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The association of the FOXE1 polyalanine tract length with the occurrence of premature ovarian insufficiency in the Greek population: A pilot, case-control study

FOXE1 polialanin yolu uzunluğunun Yunan toplumunda prematür over yetmezliği oluşumuyla ilişkisi: Pilot, olgu-kontrol çalışması

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Abstract

Objective: To investigate the relationship between the *FOXE1* gene polyalanine tract length and premature ovarian insufficiency (POI) in the Greek population.

Materials and Methods: Peripheral blood was collected from 28 women with POI and 29 healthy controls. DNA was extracted and the gene was amplified using the polymerase chain reaction (PCR) technique. The PCR product was sequenced and the number of alanine tracts and the genotypes was recorded. Statistical analysis examined differences in allele and genotype frequencies between the groups.

Results: The patients' group mean age was 31.68 years with a mean age of POI diagnosis of 25.18 years. Five alleles (8, 12, 14, 16, 17 comprising alanine residues) and seven genotypes (14/14, 14/16, 16/16, 14/17, 16/17, 8/16, 12/14) were identified. The 8-alanine allele was exclusive to patients, while the 12-alanine allele appeared only in controls. The most common genotype in the study group was 14/16 (64.29%), whereas the most common genotype in the control group was 14/14 (41.4%). No differences of statistical significance were observed in the prevalences of the allele with 14 (p=0.590) and 16 (p=0.594) residues or the genotype prevalences between the two groups (p=0.066).

Conclusion: Our preliminary findings suggest no correlation between FOXE1 polyalanine tract length and POI, but given the study's small sample size, they should be interpreted with caution. Further research is deemed necessary.

Keywords: Premature ovarian insufficiency, POI, FOXE1, polyalanine tract, genetics

PRECIS: We investigated the relationship between the *FOXE1* gene polyalanine tract length and premature ovarian insufficiency in Greek women, but no significant association was found.

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Öz

Amaç: Bu çalışmanın amacı *FOXE1* gen polialanin yolu uzunluğu ile Yunan toplumunda prematür over yetmezliği (POY) arasındaki ilişkiyi araştırmaktır.

Gereç ve Yöntemler: POY olan 28 kadından ve 29 sağlıklı kontrolden periferik kan örnekleri toplandı. DNA çıkarıldı ve gen, polimeraz zincir reaksiyonu (PZR) tekniği kullanılarak çoğaltıldı. PZR ürünü dizilendi ve alanin yolu sayısı ve genotipler kaydedildi. İstatistiksel analiz, gruplar arasındaki alel ve genotip sıklıklarındaki farklılıkları inceledi.

Bulgular: Hasta grubunun ortalama yaşı 31,68 yıl, POY tanısının ortalama yaşı ise 25,18 yıldı. Beş alel (alanin kalıntıları içeren 8, 12, 14, 16, 17) ve yedi genotip (14/14, 14/16, 16/16, 14/17, 16/17, 8/16, 12/14) tanımlandı. Sekiz-alanin aleli sadece hastalara özgüyken, 12-alanin aleli sadece kontrollerde görüldü. Çalışma grubunda en yaygın genotip 14/16 (%64,29) iken, kontrol grubunda en yaygın genotip 14/14 (%41,4) idi. On dört (p=0,590) ve 16 (p=0,594) kalıntılı alelin yaygınlıklarında veya iki grup arasındaki genotip yaygınlıklarında istatistiksel olarak anlamlı bir fark gözlenmedi (p=0,066).

Sonuç: Ön bulgularımız FOXE1 polialanin yolu uzunluğu ile POY arasında bir korelasyon olmadığını göstermektedir, ancak çalışmanın örneklem büyüklüğünün küçük olması göz önüne alındığında, bunlar dikkatli bir şekilde yorumlanmalıdır. Daha fazla araştırmanın gerekli olduğu düşünülmektedir.

Anahtar Kelimeler: Prematüre over yetmezliği, POI, FOXE1, polialanin yolu, genetik

Introduction

Premature ovarian insufficiency (POI) is defined as the loss of ovarian function before the age of 40 and impacts around 1% of the female population. The causes of POI vary, including chromosomal anomalies, gene variants, infectious and iatrogenic causes, and environmental factors. In 2016, the European Society of Human Reproduction and Embryology (ESHRE) provided diagnostic and management guidelines for POI, outlining specific criteria for its identification. The diagnostic work-up of women with POI includes testing for chromosomal anomalies, including the performance of a karyotype, testing for pre-mutations of the *FMR1* gene, and testing for the presence of adrenocortical auto-antibodies[1].

Several genes have been proposed as the causative factors for the appearance of POI. Specific variants have been identified for some of these genes; however, their association with POI has not been clearly defined and needs further investigation[2]. Different gene variants have been associated with POI. Given their low prevalence, testing is not recommended unless indicated by specific traits or a strong family history[1].

The *FOXE1* gene (forkhead box E1) is located in the long arm of chromosome 9, at position 22 (9q22). It contains a single exon, which encodes a protein of 367 amino acids with a molecular weight of 42 kDa[3]. This protein is a transcriptional regulator and belongs to the Forkhead box protein family. It contains a well-preserved domain of 110 amino acids, the "forkhead" domain, characterised by a structure known as the winged-helix motif[4]. The protein contains a polyalanine tract, a characteristic also found in other transcriptional suppressor proteins[5,6]. The polyalanine tract may contain 11 to 19 alanine residues, but the variants with 14 and 16 residues are the most prevalent. It has been proposed that changes in the count of alanine residues lead to altered functionality of the FOXE1 protein as a transcription factor[7-9].

With regard to POI, Watkins et al.[6] were the first to study the association of the *FOXE1* gene and the POI occurrence. They found that the allele with 16 residues was more common, whereas the allele with 14 residues was less common among women with POI. For the rest of the alleles, no statistically significant correlations were found, probably owing to their rarity[6]. In a later study by Qin et al.[10], this finding was confirmed. Additionally, it was found that genotype 16/16 was significantly more common, whereas genotype 14/14 was significantly less common in the study group than in the control group. Finally, in a smaller study, the roles of two different genes, FOXE1 and BMP15, in POI were studied. It was found that FOXE1 gene variants having a number of alanine residues other than 14 or 16 were significantly more common in patients with POI[11].

The study aimed to explore the possible role of the *FOXE1* gene in the occurrence of POI in the Greek population, and more specifically, to examine whether the length of the alanine tract of the *FOXE1* gene is associated with the condition. Our original hypothesis was that different *FOXE1* gene variants may contribute to a predisposition for POI.

Materials and Methods

Study Design

This was a pilot, case-control study, conducted from January 2018 until December 2021 at Alexandra General Hospital, Athens, Greece. Local Scientific Committee (an Institutional Review Board) approval was obtained (approval number: 972, date: 07.12.2018 - National and Kapodistrian University Ethics Committee). The study protocol complied with the Declaration of Helsinki and a signed informed consent was obtained from all the participants before their enrollment in the study.

The primary outcome of this study was the detection of the FOXE1 variants in women with POI and controls.

Participants

POI patients and controls were recruited for this study at the outpatient clinic of Alexandra General Hospital, Athens, Greece. Affected women were assessed for other causes of POI using the diagnostic workup suggested by ESHRE. More specifically, the diagnostic criteria were oligo/amenorrhea for at least 4 months and an elevated FSH level greater than 25 IU/l on two occasions, more than 4 weeks apart. The diagnostic work-up included testing for chromosomal anomalies through karyotype analysis, testing for pre-mutations of the *FMR1* gene, and testing for the presence of adrenocortical auto-antibodies. Patients with abnormal karyotype, positive 21-hydroxylase

autoantibodies, or pre-mutations of the *FMR1* gene were excluded. Additionally, women who had iatrogenic menopause (bilateral oophorectomy, chemotherapy, radiation therapy) were also excluded. All cases were matched with controls at 1:1 ratio.

The control group comprised healthy women of the general population, who had delivered at least once in the past, had entered menopause after the age of 45, had no serious medical conditions, and had presented for a routine gynaecological examination.

DNA Extraction and Detection of FOXE1 Polymorphism

For the purposes of the study, we collected peripheral blood samples from women with idiopathic POI and healthy controls. DNA was isolated using the PureLink Genomic DNA kit (Invitrogen). The polymerase chain reaction (PCR) amplification technique was performed to detect the FOXE1 polymorphism. All primers were designed by Eurofins Genomics and their sequences were as follows: FOXE1F, 5'GCGGAGGACATGTTCGAGA3' and FOXE1R, 5'CGCGGGGTAGTAGACTGGAG3'. The PCR protocol included 10X PCR Buffer minus Mg2+, 0.5 µL 10 mM dNTP mixture, 0.5 µL Primer Sense mix, 0.5 µL Primer Antisense mix, 2 µL Template DNA, 0.2 µL Taq DNA polymerase (OneTaq DNA polymerase kit, New England Biolabs), and 16.3 µL distilled water.

The PCR conditions were as follows: 95 °C for 15 min, 95 °C for 1 min, 53 °C for 1 min, 72 °C for 1 min for 29 cycles, and a final elongation step at 72 °C for 10 min. Subsequently, agarose electrophoresis was applied and the 249bp, PCR product was visualized under UV.

Sanger sequencing was applied in an ABI PRISM 3130xl Genetic Analyzer (Applied Biosystems™) to determine FOXE1 polymorphisms in all samples. BigDye™ Terminator v3.1 Cycle Sequencing Kit (Applied Biosystems™) was used in the sequencing reactions.

Statistical Analysis

Statistical analysis was performed using the SPSS 26.0 Software (SPSS Inc., Chicago, IL). Continuous variables were summarized using mean values with standard deviations and median with interquartile range. We used the two-sided Fisher's exact test and chi-square test to compare allele polymorphisms between the study group and the controls.

In this study, we did not perform a formal power analysis prior to data collection. While we acknowledge that power analysis is a crucial step in designing studies to ensure an adequate sample size to detect effects, the rarity of the condition studied posed significant challenges in recruiting a large sample size within a feasible timeframe.

Results

We recruited in total 28 women with idiopathic POI and 29 healthy controls. No statistically significant differences in the population characteristics were found between the two groups, apart from age (31.68±12.86 *vs.* 55.37±5.7, p<0.001). This was intentional, as the control group was composed of women with documented menopause after the age of 45.

The study group's mean age was 31.68 years, and the mean age at the onset of POI was 25.18 years. The women's average height was 1.64 meters, their average weight was 63.2 kilograms, and their average body mass index was 23.41. Nine women (32.14%) had a family history of POI. One woman had a history of melanoma, another was diagnosed with neutropenia, a third had a history of right ovarian torsion, a fourth had celiac disease, and another had short stature.

We detected 5 different alleles, with 8, 12, 14, 16, and 17 alanine residues. Seven genotypes were identified: 14/14, 14/16, 16/16, 14/17, 16/17, 8/16, and 12/14. The allele with 8 alanine residues appeared only in one patient, while the 12-residue allele appeared only in controls. The genotypes 8/16 and 14/17 were observed only in the patients' group, while the genotypes 12/14 and 16/17 were noted only in the control group. The most prevalent genotype in the study group was 14/16 (64.29%), whereas the 14/14 genotype was the most common in controls (41.4%). There were no statistically significant differences in the prevalence of the recorded genotypes between the two groups (p=0.066) (Table 1). Moreover, the individual frequencies of the alleles with 14 and 16 residues among patients and controls did not differ significantly (p=0.590 and 0.594, respectively). These results are summarized in Table 2.

Discussion

Main Findings and Comparison with Existing Literature

Although different causes of POI have been identified, in most cases, there is no causal factor, and hence these cases are termed idiopathic. Genetic studies have revealed several gene variants that predispose their carriers to developing POI. Such an example is the *FMR1* gene, for which the presence of premutations is investigated in all cases of primary ovarian insufficiency. Likewise, other potential gene variations could

Table 1. The various genotypes that were observed in the study and the control group

Genotype	Study group		Control group		p-value
	n	%	n	%	
8/16	1	3.6	0	0	-
12/14	0	0	1	3.4	-
14/14	6	21.4	12	41.4	-
14/16	18	64.3	10	34.5	-
14/17	1	3.6	0	0	-
16/16	2	7.1	5	17.2	-
16/17	0	0	1	3.4	-
Total	28	100.00	29	100.00	0.066

Table 2. Individual frequencies of alleles 14 and 16 in the study and the control group

Allele	Study group (n=56)	Control group (n=58)	p-value
	n (%)	n (%)	
14	31 (55.5)	35 (60.3)	0.59
16	23 (41.1)	21 (36.2)	0.596

be included in the diagnostic work-up of POI, depending on their prevalence and clinical significance. *FOXE1* gene variants have previously been associated with the occurrence of POI; however, the exact association and relative risk are still unclear. Repeated alanine residues have been found in several genes, where the length of the polyalanine tract is highly conserved, likely separating functional protein domains. Alterations in polyalanine length have been associated with various conditions[6,12], as seen in the *FOXL2* gene, which shares structural similarities with FOXE1, including a polyalanine tract and a well-preserved "forkhead" domain. In FOXL2, increases in polyalanine length are responsible for 25-30% of mutations leading to Blepharophimosis (BPES) type II[13,14] while decreases in length have been linked to a case of POI without BPES[15]. This evidence suggests that FOXE1 polyalanine tract length could similarly play a role in POI, although this remains uncertain.

This study examined the possible association between variations in the number of alanine residues in the *FOXE1* gene's polyalanine tract and the occurrence of POI among women from Greece. We found that the alleles with 14 and 16 residues are the most common among both patients and controls. The genotype 14/16 was the most prevalent in the study group, whereas the genotype 14/14 was the most prevalent in the control group. No statistically significant differences were noted in the prevalence of the detected genotypes or the prevalence of the most common alleles (14 and 16 residues) between the two populations.

FOXE1 is a transcription factor with multiple functions[4]. During fetal development, it is expressed in the growing thyroid, the pituitary gland, and the branchial arches, while in adulthood, it is expressed in the thyroid gland, the epidermis, the hair follicles, and the pre-pubertal testis[5,16,17]. Mutations of the gene can cause the Bamforth-Lazarus syndrome, which is characterized by congenital hypothyroidism, thyroid dysgenesis, cleft palate, spiky hair, bifid epiglottis, ocular hypertelorism, and choanal atresia[18,19]. It seems to be associated with the occurrence of various cancers, such as thyroid, colon, skin, breast, and liver cancer[20-24]. It is likely a major transcription factor with more functions than those described here.

Previous publications have proposed that variations in the *FOXE1* gene's polyalanine tract length are associated with the appearance of POI. Watkins et al.[6] found that the allele with 16 residues was significantly more common, while the allele with 14 residues was significantly less common among women with POI. Qin et al.[10] came to the same conclusion and they also found that genotype 16/16 was significantly more prevalent, whereas genotype 14/14 was significantly less prevalent in the study group than in the control group. Settas et al.[11] also found that alleles with an altered number of alanine residues (other than 14 or 16) were significantly more frequent among patients with POI.

Interestingly, the prevalence of the different genotypes among the European and the Chinese populations differed significantly, as described by the studies of Watkins et al.[6] and Qin et al.[10]. Based on the study by Watkins et al.[6], genotype 14/14 was found in 27.2% of the patients with POI and 46.5% of the control group, respectively. In the study by Qin et al.[10], the prevalence of the same genotype was 81.2% for the study and 96.4% for the control group. Additionally, the frequency of the allele with 16 residues was significantly lower in the Chinese population than in the European population, indicating a high heterogeneity between these two populations, probably owing to their geographic distance[6,10].

In our study, there were no statistically significant differences in the prevalence of the observed genotypes between the study and the control group. Additionally, no correlation was found between the detected alleles and the presence of POI. These results seem to contradict the findings of both Watkins et al.[6] and Qin et al.[10] and raise concerns as to whether the *FOXE1* gene is causally related to POI.

Study Limitations

The lack of a formal power analysis and the small sample size are two main limitations of our study. Given the rare nature of the condition under investigation and the relatively small Greek population, it was difficult to recruit a larger sample size within a feasible timeframe. Therefore, our results should be interpreted with caution. It is unclear whether the null results observed are indeed due to the absence of genetic effects or simply due to insufficient power to detect such effects. This limits the interpretability of our findings.

Implications

Our preliminary findings suggest no correlation between *FOXE1* genes and POI. Further research with larger sample sizes and appropriate power calculations is deemed necessary to confirm these findings and to draw more definitive conclusions about the genetic effects under study. Until then, *FOXE1* gene detection could not be supported as a diagnostic tool for POI. Furthermore, future studies could use whole genome sequencing to provide a more comprehensive analysis of the genetic factors involved in POI.

Conclusion

The *FOXE1* gene encodes a transcriptional factor with multiple functions. It has been associated with various conditions such as Bamforth-Lazarus syndrome, cleft palate, thyroid dysgenesis, and various forms of malignancy. Even though changes in the

polyalanine tract of the gene have been associated with the occurrence of POI, its role in the pathogenesis of POI remains unclear. Our preliminary findings seem to contradict the findings of previous studies, but they should be interpreted with caution, given the study's small sample size. Further research on the *FOXE1* gene or an extended genetic panel is necessary to elucidate the causes of POI.

Ethics

Ethics Committee Approval: Local Scientific Committee (an Institutional Review Board) approval was obtained (approval number: 972, date: 07.12.2018 - National and Kapodistrian University Ethics Committee).
Informed Consent: A signed informed consent was obtained from all the participants before their enrollment in the study.

Footnotes

Authorship Contributions

Concept: A.K., L.M., Design: A.K., P.D., L.M., Data Collection or Processing: A.K., S.I., Analysis or Interpretation: A.K., M.P., D.M., Writing: A.K., M.P., S.I., D.M., P.D., L.M.
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