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DOI: <https://doi.org/10.20883/jms.2018.289>


Genetic background of Meniere's disease


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ABSTRACT

Meniere's disease (MD) as an inner ear disorder including such symptoms as recurrent vertigo attacks, tinnitus, fluctuating or progressive sensorineural hearing loss. Its relatively frequent familial incidence implicates a genetic background. An autosomal dominant inheritance was commonly observed with a few exceptions. It was established that Meniere's disease is not a monogenic disorder. Instead a group of genes of genomic and mitochondrial genes was established as determinants of hearing loss. Another group of genes was associated with inner ear (vestibulum, labyrinth, endolymph) alterations followed by dizziness and tinnitus. Altogether, many studies suggest a multigenic interaction to predispose to develop Meniere's disease.

Keywords: meniere's disease, genetic background, gene identification T.

Meniere's disease (MD) as an inner ear disorder including such symptoms as recurrent vertigo attacks, tinnitus, fluctuating or progressive sensorineural hearing loss, and aural fullness. The latter is associated with an accumulation of endolymph forming endolymphatic hydrops. Further symptoms as nausea and vomiting seem to be a consequence of primary alterations [1, 2]. Migraine attacks observed in a subset of patients are classified as accompanying but separate condition. Altogether, patients present a clinical heterogeneity and not necessarily all particular symptoms are detected at diagnosis. Further, it has been noticed that first three symptoms are currently present in 40% of the patients only. It means a full manifestation of all symptoms is a subject of disease evolution and requires more time [3]. To facilitate diagnosis the American Academy of Otolaryngology – Head and Neck Surgery has proposed the guidelines widely accepted

[1]. Though MD remains in the frame of interest of otolaryngology, neurotology and neurology.

There are many different options of MD treatment which should be used in a determined order. The first line of treatment should always be medical conservative treatment including modification of the lifestyle (well sleeping, decreasing stress, avoiding coffee, alcohol and tobacco and adopt a low salt diet), vestibular rehabilitation, psychotherapy, pharmacotherapy (diuretic and betahistine) and pressure pulse therapy (Meniett® system). After this treatment 80% of patients are cured or in remission. The second line is intratympanic injections with steroid or with gentamicin. The third line is surgical treatment (endolymphatic sac surgery, vestibular neurectomy and labyrinthectomy), however endolymphatic sac surgery should be indicated before intratympanic gentamicin in cases with efficient hearing [4].

Although it has been described first in the middle XIXth MD poses still a serious medical problem for two reasons. First, the progressing MD contributes to serious health, psychological and social problems. Secondly, the disease affects a relatively high number of subjects. Epidemiologic studies have shown a range of prevalence from 17 (Western Europe) to 513 (Finland) cases per 100 000 individuals. Primarily it is detected in Caucasians and Eurasians. Diagnosis of MD is slightly more frequent in female population [2, 5].

Pathology of MD is not fully recognized yet that means a single or multiple casual factors have not been identified. Nevertheless it concerns inner ear with ion disequilibrium of endolymphatic fluid. An accompanying statement on disturbed ion homeostasis derived from dysfunction of ionic transport cannot serve as a definitive explanation of molecular pathology [6].

Hence further studies went in two directions aiming for a genetic background or immune deregulation in MD. We are aiming at presentation of genetic findings explaining predisposition and manifestation of MD. Clinical observations have shown a strong familial association of MD attributed up to 20% of patients. Pedigree analysis in families of MD carriers indicates an autosomal dominant inheritance with a reduced penetrance and anticipation [7].

Taking into account the above findings an attention was paid first on the already known genes attributed to individual symptoms assembling together Meniere's disease. Genes determining hearing loss provided themselves a broad spectrum of targeted investigations. Within this field vestibular disorders were found to be associated with the following loci: DFNA9, DFNA11, DFNA15, DFNA28 and DFNB102/103. Abbreviation DFNA is coming from deafness and the letter A denominates autosomal dominant tract when the letter B is attributed to autosomal recessive tract. The genes coded by the listed loci are as follows: *COCH*, *MYO7A*, *POU4F3*, *GRHL2* and *GLIC5* and all of them are associated with non-syndromic hearing loss [8]. Such attribution of genes to the symptoms of MD were first done by linkage analysis [9]. According to another publication [10] other mutations of the mentioned genes can be also extended onto vestibular dysfunction. The study was performed in a large Swedish family using whole-exome and targeted sequencing

techniques. *COCH* gene attracted more attention. An early study of Fransen et al. [11] investigating a large Belgium family, localized DFNA9 locus on chromosome 14 narrowing *COCH* (Coagulation Factor C Homolog, coded protein: cochlin) gene to 14q12-13. Gene mutation P51S (Pro-Ser) was found responsible for progressive autosomal dominant sensorineural hearing loss. Similar phenotype effect was established in American family carrying novel heterozygous missense mutation c.362>T>C, p.F121S0 [12]. All found *COCH* mutations were detected in exons 4, 5 and 12. The study of Gallant et al [13] done on large 3 generations American family with MD brought the discovery of another mutation located in 11th exon. This finding reinforced the need for genetic examination of the whole structure of *COCH*.

A specific position is taken by *SLC44A2* (chromosome locus 19p13.1) which product is a membrane transporter protein. It has a strong role in choline transport and uptake in inner ear. The research group of Tom Carey [14] has found disequilibrium at polymorphic loci rs2288904 with rs3087969 responsible for hearing loss. The defect is registered as DFNB68 that means, contrary to majority of genes responsible for hearing loss in MD, it is inherited on the autosomal recessive way. *SLC44A2* polymorphism seems also to be responsible for severity of Meniere's disease [14].

Our own study on hearing loss was done on 250 unrelated Polish subjects including a subgroup of MD patients. A sensitivity to aminoglycoside drugs was established with mutations of mitochondrial *12S rRNA* gene. Mutations m.1555 A>G, m.988 G>C and m.1453 A>G were found in all studied MD patients [15]. Our findings are consistent with the study on deafness-associated mutations by Qian and Guan [16].

Independently on hearing loss genetic studies on MD were focused on tinnitus, dizziness and motion sickness [6, 8, 10]. Initial studies performed on 5 generations Swedish family affected by MD done by genome wide linkage scan (GWAS) indicated chromosome locus 12p12.3 [17]. Later on it was shown that a finding is not having a general character as the familial MD studied in Finland was not linked to this region [18]. Further studies indicated that in very close region there is located *KCNA7* gene (12p13) encoding protein connected with a voltage-gated potassium channel [19].

Another genes also connected with ion homeostasis, aquaporin water channels (*AQP-1*), potassium channel (*KCNE1* and *KCNE3*) and $\text{Na}^+\text{-K}^+$ pump activity (*ADD1*) are under investigative attention [18]. It is necessary to add that a recent meta-analysis concluded that neither of *KCNE* variants is significantly associated with MD [20].

Looking for a background of pathology in MD some studies deal with immune system. There were published reports on association of MD with certain major histocompatibility complex (HLA) genes, namely *MICA-STR A.4* and *HLA-DRB1* [21, 22]. Also *PTPN22* (1p32; protein product: protein tyrosine phosphatase) as an integral part of immune stem could contribute to bilateral MD in east in southern European population [23]. It seems that immunologic hypothesis of MD incidence is not having a sufficient experimental support.

The reviewed list of the established or requiring further studies genes is not full. At this point a leading position in the field of laboratory headed by Jose A. Lopez-Escamez (Granada, Spain) is to be mentioned. In any case, it has become clear that Meniere's disease is not derived from a single mutated gene. A combination of genes responsible for hearing loss [12, 14, 15], dizziness [8, 10, 19] and tinnitus [24] forms a landscape for genetic background of Meniere's disease. A heterogeneous nature of genetic background makes the studies difficult to perform and complicates an interpretation of results [8, 25, 26].

Acknowledgements

Conflict of interest statement

The authors declare no conflict of interest.

Funding sources

There are no sources of funding to declare.

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Acceptance for editing: 2018-06-30
Acceptance for publication: 2018-07-02

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