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A novel homozygous frame-shift variant in the *LHCGR* gene is associated with primary ovarian insufficiency in a Pakistani family

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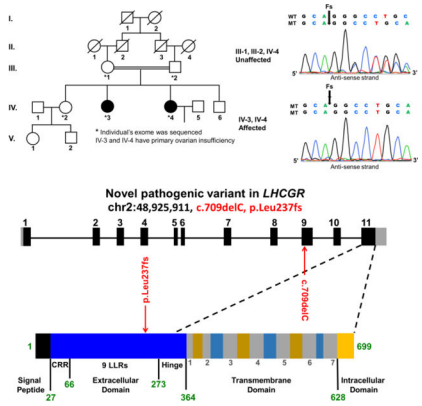
Graphical Abstract



To the Editor:

Primary Ovarian Insufficiency (POI) affects 1–2% of women and is a genetically heterogeneous condition characterized by hypergonadotropic hypogonadism, amenorrhea, and infertility. POI patients are evaluated for chromosomal, iatrogenic, endocrine, autoimmune, and infectious causes. Women with POI onset prior to age 20 are more likely to have a strong genetic component [1]. In this study, we investigated a consanguineous Pakistani family belonging to the district Hazara of Khyber Pakhtunkhwa. Parents were first cousins and had three daughters and one son. Two daughters presented with primary amenorrhea, hypergonadotropic hypogonadism, and normal 46, XX karyotypes. The Ethical

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Review Board of Khyber Medical University, approved this study and all participants provided informed consent.

The first proband presented at 20 years of age with primary amenorrhea and hormonal evaluation was consistent with hypergonadotropic hypogonadism. Luteinizing hormone (37.50 IU/L; normal follicular range is 1.8–11.78 IU/L) and follicle stimulating hormone (26.30 IU/L; normal range is 3.03–8.08 IU/L) levels were elevated, while estradiol (25 pg/mL; normal range is 21–251), anti-mullerian hormone (1.51 ng/mL; normal range is 1–4), and testosterone (17.52 ng/dL; normal range is 11–57) levels were normal. Ultrasonography showed an anteverted uterus measuring 5.5×2×3.3 cm with a thin endometrium of 0.2 cm and normal sized ovaries with an anechoic cyst (8 cm^3) in the left ovary.

The second proband presented at 24 years of age with primary amenorrhea, hypergonadotropic hypogonadism, and had a history of hot flushes. Estradiol (48 pg/mL) and testosterone (31.83 ng/dL) levels were normal, anti-mullerian hormone (1.12 ng/mL) levels were relatively low, while follicle stimulating hormone (24.42 IU/L) and luteinizing hormone (32.16 IU/L) levels were high. Ultrasonography showed a slightly small uterus with a thin endometrium. The left ovary was of normal size with few follicles and two anechoic simple cysts (12 cm^3; 18 cm^3) were seen in the right.

We performed whole exome sequencing (WES) on five family members (parents and three daughters) with an average coverage of 150 reads. We assumed autosomal recessive inheritance, with a minor allele frequency of less than 0.01%, which identified a total of seven potential variants. Four were synonymous or intronic with unlikely splicing effects, while three were exonic and non-synonymous in *LHCGR* (MIM: 152790), *PCLO* (MIM: 604918), and *OXER1* genes. The luteinizing hormone/choriogonadotropin receptor (*LHCGR*) was the only gene known to be associated with reproduction.

The *LHCGR* (chr2: 48,925,911, c.del709C, p.Leu237fs) variant was not present in dbSNP, HGMD, or general population variant databases (ExAC and gnomAD). Both patients were homozygous for the c.709delC variant, whereas the parents and unaffected sister were heterozygous, consistent with known recessive inheritance for LHCGR associated pathologies (Table 1). All individuals had high quality sequencing coverage (>35x) in this region and Sanger sequencing confirmed each genotype. The c.del709C variant is located in exon 9 and encodes a conserved leucine-rich repeat (LRR-8). The extracellular domain especially the LRR regions, is essential for LH/hCG binding affinity and specificity[2]. This variant (p.Leu237CysTer5) results in a frame-shift at amino acid 237 and is predicted to truncate the regularly sized 699 amino acid wild-type LHCGR protein. The truncated LHCGR protein lacks the highly conserved serpentine transmembrane, which is responsible for signal transduction[2]. Therefore, it is likely a loss of function variant, and co-segregation with the POI phenotype in the pedigree, further supports its likely pathogenicity.

LHCGR variant phenotype is confined to the ovaries and results in non-syndromic infertility. We report the tenth variant in LHCGR associated with female infertility and amenorrhea. Previous reports of women with LHCGR variants described phenotypes of infertility, cystic

ovaries, empty follicles, and primary/secondary amenorrhea (Table 1) in Brazilian, Canadian, Chinese, Dominican, and Turkish individuals [3, 4]. To our knowledge, this novel variant in the *LHCGR* gene was first to be described in a Pakistani family, which further supports the importance of LHCGR function in female reproduction across diverse ethnic groups.

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Table 1:

Reported LHCGR inactivating variants associated with female infertility and relevant phenotypes.

Variant	Inheritance pattern	Amenorrhea	Hormone analysis	Reproductive tract	Affected family members and associated diagnoses	Ethnic group
c.54_55insCTGCCG p.Gln18_Pro19insLeuPro	Dominant	Secondary	Normal	Recurrent ovarian cysts and inverted uterus	No siblings of same genotype	Canadian
c.34_60del / c. 1756_1758delTC p.Lys12_Pro20del / p.Ser586fs	Compound Heterozygous	Primary	Normal	Normal uterus size Normal sized cystic ovaries	Individual diagnosed with polycystic ovary syndrome; pseudo-hermaphroditism in one 46, XY sibling	Canadian
c.709delC p.Leu237fs	Recessive	Primary	High LH/FSH levels	Normal sized cystic ovaries Small atrophic uterus	Two sisters with POI	Pakistani
c.1060G>A p.Glu354Lys	Recessive	Primary	High LH levels Low E2 levels	Normal	Pseudo-hermaphroditism in two 46, XY siblings	Dominican
c.1199A>G p.Asn400Ser	Recessive	Oligo	Normal	Normal	Study reported two sisters with empty follicle syndrome	Turkish
c.1345G>A p.Ala449Thr	Recessive	Oligo	Normal	Normal uterus Ovaries of unequal sizes	Individual diagnosed with empty follicle syndrome	Chinese
c.1660T>C p.Arg554ter	Recessive	Primary	High LH levels Low E2 levels	Small uterus Unequal sized cystic ovaries	Pseudo-hermaphroditism in three 46, XY siblings	Brazilian
c.1777G>C p.Ala593Pr006F	Recessive	Primary	High LH/FSH levels Low E2/progesterone levels	Enlarged right ovary with cyst	Pseudo-hermaphroditism in two 46, XY siblings	Brazilian
c.1822_1827del p.Leu608_Val609del	Recessive	Oligo	High LH levels	Enlarged right ovary with cyst and normal uterus	Pseudo- hermaphroditism in one 46, XY sibling	Brazilian

Note: Phenotyping information was acquired from the following PMIDs: 22369774, 24849377, this study, 9626144, 21683950, 28175319, 8559204, 8923827, and 9514160, respectively.

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