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A Maternal Loss-of-Function Variant in *KHDC3L* Gene Causes a Range of Adverse Pregnancy Outcomes: A Case Report

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ABSTRACT

Background: The *KHDC3L* gene encodes a component of the subcortical maternal complex (SCMC). Biallelic mutations in this gene cause 5%–10% of biparental hydatidiform moles (BiHM), and a few maternal deletions in *KHDC3L* have been identified in women with recurrent pregnancy loss (RPL).

Method: In this study, we had a patient with a history of 10 pregnancy or neonatal losses, including spontaneous abortions, neonatal deaths, and molar pregnancy. Whole-exome sequencing (WES) was performed for genetic diagnostic testing.

Results: We found a homozygous deleterious variant in the start codon of *KHDC3L* (c. 1A>G, p.M1V), which probably results in non-translation or the production of a truncated protein.

Conclusion: This is the first report of a maternal loss-of-function variant in *KHDC3L* gene in a patient experiencing various types of pregnancy loss. This case report broadens the understanding of *KHDC3L*'s pathogenic variants and phenotypic spectrum, consistent with its crucial role during human pre- and post-implantation development.

1 | Introduction

The subcortical maternal complex (SCMC) is a multiprotein complex expressed in the oocyte and early embryo in mammals. Encoded by maternal effect genes, it plays a vital role in the maternal-to-zygotic transition (MZT) (Wu and Dean 2020). The SCMC proteins are essential components of cytoplasmic lattices (CPLs), which are sites where oocytes store essential proteins for early embryonic development (Jentoft et al. 2023). Maternal loss-of-function of genes encoding SCMC components leads to either sterility or subfertility in both mice and humans (Lu et al. 2017). So far, at least eight members of this complex have been identified in humans (Bebbere et al. 2021). *KHDC3L* (OMIM 614293) is among those members. Maternal loss of function of *Khdc3*

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(*Filia*) in mice causes a high frequency of aneuploidy and micronuclei formation in the embryos. Consequently, these embryos either do not progress beyond the cleavage-stage or experience developmental delays, leading to reduced fecundity (Zheng and Dean 2009). In humans, biallelic mutations of maternal *KHDC3L* account for 5%–10% of cases with biparental hydatidiform mole (BiHM) (Parry et al. 2011; Akoury et al. 2015; Yang et al. 2022; Rath et al. 2023). This is a recurring form of hydatidiform mole (HM), which is characterized by trophoblast overgrowth and the absence of embryo development (Murdoch et al. 2006). In our previous study, we demonstrated that in a BiHM patient with homozygous null mutation in *KHDC3L*, there was a genome-wide loss of methylation in the oocytes, that included imprinted and non-imprinted regions. Genome-wide analysis of a pre-implantation embryo and molar tissue from the same patient showed that following fertilization, methylation defects at imprinted genes persist, while most non-imprinted regions recover near-normal methylation post-implantation. This evidence highlights the critical role of *KHDC3L* in the establishment of *de novo* DNA methylation in human oocytes (Demond et al. 2019). A recent study showed that NLRP5, a core component of SCMC proteins, stabilizes UHRF1, which is essential for maintaining CpG methylation (Unoki et al. 2024). This further supports the role of SCMC in DNA methylation and epigenetic regulation.

Recurrent pregnancy loss (RPL) is the failure of two or more clinically recognized pregnancies before 20 weeks of gestation (Dimitriadis et al. 2020). Initially, there was no evidence for mutations in *NLRP7*, *NLRP2*, or *KHDC3L* in women with RPL (Aghajanova et al. 2015). Later on, only a handful of studies in the literature have found mutations in *KHDC3L* gene associated with RPL (Wang et al. 2018; Fatemi et al. 2021; Xiang et al. 2021). A study in 2019 revealed small heterozygous deletions in two women affected by RPL and demonstrated that these *KHDC3L* mutations caused severe genomic instability and apoptosis in human embryonic stem cells (hESC) (Zhang et al. 2019). Moreover, deleterious single heterozygous variant of *KHDC3L* has been associated to multilocus imprinting disorders (MLID) in one case (Pignata et al. 2022). Thus, although *KHDC3L* has been firmly established as a cause of HM, a few cases suggest that the associated phenotypes may be more heterogeneous.

Whole-exome sequencing (WES) is a powerful tool for identifying disease-causing mutations. In pregnancy, it helps detect genetic causes of developmental disorders, congenital anomalies, or pregnancy loss. Here, using WES, we report a homozygous missense pathogenic variant in *KHDC3L* gene associated with HM, RPL, and neonatal death. This is a previously reported variant, which has a founder effect on Iranian patients affected by recurrent HM (Fallahi et al. 2020). This study expands our knowledge on the involvement of *KHDC3L* in different types of pregnancy complications, going beyond HM.

2 | Materials and Methods

2.1 | Ethical Compliance and Consent to Participate

We obtained ethical approval from the Royan institute at the commencement of this study (IR.ACECR.ROYAN.REC.1398.173). We received informed consent from the patient, and she agreed to the publication of a report on the study.

2.2 | Molecular Genetic Analysis

Genomic DNA was extracted from peripheral blood cells using the conventional salting-out procedure. The extracted DNA was quantified by a nanodrop. WES of the proband was performed on the extracted DNA at IGA Technology Services (Italy) using the Agilent SureSelect Human All Exone v5 library (50 M bp of genome) and the Illumina HiSeq2500 platform. Bioinformatic analysis was done as previously reported (Cubellis et al. 2020). Briefly, reads were aligned to the human genome reference assembly (Genome Reference Consortium Human GRCh37) using the BWAmem software package v0.7.15 (Li and Durbin 2009). PCR duplicates were filtered out by Picard v2.9, and the GATK v3.7 suite was used to locally realign around inferred Insertion/Deletions and recalibrate base quality scores. Single-nucleotide variants and Insertion/Deletions were called using GATK HaplotypeCaller and GenotypeGVCFs (DePristo et al. 2011), and recalibrated with VariantRecalibrator. Recalibrated variants were annotated using wANNOVAR (Chang and Wang 2012). Genome variants with low coverage (< 20) or low quality (< 20) or in VQSRTrancheSNP99.00to99 or frequently occurring in general population (Karczewski et al. 2021) were filtered out. The effect of the variants was predicted using the sequence-based tool PolyPhen-2 (Adzhubei et al. 2010), whose scores correlate with the residual activity of the protein affected by the mutation (Cimmaruta et al. 2018). Sanger sequencing was used to confirm the identified variant in the patient.

3 | Case Presentation

The proband was a 41-year-old Iranian woman with a history of 10 pregnancy losses, who was referred to the Isfahan Infertility Center. The proband was in a consanguineous marriage (first cousin) and the couple socio-occupational status is classified as medium. In the couple's family, only the proband's sister has experienced two spontaneous abortions. Apart from that, there is no history of pregnancy loss in either family. Clinical evaluation of uterine anatomy, thrombophilia, immunologic factors, and infections in the proband showed no signs of abnormality. The proband had regular menstrual every 28–30 days. Also, the proband and her husband's karyotype was normal. The proband was referred to the Isfahan Infertility Center after her pregnancy losses, which included five spontaneous abortions before reaching 3 months, and one complete HM. The cardiac activity was not present on ultrasound scans in any of the spontaneous abortions. Additionally, she experienced four preterm births between 5 and 7 months. The first three preterm births were stillborn males delivered at 5–6 months of gestational age due to preterm premature rupture of membranes (PPROM). The last preterm birth was a male delivered at 7 months of gestational age, who passed away 5 days after birth due to neonatal respiratory distress. It is worth mentioning that there was no sign of cervical incompetence in any of pregnancies. The patient had normal hysterosalpingogram, so no anomalies were detected in her uterine cavity. She experienced repeated preterm births following the spontaneous rupture of amniotic sac. A cervical

cerclage was performed in her tenth pregnancy but was not effective. Therefore, other causes for PPROM such as uterine overactivity, infection, and inflammation might have been involved. Additionally, we did not have access to abortion products for P57 staining or ultrasound from the preterm births. The P57 staining is used to differentiate between molar pregnancies and nonmolar pregnancies. Consequently, we cannot claim with 100% certainty that the first five pregnancies were indeed abortions.

In 2012, the patient was advised to undergo assisted reproductive treatment. Briefly, oocytes were collected after ovarian stimulation using a standard gonadotropin-releasing hormone (GnRH) antagonist protocol. Oocytes were collected in G-IVF plus (Vitrolife) and cleaned in G-MOPS (Vitrolife) supplemented with 80 IU/mL hyaluronidase (HYASE-10X, Vitrolife). A total of 16 oocytes were collected (2 were at GV stage and 14 at MII stage). Using the patient's husband's sperm, 14 oocytes underwent IVF, resulting in the production of eight embryos. First, two eight-cell stage embryos were transferred but did not result in pregnancy. Then, based on the gynecologist's decision, three embryos were transferred to a surrogate uterus. Unfortunately, these embryos led to the development of a partial HM in the surrogate mother. Based on the gynecologist's advice and considering the consanguineous marriage, the proband and her husband decided to proceed with genetic testing for the proband. Further details are provided in the next section. In 2019, the patient and her husband opted for IVF with donor eggs from a healthy, non-related woman, which yielded four embryos. Two embryos at blastocyst stage were transferred to the patient's uterus. However, absence of a fetal heartbeat was diagnosed at 6 weeks of gestation. Consequently, a D&C procedure was performed. There are several potential causes of miscarriage for these embryos including developmental disorders of placenta or fetal membranes, hormonal or endocrine problems, and uterine receptivity abnormalities. Figure 1 shows the pedigree. After the failure of IVF with both the patient's oocyte and donor oocyte, the patient and her husband opted for adoption.

4 | Genetic Evaluation

Genomic DNA of the proband was analyzed by WES. We selected variants that are most probably deleterious among those found in the general population with relatively low frequency (MAF < 0.001 in gnomAD, Karczewski et al. 2021). We included frameshift insertions or deletions, non-sense mutations, mutations affecting the start codon and those classified as deleterious "D" by PolyPhen2 (Adzhubei et al. 2010). We found a previously reported homozygous pathogenic variant c. 1A>G, p.M1V in exon one of *KHDC3L* (NM_001017361.3). The variant has been recorded in ClinVar database and according to the criteria of the American College of Medical Genetics and Genomics (ACMG) (Richards et al. 2015), this variant is considered pathogenic with no possibility of being a splice variant. The identified variant was confirmed by Sanger sequencing (Figure 2).

5 | Discussion

Preimplantation embryonic development relies on maternal-effect genes to orchestrate the oocyte-to-embryo transition, with the SCMC being a maternal functional module playing a fundamental role in this transition; altering SCMC genes in mice and humans has been found to result in impaired early embryonic arrest (Bebbere et al. 2021). However, studies have demonstrated alterations in SCMC genes associated with later reproductive problems, such as BiHM, RPL, and MLID. Although the molecular mechanisms behind reproductive disorders and SCMC genes remain poorly understood, it is feasible to suggest that SCMC gene expression is important not only during early embryogenesis but also later in pregnancy (Rockenbach et al. 2023). One SCMC member is *KHDC3L*, which is primarily expressed in oocyte and early embryo (Pierre et al. 2007). Although *KHDC3L* mRNA is rarely detected in human and monkey morulae, its levels dramatically increase in blastocysts. Moreover, single-cell RNA sequencing in monkey embryos has prominently identified *KHDC3L* mRNAs in epiblast cells, with its expression remaining high until E14 at the onset of gastrulation (Nakamura

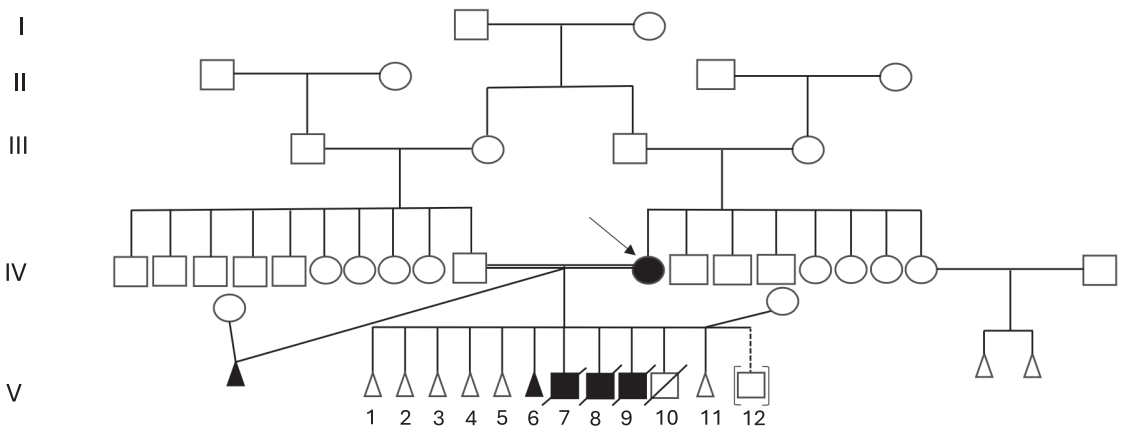

FIGURE 1 | Pedigree. The proband is indicated by an arrow. The individual on the left, attached with the diagonal line, represents the surrogate mother. The individual on the right, attached with the diagonal line, represents the egg donor. Individual V-12 is the adopted child. Unfilled triangles: Spontaneous abortion, filled triangle: Hydatidiform mole, filled square: Preterm births, unfilled square with diagonal line: Neonatal death.

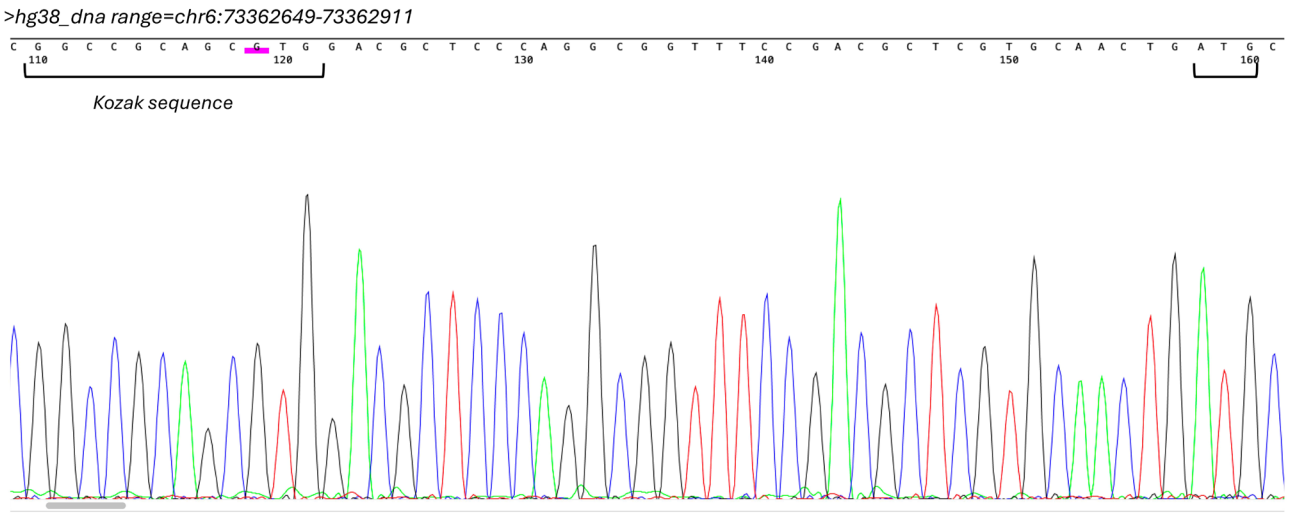

FIGURE 2 | Electropherogram from Sanger sequencing confirming the identified mutation in the proband. The mutated base is highlighted in purple. The surrounding Kozak sequence and the second start codon are enclosed in brackets.

et al. 2016). These expression patterns imply that *KHDC3L* may play a role during post-implantation embryogenesis.

Upon the implantation, the proper trophectoderm proliferation and subsequent placental development rely on both a competent blastocyst and receptive endometrium. Concerning the latter, endometrial cells undergo decidualization, which is pivotal for supporting normal placentation. Recently, it has been shown that in the chorionic villus of RPL patients, *KHDC3L* was upregulated (Rockenbach et al. 2023). On the other hand, HM (caused by mutations in *KHDC3L* or *NLRP7*) is a pregnancy complication characterized by hyperproliferation of trophectoderm. This evidence suggests a potential role of *KHDC3L* in trophectoderm proliferation and differentiation, which further could affect the placental development. In case of our patient's oocyte, it led to the development of a partial HM in the surrogate uterus, further indicating that the absence of *KHDC3L* in the female germline is the cause of HM formation.

In this study, we had a patient with complex pregnancy situation. Using WES, we identified a previously reported homozygous mutation (c. 1A>G, p.M1V) in exon one of the *KHDC3L* gene. This pathogenic variant, which is the same as in our previous work demonstrating a genome-wide loss of methylation in oocytes of a BiHM patient (Demond et al. 2019), is responsible for the HM, RPL, and neonatal death in this patient. This pathogenic variant results in the loss of the canonical start codon. Alternate start codons are rare in eukaryotic genomes (Asano 2014); hence, based on transfections experiment performed by Parry and colleagues (Parry et al. 2011), we hypothesize that the following ATG codon is utilized, which corresponds to what would be methionine 14 in the wild-type protein. However, translation from this site might not be efficient as a Kozak consensus is not found in its proximity. Therefore, the mutation leads to a deletion at the N-terminus of the resulting protein product. Amino acids 1–14 in the wild-type KHDC3L protein are crucial for the beta-sheet structure of the KH domain. Therefore, we anticipate that even if the translation starts, the protein may not fold correctly (Graphical abstract). The residual activity of this truncated protein or partial compensation from other SCMC proteins may explain the resulting variable phenotype. Additionally, as mentioned above, due to the absence of Kozak consensus near the second start codon, another possibility is the complete lack of the protein. In this case, the observed phonotype would align closely with that of *Khdc3* null mice, which show impaired preimplantation embryo development leading to fetal wastage (Zheng and Dean 2009).

This study confirms that genetic problem is one of the causes of repeated abortions. Consanguineous marriage is not recommended, especially in the families with such a background. Gynecologists must be highly vigilant and aware of the genetic causes of repeated molar pregnancies. They should request genetic testing for the responsible mutations and confirm the diagnosis promptly. On the other hand, financial considerations for implementing genetic testing for patients with a history of multiple miscarriages must be taken into account. In the country where the study was performed, the insurance does not cover the entire cost of the analysis. Therefore, adding this kind of genetic testing, at least for patients with direct indications, to government-funded patient support programs must be seriously considered. Once mutations are diagnosed, the proper treatment, including oocyte donation, should be recommended.

In conclusion, here we report a homozygous mutation (c. 1A>G, p.M1V) in *KHDC3L* gene, which is implicated in the RPL and neonatal death etiology, which was not previously reported.

Author Contributions

Zahra Anvar, Bahia Namavar Jahromi and Andrea Riccio conceived the idea. Farnoosh Jafarpour obtained the sample. Zahra Anvar and Maria Vittoria Cubellis performed molecular studies. Maria Vittoria Cubellis performed the bioinformatic analysis. Andrea Riccio and Mohammad Hossein Nasr-Esfahani interpreted the results. Mohammad Hossein Nasr-Esfahani and Bahia Namavar Jahromi identified the patient. Zahra Anvar, Farnoosh Jafarpour and Maria Vittoria Cubellis wrote the manuscript. All authors have read and approved the final manuscript.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available in ClinVar database at https://www.ncbi.nlm.nih.gov/clinvar/. These data were derived from the following resources available in the public domain: ClinVar database, https://www.ncbi.nlm.nih.gov/clinvar/.

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