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Novel Variants in *MCM8* Associated with Primary Ovarian Insufficiency, Short Stature, and Congenital Anomalies of the Kidneys in a Patient from Georgia: A Case Report

Kakha Bregvadze[1,ID], Ekaterine Kvaratshelia[2,3], Marika Mdivnishvili[1], Ani Murtskhvaladze[1], Tinatin Tkemaladze[1,4,ID]

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ABSTRACT

Primary ovarian insufficiency (POI) is a major cause of female infertility, resulting from the premature loss of ovarian function. Recently, pathogenic variants in the minichromosome maintenance (MCM) complex component 8 (*MCM8*) have been associated with POI. We report a case of a 13-year-old female from Georgia presenting with POI, short stature, and congenital kidney anomalies, in whom whole exome sequencing (WES) identified two novel heterozygous variants: a frameshift variant, c.278_281del, p.(Ile93Argfs*22), and a missense variant, c.703T>C, p.(Cys235Arg). The patient's clinical presentation, which includes previously unreported kidney anomalies, and the identification of novel variants expand the phenotypic and molecular spectrum of *MCM8*-related POI. The presented case also highlights the critical role of WES in diagnosing unexplained POI, leading to early diagnosis and management. A literature review of existing *MCM8* variants is also provided, emphasizing the necessity of additional functional studies to fully understand its role in ovarian function and related abnormalities.

Keywords: Infertility; Kidney anomalies; Minichromosome maintenance complex component 8 (*MCM8*); Primary ovarian insufficiency (POI); Whole exome sequencing (WES).

INTRODUCTION

Primary ovarian insufficiency (POI) represents a disease spectrum characterized by amenorrhea before the age of 40 due to dysfunctional ovaries caused by follicle atresia and a rapid decline in germ cells.[1] POI is one of the most common causes of female infertility. Diagnosis of POI is often delayed due to subtle clinical symptoms and limited awareness of the condition. More than 70% of POI cases are idiopathic, although various factors, including iatrogenic and environmental influences, autoimmune and endocrine diseases, and genetic defects with abnormal karyotypes (46,XY; 45,X) or normal karyotypes (fragile X syndrome and gene mutations) are known to cause it.

The overall prevalence of genetic-associated POI is reported to be approximately 20–25%.[2] More than 60 genes related to both syndromic and nonsyndromic POI are described.[3] Recently, there has been growing interest in the role of the minichromosome maintenance (MCM) complex component 8 (*MCM8*) gene in maintaining and stabilizing the genome, especially during meiosis. MCM8 and MCM9 form a functional helicase complex (MCM8/9) that plays an important role in homologous recombination, meiosis, and DNA replication.[4] Pathogenic variants in *MCM8* have been linked to autosomal recessive POI.[5] Functional studies demonstrated that these variants cause chromosomal instability and reduce the DNA repairing capacity. However, substantial research into POI-associated genes across various ethnic groups has also identified heterozygous mutations in *MCM8*. Not all these mutations have been proven detrimental; specific variants' effects remain unclear, and some are considered benign.[1]

Here, we report two novel variants in *MCM8* in a 13-year-old adolescent female with a 46,XX karyotype who presents with POI, short stature, and congenital kidney anomalies, expanding the genotype and phenotype spectrum of the disease.

CASE

We describe a 13-year-old adolescent female who was referred to us for clinical evaluation at the age of 11 due to a linear growth delay that became evident at eight years of age. She was born at term to non-consanguineous parents with a birth weight of 2900 gr and a length of 49 cm and had two healthy younger sisters. The pregnancy and delivery were uneventful, and prenatal ultrasounds revealed no intrauterine growth restriction (IUGR) or other abnormalities.

On physical examination at 11 years of age, the patient was noted to be short-statured, with a height of 122 cm (−2.0 SD). Examination of secondary sexual characteristics revealed no breast mound, no axillary hair, and stage 1 on the pubic hair scale. The labia majora and minora were hypoplastic. Additionally, mild cubitus valgus, hypermobile joints, mild shortening of the fourth metacarpals, and hypertrichosis were observed. Her intelligence was age-appropriate.

A transabdominal gynecological Doppler ultrasound of bilateral ovaries revealed a hypoplastic uterus with bilateral ovaries absent. A pelvic MRI scan confirmed these findings. An

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abdominal MRI scan showed a dystopic left kidney at the L4-S1 level and a malrotation right kidney. The skeletal survey revealed delayed bone age by three years at 11 years of age.

Laboratory investigations at 11 years of age showed elevated follicle-stimulating hormone (FSH) levels (67 IU/L) and luteinizing hormone (LH) levels (14 IU/L), as well as low anti-Müllerian hormone (AMH) levels (<0.01 ng/mL) and estradiol (E2) levels (15 ng/mL).

Routine G-banded karyotype analysis showed a normal female karyotype (46,XX). Whole exome sequencing (WES) identified a novel heterozygous frameshift variant c.278_281del, p.(Ile93Argfs*22) and a novel heterozygous missense c.703T>C, p.(Cys235Arg) variant in *MCM8* classified as "Likely Pathogenic (LP)" and "Variant of Uncertain Significance (VUS)," respectively, based on American College of Medical Genetics (ACMG) criteria.[6] Based on clinical, imaging and genetic investigation findings a diagnosis of MCM8-related POI was made.

The patient has been undergoing transdermal estrogen therapy for six months. Despite the treatment, her bone age remains delayed by two years, and her height velocity continues to be within the prepubertal range. However, there has been notable progress in breast development, and the uterus has increased in size and become more structured. The patient is being closely monitored by a multidisciplinary team, including a gynecologist, endocrinologist, geneticist, and pediatric specialists.

DISCUSSION

Recent advancements in sequencing technologies have facilitated the discovery of candidate genes associated with primary ovarian insufficiency (POI), including members of the minichromosome maintenance (MCM) family of genes, specifically *MCM8* and *MCM9*. *MCM8* (OMIM: 608187) is located on chromosome 20 and consists of 19 exons encoding 840 amino acids. It contains highly conserved amino-terminal DNA-binding and AAA+ core domains. The gene product is a DNA helicase protein that plays a critical role in DNA homologous recombination repair, particularly during the repair of DNA double-strand breaks, as well as in meiosis and DNA replication.[7] Pathogenic variants in *MCM8* lead to the absence of functional MCM8 proteins, resulting in genomic instability and errors during cell division that affect reproductive organs, particularly the ovaries. Germline biallelic MCM8variants have also been associated with early-onset Lynch-like syndrome.[8]

Currently, the medical literature has reported 15 cases from 6 families with MCM8-related disorders (Tab.1). AlAsiri et al. were the first to describe an autosomal recessive pathogenic variant in MCM8 causing POI. They reported three sisters from a consanguineous marriage who presented with idiopathic hypergonadotropic primary amenorrhea, hypothyroidism, and atrophic ovaries. Whole exome sequencing (WES) identified a missense variant c.446C>G, p.(Pro149Arg), and functional studies confirmed its pathogenicity.[7] Wang et al. described two siblings diagnosed with short stature and POI, both carrying two novel MCM8variants: c.724T>C, p.(Cys242Arg) and c.1334C>A, p.(Ser445*). The 13-year-old girl with these variants exhibited delayed puberty, short stature, and ovarian insufficiency, while her 6-year-old sister, though asymptomatic at initial presentation, carried the same variants.[9]

TABLE 1. Molecular and additional clinical findings of previously reported and current patients with MCM8-related disorder

Transcript	Nomenclature	Presentation	Genotype	Authors
NM_001282717.2	c.446C>G; p.Pro149Arg	Thyroid dysfunction	Hom	7
NM_001282717.2	c.482A>C; p.His161Pro	-	Hom	12
NM_001281522.1	c.925C>T, p.R309*	Short stature, pilomatricomas	Hom	11
NM_001282717.2 NM_001282717.2	c.724T>C(p.Cys242Arg) c.1334C>A(p.Ser445*)	Short stature	Het Het	4
NM_001282717.2	c.351_354delAAAG	-	Hom	10
NM_001282717.2	c.808C>T, p.(Arg270Ter)	Short stature	Hom	13
NM_032485.6 NM_032485.6	c.278_281del, p.(Ile93Argfs*22) c.703T>C, p.(Cys235Arg)	Congenital kidney anomalies, short stature	Het Het	Our case

Abbreviations: Het, heterozygous; Hom, homozygous

Zhang et al. reported a consanguineous Han Chinese family with healthy parents, a healthy daughter, and two daughters affected by POI. WES revealed a homozygous frameshift mutation, c.351_354 delAAAG, in *MCM8*, which segregated with POI within the family.10 Heddar et al. described a 14-year-old female presenting with short stature, lack of pubertal development, primary amenorrhea, and pilomatricomas. WES identified a c.925C>T, p.R309* variant, which leads to a truncated protein or nonsense-mediated mRNA decay. This variant was homozygous in the patient and heterozygous in her mother.[11]

Bouali et al. investigated a large consanguineous Tunisian family with five affected siblings. Targeted sequencing revealed a novel homozygous missense variant c.482A>C, p.(His161Pro) in *MCM8*. Functional studies confirmed the deleterious nature of the variant, and the parents were heterozygous carriers.[12] Mishra et al. reported two siblings with primary amenorrhea, short stature, and uterine hypoplasia. WES identified a homozygous missense variant

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c.808C>T, p.(Arg270Ter) in both sisters, further expanding the spectrum of *MCM8*-related POI.[13]

In our patient, whole exome sequencing (WES) revealed a heterozygous frameshift variant c.278_281del, p.(Ile93Argfs22), classified as "Likely Pathogenic (LP)," and a heterozygous missense variant c.703T>C, p.(Cys235Arg), classified as a "Variant of Uncertain Significance (VUS)." The p.(Ile93Argfs22) variant results from the deletion of four base pairs in exon 4, generating a frameshift that leads to a premature stop codon 22 amino acids downstream. This is predicted to result in the loss of normal protein function through either truncation or nonsense-mediated mRNA decay. This variant has been identified in 16 heterozygous individuals in gnomAD. However, it has not been described in the medical literature or reported in disease-related variation databases, such as the Human Gene Mutation Database (HGMD).

The p.(Cys235Arg) variant affects a highly conserved amino acid, with a significant physicochemical difference between cysteine and arginine (Grantham score 180, [0-215]). In silico tools consistently predict this variant to be deleterious. The p.(Cys235Arg) variant is absent from gnomAD and has not been reported in the medical literature or disease-related variation databases. Unfortunately, we could not perform a functional analysis of chromosomal instability, such as DNA damage induction, by increasing mitomycin C concentrations on cultured peripheral lymphocytes. However, there is a strong genotype-phenotype correlation, and no other pathogenic or likely pathogenic variants were identified through WES. Overall, our findings support the pathogenicity of these variants and contribute to the expanding mutational spectrum of *MCM8*-related POI.

Notably, our patient presented with a dystopic left kidney and a malrotated right kidney, features not previously reported in the context of *MCM8*-related POI. This finding broadens the known phenotypic spectrum of the disorder. POI is often described as spontaneous or idiopathic, with its etiology remaining largely undetermined.[14] Understanding the genetic basis of POI is critical for improving early diagnosis, treatment strategies, and potential preventive measures. Our study emphasizes the importance and diagnostic utility of WES in cases of unexplained POI.

CONCLUSIONS

We report two novel variants in *MCM8* in a 13-year-old adolescent female with a 46, XX karyotype who presents with POI, short stature, and congenital kidney anomalies. This expands the genotype and phenotype spectrum of the disease. Long-term follow-up studies will be necessary to further expand the phenotypic spectrum in females with *MCM8*-related POI. The exact functional mechanisms involved in the pathogenesis must also be explored further.

INFORMED CONSENT

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AUTHOR AFFILIATIONS

[1]Department of Molecular and Medical Genetics, Tbilisi State Medical University, Tbilisi, Georgia;
[2]Department of Endocrinology, Tbilisi State Medical University, Tbilisi, Georgia;
[3]Direction of Endocrinology and Pediatric Endocrinology, Ilia State University, Tbilisi, Georgia;
[4]Department of Pediatrics, Givi Zhvania Pediatric Academic Clinic, Tbilisi State Medical University, Tbilisi, Georgia.

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