第一章　緒　論

Endometriosis prevalence, etiology, and mechanism

Endometriosis is the common polygenic/multifactorial tumor in women, but its etiology remains unclear. The prevalence of endometriosis is around 10% in the general population [Goldman and Cramer, 1989] and as high as 30-40% in infertile women [Strathy et al., 1982]. Some heritable genetic defects might contribute to the development of endometriosis [Treloar et al., 1999]. Three possible theories are involved with endometriosis, including (1) retrograde menstruation through the fallopian tubes into the peritoneal cavity; (2) lymphatic and vascular metastases; (3) tissue in-situ metaplasia. Endometriosis might be caused by an interaction between hormone interaction, immunologic changes [Akoum et al., 2000], multiple genes, endocreine, and the environment [Bischoff et al., 2000]. Endometriosis displays some features of malignancy, including local invasion and aggressive spread to distant organs. Similar to tumor metastases, endometriotic implants require neovascularization to become established, grow, and invade tissue. However, there was no adequate theory to explain their complex features.

Endometriosis, a frequent estrogen-dependent disease, has been suggested to have a genetic basis for its familial tendency [Moen et al., 1993; Kennedy et al., 1995; Hadfield et al., 1997]. Estrogen secreted by the ovaries is necessary for the development of endometriosis. Endometriosis develops mostly in women of reproductive age and regresses after menopause or ovariectomy, which suggests its estrogen-dependent growth. Some genomic aberration of progesterone receptor (PR) might be related with endometriosis development [Lattuada et al., 2004]. Recent studies have suggested that abnormalities in the regulation of specific genes are involved in the development of endometriosis [Ota et al., 2000]. Some genes might be involved in the up-regulation process of the endometriosis implants, including the apoptosis [Meresman et al., 2003], cytokine, cytokine receptor [Eyster et al., 2002], tumor suppressor genes [Chang et al., 2002], etc. The protein expression spectra of eutopic endometrium from patients with endometriosis are significantly different from those of the controls [Zhang et al., 2005]. Furthermore, the histologically normal, but biochemically abnormal, endometrium during the window of implantation has been observed in some women with endometriosis [Giudice et al., 2002].

Leiomyoma prevalence, etiology, and mechanism

Uterine leiomyoma, the most common neoplasms of the uterus, occurs in around 20-30% of women over 30 years of age [Cramer, 1992]. Despite its high prevalence, the pathophysiology and proliferation of this tumor remains unclear. The leiomyoma growth might be derived from growth and proliferation of a single smooth muscle cell [Townsend et al., 1970, Mashal et al., 1994]. One possible mechanism is the different expression of estrogen-regulated genes between leiomyoma and normal myometrium [Andersen and Barbieri, 1995]. However, formation of leiomyoma is viewed as a multistep process. The neoplastic transformation of myometrium to leiomyoma likely involves somatic mutations of normal myometrium and the complex interactions of sex steroids, cytokines, local growth factors, and DNA mutatoins [Reeve et al., 1985; El-Badry et al., 1991; Maruo et al., 2004, Shushan et al., 2004]. Leiomyoma tissue appears higher sensitivity to estrogen than myometrium. The myoma growth is regulated not only by the estrogen levels in blood, but also by estrogen production in the tumor itself [Urabe et al., 1990]. The estrogen concentration in tissues is higher in leiomyoma tissues than that in the normal myometrium [Urabe et al., 1990]. Leiomyoma is related with the complex mechanism of auto- and paracrine interaction or the effect of sex-steroid hormone action on cells [El-Badry et al., 1991]. Besides the importance of estrogens for development and growth of the myoma, progesterone seems to play an important role in the modulation of mitotic activity, local growth factors and growth factor receptors, as well as other paracrine mechanisms.

Hyperprolactinemia

Some hormones might be related with the hyperprolactinemia, including estrogen, thyroid hormone, and progesterone [Williams et al., 1994]. Hyperprolactinaemia might be induced and maintained by both estrogen and progesterone administration [Williams et al., 1994]. Estrogen-progesterone synergy promotes prolactin (PRL) secretion [Williams et al.,1985]. The positive feedback effect of progesterone upon gonadotropin as well as the prolactine was noted [Nakano et al., 1989]. In contrast, progesterone also plays an inhibitory factor for the lactogenesis [Caron et al., 1998]. Progesterone could antagonize diethylstilbestrol-induced hyperprolactinemia [Piroli et al., 1996].

Single nucleotide polymorphisms (SNPs)

Single nucleotide polymorphism (SNP) is the most abundant types of DNA sequence variation in the human genome [Kwok et al., 1999]. SNP is a single base pair on the DNA varies from person to person. The SNP marker has gained more and more popularity for its quick, accurate, and inexpensive properties for the genetic analyses of different diseases [Collins et al., 1997]. The SNP marker provides a new way for the identification of complex gene-associated diseases such as endometriosis. Genetic studies of these multifactorial diseases such as endometriosis, leiomyoma, or hyperprolactinemia are difficulty to approach due to the uncertainty of a polygenic trait and genetic susceptibility. Gene polymorphisms are useful tools in the study of multifactorial disorders [Anderson et al., 1994]. The analyses of SNP can be implemented to analyze the mechanisms of complex genetic disorders.

The mechanisms of SNPs upon individual disease remain uncertain. Unlike mutations, polymorphisms are not directly linked to a certain disease, but they are useful tools in the study of multifactorial disorders, such as endometriosis, leiomyoma or hyperprolactinemia [Lehrer et al., 1993; Anderson et al., 1994]. Despite the SNPs don't alter the transcript productions, some investigator demonstrated the disequilibrium effects of certain genotypes might influence the related 3-dimentional structure and efficiency of the transcripts [Shintani et al., 1999; Kennon et al., 2004; Shirasawa et al., 2004]. Numerous polymorphism might be related with the endometriosis development, including estrogen receptor (ER) gene polymorphisms [Georgiou et al., 1999], and AR gene polymorphisms [Fujimoto et al., 1999]. Susceptibility genes are considered to interact with other genes and environment to produce the corresponding disorder [Sano et al., 1995].

1.1 Hormone/hormone receptor-related gene

Estrogen receptor

Although the pathogenesis of endometriosis remains unclear, ectopic endometrium expresses persistent ER with hormonal independence during the luteal phase and possibly altered biologic activity [Nisolle et al., 1997]. Estrogen and ER play major roles in the pathogenesis of endometriosis or leiomyoma. ER is expressed not only in the reproductive system and ovaries but also in some other tissues. ER-related genotype may determine the function of the sex-steroid system not only at the receptor level but also at the level of

hormone synthesis [Zofkova et al., 2002]. The associations between the ER polymorphism and breast carcinoma or osteoporosis have been demonstrated. The ER polymorphism is related with numerous chronic diseases, including endometriosis [Georgiou et al., 1999], breast carcinoma [Yaich et al., 1992], recurrent abortion [Berkowitz et al., 1994], ovarian dysfunction [Syrrou et al., 1999], osteoporosis [Sano et al., 1995.], and arthritis [Ushiyama et al., 1998]. Polymorphisms involved in steroid hormone biosynthesis and signaling may be useful genetic biomarkers for hormone-related diseases [Dunning et al., 1999]. The associations between the ER polymorphism and breast carcinoma or osteoporosis have been demonstrated. Sano et al. [1995] investigated the thymine-adenine (TA) repeat polymorphism and observed that the 12 repeats of TA allele had significantly lower score of bone marrow density. Using TA repeat polymorphisms for ER, Georgiou et al. [1999] firstly demonstrated that the higher percentage of patients with endometriosis had the 15 repeats of the thymine-adenine (TA) multiallele polymorphism.

Androgen receptor (AR)

AR, a member of the steroid receptor superfamily, is involved in various biological processes such as sexual differentiation, maturation and spermatogenesis [Wieacker et al., 1998]. The AR gene has a polymorphic cytosine, adenine, and guanine (CAG) microsatellite in exon one that codes for variable-length glutamine repeats in the N-terminal domain of the AR protein [Edwards et al., 1992]. The CAG repeat length for AR is related with prostate diseases, including prostate carcinoma [Stanford et al., 1997; Ingles et al., 1997; Hakimi et al., 1997] and benign prostatic hyperplasia (BPH) [Mitsumori et al., 1999]. Mitsumori et al. [1999] demonstrated that the CAG repeat length is related with the size of BPH. However, to the best of our knowledge, no investigators demonstrated the relationship between endometriosis/leiomyoma and CAG repeats for AR in Asian population. It has been demonstrated the correlations of CAG repeat length for AR gene and endometriosis [Piva et al., 1992].

Progesterone receptor

There is increasing evidences which indicate the involvement of progesterone in the pathogenesis of endometriosis [Chwalisz et al., 2005] and leiomyoma [Maruo et al., 2004].

Both estrogen and progesterone are recognized as promoters of endometriosis and leiomyoma growth [Flake et al., 2003]. Biochemical and immunocytochemical evidence revealed the hormone receptors in endometriosis and leiomyoma cells [Soules and McCarty, 1982]. Endometriosis or leiomyoma pathogenesis is a progestin-responsive process [Massart et al., 2003]. Volume decrease of leiomyoma in GnRHa-treated patients is associated with alternation in PR expression [Wu et al., 2002].

Numerous hormones could influence the hypophyseal-gonadal axis, including estrogen, progesterone, and thyroid hormones (T3, T4, TSH) [Williams et al., 1994]. Progesterone administration might suppress the hypothalamic-pituitary-ovarian axis, which further influences the prolactin (PRL) production [Smith et al., 2002]. Hyperprolactinemia might be induced and maintained by both estrogen and progesterone administration [Williams et al., 1994]. Administration of progesterone might increase the level of PRL [Schmidt et al., 2002]. In contrast, progesterone also plays an inhibitory factor for the lactogenesis [Caron et al., 1998]. Progesterone could antagonize diethylstilbestrol-induced hyperprolactinemia [Piroli et al., 1996].

PR is long known to be essential for reproduction. The PR content is related with the prognosis and survival for breast and ovarian cancers [Clark et al., 1983; Slotman et al., 1989]. The PR gene locates on chromosome 11q22-23 [Rousseau-Merck et al., 1987]. A genetic polymorphism named as PROGINS has been identified in the PR gene [Rowe et al., 1995]. The satellite gene consists of a 306-bp DNA fragment insertion of the PV/HS-1 Alu subfamily in intron G [Rowe et al., 1995]. It has been speculated that this insertion might results in the expression of an aberrant splice form of PR, since it introduces a consensus splice acceptor site downstream of a consensus splice donor site [Rowe et al., 1995]. Therefore, it is logical to suspect this polymorphism might be a candidate marker in the genetic study of disorders affecting female endocrine systems.

An Alu insertion polymorphism of the PR was reported to be associated with a reduced risk of breast cancer [Wang-Gohrke et al., 2000]. The Alu insertion variant may be associated with increased risk of ovarian cancer in carriers without exposure to oral contraceptives [Runnebaum et al., 2001]. They also suggested a small reduced or increased risk associated with the T allele, especially the rare TT genotype [Runnebaum et al., 2001]. Progesterone antagonizes estrogen action and has antiproliferative effects in reproductive tissues such as the endometrium [Persson, 2000]. Linkage disequilibrium has been reported to exist between three polymorphisms of the PR3 gene: an intronic Alu insertion, an exon 4 amino acid

substitution codon 660 T variant, and an exon 5 synonymous codon 700 T variant [Agoulnik et al., 1997].

Genetic inheritability are related with numerous diseases, including leiomyoma and hyperprolactinemia [Ligon and Morton, 2001; Limas et al., 2002]. The identified SNP correlated with individual diseases might be plausible for understanding the related complex mechanisms. Westberg et al. [2004] demonstrated that the PR*G331A but not PROGINS is associated with PRL levels. Stevens et al. [2001] also observed the correlation between PRL-1149 G allele and hyperprolactinemia. Some polymorphisms might be related with the leiomyoma development, including AR [Fujimoto et al., 2000], and ER [Kitawaki et al., 2001].

Cytochrome P450c17α gene (CYP17)

CYP17, the gene coding for the CYP17 enzyme, involved in estrogen biosynthesis [Carey et al., 1994]. CYP17 mediates both steroid 17 α-hydroxylase and 17, 20-lyase activities and functions at key steps in the genesis of human sex steroid hormones [Habuchi et al., 2000]. CYP17 gene maps to chromonsoe 10 and contains eight exons and seven introns [Picado-Leonard et al., 1987]. The 5'-untranslated region (5'-UTR) of CYP17 contains a single-bp polymorphism 34 bp upstream from the transcription start site [Carey et al., 1994]. A single (A1 to A2) nucleotide change in the 5' region of CYP17, which contains recognition site for the MspAI restriction enzyme. CYP17 polymorphism may play a crucial role in the etiology of hormone-related disease such as endometriosis.

1.2 Tumor suppressor P53 gene

Endometriosis displays features similar to malignancy, including local invasion and aggressive spread to distant organs. Genetic alterations have been identified in endometriotic lesions, which might contribute to its initiation and progression [Jiang et al., 1998]. Some somatic genetic factors might contribute to the development of endometriosis [Treloar et al., 1999].

Tumor suppressor genes, such as p53 and p21, play a role in the regulation of cell growth and prevention of carcinogenesis. Altered tumor suppressor genes might be related with the development of endometriosis [Jiang et al., 1996]. Genomic instability of p53 plays a role in

the development and progression of various tumor types. There is a hypothetical connection between apoptosis and endometriosis [Meresman et al., 2000]. Therefore, it is logical to suspect the correlation between p53/p21 poymorphism and the endometriosis formation.

P53

p53, a representative tumor suppressor, is involved in cell proliferation and progression of various tumor types. p53 is the most common genetic change reported in human cancer. However, around half of cancer does not have p53 mutation [Harris et al., 1996]. Therefore, mutations of gene situated upstream or downstream of p53 might have a similar oncogenic effect [Li et al., 1995].

There is discrepancy about this presentation of p53 polymorphism and various tumors. The p53*Arg72 homozygote is considered to be a risk factor in the development of cancer [Storey et al., 1998]. In contrast, some investigators demonstrated the non-association between the different p53 polymorphism and cancer development [Helland et al., 1998]; other studies revealed the higher risks in the Pro72 homozygotes [Yu et al., 1999; Wang et al., 1999].

Scanty literature presented the association between the endometriosis and p53 polymorphism. High frequency of loss of p53 locus was observed in the endometriosis specimens [Bischoff et al., 2002]. p53 protein abnormalities and chromosomal aberrations may be involved in malignant transformation of ovarian endometriosis [Mhawech et al., 2002]. In contrast, some investigators have demonstrated the undetectable expression of p53 in the endometriosis specimens [Vercellini et al., 1994; Schneider et al., 1998; Horiuchi et al., 1998].

P53 promoter

Loss of tumor suppressor function generally occurs in tumorogenesis. Somatic mutations in p53 gene are the most common genetic alterations found in human malignancies [Oh et al., 2000]. It is therefore reasonable to assume that naturally occurring polymorphic genetic variants in the p53 promoter region might determine an individual susceptibility to leiomyoma. Genomic instability of p53 plays a role in the development and progression of various tumor types. Recently, the tumor suppressor gene such as p53 influence growth of

leiomyoma is being investigated [Strawn et al., 1995]. Altered tumor suppressor genes might be related with the development of leiomyoma [Jiange et al., 1996]. Induction of apoptosis may be a mechanism of the effect of GnRHa in leiomyoma [Higashijima et al., 1996].

Functional inactivation of tumor suppressor genes during tumor progression has been shown to occur by either coding region mutation or promoter region. The segregation, substitution or deletion within the promoter consequences might directly or indirectly interfere with the guarantee of p53 as well as the consequent tumorgenesis. Transcriptional inactivation of the promoter region may participate in carcinogenesis [Oue et al., 2001]. Transcriptional repression by p53 promoter methylation might contribute to tumor progression [Pogribny et al., 2002]. Aberrant methylation of CpG islands within promoter regions of the gene is associated with transcriptional inactivation of various tumor suppressor genes in neoplasms [Oue et al., 2001]. Therefore, mutations in p53 promoter region might play a partial role in the process of tumorogenesis. Furthermore, the understanding of the detailed characterization of p53 promoter is useful for the elucidation of the underlying regulation of p53 expression.

Reviewing literature, few investigators demonstrated the mutation statuses of p53 promoter as well as its promoter region in leiomyoma individuals. Some investigators have demonstrated the undetectable expression of p53 in the leiomyoma specimens [Vercellini et al., 1994; Schneider et al., 1998; Horiuchi et al., 1998]. No literature revealed the association between the leiomyoma and the p53 promoter genes.

P21

P21 (also known as WAF1, Cip1, Sdi1, Mda 6 and Cap20) is a cyclin-dependent kinase inhibitor (CDK) upregulated by wild-type tumor suppressor protein p53 [el-Deiry et al., 1995; Gujuluva et al., 1994]. Scanty studies reported the relationships between p21 codon 31 polymorphisms and individual diseases. Li et al. [1995] demonstrated the p21 gene codon 31 arginine/serine polymorphisms is not associated with a colorectal cancer predisposition. Koopmann et al [1995] demonstrated that the p53 mutation is not involved in the formation of brain tumor.

1.3 Vascular/growth factor-related genes

Endometriosis displays features similar to malignancy, requiring neovascularization to local invasion and aggressive spread to distant organs. The altered vascular-related genes might be related with the development of endometriosis. Similar to tumor metastases, endometriotic implants require neovascularization to become established, grow, and invade tissues. The neovascular processes are prominent in the endometriosis tissues. Heritable genetic factors may contribute to the initiation and progression of endometriosis [Treloar et al., 1999]. Cardiovascular genes play a role in the regulation and growth of tumor. Altered vascular-related genes might be related with the development of endometriosis or leiomyoma. Although the etiology of endometriosis remains unclear, angiogenesis may be involved in the pathogenesis of extrapelvic endometriosis [Deguchi et al., 2001]. Endometrial vascularization is effected by both endocrine and paracrine pathways [Taylor et al., 2001].

Angiotensin I-converting enzyme (ACE)

The renin-angiotensin system (RAS) regulates blood pressure through its effects on vascular tone, renal hemodynamics, and fluid-electrolyte balance [Fornage et al., 1998]. Renin converts angiotensinogen to angiotensin I. ACE cleaves angiotensin I to angiotensin II, which is the key component in RAS [Berge et al., 1994]. ACE regulates the systemic circulation through angiotensin II formation and kinin metabolism. The ACE (encoded by the gene DCP1) and RAS genes are related with the regulatory pathway in cardiovascular disease [Zhu et al., 2001]; while the ACE gene is implicated as a risk factor for coronary artery disease and myocardial infarction [Zhu et al., 2001].

Renin-angiotensin system is expressed in gonadotrophs [Robberecht et al., 1992]. Renin, angiotensinogen, and ACE were present in pituitary lactotroph cells and prolactin-secreting adenomas. Angiotensin-II has also been shown to modulate prolactin release in-vitro [Denolle et al., 1990]. Angiotensin II could be released into the hypophyseal portal vessels, which further stimulate prolactin release [Franci et al., 1997]. Luteinizing hormone-releasing hormone stimulation of prolactin release might be mediated by angiotensin II [Robberecht et al., 1992]. Angiotensin II antagonist, e.g., enalapril, could decrease the formation of angiotensin II as well as increase the prolactin reserve [Dupont et al., 1987]. Therefore, it is logical to suspect the correlations between ACE and hyperprolactinemia.

Angiogenesis and vascular remodeling play critical roles in the growth, invasion and regression of endometriosis or leiomyoma [Donnez et al., 1998]. It has been demonstrated that the presence of angiotensin receptors in endometrial tissue. Angiotensin II in endometrial stromal cells was mediated via angiotensin I receptors [Braileanu et al., 2002]. Angiotensin II could increase the intracellular calcium concentration by interaction with angiotensin receptor in endometrial stromal cells [Braileanu et al., 2002]. Vasopressin also stimulates phospholipase C activity in endometrial explants [Braileanu et al., 2001].These findings suggested the underlying contributions of ACE upon the development of endometriosis and leiomyoma.

Most studies on ACE gene polymorphisms were focused on their associations with cardiovascular diseases, serum ACE level and blood pressure [Zhu et al., 2001]. Few investigators demonstrated their roles in gynecological diseases, such as endometriosis, leiomyoma or hyperprolactinemia. Recently, a 287-bp Alu insertion/deletion (I/D) restriction fragment length polymorphism (RFLP) in intron 16 of the human ACE gene has been largely surveyed in individual diseases. However, no investigator demonstrates their association with endometriosis or leiomyoma.

1.4 Aims of this survey

In this series, we aimed to investigate the SNP distribution in three common gynecological diseases, including endometriosis, leiomyoma and hyperprolactinemia. We used the techniques of polymerase chain reaction and restriction fragment length polymorphism (PCR-RFLP) and gene sequencing for the related surveys. We also tried to establish the extent of genetic variability within the promoter region of p53 gene as well as their association with these gynecological disase.

These SNPs included (1) hormone-related SNPs [ER, CYP17, PR, AR]; (2) tumor suppressor genes (p53 codon 11, 72 and 248, p53 promoter, p21)]; (3) vascular-related SNPs (ACE-related SNPs). We aimed to detect the association between different SNPs and individual gynecological diseases. We also tried to detect some sequence variations and determine whether mutations in transcription regulatory sequences of p53 gene may result in leiomyoma development. After the related surveys, we also aimed to detect the cumulative effects of genetic risk factors upon these disorder susceptibilities, and illness severities. The

related synergic, interactive and cumulative effects of these mutant genetic variations upon the illness development were also assessed.

第二章　材料與方法

2.1 Patient recruitment

Pre-menopausal Taiwan Chinese women with surgically diagnosed endometriosis, leiomyoma, hyperprolactinemia, and controls were included. Women were divided into four groups: (1) moderate/severe endometriosis (n=100-200); (2) leiomyoma (n=100-200); (3) hyperprolacinemia (n=100-200); (4) controls (n=100-200). Their polymorphisms were detected by polymerase chain reaction and restriction fragment length polymorphism (PCR-RFLP). All women accepted the peripheral blood sampling for genotype analyses.

Women with moderate-severe (III-IV) endometriosis, staged using the revised American Fertility Society (rAFS) classification system (1985) were recruited. All women had a trans-vaginal ultrasound scan (TVS) at screening followed by a laparoscopy to confirm the diagnosis (rAFS III = 101; IV = 209). Women with other ovarian cysts or ovarian cancer were excluded from the study. The leiomyoma status was diagnosed by ultrasonography and confirmed by pathological examination after myomectomy or hysterectomy. Hyperprolactinemia status was diagnosed as chronic statuses of irregular menstruation with the elevated levels of serum PRL (>30 ng/ml) without the secondary causes of hyperprolactinemia, including primary hypothyroidism (elevated TSH with low free T4) and drug use (e.g., dopamine receptor blockers such as phenothiazines or the antiemetic metoclopramide). All individuals with hyperprolactinemia accepted the medical therapy with the bromocriptine (parlodel).

2.2 PCR procedures

The genomic deoxyribonucleic acid (DNA) was extracted from peripheral blood using Genomaker DNA extractor kit (Blossom, Taipei, Taiwan) and subjected to PCR, digestion with restriction enzyme and gel electrophoresis of the PCR products. PCR procedures were carried out in a 25-μl aliquot containing 50 ng of genomic DNA, 50 pmol of each primer, 125 μM deoxynucleotide triphosphates, 1 unit of Taq polymerase (Ampli-Taq Gold DNA polymerase, PE Applied Biosystems), and 1x reaction buffer supplied by the manufacturer (PE Applied Biosystems). PCR amplification was performed in a programmable thermal cycler GeneAmp PCR System 2400 (Perkin Elmer Applied Biosystems, Foster City, USA).

The cycling condition for individual gene polymorphism was set as follows: one cycle at 94°C for 5 min, 35 cycles at 94° C for 1 minute, 55-65°C for 1 minute, 72°C for 1 minute, one final cycle of extension the repeat region at 72°C for 7 min, and hold at 4°C.

The primer sequences for fragment amplification and PCR conditions were carried out as **Table 1 and 2**. These SNPs included 5 major groups, including (A) hormone/hormone receptor-related gene polymorphisms; (B) tumor suppressor gene polymorphisms; (C) vascular-related gene polymorphisms. The variations of DNA fragments were detected by restriction fragment length polymorphism (RFLP) or DNA sequencing. The primer sequences, PCR conditions, restriction enzyme digestions, and base pairs for the wild and mutant types for individual SNPs after PCR-RFLP were listed in **Table 1 and 2.** The SNP information for the genes involved was obtained through internet (http://www.ncbi.nlm.nih.gov/LocusLink/).

2.3 Restriction enzyme digestions

The PCR products were mixed with 2 units of individual restriction enzymes and the reaction buffers for digestion for 3 hours or overnight according to the manufacturer's instructions (New England Biolabs, Inc, Beverly, MA, USA). The genotypes were designated as wild-homozygote, heterozygote, or mutant-homozygote genotype when the restriction site was absent or present. The PCR products were applied to electrophoretic analyses with the use of a 2-3% agarose gel. The PCR products were mixed together and 10 μl of this solution was loaded into 2-3% agarose gel containing ethidium bromide for electrophoresis. Each allele was recognized according to its size (**Figure 1A, B, C**).

2.4 Hormone/hormone receptor-related gene polymorphisms

The hormone/hormone receptor-related gene polymorphisms included: (1) ER*TA repeat, ER -351 A/G XbaI, ER -397 T/C PvuII; (2) CYP17 A1/A2; (3) AR CAG repeat [from 168 bp (9 CAG repeats with the 141 bp of amplified flanking sequences) to 234 bp (31 CAG repeats)]; (4) PROGINS. The ER dinucleotide (thymine-adenine, TA) repeat polymorphism located the upstream of ER gene. The ER genotypes were classified into 'A' through 'T' (TA repeats:10 to 29). The genotype for the ER was classified into 'A' through 'T' according to the number of the TA repeats from 160 base pairs (containing 10 TA repeats with the 140 bp of amplified flanking sequences) to 198 bp (29 TA repeats). The PCR was performed using

oligonucleotide primers designed to amplify the polymorphic (TA)n repeat at 1174-base pair upstream of the human ER gene [Piva et al., 1992; del Senno et al., 1992]. The genotype for the AR was classified into 'A' through 'W' according to the number of the CAG repeats from 168 bp (9 CAG repeats with the 141 bp of amplified flanking sequences) to 234 bp (31 CAG repeats) (**Table 1)**.

The amplification was performed in a programmable thermal cycler GeneAmp PCR System 2400 (Perkin Elmer, Foster City, USA). Appropriate amount of PCR products (0.75 μl) were mixed with 1.75 μl of premixed solution [formamide: loading buffer (blue dextran, 50 mg/ml; EDTA, 25 mM):standard=5:1:1]. The former was 5' end-labeled with 5-carboxyfluorescein (FAM). Genescan-350 TAMRA (6-carboxy-tetramethylrhodamine, red) (Perkin Elmer, Applied Biosystems, USA) was used as the reference molecular size standard. Electrophoretic analysis was performed with the use of a 6% denaturing polyacrylamide gel and with ABI Prism 377 DNA Sequencer (Perkin Elmer 377, USA). The data was analyzed with software GeneScan Analysis 2.1 (Perkin Elmer Applied Biosystems, Foster City, USA). At the second electrophoresis, we applied the samples in ranked order based on size and confirmed the original determinations. PROGINS is composed a Alu (306-bp DNA) insertion in intron G of PR.

2.5 Tumor suppressor gene polymorphisms

The tumor suppressor gene polymorphisms included: (1) p53 [codon 11 Glu/Gln or Lys (GAG->CAG or AAG), codon 72 Arg/Pro (CGC->CCC), codon 248 Arg/Thr (CGG->TCG), p53 promoter; (2) p21 codon 31 Ser/Arg (AGC->AGA). Genotypes were analyzed by method of RFLP. Sequence alignment was used to identify sequence variations in p53 promoter regions. PCR primers were synthesized according to the published p53 GenBank promoter sequence (Accession no. X54156) spanning a 468-basepair fragment. The sequences of the primers were listed in **Table 2**. A 468-bp PCR product of p53 promoter cloned from the population of 160 individuals with leiomyoma were sequenced and aligned for determining sequence variations.

PCR fragments were purified, cloned into pGEM-Teasy vector (Promega, Madison, WI, USA) and then cyclesequenced for sequence variations using the Thermo Sequenase dye terminator kit and reactions were analyzed on the ALF express automated DNA sequencer (Amersham Pharmacia Biotech, Amersham, UK). The 468-bp PCR products of p53 promoter

cloned from the population of 160 individuals with leiomyoma were sequenced and aligned for determining sequence variations. The resultant reads are then compared with the wild genome for Homo sapiens.

2.6 Vascular-related gene polymorphisms

The vascular-related gene polymorphisms included: ACE A2350G, ACE A-240T, and ACE intron 16 I/D) (**Table 2**).

2.7 Illness severities: association with individual SNPs

For the further evaluation of the correlations of illness severities with individual SNP, we randomly recruited 100 cases between each group for the related surveys. The illness severities include illness stages (stage III, IV endometriosis), tumor sizes (myoma<, >5 cm), and hormone levels (PRL<, >50 pg/ml). The combined percentages of wild/mutant SNPs between each group were detected and compared.

2.8 Cumulative effects of combinant SNPs upon individual illnesses

For the further evaluation of the combinant effects of mutant-type SNPs upon individual illnesses, we randomly recruited 100 cases between each group for the related surveys (**Table 11-14**). We aimed to assess the association of cumulative effects of combinant mutant SNPs upon increased susceptibilities for individual illnesses. The distributions for combined mutant SNPs between each group were detected. The percentage of different mutant genetic numbers in each groups were also graphed (**Figure 6-9**).

2.9 Statistical analyses

Genotypes and allelic frequencies for individual gene polymorphisms in each group were compared. Allelic frequencies are expressed as a percentage of the total number of alleles. Genotypes and allelic frequencies for these polymorphisms in each group were compared.

Correlations of the genotypes/alleles for individual SNPs with different gynecological diseases were evaluated. The SAS system with χ^2 test, logistic regression method, and Fisher's exact tests were utilized for statistical analyses. Logistic regression method and Fisher's exact test were used in the analyses of ER or AR genotypes. A p-value <0.05 was considered statistically significant.

第三章 結果

3.1 Hormone/hormone receptor-related gene polymorphisms

ER*E $(TA)_{14}$, I $(TA)_{18}$ and O $(TA)_{24}$ genotypes are related with higher risk of endometriosis. Their differences existed in the genotypes E (14 TA repeats), F (15 TA repeats), H (17 TA repeats), I (18 TA repeats), and O (24 TA repeats) **(Figure 2)**. Women with genotypes E, I, and O (14, 18, 24 TA repeats) have higher risk of developing endometriosis. In contrast, women with genotypes F and H (15, 17 TA repeats) have lower risk of developing endometriosis. Mutation in the ER (XbaI*G, PvuII*C) was more prevalent in the tumor groups. Higher percentages of ESR1 mutant genotypes/alleles (XbaI*G, PvuII*C) presented in the endometriosis/leiomyoma population compared to controls. Proportions of ESR1 XbaI*AA/AG/GG and PvuII TT/TC/CC in each group were: (1) 26.8/57.1/16.1% and 24.1/60.7/15.2%; (2) 19.8/52.8/27.4% and 23.6/70.8/5.6%; (4) 33.6/64.6/1.8% and 54.5/40/5.5%, respectively (**Table 3**).

The distribution of CAG repeats for AR gene in both group appeared mono-peak distributions. AR*M $(CAG)_{21}$ and AR*S $(CAG)_{27}$ genotypes are associated with higher susceptibility of endometriosis and leiomyoma, respectively. Individuals possessing one allele of genotype M (21 CAG repeats) had higher risk of developing endometriosis compared to individuals not possessing genotype M (p-value = 0.007). The genotype S (27 CAG repeats) is associated with higher susceptibility of leiomyoma. The CYP17*A1 was associated with higher risk of endometriosis, but not leiomyoma. PR T1/T2 genotypes and allele frequencies between endometriosis, leiomyoma and controls were non-significantly different. In contrast, higher percentage of PR*T2 (PROGINS)-related genotype and allele were noted in hyperprolactinemic women compared to other three groups **(Table 3)**.

3.2 Tumor suppressor-related gene polymorphisms

P53 codon 72*Pro related genotype/allele were associated with higher risk of endometriosis, but not leiomyoma. The distributions of p53 codon 11 and 248 and p21 codon 31 polymorphisms in each groups were non-significantly different. All individuals appeared the wild genotype (Glu11, Arg248) and allele. There was no mutated genotype (p53 codon 11*Glu/Glu, Glu/Lys, Glu/Gln, Lys/Lys) (p53 codon 248*Trp, Gln) observed in all

individuals (**Table 4**). The proportions of different p21 polymorphisms in both groups were non-significantly different.

A total of 15 sequence variations within p53 promoter region were identified, including -408 T/C, -382 A/G, -359 A/G, -325 T/C, -250 A/G, -216 T/C, -205 G/A, -198 G/A, -177 T/C, -103 A/G, -81 G/A, -71 G/A, -51 T/A, -33 A/G and -17 T/C **(Figure 4)** . The percentages of mutated sequences detected are ranging from 1.3% to 6.9% **(Table 5)**. Among these variations, four SNPs (-250 A/G, -216 T/C, -103 A/G and -33 A/G) were established **(Figure 5)**. The SNPs of -250 A/G, -216 T/C, -205 G/A and -33 A/G were identified by the restriction enzymes of Bgl I, Mae I, Tau I and Dde I digestion, respectively. Allele frequencies of -250*G/-216*C/-103*G/-33*G in the leiomyoma group and control group 6.9/5.0/5.9/3.8% and 3.8/1.8/2.3/4.0%, respectively. Among these four SNPs, two of them (-216*C and -103*G) are associated with higher leiomyoma susceptibility. Alleles of -216*C and -103*G within the promoter region of p53 genes were associated with higher susceptibility of leiomyoma development. **(Table 6)**.

3.3 Vascular-related gene polymorphisms

We observed the distributions of most vascular-related SNPs in each group were different, including ACE A2350G, ACE A-240T, and ACE I/D. Most common genotype and allele for ACE I/D gene polymorphisms in disease groups (endometriosis, leiomyoma, hyperprolactinemia) were I-related genotype and allele. The distribution percentages of I-related genotype and allele were highest in endometriosis group, moderate in hyperprolactinemia group, lower in leiomyoma group, and lowest in controls. These findings indicated that ACE*I-related genotype and allele were strongly associated with higher susceptibility of endometriosis as well as moderately correlated to the susceptibility of hyperprolactinemia and leiomyoma. ACE*insertion-related genotype and alleles were strikingly higher among the endometriosis and leiomyoma populations. ACE 2350*G and ACE -240*T are associated higher susceptibility of endometriosis (**Table 7**).

3.4 Illness severities: association with individual SNPs

Concering the correlations of illness severities with individual SNPs, we observed the association of combined mutant genetic variations with higher degree of illness severities for

individual diseases (**Table 10**). In endometriosis, leiomyoma, and hyperprolactinemia cases, the combined percentages of wild/mutant SNPs were 80.1/19.9% (stage III endometriosis), 66.8/33.2% (stage IV endometriosis), 76/24% (myoma<5 cm), 64.1/35.9% (myoma>5 cm), 77.6/22.4% (PRL<50 pg/ml) and 57.1/42.9% (PRL>50 pg/ml), respectively ($p<0.05$, **Table 10**).

3.5 Cumulative effects of combinant SNPs upon individual illnesses

Concering the combinant mutant-type SNPs upon individual illnesses, we observed the cumulative effects of combinant mutant SNPs upon increased susceptibilities for individual illnesses. In the endometriosis group, the distributions for combined mutant SNPs were listed as following: 5% (0 mutant SNP), 5% (1 mutant SNP), 13% (2 mutant SNP), 25% (3 mutant SNP), 30% (4 mutant SNP), 13% (5 mutant SNP), and 9% (6 mutant SNP) (**Figure 6, Table 11**). In the leiomyoma group, the distributions for combined mutant SNPs were listed as following: 3% (0 mutant SNP), 1% (1 mutant SNP), 13% (2 mutant SNP), 32% (3 mutant SNP), 27% (4 mutant SNP), 18% (5 mutant SNP), and 6% (6 mutant SNP) (**Figure 7, Table 12**). In the hyperprolactinemia group, the distributions for combined mutant SNPs were listed as following: 3% (0 mutant SNP), 2% (1 mutant SNP), 53% (2 mutant SNP), 36% (3 mutant SNP), and 6% (4 mutant SNP) (**Figure 8, Table 13**). In the controls group, the distributions for combined mutant SNPs were listed as following: 2% (0 mutant SNP), 3% (1 mutant SNP), 20% (2 mutant SNP), 34% (3 mutant SNP), 29% (4 mutant SNP), and 12% (5 mutant SNP) (**Figure 9, Table 14**). We observed the trend of cumulative effects of mutant genets upon the susceptibility of endometriosis and leiomyoma.

第四章　討論

4.1 Hormone/hormone receptor-related gene

Estrogen receptor

ER gene presented in endometrial tissue and the pelvic organs, which are the targets of endometriotic implants [Nisolle et al., 1997]. ER polymorphism is related with numberous chronic disease, including endometriosis [Georgiou et al., 1999], breast carcinoma [Yaich et al., 1992], recurrent abortion [Berkowitz et al., 1994], ovarian dysfunction [Syrrou et al., 1999], osteoporosis [Sano et al., 1995], and arthritis [Ushiyama et al., 1998; 1999]. Georgiou et al. [1999] firstly demonstrated that the higher percentage of patients with endometriosis had the 15 repeats of the thymine-adenine (TA) multiallele polymorphism. They also observed that the distributions of (TA)n repeats was bimodal, with two peaks at 15 repeats and 23 repeats, respectively. In contrast, our data revealed that the women who had 14 repeats showed higher endometriosis stage. The genotype F (15 TA repeats) appeared prominent (19.9%) in women without endometriosis. The higher prevalence of genotype E (14 TA repeats) suggested its influences upon the endometriosis formation. The genotype E at the microsatellite locus may be associated with some variation of the ER gene that causes the endometriosis formation. We also observed the mono-peak distribution instead of bimodal distribution. The different distribution may be due to the racial difference between Asians and Caucersians.

ER is also involved in metabolic pathways influencing estrogen-related tissue growth and height stature [Schuit et al., 2004]. ER alpha (ER1) and beta (ER2) mediate much estrogen action. ER1 is a member of the nuclear receptor superfamily of ligand-activated transcription factors, which mediates estrogen actions in target tissues. Different polymorphisms have been described in ER1 genes. Allelic variants of the gene encoding ER1 and ER2 may alter their expression and function, resulting in genetic variability. Several polymorphisms of the ER1 gene have been reported to be associated with alterations in receptor expression and function. The ER1 gene, which is located on chromosome 6q25, contains some gene polymorphisms, including intron 1 polymorphisms XbaI [dbSNP: rs9340799] and PvuII [dbSNP: rs2234693][Ioannidis et al., 2004; van Duijnhoven et al., 2005]. The associations between the ER1 XbaI and PvuII polymorphism and breast carcinoma or osteoporosis have been

demonstrated [Boyapati et al., 2005; Liu et al., 2001].

The mechanism of how ER genetic differences might influence individual disorders is unknown. Itronic sequences have been reported to contain regulatory elements for transcription and splicing, giving rise to varying messenger RNA levels and different isoforms of mature messenger RNA, respectively [Gasch et al., 1989; Carstens et al., 1998]. Whether this is the case for ER polymorphisms remains to be determined. ER1 XbaI and PvuII gene polymorphisms have been reported to be related with numerous estrogen-related diseases, including age of menarche [Stavrou et al., 2006], symptom of menopause [Malacara et al., 2004], breast cancer [Boyapati et al., 2005], osteoporosis [Massart, 2005], height stature [Schuit et al., 2004], osteoarthritis [Jin et al., 2004], prostate cancer [Hernandez et al., 2006], systemic lupus erythematosus [Johansson et al., 2005], cholesterol metabolism[Kajinami et al., 2005], Alzheimer's disease [den Heijer et al., 2004], ischemic heart disease and myocardial infarction [Schuit et al., 2004], aortic valve sclerosis [Nordstrom et al., 2003], etc.

Schuit et al. [2005] demonstrated that ER1 gene polymorphism might influence the serum estradiol (E2) levels in postmenopausal women. They observed that ER1 mutant alleles (XbaI*G, PvuII*C) were associated with elevated E2 production. Lorentzon et al. [1999] demonstrated that e ER1 XbaI and PvuII gene polymorphisms is related to bone density and height during late puberty and at attainment of peak bone density in young men. They suggested that the XbaI or PvuII genotypes were related with bone mineral density (BMD), but not related to the levels of estradiol [Lorentzon et al., 1999]. ER1 XbaI*G allelic variant is associated with higher BMD. They also observed that the ER1 polymorphism might influence bone development predominantly before late puberty as well as the final body height.

Accordingly, van Duijnhoven et al. [2005] demonstrated that ER1 XbaI*G and PvuII*C-related genotype or allele are associated with increased mammographic density, which might affect the breast cancer risk. Onland-Moret et al. [2005] demonstrated that some mutation in linkage disequilibrium with ER1 397 PvuII might increases breast cancer risk in postmenopausal women. The effect of ER on breast cancer was also modified by genotypes of ER1 gene [Boyapati et al., 2005]. Schuit et al. [2004] also demonstrated that postmenopausal women who carry ER1 -351 A allele and -397 T allele have an increased risk of ischemic heart disease and myocardial infarction. Zofkova et al. [2002] demonstrated the mutant genotypes for ER XbaI or PvuII polymorphisms is associated with highest levels of the estradiol compared to wild genotypes. Such relationships provide partial molecular pathways between ER1 allelic variations and endometriosis/leiomyoma pathogeneses.

Despite many epidemiological studies suggest that the ER1 genetic variants confer increased susceptibility to individual disorders; few investigators demonstrated their association with endometriosis or leiomyoma. In this survey, we observed that the genotype distributions and allele frequencies for ER1 XbaI A/G and PvuII T/C polymorphisms were significantly different between the individuals with and without endometriosis/leiomyoma. Mutant variants for both ER1 SNPs are correlated higher susceptibility of endometriosis or leiomyoma. We indicated both ER1 XbaI and PvuII gene polymorphisms might predispose to endometriosis or leiomyoma developments. The ER1 XbaI -351*G-related genotype and allele are strongly related to the occurrence of leiomyoma, compared to being moderately correlated with the occurrence of endometriosis. In contrast, the ER1 PvuII -397*C-related genetic variants are strongly correlated with endometriosis susceptibility, compared to being moderately related to leiomyoma risk. In this study, we observed that the genotype distributions and allele frequencies for ER1 XbaI A/G and PvuII T/C polymorphisms were significantly different between the individuals with and without endometriosis/leiomyoma. Mutant variants for both ER1 SNPs are correlated higher susceptibility of endometriosis or leiomyoma. It suggested that the ER and ER-related polymorphisms might substantially contribute to the pathogenesis of endometriosis or leiomyoma.

In fact, different ethnic groups might influence the gene distributions for different SNPs. There is controversial and inconsistent reports about the ER1 -351 XbaI*G and -397 PvuII*C-related genotypes distributions or association in individual diseases among different races. Ethnic variation plays a major role in genetic regulation of estrogen or ER activity and related polymorphism to individual diseases. Furthermore, the gender-specific influence of these gene polymorphisms should be concerned in the relative surveys. In the survey of Lorentzon et al. [1999], the distributions of XbaI AA/AG/GG and PvuII TT/TC/CC in 90 Caucasians boys were 8.9/40/51.1% and 22.2/44.5/33.3%, respectively. In contrast, in one Korean population survey with 174 postmenopausal women, Nam et al. [2005] demonstrated the related distribution were 3.5/29.3/67.2% and 14.9/46.0/39.1%, respectively. These different distributions might be due to the racial difference, ethical or gender variation as well as illness classification. In this study, we observed a higher percentage of ER -351 XbaI*G homozygote/allele and -397 PvuII*T heterozygote and allele in the women with endometriosis or leiomyoma, compared to controls. The presences of wild-type alleles or homozygote for ER -351 XbaI or -397 PvuII might contribute to a decreased risk for

endometriosis or leiomyoma. The mutant alleles for these two SNPs might be serving as markers of a functional variant in a nearby gene.

Cytochrome P450c17

CYP17 is a key enzyme in the sex steroid synthesis [Martucci et al., 1993]. The enzyme has both 17 -hydroxylase and 17,20-lyase activities, which is involved in the production of estrogen [Picado-Leonard et al., 1987]. CYP17 gene polymorphism may be related with numerous tumors, including breast cancer [Feigelson et al., 1997; Bergman-Jungestrom et al., 1999; Young et al., 1999], prostate cancer [Habuchi et al., 2000], etc. Some investigators have demonstrated that the A1 allele has a more andeogenic effect on men. A1 allele of the CYP17 polymorphism is associated with an increased risk of prostate cancer and BPH [Habuchi et al., 2000]. In contrast, A2 allele has an estrogenic effect on women. A2 allele is associated with an increased risk of advanced breast cancer [Feigelson et al., 1997], polycystic ovary syndrome [Feigelson et al., 1998; Haiman et al., 1999; Diamanti-Kandarakis et al., 1999], and higher levels of serum estradiol [Haiman et al., 2001].

However, some investigators indicated the non-association between CYP17 polymorphism with individual diseases, including ovarian cancer [Spurdle et al., 2000], breast cancer [Nedelcheva Kristensen et al., 1999; Weston et al., 1998; Helzlsouer et al., 1998; Techatraisak et al., 1998], polycystic ovaries [Techatraisak et al., 1997], prostate cancer [Lunn et al., 1999; Wadelius et al., 1999; Gsur et al., 2000], and steroid hormone levels [Nedelcheva Kristensen et al., 1999; Weston et al., 1998; Helzlsouer et al., 1998; Techatraisak et al., 1997; Dunning et al., 1998].

Nedelcheva Kristensen et al. [1999] demonstrated that the age at onset, tumor grade, metastases, and ER for breast cancer were not associated with the CYP17 genotype. Haiman et al. [1999] demonstrated that A2 allele of CYP17 gene is not a strong risk factor for breast cancer. Furthermore, Haiman et al. [2001] demonstrated that the A2 allele of CYP17 was at decreased risk of endometrial cancer. Although the exact reason for these contradictory results remains unclear, the identical CYP17 genotype may play either a protective or a promoting role in endometriosis given different environmental and/or genetic backgrounds. In this study, we observed a higher percentage of A1 homozygote and allele in the endometriosis women compared with the non-endometriosis women. The presence of A2 allele presented a decreased risk for endometriosis. The A1 and A2 alleles may be serving as markers of a

functional variant in a nearby gene.

Progesterone receptor (PR)

Traditionally, estrogen has been considered to be the major stimulator of leiomyoma growth. However, some biochemical, histologic, and clinical evidences highlighted the equal contributions of progesterone and estrogen upon the tumor genesis of leiomyoma [Rein, 2000]. Some investigations suggested that progesterone and PGR play important roles in the modulation of mitotic activity, local growth factors and growth factor receptors, as well as other paracrine mechanisms in leiomyoma development [Schweppe, 1999]. Furthermore, the PGR can suppress the ER signaling as well as the stimulation of leiomyoma growth [Hodges et al., 2002]. Compared to the PGR in myometrium, the PGR in the leiomyoma is more resistant to the suppression of gonadotropin releasing hormone analogus [van de Ven et al., 2001].

Progesterone is known to influence the release of PRL [Westberg et al., 2004]. The administration of progesterone could induce the elevation of PRL [Williams et al., 1994; Schmidt et al., 2002]. The stimulatory influence of progesterone on pituitary PRL release is mediated by PGRs within the brain [Westberg et al., 2004]. These intermediate factors included β-endorphin [Pecins-Thompson et al., 1996], serotonin [Pecins-Thompson and Bethea, 1997] or dopamine [Tomogane et al., 1990]. Through the PGRs in the brain, progesterone might react with these intermediate factors, which further stimulate the PRL production [Schmidt et al., 2002]. Progesterone could up-regulates the PRL-regulated gene and the subsequent PRL-expression [Tessier et al., 2000]. The PGR could regulate the PRL expression during the differentiation processes of endometrial stromal cells [Brosens et al., 1999]. Furthermore, the cooperative transcriptions and regulations between PRL and PGR have been observed [Hovey et al., 2001]. During the neonatal phase, the uterus and endometrium developments involved the combined coordination of progesterone, estrogen and PRL receptors [Taylor et al., 2000]. Endometriosis may be due to the absence of sufficient levels of functional PR in this tissue [Fang et al., 2004].

Furthermore, numerous hormones which were correlated with endometriosis and leiomyoma might also influence the hypophyseal-gonadal axis, including estrogen and progesterone [Williams et al., 1994]. Hyperprolactinemia might be induced and maintained by both estrogen and progesterone administration [Williams et al., 1994]. Estrogens stimulate

prolactin gene transcription [Benker et al., 1990]. Estrogen administration might induce the formation of pituitary prolactin-secreting adenoma [Xu et al., 2000], pituitary hyperplasia and hyperprolactinaemia, which was mediated by angiotensin II [Pawlikowski et al., 1995]. Progesterone administration might suppress the hypothalamic-pituitary-ovarian axis, which further influences the prolactin production [Smith et al., 2002]. Administration of progesterone might increase the level of PRL [Schmidt et al., 2002]. In contrast, progesterone also plays an inhibitory factor for the lactogenesis [Caron et al., 1998]. Progesterone could antagonize diethylstilbestrol-induced hyperprolactinemia [Piroli et al., 1996].

The 306-base pair insertion polymorphism in intron G of the PGR is related with development of endometriosis [Wieser et al., 2002]. Wang-Gohrke et al. [2000] suggested the dosage effect of PROGINS upon the decreased risk for breast cancer. High levels of PGRs might be associated with better survival [Mihara et al., 2000]. Recently, Lattuada et al. [2004] demonstrated that the PROGIN *T2 allele is associated with a two-fold risk of developing endometriosis. Westberg et al. [2004] also demonstrated the correlation between PGR 331*A-related genotype and higher production of PRL. Increased production of PGR-B by the G331A polymorphism might predispose women to breast cancer development through increased PGR-B-dependent stimulation of mammary cell growth [De Vivo et al., 2003]. Possession of the PGR 331*A and H770H*C alleles for PGR polymorphism are associated with an increased risk for implantation failure post embryo transfer [Cramer et al., 2003].

In this study, we observed that the genotype and allele frequencies for PGR T1/T2 between the leiomyoma and control groups were non-significantly different. In contrast, we observed the statistical association between PROGINS genotype and hyperprolactinemia risk. The PGR*T2 related genotype and allele are related with higher susceptibility of hyperprolactinemia. We also observed the PROGIN proportions in Asians were not compatible with those of Caucasians reports. The lower percentage of T2-related genotype appear in Taiwanese population. These discrepancies might be due to numerous factors, including racial variation, illness classification, environmental variation, and multiple enzymatic processes and interactions.

Androgen receptor

Numerous diseases are related with AR gene, including prostate carcinoma [Stanford et al., 1997; Ingles et al., 1997; Hakimi et al., 1997], BPH [Mitsumori et al., 1999], uterine

endometrial carcinoma [Sasaki et al., 2000], polycystic ovarian disease [Chadha et al., 1994], breast carcinoma [Yu et al., 2000], androgen insensitivity [Biancalana et al., 1992; Lobaccaro et al., 1992], hirsutism [Calvo et al., 2000], oligozoospermia [Komori et al., 1999], X-linked spinal and bulbar muscular atrophy [Belsham et al., 1992], ankylosing spondylitis [Mori et al., 2000], amyotrophic lateral sclerosis [Garofalo et al., 1993], Hypertrophic cardiomyopathy [Kaneko et al., 1993], Huntington's disease [Alonso et al., 1997]. However, scanty reports presented the association between the endometriosis and AR gene.

AR gene presented in endometrial tissue and the pelvic organs, which are the targets of endometriotic implants [Nisolle et al., 1997]. Horie et al. [1992] demonstrated that the AR was detected in endometriosis, adenomyosis, and endometrial carcinoma. Endometrial cyst is monoclonal in origin [Jimbo et al., 1997] and related to the reaction with AR [Fujimoto et al., 1999]. Fujimoto et al. [1999] demonstrated that endometrioma might be formed from an independent monoclonal ovarian endometrial cell after inactivation of AR allele in X chromosome. The proliferation and differentiation of endometrium are mediated mainly by estrogen and progesterone receptors. However, AR also play some role in modulating the cyclic change of endometrium [Horie et al., 1992].

In contrast, some investigator demonstrated the non-association between AR gene polymorphism and the individual diseases, including isolated familial breast and ovarian cancers (Menin et al., 2001), familial prostate cancer (Miller et al., 2001), cryptorchidism (Wiener et al., 1998), and impaired spermatogenesis of linefelter's syndrome (Suzuki et al., 2001). These controversies may be due to the multiple enzymatic processes and interactions, different illness classification, racial, environmental and disease variation.

In this study, we observed that the distributions of CAG repeats for AR gene were different between the individuals with leiomyoma and normal populations. We noted that the women with genotypes S (27 CAG repeats) have higher risk of developing leiomyoma. The higher prevalence of genotype S in women with leiomyoma suggested its genetic contribution upon the leiomyoma formation. Although the other CAG repeat between both groups appeared non-significantly different, their difference may exist after a larger series survey.

4.2 Tumor suppressor genes

P53

Somatic genetic alterations have been identified in endometriotic lesions, which might be related with its initiation and progression [Jiang et al., 1998]. Kosugi et al. [1999] demonstrated the increased heterogeneity and aneuploidy of chromosome 17 in endometriosis specimen. Because p53 is located in chromosome 17, the chromosome 17 aneuploidy might impair the function of p53, which influences the further progression of endometriosis.

The p53 gene and its encoded protein are related with the regulation of cell cycle, cellular growth, and apoptosis. It is a gatekeeper or guardian of the cell division [Levine, 1997]. The p53 mutations are associated with instability of cell development and cycle progression [Harris and Hollstein, 1993]. The wild-type p53 protein is a DNA-binding transcription factor that activates other tumor suppressor genes (e.g., p21, MDM2, GADD45, Bax), that are required for the regulation of cell cycle progression or apoptosis in response to DNA damage [Loging and Reisman, 1999]. Alterations of p53 are related to the induction of apoptosis in malignant tumors.

Individuals lacking functional p53 are at an increased risk of tumor development. Numerous cancers are related the abnormal p53 presentation in tumor specimens, including the cervical carcinoma [Zehbe et al., 1999], ovarian carcnioma [Kupryjanczyk et al., 1994], bladder cancer [Esrig et al., 1994], prostate cancer [Steiner et al., 2000], hepatoma [Wang et al., 1999], gastric cancer [Takeda et al., 2000], lung cancer [Wang et al., 1999], brain tumor [Nutt et al., 2000], esophageal carcinoma [Miyazaki et al., 2000], breast cancer [Pich et al., 2000], lymphoma [Boley et al., 2000], etc. Mutated p53 gene or malfunctioned p53 protein has often observed in patients with most types of malignancies [Harris and Hollstein, 1993].

Recently, Omori et al. [2004] demonstrated that the non-association between the endometriosis and p53 codon 72 polymorphism. In their study, the proportions of Arg homozygotes/heterozygotes/Pro homozygotes in endometriosis and control groups were 35.2/48.6%/16.2% and 39.4/41.7/18.9 %, respectively. We can see their controls' distributions were compatible with ours. However, the percentage in endometriosis individuals is different from that of ours. This discrepancy may be due to the different cell nature and racial variation. In this series, we observed that Arg72 homozygote is related with lower risk of endometriosis development. The Pro forms of codon 72 in p53 (Pro homozygotes or heterozygotes) are related with the higher risk of endometriosis development.

Our finding was compatible with Wang et al. [1999] and Yu et al. [1999], who demonstrated the association between the Pro homozygotes and lung or hepatocellular carcinoma. Combined these above studies, it suggested the dominant p53* Pro forms is a risk factor for the development of endometriosis in Taiwanese population.

Most cancer-related mutations of p53 are clustered in the four so-called 'hot spots', codon 175, 248, 273 and 281/282 [Kawamura et al., 1996]. Numerous reports presented the correlation statuses of p53 codon 248 polymorphism and individual diseases. In this study, we noted the mutated somatic mutation of p53 condon 11 and 248 could not be observed in the peripheral lymphocytes from endometriosis populations. Therefore, these two SNPs will not become useful candidates for the suspecting the susceptibility of endometriosis.

Estrogen may exert its mitogenic effects on leiomyoma through estrogen-dependent growth factors [Friedman et al., 1990]. However, sex steroid hormones control uterine growth mechanisms not only via an influence on proliferation but also via apoptosis [Wu et al., 2000]. Apoptosis is important for the proper maintenance of homeostasis in a tissue and the removal of damaged or excess cells from population. The balance between cell proliferation and cell death determines tumor growth. Disregulation between proliferative and apoptotic responses may contribute to the disruption of tissue homeostasis and neoplastic growth of leiomyoma [Burroughs et al., 2000]. The regulation of p53 expression might be mediated through binding of individual proteins to target sites at p53 promoter regions.

P53 gene and its encoded protein are related with the regulation of cell cycle, cellular growth, and apoptosis. It is a gatekeeper or guardian of cell division [Lane, 1992; Levine, 1997]. The p53 mutations are associated with instability of cell development and cycle progression [Harris et al., 1993]. Dysregulated p53 expression has been implicated in the pathogenesis of a number of diseases. Alterations of p53 are related to the induction of apoptosis in malignant tumors. Individuals lacking functional p53 are at an increased risk of tumor development. A mutated p53 gene or malfunctioned p53 protein has often observed in patients with numerous malignancies [Harris et al., 1993].

p53 promoter

The mutant p53 promoter could alter the p53 gene expression. The mutations might either increased or reduced promoter activity. The deregulated expressions of p53 promoter might play a role in the predisposition towards leiomyoma development. Point mutations in

the DNA element of promoter regions might eliminate protein-DNA interactions as well as nonresponsive p53 genes. However, the involvement of p53 promoter mutation upon individual diseases remains anonymous to date. Furthermore, the role of p53 promoter in p53 expression is still elusive.

P53 promoter is related with the expression of p53 transcription. However, the involvement of p53 promoter in cancers is not clearly known. Few reports are available on mutations in the p53 promoter in cancers. Deletion analysis of p53 promoter delineated sequences between +22 and +67 as being critical for regulation [Deffie et al., 1993]. Attwooll et al. [2002] identified a single nucleotide deletion within the C/EBPlike site of the promoter in human fibroblasts, which might be correlated with the susceptibility of Li-Fraumeni syndrome. They detected one silent gene polymorphism at codon 213 in exon 6 with CGA→CGG (Arg →Arg) change. They also observed this mutation is not related with p53 production. Then they suggested that this site is not utilized in wild-type P53 promoter as well as its mutation has no consequent effect [Attwooll et al., 2002].

In contrast, Kullmann et al. [1999] analyzed the sequence p53 promoter, which did not reveal any mutational base change in the 10 synovial fibroblast populations examined. This indicates that in these patients p53 mutations in synovial fibroblasts do not contribute to the proliferative and aggressive behavior of these cells. Furthermore, Nayak and Das [1999] demonstrated the absence of mutations and deletions in p53 promoter, which indicated that mutation of p53 promoter is probably not a significant factor in breast tumorigenesis. In fact, the specific mutation patterns of p53 gene appears different expression depending on the types of tissue [Kullmann et al., 1999].

In this survey, we sequenced the p53 promoter to determine whether promoter mutations could be responsible for the leiomyoma. We identified 4 novel SNPs within this region and observed two of these mutated SNPs might be associated with the susceptibility of leiomyoma. It provided the evidences that these sequence variances might have a functional effect upon p53 presentation as well as leiomyoma development. These discrepancies with some previous reports might be due to ethologic variations, illness classification, and different sample origins.

P21

p21 gene, localized at the chromosome 6p21.2, is a gene that regulates and arrests the cell

cycle [Xiong et al., 1993]. p21 is highly associated with cell death in the response to the wild type tumor suppressor protein p53. The activation of the p21 gene could inhibit the cyclin-dependent kinase complexes, which results in the inhibition of cell cycle from the G1 to the S phase [el-Deiry et al., 1995; Gujuluva et al., 1994]. Altered p21 could interrupt the p53-mediated pathway of cell cycle and influence the progression of apoptosis.

There is controversy about the correlation between p21 presentation and individual diseases. Pasz-Walczak et al. [2000] demonstrated that p21 protein is involved in the regulatory mechanisms of carcinogenesis in colorectal cancer. Li et al. [1997] demonstrated that the immunohistochemical expression of p21 is helpful for early detection and prognosis of cervical carcinoma. Cao et al. [1998] demonstrated that the deregulation of p21 protein may effect the onset and metastasis of ovarian carcinoma. Chen et al. [2000] demonstrated that the p21 is related with the activation of estrogen-signaling pathway in breast tumor. In contrast, Schneider et al. [2000] demonstrated that serum p21 protein is not a useful marker for the early detection of lung cancer. Bankfalvi et al. [2000] demonstrated the non-significantly prognostic value of immunohistochemical expression of p21 in breast carcinoma.

Numerous cancers are related the abnormal p21 presentation, including the cervical carcinoma [Li et al., 1997], ovarian carcnioma [Levesque et al., 2000], bladder cancer [Jahnson et al., 2000], prostate cancer [Cheng et al., 2000], hepatoma [Hsu et al., 1999], colorectal carcinoma [Li et al., 1995], lung cancer [Schneider et al., 2000], brain tumor [Koopmann et al., 1995], oral carcinoma [Harada et al., 2000], nasopharyngeal carcinoma [Lin et al., 2000], esophageal carcinoma [Woodward et al., 2000], breast cancer [Chen et al., 2000], lymphoma [Kanavaros et al., 2000], etc.

In this series, we firstly survey the correlation between p21 codon 31 polymorphism and endometriosis, which revealed their non-association. This may be due to that p21 expression could be activated through p53-dependent or p53-independent pathways [Xiong et al., 1993]. Although the real role of p21 upon endometriosis is unclear, it suggested that the p21 codon 31 could not become a useful genetic marker for endometriosis susceptibility. Furthermore, the roles of other p21 polymorphisms (such as at codon 14, 25, 32, 39, 64, or 149) [Koopmann et al., 1995; Bahl et al., 2000] upon endometriosis development deserved further surveys.

There is discrepancy about the distribution of p21 polymorphism in different diseases.

Koopmann et al. [1995] demonstrated that the most abundant p21 polymorphism located at codon 31, which involved the base change from AGC to AGA and amino acid changes from Ser to Arg. In the surveys of the p21 polymorphisms in human brain tumors, they observed the allelic frequencies for Ser and Arg-form amino acid were 90.5 % and 8.5 %, respectively [Koopmann et al., 1995]. Li et al. [1995] demonstrated the 18% of the Arg-form amino acid in colorectal cancer. Bahl et al. [2000] and Li et al. [1995] observed the 4% and 18% of the Arg-form amino acid in the patients with esophageal and colorectal cancer, respectively. In this series, we observed the around 50% Arg distribution in endometrioisis patients, which was different from that of Koopmann et al. [1995]. The difference of the Ser/Arg distribution may be due to the racial or disease variations.

4.3 Vascular/growth factor-related genes

Angiotensin-converting enzyme (ACE)

The endometrium, which has prominent vessels and blood flow, is one of the few adult tissues that exhibit regular intervals of rapid growth. Therefore, angiogenesis is an important component of the growth and function of these tissues. Endometriosis is a disease of endometrium tissues shedding outside the uterus during menstruation. These explants require a rich blood supply, which enables them to survive and grow. Therefore, the activation of angiogenesis might be a key factor in the pathogenesis of endometriosis [Inan et al., 2003]. Therefore, it is logical to expect that ACE might appear to be an angiogenic factor in the female reproductive organs. The ACE gene, which is located on chromosome 17q23, contains some gene polymorphism and candidate markers for hypertension and related diseases [Doria et al., 1994]. The ACE gene polymorphism located on the intron 17 of ACE gene. ACE gene polymorphisms are related to numerous diseases, including carotid artery wall thickness [Sayed-Tabatabaei et al., 2003], post-transplant erythrocytosis [Yildiz et al., 2003], diabetic nephropathy [Chang et al., 2003], Alzheimer's disease [Kehoe et al., 2003], ischemic cerebrovascular disease [Um et al., 2003], dementia [Choi et al., 2003], segmental glomerulosclerosis [Dixit et al., 2002], cystic fibrosis [Arkwright et al., 2003], etc. ACE I/D polymorphism affects uteroplacental and umbilical flows and the recurrence of an adverse pregnancy outcome in women with preeclampsia [Mello et al., 2003]. The ACE insertion/deletion and M235T polymorphisms are associated with an increased risk of developing coronary heart disease, hypertension, and ventricular hypertrophy [Alvarez et al.,

2000; Sethi et al., 2003]. Three ACE gene polymorphisms [Alu insertion/deletion, 23949 (CT), 10698 (G)] might influence the development of systemic lupus erythematosus and nephritis [Parsa et al., 2002].

In contrast, some investigators have demonstrated the non-associations between the ACE gene polymorhpisms with individual diseases, including hypertension [Harrap et al., 1993], left ventricular hypertrophy [West et al., 1997], pregnancy outcome, pregnancy-induced hypertension [Tamura et al., 1996], and nephronophthisis [Omran et al., 1999]. ACE-5466C and 4656 gene polymorphisms are not directly related with the occurrence of sarcoidosis [Schurmann et al., 2001]. In fact, different ethnic groups might influence the ACE gene distributions [McKenzie et al., 2001]. Ethnic variation plays a major role in genetic regulation of serum ACE activity and ACE gene polymorphism to cardiovascular disease [Bloem et al., 1996]. Zhu et al. [2001] demonstrated that two polymorphisms (ACE A2350G and A-240T) are significantly associated with blood pressure and ACE concentration. The G allele for ACE 2350 gene polymorphism is significantly associated with higher blood pressure and ACE concentration [Zhu et al., 2001]. They suggested that allelic interaction of these gene polymorphisms might play an important role in the dissection of complex traits such as blood pressure. They also indicated these associations were more obvious in female individuals than in male patients. Therefore, the gender-specific influence of these gene polymorphisms should be concerned in the relative surveys.

In this study, we noted that the genotype distributions for ACE A2350G gene polymorphisms were significantly different between the individuals with and without endometriosis. This finding is the first indication that ACE gene polymorphism indicates a predisposition to endometriosis development. We also observed the G-related genotypes and G allele appeared higher percentage among the endometriosis populations. This finding is compatible with the result of Zhu et al. [2001], who suggested that the ACE 2350*G allele might be associated with higher risk of Vascular lesion (higher systolic blood pressure) and higher ACE concentrations. Therefore, our data strongly suggests that the ACE gene polymorphisms may substantially contribute to the pathogenesis of endometriosis. It also suggests that RAS might be involved in the pathogenesis of endometriosis.

Most studies have associated the presence (insertion, I) or absence (deletion, D) of a 287-bp Alu repeat element in intron 16 with the levels of circulating enzyme or cardiovascular pathophysiologies. ACE I/D polymorphism affects the uteroplacental and umbilical flows as well as the recurrence of an adverse pregnancy outcome in women with

preeclampsia [Mello et al., 2003]. Individuals with the DD genotype show a significantly increased left-ventricular mass in response to physical training, compared to the II or ID genotype as well as the lowest plasma ACE levels [Alvarez et al., 2000]. ACE I/D genotype DD might be a promoter to clinical manifestation of sarcoidosis. A significant association was observed between the presence of ACE*D genotype/allele and an elevation of serum ACE activity [Martinez et al., 2000].

Despite many epidemiological studies suggest that the ACE*D allele confers increased susceptibility to cardiovascular disease; however, other reports have found no such association or even a beneficial effect [Rieder et al., 1999]. ACE polymorphism may be associated with the development of endometrial carcinoma [Freitas-Silva et al., 2004]. The presence of I allele (genotypes ID and II) is significantly associated to an earlier age of onset of endometrial carcinoma [Freitas-Silva et al., 2004]. In contrast, the D-related genotype (DD, ID) exhibited higher risk of breast cancer [Koh et al., 2003] and advanced progression of prostate cancer [Medeiros et al., 2004]. Furthermore, some investigators have demonstrated the non-associations between the ACE gene polymorphisms with individual diseases, including hypertension [Mondorf et al., 1998; Berge et al., 1994; Harrap et al., 1993], myocardial infarction [Foy et al., 1997], left ventricular hypertrophy [West et al., 1997], pregnancy outcomes, pregnancy-induced hypertension [Tamura et al., 1996], nephronophthisis [Omran et al., 1999], and sarcoidosis [Schurmann et al., 2001].

In this study, we further observed that the genotype distributions and allele frequencies for ACE I/D polymorphisms were significantly different between the individuals with and without endometriosis/leiomyoma. The ACE*I-related genotype and allele are strongly related to the occurrence of endometriosis, compared to being moderately correlated with the occurrence of leiomyoma. Our results firstly indicated the ACE gene polymorphisms might predispose to the developments of these gynecological diseases. This finding is also compatible with some previous reports, who suggested that the ACE*I allele might be associated with higher susceptibility of individual diseases. Therefore, our data strongly suggests that the ACE gene polymorphisms might substantially contribute to the pathogenesis of endometriosis, leiomyoma or hyperprolactinemia. It also suggests that RAS might be involved in the pathogenesis of these diseases.

4.4 Cumulative effects of SNPs

Concerning the correlations of illness severities with individual SNPs, in our surveys, we observed the association of combined mutant genetic variations with higher degree of illness severities for endometriosis, leiomyoma, and hyperprolactinemia.

In the cases with more severe endometriosis (rAFS IV), larger leiomyoma (>5cm), or higher serum levels of prolactinemia (PRL>50 pg/ml), the higher percentage ofcombinant mutant SNPs. Concering the combinant mutant-type SNPs upon individual illnesses, we observed the association of cumulative effects of combinant mutant SNPs upon increased susceptibilities for endometriosis, leiomyoma, and hyperprolactinemia. We observed the trend of additional effects of mutant genets upon the susceptibility of endometrios, leiomyoma and hyperprolactinemia.

Recently, there were some literatures dealed with the cumulative effects of combinant genetic variations upon the illness susceptibilities [Borroni et al., 2006; Calhoun et al., 2006; Juyal et al., 2006; Tao et al., 2006; Vineis and McMichael, 1996]. It has been demonstrated a cumulative contribution of genetic variations in genes from the dopaminergic pathway upon comferring the susceptibility to Parkinson's disease [Juyal et al., 2006]. There existed a synergic, interactive and cumulative effects of COMT*H and 5-HTTLPR*S polymorphisms upon the disease severity, comorbidities and risk of psychosis in Alzheimer disease [Borroni et al., 2006]. Despite of the individual small effects, the cumulative contribution of multiple DNA sequence polymorphisms might results in the the allele-specific expression differences through a series of complex trait [Tao et al., 2006].

第五章 結論

In conclusion, in our preliminary surveys, we observed some SNPs were correlated with the susceptibilities for some gynecological diseases. ER -351*G, ER -397*C, and ACE* insertion-genotypes/alleles are associated with higher risk of both endometriosis and leiomyoma. ER*$(TA)_{14}$, ER $(TA)_{18}$, ER$(TA)_{24,}$ AR*$(CAG)_{21,}$ CYP17*A2, P53 codon 72*Pro, ACE 2350*G, and ACE -240*T related genotypes/alleles are related with higher risk of endometriosis. AR*$(CAG)_{27}$ related genotypes/alleles are associated with higher susceptibility of leiomyoma. Some sequence variations were observed within the promoter region of p53 gene. The SNPs of -216*C and -103*G among the identical sequence variations are associated with leiomyoma development. Higher percentage of PR*T2 and ACE*insertion-related genotype and allele were noted in hyperprolactinemic women.

We also identified as many as 15 mutation points within p53 promoter region. Among these mutations, a total of 4 SNPs might be established. We also observed p53 promote -216*C and -103*G related genotypes and alleles might be associated with leiomyoma development. It suggested that sequence variations of p53 promoter might be useful markers for predicting leiomyoma susceptibility. These novel SNPs deserved further detailed disease-association studies to determine their linkage with individual diseases.Other SNPs were not associated with susceptibility for endometriosis or leiomyoma, including p53 codon 11 and 248, and p21 codon 31. All these polymorphisms are not useful markers for predicting the development of these gynecological diseases.

In our survey, we observed an association of combined mutant genetic variations with higher degree of illness severities, including more severe endometriosis, larger leiomyoma size, and higher levels of serum prolactin. We observed the cumulative effects of combinant mutant SNPs upon increased susceptibilities for individual illnesses. There is a trend of additional effects of mutant genets upon the development risk of endometrios, leiomyoma and hyperprolactinemia.

Some associated gene polymorphisms likely contributes to the pathogenesis of these gynecological disorders. However, correlation between SNPs in the p53 promoter region and illness susceptibility remains to be explored. Future studies need to determine if the polymorphisms in p53 promoter region have direct effect on the level of p53 transcription and ultimately tumor pathology. Lager cohort recruitment is request for its further clarification. After the elucidation of these issues, some gene polymorphismss might become useful

markers to predict the future development of these diseases as well as the development and intervention of genetic therapy. This study could be extended to know whether and how the pathophysiology for these gynecological disease formation and the valuable insight into the pathogenesis of leiomyoma.

We alos observed the cumulative effects of mutant genetic factors upon the disorder susceptibilies, illness severities and syptoms. Patients suffering from endometriosis, leiomyoma or hyperprolactinemia showed a cumulation of high risk genotypes at horomne/hormone receptor, tumor suppressor, and vascular-related gene polymorphisms. Our findings indicated the determinational effects of these genetic events (mutations and deletions) in hormone homogenesis, regulations of tumor suppressor genes and vascular events in the pathogenesis of these disorders. It also suggests a crucial contribution for these mutations upon the induction or progression of these tumors or hormone changes.

After the clarification of these issues, some gene polymorphism may become a useful marker to predict the future development of endometriosis and to permit early therapeutic intervention. These polymorphisms with presentation differences might become useful markers for predicting endometriosis, leiomyoma or hyperprolactinemia susceptibility. Moreover, an important aim in future work will be to define their functional molecular consequences and their interaction with the environment in the causation of the endometriosis, leiomyoma or hyperprolactinemia phenotype. A further promising application of these polymorphisms comes from their pharmacogenomic implications, with the possibility of providing better guidance for therapeutic regimens, such as selective ER modulators and ER antagonist transfection therapy.

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Table 1. The primer sequences, polymerase chain reaction and restriction fragment length polymorphism (PCR-RFLP) conditions for hormone/hormone receptor-related gene polymorphisms.

Polymorphisms	Primers sequences (5'->3') [a]	Tm (^oC) [b]	Restriction enzymes [c]	Allele	DNA fragment size (bp)	參考文獻
Estrogen receptor TA repeat	F-GACGCATGATATACTTCACC R-GCAGAATCAAATATCCAGATG	58	-	$(TA)_{10-29}$	140 bp [$(TA)_{10,}$ A allele]~ [198 $(TA)_{29,}$ T allele]	Piva et al., 1992; del Senno et al., 1992
Androgen receptor CAG repeat	F-TGCGCGAAGTGATCCAGAAC R-CTTGGGGAGAACCATCCTCA	60	-	$(CAG)_{9-31}$	168 bp [$(CAG)_{9,}$ A allele]~ 234 bp [$(CAG)_{31,}$ W allele]	Stanford et al., 1997
Cytochrome P450c17α (CYP17)	F-CCACAAGGCAAGAGATAACA R-AGGGTAAGCAGCAAGAGAGC	58	MspA1I (37 ^oC)	A1 A2	169 102+67	Carey et al., 1994
Estrogen receptor -351 A/G XbaI intron 1	F-CTGCCACCCTATCTGTATCTTTT CCTATTCTCC; R-TCTTTCTCTGCCACCCTGGCGTC GATTATCTGA	58	XbaI (37^oC)	A G	1300 239+140	Lorentzon et al., 1999;
Estrogen receptor -397T/C PvuII exon 2			PvuII (65^oC)	T C	1300 160+119	Kobayashi et al., 1996
PROGINS	F-GGC AGA AAG CAA AAT AAA AAG A R-AAA GTA TTT TCT TGC TAA ATG TC	58	-	T1 (wild type) T2 (PROGINS)	159 465 (306-bp Alu insertion)	Rowe et al., 1995

[a] F and R indicate forward and reverse primers; [b] Tm= mean melting temperature of primers; [c] One unit of restriction enzyme in 10 μL buffer for 2 hours digestion

Table 2. The primer sequences, polymerase chain reaction and restriction fragment length polymorphism (PCR-RFLP) conditions for tumor suppressor and angiotensin I-converting enzyme (ACE)-related gene polymorphisms.

Polymorphisms	Primers sequences (5'->3') [a]	Tm (^{o}C) [b]	Restriction enzymes [c]	Allele	DNA fragment size (bp)	參考文獻
p53 codon 11	F-CTTGGGTTGTGGTGAAACATTG; R- GTCAGTCCCATGAATTTTCGCT	55	Taq I (65^{o}C)	Glu Gln/Lys	239+140 379	Butz et al., 2003
p53 codon 72	F-TCCCCCTTGCCGTCCCAA; R-CGTGCAAGTCACAGACTT	58	BstU I (37^{o}C)	Arg Pro	279 160+119	Storey et al., 1998
p53 codon 248 (exon 7)	F- TAGGTTGGCTCTGACTGTACCA; R-TGTGATGAGAGGTGGATGGGTA	58	Hap II (65^{o}C)	Arg Trp/Gln	164+69 233	Butz et al., 2003
P53 promoter	F-GAT ATT ACG GAA AGC CTT C R-AGC CCG AAC GCA AAG TGT	58	-	-	468	-
p21 codon 31	F-GTCAGAACCGGCTGGGGATG R-CTCCTCCCAACTCATCCC GG	57	Blp I (37 ^{o}C)	Ser (AGC) Arg (AGA)	183+89 272	Li et al., 1997
ACE A2350G exon 17	F-CTGACGAATGTGATGGCCGC R-TGATGAGTTCCACGTATTTCG	62	BstUI (60 ^{o}C)	A G	122 103+19	Zhu et al., 2001
ACE A-240T	F-TCGGGCTGGGAAGATCGAGC R-GAGAAAGGGCCTCCTCTCTCT	58	XbaI (37℃)	A T	137 114+23	Yildiz et al., 2003
ACE I/D intron 17	F-CTGGAGACCACTCCCATCCTTT CT R-GATGTGGCCATCACATTCGTCA GAT	58	-	I (insertion) D (Deletion)	490 190	Abbud et al., 1998

[a] F and R indicate forward and reverse primers; [b] Tm= mean melting temperature of primers; [c] One unit of restriction enzyme in 10 μL buffer for 2 hours digestion

Table 3. Genotypes/allelic variations for hormone/hormone receptor-related gene polymorphisms in women with gynecological diseases.

SNPs*	Endometriosis (%)	Leiomyoma (%)	Hyperprolactinemia (%)	Controls (%)	p-values
Estrogen receptor -351 XbaI	n=112	n=106	n=102 (%)	n=110	
AA	30 (26.8)	21 (19.8)	29 (28.4)	37 (33.6)	NS[a]
AG	64 (57.1)	56 (52.8)	55 (54)	71 (64.6)	<0.005[b,c]
GG	18 (16.1)	29 (27.4)	18 (17.6)	2 (1.8)	
A	124 (55.4)	98 (46.2)	113 (55.4)	145 (65.9)	NS[a]
G	100 (44.6)	114 (53.8)	91 (44.6)	75 (34.1)	<0.005[b,c,d]
Estrogen receptor -397 PvuII	n=112	n=106	n=102 (%)	n=110	NS [a]
TT	27 (24.1)	25 (23.6)	34 (33.3)	60 (54.5)	<0.005 [b,c,d]
TC	68 (60.7)	75 (70.8)	58 (56.9)	44 (40)	
CC	17 (15.2)	6 (5.6)	10 (9.8)	6 (5.5)	NS [a]
T	122 (54.5)	125 (59)	126 (61.8)	164 (74.5)	<0.005 [b,c,d]
C	102 (45.5)	87 (41)	78 (38.2)	56 (25.5)	
CYP17	n=119 (%)	n=159 (%)	n=102 (%)	n=108 (%)	<0.05 [a]
A1/A1	31 (26.1)	27 (17.0)	20 (19.6)	16 (14.8)	NS[b]
A1/A2	55 (46.2)	74 (46.5)	47 (46.1)	48 (44.5)	<0.005 [c]
A2/A2	33 (27.7)	58 (36.5)	35 (34.3)	44 (40.7)	<0.05 [a]
A1	117 (49.2)	128 (40.3)	87 (42.6)	80 (37.1)	NS [b]
A2	121 (50.8)	190 (59.7)	117 (57.4)	136 (62.9)	<0.005 [c]
PROGINS	n=159	n=192 (%)	n=178 (%)	n=252 (%)	NS [b,c]
T1/T1	151 (95)	183 (95.3)	152 (85.4)	243 (96.4)	<0.0005[d]
T1/T2	7 (4.4)	7 (3.6)	19 (10.7)	8 (3.2)	
T2/T2	1 (0.6)	2 (1.1)	7 (3.9)	1 (0.4)	
T1	309 (97.2)	373 (97.1)	323 (90.7)	494 (98)	NS [b,c]
T2	9 (2.8)	11 (2.9)	33 (9.3)	10 (2)	<0.0005 [d]

[a] Endometriosis vs. leiomyoma vs. hyperprolactinemia; [b]leiomyoma vs. controls; [c] Endometriosis vs. controls; [d] hyperprolactinemia vs. controls;
*p-value were calculated by χ^2 test.

Table 4. Genotypes and allelic variations for tumor suppressor gene polymorphisms in women with individual gynecological diseases.

	Endometriosis (%)	Leiomyoma (%)	Controls (%)	p-values
p53 codon 11†	n=148 (%)	n=159 (%)	n=150 (%)	
Glu/Glu	148 (100)	159 (100)	150 (100)	NS
Glu /Gln, Glu/Lys,	0	0	0	
Gln/Gln, Lys /Lys	0	0	0	
Glu	296 (100)	318 (100)	300 (100)	NS
Gln	0	0	0	
Lys	0	0	0	
p53 codon 72*	n=148 (%)	n=159 (%)	n=150 (%)	
Arg/Arg	14 (9.5)	52 (32.7)	47 (31.4)	<0.005[a,c]
Arg /Pro	98 (66.2)	67 (42.1)	74 (49.3)	NS[b]
Pro/Pro	36(24.3)	40 (25.2)	29 (19.3)	
Arg	126 (42.6)	171 (53.8)	168 (56)	<0.005 [a,c]
Pro	170 (57.4)	147 (46.2)	132 (44)	NS[b]
p53 codon 248*	n=148 (%)	n=159 (%)	n=150 (%)	
Arg/Arg	148 (100)	159 (100)	150 (100)	NS
Arg/Trp, Arg/Gln	0	0	0	
Trp/Trp, Gln/Gln	0	0	0	
Arg	296 (100)	318 (100)	300 (100)	NS
Trp	0	0	0	
Gln	0	0	0	
p21 codon 31*	n=102 (%)	n=112 (%)	n=119 (%)	
Ser/Ser	27 (26.5)	24 (21.4)	21 (17.7)	NS
Ser/Arg	49 (48.0)	57 (50.9)	60 (50.4)	
Arg/Arg	26 (25.5)	31 (27.7)	38 (31.9)	
Ser	103 (50.5)	105 (46.9)	102 (42.9)	NS
Arg	101 (49.5)	119 (53.1)	136 (57.1)	

[a] Endometriosis vs. leiomyoma; [b]leiomyoma vs. controls; [c] Endometriosis vs. controls; p-value were calculated by χ^2 test* and Fisher's exact test†.

Table 5. The percentages of mutated p53 promoter genes in the population (n=160) of leiomyoma group. The sequence was detected by the method of DNA sequencing.

Position	Wild-type → Mutated-type	Case No. (%) of mutated-type
-408	T → C	5 (3.13)
-382	A → G	2 (1.25)
-359	A → G	4 (2.50)
-325	T → C	3 (1.88)
-250	A → G	11 (6.88)*
-216	T → C	9 (5.63)*
-205	G → A	2 (1.25)
-198	G → A	2 (1.25)
-177	T → C	5 (3.13)
-103	A → G	9 (5.63)*
-81	G → A	7 (4.38)
-71	G → A	6 (3.75)
-51	T → A	7 (4.38)
-33	A → G	8 (5.00)*
-17	T → C	2 (1.25)

Identified single nucleotide polymorphism

Table 6. The cutting sequences, restriction enzymes, and DNA fragments after digestion for p53 promoter -250 A/G, -216 T/C, -103 A/G and -33 A/G polymorphisms and their allelic frequency between women with and without endometriosis.

SNPs	Sequence of cutting site	Restriction enzyme	Allele type (No. of cutting site)	DNA fragment (bp)	Leiomyoma Allele No.=320 (%)	Controls Allele No.=400 (%)	p-value
-250 A/G	GCC$(N)_4$^NGGC	Bgl I	WT (0)	468	22 (6.9)	15 (3.8)	0.059
			MT (1)	153, 315			
-216 T/C	C^TAG	Mae I	WT (1)	61, 407	16 (5.0)	7 (1.8)	0.014
			MT (2)	61, 189, 218			
-103 A/G	GCSG^C	Tau I	WT (0)	468	19 (5.9)	9 (2.3)	0.011
			MT (1)	166, 302			
-33 A/G	C^TNAG	Dde I	WT (1)	60, 408	12 (3.8)	16 (4.0)	0.86
			MT (2)	40, 60, 368			

N indicates G, A, T or C.

WT: wild type; MT: mutant type

Table 7. Genotypes and allelic variations for vascular/growth factor gene polymorphisms in women with individual gynecological diseases.

	Endometriosis (%)	Leiomyoma (%)	Hyperprolactinemia (%)	Controls (%)	p-values
ACE A2350G	n =150 (%)	n=105 (%)	n=102 (%)	n =159 (%)	
A/A	100 (66.7)	78 (74.3)	81 (79.4)	153 (96.2)	<0.005 [b,c,d]
A/G	44 (29.3)	20 (19)	17 (16.7)	5 (3.1)	
G/G	6 (4.0)	7 (6.7)	4 (3.9)	1 (0.7)	
A	244 (81.3)	176 (83.8)	179 (87.7)	311 (97.8)	<0.005 [b,c,d]
G	56 (18.7)	34 (16.2)	25 (12.3)	7 (2.2)	
ACE A-240T	n =150 (%)	n=105 (%)	n=102 (%)	n =159 (%)	
A/A	65 (43.3)	47 (44.8)	51 (50)	100 (62.9)	<0.005 [b,c,d]
A/T	69 (46)	50 (47.6)	39 (38.2)	57 (35.8)	
T/T	16(10.7)	8 (7.6)	12 (11.8)	2 (1.3)	
A	199 (66.3)	144 (68.6)	141 (69.1)	257 (81.8)	<0.005 [b,c,d]
T	101 (33.7)	66 (31.4)	63 (30.9)	61 (18.2)	
ACE I/D	n=125 (%)	n=120 (%)	n=138 (%)	n=128 (%)	
Insertion/Insertion	63 (50.4)	30 (25)	54 (39.1)	13 (10.2)	<0.005 [b,c,d]
Insertion/Deletion	30 (24)	28 (23.33)	38 (27.6)	38 (29.7)	
Deletion/Deletion	32 (25.6)	62 (51.67)	46 (33.3)	77 (60.1)	
Insertion	156 (62.4)	88 (36.7)	146 (52.9)	64 (25)	<0.005 [b,c,d]
Deletion	94 (37.6)	152 (63.3)	130 (47.1)	192 (75)	

Endometriosis vs. leiomyoma; [b]leiomyoma vs. controls; [c] Endometriosis vs. controls; [d] hyperprolactinemia vs. controls
p-value were calculated by χ^2 test* and Fisher's exact test†.

Table 8. Distributions of wild/mutant allele for individual genes between individual illness and controls

Gene	Endometriosis	Leiomyoma	Hyperprolactinemia	Controls
ER -351 A/G	55/45	46/54	55/45	66/34
ER -397 T/C	54/46	59/41	62/38	74/26
CYP17 A1/ A2	49/51	40/60	43/57	37/63
PROGINS T1/T2	97/3	97/3	90/10	98/2
p53 codon 11 Glu/Mut	100/0	100/0	-	100/0
p53 codon 72 Arg/Pro	42/58	54/46	-	56/44
p53 codon 248 Arg/mutant	100/0	100/0	-	100/0
p21 codon 31 Ser/Arg	51/49	47/53	-	43/57
ACE 2350 A/G	82/18	84/16	88/12	98/2
ACE -240 A /T	66/34	70/30	69/31	82/18
ACE I/D	62/38	37/63	53/47	25/75

Table 9. Clinical characteristics of study subjects (n=100) in each group (characteristics mean value ± SEM).

	Endometriosis (n=100)	**Leiomyoma (n=100)**	**Hyperprolactinemia (n=100)**	**Controls (n=100)**	**p-value**
Age (y)	32.7 ± 3.7	31.6 ± 3.7	29.3 ± 3.2	29.3 ± 3.2	NS
BMI (kg/m2)	20.5 ± 2.1	20.9 ± 2.8	19.8 ± 2.9	21.2 ± 3.1	NS
Severe status	stage IV n=16	Huge myoma (>5 cm) n=78	PRL >50 n=58	-	
Moderate status	stage III n=84	Small myoma (<5 cm) n=22	PRL <50 n=42	-	

Table 10. Correlations of gene polymorphisms and illness severities for endometriosis, leiomyoma, and hyperprolactinemia.

Gene	Allele	Endometriosis		Leiomyoma		Hyperprolactinemia	
		stage III (n=16) *	**stage IV (n=84) ***	**Size <5 cm (n=22) †**	**Size >5 cm (n=78) †**	**PRL <50** (n=42) ‡	**PRL >50** (n=58) ‡
ER -351	A	11	44	12	34	34	21
	G	5	40	10	44	8	37
ER -397	T	10	44	13	46	34	28
	C	6	40	9	32	8	30
CYP17	A1	12	37	14	26	25	18
	A2	4	47	8	52	17	40
PROGINS	T1	16	81	22	75	40	50
	T2	0	3	0	3	2	8
p53 codon 11	Glu	16	84	22	78	-	-
	Mutant	0	0	0	0	-	-
p53 codon 72	Arg	12	30	17	37	-	-
	Pro	4	54	5	41	-	-
p53 codon 248	Arg	16	84	22	78	-	-
	Mutant	0	0	0	0	-	-
p21 codon 31	Ser	13	38	14	33	-	-
	Arg	3	46	8	45	-	-
ACE A2350G	A	10	72	19	65	35	53
	G	6	12	3	13	7	5
ACE A-240T	A	13	53	19	51	31	38
	T	3	31	3	27	11	20
ACE I/D	I	12	50	10	27	29	24
	D	4	34	12	51	13	34
Sum (%)	**Wild**	**141 (80.1%)**	**617 (66.8%)**	**184 (76%)**	**550 (64.1%)**	**228 (77.6%)**	**232 (57.1%)**
	Mutant	**35 (19.9%)**	**307 (33.2%)**	**58 (24%)***	**308 (35.9%)**	**66 (22.4%)***	**174 (42.9%)**

*, †, ‡: $p<0.05$

Table 11. Endometriosis individuals with wild (represent :0) or mutant (represent :1) gene polymorphisms.

Case	ER-351	ER-397	CYP17	PROGIN	p53cod11	p53cod72	p53 cod 248	p21cod31	ACE2350	ACE-240	ACE I/D	Sum
1.	1	0	1	1	0	1	0	0	0	1	0	**5**
2.	1	1	0	1	0	1	0	0	0	1	1	**6**
3.	1	1	1	0	0	1	0	0	0	1	1	**6**
4.	1	1	1	0	0	1	0	1	0	0	1	**6**
5.	1	0	1	0	0	1	0	1	0	0	1	**5**
6.	1	1	0	1	0	1	0	0	0	1	1	**6**
7.	1	0	0	0	0	1	0	1	0	1	0	**4**
8.	1	0	0	0	0	0	0	1	0	1	1	**4**
9.	1	0	0	0	0	0	0	1	0	1	0	**3**
10.	0	0	1	0	0	0	0	0	0	1	1	**3**
11.	0	0	0	0	0	1	0	1	1	1	1	**5**
12.	0	0	0	0	0	1	0	1	1	1	1	**5**
13.	0	0	0	0	0	1	0	1	1	1	1	**5**
14.	0	0	0	0	0	1	0	0	1	1	1	**4**
15.	0	0	0	0	0	1	0	1	1	1	1	**5**
16.	0	0	0	0	0	1	0	1	1	1	1	**5**
17.	1	0	0	0	0	1	0	1	0	0	1	**4**
18.	1	1	0	0	0	1	0	1	0	0	1	**5**
19.	1	1	1	0	0	0	0	1	1	0	1	**6**
20.	1	1	1	0	0	1	0	0	1	0	1	**6**
21.	1	1	1	0	0	0	0	0	1	1	1	**6**
22.	1	1	0	0	0	0	0	0	0	1	1	**4**
23.	1	0	0	0	0	1	0	0	0	1	0	**3**

24.	0	1	0	0	0	0	0	0	1	1	0	**3**
25.	0	0	1	0	0	0	0	0	1	0	0	**2**
26.	0	0	1	0	0	0	0	1	1	0	0	**3**
27.	0	0	1	0	0	0	0	1	1	0	1	**4**
28.	0	0	0	0	0	0	0	1	1	1	1	**4**
29.	0	1	0	0	0	0	0	0	1	1	1	**4**
30.	0	1	0	0	0	1	0	1	0	1	0	**4**
31.	1	1	0	0	0	1	0	1	0	0	0	**4**
32.	1	0	0	0	0	1	0	1	0	0	0	**3**
33.	1	0	0	0	0	0	0	1	1	1	1	**5**
34.	1	0	0	0	0	0	0	1	1	1	1	**5**
35.	1	0	1	0	0	0	0	1	1	1	1	**6**
36.	1	0	1	0	0	0	0	0	0	0	0	**2**
37.	1	0	1	0	0	1	0	0	0	0	0	**3**
38.	0	0	1	0	0	1	0	1	0	0	0	**3**
39.	0	0	0	0	0	1	0	0	0	1	0	**2**
40.	0	1	0	0	0	1	0	0	0	1	0	**3**
41.	0	1	0	0	0	1	0	0	0	1	0	**3**
42.	0	1	1	0	0	1	0	1	0	0	0	**4**
43.	0	1	1	0	0	0	0	1	0	0	0	**3**
44.	0	0	1	0	0	1	0	1	0	0	1	**4**
45.	1	0	1	0	0	1	0	0	0	0	1	**4**
46.	1	0	0	0	0	1	0	1	0	0	1	**4**
47.	1	1	0	0	0	1	0	1	0	0	0	**4**
48.	1	1	0	0	0	1	0	1	0	0	0	**4**
49.	1	1	0	0	0	1	0	1	0	0	0	**4**
50.	1	1	0	0	0	1	0	1	0	0	0	**4**

51.	1	1	0	0	0	1	0	0	0	0	0	**3**
52.	1	0	0	0	0	1	0	0	0	0	1	**3**
53.	1	0	1	0	0	1	0	0	0	0	1	**4**
54.	0	1	1	0	0	0	0	0	0	0	1	**3**
55.	0	1	1	0	0	1	0	0	0	0	0	**3**
56.	0	1	1	0	0	1	0	0	0	0	1	**4**
57.	0	1	1	0	0	1	0	0	0	0	1	**4**
58.	0	1	1	0	0	0	0	0	0	1	1	**4**
59.	1	1	1	0	0	0	0	0	0	1	0	**4**
60.	1	1	1	0	0	1	0	0	0	1	0	**5**
61.	1	0	1	0	0	1	0	0	0	0	0	**3**
62.	1	0	1	0	0	1	0	0	0	0	0	**3**
63.	1	0	1	0	0	0	0	1	0	0	0	**3**
64.	0	1	1	0	0	0	0	1	0	0	0	**3**
65.	0	1	1	0	0	0	0	1	0	1	0	**4**
66.	0	1	1	0	0	0	0	0	0	1	0	**3**
67.	0	1	1	0	0	1	0	0	0	1	0	**4**
68.	0	1	1	0	0	1	0	0	0	0	0	**3**
69.	1	1	1	0	0	1	0	0	0	0	0	**4**
70.	1	1	1	0	0	1	0	0	0	0	0	**4**
71.	1	1	1	0	0	1	0	0	0	0	0	**4**
72.	1	0	1	0	0	1	0	0	0	0	0	**3**
73.	0	0	1	0	0	0	0	0	0	0	0	**1**
74.	0	0	1	0	0	0	0	1	0	0	0	**2**
75.	0	0	1	0	0	0	0	1	0	0	0	**2**
76.	0	0	1	0	0	0	0	1	0	0	0	**2**
77.	0	1	1	0	0	0	0	0	0	0	0	**2**

78.	0	1	0	0	0	0	0	1	0	0	0	**2**
79.	1	1	1	0	0	0	0	1	0	0	0	**4**
80.	1	1	1	0	0	0	0	1	0	0	1	**5**
81.	1	1	1	0	0	1	0	0	0	0	1	**5**
82.	1	1	1	0	0	1	0	1	0	0	1	**6**
83.	0	1	1	0	0	1	0	0	0	0	0	**3**
84.	0	0	0	0	0	1	0	0	0	0	0	**1**
85.	0	1	1	0	0	1	0	1	0	0	0	**4**
86.	0	0	0	0	0	1	0	1	0	0	0	**2**
87.	0	0	0	0	0	0	0	1	0	0	0	**1**
88.	0	1	0	0	0	0	0	1	0	0	0	**2**
89.	0	0	0	0	0	1	0	1	0	0	0	**2**
90.	0	0	0	0	0	1	0	0	0	1	0	**2**
91.	0	0	1	0	0	1	0	1	0	0	0	**3**
92.	0	0	1	0	0	1	0	1	0	0	0	**3**
93.	0	0	1	0	0	0	0	1	0	0	0	**2**
94.	0	0	1	0	0	0	0	0	0	0	0	**1**
95.	0	0	0	0	0	0	0	0	0	0	1	**1**
96.	0	0	0	0	0	0	0	0	0	0	0	**0**
97.	0	0	0	0	0	0	0	0	0	0	0	**0**
98.	0	0	0	0	0	0	0	0	0	0	0	**0**
99.	0	0	0	0	0	0	0	0	0	0	0	**0**
100.	0	0	0	0	0	0	0	0	0	0	0	**0**
Sum	**45**	**46**	**54**	**3**	**0**	**58**	**0**	**49**	**18**	**34**	**38**	

Table 12. Leiomyoma individuals with wild (represent :0) or mutant (represent :1) gene polymorphisms.

Case	ER-351	ER-397	CYP17	PROGIN	p53cod11	p53cod72	p53 cod 248	p21cod31	ACE2350	ACE-240	ACE I/D	Sum
1.	1	0	1	1	0	1	0	1	0	1	0	**6**
2.	1	0	0	1	0	1	0	0	0	1	1	**5**
3.	1	1	1	0	0	1	0	1	0	0	1	**6**
4.	1	1	1	0	0	1	0	0	1	0	1	**6**
5.	1	0	1	0	0	0	0	1	0	0	1	**4**
6.	1	1	0	0	0	1	0	0	0	1	1	**5**
7.	1	0	0	0	0	1	0	1	1	1	0	**5**
8.	1	0	0	0	0	0	0	1	0	1	1	**4**
9.	1	0	0	0	0	0	0	1	0	1	0	**3**
10.	0	0	1	1	0	0	0	0	1	0	1	**4**
11.	0	0	0	0	0	1	0	0	0	1	1	**3**
12.	0	0	0	0	0	1	0	1	0	1	1	**4**
13.	0	0	0	0	0	1	0	0	1	1	1	**4**
14.	0	0	0	0	0	0	0	1	0	1	1	**3**
15.	0	0	0	0	0	1	0	1	0	1	1	**4**
16.	0	0	0	0	0	0	0	1	1	1	1	**4**
17.	1	0	0	0	0	1	0	1	0	0	1	**4**
18.	1	1	0	0	0	1	0	1	0	0	1	**5**
19.	1	1	1	0	0	0	0	1	1	0	1	**6**
20.	1	0	1	0	0	1	0	0	1	0	1	**5**
21.	1	0	1	0	0	0	0	1	1	1	1	**6**
22.	1	1	0	0	0	0	0	0	0	1	1	**4**
23.	1	0	0	0	0	1	0	0	1	1	0	**4**

24.	0	1	0	0	0	0	0	1	1	1	0	**4**
25.	0	0	1	0	0	0	0	0	1	0	1	**3**
26.	0	0	1	0	0	0	0	1	1	0	0	**3**
27.	0	0	1	0	0	0	0	1	0	0	1	**3**
28.	0	0	0	0	0	0	0	1	0	1	1	**3**
29.	0	1	0	0	0	0	0	0	1	1	1	**4**
30.	0	1	0	0	0	1	0	1	0	1	1	**5**
31.	1	1	0	0	0	1	0	1	0	0	1	**5**
32.	1	0	0	0	0	1	0	1	0	0	1	**4**
33.	1	0	0	0	0	0	0	1	1	0	1	**4**
34.	1	0	0	0	0	0	0	1	1	0	1	**4**
35.	1	0	1	0	0	0	0	1	1	1	1	**6**
36.	1	0	1	0	0	0	0	0	0	0	0	**2**
37.	1	0	1	0	0	1	0	0	0	0	0	**3**
38.	0	0	1	0	0	1	0	1	0	0	0	**3**
39.	0	0	0	0	0	1	0	0	0	1	0	**2**
40.	0	1	0	0	0	1	0	0	0	1	0	**3**
41.	0	0	0	0	0	1	0	0	0	1	0	**2**
42.	0	0	1	0	0	0	0	1	0	0	0	**2**
43.	0	1	1	0	0	0	0	1	0	0	0	**3**
44.	0	0	1	0	0	0	0	1	0	0	1	**3**
45.	1	0	1	0	0	0	0	0	0	0	1	**3**
46.	1	0	0	0	0	1	0	1	0	0	1	**4**
47.	1	1	0	0	0	1	0	1	0	0	1	**5**
48.	1	1	0	0	0	1	0	1	0	0	1	**5**
49.	1	1	0	0	0	1	0	1	0	0	1	**5**
50.	1	1	0	0	0	1	0	1	0	0	1	**5**

51.	1	1	0	0	0	1	0	0	0	0	0	**3**
52.	1	0	0	0	0	1	0	0	0	0	1	**3**
53.	1	0	1	0	0	1	0	0	0	0	1	**4**
54.	0	1	1	0	0	0	0	0	0	0	1	**3**
55.	0	1	1	0	0	1	0	0	0	0	0	**3**
56.	0	1	1	0	0	1	0	0	0	0	1	**4**
57.	0	1	1	0	0	1	0	0	0	0	1	**4**
58.	0	1	1	0	0	0	0	0	0	1	1	**4**
59.	1	1	1	0	0	0	0	0	0	1	0	**4**
60.	1	1	1	0	0	1	0	0	0	1	0	**5**
61.	1	0	1	0	0	1	0	0	0	0	0	**3**
62.	1	0	1	0	0	1	0	0	0	0	0	**3**
63.	1	0	1	0	0	0	0	1	0	0	0	**3**
64.	0	1	1	0	0	0	0	1	0	0	0	**3**
65.	0	1	1	0	0	0	0	1	0	1	0	**4**
66.	0	1	1	0	0	0	0	0	0	1	0	**3**
67.	0	1	1	0	0	1	0	0	0	1	0	**4**
68.	0	1	1	0	0	1	0	0	0	0	0	**3**
69.	1	1	1	0	0	0	0	0	0	0	0	**3**
70.	1	1	1	0	0	1	0	0	0	0	1	**5**
71.	1	1	1	0	0	1	0	0	0	0	1	**5**
72.	1	0	1	0	0	1	0	0	0	0	1	**4**
73.	0	0	1	0	0	0	0	0	0	0	1	**2**
74.	0	0	1	0	0	0	0	1	0	0	0	**2**
75.	0	0	1	0	0	0	0	1	0	0	0	**2**
76.	0	0	1	0	0	0	0	1	0	0	0	**2**
77.	0	1	1	0	0	0	0	0	0	0	0	**2**

78.	0	1	1	0	0	0	0	1	0	0	0	**3**
79.	1	1	1	0	0	0	0	1	0	0	1	**5**
80.	1	1	1	0	0	0	0	1	0	0	1	**5**
81.	1	1	1	0	0	1	0	0	0	0	1	**5**
82.	1	1	1	0	0	0	0	1	0	0	1	**5**
83.	0	1	1	0	0	0	0	0	0	0	0	**2**
84.	0	0	0	0	0	0	0	0	0	0	0	**0**
85.	0	1	1	0	0	0	0	1	0	0	1	**4**
86.	0	0	0	0	0	1	0	1	0	0	1	**3**
87.	0	0	0	0	0	0	0	1	0	0	1	**2**
88.	0	1	0	0	0	0	0	1	0	0	1	**3**
89.	0	0	1	0	0	0	0	1	0	0	1	**3**
90.	0	0	1	0	0	1	0	0	0	1	0	**3**
91.	0	0	1	0	0	1	0	1	0	0	1	**4**
92.	0	0	1	0	0	1	0	1	0	0	1	**4**
93.	0	0	1	0	0	0	0	1	0	0	1	**3**
94.	0	0	1	0	0	0	0	0	0	0	1	**2**
95.	0	0	0	0	0	0	0	0	0	0	1	**1**
96.	0	0	1	0	0	0	0	1	0	0	1	**3**
97.	0	0	1	0	0	0	0	1	0	0	1	**3**
98.	0	0	1	0	0	0	0	0	0	0	1	**2**
99.	0	0	0	0	0	0	0	0	0	0	0	**0**
100.	0	0	0	0	0	0	0	0	0	0	0	**0**
Sum	**54**	**41**	**60**	**3**	**0**	**46**	**0**	**53**	**16**	**30**	**63**	

Table 13. Hyperprolactinemia individuals with wild (represent :0) or mutant (represent :1) gene polymorphisms.

Case	ER-351	ER-397	CYP17	PROGIN	ACE2350	ACE-240	ACE I/D	Sum
1.	1	0	1	1	0	1	0	**4**
2.	1	0	0	1	0	1	0	**3**
3.	1	0	1	0	0	0	1	**3**
4.	1	1	1	0	0	0	1	**4**
5.	1	0	1	0	0	0	1	**3**
6.	1	1	0	0	0	1	0	**3**
7.	1	0	0	0	1	1	0	**3**
8.	1	0	0	0	0	1	1	**3**
9.	1	0	0	0	0	1	0	**2**
10.	0	0	1	1	1	0	1	**4**
11.	0	0	0	0	0	1	1	**2**
12.	0	0	0	0	0	1	1	**2**
13.	0	0	0	0	1	1	1	**3**
14.	0	0	0	0	0	1	1	**2**
15.	0	0	0	0	0	1	1	**2**
16.	0	0	0	0	1	1	0	**2**
17.	1	0	0	0	0	0	1	**2**
18.	1	1	0	0	0	0	0	**2**
19.	1	1	1	0	0	0	0	**3**
20.	1	0	1	0	0	0	1	**3**
21.	1	0	1	0	1	1	0	**4**
22.	1	1	0	0	0	1	0	**3**
23.	1	0	0	0	1	1	0	**3**

24.	0	1	0	0	1	1	0	**4**
25.	0	0	1	0	1	0	1	**3**
26.	0	0	1	0	1	0	0	**3**
27.	0	0	1	0	0	0	1	**3**
28.	0	0	0	0	0	1	1	**3**
29.	0	1	0	0	1	1	1	**4**
30.	0	1	0	0	0	1	1	**5**
31.	1	1	0	0	0	0	1	**5**
32.	1	0	0	0	0	0	1	**4**
33.	1	0	0	0	1	0	1	**4**
34.	1	0	0	0	1	0	1	**4**
35.	1	0	1	0	1	1	1	**6**
36.	1	0	1	0	0	0	0	**2**
37.	1	0	1	0	0	0	0	**3**
38.	0	0	1	0	0	0	0	**3**
39.	0	0	0	0	0	1	0	**2**
40.	0	1	0	0	0	1	0	**3**
41.	0	0	0	0	0	1	0	**2**
42.	0	0	1	0	0	0	0	**2**
43.	0	1	1	0	0	0	0	**3**
44.	0	0	1	0	0	0	1	**3**
45.	1	0	1	0	0	0	1	**3**
46.	1	0	0	0	0	0	1	**4**
47.	1	1	0	0	0	0	1	**5**
48.	1	1	0	0	0	0	1	**5**
49.	1	1	0	0	0	0	1	**5**
50.	1	1	0	0	0	0	1	**5**

51.	1	1	0	0	0	0	0	**3**
52.	1	0	0	0	0	0	1	**3**
53.	1	0	1	0	0	0	1	**4**
54.	0	1	1	0	0	0	1	**3**
55.	0	1	1	0	0	0	0	**3**
56.	0	1	1	0	0	0	1	**4**
57.	0	1	1	0	0	0	1	**4**
58.	0	1	1	0	0	1	1	**4**
59.	1	1	1	0	0	1	0	**4**
60.	1	1	1	0	0	1	0	**5**
61.	1	0	1	0	0	0	0	**3**
62.	1	0	1	0	0	0	0	**3**
63.	1	0	1	0	0	0	0	**3**
64.	0	1	1	0	0	0	0	**3**
65.	0	1	1	0	0	1	0	**4**
66.	0	1	1	0	0	1	0	**3**
67.	0	1	1	0	0	1	0	**4**
68.	0	1	1	0	0	0	0	**3**
69.	1	1	1	0	0	0	0	**3**
70.	1	1	1	0	0	0	1	**5**
71.	1	1	1	0	0	0	1	**5**
72.	1	0	1	0	0	0	1	**4**
73.	0	0	1	0	0	0	1	**2**
74.	0	0	1	0	0	0	0	**2**
75.	0	0	1	0	0	0	0	**2**
76.	0	0	1	0	0	0	0	**2**
77.	0	1	1	0	0	0	0	**2**

78.	0	1	1	0	0	0	0	**3**
79.	1	1	1	0	0	0	1	**5**
80.	1	1	1	0	0	0	1	**5**
81.	1	1	1	0	0	0	1	**5**
82.	1	1	1	0	0	0	1	**5**
83.	0	1	1	0	0	0	0	**2**
84.	0	0	0	0	0	0	0	**0**
85.	0	1	1	0	0	0	1	**4**
86.	0	0	0	0	0	0	1	**3**
87.	0	0	0	0	0	0	1	**2**
88.	0	1	0	0	0	0	1	**3**
89.	0	0	1	0	0	0	1	**3**
90.	0	0	1	0	0	1	0	**3**
91.	0	0	1	0	0	0	1	**4**
92.	0	0	1	0	0	0	1	**4**
93.	0	0	1	0	0	0	1	**3**
94.	0	0	1	0	0	0	1	**2**
95.	0	0	0	0	0	0	1	**1**
96.	0	0	1	0	0	0	1	**3**
97.	0	0	1	0	0	0	1	**3**
98.	0	0	1	0	0	0	1	**2**
99.	0	0	0	0	0	0	0	**0**
100.	0	0	0	0	0	0	0	**0**
Sum	**45**	**38**	**57**	**10**	**12**	**31**	**47**	

Table 14. Controlled individuals with wild (represent :0) or mutant (represent :1) gene polymorphisms.

Case	ER-351	ER-397	CYP17	PROGIN	p53cod11	p53cod72	p53 cod 248	p21cod31	ACE2350	ACE-240	ACE I/D	Sum
1.	0	0	1	0	0	1	0	1	0	0	1	**4**
2.	0	1	1	0	0	0	0	0	0	0	1	**3**
3.	1	0	0	0	0	1	0	1	0	0	1	**4**
4.	0	0	0	0	0	0	0	1	0	0	1	**2**
5.	1	0	0	0	0	1	0	1	0	0	1	**4**
6.	1	0	1	0	0	0	0	0	0	1	1	**4**
7.	0	0	0	0	0	1	0	1	0	0	1	**3**
8.	0	1	1	0	0	1	0	0	1	0	0	**4**
9.	0	0	0	0	0	1	0	1	0	1	1	**4**
10.	0	0	0	0	0	0	0	0	0	0	1	**1**
11.	1	0	0	0	0	0	0	1	0	0	1	**3**
12.	0	1	0	0	0	1	0	0	0	0	1	**3**
13.	0	0	1	0	0	0	0	0	0	0	1	**2**
14.	0	0	0	0	0	1	0	1	0	0	1	**3**
15.	1	0	0	0	0	1	0	1	0	0	0	**3**
16.	1	0	1	0	0	0	0	0	0	1	1	**4**
17.	1	1	1	0	0	1	0	1	0	0	1	**6**
18.	0	1	0	0	0	0	0	1	0	1	0	**3**
19.	0	1	1	0	0	1	0	0	0	0	1	**4**
20.	0	0	1	0	0	0	0	1	0	0	1	**3**
21.	1	0	1	0	0	1	0	1	0	0	0	**4**
22.	1	0	0	1	0	0	0	1	0	1	0	**4**
23.	0	1	1	0	0	1	0	1	0	0	1	**5**
24.	0	1	1	0	0	0	0	1	0	0	1	**4**

25.	1	0	1	0	0	1	0	1	0	0	0	**4**
26.	1	0	0	0	0	0	0	0	0	0	0	**1**
27.	0	1	1	0	0	1	0	1	0	0	1	**5**
28.	0	0	0	0	0	0	0	1	0	1	1	**3**
29.	0	0	1	0	0	0	0	0	0	0	1	**2**
30.	1	0	1	0	0	0	0	0	0	0	1	**3**
31.	1	0	1	0	0	0	0	0	0	0	0	**2**
32.	0	1	0	0	0	0	0	0	0	0	1	**2**
33.	0	0	1	0	0	1	0	1	0	0	0	**3**
34.	1	0	1	0	0	1	0	1	0	0	1	**5**
35.	1	0	0	0	0	0	0	1	0	1	1	**4**
36.	0	1	1	0	0	1	0	0	0	0	1	**4**
37.	0	0	1	0	0	1	0	1	0	0	1	**4**
38.	0	0	1	0	0	1	0	0	0	0	0	**2**
39.	0	0	1	0	0	0	0	1	0	0	1	**3**
40.	0	0	0	0	0	1	0	0	0	0	1	**2**
41.	0	0	1	0	0	0	0	1	0	0	1	**3**
42.	0	1	0	0	0	1	0	0	0	0	0	**2**
43.	0	1	1	0	0	0	0	1	0	0	0	**3**
44.	1	0	1	0	0	0	0	1	0	0	0	**3**
45.	1	0	1	0	0	1	0	0	0	0	1	**4**
46.	0	0	1	0	0	0	0	0	0	0	1	**2**
47.	0	0	1	0	0	1	0	0	0	0	1	**3**
48.	0	0	0	0	0	0	0	1	0	1	1	**3**
49.	1	1	0	0	0	1	0	1	0	0	1	**5**
50.	1	0	1	0	0	0	0	1	0	0	1	**4**
51.	0	0	1	0	0	0	0	0	0	0	0	**1**

52.	0	0	1	0	0	0	0	0	0	0	1	**2**
53.	0	0	0	0	0	0	0	1	0	0	0	**1**
54.	0	0	0	0	0	0	0	1	0	0	0	**1**
55.	0	0	1	0	0	1	0	0	1	0	1	**4**
56.	1	0	1	0	0	0	0	0	0	0	1	**3**
57.	1	0	0	0	0	1	0	0	0	0	1	**3**
58.	0	0	0	0	0	0	0	1	0	0	0	**1**
59.	0	0	1	0	0	0	0	1	0	0	1	**3**
60.	1	1	0	0	0	0	0	1	0	0	1	**4**
61.	0	0	1	0	0	0	0	0	0	1	1	**3**
62.	0	0	1	0	0	0	0	1	0	0	1	**3**
63.	1	1	0	0	0	1	0	1	0	0	1	**5**
64.	1	1	1	0	0	0	0	0	0	0	1	**4**
65.	0	0	1	0	0	1	0	0	0	0	1	**3**
66.	1	1	1	0	0	0	0	0	0	0	0	**3**
67.	1	0	1	0	0	0	0	1	0	0	0	**3**
68.	0	0	1	0	0	0	0	1	0	0	1	**3**
69.	0	0	1	0	0	0	0	1	0	0	1	**3**
70.	0	1	1	0	0	0	0	0	0	0	1	**3**
71.	0	0	1	0	0	1	0	1	0	0	1	**4**
72.	0	0	1	0	0	1	0	1	0	0	1	**4**
73.	0	1	1	0	0	0	0	1	0	1	1	**5**
74.	0	0	0	0	0	1	0	1	0	0	0	**2**
75.	0	0	0	0	0	0	0	0	0	1	1	**2**
76.	1	0	1	1	0	1	0	0	0	0	1	**5**
77.	1	0	1	0	0	1	0	0	0	0	1	**4**
78.	0	0	1	0	0	0	0	1	0	0	0	**2**

79.	1	0	1	0	0	0	0	1	0	0	0	**3**
80.	0	1	0	0	0	1	0	1	0	0	1	**4**
81.	0	0	1	0	0	0	0	0	0	1	1	**3**
82.	0	1	1	0	0	1	0	1	0	1	1	**6**
83.	1	1	0	0	0	0	0	1	0	1	1	**5**
84.	1	1	1	0	0	1	0	1	0	1	1	**7**
85.	1	1	1	0	0	1	0	0	0	0	0	**4**
86.	0	0	0	0	0	1	0	0	0	0	1	**2**
87.	0	0	1	0	0	0	0	0	0	0	1	**2**
88.	0	0	0	0	0	0	0	1	0	0	1	**2**
89.	1	0	1	0	0	0	0	1	0	0	0	**3**
90.	0	0	0	0	0	0	0	0	0	0	1	**1**
91.	1	0	0	0	0	1	0	1	0	1	1	**5**
92.	0	0	0	0	0	0	0	1	0	0	0	**1**
93.	0	0	1	0	0	1	0	1	0	0	1	**4**
94.	0	0	1	0	0	0	0	0	0	0	1	**2**
95.	0	0	0	0	0	0	0	1	0	0	1	**2**
96.	0	1	0	0	0	1	0	1	0	0	1	**4**
97.	0	0	1	0	0	0	0	0	0	0	1	**2**
98.	0	0	1	0	0	1	0	0	0	0	1	**3**
99.	0	0	1	0	0	1	0	0	0	1	1	**4**
100.	0	0	1	0	0	0	0	0	0	1	1	**3**
Sum	**34**	**26**	**63**	**2**	**0**	**44**	**0**	**57**	**2**	**18**	**75**	

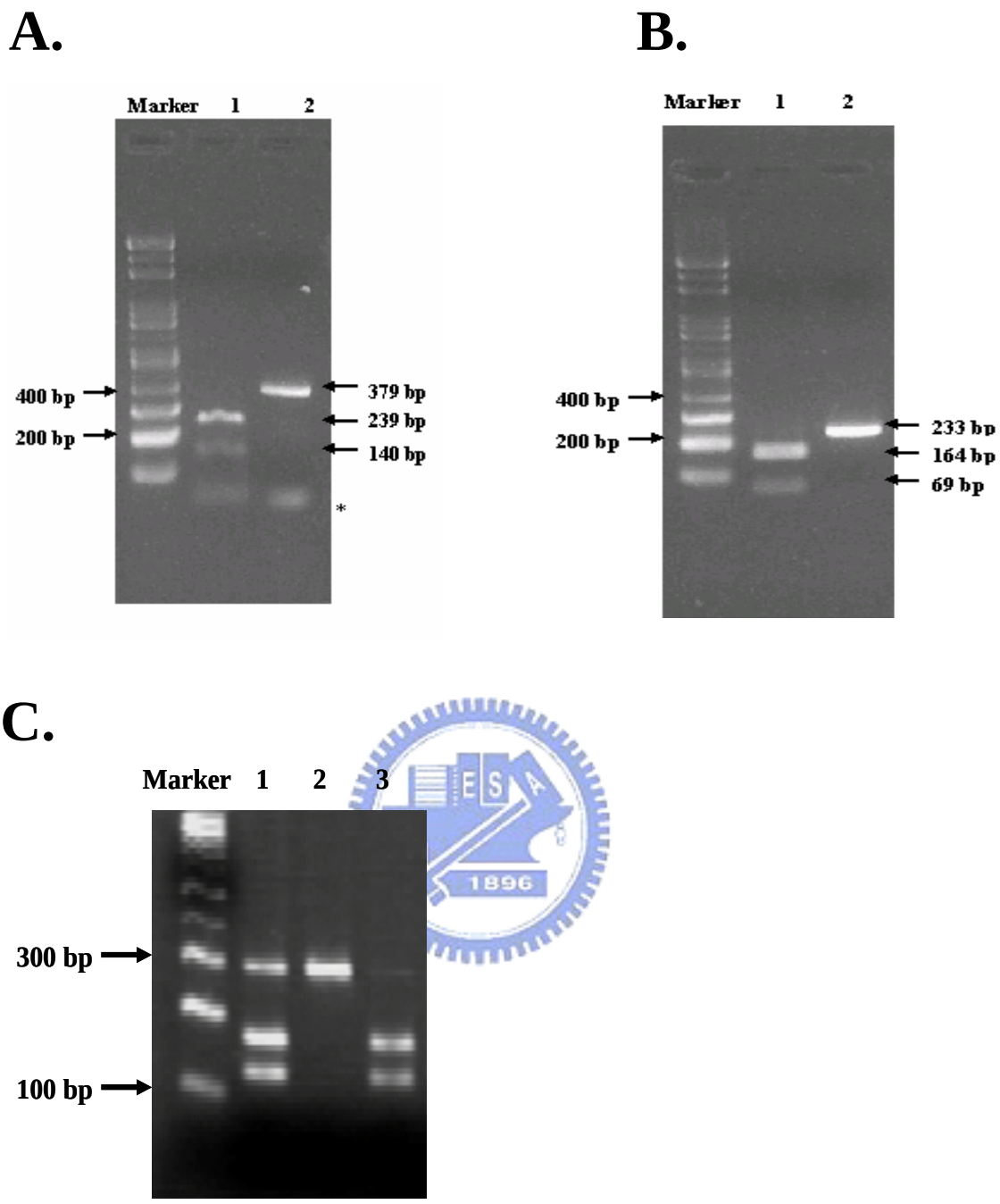

Figure 1. Polymorphism of p53 codon 11, 72, and 248. (**A)** Electrophoresis of p53 codon 11 (marker 1. Glu homozygote; 2. Gln/Lys heterozygote) (*signals from non-complete reaction of the primers). (**B)** Electrophoresis of p53 codon 72 (marker 1. Arg/Pro heterozygosity; 2. Arg homozygosity; 3. Pro homozygosity). (**C)** Electrophoresis of p53 codon 248 (marker 1. Trp/Gln heterozygosity; 2. Arg homozygosity).

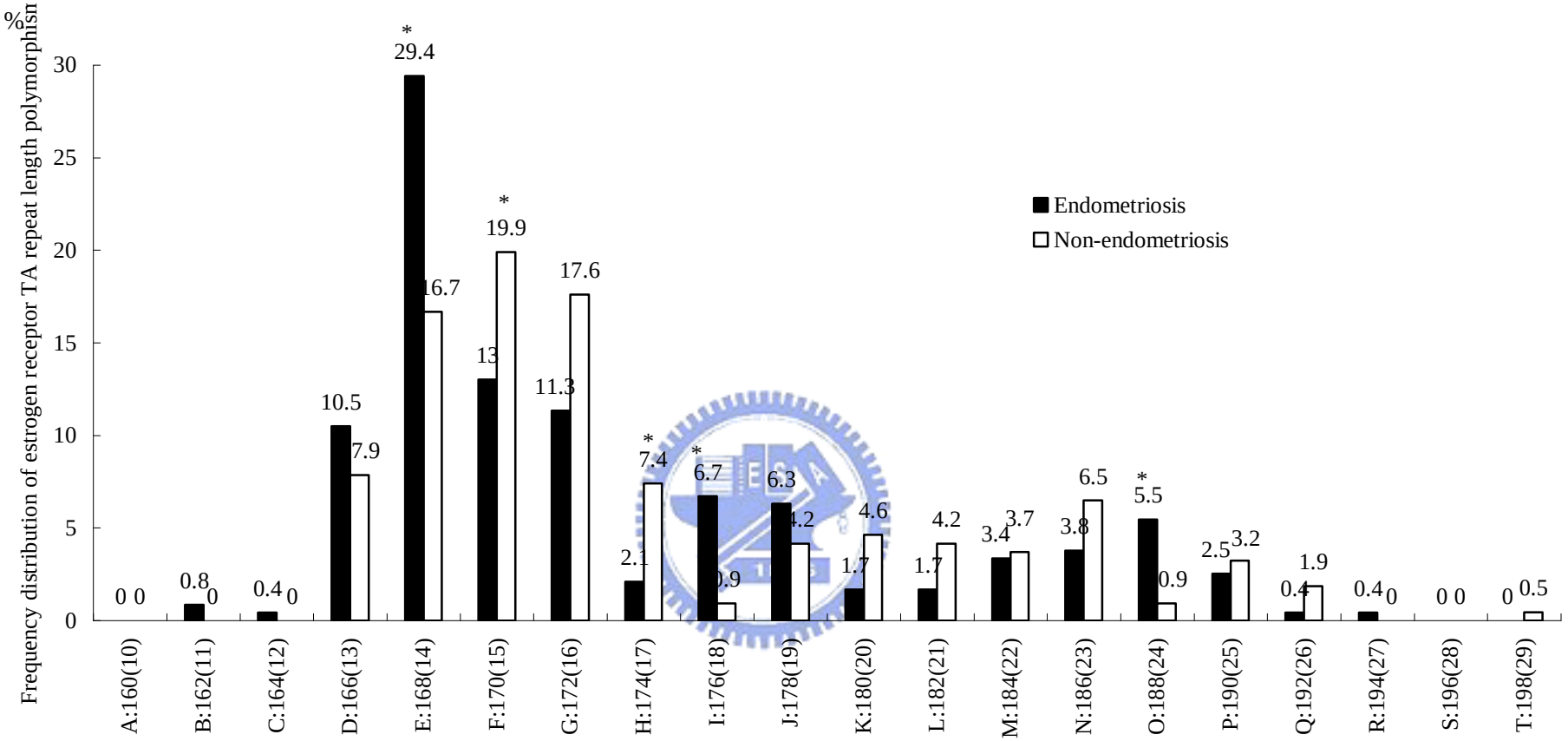

Figure 2. Frequency distributions of TA repeat polymorphism for estrogen receptor in patients with and without endometriosis. The PCR products ranged in length from 160 bp (10 repeats, genotype A) to 198 bp (27 repeats, genotype T) (*difference existed in the genotype between both groups) (The logistic regression method was used in the analyses of all genotypes. The Fisher's exact test was used in the analyses of genotype B, C, O, P, Q, R, and T.)

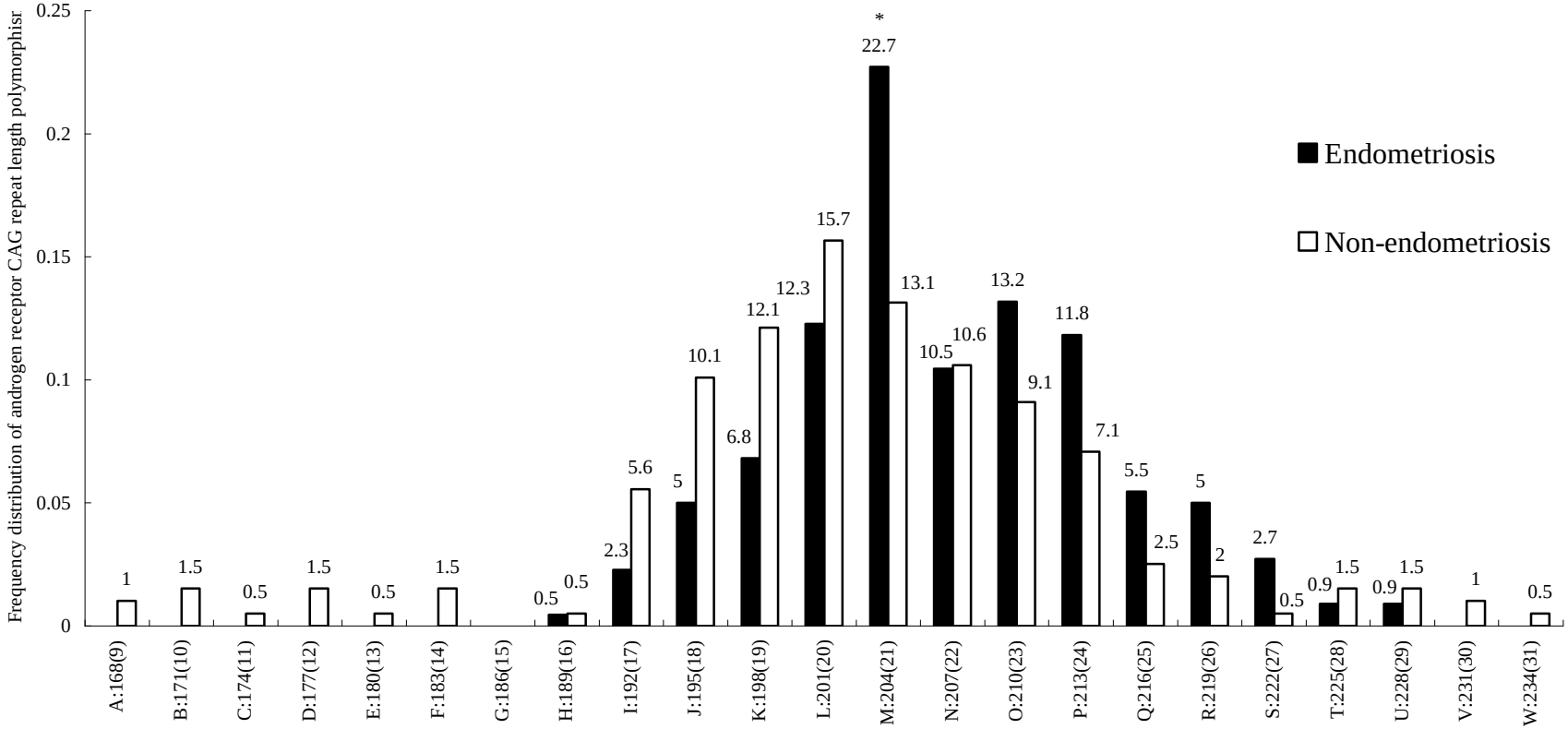

Figure 3. Frequency distributions of androgen receptor CAG repeat length polymorphism in patients with endometriosis (n=110) and without endometriosis (n=99). The PCR products ranged in length from 168 bp (9 CAG repeats, genotype A) to 234 bp (31 CAG repeats, genotype W). The number demonstrates the percentage of individual genotype in each group (*difference existed in the genotype M between both groups). (The Fisher's exact test was used in the analyses of genotype A, B, C, D, E, F, H, S, T, U, V, and W. The χ^2 test were used in the analyses of genotype I, J, K, L, M, N, O, P, Q, and R).

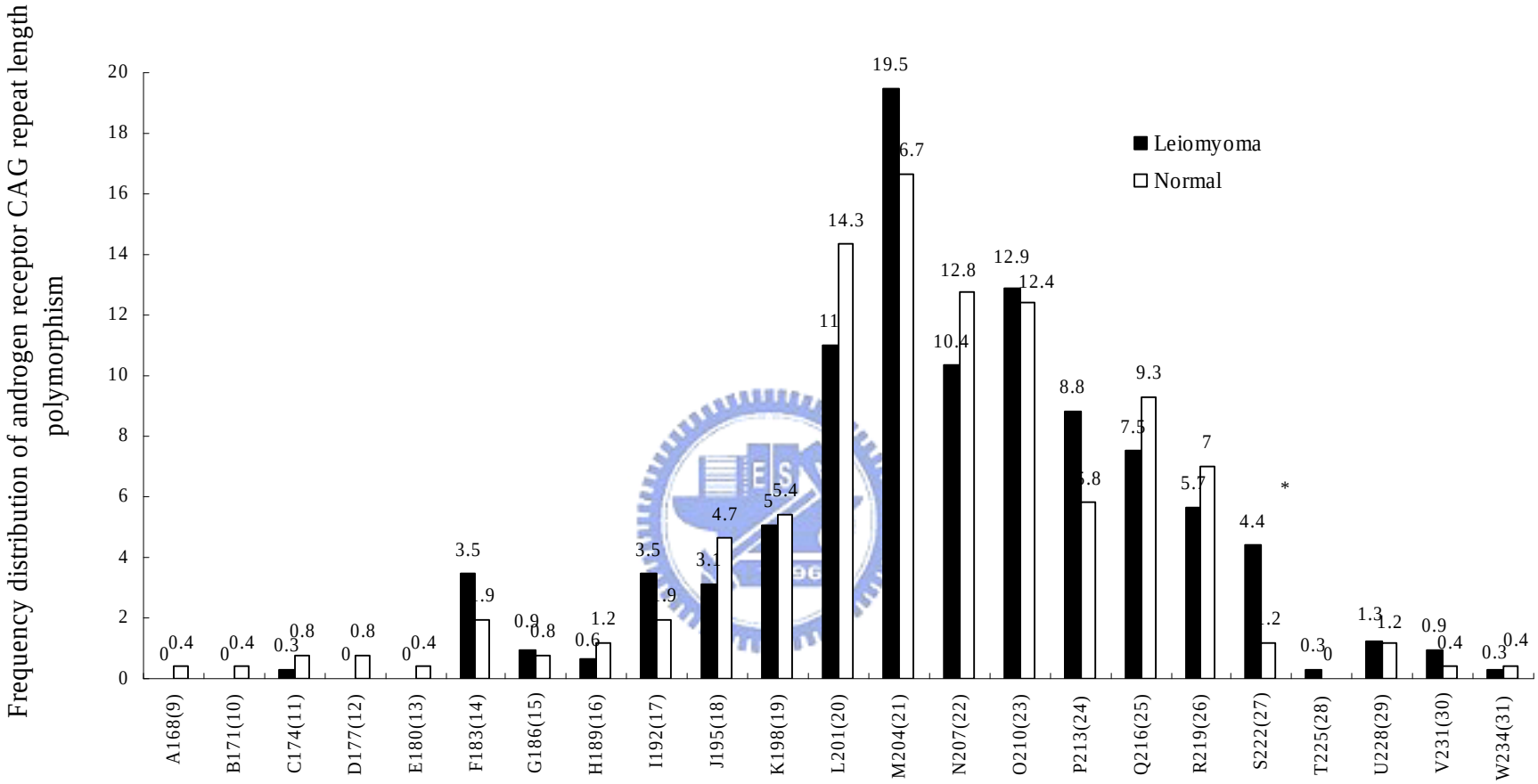

Figure 4. Frequency distributions of androgen receptor CAG repeat length polymorphism in patients with leiomyoma (n=159) and without leiomyoma (n=129). The PCR products ranged in length from 168 bp (9 CAG repeats, genotype A) to 234 bp (31 CAG repeats, genotype W). The number demonstrates the percentage of individual genotype in each group (*difference existed in the genotypes between both groups).

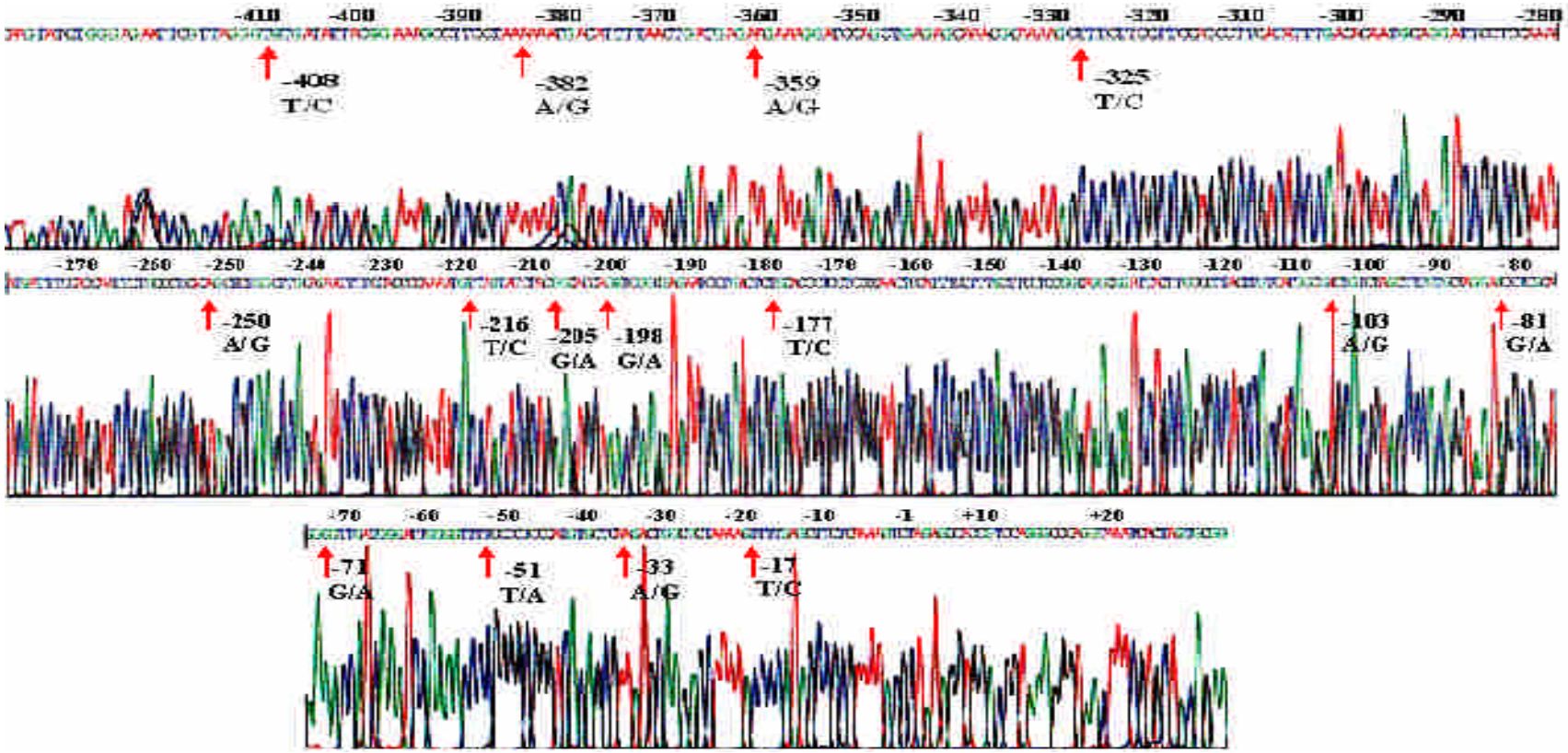

Figure 5. A total of 15 sequence variations identified in the p53 promoter region. These SNP located at -408 T/C, -382 A/G, -359 A/G, -325 T/C, -250 A/G, -216 T/C, -205 G/A, -198 G/A, -177 T/C, -103 A/G, -81 G/A, -71 G/A, -51 T/A, -33 A/G and -17 T/C.

Figure 6. Four single nucleotide polymophisms (-250 A/G, -216 T/C, -103 A/G, and -33 A/G) were identified within the promoter region of p53 gen

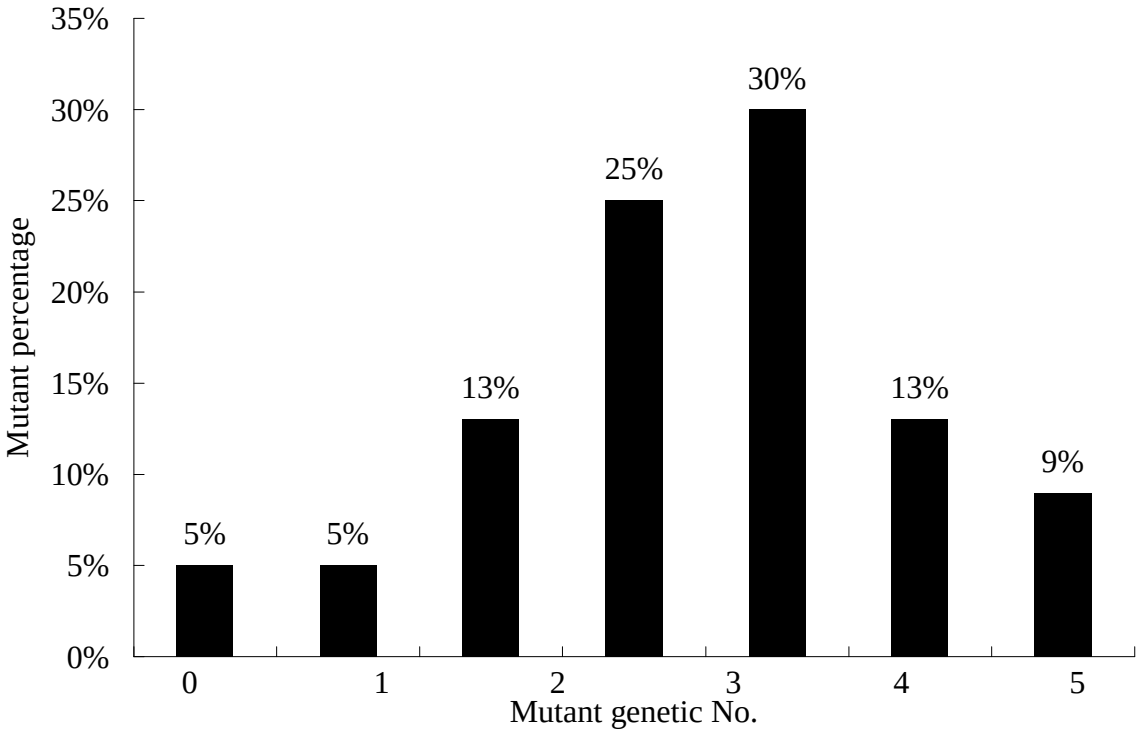

Figure 7. Distributions of cases numbers for endometriosis patients with different mutant genetic numbers

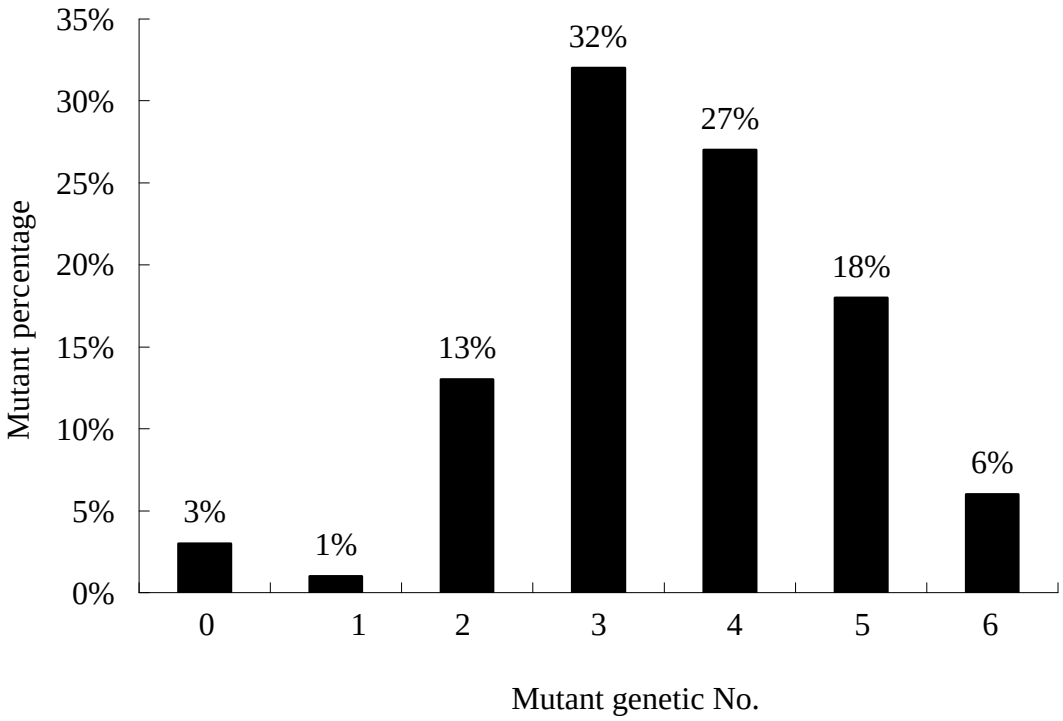

Figure 8. Distributions of cases numbers for leiomyoma patients with different mutant genetic numbers.

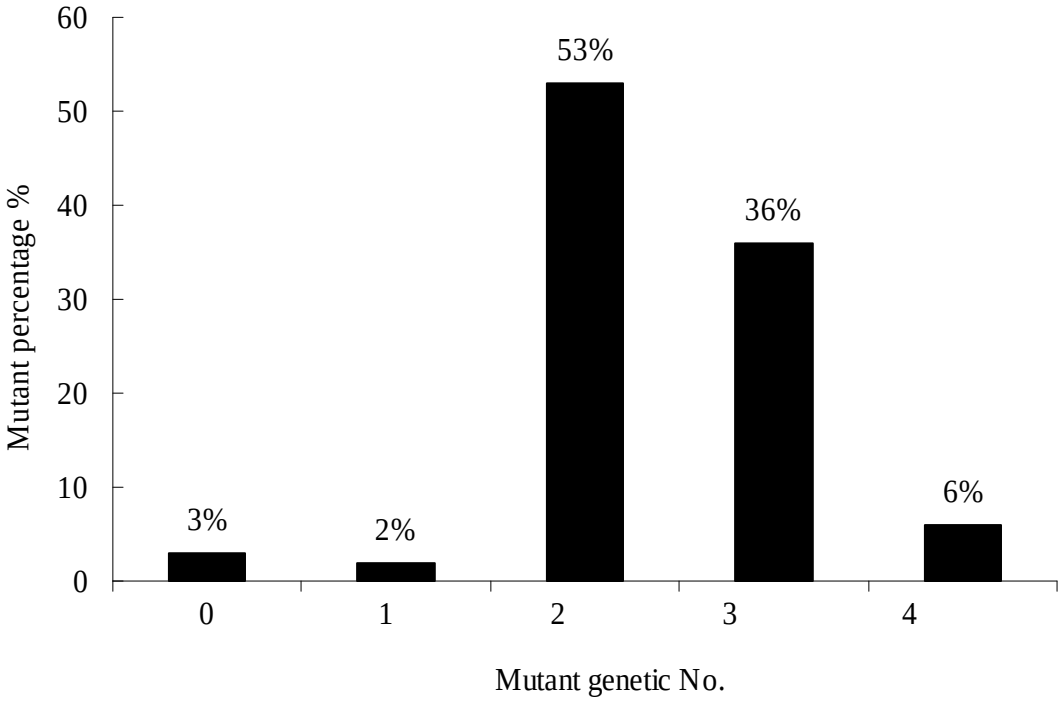

Figure 9. Distributions of cases numbers for hyperprolactinemia patients with different mutant genetic numbers.

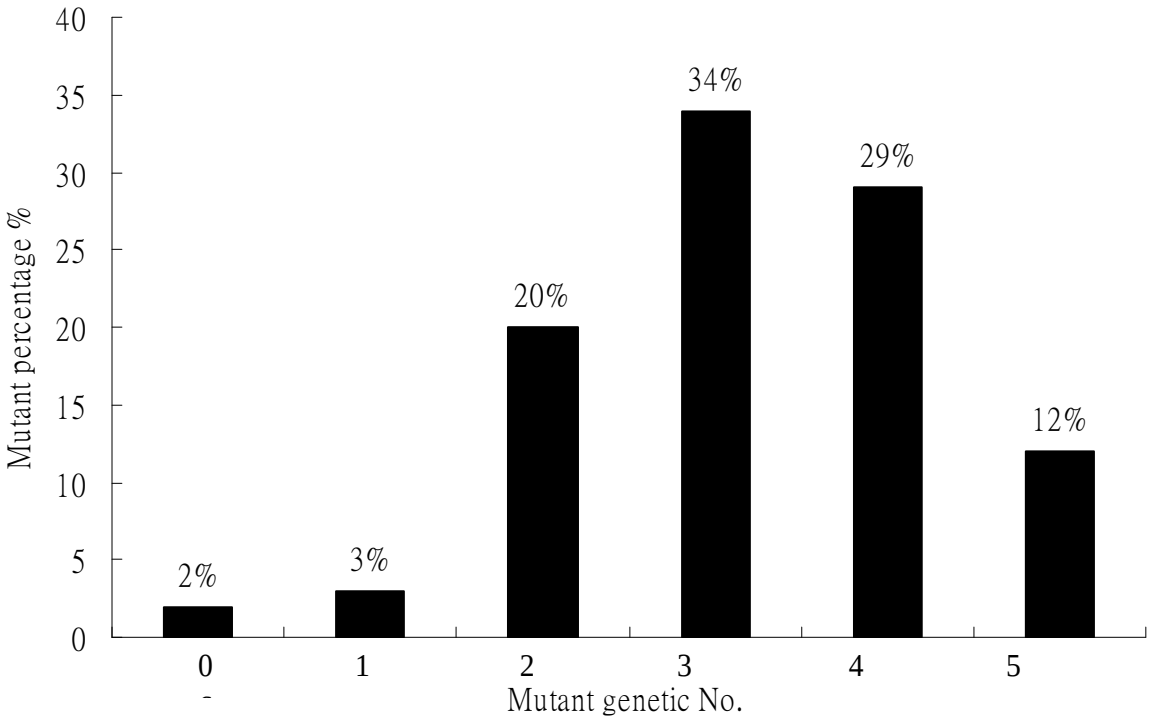

Figure 10. Distributions of cases numbers for controls with different mutant genetic numbers

自　　傳

謝耀元 學經歷

生日：58 年 6 月 24 日

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90, 91，92，94，95 年度國科會研究計畫主持人

89 年度國度國科會研究計畫共同主持人

89,90,91 年度連續獲得國科會研究獎勵金

發表論文共計 90 餘篇，包括 SCI/MI 級論文共計 80 餘篇

我，謝耀元，年三十八歲，祖籍台灣屏東，成長於小康之家，父母均為教師，自幼父母對我之課業要求頗為嚴格，亦提供我音樂美術與諸多才藝之廣泛性學習，造就我日後對於諸多藝術活動之喜好與廣泛之興趣，國小畢業後，隻身前往台南天主教學校黎明中學就學，初中畢業後考取台南一中，仍選擇直升母校高中部，歷經三年辛苦研習，於畢業那年應屆考取中國醫藥大學醫學系。大學時代匆促而短暫，畢業後選擇母校之附設醫院婦產科研習，於住院醫師期間，開始廣泛涉獵相關期刊，亦開始接受醫學研究之啟蒙，完成數篇報告於國際級重要期刊，於住院醫師開始研習不孕生殖科技，學習日新月異之胚胎臨床技術，並發表多篇研究論文於不孕症界重量級期刊(Fertil Steril)中。

本人深感在醫學研究計畫日趨龐大複雜之年代，研究之執行除研究方向，慨念，相關技術之完備之外，仍須相當多研究人員與環境之配合，一位有前瞻性之研究人員除了努力充實自我外，亦應屏除成見以誠懇虛心之態度與其他研究團隊進行互補性之交流與合作，因此於主治醫師階段，開始申請並多次主持執行國科會研究計畫，專注於基礎與臨床醫學之合併研究，亦充分與院內醫師與院外研究團隊進行緊密之合作，四年之住院醫師訓練結束，於研究員醫師那一年順利考取中國醫藥大學臨床醫學研究所，研究所研習期間接受指導教授吳介信與林志生老師之基因轉殖治療概念，完成基因轉植老鼠子宮內膜之研究實驗。數年期間發表數十餘篇 SCI/MI 級之研究論文，發表於國際期刊中。

最後我深深的感謝承蒙指導老師林志生教授的提拔，使我有機會在從事臨床醫療時也可以進一步接受研究所博士班之基礎研究訓練，學習獨立思考的能力、研究計畫的擬定和分子生物的實驗方法及認識各種研究工具。感謝林志生教授在分子生物的頃囊相授，開啟了我對知識探求方法的一扇門。指導及啟發我實驗方法的構思；使我對於此一有更深一層之了解。感謝我的家人，於臨床研究方面給予我百分之百之支持，並照顧好我的家庭使我無後顧之憂，蔡鴻德教授，吳介信教授，蔡輔仁教授在學術領域上所給我諸多協助於有關婦產科學與人工生殖科技的一切知識，勇敢面對與解決問題。