Clinical Investigation / Araştırma

DOI: 10.4274/tjod.galenos.2025.40456

Turk J Obstet Gynecol

The retrospective data analysis of NLRP7 and KHDC3L mutations in Turkish patients with recurrent hydatidiform mole

Tekrarlayan mol hidatidiformlu Türk hastalarda NLRP7 ve KHDC3L mutasyon verilerinin retrospektif analizi

Leyla Özer[1], Süleyman Aktuna[1], Evrim Ünsal[2]

[1]*Mikrogen Genetic Diagnosis Center, Ankara, Türkiye*

[2]*Yüksek İhtisas University Faculty of Medicine, Department of Medical Genetics, Ankara, Türkiye*

Abstract

Objective: Recurrent hydatidiform mole (RHM) is a rare disorder which is characterized by the presence of at least two molar pregnancies. The mutations in the *NLRP7* and *KHDC3L* genes are responsible for the majority of recurrent molar pregnancies. This study aimed to demonstrate the diversity and frequency of NLRP7 and KHDC3L gene mutations in our Turkish cohort with recurrent molar pregnancies, and to establish genotype-phenotype correlation.

Materials and Methods: It was aimed to represent the detected *NLRP7* and *KHDC3L* gene variants and reproductive history of 32 recurrent mole hydatidiform patients. We analysed the retrospective clinical and sequence data of 32 patients, who were referred to the laboratory for NLRP7 and KHDC3L sequencing.

Results: Among the detected 32 patients with recurrent molar pregnancy, 18 of 32 patients had no mutation in these two genes; we found 7 cases of homozygous NLRP7 variant, 1 case of heterozygous NLRP7 variant, 3 cases of homozygous *KHDC3L* gene variant, and 1 case of heterozygous *KHDC3L* gene variant. Among the detected NLRP7 variants, 3 of 11 variants were classified as pathogenic, 7 of 11 variants were classified as likely pathogenic, and 1 of 11 variants was classified as variant of unknown significance (VUS). Among the detected KHDC3L variants, 1 of 4 was classified as pathogenic, 2 of 4 were classified as likely pathogenic, and 1 of 4 was classified as VUS. Seven unpublished *NLRP7* gene variants and two unpublished *KHDC3L* gene variants were first reported in this study.

Conclusion: Here we report new RHM patients with NLRP7 and KHDC3L mutations. The current study highlights the importance of defining new cases and novel mutations in the pathogenesis and clinical management of RHM. Understanding genotype-phenotype correlations in RHM patients will also contribute to the selection of treatment methods and patient management.

Keywords: NLRP7 protein, KHDC3L protein, recurrent mole hydatidiform, next generation sequencing

Öz

Amaç: Tekrarlayan mol gebeliklerin (RHM) büyük bir kısmından NLRP7 ve KHDC3L genlerinin mutasyonları sorumludur. Bu çalışmada tekrarlayan mol gebelikli Türk kohortumuzdaki NLRP7 ve KHDC3L gen mutasyonlarının çeşitliği ve sıklığının gösterilmesi ve genotip-fenotip korelasyonunun kurulması amaçlandı.

Gereç ve Yöntemler: Otuz iki tekrarlayan mol hidatidiform hastanın *NLRP7* ve *KHDC3L* gen varyantları ve üreme geçmişleri sunulmuştur. NLRP7 ve KHDC3L dizilmesi için laboratuvara sevk edilen 32 hastanın retrospektif klinik ve dizi verilerini analiz ettik.

PRECIS: Retrospective analysis of NLRP7 and KHDC3L sequence data revealed novel variants. The findings support genotype-phenotype correlations and have important implications for diagnosis, genetic counseling, and clinical management in recurrent molar pregnancies.

Corresponding Author/Sorumlu Yazar: Leyla Özer MD,
Mikrogen Genetic Diagnosis Center, Ankara, Türkiye
E-mail: leyla_ozer@yahoo.com **ORCID ID:** orcid.org/0000-0001-8763-5268

Received/Geliş Tarihi: 09.05.2025 **Accepted/Kabul Tarihi:** 07.07.2025 **Epub:** 10.07.25025

Cite this article as: Özer L, Aktuna S, Ünsal E. The retrospective data analysis of NLRP7 and KHDC3L mutations in Turkish patients with recurrent hydatidiform mole. Turk J Obstet Gynecol. [Epub Ahead of Print]

Bulgular: Tespit edilen 32 tekrarlayan molar gebelik hastası arasında 32 hastanın 18'inde bu iki gende mutasyon saptanmamış olup, 7 olguda homozigot NLRP7 varyantı, 1 olguda heterozigot NLRP7 varyantı, 3 olguda homozigot *KHDC3L* gen varyantı ve 1 olguda heterozigot *KHDC3L* gen varyantı saptandı. Tespit edilen NLRP7 varyantlarından 11 varyanttan 3'ü patojenik, 11 varyanttan 7'si muhtemel patojenik ve 11 varyanttan 1'i önemi bilinmeyen varyant (VUS) olarak sınıflandırıldı. Tespit edilen KHDC3L varyantlarından 4 varyanttan 1'i patojenik, 4 varyanttan 2'si olası patojenik ve 4 varyanttan 1'i VUS olarak sınıflandırıldı. Bu çalışmada ilk kez 7 adet yayınlanmamış *NLRP7* gen varyantı ve 2 adet yayınlanmamış *KHDC3L* gen varyantı bildirildi.

Sonuç: Bu çalışmada NLRP7 ve KHDC3L mutasyonları olan yeni RHM hastalarını bildirilmektedir. Mevcut çalışma, RHM'nin patogenezinde ve klinik yönetiminde yeni olguların ve yeni mutasyonların tanımlanmasının önemini göstermektedir. RHM hastalarında genotip-fenotip korelasyonlarının anlaşılması tedavi yöntemlerinin seçimi ve hasta yönetimine de katkı sağlayacaktır.

Anahtar Kelimeler: NLRP7 protein, KHDC3L protein, tekrarlayan mol hidaditiform, yeni-nesil sekanslama

Introduction

Molar pregnancy or mole hydatidiform is a gestational trophoblastic disease characterized by abnormal embryonic development and excessive proliferation of trophoblasts. Most cases of molar pregnancy are sporadic, occurring in approximately 1 in 600 pregnancies[1,2]. A hydatidiform mole is histopathologically classified into two main categories based on parental origin: complete hydatidiform mole and partial hydatidiform mole. Complete mole hydatidiform is characterized by excessive trophoblastic proliferation and the absence of extra-embryonic membranes. In contrast, partial molar hydatidiform shows mild trophoblastic proliferation and may contain extra-embryonic membranes and embryonic tissue. Most complete mole hydatidiform cases are diploid androgenetic, while most partial mole hydatidiform cases are dispermic triploid. Recurrent mole hydatidiform (RHM) is defined as the occurrence of ≥2 molar pregnancies[1,2]. Although the frequency varies among the different ethnicities, RHM accounts for approximately 1-10% of all molar hydatidiform cases[3]. The most common genetic cause of recurrent molar hydatidiform is a homozygous mutation of the *NLRP7* gene (OMIM 231090), which accounts for approximately 55% of cases[4-6]. The second most common cause is homozygous mutations of the *KHDC3L* gene (OMIM 611687), accounting for 5% of cases. In cases with mutations in *NLRP7* or *KHDC3L*, molar hydatidiform tissues are found to be diploid biparental[6-9]. Both genes regulate gene expression during oocyte and embryo development through genomic imprinting or epigenetic mechanisms. The *NLRP7* and *KHDC3L* genes are maternal-effect genes and components of the subcortical maternal complex, playing roles in the epigenetic reprogramming of the oocyte and the activation of embryonic development[6,10]. Mutations in the *NLRP7* and *KHDC3L* genes contribute to the pathogenesis of molar pregnancy by disrupting cytokine secretion and the implantation process. In addition to playing a role in oocyte and embryo development, *NLRP7* also regulates the release of interleukin-1 beta, contributing to inflammation and immune responses[8]. Mutations in the *NLRP7* or *KHDC3L* genes lead to the inactivation of the maternal allele and the expression of only the paternal allele. Monoallelic paternal expression of these genes causes defective placenta-specific imprinting and recurrent molar pregnancies[10,11]. Several studies have demonstrated that mutations in the *NLRP7* gene negatively impact oocyte quality and lead to arrest in embryonic development. *NLRP7* plays a role in sustaining genomic stability by regulating the alternative splicing of genes involved in homologous recombination repair[12]. Similarly, the *KHDC3L* mutation causes genomic instability in embryonic cells, which can result in increased DNA damage and subsequent embryonic developmental arrest[13]. Mutations in both *NLRP7* and *KHDC3L* disrupt DNA repair mechanisms, thereby contributing to impaired embryonic development[9]. Mutations of the *NLRP7* and *KHDC3L* genes have been reported to be associated with recurrent pregnancy losses and recurrent molar pregnancies.

It is not easy to clinically and histologicallydistinguish recurrent from spontaneous molar pregnancies. Therefore, the diagnosis of RHMs is often delayed. Although the mechanisms leading to molar pregnancy are not fully known, screening for known genetic factors is necessary to establish the genetic diagnosis of recurrent molar pregnancies. Late diagnosis in these patients may lead to recurrent molar pregnancies, unnecessary medications, and in vitro fertilization (IVF) treatments. Early diagnosis of recurrent molar pregnancies is essential for patients to receive appropriate treatment. The aim was to highlight the importance of the genetic diagnosis of RHM in clinical decision-making by reporting new cases. Here, we present the reproductive history and genomic variants, specifically NLPR7 and *KHDC3L* mutations, in Turkish patients with RHMs, including nine previously unpublished variants.

Materials and Methods

Patient Selection

A total of 32 patients with recurrent hydatidiform mole who were referred to the Mikrogen Genetic Diagnosis Center for *NLPR7* and *KHD3L* gene sequencing were retrospectively analyzed. Thirty-one patients had at least two molar pregnancies, and one patient had a history of choriocarcinoma. This study was approved by the Yüksek İhtisas University Medical School Ethical Committee (approval no: 295, date: 14.04.2025), and written consent was obtained. This study was conducted in accordance with the Declaration of Helsinki.

NLRP7 and *KH3DL* Gene Sequencing

Genomic DNA was isolated from peripheral blood samples using the QIAamp DNA Blood Kit (QIAGEN, Germany). Next-generation sequencing of the *NLRP7* and *KHD3L* genes was

performed on an Illumina MiSeq sequencing platform (Illumina Inc., San Diego, CA, USA) by following the manufacturer's instructions. The exon/exon-intron junctions of *NLRP7* and *KHDC3L* genes were sequenced to obtain a minimum read depth of 20x for >98% of the targeted bases. The Hg19 (GRCh37) sequence was used as a reference genome. FASTQ and VCF files were obtained. Bioinformatic solutions such as NextGENe (Version 2.4.2.3/SoftGenetics LLC-USA), Geneticist Assistant (Version 1.8.1.0/SoftGenetics LLC-USA), and Franklin Genoxx (Genoox, Israel) were used for VCF data analysis. All detected variants were evaluated according to their pathogenicity and classified according to the recommendations of international guidelines. Detected *NLRP7* and *KHDC3L* variants have been classified into five categories based on international standards, which are determined by their pathogenic effects (ACMG 2015): pathogenic, likely pathogenic, variant with unknown clinical significance (VUS), likely benign, and benign. A pathogenic variant is defined as a genetic change for which there is strong and well-established evidence indicating a direct causative role in disease. A likely pathogenic (LP) variant has greater than 90% certainty, of being disease-causing, based on available evidence. Conversely, a likely benign variant also has greater than 90% certainty; however, in this case, the evidence suggests that the variant is not associated with disease. A benign variant is one for which there is conclusive evidence demonstrating that it does not cause disease. A VUS refers to a genetic alteration for which the current evidence is either insufficient or conflicting regarding its role in disease. Identification of a VUS does not confirm or exclude a diagnosis. The variant classification is made according to the mutation type, its functional effect, whether it is defined in relevant databases and literature, and whether it is compatible with the patient's clinical findings.

Results

A total of 32 patients with RHMs were analyzed for mutations in *NLRP7* and *KHDC3L* genes. 7 of 32 patients (21.8%) had a homozygous *NLRP7* variant, 1 of 32 patients (3.1%) had compound heterozygous *NLRP7* variants, 2 of 32 patients (6.2%) had a heterozygous *NLRP7* variant, 3 of 32 patients (9.3%) had a homozygous *KHDC3L* variant and 1 of 32 patients (%) had a heterozygous *KHDC3L* variant (Figure 1). No mutation was found in 56.2% of patients (18/32). Among the detected *NLRP7* variants, 3 of 11 variants were classified as pathogenic, 7 of 11 variants were classified as LP, and 1 of 11 variants was classified as VUS. Regarding the type of *NLRP7* gene variants, one missense, five frameshift, two nonsense, and three splice variants were reported. Among the detected *KHDC3L* variants, 3 out of 4 were classified as LP, and 1 out of 4 was classified as VUS. Regarding the type of *KHDC3L* gene variants, one missense and three frameshift variants have been reported. Seven unpublished *NLRP7* gene variants and two unpublished *KHDC3L* gene variants were first reported in this study (Table 1).

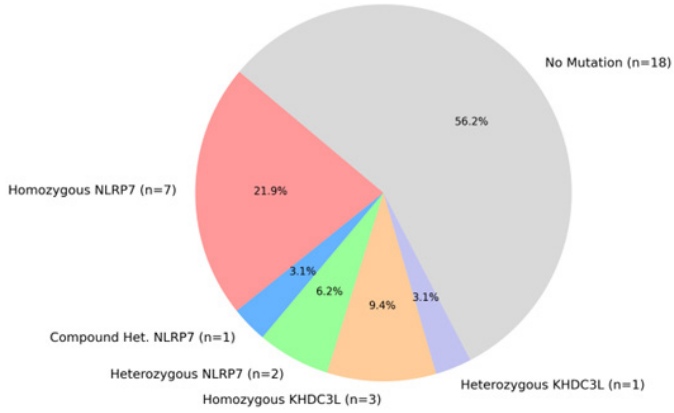

Figure 1. Distribution of genetic findings in RHM patients

RHM: Recurrent hydatidiform mole, NLRP7: NLR family, pyrin domain-containing 7, KHDC3L: KHDC3L like protein, subcortical maternal complex member

The clinical phenotypes of patients with *NLRP7* or *KHDC3L* gene variants are presented in Table 1. Eighteen of 32 patients had no variant in the *NLRP7* or *KHDC3L* genes. Seventeen of 18 patients (17/18), had at least two molar pregnancies, and one of them had a history of choriocarcinoma.

Discussion

Here, we have reported the retrospective data of 32 patients with RHM referred to the Mikrogen Genetic Diagnosis Center. Seven patients had a homozygous *NLRP7* variant, one patient had a compound heterozygous *NLRP7* variant, and two had a heterozygous *NLRP7* variant. Individuals with *NLRP7* variants exhibit a broad spectrum of reproductive outcomes, including stillbirth, spontaneous abortion, blighted ovum, partial hydatidiform mole, complete hydatidiform mole, and, in rare instances, live birth. The underlying mechanisms through which specific mutation types in *NLRP7* contribute to the pathogenesis of molar pregnancies remain to be elucidated[14]. Biallelic *NLRP7* variants cause recurrent hydatidiform mole disease. Still, female carriers have an increased risk of reproductive failure, recurrent pregnancy loss, or having offspring with aberrant methylation and imprinting disorders. Limited data are reported regarding the effect of heterozygous *NLRP7* variants on phenotype. These studies suggested that female heterozygous carriers have a history of reproductive failure without molar pregnancy. Hayward et al.[15] demonstrated aberrant methylation in embryonic tissues of *NLRP7* heterozygous carriers, and they stated that the *NLRP7* gene regulates oocyte growth or controls the transduction of signals to initiate imprinting. Some studies have demonstrated that reproductive failure in heterozygous carriers of *NLRP7* variants is consistent with imprinting defects in placental tissues and increased maternal methylated transcripts[16,17]. Soellner et al.[18] reported a case of reproductive failure and fetal

Table 1. Clinical and genotypic data of RHM cases with NLRP7 and KHDC3L variants and our cases

Patient no	Age	Clinical features	Gene	Variant	Zygosity	Variant type	Classification	References
1	26	Recurrent mole hydtatiform	*NLRP7*	c.241delA	Homozygous	Frameshift	Likely pathogenic	Recent study
2	39	Recurrent mole hydtatiform	*NLRP7*	c.1557delA	Homozygous	Frameshift	Likely pathogenic	Recent study
3	27	Recurrent mole hydtatiform and have 3 sisters with same condition	*NLRP7*	c.368G>A c.2471+1G>A	Compound heterozygous	Nonsense Splice altering	Likely pathogenic Pathogenic	Recent study Murdoch et al.[20], Kocabey et al.[21]
4	28	Recurrent mole hydtatiform	*NLRP7*	c.368G>A	Homozygous	Nonsense	Likely pathogenic	Recent study
5	41	Recurrent mole hydtatiform	*NLRP7*	c.1374_1375del	Homozygous	Frameshift	Likely pathogenic	Recent study
6	29	Recurrent mole hydtatiform	*NLRP7*	c.2471+1G>A	Homozygous	Splice altering	Pathogenic	Murdoch et al.[20], Kocabey et al.[21]
7	38	Recurrent mole hydtatiform	*NLRP7*	c.994del	Homozygous	Frameshift	Likely pathogenic	Recent study
8	39	Recurrent mole hydtatiform, ectopic pregnancy, IVF failure	*NLRP7*	c.2471+1G>A	Homozygous	Splice altering	Pathogenic	Murdoch et al.[20], Kocabey et al.[21]
9	26	She had an affected daughter with neurological problems and her sister had a homozygous NLRP7 variant	*NLRP7*	c.2063delC	Heterozygous	Frameshift	Likely pathogenic	Wang et al.[5]
10	27	recurent pregnancy losses and one molar pregnancy	*NLRP7*	c.799C>G	Heterozygous	Missense	VUS	Recent study
11	23	Recurrent mole hydtatiform	*KHDC3L*	c.322_325del	Homozygous	Frameshift	Likely pathogenic	Fallahian et al.[23], Reddy et al.[7], Landolsi et al.[9], Parry et al.[10], Wang et al.[5]
12	27	Recurrent mole hydtatiform	*KHDC3L*	c.322_325del	Homozygous	Frameshift	Likely pathogenic	Fallahian et al.[23], Reddy et al.[7], Landolsi et al.[9], Parry et al.[10], Wang et al.[5]
13	26	Recurrent mole hydtatiform	*KHDC3L*	c.396_397dup	Homozygous	Frameshift	Likely pathogenic	Recent study
14	28	Recurrent pregnancy losses	*KHDC3L*	c.572C>A	Heterozygous	Missense	VUS	Recent study

NLRP7: NLR family, pyrin domain-containing 7, KHDC3L: KHDC3L like protein, subcortical maternal complex member, VUS: Variant of uncertain significance, RHM: Recurrent hydatidiform mole, IVF: In vitro fertilization

aberrant methylation. They stated that heterozygous variants of the *NLRP7* gene are associated with reproductive failures. The reported index patient had a frameshift mutation in *NLRP7* (NM_001127255.1: c.2010_2011del, p.(Phe671Glnfs*18)), resulting in a stop codon. In silico prediction tools suggested nonsense-mediated mRNA decay as the mechanism for the translated mRNA product. Qian et al.[19] also reported a female patient with a heterozygous *NLRP7* variant (c.295G>T, p.Glu99*) who had one stillbirth and three normal pregnancies. In the current study, we found heterozygous NLPR7 variants

in 2 cases. One of them had no reproductive failures, but she had an affected daughter with neurological problems (epilepsy, hypotonia, cerebellar atrophy), and her sister had a history of recurrent molar pregnancies. Another heterozygous carrier in our study had a missense mutation in the *NLRP7* gene and had a history of recurrent pregnancy losses and one molar pregnancy. Our case is also compatible with previously reported cases of heterozygous *NLRP7* mutations associated with reproductive failure.

The homozygous *NLRP7* variant (c.2471+1G>A) was first reported in a Pakistani patient with spontaneous abortion and complete hydatidiform mole[20]. Kocabey et al.[21] reported homozygous *NLRP7* c.2471+1G>A splice site variant in two Turkish patients with recurrent molar pregnancies. In the current study, we reported two different patients with homozygous *NLRP7* variants and one patient with a heterozygous *NLRP7* variant, all with the c.2471+1G>A mutation. One of the patients with a homozygous variant has a history of recurrent hydatidiform mole and one ectopic pregnancy. Another case with a homozygous variant has a history of recurrent hydatidiform mole (more than two hydatidiform moles). The patient with a heterozygous *NLRP7* variant (c.2471+1G>A) also had a LP heterozygous *NLRP7* variant (c.368G>A). The compound heterozygous patient had recurrent hydatidiform moles, and her three sisters also had recurrent molar pregnancies.

Wang et al.[5] reported a case with a homozygous *NLRP7* c.2147delC variant. The patient had 4 CHM and 2 PTD. Our study reported a patient with a heterozygous *NLRP7* variant (c.2147delC) who had no recurrent molar pregnancy, but she had a sister with a history of recurrent hydatidiform mole. Human epidermal growth factor receptor 2-year-old boy had a heterozygous *NLRP7* variant (c.2147delC) and neurological abnormalities.

We reported three patients with a homozygous *KHDC3L* variant (c.322_325delGACT) and one patient with a heterozygous *KHDC3L* variant (c.572C>A). Biallelic *KHDC3L* variants are associated with early embryonic arrest, recurrent hydatidiform moles, and recurrent pregnancy loss[11,19]. The *KHDC3L* variant (c.322_325delGACT) was reported in several studies[10,13,22,23]. Fatemi et al.[8] reported a large pedigree with a homozygous *KHDC3L* (c.322_325delGACT) variant and a history of recurrent molar pregnancies. Wang et al.[13] reported another patient with four recurrent molar pregnancies (complete hydatidiform mole). Wang et al.[13] reported another patient with four recurrent molar pregnancies who was compound heterozygous for *KHDC3L* variants (c.1A>G and c.322_325delGACT). In the current study, we found a homozygous *KHDC3L* (c.322_325delGACT) variant in two patients with recurrent molar pregnancies. Our patient with a heterozygous *KHDC3L* variant (c.572C>A) had recurrent pregnancy losses but no hydatidiform mole.

Previous studies suggest that patients with biallelic *KHDC3L* mutations may have a more severe phenotype compared to patients with biallelic *NLRP7* mutations. Fatemi et al.[8] reported that patients with a biallelic truncating *KHDC3L* variant, could not have a successful pregnancy and suffer from PL and HM; however, heterozygosity of the same variant does not result in HM and causes recurrent pregnancy losses[9]. Our patient with a heterozygous missense *KHDC3L* mutation had recurrent pregnancy losses but no HM, and the phenotype is consistent with the previously reported heterozygous cases.

Limited studies were reported in Turkish patients with *KHDC3L* and *NLRP7* gene variants. To date, no *KHDC3L* gene variant has been reported in Turkish patients with recurrent hydatidiform mole. Some of the variants detected in the *NLRP7* gene in our study were reported for the first time in Turkish patients. Kocabey et al.[21] reported a homozygous *NLRP7* splice site variant (c.2471+1G>A) and homozygous frameshift variant (c.2571dupC) in three Turkish patients with recurrent molar pregnancies. Balci et al.[24] found a homozygous *NLRP7* variant (c.3024_3025insC) in a Turkish patient with six hydatidiform moles and five missed abortions[24].

The likelihood of a normal pregnancy in women with a history of recurrent molar pregnancies has been reported to be very low[23,25]. Several studies have demonstrated that oocyte donation is the best treatment option for women carrying biallelic *NLRP7* variants; however, some women with these variants have been reported to have live births from their own oocytes, albeit rarely[25,26]. Although oocyte donation is considered the most effective treatment for *NLRP7* homozygous individuals, live birth cannot be achieved in all these patients. The reported live birth from women with biallelic *NLRP7* variants was attributed to different types of mutations. Missense, splice variants, or protein-truncating mutations of the *NLRP7* gene are expected to cause a milder functional effect[5,24,25].

Study Limitations

The current study has some limitations. Mutations in the *NLRP7* and *KHDC3L* genes are responsible for most RHM cases; however, other genes have been reported in rare cases. We sequenced only the *NLRP7* and *KHDC3L* genes, but sequencing of other responsible genes is necessary to exclude the presence of mutations in *NLRP7-KHDC3L* mutation-negative cases. Another limitation of the current study is the lack of population-based data on the prevalence of *NLRP7* and *KHDC3L* mutations in the Turkish population. As no prior large-scale epidemiological studies exist, a power analysis could not be performed. Additionally, only a few published reports have described these mutations in Turkish patients. Nevertheless, this study includes the largest Turkish cohort to date screened for *NLRP7* and *KHDC3L* mutations, and offers preliminary but valuable data that may guide future studies aiming to establish

national prevalence rates and explore genotype–phenotype correlations. Furthermore, there was no information available on treatment options or live birth rates in cases with mutations. Further studies with large cohorts are needed to understand the etiopathogenesis of RHM and develop effective treatment options.

Conclusion

Genetic counseling for RHM associated with pathogenic variants in the *NLRP7* and *KHDC3L* genes is a highly complex process that plays a crucial role in the clinical management of patients with RHM. Given the markedly low likelihood of successful pregnancy outcomes in patients with biallelic variants of these genes, it is essential to provide comprehensive counseling regarding reproductive options and the limited probability of achieving a live birth. Although there is no treatment addressing the genetic causes in RHMs with a genetic diagnosis, oocyte donation is the best reproductive method for pregnancy success. Most biallelic variants in *NLRP7* and *KHDC3L* are incompatible with live birth; therefore, studies aimed at identifying clinically relevant genetic variants will aid in the genetic counseling of these patients. Reporting additional cases with confirmed pathogenic variants will not only expand the understanding of genotype-phenotype correlations but also guide patients toward appropriate reproductive strategies, such as oocyte donation. Moreover, such data will help to prevent the patients from unnecessary IVF cycles, medications, and pregnancy expectations.

Ethics

Ethics Committee Approval: This study was approved by the Yüksek İhtisas University Medical School Ethical Committee (approval no: 295, date: 14.04.2025).
Informed Consent: Written consent was obtained.

Footnotes

Authorship Contributions

Concept: L.Ö., E.Ü., S.A., Design: L.Ö., Data Collection or Processing: L.Ö., E.Ü., S.A., Analysis or Interpretation: L.Ö., E.Ü., S.A., Literature Search: L.Ö., Writing: L.Ö., E.Ü., S.A.
Conflict of Interest: No conflict of interest was declared by the authors.
Financial Disclosure: The authors declared that this study received no financial support.

References

1. Kronfol NM, Iliya FA, Hajj SN. Recurrent hydatidiform mole: a report of five cases with review of the literature. J Med Liban. 1969;22:507-20.
2. Horn LC, Kowalzik J, Bilek K, Richter CE, Einenkel J. Clinicopathologic characteristics and subsequent pregnancy outcome in 139 complete hydatidiform moles. Eur J Obstet Gynecol Reprod Biol. 2006;128:10-4.
3. Eagles N, Sebire NJ, Short D, Savage PM, Seckl MJ, Fisher RA. Risk of recurrent molar pregnancies following complete and partial hydatidiform moles. Hum Reprod. 2015;30:2055-63.
4. Aguinaga M, Rezaei M, Monroy I, Mechtouf N, Pérez J, Moreno E. The genetics of recurrent hydatidiform moles in Mexico: further evidence of a strong founder effect for one mutation in NLRP7 and its widespread presence. J Assist Reprod Genet. 2021;38:1879-86.
5. Wang CM, Dixon PH, Decordova S, Hodges MD, Sebire NJ, Ozalp S, et al. Identification of 13 novel NLRP7 mutations in 20 families with recurrent hydatidiform mole; missense mutations cluster in the leucine-rich region. J Med Genet. 2009;46:569-75.
6. Bahutair SNM, Dube R, Kuruba MGB, Salama RAA, Patni MMAF, Kar SS, et al. Molecular basis of hydatidiform moles—a systematic review. Int J Mol Sci. 2024;25:8739.
7. Reddy R, Akoury E, Nguyen NMP, Abdul-Rahman OA, Dery C, Gupta N. Report of four new patients with protein-truncating mutations in C6orf221/KHDC3L and colocalization with NLRP7. Eur J Hum Genet. 2013;21:957-64.
8. Fatemi N, Ray PF, Ramezanali F, Shahani T, Amiri-Yekta A, Kherraf ZE, et al. KHDC3L frame-shift mutation causes both recurrent pregnancy loss and hydatidiform mole. Eur J Obstet Gynecol Reprod Biol. 2021;259:100-4.
9. Landolsi H, Rittore C, Philibert L, Hmissa S, Gribaa M, Touitou I, et al. NLRP7 mutation analysis in sporadic hydatidiform moles in Tunisian patients. Arch Pathol Lab Med. 2012;136:646-51.
10. Parry DA, Logan CV, Hayward BE, Shires M, Landolsi H, Diggle C, et al. Mutations causing familial biparental hydatidiform mole implicate C6orf221 as a regulator of genomic imprinting in the oocyte. Am J Hum Genet. 2011;89:451-8.
11. Florea A, Caba L, Grigore AM, Antoci LM, Grigore M, Gramescu M, et al. Hydatidiform mole—Between chromosomal abnormality, uniparental disomy, and monogenic variants: a narrative review. Life. 2023;13:2314.
12. Chen Z, Jiang L, Su M, Zeng O, Luo P, Chu L. NLRP7 maintains genomic stability during early embryogenesis via mediating alternative splicing. Commun Biol. 2025;8:125.
13. Wang X, Song D, Mykytenko D, Kuang Y, Lv Q, Li B, et al. Novel mutations in subcortical maternal complex proteins may cause embryonic developmental arrest. Reprod Biomed Online. 2018;36:698-704.
14. Mehta S, Mahay SB, Satapathy A, Arora K. Decoding the genetics of recurrent molar pregnancy. J Hum Reprod Sci. 2024;17:61-4.
15. Hayward BE, De Vos M, Talati N, Abdollahi MR, Taylor GR, Meyer E, et al. Genetic and epigenetic analysis of recurrent hydatidiform mole. Hum Mutat. 2009;30:E629-39.
16. Sanchez-Delgado M, Martin-Trujillo A, Tayama C, Vidal E, Esteller M, Iglesias-Plataset I, et al. Absence of maternal methylation in biparental hydatidiform moles from women with NLRP7 mutations reveals placenta-specific imprinting. PLoS Genet. 2015;11:e1005644.
17. Kou YC, Shao L, Peng HH, Rosetta R, Gaudio D, Wagner AF, et al. Novel mutations in NLRP7 and imprinting defects in biparental hydatidiform moles. Mol Hum Reprod. 2008;14:33-40.
18. Soellner L, Begemann M, Degenhardt F, Geipel A, Eggermann T, Mangold E. Maternal heterozygous NLRP7 variant results in

reproductive failure and imprinting disturbances in offspring. Eur J Hum Genet. 2017;25:924-9.

19. Qian J, Deveault C, Bagga R, Xie X, Slim R. Women heterozygous for NLRP7 mutations are at risk for reproductive wastage. Hum Mutat. 2007;28:741.
20. Murdoch S, Djuric U, Mazhar B, Seoud M, Khan R, Kuick R, et al. Mutations in NALP7 cause recurrent hydatidiform moles and reproductive wastage. Nat Genet. 2006;38:300-2.
21. Kocabey M, Gulhan I, Koc A, Cankaya T, Karatasli V, Ileri A. High risk of gestational trophoblastic neoplasia development in recurrent hydatidiform moles with NLRP7 pathogenic variations. Balkan J Med Genet. 2023; 25:45-50.
22. Zhang W, Chen Z, Zhang D, Zhao B, Liu L, Xie Z, et al. KHDC3L mutation causes recurrent pregnancy loss by inducing genomic instability. PLoS Biol. 2019;17:e3000468.
23. Fallahian M, Sebire NJ, Savage PM, Seckl MJ, Fisher RA. Mutations in NLRP7 and KHDC3L confer a complete mole phenotype on digynic triploid conceptions. Hum Mutat. 2013;34:301-8.
24. Balci MF, Kaya ÖÖ, Gezici AE, Oral S, Akpak YK, Karaduman AB, et al. Recurrent hydatidiform moles: detection of a new mutation in the NLRP7 gene in the family. Int J Reprod Contracept Obstet Gynecol. 2023;12:2251-4.
25. Akoury E, Gupta N, Bagga R, Brown S, Déry C, Kabra M, et al. Live births in women with recurrent hydatidiform mole and two NLRP7 mutations. Reprod Biomed Online. 2015;31:120-4.
26. Cozette C, Scheffler F, Lombart M, Massardier J, Bolze PA, Hajri T, et al. Pregnancy after oocyte donation in a patient with NLRP7 mutations and recurrent molar pregnancies. J Assist Reprod Genet. 2020;37:2273-7.