Genetic foundations of Ménière's disease: changing the game

BY JOSE ANTONIO LOPEZ ESCAMEZ

Sydney researchers reveal genetic roots of Ménière's disease. Familial patterns and gene discoveries highlight autosomal inheritance in rare cases, transforming molecular insights.

Ménière's disease (MD) is a chronic disorder of the inner ear defined by clinical criteria of episodic vertigo associated with sensorineural hearing loss and tinnitus. Exciting clinical and translational research on the condition during the last 10 years has been transformative in our molecular understanding.

With an estimated prevalence of 75 cases per 100,000 individuals in Europe and lower in Asia, MD is a rare syndrome with several comorbidities such as migraine or immune-related disorders with a significant genetic contribution [1].

Familial clustering is observed in Western European and East Asian cohorts and exome sequencing studies have identified ~20 genes in families. Most of these families have been identified by the Ménières Disease Consortium in Spain, showing autosomal dominant, autosomal recessive and digenic inheritance patterns. Rare mutations in four genes have been found in several MD families including OTOG, MYO7A and TECTA, which are three well-studied genes previously associated with non-syndromic sensorineural hearing loss [2]. OTOG, the most important familial MD, was found in 15 unrelated families, showing missense variants with compound recessive inheritance. It encodes for otogelin, a structural protein specific to the inner ear involved in the organisation of the tectorial and otolithic membranes, which play a role in the anchorage of the stereocilia tips to the tectorial membrane in the organ of Corti. These discoveries have been made combining gene burden tests showing an overload of rare variants (allelic frequency <0.05) in multiplex families with segregation analysis.

Recently, GJD3 has been discovered as a novel familial MD gene with a rare haplotype (TGAGT) composed of two missense, two synonymous and one downstream variant, segregating the MD phenotype in a total of 10 individuals from three unrelated families and in another eight non-familial MD individuals [3]. Immunofluorescence studies in mice revealed that GJD3 was expressed in the organ of Corti and vestibular organs, particularly in the tectorial membrane, the base of inner and outer hair cells and their nerve endings. Moreover, the GJD3 variant overlaps in familial and non-familial MD individuals. Rare shared variants have been also observed for other hearing loss genes such as OTOG, MYO7A, CDH23, ADGRV1 and TECTA, suggesting a hidden inheritance in 30-40% of sporadic cases.

Despite these advances in the MD gene discovery, >65% of families remain undiagnosed, and almost no gene has been reported in individuals with non-European ancestry. This situation requires a multilateral sequencing initiative that we are leading at the University of Sydney to include Australasian populations, offering a more inclusive genetic approach for underrepresented populations in genetic databases.

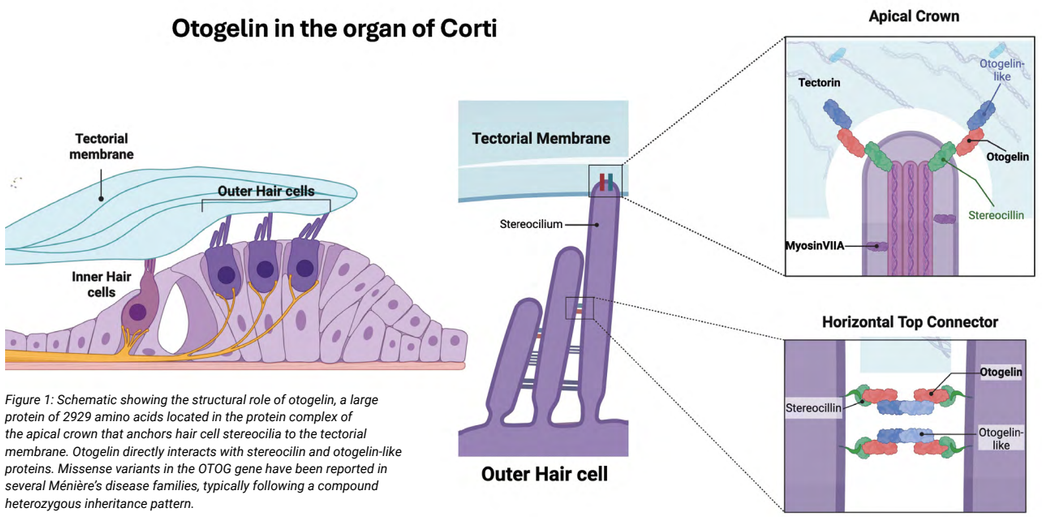

Figure 1: Schematic showing the structural role of otogelin, a large protein of 2929 amino acids located in the protein complex of the apical crown that anchors hair cell stereocilia to the tectorial membrane. Otogelin directly interacts with stereocilin and otogelin-like proteins. Missense variants in the OTOG gene have been reported in several Ménière's disease families, typically following a compound heterozygous inheritance pattern.

Attribution: Otogelin in the organ of Corti by JA Lopez-Escamez (2025) created in BioRender (https://biorender.com/yfrjs8r) is licensed under CC BY 4.0.

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Nevertheless, additional exciting insights have been unveiled in patients with MD: the discovery of a persistent systemic inflammatory response in 60% of MD patients supports a central role of the immune system in MD, beyond the inflammatory process in the inner ear.

Several epidemiological studies have reported a high prevalence of autoimmune disorders in MD patients, including autoimmune thyroiditis, rheumatoid arthritis and psoriasis, among other conditions.

However, a prospective two-year follow-up longitudinal study has led to the identification of three groups of MD patients according to epigenomic, transcriptomic and proteomic data, supporting: (1) an allergic cluster with chronic-persistent inflammation associated with type 2 immune cytokines (IL4, IL6, IL9, IL13) and high levels of IgE; (2) a monocyte-driven cluster associated with autoinflammation and high levels of IL1ß; as well as (3) a non-immune cluster [4]. Furthermore, these results were confirmed in another study using peripheral mononuclear cells from MD patients. Single-cell transcriptomic and single-cell ATAC-seq analyses, which profile RNA and chromatin accessibility at the single-cell level, showed that vestibular migraine and MD have distinct transcriptomic profiles.

The Ménière's Disease Atlas

To integrate all this multiomic information and facilitate the precise diagnosis for MD patients, we have been building the MD Atlas website https://multiomic-md.sydney.edu.au. This is an open resource which provides access to anonymised multiomic data obtained from MD patients. The MD Atlas integrates three datasets: genome aggregated MD variants (GRCh38-aligned, annotated for position, consequence, gnomAD frequencies); epigenomic data with methylated CpG sites from MD patients; and transcriptomic data including bulk RNA-seq from mononuclear cells and single-cell RNA-seq from B cells, CD4/CD8 T cells, monocytes and NK cells of MD participants. Datasets have been curated, standardised and paired with visualisation tools for each omics layer. Future updates will allow users to upload datasets for comparison with MD Atlas.

The link between the immune response and genetic mutations remains to be established, but ongoing experimental data in human and non-human models will clarify this issue.

A precise molecular diagnosis beyond clinical symptoms is needed for MD. Current research will be the first to generate a reference database for genetic diagnosis of MD and to implement a decision support system to classify patients according to multiomic datasets.

Conclusions

The implementation of genetic and cytokine testing for MD in clinical practice will revolutionise the diagnosis of MD by facilitating personalised treatment strategies. In the near future, patients will benefit from gene therapy and immune phenotype-based treatments including anti-IgE/IL-4R drugs (dupilumab, omalizumab) in IgE/type2 cytokine patients, or TNF-α or IL-1 ß blockers (adalimumab, anakinra) in autoimmune / autoinflammatory patients.

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