

Clinical variant Answer

- 1. Document that the allele or genotype was classified according to a comprehensive review of evidence consistent with, or more thorough than, current practice guidelines (e.g. review of case data, genetic data and functional evidence from the literature and analysis of population frequency and computational predictions)**

The following two variants were identified by WES (Sureselect Agilent capture kit and SOLiD 5500xd sequencing technology) of three individuals with familiar Meniere's disease (MD). Both variants were not found in 2 familial controls. The variants were selected as candidate mutations after bioinformatic analysis described in "Combining multiple strategies for prioritizing heterozygous variants using exome sequencing data in autosomal dominant sensorineural hearing loss" (paper in preparation). Briefly, this filtering and prioritizing strategies were: 1) a composite score including 7 criteria to consider a variant pathogenic (PAVAR score), 2) Exomiser, 3) VAAST and 4) Phevor software. After confirming that both variants were not present in our in-house exome database (30 controls exomes and 20 cases from Spain), these variants were validated by Sanger sequencing (published results are provided in point 3).

Moreover, the presence of both mutations was assessed in different populations with the use of three databases: 1000 Genomes, the National Heart, Lung, and Blood Institute Exome Variant Server as well as additional analyses which were performed to calculate the frequency of these two new variants.

NM_032822.2 (FAM136A): c.226C>T (p.Gln76Ter) →1000 (MD) cases and 500 healthy control of Spanish population were screened by Taqman assay and the nonsense variant only was found in the three cases of Familiar MD. FAM136 variant could be assigned with the level of a pathogenic variant.

Recently, the Exome Aggregation Consortium (ExAC) has allowed us to screen in 65000 WES data for both variants. Only the variant NM_001198938.1 (DTNA):c.1963G>T (p.Val655Phe) was found in 2 individual which phenotype is unknown. This is the reason that the missense variant in DTNA gene could be assigned with the level of uncertain significance variant.

Furthermore several functional analysis to study the effect of both variants were performed and are described in paper provide in point 3.

- 2. Include a clinical significance assertion using a variant scoring system with a minimum of three levels for monogenic disease variants (pathogenic, uncertain significance, benign) or appropriate terms for other types of variation.**

Both sequence variants could be classified as damaging (alters the normal levels or biochemical function of a gene or gene product) according to (MacArthur, et al. 2014)

NM_032822.2 (FAM136A): c.226C>T (p.Gln76Ter) → Clinical significance for this nonsense variant is pathogenic and damaging since it generates a stop codon.

NM_001198938.1 (DTNA):c.1963G>T (p.Val655Phe) → Clinical significance for this missense variant is pathogenic and probably damaging since it leads to a novel acceptor splice-site.

- 3. Provide a publication or other electronic document (such as a PDF) that describes the variant assessment terms used (e.g. pathogenic, uncertain significance, benign or appropriate terms for other types of variation) and the criteria required to assign a variant to each category. This document will be available to ClinVar users via the ClinVar website (link provided for all submitted assertions).**

Requena T, Cabrera S, Martín-Sierra C, Price SD, Lysakowski A, Lopez-Escamez JA. Identification of two novel mutations in FAM136A and DTNA genes in autosomal-dominant familial Meniere's disease. Hum Mol Genet. 2015 Feb 15;24(4):1119-26. doi: 10.1093/hmg/ddu524.

- 4. Submit available supporting evidence or rationale for classification (e.g. literature citations, total number of case observations, descriptive summary of evidence, web link to site with additional data, etc.) or be willing to be contacted by ClinVar users to provide supporting evidence. In other words, contact information for one person on the submission must be submitted as "public".**

Requena T, Cabrera S, Martín-Sierra C, Price SD, Lysakowski A, Lopez-Escamez JA. Identification of two novel mutations in FAM136A and DTNA genes in autosomal-dominant familial Meniere's disease. Hum Mol Genet. 2015 Feb 15;24(4):1119-26. doi: 10.1093/hmg/ddu524.

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Our group website→<http://www.genyo.es/en/content/view-research-group?id=5>

OTHER REFERENCES

MacArthur, D. G., et al.

2014 Guidelines for investigating causality of sequence variants in human disease. Nature 508(7497):469-76.