



**MARMARA UNIVERSITY  
INSTITUTE FOR GRADUATE STUDIES  
IN PURE AND APPLIED SCIENCES**



**Computational Prediction of Genomic and Proteomic  
Biomarker Candidates for Reproductive System  
Associated Women Diseases**

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MEDİ KORİ

**M.Sc. THESIS**  
Department of Bioengineering

**ADVISOR**  
Assoc. Prof. Dr. KAZIM YALÇIN ARĞA

**ISTANBUL, 2015**

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**PURE AND APPLIED SCIENCES**

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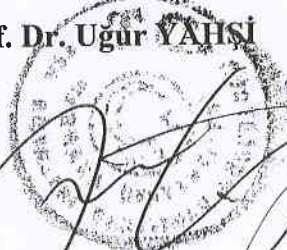
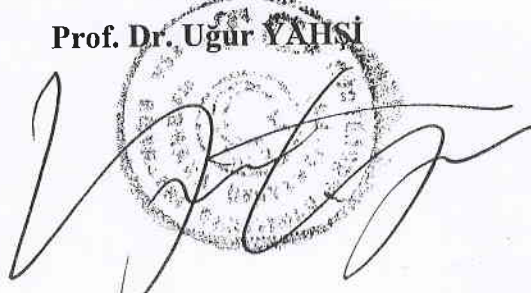
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**April, 2015**

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## ÖZET

### Üreme Sistemiyle İlişkili Kadın Hastalıkları için Genomik ve Proteomik Aday Biyobelirteçlerin Hesapsal Olarak Öngörülmesi

Kısırlık dünyada birçok çifti etkileyen ve gittikçe büyüyen bir tıbbi problemdir. Güncel çalışmalar, 2010 yılında dünyada 48,5 milyon çiftin 5 yılın sonunda canlı bir doğum gerçekleştiremediğini göstermiştir. Kısırlığın sebebi çiftler olduğu gibi bireysel yani kadına ve erkeğe bağlı nedenler de olabilmektedir. Ama yapılan çalışmalar kadına bağlı kısırlık sebeplerinin diğer kısırlık sebeplerine oranla daha yüksek olduğunu göstermiştir. Kadın kısırlık nedenleri çok fazla olmakla beraber, kadın kısırlığıyla ilişkilendirilmiş, klinik veya klinik belirtiler göstermeyen, çok çeşitli hastalıklar vardır. Bu çalışmada, kadın kısırlığı ile ilişkilendirilmiş hastalıkların: rahim ağzı kanseri, yumurtalık kanseri, rahim fibroidleri, endometriosis, polikistik over sendromu ve ayrıca insülin direncinin, biyolojik mekanizmasında anahtar rol alan, önemli biyolojik birimleri (gen, protein, yolak v.b.) tanımlayabilmek için bir sistem biyolojisi yaklaşımı uygulandı. Buna göre, rapor edilmiş transkriptom veri setlerinin (rahim ağzı kanseri 2 veri seti, yumurtalık kanseri 2 veri seti, rahim fibroidleri 2 veri seti, endometriosis 3 veri seti, polikistik over sendromu 7 veri seti ve insülin direnci 3 veri seti) istatistiksel olarak analiziyle her bir veri seti için gen ifadesi anlamlı düzeyde değişen genler saptandı. Hastalıklar ve biyolojik yolaklar arasındaki ilişkiyi haritalamak için zenginleştirme analizleri yapıldı. Daha sonra, anlatımı anlamlı derecede farklılık gösteren genlerin etrafında protein-protein etkileşim ağı oluşturuldu. Oluşturulan protein-protein etkileşim ağının değişik metrikler kullanılarak topolojik analiziyle merkezi proteinler saptandı. Son olarak, tüm bulunanlar göz önünde bulundurularak incelenen hastalıklar için aday biyobelirteçler ve/veya ilaç tasarımına yönelik önemli olabilecek genler ve proteinler önerildi.

Nisan, 2015

Medi Kori

## **ABSTRACT**

### **Computational Prediction of Genomic and Proteomic Biomarker Candidates for Reproductive System Associated Women Diseases**

Infertility is a worldwide growing medical problem which affects many couples around the world. Current studies predicted that, at 2010 there were 48.5 million couples throughout the world, who unable to have a live birth at the end of the 5 years experience. Infertility can be caused by couples or individually, namely by female and male related reasons. However, it was shown that, the ratio of the female infertility related causes is relatively higher than the other infertility related reasons. Although, female infertility causes are substantially variable there are wide range of women diseases, either clinical or subclinical, that were associated with female infertility. In the present study, a systems biology approach was applied to identify the significant biologically relevant entities (genes, proteins, pathways etc.) taking key roles in biological mechanisms of the infertility-associated woman diseases: cervical cancer, ovarian cancer, uterine fibroid, endometriosis, polycystic ovary syndrome, besides insulin resistance. According to this, reported transcriptomics datasets (cervical cancer 2 datasets, ovarian cancer 2 datasets, uterine fibroid 2 datasets, endometriosis 3 datasets, polycystic ovary syndrome 7 datasets and insulin resistance 3 datasets) were analyzed statistically to identify differentially expressed genes (DEGs) for each dataset. Enrichment analyses were performed to map the interconnectivities between diseases and biological pathways. Later, protein-protein interaction networks around the DEGs were reconstructed. Topological analyses of the reconstructed protein-protein interaction network with different topological metrics indicated the presence of the hub (central) proteins. Finally, via discussion of the findings in overall, significant genes and encoded proteins, which may be considered as candidate biomarkers and/or drug targets for the inspected diseases, were suggested.

**April, 2015**

**Medi Kori**

## **SYMBOLS**

**$\alpha$ :** Alpha

**$\beta$ :** Beta

**$\varepsilon$ :** Epsilon

**$\gamma$ :** Gamma

**$\eta$ :** Eta

**$\tau$ :** Tau

**$\zeta$ :** Zeta

**$\sigma$ :** Sigma

## **ABBREVIATIONS**

<b>WHO</b>	: World Health Organization
<b>FSH</b>	: Follicle Stimulating Hormone
<b>AMH</b>	: anti- Mullerian Hormone
<b>POF/POI</b>	: Premature Ovarian Failure/Primary Ovarian Insufficiency
<b>BMI</b>	: Body Mass Index
<b>LH</b>	: Luteinizing Hormone
<b>IARC</b>	: International Agency for Research on Cancer
<b>HPV</b>	: Human Papillomavirus
<b>FIGO</b>	: The International Federation of Gynaecology and Obstetrics
<b>PCOS</b>	: Polycystic Ovary Syndrome
<b>GnRH</b>	: Hypothalamic Gonadotropin Releasing Hormone
<b>SHBG</b>	: Sex Hormone-Binding Globulin
<b>ASRM</b>	: American Society of Reproductive Medicine
<b>ESHRE</b>	: European Society for Human Reproduction
<b>NIH</b>	: National Institutes of Health
<b>GEO</b>	: Gene Expression Omnibus
<b>NCBI</b>	: The National Center for Biotechnology Information
<b>Biodbnet</b>	: Biological Database Network
<b>DAVID</b>	: The Database for Annotation, Visualization and Integration Discovery
<b>OMIM</b>	: Online Mendelian Inheritance in Man
<b>KEGG</b>	: Kyoto Encyclopedia of Genes and Genomes

<b>GO</b>	: Gene Ontology
<b>EBI</b>	: European Bioinformatics Institute
<b>GOA</b>	: The Gene Ontology Annotation
<b>RMA</b>	: Robust Multi-Array Average
<b>DEG</b>	: Differentially Expressed Gene
<b>BIND</b>	: Biomolecular Interaction Network Database
<b>BioGRID</b>	: Biological General Repository for Interaction Dataset
<b>DIP</b>	: Database of Interacting Proteins
<b>HPRD</b>	: Human Protein Reference Database
<b>CORUM</b>	: Comprehensive Resource of Mammalian Protein Complexes
<b>MPPI</b>	: Mammalian Protein-Protein Interaction Database
<b>OPHID</b>	: The Ontario Population Health Index of Databases
<b>MINT</b>	: Molecular Interaction database
<b>RT-PCR</b>	: Real Time Polymerase Chain Reaction

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# 1. INTRODUCTION

## 1.1. Aim

Infertility is a growing medical problem affecting many couples in the worldwide. Current studies predicted that, at 2010 there were 48.5 million couples throughout the world, who unable to have a live birth at the end of the 5 years experience (Mascarenhas et al., 2012). According to Turkish Ministry of Health, in Turkey approximately 2 million couples are unable to have a child. Infertility clinically described as “a disease of the reproductive system defined by the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse” (Zegers-Hochschild et al., 2009). Besides Practice Committee of the American Society for Reproductive Medicine defined infertility as a, failure to become pregnant after 12 months regular intercourse for women who is under age 35 and 6 months women who is over age 35, without using any contraception (Practice Committee of American Society for Reproductive Medicine, 2013). In general there are 2 types of infertility which are primary and secondary infertility. Primary infertility is described as the inability to have any live birth, and secondary infertility is an inability to have a child once again providing that the prior live birth didn't require any infertility treatment (Mascarenhas et al., 2012; Katib et al., 2014). Infertility can be produced by couple or separately female and male causes, but studies have shown that, ratio of the infertility by female causes is relatively higher than others (Cozaru et al., 2012). Despite female infertility causes are substantially variable; most common factors associated with female infertility are lifestyle factors and several diseases.

Although several women diseases are associated with female infertility and some experimental studies reporting transcriptome analysis for each of these diseases exist, these diseases were not analyzed from an integrated and comparative perspective. Therefore, these individual studies are far away to map the interconnectivities between complex diseases and to identify genomic and proteomic biomarkers. The aim of the study is to perform comparative analysis via integration of transcriptomics and proteomics datasets for infertility-associated women diseases and identify candidate genes and proteins that have the potential for being biomarker for infertility-associated

women diseases. Also the study has the potential to identify the interconnectivities between/among complex human diseases and biological pathways. Furthermore results of this study will be used to design new experiments with the final goal of manufacturing diagnostic kits and biomedical devices for the inspected diseases.

## **1.2. Female Infertility**

For a women, infertility can be described as, (i) the inability to become pregnant, (ii) an inability to sustain a pregnancy, (iii) an inability to resume pregnancy which results to a live birth according to World Health Organization (WHO) (<http://www.who.int/topics/infertility/en/>).

Researchers mainly focus and deal with the causes and risk factors of female infertility. Besides, female infertility causes and risk factors are varying, these causes and risk factors are differing from person to person. Mainly encountered, seen and investigated as infertility causes that are associated with female infertility are shown in the Table 1.1.

### **1.2.1. Changeable Lifestyle Factors**

Lifestyle factors reflect a person's attitudes and values, and it can easily affect person's general health and reproduction. Although these lifestyle factors are comprehensive and modifiable, some of them, including delayed child bearing, body weight, smoking, caffeine and alcohol consumption can directly affect women's reproduction ability (Petraglia et al., 2013).

#### **1.2.1.1. Delayed Child Bearing**

In today's conditions, in particular, women who live in metropolitan areas are postponing child bearing to have a well education, career or to advance in career. However the studies have shown that, number and quality of the oocytes are decreasing in aging women; therefore, their fertility capacity were declined depending on their growing age (Velde and Pearson, 2002). Compared by maternal age, women aged 35-39 have two fold less chance than women who aged 19-26 (Dunson et al., 2002).

**Table 1.1.** Some causes of female infertility.

CHANGEABLE LIFESTYLE FACTORS	Delayed Child Bearing, Body Weight, Smoking, Caffeine and Alcohol Consumption
OVARIAN REGION ASSOCIATED WOMEN DISEASES	Premature Ovarian Failure, Polycystic Ovarian Syndrome, Ovarian Cancer
UTERINE and TUBAL REGIONS ASSOCIATED WOMEN DISEASES	Uterine Fibroid, Uterine Cancer, Fallopian Tube Blockage
CERVICAL REGION ASSOCIATED WOMEN DISEASES	Cervical Cancer
ALL ABDOMEN ASSOCIATED WOMEN DISEASES	Endometriosis
ENDOCRINE ASSOCIATED WOMEN DISEASES	Thyroid Disorder, Cushing Syndrome, Acromegaly, Addison Disease
OTHERS	Cancer Treatment, Diabetes Mellitus, Celiac Disease, Beta-Thalassemia Disease, Turner Syndrome, Kallmann Syndrome, Recurrent Pregnancy Lost

Females are born with apparent ovarian reserve which is approximately 1-2 million oocytes. As time passes, women's oocyte number decreases, namely the decrease starts with menarche and proceeds through the menses. It's terminating when only a several hundred oocytes left over (which is called menopause) and generally the mean age of menopause accepted as 51 (The American College of Obstetricians and Gynecologists Committee on Gynecologic Practice and The Practice Committee of the American Society for Reproductive Medicine, 2014).

Ovarian age describes women's remaining fertility ability, which is directly related with women's total ovarian reserve (Gleicher et al., 2011). While the ovarian reserve depleted related to advancing age, usually 6-7 years before menopause, women experience menstrual irregularities and long intermittent menstrual cycles. Namely women's child bearing ability starts to decline 10 years before menopause which is equal to women's late-30's (Liu and Case, 2011). There are countless tests to detect women's total ovarian reserve in order to comprehend their fertility ability. The most preferred tests are

measurement of follicle stimulating hormone (FSH) and anti-Mullerian hormone (AMH) in serum levels. If the serum FSH level equal or greater than 10mIU/ml, it is accepted that ovarian reserve is decreased (Sengul et al., 2014). AMH is a dimeric glycoprotein which is produced by granulosa cells during the reproductive ages, in this manner any reduction of AMH serum levels reflect reduction of ovarian reserve (Aboulgar, 2014).

Except menopause, ovarian reserve depletion can occur in another ways, for instance chemotherapy, radiation or depending on the disease which is named premature ovarian failure (POF)/primary ovarian insufficiency (POI). POF is described depletion of functional primordial follicles or loss of ovarian function and reserve before the age 40. Although the causes are various, it can be divided in 5 categories such as genetic, autoimmune, infectious, metabolic dysfunctions or iatrogenic. POF affects approximately %1 of women and patients have low levels of AMH, high levels of FSH and they experience at least 6 months amenorrhea before the age 40 (Tilly and Sinclair, 2013; Wood and Rajkovic, 2013; Cox and Liu, 2014; Caburet et al., 2014). Eventually, POF disease obstructed women's fertility ability before the age 40 or before their spontaneously menopause age (Pouresmaeili and Fazeli, 2014).

Due to the increase of women age, the possibility of occurrence chromosomal abnormalities and aneuploidy in the oocytes considerably increases and this situation increased the probability of infertility, miscarriages and birth defects (Selesniemi et al., 2011).

For fertilization oocytes pass through two meiotic division, meiosis I and II. In meiosis I, chromosomes reduce its number in one in half and become haploid to prepare itself to the fertilization, because if the oocyte is fertilizing by the sperm it can form a diploid embryo which is expected. Unfortunately depending on advance women age, meiotic cell cycle errors occurrence excessively increases such as nondisjunction or chromosome segregation errors. These errors decline the quality of the oocytes, therefore incidences of infertility, miscarriages or birth defects is increased (Hunt, 1998). Down syndrome, trisomy 21 is most known chromosome nondisjunction which is mostly connected with advance maternal age (Allen et al., 2010).

### **1.2.1.2. Body Weight**

Body weight reflects a person's feeding behavior and physical activity (Spiegelman and Flier, 2001). Body weight cause many health problems, including reproductive health problems in both male and female. Generally body weight defined by using body mass index (BMI) measurement. BMI calculated as weight in kilograms and divided the square of height which is in meters. If BMI is below 18.5 its considered underweight, between 18.5 and 24.9 normal, between 25 and 29.9 overweight and over 30 obese.

Being underweight have negatively affect on reproduction health. It can cause ovulatory dysfunctions, menstrual irregularities and hormone imbalances and these causes increased infertility frequencies (Sharma et al., 2013).

Obesity usually associated with menstrual cycle irregularities s and principally connects with ovulatory dysfunction (Practice Committee of American Society for Reproductive Medicine, 2008). Obesity influence menarche time and cause hirsutism. Also it was found that generally polycystic ovary syndrome patients have high BMI value (Pasquali et al., 1997). Obesity increases the probability of miscarriages and inborn defects. Besides, obesity enhances time to conceive even women with regular menstrual cycles. Obesity can affect oocyte maturation depending on the various hormonal imbalances, especially steroid hormone. Steroid is necessary for oocyte maturation and adipose tissue is a crucial tissue for steroid production. Due to the increased BMI value, excessive serum insulin levels develops in the cells which is associated with steroid hormone binding globulin (SHBG) reduce. This SHBG decrease can cause raise in androgens in follicular fluid which is unlikely event (Purcell and Moley, 2011).

### **1.2.1.3. Smoking**

Cigarette smoke includes approximately 4000 compounds and the cigarette's major components that affect people's health is nicotin. Multiple studies have shown that the negative relation between smoke and reproduction health, namely their fertility capacity. Maternal smokers have more menstrual irregularities and pregnancy complications such as premature birth, harm to the developing embryo and miscarriages than non-smokers (Mostafa, 2009; Agarwal et al., 2012). Furthermore their chance to conceive is decreased. Smoker's spontaneous menopause age is lower than non-

smokers. Also in a study, when AMH serum levels compared with smokers and non-smokers they found smokers have lower AMH levels which means that, smokers have poor ovarian reserve than the non-smokers. Also maternal smokers have nicotine in their endometrium and follicular fluid therefore; their fetal development begins in poisonous place which can pose a problem (Dechanet et al., 2010). Besides, maternal smokers response to the infertility treatment is low and even passive smoking can affect embryo quality in in-vitro fertilization treatments (Wdowiak et al., 2013).

#### **1.2.1.4. Caffeine and Alcohol Consumption**

Caffeine can cause hormonal changes and this may affect menstrual function. Maternal caffeine consumers' probability to have menstrual abnormalities and heavy menses (such as oligomenorrhea) are higher than non-consumers. Researchers explain this relation through on sex hormones and receptors because, coffee's components are found slightly oestrogenic. Caffeine may inhibit the adenosine action which can impress FSH and luteinizing hormone (LH). Consequently these can influence menstrual cycles (Mahmoud et al., 2014).

Studies indicated that high alcohol intake associated with higher risks of infertility and low consumers have considerable lower risks. That's why the amount of alcohol intake is important; however there isn't any specific deterministic alcohol intake (Eggert et al., 2004). Maternal alcohol consumption give rise to maturation disorders, difficulties to conceive, complications during the pregnancy and embryo development problems. Studies showed that restriction or stop to consumption alcohol can increase the embryo quality therefore, achievement rates in in-vitro fertilization treatments are increased (Wdowiak et al., 2014). Besides, another study found a relation between alcohol intake and ovulatory disorder that is associated with infertility (Chavarro et al., 2009).

#### **1.2.2. Infertility Associated Women Diseases**

There is wide range of women diseases, either clinical or subclinical, that associated with infertility. Although the diseases are vary, diseases can be classified by their region, in other words where the disease occurs. Basically diseases can classify by uterine, ovarian and cervical regions, besides the disease can occur all abdominal

region. Certain significant infertility associated women diseases that underlying all abdominal regions is endometriosis and for uterine region is uterine fibroids. Likewise some considerable infertility associated women diseases that lying underneath ovarian region are polycystic ovarian syndrome and ovary cancer and for cervical region most known disease is cervical cancer.

### **1.2.2.1. Cervical Cancer**

Cervical cancer is one of the major and fatal health problems among women. Cervical cancer is the second most common cause of cancer among women in the worldwide and frequent cause of cancer death, especially when cervical cancer diagnosed in advanced stages foregone conclusion is death (Ancuta et al., 2014). According to International Agency for Research on Cancer, (IARC) 266000 women death occurred because of cervical cancer and approximately 528000 new cases are developed in 2012 throughout the world (The International Agency for Research on Cancer, 2012).

Cervical cancer arises from Human Papillomavirus (HPV) infection and in the world wide 99.7% of cervical cancer cases originate from HPV infection (Van Krieking et al., 2014). HPV infection can occur mainly with sexual intercourse also it's occurrence rises corresponding to higher number of sexual partners, initiation of sexual intercourse at age 18 or before 18, have first full term pregnancy before 18, 4 or more natural childbirth, using combined hormonal oral contraceptives 5 or more than 5 years and history of other sexually transmitted infections for example HIV infection (McGraw and Ferrante, 2014). Besides these causes, body mass index and educational background factors can affect cervical cancer development. Moreover several genes such as interferon regulatory factor 1 (IRF-1) and fragile histidine triad (FHIT) are associated with cervical cancer (Hu et al., 2014). HPV is a small double stranded DNA virus which can induce differentiating various lesions and constitute hyperproliferative tissues. It was estimated that in 2008 approximately 12.7 million new cancer cases occurred and 4.8% cases were arises from HPV infection. In 1977 it was found that HPV is an important factor for cervical cancer and HPV16 and HPV18 are discovered in cervical cancer in 1983-84. Now HPV16 and 18 are mostly known viruses that associated with influencing cause of cervical cancer development. As well as, HPV6 and HPV11 identified as a chiefly cause of genital warts, which is common among women. The other HPV types

in different qualifications are as shown in the Table 1.2 (Bazarra-Fernandez, 2010; Morshed et al., 2014). HPV16 mainly cause squamous cell carcinoma, HPV18 cause adenocarcinoma which is more aggressive and less common than squamous cell carcinoma (McGraw and Ferrante, 2014). Usually HPV infection happens in early 20's or 30's but consisted of lesion changes may cause cervical cancer after 20 or more years so generally HPV infection that causes cancer generally not show any symptoms except the late stages of the cancer (Nnadi et al., 2014).

Medical diagnosis of cervical cancer in late stages can derives almost one year survival, but treatment of cervical cancer with early stages is more feasible and successful. Therefore in cervical cancer screening is crucial for early detection (Haedicke and Iftner, 2013). For screening various tests can be used, most commonly cervical cytology is preferred, except this direct visual inspection, visual inspecting with using acetic acid or lugol's iodine, HPV DNA testing, speculoscopy and polar probes can be used. If these tests culminate with abnormal results, colposcopy, microcolpohysteroscopy and cervicography can be used afterwards (Aggarwal, 2014). Generally, it is suggested that for a women who aged between 21- 65 should screen only with cytology every 3 years. However women between ages 30-65 should prefer to screen with cytology and HPV testing every 5 years (Saslow et al., 2012).

Like screening methods treatment methods are varies. Due to the cervical cancer affects reproductive age women, it's important to select convenient treatment according to the cancer stage and women's fertility prevention desire. Radiotherapy and chemotherapy is most applied and known cervical cancer treatments (Ganesh et al., 2013). Besides, there are alternative surgical options which purpose to remove cervical cancer tissues for example, conization, cryosurgery, laser vaporization, and loop electrosurgical excision. However both radiotherapy/chemotherapy and surgical treatments will cause damage or disappearances in some healthy cervical tissues too. Correspondingly, cervical tissues structure and functions (especially mucus production function), which provides to sperm transport from the vagina, is destroyed (Spracklen et al., 2013). That's why treatments like radiotherapy/chemotherapy or surgical may cause infertility so, these treatments inconvenient for reproductive women who want to preserve their fertility.

**Table 1.2.** HPV types in different oncogenic qualifications (Morshed et al., 2014).

HPV's ACCORDING TO ONCOGENIC POTENTIAL	
LOW ONCOGENIC POTENTIAL	6, 11, 42, 43, 44
INTERMEDIATE ONCOGENIC POTENTIAL	31, 33, 35, 51, 52
HIGH ONCOGENIC POTENTIAL	16, 18, 45, 56

Reproductive women with a diagnosis of early stage cervical cancer have feasibility to conserve fertility due to the developing methods so, early diagnosis is significant again especially in young women. Radical trachelectomy is a surgical treatment which can applied abdominally, vaginally, laparoscopically or robotically in early cervical cancer stages and the treatment provides fertility preservation because of this, it's applied especially in young women who wants to preserve their fertility capacity (Mejia-Gomez, 2012). For cervical cancer protection scientists developed HPV vaccines which are also avail to protect from genital warts. There are two types of HPV vaccines, which are bivalent vaccine (called Cervarix) and quadrivalent vaccine (called Gardasil). Both are given in 3 doses at certain times. Although the vaccine should be given before sexual debut for optimal benefit, there isn't any certain age to apply besides, vaccines application changes from country to country (Dochez et al., 2014).

#### **1.2.2.2. Ovarian Cancer**

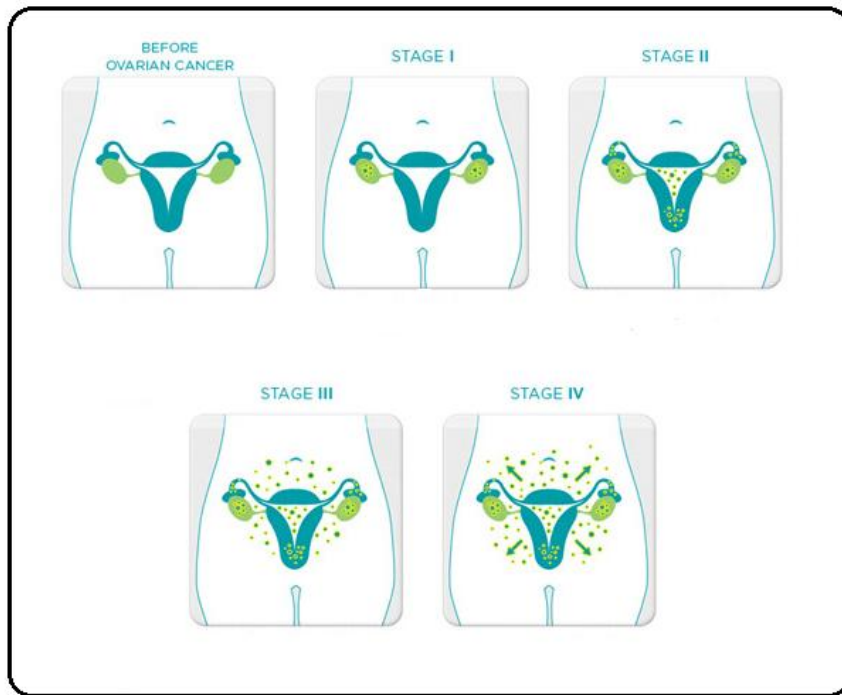
Ovarian cancer is the second most encountered gynecologic cancer type throughout the world. Approximately in the worldwide ovarian cancer prevalence access; 6.1 per 100,000 women and mortality rate access 3.8 per 100,000 women (Didžiapetrienė et al., 2014).

Ovarian cancer starts in the ovaries then bounce to pelvic organs later to the abdominal cavity and at the end cancer can spread beyond to these regions. Ovarian cancer is separated in 4 stages based on The International Federation of Gynaecology and Obstetrics (FIGO) staging system. Accordingly to this system, if cancer only remains in

ovaries it is stage I, if cancer spread to the pelvis stage II, if it bounce to the abdominal organs stage III and finally if it's spread in abdominal cavity it is stage IV (Figure 1.1) (Rossing et al., 2010). The Gynecologic Cancer Foundation, the Society of Gynecologic Oncologists, and the American Cancer Society declared an agreement about certain ovarian cancer indications in 2007. According to this ovarian cancer apparent symptoms are bloating, pelvic or abdominal pain, difficulty eating or feeling full rapidly, and urinary urgency or frequency. Moreover they recommend that if these symptoms proceed more than a few weeks and persistent patient should get examined (Kurman et al., 2008).

There are some risk factors that associated with ovarian cancer. These factors contain an ovulation, infertility, infertility drugs, women who have menstrual abnormalities or never give a birth, polycystic ovary syndrome, endometriosis and pelvic inflammatory diseases. It was reported that women that never give a birth have two or three fold increased ovarian cancer risk compared to women who have a child (Brinton et al., 2003; Tomao et al., 2014). Furthermore a lot of study reported that there is relation between genetic alterations and ovarian cancer. P53 gene mutations highly appeared in ovarian cancer. Moreover BRCA1 and BRCA2 were highly encountered in ovarian cancer patients. BRAF and KRAS genes mutations are considerable genetic alterations that associated with stage I ovarian cancer. Also it was shown that PTEN, NF1, RB1, FAT3, CSMD3, GABRA6, PIK3CA, NRAS, AKT2 and CDK12 mutations and HER2/neu amplification can occurred in ovarian cancer (Lee et al.,2013).

Like all types of cancers, early diagnosis of the ovarian cancer provides more efficient treatments so high survival rates and approximately 10% ovarian cancer deaths can preventable. However often ovarian cancer diagnosed in stage III or IV, and unfortunately under than 30% of women diagnosed in stage I. 20% patients who diagnosed in stage III will survive up to five years whereas if women diagnosed in stage I their 5 year survival rise to 90%. Several screening methods suggested for early detection such as; abdominal and transvaginal ultrasonography, computed tomography, or magnetic resonance imaging. As well as, National Institute for Health and Clinical Excellence recommend examining CA125 serum marker concentrations especially for symptomatic women (Hippisley-Cox and Coupland 2012).



**Figure 1.1** 4 stages of ovarian cancer (<http://smrfteal.org/about-ovarian-cancer/stages/>)

Essentially CA125 marker was developed to observe already diagnosed ovarian cancer patient, not for early diagnosis because CA125 is screening method which is not convenient and sensitive for early screening. It is estimated that only 50–60% of the stage I patients CA125 serum levels increased whereas, 90% of the advanced stage patients have elevated CA125 concentration. Moreover noncancerous diseases like endometriosis, adenomyosis, ovarian cysts, uterine fibroids, renal dysfunction and hepatic diseases can cause elevated CA125 serum levels (Das and Bast, 2008).

Ovarian cancer can be treated in several ways depending on diseased women's cancer stage. Ovarian cancer treatment includes chemotherapy, medical surgery or drug treatment (Luvero et al., 2014). However, it is estimated that 10% of the ovarian cancer case occur in reproductive aged women so especially for young women early diagnosis is significant because early diagnosis enables treatments that can conserve women's fertility ability. For this fertility sparing surgery was applied if reproductive aged women have a strong desire to conserve her fertility ability (Lee et al., 2014).

### 1.2.2.3. Uterine Fibroids

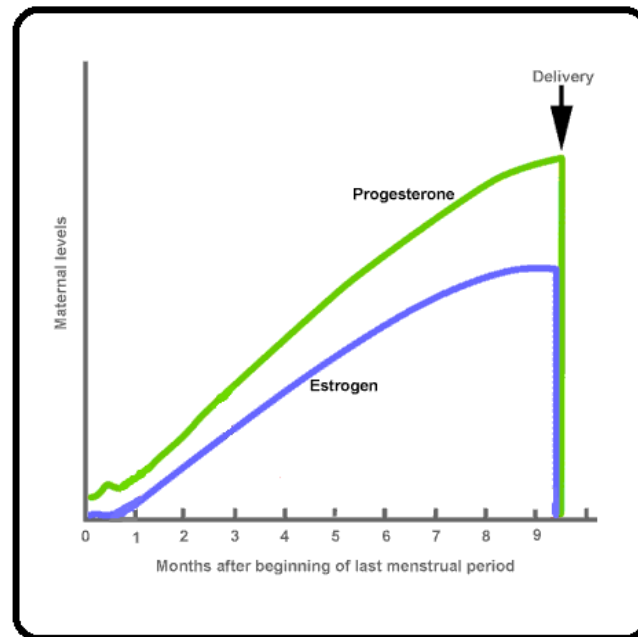
Uterine fibroids (fibroid tumors, fibromyomas, myomas or leiomyomas) are the benign tumors of the uterus which was known since in ancient times, it was reported that Hippocrates mentioned uterine fibroids as a "uterine stones". A German pathologist, Virchow used the term myoma for the first time and discovered that these fibroids were consisted from the smooth muscle cells. As well as the term fibroid was firstly used and introduced by Rokitansky in 1860 and Klob in 1863 (Bozini and Baracat, 2007). Uterine fibroids described as benign smooth muscle tumors of the uterus myometrium which is frequently encountered in women (Marino et al., 2004). Uterine fibroids are consisted abounded quantities of extracellular matrix. It contains fibronectin, proteoglycan and mostly collagen, especially collagen I and III and it is known that the collagen fibrils are formed abnormally and in keloid formation in diseased myometrium (Parker, 2007). In women, uterine fibroid generally diagnosed incidentally that's why, many women unaware that they have the disease. According to this, knowing the accurate prevalence of disease is difficult and limited, nevertheless it is estimated that approximately 20%-40% reproductive women has the disease (Mavrelou et al., 2010). However, it is known that the prevalence increase depending on women's descent and age. Black women have 2 to 3 fold higher risk of developing uterine fibroid than white women and among the premenopausal women, incremental age causes greater risk for uterine fibroids (Wise et al., 2005).

Uterine fibroid's certain cause or causes are unknown but it's generally associated with hormonal, epigenetic or genetic and modifiable life factors. It's usually admitted that human sex hormones and steroids are induced uterine fibroid enhance. It's generally thought that, an estrogen; 17 $\beta$ -estradiol (E2) is associated with uterine fibroid. This association is explained like that, (i) uterine fibroids compromised after puberty due to the increased E2 levels, (ii) uterine fibroids are declined after menopause because of reducing E2 and (iii) estrogen receptors antagonists including selective estrogen receptors modulators, induce proliferation of uterine fibroids due to the E2 decreasing. Moreover progesterone can stimulate the fibroid growth (Nierth-Simpson et al., 2009). During pregnancy the levels of the estrogen and progesterone increased. That is to say, generally pregnancy give rise to the uterine fibroid growth, but this growth often occurs

in first 12 weeks of gestation and most of the fibroids (especially the huge ones) regress after pregnancy, because after pregnancy increased hormone levels decreased abruptly as seen in the Figure 1.2., therefore fibroids were regress after pregnancy. Correspondingly, it can be said that pregnancy has protector effect on uterine fibroid formation (Practice Committee of American Society for Reproductive Medicine in collaboration with Society of Reproductive Surgeons, 2008; Walker et al., 2001). Also, premenopausal black women have higher sex hormone levels than white women. Therefore, black women have higher risk of fibroid development and disease incidence is higher than white women because of incremental hormone levels (Wise et al., 2004). Apart from hormones genetic factors can cause uterine fibroid formation. It's been reported that approximately 70% of the uterine fibroid cases consisted of transcriptional mediator subunit, MED12, mutations (Turunen et al., 2014). Germline mutations in fumarate hydratase gene (FH) can cause uterine fibroid (Lehtonen et al., 2004). Also studies show that chromosomal rearrangements (for example translocations involving the HMGA2 gene) can cause uterine fibroid development (Cirilo et al., 2013). Moreover, modifiable risk factors such as smoking and alcohol consumption can increase uterine fibroid possibility due to the changes in hormone levels (Wise et al., 2004). Although menarche, number of child delivery, menopause, oral contraceptives and excess body weight can affect uterine fibroid's formation (Flake et al., 2003).

Uterine fibroids generally remained undiagnosed, because in most cases women not have any symptoms. Despite that, women who experience symptoms are variable person to person depending on fibroid's number, location and size. Women may have one or more than one fibroid and multiple fibroids increased the symptoms occurrence. Fibroids classified as a sub-mucous, intramural and subserosal fibroids related to their location and sub-mucous fibroids are generally showing more symptoms than other two (Bajekal and Li, 2000). Women who have 5 or greater than 5 cm diameter fibroid, which means that widen the uterus like 12 week pregnancy, would likely to have more symptoms (Davis et al., 2009). Diseased women experience difficulties to conceive, preterm birth, spontaneous abortion, pelvic pain, heavy, painful menstrual bleeding, often leading to anemia, dyspareunia and dysmenorrhea (Laughlin et al., 2009; Lippman et al., 2003, Wechter et al., 2011). As well as uterine fibroids were the single factor that cause infertility in <10% infertility cases (Flake et al., 2003).

Uterine fibroids have miscellaneous treatments such as medical therapy, hysteroscopic and laparoscopic myomectomy, uterine artery embolization and focused ultrasound. For medical therapy non-steroidal anti-inflammatory drugs, gonadotropin releasing hormone agonists, progesterone mediated medical treatments are used and for surgical treatments generally myomectomy is preferred (Parker, 2007).



**Figure 1.2.** Progesterone and estrogen hormone changes after giving a birth ([http://www.medicine.mcgill.ca/physio/vlab/other\\_exps/endo/reprod\\_horm.htm](http://www.medicine.mcgill.ca/physio/vlab/other_exps/endo/reprod_horm.htm))

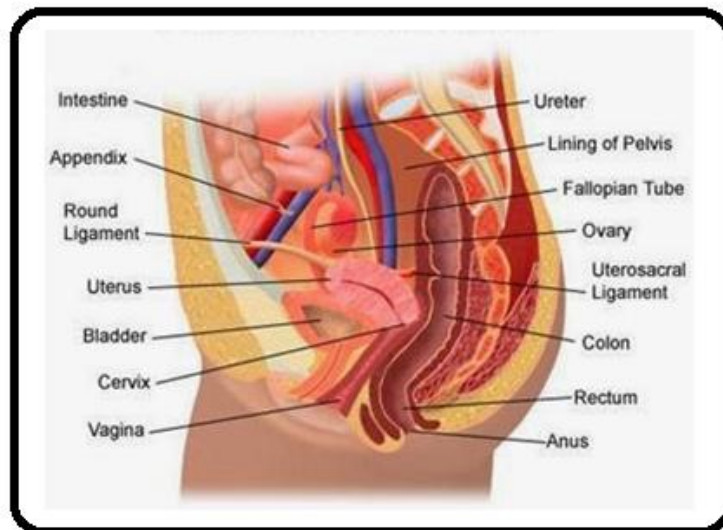
#### 1.2.2.4. Endometriosis

It has been 154 years since endometriosis's most inclusive definition defined (at the same time, first known publication published) by German scientist Carl von Rokitansky (Knapp, 1999). Despite the elapsed time there are still unknown things about the disease. There aren't certain causes and symptoms or specific region that disease occurs. Therefore the disease usually accepted as a heterogeneous disease (Becker et al., 2014). Although determination of endometriosis prevalence is little unfeasible, it is estimated that at 2010 approximately 176 million women in reproductive age affected from the disease throughout the world (Johnson and Hummelshoj, 2013).

Endometriosis is conventionally defined by presence of a tissue that is similar to uterine endometrial tissue in extra-uterine sites (Simoens et al., 2007). Also it's described as an inflammatory disease which is chronic, benign and estrogen-dependent (Sourial et al., 2014). Endometriosis can occur in all abdominal regions for instance ovaries, peritoneum, uterosacral ligaments, retro-cervical area, retro-vaginal septum, rectum, bladder, appendix and ureters (Bellelis et al., 2011) as seen in the Figure 1.3. However endometriosis mostly encountered at ovaries and pelvic peritoneum (Said and Azzam, 2013). Though endometriosis patients have experience variety symptoms in different severities, sometimes they not experience any symptoms. Basically endometriosis symptoms include dysmenorrhea, chronic pelvic pain, irregular uterine bleeding and/or infertility but, disease's primary symptoms are infertility and pain. It is estimated that 35%-50% endometriosis patients experience pain and/or infertility (Bellelis et al., 2011; Burney and Giudice, 2012). There are several recommended mechanisms that clarify endometriosis and infertility association. Existence of endometriosis, can ruin oocyte release from the ovary due to the deformed pelvic anatomy, negatively affect oocyte and fallopian tube function, give rise to ovulatory and endocrine disorders, decreased oocyte and embryo quality and reduce endometrial receptivity (American Society for Reproductive Medicine, 2012). Endometriosis is classified into four stages (I-minimal, II-mild, III-moderate, and IV-severe) according to American Society for Reproductive Medicine due to the location, extent and intensity of the disease and stage IV patients, infertility incidence is higher than the other stages (American Society for Reproductive Medicine, 2012).

There aren't any particular causes for endometriosis but, multiple hypotheses formed from researchers. First remarkable hypothesis formed by John A.Sampson at 1927. He gave a consideration after he realized that several extra-uterine tissues were relative to endometrial tissues. Sampson comprehended this, while he was operating a woman in her menstrual period. He observed that peritoneum regions were bleeding just like uterine endometrial tissues. Therefore, Sampson hypothesize that the endometrial like tissues was in extra-uterine regions because of, endometrial tissues retro-gated from the fallopian tubes with menstrual debris and permeated to extra-uterine regions during the menstrual cycles (Brosens and Benagiano, 2011). However when some researchers evaluated Sampson's theory, they believed that it couldn't be the only reason and

thought that, there should be something else because, virtually all women experience menstruation and practically most of the women's menstrual debris is retro-gated but, some of them come down with endometriosis. Consequently they hypothesize that patients could have functional abnormalities in the uterus endometrial tissues or the mechanism that responsible for identify and exterminate the extra-uterine endometrial tissues was withered (Fraser and Crei, 2008). Apart from that, researchers hypothesize that endometriosis can occur depending on; early menarche age, high body weight in pre-adolascence period, positive family history, environmental and lifestyle factors (Janssen et al., 2013). A study, among nearly 3000 female twins was created to indicate responsibility of genetic factors in endometriosis over familial connections and they found that genes can influence disease feasibility (Treloar et al., 1999).



**Figure 1.3.** Possible sites of the endometriosis disease

(<http://www.infertility2pregnancy.com/p/endometriosis.html>)

Due to the endometriosis disease haven't got any certain sign or symptoms, the diagnosis and treatment is difficult and varies from patient to patient. Endometriosis generally diagnosed by clinically and visualizes examinations such as ultrasound or blood tests, although there aren't any totally specific blood tests for endometriosis. In order to endometriosis treatment, surgical procedures such as laparoscopy and laparotomy can be used (Acién and Velasco, 2013). In reproductive age women generally laparoscopic surgery is preferred; because it's known that laparoscopy

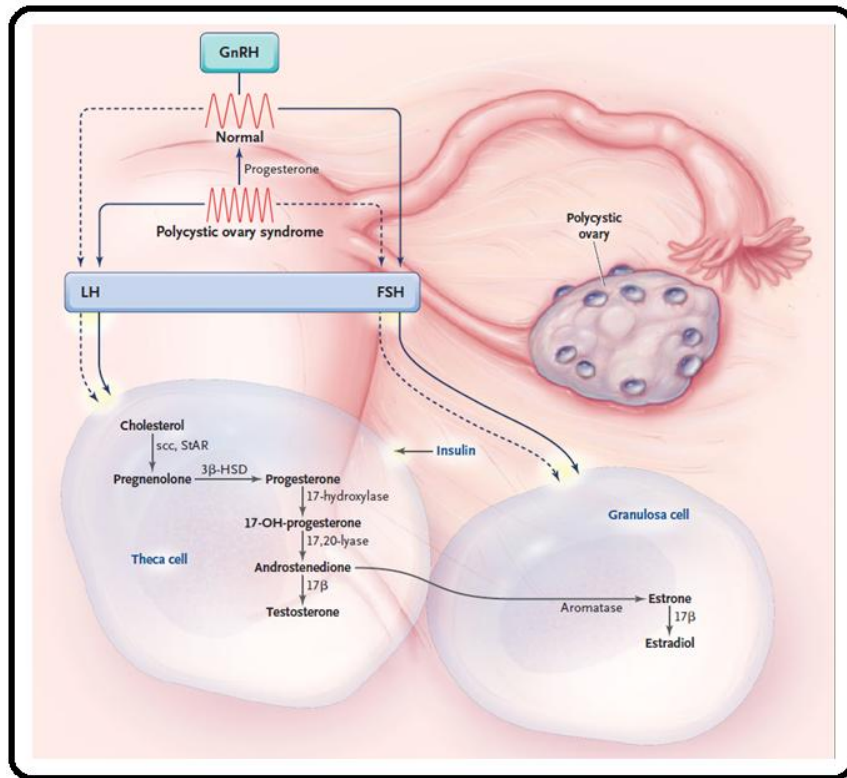
surgeries can increase women's chance of conceiving (Kim et al., 2013). Besides, pharmacological agents are convenient (especially for endometriosis associated pelvic pain treatments) which are non-steroidal anti-inflammatory drugs, aromatase inhibitors, immunomodulators, selective progesterone receptor modulators and histone deacetylase inhibitors (Zito et al., 2014). Lastly several studies have indicated that endometriosis can improve different kind of cancers, particularly ovarian cancer due to the recurrent ovulation trauma and high levels of estrogen. Furthermore, with uncertainty, some studies considered that, using ovulating stimulating drugs for endometriosis associated infertility treatments also hormonal drugs can improve ovarian cancer risk (Melin et al., 2007).

#### **1.2.2.5. Polycystic Ovary Syndrome**

Polycystic Ovary Syndrome (PCOS) is a complicated, multifactorial disorder that affects reproductive age women (Sørensen et al., 2014). PCOS was firstly described in 1935 by Irving Freiler Stein and Michael Leo Leventhal, that's why the syndrome also known as Stein-Leventhal syndrome. They described the syndrome by menstrual irregularities, infertility, hyperandrogenization, obesity, polycystic ovaries, and other factors (Adi and Tank, 2010). Although PCOS described nearly 80 years ago there isn't any universal definition for the disease. There are 3 proposed definitions for the syndrome which were constituted by National Institutes of Health (NIH) in 1990, European Society for Human Reproduction (ESHRE) and American Society of Reproductive Medicine (ASRM) in 2003 and Androgen Excess and PCOS (AE-PCOS) in 2009. NIH described PCOS as a clinical and/or biochemical hyperandrogenism with chronic absence of ovulation when the other related disorders eliminated. ESHRE/ASRM defined PCOS by 3 criteria and they suggested that PCOS patient must have at least 2 of the 3 following criteria which are clinical and/or biochemical hyperandrogenism, polycystic ovaries and oligo and/or anovulation. Finally AE-PCOS described PCOS with hyperandrogenism; hirsutism and/or hyperandrogenemia, ovarian dysfunction; oligoanovulation and/or polycystic ovaries with excluded androgen excess or associated diseases (Azziz et al., 2009). The prevalence of the disease is varying due to the using different definitions but most of the studies determined PCOS prevalence between 6-20% (Johansson and Stener-Victorin, 2013).

Polycystic ovaries are required for the syndrome. Although deuced women have polycystic ovaries some of them have PCOS because, except polycystic ovaries PCOS indicate different biochemical, clinical symptoms and features (Franks, 1997). Clinical or biochemical hyperandrogenism and chronic anovulation are main symptoms of the disease. Clinical hyperandrogenism includes hirsutism, persistent acne and/or alopecia. Hirsutism described as an excessive/increased male pattern hair growth in women and 70% women with PCOS have hirsutism. In women persistent acne and male pattern alopecia are associated with PCOS. Chronic anovulation includes amenorrhea, oligomenorrhea, dysfunctional uterine bleeding and/or infertility. It was estimated that 85–90% women with PCOS experience oligomenorrhea and 30–40% amenorrheic patient have the syndrome. PCOS is the frequent cause of anovulatory infertility (Sheehan, 2004; Allahbadia and Merchant, 2010). The incidence of anovulatory infertility in PCOS women varies between 35% and 94% (Sheikhha et al., 2007).

There isn't any unique reason that completely related to PCOS, but it's known that excessive ovarian androgen production is main cause of the syndrome. The hypothalamic gonadotropin releasing hormone (GnRH) pulse frequency regulates LH and FSH secretion. LH secretion provides ovarian androgen production in ovarian theca cells. FSH stimulates aromatase activity in ovarian granulosa cells and by aromatase activity androgenic steroid, androstenedione, constitutes to estrone (Figure 1.4). High GnRH pulse frequency causes LH secretion whereas low GnRH pulse frequency leads FSH secretion. It was known that, PCOS patients have increased LH secretion for this reason their GnRH pulse frequency must be high. It is not clear what cause GnRH acceleration but it was thought that low progesterone levels can cause high GnRH pulse frequency. As a result low progesterone levels leads high GnRH pulse frequency, this situation give rise to LH secretion and ovaries produce more androgen. The relative decline in FSH secretion cause less aromatization of androstenedione to estrone therefore this ruined follicular development and induce infrequent menstrual cycles (David and Ehrmann, 2005). Moreover there are several studies reported that some genes are play a part in PCOS development. However there aren't any certain genes that accepted by everybody. These proposed genes usually involved in ovarian and adrenal steroidogenesis, steroid hormone action, energy homeostasis, gonadotropin action and regulation and insulin action and secretion (Prapas et al., 2009).



**Figure 1.4.** A brief scheme describing the main mechanism of PCOS (David and Ehrmann, 2005)

PCOS occurrence possibilities are associated with number of situations. Syndrome's occurrence is rises if women have hyperinsulinemia or insulin resistance. Also being overweight or obese affects PCOS probability. Hyperinsulinemia, excessive levels of insulin in blood, is related with ovulation disorders, multiple small follicle formation and high ovarian androgen secretion (Homburg, 2009). Insulin resistance is a state which body cells become resistant to insulin, cells normally produce insulin but unable to biological responds so briefly, this condition leads to high blood insulin (Panag et al., 2014). It has been reported that approximately 50–75% women with PCOS have insulin resistance (Belani et al., 2014). High insulin levels is enhanced ovarian androgen synthesis because it's acts like LH and high insulin levels inhibits SHBG production which cause biocompatible, free testosterone increasing (David and Ehrmann, 2005). Obesity or being overweight is associated with further hyperandrogenism, high free testosterone levels and low FSH secretion. Also the studies have been show that being overweight or obese can improve insulin resistance development as well as PCOS development. It was estimated that between 38% and 88% women with PCOS are

overweight or obese. Moreover studies show that overweight or obese PCOS women have more severe symptoms than ideal weight women. Even 5% weight loss can decrease symptoms severities (Mahmoud et al., 2015).

Ideally for the PCOS treatment, patient should firstly exclude all other etiologies like insulin resistance or obesity. If these etiologies are observed in patient, patient primarily change her lifestyle. Diseased women should go on diet to lose a weight and lower blood insulin levels. These should give rise to nearly normal ovulatory and decreased hyperandrogenism severity (Kawwass et al., 2010). Thereafter drug therapies are initiated. Generally clomiphene citrate is used to induce ovulation. Gonadotrophins are used for clomiphene citrate ineffectiveness (Connolly et al., 2014). Also as drug treatments, anti-androgens glucocorticoids, oral contraceptives and metformin are preferred (David and Ehrmann, 2005).

There are few studies, hypothesis that PCOS can increased the ovarian cancer risk. PCOS women's ovulation rate is low therefore it is assumed that their ovarian cancer occurrence possibility is less than women without syndrome. However applied treatments to induce ovulation can increase the ovarian cancer risk. The study has shown that by using clomiphene, PCOS women increased their ovarian cancer risk (Daniilidis and Dinas, 2009)

## 2. MATERIALS AND METHODS

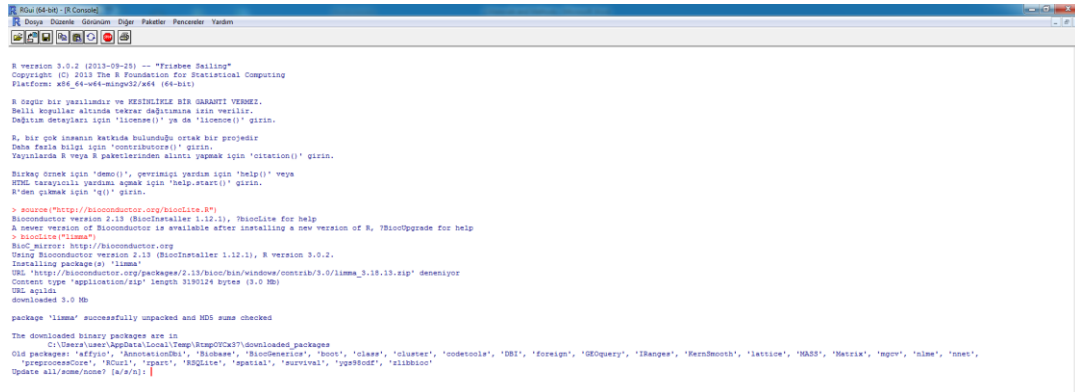
### 2.1 Bioinformatics Database and Tools

#### 2.1.1 Gene Expression Omnibus

Gene Expression Omnibus (GEO) is a public repository database which is constituted by The National Center for Biotechnology Information (NCBI) at 2000. Database contains high-throughput gene expression datasets that are manufactured generally by microarray based experiments. GEO contains approximately one billion individual gene expression measurements and 13 million gene expression profiles. GEO platform offers to the researchers' spacious varieties of gene expressions profiles of biological events such as diseases, development, immunity, ecology etc. (Barrett and Edgar, 2006a; Barrett and Edgar, 2006b).

#### 2.1.2 Bioconductor

Bioconductor is open software which is using a high level interpreted language named R (Gentleman et al., 2004). Bioconductor provides to comprehend, annotate, visualize and analyze of high throughput genomic datasets such as microarray datasets (González-Beltrán et al., 2014). Its offers hundreds of useful packages like Affy and Linear Models for Microarray Data (Limma). These packages are main Bioconductor packages. Affy is a package for normalizing and reading expression values of Affymetrix microarray datasets. Limma package provides to analyze gene expression data sets that are originating from microarray experiments (Smyth et al., 2014).



```
RGui (64-bit) - R Console
Dosya | Diyarlar | Gecelem | Diyer | Paletler | Penceler | Yardm

R version 3.0.2 (2013-09-13) -- "Firebee Sailing"
Copyright (C) 2013 The R Foundation for Statistical Computing
Platform: x86_64-w64-mingw32/x64 (64-bit)

R çöğür bir yarılandır ve KESİMLİKLE BİR GARANTİ VERMEZ.
Belli kuralılar altında destek sağlanmasına izin verilir.
Değitim detayları için 'license()' ya da 'license()' girin.

R, bir çok insanın katkıda bulunduğu ortak bir projedir
Tümde destek bulup için 'contrib.bior()' girin.
Yayınlarda R veya R paketlerinden alıntı yapmak için 'citation()' girin.

Biraz örnek için 'demo()', çevrimiçi yardım için 'help()' veya
HTML tarayıcıları yardımı için 'help.start()' girin.
R'den çıkmak için 'q()' girin.

> source("http://bioconductor.org/biocLite.R")
Bioconductor version 2.13 (BioCInstaller 1.12.1), ?biocLite for help
A newer version of Bioconductor is available after installing a new version of R. ?biocUpgrade for help
> biocLite("limma")
BioC_mirror: http://bioconductor.org
Using Bioconductor version 2.13 (BioCInstaller 1.12.1), R version 3.0.2.
Installing package(s) "limma"
URL: http://bioconductor.org/packages/2.13/bioc/bin/windows/contrib/3.0/limma_3.18.13.zip#download
Content type "application/zip" length 3190124 bytes (3.0 MB)
URL applied
downloaded 3.0 Mb
package "limma" successfully unpacked and MD5 sums checked

The downloaded binary packages are in
  C:\Users\user\AppData\Local\Temp\Rtmp07Ck37\downloaded_packages
Old packages: "affy", "biomart", "Biobase", "BiocGenerics", "biov", "class", "cluster", "codetools", "DNI", "foreign", "GSDQuery", "Ikanpays", "KernSmooth", "lattice", "MASS", "Matrix", "mpow", "nlme", "ones",
"preprocessCore", "RColor", "rpart", "RSQLite", "spatial", "survival", "yags80df", "zlibbioc"
Update all/none/none? [y/n/d]: |
```

Figure 2.1. A snapshot from R version 3.0.2.

### **2.1.3 GeneCards**

Gene Cards is freely available integrated web-server presenting information on human genes. It includes enormous information on human genes and proteins, such as their molecular functions, cellular location, involvement in pathways and diseases (Rebhan et al., 1998).

### **2.1.4 Biological Database Network**

Biological Database Network (Biodbnet) is totally free comprehensive web resource which contains gene based database identifiers such as Entrez Gene, Gene ID, Ensembl Gene ID, etc. Furthermore it's including protein, microarray, sequence and pathway database identifiers. Biodbnet includes several specialized conversion tools like db2db and dbFind. DbFind is preferred for unknown or mixed gene id lists because it provides to the researchers to convert any kind of identifiers to another identifier without indicating identifier type of their list (Mudunuri et al., 2009).

### **2.1.5 The Database for Annotation, Visualization and Integration Discovery**

The Database for Annotation, Visualization and Integration Discovery (DAVID) is an open access website which launched in 2003. DAVID software enables extensive analytic features and tools for instance gene functional classification and annotation tools. It provides researchers to discover and obtain information in both biological and extension meanings of their investigational large gene lists (Huang et al., 2007).

### **2.1.6 Online Mendelian Inheritance in Man**

Online Mendelian Inheritance in Man (OMIM) was created in Johns Hopkins University School of Medicine. It does freely exist first from Johns Hopkins since 1987 and since 1995 from the NCBI. OMIM provides a brief summary about genetic disorders and genes (Hamosh et al., 2002).

### **2.1.7 Kyoto Encyclopedia of Genes and Genomes**

Kyoto Encyclopedia of Genes and Genomes (KEGG) is an integrated free database which's development started in Japan at 1995 (Kanehisa and Goto, 2000). KEGG provides to comprehend features and functions of the biological systems. KEGG is comprised mainly 4 categories (genomic, chemical, systems and health information) and these categories are divided into 15 databases (Kanehisa et al., 2013). KEGG Pathway Database is under the systems information category and includes a collection of manually drawn pathway maps.

### **2.1.8 Quick GO**

Due to the requirements, in 1998, the Gene Ontology (GO) project was founded to guide researchers for the gene products related functional descriptions. GO project provides to describe the features of gene products in 3 terms which are biological process, cellular component and molecular function. After 3 years, the European Bioinformatics Institute (EBI) started The Gene Ontology Annotation (GOA) project and now GOA database become a GO annotation resource. The QuickGO browser which was launched by GOA in 2001 is one of the first and fastest browsers for GO terms. The QuickGO, which is freely available, provides researchers comprehensive descriptions of all GO annotation terms (Barrell et al., 2009; Binnis et al., 2009; Huntley et al., 2009).

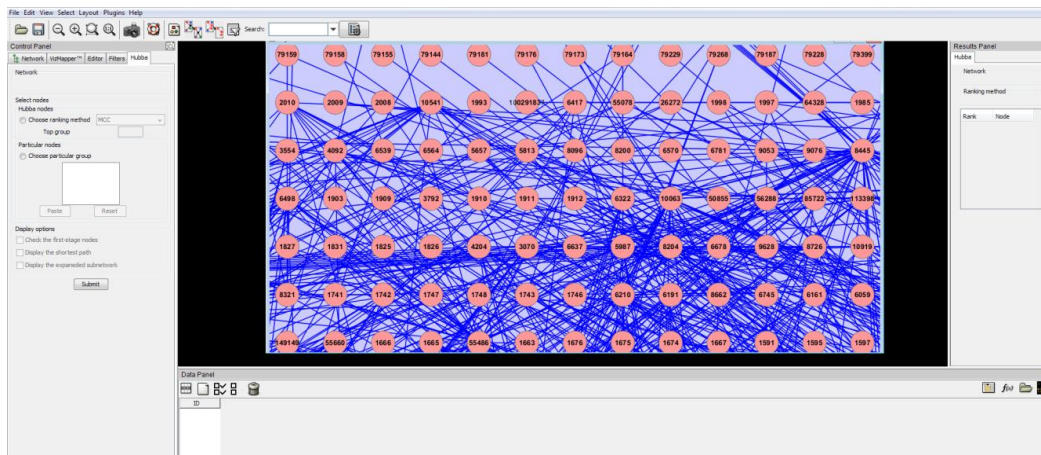
### **2.1.9 iRefIndex**

iRefIndex provides a wide context of protein-protein interactions. These protein-protein interaction data are obtained from 10 different interaction databases, which are Bimolecular Interaction Network Database (BIND), Biological General Repository for Interaction Datasets (BioGRID), Database of Interacting Proteins (DIP), Human Protein Reference Database (HPRD), Protein Interaction database at EBI (IntAct), the Comprehensive Resource of Mammalian protein complexes (CORUM), the Molecular Interaction database (MINT), MIPS (Munich Information Center for Protein Sequences) Protein interaction Resource on Yeast (MPact), Mammalian Protein-Protein Interaction

Database (MPPI) and The Ontario Population Health Index of Databases (OPHID) (<http://irefindex.org>).

### 2.1.10 Cytoscape

High-throughput experiments enables spacious information about biological interactions exemplarily protein-protein, protein-DNA or genetic interactions. Therefore, to use these data sets computational tools are required such as Cytoscape. Cytoscape is open software which provides an environment for integration of the biological interaction networks. As well as it has allows to the researchers to visualize and analyze the networks. A wide range of plugins were created in order to obtain researchers new characteristic infers to their studies (Shannon et al., 2003; Saito et al., 2012). Cyto-Hubba plugin provides to explore significant nodes or hubs in a protein-protein network,; besides this, it also offers to the researchers to analyze their networks using diverse topological analyses (Chen et al., 2009).



**Figure 2.2.** A snapshot from Cytoscape (Version 2.8.3)

## 2.2 Datasets

### 2.2.1 Transcriptome Datasets

19 transcriptomics (mRNA expression) datasets were obtained from the GEO database (Edgar et al., 2002; Barrett et al., 2002), which are shown in the Table 2.1.

**Table 2 .1.** Gene expression datasets considered in the present study

Dataset Number	Disease State	Description	Sample Subsets	Array	Reference
GDS3233	Cervical Cancer	Analysis of cervical cancer primary tumors and cell lines	28 Diseased (Primary Tumors), 24 Control (Normal Cervical Epithelium)	Affymetrix Human Genome U133A Array	Scotto et al., 2008
GDS3292	Cervical Cancer	Analysis of LCM-harvested high-grade squamous intraepithelial lesions and invasive squamous cell carcinomas from cervixes	21 Diseased (Invasive Squamous Cell Carcinomas), 10 Control (Normal Squamous Cervical Epithelia)	Affymetrix Human Genome U133A Array	Zhai et al., 2007
GDS2785	Ovarian Cancer	Analysis of malignant ovarian cancer tumors from patients who are untreated or receiving neo-adjuvant chemotherapy	9 Diseased (Pre-Treated Adenocarcinomas), 10 Control (Pre-Treated Benign Serous Cystadenomas)	Affymetrix Human Genome U95 Version 2 Array	Moreno et al., 2007
GDS3592	Ovarian Cancer	Comparison of normal ovarian surface epithelia and ovarian cancer epithelial cells	12 Diseased (Ovarian Cancer Epithelial Cells), 12 Control (Normal Ovarian Surface Epithelial)	Affymetrix Human Genome U133 Plus 2.0 Array	Bowen et al., 2009
GDS2245	Uterine Fibroid	Analysis of uterine fibroids with mutations in the fumarate hydratase gene	7 Diseased (Fibroid Myometrium Samples with FH Mutations), 11 Control (Normal Myometrium Samples)	Affymetrix Human Genome U133 Plus 2.0 Array	Vanharanta et al., 2006

**Table 2.1:** Gene expression datasets considered in the present study (continued)

Dataset Number	Disease State	Description	Sample Subsets	Array	Reference
GDS2246	Uterine Fibroid	Analysis of uterine fibroids with mutations in the fumarate hydratase gene	5 Diseased (Fibroid Myometrium Samples with FH Mutations), 3 Control (Normal Myometrium Samples)	Affymetrix Human Genome U133 Plus 2.0 Array	Vanharanta et al., 2006
GDS2737	Endometriosis	Analysis of endometrial specimens from women with endometriosis	21 Diseased (6 Proliferative, 6 Early Secretory, 9 Mid Secretory Endometrium), 16 Control (5 Proliferative, 3 Early Secretory, 8 Mid Secretory Endometrium)	Affymetrix Human Genome U133 Plus 2.0 Array	Burney et al., 2007
GDS2835	Endometriosis	Comparison of endometriosis lesions to normal endometrial tissues obtained from the same patient at the same time	10 Diseased (Ovarian Endometriosis Tissue), 10 Control (Normal Endometrium Tissue)	Affymetrix Human Genome U133 Plus 2.0 Array	Hever et al., 2007
GDS3060	Endometriosis	Analysis of cultured endometrial endothelial cells derived from the eutopic endometria of patients with endometriosis	5 Diseased (Eutopic Endometrium Cells with Endometriosis), 5 Control (Eutopic Endometrium Cells without Endometriosis)	Affymetrix Human Genome U133 Plus 2.0 Array	Sha et al., 2007
GDS1050	PCOS	Analysis of normal theca cells treated with 500 uM valproic acid, an anti-epilipetic that induces PCOS-like symptoms	5 Diseased (Untreated), 4 Control (Untreated)	Human Genome U133A Array	Wood et al., 2005

**Table 2.1:** Gene expression datasets considered in the present study (continued)

Dataset Number	Disease State	Description	Sample Subsets	Array	Reference
GDS1051	PCOS	Analysis of normal theca cells treated with 500 $\mu$ M valproic acid, an anti-epilipetic that induces PCOS-like symptoms	5 Diseased (Untreated), 4 Control (Untreated)	Human Genome U133B Array	Kenigsberg et al., 2009
GDS3104	PCOS	Analysis of vastus lateralis muscles from women with PCOS plus insulin-resistant	16 Diseased (Obese+Insulin resistant+PCOS), 13 Control (Obese)	Affymetrix Human Genome U133 Plus 2.0 Array	Skov et al., 2008
GDS3841	PCOS	Analysis of cumulus cells from lean and overweight-obese PCOS patients undergoing in vitro fertilization	12 Diseased (5 Lean+7 Obese), 11 Control (6 Lean+5 Obese)	Affymetrix Human Genome U133 Plus 2.0 Array	Kaur ert al., 2012
GDS4133	PCOS	Analysis of skeletal muscle from obese women with PCOS and obese, healthy women	10 Diseased (Obese), 13 Control (Obese)	Affymetrix Human Genome U133 Plus 2.0 Array	Piltonen et al., 2013
GDS4399	PCOS	Analysis of granulosa cells from ovarian aspirates from PCOS women undergoing in vitro fertilization	7 Diseased (Insulin resistant+Insulin Sensivity), 3 Control	Affymetrix Human Genome U133 Plus 2.0 Array	Wu et Al., 2011

**Table 2.1:** Gene expression datasets considered in the present study

Dataset Number	Disease State	Description	Sample Subsets	Array	Reference
GDS4987	PCOS	Analysis of FACS-sorted endometrial cell types from proliferative phase endometrial biopsies collected from overweight/obese women with PCOS	14 Diseased (Overweight+Obese), 15 Control (Overweight+Obese)	Affymetrix Human Gene 1.0 ST Array [transcript (gene) version]	Kenigsberg et al., 2009
GDS3715	Insulin Resistance	Analysis of vastus lateralis muscle biopsies from insulin-sensitive and insulin-resistant subjects	20 Diseased (Untreated), 20 Control (Untreated)	Affymetrix Human Genome U95A Array	Skov et al., 2008
GDS3781	Insulin Resistance	Analysis of subcutaneous and visceral adipose tissues from, obese patients who were insulin-sensitive or insulin-resistant	19 Diseased (11 Obese Female+8 Obese Male), 20 Control (16 Obese Female+4 Obese Male)	Affymetrix Human Genome U133 Plus 2.0 Array	Kaur ert al., 2012
GDS3962	Insulin Resistance	Analysis of omental and subcutaneous adipose tissue samples from, morbidly-obese cohort patients that are either insulin-sensitive or insulin-resistant	9 Diseased (5 Obese Female+4 Obese Male), 10 Control (Obese Female)	Affymetrix Human Genome U133 Plus 2.0 Array	Piltonen et al., 2013

## **2.2.2 Protein-Protein Interaction Data**

The interaction dataset of *Homo sapiens* was obtained from iRefIndex Database (Razick et al., 2013). A reconstructed human protein-protein interaction network was consisting of 288033 physical protein-protein interactions between 21052 proteins.

## **2.3 Methods**

### **2.3.1 Identification of Differential Expressed Genes**

For the analysis of transcriptome data, CEL files were normalized. For the normalization Robust Multi-Array Average (RMA) (Bolstad et al., 2003) was used as implemented in the R/Bioconductor platform's (version Rx64 3.0.2) (Gentleman et al., 2004) affy package (Gautier et al., 2004).

For each dataset differentially expressed genes (DEGs) were identified by using R/Bioconductor platform's (Gentleman et al., 2004) LIMMA package (Smyth, 2005). To determine statistical significance of the DEGS, p-value threshold was used and defined as a 0.01 ( $p < 0.01$ ) in all DEG analyses. In addition, fold change threshold was used to determine the direction of regulation of the DEGs (down or up-regulated). If the fold-change was less than 0.67, it's accepted as a down-regulated, and greater than 1.5 was accepted as an up-regulated DEG.

### **2.3.2 Functional Enrichment Analyses**

Determined DEGs which were defined by Gene Symbols or Affymetrix gene IDs were converted to Entrez Gene ID by using Biodbnet's dbFind tool (Mudunuri et al., 2009). Disease, gene ontology (biological process, cellular component, molecular function) and pathway enrichment analyses were performed using DAVID's functional annotation tool (Huang et al., 2009a; Huang et al., 2009b) and the results were interpreted by using OMIM (Amberger et al., 2011), KEGG (Kanehisa et al., 2014; Kanehisa and Goto, 2000) and Quick GO (Binns et al., 2009) tools and databases. DAVID enrichment tool was used to map interconnectivity's between inspected diseases and in functional enrichment analyses, p-value threshold was used to determine statistical significance ( $p < 0.01$ ).

### **2.3.3 Reconstruction and Topological Analysis of Protein-Protein Interaction Networks**

Protein-protein interaction network around DEGs (i.e., DEGs and their first neighbors) were reconstructed using data from iRefIndex Database (Razick et al., 2008) and visualized via Cytoscape software (version 2.8.3) (Smoot et al., 2011). The topological analyses of the networks were performed via Cyto-Hubba plugin. Two different topological metrics, which are degree and betweenness centrality, were employed simultaneously to define hub proteins.

### **2.3.4 Correlation Analysis of Hub Proteins Expression**

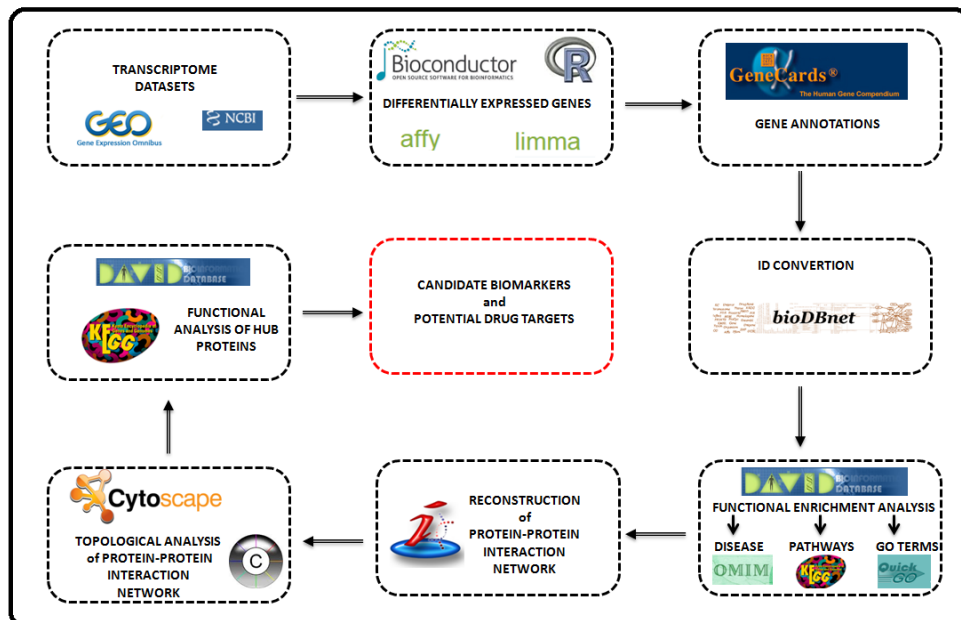
To determine the correlation between hub proteins, Pearson correlation coefficient was employed.

### **2.3.5 Hub Proteins Enrichment and Pathway Analysis**

Predetermined hub protein's pathway enrichment analyses were performed in DAVID's functional enrichment annotation tool (Huang et al., 2009a; Huang et al., 2009b). With respect to DAVID's pathway enrichment results ( $p < 0.01$ ), pathway resultants were examined in KEGG pathway database (Kanehisa et al., 2014; Kanehisa and Goto, 2000).

### 3. RESULTS AND DISCUSSION

In the present study, a systems biology approach was employed to identify the biological entities significantly taking roles in biological mechanisms associated with five infertility-associated woman diseases (cervical cancer, ovarian cancer, uterine fibroid, endometriosis, polycystic ovary syndrome) as well as insulin resistance (Figure 3.1). Statistical analyses were performed to identify DEGs for each dataset. Proteins encoded by DEGs were examined and required naming conversions were done. Functional enrichment analyses of DEG sets, such as disease, gene ontology (biological process, cellular component and molecular function) and pathway annotations were also performed to identify statistically important biological processes affected from disease states. Later, protein-protein interaction networks around the DEGs were reconstructed. Topological analyses of the reconstructed protein-protein network with different topological metrics indicated the presence of central proteins, so-called “hubs”. These proteins presented significant associations between infertility-associated women diseases. Finally, via discussion of the findings in overall, the candidate biomarkers and potential drug targets were suggested.



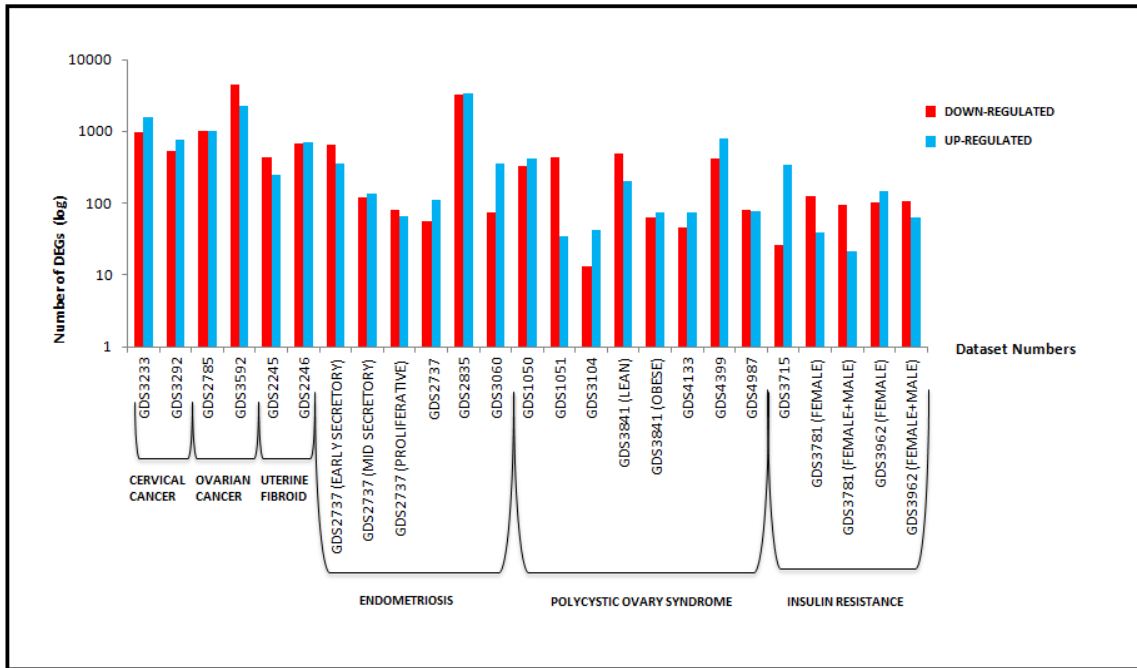
**Figure 3.1.** The overall methodology employed in the present study

### **3.1. Identification of Differentially Expressed Genes**

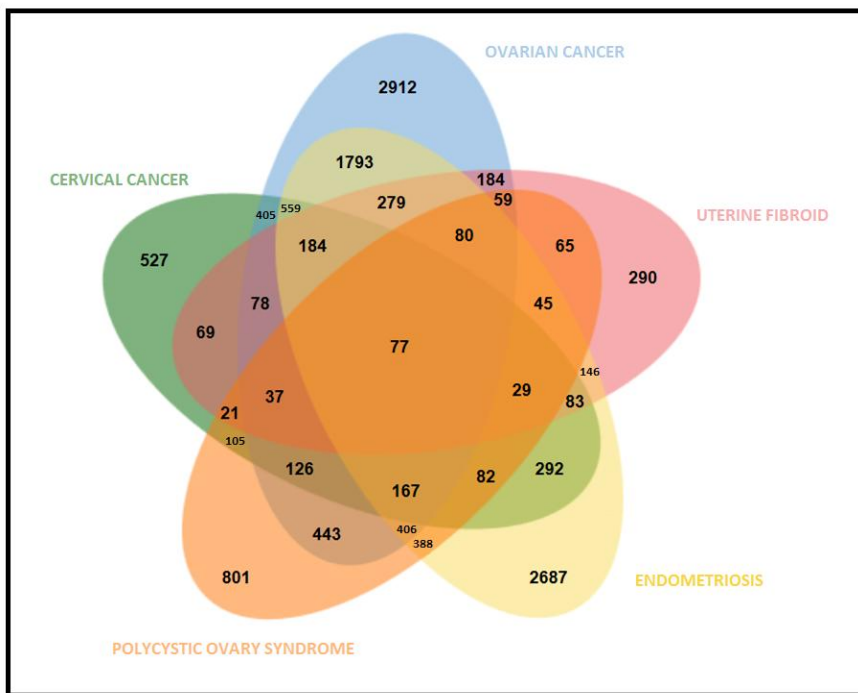
For 6 disease cases, totally 19 different transcriptome datasets were obtained from GEO database. These datasets were associated with cervical cancer (2 datasets), ovarian cancer (2 datasets), uterine fibroid (2 datasets), endometriosis (3 datasets), polycystic ovary syndrome (7 datasets) and insulin resistance (3 datasets). Four datasets (GDS2737 in endometriosis, GDS3841 in polycystic ovary syndrome, GDS3781 and GDS3962 in insulin resistance) were divided into several subsets due to their nature and each subset was analyzed separately. GDS2737 dataset was separated into four subsets since it included data on the three phases of the menstrual cycles which were early secretory (GDS2737 early secretory), mid secretory (GDS2737 mid secretory) and proliferative (GDS2737 proliferative) phases. In addition, the dataset was also analyzed as a whole without considering these features (GDS2737). GDS3841 dataset was analyzed in two different ways depending on diseased samples BMI (GDS3841 lean/GDS3841 obese). Moreover insulin resistance datasets GDS3781 and GDS3962 analyzed separately upon samples gender (GDS3781 female/GDS3781 female+male/GDS3962 female/ GDS3962 female+male). As a result, totally 25 transcriptome datasets were analyzed. Statistical analyses were performed to identify DEGs for each transcriptome dataset. Also situated DEGs were inspected as down or up regulated depending on their expression profiles (down or up-regulated) (Figure 3.2).

### **3.2. Common DEGs between Diseases**

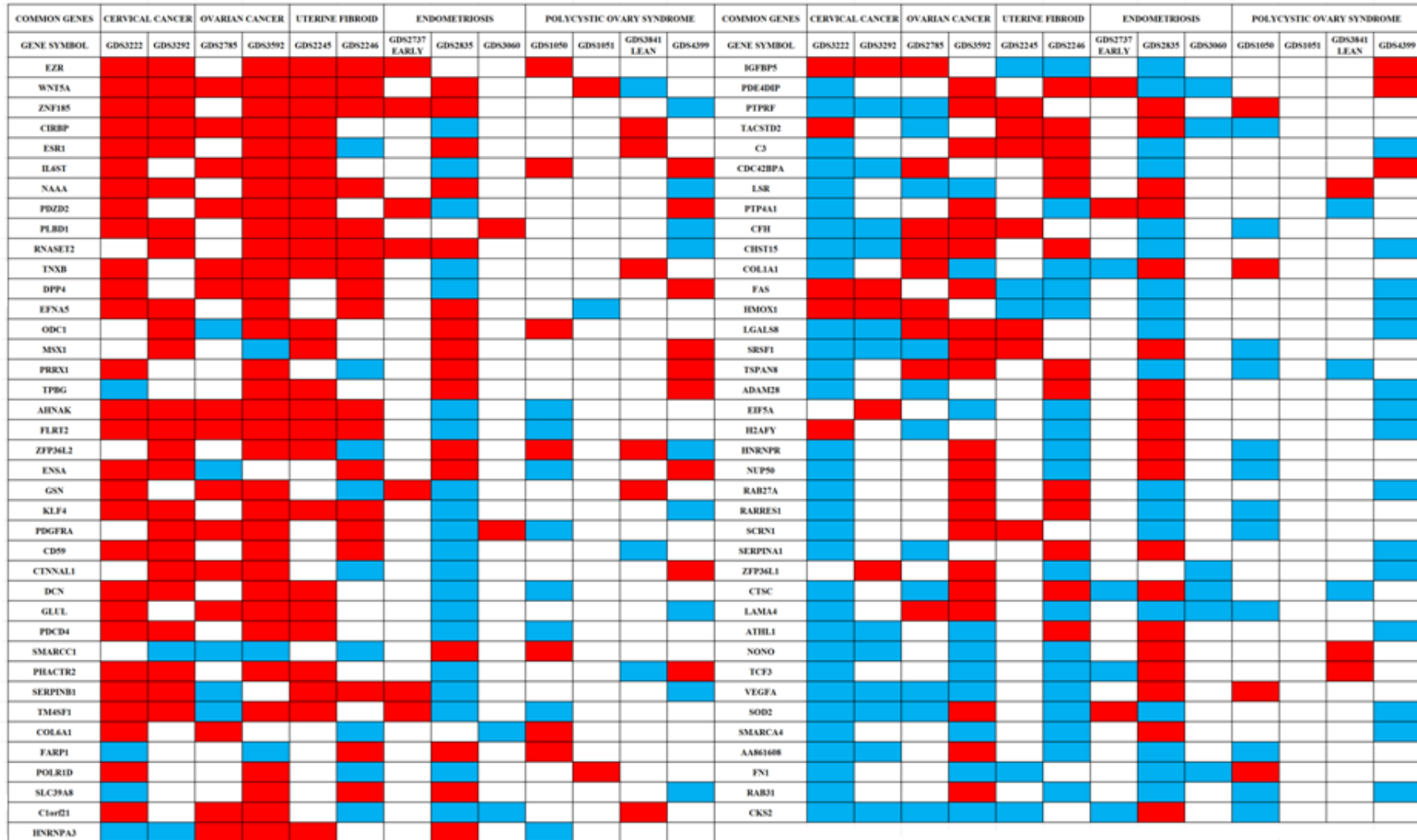
77 common DEGs were found between the investigated women diseases depending on this case; if any gene resulted as a DEG at least in one dataset of the each disease's all datasets was adequately acceptable consideration to investigate the intersection among the 5 diseases (Figure 3.3). Seven datasets (GDS2737, GDS2737 mid secretory, GDS2737 proliferative, GDS3104, GDS3841 obese, GDS4133 and GDS4987) were excluded in this analysis since they limited the analysis results significantly due to very low numbers of DEGs (i.e., less than 250) (Figure 3.2). In addition, the expression profiles of these common DEGs across diseases were examined (Figure 3.4). Apart from these 5 diseases, common DEGs of insulin resistance datasets were also analyzed, however we couldn't find an intersection between two DEGs lists.



**Figure 3.2.** The distribution of down-regulated and up-regulated DEGs in 25 transcriptome datasets



**Figure 3.3.** Venn diagram representing common DEGs between the investigated diseases



**Figure 3.4.** Heat map representing the clustering of the 77 common DEGs upon their expression profiles across diseases. Down-regulation and up-regulation were represented by red and blue colors, respectively.

### **3.3. Functional Enrichment Analyses of DEGs**

Functional enrichment analyses were performed through DAVID bioinformatics tool for each list of DEGs in order to identify enriched diseases, pathways and GO terms; biological processes, cellular components and molecular functions. As mentioned before for functional enrichment analyses, statistical significance was considered with p-value threshold ( $p < 0.01$ ). However in the tables, which were related to functional enrichment analysis, top 10 outcomes were presented according to ranking based on their statistical significance.

Disease functional enrichment analysis provides the diseases that are associated with genes products. Pathway functional enrichment analysis gives information about the pathways gene products attended. The GO functional enrichment analyses cover genes in 3 different categories, which are biological process, cellular component and molecular function and all three describe features of gene products. Biological processes provide to understand which processes the gene products involved in. Cellular component describes where the gene products act in the cell or which organelle gene products perform their functions in. Lastly, molecular function describes the functions that are carried out by gene products.

#### **3.3.1. Functional Enrichment Analysis for Cervical Cancer**

Several cancers, including bladder, breast, colorectal, esophageal, lung, ovarian and stomach cancer, were among the enriched diseases in both cervical cancer datasets (Table 3.1). In addition, all these diseases were associated with up-regulated DEGs. On the other hand, significant enrichment results couldn't be obtained for down-regulated DEGs.

**Table 3.1.** Disease enrichment analysis results for cervical cancer

RELATED DISEASE	DATASET NUMBER	DOWN-REGULATED DEGs	UP-REGULATED DEGs	ALL DEGs
CERVICAL CANCER	3233	-	Colorectal Cancer, Lung Cancer, Breast Cancer, Ovarian Cancer, Bladder Cancer, Rheumatoid Arthritis, Periodontitis, Subarachnoid Hemorrhage, Brain Aneurysm, Atherosclerosis (Coronary)	Colorectal Cancer, Lung Cancer, Periodontitis, Bladder Cancer, Breast Cancer, Ovarian Cancer, Esophageal Cancer, Head and Neck Cancer, Stomach Cancer, Atherosclerosis(coronary), Normal Variation, Subarachnoid Hemorrhage, Asthma, Cancer
	3292	-	Lung cancer, Colorectal Cancer, Bladder Cancer, Breast Cancer, Ovarian Cancer, Stomach Cancer	Lung Cancer, Colorectal Cancer, Stomach Cancer, Esophageal Cancer, Bladder Cancer, Colon Cancer, Breast Cancer, Ovarian Cancer

In functional enrichment analyses for pathways, KEGG database was employed. According to the pathway enrichment analyses, down-regulated DEGs were generally enriched with the pathways that attended in different metabolic pathways (fatty acid metabolism, linoleic acid metabolism, drug metabolism, arachidonic acid metabolism, etc.), whereas the up-regulated DEGs were enriched with the pathways which related to cell cycle, DNA replication, p53 signaling pathway, or pathways in cancer (Table 3.2).

**Table 3.2.** Pathway enrichment analysis results for cervical cancer

RELATED DISEASE	DATASET NUMBER	DOWN-REGULATED DEGs	UP-REGULATED DEGs	ALL DEGs
CERVICAL CANCER	3233	Fatty Acid Metabolism, Linoleic Acid Metabolism, Drug Metabolism, Arachidonic Acid Metabolism, Pathogenic Escherichia. Coli Infection, Valine, Leucine and Isoleucine Degradation, Limonene and Pinene Degradation, Butanoate Metabolism, Histidine Metabolism, Biosynthesis of Unsaturated Fatty Acids	Cell Cycle, DNA Replication, Spliceosome, Small Cell Lung Cancer, Mismatch Repair, Pathways in Cancer, p53 Signaling Pathway, Homologous Recombination, Nucleotide Excision Repair, ECM-Receptor Interaction	Cell Cycle, DNA Replication, p53 Signaling Pathway, Small Cell Lung Cancer, Pathways in Cancer, Mismatch Repair, Spliceosome, ECM-Receptor Interaction, Oocyte Meiosis, Biosynthesis of Unsaturated Fatty Acids
	3292	Ribosome, Butanoate Metabolism, Drug Metabolism, Fatty Acid Metabolism, Arginine and Proline Metabolism, Arachidonic Acid Metabolism, Pathogenic Escherichia Coli Infection, Linoleic Acid Metabolism, p53 Signaling Pathway	Cell Cycle, DNA replication, Spliceosome, Pathways In Cancer, One Carbon Pool by Folate, Base Excision Repair, p53 Signaling Pathway, Oocyte Meiosis	Cell Cycle, p53 Signaling Pathway, DNA Replication, Oocyte Meiosis, Pathways in Cancer, Spliceosome, Prostate Cancer, Epithelial Cell Signaling in Helicobacter Pylori Infection

Biological process enrichment analyses based on GO biological process terminology resulted that the down-regulated DEGs associated with cervical cancer were significantly enriched with the developmental and differentiation processes such as ectoderm, epidermis, organ, tissue, system developments and epidermal and epithelial cell differentiation (Table 3.3). Up-regulated DEGs were enriched with the biological processes that associated with cell cycle processes. Moreover all down and up regulated DEGs usually enriched the processes that associated with cell cycle biological processes. The biological processes, i.e., anatomical structure development, cell cycle, cell cycle phase, cell cycle process, DNA metabolic process, ectoderm development, epidermal cell differentiation, epidermis development, epithelial cell differentiation, keratinocyte differentiation, M phase, mitosis, mitotic cell cycle, nuclear division, organ development, organelle fission, system development and tissue development, outcome both in datasets.

**Table 3.3.** GO-biological process enrichment analysis results for cervical cancer

RELATED DISEASE	DATASET NUMBER	DOWN-REGULATED DEGs	UP-REGULATED DEGs	ALL DEGs
CERVICAL CANCER	3233	Ectoderm Development, Epidermis Development, Tissue Development, Epidermal Cell Differentiation, Organ Development, Anatomical Structure Development, Epithelial Cell Differentiation, Keratinocyte Differentiation, System Development, Fatty Acid Metabolic Process	Cell Cycle, Cell Cycle Phase, Cell Cycle Process, DNA Metabolic Process, M Phase, Mitotic Cell Cycle, M Phase of Mitotic Cell Cycle, Organelle Fission, Mitosis, Nuclear Division	Cell Cycle, Cell Cycle Phase, Cell Cycle Process, Mitotic Cell Cycle, M Phase, DNA Metabolic Process, Organelle Fission, Nuclear Division, Mitosis, M Phase of Mitotic Cell Cycle
	3292	Ectoderm Development, Epidermis Development, Organ Development, Epidermal Cell Differentiation, Epithelial Cell Differentiation, Tissue Development, Anatomical Structure Development, System Development, Keratinocyte Differentiation, Multicellular Organismal Development	Cell Cycle, DNA Metabolic Process, Cell Cycle Phase, Cell Cycle Process, Mitotic Cell Cycle, M Phase, DNA Replication, Nuclear Division, Mitosis, Organelle Fission	Cell Cycle, Cell Cycle Phase, Mitotic Cell Cycle, Cell Cycle Process, DNA Metabolic Process, M Phase, DNA Replication, Mitosis, Nuclear Division, Organelle Fission

Cellular component enrichment analysis based on GO cellular component terminology demonstrated that usually down-regulated DEGs were enriched with cytoplasm, cornified envelope and intracellular part, whereas up-regulated DEGs were enriched with the nucleus, nuclear and organelle part cellular components (Table 3.4). All DEGs of either cervical cancer datasets were generally enriched with the intracellular and organelle parts as cell components. Cell fraction, cornified envelope, cytoplasm, desmosome, intracellular, intracellular membrane-bounded organelle, intracellular organelle, intracellular organelle part, intracellular part, membrane-bounded organelle, membrane-enclosed lumen, nuclear part, nucleus, organelle and organelle part were the cellular components that were enriched in both datasets.

**Table 3.4.** GO-cellular component enrichment analysis results for cervical cancer

RELATED DISEASE	DATASET NUMBER	DOWN-REGULATED DEGs	UP-REGULATED DEGs	ALL DEGs
CERVICAL CANCER	3233	Cytoplasm, Cornified Envelope, Cell Fraction, Desmosome, Insoluble Fraction, Membrane Fraction, Intracellular, Intracellular Part, Cytoskeleton, Cell-Cell Junction	Nuclear Part, Intracellular Part, Nucleus, Intracellular, Membrane-Bounded Organelle, Intracellular Membrane-Bounded Organelle, Intracellular Organelle Part, Organelle Part, Membrane-Enclosed Lumen, Organelle	Intracellular Part, Intracellular, Cytoplasm, Nuclear Part, Intracellular Organelle Part, Intracellular Organelle, Organelle, Organelle Part, Membrane-Bounded Organelle, Intracellular Membrane-Bounded Organelle
	3292	Cytoplasm, Cornified Envelope, Cytoplasmic Part, Desmosome, Cytosol, Extracellular Region, Cytosolic Ribosome, Extracellular Region Part, Cell Fraction, Intracellular Part	Nucleus, Nuclear Part, Nucleoplasm, Intracellular, Nuclear Lumen, Intracellular Part, Intracellular Organelle Part, Intracellular Membrane-Bounded Organelle, Membrane-Bounded Organelle, Organelle Part	Intracellular, Intracellular Part, Nuclear Part, Intracellular Organelle Part, Organelle Part, Organelle, Intracellular Organelle, Nucleoplasm, Nuclear Lumen, Membrane-Enclosed Lumen

In molecular function enrichment analysis, it was indicated that DEGs were usually enriched with the binding activities (Table 3.5). Down-regulated DEGs were enriched with enzymatic activities (catalytic activity, endopeptidase inhibitor activity, oxidoreductase activity, etc.), besides up-regulated DEGs were enriched with DNA, RNA and ATP binding activities. All DEGs were associated with diverse molecular functions that related to binding. Two datasets were enriched with several common functions such as; ATP binding, binding, catalytic activity, endopeptidase inhibitor activity, nucleotide binding, oxidoreductase activity, protein binding, bridging, purine nucleoside binding, RNA binding, serine-type endopeptidase inhibitor activity, single-stranded DNA binding, structural molecule activity and structure-specific DNA binding functions.

**Table 3.5.** GO-molecular function enrichment analysis results for cervical cancer

RELATED DISEASE	DATASET NUMBER	DOWN-REGULATED DEGs	UP-REGULATED DEGs	ALL DEGs
CERVICAL CANCER	3233	Protein Binding, Binding, Structural Molecule Activity, Protein Binding and Bridging, Oxidoreductase Activity, C-Acyltransferase Activity, Protein Dimerization Activity, Endopeptidase Inhibitor Activity, Oxidoreductase Activity, Acting on Paired Donors with Incorporation or Reduction of Molecular Oxygen, Serine-Type Endopeptidase Inhibitor Activity	Protein Binding, Binding, Nucleotide Binding, ATP Binding, Adenyl Ribonucleotide Binding, Adenyl Nucleotide Binding, Nucleoside Binding, Single-Stranded DNA Binding, Purine Nucleoside Binding, RNA Binding	Protein Binding, Binding, Nucleotide Binding, Structure-Specific DNA Binding, Catalytic Activity, Purine Ribonucleotide Binding, Ribonucleotide Binding, Single-Stranded DNA Binding, Purine Nucleotide Binding, Nucleoside Binding
	3292	Structural Molecule Activity, Protein Binding, Endopeptidase Inhibitor Activity, Oxidoreductase Activity, Peptidase Inhibitor Activity, Protein Binding and Bridging, Serine-Type Endopeptidase Inhibitor Activity, Enzyme Inhibitor Activity, Structural Constituent of Cytoskeleton, Tetrapyrrole Binding	Protein Binding, Nucleic Acid Binding, Structure-Specific DNA Binding, Binding, RNA Binding, Double-Stranded DNA Binding, Single-Stranded DNA Binding, DNA Binding, DNA Binding, Nucleotide Binding, ATP Binding	Protein Binding, Binding, Structure-Specific DNA Binding, RNA Binding, Double-Stranded DNA Binding, Single-Stranded DNA Binding, Nucleotide Binding, Nucleic Acid Binding, Catalytic Activity, Purine Nucleoside Binding

### 3.3.2. Functional Enrichment Analysis for Ovarian Cancer

The analysis of GDS3592 dataset associated with ovarian cancer resulted in limited findings. Only up-regulated DEGs were enriched with neural tube defect disease. However, in the other dataset of ovarian cancer (GDS2785), down-regulated genes were enriched with diabetes and type 2 liver diseases, and disease enrichment analysis of up-regulated DEGs resulted in several diseases including rheumatoid arthritis, colorectal cancer, Crohn's disease and multiple sclerosis (Table 3.6).

**Table 3.6.** Disease enrichment analysis results for ovarian cancer

RELATED DISEASE	DATASET NUMBER	DOWN-REGULATED DEGs	UP-REGULATED DEGs	ALL DEGs
OVARIAN CANCER	2785	Diabetes, Type 2 Liver Disease	Rheumatoid Arthritis, Arthritis, Periodontitis, Lupus Erythematosus, Colorectal Cancer, Arthritis- Rheumatoid, Systemic Lupus Erythematosus, Crohn's Disease, Multiple Sclerosis, Lupus Erythematosus; Nephrotic Syndrome; Agranulocytosis-Drug Induced	Colorectal Cancer, Periodontitis, Arthritis-Rheumatoid, Hepatitis B-Chronic, Arthritis, Crohn's Disease, Rheumatoid Arthritis, Lupus Erythematosus; Nephrotic Syndrome; Agranulocytosis- Drug Induced, Clubfoot, Bone Density
	3592	-	Neural Tube Defects	-

**Table 3.7.** Pathway enrichment analysis results for ovarian cancer

RELATED DISEASE	DATASET NUMBER	DOWN-REGULATED DEGs	UP-REGULATED DEGs	ALL DEGs
OVARIAN CANCER	2785	Ribosome, Focal Adhesion, MAPK Signaling Pathway, Vascular Smooth Muscle Contraction	Cell Cycle, Systemic Lupus Erythematosus, Proteasome, Alzheimer's Disease, p53 Signaling Pathway, Toll-Like Receptor Signaling Pathway, Oxidative Phosphorylation, Huntington's Disease, Fc Gamma R-Mediated Phagocytosis, Antigen Processing and Presentation	Systemic Lupus Erythematosus, Cell Cycle, Pathways in Cancer, Ribosome, ECM-Receptor Interaction, Prostate Cancer, p53 Signaling Pathway, Focal Adhesion, Proteasome, Viral Myocarditis
	3592	Ribosome, Spliceosome, Ubiquitin Mediated Proteolysis, Focal Adhesion, Endocytosis, Adherens Junction, Proteasome, Wnt Signaling Pathway	Cell Cycle, ECM-Receptor Interaction, DNA Replication	Ribosome, Cell Cycle, Focal Adhesion, Oocyte Meiosis, Axon Guidance, Ubiquitin Mediated Proteolysis, Endocytosis, Pathways in Cancer, Progesterone-Mediated Oocyte Maturation, Regulation of Actin Cytoskeleton

In pathway enrichment analyses down-regulated DEGs of GDS2785 dataset were enriched with ribosome, focal adhesion and MAPK signaling pathways. Up-regulated DEGs were enriched with the cell cycle, Alzheimer’s disease, p53 signaling pathway, oxidative phosphorylation and Huntington’s disease pathways (Table 3.7). In addition to these pathways, the DEGs of GDS3592 dataset were enriched with pathways charged in oocyte meiosis, ubiquitin mediated proteolysis, pathways in cancer and progesterone-mediated oocyte maturation. The down-regulated DEGs were enriched with the ribosome, spliceosome, adherens junction and Wnt signaling pathway and up-regulated DEGs were enriched with pathways like cell cycle, ECM-receptor interaction and DNA replication. DEGs of both datasets were enriched with pathways of ribosome, proteasome, cell cycle, focal adhesion, ECM-receptor interaction and pathways of cancer.

**Table 3.8.** GO-biological process enrichment analysis results for ovarian cancer

RELATED DISEASE	DATASET NUMBER	DOWN-REGULATED DEGs	UP-REGULATED DEGs	ALL DEGs
OVARIAN CANCER	2785	Translational Elongation, Developmental Process, Multicellular Organismal Development, Anatomical Structure Development, System Development, Cellular Process, Negative Regulation of Biosynthetic Process, Negative Regulation of Cellular Biosynthetic Process, Cell Adhesion, Biological Adhesion	Mitotic Cell Cycle, Cell Cycle, Cell Cycle Process, Response to Stress, Cellular Component Organization Immune System Process, Organelle Organization, Macromolecular Complex Assembly, Response to Chemical Stimulus, Defense Response	Cellular Process, Cellular Component Organization, Response to Chemical Stimulus, Positive Regulation of Biological Process, Organelle Organization, Negative Regulation of Cellular Process, Positive Regulation of Cellular Process, Response to Organic Substance, Negative Regulation of Biological Process, Mitotic Cell Cycle
	3592	Cellular Process, Cellular Metabolic Process, Cellular Protein Metabolic Process, Cellular Macromolecule Metabolic Process, Metabolic Process, Macromolecule Metabolic Process, Protein Metabolic Process, Translational Elongation, Primary Metabolic Process, Translation	Cell Cycle, Cell Cycle Phase, M Phase of Mitotic Cell Cycle, M Phase, Mitosis, Nuclear Division, Cell Cycle Process, Organelle Fission, Cell Division, Mitotic Cell Cycle	Cellular Process, Cell Cycle, Mitotic Cell Cycle, Cell Cycle Process, Cell Division, Cellular Component Organization, Cellular Metabolic Process, Organelle Organization, M Phase of Mitotic Cell Cycle, Cellular Macromolecule Metabolic Process

The functional enrichment analyses based on GO biological process terms indicated similar results in both datasets, i.e., several biological processes like cell cycle, cell cycle process, cellular process, cellular component organization, mitotic cell cycle, translational elongation and organelle organization were common results (Table 3.8). The down-regulated DEGs were enriched with developmental processes such as multicellular organismal, anatomical structure and system development of biological processes. Except these enrichments, they were also enriched with cellular and metabolic processes including negative regulation of biosynthetic process, cellular biosynthetic process, cell and biological adhesion of biological processes, protein metabolic process, etc. On the other hand, up-regulated DEGs were enriched with cell cycle processes, cellular component organization, immune system process and organelle organization.

**Table 3.9.** GO-cellular component enrichment analysis results for ovarian cancer

RELATED DISEASE	DATASET NUMBER	DOWN-REGULATED DEGs	UP-REGULATED DEGs	ALL DEGs
OVARIAN CANCER	2785	Intracellular Part, Intracellular, Cytoplasm, Non-Membrane-Bounded Organelle, Intracellular Non-Membrane-Bounded Organelle, Cytosolic Ribosome, Extracellular Region Part, Organelle, Intracellular Organelle, Cytoskeleton	Cytoplasm, Intracellular Part, Cytoplasmic Part, Intracellular, Cytosol, Organelle Part, Intracellular Organelle Part, Membrane-Bounded Organelle, Intracellular Membrane-Bounded Organelle, Macromolecular Complex	Cytoplasm, Intracellular Part, Intracellular, Cytoplasmic Part, Cytosol, Organelle, Organelle Part, Intracellular Organelle, Intracellular Organelle Part, Macromolecular Complex
	3592	Intracellular, Intracellular Part, Cytoplasm, Intracellular Organelle, Organelle, Cytoplasmic Part, Intracellular Membrane-Bounded Organelle, Membrane-Bounded Organelle, Cell, Cell Part	Chromosome, Chromosomal Part, Chromosome-Centromeric Region, Condensed Chromosome, Condensed Chromosome-Centromeric Region, Condensed Chromosome-Kinetochore, Spindle, Kinetochore, Intracellular Non-Membrane-Bounded Organelle, Non-Membrane-Bounded Organelle	Intracellular, Intracellular Part, Cytoplasm, Organelle, Intracellular Organelle, Intracellular Membrane-Bounded Organelle, Membrane-Bounded Organelle, Cytoplasmic Part, Organelle Part, Intracellular Organelle Part

GO cellular component enrichment analyses results demonstrated that down-regulated DEGs were enriched in components suchlike intracellular part, cytoplasm, intracellular and non-membrane-intracellular bounded organelle and cytosolic ribosome. Up-

regulated and all DEGs were enriched with components like cytoplasm, intracellular part, organelle part and macromolecular complex of cellular components. In addition, up-regulated DEGs were enriched in cellular components that were associated with chromosome parts and regions (Table 3.9).

Binding activities (adenyl nucleotide binding, ATP binding, nucleoside binding, nucleotide binding, protein binding, purine nucleoside binding, RNA binding), catalytic activity and structural constituent of ribosome were the molecular functions outcomes of enrichment analyses for ovarian cancer (Table 3.10). Analyses indicated that down- and up-regulated DEGs were enriched with the binding processes. Down-regulated DEGs were also enriched with cytoskeleton protein, RNA, growth factor and insulin-like factors binding activities, while up-regulated DEGs were enriched in ribonucleotide, purine nucleotide, nucleotide and ATP binding activities.

**Table 3.10.** GO-molecular function enrichment analysis results for ovarian cancer

RELATED DISEASE	DATASET NUMBER	DOWN-REGULATED DEGs	UP-REGULATED DEGs	ALL DEGs
OVARIAN CANCER	2785	Protein Binding, Binding, Cytoskeletal Protein Binding, Structural Molecule Activity, Structural Constituent of Ribosome, RNA Binding, Growth Factor Binding, Insulin-Like Growth Factor Binding, Actin Binding, Transmembrane Receptor Protein Tyrosine Kinase Activity	Protein Binding, Catalytic Activity, Purine Nucleotide Binding, Ribonucleotide Binding, Purine Ribonucleotide Binding, Nucleoside Binding, Purine Nucleoside Binding, Adenyl Nucleotide Binding, Nucleotide Binding, ATP Binding	Protein Binding, Binding, Identical Protein Binding, Receptor Binding, Nucleotide Binding, Cytoskeletal Protein Binding, Protein Dimerization Activity, Protein Complex Binding, Integrin Binding, Purine Nucleotide Binding
	3592	Protein Binding, Binding, RNA Binding, Structural Constituent of Ribosome, Translation Factor Activity, Nucleic Acid Binding, Nucleotide Binding, Small Conjugating Protein Ligase Activity, Catalytic Activity, Hydrolase Activity Acting on Acid Anhydrides in Phosphorus-Containing Anhydrides, Pyrophosphatase Activity	Protein Binding, Binding, GTPase Regulator Activity, Nucleoside-Triphosphatase Regulator Activity, Small GTPase Regulator Activity, ATP Binding, Adenyl Ribonucleotide Binding, Adenyl Nucleotide Binding, Purine Nucleoside Binding, Nucleoside Binding	Protein Binding, Binding, Nucleotide Binding, GTPase Regulator Activity, Nucleoside-Triphosphatase Regulator Activity, Enzyme Regulator Activity, Pyrophosphatase Activity, Hydrolase Activity, Acting on Acid Anhydrides in Phosphorus-Containing Anhydrides, Hydrolase Activity Acting on Acid Anhydrides, Nucleoside-Triphosphatase Activity

### 3.3.3. Functional Enrichment Analysis for Uterine Fibroid

Disease enrichment analysis for uterine fibroid resulted in associations with several diseases including cancers and metabolic disorders (Table 3.11). Down-regulated DEGs were not enriched in any diseases, whereas the up-regulated DEGs were associated with certain types of cancers such as lung, esophageal, head and neck, prostate, bladder cancer, leukemia and ovarian cancer, and also metabolic disorders.

**Table 3.11.** Disease enrichment analysis results for uterine fibroid

RELATED DISEASE	DATASET NUMBER	DOWN-REGULATED DEGs	UP-REGULATED DEGs	ALL DEGs
UTERINE FIBROID	2245	-	Lung Cancer, Esophageal Cancer, Head and Neck Cancer, Prostate Cancer, Bladder Cancer, Leukemia, Juvenile Idiopathic Arthritis, Urolithiasis, Migraine	Esophageal Cancer, Cleft Lip with Cleft Palate Cleft Lip without Cleft Palate Cleft Palate, Lung Cancer, Head and Neck Cancer, Prostate Cancer, Skin Cancer (Non-Melanoma), Urolithiasis, Parkinson's Disease
	2246	-	Metabolism Disorders	Ovarian Cancer, Longevity

Pathway enrichment analyses of down-regulated DEGs in uterine fibroid culminated pathways in cancer, focal adhesion pathway, complement and coagulation cascades, nicotinate and nicotinamide metabolism, gap junction and basal cell carcinoma. On the other hand, up-regulated DEGs were related with central carbon metabolism, fructose and mannose metabolism, glutathione metabolism, ECM-receptor interaction, signaling pathways (MAPK and p53 signaling), and apoptosis. According to analysis results for up-regulated DEGs, genes were also enriched in pathways that charged in cancer processes like chronic myeloid leukemia, prostate, pancreatic and non-small cell lung cancer (Table 3.12).

**Table 3.12.** Pathway enrichment analysis results for uterine fibroid

RELATED DISEASE	DATASET NUMBER	DOWN-REGULATED DEGs	UP-REGULATED DEGs	ALL DEGs
UTERINE FIBROID	2245	Pathways in Cancer, Focal Adhesion	Glycolysis/Gluconeogenesis, Pentose Phosphate Pathway, Fructose and Mannose Metabolism, Glutathione Metabolism, ECM-Receptor Interaction, Metabolism of Xenobiotics by Cytochrome P450	Glycolysis/Gluconeogenesis, Pentose Phosphate Pathway, ECM-Receptor Interaction, Pathways in Cancer, Focal Adhesion, Fructose and Mannose Metabolism, Colorectal Cancer, Small Cell Lung Cancer, MAPK Signaling Pathway, Prostate Cancer
	2246	Complement and Coagulation Cascades, Pathways in Cancer, Nicotinate and Nicotinamide Metabolism, Gap Junction, Inositol Phosphate Metabolism, Basal Cell Carcinoma, Melanogenesis	Chronic Myeloid Leukemia, MAPK Signaling Pathway, Pathways in Cancer, p53 Signaling Pathway, Neurotrophin Signaling Pathway, Glycolysis/Gluconeogenesis, Focal Adhesion, Pancreatic Cancer, Non-Small Cell Lung Cancer, Apoptosis	Pathways in Cancer, MAPK Signaling pathway, Prostate Cancer, Colorectal Cancer, Gap Junction, Melanoma, Phosphatidylinositol Signaling System, Chronic Myeloid Leukemia, Endometrial Cancer, Pancreatic Cancer

Down-regulated DEGs of uterine fibroid were generally attended in developmental and regulatory biological processes, which include anatomical structure, multicellular organismal, system, organ development, etc. (Table 3.13). The down-regulated DEGs were also enriched with response processes like response to wounding, stress and immune. On the other hand, up-regulated DEGs were participated in metabolic processes, especially catabolic processes, such as glucose, hexose, and alcohol catabolic processes, glycolysis, and monosaccharide metabolic processes. The enrichment results of these DEGs indicated that, they were also enriched with regulatory processes such as positive and negative regulation of cellular process, regulation of programmed cell death, cell death, and positive regulation of apoptosis. Alike to up-regulated DEGs enrichment results all DEGs enriched with regulatory biological processes. Anatomical structure development, anatomical structure morphogenesis, negative regulation of cellular process, regulation of apoptosis and system development were the biological processes that were common in enrichments results of either datasets.

**Table 3.13.**GO-biological process enrichment analysis results for uterine fibroid

RELATED DISEASE	DATASET NUMBER	DOWN-REGULATED DEGs	UP-REGULATED DEGs	ALL DEGs
UTERINE FIBROID	2245	Developmental Process, Anatomical Structure Development, Multicellular Organismal Development, System Development, Organ Development, Anatomical Structure Morphogenesis, Negative Regulation of Cell Proliferation, Negative Regulation of Cellular Process, Positive Regulation of Cell Adhesion, Cell Adhesion	Glucose Catabolic Process, Hexose Catabolic Process, Monosaccharide Catabolic Process, Alcohol Catabolic Process, Cellular Carbohydrate Catabolic Process, Glycolysis, Carbohydrate Catabolic Process, Glucose Metabolic Process, Hexose Metabolic Process, Monosaccharide Metabolic Process	Anatomical Structure Development, Developmental Process, Multicellular Organismal Development, System Development, Organ Development, Glucose Catabolic Process, Anatomical Structure Morphogenesis, Hexose Catabolic process, Regulation of Apoptosis, Negative Regulation of Apoptosis
	2246	Anatomical Structure Morphogenesis, Response to Wounding, Response to Stress, Anatomical Structure Development, Immune Response, Protein Maturation, Response to External Stimulus, Regulation of Signal Transduction, System Development, Immune Effector Process	Positive Regulation of Cellular Process, Cellular Process, Positive Regulation of Biological Process, Negative Regulation of Biological Process, Negative Regulation of Cellular Process, Regulation of Apoptosis, Regulation of Programmed Cell Death, Regulation of Cell Death, Positive Regulation of Apoptosis, Positive Regulation of Programmed Cell Death	Regulation of Programmed Cell Death, Regulation of Cell Death, Regulation of Apoptosis, Negative Regulation of Biological Process, Negative Regulation of Cellular Process, Positive Regulation of Biological Process, Anatomical Structure Development, Positive Regulation of Cellular Process, Negative Regulation of Programmed Cell Death, Anatomical Structure Morphogenesis

All DEGs associated with uterine fibroid were significantly enriched in cellular components of extracellular matrix, cytoplasm and neuron projection components. Genes associated with extracellular components were down-regulated, while up-regulated DEGs were enriched in cytoplasm, cytosol, soluble fraction and several membrane-bound organelles (Table 3.14).

**Table 3.14.** GO-cellular component enrichment analysis results for uterine fibroid

RELATED DISEASE	DATASET NUMBER	DOWN-REGULATED DEGs	UP-REGULATED DEGs	ALL DEGs
UTERINE FIBROID	2245	Extracellular Matrix, Extracellular Region Part, Proteinaceous Extracellular Matrix, Extracellular Region, Extracellular Space, Cell-Cell Junction, Plasma Membrane Part	Cytoplasm, Cytosol, Cytoplasmic Part, Soluble Fraction, Intracellular, Intracellular Part, Neuron Projection, Extracellular Region Part, Cell Fraction, Extracellular Space	Extracellular Region Part, Extracellular Matrix, Proteinaceous Extracellular Matrix, Extracellular Region, Cytoplasm, Cytosol, Extracellular Space, Soluble Fraction, Neuron Projection, Platelet Alpha Granule Lumen
	2246	Cytoplasm, Extracellular Matrix, Cytoplasmic Part, Extracellular Region Part, Extracellular Region, Proteinaceous Extracellular Matrix, Golgi Apparatus, Endoplasmic Reticulum, Extracellular Space, Myelin Sheath	Intracellular Part, Intracellular, Cytoplasm, Cytosol, Cytoplasmic Part, Membrane-Bounded Organelle, Intracellular Membrane-Bounded Organelle, Organelle, Intracellular Organelle, Nucleus	Cytoplasm, Cytoplasmic Part, Intracellular Part, Intracellular, Cytosol, Soluble Fraction, Cell Fraction, Golgi Apparatus, Vesicle, Extracellular Matrix

Binding activities (carbohydrate binding, glycosaminoglycan binding, extracellular matrix binding, heparin binding, polysaccharide and protein binding) and catalytic activity were the common molecular functions that resulted in analyses (Table 3.15). Down-regulated DEGs were enriched in catalytic activity beside several binding activities, whereas up-regulated DEGs were enriched in enzymatic activities (especially, oxidoreductase activity and protein kinase activity) binding and transcription factor activities.

**Table 3.15.** GO-molecular function enrichment analysis results for uterine fibroid

RELATED DISEASE	DATASET NUMBER	DOWN-REGULATED DEGs	UP-REGULATED DEGs	ALL DEGs
UTERINE FIBROID	2245	Protein Binding, Glycosaminoglycan Binding, Extracellular Matrix Binding, Heparin Binding, Pattern Binding, Polysaccharide Binding, Transcription Factor Activity, Extracellular Matrix Structural Constituent, Binding, Integrin Binding	Oxidoreductase Activity-Acting on the CH-OH Group of Donors NAD or NADP as Acceptor, Oxidoreductase Activity-Acting on CH-OH Group of Donors, Oxidoreductase Activity, Catalytic Activity, Steroid Dehydrogenase Activity-Acting on the CH-OH Group of Donors NAD or NADP as Acceptor, Oxidoreductase Activity-Acting on Paired Donors with Incorporation or Reduction of Molecular oxygen, Steroid Dehydrogenase Activity, Aldo-Keto Reductase Activity ,Trans-1,2-Dihydrobenzene-1,2-diol Dehydrogenase activity ,NADP or NADPH binding	Protein Binding, Extracellular Matrix Structural Constituent, Binding, Glycosaminoglycan Binding, Heparin Binding, Oxidoreductase Activity-Acting on the CH-OH Group of Donors, NAD or NADP as Acceptor, Polysaccharide Binding, Pattern Binding, Carbohydrate Binding, Oxidoreductase Activity-Acting on CH-OH group of Donors
	2246	Calcium Ion Binding, Catalytic Activity, Carbohydrate Binding, Heparin Binding, Enzyme Regulator Activity, Growth Factor Binding, Glycosaminoglycan Binding, Oxidoreductase Activity- Acting on the Aldehyde or Oxo Group of Donors, Protein Dimerization Activity, Endopeptidase Inhibitor Activity	Protein Binding, Binding, Kinase Activity, Phosphotransferase Activity-Alcohol Group as Acceptor, Enzyme Binding, Transferase Activity-Transferring Phosphorus-Containing Groups, Transcription Regulator Activity, Transcription Repressor Activity, Transcription Factor Binding, Protein Kinase Activity	Protein Binding, Binding, Kinase Activity, Phosphotransferase Activity-Alcohol Group as Acceptor, Transferase Activity-Transferring Phosphorus-Containing Groups, Catalytic Activity, Protein Kinase Activity, Enzyme Binding, Nucleotide Binding, Calcium Ion Binding

### 3.3.4. Functional Enrichment Analysis for Endometriosis

The DEGs associated with endometriosis were significantly related with several diseases including various types of cancers, auto-immune diseases, cardiovascular disorders and others (Table 3.16). Down-regulated DEGs (GDS2835) were enriched with lung, breast and colorectal cancer, as well as ovarian cancer. On the other hand, up-regulated DEGs were enriched in some diseases such as atherosclerosis (coronary), macular degeneration, retinopathy (diabetic), myocardial infarct, cardiomyopathy, multiple sclerosis, osteoarthritis, neural tube defects, thalassemia, brain aneurysm, breast, colorectal and bladder cancers.

**Table 3.16.** Disease enrichment analysis results for endometriosis

RELATED DISEASE	DATASET NUMBER	DOWN-REGULATED DEGs	UP-REGULATED DEGs	ALL DEGs
ENDOMETRIOSIS	GDS2737	-	-	-
	GDS2737 (EARLY SECRETORY)	-	Breast Cancer, Neural Tube Defects, Colorectal Cancer, Bladder Cancer	Neural Tube Defects
	GDS2737 (MID SECRETORY)	-	-	Hematology Indices
	GDS2737 (PROLIFERATIVE)	-	Thalassemia, Atherosclerosis-Coronary	Thalassemia
	GDS2835	Lung Cancer, Breast Cancer, Colorectal Cancer, Ovarian Cancer	Atherosclerosis-Coronary, Osteoarthritis, Macular Degeneration, Myocardial Infarct, Cardiomyopathy, Retinopathy-Diabetic, Stroke, Multiple Sclerosis, Systemic Lupus Erythematosus, Abdominal Aortic Aneurysm	Osteoarthritis, Colorectal Cancer
	GDS3060	-	Myocardial Infarct; Atherosclerosis-Coronary, Brain Aneurysm	-

**Table 3.17.** Pathway enrichment analysis results for endometriosis

RELATED DISEASE	DATASET NUMBER	DOWN-REGULATED DEGs	UP-REGULATED DEGs	ALL DEGs
ENDOMETRIOSIS	GDS2737	-	-	-
	GDS2737 (EARLY SECRETORY)	-	Cell cycle, DNA Replication, Oocyte Meiosis, Progesterone-Mediated Oocyte Maturation, Pyrimidine Metabolism, Base Excision Repair	Cell Cycle, DNA Replication, Progesterone-Mediated Oocyte Maturation, Oocyte Meiosis
	GDS2737 (MID SECRETORY)	-	Amyotrophic Lateral Sclerosis (ALS)	-
	GDS2737 (PROLIFERATIVE)	-	-	-
	GDS2835	Cell Cycle, DNA Replication, Spliceosome, Oocyte Meiosis, p53 Signaling Pathway, Mismatch Repair, Proteasome, Alzheimer's Disease, Nucleotide Excision Repair, Purine Metabolism	Complement and Coagulation Cascades, Cell Adhesion Molecules (CAMs), Focal Adhesion, MAPK Signaling Pathway, Asthma, Leukocyte Transendothelial Migration, Chemokine Signaling Pathway, Adherens Junction, Systemic Lupus Erythematosus, Fc Gamma R-Mediated Phagocytosis	Cell Cycle, p53 Signaling Pathway, Pathways in Cancer, Oocyte Meiosis, DNA Replication, Adherens Junction, Progesterone-Mediated Oocyte Maturation, Cell Adhesion Molecules (CAMs), Tight Junction, Fc Gamma R-Mediated Phagocytosis
	GDS3060	Lysosome, Melanoma	Focal Adhesion, ECM-Receptor Interaction, Gap Junction, Vascular Smooth Muscle Contraction, Calcium Signaling Pathway, Hypertrophic Cardiomyopathy (HCM), Apoptosis, Dilated Cardiomyopathy, p53 Signaling pathway, Long-Term Depression	Focal Adhesion, ECM-Receptor Interaction, Gap Junction, Melanoma, Vascular Smooth Muscle Contraction, Calcium Signaling Pathway, Axon Guidance, Glioma, Prostate Cancer, Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC)

Among six datasets related to endometriosis, GDS2835 dataset resulted with significantly higher number of DEGs compared to all other datasets, and functional enrichment analyses resulted with diverse set of pathways and processes. On the other hand, any significant enrichment couldn't be obtained as a result of the pathway enrichment analysis of GDS2737 dataset.

Diverse pathways were affected in endometriosis (Table 3.17). Genes associated with pathways, including cell cycle, DNA replication, oocyte meiosis, and p53 signaling pathway, were differentially expressed in endometriosis. Down-regulated genes were enriched with mismatch repair, proteasome, Alzheimer's disease, nucleotide excision repair, purine metabolism, lysosome and melanoma. On the other hand, pyrimidine metabolism, amyotrophic lateral sclerosis (ALS), progesterone-mediated oocyte maturation, complement and coagulation cascades, cell adhesion molecules (CAMs), focal adhesion, MAPK signaling pathway, chemokine signaling pathway, ECM-receptor interaction, vascular smooth muscle contraction and calcium signaling pathways were enriched with up-regulated DEGs.

Biological process enrichment analyses of six datasets for endometriosis indicated diverse biological processes. In general cell cycle processes, organizational and developmental processes, response systems, transport mechanisms, and regulation of several biological processes were significantly affected in endometriosis (Table 3.18). In the early secretory phase of endometriosis, ion transport and homeostasis, and response to chemical stimulus processes were down-regulated, whereas cell cycle processes were significantly up-regulated. In the mid secretory phase, phosphate metabolism and dephosphorylation processes were down-regulated, whereas up-regulated DEGs were enriched with regulation of several biological processes. In the proliferative phase of the disease, down-regulated DEGs were enriched with organelle and actin cytoskeleton processes, however response processes such as inflammatory response, immune system, response to external stimulus and response to wounding were up-regulated as well as oxygen transport, several organizational and developmental processes.

Proteins encoded by the DEGs in endometriosis were located in several parts of the biological systems. Down-regulated DEGs were enriched with plasma membrane

associated terms (apical plasma membrane, apical junction complex, apical part of cell, apicolateral plasma membrane, membrane fraction, insoluble fraction), intracellular component terms (including cytoskeleton, cytoplasm, cytoplasmic part, intracellular part, intracellular organelle part), and organelle terms (endoplasmic reticulum, membrane-bounded organelle, intracellular organelle). On the other hand, chromosomal (chromosome, chromosomal part, centromeric region, condensed chromosome, etc.) and extracellular location terms (extracellular region, extracellular matrix, extracellular space, cell surface, proteinaceous extracellular matrix, cell leading edge) were significantly enriched with up-regulated DEGs in endometriosis (Table 3.19).

Results of molecular function enrichment analyses indicated that proteins associated with binding activities (especially for cadmium and copper ions, cytoskeleton protein, actin, RNA, nucleotide, ATP, adenylyl ribonucleotide), catalytic activities (especially, hydrolase and phosphatase), protein kinase regulator activity and transmembrane transporter activity were down-regulated. Moreover, up-regulated DEGs were significantly enriched with several binding activities (ATP, adenylyl ribonucleotide, purine nucleoside, nucleoside, purine ribonucleotide, ribonucleotide and purine nucleotide, protein, cytoskeletal protein, actin, fibronectin, pattern, polysaccharide, carbohydrate, growth factor, oxygen), peptidase activity, oxygen transporter activity, enzyme regulator activity and kinase activity (Table 3.20).

**Table 3.18.** GO-biological process enrichment analysis results for endometriosis

RELATED DISEASE	DATASET NUMBER	DOWN-REGULATED DEGs	UP-REGULATED DEGs	ALL DEGs
ENDOMETRIOSIS	GDS2737	-	Response to Wounding, Response to External Stimulus, Response to Stress, Acute-Phase Response, Inflammatory Response, Defense Response	Response to Wounding, Inflammatory Response, Acute-Phase Response, Acute Inflammatory Response, Response to External Stimulus
	GDS2737 (E.S.)	Inorganic Anion Transport, Anion Transport, Regulation of Biological Quality, Amine Catabolic Process, Cellular Ion Homeostasis, Response to Chemical Stimulus, Cellular Cation Homeostasis, Cellular Chemical Homeostasis, Cation Homeostasis, Cellular Homeostasis	Cell Cycle, M Phase, Cell Cycle Phase, Cell Cycle Process, Nuclear Division, Mitosis, M Phase of Mitotic Cell Cycle, Organelle Fission, Mitotic Cell Cycle, Cell Division	M Phase, Cell Cycle, Cell Cycle Phase, Nuclear Division, Mitosis, M Phase of Mitotic Cell Cycle, Organelle Fission, Cell Cycle Process, Mitotic Cell Cycle, Cell Division
	GDS2737 (M.S.)	Phosphate Metabolic Process, Phosphorus Metabolic Process, Dephosphorylation	Biological Regulation, Positive Regulation of Cellular Process, Regulation of Cellular Process, Positive regulation of Biological Process, Positive Regulation of Macromolecule Biosynthetic Process, Regulation of Biological Process, Positive Regulation of Transcription, Positive Regulation of Transcription-DNA Dependent, Positive Regulation of RNA Metabolic Process	Dephosphorylation, Positive Regulation of Biosynthetic Process, Phosphate Metabolic Process, Phosphorus Metabolic Process, Positive Regulation of Macromolecule Biosynthetic Process, Positive Regulation of Metabolic Process
	GDS2737 (P.)	Organelle Organization, Cellular Component Organization, Actin Cytoskeleton Organization	Response to Wounding, Inflammatory Response, Response to External Stimulus, Defense Response, Response to Stress, Acute Inflammatory Response, Oxygen Transport, Leukocyte Migration, Immune System Process, Gas Transport	Response to Wounding, Inflammatory Response, Oxygen Transport, Gas Transport, Response to External Stimulus, Regulation of Developmental Process, Response to Stress, Cellular Component Organization, Defense Response, Negative Regulation of Cell Differentiation
	GDS2835	Mitotic Cell Cycle, M Phase, Cell Cycle, Cell Cycle Phase, Cell Cycle Process, Mitosis, Nuclear Division, M phase of Mitotic Cell Cycle, Organelle Fission, Cell Division	Response to Wounding, Positive Regulation of Biological Process, Immune System Process, Response to External Stimulus, Cell Adhesion, Biological Adhesion, Response to Chemical Stimulus, Anatomical Structure Development, Inflammatory Response, System Development	Cell Cycle, Cellular Component Organization, Mitotic Cell Cycle, Cell Cycle Process, Mitosis, Nuclear Division, Cellular Process, M Phase of Mitotic Cell Cycle, Cell Division, Organelle Fission
	GDS3060	Lysosome, Melanoma, Regulation of Nitric-Oxide Synthase Activity, Regulation of Monooxygenase Activity, Purine Nucleotide Metabolic Process, Heterocycle Metabolic Process, Tube Development	Anatomical Structure Development, System Development, Organ Development, Multicellular Organismal Development, Developmental Process, Blood Vessel Development, Anatomical Structure Morphogenesis, Vasculature Development, Blood Vessel Morphogenesis	System Development, Organ Development, Anatomical Structure Development, Multicellular Organismal Development, Developmental Process, Anatomical Structure Morphogenesis, Blood Vessel Development, Blood Vessel Morphogenesis, Vasculature Development, Cell

**Table 3.19.** GO-cellular component enrichment analysis results for endometriosis

RELATED DISEASE	DATASET NUMBER	DOWN-REGULATED DEGs	UP-REGULATED DEGs	ALL DEGs
ENDOMETRIOSIS	GDS2737	Cytoplasmic Membrane-Bounded Vesicle, Membrane-Bounded Vesicle	-	-
	GDS2737 (E.S.)	Cytoplasm, Apical Plasma Membrane, Apical Junction Complex, Apical Part of Cell, Apicolateral Plasma Membrane, Cytoskeleton, Cytoplasmic Part, Membrane Fraction, Insoluble Fraction, Endoplasmic Reticulum	Chromosome, Chromosomal Part, Condensed Chromosome, Spindle, Chromosome-Centromeric Region, Microtubule Cytoskeleton, Intracellular Non-Membrane-Bounded Organelle, Non-Membrane-Bounded Organelle, Condensed Chromosome, Centromeric Region, Condensed Chromosome Kinetochore	Microtubule Cytoskeleton, Spindle, Condensed Chromosome, Chromosome, Chromosomal Part, Chromosome-Centromeric Region, Condensed Chromosome-Centromeric Region, Cytoskeletal Part, Condensed Chromosome Kinetochore, Kinetochore
	GDS2737 (M.S.)	-	-	Integral to Plasma Membrane, Intrinsic to Plasma Membrane, Plasma Membrane Part
	GDS2737 (P.)	Intracellular Part	Extracellular Region, Hemoglobin Complex, Plasma Membrane Part, Anchored to Membrane, Apical Plasma Membrane	Hemoglobin Complex, Extracellular Region
	GDS2835	Intracellular Part, Intracellular, Organelle Part, Intracellular Organelle Part, Cytoplasm, Membrane-Bounded Organelle, Intracellular Membrane-Bounded Organelle, Organelle, Intracellular Organelle, Chromosome-Centromeric Region	Cytoplasm, Extracellular Region Part, Plasma Membrane Part, Extracellular Matrix, Cell Surface, Proteinaceous Extracellular Matrix, Plasma Membrane, Cell Leading Edge, Platelet Alpha Granule, Extracellular Space	Cytoplasm, Intracellular Part, Intracellular, Cytoplasmic Part, Membrane-Bounded Organelle, Intracellular Membrane-Bounded Organelle, Intracellular Organelle, Organelle, Chromosome-Centromeric Region, Intracellular Organelle Part
	GDS3060	-	Cell-Substrate Adherens Junction, Cell-Substrate Junction, Anchoring Junction, Adherens Junction, Basolateral Plasma Membrane, Extracellular Matrix, Focal Adhesion, Proteinaceous Extracellular Matrix, Smooth Muscle Contractile Fiber, Intrinsic to Plasma Membrane	Anchoring Junction, Cell-Substrate Adherens Junction, Basolateral Plasma Membrane, Adherens Junction, Cell-Substrate Junction, Intrinsic to Plasma Membrane, Focal Adhesion, Cell Projection, Cytoplasmic Membrane-Bounded Vesicle Lumen, Plasma Membrane Part

**Table 3.20.** GO-molecular function enrichment analysis results for endometriosis

RELATED DISEASE	DATASET NUMBER	DOWN-REGULATED DEGs	UP-REGULATED DEGs	ALL DEGs
ENDOMETRIOSIS	GDS2737	-	-	-
	GDS2737 (E.S.)	Cadmium Ion Binding, Catalytic Activity, Copper Ion Binding, Cytoskeletal Protein Binding, Actin Binding, Hydrolase Activity, CAMP-Dependent Protein Kinase Regulator Activity	Adenyl Ribonucleotide Binding, ATP Binding, Adenyl Nucleotide Binding, Purine Nucleoside Binding, Nucleoside Binding, Protein Binding, Purine Ribonucleotide Binding, Ribonucleotide Binding, Purine Nucleotide Binding, Microtubule Motor Activity	ATP Binding, Adenyl Ribonucleotide Binding, Adenyl Nucleotide Binding, Purine Nucleoside Binding, Nucleoside Binding, Purine Ribonucleotide Binding, Ribonucleotide Binding, Purine Nucleotide Binding, Catalytic Activity, Protein Binding
	GDS2737 (M.S.)	Binding	-	-
	GDS2737 (P.)	RNA Binding, Nucleotide Binding, Cytoskeletal Protein Binding	Cysteine-Type Endopeptidase Activity, Oxygen Binding, Oxygen Transporter Activity, Cysteine-Type Peptidase Activity, Protein Complex Binding, Endopeptidase Activity, Peptidase Activity, Kininogen Binding	Oxygen Transporter Activity, Oxygen Binding, Cysteine-Type Endopeptidase Activity, Binding, RNA Binding, Heme Binding
	GDS2835	Catalytic Activity, Protein Binding, Hydrolase Activity, Pyrophosphatase Activity, Nucleotide Binding, Hydrolase Activity-Acting on Acid Anhydrides, Hydrolase Activity-Acting on Acid Anhydrides in Phosphorus-Containing Anhydrides, Nucleoside-Triphosphatase Activity, ATP Binding, Adenyl Ribonucleotide Binding	Protein Binding, Binding, Cytoskeletal Protein Binding, Growth Factor Binding, Actin Binding, Pattern Binding, Polysaccharide Binding, Glycosaminoglycan Binding, Carbohydrate Binding, Enzyme Regulator Activity	Protein Binding, Binding, Cytoskeletal Protein Binding, Catalytic Activity, Nucleotide Binding, Polysaccharide Binding, Pattern Binding, Glycosaminoglycan Binding, Purine Ribonucleotide Binding, Ribonucleotide Binding
	GDS3060	Active Transmembrane Transporter Activity	Protein Binding, Binding, Cytoskeletal Protein Binding, Enzyme Activator Activity, GTPase Activator Activity, Actin Binding, Growth Factor Binding, Fibronectin Binding, Protein Kinase Activity, Transmembrane Receptor Protein Tyrosine Kinase Activity	Protein Binding, Cytoskeletal Protein Binding, Transmembrane Receptor Protein Tyrosine Kinase Activity, Actin Binding, Growth Factor Binding, Enzyme Activator Activity, GTPase Activator Activity, Protein Kinase Activity, Phosphotransferase Activity-Alcohol Group as Acceptor, Binding

### 3.3.5. Functional Enrichment Analysis for Polycystic Ovary Syndrome

Disease enrichment results of individual dataset were not consistent, i.e., common enrichment within at least two datasets couldn't be achieved. Even, no significant disease enrichment was obtained for three datasets (GDS1051/GDS3841 lean/GDS4987). Keloid disease, Dupuytren's disease, congenital heart anomalies, brain aneurysm, type 2 diabetes, liver disease and hypertension were enriched in individual down-regulated DEG sets. On the other hand, up-regulated DEGs in PCOS were enriched in, beta-thalassemia, fetal hemoglobin, type 2 diabetes, hypertension, obesity, triglycerides, arterial blood pressure, periodontitis, multiple sclerosis, lupus erythematosus, tuberculosis, sarcoidosis, HIV, and Crohn's diseases (Table 3.21).

**Table 3.21.** Disease enrichment analysis results for PCOS

RELATED DISEASE	DATASET NUMBER	DOWN-REGULATED DEGs	UP-REGULATED DEGs	ALL DEGs
POLYCYSTIC OVARY SYNDROME	GDS1050	Keloid Disease, Dupuytren's Disease, Heart Anomalies-Congenital, Brain Aneurysm	-	Keloid Disease, Heart Anomalies-Congenital
	GDS1051	-	-	-
	GDS3104	-	Beta-Thalassemia, Fetal Hemoglobin	Beta-Thalassemia
	GDS3841 (LEAN)	-	-	-
	GDS3841 (OBESE)	-	Insulin; Polycystic Ovary Syndrome, Diabetes- Type 2; Hypertension; Insulin; Obesity, Body Mass; Cholesterol; Triglycerides; Insulin; Glucose; Blood Pressure, Arterial	-
	GDS4133	Diabetes, Type 2; Liver Disease, Hypertension	-	-
	GDS4399	-	Periodontitis, Multiple Sclerosis, Rheumatoid Arthritis, HIV, Systemic Lupus Erythematosus, Sarcoidosis, Lupus Erythematosus, Crohn's Disease, Arthritis, Tuberculosis	Periodontitis, Multiple Sclerosis, Lupus Erythematosus, Sarcoidosis, HIV, Rheumatoid Arthritis, Systemic Lupus Erythematosus, Crohn's Disease, Arthritis, Tuberculosis
	GDS4987	-	-	-

Significant pathway enrichment results were obtained for five datasets. Pathways in cancer and several signaling pathways (MAPK, Insulin, VEGF, TGF-Beta) as well as cell cycle and proteasome were enriched with down-regulated DEGs. On the other hand, up-regulated DEGS were enriched in oxidative phosphorylation, calcium signaling pathway and several disease pathways, including Parkinson’s disease, Huntington’s disease, Alzheimer’s disease, and Type I diabetes mellitus (Table 3.22).

**Table 3.22.** Pathway enrichment analysis results for PCOS

RELATED DISEASE	DATASET NUMBER	DOWN-REGULATED DEGs	UP-REGULATED DEGs	ALL DEGs
POLYCYSTIC OVARY SYNDROME	GDS1050	Focal Adhesion, ECM-Receptor Interaction, Pathways in Cancer, Chronic Myeloid Leukemia, Thyroid Cancer, Adherens Junction, MAPK Signaling Pathway, Insulin Signaling Pathway, VEGF Signaling Pathway, TGF-Beta Signaling Pathway	Oxidative Phosphorylation, Parkinson's Disease, Huntington's Disease, Alzheimer's Disease, Spliceosome, Ribosome, Proteasome	Oxidative Phosphorylation, Parkinson's Disease, Huntington's Disease, Alzheimer's Disease, Spliceosome, Ribosome, Focal Adhesion, Proteasome, Adherens Junction
	GDS1051	-	-	-
	GDS3104	-	Calcium Signaling Pathway	-
	GDS3841 (LEAN)	Small Cell Lung Cancer, Pathways in Cancer, MAPK Signaling Pathway	Systemic Lupus Erythematosus	Small Cell Lung Cancer, Pathways in Cancer
	GDS3841 (OBESE)	-	-	-
	GDS4133	-	-	-
	GDS4399	Gap Junction	Allograft Rejection, Viral Myocarditis, Antigen Processing and Presentation, Graft-Versus-Host Disease, Type I Diabetes Mellitus, Autoimmune Thyroid Disease, B Cell Receptor Signaling Pathway, Fc Gamma R-Mediated Phagocytosis, Cell Adhesion Molecules (CAMs), Natural Killer Cell Mediated Cytotoxicity	Graft-Versus-Host Disease, Type I Diabetes Mellitus, Autoimmune Thyroid Disease, B Cell Receptor Signaling Pathway, Fc Gamma R-Mediated Phagocytosis, Cell Adhesion Molecules (CAMs), Natural Killer Cell Mediated Cytotoxicity
	GDS4987	Proteasome, Cell Cycle	-	Proteasome

**Table 3.23.** GO-biological process enrichment analysis results for PCOS

RELATED DISEASE	DATASET NUMBER	DOWN-REGULATED DEGs	UP-REGULATED DEGs	ALL DEGs
POLYCYSTIC OVARY SYNDROME	GDS1050	Cellular Process, Blood Vessel Development, Vasculature Development, Regulation of Developmental Process, Positive Regulation of Cellular Process, Developmental Process, Response to Organic Substance, Wound Healing, Positive Regulation of Biological Process, Anatomical Structure Development	Oxidative Phosphorylation, Mitochondrial ATP Synthesis Coupled electron Transport, ATP Synthesis Coupled Electron Transport, RNA Splicing-via Transesterification Reactions, RNA Splicing-via Transesterification Reactions with Bulged Adenosine as Nucleophile, Nuclear mRNA Splicing-via Spliceosome, Respiratory Electron Transport Chain, Generation of Precursor Metabolites and Energy, Electron Transport Chain, Mitochondrial Electron Transport-NADH to Ubiquinone	Cellular Process, Cellular Metabolic Process, Oxidative Phosphorylation, RNA Splicing-via Transesterification Reactions with Bulged Adenosine as Nucleophile, RNA Splicing-via Transesterification Reactions, Nuclear mRNA Splicing-via Spliceosome, Mitochondrial ATP Synthesis Coupled Electron Transport, ATP Synthesis Coupled Electron Transport, Regulation of Programmed Cell Death, Regulation of Cell Death
	GDS1051	Cellular Macromolecule Metabolic Process, Macromolecule Metabolic Process, Primary Metabolic Process, Cellular Protein Metabolic Process, Protein Metabolic Process, Cellular Metabolic Process, Golgi Vesicle Transport, Protein Catabolic Process, Metabolic Process, Cellular Protein Catabolic Process	-	Cellular Macromolecule Metabolic Process, Macromolecule Metabolic Process, Cellular Protein Metabolic Process, Primary Metabolic Process, Cellular Metabolic Process, Protein Metabolic Process, Protein Catabolic Process, Golgi Vesicle Transport, Cellular Macromolecule Biosynthetic Process, Cellular Protein Catabolic Process
	GDS3104	-	Regulation of Skeletal Muscle Tissue Development, Regulation of Striated Muscle Tissue Development, Regulation of Muscle Development, Muscle System Process	Regulation of Skeletal Muscle Tissue Development
	GDS3841 (LEAN)	Cellular Macromolecule Metabolic Process, Transcription, Cellular Metabolic Process, Cellular Process, Regulation of Transcription, Regulation of Macromolecule Biosynthetic Process, Nucleobase-Nucleoside-Nucleotide and Nucleic Acid Metabolic Process, Macromolecule Metabolic Process, Regulation of Gene Expression, Transcription-DNA Dependent	Nucleosome Assembly, Chromatin Assembly, Cellular Process, Chromatin Assembly or Disassembly, Protein-DNA Complex Assembly, Nucleosome Organization, Response to Biotic Stimulus, Immune Response, DNA Packaging, Localization	Cellular Process, Transcription- DNA Dependent, RNA Biosynthetic Process, Cellular Metabolic Process, Positive Regulation of Cellular Process, Organelle Organization, Cellular Macromolecule Metabolic Process, Positive Regulation of Biological Process, Chromatin Organization, Wnt Receptor Signaling Pathway
	GDS3841 (OBESE)	Cellular Metabolic Process, Metabolic Process	Positive Regulation of Cellular Catabolic Process, Negative Regulation of Biological Process, Positive Regulation of Catabolic Process, Regulation of Protein Metabolic Process, Cellular Process, Regulation of Signal Transduction, Regulation of Transcription from RNA Polymerase II Promoter, Positive Regulation of Cellular Metabolic Process, Regulation of Cellular Catabolic Process, Regulation of Cellular Protein Metabolic Process	Cellular Process, Primary Metabolic Process, Cellular Metabolic Process, Mesoderm Development, Positive Regulation of Cellular Catabolic Process, Negative Regulation of Biological Process, Metabolic Process, Positive Regulation of Catabolic Process, Negative Regulation of Macromolecule Metabolic Process, Cellular Macromolecule Metabolic Process

**Table 3.23.** GO-biological process enrichment analysis results for PCOS (continued)

RELATED DISEASE	DATASET NUMBER	DOWN-REGULATED DEGs	UP-REGULATED DEGs	ALL DEGs
POLYCYSTIC OVARY SYNDROME	GDS4133	Positive Regulation of Cholesterol Storage	-	Cellular Process, Carboxylic Acid Transport, Organic Acid Transport
	GDS4399	Intracellular Signaling Cascade, Protein Modification Process, Biopolymer Modification, Developmental Process, Neuron Recognition, Response to Hormone Stimulus, Post-Translational, Protein Modification, Enzyme Linked Receptor Protein Signaling Pathway, Cell Projection Morphogenesis, Central Nervous System Development	Immune System Process, Immune Response, Defense Response, Inflammatory Response, Response to Wounding, Response to External Stimulus, Response to Stimulus, Response to Stress, Regulation of Immune System Process, Regulation of Immune Response	Immune System Process, Immune Response, Defense Response, Inflammatory Response, Response to Wounding, Response to External Stimulus, Response to Stress, Response to Stimulus, Regulation of Immune Response, Regulation of Immune System Process
	GDS4987	Mitotic Cell Cycle, Cell Cycle Process, Cell Cycle, M Phase, Anaphase-Promoting Complex-Dependent Proteasomal Ubiquitin-Dependent Protein Catabolic Process, Negative Regulation of Ubiquitin-Protein Ligase Activity During Mitotic Cell Cycle, Negative Regulation of Ligase Activity, Negative Regulation of Ubiquitin-Protein Ligase Activity, Regulation of Ubiquitin-Protein Ligase Activity During Mitotic Cell Cycle, Negative Regulation of Protein Ubiquitination	Neurological System Process, Sensory Perception of Light Stimulus, Visual Perception, System Process, Cognition	Mitotic Cell Cycle, Cell Cycle Process, Negative Regulation of Ubiquitin-Protein Ligase Activity During Mitotic Cell Cycle, Anaphase-Promoting Complex-Dependent Proteasomal Ubiquitin-Dependent Protein Catabolic Process, Negative Regulation of Ubiquitin-Protein Ligase Activity, Negative Regulation of Ligase Activity, Regulation of Ubiquitin-Protein Ligase Activity During Mitotic Cell Cycle, Negative Regulation of Protein Ubiquitination, Cell Cycle, Regulation of Ubiquitin-Protein Ligase Activity

Down-regulated DEGs of PCOS dataset, GDS1050, were enriched in biological processes of cellular process, blood vessel development, vasculature development, response to organic substance, wound healing and anatomical structure development. Up-regulated and all DEGs were enriched in some common processes like oxidative phosphorylation, ATP synthesis coupled electron transport and nuclear mRNA splicing-via spliceosome processes. Down-regulated DEGs of GDS1051 dataset were enriched in generally metabolic processes, like cellular macromolecule, macromolecule, cellular protein, primary and cellular metabolic processes. Up-regulated and all DEGs of GDS3104 dataset were enriched in regulation of skeletal muscle tissue development and except this process, they were enriched in regulation of striated muscle tissue development, regulation of muscle development and muscle system processes.

GDS3841 dataset which contain just lean samples were enriched in biological processes of cellular macromolecule metabolic process, transcription, nucleobase-nucleoside-nucleotide and nucleic acid metabolic process, macromolecule metabolic process and regulation of gene expression processes, whereas up-regulated DEGs were enriched in nucleosome assembly, chromatin assembly, cellular process, chromatin assembly or disassembly, protein-DNA complex assembly and DNA packaging as a biological processes. All DEGs were enriched in biological processes like cellular process, transcription-DNA dependent RNA biosynthetic process, cellular metabolic process, positive regulation of cellular process, organelle organization and chromatin organization processes. Down-regulated DEGs of the subset of this dataset, which contain only obese women samples (GDS3841 obese), were enriched in metabolic processes, while up-regulated DEGs were enriched in positive regulation of cellular catabolic process, positive regulation of catabolic process, regulation of protein metabolic process, regulation of signal transduction and regulation of transcription from RNA polymerase II promoter processes. All DEGs were enriched in biological processes of cellular process, primary metabolic process, cellular metabolic process and mesoderm development. Analyses results of GDS4133 dataset showed that down-regulated DEGs were enriched with positive regulation of cholesterol storage, while all DEGs were enriched in cellular process, carboxylic acid transport and organic acid transport processes. Down regulated DEGs of GDS4399 dataset were enriched in processes such as intracellular signaling cascade, protein modification process, biopolymer modification, neuron recognition, response to hormone stimulus, post-translational, protein modification and central nervous system development biological processes. On the other hand, up-regulated and all DEGs were enriched in cellular response processes such as immune system process, immune response, defense response, inflammatory response, response to wounding and response to stress processes. Down-regulated and all DEGs of GDS4987 dataset were enriched in biological processes including mitotic cell cycle, cell cycle process, negative regulation of ubiquitin-protein ligase activity and regulation of ubiquitin-protein ligase activity during mitotic cell cycle, whereas up-regulated DEGs were enriched in biological processes of neurological system process, visual perception, system process and cognition processes. Eventually, cellular metabolic process, cellular process and

cellular macromolecule metabolic process were the biological processes that were enriched in 4 and 3 datasets, respectively. Developmental process, immune response, macromolecule metabolic process, metabolic process, positive regulation of biological process, positive regulation of cellular process and primary metabolic process were outcomes in two datasets (Table 3.23).

Proteins encoded by the DEGs in PCOS were mostly located in the intracellular part of the cells (Table 3.24). Cytoplasm, intracellular organelle and intracellular part terms were the cellular components that enriched in 5 datasets out of 7. Cellular components of intracellular membrane-bounded organelle and membrane-bounded organelle were enriched in 4 datasets, whereas cytoplasmic part, cytoskeleton, intracellular organelle part, nucleus and organelle part were enriched with 3 datasets. Lastly cytosol, macromolecular complex, nuclear part and nucleoplasm outcomes were enriched with 2 datasets.

Molecular function enrichment analyses indicated that proteins associated with protein, enzyme, actin, ion, transcription factor, kinase and DNA binding activities were down-regulated in PCOS. On the other hand, catalytic activities (especially, dehydrogenase and oxidoreductase), ion (especially, cation) transporter activity, signaling activities (including signal transducer and receptor activities) and binding activities for calmodulin, cytokine and carbohydrates were significantly up-regulated (Table 3.25). Molecular functions of protein binding, and cytoskeletal protein binding were enriched with 4 and 3 datasets, respectively. Except these functions, actin binding, molecular transducer activity, nucleotide binding, protein kinase activity, protein serine/threonine kinase activity, receptor activity, signal transducer activity, small conjugating protein ligase activity, transcription factor binding, transferase activity and zinc ion binding were enriched in two datasets. Down-regulated DEGS of GDS1050 dataset were generally enriched in molecular function of binding such as protein, enzyme, protein, transcription factor, kinase and cytoskeletal protein binding, whereas up-regulated DEGs were enriched in activities including NADH dehydrogenase, oxidoreductase and ion transmembrane transporter activities. Down-regulated DEGs of GDS1051 dataset were enriched in transferase activity, actin binding and zinc ion binding; up-regulated DEGs were enriched in calmodulin binding.

**Table 3.24.** GO-cellular component enrichment analysis results for PCOS

RELATED DISEASE	DATASET NUMBER	DOWN-REGULATED DEGs	UP-REGULATED DEGs	ALL DEGs
POLYCYSTIC OVARY SYNDROME	GDS1050	Cytoplasm, Intracellular Part, Cytoskeleton, Non-Membrane-Bounded Organelle, Intracellular Non-Membrane-Bounded Organelle, Intracellular, Basolateral Plasma Membrane, Cytosol, Focal Adhesion, Actin Cytoskeleton	Intracellular Part, Intracellular Organelle, Organelle, Macromolecular Complex, Cytoplasm, Mitochondrial Membrane Part, Intracellular, Organelle Part, Intracellular Membrane-Bounded Organelle, Membrane-Bounded Organelle	Cytoplasm, Intracellular Part, Intracellular Organelle, Intracellular, Organelle, Cytoplasmic Part, Macromolecular Complex, Intracellular Organelle Part, Organelle Part, Intracellular Membrane-Bounded Organelle
	GDS1051	Intracellular, Intracellular Part, Intracellular Organelle, Intracellular Membrane-Bounded Organelle, Organelle, Membrane-Bounded Organelle, Cytoplasm, Golgi Apparatus Part, Nucleus, Cytoplasmic mRNA Processing Body	-	Intracellular, Intracellular Part, Intracellular Organelle, Organelle, Intracellular Membrane-Bounded Organelle, Membrane-Bounded Organelle, Cytoplasmic mRNA Processing Body, Cytoplasm, Nucleus, Golgi Apparatus Part
	GDS3104	-	Sarcomere, Myofibril, Contractile Fiber Part, Contractile Fiber, Cytoplasm, Cytoskeleton	Sarcomere, Myofibril, Contractile Fiber, Cytoplasm
	GDS3841 (LEAN)	Intracellular, Nucleus, Intracellular Part, Intracellular Organelle, Organelle, Nuclear Part, Membrane-Bounded Organelle, Nuclear Lumen, Intracellular Membrane-Bounded Organelle, Nucleolus	Endoplasmic Reticulum, Cytoplasmic Part, Nucleosome, Cytoplasm, Protein-DNA Complex, Endoplasmic Reticulum Part, Intracellular Membrane-Bounded Organelle, Membrane-Bounded Organelle, Integral to Membrane, Chromatin	Intracellular, Intracellular Part, Intracellular Organelle, Organelle Membrane-Bounded Organelle, , Intracellular Membrane-Bounded Organelle, Organelle Part, Nucleus, Cell Part
	GDS3841 (OBESE)	Intracellular Membrane-Bounded Organelle, Membrane-Bounded Organelle	Nucleoplasm	Intracellular Membrane-Bounded Organelle, Membrane-Bounded Organelle, Intracellular Part, Nucleus, Intracellular, Integral to Endoplasmic Reticulum Membrane, Nuclear Part, Intracellular Organelle, Organelle, Intrinsic to Endoplasmic Reticulum Membrane
	GDS4133	-	-	Cell Fraction, Membrane Fraction, Insoluble Fraction
	GDS4399	Cell Projection, Cell Junction, Synapse, Plasma Membrane Part, Cell-Cell Junction, Plasma Membrane, Synapse Part, Cytoskeleton, Cell Leading Edge, Microvillus	Plasma Membrane, Plasma Membrane Part, Membrane, Integral to Plasma Membrane, Intrinsic to Plasma Membrane, Membrane Part, Intrinsic to Membrane, MHC Protein Complex, Lytic Vacuole, Lysosome	Plasma Membrane, Plasma Membrane Part, Membrane, Intrinsic to Membrane, Integral to Plasma Membrane, Membrane Part, Cell Surface, Cell Leading Edge, Intrinsic to Membrane, MHC Protein Complex
	GDS4987	Macromolecular Complex, Cytoplasm, Cytoplasmic Part, Protein Complex, Cytosol, Intracellular Part, Intracellular, Intracellular Organelle Part, Organelle Part, Intracellular Organelle	-	Macromolecular Complex, Protein Complex, Cytosol, Proteasome Core Complex, Proteasome Complex

Analysis of GDS3841 dataset, which includes only lean women samples, resulted in molecular functions of protein, zinc ion, cytoskeletal protein binding and protein serine/threonine kinase activity for down-regulated DEGs. Except these functions, all DEGs were enriched in functions like RNA polymerase II transcription factor activity and transferase activity. Up-regulated DEGs of the same dataset that contain only obese samples were enriched in molecular function of small conjugating protein ligase activity. All DEGs of GDS4133 dataset were enriched in carboxylic acid binding. The DEGs in GDS4399 dataset were enriched in molecular functions of binding and activity functions. Down-regulated DEGs were enriched in protein binding, cytoskeletal protein binding, actin binding and protein kinase activity, while up-regulated DEGs were enriched in molecular transducer activity, receptor activity, carbohydrate binding, lipoprotein binding and GTPase activator activities. All DEGs were enriched in molecular functions like signal transducer activity, cytokine binding and sugar binding. Finally, down-regulated DEGs of GDS4987 dataset were enriched in binding activity, whereas up-regulated DEGs were enriched in signaling activities. Down-regulated DEGs were enriched in threonine-type endopeptidase and threonine-type peptidase activities.

**Table 3.25.** GO-molecular function enrichment analysis results for PCOS

RELATED DISEASE	DATASET NUMBER	DOWN-REGULATED DEGs	UP-REGULATED DEGs	ALL DEGs
POLYCYSTIC OVARY SYNDROME	GDS1050	Protein Binding, Binding, Enzyme Binding, Protein Dimerization Activity, Transcription Factor Binding, Kinase Binding, Cytoskeletal Protein Binding, Identical Protein Binding, Protein Complex Binding, Protein Kinase Binding	NADH Dehydrogenase Activity, NADH Dehydrogenase (quinone and ubiquinone) Activity, Oxidoreductase Activity Acting on NADH or NADPH-Quinone or Similar Compound as Acceptor, RNA Binding, Structural Constituent of Ribosome, Oxidoreductase Activity, Acting on NADH or NADPH, Hydrogen Ion Transmembrane Transporter Activity, Monovalent Inorganic Cation Transmembrane Transporter Activity, Protein Binding	Protein Binding, NADH Dehydrogenase (ubiquinone) Activity, NADH Dehydrogenase Activity, NADH Dehydrogenase (quinone) Activity, Oxidoreductase Activity Acting on NADH or NADPH-Quinone or Similar Compound as Acceptor, Transcription Factor Binding, RNA Binding, Structural Constituent of Ribosome, Oxidoreductase Activity Acting on NADH or NADPH, Single-Stranded DNA Binding
	GDS1051	Actin Binding, Binding, Transferase Activity, Small Conjugating Protein Ligase Activity, Zinc Ion Binding	-	Transferase Activity, Actin Binding, Zinc Ion Binding, Binding
	GDS3104	-	Calmodulin Binding	Calmodulin Binding, Magnesium Ion Binding
	GDS3841 (LEAN)	Protein Binding, Binding, Zinc Ion Binding, Cytoskeletal Protein Binding, Protein Serine/Threonine Kinase Activity, Nucleotide Binding, Nucleic Acid Binding, Protein Kinase Activity, Transcription Factor Binding, DNA Binding	-	Protein Binding, Binding, Cytoskeletal Protein Binding, RNA Polymerase II Transcription Factor Activity, Protein Serine/Threonine Kinase Activity, Transferase Activity- Transferring Acyl Groups Other Than Amino Acyl Groups, Zinc Ion Binding, Transferase Activity- Transferring Acyl Groups
	GDS3841 (OBESE)	-	Small Conjugating Protein Ligase Activity, Acid-Amino Acid Ligase Activity	Small Conjugating Protein Ligase Activity
	GDS4133	-	-	Carboxylic Acid Binding
	GDS4399	Protein Binding, Cytoskeletal Protein Binding, Actin Binding, Binding, Protein Kinase Activity, Protein Serine/Threonine Kinase Activity, Transmembrane Receptor Protein Tyrosine Kinase Activity	Molecular Transducer Activity, Signal Transducer Activity, Receptor Activity, Carbohydrate Binding, Lipoprotein Binding, Cytokine Binding, GTPase Activator Activity, Sugar Binding, GTPase Regulator Activity, Enzyme Activator Activity	Signal Transducer Activity, Molecular Transducer Activity, Receptor Activity, Protein Binding, Cytokine Binding, Carbohydrate Binding, Lipoprotein Binding, GTPase Activator Activity, GTPase Regulator Activity, Sugar Binding
	GDS4987	Ribonucleotide Binding, Purine Ribonucleotide Binding, Threonine-Type Endopeptidase Activity, Threonine-Type Peptidase Activity, Purine Nucleotide Binding, Nucleotide Binding,-Hydrolase Activity	Receptor Activity, Molecular Transducer Activity, Signal Transducer Activity, Transmembrane Receptor Activity, Steroid Hormone Receptor Activity, G-Protein Coupled Receptor Activity	Threonine-Type Endopeptidase Activity, Threonine-Type Peptidase Activity

### 3.3.6. Functional Enrichment Analysis for Insulin Resistance Datasets

Consistent disease enrichment results couldn't be achieved among insulin resistance datasets (Table 3.26). On the other hand, down-regulated DEGs of individual datasets were enriched in either emphysema or mastocytosis, whereas up-regulated DEGs of GDS3962, which included only female samples, were enriched with nephrolithiasis, inflammatory Bowel disease, liver and heart transplant, leishmaniasis, Hepatitis C, and multiple sclerosis.

**Table 3.26.** Disease enrichment analysis results for insulin resistance datasets

RELATED DISEASE	DATASET NUMBER	DOWN-REGULATED DEGs	UP-REGULATED DEGs	ALL DEGs
INSULIN RESISTANCE	GDS3715	Emphysema	-	-
	GDS3781 (FEMALE)	-	Nephrolithiasis	-
	GDS3781 (FEMALE+ MALE)	-	-	-
	GDS3962 (FEMALE)	-	Inflammatory Bowel Disease, Liver Transplant, Leishmaniasis, Hepatitis C, Heart Transplant, Measles Vaccine Immunity, Multiple Sclerosis	Liver Transplant, Heart Transplant, Renal Transplant, Leishmaniasis, Inflammatory Bowel Disease, Lung Transplant Complications
	GDS3962 (FEMALE+ MALE)	Mastocytosis	-	-

Similar to disease enrichment analyses, pathway enrichment results were also inconsistent. Down-regulated DEGs of individual datasets were enriched in oxidative phosphorylation, endocytosis or fatty acid biosynthesis. On the other hand, up-regulated DEGs were enriched with proteasome as well as several signaling pathways including Jak-STAT signaling, T-cell receptor signaling, chemokine signaling, and Toll-like receptor signaling pathways (Table 3.27).

**Table 3.27.** Pathway enrichment analysis results for insulin resistance datasets

RELATED DISEASE	DATASET NUMBER	DOWN-REGULATED DEGs	UP-REGULATED DEGs	ALL DEGs
INSULIN RESISTANCE	GDS3715	Oxidative phosphorylation	Proteasome	Proteasome, Spliceosome
	GDS3781 (FEMALE)	Endocytosis	-	Endocytosis
	GDS3781 (FEMALE+ MALE)	-	-	-
	GDS3962 (FEMALE)	Fatty Acid Biosynthesis	Cytokine-Cytokine Receptor Interaction, Natural Killer Cell Mediated Cytotoxicity, Jak-STAT Signaling Pathway, T Cell Receptor Signaling Pathway, Allograft Rejection, Chemokine Signaling Pathway, Toll-Like Receptor Signaling Pathway	Cytokine-Cytokine Receptor Interaction, Natural Killer Cell Mediated Cytotoxicity, Fatty Acid Biosynthesis, T Cell Receptor Signaling Pathway, Chemokine Signaling Pathway
	GDS3962 (FEMALE+ MALE)	-	-	Focal adhesion

Biological process enrichment analyses of insulin resistance datasets indicated a wide range of processes associated with insulin resistance (Table 3.28). In general, down-regulated DEGs were enriched with developmental and organizational processes, transport processes, several signaling pathways, and organic acid and lipid metabolism. On the other hand, general metabolic processes, immune system and defense response processes, cell death and apoptosis processes as well as their regulatory systems were up-regulated in insulin resistance.

Individually, immune response and immune system process were the biological processes that enriched with three datasets. Biological processes of cell differentiation, cellular developmental process, enzyme linked receptor protein signaling pathway, cellular process, locomotory behavior, negative regulation of biological process, regulation of apoptosis, regulation of cell death, regulation of cell proliferation, regulation of programmed cell death, response to external stimulus, response to stimulus and vasculature development were the outcomes that common in two datasets. In biological process enrichment analyses, down-regulated DEGs in GDS3715 dataset were enriched in processes like negative regulation of cellular component organization,

ATP synthesis coupled proton transport, ion transmembrane transport, negative regulation of cytoskeleton organization and proton transport; whereas up-regulated and all DEGs were enriched in some common processes like cellular metabolic process, RNA splicing, cellular macromolecule metabolic process and mRNA metabolic processes. In GDS3781-female dataset biological process enrichment analyses showed that down-regulated and all DEGs were enriched in certain common processes suchlike activation of MAPK activity, smooth muscle tissue development, regulation of localization, cellular developmental process and protein modification processes; whereas up-regulated DEGs were enriched in processes of response; for example, response to stimulus, immune, wounding and regeneration. Down-regulated DEGs in GDS3962 female dataset were enriched in metabolic processes for example carboxylic acid, organic acid, cellular ketone, monocarboxylic acid and fatty acid metabolic processes. Dataset's up-regulated DEGs were enriched generally with biological processes of response and regulation, such as immune response, defense response, and response to external stimulus, regulation of apoptosis, regulation of programmed cell death and regulation of cell death processes. All DEGs were enriched with immune system process, monocarboxylic acid metabolic process, protein kinase cascade, defense response, carboxylic acid metabolic process and oxoacid metabolic processes. Analysis of GDS3962 dataset, which includes female and male samples, resulted that up-regulated DEGs were enriched in death, apoptosis, programmed cell death, cell death, response to protein stimulus, regulation of apoptosis and regulation of programmed cell death processes.

The cellular component enrichment analysis results indicated that only each of the two datasets was enriched with cellular components of cytoplasm, intracellular and intracellular part (Table 3.29).

**Table 3.28.** GO-biological process enrichment analysis results for insulin resistance datasets

RELATED DISEASE	DATASET NUMBER	DOWN-REGULATED DEGs	UP-REGULATED DEGs	ALL DEGs
INSULIN RESISTANCE	GDS3715	Negative Regulation of Cellular Component Organization, ATP Synthesis Coupled Proton Transport, Energy Coupled Proton Transport-Down Electrochemical Gradient, Ion Transmembrane Transport, Negative Regulation of Cytoskeleton Organization, Proton Transport, Hydrogen Transport, Negative Regulation of Organelle Organization, ATP Biosynthetic Process	Cellular Metabolic Process, Cellular Process, Cellular Macromolecule Metabolic Process, RNA Splicing, mRNA Metabolic Process, mRNA Processing, Macromolecule Metabolic Process, Primary Metabolic Process, RNA Splicing via Transesterification Reactions, Nuclear mRNA Splicing via Spliceosome	Cellular Metabolic Process, RNA Splicing, Cellular Macromolecule Metabolic Process, mRNA Metabolic Process, Cellular Process, mRNA Processing, Macromolecule Metabolic Process, RNA Metabolic Process, Posttranscriptional Regulation of Gene Expression, Metabolic Process
	GDS3781 (FEMALE)	Activation of MAPKK Activity, Smooth Muscle Tissue Development, Regulation of Localization, Cell Differentiation, Enzyme Linked Receptor Protein Signaling Pathway, Protein Amino Acid Phosphorylation, Cellular Developmental Process, Activation of Protein Kinase Activity, Post-Translational Protein Modification, Regulation of Cell Motion	Response to Stimulus, Immune System Process, Multi-Organism Process, Immune Response, Response to Wounding, Regeneration, Response to External Stimulus	Regulation of Cell Proliferation, Cell Differentiation, Activation of MAPKK Activity, Response to Chemical Stimulus, Cellular Developmental Process, Negative Regulation of Biological Process, Regulation of Localization, Smooth Muscle Tissue Development, Post-Translational Protein Modification, Vasculature Development
	GDS3781 (FEMALE +MALE)	Regulation of Cell Proliferation, Cell Differentiation, Developmental Process, Cellular Developmental Process, Positive Regulation of Cell Proliferation, System Development, Anatomical Structure Development, Enzyme Linked Receptor Protein Signaling Pathway, Anatomical Structure Morphogenesis, Regulation of Epithelial Cell Proliferation	Immune System Process, Immune Response, Response to Stimulus	Cell Differentiation, Locomotory Behavior, Cellular Developmental Process, Developmental Process, Immune System Process, Vasculature Development, Regulation of Cell Proliferation, Cell Morphogenesis, System Development, Anatomical Structure Morphogenesis
	GDS3962 (FEMALE)	Carboxylic Acid Metabolic Process, Organic Acid Metabolic Process, Cellular Ketone Metabolic Process, Monocarboxylic Acid Metabolic Process, Fatty Acid Metabolic Process, Cellular Lipid Metabolic Process, Carboxylic Acid Biosynthetic Process, Organic Acid Biosynthetic Process, Lipid Metabolic Process	Immune Response, Immune System Process, Defense Response, Response to External Stimulus, Chemotaxis, Taxis, Regulation of Apoptosis, Regulation of Programmed Cell Death, Regulation of Cell Death, JAK-STAT Cascade	Immune Response, Immune System Process, Monocarboxylic Acid Metabolic Process, Protein Kinase Cascade, Defense Response, Carboxylic Acid Metabolic Process Oxoacid Metabolic Process, Organic Acid Metabolic Process, Cellular Ketone Metabolic Process, Organic Acid Biosynthetic Process
	GDS3962 (FEMALE + MALE)	-	Death, Apoptosis, Programmed Cell Death, Cell Death, Response to Protein Stimulus, Regulation of Apoptosis, Negative Regulation of Biological Process, Regulation of Programmed Cell Death, Regulation of Cell Death	Death, Behavior, Programmed Cell Death, Cell Death, Gliogenesis, Locomotory Behavior

**Table 3.29.** GO-cellular component enrichment analysis results for insulin resistance datasets

RELATED DISEASE	DATASET NUMBER	DOWN-REGULATED DEGs	UP-REGULATED DEGs	ALL DEGs
INSULIN RESISTANCE	GDS3715	Intracellular Organelle Part, Intracellular, Organelle Part, Intracellular Part, Proton-Transporting Two-Sector ATPase Complex, Intracellular Organelle, Organelle, Organelle Membrane, Cytoplasmic Part, Macromolecular Complex	Intracellular Part, Intracellular, Intracellular Membrane-Bounded Organelle, Membrane-Bounded Organelle, Cytoplasm, Intracellular Organelle, Organelle, Nucleus, Cytoplasmic Part, Nuclear Part	Intracellular, Intracellular Part, Cytoplasm, Intracellular Membrane-Bounded Organelle, Membrane-Bounded Organelle, Intracellular Organelle, Organelle, Cytoplasmic Part, Nucleus, Organelle Part
	GDS3781 (FEMALE)	Intracellular, Cytoplasm, Intracellular Part	-	Cytoplasm
	GDS3781 (FEMALE +MALE)	-	-	-
	GDS3962 (FEMALE)	-	-	-
	GDS3962 (FEMALE +MALE)	-	-	-

Molecular function enrichment analyses showed that hydrogen ion and inorganic cation transporter activities were enriched with down-regulated DEGs. In addition, down-regulated DEGs were also enriched in ion and carboxylic acid binding activities, metalloproteinase activity, and carboxylase activities. On the other hand, several binding activities (protein, DNA, urine nucleoside, purine nucleotide, etc.), helicase activity, and cytokine and chemokine activities were enriched with up-regulated DEGs (Table 3.30).

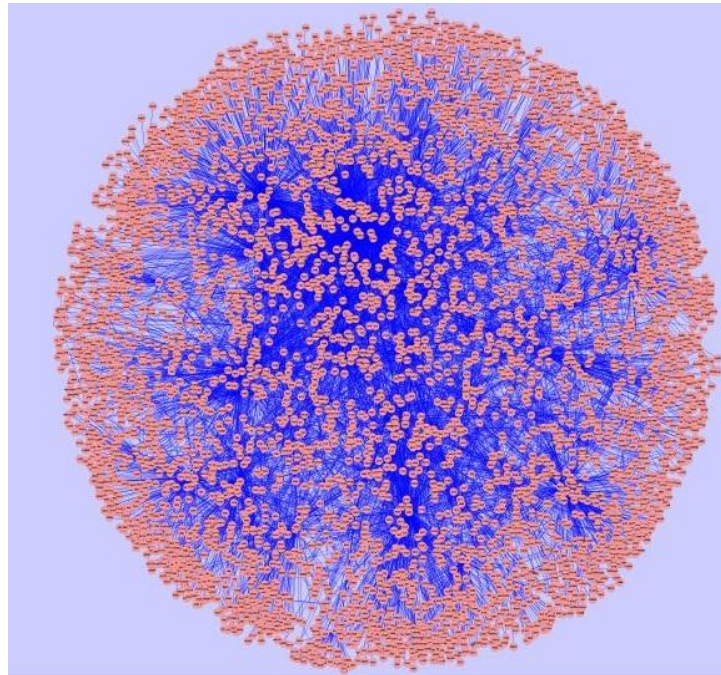
**Table 3.30.** GO-molecular functionenrichment analysis results for insulin resistance datasets

RELATED DISEASE	DATASET NUMBER	DOWN-REGULATED DEGs	UP-REGULATED DEGs	ALL DEGs
INSULIN RESISTANCE	GDS3715	Hydrogen Ion Transmembrane Transporter Activity, Monovalent Inorganic Cation Transmembrane Transporter Activity, Inorganic Cation Transmembrane Transporter Activity, Coumarin 7-Hydroxylase Activity, Cation TransmembraneTransporter Activity	Protein Binding, Nucleotide Binding, RNA Binding, Binding, Unfolded Protein Binding, Helicase Activity, Urine Nucleoside Binding, Nucleoside Binding, Adenyl Nucleotide Binding ,Purine Nucleotide Binding	Protein Binding, Nucleotide Binding, RNA Binding, Binding, Unfolded Protein Binding, ATPase Activity, Helicase Activity, Nucleic Acid Binding, Purine Nucleotide Binding, Nucleoside-Triphosphatase Activity
	GDS3781 (FEMALE)	Catalytic Activity, Transition Metal Ion Binding, Carboxylic Acid Binding, Ion Binding	-	Catalytic Activity, Transition Metal Ion Binding, Protein Kinase Activity
	GDS3781 (FEMALE+ MALE)	Metallopeptidase Activity	-	Metallopeptidase Activity
	GDS3962 (FEMALE)	Catalytic Activity, Carboxylic Acid Binding, Acetyl-CoA Carboxylase Activity	Cytokine Activity, Chemokine Activity, Chemokine Receptor Binding	Cytokine Activity
	GDS3962 (FEMALE+ MALE)	-	SMAD Binding	Structure-Specific DNA Binding

### 3.4. Reconstruction of Protein-Protein Interaction Networks

Protein-protein interaction networks around the DEGs of each dataset were reconstructed (see Materials and Methods section for details). The numbers of DEGs identified in statistical analyses of some datasets (endometriosis: GDS2737, GDS2737 mid secretory, GDS2737 proliferative; PCOS: GDS3104, GDS3841 obese, GDS4133, GDS4987; and insulin resistance: GDS3962) were not sufficient to construct a reliable network, consequently these datasets were not incorporated in network reconstruction therefore; further analyses were carried out with 16 transcriptome datasets.

In a protein-protein network, nodes represent proteins and edges represent physical interactions between the proteins. Reconstructed protein-protein interaction networks related with the investigated diseases situated different number of nodes and edges (Table 3.31). Among those, GDS3592 dataset which associated with ovarian cancer was gained the highest network with 19031 nodes and 144252 edges as well as, GDS3781 (female and male) dataset associated with insulin resistance was gained the least network with 1764 nodes and 2292 edges. The protein-protein interaction network around DEGs in endometriosis GDS3060 dataset was given as an example in Figure 3.5.



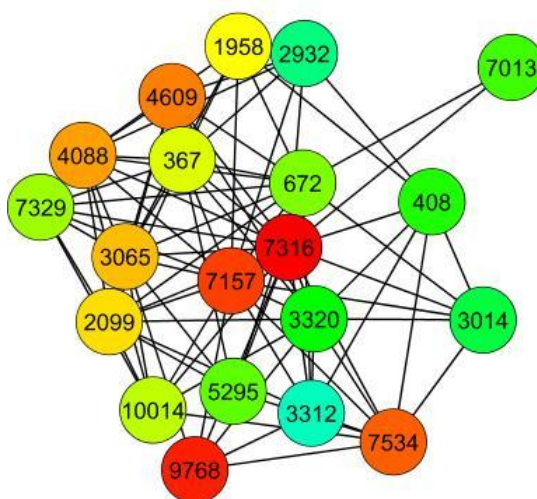
**Figure 3.5.** Protein-protein interaction network for endometriosis GDS3060 dataset

**Table 3.31.** The sizes of the reconstructed protein-protein interaction networks

Related Disease	Dataset Number	Number of Proteins (Nodes)	Number of Protein-protein Interactions (Edges)
Cervical Cancer	3233	14246	86005
	3292	15804	59052
Ovarian Cancer	2785	13758	77684
	3592	19031	144252
Uterine Fibroid	2245	8122	22199
	2246	11207	45916
Endometriosis	GDS2737(Early Secretary)	8031	21517
	GDS2835	16670	124365
	GDS3060	4588	9165
PCOS	GDS1050	9999	36190
	GDS1051	5122	9799
	GDS3841(Lean)	7012	16465
	GDS4399	9609	20818
Insulin Resistance	GDS3715	6829	18269
	GDS3781(Female)	2433	3614
	GDS3781(Female+Male)	1764	2292

### 3.5. Topological Analyses of Reconstructed Protein-Protein Interaction Networks

Topological analyses of the reconstructed protein-protein interaction networks were investigated to define central proteins (i.e., hubs) that play role in biological mechanisms of the examined diseases (Figure 3.6). Degree and betweenness centrality metrics were the features employed in identification of hub proteins. It is possible to indicate the highly connected proteins by examining these two properties. Degree metric describes the number of the edges between the nodes. Therefore, a higher degree node indicates that the node have a central role in the network. Betweenness centrality metric is defined as the ratio of the number of shortest paths passing through a node to the total number of paths passing through the nodes. Accordingly highest betweenness nodes are the significant nodes that control most of the information in the network.



**Figure 3.6.** Hub proteins of the reconstructed protein-protein interaction network for GDS3233 dataset of cervical cancer (Top 20 proteins based on degree metric were presented with their Entrez gene IDs).

#### 3.5.1. Topological Analyses for Cervical Cancer

The hub proteins of the reconstructed protein-protein interaction networks associated with cervical cancer datasets (GDS3233 and GDS3292) were tabulated in Tables 3.32-33. Topological analysis results indicated that there were 17 common hub proteins between the two datasets (Table 3.34).

**Table 3.32.** The hub proteins of the reconstructed protein-protein interaction network associated with cervical cancer GDS3233 dataset

Nodes		Ranking Based On Degree Metric	Ranking Based On Betweenness Centrality Metric	Direction of the Regulation (Down or Up Regulated)
Entrez ID	Gene Symbol ID			
7316	UBC	1	1	-
9768	KIAA0101	2	2	UP
7157	TP53	3	3	UP
7534	YWHAZ	4	4	DOWN
4609	MYC	5	6	DOWN
4088	SMAD3	6	7	UP
3065	HDAC1	7	8	UP
2099	ESR1	8	9	DOWN
1958	EGR1	9	5	DOWN
367	AR	10	13	DOWN
10014	HDAC5	11	18	DOWN
7329	UBE2I	12	12	UP
672	BRCA1	13	-	UP
5295	PIK3R1	14	10	DOWN
7013	TERF1	15	11	UP
408	ARRB1	16	16	DOWN
3320	HSP90AA1	17	17	UP
3014	H2AFX	18	-	UP
2932	GSK3B	19	14	UP
3312	HSPA8	20	-	DOWN
5359	PLSCR1	-	15	UP
7083	TK1	-	19	UP
60	ACTB	-	20	DOWN

**Table 3.33.** The hub proteins of the reconstructed protein-protein interaction network associated with cervical cancer GDS3292 dataset

Nodes		Ranking Based On Degree Metric	Ranking Based On Betweenness Centrality Metric	Direction of the Regulation (Down or Up Regulated)
Entrez ID	Gene Symbol ID			
7316	UBC	1	1	DOWN
9768	KIAA0101	2	5	UP
7534	YWHAZ	3	3	DOWN
4088	SMAD3	4	4	UP
2099	ESR1	5	9	DOWN
1958	EGR1	6	2	DOWN
367	AR	7	15	DOWN
1387	CREBBP	8	8	UP
672	BRCA1	9	-	UP
5295	PIK3R1	10	6	DOWN
7013	TERF1	11	12	UP
3320	HSP90AA1	12	-	UP
3014	H2AFX	13	-	UP
4086	SMAD1	14	10	Up
2932	GSK3B	15	13	UP
3312	HSPA8	16	-	DOWN
983	CDK1	17	-	UP
1937	EEF1G	18	20	DOWN
60	ACTB	19	18	DOWN
5925	RB1	20	-	UP
5359	PLSCR1	-	7	UP
351	APP	-	11	UP
7083	TK1	-	14	UP
25913	POT1	-	16	UP
2353	FOS	-	17	DOWN
4067	LYN	-	19	UP

**Table 3.34.** Common hub proteins of cervical cancer datasets

Nodes		Ranking Based On Degree Metric GDS3233&GDS3292	Ranking Based On Betweenness Centrality Metric GDS3233&GDS3292	Direction of the Regulation (Down or Up Regulated) GDS3233&GDS3292
Entrez ID	Gene Symbol ID			
7316	UBC	1&1	1&1	NONE&DOWN
9768	KIAA0101	2&2	2&5	UP
7534	YWHAZ	4&3	4&3	DOWN
4088	SMAD3	6&4	7&4	UP
2099	ESR1	8&5	9&9	DOWN
1958	EGR1	9&6	5&2	DOWN
367	AR	10&7	13&15	DOWN
672	BRCA1	13&9	NONE&NONE	UP
5295	PIK3R1	14&10	10&6	DOWN
7013	TERF1	15&11	11&12	UP
3320	HSP90AA1	17&12	17&NONE	UP
3014	H2AFX	18&13	NONE&NONE	UP
2932	GSK3B	19&15	14&13	UP
3312	HSPA8	20&16	NONE&NONE	DOWN
60	ACTB	NONE&19	20&18	DOWN
5359	PLSCR1	NONE&NONE	15&7	UP
7083	TK1	NONE&19	NONE&14	UP

### 3.5.2 Topological Analyses for Ovarian Cancer

The hub proteins of the reconstructed protein-protein interaction networks associated with ovarian cancer datasets (GDS2785 and GDS3592) were tabulated in Tables 3.35-36. Topological analysis results indicated that there were 11 common hub proteins between the two datasets (Table 3.37).

**Table 3.35.** The hub proteins of the reconstructed protein-protein interaction network associated with ovarian cancer GDS2785 dataset

Nodes		Ranking Based On Degree Metric	Ranking Based On Betweenness Centrality Metric	Direction of the Regulation (Down or Up Regulated)
Entrez ID	Gene Symbol ID			
7316	UBC	1	1	-
9768	KIAA0101	2	2	UP
7534	YWHAZ	3	3	UP
7341	SUMO1	4	4	UP
4088	SMAD3	5	6	DOWN
1956	EGFR	6	5	DOWN
2534	FYN	7	9	DOWN
808	CALM3	8	15	DOWN
801	CALM1	9	16	UP
367	AR	10	10	DOWN
7329	UBE2I	11	14	DOWN
25	ABL1	12	12	DOWN
5499	PPP1CA	13	8	UP
7013	TERF1	14	11	DOWN
5594	MAPK1	15	17	UP
6310	ATXN1	16	7	DOWN
4734	NEDD4	17	13	DOWN
3014	H2AFX	18	-	UP
207	AKT1	19	19	UP
4690	NCK1	20	-	UP
7083	TK1	-	18	UP
5578	PRKCA	-	20	DOWN

**Table 3.36.** The hub proteins of the reconstructed protein-protein interaction network associated with ovarian cancer GDS3592 dataset

Nodes		Ranking Based On Degree Metric	Ranking Based On Betweenness Centrality Metric	Direction of the Regulation (Down or Up Regulated)
Entrez ID	Gene Symbol ID			
7316	UBC	1	1	DOWN
9768	KIAA0101	2	2	UP
51547	SIRT7	3	-	UP
4087	SMAD2	4	7	DOWN
4088	SMAD3	5	6	DOWN
2099	ESR1	6	8	DOWN
1956	EGFR	7	5	DOWN
2534	FYN	8	3	DOWN
805	CALM2	9	14	DOWN
801	CALM1	10	15	DOWN
6613	SUMO2	11	-	-
7329	UBE2I	12	-	DOWN
6667	SP1	13	19	UP
5295	PIK3R1	14	10	DOWN
7013	TERF1	15	13	DOWN
3106	HLA-B	16	-	DOWN
5594	MAPK1	17	-	DOWN
6310	ATXN1	18	4	DOWN
3320	HSP90AA1	19	-	DOWN
4734	NEDD4	20	-	DOWN
1385	CREB1	-	9	DOWN
5359	PLSCR1	-	11	DOWN
56893	UBQLN4	-	12	UP
1398	CRK	-	16	DOWN
4089	SMAD4	-	17	DOWN
2932	GSK3B	-	18	DOWN
2335	FN1	-	20	UP

**Table 3.37.** Common hub proteins of ovarian cancer datasets

Nodes		Ranking Based On Degree Metric GDS2785&GDS3592	Ranking Based On Betweenness Centrality Metric GDS2785&GDS3592	Direction of the Regulation (Down or Up Regulated) GDS2785&GDS3592
Entrez ID	Gene Symbol ID			
7316	UBC	1&1	1&1	NONE&DOWN
9768	KIAA0101	2&2	2&2	UP
4088	SMAD3	5&5	6&6	DOWN
1956	EGFR	6&7	5&5	DOWN
2534	FYN	7&8	9&3	DOWN
801	CALM1	9&10	16&15	UP&DOWN
7329	UBE2I	11&12	14&NONE	DOWN
7013	TERF1	14&15	11&13	DOWN
5594	MAPK1	15&17	17&NONE	UP&DOWN
6310	ATXN1	16&18	7&4	DOWN
4734	NEDD4	17&20	13&NONE	DOWN

### 3.5.3 Topological Analyses for Uterine Fibroid

The hub proteins of the reconstructed protein-protein interaction networks associated with uterine fibroid datasets (GDS2245 and GDS2246) were tabulated in Tables 3.38-39. Topological analysis results indicated that there were 7 common hub proteins between the two datasets (Table 3.40).

**Table 3.38.** The hub proteins of the reconstructed protein-protein interaction network associated with uterine fibroid GDS2245 dataset

Nodes		Ranking Based On Degree Metric	Ranking Based On Betweenness Centrality Metric	Direction of the Regulation (Down or Up Regulated)
Entrez ID	Gene Symbol ID			
2099	ESR1	4	1	DOWN
1956	EGFR	3	2	DOWN
1958	EGR1	2	3	DOWN
367	AR	6	4	UP
5295	PIK3R1	5	5	UP
7316	UBC	1	6	-
2908	NR3C1	13	7	DOWN
7531	YWHAE	8	8	DOWN
5578	PRKCA	7	9	DOWN
1026	CDKN1A	9	10	UP
5111	PCNA	10	11	UP
2353	FOS	11	12	DOWN
8848	TSC22D1	12	13	DOWN
8878	SQSTM1	16	14	UP
3303	HSPA1A	14	15	DOWN
2335	FN1	18	16	UP
2597	GAPDH	15	17	UP
5590	PRKCZ	-	18	UP
1400	CRMP1	-	19	UP
596	BCL2	-	20	DOWN
773	CACNA1A	17	-	UP
9759	HDAC4	19	-	DOWN
6446	SGK1	20	-	DOWN

**Table 3.39.** The hub proteins of the reconstructed protein-protein interaction network associated with uterine fibroid GDS2246 dataset

Nodes		Ranking Based On Degree Metric	Ranking Based On Betweenness Centrality Metric	Direction of the Regulation (Down or Up Regulated)
Entrez ID	Gene Symbol ID			
7157	TP53	2	1	UP
7316	UBC	1	2	-
4088	SMAD3	3	3	UP
2099	ESR1	5	4	UP
5970	RELA	7	5	UP
1956	EGFR	4	6	DOWN
6714	SRC	6	7	UP
2534	FYN	8	8	UP
25	ABL1	9	9	UP
5295	PIK3R1	12	10	UP
3320	HSP90AA1	10	11	UP
207	AKT1	15	12	UP
5829	PXN	16	13	UP
7531	YWHAE	13	14	UP
1026	CDKN1A	14	15	UP
10524	KAT5	18	16	UP
1385	CREB1	11	17	UP
6597	SMARCA4	19	18	UP
6772	STAT1	-	19	DOWN
5111	PCNA	17	20	UP
11140	CDC37	20	-	UP

**Table 3.40.** Common hub proteins of uterine fibroid datasets

Nodes		Ranking Based On Degree Metric GDS2245&GDS2246	Ranking Based On Betweenness Centrality Metric GDS2245&GDS2246	Direction of the Regulation (Down or Up Regulated) GDS2245&GDS2246
Entrez ID	Gene Symbol ID			
7316	UBC	1&1	6&2	-
1956	EGFR	3&4	2&6	DOWN
2099	ESR1	4&5	1&4	DOWN&UP
5295	PIK3R1	5&12	5&10	UP
7531	YWHAE	8&13	8&14	DOWN&UP
1026	CDKN1A	9&14	10&15	UP
5111	PCNA	10&17	11&20	UP

### 3.5.4 Topological Analyses for Endometriosis

The hub proteins of the reconstructed protein-protein interaction networks associated with endometriosis datasets (GDS2737 early secretory, GDS2835, GDS3060) were tabulated in Tables 3.41-43.

**Table 3.41.** The hub proteins of the reconstructed protein-protein interaction network associated with endometriosis GDS2737 (early secretory) dataset

Nodes		Ranking Based On Degree Metric	Ranking Based On Betweenness Centrality Metric	Direction of the Regulation (Down or Up Regulated)
Entrez ID	Gene Symbol ID			
9768	KIAA0101	1	2	UP
1387	CREBBP	2	3	UP
7316	UBC	3	1	-
672	BRCA1	4	4	UP
3014	H2AFX	5	5	UP
983	CDK1	6	6	UP
5111	PCNA	7	8	UP
7083	TK1	8	7	UP
5347	PLK1	9	9	UP
6929	TCF3	10	11	UP
8850	KAT2B	11	17	DOWN
875	CBS	12	20	UP
5901	RAN	13	10	UP
604	BCL6	14	12	DOWN
4176	MCM7	15	-	UP
57562	KIAA1377	16	19	DOWN
10155	TRIM28	17	16	UP
5888	RAD51	18	-	UP
203068	TUBB	19	15	UP
891	CCNB1	20	-	UP
3838	KPNA2	-	13	UP
658	BMPR1B	-	14	DOWN
7430	EZR	-	18	DOWN

**Table 3.42.** The hub proteins of the reconstructed protein-protein interaction network associated with endometriosis GDS2835 dataset

Nodes		Ranking Based On Degree Metric	Ranking Based On Betweenness Centrality Metric	Direction of the Regulation (Down or Up Regulated)
Entrez ID	Gene Symbol ID			
7316	UBC	1	1	-
9768	KIAA0101	2	2	DOWN
7157	TP53	3	3	DOWN
7534	YWHAZ	4	4	DOWN
2099	ESR1	5	11	DOWN
1956	EGFR	6	6	DOWN
1958	EGR1	7	5	UP
2534	FYN	8	8	UP
1457	CSNK2A1	9	9	DOWN
7428	VHL	10	12	DOWN
1499	CTNNB1	11	10	UP
4193	MDM2	12	18	DOWN
10971	YWHAQ	13	19	DOWN
10014	HDAC5	14	-	UP
7329	UBE2I	15	15	UP
7046	TGFBR1	16	13	UP
6613	SUMO2	17	-	-
5499	PPP1CA	18	7	DOWN
672	BRCA1	19	-	DOWN
6667	SP1	20	20	DOWN

**Table 3.43.** The hub proteins of the reconstructed protein-protein interaction network associated with endometriosis GDS3060 dataset

Nodes		Ranking Based On Degree Metric	Ranking Based On Betweenness Centrality Metric	Direction of the Regulation (Down or Up Regulated)
Entrez ID	Gene Symbol ID			
1956	EGFR	1	3	DOWN
2534	FYN	2	2	UP
2908	NR3C1	3	4	UP
836	CASP3	4	5	UP
2064	ERBB2	5	9	UP
3688	ITGB1	6	8	UP
2335	FN1	7	7	UP
1021	CDK6	8	6	UP
7316	UBC	9	1	-
1647	GADD45A	10	12	UP
83737	ITCH	11	11	UP
5921	RASA1	12	15	UP
3843	IPO5	13	10	UP
3643	INSR	14	-	UP
2643	GCH1	15	14	DOWN
3480	IGF1R	16	-	UP
2963	GTF2F2	17	13	UP
6711	SPTBN1	18	20	UP
5690	PSMB2	19	16	UP
27292	DIMT1	20	17	UP
10253	SPRY2	-	18	DOWN
5565	PRKAB2	-	19	UP

In endometriosis, 3 datasets were investigated. The only common hub protein was UBC when all datasets were considered (Table 3.44). Moreover, according to analysis results for GDS2737 (early secretory) and GDS2835 datasets, 2 proteins (KIAA0101 and BRCA1) culminated in common (Table 3.45). On the other hand, EGFR and FYN proteins were observed as common hubs of GDS2835 and GDS3060 datasets (Table 3.46).

**Table 3.44.** Common hub proteins of endometriosis datasets

Nodes		Ranking Based On Degree Metric GDS2737(E.S.)& GDS2835&GDS3060	Ranking Based On Betweenness Centrality Metric GDS2737(E.S.)& GDS2835&GDS3060	Direction of the Regulation (Down or Up Regulated) GDS2737(E.S.)& GDS2835&GDS3060
Entrez ID	Gene Symbol ID			
7316	UBC	3&1&9	1&1&1	NONE

**Table 3.45.** Common hub proteins of endometriosis GDS2737 (early secretory) and GDS2835 datasets

Nodes		Ranking Based On Degree Metric GDS2737(E.S.)&GDS2835	Ranking Based On Betweenness Centrality Metric GDS2737(E.S.)&GDS2835	Direction of the Regulation (Down or Up Regulated) GDS2737(E.S.)&GDS2835
Entrez ID	Gene Symbol ID			
9768	KIAA0101	1&2	2&2	UP&DOWN
672	BRCA1	4&19	4&NONE	UP&DOWN

**Table 3.46.** Common hub proteins of endometriosis GDS2835 and GDS3060 datasets

Nodes		Ranking Based On Degree Metric GDS2835&GDS3060	Ranking Based On Betweenness Centrality Metric GDS2835&GDS3060	Direction of the Regulation (Down or Up Regulated) GDS2835&GDS3060
Entrez ID	Gene Symbol ID			
1956	EGFR	6&1	6&3	DOWN
2534	FYN	8&8	8&2	UP

### 3.5.5 Topological Analyses for Polycystic Ovary Syndrome

The hub proteins of the reconstructed protein-protein interaction networks associated with PCOS datasets (GDS1050, GDS1051, GDS3841 lean and GDS4399) were tabulated in Tables 3.47-50. Topological analysis results indicated that 2 proteins (UBC and ACTB) were common hubs of all 4 datasets (Table 3.51).

**Table 3.47.** The hub proteins of the reconstructed protein-protein interaction network associated with PCOS GDS1050 dataset

Nodes		Ranking Based On Degree Metric	Ranking Based On Betweenness Centrality Metric	Direction of the Regulation (Down or Up Regulated)
Entrez ID	Gene Symbol ID			
6613	SUMO2	1	2	UP
7157	TP53	2	3	DOWN
7341	SUMO1	3	4	UP
5970	RELA	4	7	DOWN
6714	SRC	5	5	DOWN
7316	UBC	6	1	-
9641	IKBKE	7	6	DOWN
7046	TGFBR1	8	8	DOWN
5594	MAPK1	9	10	DOWN
4086	SMAD1	10	11	DOWN
7529	YWHAB	11	9	UP
3692	EIF6	12	18	UP
5829	PXN	13	15	DOWN
1432	MAPK14	14	12	DOWN
60	ACTB	15	13	DOWN
6464	SHC1	16	20	DOWN
6500	SKP1	17	-	UP
3837	KPNB1	18	-	UP
7874	USP7	19	17	UP
998	CDC42	20	16	UP
351	APP	-	14	UP
3308	HSPA4	-	19	DOWN

**Table 3.48.** The hub proteins of the reconstructed protein-protein interaction network associated with PCOS GDS1051 dataset

Nodes		Ranking Based On Degree Metric	Ranking Based On Betweenness Centrality Metric	Direction of the Regulation (Down or Up Regulated)
Entrez ID	Gene Symbol ID			
60	ACTB	1	3	DOWN
7014	TERF2	1	2	DOWN
30011	SH3KBP1	3	4	DOWN
7316	UBC	4	1	-
84172	POLR1B	5	6	DOWN
1021	CDK6	6	5	DOWN
26260	FBXO25	7	7	DOWN
1656	DDX6	8	11	UP
3069	HDLBP	9	13	DOWN
3735	KARS	10	15	DOWN
26277	TINF2	10	8	DOWN
11091	WDR5	12	9	DOWN
8573	CASK	13	-	DOWN
29927	SEC61A1	13	-	DOWN
51082	POLR1D	15	-	DOWN
84916	CIRH1A	16	12	DOWN
375	ARF1	17	19	DOWN
5581	PRKCE	18	14	UP
11124	FAF1	18	20	DOWN
51154	MRTO4	20	-	DOWN
8537	BCAS1	-	10	-
84557	MAP1LC3A	-	17	DOWN
2260	FGFR1	-	18	DOWN
54472	TOLLIP	-	16	DOWN

**Table 3.49.** The hub proteins of the reconstructed protein-protein interaction network associated with PCOS GDS3841 (lean) dataset

Nodes		Ranking Based On Degree Metric	Ranking Based On Betweenness Centrality Metric	Direction of the Regulation (Down or Up Regulated)
Entrez ID	Gene Symbol ID			
4609	MYC	1	2	DOWN
2099	ESR1	2	3	DOWN
10014	HDAC5	3	4	DOWN
7316	UBC	4	1	-
60	ACTB	5	5	DOWN
10399	GNB2L1	6	6	DOWN
25942	SIN3A	7	8	DOWN
5747	PTK2	8	10	DOWN
8878	SQSTM1	9	7	DOWN
1973	EIF4A1	10	11	DOWN
6929	TCF3	11	9	DOWN
5894	RAF1	12	12	DOWN
2316	FLNA	13	13	DOWN
8175	SF3A2	14	15	DOWN
3575	IL7R	15	14	UP
57562	KIAA1377	16	16	DOWN
9978	RBX1	17	17	UP
472	ATM	18	20	DOWN
11030	RPMS	19	-	DOWN
4905	NSF	19	18	DOWN
821	CANX	-	19	UP

**Table 3.50.** The hub proteins of the reconstructed protein-protein interaction network associated with PCOS GDS4399 dataset

Nodes		Ranking Based On Degree Metric	Ranking Based On Betweenness Centrality Metric	Direction of the Regulation (Down or Up Regulated)
Entrez ID	Gene Symbol ID			
2885	GRB2	1	1	UP
1956	EGFR	2	3	DOWN
409	ARRB2	3	4	UP
408	ARRB1	4	6	UP
5594	MAPK1	5	5	UP
7316	UBC	6	2	-
5566	PRKACA	7	8	UP
5359	PLSCR1	8	11	UP
1958	EGR1	9	7	UP
4215	MAP3K3	9	9	UP
6597	SMARCA4	11	10	UP
3106	HLA-B	12	12	UP
1107	CHD3	13	14	UP
5580	PRKCD	14	13	UP
6256	RXRA	15	17	UP
382	ARF6	16	-	UP
4067	LYN	17	15	UP
5914	RARA	18	18	UP
3304	HSPA1B	19	16	UP
6850	SYK	20	-	UP
7132	TNFRSF1A	-	19	UP
60	ACTB	-	20	UP

**Table 3.51** Common hub proteins of PCOS datasets

Nodes		Ranking Based On Degree Metric GDS1050&GDS1051 &GDS3841(LEAN) &GDS4399	Ranking Based On Betweenness Centrality Metric GDS1050&GDS1051 &GDS3841(LEAN) &GDS4399	Direction of the Regulation (Down or Up Regulated) GDS1050&GDS1051 &GDS3841(LEAN) &GDS4399
Entrez ID	Gene Symbol ID			
7316	UBC	6&4&4&6	1&1&1&2	NONE
60	ACTB	15&1&5&NONE	13&3&5&20	DOWN&DOWN& DOWN&UP

### 3.5.6. Topological Analyses for Insulin Resistance Datasets

The hub proteins of the reconstructed protein-protein interaction networks associated with insulin resistance datasets (GDS3715, GDS3781 female, GS3781 female+male) were tabulated in Tables 3.52-54. UBC was the only hub protein that was common in all datasets (Table 3.55). On the other hand, 11 common hub proteins were observed, when the dataset GDS3715 were excluded in comparisons (Table 3.56).

**Table 3.52.** The hub proteins of the reconstructed protein-protein interaction network associated with insulin resistance GDS3715 dataset

Nodes		Ranking Based On Degree Metric	Ranking Based On Betweenness Centrality Metric	Direction of the Regulation (Down or Up Regulated)
Entrez ID	Gene Symbol ID			
7341	SUMO1	1	2	UP
808	CALM3	2	3	UP
3320	HSP90AA1	3	4	UP
2908	NR3C1	4	6	UP
5684	PSMA3	5	8	UP
5885	RAD21	6	7	UP
7316	UBC	7	1	-
5781	PTPN11	8	10	UP
5597	MAPK6	9	5	UP
3178	HNRNPA1	10	11	UP
7514	XPO1	11	15	UP
3688	ITGB1	12	12	UP
5501	PPP1CC	13	14	UP
5701	PSMC2	14	-	UP
7323	UBE2D3	15	9	UP
26986	PABPC1	16	19	UP
10987	COPS5	17	13	UP
857	CAV1	18	17	UP
2316	FLNA	19	16	DOWN
55660	PRPF40A	20	18	UP
4869	NPM1	-	20	UP

**Table 3.53.** The hub proteins of the reconstructed protein-protein interaction network associated with insulin resistance GDS3781 (female) dataset

Nodes		Ranking Based On Degree Metric	Ranking Based On Betweenness Centrality Metric	Direction of the Regulation (Down or Up Regulated)
Entrez ID	Gene Symbol ID			
1956	EGFR	1	1	DOWN
3932	LCK	2	4	UP
23327	NEDD4L	3	3	DOWN
604	BCL6	4	5	DOWN
1487	CTBP1	5	6	DOWN+UP
6696	SPP1	6	7	UP
3689	ITGB2	7	12	UP
267	AMFR	8	8	DOWN
8204	NRIP1	9	10	DOWN
6711	SPTBN1	9	9	DOWN
10912	GADD45G	11	11	DOWN
3937	LCP2	12	-	UP
83593	RASSF5	13	18	UP
80321	CEP70	14	15	DOWN
10318	TNIP1	14	17	UP
5588	PRKCQ	14	-	UP
57563	KLHL8	17	14	DOWN
6160	RPL31	18	16	DOWN
2247	FGF2	19	13	DOWN
7316	UBC	19	2	-
122622	ADSSL1	-	19	DOWN
178	AGL	-	20	DOWN

**Table 3.54.** The hub proteins of the reconstructed protein-protein interaction network associated with insulin resistance GDS3781 (female + male) dataset

Nodes		Ranking Based On Degree Metric	Ranking Based On Betweenness Centrality Metric	Direction of the Regulation (Down or Up Regulated)
Entrez ID	Gene Symbol ID			
1956	EGFR	1	1	DOWN
604	BCL6	2	3	DOWN
1487	CTBP1	3	5	DOWN+UP
3659	IRF1	4	4	UP
3689	ITGB2	5	8	UP
10912	GADD45G	6	7	DOWN
2308	FOXO1	7	9	DOWN
10318	TNIP1	8	12	UP
57563	KLHL8	9	10	DOWN
6160	RPL31	10	11	DOWN
2247	FGF2	11	6	DOWN
5329	PLAUR	12	14	UP
2043	EPHA4	13	15	DOWN
122622	ADSSL1	13	13	DOWN
7403	KDM6A	15	16	DOWN
7316	UBC	16	2	-
4299	AFF1	17	-	DOWN
2289	FKBP5	18	-	DOWN
9588	PRDX6	19	-	DOWN
7049	TGFBR3	20	-	DOWN
5594	MAPK1	-	17	-
2669	GEM	-	18	UP
7534	YWHAZ	-	19	-
7530	YWHAD	-	20	-

**Table 3.55.** Common hub proteins of insulin resistance datasets

Nodes		Ranking Based On Degree Metric GDS3715& GDS3781(F) &GDS3781(F+M)	Ranking Based On Betweenness Centrality Metric GDS3715& GDS3781(F) &GDS3781(F+M)	Direction of the Regulation (Down or Up Regulated) GDS3715& GDS3781(F)& GDS3781(F+M)
Entrez ID	Gene Symbol ID			
7316	UBC	7&19&16	1&2&2	NONE

**Table 3.56.** Common hub proteins of insulin resistance GDS3781 (female) and GDS3781 (female + male) datasets

Nodes		Ranking Based On Degree Metric GDS3781(F)& GDS3781(F+M)	Ranking Based On Betweenness Centrality Metric GDS3781(F)& GDS3781(F+M)	Direction of the Regulation (Down or Up Regulated) GDS3781(F)& GDS3781(F+M)
Entrez ID	Gene Symbol ID			
1956	EGFR	1&1	1&1	DOWN
604	BCL6	4&2	5&3	DOWN
1487	CTBP1	5&3	6&5	DOWN+UP
3689	ITGB2	7&5	12&8	UP
10912	GADD45G	11&6	11&7	DOWN
10318	TNIP1	14&8	17&12	UP
57563	KLHL8	17&9	14&10	DOWN
6160	RPL31	18&10	16&11	DOWN
2247	FGF2	19&11	13&6	DOWN
7316	UBC	19&16	2&2	NONE
122622	ADSSL1	NONE&13	13&13	DOWN

### 3.6. Comparative Analysis of Common DEGs

In the present study, 77 common DEGs were found between the investigated 5 women diseases (except insulin resistance datasets). These DEGs can be classified into nine major groups: 6 binding proteins (IGFBP5, HNRNPR, CTNNAL1, GSN, ZFP36L1, and ZFP36L2), 2 cytokines (C3 and IL6ST), 15 enzymes (NAAA, PLBD1, CHST15, CTSC, DPP4, GLUL, HMOX1, ODC1, POLR1D, PTP4A1, PTPRF, RNASET2, SMARCA4, SOD2, and CDC42BPA), 4 enzyme inhibitor and modulators (SERPINA1, SERPINB1, CKS2, and PHACTR2), 10 receptors (LSR, PDGFRA, AA861608, DCN, LAMA4, TACSTD2, TPBG, ESR1, FLRT2 and FAS), 7 signaling molecules (TSPAN8, LGALS8, TNXB, WNT5A, CD59, EFNA5 and FN1), 11 transcription factors and cofactors (CIRBP, HNRNPA3, NONO, SRSF1, SMARCC1, KLF4, MSX1, PRRX1, TCF3, PDCD4, EIF5A), 4 transporters (COL1A1, COL6A1, NUP50 and SLC39A8) and 18 unclassified genes (ADAM28, AHNAK, ATHL1, C1orf21, ENSA, PDE4DIP, SCRNI, TM4SF1, ZNF185, VEGFA, RARRES1, EZR, CFH, FARP1, H2AFY, PDZD2, RAB27A and RAB31).

For 77 common DEGs functional enrichment analyses were performed via DAVID bioinformatic tool (Table 3.57).

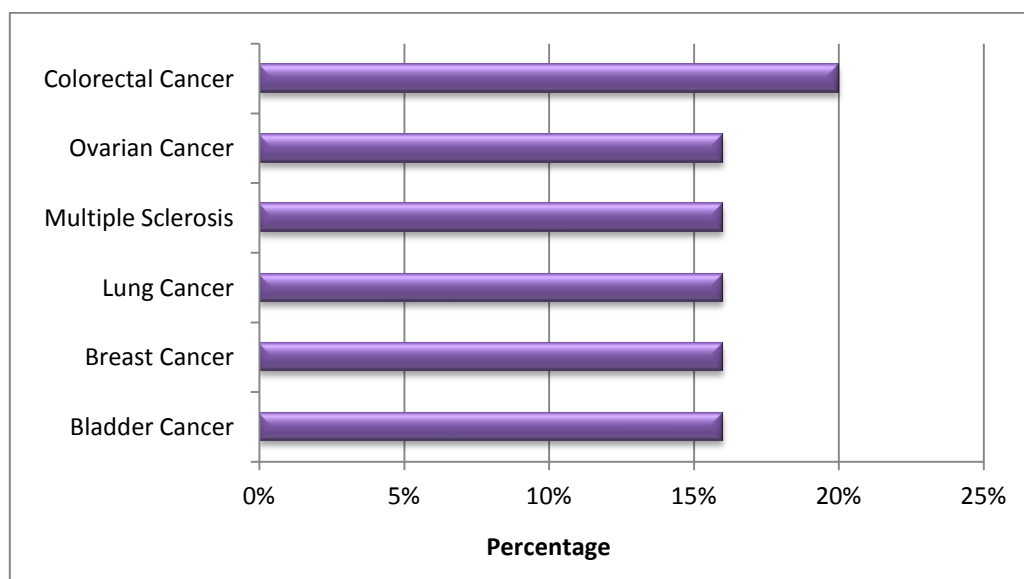
**Table 3.57.**Enrichment analysis results for 77 common DEGs

Category	Enrichment Results
Disease	Longevity, Heart Transplant Complications, Cirrhosis, Lung Cancer, Pregnancy Lost, Recurrent
Pathway	Focal Adhesion, ECM-Receptor Interaction, Complement and Coagulation Cascades
GO-Biological Process	Organ Development, Regulation of Cell Proliferation, Regulation of Cell Migration, Wound Healing, Regulation of Locomotion, Regulation of Cell Motion, Response to External Stimulus, System Development, Response to Nutrient Levels, Developmental Process
GO-Cellular Component	Extracellular Region Part, Extracellular Region, Extracellular Space, Proteinaceous Extracellular Matrix, Extracellular Matrix, Extracellular Matrix Part, Plasma Membrane Part
GO-Molecular Function	Identical Protein Binding, Protein N-Terminus Binding, Platelet-Derived Growth Factor Binding, Protein Binding, Growth Factor Binding, RNA Binding, Extracellular Matrix Structural Constituent

According to disease enrichment analyses 77 common DEGs were associated with several diseases including longevity, heart transplant complications, cirrhosis, lung cancer and pregnancy loss (recurrent). Pathway enrichment analysis for common DEGs resulted in only 3 pathways which were focal adhesion, ECM-receptor interaction, and complement and coagulation cascades. In biological enrichment, generally developmental, regulation and response processes (i.e. organ development, regulation of cell proliferation, response to external stimulus) were enriched in common DEGs. Usually cellular components that associated with extracellular region, space and matrix were enriched with 77 common DEGs. The molecular function enrichment analyses resulted with functions that were related to binding processes such as identical protein binding, platelet-derived growth factor binding, protein binding, growth factor binding and RNA binding.

### 3.7. Comparative Analyses of Functional Enrichment Analyses of DEGs

As a consequences of the functional enrichment analyses for all 6 diseases namely for 25 transcriptome datasets DEGs (includes all expression profiles) number of disease, pathway, biological process, cellular component and molecular function analyses results which outcomes at least in 4 transcriptome datasets represented in the Figure 3.7.,Figure 3.8, Figure 3.9, Figure 3.10 and Figure 3.11.



**Figure 3.7.** Disease enrichment analyses

Due to the diagnosis of colorectal cancer is considerably high; colorectal cancer becomes one of the significant public health problems in the worldwide. Among the all types of cancers, colorectal cancer is second most commonly diagnosed cancer in females and the third in men. It's malignant tumor, which located in the colon and rectum and most known colorectal cancer risk factors include age, obesity, alcohol consumption, physical inactivity and false dietary (Mylonas and Lazaris, 2014;Zulig et al., 2015).

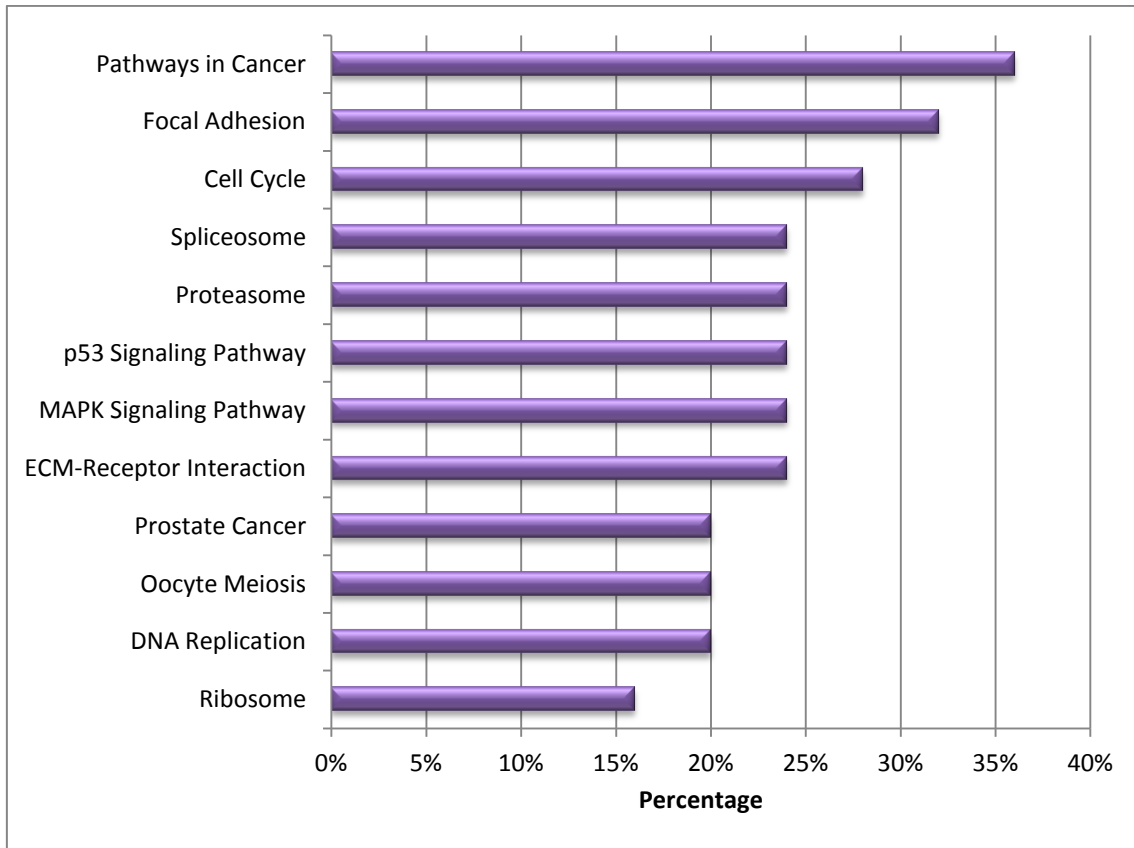
As mentioned before ovarian cancer is the second most encountered gynecologic cancer type in the worldwide (Didžiapetrienė et al., 2014). Ovarian cancer starts in the ovaries then bounce to pelvic organs later to the abdominal cavity (Rossing et al., 2010). There are several risk factors for ovarian cancer which include infertility drugs, women who have menstrual abnormalities, women who never give a birth and genetic alterations such as p53, BRCA1 and BRCA1 mutations (Brinton et al., 2003; Tomao et al., 2014; Lee et al., 2013).

Multiple Sclerosis is one of the nervous systems chronic disease that affect generally young adults (Dong et al., 2015). Approximately 2.5 million impressed Multiple Sclerosis in the worldwide and it wasn't known that where the disease originate from (Ajami et al., 2015).

Lung cancer is one of the most widespread and lethal cancer throughout the world. It was estimated that more than 1.3 million deaths occurs each year. In lung cancer, cigarette smoking and age were the prevalent risk factors (Zulig et al., 2015).

Although deaths from breast cancer decreased day after day, it's still the second main cause of cancer death among women in the Western World (Spano et al., 2015). At most it was known that breast cancer originate from BRCA1 and BRCA2 inherited mutations. Besides, obesity, hormone therapy and alcohol consumption are the feasible breast cancer risk factors (Majeed et al., 2014).

Every year approximately 430.000 patients were diagnosed with bladder cancer throughout the world and it was known that the rate of bladder cancer in men is high as twice when compared to women. According to National Institutes of Health-AARP Diet and Health Study Cohort, cigarette smoking is the only risk factor for bladder cancer (Ye et al., 2015).



**Figure 3.8.** Kegg pathway enrichment analyses

According to KEGG pathway database, Pathways in cancer pathway map representing several cancer types which this includes; colorectal, pancreatic, thyroid, bladder, prostate, endometrial, small cell and non-small cell cancers, glioma, acute myeloid leukemia, chronic myeloid leukemia, melanoma, basal and renal cell carcinomas.

Extracellular matrix provides biochemical and structural support to the cells by surrounding them and cell adhesion to the extracellular matrix plays crucial roles in cellular migration, proliferation, survival, differentiation and morphology. Cell adhesion to the extracellular matrix is mediated by extracellular matrix receptors such as integrins and discoidin domain receptors. In integrin mediated cell adhesion to extracellular matrix, specialized structures are formed and termed as focal adhesions; therefore basically focal adhesions serve as the mechanical connection to the extracellular matrix (Nagano et al., 2012; Petit and Thiery, 2000).

Briefly, cell cycle progression accomplished via repeatable serried events. In each cell cycle, chromosomes are replicated once which called DNA replication (S phase) and separated to constitute two genetically identical daughter cells which known as mitosis (M phase) (Collins et al., 1997).

After first step of the gene expression, transcription, eukaryotic mRNA precursors (pre-mRNAs) consisted protein coding exons and non-coding introns, so in eukaryotic gene expression removal of introns and ligation of exons are crucial steps. Spliceosome, a molecular machine which consisted of five small nuclear ribonucleoprotein particles, provides removal of introns from a transcribed pre-mRNA (Shcherbakova et al., 2013).

A multi-subunit enzyme complex, proteasome, plays essential role in protein regulation that control cellular functions such as cell cycle regulation and apoptosis. Before protein degradation, generally targeted proteins are modified by ubiquitin chain and proteasome's 19S regulatory cap binds to ubiquitin chain. Then simply, ubiquitinated proteins denatured and degraded by proteasome (Adams, 2003).

Either internal or external stresses signals, which may cause DNA damage, can activate p53 pathway. As a result of stress signals, p53 protein is activated in a particular manner by post-translational modifications and this lead to three cases; cell cycle arrest, cellular senescence or apoptosis. Except from these three responses, p53 signaling pathway proteins communicate with neighbored cells, because may be also their cellular environment have been changed, so they produce proteins that can assistance DNA repair (Harris and Levine, 2005).

Mitogen activated protein kinase (MAPK), signaling pathway is a highly conserved pathway which is attended in various processes including cell differentiation, proliferation, survival and migration. The pathway activated by hormones, cytokines and growth factors. MAPKs have 5 main groups which were ERK (ERK1/ERK2), c-Jun N (JNK/SAPK), p38MAPK, ERK3/ERK4 AND ERK5. Furthermore, the MAPK pathway compromised of three components; MAP3K, MAP2K and MAPK (Pati and Page, 2013; Cseh et al., 2014).

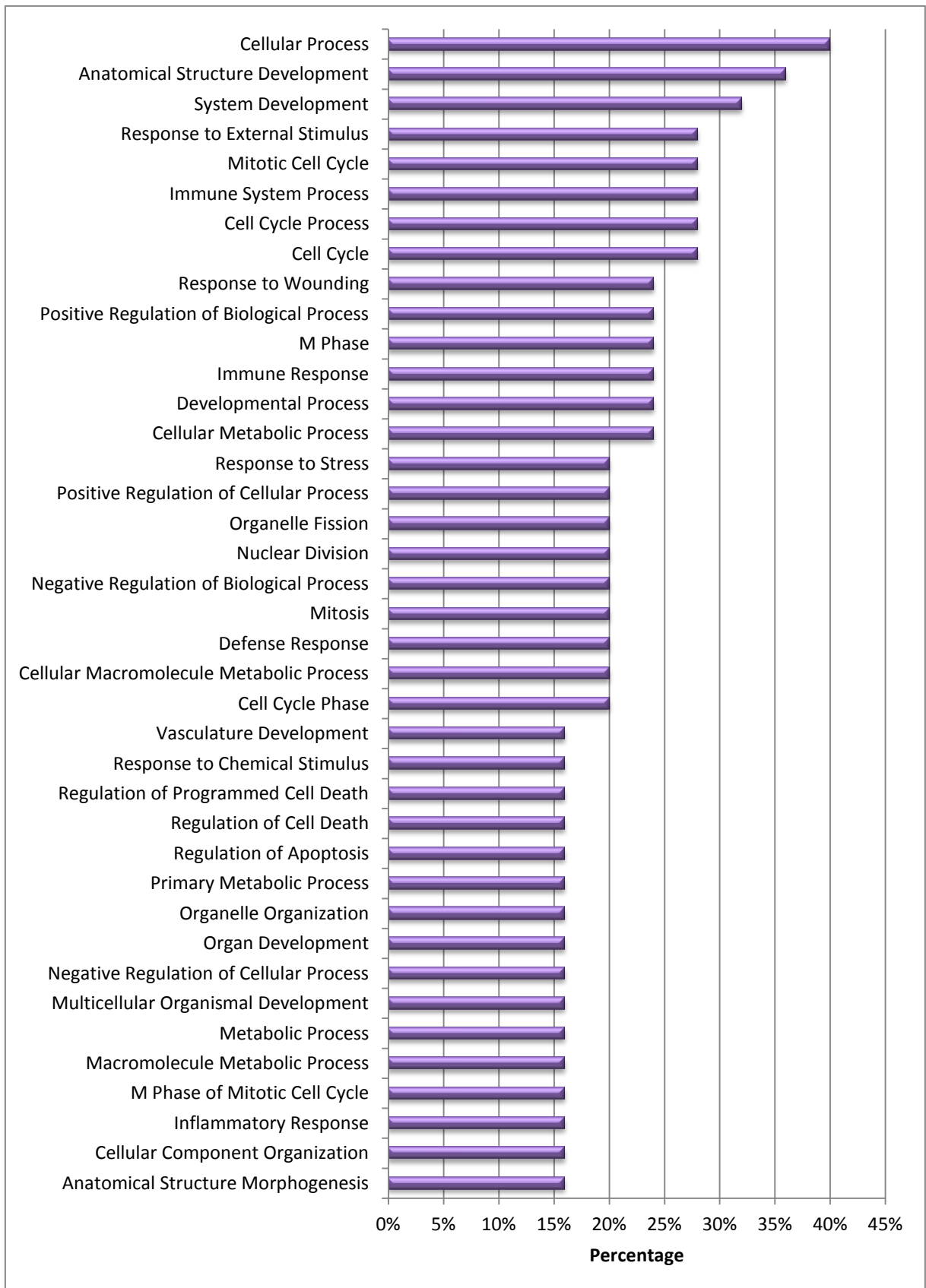
As mentioned before, extracellular matrix (ECM) provides biochemical and structural support to the cells by surrounding them. ECM, interacts with the cell surfaces by binding to certain receptors. These receptors mainly include integrins and perhaps also CD36, proteoglycans and others. These interactions can lead to control of the some processes like cell migration, proliferation and apoptosis (Gullberg and Ekblom, 1995).

Prostate cancer is the most commonly diagnosed cancer and the second death cause (29%) among all male cancer deaths. Like other cancer types prostate cancer is occurs, because of genetic alterations and certain genes and genetic alteration have been suggested for prostate cancer. The androgen signaling pathway may play a key role in prostate cancer and except these several prostate cancer susceptibility genes have been described including, CDKN1B, NKX3.1, PTEN, p53, GSTP1 as a tumor suppressors and AR, c-MYC, Bcl-2 as a oncogenes (Mazaris and Tsiotras, 2013).

Oocytes in the ovary were arrested in first meiotic prophase phase in prenatal, until the FSH and LH were synthesized from the pituitary gland and induced follicular growth and development. Certain period of times ovarian follicles, which were arrested in the first meiotic prophase phase, reentry meiosis and continues to grow-up. Follicles grow-up, until to metaphase II then, they arrested again. If follicles fertilized, it completes meiotic maturation (Mehlmann, 2005; Jamnongjit and Hammes, 2005).

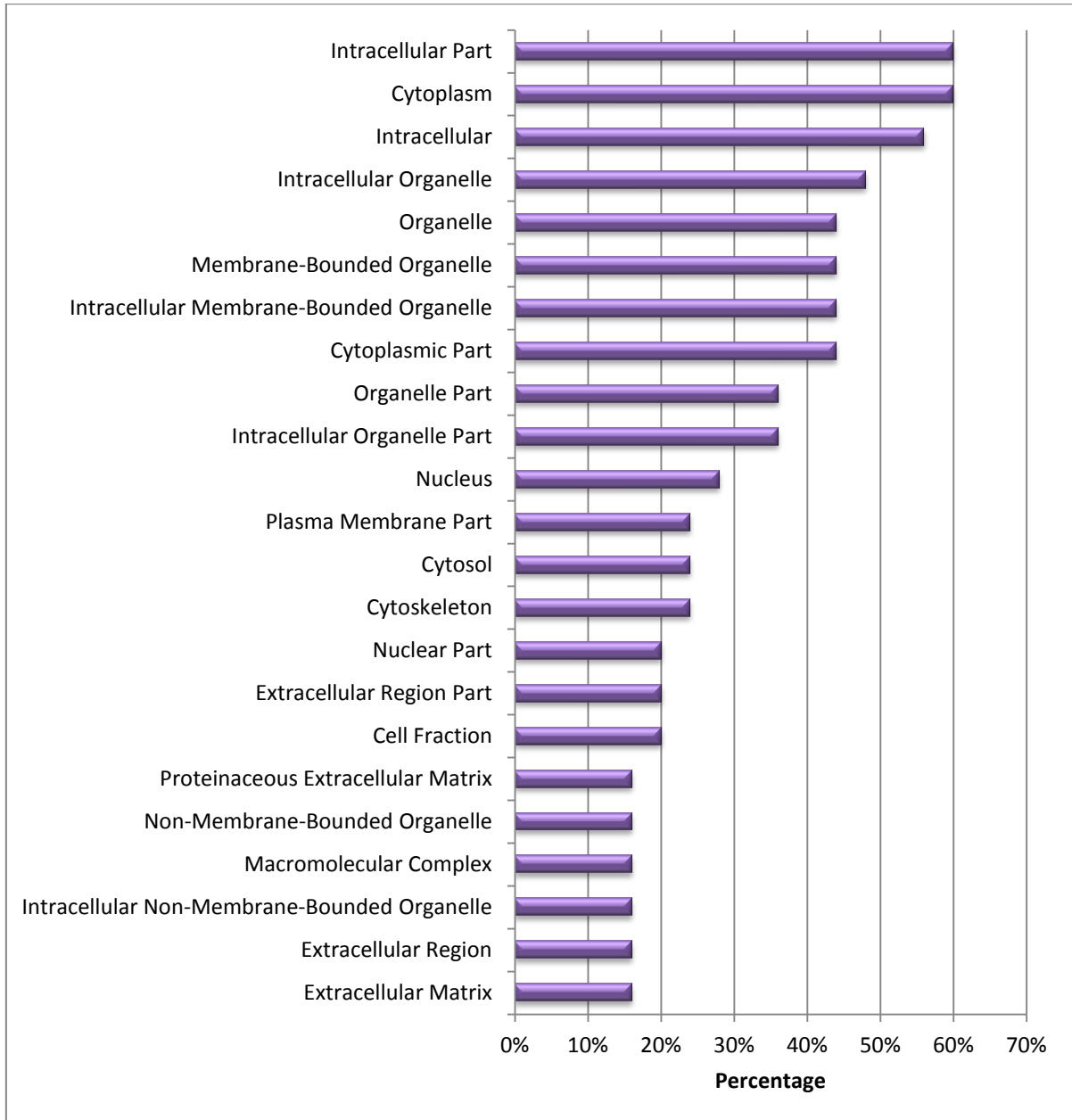
DNA replication is a process which occurs in all living organisms that provide genetic heritage. In short, in this process two identical replicas were produce from one DNA molecule. A double-stranded DNA molecule's each strands act as a template for the production of new strand. For DNA replication many proteins and enzymes were required and it's a multistep enzymatic pathway.

After first step of the gene expression, namely transcription, messenger RNAs (mRNAs) exceed in translation process. In translation process, mRNAs decoded to produce a certain amino acid or polypeptide, so in translation process biological protein synthesis occurs which this accrues in ribosome, a cellular machine which is complex.



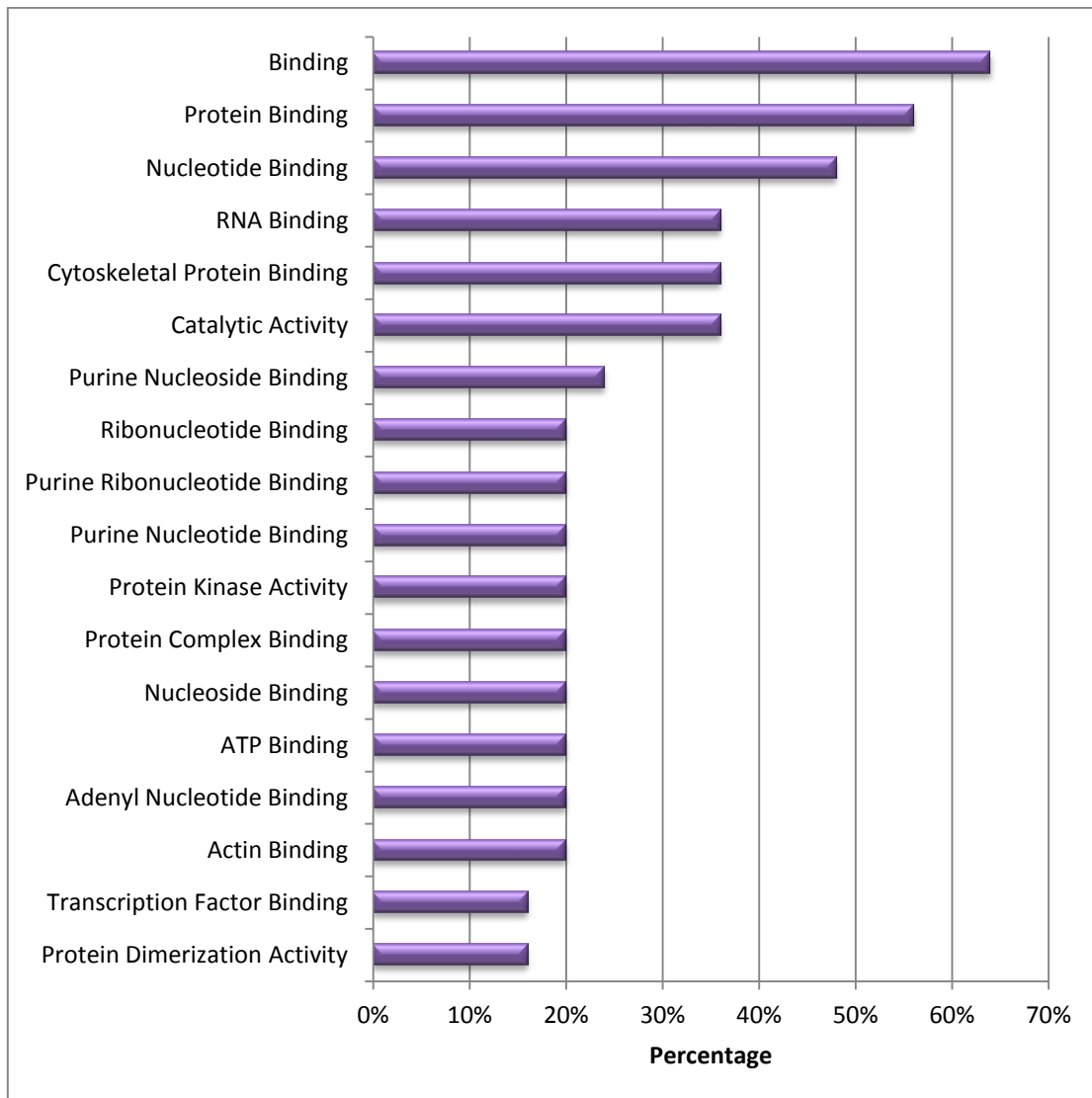
**Figure 3.9.** Biological process enrichment analyses

The functional enrichment analyses (for all 6 diseases) based on GO biological process terms indicated that mostly datasets were enriched with cellular processes, developmental processes and cell cycle processes (Figure 3.9).



**Figure 3.10.** Cellular component enrichment analysis

GO cellular component enrichment analyses results demonstrated that for all 6 diseases DEGs were enriched in components suchlike intracellular parts, cytoplasm and organelle (Figure 3.10).



**Figure 3.11.** Molecular function enrichment analyses

The molecular function enrichment analysis results indicated that 25 transcriptome datasets were usually enriched with binding processes such as protein, nucleotide, RNA and cytoskeleton proteins (Figure 3.11).

Comparative analyses of functional enrichment analyses for all inspected diseases were tabulated in Tables 3.58.

**Table 3.58.** Comparative analyses of functional enrichment analyses for all inspected diseases (continued)

Category	Expression Profile	Cervical Cancer	Ovarian Cancer	Uterine Fibroid	Endometriosis	PCOS	Insulin Resistance
Disease	Down-Regulated	-	Diabetes, Liver disease	-	Ovarian cancer	-	-
	Up-Regulated	Colorectal, lung, ovarian, breast and bladder cancer	Arthric Diseases, Colorectal Cancer, Crohn's Disease, Multiple Sclerosis	Arthric diseases, metabolic disorders, lung, bladder and prostate cancer	Thalassemia, Atherosclerosis, Multiple Sclerosis, Myocardial Infarct, Retinopathy-Diabetic	Type-2 Diabetes, obesity, Cholesterol	-
Pathway	Down-Regulated	Metabolic pathways	Ribosome, MAPK signaling	Complement and coagulation cascades, nicotine and nicotinamide metabolism	Cell cycle	Pathways in cancer, signaling pathways (MAPK, insulin, VEGF), cell cycle, proteosome	Oxidative phosphorylation, fatty acid biosynthesis, endocytosis
	Up-Regulated	Cell cycle, DNA replication, signaling and cancer pathways	Cell cycle, ECM-receptor interaction, Toll-like receptor signaling, DNA replication, oxidative phosphorylation	ECM-receptor interaction, central carbon metabolism, sugar metabolism, apoptosis, p53 and MAPK signaling pathways	Apoptosis, signaling pathways, cell cycle	Oxidative phosphorylation, calcium signaling pathway, disease pathways(Parkinson, Huntington, Alzheimer)	Proteosome, signaling pathways(Toll-like receptor, Jak STAT, T Cell Receptor)

**Table 3.58.** Comparative analyses of functional enrichment analyses for all inspected diseases (continued)

Category	Expression Profile	Cervical Cancer	Ovarian Cancer	Uterine Fibroid	Endometriosis	PCOS	Insulin Resistance
Biological Process	Down-Regulated	Developmental and differentiation processes	Developmental and metabolic processes	Developmental and response processes (immune response, response to stress and wounding)	Early: Ion transport, response to chemical stimulus Mid: Phosphate metabolism and dephosphorylation Proliferative: Organizational processes	Cell cycle, developmental and metabolic processes	Developmental, transport, organizational processes, signaling pathways
	Up-Regulated	Cell cycle	Cell cycle and response processes	Catabolic processes, regulatory pathways of cellular processes, apoptosis and programmed cell death	Early: Cell cycle Mid: Regulatory processes Proliferative: Organizational, developmental, and response processes (immune response), transport	Energetic, regulatory processes (metabolic and signaling), immune response	Metabolic processes, regulation of apoptosis, apoptosis and cell death

**Table 3.58.** Comparative analyses of functional enrichment analyses for all inspected diseases (continued)

Category	Expression Profile	Cervical Cancer	Ovarian Cancer	Uterine Fibroid	Endometriosis	PCOS	Insulin Resistance
Cellular Component	Down-Regulated	Cytoplasm	Cytoplasm and organelle	Extracellular matrix	Cytoplasm and intracellular part	Intracellular part	Intracellular part
	Up-Regulated	Nucleus and other organelles	Chromosome regions and cytoplasm	Cytoplasm and intracellular part	Chromosome and extracellular region	Intracellular part	Intracellular part
Molecular Function	Down-Regulated	Enzymatic activities	Protein binding, kinase and catalytic activities	Binding, enzyme regulator and transcription factor activities	Binding(calcium and copper ions), transmembrane transport and catalytic activities	Binding activities(protein, actin, ion, kinase, DNA)	Transporter activities, carboxylic binding and enzyme activities
	Up-Regulated	DNA and RNA binding	Binding (protein) and regulator activity	Binding and transcription factor activities	Binding (fibronectin, growth factor, oxygen), oxygen transporter and kinase activities	Signaling (receptor), binding (cytokine, calmodulin, sugar)and enzyme activities	Binding activities(protein, RNA), helicase activity, cytokine and chemokine activity

### 3.8. Comparative Analysis of Hub Proteins

When the topological analysis results of the 5 infertility associated women diseases (excluding insulin resistance) were comparatively investigated, 27 different proteins were observed as hubs.

According to 27 hub proteins pathway enrichment analyses via DAVID bioinformatic tool, it was found that they were functioning in diverse pathways (Table 3.59).

The expression profiles of these hub proteins in all diseases were also investigated (Figure 3.12). Most of the hub proteins were differentially expressed in more than one disease. In addition, several hub proteins, including ACTB and EGFR, were down-regulated in several diseases. On the other hand, several hubs, including ATXN1, NEDD4 and CALM1, were specific for a disease (i.e., ovarian cancer in this case).

To find the co-expression relations between 11 hub proteins, which indicate differential gene expression in at least two diseases (Figure 3.12), the Pearson correlation coefficients were determined based on their expression profiles (i.e., Fold Changes) in transcriptome datasets. Pearson correlation coefficients greater than 0.75 represent positive correlation between genes, while Pearson correlation coefficients less than -0.75 represent negative correlation between genes. Significant positive and negative correlation relationships were obtained for 11 hub proteins (Table 3.60).

**Table 3.59.** Pathway enrichment results of hub proteins (P-value<0.01)

KEGG Pathway Name	Number of Hubs	PValue	KEGG Pathway Name	Number of Hubs	PValue
Prostate cancer	7	$1.07 \times 10^{-6}$	Prion diseases	3	$8.90 \times 10^{-3}$
Glioma	7	$1.09 \times 10^{-4}$	T cell receptor signaling pathway	4	$9.38 \times 10^{-3}$
Neurotrophin signaling pathway	5	$1.18 \times 10^{-4}$	Bladder cancer	3	$1.27 \times 10^{-2}$
Cell cycle	6	$1.23 \times 10^{-4}$	Insulin signaling pathway	4	$1.72 \times 10^{-2}$
Pathways in cancer	6	$2.30 \times 10^{-4}$	Non-small cell lung cancer	3	$2.04 \times 10^{-2}$
Adherens junction	8	$2.39 \times 10^{-4}$	Pathogenic Escherichia coli infection	3	$2.26 \times 10^{-2}$
Colorectal cancer	5	$3.35 \times 10^{-4}$	B cell receptor signaling pathway	3	$3.76 \times 10^{-2}$
ErbB signaling pathway	5	$3.83 \times 10^{-4}$	Fc epsilon RI signaling pathway	3	$4.04 \times 10^{-2}$
Oocyte meiosis	5	$9.34 \times 10^{-4}$	Progesterone-mediated oocyte maturation	3	$4.82 \times 10^{-2}$
Focal adhesion	5	$1.11 \times 10^{-3}$	Regulation of actin cytoskeleton	4	$5.66 \times 10^{-2}$
Endometrial cancer	6	$1.18 \times 10^{-3}$	GnRH signaling pathway	3	$6.09 \times 10^{-2}$
Melanoma	4	$2.90 \times 10^{-3}$	Melanogenesis	3	$6.20 \times 10^{-2}$
Pancreatic cancer	4	$3.01 \times 10^{-3}$	Axon guidance	3	$9.81 \times 10^{-2}$
Chronic myeloid leukemia	4	$3.39 \times 10^{-3}$	Dorso-ventral axis formation	2	$9.85 \times 10^{-2}$

COMMON HUB PROTEINS	CERVICAL CANCER		OVARIAN CANCER		UTERINE FIBROID		ENDOMETRIOSIS			POLYCYSTIC OVARY SYNDROME			
	GDS3222	GDS3292	GDS2785	GDS3592	GDS2245	GDS2246	GDS2737 EARLY	GDS2835	GDS3060	GDS1050	GDS1051	GDS3841 LEAN	GDS4399
ACTB	Red	Red					Red			Red	Red	Red	Red
EGFR			Red	Red	Red	Red			Red				Red
EGR1	Red	Red			Red			Blue					Red
ESR1	Red	Red	Red		Red	Blue		Red				Red	
HSPA8	Red	Red		Red				Red					
AR	Red	Red	Red		Blue								
YWHAE				Red	Red	Blue		Red					
ATXN1			Red	Red									
NEDD4			Red	Red									
UBC		Red		Red									
YWHAZ		Red	Blue					Red					
MAPK1			Blue	Red				Red		Red			Blue
CALM1			Blue	Red									
PIK3R1	Red	Red		Red	Blue	Blue		Blue					
UBE2I	Blue		Red	Red				Blue					
FYN			Red	Red		Blue		Blue	Blue				
SMAD3	Blue	Blue	Red	Red		Blue							
TERF1	Blue	Blue	Red	Red				Blue					
GSK3B	Blue	Blue		Red									
BRCA1	Blue	Blue					Blue	Red					
CDKN1A				Red	Blue	Blue		Blue					
HSP90AA1	Blue	Blue		Red		Blue							
PLSCR1	Blue	Blue		Red				Blue					Blue
H2AFX	Blue	Blue	Blue	Blue			Blue	Red					
KIAA0101	Blue	Blue		Blue			Blue	Red					
TK1	Blue	Blue	Blue	Blue			Blue	Red					
PCNA	Blue	Blue	Blue		Blue	Blue	Blue	Red					

**Figure 3.12.** Heat map representing the clustering of the 27 hub proteins upon their expression profiles. Down-regulation and up-regulation were represented by red and blue colors, respectively

**Table 3.60.** Pearson correlation coefficients representing the co-expression levels of several hub proteins (Pearson > 0.75 represents significant positive correlation, Pearson < -0.75 represents significant negative correlation)

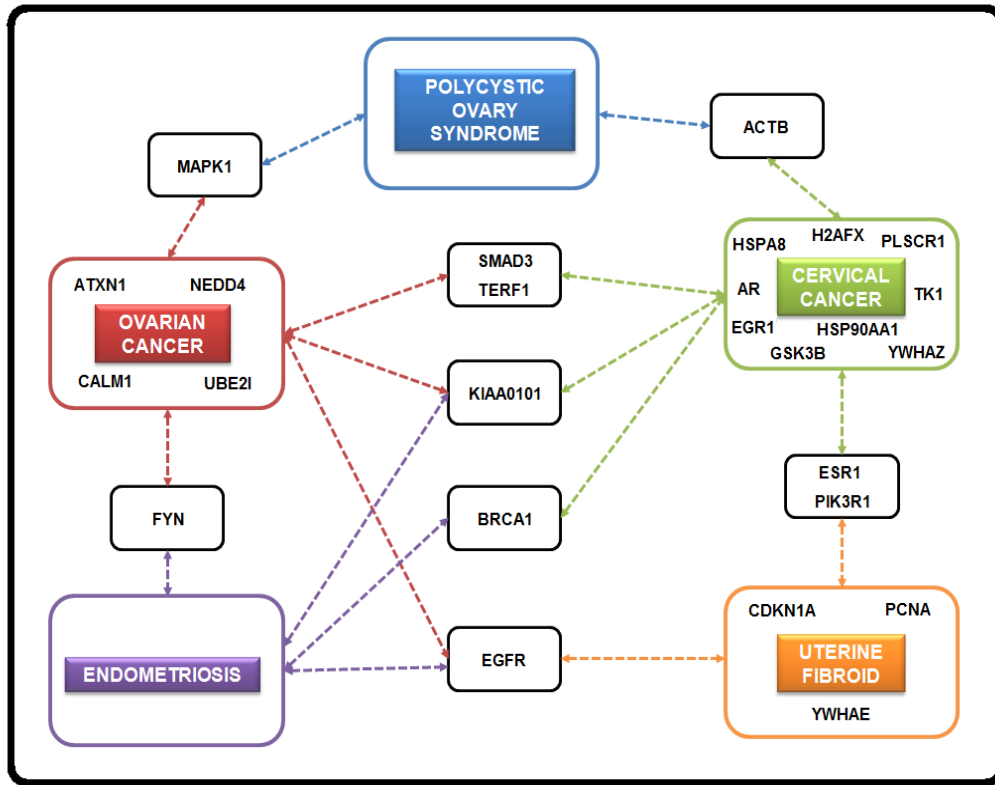
	ESR1	TERF1	UBC	FYN	KIAA0101	EGFR
ACTB	-0.987	-	-	-0.991	-0.961	-0.924
BRCA1	0.994	-0.899	-	-	-0.998	-
KIAA0101	-0.982		-0.768	0.997	-	-
MAPK1	0.974	0.992	-	0.994	-	-
PIK3R1	-	-	0.999	-	-	-
SMAD3	0.774	-0.771	0.918	0.989	-	-
UBC	-0.852	0.957	-	-	-	-
ESR1	-	-0.799	-0.852	-	-	-

### 3.9. Significant Genes/Proteins Associated with Diseases

We analyzed the significance of proteins in terms of their expression levels and topological importance within the protein interaction networks in each disease, and identified significant genes and encoded proteins, which may be considered as candidate biomarkers and/or can be used for design of drug targets and have utility for development of diagnostic tests for the inspected diseases.

Due to the UBC have more than 10.000 interactions in protein- protein interaction database we excluded UBS and as a result, 26 hub proteins came into prominence as seen in the Figure 3.13. Among those, 16 proteins were disease-specific: 9 proteins (AR, EGR1, GSK3B, HSP90AA1, HSPA8, H2AFX, PLSCR1, TK1 and YWHAZ) for cervical cancer, 4 proteins (ATXN1, CALM1, NEDD4 and UBE2I) for ovarian cancer; and 3 proteins (CDKN1A, PCNA and YWHAZ) for uterine fibroid. We couldn't pair any specific protein to PCOS or endometriosis. On the other hand, 10 proteins were associated with more than one disease: KIAA0101 was detected in endometriosis, ovarian and cervical cancer; SMAD3 and TERF1 were detected in both ovarian and cervical cancers; ESR1 and PIK3R1 culminated in both cervical cancer and uterine fibroid; BRCA1 resulted as common in endometriosis and cervical cancer; EGFR was

detected in endometriosis and uterine fibroid; ACTB was detected in cervical cancer and PCOS. FYN was detected in ovarian cancer and endometriosis, and MAPK1 resulted as common in ovarian cancer and PCOS.



**Figure 3.13.** Significant proteins identified in the present study

### 3.9.1. Significant Proteins Specific to Cervical Cancer

9 significant proteins (AR, EGR1, GSK3B, HSP90AA1, HSPA8, H2AFX, PLSCR1, TK1 and YWHAZ) were cervical cancer-specific.

Androgens bring up their effects by binding to the androgen receptor (AR) (Chang, et al., 2013). AR is a steroid receptor and related to nuclear hormone receptor family which this family includes estrogen, progesterone and glucocorticoid receptors (Aragon-Ching, 2014). It was known that AR plays a significance role in all stages of prostate cancers (Daniels, et al., 2014). In females, androgens are required for normal follicular development, function and fertility. However in females except androgens existence, androgens balance is important, too. Redundant androgens increase dysfunctional follicular development which may induce PCOS possibility, while low levels lead

aberrant follicular growth and poor ovarian reserve. Eventually both conditions affect female's fertility capacity negatively (Prizant, et al., 2014). AR is expressed in mammary gland, ovary, uterus, fallopian tubes and vagina in mammals (Chang, et al., 2013). Aromatase enzyme which is generally expressed in ovaries are accountable for the conversion of androgens to estrogens and it was proposed that up-regulation of aromatase enzyme may cause estrogen-sensitive cancers (Nair, et al., 2005). In females, AR expression was related to breast cancer and it was estimated that AR was expressed up to 90% of estrogen-sensitive breast cancer, while up to 55% of non-estrogen-sensitive tumors (Secreto, et al., 2012). There was a thought that AR expression changes in the ovary would be associated with HPV infection, which is cervical cancer's most known reason (Mendez, et al., 2013).

Early growth response protein 1 (EGR1), which is also known as a nerve growth factor-induced protein A (NGFI-A) or zinc finger protein 225 (ZIF268) or Krox-24 or TIS8, is belongs to EGR family of zinc-finger transcription factors. EGR1 consists of a considerably conserved DNA binding domain with three zinc fingers. EGR1 binds to these zinc fingers via GC-rich DNA consensus sequences. In non-stimulated condition, EGR1 has low expression pattern in almost all tissues except brain. However, EGR1 expression can be induced straight away by a numerous growth factors, cytokines or injurious stimulant (Gitenay and Baron, 2009; Silverman and Collins, 1999). EGR1 is associated with various biological processes including cell proliferation, differentiation, and apoptosis. Except these, it was demonstrated that EGR1 was crucial for regulating the transcription of luteinizing hormone  $\beta$  subunit (LH $\beta$ ). They showed that EGR1 deficient mice were infertile, because LH $\beta$  was absent and this caused anovulation problem (Kim, et al., 2014). EGR1 can directly bind to TGF $\beta$ 1, PTEN, p53 and AR (Baron, et al., 2006; Adamson et al., 2003). It was known that EGR1 is also one of the tumor suppressor genes. EGR1 may suppress lung cancer, breast cancer, and glioma; however its induction of prostate cancer progression was also reported (Kim, et al., 2014).

Glycogen synthase kinase 3 beta (GSK3B) is a proline-directed serine/threonine protein kinase and is one of two mammalian isoforms of glycogen synthase kinase 3 (GSK3) (Frizzo, 2013). GSK3 was known as a significant kinase that attended in various signaling pathways including protein synthesis, glycogen metabolism, cell motility,

proliferation and survival. Differently from other kinases, GSK3B is active in resting cells. Due to cellular responses, it was inactivated and its activity was regulated by certain site phosphorylation. If it is phosphorylated at tyrosine216 it would be active, whereas if it is phosphorylated at serine9 it would be inactive. GSK3B attended in comprehensive processes containing glycogen metabolism cytoskeletal regulation, cell differentiation, proliferation and apoptosis. GSK3B have approximately more than 40 substrates and the best knowns are  $\beta$ -catenin and p53, which play important roles in cancer development. Moreover, GSK3B play a part in some human diseases including diabetes, cardiovascular disease, some neurodegenerative diseases, bipolar disorder and cancer development (Luo, 2009). Curiously in cancer development, due to the cancer type, GSK3B may behave like as a tumor suppressor or as a promoter. In breast cancer development, up regulation of inactive GSK3B and active GSK3B suppressed tumor development. In ovarian cancer, GSK3B expression increases and promotes cancer cells division so it acts like a tumor promoter (Mishra, 2010). According to our results, its expression was significantly down-regulated in cervical cancer.

Heat shock protein 90kDa alpha is a member of heat shock protein 90 (HSP90) family which is encoded by heat shock protein 90kDa alpha (cytosolic), class A member 1 (HSP90AA1). Like other heat shock protein (HSPA8), HSP90 family members have collaboration with co-chaperones and playing significance roles in protein folding or unfolding under stress conditions (Chen, et al., 2005). Between heat shock proteins, HSP90 family have particular feature; HSP90 is not essential for the biogenesis of almost all polypeptides. HSP90 family can interact with various proteins including SRC family kinases (SRC, FYN), receptor tyrosine kinases (EGFR, HER2), serine/threonine kinases (RAF1, AKT), transcription factors (p53), steroid hormone receptors (AR, ER) and telomerase (Bagatell and Whitesell, 2004). Like other heat shock proteins, HSP90 family was attended in cancer development as well and its expression was related with various tumors containing breast cancer and pancreatic cancer, leukemia, and systemic lupus erythematosus (Chen, et al., 2005). In addition, it was known that HSP90AA1 was attended in cancer development and it's over-expressed, because it would repair unfolded proteins in oncogenic cells for survival. Several HSP90AA1 inhibitors such as 17-AAG and SNX-2112 show promising results in cancer therapies, because these

inhibitors bind HSP90AA1 and repress its misfolded protein repair mission in cancer cells, which inhibit cancer cell survival (Shen, et al., 2014).

Heat shock 70 kDa proteins 8 (HSPA8), also known as HSC70 or HSP73 or HSPA10, is another member of heat shock protein 70 (HSP70) family. HSP70's family proteins were the proteins that mostly conserved through the evolution and existed in all organisms. HSPA8 have various cellular functions; however most of these functions include collaboration with co-chaperones. The main function of HSPA8 is to attend in protein folding or unfolding. Chaperones can shuttles between cytoplasm and nucleus, so this feature allows HSPA8 to move in and out of nucleus and take cytoplasm proteins to the nucleus which this includes karyophilic proteins (Stricher, et al., 2013). However, the transport of HSPA8 was obstructed during stress conditions (for example; heat shock) which results with incarcerates HSPA8 in nucleus and after this stress condition ended, HSPA8 can move into cytoplasm again. Moreover, heat causes HSPA8 to bind cytoplasmic structures that were different from internal cell membrane and cytoskeleton rapidly (Tanaka, et al., 2014). Additionally, it's attended in cellular protein degradation; it's providing this function by inserting protein in ubiquitin proteasome pathway. Actin, crystallin  $\alpha$  and H2A are among some proteins that are needed for HSPA8 in ubiquitination and degradation (Stricher, et al., 2013). It was known that HSP70 family was attended in cancer development, even some inhibitors which targets HSP70 family was generated as anti-cancer agents. Oncogenic cells should overcome with proteotoxic stress conditions which this condition arises from misfolded proteins and it was known that under proteotoxic stress conditions HSPA8's protein folding mission interrupted and instead of that, it's began to repair misfolded proteins. According to this, in cancer cells HSPA8 was up regulated to repair unfolded proteins, mainly for cancer cell survival (Tanaka, et al., 2014). Except various cancers, HSPA8 was associated with Alzheimer's or Corea Huntington diseases (Schlecht, et al., 2013). HSPA8 was also associated with BAG-1, which is up regulated in cervical and various cancers (Yang, et al., 2000).

H2A histone family member X (H2AFX), which is also known as H2AX, is one of genes that encode the principal histone proteins: H2A, H2B, H3 and H4 families (Ibuki and Toyooka, 2014). H2AFX attended in DNA repair, DNA replication and DNA recombination (Ausio, 2006; Dickey, et al., 2009). Depending on double stranded DNA

break, H2AFX's one residue is phosphorylated quickly by several Class IA phosphoinositide 3-kinases and this revised structure is named as gamma-H2AFX. Gamma-H2AFX determines the broken sites and mediates other DNA repair proteins at the site of damage, and this lack of H2AFX cause chromosome instability and cancer. So it was known that gamma-H2AFX was up regulated in various types of cancers including cervical cancer (Dickey, et al., 2009; Fragkos, et al., 2009; Banath et al., 2004). Gamma-H2AFX has been described as a suitable candidate biomarker, because it's susceptible in determining DNA break and also H2AFX is now being used in drug development (Dickey, et al., 2009).

Phospholipid scramblase 1 is described as calcium ion dependent plasma membrane protein encoded by PLSCR1 (Kuo, et al., 2011). The plasma membrane was formed with phospholipids that spread out asymmetrically in its outer and inner leaflets. Phosphatidylcholine and sphingomyelin phospholipids fundamentally were located in outer leaflet whereas phosphatidylserine and other amino phospholipids was located inner leaflet (Zhao, et al., 1998). According to intracellular calcium ion rising, the phospholipids quickly start to redistribute between outer and inner leaflets (Ying, et al., 2006). PLSCR1 provided redistribution of phosphatidylserine and other amino phospholipids from inner leaflet to outer leaflet due to the rising of calcium ion concentration (Kuo, et al., 2011). Calcium ion rising accrue due to the cell activation, cell injury or apoptosis and this redistribution response play a considerable role in platelet procoagulant activity (Zhao, et al., 1998). PLSCR1 protein may be induced by interferons and interact with multiple proteins including epidermal growth factor receptor, the proto-oncogene c-Abl tyrosine kinase and onzin (negative c-Myc target gene) (Ying, et al., 2006). Except PLSCR1's membrane phospholipids movement task, several studies indicated that PLSCR1 attended in cell proliferation, differentiation, apoptosis, and the cancer development and progression. When PLSCR1's connection with cancers was considered, it was found that PLSRC1 expression profile varies in different tumor types (Cui, et al., 2012). It's up regulation in myeloid leukemia support its role in apoptosis and inhibition of tumorigenesis. Furthermore PLSRC1 up regulation provide myeloid cells differentiation to granulocytes (Li, et al., 2006). Also in ovarian cancer, PLSRC1 over expression inhibits cancer cells to grow, however in

colorectal and liver cancer patients it was found that PLSRC1 was over expressed when compared with healthy tissues (Kuo, et al., 2011; Cui, et al., 2012).

Thymidine triphosphate (dTTP) formation occurs by a series of phosphorylation processes of the thymidine (Brockenbrough, et al., 2009) and thymidine kinase 1 (TK1), which is an enzyme that attended one of the salvage pathways that provides dTTP formation (Huang and Chang, 2001). dTTP formation is having a high regulation profile during DNA replication and repair in all living cells (Chen, et al., 2010). TK1 expression profile was low during cell cycle's G1-phase, reaching its peak in S-phase and start to decrease in G2/M-phase, so TK1 expression is low even lack in non-proliferating cells, except in some conditions. In tumor cells, TK1 is over-expressed due to the DNA damage response, because dTTP synthesis was required for this response, so TK1 was proposed as an efficient biomarker for tumor cells (Zhou, et al., 2013; Huang and Chang, 2001). TK1 concentration in serum levels has been used since 1980 as a biomarker of lymphoma and leukemia cancers. It has been used to decide tumor cells growth for tumor prognosis and treatment (Chen, et al., 2011). The over-expression of TK1 in serum levels was associated with various types of cancers including breast, cervical, esophageal, prostate, bladder and lung cancers (Zhou, et al., 2013; Chen, et al., 2013). In cervical cancer it was found that, TK1 concentration in serum levels were considerable raised, and after surgery it was reduced and almost became healthy women's TK1 concentration (Zhou, et al., 2013).

YWHAZ was the members of the 14-3-3 protein family, which has 7 isoforms in mammals encoded by 7 different genes. The isoforms were  $\beta$ ,  $\epsilon$ ,  $\gamma$ ,  $\eta$ ,  $\tau$ ,  $\zeta$ ,  $\sigma$ , and they encoded by YWHAB, YWHAE, YWHAG, YWHAH, YWHAQ, YWHAZ and YWHAS genes, respectively (De et al., 2012). 14-3-3 protein family is acidic, highly conserved, expressed in all eukaryotic cells, and may presented as a homodimer or heterodimer (Pozuelo-Rubio, 2012). 14-3-3 protein family identifies multifarious molecules including kinases, phosphatases, transmembrane receptors and transcription factors, which have certain phosphoserine/phosphothreonine motifs (Zhao et al., 2011). After binding, 14-3-3 protein family generally provided 3 different functional modulations. First, because 14-3-3 proteins were very rigid they could change the conformation of binding molecule, so if the binding protein is an enzyme this event may

affect enzymatic properties. Second, by binding its partner, they could physically block significant properties of the surface of the target protein. Finally, 14-3-3 proteins may behave like a scaffold which provides interactions between proteins (Obsilová et al., 2008). Herewith, 14-3-3 protein family includes key regulatory proteins which may stimulate the functions of comprehensive molecules with the same time control many biological processes containing cell cycle regulation, metabolic regulation, protein trafficking, cell proliferation and cell apoptosis (Freeman and Morrison, 2011). Since the 14-3-3 protein family attended countless processes, surely there are link between diverse human diseases and 14-3-3 proteins. The isoform  $\zeta$ , that encoded by YWHAZ gene have a causing role in cancer development. It was known that 14-3-3 $\zeta$  can bind oncogene and proto-oncogene molecules including  $\beta$ -catenin, c-Raf1, BCR/abl, IGF-IR and hTERT. Up regulation of 14-3-3 $\zeta$  may activate growth signaling pathways, separate tumor suppressor proteins and inhibit apoptosis. The over expression of 14-3-3 $\zeta$  was related with some types of cancers, considerable related with recurrence and chemotherapeutic agents resistance. It was found that 14-3-3 $\zeta$  up regulation associated with pancreas, colon, esophageal, stomach, oral, head and neck, urothelial, and breast cancers, papillomavirus-induced carcinomas (cervical cancer) and chronic myeloid leukemia (Neal and Yu, 2010).

### **3.9.2. Significant Proteins Specific to Ovarian Cancer**

4 significant proteins (ATXN1, CALM1, NEDD4 and UBE2I) were ovarian cancer-specific.

Ataxin 1 is a nuclear protein that is encoded by ATXN1 gene. ATXN1 gene has been described as a gene that causes spinocerebellar ataxia type 1 (SCA1), which is a lethal neurodegenerative disorder. SCA1 disorder is characterized by loss of motor coordination that results with cerebellum degeneration. SCA1 disorder comes up when, expansion of CAG trinucleotides repeats encode an abnormal prolonged stretch of glutamine amino acid in ATXN1 (Bergeron et al., 2013; Lee et al., 2011). Pathogenic ATXN1 have 39-83 CAG repeats whereas non-pathogenic ATXN1 have 6-44 repeats. ATXN1 have at least 3 functional structures including a nuclear localization sequence, conserved AXH domain and Ser<sup>776</sup>. Ser<sup>776</sup> provides a site for phosphorylation and it was known that phosphorylation of Ser<sup>776</sup> is required for the disorder (Zoghbi and Orr,

2009). Except this, nuclear localization of the pathogenic ATXN1, namely abnormal prolonged stretch of polyglutamine in ATXN1, is required for the SCA1 pathology. The function of non-pathogenic ATXN1 is indefinite (Bergeron et al., 2013).

Calmodulin 1 (CALM1) is one of the proteins that encode the calmodulin (CaM) in human. CaM is a small, highly conserved, calcium binding protein, and is main intermediary of the calcium signaling pathways. It exists in all eukaryotic cells ubiquitously (Toutenhoofd, et al., 1998; Kortvely and Gulya, 2004). Almost all calcium responsive proteins couldn't bind free calcium. They need an intermediary protein to bind for signal transmission and the most significance intermediary protein is CaM. CaM has four E-F hand motifs which these domains provide calcium to bind itself. Due to the temporary intracellular calcium increase, calcium binds CaM by the four E-F hand motifs which this leads conformational change in CaM for activation of its target proteins (Seales et al., 2006). It was known that CaM can interact with at least 40 different types of proteins. The interactions between CaM and its target proteins activate various cellular processes containing hormone and protein synthesis, gene expression, cell motility, cell proliferation and apoptosis (Huoet al., 2005). In cell cycle proliferation during G1/S phase CaM reaches in elevated levels and remains high and in apoptosis processes, and it regulates apoptosis in both positively and negatively ways (Yokokura et al., 2014). It was reported that, CaM levels were considerable high in Alzheimer disease in contrast to other neurodegenerative disorders. Therefore, previously calmodulin levels in blood were proposed as a potential biomarker for Alzheimer disease (Esteras et al., 2013). Moreover it was reported that CaM levels were less in normal cells when compared with cancer cells, and there is a positive correlation among CaM levels and cancer cells growth rate (Liu et al., 1996).

NEDD4, neural precursor cell expressed developmentally down-regulated protein 4, is a member of HECT (Homologous to the E6-AP Carboxyl Terminus) E3 ubiquitin ligase family. It's contains C2 domain in N-terminal for membrane binding, WW2 domain for protein-protein interaction and HECT domain in C-terminal for ubiquitin protein ligation (Shi and Grossman, 2010). NEDD4 is considerably expressed in mammals. As the name gene suggest, it's substantially expressed in central nervous system and have an essential role in neuronal development. Moreover it's attended in regulation of cell differentiation, proliferation, survival and motility processes and attended in hippo

pathway and IGF-1 signaling (Boase and Kumar, 2015). It has been shown that, there is an interaction between NEDD4 and PTEN, which is generally deleted or mutated in miscellaneous cancers to develop tumor cells. NEDD4 negatively regulates PTEN by degradation. Namely in respect to PTEN, its acts like a proto-oncogene so, NEDD4's exceptional high regulation may prevent tumor growth with regard to PTEN (Wang et al., 2007). Increased and decreased levels of NEDD4 were associated with various types of cancers: an increase in NEDD4 expression and corresponding decrease in PTEN expression was observed in breast and prostate cancer cell lines. In certain conditions, increased levels of NEDD4 were related to cervical, colorectal, gastric and hepatocellular carcinoma, while decreased level of NEDD4 was related to pancreatic cancer (Boase and Kumar, 2014).

UBE2I gene encodes SUMO-conjugating enzyme UBC9, which is crucial for sumoylation. Post-translational modifications were required in various cellular processes and sumoylation is one of the post-translational modifications which include small ubiquitin related polypeptide (SUMO) (Wu et al., 2009). SUMO is covalently attached or detached to their target proteins to modify their functions. Sumoylation process play significance roles in cellular processes including nuclear transport, cell cycle control, transcriptional regulation and maintenance of genome integrity through modulating protein-protein interactions of target proteins (Chen et al., 2011). UBC9 is the single declared protein that attended in sumolytion (Wozniak et al., 2014). However, it can regulate pathways which were unconnected to sumoylation processes (Zhu et al., 2010). UBC9 attended biological processes including DNA damage repair, chromosome segregation and p53, Rad51, SMAD4, c-Jun and sex hormone receptors are the target proteins of UBC9 (Moschos et al., 2010). UBC9 is usually over expressed in some type of cancers including breast, colon, prostate, lung, head and neck and ovarian (Zhu et al., 2010; Wozniak et al., 2014). On the other hand, our results indicated that it was down-regulated in ovarian cancer, whereas up-regulated in cervical cancer and endometriosis.

### 3.9.3. Significant Proteins Specific to Uterine Fibroid

3 significant proteins (CDKN1A, PCNA and YWHAE) were uterine fibroid-specific.

The cyclin-dependent kinase inhibitor 1A gene (CDKN1A), also known as a TP21 or WAF1 or CIP1 or CDKN1, encodes p21 protein. In general, CDK inhibitors are the extremely important check points, because during cell cycle stages they can prohibit the replication or proliferation of the damaged DNA, but cancer cells should get over these check points. p21 may directly regulated by two ways: (i) p53 protein can directly bind p21 promoter and activates p21 (Abukhdeir and Park, 2009). DNA damage cause p53 activation and as a result p21 up regulation occurs and p21 provides cell cycle closure in G1 phase for feasible DNA repair or initiating apoptosis (Pérez-Sayáns et al., 2013). (ii) p21 may be regulated by p53 independent pathways. p21 can be regulated by MYC or phosphorylation of certain site may cause p21 inactivation (Abukhdeir and Park, 2009). Like KIAA0101, p21 can interact with PCNA and it competes with p21 for binding PCNA. However they can bind together at the same time (Yu et al., 2001). p21 has important roles in many cancer types. p21 generally act as a tumor suppressor, but also display oncogenic activities. In a mice dependent experiment, it has been shown that p21 can act as a tumor suppressor and CDKN1A deficiency cause spontaneous tumors (Abukhdeir and Park, 2009). Also high p21 expression in cancer cells was associated with higher 5 year survival rate (Pérez-Sayáns et al., 2013). Apart from its role in cancer development, it was reported that CDKN1A is one of the important agent in uterine fibroids which take a role in growth control and genomic stability of the uterine fibroids (Markowski et al., 2010).

Proliferation cell nuclear antigen (PCNA) is a well conserved protein, which generates a ring around the DNA to control and simplify DNA replication. PCNA can interact with excessive proteins, especially DNA replication proteins (for instance; DNA ligase, cell cycle regulator proteins such as p21 and KIAA0101, DNA repair proteins, metabolic enzymes, chromatin assembly and maintenance proteins, sister-chromatid cohesin proteins and transcription factor proteins) (Stoimenov and Helleday, 2009). Many of these proteins couldn't identify DNA sequences in high specificity, so PCNA binds to DNA and provides a base to polymerases during DNA synthesis. Therefore, PCNA is a crucial protein in DNA replication processes (Yu et al., 2001). Except it have DNA

replication related functions, PCNA attended in various and extremely important cellular processes such as DNA repair, cell cycle control, chromatin remodeling and sister-chromatid cohesion (Stoimenov and Helleday, 2009). The regulation of PCNA was increased during cell cycle and reached a peak in S phase. Since the PCNA expression is high in proliferating cells, it's accepted that in cancer cells PCNA is up regulated (Moldovan et al., 2007). Moreover, PCNA expression is higher in uterine fibroids when compared to normal myometrium (Hassan et al., 2011). Also, PCNA and endometriosis relation was reported in a study, where they demonstrated that PCNA was expressed during proliferative phase in fertile control group and then its expression decreased in secretory phase, whereas either in two phases PCNA expression was considerably constant in women with endometriosis (Hapangama et al., 2009).

YWHAZ was also one of the members of the 14-3-3 protein family, which has 7 isoforms in mammals encoded by 7 different genes which is mentioned before. The isoform 14-3-3 $\epsilon$ , which is encoded by YWHA $\epsilon$  gene, may act either as an oncogene or a tumor suppressor gene (Leal et al., 2012). 14-3-3 $\epsilon$  was over expressed in breast, lung, thyroid, hepatocellular and renal cancers. However it was down regulated in gastric cancer and medulloblastoma (Liu et al., 2013, Neal and Yu, 2012).

#### **3.9.4. Significant Proteins Associated with More than One Disease**

In the present study, KIAA0101 (p15PAF, L5, OEATC-1 and PAF15) was detected in endometriosis, ovarian and cervical cancer. KIAA0101 is a nuclear protein, which interacts with PCNA. KIAA0101 is related with regulation of DNA repair, cell cycle progression, cell proliferation and migration. Up-regulation of KIAA0101 protein can defend cells from UV stimulated cell death (Cheng et al., 2013). Moreover, KIAA0101 considerably has high expression profile in several types of cancers including esophageal, breast, uterine, cervix, brain, kidney and lung cancers (Yu et al., 2001; De Biasio et al., 2014). In addition, KIAA0101 is also defined as an anaphase-promoting complex/cyclosome (APC/C) substrate (Emanuele, 2011). APC/C is attended in almost every degradation events that control mitosis and meiosis cycles and depending APC/C's task it's attended almost every phases of mammalian oocyte development (Min et al., 2013; Whitfield et al., 2013; Homer, 2013). However KIAA0101 exists only in S and G2/M phases of the cell cycle (Emanuele, 2011).

SMAD3 and TERF1 were detected in both ovarian and cervical cancers.

SMAD3 is one of the receptor regulated SMAD (R-Smad) member which attended in transforming growth factor- $\beta$  (TGF- $\beta$ ) super family signaling pathway. TGF- $\beta$  super family ligands bind to type II receptor and recruits type I receptor. Thereby type I receptor is phosphorylated and activated by type II receptor. Type I receptor phosphorylates R-Smads, phosphorylated R-SMADs (SMAD1, 2, 3, 5, 8) bind the co-mediator SMAD (co-SMAD), which is SMAD4. This complex migrated to nucleus and with other nuclear cofactors; they regulate the target genes (Shi and Massague, 2003). TGF- $\beta$  signaling pathway has crucial roles in female reproduction and this pathway disturbance can cause infertility-associated female diseases. In general pathway provides; embryonic, uterine and follicular development, oocyte maturation, ovulation and pregnancy (Li, 2014). TGF- $\beta$  super family ligands were variable and included activin/inhibin, growth differentiation factors (GDFs), bone morphogenetic proteins (BMPs), TGF- $\beta$ s, Mulerian inhibiting substance (MIS) and nodal proteins (Li et al., 2008; Shi and Massague, 2003). Studies have been showed that TGF- $\beta$  super family ligands were relevant to ovarian events. Several GDFs and BMPs were expressed in folliculogenesis, maturation and development of ovarian follicles (Piotrowska et al., 2013). GDF9 and BMP15 were the significant ligands which regulate female reproduction by regulating oocyte functions (Peng et al., 2013). Besides, activins/inhibins play important regulating roles in FSH biosynthesis from the pituitary (Pangas et al., 2013). TGF- $\beta$ 1, TGF- $\beta$ 2 and TGF- $\beta$ 3 were produced from the ovarian cells and in some studies it have been reported that TGF- $\beta$ 1 have an inhibitory effect on primary follicle survival to the early antral stage (Knight and Glister, 2006), whereas TGF- $\beta$ 2 is necessary for normal embryo growth, TGF- $\beta$ 3 promoting cell growth and fibrogenic process, and can cause uterine fibroids (Li, 2014). Nodal is a secretory protein which provides a signal transmission of a node to lateral plate mesoderm (Kawasumi et al., 2014). In development of reproductive organs, Mulerian inhibiting substance acts as a repressor (Josso and Clemente, 2003). SMAD2 and SMAD3 were mainly attended as substrates for the TGF- $\beta$ s, activins, some GDFs and nodal proteins (Shi and Massague, 2003). The experiments in mice have showed that SMAD3 is essential for folliculogenesis. SMAD3 deficiency causes decrease of follicle growth rate, increase failure of a follicle to rupture or ovulate which induces oocyte degeneration and

increased immature oocytes. Moreover, SMAD3 deficiency causes decrease of inhibin- $\alpha$  and ESR2 and increase of ESR1 expressions in ovary and antral follicles. SMAD3 deficient mice didn't ovulate even with exogenous gonadotropins ovulatory induction (Tomic et al., 2004). When considering SMAD3 expression with the diseases, it was reported that SMAD3 can regulate syntheses of multiple extracellular matrix proteins such as collagens, so it's purposed that SMAD3 may have a role in certain fibroses pathologies (Roberts et al., 2006). Additionally, due to the SMAD3's crucial role in TGF- $\beta$  signaling pathway, it has been associated with cancer development. It was reported that, abnormal expression in SMAD3 is encountered in breast cancers. Also induced expression of SMAD3 expression by TGF- $\beta$  in breast cancers directly related wit metastasis to other organ systems or lymph node metastasis (Xue et al., 2014). Except breast cancer, down regulated SMAD3 expression has been encountered in endometrial, gastric, parathyroid cancers and up regulated SMAD3 expression has been associated with prostate cancer (Malkoski and Wang, 2012; Lu et al., 2007). Moreover, SMAD3 mutations were related with colon, cervical and familial thoracic aortic aneurysms (Xue et al., 2014; Hariharan et al., 2009).

Telomeric repeat binding factor 1 (TERF1), also known as a TRF1, is one of the mammalian telomere proteins. Telomeres were the structures which were localized at the end of the chromosomes. These chromosomes' ends should be protected from degradation and recombination events. In human, telomeres were formed by TTAGGG repeats. However telomeres (due to the telomeric DNA replication) regularly lose their telomeric TTAGGG repeats, because of the "end replication problem" which arises from DNA polymerase. In every telomeric DNA replication, approximately 100-200 bp telomeric DNA was lost which this cause 10-15 to 2-5 kb shortening of telomeres. As a result telomeres describe cell's replicative lifetime. Moreover its advancing shortening indicates organism ageing. After certain telomerase shortening, cell exits from cell cycle, which gives raise to loss of cell vitality and chromosomal uncertainty. Hence some cancer and germ cells produced telomerase superfluously, to obstruct telomere shortening and to sustain cell vitality (Liu and Li, 2010; Blasco, 2005). Moreover, there was no consensus between researchers on the presence or absence of telomerase activity in oocytes (Reig-Viader et al., 2012). TERF1 is one of the telomere specific proteins which can directly bind to the telomeric repeats. TERF1 existed in all human cells and

tissues. It regulates telomere maintenance in negative manner and it is proposed that TERF1 enables this by inhibiting the individual telomeres telomerase activity (Bianchi et al., 1997). In human, TERF1 causes advancing telomerase shortening (Iwano et al., 2004).

As mentioned before telomere length is associated with biological aging and it was known that after certain time female fertility ability decreased and then finished depending on growing age, because quantity and quality of oocytes are decreases. Referring the relation between telomeres and oocyte quality, it was thought that telomere dysfunction due to the growing maternal age, induced meiotic dysfunction, decline fertility rate, birth defects and give rise to aneuploidies which can results with miscarriages. Besides, telomere shortening in oocytes results with, cell cycle arrest, apoptosis and aberrant meiotic spindles. The quantity of the oocytes was related to women's ovarian reserve and this reserve determined during fetal development. Referring to the correlation between telomere and ovarian reserve it was thought that, different telomere length in primordial germ cells might outcomes with varied ovarian reserve. According to this, short telomere can restrict mitotic cycles in fetal development which results in poor ovarian reserve (Aydos, 2012). In another study it was shown that women who have deficient telomerase activity in her granulosa cells have 11 times more poor ovarian reserve than women who have normal telomerase activity (Butts et al., 2009). When we consider the relation between telomerase enzyme and telomeres expression and human diseases, it was known that telomerase enzyme is frequently inactive in somatic cells; however the enzyme was expressed in approximately 90% of the human tumors (Harris et al., 2012). It was found that shorter telomeres in leukocytes was associated with some cancers including gastric, head and neck, renal, bladder, esophageal and ovarian (Terry et al., 2012; Wentzensen et al., 2011). Moreover, limited studies reported the down regulation of TRF1 expression and they proposed that decreased TRF1 expression could be a common fact in tumorigenesis (Jian et al., 2009; Chuang et al., 2010). Furthermore in another study it was reported that, abnormal expression of telomerase enzyme and telomere lengthening was associated with endometriosis (Hapangama et al., 2009).

ESR1 and PIK3R1 culminated in both cervical cancer and uterine fibroid.

Estrogens play a considerable role in female reproduction system. Granulosa cells synthesize estrogen in the grip of LH and FSH. Although deuced hormones, estrogen needs a receptor to bind to carry out its mission. There are two estrogen receptors identified in human which were estrogen receptor  $\alpha$  (ER $\alpha$ ) and estrogen receptor  $\beta$  (ER $\beta$ ), which were coded by ESR1 and ESR2 genes, respectively (Ayvaz et al., 2009). These two receptors were related to class I member of the nuclear hormone receptor family and act as a nuclear transcription factor. Compared to ESR2, ESR1 have wide expression profile (Krege et al., 1998). Estrogen biosynthesis occurred, when cholesterol accessed into mitochondria and undergo six enzymatic steps. In the last step C19 steroids were converted to estrone or estrediol (17- $\beta$  estradiol), more briefly steroids were converted to estrogens, and this step catalyzes by aromatase enzyme. In this biosynthesis, aromatase was crucial and its inhibition causes estrogen annihilation (Yilmaz et al., 2009). Aromatase inhibitors cause approximately 98% reductions in estrogen levels (Robinson et al., 2013). It was reported that loss of ESR1 is related with cancer progression in several cancer types. In breast and endometrial cancers, ESR1 over expression provide a decrease in cancer's invasiveness. Moreover ESR1 up regulation may affect cancer's proliferation, for instance in cervical cancer ESR1 over expression provides proliferation inhibition (Zhai et al., 2010). Furthermore, in uterine fibroids, estrogen receptors were more in fibroid tissues when compared to myometrium tissues (Medikare et al., 2011). Also the estrogens play significant roles in endometriosis development; however there were some studies that propose positive correlation between ESR1 and endometriosis, whereas some studies reported the negative case (Matsuzaka et al., 2012). Aromatase inhibitors are preferred for estrogen-dependent diseases, for example breast cancer, endometrial cancer, uterine fibroid and endometriosis (Bulun et al., 2005). Apart from aromatase inhibitors, selective estrogen receptor modulators (SERMS) or estrogen analogs or anti-estrogens were used for treatment. SERMS attached to estrogen receptors and block (antagonist) or activate (agonist) estrogens action by the status of the target tissues. For instance, some of these agents act agonist in serum lipoproteins whereas act like antagonist in reproductive tissues (Cosman and Lindsay et al., 1999). In some resources it have been described that estrogens were accountable for ovarian follicular development, FSH and LH receptor expression, steroidogenesis, granulosa cell gap junction formation and granulosa cell

apoptosis inhibition (Rosenfeld et al., 2013). Moreover estrogen receptors and 17- $\beta$  estradiol were required for reproduction, continuation of the pregnancy and formation of secondary female characterization. Also estradiol was the main component for embryo development (Lubahn et al., 1993). The experiments that based on mice have showed that ESR1 knockout affect breast development negatively and cause infertility in both sexes by accruing abnormalities in reproductive track and gonadols (Krege et al., 1998). Again in another study it has been shown that ESR1 knockout in mice affected the estrous cycles which this may resulted in infertility (Shughrue et al., 1998).

Class IA phosphoinositide 3-kinase (PI3K) was compromised of catalytic and regulatory subunits. Catalytic subunit which is 110-kDa defined as a p110 $\alpha$  and encoded by PIK3CA gene while regulatory subunit have different isoforms and one of them is defined as a p85 $\alpha$  which is encoded by PIK3R1 (Ueki et al., 2003). PIK3R1 and PIK3CA complex get regulatory stimulation from tyrosine kinases transmembrane receptors including growth factor receptors like EGFR and Src family protein tyrosine kinases (Liu et al., 2014). PI3K was related to lipid kinases and have essential roles in various processes including cell growth, survival and migration (Philp et al., 2001). It was demonstrated that in some cell types, PI3K activity was induced in early M phase to regulate mitosis entry. However the increase in p85 $\alpha$  (PIK3R1) expression may cause decrease in PI3K activity by diminishing S phase entry. Apart from that it's behave like a catalyst in M to G1 migration. According to this in a study, they supported that p85 $\alpha$  was attended in cell cycle termination, and they showed that, its deficiency cause cell accumulation in telephase and postponed cytokinesis (García et al., 2006). Moreover it was known that PI3K also plays crucial role in insulin based events suchlike, glucose transport and glycogen synthesis (Ueki et al., 2003). It has been found that, in specific conditions increased levels of p85 $\alpha$  have a significant role in insulin resistance development (Draznin, 2006). PI3K is also one of the significance players in cancer development. Up regulation of PI3K was related with colon, bladder and ovarian cancers. Also p110 $\alpha$  (PIK3CA) have an oncogenic potential and it was reported that, up regulation of PIK3CA may cause ovarian and cervical cancers. However, p85 $\alpha$  act as a tumor suppressor gene, because p85 $\alpha$  may stabilize p110 $\alpha$  subunit. Also it reported that, PIK3R1 was mutated in breast, colon ovarian and urothelial cancers (Philp et al., 2001; Cizkova et al., 2013; Ross et al., 2013). Furthermore, a lipid phosphatase PTEN act as a

tumor suppressor gene generally mutated in human cancer cells and inactivates PI3K (Shi and Grossman, 2010).

BRCA1 resulted as common significant protein in endometriosis and cervical cancer. It was known that, breast cancer associated gene 1 (BRCA1) germ line mutations get inclined women to breast cancer. Moreover BRCA1 germ line mutations have been increased the ovarian cancer occurrence possibility. Beyond that it was reported that BRCA1 plays a significance role in DNA damage repair and transcriptional regulation processes (Welch and King, 2001). BRCA1 can interact with various molecules directly or indirectly. It can interact with DNA damage repair proteins, cell cycle regulators, tumor suppressors and activator, transcriptional activators, and repressors. Therefore, mutations that cause BRCA1's function loss might induce apoptosis, DNA damage repair and cell cycle checkpoint false, chromosome damage and aneuploidy. Since BRCA1 interact with tumor suppressors, it was thought that BRCA1 mutations directly don't cause tumor formation, they cause genetic stability in cells that exposed the mutation which this give raise to malignant transformation (Deng, 2006). Except breast and ovarian cancer elevated risks, several studies reported that BRCA1 mutation carriers have a high risk for some cancer types which includes colon, prostate, pancreatic, uterus and cervical cancers. In cervical cancer patients, it was found that loss of BRCA1 gene's chromosome was common and BRCA1 promoter methylation may associated with worse prognosis (Thompson and Easton, 2002; Zhang et al., 2005). Moreover it was thought that endometriosis and BRCA1 may be related with each other, it was proposed that reduced BRCA1 expression might play a substantial role in endometriosis pathophysiology (Govatati et al., 2014). However in another study, researchers couldn't find any relation with BRCA1 and endometriosis (Aviel-Ronen et al., 2014). Based on BRCA1's role in DNA damage repair, it may be proposed that its absence brings developmental problems like embryonic lethality which may cause infertility and tumorigenesis. When correlation between BRCA1 and embryonic lethality was examined, it's believed that BRCA1 deficiency negatively impresses DNA damage repair system, which this cause genetic instability and as according to this, p53 gene is activated. p53 gene activation causes cell cycle arrest and apoptosis which give rise to embryonic lethality (Deng and Wang, 2003). Moreover, in females BRCA1 mutation may cause poor ovarian reserve which this may cause premature ovarian

failure. Due to the oocytes were more inclined to DNA damage it was known that, DNA damage repair was lacking in women with BRCA1 mutations. Therefore when DNA damage intensive and couldn't fix, oocytes may entered to apoptotic pathway which this trigger with early ovarian reserve depletion or premature ovarian failure in consequences of female infertility (Oktay et al., 2010).

Epidermal growth factor receptor (EGFR), also known as ErbB-1 or HER1, was detected in endometriosis and uterine fibroid. It is one of the members of ErbB (HER) receptor which is related to tyrosine kinase receptor group (Ferguson et al., 2003). Mammalian oocytes become mature in the ovarian follicles and certain periods of time mature oocytes released from the ovary which this called ovulation (Ogiwara et al., 2013). Oocytes in the ovary were arrested in first meiotic prophase phase in prenatal, until the FSH and LH were synthesized from the pituitary gland and induced the follicular growth and development. Certain period of times ovarian follicles, which were arrested in the first meiotic prophase phase, reentry meiosis and continues to grow-up. They continue to grow-up, until to metaphase II. Then they arrested again, until fertilization. If follicles fertilized, it completes meiotic maturation. This meiosis division resumes by LH synthesize and by this oocyte maturation started again. Therefore synthesis of LH from the pituitary gland triggers oocyte maturation which is required for reproduction. Since metaphase II meiotic arrest has a short lifetime, the timing of oocyte meiotic arrest is very important; therefore, LH synthesis must be under control (Mehlmann, 2005; Jamnongjit and Hammes, 2005). Epidermal growth factor (EGF) was the agent which provides LH secretion to generate mature oocytes. EGFR was expressed necessarily for LH induced oocyte maturation and ovulation. Eventually EGFR and LH cooperated to oocytes meiotic division reentry to form mature oocyte (Hsieh et al., 2011). Several studies have showed that the failure or mistiming of oocyte meiosis resumption or oocyte maturation arrest can cause infertility. Even this event could be encountered in couples that they have unexplained infertility before. For these patients oocyte donation was the truest option however, because of the some considerations it was not preferred (Levrán et al., 2002). Moreover, it was known that excess of EGFR is frequently related to high tumor grade, poor treatment results including chemotherapy and hormonal therapy resistance. EGFR over expression has been determined as a powerful marker in head and neck, bladder, esophageal, ovarian

and cervical cancers, while it is a modest marker in gastric, endometrial, colorectal cancers. In addition, it's insufficient marker in non-small-cell lung cancer (Correia et al., 2014). Furthermore, it was reported that in uterine fibroids progesterone and  $17\beta$ -estradiol behave in combination to motivate uterine fibroid's cell proliferation via EGF and EGFR expressions (Maruo et al., 2004). AG1478, a selective inhibitor of the EGFR is proposed as a potential therapy for uterine fibroids (Shushan et al., 2004). Due to the EGFR expressed nearly in all of the cells, it's also expressed in endometriosis cells as expectedly. Goserelin was used in endometriosis patients as a treatment method which this provide decline in EGFR expression was observed in ectopic endometrial tissues (Augustin et al., 2001).

$\beta$ -actin, encoded by ACTB gene, was detected as a significant protein in cervical cancer and PCOS. It is one of the actin isoforms which have been identified in humans. Actins were crucial cytoskeleton constituent parts which were attended in comprehensive processes including cell migration, cell division, embryonic development, wound healing, immune response and gene expression (Bunnell et al., 2011;Guo et al., 2014). It has been described that eukaryotes have six different actin isoforms which were coded by different genes. Out of those six actin isoforms, two were striated muscle related, two smooth muscles related and two actins were cytoplasmic (which were  $\alpha$ -actin and  $\beta$ -actin). The four actin isoforms which related to muscles were expressed tissue specific while  $\alpha$ -actin and  $\beta$ -actin could expressed in anywhere and encoded by ACTB and ACTG1, respectively.  $\alpha$ -actin and  $\beta$ -actin were crucial for cell viability and differ from out of four amino acids.  $\beta$ -actin exist as a filamentous actin (F-actin) or globular actin (G-actin) and it was known that it's deficiency can cause embryonic lethality (Joseph et al., 2014). In a study, it was shown that ACTB deficiency was directly related with alive born, and therefore ACTB was essential for embryogenesis (Bunnell et al., 2011). Moreover, in the same study they demonstrated that deletion of  $\beta$ -actin in two different primary cell types causes extraordinary migration problems which show ACTB necessity in cell motility. In addition, it was shown that  $\alpha$  and  $\beta$ -actins were required for the meiotic spindle positioning and this was essential for healthy reproduction (Yi and Li, 2012, Brockmann et al., 2011). On the other hand, ACTB is usually regarded as a housekeeping gene; its expression is generally not affected by most of the different conditions, so ACTB is preferred as a reference gene for

quantification of the genes expression changes in the cells gene (Bürkle et al., 2013; Depalo et al., 2009). However, ACTB expression was differentially expressed in various types of cells under specific circumstances. It was found that ACTB were expressed differentially in some type of cancers including leukemia, lymphoma gastric, pancreatic, esophageal, liver, melanoma, renal, colorectal, lung, breast, prostate, ovarian cancers: up-regulated in liver, renal, gastric, pancreatic, esophageal, lung and ovarian cancer, while down-regulated in colorectal cancers (Guo et al., 2014).

FYN was detected in ovarian cancer and endometriosis. FYN is a member of the Src family protein tyrosine kinases (SFKs) comprised of non-receptor tyrosine kinases. SFKs consisted of 9 members including Blk, Fgr, Fyn, Hck, Lck, Lyn, c-Src, Yes and Yrk. Fyn, Src, Yes and Yrk could expressed in every cell, while Blk expressed in B cells, Fgr in myeloid and B cells, Hck in myeloid cells, Lck in T cells, NK cells and brain, and Lyn in brain, myeloid and B cells. SFKs could regulate cellular processes like cell growth, differentiation, cell shape, migration and survival, and specialized cell signals (Parsons and Parsons, 2004). SFKs all have common protein structure which contains SH1-2-3-4 and unique domains and unique domains N terminus determined each proteins identity. Fyn has various functions; in general it attended in immune and neurological functions. Furthermore, Fyn attended in biological processes such as growth and proliferation, cell-cell adhesion, cell cycle entry, mitogenic signaling and integrin-mediated interactions. It was known that Fyn is showed an up regulation expression pattern in some types of cancers such like melanoma, glioblastoma multiformae, prostate cancer, squamous cell carcinoma of the head and neck (Saito et al., 2010). SRC family kinases were associated with cancer development and progression; therefore its inhibitors were developed and most known was dastinab. It tested for several cancers like ovarian, cervical, skin, pancreatic, non-small lung and hepatocellular cancers and for cervical and ovarian cancers, some SRC family kinase inhibitors provide successful results (Szalmás et al., 2013). Moreover it was reported that one of the SRC family kinase, c-Src, was attended in uterine fibroid formation (Zhu et al., 2010). Also Fyn protein has been identified in mammalian oocytes. The experiments based on female mice have shown that Fyn deficiency may cause decrease in fertility. Fyn deficiency caused meiosis defects like chromosome disjunction and spindle microtubules organization irregularities (McGinnis et al., 2008). In another

study it was mentioned that Fyn is necessary for microtubule regulation and spindle organization, and attended in metaphase exit through meiosis and early embryo development (Levi and Shalgi, 2010).

MAPK1 resulted as common in ovarian cancer and PCOS. The two, mitogen activated protein kinases (MAPK) (also known as a extracellular signal regulated kinases; ERK), MAPK1 (ERK2) and MAPK3 (ERK1), are expressed ubiquitously and key regulators that attended in embryogenesis proliferation, differentiation and survival processes (Lei et al., 2014; Pearson et al., 2001). Both MAPKs were attended in MAPK/ERK, also known as a Ras-Raf-MEK-ERK, pathway. In this pathway activated Ras activates Raf; Raf activates MEK1/2, and MEK1/2 activates ERK1/2. MEK1/2 activates ERK1/2 by phosphorylated Tyr and Thr residues, and activated ERK1/2 can phosphorylate at least 160 substrates, containing transcription factors, kinases, phosphates, cytoskeleton proteins, scaffolds, receptors and other molecular switches. Therefore this pathway can regulate spacious processes (Park, 2014). It was known that Ras and Raf mutations are common in cancers and since the ERK mutations never reported in cancer development. It was thought that Ras and Raf oncogenes raises the cancer development by activated ERKs. In cancers ERKs behave in both manner, such that as oncogenes or anti-oncogenes (Deschenes-Simard et al., 2014). It was reported that altered MAPK/ERK signaling pathway plays a considerable role in distinguishing, low grade ovarian cancers from high grade ovarian cancers (Lei et al., 2014). Furthermore, MAPK/ERK signaling pathway attended in both pathogenesis and development of endometriosis (Zhang et al., 2010). As mentioned before EGFR and LH were required for oocyte meiotic maintenance to form fertilizable egg. There were other mechanisms that control oocytes meiotic division reentry. In granulosa cells the MAPK1-MAPK3 (ERK2-ERK1) activation was required for this resumption. Basically, EGFR dependent MAPK1-MAPK3 activation was required for oocyte maturation, but not enough for meiotic division reentry (Hsieh et al., 2011). In a mutant mouse models study, it was shown that in a mouse the MAPK3 absence resulted in a viable and fertile mouse, but MAPK1 mutation causes embryonic lethal mouse (Fan et al., 2009).



## 4. CONCLUSIONS

This thesis aims to identify significant genes and encoded proteins, which may be considered as a candidate biomarker and/or can be used for to design drug targets, for infertility-associated woman diseases (cervical cancer, ovarian cancer, uterine fibroid, endometriosis, polycystic ovary syndrome). According to this, in the present study, briefly we integrated disease specific gene expression data with comprehensive human protein-protein interaction network.

We analyzed the significant biological processes and pathways critically affected in diseases. Our analyses suggested that pathways like; focal adhesion, cell cycle, spliceosome, proteasome, p53 and MAPK signaling pathways, biological processes like; developmental (anatomical structure, system, vasculature etc.), cell cycle, response (wounding, immune, defense etc.) and regulation (programmed cell death, apoptosis processes and binding (protein, nucleotide, RNA etc.) molecular functions are conserved in almost all diseases.

We mapped the possible interconnections between diseases. Our analyses proposed that cervical cancer, ovarian cancer and endometriosis have more apparent association with each other than the other diseases relation. Apart from that we can say that, there are some correlations between cervical cancer and uterine fibroid, endometriosis and uterine fibroid and PCOS with ovarian and cervical cancer.

We analyzed the significance of proteins in terms of their expression levels and topological importance within the protein interaction networks in each disease, and identified significant genes and encoded proteins. We proposed 26 proteins which may be considered as candidate biomarkers and/or can be used for design of drug targets and have utility for development of diagnostic tests for the inspected diseases. We suggested 16 proteins that were disease-specific: 9 proteins (AR, EGR1, GSK3B, HSP90AA1, HSPA8, H2AFX, PLSCR1, TK1 and YWHAZ) for cervical cancer, 4 proteins (ATXN1, CALM1, NEDD4 and UBE2I) for ovarian cancer; and 3 proteins (CDKN1A, PCNA and YWHAE) for uterine fibroid. Furthermore, we proposed 10 proteins that were associated with more than one disease, 1 protein (KIAA0101) for endometriosis, ovarian and cervical cancer, 2 proteins (SMAD3 and TERF) for ovarian and cervical

cancers, 2 proteins (ESR1 and PIK3R1) for cervical cancer and uterine fibroid, 1 protein (BRCA1) for endometriosis and cervical cancer, 1 protein (EGFR) for endometriosis and uterine fibroid, 1 protein (ACTB) for cervical cancer and PCOS, 1 protein (FYN) for ovarian cancer and endometriosis and 1 protein (MAPK1) for ovarian cancer and PCOS.

As a result of this study several candidate biomarkers which had statistically significant changes in terms of their expression profiles among diseased and healthy samples were discovered. However it's insufficient for clinical application, therefore in future studies discovered candidate biomarkers should be supported with some experimental studies. For biomarker assay analysis, generally technologies such as ELISA, real time polymerase chain reaction (RT-PCR), enzymatic and protein assays and the others were used. Among these technologies, ELISA and RT-PCR biomarker assays studies have more feasibility than the others, so in further studies ELISA and RT-PCR assays between patients and healthy individuals should be done to check discovered biomarkers presence.

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2. Kori M., Arga K.Y., “Uncovering the Interconnectivity Between Infertility-Associated Woman Diseases”, The 13th European Conference on Computational Biology (ECCB 2014) , 7-10 September 2014, Strasbourg, France (accepted as a poster presentation)
3. Kori M., Arga K.Y., “Uncovering the Interconnectivity Between Infertility-Associated Woman Diseases”, FEBS–EMBO 2014 Conference, 30 August-4 September 2014, Paris, France (accepted as a poster presentation)