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Current Approach to Genetic Causes of Female Infertility and Genetic Counseling

Kadın İnfertilitesinin Genetik Nedenlerine Güncel Yaklaşım ve Genetik Danışmanlık

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ABSTRACT

Infertility is a disease of the male or female reproductive system and is defined as the inability to achieve pregnancy after 12 months or more of regular and unprotected sexual intercourse. Data shows that more than 186 million people worldwide are infertile. About 10% of the women of reproductive age are unable to conceive or maintain a pregnancy. In this study, the causes of female infertility were reviewed under several headings and the importance of genetic counseling in infertility was also mentioned. There are many different causes of female infertility, including both genetic and non-genetic causes. In this review, current developments and approaches in the genetic etiology of female infertility were reviewed under six main headings, chromosomal abnormalities, female genital system disorders, hypogonadotropic hypogonadism, primary ovarian failure, polycystic ovary syndrome, and gonadal dysgenesis. Also, the role of genetic counseling in these diseases was discussed. The aim of genetic counseling is to inform people with a hereditary disease or at high risk of carrying it about the course of the disease and treatment methods, and also to guide future generations and family members about their risks. After all tests and examinations, genetic counseling has a very important place in reproductive health.
Keywords: Female; genetics; infertility; genetic counseling.

ÖZ

İnfertilite, erkek veya kadın üreme sisteminin bir hastalığı olup, 12 ay veya daha uzun süre düzenli ve korunmasız cinsel ilişkiden sonra gebelik elde edilememesi olarak tanımlanır. Veriler, dünya çapında 186 milyondan fazla insanın infertil olduğunu göstermektedir. Üreme çağındaki kadınların yaklaşık %10'u gebe kalamaz veya hamileliğini sürdüremez. Bu çalışmada kadın infertilitesinin nedenleri çeşitli başlıklar altında incelenmiş ve ayrıca infertilitede genetik danışmanlığın önemine de değinilmiştir. Kadın infertilitesinin hem genetik ve hem de genetik olmayan nedenler de dahil olmak üzere birçok farklı nedeni vardır. Bu derlemede kadın infertilitesinin genetik etiyolojisindeki güncel gelişmeler ve yaklaşımlar, kromozom anomalileri, kadın genital sistem bozuklukları, hipogonadotropik hipogonadizm, primer over yetmezliği, polikistik over sendromu ve gonadal disgenezi olmak üzere altı ana başlık altında incelenmiştir. Ayrıca bu hastalıklarda genetik danışmanlığın rolü de tartışılmıştır. Genetik danışmanlığın amacı, kalıtsal bir hastalığı olan veya taşıyıcı olma riski yüksek olan kişileri hastalığın seyri ve tedavi yöntemleri hakkında bilgilendirmek, aynı zamanda gelecek nesillere ve aile bireylerine de riskleri konusunda rehberlik etmektir. Tüm test ve tetkiklerden sonra, üreme sağlığında genetik danışmanlık çok önemli bir yere sahiptir.
Anahtar kelimeler: Kadın; genetik; infertilite; genetik danışmanlık.

INTRODUCTION

Infertility is a disease of the male or female reproductive system and is defined as the inability to achieve pregnancy after 12 months or more of regular and unprotected sexual intercourse (1). Infertility has been an important medical, religious, political, and social problem since the existence of humanity. Data show that 48 million couples and 186 million people worldwide have infertility. About 10% of women of reproductive age are unable to conceive or maintain a pregnancy to term (2). Although infertility is a disease of both gender, most fertility tests and treatments have been applied to females due to infertility has been almost synonymous with women for centuries (3). Only women were blamed for not being able to have children and especially in societies where children are emotionally valued, this has always created a feeling of shame or guilt in women due to reproductive failure and it has been very rare for males to be cited as the reason. Therefore, significant efforts have been made to achieve pregnancy, and the female body has always been the center of attention (4).

Genetic counseling is an educational process that aims to provide patients and their relatives at risk of development with recent genomic information about the consequences of the disease, the risk of developing the disease, the preventability of this risk, and the methods of prevention or treatment (5).

In this study, we gathered the causes of female infertility under several headings and mentioned the importance of genetic counseling in infertility.

The causes of infertility have been investigated for centuries by learning the physiology and pathology of the female reproductive system. Embryology of the female reproductive system and oogenesis should be reviewed in order to understand the cause of infertility.

EMBRYOLOGY OF THE FEMALE REPRODUCTIVE SYSTEM DEVELOPMENT

The chromosome effect on the developing gonad is uncertain, regardless of whether it is XX or XY up to the sixth week of gonadal development; this stage is also known as the indifferent stage. By the sixth week of development, primordial germ cells develop into the epiblast migrate from their previous extraembryonic position to the lateral part of the genital ridges, and are surrounded by sex cords to form a pair of primitive gonads there. Since females do not have a Y chromosome, the gonad begins to develop in the direction of the ovary in a process that starts in the eighth week of pregnancy and continues for a few weeks. During this period, the cortex develops, the medullary structure shows regression, and the oogonia begin to develop into the follicular cell. About the third month of intrauterine development, oogonia enter meiosis I and remains in this stage until puberty.

The absence of testis and Y chromosome in the female embryo results in the absence of Anti-Müllerian hormone (AMH) and thus, the Müllerian duct develops from the nephrogenic ridge lateral to the genital protrusions. This canal gives the beginning of the fallopian tubes, the uterus, and the upper third of the vagina. The lower 2/3 of the vagina develops from synovaginal bulbs. In the absence of a testicle (or more specifically, in the absence of androgens), the female external genitalia (clitoris, labia major, and labia minora) develop from the genital tubercle regardless of the presence or absence of an ovary (6,7).

Oogenesis

Gametes originate from primitive germ cells that form in the epiblast during the second week of pregnancy and migrate to the yolk sac. Oogenesis is the process of transforming oogonia into mature oocytes, which can be examined in two parts, prenatal and postnatal (8).

Prenatal Period

Oogonia are reproduced continuously by mitosis in the gonadal prominences. Meanwhile, some of them enter the 1st meiotic division; remain in the prophase, and develop into primary oocytes. The oocytes are surrounded by squamous epithelial cells and are defined as primordial follicles. A newborn female has primordial follicles and primary oocytes. All of these oocytes remain in the prophase of the first meiosis and do not complete the first meiosis until puberty. They remain at this stage due to the oocyte maturation inhibitory (OMI) factor, which is secreted from the follicle epithelial cells. By puberty, some of these follicles undergo atresia and only 400,000 of them reach puberty.

Postnatal Period

Approximately 15-20 of the primordial follicles that reach puberty begin to mature in each ovarian cycle under the influence of follicle stimulating hormone (FSH) and form the primary follicle. Usually, only one of the primary follicles develops into a mature follicle. In the process of maturation, it goes through the secondary and tertiary follicle stages, respectively. The oocyte is expelled by ovulation as a tertiary follicle (Graaf's follicle). The secondary oocyte which completes the first meiosis just before ovulation, begins the second meiotic division and remains at the metaphase. The oocyte completes the second meiosis only if fertilization occurs. A menstrual cycle is crucial for human reproduction as it is required for oocyte selection, maturation, and ovulation in preparation for fertilization and subsequent pregnancy. The median menstrual cycle has two distinct ovarian phases; the follicular and luteal phases that are separated by ovulation. After these consecutive stages, fertilization usually takes place in the ampulla of the fallopian tubes (9).

CAUSES OF FEMALE INFERTILITY

There are many distinct causes of female infertility, including both genetic and non-genetic reasons. In this review, current developments and approaches in the genetic etiology of female infertility are reviewed in six main headings, which are: chromosomal abnormalities, female genital system disorders, hypogonadotropic hypogonadism, primary ovarian failure, polycystic ovary syndrome (PCOS), and gonadal dysgenesis. Chromosomal abnormalities are the most common disorders among the genetic causes that cause infertility.

Chromosomal Abnormalities

The frequency of chromosomal abnormalities, including chromosomal polymorphisms, is relatively high, which has been found in 1.3-15.0% of couples failing to conceive. The incidence of chromosomal anomalies in women is 10.0% (10). Since ova are prone to genetic changes due to aging, the risk of chromosomal abnormality

increases with maternal age. Besides aging, environmental factors and lifestyle can also affect the pathogenesis of chromosomal abnormalities (11).

Chromosomal abnormalities are classified as numerical and structural, and numerical abnormalities are the most common chromosomal abnormalities which are divided into two groups, aneuploidy, and polyploidy. Chromosomal aneuploidy is the most common identified cause of spontaneous abortion and developmental errors in humans. Aneuploidies generally occur during oogenesis and are generally subdivided into two groups, trisomy, and monosomy (11).

Triple X syndrome (47,XXX) is a sex chromosome aneuploidy which is the most common chromosomal abnormality in females with an additional X chromosome. It is usually not inherited and is mainly caused by the non-segregation of chromosomes during maternal meiosis. However, an additional X chromosome, seen in almost 20% of cases and caused by post-zygotic segregation, is seen in only some cells of the affected individuals, resulting in 46,XX/47,XXX mosaicism. Therefore, mosaic cases are usually fertile with milder clinical manifestations and have offspring with normal chromosome numbers. Females with triple X syndrome have a rapid increase in height until puberty due to the extra *SHOX* gene. In some cases, primary infertility is accompanied by tall stature, congenital urogenital anomalies, premature ovarian insufficiency (POI), amenorrhea, and early menopause (11).

Turner syndrome (TS), also known as monosomy X, occurs when the X chromosome is partially or completely missed in females. Its main clinical manifestations include growth disorders, reproductive system abnormalities, cardiovascular abnormalities, and autoimmune diseases (12). Females with TS have an extremely high risk for POI and infertility. Although approximately 70-80% of affected individuals do not have spontaneous pubertal development and 90% have primary amenorrhea, the remaining individuals may have a small remnant of ovarian follicles at birth or in early childhood (13). Various karyotype findings are seen in cytogenetic analyzes performed in TS cases. About 40-50% of affected females have the karyotype 45,X; 15-25% have mosaicism (45,X/46,XX); 20% have isochromosomes, and a small percentage of them have ring X chromosomes. In addition, 10-12% of women also have varying amounts of Y chromosome material (14).

Structural chromosomal abnormalities are classified into two groups: balanced and unbalanced abnormalities. Since there is no segment loss in balanced chromosomal abnormalities, it does not cause a phenotypical change or disease at the balanced abnormality carrier. However, individuals with this balanced chromosomal abnormality can form unstable gametes due to segmental loss or gains and cause disease in subsequent generations (14).

Chromosome deletion is an abnormality in which a segment of the chromosome is deleted. The length of the deleted region affects the number of genes deleted and the severity of the predicted phenotype. Chromosomal deletions affecting the sex chromosomes will most likely impair reproductive development. Deletion in X chromosomes can cause defective chromosomal synapses, meiotic arrest, as well as POI, gonadal dysgenesis, and infertility (14).

Chromosomal duplications occur when a region of the chromosome is duplicated. As the gene dose increases in the affected area, the amount of protein also produced increases, and the increased protein dose may cause toxic effects. Because embryogenesis is controlled by balanced protein levels, additional gene copies can impair gametogenesis and fetal development (15).

The ring chromosome is formed by breaking both ends of the chromosomes and joining these broken ends. It is rarely inherited and is usually lost during cell division. However, if passed on to the next generation, it can form new rings that coexist with the normal cell line in the offspring. This can result in a mosaic karyotype. Women with ring chromosome may have subfertility and low ovarian reserve (15).

Female Genital System Disorders

The mammalian female reproductive system; fallopian tubes, uterus, cervix, and upper part of the vagina develop from the Mullerian ducts. Defects during the development of Mullerian structures can lead to varying severity of congenital defects in the female genital tract (2).

Abnormalities in the female reproductive system can be classified as agenesis, atresia and embryologically abnormal septation of the fallopian tubes, uterus, cervix, or vagina originating from the Mullerian duct. A few genes are well defined, which affect the development of the Mullerian duct (2).

Heterozygous sequence variants, deletions and expansions in the polyadenosine tail of the *HOXA13* gene are well-known causes of the hand-foot-genital syndrome, which is characterized by a fusion of Mullerian structure and uterine malformations with extremity anomalies (16).

Abnormal expression of HOXA11-AS1 antisense RNA (a long non-coding RNA) and rare variants in other Homeobox A family genes (*HOXA10* and *HOXA11*) have been identified in individuals with sporadic uterine malformations, and in infertile women with endometriosis (2).

Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome, also called Mullerian agenesis, is the second most common cause of primary amenorrhea. It is characterized by congenital absence of the uterus, cervix, and upper part of the vagina in phenotypically normal 46,XX females. The incidence of MRKH syndrome is approximately 1 in 4,500-5,000 newborn females and is generally divided into two subtypes: MRKH type 1, in which only the upper vagina, cervix, and uterus are affected and MRKH type 2, which is associated with comorbidities. MRKH type 2 usually includes Mullerian renal cervical somite (MURCS), characterized by cervix-thoracic defects as well as malformations affecting the kidney and skeletal systems. The association of abnormalities in Mullerian duct development with defects in other organs indicates disruption of pathways involved in the embryonic development of structures derived from the intermediate mesoderm (17).

The etiology of MRKH syndrome is unclear and conflicting; most cases are sporadic, however, several reports of familial clustering suggest a genetic cause (17). These cases of familial clustering appear to occur by autosomal dominant inheritance with incomplete penetrance and variable expressivity. Investigations based

on these cases have subsequently been directed to certain candidate genes (18). Defects in the *LHX1*, *HNF1β*, *TBX6*, *HOX* (Hoxa9-13 and Hoxb9-13), *SHOX*, *WNT* (*WNT4*, *WNT9B*, and *WNT7*), *MMP14*, and *LRP10* genes are some of the possible causes (17). *WNT4* mutations are associated with Mullerian aplasia, hyperandrogenism, and renal malformations due to failure to suppress androgens in the ovary (18). Mutations in *HNF1β* (also known as *TCF2*) have been associated with maturity-onset diabetes of the young renal dysfunction and Mullerian aplasia (18). *WNT7A* mutations have recently been recognized as causing Al-Awadi/Raas-Rothschild/Schinzel phocomelia syndrome; which is characterized by several limb deformities beside the uterine hypoplasias/aplasia (18).

Nik-Zainal et al. (19) identified three microdeletions at 16p11.2, 17q12, and 22q11.2 that were significantly more frequent in the syndromic Mullerian aplasia case population compared to a healthy control group. *TBX6*, an important gene in paraxial mesoderm development, is located on 16p11.2, while 17q12 covers the genes *HNF1β* and *LHX1*.

Endometriosis is another anatomical cause of female infertility. In a study conducted in Japan, it was shown that the rs10965235 SNP of the *CDKN2B-AS* gene may be associated with the development of endometriosis. Hypermethylation of the promoter region of the gene may also be associated with endometriosis (20). In addition *WNT4*, *NFE2L3*, *HOXA10*, growth-regulating estrogen receptor binding 1 (*GREB1*), *ID4*, and *VEZT* genes are associated with endometriosis (20-22). In addition, *AMH* gene polymorphism has been associated with endometriosis-associated infertility (23).

Hypogonadotropic Hypogonadism

Hypogonadotropic hypogonadism is a rare disease characterized by a decrease in the release of gonadotrophin releasing hormone (GnRH) or disruption of its function (24,25). This disease is often manifested by underdevelopment of puberty and infertility. Hypogonadotropic hypogonadism is a genetic heterogeneous disease with more than 25 identified genes, which has both sporadic and familial cases. The most commonly affected genes are *ANOS1* (*KAL1*), *SOX10*, *IL17RD*, *FGFR1*, *CHD7*, *PROKR2*, *GHRHR*, *FGF8*, and *WDR11* (24). Kallmann syndrome includes a significant part of patients with hypogonadotropic hypogonadism with anosmia, a characteristic feature (24,26). The presence of anosmia should alert clinicians to possible congenital hypogonadotropic hypogonadism (CHH), and molecular genetic testing in affected patients may facilitate diagnosis (24).

Primary Ovarian Failure

Primary ovarian failure, known as early ovarian failure or early menopause, is defined as the termination of menstruation before the expected age of menopause. The expected age of menopause is defined as before the age of 40, and the diagnosis is confirmed by a high level of FSH. About 1% of women are affected by POI before the age of 40, and 0.1% before the age of 30 (27,28). Necessary tests should be performed for TS, triple X, and Fragile X premutation carriage, which are the genetic conditions that most often cause this condition in a patient with primary ovarian failure (29).

FMR1 is an mRNA-binding protein that regulates translation. CGG premutation at 5'UTR of the *FMR1* gene increases mRNA expression in females, and the *FMR1* protein is overexpressed in neuron and granulosa cells, which leads to premature ovarian failure and infertility. *FMR1* premutation carriage frequency is 1/150-300 (24), while *FMR1* premutation carriage is detected in 2% to 15% of women with isolated POI, and in 14% to 20% of women with familial POI (29).

Triple X, the other sex chromosome aneuploidy that causes POI, is a chromosomal anomaly that occurs in about one of 1,000 females due to maternal meiosis nondisjunction error, which advanced maternal age is an important risk factor (29). Although there are no structural and functional pathologies in the reproductive system, POI is frequently observed in triple X patients (30). It is thought that genes that escape from X inactivation in patients with triple X syndrome may cause POI (31). Although most patients with triple X syndrome can achieve pregnancy, the prevalence of sex chromosome anomaly, genitourinary system anomaly, neural tube defects, and cardiac malformation is high compared to the healthy population (31,32).

There are many examples of other syndromic diseases that occur with POI, such as galactosemia, Perrault syndrome, ataxia telangiectasia, and McKusick-Kaufman syndrome. Also, many studies have shown that DNA repair genes are associated with follicle maturation-follicle quality, reproductive aging, and the age of onset of menopause. Fanconi anemia, Warsaw fracture syndrome, ataxia telangiectasia, and xeroderma pigmentosum are examples (24,33,34).

Polycystic Ovary Syndrome

PCOS is an endocrinopathy characterized by increased ovarian androgen biosynthesis, anovulation, and infertility (34,35). It is the most common form of female infertility, affecting about 10% of women of reproductive age. It is associated with high pregnancy loss rates despite low pregnancy rates (33). PCOS has a significant hereditary component based on familial clustering and twin studies. Studies have shown that the risk of developing PCOS in daughters of women with PCOS is five times higher than in a healthy society (36). Similarly, it has been observed that PCOS disease develops in approximately 60-70% of the daughters of women with PCOS (37). PCOS-related candidate genes (*DENND1A*, *LHCGR*, *FSHR*, *ZNF217*, *YAP1*, *INSR*, *RAB5B*, *C9orf3*) have been identified via genome-wide association studies. Some recent studies about the expression of miRNAs have shown that there is a difference between women whit PCOS and healthy women, and the plasma miRNA may play an important role in the formation and development of PCOS (34).

Gonadal Dysgenesis

Gonadal dysgenesis is a genetic defect that causes a complete or partial loss of gonadal development during fertilization or the early embryonic development period (34). 46,XY complete gonadal dysgenesis (Swyer's syndrome) is a sexual differentiation disorder with a female phenotype. The vagina, uterus, and fallopian tube are developed in the female gender in a hypoplaztic manner. The gonads consist of fibrous stroma, also usually there is no breast development (37,38). The phenotypic

difference between complete and incomplete gonadal dysgenesis depends on the level of differentiation of the testicular tissue and the production of testosterone and AMH by the fetal testicle (37).

The *SRY* gene encodes the testis specific testis determining factor (TDF), which plays an important role in sexual differentiation and development in males. About 15% of Swyer's syndrome has an *SRY* gene mutation associated with the high mobility group (HMG) box on the Y chromosome (34,37). It is thought that Y chromosome structural changes and *DHH*, *MAP3*, *DEC1*, *SOX9*, *GATA4*, *AR*, *DMRT1*, *DMRT2*, *NROB1*, *FOG2*, *WT1*, *NR5A1* genes may be associated with other causes of the syndrome (37,38).

WHAT IS THE ROLE OF GENETIC COUNSELING IN FEMALE INFERTILITY?

The aim of genetic counseling is to provide information about the progress of the disease and treatment methods for people with a hereditary disease or at high risk of carrying it, as well as to guide the next generation and family members about the risks of recurrence through to anamnesis and pedigree analysis. The purpose of a medical geneticist is to ensure the understanding of the information about the disease by the family accurately and completely and to offer solutions. In reproductive health, the most important indications for genetic counseling are infertility and recurrent pregnancy losses such as stillbirths, miscarriages, and premature infant deaths. Advanced maternal age due to a higher risk of aneuploidy, neural tube defects, the presence of ultrasound-identified soft markers, and elevated risk in maternal serum screening are the other main indication for genetic testing for reproductive genetics. Also, being a carrier of a certain genetic condition (for example, balanced chromosomal rearrangements), an affected first child or family history of mental retardation, chromosomal abnormalities, congenital malformations such as cleft palate, neural tube defects, or congenital heart defects; single-gene disorders, subfertility or a wide range of different genetic disorders should be considered as important indications for genetic counseling. Premarital counseling or preconception counseling is recommended for couples with a higher probability of genetic disorders, especially for consanguineous couples (39).

Karyotype analysis is always recommended as a first step genetic test when considering that chromosomal disorders significantly affect fertility and miscarriage risk. Patients with reciprocal translocations or any other structural chromosomal abnormality have a significantly increased risk of infertility, including primary or secondary amenorrhoea or hypogonadotropic hypogonadism with oligomenorrhea. Balanced rearrangements do not cause health problems for their carriers as they do not cause loss or duplication of genetic material, but can lead to gametes in which genetic information is unbalanced, thus causing infertility or multiple miscarriages (39). Some abnormalities, such as the triple X karyotype, could not be clearly associated with infertility. The primary cause of fertility loss in individuals with TS is thought to be accelerated germ cell loss and impaired folliculogenesis in fetal life.

However, depending on the percentage of cells with 46,XX karyotype remaining in the ovaries, although spontaneous puberty and pregnancy may occur in some individuals, pregnancy cannot be completed in these individuals. This situation is due to the insufficiency of the endometrium and uterus (40).

Unlike male infertility, little is known about the genetic basis of female infertility. Therefore, first tier tests are recommended to determine chromosomal disorders; and specific or single-gene tests are less approved in infertile women. Isolated infertility due to genetic causes is rare; more commonly, syndromic diseases cause female infertility. Currently, genetic tests are mainly used for patients with POI, chromosomal abnormalities, and *FMR1* premutation carriers (41).

Females with a normal karyotype produce a variable percentage of oocytes with chromosomal abnormalities because of crossing-over and/or meiotic nondisjunction errors. The three main groups of abnormalities are 45X, trisomy, and polyploidy. These abnormalities are associated with advanced maternal age. While applying assisted reproductive technology (ART), gametes or embryos are analyzed with preimplantation genetic testing (PGT), and healthy gametes or embryos can be obtained. Aneuploid embryos need to be screened, and only euploid embryos are transferred to increase the chances of healthy pregnancies (41).

MRKH syndrome is considered a multifactorial condition caused by both genetic and environmental factors during embryonic development, resulting in a range of phenotypes and severities. Most studies have been conducted in small groups without analyzing unaffected relatives. Ultimately the etiology of MRKH syndrome has not been clearly elucidated, and it is difficult to demonstrate the roles of identified candidate gene variants in impairing urogenital development or differentiation. For the individual affected by MRKH syndrome and their relatives, a multidisciplinary approach is required. Recent discoveries, including whole genome/exome sequencing and genome editing, have contributed to the identification of molecular factors regulating the development of Mullerian ducts, characterizing their roles, and facilitating the clinical diagnosis of MRKH syndrome (42).

CHH has a heterogeneous clinical phenotype and genetic background. Genetic data on hypogonadotropic hypogonadism is increasing with the increasing use of next-generation sequencing (NGS), but these results must be interpreted correctly in clinical practice. According to recent data, in more than 50% of cases, the disease-causing genetic changes can be found via NGS. In analyses with NGS-based methods, variants of unknown significance can be difficult to interpret. Proving the disease-causing effects of potential candidate genes and variants may be possible through extensive clinical genotype-phenotype studies and in vitro or in vivo animal experiments. Another major challenge in CHH is to distinguish accurate oligogenic inheritance from incidental findings unrelated to CHH. It can be difficult to determine the inheritance pattern due to non-complete penetrance and variable expressivity besides the oligogenicity. This could be a struggling issue for genetic counselors. However, over time, with increasing genetic data associated with clinical information, CHH will be deciphered, and variant interpretation will be easier (43).

FMR1 gene is one of the well-known genes related to POI. Therefore, it is necessary to analyze the *FMR1* gene in women presenting signs of ovarian dysfunction of unknown cause. This would also be useful for detecting intermediate and premutation alleles that lead to a mutation and thus fragile X syndrome. In addition, detection of these alleles among young women allows for genetic counseling necessary for planning their reproductive lives, taking into account possible ovarian dysfunction (44).

CONCLUSION

Genomic medicine applications require multidisciplinary applications in current approaches At Medical Genetics High-Risk Polyclinics, each patient is evaluated with detailed family history as well as clinical findings. The necessary genetic tests are selected with effective genetic counseling, and preventive medicine is applied by determining other family members who are at risk besides the patients.

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