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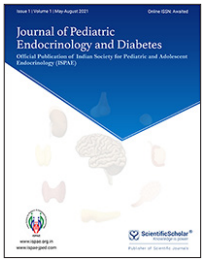

Case Report

A novel *STAG3* variant associated with primary ovarian insufficiency

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ABSTRACT

Primary ovarian insufficiency (POI) is a complex condition affecting women under the age of 40 years, characterized by ovarian dysfunction and reduced fertility. Genetic mutations, including those in the *STAG3* gene, have been increasingly recognized as contributors to POI, particularly in populations with consanguinity. Here, we report a novel *STAG3* homozygous missense variant, c.926T>C (p.Phe309Ser), in a 15-year-old Indian girl presenting with delayed menarche, features of gonadal dysgenesis, and 46,XX karyotype. This variant, located in the Regulator of Chromosome Condensation 1 (RCC1) domain of the STAG3 protein, likely disrupts the cohesin complex's function in meiosis, leading to premature depletion of ovarian follicles and POI. This case highlights the importance of genetic testing in young patients with unexplained gonadal dysgenesis and emphasizes the need for further studies to explore the molecular mechanisms underlying *STAG3*-associated POI.

Keywords: Cohesin complex, Gonadal dysgenesis, Primary ovarian insufficiency, *STAG3* mutation

INTRODUCTION

Primary ovarian insufficiency (POI) is characterized by ovarian dysfunction leading to reduced fertility in women under 40 years of age. For the diagnosis, there must be 4–6 months of amenorrhea in a woman under the age of 40 years with elevated gonadotropins and low estradiol.[1] POI contributes to the causes of primary and secondary amenorrhea. Symptoms are similar to those of postmenopausal, such as menstrual irregularities and oligomenorrhea, and menopausal-like symptoms such as hot flashes, vaginal dryness, mood changes, and decreased bone density. Fertility issues are often a key concern, as women with POI may have difficulty conceiving due to low ovarian follicle reserve. In cases of primary amenorrhea, delayed or incomplete breast development may be observed. Diagnosing POI in adolescents can be delayed as irregular menstrual cycles can either indicate early adolescence or early POI.[2]

POI occurs in approximately 1% of women who have not reached 40 years of age. The frequency is roughly 4–8% in women experiencing secondary amenorrhea and 10–28% in cases of primary amenorrhea.[3,4] The etiology of POI is heterogeneous, and known causes include genetic factors, iatrogenic (such as surgery, chemotherapy and radiotherapy), autoimmune disorders, and idiopathic causes.[1] The overall prevalence of POI associated with genetic mutations is approximately 20–25%.[2,5] Chromosomal abnormalities such as monosomy or mosaic forms of trisomy X and fragile X syndrome are well-established causes of POI, and their frequency

is approximately 10–13%.[6] Mutations of >60 genes have been linked with POI.[7] One gene of interest is *STAG3*, and mutation in this gene leads to abnormal folliculogenesis and, eventually, POI.[5] *STAG3* encodes a protein, which functions as a subunit of the cohesin complex in meiosis.[5,8] The mutations in *STAG3* gene are uncommon and are seen in ethnicities such as Middle Eastern, Asian, and Caucasian populations where consanguineous marriages are high.[8-11]

CASE REPORT

A 15-year and 7-month-old Kashmiri girl with normal perinatal and postnatal development presented with the parental concern regarding delayed menarche. The patient's mother reported the development of breast buds 4 years ago, which progressed for 2 years before stagnating. Pubic and axillary hair appeared 4 years ago. There were no concerns regarding short stature. There was no history of muscle weakness, a round face, easy bruising, headache, or visual field defects. She was born of non-consanguineous marriage, but there was a history of skin cancer and eye cancer each in two maternal uncles and kidney disease in one maternal uncle and maternal aunt.

On examination, the patient's height was 158.3 cm (50th–75th percentile), weight 55.5 kg (75th percentile), Tanner staging A3, P3, B2, normal female external genitalia, no physical features of Turner syndrome, and no thyromegaly. Systemic examination was unremarkable. Laboratory investigations revealed elevated follicle-stimulating hormone (FSH) at 78.3 mIU/mL and luteinizing hormone (LH) at 20.3 mIU/mL, with low estradiol (E2) <11.8 pg/mL and anti-Mullerian hormone (AMH) <0.02 ng/mL. Thyroid-stimulating hormone (TSH) and cortisol levels were within normal ranges. Magnetic resonance imaging (MRI) and ultrasound visualized the hypoplastic uterus (endometrial thickness 2 mm), but the ovaries were not visualized.

Based on the clinical presentation and laboratory findings, a provisional diagnosis of "46,XX gonadal dysgenesis" was considered. Karyotype was 46,XX and whole genome sequencing revealed a *STAG3* mutation. In this case, homozygous missense variant in exon 9 of the *STAG3* gene (chr7: g.100195367T>C; Depth: 124×) that results in the amino acid substitution of serine for phenylalanine at codon 309 (p.Phe309Ser; ENST00000615138.5) was detected. The observed variant lies in the "Regulator of chromosome condensation 1 (RCC1) repeat" domain of the *STAG3* protein. This variant has not been reported in the 1000 genomes, gnomAD (v3.1), and gnomdAD (v2.1), TOPMed. This *STAG3* variant is classified as a variant of uncertain significance.

DISCUSSION

POI is a complex condition that results in diminished ovarian function before the age of 40 years, with genetic factors contributing to 20–25% of cases.[3] *STAG3* gene mutations are among the recognized causes of POI, which encodes a crucial component of the cohesin complex. This complex plays an essential role in chromosome cohesion during meiosis, and disruption of this process can lead to errors in chromosomal segregation, resulting in gonadal dysfunction and ovarian insufficiency.[7,12]

The present case of a 15-year and 7-month-old Kashmiri girl with delayed menarche and clinical features of gonadal dysgenesis is significant due to the identification of a novel homozygous missense mutation in *STAG3*, c.926T>C (p.Phe309Ser). This mutation is located in the RCC1 domain of the STAG3 protein. The RCC1 domain is vital for the cohesin complex's integrity during meiosis, and mutations within this region could disrupt chromosomal segregation. Specifically, the substitution of phenylalanine with serine at codon 309 likely alters the protein's structural stability or folding, impairing its function in maintaining sister chromatid cohesion during oocyte development. This disruption ultimately leads to premature depletion of ovarian follicles, manifesting as POI.

The *STAG3* mutation spectrum in POI is diverse, with various mutations identified across different ethnicities [Table 1].[11-18] Notably, the p.Phe309Ser mutation found in this patient represents a novel addition to the Asian genetic landscape, as previously reported *STAG3* mutations have been more commonly identified in populations from the Middle East and Europe. For instance, Caburet *et al*.[12] described a c.968delC mutation in a Middle Eastern Palestinian cohort, while Colombo *et al*.[13] reported a c.677C>G mutation in Asian individuals. This expanding catalog of *STAG3* mutations underscores the gene's importance in ovarian function across diverse populations. Comparing this case with previous reports highlights the heterogeneity of *STAG3* mutations in terms of both the nature of the mutations and the ethnic backgrounds of the affected individuals. For example, mutations such as c.291dupC (p.Asn98Glnfs*2) in a Brazilian patient[9] and c.877_885del (p.293_295del) in a Chinese individual[11] demonstrate the widespread occurrence of *STAG3* mutations. The p.Phe309Ser mutation identified in this patient contributes to the understanding of POI pathogenesis, particularly within Asian populations, where consanguinity may increase the risk of autosomal recessive mutations such as this one.

Genetic spectrum of *STAG3* mutations

The *STAG3* gene has been implicated in POI in a variety of ethnic groups, with mutations spanning deletions, duplications, and missense variants. Table 1 outlines some of the known mutations and their ethnic associations. The novel c.926T>C (p.Phe309Ser) mutation identified in this case adds to the growing list of *STAG3* mutations linked to POI. This

Table 1: Spectrum of stromal antigen 3 (*STAG3*) mutations associated with POI.

S. No.	First author	Year	Variant	Ethnicity
1.	Present case	2024	c. 926T >C (p.Phe309Ser)	Asian
2.	Xiao *et al.*[11]	2019	[c. 877_885del (p. 293_295del) (Hom)] and [c. 891_893dupTGA (p. 297_298insAsp) (Hom)]	Chinese
3.	França *et al.*[9]	2019	[c. 291dupC (p.Asn98Glnfs*2) ([Het)] and [c. 1950C >A (p.Tyr650*) (Het)]	Brazil
4.	Caburet *et al.*[12]	2014	c. 968delC (p.Gln188Argfs*8) (Hom)	Middle Eastern, Palestinian
5.	Colombo *et al.*[13]	2017	c. 677C >G (p.Ser227*) (Hom)	Asian
6.	He *et al.*[15]	2018	c. 1573+5G >A (p.Leu490Thrfs*10) (Hom)	Chinese
7.	Le Quesne Stabej *et al.*[8]	2016	c. 1947_48dupCT (p.Tyr650Serfs*22) (Hom)	Lebanese
8.	Mellone *et al.*[16]	2021	c. 3381_3384delAGAA, p.Glu1128Metfs*42	Senegal (Africa)
9.	Demain *et al.*[17]	2021	c. 1336G >T, p.Glu446Ter (Hom)	White British
10.	Heddar *et al.*[18]	2019	(c. 3052delC, p.Arg1018Aspfs*14) and (c. 659T >G, p.Leu220Arg. Leu220)	Caucasian

POI: Primary ovarian insufficiency

variant may disrupt the cohesin complex during meiosis, leading to ovarian insufficiency. The functional significance of this specific mutation requires further investigation, but its location within the RCC1 domain suggests that it may interfere with protein–protein interactions necessary for chromosomal cohesion. In addition, *STAG3* mutations (both homozygous and heterozygous) are implicated in male infertility.[14]

Clinical implications

The identification of the *STAG3* mutation in this patient has important implications for clinical management and genetic counseling. Given that *STAG3* mutations follow an autosomal recessive inheritance pattern, genetic counseling is essential for the patient's family to understand the recurrence risk in future pregnancies, particularly in populations with high rates of consanguineous marriages. In these communities, genetic screening for *STAG3* mutations might be beneficial to inform reproductive planning and prevent recurrence in subsequent generations. Hormone replacement therapy (HRT) is a cornerstone of management for estrogen deficiency associated with POI, and in this case, it could help alleviate symptoms such as hot flashes, vaginal dryness, and decreased bone density. Since this patient is still in her teenage years, early initiation of HRT may be particularly important to ensure proper bone development, uterine development (for future assisted pregnancy), and breast development and prevent osteoporosis later in life. In addition, psychological support should be provided to help the patient cope with the emotional and psychological impact of POI, particularly in relation to fertility concerns. From a fertility standpoint, women with POI, especially those with *STAG3* mutations, have a significantly reduced chance of spontaneous conception. Assisted reproductive technologies, such as *in vitro* fertilization with donor oocytes, may be an option if the patient desires to conceive in the future. Fertility counseling and exploration of options like oocyte preservation might also be relevant for this patient.

CONCLUSION

This case adds to the growing evidence of the genetic basis of POI and emphasizes the importance of *STAG3* mutations in its pathogenesis. The discovery of the c.926T>C (p.Phe309Ser) variant in an Asian female with delayed menarche underscores the importance of considering genetic testing in young patients presenting with unexplained gonadal dysgenesis. As more cases of POI linked to *STAG3* mutations are reported across different ethnicities, a deeper understanding of the gene's role in ovarian biology and its diverse phenotypic presentations will emerge, guiding more personalized approaches to management and treatment. Further studies are needed to delineate the precise molecular consequences of the p.Phe309Ser mutation and its impact on cohesin complex function.

Ethical approval

Institutional Review Board approval is not required.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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