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A rare *PRDM9* frameshift variant in a woman with diminished ovarian reserve

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ABSTRACT

PRDM9 directs meiotic recombination hotspots through its C2H2 zinc-finger (ZF) array, but the clinical significance of heterozygous loss-of-function variants remains uncertain. We identified an extremely rare heterozygous terminal-exon PRDM9 frameshift variant (NM_001310214.2:c.1683del [p.(Phe561LeufsTer378)]; rs1300895286) in a woman with diminished ovarian reserve. The variant lies within the third annotated C2H2 zinc-finger motif according to the UniProtKB Q9NQV7 annotation and is predicted to replace the normal amino acid sequence from Phe561 onward with an aberrant sequence, thereby altering the C-terminal ZF array. The variant was conservatively classified as a variant of uncertain significance. Serum anti-Müllerian hormone levels were 0.31 ng/mL in 2018 and 0.05 ng/mL in 2023. Despite 35 ovarian stimulation cycles, including 23 cycles with planned oocyte retrieval, the patient achieved two live births. This case documents the coexistence of an extremely rare PRDM9 frameshift variant and diminished ovarian reserve but does not establish a causal relationship between them. This hypothesis-generating observation provides additional clinical information for future studies evaluating the potential reproductive significance of rare PRDM9 variants.

1. Introduction

Meiotic recombination is initiated by programmed DNA double-strand breaks and is essential for accurate pairing and segregation of homologous chromosomes (Murakami and Keeney, 2008; Borde and Massy, 2015). In many mammals, PRDM9 directs recombination hotspots through sequence-specific DNA binding mediated by its polymorphic C_2H_2 zinc-finger (ZF) array and catalyzes histone H3K4 and H3K36 trimethylation through its PR/SET domain (Paigen and Petkov, 2018). In mice, *Prdm9* deficiency is frequently associated with meiotic arrest and infertility, although the severity of the phenotype varies according to genetic background (Paigen and Petkov, 2018). Experimental studies have also demonstrated sexual dimorphism in the requirement for PRDM9, with female meiosis showing greater tolerance to altered PRDM9 activity than male meiosis (Powers et al., 2020).

In humans, however, the requirement for PRDM9 in meiosis appears less stringent, and the clinical significance of *PRDM9* loss-of-function (LoF) variants in human reproduction remains uncertain. Heddar et al. reported a woman with primary ovarian insufficiency (POI) carrying a

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Abbreviations

ACMG	American College of Medical Genetics and Genomics
AMH	anti-Müllerian hormone
AMP	Association for Molecular Pathology
BWA	Burrows–Wheeler Aligner
DSB	double-strand break
GATK	Genome Analysis Toolkit
LoF	loss of function
NMD	nonsense-mediated mRNA decay
POI	primary ovarian insufficiency
VUS	variant of uncertain significance
WES	whole-exome sequencing
ZF	zinc finger

heterozygous *PRDM9* truncating variant (Heddar et al., 2025), and Wang et al. identified deleterious *PRDM9* variants in a large POI cohort with supporting functional evidence (Wang et al., 2021). Conversely, population-based studies have identified fertile individuals homozygous for predicted *PRDM9* LoF alleles (Narasimhan et al., 2016), suggesting that the reproductive consequences of *PRDM9* variants may be incompletely penetrant and dependent on additional genetic or physiological factors. We therefore report the molecular and reproductive phenotype of a woman carrying an extremely rare terminal-exon *PRDM9* frameshift variant.

2. Materials and methods

2.1. Study participants and genetic screening

This study included 175 individuals enrolled in ongoing genetic studies of reproductive disorders at our institutions. The cohort was not specifically recruited for PRDM9-associated phenotypes. WES data were available for 79 participants (55 women and 24 men), in whom *PRDM9* variants were evaluated from the exome data. For the remaining 96 participants without WES data, targeted Sanger sequencing was performed specifically to determine the presence or absence of c.1683del. All WES datasets included in the analysis had passed the sequencing provider's routine quality-control assessment before downstream analysis. For both targeted screening and independent validation of the WES-identified c.1683del variant, a 150-bp fragment encompassing the variant site was amplified using the forward primer 5′-ATGGAGAGTGTGGACAAGGT-3′ and reverse primer 5′-CCTGTGTGTATCCTCTGGTGAA-3′, followed by Sanger sequencing.

2.2. Whole-exome sequencing and variant annotation

Genomic DNA was extracted from whole-blood samples using the ISOSPIN Blood & Plasma DNA kit (NIPPON GENE Co., Ltd., Tokyo, Japan), and quality control was conducted before sequencing at Macrogen Co., Ltd. (Tokyo, Japan). Libraries were prepared using the Agilent SureSelectXT Low Input Target Enrichment protocol with the SureSelect Human All Exon V6 (V6-Post) capture kit and sequenced on an Illumina NovaSeq platform with paired-end 151-bp reads. Sequencing reads were aligned to the human reference genome GRCh38/hg38 using BWA-MEM (v0.7.17). PCR duplicates were marked using Picard MarkDuplicates (v3.1.1), and base quality score recalibration was performed using GATK. Variant calling was conducted using GATK HaplotypeCaller (v4.5.0.0), followed by VariantFiltration. Variants were annotated using SnpEff (v5.2), with reference to dbSNP156, 1000 Genomes Phase 3, ClinVar (2024-07-16), and dbNSFP v4.5c. Transcript and protein information was derived from NCBI RefSeq. The PRDM9 variant was described according to the RefSeq transcript NM_001310214.2 and its corresponding protein reference sequence NP_001297143.1. Protein domain positions and zinc-finger numbering were based on the UniProtKB human PRDM9 entry Q9NQV7 (894 amino acids).

2.3. Variant interpretation

Variant interpretation was performed according to the American College of Medical Genetics and Genomics/Association for Molecular Pathology (ACMG/AMP) framework and current ClinGen recommendations (Richards et al., 2015; Abou Tayoun et al., 2018). Population frequency, predicted molecular consequence, transcript location, predicted susceptibility to nonsense-mediated mRNA decay (NMD), and the current evidence for LoF as a disease mechanism for PRDM9 were considered. The c.1683del variant was conservatively classified as a variant of uncertain significance (VUS). PM2_Supporting was considered applicable based on the extreme rarity of the variant in population databases (AC = 2, AN = 42,504; AF = 0.00004705 in the East Asian ancestry group of gnomAD v4 exomes) and its absence from the Japanese 38KJPN reference dataset. However, this evidence was interpreted cautiously because of the relatively limited representation of East Asian individuals in gnomAD and differences in ancestry composition and database coverage. Although the variant is predicted to alter the amino acid sequence of most of the C-terminal ZF array, application of PVS1 requires caution because the variant occurs in the terminal exon and is predicted to escape NMD based on its transcript location; however, this prediction has not been experimentally validated at the RNA level. Furthermore, LoF has not been unequivocally established as a disease mechanism for heterozygous *PRDM9* variants associated with ovarian dysfunction.

2.4. Clinical assessment

Clinical information was obtained from the patient's medical records, including age, menstrual status, serum anti-Müllerian hormone (AMH) and basal follicle-stimulating hormone (FSH) concentrations, available antral follicle count (AFC) data, ovarian stimulation and oocyte retrieval history, and reproductive outcomes. Serum AMH concentrations were measured in-house using the cobas e 402 analyzer (Roche Diagnostics, Mannheim, Germany). Diminished ovarian reserve was clinically characterized based on the combination of markedly reduced AMH concentrations, elevated basal FSH concentrations, and very low AFCs in the available records.

3. Results

3.1. Identification and molecular interpretation of the PRDM9 variant

WES identified a heterozygous 1-bp deletion in the terminal exon of *PRDM9* in one woman (NM_001310214.2:c.1683del [p.(Phe561LeufsTer378)]; rs1300895286) (Fig. 1A). The variant was confirmed by Sanger sequencing (Fig. 1C). The canonical human PRDM9 protein annotated in UniProtKB (Q9NQV7) is 894 amino acids long and contains a KRAB-related domain at residues 23–86, a PR/SET domain at residues 244–358, and 14 annotated C_2H_2 zinc-finger motifs (UniProt Consortium, 2025). According to the UniProtKB Q9NQV7 annotation, Phe561 lies within the third annotated C_2H_2 zinc-finger motif (residues 552–574) (Fig. 1B). The frameshift is predicted to replace the normal amino acid sequence from Phe561 onward with an aberrant sequence, thereby altering the C-terminal zinc-finger array. Although this sequence alteration may affect sequence-specific DNA recognition, its effect on DNA-binding activity has not been experimentally determined. Based on its location in the terminal exon, the mutant transcript is predicted to escape NMD; however, transcript stability was not experimentally assessed. The frameshift is predicted to alter the C-terminal portion of PRDM9, but expression and stability of the resulting protein,

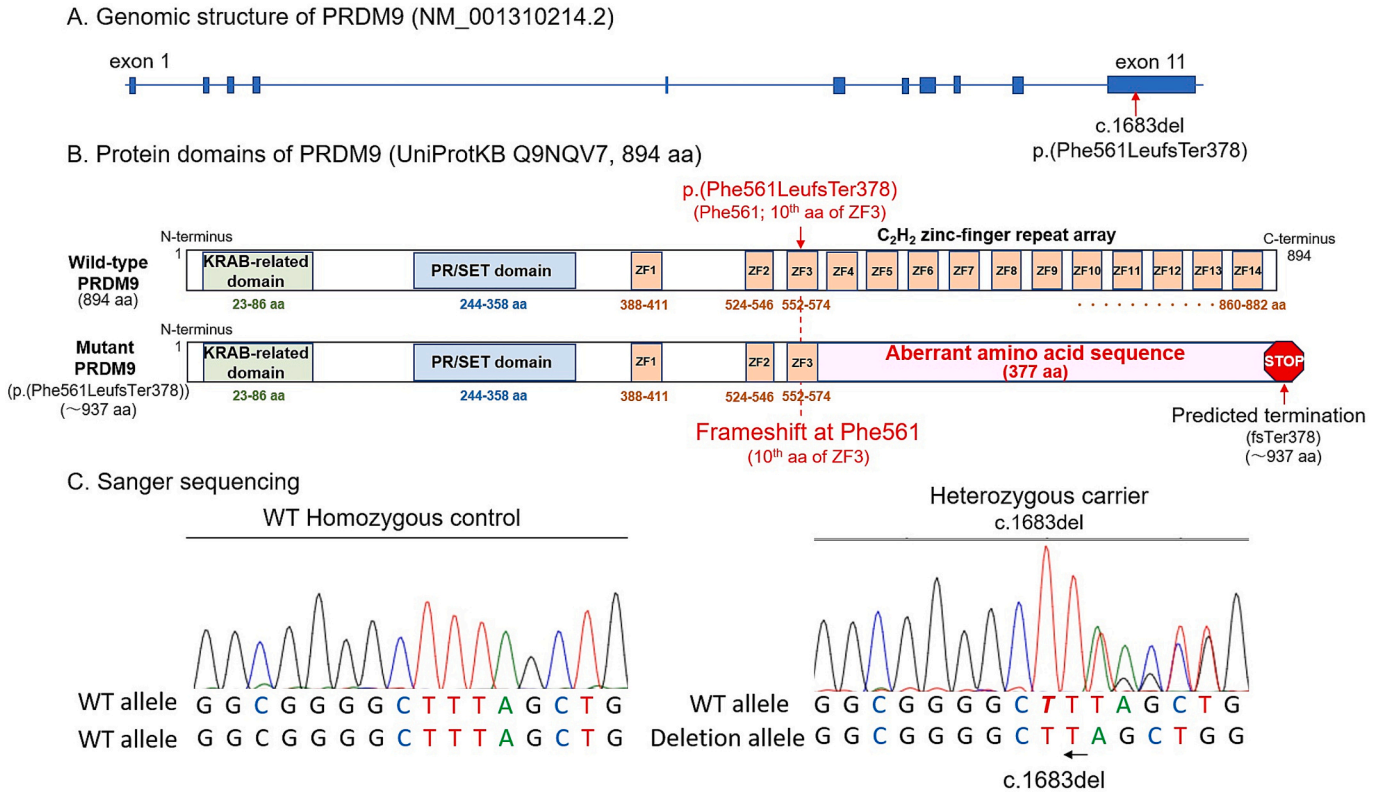


Fig. 1. Identification and localization of the *PRDM9* frameshift variant. (A) Genomic structure of *PRDM9* (NM_001310214.2). The heterozygous frameshift variant c.1683del [p.(Phe561LeufsTer378)], located in the terminal exon, is indicated by a red arrow. (B) Schematic representation of the PRDM9 protein and the predicted consequence of the c.1683del variant. Zinc-finger numbering and residue positions follow the UniProtKB Q9NQV7 annotation. Phe561 lies within the third annotated C_2H_2 zinc-finger motif (residues 552–574). The variant is predicted to result in p.(Phe561LeufsTer378), replacing the normal amino acid sequence from Phe561 onward with an aberrant sequence and introducing a predicted termination codon after 378 codons in the new reading frame. The predicted termination point is indicated. (C) Representative Sanger sequencing chromatograms confirming the heterozygous 1-bp deletion in the patient compared with a wild-type control. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

if produced, remain unknown. Therefore, the variant cannot automatically be considered a conventional null allele. Furthermore, LoF has not been unequivocally established as a disease mechanism for heterozygous *PRDM9* variants in humans. Accordingly, interpretation according to the ACMG/AMP framework requires caution, particularly with respect to the application and strength of PVS1 evidence (Richards et al., 2015; Abou Tayoun et al., 2018). We therefore regard c.1683del as an extremely rare frameshift VUS predicted to substantially alter the amino acid sequence of the C-terminal ZF array rather than as an established pathogenic variant. The c.1683del variant was extremely rare in population databases. In gnomAD v4 exomes, the variant was observed exclusively in the East Asian ancestry group, with an allele count of 2 among 42,504 alleles (AC = 2, AN = 42,504; AF = 0.00004705); no alternate alleles were reported in the other ancestry groups. Therefore, these population data support the rarity of the variant but should be interpreted cautiously and do not provide evidence of pathogenicity by themselves. The patient also carried a homozygous *PRDM9* missense variant, rs6875787 (p.Thr681Ser), within the ZF repeat array. This variant was also observed in other individuals in our cohort and is common in population databases. The frequency of the G allele was 0.54853 in the 38KJPN Japanese reference population (70,740 samples), and the allele frequency reported in gnomAD was 0.74556. In ClinVar (Variation ID 436411), rs6875787 is classified as benign/likely benign based on three submissions without conflicting classifications. No direct functional evidence demonstrating a deleterious effect of rs6875787 was identified. Together with its high population frequency and benign/likely benign ClinVar classification, these findings support its interpretation as common allelic variation rather than as a likely pathogenic variant contributing independently to the phenotype.

3.2. Clinical phenotype and reproductive course

Clinically, the woman carrying the frameshift variant first presented to our clinic in October 2018 at 34 years of age. Her menstrual cycles were irregular. At initial evaluation, her serum AMH concentration was 0.31 ng/mL and her basal serum FSH concentration was 15.0 mIU/mL. At 39 years of age in July 2023, her AMH concentration had decreased to 0.05 ng/mL, with a basal FSH concentration of 27.0 mIU/mL. AFC was not systematically assessed or documented throughout treatment; among the six cycles for which AFC was recorded, it was 0 in four cycles and 1 in two cycles. Taken together, the markedly reduced AMH concentrations, elevated basal FSH concentrations, and very low AFCs in the available records were considered consistent with diminished ovarian reserve. Thyroid function and serum prolactin levels were within the normal range. Between 35 and 41 years of age, the patient underwent 35 ovarian stimulation cycles. Treatment predominantly involved mild stimulation protocols designed to retrieve a limited number of oocytes, generally one to two and at most approximately four per cycle. Of the 35 stimulation cycles, 23 were assigned OPU numbers. Among these, three cycles were converted to intrauterine insemination (IUI) because ovulation had already occurred before the planned retrieval (two cycles) or follicular puncture could not be performed (one cycle). Of the remaining 12 cycles, 10 were cancelled, one was converted to IUI after ovulation, and one proceeded directly to IUI. Consequently, oocyte retrieval was attempted in 20 cycles, and at least one oocyte was obtained in 17 cycles. A detailed treatment timeline, including available AFC data, is provided in Supplementary Table S1. The male partner had normal semen findings, with no clinically significant male-factor infertility identified.

Despite this prolonged treatment course, the patient achieved two live births. The first pregnancy was achieved by fresh embryo transfer following the 13th oocyte retrieval and resulted in a live birth. Subsequently, she underwent a further 10 oocyte retrievals. An oocyte obtained at the 23rd retrieval developed to the blastocyst stage, and subsequent frozen-thawed blastocyst transfer resulted in a second pregnancy and live birth.

4. Discussion

The present case provides an additional clinical observation of an extremely rare *PRDM9* frameshift variant in a woman with markedly diminished ovarian reserve. Heterozygous truncating *PRDM9* variants have been reported in women with POI (Heddar et al., 2025; Wang et al., 2021), whereas fertile individuals carrying predicted *PRDM9* LoF alleles have also been described (Narasimhan et al., 2016).

In the present patient, the coexistence of the *PRDM9* variant and DOR does not establish a causal relationship between the two. Rather, this case represents a hypothesis-generating observation that may help inform future studies investigating the potential reproductive significance of rare PRDM9 variants.

Importantly, the predicted molecular consequence of the present variant should be distinguished from its clinical pathogenicity. The p.(Phe561LeufsTer378) frameshift begins within the third annotated C_2H_2 zinc-finger motif according to the UniProtKB Q9NQV7 annotation and is predicted to replace the normal amino acid sequence from Phe561 onward with an aberrant sequence, thereby altering the C-terminal zinc-finger array. Because the variant occurs in the terminal exon, the mutant transcript is predicted to escape NMD based on its transcript location. However, neither mutant transcript stability nor expression of an altered PRDM9 protein was experimentally assessed in the present study. Therefore, NMD escape and production of an altered protein remain untested predictions. If an altered protein is produced, its stability and functional consequences would also require experimental evaluation. Thus, although the predicted sequence alteration is substantial, its clinical pathogenicity remains uncertain. This uncertainty is reflected in its conservative classification as a VUS under the ACMG/AMP framework.

One testable hypothesis for future investigation is that an altered PRDM9 protein, if expressed, might exert a dominant-negative effect. The N-terminal KRAB domain of PRDM9, which is retained in the predicted altered protein, is known to mediate interactions with proteins involved in meiotic recombination, including CXXC1, EWSR1, EHMT2, and CDYL (Parvanov et al., 2017; Imai et al., 2017). The predicted changes in the C-terminal ZF array could potentially affect its DNA-binding properties. However, neither mutant protein expression, protein–protein interactions, nor DNA-binding specificity or activity was assessed in the present study. Therefore, this model remains speculative and requires experimental validation.

The patient was also homozygous for rs6875787, a common variant classified as benign/likely benign. Although a potential modifier effect of rs6875787 on the consequences of the rare frameshift variant cannot be excluded, no direct functional or clinical evidence currently supports such an interaction. Its potential modifying effect therefore remains uncertain and cannot be evaluated from this single case.

More broadly, ovarian reserve and reproductive aging are regulated by evolutionarily conserved pathways that integrate metabolic and cellular signals. Among these, mechanistic target of rapamycin (mTOR) signaling plays an important role in primordial follicle activation and maintenance of the follicular reserve, and dysregulation of this pathway has been implicated in accelerated follicular depletion and ovarian aging (Sato and Kawamura, 2020; Goldman et al., 2017). Recent studies have further demonstrated the role of mTORC1 as a conserved nutrient-sensing pathway linking extracellular nutrient availability to cellular growth and function through downstream targets such as PDX1 (Fan et al., 2022; Fan et al., 2026). Although no direct relationship between PRDM9 and mTOR signaling has been established, future studies integrating meiotic genetic factors with pathways regulating follicular activation and reproductive aging may help clarify the biological context of diminished ovarian reserve.

Several limitations should be acknowledged. Chromosomal analysis was not documented in the available clinical records, and dedicated copy-number variant analysis was not performed. Although WES did not identify potentially relevant rare variants in the major meiotic genes examined, other genetic contributors to DOR cannot be excluded. In addition, DNA samples and detailed reproductive phenotypes from family members were unavailable, precluding segregation analysis and assessment of genotype–phenotype relationships within the family.

Causality cannot be established from a single carrier, and other genetic, age-related, treatment-related, and physiological factors may have contributed to the clinical phenotype. Further accumulation of individuals carrying rare *PRDM9* frameshift variants, together with detailed reproductive phenotyping and functional analyses, will be required to clarify whether such variants have any relevance to human reproductive disorders.

5. Conclusion

We identified an extremely rare terminal-exon *PRDM9* frameshift variant, c.1683del [p.(Phe561LeufsTer378)], conservatively classified as a VUS, in a woman with diminished ovarian reserve who ultimately achieved two live births after extensive fertility treatment. This case provides an additional clinical observation of a rare *PRDM9* variant in a patient with DOR but does not establish a causal relationship between the variant and DOR. Further studies involving additional well-phenotyped carriers and functional analyses are required to determine the biological and clinical significance of rare *PRDM9* variants in human reproductive disorders.

CRediT authorship contribution statement

Ai Yamada: Validation, Investigation. **Junko Otsuki:** Writing – review & editing, Writing – original draft, Validation, Investigation, Funding acquisition, Formal analysis. **Thu Nu Anh Le:** Validation, Formal analysis. **Yasuhiro Fujiwara:** Writing – review & editing, Validation, Investigation. **Noritoshi Enatsu:** Data curation. **Koji Yamada:** Data curation. **Mariko Iwamoto:** Validation. **Sanae Ichihashi:** Validation. **Ryo Kitajima:** Validation. **Hayato Asama:** Validation. **Daigaku Kamibayashi:** Data curation. **Mikiya Nakatsuka:** Data curation. **Masahide Shiotani:** Validation, Supervision. **Tetsuo Kunieda:** Writing – review & editing, Writing – original draft, Validation, Investigation, Funding acquisition, Conceptualization.

Consent for publication

All participants provided written informed consent for genetic analysis and the use of clinical information for research purposes. Written informed consent for publication was obtained from all patients.

Ethical approval

This study was approved by the Okayama University Institutional Review Board (Approval numbers K2006-036 and K2306-019) and Hanabusa Women's Clinic Institutional Review Board (Approval number 2020-02).

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Declaration of competing interest

All authors declare no competing interests.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.genrep.2026.102685.

Data availability

Data will be made available on request.

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