A rare **BMP15** genetic variant in a patient with premature ovarian insufficiency and two spontaneous pregnancies

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Summary

**Introduction:** Premature ovarian insufficiency (POI) is characterized by an unusually early depletion of the ovarian follicular pool in women. Genetic progress in recent years has allowed the identification of different genes that can predispose to the development of POI. Bone morphogenetic protein 15 (**BMP15**) genetic variants have been associated with diminished ovarian reserve and subfertility in animals and humans. **Materials and Methods:** Herein, the authors present a 34-year-old Caucasian woman with normal pubertal development, one uncomplicated pregnancy and two spontaneous pregnancies after POI diagnosis. **Results:** A very rare variant c.269T>C (p.Ile90Thr) in exon 1 of the **BMP15** gene was detected. **Conclusions:** The proper differentiation between genetic variants associated with premature ovarian ageing and mutations that can attribute to irreversible early gonadal impairments is an important task of future studies.

Key words: Premature ovarian insufficiency; Fertility; **BMP15** genetic variants.

Introduction

Premature ovarian insufficiency (POI) is characterized by an early depletion of the ovarian function in women younger than 40 years. The hormonal constellation of POI includes increased follicle-stimulating hormone (FSH) levels and hypoestrogenism. The clinical manifestations of POI include menstrual disturbances, such as oligomenorrhea or amenorrhea [1]. Infertility is common among the affected patients, but an intermittent restoration of the folliculogenesis may occur in a subset of patients. Thus, the estimated pregnancy rate in women with idiopathic POI varies between 3.5% and 4.4% [2, 3]. Different genetic variants may predispose to POI development; however, it is not clear which of them can be associated with a higher probability of intermittent POI.

Herein, the authors present a patient with two pregnancies after POI diagnosis, as well as a rare genetic variant of the bone morphogenetic protein 15 gene (**BMP15**, OMIM (Online Mendelian Inheritance in Man) *300247*).

Materials and Methods

The patient was a 34-year-old healthy Caucasian woman with secondary amenorrhea. Gynecological history revealed normal pubertal development with menarche occurring at the age of 14 years. The patient had regular periods and one successful pregnancy without any complications. At the age of 28 years, the patient began to complain of hot flushes, profuse night sweats and four months of amenorrhea. Hormonal tests showed increased serum blood levels of FSH: 121.3 IU/L and luteinizing hormone (LH): 66.8 IU/L; the anti-Müllerian hormone (AMH) serum blood level was below the lower reference range. Pelvic ultrasound described reduced ovarian volume bilaterally. Hormone replacement therapy with transdermal estradiol and cyclic progestin was begun and the subjective complaints of the patient disappeared quickly.

At the age of 30 years, the patient became pregnant spontaneously, but decided to terminate the pregnancy, because of a concomitant acute lung infection treated with possible teratogenic drugs. After the abortion, the patient had three regular periods followed by amenorrhea and restoration of the vegetative complaints; thus, the hormone replacement therapy which had been stopped during pregnancy was restarted. One year later, a new pregnancy was detected and the patient developed preeclampsia during the third trimester leading to a premature birth of a healthy child. After the birth, the patient was amenorrheic and normotensive. The hormonal tests displayed similar previous results; FSH: 110.6 IU/L, LH: 77.0 IU/L; estradiol: 248 pmol/L and AMH: below the lower reference range. Pelvic ultrasound showed reduced ovaries bilaterally without fol-
On general examination, the patient had a good overall health condition; no malformative signs were detected. Clinical examination showed no abnormalities in the various body organs and systems. The only concomitant disease was a mild bronchial asthma that was occasionally treated with inhaled corticosteroids; systemic corticosteroids had never been administered. No other diseases including systemic autoimmune, thyroid or adrenal disorders were found. The hormone replacement therapy was continued considering the age of the patient.

After receiving a written informed consent, a blood sample for genetic testing was collected from the patient; other family members were not available for testing. Deoxyribonucleic acid (DNA) was isolated from peripheral blood using standard salt-extraction procedures. Both coding exons 1 and 2 and exon/intron boundaries of the BMP15 gene were amplified by polymerase chain reaction (PCR) followed by Sanger sequencing. The amplified products were purified by ExoSAP-IT and sequenced by ABI BigDye Terminator Cyclesequencing Kit v3.1. The sequencing analysis was performed on ABI genetic analyser 3130 and the obtained results were interpreted by the Sequencing Analysis v5.1.1. software. The generated sequences were compared with the published BMP15 gene sequence (NM_005448.2).

**Results**

Turner syndrome and a premutation of the fragile X mental retardation 1 (FMR1) gene were previously excluded. The patient was tested for genetic mutations involving the BMP15 gene. A nucleotide change c.269T>C in exon 1 of the BMP15 gene was detected, resulting in a replacement of an isoleucine residue by a threonine residue at the amino acid position 90 (p.Ile90Thr). This variant (rs377085803) was reported with an extremely low frequency of the mi-
nor allele, which was found in one out of 10549 investigated chromosomes (http://evs.gs.washington.edu/EVS/; http://databases.lovd.nl).

To predict the potential functional impact of the amino acid change on the structure and/or function of the BMP15 protein, a pathogenicity prediction algorithm was used. The identified variant p.Ile90Thr was evaluated as possibly damaging by the in silico PolyPhen-2 software predicting functional effects. The obtained pathogenicity score was 0.907. Exon 1 of the BMP15 gene was analyzed in additional 43 unrelated Bulgarian females; 22 of them had clinical manifestations of POI. However, the variant c.269T>C (p.Ile90Thr) was not detected.

Discussion

BMP15 is an important oocyte-derived protein that can regulate early follicular growth and development [4]. BMP15 genetic variants in heterozygous states have been described in patients with ovarian dysgenesis, but more often in women with decreased ovarian reserve [5, 6]. Persiani et al. summarized the available data published before 2014 and showed the prevalence of BMP15 genetic variants was 4.5% in POI patients and only 0.43% in women with normal ovarian function [4]. Herein, a heterozygous carrier of c.269T>C (p.Ile90Thr) variant of the BMP15 gene is presented. The substitution is located on the gene sequence encoding the pro-region of the BMP15 protein (Figure 1), which is important for its processing and dimerization [7]. The same genetic variant was found in one out of 6719 individuals of European descent (http://evs.gs.washington.edu/EVS/; http://databases.lovd.nl). However, no clinical information regarding age, sex and reproductive health of the individual carrier had been published.

The clinical phenotype of the presented patient resembled that of an African patient with c.443T>C (p.Leu148Pro) variant of the BMP15 gene [8]. Both patients had normal pubertal development, several spontaneous pregnancies and secondary amenorrhea. The presented patient also had a successful pregnancy after POI diagnosis, suggesting an intermittent restoration of normal folliculogenesis. However, the p.Leu148Pro variant was described in patients with much severe clinical manifestations, including streak gonads and primary amenorrhea. On the contrary, opposite healthy p.Leu148Pro carriers had also been identified [9]. Thus, the precise distinction between the BMP15 genetic mutations with clinical significance and rare neutral polymorphisms might be difficult in some cases [10]. Other genetic and epigenetic factors could be involved in the modulation of the clinical picture in patients with identical BMP15 genetic variants.

In conclusion, the authors presented a case of woman with a rare BMP15 c.269T>C (p.Ile90Thr) variant who delivered a healthy baby several years after initial symptoms of POI. The proper differentiation between genetic variants associated with premature ovarian ageing and genetic mutations causing irreversible early gonad impairment might be an important task of future studies.

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Conflict of Interest

The authors declare no competing interests.

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