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LETTER TO THE EDITOR

# A known pathogenic variant in the essential mitochondrial translation gene *RMND1* causes a Perrault-like syndrome with renal defects

*To the Editor*:

Perrault syndrome is a rare autosomal recessive condition characterized by sensorineural hearing loss (SNHL) in both sexes and primary ovarian insufficiency (POI) in 46, XX females. Additional phenotypes, especially progressive neurological features affect some individuals. Six genes have been identified as causative for Perrault syndrome: *HSD17B4*, *HARS2*, *LARS2*, *CLPP*, *C10orf2* and *ERAL1*, the latter 5 of which function in mitochondrial translation.[1,2] As many cases of Perrault syndrome are unresolved at a genetic level it is suggested that additional Perrault genes are undiscovered.[1]

We present a case with the defining clinical features of Perrault syndrome, in addition to renal dysfunction and short stature, associated with a known pathogenic variant, *RMND1* c.713A>G p.(Asn238Ser).[3] Patients provided written informed consent in accordance with local regulations. Ethical approval was granted by the National Health Service Ethics Committee (16/WA/0017) and the University of Manchester. The proband is from a non-consanguineous Portuguese family with unaffected parents and 2 unaffected brothers. SNHL was noted at 7 years of age and was moderate to severe at 16 years of age. At 10 years of age short stature, growth hormone deficiency and POI were observed. She also had distal renal tubular acidosis, renal dysfunction has not been previously associated with Perrault syndrome. The proband had 2 measurements of lactic acid with elevated/borderline results; postprandial: 2.01 mmol/L (reference: <1.8) and 1.9 mmol/L (reference: 0.5-1.6). A full neurological evaluation, including electromyography, was performed with no neurological phenotype noted. The proband attends a mainstream school and undertakes age appropriate work with no additional assistance. No additional members of the family reported any health problems.

Whole exome sequencing was performed on the proband (SureSelect Human All Exon V5 Panel [Agilent, Santa Clara, California] and HiSeq 2500 [Illumina, San Diego, California]).[1] No putative pathogenic variants were identified in known Perrault syndrome genes. We classified the homozygous known pathogenic variant, *RMND1* c.713A>G p.(Asn238Ser) (NM_017909) as the likely cause of the phenotype in the proband. The variant segregated with the phenotype (Sanger sequencing using ABI big Dye v3.1 technology [ThermoFisher Scientific Inc.]); both parents and both unaffected siblings were heterozygous.

*RMND1* has been proposed to tether the mitoribosome to the mitochondrial inner matrix.[4] Variants in *RMND1* are associated with a wide phenotypic range including SNHL, hypotonia, developmental delay, lactic academia and renal dysfunction. Many patients have a defect in mitochondrial translation.[3]

The variant *RMND1* c.713A>G has been observed as homozygous in 2 unrelated families (Table 1). In both families SNHL, developmental delay, hypotonia and peripheral spasticity were observed, one patient had renal dysfunction. All 3 affected individuals are prepubertal, including 1 affected female.[3] The phenotypic range associated with this *RMND1* variant suggests modifying factors, which may be components of the mitochondrial translation pathway.

POI has not been previously associated with variants in *RMND1*. In most reported cases of *RMND1*-related disorders, patients have been of pre-pubertal age so POI may not have yet become apparent.[3] In 2 affected sisters, aged 17 and 14 years, with the *RMND1* c.713A>G variant compound heterozygous with another variant, the absence or presence of POI was not commented upon.[3,5] This may indicate that POI is not a feature of all cases of *RMND1*-associated mitochondrial dysfunction.

We suggest that patients with Perrault syndrome are screened for variants in *RMND1* alongside the known Perrault syndrome genes. Renal phenotypes in women with Perrault syndrome features may indicate the causative variant is in *RMND1* but the absence of renal dysfunction should not preclude *RMND1* screening. We also suggest that POI may be an unrecognized feature of *RMND1*-related mitochondrial dysfunction and female patients should be monitored for POI.

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**TABLE 1** Clinical features of individuals homozygous for the variant *RMND1* c.713A>G p.(Asn238Ser)

| Individual ID | 4.1 | 4.2 | 5 | II-1 |
|---|---|---|---|---|
| Reference | 3 | | | This report |
| Ethnicity | Caucasian | Caucasian | Caucasian, Native American | Caucasian (Portuguese) |
| Consanguinity | N | N | N | N |
| Sex | M | M | F | F |
| Onset (y) | 0.5 | Birth | Birth | 7 |
| Age (y) at last assessment | 8 | 6 | 9 | 16 |
| SNHL | Bilateral SNHL | Bilateral SNHL | Congenital bilateral progressive SNHL, mid to high frequencies | Bilateral progressive moderate/severe SNHL |
| Gonadal dysfunction | NR | NR | NR | Ovarian atrophy and hypergonadotropic hypogonadism |
| Renal dysfunction | N | N | Cystic dysplasia, possible renal tubular acidosis, end stage renal failure, renal transplant | 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 |
| Developmental delay | Y | Yes with regression at 4 y | Yes with failure to thrive | N |
| Neurological features | Y | Y | Y | N |
| Tone | Central hypotonia and peripheral spasticity | Central hypotonia and peripheral spasticity | Central hypotonia and peripheral spasticity | Normal |
| Epilepsy | Febrile seizures | Febrile seizures | Y | N |
| MRI | Leukoencephalopathy temporal lobe cyst | NR | Cerebral atrophy and white matter changes | Normal (spectroscopy not performed) |
| Additional features | NR | Torticollis and plagiocephaly | Microcephaly, hypertension, mild ventricular hypertrophy | Growth hormone deficiency, autoimmune thrombocytopenia, non-immune hypothyroidism, femoral epiphysiolysis (13 y of age), ECG normal |

Abbreviations: ECG, electrocardiogram; F, female; M, male; MRI, magnetic resonance imaging; N, no; NR, not recorded; SNHL, sensorineural hearing loss; Y, yes.

## Conflict of interest

The authors declare no conflicts of interest.


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