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CASE REPORT

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RMND1 and *PLN* variants are the underlying cause of Perrault-like syndrome and cardiac anomalies in a patient

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Key Clinical Message

Recent studies have established an association between *RMND1* variants and Perrault syndrome. In this case report, we present a female patient with Perrault syndrome and cardiomyopathy, resulting from variants in *RMND1* and *PLN*, respectively.

KEYWORDS

dual diagnosis, hearing loss, ovarian insufficiency, Perrault syndrome, PLN (phospholamban), RMND1 (required for meiotic nuclear division 1 homolog)

1 | INTRODUCTION

Rare genetic diseases affect at least 1 in 50 individuals worldwide (http://orphanet.net). It is estimated that about 50% of patients with a rare genetic disease never receive a diagnosis.[1] Exome sequencing (ES) has significantly enhanced the diagnostic rate of genetic disorders, with improvements reported up to 42.7%.[2] ES has also been shown to identify pathogenic variants in known disease genes in 29% of childhood-onset patients, ending the diagnostic odyssey.[3] Moreover, the diagnostic rate of two genetic conditions in a single individual through exome testing is estimated to range from 1.8% to 7%.[4–7]

The *RMND1* (*required for meiotic nuclear division 1 homolog*) gene encodes an inner membrane protein in the mitochondria, which supports the translation and assembly of the oxidative phosphorylation complex. Biallelic pathogenic variants in *RMND1* cause mitochondrial translation defects, and result in combined oxidative phosphorylation deficiency 11 (COXPD11; MIM#614922). COXPD11 typically presents with neonatal-onset severe symptoms, characterized by encephalopathy, lactic acidosis, seizures, hearing loss, myopathy, and renal failure, leading to death in the first few years of life.[8–10] Recently, older individuals with biallelic pathogenic variants in *RMND1* have been reported to have renal abnormalities

and symptoms resembling Perrault syndrome, including sensorineural hearing loss (SNHL) and primary ovarian insufficiency (POI).[11–14] Perrault syndrome is a rare autosomal recessive condition characterized by SNHL in both males and females and ovarian dysgenesis in females. The diagnosis of Perrault syndrome in individuals with these clinical findings can be confirmed by the identification of biallelic pathogenic variants in one of six genes, including *CLPP*, *ERAL1*, *HARS2*, *HSD17B4*, *LARS2*, and *TWNK*. As with *RMND1*, these genes play roles in the normal functioning of mitochondria, particularly in mitochondrial translation and protein homeostasis suggesting a critical relationship between mitochondrial functions and the development of Perrault syndrome. The proteins CLPP and ERAL1 are involved in mitochondrial ribosome formation, while HARS2 and LARS2 are crucial for translating mitochondrial proteins. TWNK plays a role in maintaining mitochondrial DNA. Still, the genetic cause of Perrault syndrome is unknown for ~60% of affected individuals.[15] Interestingly, a female with a clinical diagnosis of Perrault syndrome was found to be homozygous for pathogenic variants in two unlinked genes, *CLDN14* and *SGO2*, which collectively explained her deafness and POI, highlighting the genetic complexity of this condition.[16]

The *PLN* gene codes Phospholamban, a regulator of Ca2+-ATPase, which mediates calcium sequestration within the sarcoplasmic reticulum. Pathogenic *PLN* variants lead to dilated cardiomyopathy 1P (MIM#609909) and hypertrophic cardiomyopathy 18 (MIM#613874).[17–19] Patients with dilated cardiomyopathy 1P have been associated with *PLN* pathogenic variants in homozygous or heterozygous states.[20–23] Several large cohort studies revealed heterozygous *PLN* pathogenic variants in patients with hypertrophic cardiomyopathy 18, but not in the controls.[24,25]

This report describes a patient with a complex clinical presentation due to homozygous pathogenic variants in *RMND1* and a pathogenic variant in *PLN*. The patient exhibits symptoms such as sensorineural hearing loss, ovarian insufficiency, microcephaly, mild developmental delay, heart abnormalities, and chronic kidney disease. The case underscores the effectiveness of exome sequencing in identifying multiple genetic causes for patients with intricate phenotypes.

2 | CASE HISTORY/EXAMINATION

Our patient is a 14-year-old female who was born full-term to a gravida 2, para 1 (G2P1) mother via C- section due to breech presentation. Birth weight was 2.77 kg. At the birth hospital, she failed the initial newborn hearing screen but passed a subsequent auditory brainstem response (ABR). At 20 months old, she presented for an audiometry exam due to parental concern for speech delay and was diagnosed with moderate-profound SNHL of her right ear and moderate to severe-profound SNHL of her left ear. A follow-up ABR showed no responses bilaterally. Magnetic resonance imaging (MRI) of the brain demonstrated normal cochlea and semicircular canals but noted marked tortuosity of the carotid arteries bilaterally at the level of C2 vertebral body. Bilateral cochlear implantation occurred at 3 years of age. A genetics evaluation at the time was unremarkable with negative *GJB2*, *GJB6*, and 12SrRNA & tRNAser mitochondrial mutation testing. She had an episode of intussusception at age five and required ileocecal resection.

The proband presented at age 14 due to chronic weight loss and vomiting. She presented to the emergency department and urgent care with complaints of blurred vision and right-sided Bell's palsy. Upon admission, she had elevated creatinine and blood pressure. She was transferred to the PICU where she was treated for hypertensive emergency. A renal biopsy noted significant chronic injury on pathology. Electron microscopy did not demonstrate basement membrane features, limiting suspicion of Alport syndrome. An electrocardiogram (ECG) completed during admission showed left ventricular hypertrophy (LVH) with right atrial enlargement. A follow-up ECG showed mild aortic root dilation, moderate aortic sinotubular junction dilatation, moderately dilated ascending aorta, and mild hypertrophy of the left ventricle.

Concern for an underlying connective tissue disorder prompted human genetics consult. On physical exam, the clinical geneticist noted arachnodactyly and lack of development of secondary sexual characteristics. She has not had menarche and had no signs of breast development and no pubic hair. The proband was also noted to have microcephaly, short nose with anteverted nares, mild bilateral ptosis, asymmetric ears with the right ear cupped, and full lips. A comprehensive three-generation pedigree was unremarkable. She had no history of seizures, and mild developmental delay with more severe involvement of expressive and receptive communication. Her parents reported increased difficulty with comprehension compared to her siblings and peers. The family has consent for the clinical diagnostic testing per local hospital protocol. Written consent was obtained from the family for case report publication.

3 | METHODS

Clinical ES was performed on the proband and her parents' DNA with the SureSelect Human All Exon V5 Panel kit [Agilent, Santa Clara, California] and an Illumina

sequencing system [Illumina, San Diego, California] with paired-end reads at Cincinnati Children's Hospital Medical Center (CCHMC) Genetics and Genomics Diagnostic Laboratory (GGDL). Alignment and variant calling were performed with a GATK-based in-house bioinformatics pipeline (human reference genome version hg37). Variants were then uploaded to the Fabric Genomics Analysis platform [Fabric Genomics, Oakland, California], which was used to annotate and analyze the identified variants. Sanger sequencing confirmation was performed at the CCHMC DNA Sequencing and Genotyping Core. Identified variants were classified based on ACMG-AMP (2015) guidelines.[26]

Homozygous *RMND1* missense variants, NM_017909.3:c.713A > G,p.(Asn238Ser), were identified in the proband, which were inherited from non-consanguineous carrier parents (Figure 1 and Figure 2). At the time of the trio ES analysis, the minor allele frequency was 0.04 in the Genome Aggregation Database (Gnomad v2.1.1) with no homozygotes. This variant was reported in Human Gene Mutation Database (HGMD) as a disease-causing mutation (CM147820) and in ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/; variant ID: 225255) with conflicting classification of pathogenicity, four times as pathogenic and twice as uncertain significance. Based on the available evidence, this variant was classified as likely pathogenic (ACMG: PM2 + PP + PS4m + PP5/PS1p). ES also identified a de novo heterozygous *PLN* deletion variant, NM_002667.4:c.95_98del,p.(Phe32Serfs*7). This variant has not been reported previously in the literature and is absent from the NCBI database of genetic variation (dbSNP), GnomAD, HGMD, and ClinVar. It is speculated to disrupt the translational reading frame and lead to nonsense-mediated mRNA decay. This variant was classified as pathogenic (ACMG: PVS1 + PS2 + PM2). A recent entry in ClinVar classifies the same *PLN* variant as pathogenic (variant ID: 1453340).

4 | CONCLUSION AND RESULTS

Perrault syndrome is an autosomal recessive condition characterized by SNHL in both males and females and ovarian dysgenesis in females. In this report, we present a female patient with Perrault-like features, including hearing loss and primary ovarian insufficiency. Additionally, the proband has LVH and chronic kidney disease. Through clinical exome sequencing, we identified a homozygous c.713A > G,p.(Asn238Ser) variant in the *RMND1* gene, and a novel de novo heterozygous variant c.95_98del,p.(Phe32Serfs*7) in the *PLN* gene. To our knowledge, she is the first individual reported to have this type of multiple molecular diagnosis. In addition, our proband has marked bilateral carotid arteries tortuosity noticed via MRI, which has not been reported in individuals with pathogenic variants in *RMND1* or *PLN*. Thus, whether this vascular anatomical variation is associated with the proband's clinical features or just an incidental finding is unclear.

5 | DISCUSSION

The association between *RMND1* and human disease was established in 2012 through pedigree-based gene mapping and exome sequencing studies.[9,10] Since then, most of the disease-causing *RMND1* variants have been

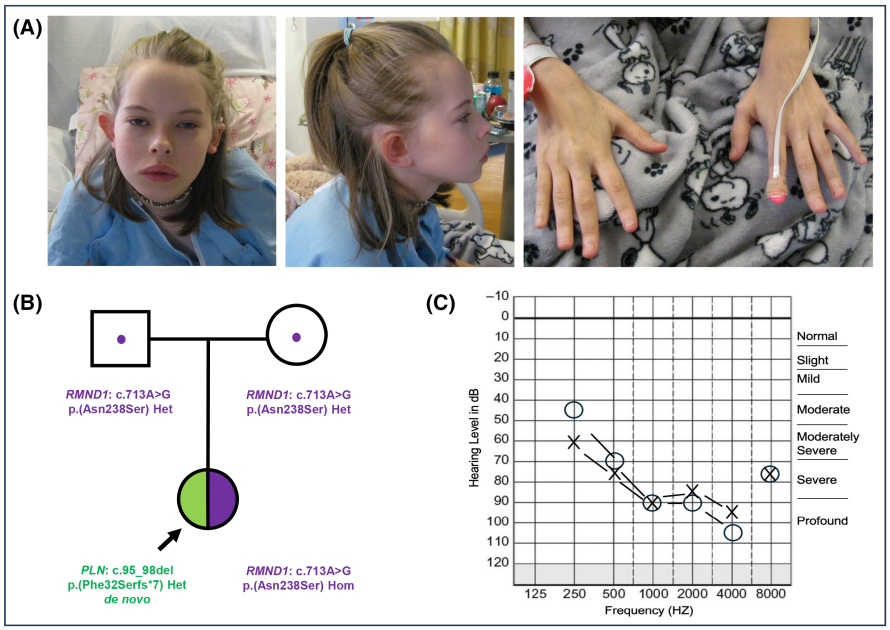

FIGURE 1 Clinical and genetic findings in the proband. (A) Craniofacial findings include microcephaly, flat midface, mild bilateral ptosis, asymmetric ears with the right ear cupped, and full lips. The hands demonstrate arachnodactyly. (B) A pedigree indicates relevant variants identified by exome sequencing. (C) Audiological data of the proband at 20 months of age. Air conduction. Signs: Cross, left ear. Circle, right ear. We have obtained informed consent to publish the full-face photograph of the proband.

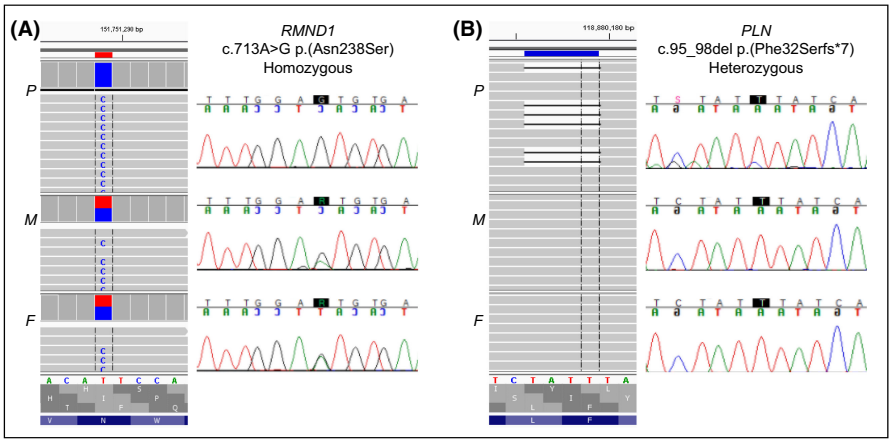

FIGURE 2 Genetic testing results of the exome trio. Results of ES and Sanger sequencing showing c.713A > G, p.(Asn238Ser) in *RMND1* (A) and c.95_98del, p.(Phe32Serfs*7) in *PLN* (B). P-proband; M-mother; F-father.

identified through exome sequencing. Currently, 22 disease-causing *RMND1* variants are listed in HGMD, linked to conditions such as encephalopathy, hearing impairment, Perrault syndrome, mitochondrial disease, and renal disease.[10,27–29] To date, the specific homozygous *RMND1* variant, c.713A>G, p.Asn238Ser, identified in the current proband, has also been reported in seven other individuals (three males and four females) from six unrelated families.[11,12,14,30,31] The clinical features associated with this variant include SNHL (7/7), leukoencephalopathy with or without seizures (4/7), LVH (1/7), renal disease (4/7), and ovarian atrophy and hypergonadotropic hypogonadism (1/7). This underscores the variant's significance in contributing to a spectrum of clinical manifestations.

Hearing loss is a primary clinical presentation observed in the proband, consistent with other reported individuals. She previously had negative genetic testing on an SNP microarray and a hearing loss gene panel composed of *GJB2*, *GJB6*, and several mitochondria variants. Hearing loss is typical for patients with *RMND1*-related disorders.[27–29] Early identification of *RMND1*-related hearing loss may be informative to monitoring and early intervention of possible renal and ovarian dysfunction in the affected individuals. Currently, *RMND1* is only offered by a few laboratories on hearing loss next-generation sequencing (NGS) panels. We propose the inclusion of the *RMND1* gene in the PanelApp (Version 4.50: https://panelapp.genomicsengland.co.uk/panels/126/) list for monogenic hearing loss, which currently includes 147 genes. This addition can potentially enhance the comprehensiveness and accuracy of genetic testing panels for hearing loss.

In reviewing cases of *RMND1*-related disorders, it is notable that all documented *RMND1* c.713A>G homozygous females, except for one pre-pubertal girl, have exhibited ovarian failure or insufficiency ([11,12,14,30]; Table 1: patient 1, patient 4, and patient 5). This consistency is further supported by findings from another study that reported two siblings with compound heterozygous *RMND1* variants, c.583G>A,p.Gly195Arg and c.818A>C,p.Tyr273Ser, both sisters presented with ovarian insufficiency ([13]; Table 1: patient 2 and patient 3). The current proband represents the fourth female with ovarian insufficiency linked to homozygous *RMND1* c.713A>G (Table 1: patient 6). These observations suggest that ovarian insufficiency is a consistent clinical feature among older females with *RMND1*-related disorders, warranting the inclusion of *RMND1* in multigene panels for POI and related endocrine disorders. Previously, six genes (*CLPP*, *ERAL1*, *HARS2*, *HSD17B4*, *LARS2*, or *TWNK*) have been associated with Perrault syndrome, but the compelling evidence from various cases supports adding *RMND1* as the seventh gene linked to this syndrome.[11–15] Furthermore, renal involvement, observed in both the current proband and other cases, is highlighted as a distinguishing feature of *RMND1*-related Perrault syndrome, setting it apart from other known genetic causes of the condition.

In addition to the *RMND1* c.713A>G variant, ES revealed a de novo pathogenic variant, in the *PLN* gene, c.95_98del,p.Phe32Serfs*7, which may account for the LVH observed in the proband. Although *PLN* has been linked to cardiomyopathy since 2007, pathogenic variants in this gene are relatively rare, with only 17 disease-causing variants listed in HGMD. The identified *PLN* c.95_98del variant is located upstream of a known nonsense variant (c.116T>G,p.L39*) frequently associated with hypertrophic cardiomyopathy and dilated cardiomyopathy.[32,33] The proband also has high blood pressure, a common feature in *RMND1* patients, which could further exacerbate LVH.[28,30] This combination of genetic findings underlines the complexity of the proband's clinical presentation, where both *RMND1* and *PLN* variants contribute to her cardiovascular issues.

In summary, the current patient has a dual diagnosis of two rare genetic disorders, *RMND1*-related Perrault syndrome and *PLN*-related cardiomyopathy, with pathogenic variants in both genes contributing to a complex array of clinical features such as microcephaly, hearing loss,

TABLE 1 Summary of patients with *RMND1*-related disease and ovarian dysfunction.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Patient (Reference)	Proband[12]	Proband[13]	Proband's sister[13]	Proband[11]	Proband[14]	Current proband
Gender	Female	Female	Female	Female	Female	Female
Age of onset	7 years	4 years	3 years	17 years	61 years	20 months
Ethnicity	Caucasian (Portuguese)	Polish	Polish	Belgian origin	Caucasian	Caucasian
Consanguinity	N	N	N	N	N	N
RMND1 variants (NM_017909.3) (nucleotide change, amino acid change)	Homozygous c.713A > G, p.Asn238Ser	Compound Heterozygous c.583G > A, p.Gly195Arg; c.818A > C, p.Tyr273Ser	Compound Heterozygous c.583G > A, p.Gly195Arg; c.818A > C, p.Tyr273Ser	Homozygous c.713A > G, p.Asn238Ser	Homozygous c.713A > G, p.Asn238Ser	Homozygous c.713A > G, p.Asn238Ser
Short Stature	Y	N	N	N	N	N
Dysmorphic features	U	U	U	U	U	Mildly distinct facial features: mild facial swelling, flat midface, microcephaly, short nose with anteverted nares, mild bilateral ptosis, asymmetric ears with the right ear cupped, full lips
Hands	U	U	U	U	U	Arachnodactyly
Lactic acidosis	Y	Y	N	N	N	N
Hypertension	N	Y	Y	N	N	Y
Renal abnormalities	Distal renal tubular acidosis with hyperchloremic metabolic acidosis and a normal anion gap, uric acid mildly elevated, low urine citrate levels, normal calcium levels and a normal renal ultrasound	Chronic kidney disease	Chronic kidney disease	Renal insufficiency stage III was diagnosed at age of 4. Normal renal ultrasound	Renal failure progressed linearly for over 40 years. Mild kidney atrophy reported at age 24	Small kidneys, elevated creatinine 2.39 mg/dL, Stage 4 chronic kidney disease; biopsy was not consistent with Alport syndrome
Neurologic features (developmental delay, hypotonia, seizures)	N	N	N	Y	N	Y
Gonadal dysfunction	Ovarian atrophy, hypergonadotropic hypogonadism	Menarche at age 14, hypergonadotropic hypogonadism, small ovaries and uterus, Infertility	Gonadal dysgenesis	At age 17, absent pubertal development and laboratory investigations revealed primary ovarian insufficiency	At age 16, failure to menstruate (primary XX amenorrhea by showing increased serum levels of FSH and LH)	At age 14, a complete lack of development of secondary sexual characteristics and no menarche

Note: Variant nomenclature is based on the recommendations set forth by the Human Genome Variation Society.

Abbreviations: N, no/not present; Y, yes/present; U, unknown.

absence of menarche, kidney disease, aortic root dilation, and left ventricular hypertrophy. This study supports adding the *RMND1* gene in Perrault syndrome genetic testing and its addition to various multigene panels specific to related diseases. Notably, this case is the first to document concurrent pathogenic variants in *RMND1* and *PLN*, highlighting the utility of comprehensive genetic testing techniques like exome sequencing in uncovering complex conditions that may arise from multiple genetic factors.

AUTHOR CONTRIBUTIONS

Xiaoli Du: Investigation; methodology; writing – original draft; writing – review and editing. **Cara L. Barnett:** Conceptualization; data curation; methodology; writing – original draft; writing – review and editing. **Kimberly M. Widmeyer:** Investigation; methodology. **Xinjian Wang:** Investigation; methodology. **Diana S. Brightman:** Investigation; methodology; writing – review and editing. **Carolee W. Noonan:** Writing – review and editing. **Kathryn N. Weaver:** Investigation; methodology; writing – review and editing. **Robert J. Hopkin:** Investigation; methodology; writing – review and editing. **Yaning Wu:** Conceptualization; data curation; formal analysis; investigation; methodology; project administration; supervision; writing – review and editing.

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N/A.

CONFLICT OF INTEREST STATEMENT

N/A.

DATA AVAILABILITY STATEMENT

All data generated or analyzed in this case report are included in this published article.

ETHIC STATEMENT

The family has consent for the clinical diagnostic testing per local hospital protocol. Written consent was obtained from the family for journal case report publication.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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