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Variant: NC_012920.1(MT-ND1):m.1555A>G

Version: 1.3

CA120590

9628 (ClinVar)

Gene: MT-RNR1 (HGNC:4549)
Condition: mitochondrial disease (MONDO:0044970)
Inheritance Mode: Mitochondrial inheritance
UUID: 1eeeeb29-f4bc-4e59-a301-29403e850a3c
Approved on: 2022-12-15
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HGVS expressions

NC_012920.1:m.1555A>G
J01415.2:m.1555A>G

Pathogenic

Met criteria codes 3

PS3_Moderate PS4 PP3

Not Met criteria codes 4

PS2 PP1 PM6 PM2

Evidence Links 4

Expert Panel

Mitochondrial Diseases VCEP

Criteria Specification Information

Criteria Specification: *ClinGen Mitochondrial Disease Nuclear and Mitochondrial Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines Version 1_mtDNA*
Criteria Specification Approval History
Criteria Specifications for this VCEP

Evidence submitted by expert panel

Mitochondrial Diseases VCEP

The m.1555A>G variant in MT-RNR1 has been reported in more than 65 individuals with primary mitochondrial disease, and the only consistent reported feature in affected individuals was hearing loss (PS4; PMIDs: 7689389, 1613771, 8285309, 8414970, 9111378, 9040738, 9490575, 9831149, 10661905, 12031626, 12920080, 16935512, 20123042, 22317974, 23357420, 24252789, 11870684). Some individuals with this variant have normal hearing, others have hearing loss following aminoglycoside exposure, and others have hearing loss and no known aminoglycoside exposure. Age of onset of hearing loss ranged from infancy (after aminoglycoside exposure) to adulthood. Hearing loss has been reported to be variable, stable in some individuals and progressive in others. Several reports of individuals receiving cochlear implants had good outcomes (PMIDs: 9831149, 16935512, 24252789). While most affected individuals have this variant present at homoplasmy, there have been some reports of heteroplasmic occurrences in those with hearing loss. There are isolated reports of individuals with this variant having other medical concerns, however there is not sufficient evidence currently that this variant was causative of these other concerns. These concerns include chronic progressive external ophthalmoplegia and myopathy (PMID:

11870684), cardiomyopathy (PMIDs: 28104394, 24252789), neural tube defect (PMID: 10661905), hypertension (PMID: 22317974), type 2 diabetes (PMID: 23357420), Parkinson disease (abstract only, Shoffner et al., 1996), autism spectrum disorder and intellectual disability (PMID: 29340697), and Leigh syndrome (PMID: 32867169). There are no de novo occurrences of this variant reported to our knowledge. Many extended families have been reported in the medical literature however the variant was present at homoplasmy in both affected and unaffected family members, thus preventing consideration for PP1. The computational predictor HmtVAR predicts it to be pathogenic score of 1 (PP3). This variant is present in the healthy population, which is to be expected given the known reduced penetrance of this variant. Several studies in patient cells (PMIDs: 8817331, 9915970), cybrids (PMIDs: 8687424, 11230176), and single fiber testing (PMID: 9915970) support the functional impact of this variant (PS3_moderate). This variant meets criteria to be classified as likely pathogenic however this Expert Panel elected to modify the classification to pathogenic given the overwhelming evidence of pathogenicity. Furthermore, the mitochondrial DNA variant specifications are known to not be optimized for pathogenic variants that tend to be homoplasmic in nature and/or have reduced penetrance. This classification was approved by the NICHD/NINDS U24 ClinGen Mitochondrial Disease Variant Curation Expert Panel on December 15, 2022. Mitochondrial DNA-specific ACMG/AMP criteria applied (PMID: 32906214): PS4, PP3, PS3_moderate.

Met criteria codes

PS3_Moderate ✔

Several studies in patient cells (PMIDs: 8817331, 9915970), cybrids (PMIDs: 8687424, 11230176), and single fiber testing (PMID: 9915970) support the functional impact of this variant (PS3_moderate).

Cybrids were generated using rho0 HeLa cells and mother of a Japanese individual with aminoglycoside-induced hearing loss. Controls used were from unrelated individuals. Streptomycin progressively inhibited translation in mother's cells. Cybrids were homoplasmic for the variant. Mitochondrial translation was also inhibited in cybrids generated from mother's cells. PubMed:8687424

This paper describes studies in lymphoblastoid cell lines from the Arab-Israeli family described in Jaber et al., 1992 and Prezant et al., 1993. Cell lines from individuals with the variant and hearing loss, individuals with the variant and normal hearing, individuals who married into the family, and unrelated control individuals were assessed. All cell lines from individuals with the variant (with and without hearing loss) showed reduced labeling of mitochondrial translation products. The decrease in the rate of labeling of mitochondrially-synthesized polypeptides, in lines from those with the variant and hearing loss and those with the variant and without hearing loss, compared to controls was statistically significant. There was also decreased growth on galactose media in those with the variant and hearing loss. Doubling time values were slightly shorted in cells from those with hearing loss and the variant compared to those without hearing loss and the variant, but did not reach statistical significance. Oxygen consumption was reduced in cell lines from those with the variant with and without hearing loss. In the cell lines from those with the variant and hearing loss, the rate of malate/glutamate-driven respiration (normally reflecting complex I activity) was decreased, relative to the control cell lines, by an average of 56% (P = 0.00016), the rate of succinate/glycerol-3-phosphate (G-3-P)-driven respiration (normally reflecting complex III activity), by an average of 44% (P = 0.00014), and the rate of N,N,N4,N4-tetramethyl-p-phenylenediamine (TMPD)/ascorbate-driven respiration (normally reflecting the activity of complex IV) was reduced by an average of 32% (P = 0.020). The corresponding rates for the cell lines from individuals without hearin gloss were also reduced relative to those from the control cell lines, but these decreases were lower than those observed for the cell lines from those with hearing loss (50%, P = 0.020 for complex I, 27%, P = 0.021 for complex III, and 13%, P = 0.2717 for complex IV). Cells from individuals with the variant showed decreased growth in the presence of an antibiotic. In particular, the doubling time ratios in the presence or absence of neomycin were increased on average by ~16% in both groups of cell lines with the variant (P = 0.01), while the doubling time ratios in the presence or absence of paromomycin were increased by 30% (P = 0.001) and 26% (P <0.001) in the symptomatic derived and asymptomatic-derived cell lines, respectively. PubMed:8817331

Cybrids were generated from patients' lymphoblastoid cell lines (from large Arab-Israeli family previously described). Cybrids showed (1) decreased growth in galactose media compared to glucose, (2) decreased mito protein synthesis, (3) decreased substrate-dependent respiration, and (4) this was similar to cybrids generated from three healthy family members. PubMed:11230176

Single fiber testing showed higher levels of the variant in abnormal muscle fibers than normal muscle fibers. They also looked at translation capacity in patient fibroblasts in the presence and absence of aminoglycodsides

(gentamicin). The relative labeling ratios and electrophoretic mobility of mitochondrial translation products in cell lines harboring 60% heteroplasmy for the variant did not differ significantly from those observed in controls in three independent measurements. There was an overall decrease in the rate of protein labeling, with an average decrease of 35%, which became more apparent (40%) when aminoglycoside was added. PubMed:9915970

PS4	ℹ	✔	The m.1555A>G variant in MT-RNR1 has been reported in more than 65 individuals with primary mitochondrial disease, and the only consistent reported feature in affected individuals was hearing loss (PS4; PMIDs: 7689389, 1613771, 8285309, 8414970, 9111378, 9040738, 9490575, 9831149, 10661905, 12031626, 12920080, 16935512, 20123042, 22317974, 23357420, 24252789, 11870684). Some individuals with this variant have normal hearing, others have hearing loss following aminoglycoside exposure, and others have hearing loss and no known aminoglycoside exposure. Age of onset of hearing loss ranged from infancy (after aminoglycoside exposure) to adulthood. Some individuals with this variant remain unaffected, while others have hearing loss (with aminoglycoside exposure and without). Hearing loss has been reported to be variable, stable in some individuals and progressive in others. Several reports of individuals receiving cochlear implants had good outcomes (PMIDs: 9831149, 16935512, 24252789). While most affected individuals have this variant present at homoplasmy, there have been some reports of heteroplasmic occurrences in those with hearing loss. There are isolated reports of individuals with this variant having other medical concerns, however there is not sufficient evidence currently that this variant was causative of these other concerns. These concerns include chronic progressive external ophthalmoplegia and myopathy (PMID: 11870684), cardiomyopathy (PMIDs: 28104394, 24252789), neural tube defect (PMID: 10661905), hypertension (PMID: 22317974), type 2 diabetes (PMID: 23357420), Parkinson disease (abstract only, Shoffner et al., 1996), autism spectrum disorder and intellectual disability (PMID: 29340697), and Leigh syndrome (PMID: 32867169).
PP3	ℹ	✔	The computational predictor HmtVAR predicts it to be pathogenic score of 1 (PP3).

Not Met criteria codes

PS2	ℹ	✖	There are no de novo occurrences of this variant reported to our knowledge.
PP1	ℹ	✖	Many extended families have been reported in the medical literature however the variant was present at homoplasmy in both affected and unaffected family members, thus preventing consideration for PP1.
PM6	ℹ	✖	There are no de novo occurrences of this variant reported to our knowledge.
PM2		✖	This variant is present in the healthy population, which is to be expected given the known reduced penetrance of this variant.

Curation History

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