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Screening of Premature Ovarian Insufficiency-Associated Genes in Turkish Patients

Türk Hastalarda Prematür Over Yetmezliği ile İlişkili Genlerin Taranması

Emine İkbal ATLI, Hakan GÜRKAN, Sinem YALÇINTEPE, Selma DEMİR, Hazal SEZGİNER GÜLER, Drenushe ZHURİ, Engin ATLI, Koray ELTER, Sinan ATEŞ

Trakya University Faculty of Medicine, Department of Medical Genetics, Edirne, Türkiye

ABSTRACT

Aim: Infertility is primarily caused by premature ovarian insufficiency (POI). Since multiple genes have been linked to the genetic foundation of POI, the genetic investigation of the condition needs to be a component of the clinical diagnosis. Analyzing the genetic background of POI in a Turkish cohort was the goal of our investigation.

Materials and Methods: The onset age ranged from 18 to 39 years old. Every patient was prescreened for the most common POI-associated fragile-X premutation premutation and had the karyotype 46,XX. Next-generation sequencing (NGS) of 26 genes previously linked to POI was performed on 68 unrelated individuals from Türkiye in order to detect genetic changes.

Results: We examined the DNA samples of 68 unrelated POI patients in order to use targeted panel sequencing to find possible causal variations of the disease. Three POI-related genes in our sample had three heterozygous variants of unclear significance and one heterozygous potentially pathogenic gene. These variants were related to 3 genes: *Newborn ovary homeobox (NOBOX),* GDF9 and STAG3.

Conclusion: POI is distinguished by a complex genetic background with an increasing number of genes and diverse phenotypic traits. This is the first genetic epidemiology study in Türkiye focusing on the effects of 26 genes related to POI. Among the variations we detected in our patient group, the variation we detected in the *STAG3* gene has not been reported before. Two separate variations were detected in the *NOBOX* gene in two patients. Finally, one variation was detected in the *GDF9* gene. The variation in the *STAG3* gene was classified as likely pathogenic. The variations in the *NOBOX* and *GDF6* genes are classified as of unknown clinical significance. Due to the intricate network governing human folliculogenesis, individual patients exhibit significant phenotypic diversity, necessitating the development of NGS sequencing methods to aid in POI diagnosis.

Keywords: Premature ovarian insufficiency, genetic investigation, next-generation sequencing

ÖZ

Amaç: İnfertilite esas olarak prematür over yetmezliğinden (POI) kaynaklanır. POI'nin genetik temelinde birden fazla gen bulunduğundan, durumun genetik incelemesi klinik tanının bir bileşeni olmalıdır. Araştırmamızın amacı, POI'nin genetik geçmişini bir Türk kohortunda analiz etmekti. **Gereç ve Yöntem:** Başlangıç yaşı 18 ila 39 arasında değişen hastalar çalışmaya dahil edildi. Her hasta POI ile ilişkili Frajil X ön mutasyonu premutasyonu için önceden tarandı ve karyotipler 46,XX idi. Genetik değişiklikleri tespit etmek için POI ile bağlantılı 26 genin yeni nesil dizilemesi (NGS) aralarında akrabalık bulunmayan 68 bireyde gerçekleştirildi.

Bulgular: Hastalığın olası nedensel varyasyonlarını bulmak için hedefli panel dizilemesini kullanmak amacıyla 68 akrabalık ilişkisi bulunmayan POI hastasının DNA örneklerini inceledik. Hasta grubunda POI ile ilişkili 3 gende 3 heterozigot klinik önemi bilinmeyen varyant ve bir heterozigot olası patojenik varyasyon saptanmıştır. Bu varyantlar 3 genle ilişkiliydi: *Yenidoğan yumurtalık homeoboks geni* (*NOBOX),* GDF9 ve STAG3.

Sonuç: POI, giderek artan sayıda gen ve çeşitli fenotipik özelliklerle karmaşık bir genetik geçmişe sahiptir. Bu, POI ile ilgili 26 adet genin etkisine odaklanan Türkiye'nin ilk genetik epidemiyoloji çalışmasıdır. Hasta grubumuzda tespit ettiğimiz varyasyonlar arasında, *STAG3* geninde tespit ettiğimiz varyasyon daha önce bildirilmemiştir. *NOBOX* geninde 2 hastada 2 ayrı varyasyon saptanmıştır. Son olarak *GDF9* geninde bir adet varyasyon

Address for Correspondence: Emine İkbal ATLI MD, Trakya University Faculty of Medicine, Department of Medical Genetics, Edirne, Türkiye
E-mail: emine.ikbal@gmail.com **ORCID ID:** orcid.org/0000-0001-9003-1449
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saptanmıştır. STAG3 genindeki varyasyon olası patojenik olarak sınıflandırılmıştır. *NOBOX* ve GDF6 genlerindeki varyasyonlar klinik önemi bilinmeyen sınıfında yer almaktadır. İnsan folikülogenezini yöneten karmaşık ağ nedeniyle, bireysel hastalar önemli fenotipik çeşitlilik göstermektedir ve bu durum POI tanısına yardımcı olmak için dizileme yöntemlerinin geliştirilmesini gerekli kılmaktadır. NGS taramasının kapsamını daha önce infertilite ile ilişkilendirilen genleri de kapsayacak şekilde genişletmek, POI için daha kesin, hızlı ve uygun fiyatlı genetik tanılamalara olanak sağlayabilir. Hastaların genomik analizi klinik karar almada yardımcı olabilir ve yaklaşan klinik denemeler ve tedaviler için kapıyı açabilir.

Anahtar Kelimeler: Prematüre over yetmezliği, genetik araştırma, yeni nesil dizileme

INTRODUCTION

Premature ovarian insufficiency (POI), also referred to as premature ovarian failure, denotes the cessation of ovarian function before the age of 40 years. By the end of the 2000s, the term POI was adopted to describe this condition of premature ovarian ageing more accurately. This terminology highlights that women with this dysfunction may occasionally experience spontaneous follicular development, the return of menses, and even conception following the diagnosis[1,2]. POI is characterized by the depletion of ovarian follicles, leading to infertility before the age of 40 years, and presents with a diverse range of clinical phenotypes[3]. This condition is defined by the absence of menses (amenorrhea or oligomenorrhea) for a minimum of four months, elevated gonadotropin levels [follicle-stimulating hormone (FSH) > luteinizing hormone], and hypoestrogenism[4]. Primary amenorrhea, typically identified early in life in individuals with delayed puberty, absent breast development, and menarche, can be the first warning sign. The most common POI phenotype, secondary amenorrhea, however, manifests between the ages of 20 years and 40 years and is characterized by an irregular menstrual cycle followed by amenorrhea alongside normal pubertal development[3]. The studies showed that the global overall prevalence of POI among women was 3.5%. By subgroup analysis, the prevalence of POI among women with iatrogenic etiology was 11.2%, followed by autoimmunity (10.5%); the prevalence of POI by region was 11.3% at the highest in North America followed by South America (5.4%); and the prevalence of POI was 5.3% in a developing country, higher than 3.1% in a developed country. The trend of prevalence of POI over the past 20 years was on the rise (although $p>0.05$)[5].

Genetic flaws, autoimmune disorders, iatrogenic causes (such as chemotherapy or radiation therapy), viral infections, poisons, or even idiopathic conditions can all contribute to POI[5].

Nonetheless, many impacted women have a positive family history. POI with various genetic etiologies may suggest a hereditary status of the cases[6]. Surgical, medical, infectious or autoimmune ovarian damages are the other well-known reasons for POI[7].

Regarding genetic factors, the POI phenotype can be instigated by chromosomal abnormalities and monogenic disorders. Following the confirmation of a clinical diagnosis of POI, chromosome analysis, fragile-X premutation (FMR1) testing, evaluation of thyroid and adrenal (21-hydroxylase) antibodies, and pelvic ultrasonography should all be performed[3]. Approximately 10-13% of individuals exhibit chromosomal abnormalities[8]. In terms of chromosomal origins, X-chromosome abnormalities account for 12% of POI cases. These abnormalities encompass monosomy, trisomy, deletions, duplications, and X-autosome translocations[9]. Critical X chromosomal regions potentially correlating with POI have been identified through cytogenetic studies. POI has been associated with deletions in the Xq21.3-q27 region or X-autosome translocations in the Xq13.3-q21.1 region. Additionally, POI has been linked to the deletion of the p arm of the X chromosome. Cytogenetic analysis can be utilized to evaluate karyotypes for numerical alterations, and various methods, including array comparative genomic hybridization, have been developed to identify copy number variants within the context of POI[10].

Furthermore, expanding a cytosine-guanine-guanine repeat in the 5′ regulatory region of the *FMR1* gene, which results in Fragile-X syndrome, may also contribute to syndromic POI. Since the *FMR1* premutation is linked to POI in approximately 20% of affected women, its presence in those diagnosed with POI should be investigated[11]. Microdeletions in the *FMR2* gene may also significantly contribute to POI, as suggested by another study[12]. Most cases of POI remain without a clear underlying cause; however, this screening might be useful in identifying the etiology of POI. Genetic disorders involved include not only Turner syndrome and *FMR1* gene premutation, but also monogenic disorders. Karyotype analysis is insufficient to resolve all cases of POI due to low resolution. Since *FMR1* gene premutation analysis can only resolve some of the cases (3% to 15% of cases of POI), monogenic gene analysis appears to be the most accurate method choice[13]. Therefore, monogenic analysis should be the next step if the tests do not provide any positive findings substantiating the POI diagnosis.

Given that the intricate network governing human folliculogenesis leads to significant phenotypic variance in POI syndrome with a diverse genetic etiology, NGS analysis could offer a more accurate, rapid, and cost-effective genetic diagnosis for POI[14-2]. Furthermore, a theory positing oligogenic

origins for this condition has been proposed, highlighting the necessity for multigene panel sequencing[15,16]. Previous studies suggest that these genes may be clustered in the POI1 and POI2 loci on the female sex chromosome[17]. It is suggested that several X- and autosome-encoded genes are critical candidates for POI, as they may play a role in human folliculogenesis. A more effective diagnostic pathway could be developed by further investigating their functional contributions to the genetic etiology of POI in clinical settings.

Our understanding of the genetic causes of idiopathic POI has significantly increased in the Next-generation sequencing (NGS) era. Numerous novel pathogenic variants of well-known genes [*FSHR, GDF9, BMP15, FIGLA*, and *Newborn ovary homeobox (NOBOX*)] have been linked to POI through high-throughput sequencing approaches[3]. Due to their roles in sex chromosome remodeling, metabolism, autoimmune associations, meiosis and DNA repair, oogenesis, folliculogenesis, hormone signaling, and germ cell development, these genes have been proposed to play a part in the etiology of POI. Furthermore, extensive genomic research paves the way for discovering additional gene variants underlying currently unknown POI. Our expanding knowledge may lead to more promising results when analyzing the genetic makeup of POI patients and may unveil new pathways for discovering potential treatments for women with POI. This is the only comprehensive genomic investigation to date on Turkish POI patients that utilizes the potential of the NGS method.

MATERIALS AND METHODS

Subjects

Sixty-eight Turkish-unrelated patients diagnosed with POI, who experienced amenorrhea for at least six months before the age of 40 years and had FSH plasma levels exceeding 40 IU/L, were recruited. The age of onset ranged from 18 to 39 years. Each patient underwent an *FMR1* molecular analysis and had at least 20 cells karyotyped. We excluded patients found to have Turner syndrome based on the karyotype or any other karyotype abnormality, as well as patients with a FMR1 premutation. Patients who previously underwent a gonadotoxic treatment (chemotherapy or pelvic radiation) or extensive ovarian surgery were also excluded from the study. NGS analysis was performed after all these exclusion criteria were met. Each patient signed a paper granting informed consent. The local ethics committee approved the study. All procedures performed in the study involving human participants were approved by the Ethics Committee for Scientific Research, Faculty of Medicine, Trakya University (decision no: TÜTF-BAEK 2018/319, date: 01.10.2018) and followed the Declaration of Helsinki. Targeted panel sequencing was performed on 68 POI patients (P01∼P68).

Targeted Panel Sequencing

Our goal has been to cover every known POI risk locus. Based on information from the literature, a list of 26 genes under investigation was compiled (Table 1).

Sixty-eight samples were sequenced using the QIAseq Targeted DNA Custom Panel (Qiagen, Hilden, Germany). Two milliliters (2 mL) of peripheral blood were collected and preserved in anticoagulation tubes. Genomic DNA was isolated from peripheral whole blood using the EZ1 DNA Investigator Kit (Qiagen, Hilden, Germany). After DNA extraction, target sequences were enriched using customized capture probe chips (Illumina, San Diego, CA). This kit included 26 genes associated with the disease. Libraries covering the target genes were prepared according to the QIAseq Targeted DNA Panel Protocol (Qiagen, Hilden, Germany). Following the target enrichment process, libraries were sequenced on the MiSeq system (Illumina, San Diego, CA, USA). Obsessive compulsive

Table 1. A panel of 26 candidate genes

Gene name	Transcript ID	Protein ID
BMP15	NM_005448.2	NP_005439.2
CYP17A1	NM_000102.3	NP_000093.1
CYP19A1	NM_000103.3	NP_000094.2
DIAPH2	NM_007309.3	NP_009293.1
ERCC6	NM_000124.3	NP_000115.1
FIGLA	NM_001004311.3	NP_001004311.2
FMR1	NM_002024.5	NP_002015.1
FOXL2	NM_023067.3	NP_075555.1
FSHR	NM_000145.3	NP_000136.2
GALT	NM_000155.3	NP_000146.2
GDF9	NM_005260.5	NP_005251.1
GNAS	NM_080425.3	NP_536350.2
HFM1	NM_001017975.4	NP_001017975.4
LHCGR	NM_000233.3	NP_000224.2
LMNA	NM_170707.3	NP_733821.1
MCM8	NM_182802.2	NP_877954.1
MSH5	NM_172165.3	NP_751897.1
NOBOX	NM_001080413.3	NP_001073882.3
NR5A1	NM_004959.4	NP_004950.2
POF1B	NM_024921.3	NP_079197.3
POLG	NM_002693.2	NP_002684.1
POR	NM_000941.2	NP_000932.3
PSMC3IP	NM_016556.3	NP_057640.1
STAG3	NM_001282716.1	NP_001269645.1
STAR	NM_000349.2	NP_000340.2
SYCE1	NM_130784.3	NP_570140.1
WT1	NM_024426.4	NP_077744.3

inventory analysis (Qiagen, Hilden, Germany) was employed to control quality and generate Variant Call Format files. In silico evaluation of the pathogenicity of nucleotide changes in exons was performed using Polymorphism Phenotyping v2 (PolyPhen-2, http:// genetics.bwh.harvard.edu/pph2/), Sorting Intolerant from Tolerant (SIFT, https://sift.bii.a-star.edu.sg/), and MutationTaster (http://www.mutationtaster.org). Minor allele frequencies were checked in the Genome Aggregation Database gnomAD (http://gnomad.broadinstitute.org/). Variant analysis was conducted using Ingenuity software (Qiagen, Hilden, Germany). Variants were interpreted according to the American College of Medical Genetics and Genomics (ACMG) recommended standard. Sanger sequencing was performed for confirmation when target region coverage was less than 15 reads. Nucleotide alterations were analyzed and validated by Sanger sequencing. After confirmation, each variant was classified as a pathogenic, likely pathogenic, variant of unknown significance (VUS), likely benign, or benign, according to the ACMG guidelines. Coding genomic regions that were sequenced with coverage less than 15X were eventually re-sequenced using Sanger technology. All detected variations were confirmed to be accurate by Senger sequencing.

NGS assays produced ~14,5 GB data for 68 samples for each individual as pair-end reads, having up to 97 bp mean read length, and about 90% (0.2 Mb length) of the targeted bases were covered, thereby sufficiently passing our thresholds for calling single nucleotide polymorphisms and short insertions or deletions (indels).

Primer sets were created for all required areas in order to execute Sanger sequencing on an ABI 3130 (Applied Biosystems, USA) capillary electrophoresis machine and validate the variations and segregation analyses.

RESULTS

We examined the DNA samples of sixty-eight unrelated patients with POI using targeted panel sequencing to identify potential causal variations of the disease. Within our sample, three POI-related genes exhibited three heterozygous VUS and one heterozygous gene that may be pathogenic. With the assistance of Franklin (available online at https://franklin.genoox.com) and VarSome[18], we detailed the clinical interpretation and implications for the identified variants. All variants identified were heterozygous, with most classified as missense (Table 2).

A total of one likely pathogenic variant (STAG3) was identified in 1.47% (1 of 68) of POI patients, which is regarded as a molecular genetic diagnosis of POI. VUS were detected in two genes in three patients from the total patient group. The genes identified were *NOBOX* and *GDF9*. A frameshift was recognized in one of the 68 patients.

Statistical Analysis

Characteristics of patients were gathered through a review of electronic medical records. Descriptive statistics, such as medians, ranges, and frequencies, were employed.

DISCUSSION

POI is characterized by a robust genetic background with increasing genes and diverse phenotypic traits[3]. The POI phenotype is associated with detrimental gene variations affecting meiosis, DNA repair, gonadal development (oogenesis and folliculogenesis), hormone signaling, immunological function, and metabolism[3]. This study represents, to our knowledge, the first genetic epidemiology study in Türkiye focusing on 26 genes in a single panel associated with POI, and several genetic alterations have been identified in genes associated with this condition. Sixty-eight Turkish patients with a clinical diagnosis of POI, who had undergone prescreening for *FMR1* pathogenic expansion, were included in our investigation.

The NM_001282717.2 (*STAG3*):c.1237_1238insAA variation identified in one of our patients constitutes a frameshift alteration that has not previously been reported for POI.

The meiosis-specific subunit of the cohesin complex, encoded by *STAG3*, comprises SMC1α/SMC1β, SMC*3*, RAD21/REC8, or RAD21L[19]. Sister chromatids are held together during mitosis and meiosis by the multiprotein cohesin complex encircles them in a ring. SMC1β, REC8, and RAD21L are exclusively present in meiotic cells, while SMC1α and RAD21 are ubiquitously found[20]. Although *STAG3* is restricted to the testes and ovaries[21,22], *STAG1/2* is present in mitotic cells[23]. The phenotypic effect of the *STAG3* gene exhibits recessive inheritance.

Table 2. Potential causal variants found in 4 POI patients via targeted panel sequencing

Gene	ACMG	dbSNP ID	Sequence change	Type
GDF9	VUS (PM2, PP3)	-	NM_005260.7:c.1297G>A (p.E433K)	Missense
NOBOX	VUS (PM1, PP3)	rs749172175	NM_001080413.3: c.1067G>A (p.R356Q)	Missense
STAG3	Likely Pathogenic (PM2, PVS1)	-	NM_001282717.2:c.1237_1238insAA p. (Ile413LysfsTer10)	Frameshift
NOBOX	VUS (PM2, PP3)	-	NM_001080413.3:c.1788G>C (p.Trp596Cys)	Missense

POI: Premature ovarian insufficiency, VUS: Variant of unknown significance, ACMG: American College of Medical Genetics and Genomics

Table 3. Clinical features (patient group average)	
Actual age	**29**
Amenorrhea	Primary
FSH, IU/L	96.2
LH, IU/L	20.8
E2 pg/mL	16
FSH: Follicle-stimulating hormone, LH: Luteinizing hormone	

In the study by Caburet et al.[22], the identified homozygous STAG3 variant leads to a premature stop codon, and autosomal recessive inheritance was demonstrated in four sisters of consanguineous parents. In another more recent study, a homozygous donor splice-site variant of STAG3 was reported leading to POI in two females[25].

There was no anomaly other than POI in our patient, for whom we detected *STAG3* heterozygous frameshift variation. However, the contribution of variations in the *STAG3* gene to the POI has been reported in the literature. Our finding is consistent with this finding. However, due to the recessive inheritance of STAG3, we do not expect any phenotypic effects[13,26].

Variations in the *NOBOX* gene were identified in two patients, both classified as VUS. The *NOBOX* gene is believed to be one of the primary genetic contributors to POI[27,28]. This ovarian *homeobox* gene is involved in the early stages of folliculogenesis, with the phenotypic effect of the *NOBOX* gene exhibiting dominant inheritance. Although the variant detected in our patient (rs749172175) is defined as VUS according to ACMG criteria, it is evaluated as "pathogenic" in variant evaluation prediction tools and the allele frequency given as 0.00000881 in the gnomAD database supports this possibility. The variations we detected in the *NOBOX* gene are consistent with the studies in the literature. Another variation detected in *NOBOX*, c.1788G>C (p.(Trp596Cys), was evaluated as VUS. However, there are values in the databases suggesting pathogenicity (SIFT: Damaging, CADD (phred): 27.10). However, since both variations were reported as VUS, their clinical significance is unknown[29].

A variation classified as a VUS was identified in the *GDF9* gene in one of our patients. Clinical evaluation of the patient revealed POI. According to Qin et al.[28] and Jiao et al.[30], variations in *GDF9* are frequently cited among the top 20 common genetic causes of POI. Notably, various *GDF9* variations have been found globally, albeit with a slightly uneven distribution by geography and ethnicity. The phenotypic effect of the *GDF9* gene exhibits recessive inheritance. Since the *GDF9* variation in our patient was both heterozygous and classified as a VUS, we did not consider it likely to have a phenotypic effect. The c.1297G>A variation detected in GDF9 has not been reported before. Therefore, a comparison with the literature could not be made.

High-throughput methods have been essential for identifying novel variants in candidate genes and genes previously linked to POI. The encoded proteins' primary functions are meiosis and DNA repair, gonadal development (oogenesis and folliculogenesis), hormone signaling, immunological response, and metabolism. As shown in several animal models, changes in genes related to meiosis and DNA repair may result in distinct symptoms of ovarian insufficiency because of the resting state of oocytes[31].

Study Limitations

There are certain limitations in our study. One of them is the number of the patients. There may not be enough power to detect rare variants with a frequency of less than 5% in 68 patients. We could obtain more results with an increased number of patients. A setting of risk prediction, routine diagnosis, and early intervention will benefit greatly from targeted panels of hotspot mutations and/or validated causal genes, as well as broader analysis like whole-exome and whole genome sequencing in the future.

CONCLUSION

POI is a highly diverse disorder that may have a complex array of genetic variants due to its many contributing causes. Furthermore, phenotypic variability is complicated by the unclear definition and nomenclature of POI, which exacerbates the genetic heterogeneity of POI and vice versa. It is uncertain if different phenotypes-like ovarian dysgenesis, primary or secondary amenorrhea, or early or late onset POI-share the same genetic makeup but have differing cumulative effects. A very large number of variations with unclear significance will surface in the NGS era. Data analysis and filtering will be quite difficult but crucial. Mutation-directed transgenic models or transformation experiments should be used to confirm causal relevance. However, it is getting more and harder to identify a single genetic alteration in any one POI patient as "causative" because many of the known POI genes appear to work in concert while exhibiting characteristics of incomplete penetrance or variable expressivity on their own. The relationship between genetics and phenotype requires more investigation.

Determining who is at risk for POI is still difficult. The potential of NGS technologies in clinical practice is huge.

Ethics

Ethics Committee Approval: All procedures performed in the study involving human participants were approved by the Ethics Committee for Scientific Research, Faculty of Medicine, Trakya University (decision no: TÜTF-BAEK 2018/319, date: 01.10.2018) and followed the Declaration of Helsinki.

Informed Consent: Each patient signed a paper granting informed consent.

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Footnotes

Authorship Contributions

Surgical and Medical Practices: H.G., S.Y., K.E., S.A., Concept: H.G., E.A., K.E., S.A., Design: E.İ.A., Data Collection or Processing: E.İ.A, H.G., S.Y., H.S.G., D.Z., E.A., Analysis or Interpretation: E.İ.A, S.D., Literature Search: E.İ.A., Writing: E.İ.A.

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