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Elina Hietikko

GENETIC AND CLINICAL FEATURES OF FAMILIAL MENIERE'S DISEASE IN NORTHERN OSTROBOTHNIA AND KAINUU

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DEPARTMENT OF OTORHINOLARYNGOLOGY

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Abstract

Meniere's disease (MD) is an inner ear disorder characterized by vertigo, tinnitus and sensorineural hearing impairment. An inherited form of the disease is called familial Meniere's disease (FMD). The aim of this thesis was to describe the clinical and genetic features of Finnish FMD and to study its prevalence in Finland. In addition genetic factors previously associated with MD were studied in Finnish MD patients.

A total of 38 Meniere-families were analysed in this study. In most of the families the mode of inheritance was found to be autosomal dominant. Meniere-like symptoms such as tinnitus or vertigo were common in these families even in individuals without a full triad of MD. Familial patients were affected earlier, suffered from longer spells of vertigo and had more autoimmune diseases compared to sporadic MD patients.

The prevalence of FMD was studied among the patients treated in the Oulu University Hospital and Kainuu Central Hospital during the years 2005-2010. A family history of MD was probable in 23.4% of the cases, but only 9.3% could be confirmed, as it was not possible to gain information from deceased generations.

Six candidate genes previously associated with MD were screened for mutations in Finnish MD patients. Two possibly adverse variations were observed in the *KCNE1* gene in two patients but in none of the controls. The role of these variations in MD is still unclear and needs further study. The association of MD to the five other genes could not be confirmed, nor was Finnish FMD linked to a previously suggested locus on chromosome 12.

Keywords: candidate gene analysis, familial Meniere's disease, hearing impairment, KCNE1, sporadic Meniere's disease, vertigo

Hietikko, Elina, Menieren taudin perinnöllisyyden ominaispiirteet Pohjois-Pohjanmaalla ja Kainuussa.

Oulun yliopiston tutkijakoulu; Oulun yliopisto, Lääketieteellinen tiedekunta, Biolääketieteen laitos, Lääketieteellinen biokemia ja molekyylibiologia; Kliinisen lääketieteen laitos, Korva-nenä- ja kurkkutaudit; Oulun yliopistollinen sairaala, PL 5000, 90014 Oulun yliopisto; Kainuun keskussairaala, Korva -, nenä - ja kurkkutautien poliklinikka, Sotkamontie 13, 87300 Kajaani
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Tiivistelmä

Menieren tauti on sisäkorvan sairaus, jolle on tyypillistä huimaus, korvien soiminen ja kuulon heikkeneminen. Tauti voi esiintyä myös perinnöllisenä. Tutkimustyön tavoitteena oli selvittää perinnöllisyyden osuutta Menieren taudissa, kuvata suomalaisen perinnöllisen Menieren taudin tyypilliset piirteet ja tutkia suomalaisessa aineistossa aikaisemmin tautiin yhdistettyjä perinnöllisiä tekijöitä.

Tutkimuksessa analysoitiin 38 sukua, joissa Menieren tautia esiintyi perinnöllisenä. Suurimmassa osassa tapauksista periytyminen tapahtui vallitsevasti. Suvuissa esiintyi paljon Menieretyypistä oirehdintaa, kuten tinnitusta ja huimausta, ilman Menieren taudin koko taudinkuvaa. Meniere-suvuissa potilaat sairastuivat keskimääräistä aikaisemmin, kärsivät pidemmistä huimauskohtauksista ja sairastivat enemmän autoimmuunitauteja.

Perinnöllisen Menieren taudin yleisyyttä tutkittiin Kainuun keskussairaalassa ja Oulun yliopistollisessa sairaalassa vuosina 2005−2010 hoidettujen potilaiden keskuudessa. Potilaista 23,4 %:lla Menieren taudin sukuhistoria oli positiivinen; kuitenkin vain 9,3 % pystyttiin vahvistamaan, sillä tietojen kerääminen edesmenneiltä sukupolvilta ei ollut mahdollista.

Kuuden Menieren tautiin aikaisemmin yhdistetyn geenin merkitystä tutkittiin suomalaisessa aineistossa mutaatio- ja ehdokasgeenianalyysillä. *KCNE1*-geenistä löydettiin kaksi mahdollisesti proteiinia vaurioittavaa sekvenssinvaihtelua, joita ei havaittu kontrollihenkilöillä. Muutosten merkitys Menieren taudin synnyssä jäi kuitenkin epävarmaksi ja vaatii jatkotutkimuksia. Muiden geenien yhteyttä sairauteen ei pystytty vahvistamaan. Suomalainen Menieren tauti ei myöskään kytkeytynyt aikaisemmin ehdotettuun lokukseen kromosomissa 12.

Asiasanat: ehdokasgeenianalyysi, familiaalinen, genetiikka, huimaus, KCNE1, kuulonalenema, Menieren tauti, perinnöllisyys

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Oulu, April 2013 Elina Hietikko

Abbreviations

AAO-HNS	American Academy of Otolaryngology –Head and Neck Surgery
ABR	auditory brain stem response
ADD1	alpha adducin 1
AF	aural fullness
AQP	aquaporin
ARHI	age related hearing impairment
BMP	bone morphogenetic protein
BPPV	benign paroxysmal positional vertigo
CACNA1A	calsium channel alpha 1A subunit
CAT	catalase
CD4	cluster of differentation 4
CI	confidence interval
COCH	coagulation factor C homolog
COL1A1	collagen type 1 alpha 1
CSC	Center for Science Computing
CSGE	conformation sensitive gel electrophoresis
CT	computer tomography
dB	decibel
DFNB1	autosomal recessive non-syndromic hearing loss 1
DFNA9	autosomal dominantly inherited cochleo-vestibular dysfunction 9
DNA	deoxyribonucleic acid
EDTA	ethylenediaminetetraacetic acid
EH	endolymphatic hydrops
ENT	ear-nose-throat
FMD	familial Meniere's disease
GJB2	gap junction protein beta 2
GWAS	genome wide association analysis
HCFC1	host cell factor C1
HCFC1	heat shock protein 1
HLA	human leucocyte antigens
HLOD	heterogenic logarithm of odds
HSP	heat shock protein
HWE	Hardy–Weinberg equilibrium
ICD10	International Statistical Classification of Disease 2010

IgE	immunoglobulin E
IL1	interleukin 1
IHS	International Headache Society
KCNA1	potassium voltage-gated channel subfamily A member 1, Shaker-related subfamily 1
KCNE	potassium voltage-gated channel subfamily E member 1, Isk-related family
kHz	kilohertz
LMH	low-mid-low
LOD	logarithm of odds
MD	Meniere's disease
MRI	magnetic resonance imaging
NCBI	National Center for Biotechnology Information
NIHI	noise induced hearing impairment
NOS	nitric oxide synthase
NPL	nonparametric linkage
NSHL	non-syndromic hearing loss
PARP1	poly (ADP-ribose) polymerase 1
PCR	polymerase chain reaction
PTPN22	protein tyrosine phosphatase, non-receptor type 22
ROS	reactive oxygen species
SD	standard deviation
SHL	syndromic hearing loss
SMD	sporadic Meniere's disease
SNP	single nucleotide polymorphism
TGFB1	transforming growth factor beta 1
VM	vestibular migraine

List of original publications

This thesis is based on the following articles, which are referred to in the text by their Roman numerals

I Hietikko E, Kotimäki J, Sorri M & Männikkö M (2013) High incidence of Meniere-like symptoms in relatives of Meniere patients in the areas of Oulu University Hospital and Kainuu Central Hospital in Finland. European Journal of Medical Genetics. In Press.

II Hietikko E, Sorri M, Männikkö M & Kotimäki J (2013) Higher prevalence of autoimmune diseases and longer spells of vertigo in patients affected with familial Meniere's disease – a clinical comparison of familial and sporadic Meniere's disease. Manuscript.

III Hietikko E, Kotimäki J, Kentala E, Klockars T, Sorri M & Männikkö M (2011) Finnish familial Meniere disease is not linked to chromosome 12p12.3, and anticipation and cosegregation with migraine are not common findings. Genet Med 13(5): 415–20.

IV Hietikko E, Kotimäki J, Okuloff A, Sorri M & Männikkö M (2012) A replication study on proposed candidate genes in Ménière's disease, and a review of the current status of genetic studies. Int J Audiol 51(11): 841–5.

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1 Introduction

Meniere's disease (MD) is an inner ear disorder characterized by a triad of spinning vertigo, sensorineural hearing impairment and tinnitus. The French physician Prosper Ménière first described the disease in 1861. Despite relentless study the aetiology of MD has remained unknown. Although a fluid overload of the inner ear called endolymphatic hydrops has been observed in MD patients, the exact mechanism behind the symptoms of MD are unknown and treatment modalities of MD can only relieve the patient´s symptoms.

Reports on hereditary MD have been published since the 1940s and at present inherited, i.e., familial MD (FMD) is estimated to represent 5–20% of all MD cases. Most studies concerning FMD to date are case reports describing single families and only a few systematic studies exist. More detailed information about FMD is needed in order to provide patients with accurate information about the heredity of MD and facilitate future genetic studies. Although genetic factors responsible for the disease have not been identified, modern genetics may prove useful in the aetiologic study of MD.

The aim of this thesis was to describe genetic and clinical features of FMD in Finland, to estimate the prevalence of FMD and Meniere-like symptoms in the patients´ families, and to clarify whether clinical differences between familial and sporadic forms of the disease exist. In addition genetic factors previously associated with MD are reviewed and studied in a set of Finnish MD patients. The results of these studies add information about the significance of genetic factors in MD and lay a foundation for future genetic studies on Finnish MD patients.

2 Review of the literature

2.1 Meniere's disease

2.1.1 Definition

The Committee of Hearing and Equilibrium of the American Academy of Otolaryngology -Head and Neck Surgery (AAO-HNS) has published recommendations on the diagnostic criteria and guidelines on reporting results of scientific studies of MD on three occasions (AAO-HNS 1972, Pearson & Brackmann 1985, AAO-HNS 1995). The latest criteria for MD are presented in Table 1.

Table 1. Diagnostic criteria for MD.

Probability	Description
Certain	Definite MD and histopathologic confirmation
Definite	At least two definite episodes of vertigo 20 minutes or longer
	Audiometrically documented hearing loss
	Tinnitus or aurall fullness in the affected ear
	Other causes excluded
Probable	One definite episode of vertigo 20 minutes or longer
	Otherwise same as definite
Possible	Meniere-like episodic vertigo without documented hearing loss or sensorineural hearing loss, fluctuating or fixed, with dysquilibrium but without definite episodes
	Other causes excluded

The AAO-HNS 1995 criteria are widely accepted and present the "gold standard" in admitting and evaluating patients affected with MD in scientific studies. Although, these criteria have been criticized for deviating from Prosper Ménierè's original criteria (Stapleton & Mills 2008) and for the lack of guidelines on what differential studies should be performed to adequately diagnose MD (Matejsen 2001), by 2003 approximately 85% of all studies concerning MD have followed the diagnostic criteria applied by the AAO-HNS in 1995 (Thorp *et al.* 2003).

2.1.2 Natural course

The classic symptoms of MD are rotational vertigo, sensorineural hearing loss and tinnitus (Ménière 1861). Vertigo is often accompanied by nausea and vomiting. Patients may also experience aural fullness in the affected ear (Paparella 1984). The classic symptoms can be accompanied by drop attacks (Baloh *et al.* 1990) and a reduction in vestibular function (Hulshof & Baarsma 1981). MD begins with manifestation of the whole triad in only 27–44% of the cases (Friberg *et al.* 1984, Haid *et al.* 1995, Belinchon *et al.* 2012). Patients can suffer from separate symptoms even for years before the appearance of the whole triad (Friberg *et al.* 1984), which makes MD a diagnostic challenge.

The natural history of each of the symptoms is reviewed below. It should, however, be noted that since a majority of the studies on the natural course of MD have been published before the current diagnostic criteria, the picture of MD presented by these studies might be slightly different if the current diagnostic criteria were applied.

Vertigo

Of all the symptoms of MD, vertigo has been reported to have the most negative effect on everyday life (Cohen *et al.* 1995); however, most studies suggest a benign course of vertigo attacks over time (Green *et al.* 1991, Perez-Garrigues *et al.* 2008, Stahle *et al.* 1991). The duration and severity of the attacks seems to stay the same (Perez-Garrigues *et al.* 2008), while the percentage of patients without vertigo attacks increases over time (Green *et al.* 1991, Tokumasu *et al.* 1996). However, some patients can have severe vertigo even after 20 years of the disease (Havia & Kentala 2004). Duration of the attacks varies anywhere from 20 minutes to several days (AAO-HNS 1995). Estimations of the frequency of the attacks have varied from 1–4 attacks a month to 3–11 attacks a year (Stahle *et al.* 1991, Green *et al.* 1991, Havia & Kentala 2004). However, remissions lasting for over two years have also been described (Tokumasu *et al.* 1996)

Hearing impairment

Meniere's disease is characterized by sensorineural hearing impairment that develops over the duration of the illness. The majority of studies suggest that most of the deterioration occurs in the first few years of MD followed by

stabilization after 5 to 10 years to an average level of 50–60 dB (Enander & Stahle 1967, Stahle & Bergman 1967, Stahle 1976, Thomas & Harrison 1971, Sumi *et al.* 2012). Fluctuation in hearing is common especially in the first years after diagnosis (AAO-HNS 1995). In the early stages lower frequencies are mainly involved, but later higher frequencies are also affected (Eliachar *et al.* 1973, Goodman 1965). A flat type audiogram is suggested to be the most common especially in the long course of the disease; however, no particular type of audiogram seems to be characteristic of MD (Stahle *et al.* 1991, Thomas & Harrison 1971). Most studies indicate that the frequency of second ear involvement increases with time, but there has been a considerable variation in the percentage of bilateral cases from 2 to 47% in different studies as reviewed recently by Huppert *et al.* (2010).

Tinnitus

Tinnitus in MD is not as consistently described as vertigo and hearing loss. Most studies suggest tinnitus in MD to be of moderate severity and identified in low and mid frequencies' (Herraiz *et al.* 2006, Romero Sanchez *et al.* 2010, Vernon *et al.* 1980). The severity of tinnitus is influenced by the duration and stage of the disease (Romero Sanchez *et al.* 2010). Intense tinnitus is more commonly seen in late stages of the disease (Havia *et al.* 2002). Tinnitus primarily affects psychological factors and mood such as sleep, depression and anxiety (Stephens *et al.* 2012). High frequency tonality, depression and youth have been identified as negative prognostic factors of tinnitus (Romero Sanchez *et al.* 2010).

Aural fullness

Aural fullness (AF) is a subjective sensation of pressure in the ear. AF is not exclusive for MD, as it has also been reported by patients with acute sensorineural hearing loss and otitis media (Sakata & Kato 2006). The mechanism of AF is unknown. In different studies 50–74.1% of MD patients have been reported to suffer from AF (Schmid *et al.* 1979, Paparella 1984, Haid *et al.* 1995).

Drop attacks

Drop attacks are sudden falling spells that can occur in patients affected with MD. They rarely occur in the early stages of the disease and are most common in late

stages (Black *et al.* 1982). It has been theorised that drop attacks result from a sudden mechanical deformation of the otolithic membranes (Baloh *et al.* 1990). Prevalence of drop attacks among MD patients was estimated in a current review to be 3–7% (Huppert *et al.* 2010).

2.1.3 Differential diagnosis

There is no widely accepted standard for differential diagnostic studies of MD. In Finnish health care a clinical examination, an audiometry and imaging of the head or measurement of auditory brain stem responses (ABR) are recommended for the differential diagnosis of MD (Kotimäki 2004). Some authors feel that more extensive studies such as electrocochleography, caloric testing and wide spectrum laboratory tests are needed (Syed & Aldren 2012). A wide number of diseases can cause vertigo, hearing loss or tinnitus. Entities that can be confused with MD are presented below.

Vestibular migraine

Vestibular migraine (VM) or migraine-associated vertigo is estimated to be one of the most common causes of episodic vertigo (Bisdorff 2011). Although VM is not recognized by the International Headache Society (IHS) (Headache Classification Subcommittee of the International Headache Society 2004), about 10% of migraine patients also suffer from vertigo (Neuhauser *et al.* 2001). Vertigo in VM can be rotational or positional and last from seconds to several hours, even days (Lempert & Neuhauser 2009). Vertigo can occur with or without a headache (Cutrer & Baloh 1992). Even cochlear symptoms can present, which makes it even harder to differentiate VM from MD, but hearing loss is usually mild and non-progressive (Kayan & Hood 1984). Patients with VM are also more susceptible to motion sickness and moving visual stimuli (Lewis *et al.* 2011). The pathophysiology of VM is unknown. Ion-channel pathology has been suspected since mutations in a calcium channel component alpha 1 subunit (*CACNA1A*) are known to cause episodic ataxia type 2, with both migraine and vestibular symptoms (Jen *et al.* 2004). This is particularly interesting since ion channel pathology has also been discussed as one possible cause of MD (Ishiyama *et al.* 2006).

Otosclerosis

Otosclerosis is a disorder of bone metabolism that affects the normally inactive otic capsule (Karosi & Sziklai 2010). It is one of the most common causes of acquired hearing loss with a clinical prevalence of 0.3–0.4% in Caucasians (Ealy & Smith 2011). Hearing loss is commonly conductive or mixed-type but even sensorineural hearing loss can occur (Cureoglu *et al.* 2010). Otosclerosis is often accompanied by tinnitus (Deggouj *et al.* 2009). In addition, Cawthorne described vestibular symptoms in 24% of patients with otosclerosis as early as the 1950s (Cawthorne 1955). Otosclerotic involvement of the vestibular organ has been thought to cause the vestibular symptoms (Cureoglu *et al.* 2010) but it has also been theorised that otosclerotic lesions involving the vestibular duct can obstruct endolymph absorption resulting in hydrops and possibly vertigo (Makarem & Linthicum 2008). Otosclerosis with vestibular symptoms can be referred to as cochlear otosclerosis, which could be confused with MD.

Vestibular nerve tumour

Vestibular nerve tumour, e.g., vestibular schwannoma is a benign tumour that can arise from anywhere along the course of the axons of the eighth cranial nerve (Roosli *et al.* 2012). The most common symptoms associated with vestibular nerve tumours are tinnitus and sensorineural hearing impairment (Stangerup & Caye-Thomasen 2012). It has been reported that half of the patients can have vertigo attacks lasting from minutes to several hours (Kentala & Pyykkö 2001), although dizziness is the most common vestibular complaint in vestibular nerve tumour patients (Loyd *et al.* 2010). Vertigo and tinnitus have been associated with tumour growth (Breivik *et al.* 2012). A differential diagnosis between vestibular schwannoma and MD can be done using magnetic resonance imaging (MRI). Bilateral vestibular schwannoma is characteristic for neurofibromatosis type II, which is a tumour predisposition syndrome caused by mutations in the *NF2* gene on chromosome 22, and which can also be confused with MD (Evans 2009). Treatment of small and intracanalicular vestibular nerve tumours in most cases involves “watchful waiting” and management of the symptoms (Quesnel & McKenna 2011). Large, rapidly growing or highly symptomatic tumours require active treatments such as surgery or radiation therapy (Arthurs *et al.* 2011).

Benign paroxysmal positional vertigo

Benign paroxysmal positional vertigo (BPPV) is a disorder characterized by recurrent spells of vertigo caused by calcium carbonate crystals in the semi-circular canals (Fife 2009). Typically vertigo attacks in BPPV are shorter and milder than in MD, but there is a huge overlap in the duration of vertigo between the two groups (Brantberg & Baloh 2011). If severe BPPV is thought to be early symptoms of developing MD, the condition can be misdiagnosed (Jin *et al.* 2012). BPPV is diagnosed using history and clinical examination including position-provoking tests (Tian *et al.* 2012).

Other

Other rare causes such as labyrinthine fistula (Minor 2003), Chiari malformation of the brain (Levo *et al.* 2010), multiple sclerosis (Peyvandi *et al.* 2010), sudden sensorineural hearing loss (Koc & Sanusoglu 2003), vertebrobasilar ischaemia (Kim & Lee 2009), superior canal dehiscence syndrome (Cuncha *et al.* 2006) and Ramsay-Hunt syndrome (Williams 2010) can manifest Meniere-like symptoms.

2.2 Epidemiology of Meniere's disease

2.2.1 Prevalence and geographical distribution

The prevalence rates of MD have varied from 17 to 513 per 100 000 in different studies. The vast variation is probably caused by changing diagnostic criteria and methodological differences as pointed out by a recent review (Alexander & Harris 2010). However, differences in geographical distribution could also be affected by genetic variation among populations since the prevalence's seem to be much higher in Caucasians (Radtke *et al.* 2008) than in Asians (Shojaku *et al.* 2005) as also seen in Table 2.

In Finland the prevalence of MD has been studied on two occasions. Kotimäki *et al.* (1999) observed a prevalence of 43 per 100 000 when reviewing patient records of seven Finnish hospitals covering a population of 1.5 million (Kotimäki *et al.* 1999). The writers concluded that the true prevalence is probably somewhat higher as the study did not include patients in private clinics and in addition some patients with long remissions could have been left out of the study. In a more recent study by Havia *et al.* (2005) a much higher prevalence of 513 per

100 000 was observed in a population based survey in southern Finland (Havia *et al.* 2005).

Table 2. Studies on the prevalence of MD.

Prevalence per 10^5	Population	Diagnostic criteria	Study method	Reference
190	United States	ICD-9+ diagnose number 386.9x, no clinical data available	nation-wide case series	Harris & Alexander 2010
120	Germany, Berlin	AAO-HNS[X] 1995	case series	Radtke *et al.* 2008
220	Nigeria, Ibadan	Own	case series	Ibekwe & Ijaduola 2007
34.5	Japan, Nishikubiki	Japanese Society for Equilibrium research	retrospective survey	Shojaku *et al.* 2005
513	Finland, Helsinki	AAO-HNS 1995	population-based survey	Havia *et al.* 2005
75	Spain, Cantabria	AAO-HNS 1995	case series	Morales *et al.* 2003
43	Finland	AAO-HNS 1995	nation-wide case series	Kotimäki *et al.* 1999
36.6[1] 21.4[2]	Japan, Hida and Nishibiki	M.C.J#	case series	Shojaku & Watanabe 1997
17	Japan, Toyama	M.C.J.#	nation-wide survey	Shojaku *et al.* 1995
82	Italy, South-eastern Latium	A.A.O.O.* 1972	case series	Celestino & Ralli 1991
218.2	UK, Rochester	AAO-HNS 1972	case series	Wladislavosky-Waserman *et al.* 1984

+ International Classification of Disease 9

[X] American Academy of Otolaryngology – Head and Neck Surgery

*American Academy of Ophthalmology and Otolaryngology

Meniere's disease committee of Japan, 1 Hida, 2 Nishibiki

2.2.2 Age at onset

MD is a disorder that most commonly occurs in middle-aged adults, but reports on paediatric cases in children 4–15 years old have been published (Hausler *et al.* 1987, Akagi *et al.* 2001, Brantberg *et al.* 2012). MD usually manifests between 20 and 70 years of age and the peak age at onset has been observed in the fourth and

fifth decade (Celestino & Ralli 1991, Harris & Alexander 2010, Shojaku *et al.* 1995, Watanabe *et al.* 1995, Wladislavosky-Waserman *et al.* 1984). The prevalence of the disease increases with age (Harris & Alexander 2010). It has been estimated that 1% of all MD cases manifest in children aged 14 years or younger (Hausler *et al.* 1987). Not all cases start with a complete triad of symptoms and there can be a delay between the onset of the first symptoms and the diagnosis (Friberg *et al.* 1984). It has also been suggested that familial cases are affected earlier and have a greater prevalence of childhood onset cases (Morrison *et al.* 2009).

2.2.3 Sex distribution

Studies on the sex distribution of MD have reported conflicting results. Both female (Watanabe *et al.* 1995) and male (Stahle 1976) preponderances and equal sex distribution have been reported as seen in Table 3. A slight female preponderance has been observed in all studies since the 1990s, which could imply that hormonal factors have a role in the development of MD. However, statistically significant differences between the sex distributions in MD have not been proven.

Table 3. Studies on the sex distribution in MD.

Reference	Cases	Females	Males	Ratio
Harris & Alexander 2010	473 000	65%	35%	1.9:1
Ibekwe & Ijaduola 2007	25	64%	36%	1.8:1
Shojaku *et al.* 2005	375	56%	43%	1.3:1
Havia *et al.* 2005	16	81%	19%	4.3:1
Kotimäki *et al.* 1999	121	58%	42%	1.4:1
Tokumasu *et al* 1996	151	56%	46%	1.2:1
Watanabe *et al.* 1995	953	72%	28%	2.6:1
Celestino & Ralli 1991	111	53%	47%	1.1:1
Wladislavosky-Waserman *et al.* 1984	180	61%	39%	1.6:1
Stahle *et al.* 1978	257	60%	40%	1.5:1
Stahle 1976	356	43%	57%	0.8:1
Cawthorne & Hewlett 1954	900	46%	54%	0.9:1

2.3 Concomitant diseases

2.3.1 Migraine and benign paroxysmal positional vertigo

Several studies have observed an association between migraine and MD (Atkinson 1962, Hinchcliffe 1967, Rassekh & Harker 1992, Parker 1995). It has even been suggested that MD develops as a complication of migraine (Cha *et al.* 2007). The overrepresentation of migraine in MD patients could also be explained by migraine-associated symptoms mimicking MD (Lempert & Neuhauser 2009).

Patients with MD also have a high prevalence of BPPV (Paparella 2008). In MD, BPPV has been suspected to be secondary to the inner ear disease (Lee *et al.* 2010). It has been theorised that hydropic distension or rupture could damage the otolithic apparatus leading to the release of otoconia debris in the semi-circular canals (Psillas *et al.* 2011). BPPV has also been associated with migraine. In a study by Lempert *et al.* (2000) migraine was twice as common in patients with BPPV than in age- and sex matched controls (Lempert *et al.* 2000).

Epidemiological evidence has been accumulating on the link between vertigo and migraine as reviewed recently (von Brevern & Neuhauser 2011). Both migraine and vertigo are common complaints in the general population and thus can affect the same person without a common background. Neuhauser *et al.* observed, however, that comorbidity of migraine and vertigo (3.2%) was higher than can be expected by chance (1.1%) (Neuhauser *et al.* 2006). It is possible that a pathophysiological link between migraine and vertigo and thus between migraine and MD exist.

2.3.2 Otosclerosis

An association between otosclerosis and MD has been suspected by a few authors (Franklin *et al.* 1990, Liston *et al.* 1984). Families with both otosclerosis and MD have been described implying a possible link between the two disorders (Klockars & Kentala 2007a).

2.3.3 Allergy

Association between MD and allergy has been suggested as an increased prevalence of allergy in MD patients has been observed in several studies (Duke 1923, Powers 1973, Derebery & Berliner 2000). Elevated levels of antibodies to

different food allergens, inhalants and prick test sensitivity to gluten have been observed in MD patients (Di Berardino & Cesarani 2012, Gibbs *et al.* 1999, Keles *et al.* 2004). Negative results when studying antifood antibodies or prick test responses have also been reported (Boulassel *et al.* 2001, Moffat *et al.* 1979). Immunoglobulin E (IgE) mediated allergy has even been proposed as a cause of MD in some cases (Banks *et al.* 2012). Derebery *et al.* reported improvement in symptoms of MD after treating for inhalant and food allergens (Derebery 2000). Individual results have not been replicated, however, and no specific allergens have been identified. It remains undecided whether allergies and MD are actually associated.

2.3.4 Other concomitant diseases

Björne & Agenberg observed a higher prevalence of signs and symptoms of craniomandibular disorders such as pain in the face or jaw, pain on movement of the mandible and fatigue of the jaws in MD patients than in the general population (Bjorne & Agerberg 1996). Kotimäki *et al.* found an increased prevalence of ischaemic heart disease in MD patients (Kotimäki 2003). Most recently a higher prevalence of systemic autoimmune diseases was observed in MD patients (Gazquez *et al.* 2011).

2.4 Aetiopathogenesis of Meniere's disease

2.4.1 Pathophysiological findings

The role of endolymphatic hydrops

Endolymphatic hydrops (EH) has been considered responsible for the symptoms of MD since 1938, when it was first described by two independent temporal bone studies on MD patients (Yamakawa 1938, Hallpike & Cairns 1938). Histopathological evidence of EH in MD patients has since been reported by several authors (Cawthorne 1947, Day & Lindsay 1949, Salt & Plontke 2010).

EH is defined as a state where the structures bordering the endolymphatic space are distended by the increased endolymphatic volume (Salt & Plontke 2010). It was originally hypothesised that EH derives from blockage of the longitudinal flow of the endolymph from the cochlea to the endolymphatic sac

either by increased production or decreased absorption of the endolymph (Cawthorne 1947, Day & Lindsay 1949).

The role of EH as the symptom causing factor has been challenged, however, as since 1989 EH has been observed in patients without symptoms of MD (Rauch *et al.* 1989). In the work of Merchant *et al.* (2005) 1750 temporal bones from 963 deceased subjects were studied with light microscopy and evidence of EH was found in 79 cases (Merchant *et al.* 2005). All MD patients in the series had EH, but a full triad of MD was only present in 28 of the 79 cases with EH. In this series sensorineural hearing impairment was highly associated with EH as only one subject with EH had normal hearing, but vertigo was not present in all cases. In addition to the work of Merchant *et al.*, several reports on asymptomatic hydrops exist (Sperling *et al.* 1993, Alpay & Linthicum 2007). MD cases with EH in the asymptomatic contralateral ear have been published (Friedrich & Thornton 2001). The previous suggests that EH is not the sole cause of the symptoms in MD.

Besides the temporal bone studies, information from inner ear homeostasis and its disturbances have been gained by studying several animal models of EH (Salt & Plontke 2010). Based on animal studies the original hypothesis of imbalance between endolymph secretion and resorption has also been challenged. Measurements of the endolymphatic flow in guinea pigs have shown that the volume of the secretion of endolymph and the rate of its flow are not sufficient to have physiological significance (Salt 2001).

The aquaporin/vasopressin system and EH

The role of water- and ion channels in the development of EH has been discussed. The aquaporin water channel family is among the most studied since several aquaporins are expressed in the endolymphatic sac (Couloigner *et al.* 2004, Ishiyama *et al.* 2006). Some studies have suggested a role of vasopressin in the development of EH, since the administration of vasopressin resulted in EH in guinea pigs (Takeda *et al.* 2000). In addition the administration of a vasopressin antagonist has been shown to reverse hydrops caused by endolymphatic sac ablation (Takeda *et al.* 2003). The effects of vasopressin are thought to be mediated via aquaporin 2, since vasopressin increases its activity (Sawada *et al.* 2002). While the vasopressin/aquaporin system is possibly involved in the development of EH, more information is still needed before definitive conclusions can be drawn.

The role of oxidative stress

The role of oxidative stress in the pathogenesis of MD has been studied recently (Semaan *et al.* 2005). An increased expression of nitric oxide synthase II (NOS II), an enzyme that produces nitric oxide, in the inner ear has been observed in several studies during surgically induced EH in guinea pigs (Michel *et al.* 2000, Watanabe *et al.* 2001). Large amounts of nitric oxide and other oxidative side products are known as possible triggers of mitochondrial pathways of apoptosis (Bras *et al.* 2005). It has been observed earlier that during the course of EH a loss of the stereocilia of the hair cells occurs followed by a loss of outer- and finally inner hair cells in the cochlea (Albers *et al.* 1988, Horner *et al.* 1988). Oxidative stress could result in hair cell apoptosis. However, no definite evidence exists and further studies are needed.

2.4.2 Imaging of the inner ear

The inner ear is located deep in the temporal bone and study of the pathological changes in MD in living subjects was not possible until the recent development of imaging techniques. The earliest images of the inner ear were taken using computer tomography (CT). As CT images have a limited ability to visualise soft tissues the structures of the inner ear were not visualised until the development of MRI techniques. Reports on imaging of the inner ear in MD with MRI have been published since the late 1980s.

In several early studies using high-resolution MRI less frequent visualisation of the endolymphatic duct in MD patients compared to healthy controls was suggested (Tanioka *et al.* 1992, Welling *et al.* 1996, Xenellis *et al.* 2000). A significantly smaller distance between the vertical part of the posterior semi-circular canal and the posterior fossa in both ears of MD patients compared to controls has also been observed and this distance did not correlate to the duration or the symptoms of the disease (Lorenzi *et al.* 2000). These findings imply that variations in anatomy could possibly predispose to the disease.

Endolymphatic hydrops was first visualised in vivo using high-resolution MRI 1.5T imaging with intravenous gadodiamide contrast agent in guinea pigs by Niyazov *et al.* in 2001. Endolymphatic hydrops in living MD patients was first visualised by Nakashima *et al.* in 2007 using intratympanically administered gadolinium to enhance the fluid attenuated inversion recovery three-dimensional MRI (Nakashima *et al.* 2007). Reports on even better quality images have been

published since and the field is developing quickly. In a recent study increased prevalence and severity of EH was associated with the duration of MD (Fiorino *et al.* 2011). Preliminary results on the effects of treatments on MRI findings have already been published. In these studies neither a standard dose of betahistine nor intratympanic gentamicin treatment had any effect on endolymphatic hydrops (Fiorino *et al.* 2012, Gurkov *et al.* 2012).

As also discussed in the review of Pyykkö *et al.* (2010), standardizing the MRI process (e.g. concentration and amount of the contrast agent and optimal time of imaging after administration of the agent), determining the risk factors associated with imaging and image interpretation guidelines are needed before wider use of MRI in the imaging of the inner ear in patients is justified (Pyykkö *et al.* 2010). It seems quite likely, however, that imaging studies may change the diagnosis and evaluation of therapy results in MD in the near future.

2.4.3 Autoimmune factors

Several factors support the role of an immunological mechanism in the development of MD: 1) the association of MD with human leukocyte antigen (HLA) types, 2) the elevated levels of antibodies observed in MD patients compared to controls, 3) the increased prevalence of autoimmune diseases among MD patients and 4) the positive response to corticosteroids observed in some MD patients. These factors are reviewed below.

HLA-types

Different HLA types have been associated with MD in several studies. Koyama *et al.* found a higher frequency of HLA-DRB1*1602 in MD patients compared to controls (Koyama *et al.* 1993). An increased frequency of HLA-CW*0303 and HLA-CW*0602 as well as a decreased frequency of HLA-B44 and HLA-CW*0102 were observed in South Korean MD patients than in controls (Yeo *et al.* 2002). Melchiorri *et al.* (2002) found an association of MD with HLA-CW*07 (Melchiorri *et al.* 2002). In 2001 Khorsandi and colleagues observed an increased prevalence of HLA-CW*04 in MD patients (Khorsandi *et al.* 2011). In the above mentioned studies the numbers of subjects have been small (22–80 subjects) and controls have not always been appropriately matched. The results of the studies are not consistent and no HLA type associations have been replicated. There is no evidence of a single HLA type associated with MD. More studies are still needed

with larger study samples and with better-matched controls to determine if HLA types have significant relevancy in MD.

Antibodies

Animal experiments have demonstrated antibody production in the inner ear (Harris 1983, Harris 1984) as well as shown that the endolymphatic sac is capable of generating an immune response (Tomiyama & Harris 1986). Autoantibodies to the endolymphatic sac have been observed in MD patients (Alleman *et al.* 1997). In addition, an increase in CD4 (cluster of differentiation 4) cells observed during an acute attack of MD (Mamikoglu *et al.* 2002) and increased natural killer cell activity support the hypothesis that immunologic processes are important in MD (Fuse *et al.* 2003). Several different autoantibodies have been observed in the sera of MD patients.

Several researchers have observed increased frequencies of antibodies against the heat shock protein 70 (HSP70) (Atlas *et al.* 1998, Rauch *et al.* 1995). On the other hand several reports that find no association to HSP70 antibodies have also been published (Garcia Berrocal *et al.* 2002, Hornibrook *et al.* 2011b, Rauch *et al.* 2000). A review by Hornibrook *et al.* (2011b) noted that reports with negative association to HSP70 have been performed with purified HSP70 antigens and reports with positive association with less-than-pure HSP70, which might account for the conflicting results (Hornibrook *et al.* 2011b). No convincing evidence exists on an association of HSP70 with MD.

Collagen II is widely expressed in the inner ear and collagen II autoimmunity in MD has been suspected by several authors (Muino *et al.* 1999, Yoo *et al.* 1982, Yoshino 1994). EH has been established by collagen II autoimmunisation in guinea pigs (Ohashi *et al.* 1989), but limitations of this model have been discussed since different researchers have obtained conflicting results using the model (Soliman 1990). A negative result regarding collagen II antibodies in MD patients has also been published (Herdman *et al.* 1993). Collagen II antibodies have been associated with otosclerosis and progressive sensorineural hearing loss (Muino *et al.* 1999, Yoo *et al.* 1982). It remains unclear if antibodies to collagen II have significance in the development of MD or if they are just indicators of inner ear damage.

Antibodies to several other inner ear antigens have also been observed in MD patients (Atlas *et al.* 1998, Yoo *et al.* 2001). Specific reports on antigens such as sialyl-1 (Ikeda *et al.* 2000), Raf-1-protein (Cheng *et al.* 2000) and *COCH5B2*

gene product expressed in the cochlea and vestibule (Boulassel *et al.* 2001) have been published. In addition, elevated antithyroid peroxidase and antinuclear autoantibody titres have been observed in MD patients (Nacci *et al.* 2010). No antibodies have been identified, however, that are exclusively found in MD patients or common to all MD patients.

Co-occurrence of immunomediated diseases

An increased prevalence of allergies in MD patients has been observed (Derebery & Berliner 2000) as discussed earlier in chapter 2.3.3. Quite recently Gazquez *et al.* observed an increased prevalence of systemic autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus and ankylosing spondylitis in MD patients compared to the general population (Gazquez *et al.* 2011). Autoimmune diseases have been observed to co-occur with individuals and families (Somers *et al.* 2006). Concomitant occurrence of immunomediated diseases supports the possibility of an immunological origin in MD.

Steroid response

Steroid use in the treatment of MD has gained popularity since studies supporting the theory that MD is an immune-mediated disorder. The benefits of steroids in a subpopulation of MD patients have been reported (Garduno-Anaya *et al.* 2005, Herraiz *et al.* 2010, Lu *et al.* 2010). Although some MD patients seem to benefit from treatment with glucocorticoids, a recent Cochrane review pointed out the lack of randomized placebo controlled trials on steroid use in MD and concluded that only a limited amount of evidence on the benefits of steroids in MD exists (Phillips & Westerberg 2011).

2.4.4 Hormonal factors

Recently evidence on hormonal regulation of the auditory system has been accumulating (Al-Mana *et al.* 2008). Higher levels of serum antidiuretic hormone, e.g., vasopressin, have been reported in MD patients by several authors (Takeda *et al.* 2010). Vasopressin levels have been reported to be higher in the acute phase of the disease than during remission (Aoki *et al.* 2007, Kakigi & Takeda 2009). A significant difference in vasopressin levels between MD patients and controls has not been detected in several studies (Lim *et al.* 2003, Hornibrook *et al.* 2011a).

The link between the vasopressin-aquaporin system and EH was previously discussed in chapter 2.3.1. Vasopressin is known to affect inner ear gene expression (Gu *et al.* 2006). Kitahara *et al.* (2008) suggested that overexpression of vasopressin receptors in the inner ear could be more significant in the development of MD than the level of serum vasopressin (Kitahara *et al.* 2008). Vasopressin has also been associated with higher levels of stress, which raises the possibility that an increase in vasopressin levels could be a reaction to discomfort, i.e., a consequence of the symptoms rather than the cause of MD (Sawada *et al.* 1997). More studies on the vasopressin system are still needed to determine its role in MD.

In addition to the vasopressin system, MD has also been associated with higher cortisol levels (Aoki *et al.* 2011), but since the levels seem to grow higher over the course of the disease, it has been suggested that the rise in cortisol level is a result rather than a cause of the disease (van Cruijsen *et al.* 2005). Higher prevalences of hypothyroidism (Brenner *et al.* 2004) and hyperprolactinemia (Horner *et al.* 2002) have also been reported in MD patients, which further supports the role of hormones in inner ear dysregulation. It seems clear that hormones are important regulators of the inner ear, but their role in MD still needs further study.

2.5 Genetics of hearing impairment, vertigo and Meniere's disease

2.5.1 Genetics of hearing impairment

Hereditary hearing impairment

Hearing loss was suspected to have a genetic basis long before the development of modern genetic methods and identification of hearing impairment causing genes (Gorlin *et al.* 1995). To date more than 120 independent genes causing hearing impairment have been identified (Van Camp & Smith 2012) and genetic studies have significantly increased our knowledge about the auditory system.

Genetic hearing impairment can be classified as syndromic or non-syndromic hearing loss (NSHL). Mutations in the gap juction protein beta 2 gene (*GJB2*) encoding connexin 26 are the most common cause of autosomal recessive NSHL accounting for almost 50% of the cases (Frei *et al.* 2004). Connexin-26 is a gap junction protein important in the potassium cycling of the inner ear and the

mutations cause defects in the ability of the hair cells to generate action potentials in response to sound, which leads to severe-profound hearing impairment (Apps *et al.* 2007). Some of the most common forms of syndromic hearing loss (SHL) are presented in Table 4.

Mitochondrial hearing loss is a rare cause of pre-lingual hearing loss accounting for less than 1% of the cases, but is more common at later ages (Kokotas *et al.* 2007). Mitochondrial mutations can cause nonsyndromic-hearing impairment but can also lead to multisystem syndromes such as Kearns-Sayre or MELAS (Schapira 2012).

Table 4. Some of the most common forms of syndromic hearing loss.

Name	Symptoms	Gene	Reference
Usher Syndrome	Moderate to severe hearing loss, vestibular dysfunction, progressive degeneration of the retina (retinitis pigmentosa)	*MYO7A* *USH1C, 2A, 3* *CDH23* *PCDH15*	Friedman *et al.* 2011
Pendred Syndrome	Severe congenital hearing loss, euthyroid goitre and labyrinth bone abnormality (Mondini dysplasia)	*SLC26A4*	Bizhanova & Kopp 2010
Jervell and Lange-Nielsen Syndrome	Congenital hearing loss and elongation of QT interval that can increase the risk of arrhythmias	*KVLQT1* *KCNE1*	Tranebjaerg *et al.* 1999
Stickler Syndrome	Progressive sensorineural hearing loss, cleft palate, abnormal development of the epiphysis and osteoarthritis	*COL11A1* *COL11A2* *COL2A1*	Liberfarb *et al.* 2003
Alport Syndrome	Progressive sensorineural hearing loss, glomerulonephritis and macular abnormalities	*COL4A3* *COL4A4* *COL4A5*	Kashtan 2000

Age-related hearing impairment

Age-related hearing impairment (ARHI) is a very common multifactorial condition associated with degenerative changes of the auditory system (Roth *et al.* 2011). It has been speculated that changes in the mitochondrial DNA caused by reactive oxygen species (ROS) and free radicals have an important role in the development of ARHI (Uchida *et al.* 2011). The aetiology is multifactorial and the

development of ARHI is dependent on both environmental factors and genetic susceptibility. Genetic research of ARHI has increased in popularity recently. The most significant genetic risk factors of ARHI identified by association and candidate gene studies are presented in Table 5. Three genome wide linkage analyses of ARHI have been performed (DeStefano *et al.* 2003, Garringer *et al.* 2006, Huyghe *et al.* 2008). Only one region on chromosome 8 reached statistical significance, but no associated variations were detected from the region (Huyghe *et al.* 2008).

Table 5. Genetic risk factors associated with age-related hearing impairment.

Gene	Variation	Gene function	Reference
mtDNA^{4977}	deletion	Oxidative phosphorylation, control of oxidative stress and apoptosis	Bai *et al*. 1997
NAT2	*6A	Detoxification and metabolic activation of numerous drugs and chemicals	Unal *et al*. 2005
KCNQ4	g.11249550A>T	Possible role in the potassium recycling of the inner ear	Van Eyken *et al.* 2006
GST	M1 &T1	Antioxidative protection of the cochlea	Van Eyken *et al.* 2007
GRHL2	rs109552552	Transcription factor widely expressed in epithelial tissue	Van Laer *et al.* 2008
EDN1	rs5370	Vasoactive peptide, with possible effect on inner ear circulation	Uchida *et al.* 2009
GRM7	rs11928865	Encodes a glutamate receptor assumed to modulate hair cell excitability and synaptic efficiency	Friedman *et al*. 2009
UCP2	Ala55Val	Mitochondrial proteins that may regulate energy metabolism and thermal control	Sugiura *et al.* 2010

Noise-induced hearing impairment

Noise-induced hearing impairment (NIHI) has risen to be a world-wide health risk after the industrial and electronic revolution (Moudon 2009). Although recent legislation and the development of hearing protectors have decreased the incidence of work-related NIHI, people are increasingly exposed to noise in their

leisure-time (Dalton *et al.* 2001). Multiple environmental and medical factors such as organic solvents, smoking, high blood pressure and hypercholesterolemia have been associated with NIHI (Konings *et al.* 2009). Genetic factors are thought to affect the susceptibility to NIHI since susceptibility to noise is highly variable among individuals. Identical exposure to noise can cause substantial hearing impairment in some, whereas others experience no effect after the same exposure (ISO 1999). This is supported by studies done on mice, where certain mouse strains have been observed to be more susceptible (Erway *et al.* 1996) or more resistant (Candreia *et al.* 2004) to NIHI after an identical exposure to noise.

Cochlear hair-cell damage by oxidative stress after noise exposure has been proposed as a possible mechanism for NIHI since antioxidant substances decreased (Choi *et al.* 2008) and chemicals that produce oxidative stress potentiated (Chen 2002) NIHI in mice. Several genes involved in oxidative stress have been studied as candidate genes of NIHI as reviewed by Konings *et al.* (2009). To date association with only one gene, *CAT*, which encodes the catalase enzyme that is key in the body's defence against oxidative stress, has been observed in two independent sample sets (Konings *et al.* 2005).

Genes involved in the potassium recycling pathways vital for hearing such as the potassium channel component encoding gene potassium voltage-gated channel subfamily E member 1 (*KCNE1*) have also been associated with NIHI. The p.85N variant of the *KCNE1* gene was only observed in NIHI susceptible subjects, and further studies have shown that compared to the p.85D channels the p.85N channels open more rapidly and the normalized current through the channel was significantly higher (Van Laer *et al.* 2006). The *KCNE1* gene has also been studied as a potential candidate gene for MD (Doi *et al.* 2005).

In addition, NIHI has been associated with variations of the heat shock protein coding gene 70 (*HSP70*). The heat shock protein family is a group of conserved proteins with multiple functions as chaperones of synthesis, folding and transport of several proteins (Gething & Sambrook 1992). It has been suggested that heat shock proteins can protect the cochlea from damage after severe noise exposure (Yoshida *et al.* 1999). Certain haplotypes and SNPs (single nucleotide polymorphisms) of the *HSP70* gene have been associated with NIHI (Konings *et al.* 2008), but functional studies are still needed to confirm the finding.

Otosclerosis

It has been estimated that 50% of otosclerosis cases are familial (Cawthorne 1955). Familial otosclerosis is considered an autosomal dominant disease with incomplete penetrance (Morrison 1967), although other inheritance patterns have been suggested (Hernandez-Orozco & Courtney 1964). To date familial otosclerosis has been linked to eight loci, OTSC 1–5, 7, 8 and 10 (Table 6), but no otosclerosis causing mutations have been identified. Only 2% of the genes in the linked regions have been screened so far, however, as pointed out by a recent review (Ealy & Smith 2010). Numerous genes such as collagen type 1 alpha 1 (*COL1A1*), transforming growth factor beta 1 (*TGFB1*) and bone morphogenetic proteins 2 and 4 (*BMP* 2 & 4) have been associated with otosclerosis in candidate gene studies but no variations with a large effect on disease development have been identified (Schrauwen & Van Camp 2010) and the exact aetiology of otosclerosis is still unknown.

Table 6. Linkage studies on familial otosclerosis.

Locus	Position	Possible candidate genes	Reference
OTSC1	15q25-26	Aggregan	Tomek *et al.* 1998
OTSC2	7q34-36	*TIF1a, PLOD3*	Van Den Bogaert *et al.* 2001
OTSC3	6p21.3-22.3	HLA-genes	Chen *et al.* 2002
OTSC4	16q21-23.2	*COG4 & 8*, DEAD box protein genes	Brownstein *et al.* 2006
OTSC5	3q22-24	*PCOLCE2, CHST2*	Van Den Bogaert *et al.* 2004
OTSC6	Unpublished	-	-
OTSC7	6q13-16.1	*COL12A1*	Thys *et al.* 2007
OTSC8	9p13.1-q21.11	*TJP2, TRMP3, KLF9*	Bel Hadj Ali *et al.* 2008
OTSC9	Unpublished	-	-
OTSC10	1q41-44	*TGFB2, AGT*	Schrauwen *et al.* 2011

2.5.2 Genetics of vertigo

The genetics of vertigo is a rather new area of research and only a few genetic studies have been performed. The genes identified are responsible for syndromes manifesting with a variety of symptoms in addition to vertigo, such as forms of familial episodic ataxia, familial hemiplegic migraine and hereditary hearing loss (Jen 2008).

Familial episodic ataxias are a group of autosomal dominant disorders characterized by vertigo and neurological symptoms such as ataxia, lack of

coordination and slurring of speech (Baloh 2012). Familial episodic ataxia type I is caused by mutations of the potassium voltage-gated channel subfamily a member 1 gene (*KCNA1*) encoding a voltage-gated potassium channel, and type II is caused by mutations in the *CACNA1A* gene encoding a voltage-gated calcium channel (Cricchi *et al.* 2007). Mutations of the *CACNA1A* gene are also responsible for familial hemiplegic migraine (Freilinger *et al.* 2011).

It was recently reported that subjects with DFNB1 (non-syndromic autosomal recessive hearing loss 1) had a high frequency of vestibular symptoms (Dodson *et al.* 2011). A recent review suspected that vestibular dysfunction might be a common but unrecognized component of non-syndromic hearing loss (Eppsteiner & Smith 2011). Other forms of hereditary hearing loss with known vestibular symptoms are Ushers syndrome and DFNA9 (autosomal dominantly inherited cochleo-vestibular dysfunction 9). The associated symptoms and genes responsible for Ushers syndrome are presented in Table 4. Mutations of the coagulation factor C homolog (*COCH*) gene are responsible for DFNA9, with associated high-frequency hearing loss, tinnitus and vertigo (Usami *et al.* 2003). In addition, benign paroxysmal vertigo has been linked to chromosome 22q12 in affected families (Lee *et al.* 2006), but BPPV associated variations have not been reported.

2.5.3 Genetics of Meniere's disease

Familial MD

Most cases of MD seem to be sporadic (SMD), but familial clustering of MD has been recognized for decades (Vrabec 2010). Only a handful of studies on familial MD (FMD) exist and most studies have been case reports on a few individual families.

The first reports on FMD were published by Brown in 1949 and Bernstein in 1965 (Brown 1949, Bernstein 1965). In these studies an association with migraine was suggested, but comprehensive family studies were not performed. Migraine has been since associated with FMD on several occasions.

In 1992 Oliveira and Braga observed autosomal dominant inheritance of MD and migraine-like headaches in one family (Oliveira & Braga 1992). Oliveira *et al.* (2002) also studied the family histories of eight MD patients and found a high incidence of migrainous headaches and Meniere-like symptoms (Oliveira *et al.*

2002). Migraine was again associated with FMD in the study of Cha *et al.* in 2008 (Cha *et al.* 2008), but an association between migraine and FMD has not been observed in all studies (Birgerson *et al.* 1987).

In 1995 Morrison described the largest published series of 41 MD families and reported autosomal dominant inheritance. In the previous series incomplete penetrance was suspected, as some of the family members were assumed to carry the disease causing variation without expressing MD. In the study of Morrison (1995) female preponderance was observed and anticipation, where the symptoms of a genetic disorder become apparent at an earlier age as it is passed on to the next generation, was suspected. Anticipation was supported by a higher incidence of childhood onset and diminishing age at onset with successive generations. Previous findings were further supported by later updates of the series (Morrison & Johnson 2002, Morrison *et al.* 2009).

In addition to the studies by Morrison, an autosomal dominant mode of inheritance has been described in most MD families (Oliveira & Braga 1992, Arweiler *et al.* 1995, Frykholm *et al.* 2006), but other modes of inheritance have also been suspected (Birgerson *et al.* 1987). Anticipation was also described in two North American families by Fung *et al.* (2002) and yet again when Frykholm *et al.* described a family with five FMD affected generations in 2006 consistent with autosomal dominant inheritance and anticipation (Frykholm *et al.* 2006).

Numbers on the prevalence of FMD have varied from 2.6–19.2% of all MD cases as seen in Table 7. It has been established that FMD is a small, but significant subform of MD.

Table 7. Estimations on the proportion of familial MD.

Country	Proportion of FMD	Reference
Sweden	14%	Birgerson *et al.* 1987
Germany	10.4%	Arweiler *et al.* 1995
United Kingdom	2.6-5%	Morrison *et al.* 2009
Finland	15%	Klockars & Kentala 2007b
Germany	19.2%	Arweiler-Harbeck *et al.* 2011

Candidate gene studies

Since the symptoms of MD are thought to be caused by disturbances in the inner ear homeostasis, several genes regulating the ionic composition or water transport of the inner ear have been studied as candidate genes for MD. The targets of

research have been the aquaporin water channel genes *AQP1-4* (Mhatre *et al.* 2002, Candreia *et al.* 2010), the potassium channel genes *KCNE1* and *KCNE3* (Doi *et al.* 2005), and the Na+-K+ pump activity regulator alpha adducing 1 (*ADD1*) (Teggi *et al.* 2008).

MD has also been connected with mutations in the *COCH* gene widely expressed in the inner ear (Fransen *et al.* 1999), however, the absence of *COCH* mutations has been reported in several families. According to the current knowledge, *COCH* mutations are the cause of DFNA9, an autosomal dominantly inherited cochleo-vestibular dysfunction, but not MD (Usami *et al.* 2003 Sanchez *et al.* 2004).

Since MD has been suspected to have an autoimmune basis, many genes previously associated with autoimmunity and inflammation have been studied as candidate genes of MD. An association of MD with the host cell factor C1 (*HCFC1*) gene earlier associated with reactivation of herpes virus infections has been reported (Vrabec *et al.* 2008). Kawaguchi *et al.* (2008) associated MD with a single nucleotide polymorphism (SNP) of the heat-shock protein 70 gene *HSPA1A* earlier associated with oxidative stress and autoimmunity (Kawaguchi *et al.* 2008). In addition, Lopez-Escamez *et al.* (2010) associated MD with a polymorphism in *PTPN22*, encoding a lymphoid protein tyrosine phosphatase previously associated with several autoimmune diseases such as rheumatoid arthritis and systemic lupus erythematosus (Lopez-Escamez *et al.* 2010). In the latest work the interleukin-1 gene (IL1) -889C>T polymorphism was associated with both MD and sudden sensorineural hearing loss (Furuta *et al.* 2011). IL1 is an important mediator of inflammation and the authors hypothesised that it may predispose carriers to autoimmune processes by enhancing the inflammation process.

Even though the patients in all candidate gene studies have been well defined and diagnosed using the strict criteria compiled by the AAO-HNS (1995), candidate gene analyses have been characterized by a limited number of subjects and poorly matched controls as seen in Table 8. No positive replications of previously reported candidate genes have been published, however, and only a few replication studies have been performed with negative results (Campbell *et al.* 2010, Sanchez *et al.* 2004). No convincing evidence on the association of MD with any gene exists.

Table 8. Reports on candidate genes in MD.

Reference	Set-up	Patients		Controls		Gene		
		B/U	n	ASM	n	name *	effect	p-value
Mhatre *et al.* 2002	mutation analysis	B+U	12	-	-	*AQP2*	-	-
Lynch *et al.* 2002	mutation analysis	B+U	14	-	-	*ATQ1*	-	-
Doi *et al.* 2005	case & control	B+U	63	NO	237	*KCNE1*	PD	<0.001
						KCNE3		0.0015
Lopez-Escamez *et al.* 2007	case & control	B	37	NO	145	*HLA- DRB1*	PD	0.029
			43		105			
Teggi *et al.* 2008	case & control	U	28	YES	48	*ADD1*	PD	0.035
				NO	1713			0.021
Vrabec *et al.* 2008	case & control	B+U	21	NM	33	*HCFC1*	PR	0.003
			30		40	*HCFC1*	-	NM
						HCFC1	PR	0.004
						HCFC1	PR	0.015
Kawaguchi *et al.* 2008	case & control	B+U	49	NO	100	*HSPA1A*	PD	<0.001
Lopez-Escamez *et al.* 2009	case & control	B	37	NO	371	*PARP-1*	PR	0.012
			43					
Lopez-Escamez *et al.* 2010	case & control	U	52	NO	348	*PTPN22*	PD	0.04
Campbell *et al.* 2010	case & control	B+U	180	YES	180	*KCNE1*	-	NS
						KCNE3	-	NS
Candreia *et al.* 2010	case & control	NM	34	NM	100	*AQP3*	PD	NM
Furuta *et al.* 2011	case & control	NM	68	NO	2202	*IL1A*	PD	0.0001
Lopez-Escamez *et al.* 2011	case & control	B+U	156	YES	626	*CD32*	-	NS
			112		144	*CD16A*	-	
Gazquez *et al.* 2011b	case & control	B+U	163	NO	407	NOS1	-	NS
			110		143	NOS2A	-	

ASM= age & sex matched, NM= not mentioned, B= bilateral, U= unilateral, PD= predisposing, PR= protective, NS= not statistically significant, * rs numbers of the associated SNPs can be seen in Table4 of article IV.

Linkage studies

FMD has been linked to chromosome 12p12.3 in affected Swedish families (Klar *et al.* 2006), and the finding was later supported by Gabrikova *et al.* (2010). Quite recently a possible linkage to chromosome 5 and a second locus on chromosome 12 were observed in an analysis of 17 German FMD families (Arweiler-Harbeck *et al.* 2011). However, no predisposing genetic factors have been identified in the areas of linkage to date. Modern genetics, genome-wide association and next generation sequencing studies may, however, help discover the biologic processes underlying MD in the future (Vrabec *et al.* 2008).

3 Aims of the present study

MD is an incurable inner ear disorder characterized by a triad of vertigo, tinnitus and sensorineural hearing loss. In Finland at least 43 people per 100 000 are affected, many of whom are middle-aged. Thus, MD is a significant entity in need of better diagnostic tools and more effective treatments. Despite relentless study, the aetiology of MD remains unresolved. The role of genetics factors has been established, but only a handful of genetic studies exist. More detailed information about the genetics of MD is needed in order to furnish patients with accurate information about the heredity of MD, offer appropriate genetic counseling to patients affected with FMD and provide a background on which to base future genetic studies. The present study aimed to increase the knowledge of the genetics of Finnish MD and to lay a foundation for future genetic research on MD in Finland.

The specific aims were:

1. To study the prevalence of FMD and Meniere-like symptoms in the families of MD patients.
2. To describe the genetic and clinical features of Finnish FMD and to study whether differences exist between sporadic and familial MD.
3. To study the significance of six genes previously associated with MD in a population of Finnish MD patients and to study whether Finnish FMD families are linked to the previously suggested locus on chromosome 12p12.3.

4 Materials and methods

4.1 Clinical studies

4.1.1 Subjects (I, II)

When studying the prevalence of FMD and Meniere-like symptoms in the families of MD patients, all patients (n=640) treated for MD at Oulu University Hospital and Kainuu Central Hospital in Finland during the period June 30th 2005- June 30th 2010 were included in the initial study sample. This was done by searching the two hospitals' digital patient archives using the International Classification of Disease 2010 (ICD10) diagnosis code H81.0 for MD. Patients treated in the Oulu University Hospital were from the primary area of Northern Ostrobothnia, not from the whole area served by the university hospital.

Out of the 640 patients, 149 definite MD patients according to the criteria set by AAO-HNS (1995) with no family history of MD or Meniere-like symptoms were used as sporadic patients in the clinical comparison of sporadic and familial MD. To compile a sufficiently large set of familial patients for the analysis, affected members of 32 MD families recruited from the primary area of Oulu University Hospital and Kainuu Central Hospital during the years 2001–2010 and six families recruited from the meetings of the Finnish Meniere Association during 2009–2011 were used in the analyses. As a result, a total of 101 definite FMD patients were studied (Table 9).

Table 9. Subjects.

Article	All subjects	Questionnaire responders	Sporadic patients	MD Families	Familial patients
I	640	402 (62.8%)	161	16	26
II	250	245 (98%)	149*	38	101

*Sporadic patients in articles I and II are the same patients, with the exception that patients with a possible secondary onset of the disease were excluded from article II

4.1.2 Collection of data from the hospital records (I-IV)

All the relevant patient records were studied to confirm the diagnosis and the differential diagnosis of all patients. The differential diagnosis was considered sufficient if an interview, a clinical examination and an audiometry had been

conducted by an otorhinolaryngologist or a resident in otorhinolaryngology, and a head MRI or auditory brain stem response (ABR) measurements were done to exclude vestibular nerve tumours.

Descriptions of vertigo, tinnitus and aural fullness were documented from the patient records. An audiogram from the initial evaluation, from the time of diagnosis, from the time of second ear involvement, every five years since and the latest audiogram were copied from the patient record. The patients were then classified using the criteria compiled by the American Academy of Otolaryngology – Head and Neck Surgery (1995).

4.1.3 Collection of data using a postal questionnaire (I, II)

To gain more information concerning the age at onset, family history, concomitant diseases, severity of the symptoms, treatments and their effect, a questionnaire (Appendix 1) was mailed to all patients.

4.1.4 Studying the family histories of the patients (I)

Out of the 640 patients, all patients who reported a positive family history of vertigo, tinnitus or hearing loss in the questionnaire (n=148) were interviewed by telephone if possible to further clarify the probability of FMD and Meniere-like symptoms in the family.

If the family history of MD seemed convincing a pedigree was drawn and the patients were asked to recruit both healthy and affected first to third degree relatives who would be willing to participate in the study. All relatives with MD or Meniere-like symptoms were interviewed by telephone and their patient records were examined as explained above.

Since not all the relatives with Meniere-like symptoms were available for further study, a classification system was created to estimate the probability of MD in a relative on the basis of the information given by the index patient in the telephone interview. This system employed a three level scale: probable, possible or unlikely MD. The basis of the classification system is explained in more detail in the article I.

4.1.5 Statistical analyses of clinical data (I, II)

Data was analysed using IBM SPSS statistics version 19 (IBM Corporation, United States). Clinical data was compared between SMD and FMD patients using the chi-square-, Fisher's-, Mann-Whitney-tests and logistic regression analyses. P-values >0.05 were considered significant. The means of the low (0.125–0.5 kHz), mid (1–2 kHz) and high frequencies (3–8 kHz) and four tone average (0.5–3kHz) from the latest audiograms were compared between SMD and FMD patients using logistic regression analysis adjusted to the time passed since the diagnosis. As some of the patients in the early stages of the disease had normal hearing in the latest evaluation configurations of the audiograms with the most severe hearing loss were compared between FMD and SMD patients using a LMH (low-mid-high) matrix as previously described by Sorri *et al.* 2000.

4.1.6 Ethics

The Ethics Committee of the Northern Ostrobothnia Hospital District approved this study. All the people answering the questionnaire and all the relatives of the MD patients gave their written consent to participate.

4.2 Genetic studies

4.2.1 Subjects and controls (III, IV)

MD patients were recruited for the genetic studies over the years 2001–2004 from the otorhinolaryngology clinics of Oulu University Hospital and Kainuu Central Hospital. The dataset used in candidate gene studies included deoxyribonucleic acid (DNA) samples from 38 sporadic and from 21 non-related familial MD patients. A familial series of 16 MD families comprised of 42 affected individuals, 10 healthy relatives and 15 relatives with some Meniere-like symptoms was used for linkage studies. All patients described as MD patients met the diagnostic criteria of the American Academy of Otolaryngology – Head and Neck Surgery (AAO-HNS, 1995) for definite Meniere's disease (Table 10). A control sample set with DNA samples from 98 individuals with a similar sex distribution and no MD was collected from the same geographical area.

Table 10. Subjects.

Article	All subjects	Sporadic patients	Familial patients	MD families	Controls
III	67	-	42	16	25 relatives
IV	157	38	21	21*	98 healthy individuals

* Sixteen families from article I are included in the 21 families together with 5 additional families

4.2.2 Polymerase chain reaction (PCR) (III, IV)

The coding regions and exon flanking areas of the studied candidate genes (*AQP2*, *KCNE1*, *KCNE3*, *COCH*, *HCFC1* and *ADD1*) and microsatellite markers used in linkage studies were amplified using the polymerase chain reaction (PCR) technique. Primers were designed using the genomic and cDNA sequences from the Ensembl and National Center for Biotechnology Information (NCBI) databases. Genomic DNA extracted from EDTA anti-coagulated blood samples with a standard protocol was used in the PCR reactions. PCR products were checked for quality using agarose gel electrophoresis.

4.2.3 Conformation sensitive gel electrophoresis (CSGE) (IV)

Mutation screening of candidate genes was done by conformation-sensitive gel electrophoresis (CSGE) as previously described by Körkkö *et al.* (1998). DNA samples were first amplified using PCR. PCR products were loaded onto the gel and electrophoresed overnight. The gel was then stained and the DNA bands were detected and photographed under an ultraviolet-light. Regions with heteroduplexes were sequenced as described in chapter 4.2.4 to define the underlying sequence variations and genotypes.

4.2.4 Sequencing (III, IV)

Sequencing for all the samples was performed using a BigDye Terminator v1.1 cycle sequencing kit and ABI PRISM 3130XL Genetic Analyzer (Applied Biosystems). Sequence variations are indicated on the basis of their Gene Bank sequence accession numbers and follow the nomenclature proposed by den Dunnen and Antonarakis (den Dunnen & Antonarakis 2001).

4.2.5 Linkage analysis (III)

Fourteen highly polymorphic microsatellite markers selected from the MAP-O-MAT database (Kong & Matise 2005) were analysed from the chromosomal 12p12.3 region. Markers were amplified by PCR. The PCR products from the same individual were pooled and combined with formamide and an internal size standard (GeneScan-500LIZ, Applied Biosystems). The pooling was designed in such a way that markers could be identified based on their size and/or different fluorescent dyes. After denaturation, the pooled products were separated on an Applied Biosystems 3130XL Genetic analyzer. The genotyping results were analysed using Genemapper Software, version 4.0 (Applied Biosystems).

4.2.6 Statistical analyses of genetic data (III, IV)

When analysing the genotype data from candidate gene studies (IV) potential deviations from the Hardy-Weinberg equilibrium (HWE) were tested using the chi-square test. Allele and genotype frequencies were compared between the patients and controls using the chi-square or Fisher's test. Haplotypes were reconstructed statistically using the PHASE program with the Markov-chain method for haplotype assignments (Stephens *et al.* 2001). The associations between MD and individual SNP markers or haplotypes were analysed using logistic regression analyses. Odds ratios and their 95% confidence intervals (CIs) were calculated using the SNPStats (Sole *et al.* 2006) and SAS version 9.2 (SAS Institute Inc., Cary, NC, United States) programs. The Bonferroni-Holm method for multiple testing corrections was used for genes with more than one SNP (Holm 1979). The significance of observed novel variations to the coded protein was estimated using PolyPhen (Adzhubei *et al.* 2010) and Mutation taster (Schwarz *et al.* 2010) functional effect analyses.

Analysis of the data on chromosome 12p12.3 (III) was done with programs provided by IT Center for Science (CSC) with remote access to their mega computers MURSKA and HIPPU. Mendelian consistency was checked using PedCheck V.1.1. Allele frequencies were estimated from the data using observed and reconstructed genotypes for the founders within the pedigrees. Both parametric and non-parametric LOD/HLOD/NLP scores were calculated using GENEHUNTER, version 2.1.R5 employing two inheritance models: autosomal dominant with 95% and autosomal dominant with 60% penetrance. The disease allele frequency was estimated to be 0.0005 in the autosomal dominant model

with 95% penetrance and 0.0007 in the autosomal dominant model with 60% penetrance.

4.2.7 Ethics

The Ethics Committee of the Northern Ostrobothnia Hospital District approved this study. All patients were informed of the risks involved in obtaining a venous blood sample. A written consent was obtained from all participants.

5 Results

5.1 Prevalence of familial Meniere's disease and Meniere-like symptoms in the relatives of Meniere-patients (I)

Out of the 640 patients identified from the archives, 402 (62.8%) responded to the family history questionnaire and 148 (36.8%) of these reported tinnitus, hearing loss or vertigo in their family. Further interviews were conducted with 138 (94.2%) of these patients. Ten patients were not available for further study (6.8%).

In all, 30 MD patients recruited their family members to the study and as a result FMD was confirmed in 26 (18.8%) and excluded in 4 (2.9%) out of the 138 patients. Confirmed FMD patients represented 16 FMD families.

The probability of MD in a relative with regards to the remaining 108 patients was estimated on the basis of the information given by the index patient according to criteria presented in Table 11.

Table 11. Probability of MD in a relative on the basis of the interview.

Points	Patient knows that a relative (1st, 2nd or 3rd degree) has suffered from
+1p	Several spells of vertigo lasting for more than 30 minutes. Patient has to describe vertigo that is disabling in nature or includes vomiting or nausea
+1p	Tinnitus or aural fullness
+1p	Bilateral hearing loss under the age of 60, hearing loss should not be associated with noise, injury or infection
+1p	Unilateral hearing loss without age limitation, hearing loss should not be associated with noise, injury or infection
-1p	Bilateral hearing loss after the age of 70
-1p	The relative has undergone ear surgery or has a diagnosis of otosclerosis
Total	3p Probable MD, 2p Possible MD, 0-1p Unlikely MD

According to the latter classification system, 26 (18.8%) of the 138 patients had a confirmed family history of MD, 40 (29.0%) a probable history, 39 (28.3%) a possible history and 33 (23.9%) an unlikely family history of MD. The results of the family history study are presented in Table 12 with regard to MD patients.

Table 12. Family history of MD.

	All MD patients n=334	Definite MD n=248	Probable MD n=5	Possible MD n=81
Confirmed	26 (7.8%)	23 (9.3%)	0 (0%)	3 (3.7%)
Probable	38 (11.4%)	35 (14.1%)	0 (0%)	3 (3.7%)
Possible	34 (10.2%)	23 (9.3%)	0 (0%)	11 (13.6%)
Unconfirmed	9 (2.2%)	6 (2.4%)	0 (0%)	3 (3.7%)
No family history	227 (68.0%)	161 (64.9%)	5 (100%)	61 (75.3%)

5.2 Finnish familial Meniere's disease (I-III)

A total of 38 FMD families were studied in this thesis. Each family had at least two subjects with definite MD according to AAO-HNS (1995) criteria. Pedigrees of the families are presented in articles I, II and III.

Anticipation was hard to evaluate, as information from a limited amount of generations was available. Descending age among generations was observed in three generations strongly implying anticipation only in two families (5.3%). Anticipation was possible in five more families (13.2%), as descending age was seen in two generations. No anticipation was observed in ten families (26.3%).

There were subjects with Meniere-like symptoms such as tinnitus, hearing loss, or vertigo episodes that did not fulfil AAO-HNS (1995) criteria for MD in 22 (57.9%) of the families. These patients were considered a separate group with "partial syndromes" possibly related to the MD inherited in these families (other causes excluded). Three families had both MD and otosclerosis patients. The age at onset, penetrance of the disease and its severity varied among families. Information from individual families is presented in Table 13.

Possible co-segregation with migraine was not common, since all the affected individuals had migraine in only four (10.5%) families. Thus in two of these families, there were subjects with "partial syndromes", but not migraine. Migraine was common since 25% of all affected patients had migraine.

Most families were suggestive of autosomal dominant inheritance (92.1%), however, mitochondrial inheritance was also possible in 14 (40%) of these 35 families. Two families were suggestive of autosomal recessive inheritance. In one family both autosomal recessive and autosomal dominant inheritance were possible, since it was not clear if subjects in earlier generation were affected with MD or otosclerosis.

Table 13. Finnish MD-families.

Article	Family n=38	Mode of inheritance	Possibility of mitochondrial inheritance	Partial syndromes	Otosclerosis	Anticipation	Co-segregation with migraine
I	1	D	-	+	-	No	-
I	2	D	+	+	-	Yes	-
I	3	D	+	-	-	N	-
I	4	D	+	+	-	N	-
I	5	D	-	+	-	Possible	+
I	6	D	-	+	-	No	-
I	7	D	-	-	+	N	-
I	8	D	+	+	-	N	+
I	9	D	-	+	-	Possible	-
I	10	D	-	+	-	Possible	-
I	11	D	-	+	-	N	+
I	12	D	-	+	-	N	-
I	13	D	+	+	-	N	-
I	14	R	N	-	-	N	-
I	15	D	-	+	-	N	-
I	16	R	N	+	-	N	-
II	1	D	-	+	-	N	-
II	2	D	-	+	-	N	-
II	3	D/R	-	+	+	N	-
II	4	D	+	+	-	N	-
II	5	D	+	+	-	N	-
II	6	D	+	+	-	N	-
III	1	D	+	-	-	N	+
III	2	D	-	-	-	Yes	-
III	3	D	-	+	-	Possible	-
III	4	D	-	-	-	No	-
III	5	D	-	-	-	No	-
III	6	D	+	+	-	No	-
III	7	D	-	+	-	No	-
III	8	D	+	-	-	N	-
III	9	D	-	-	-	No	-
III	10	D	-	-	-	No	-
III	11	D	+	-	-	Possible	-
III	12	D	-	-	-	N	-
III	13	D	-	-	+	N	-
III	14	D	+	-	-	No	-
III	15	D	-	-	-	No	-
III	16	D	+	-	-	No	-

D= autosomal dominant, R= autosomal recessive, N=evaluation not possible

5.3 Comparison of familial and sporadic Meniere's disease (IV)

Patient records and questionnaire answers were compared between 149 sporadic and 101 familial MD patients. Out of all patients 144 (57.7%) were female and 106 (42.4%) were male. The age of the patients varied from 24 to 89 years. The average follow up time of the patients was 11.5 years (0.5–38 years, SD ±9.2 years). There were no statistical differences in the treatments or their subjective benefits, gender distribution or follow up time between FMD and SMD patients.

There was no difference between FMD and SMD patients in the delay between the first visit to the otolaryngology clinic and the time when AAO-HNS (1995) diagnostic criteria were fulfilled. There was no statistical difference between the ages of the FMD and SMD patients (mean age 64.6 years compared to 67.5 years, p=0.082). The ages at which AAO-HNS (1995) diagnostic criteria were fulfilled were significantly younger in FMD patients than in SMD patients (p=0.002).

FMD and SMD patients assessed their vertigo spells to be equally disabling (p=0.949) and reported to suffer from vertigo as often (p=0.857). However, both the typical length (p=0.004) of vertigo and the longest vertigo spells (p=0.011) were significantly longer in FMD patients. There was no difference in the self-reported severity of tinnitus between FMD and SMD patients (p=0.333).

There was no statistically significant difference in the level of hearing loss between SMD and FMD patients (p=0.451), nor was there a difference in the latest audiogram configurations (p=0.315). The number of bilateral cases did not differ either.

FMD patients had significantly more rheumatoid arthritis (p=0.002) and autoimmune diseases in general (p=0.046) than SMD patients. There was no difference in the prevalence of other concomitant diseases. However, FMD patients reported more migraine than SMD patients (51.5% compared to 37.0%, p=0.036) as well as other hearing loss causing diseases besides MD and otosclerosis (60.9% compared to 37.6%, p=0.002) in their families.

There was no difference in noise exposure at work (p=0.522) or during leisure time (p=0.737), head injuries (p=0.330) or a tendency to feel stressed (p=0.768) between FMD and SMD patients. When asked about factors provoking symptoms of MD, FMD patients reported tension of the shoulder- and neck muscles and fast head movements more often than SMD patients. FMD patients also considered their symptoms to be affected by stress more often than SMD patients (74.7% FMD vs. 57.8% SMD patients, p=0.010).

The main results on the comparison of sporadic and familial patients are presented in Table 14. The data are presented in more detail in article II.

Table 14. Comparison of familial and sporadic MD.

Variable	FMD n=101	SMD n=149	p-value
Age at the time of diagnosis (years)			
mean ±SD	48.6 ±12.7	54.2 ±12.9	0.002
Four tone average (0.5-3kHz)			
mean	52.5 dB	54.6 dB	0.451*
median	55.6 dB	57.5 dB	
95% CI	47.1-57.8	50.8-58.4	
Bilateral cases			
n (%)	37 (36.6%)	64 (43.0%)	0.465*
Typical length of vertigo (hours)			
mean	8.7	7.6	0.004*
median	3.5	2.0	
Length of the longest vertigo spell (hours)			
mean	42.2	40.3	0.011*
median	24	12	
Rheumatoid arthritis			
n (%)	15 (16.9%)	6 (4.5%)	0.002#
Autoimmune diseases			
n (%)	25 (24.7%)	22 (14.8%)	0.046#

*adjusted for the time since the diagnosis, # age and sex adjusted

5.4 Significance of genetic factors previously associated with Meniere's disease in Finnish Meniere-patients

5.4.1 Candidate gene studies (IV)

A total of 13 common sequence variations were observed in the studied genes (*AQP2*, *KCNE1*, *KCNE3*, *COCH*, *HCFC1* and *ADD1*). Two variations in the *KCNE1* gene (rs11702354 and rs1805127), suggested associations with MD in genotype analyses, but only rs1805127 remained significant after correction for multiple testing (Table 15). No association with MD was observed for any of the other genes and no significant haplo/diplotypes were observed (data not shown).

Table 15. Genotype analysis of *KCNE1* rs1805127.

KCNE1	Patients n (%)			Controls n (%) n=98			Sex adjusted p-value
	G/G	G/A	A/A	G/G	G/A	A/A	Recessive
rs1805127							
All	20	37	2	37	41	12	0.03/*0.06**
(n=59)	(34)	(63)	(3)	(41)	(46)	(13)	
SMD	14	24	0				0.0021 / *0.011**
(n=38)	(37)	(63)	(0)				
FMD	6	13	2				0.62
(n=21)	(29)	(62)	(1)				

* = p-value after multiple testing correction

In addition, four novel sequence variations in the *KCNE1* gene were found in three SMD patients and in one FMD patient (Table 16), none of which were observed in the control population or have been reported in the NCBI database (National Center for Biotechnology Information 2012) or in the Hereditary hearing loss database (Van Camp & Smith 2012).

The affected family members of the one FMD patient with the p.Val80Ile change were studied, but the change had evidently not been inherited with the disease. The results of PolyPhen functional effect analysis (Adzhubei *et al.* 2010) indicated that the variation c.259T>C; p.Trp87Arg observed in one SMD patient was probably damaging to the coded protein. Mutation taster analysis (Schwarz *et al.* 2010) predicted both coding variations observed from sporadic patients (c.259T>C; p.Trp87Arg and c.257C>T; p.Ala86Leu) to be disease causing.

Table 16. Rare variants observed in the *KCNE1*[1] gene.

SNP	Change in amino acid	Patient	Result of PolyPhen analysis	Result of Mutation Taster analysis
c.-223C>T	-	Sporadic	-	-
c.238G>A	p.Val80Ile	Familial	Benign	Benign
c.257C>T	p.Ala86Leu	Sporadic	Benign	Disease causing
c.259T>C	p.Trp87Arg	Sporadic	Probably damaging	Disease causing

1= Gene Bank Accession Number NM_000219.3

5.4.2 Linkage studies (III)

No linkage to chromosome 12p12.3 was observed in the Finnish series of FMD patients. The cumulative LOD/HLOD scores were negative in all models when using the GENEHUNTER protocol. At the level of individual families, a positive LOD score was obtained for three families, with a maximum value of 0,59. Haplotype analysis excluded a shared chromosomal region for the affected members of two families, but this was not possible for one family due to the limited number of affected individuals. None of the NPL scores were statistically significant.

6 Discussion

6.1 Finnish familial Meniere's disease

6.1.1 Genetic and clinical characteristics of Finnish familial Meniere's disease (I-III)

Prevalence of FMD

The prevalence of FMD has been estimated previously to be between 2.6 and 19.2% (Birgerson *et al.* 1987, Klockars & Kentala 2007b, Morrison *et al.* 2009, Arweiler-Harbeck *et al.* 2011). In the present study FMD was identified in 9.3% of definite MD cases, but a family history of Meniere-like symptoms was observed in a much higher proportion of patients. Although we were unable to confirm all the cases, a family history of MD was convincing in 23.4% of the patients. Most likely even some of the relatives classified as having possible MD, actually do have MD, since family members may not have full knowledge of their relatives' symptoms. Moreover, as there can be a delay between the manifestations of the first symptoms and the whole triad of MD (Friberg *et al.* 1984), some of the relatives with part of the triad may be in the early stages of MD.

The study of the inheritance of MD proved to be challenging in many ways. Due to the late onset of MD, the information available usually applies to only one living generation. As can be seen from Table 1 of Article I, the listings from hospital records cannot be solely used to confirm diagnoses as only 358 from the 640 patients listed in the archives as MD patients had definite MD according to AAO-HNS (1995). Detailed patient records from several decades back are usually no longer available and therefore it is not possible in many cases to confirm a diagnosis of MD in a relative belonging to an earlier generation and thereby confirm FMD.

The difficulties in studying the prevalence of FMD have not been discussed in previous studies on the prevalence of FMD and it is unclear what was done to the "uncertain cases" in these studies. This could account for the high variability of the prevalence in different studies. Only a long prospective follow-up study on the patients and their families evaluated in this study would uncover the true

prevalence of FMD in Finland. Regardless, the genetic proposition seems to be significant in MD.

Mode of inheritance

An autosomal dominant mode of inheritance has been the most commonly suggested pattern of inheritance for MD (Vrabec 2010). Most of the families studied here seem to present with autosomal dominant inheritance with incomplete penetrance as well. However, the possibility of mitochondrial inheritance should be discussed, as it was also possible in 14 of the 38 families. Mitochondrial mutations are known to cause both syndromic and non-syndromic hearing loss (Mutai *et al.* 2011). In most diseases caused by such mutations a heteroplasmic mitochondrial DNA population exists, with both normal and mutant molecules and it is their ratio that determines the phenotype of the patient (Kokotas *et al.* 2007). Mitochondrial mosaicism could also explain the partial syndromes seen in several families with FMD. In addition to autosomal dominant and mitochondrial inheritance, recessive inheritance was also possible in a few Finnish families, although, the lack of information on previous generations may have given us a false impression of recessive inheritance. Families expressing autosomal dominant inheritance usually have more affected individuals and are therefore easier to find. It is also possible that the study method has directed us towards finding more autosomal dominant families than recessive ones.

Anticipation

Genetic anticipation, characterized by earlier onset and more severe manifestation of the disease as it is passed on to the next generation, is a genetic phenomenon verified in small number of neurological diseases such as myotonic dystrophies (Machuca-Tzili *et al.* 2005). In addition to MD, anticipation has also been suspected in familial forms of several diseases considered to have a multifactorial origin, such as familial diabetes mellitus type II and familial rheumatoid arthritis (Yaturu *et al.* 2005, McDermott *et al.* 1996).

Anticipation has been described in several FMD families (Frykholm *et al.* 2006, Morrison 1995). However, in the present study descending age at onset among three generations strongly implying anticipation was observed only in two of the 38 families. Evaluation of anticipation was not easy, since information from a limited number of generations was available. In addition, the availability of

health-care services has increased significantly among generations improving the diagnostic possibilities of MD and possibly causing a bias of anticipation among families. The natural progression of the disease must also be considered before comparing the severity of symptoms between generations. Taking these factors into consideration anticipation was not commonly seen in Finnish families.

Bias in the evaluation of anticipation has also been a matter of discussion in other diseases since evaluations of large sets of families with a long follow up time failed to support anticipation in heritable pulmonary arterial hypertension (Larkin *et al.* 2012) and familial rheumatoid arthritis (Deighton *et al.* 2007). As Finland is a well-known genetic isolate it may be that genetic factors possibly responsible for FMD and anticipation in some families are not common in our gene pool. In any case more extensive evaluations of multi-generation families with longer follow up time are needed to determine whether anticipation really exists in FMD.

Migraine

Migraine has been associated with MD in numerous studies (Cha *et al.* 2007, Gopen *et al.* 2009, Ibekwe *et al.* 2008) and clustering of migraine and episodic vertigo has been reported in family members of MD patients (Cha *et al.* 2008). In the present study only four of the 38 families showed possible co-segregation of migraine and FMD. There were MD families that did not manifest migraine at all. The lack of association to migraine could be caused by genetic heterogeneity but it is also possible that the strict diagnostic criteria applied for MD in this study has pruned some of the cases of vestibular migraine possibly mimicking MD. A population base survey on the prevalence of headache and migraine was conducted in Finland in 1993 and a 10.1% prevalence of migraine was observed (Honkasalo *et al.* 1993). Migraine was common in FMD families when compared to the general population; 25% of the familial patients had migraine. It is possible that mix up of vestibular migraine and MD still occurs despite the diagnostic criteria applied. In light of the current diagnostic criteria it seems, however, that migraine can be an associated factor in some families affected by FMD, but not in all cases.

Differences between familial and sporadic MD

A comprehensive comparison of sporadic and familial MD was conducted. Clinical manifestation of FMD proved to be very similar to SMD. There was no difference in the level or type of hearing loss, severity of tinnitus or frequency of the vertigo attacks. However, familial patients seem to be affected earlier and suffer from longer spells of vertigo. MD is a well-known disorder among MD families and it is possible that greater knowledge of it may have led to an earlier diagnosis, although, this is not supported by the equal delay between the first visit to the otolaryngology clinic and the diagnosis seen in our subject.

Autoimmunity has been suspected to play a role in the development of MD as discussed in chapter 2.3.3. In our study a significantly higher prevalence of rheumatoid arthritis and other autoimmune disease was observed in familial patients compared to sporadic patients. Our results imply that autoimmune factors might have a larger role in the development of FMD. Since studies supporting the theory of MD being an immune-mediated disorder, steroid use in the treatment of MD has gained popularity as discussed in chapter 2.4.3. Under the light of our results, it would be interesting to study if differences in steroid response exist between FMD and SMD. If FMD is more affected by immune-mediated factors, perhaps FMD patients might benefit more from glucocorticoid treatment.

6.1.2 Future aspects on studying familial Meniere's disease

The most concerning issue in the study of FMD is the rarity of the disease. Not enough families with available information from several generations are available for study in the area of a single hospital district. This emphasises the need to combine data from different studies. Family registries have combined information from familial breast cancer and familial colorectal cancer for many decades (National Cancer Institute 2012). The study of familial MD would greatly benefit from such a registry. This would enable more in-depth analysis of anticipation, migraine and inheritance patterns. Such a registry would also benefit the genetic research of MD. The combined effort of researchers is needed to collect a larger well-defined sample set of patients for future studies of familial and sporadic MD.

6.2 Genetic studies on Meniere's disease

6.2.1 The knowledge of genetic factors associated with Meniere's disease is currently modest (IV)

The field has been very successful in determining the genetic factors underlining profound hearing impairment (Shearer *et al.* 2011). However, efforts to determine genetic factors associated with late onset multifactorial diseases such as MD have not been as successful. All the genes associated with MD have been identified with candidate gene analyses (article IV, Table 4). Genes have been selected on the basis of the current knowledge of the auditory system and theories about the aetiology of MD. Bearing in mind the number of genes in the genome, this method is very ineffective. The numbers of subjects in genetic studies of MD have not been sufficient to verify or exclude association. Genome wide association analyses of MD have not been performed. Only two genome wide linkage analyses have been performed, but no associated variations have been identified from the areas of linkage (Klar *et al.* 2006, Arweiler-Harbeck *et al.* 2011). Although the role of genetic factors in MD is well documented, no convincing evidence for an association with any gene exists.

6.2.2 General difficulties in genetic studies of Meniere's disease, late onset hearing impairment and vestibular disorders

One of the major difficulties in studying the genetics of hearing impairment and vestibular disorders is determining the phenotype. MD can overlap with a number of disorders as discussed in chapter 2.1.3. Insufficient diagnostic criteria and mixture of phenotypes can impair the results of even the best-designed association studies. The phenotypic diversity of hearing impairment and vestibular disorders makes the selection of patients for genetic studies a challenge in itself, but the late onset of MD and ARHI can also complicate the gathering of appropriate control groups. The reduced penetrance suggested for FMD (Morrison 2009) can also complicate the use of linkage analyses, if individuals characterized as healthy are actually unaffected carriers of the predisposing variation.

Several factors may predispose to MD, ARHI and NIHI and the predisposing factors may vary among individuals and populations. Locus heterogeneity seen in many diseases causing hearing impairment can also complicate the genetic studies.

Even with a very distinctive clinical manifestation, such as the Ushers syndrome, several genes have been found to cause the same disease (Friedman *et al.* 2011). Genetic heterogeneity has also been suspected for MD (Arweiler-Harbeck *et al.* 2011). This means that even greater numbers of subjects are needed for genome wide linkage analyses and association studies so that adequate power can be achieved to gain reliable results.

Even the use of modern methods such as genome-wide linkage analyses has not always paid off. Eight loci have been identified for otosclerosis, but no otosclerosis causing variations or variations with a large effect on disease development have been found (Ealy & Smith 2011). The genetic factors predisposing to these diseases may not lie in the protein coding areas of the genome. Variations with associated high-risk to disease development might not even exist or might be unique to individual patients making them hard to discover. All these considerations taken together illustrate the challenges involved in the genetic approach to the study of MD, ARHI and vestibular disorders.

6.2.3 The role of KCNE1 in Meniere's disease (IV)

The *KCNE1* protein operates as part of a K+ ion channel expressed in the inner ear (Wangemann 2002). *KCNE1* has previously been associated with noise-induced hearing loss (Van Laer *et al.* 2006) and mutations in its crucial areas are known to cause long QT syndromes, some of them with accompanying hearing loss such as Jervel and Lange-Nielsen syndrome (Henrion *et al.* 2009). Most recently *KCNE1* variation rs915539 was associated with tinnitus (Pawelczyk *et al.* 2012). When considering the gene function, *KCNE1* has many qualities that make it a noteworthy candidate gene for MD. The *KCNE* gene family was originally suggested as a candidate gene for MD by Doi *et al.* in 2005.

In the present study four novel variations of the *KCNE1* gene were observed in MD patients but in none of the controls. According to the PolyPhen and Mutation Taster analyses two of the novel *KCNE1* variations (c.259T>C; p.Trp87Arg and c.257C>T; p.Ala86Leu) observed in sporadic patients were probably damaging to the coded protein. A mutation analysis of a larger sample set, together with functional studies, is needed in order to assess the relevance of the novel variations observed in the *KCNE1* gene.

Association of SMD to a sequence variant in the *KCNE1* gene was also observed but the lack of statistical power is, however, an obvious limitation of the association analysis. Campbell *et al.* (2010) failed to replicate the association

between MD and *KCNE1*, although their study and control groups were considerably larger. It is possible that the association seen in this study is only a bias caused by the small sample size.

6.2.4 Linkage to chromosome 12p12.3 (III)

Klar *et al.* (2006) reported the first linkage of MD to chromosome 12p12.3 in three Swedish families and their finding was further supported by Gabriková *et al.* (2010). Our series nevertheless failed to provide any evidence of linkage to chromosome 12p12.3. Given that anticipation was common in the Swedish families but rare in Finnish families, the lack of both anticipation and linkage to chromosome 12p12.3 in the Finnish families may suggest locus heterogeneity in FMD. The small number of families, however, causes limitations to both studies. Additional constraint may arise from the selection of markers in our study since only the peak region indicated by Klar *et al.* (2006) was studied. The negative LOD scores in 13 of the 16 families and the maximum cumulative LOD score of −7,29/ HLOD −0,95 alpha=0,4 (in the autosomal dominant model with 60% penetrance) indicate that genetic susceptibility to MD in these Finnish families must be located elsewhere.

6.2.5 Future aspects on studying the genetics of Meniere's disease

Genome wide association analyses –worth the resources?

In the last five years genome wide association analyses (GWASs) have identified over 2000 loci associated with human disease (Van Camp & Smith 2012). These studies aimed to detect association between common SNPs and common diseases. However, the vast majority of variants identified via GWASs have no established biological relevance to disease nor have they had the hoped effect of finding treatment targets or predicting disease prognosis as most variations identified with GWASs seem to have a very small effect on disease development (Vissher *et al.* 2012). Although in a few cases variations identified via GWASs have led to finding new biological pathways such as the autophagy pathway in Crohn's disease (Fritz *et al.* 2011). In general GWAS studies have not fulfilled their expectations. To conduct a GWAS on MD patients a dataset of thousands of sporadic MD patients should be gathered together with a control set of subjects

preferably without any hearing impairment or vestibular symptoms. Considering the cost and effort needed to evaluate and collect such patient sets together with the possibility that the results could have minimal effect on the development of treatments for MD in the future, this approach does not seem ideal.

Next generation sequencing – the answer?

Studying the genetics of FMD in a single MD family with multiple generations and several affected individuals would solve many of the problems in the genetic study of MD presented in chapter 6.2.1 since these patients affected with MD most likely share the predisposing genetic factors. Exome sequencing has proved to be a powerful tool in discovering the genetic basis of rare Mendelian diseases (Bamshad *et al.* 2011). However, until a recent abstract published in the 62nd Annual Meeting of the American Society of Human Genetics, it has not been clear whether a single mutation can cause MD. The abstract presented a finding of a *SLC45A3* gene deletion segregating with FMD in a Chilean family (Campbell *et al.* unpublished). The same deletion was also found in two out of 250 sporadic MD patients. The previous findings and the clinical heterogeneity of FMD families also observed in this study support the theory that multiple rare variants might predispose to the disease. However, if some of the variants lie in the non-protein coding areas of the genome exome sequencing might not be enough to discover the underlying variants. In that case genome-wide linkage analysis combined with targeted genomic sequencing might be one of the ways to study the genetics of MD in the future. In any case, approaches applying next generation sequencing might be the best and most cost effective method in genetics to gain information from the biological pathways involved in the pathogenesis of MD in the future. Thus far no studies employing next generation sequencing methods in MD research have been published.

Epigenetics

Epigenetics is a field that studies heritable changes of gene expression that, unlike mutations and polymorphisms, are not associated with changes of the DNA sequence (Hamilton 2011). Such heritable changes include, for example, DNA methylation, modifications of chromatin and non-coding RNA (Gibney &Nolan 2010). Environmental factors might effect epigenetic regulation and could explain the correlation between environmental factors and risk of disease (Jirtle &Skinner

2007). As both genetic and environmental factors are likely involved in the pathogenesis of MD, it would be interesting to pursue epigenetic studies of MD in the future.

7 Conclusions

At least 9.3% of the definite MD patients in the areas of Northern Ostrobothnia and Kainuu are affected by FMD, and the percentage may be as high as or higher than 23.4%. Genetic factors seem to have a significant role in the development of MD.

A total of 38 Meniere families were studied in this thesis. Finnish Meniere families proved to be highly heterogeneous. The most common mode of inheritance was autosomal dominant, although other modes of inheritance could not be fully excluded. Anticipation and co-segregation with migraine are not common in Finnish FMD. A high tendency of relatives to manifest Meniere-like symptoms was observed in these families.

Familial patients are affected earlier and suffer from longer spells of vertigo than SMD patients. Autoimmune factors may play a larger role in the development of FMD, since the prevalence of autoimmune diseases especially rheumatoid arthritis seems higher in this population. This might also have relevancy in medical treatment of FMD with steroids. Different aetiologic factors might predispose to the development of FMD and SMD and therefore it might be reasonable to study these patient groups separately in the future.

Finnish FMD is not linked to chromosome 12p12.3. A role of the *KCNE1* gene in MD was implied in this study, but the results are not conclusive and need further investigation.

The genetic study of MD is greatly complicated by its multifactorial origin, genetic heterogeneity and reduced penetrance. Existing candidate gene reports provide very little information on the aetiology of MD. There are probably several genetic variations that predispose subjects to MD.

Future studies should emphasize the need to collect larger, well-defined case-control groups and multigenerational families affected with FMD for use in genome-wide linkage analyses and next generation sequencing. Currently the aetiology of MD is unknown but modern genetic studies may provide the information required to trace the aetiology of the disease in the future.

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Appendix

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Meniere tutkimuksen kyselylomake

Olkaa hyvä ja merkitkää rasti teitä parhaiten kuvaavan vaihtoehdon kohdalle ☑

Tutkimuspotilaiden luokittelu

☐ Minulla on Menieren tauti

☐ Minulla on osa Menieren taudin oireista (korvien soiminen, huimaus, heikko kuulo tai huono tasapaino), mutta Menieren taudin diagnoosia ei ole asetettu.

☐ Olen Meniere potilaan terve sukulainen

Sukupuoli ☐ mies ☐ nainen Ikä _____v

Perinnöllisyys

Kyllä	**Ei**	
☐	☐	Minulla on Menieren tautia sairastavia sukulaisia.
☐	☐	Minulla on sukulaisia, joilla on osa Menieren taudin oireista, mutta Menieren taudin diagnoosia ei ole asetettu.
☐	☐	Minulla on perheenjäseniä, jotka sairastavat migreeniä.
☐	☐	Minulla on sukulaisia, joilla on korvan otoskleroosi.
☐	☐	Suvussamme on muita kuulosairauksia.

Jos vastasitte **kyllä** johonkin yllä olevista kysymyksistä, selittäkää alla olevaan tilaan kuka/ketkä suvustanne ovat sairastuneet (esim. Menieren tautia on suvussamme äitini sisarella, hänen pojallaan ja tyttärelläni.).

_____
_____
_____
_____
_____
_____

Men_____ pv _____

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Ulkopuoliset altisteet

Jos ette ole enää työelämässä, vastatkaa työhistorianne perusteella.

Koulutus ja ammatti: _____

	En	Kyllä	Mikä aiheuttaa melun/vamman?
Oletteko työssä, jossa on suotavaa käyttää kuulosuojaimia?	☐	☐	_____
Altistutteko vapaa-ajallanne koville äänille (esim. ammunta)?	☐	☐	_____
Oletteko koskaan saaneet lääkärin hoitoa vaativaa päänvammaa?	☐	☐	_____

	Usein	Joskus	En juuri koskaan
Oletteko taipuvainen kokemaan stressiä?	☐	☐	☐

Onko teillä koskaan todettu

	Kyllä	Ei	
Kilpirauhasen vajaatoiminta	☐	☐	
Hyvänlaatuinen asentohuimaus	☐	☐	
Allergioita	☐	☐	
Reuma	☐	☐	
Migreeni	☐	☐	
Diabetes (tyyppi I)	☐	☐	
Aikuistyypin diabetes (tyyppi II)	☐	☐	
Otoskleroosi	☐	☐	
Muita perussairauksia, mitä?	☐	☐	_____
			_____
			_____

Men_____ pv _____

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Menieren taudille tyypillisten oireiden kartoitus

Oletteko koskaan tuntenut paineentunnetta korvassa?

En koskaan	Yksittäisiä kertoja	Silloin tällöin	Usein
☐	☐	☐	☐

Onko teillä koskaan tinnittänyt (korvien sointi, suhina, humina)?

Ei koskaan	Yksittäisiä kertoja	Silloin tällöin	Usein
☐	☐	☐	☐

Onko teitä koskaan huimannut ilman erityistä syytä?

Ei koskaan	Yksittäisiä kertoja	Silloin tällöin	Usein
☐	☐	☐	☐

Oletteko koskaan äkillisesti menettänyt tajuntanne ilman erityistä syytä?

En koskaan	Yksittäisiä kertoja	Silloin tällöin	Usein
☐	☐	☐	☐

Oletteko koskaan kokenut kuulonne heikentyneen väliaikaisesti?

En koskaan	Yksittäisiä kertoja	Silloin tällöin	Usein
☐	☐	☐	☐

Kuuletteko mielestänne hyvin?

Hyvin	Vaihtelevasti	Huonosti	Erittäin huonosti
☐	☐	☐	☐

Onko tasapainonne mielestänne hyvä?

Hyvä	Vaihteleva	Huono	Erittäin huono
☐	☐	☐	☐

Jos teillä on ollut edellä mainittuja oireita tai jos teillä on todettu Menieren tauti,
olkaa hyvä ja vastatkaa myös seuraavien sivujen kysymyksiin.

Men_____ pv _____

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Milloin oireenne ovat alkaneet?

	alle 20v	20-29v	30-39v	40-49v	50-59v	60-65v	yli 65v
Huimaus	☐	☐	☐	☐	☐	☐	☐
Korvien soiminen	☐	☐	☐	☐	☐	☐	☐
Kuulon heikkeneminen	☐	☐	☐	☐	☐	☐	☐
Menieren tauti todettiin	☐	☐	☐	☐	☐	☐	☐

Hoitotoimenpiteet

	Ei	Kyllä	Kokeiltu, ei käytössä
Noudatan vähäsuolaista ruokavaliota.	☐	☐	☐
Minulla on nesteenpoistolääkitys.	☐	☐	☐
Minulla on beetahistiini (Betaserc) lääkitys.	☐	☐	☐
Olen saanut gentamysiinihoitoa.	☐	☐	☐
Minulle on tehty sisäkorvan leikkaus.	☐	☐	☐
Minulla on Vertipam lääkitys.	☐	☐	☐
Muuta? _____	☐	☐	☐

Hoidosta saatu hyöty

	Merkittävä hyöty	Vähäinen hyöty	Ei hyötyä
Vähäsuolainen ruokavalio	☐	☐	☐
Nesteenpoistolääkitys	☐	☐	☐
Beetahistiini (Betaserc)	☐	☐	☐
Gentamysiini	☐	☐	☐
Leikkaushoito	☐	☐	☐
Vertipam	☐	☐	☐
Muu	☐	☐	☐

Puolisuus ja kuulon apuvälineet

	Oikea	Vasen	Molemmat	En tiedä
Kumpi korva teillä on sairas?	☐	☐	☐	☐

	Oikea	Vasen	Ei kuulolaitetta
Onko teillä kuulolaitetta?	☐	☐	☐

	alle 30v	30-39v	40-49v	50-59v	yli 60v
Kuulolaitteen käyttö aloitettu	☐	☐	☐	☐	☐

Men_____ pv _____

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Huimauksen vaikeusaste (valitse parhaiten kuvaava vaihtoehto)

- ☐ Huimauksella ei ole vaikutusta päivittäiseen elämääni.
- ☐ Huimauksen aikana tekeminen keskeytyy, mutta en joudu muuttamaan suunnitelmia.
- ☐ Huimauksen aikana tekeminen keskeytyy ja joudun muuttamaan päivän suunnitelmia.
- ☐ Huimaus häiritsee päivittäistä elämääni. Pystyn pitämään huolta perheestäni ja matkustamaan, mutta se vie valtavati energiaa.
- ☐ En kykene työskentelemään tai ajamaan autoa. En voi pitää muista huolta.
- ☐ Olen ollut vuoden kykenemätön tekemään mitään, saan avustusta./ Olen joutunut sairaseläkkeelle Menieren taudin vuoksi

Kuinka usein teillä on huimauskohtauksia?

	Päivittäin	Viikoittain	Kuukausittain	Muutaman kerran vuodessa	Harvemmin kuin vuosittain
NYT	☐	☐	☐	☐	☐
PAHIMMILLAAN	☐	☐	☐	☐	☐

Kuinka pitkään huimauskohtauksenne kestävät (min/tunteja/päiviä)?

_____ tyypillisesti

_____ pisimmillään

Tinnituksen vaikeusaste

	Jatkuvasti	Vain kohtauksen aikana	Ei tinnitusta
Oikeassa korvassa	☐	☐	☐
Vasemmassa korvassa	☐	☐	☐

Oireita provosoivat tekijät

	Kyllä	Ei
Onko stressillä vaikutusta oireidenne ilmaantumiseen tai vaikeusasteeseen?	☐	☐

Jos olette tunnistaneet muita oireita laukaisevia tekijöitä, olkaa hyvä ja luetelkaa niitä tähän.

_____

_____

Kiitos vastauksistanne! Lomakkeen voi palauttaa mukana tulleella vastauskuorella.

Men_____ pv _____

Original articles

I Hietikko E, Kotimäki J, Sorri M & Männikkö M (2013) High incidence of Meniere-like symptoms in relatives of Meniere patients in the areas of Oulu University Hospital and Kainuu Central Hospital in Finland. European Journal of Medical Genetics. In Press.

II Hietikko E, Sorri M, Männikkö M & Kotimäki J (2013) Higher prevalence of autoimmune diseases and longer spells of vertigo in patients affected with familial Meniere's disease – a clinical comparison of familial and sporadic Meniere's disease. Manuscript.

III Hietikko E, Kotimäki J, Kentala E, Klockars T, Sorri M & Männikkö M. (2011) Finnish familial Meniere disease is not linked to chromosome 12p12.3, and anticipation and cosegregation with migraine are not common findings. Genet Med. 13(5): 415–20.

IV Hietikko E, Kotimäki J, Okuloff A, Sorri M & Männikkö M (2012) A replication study on proposed candidate genes in Ménière's disease, and a review of the current status of genetic studies. Int J Audiol. 51(11): 841–5.

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1193. Kaakinen, Marika (2012) Genetic and life course determinants of cardiovascular risk factors : structural equation modelling of complex relations

1194. Nevalainen, Mika (2012) Gene product targeting into and membrane trafficking from the endoplasmic/sarcoplasmic reticulum in skeletal myofibers

1195. Meriläinen, Sanna (2013) Experimental study of acute pancreatitis in a porcine model, especially tight junction structure and portal vein cytokines

1196. Koivikko, Minna (2013) Cardiac autonomic regulation and repolarisation during hypoglycaemia in type 1 diabetes

1197. Aro, Ellinoora (2013) Prolyl 4-hydroxylases, key enzymes regulating hypoxia response and collagen synthesis : the roles of specific isoenzymes in the control of erythropoiesis and skeletogenesis

1198. Koivumäki, Janne (2013) Biomechanical modeling of proximal femur : development of finite element models to simulate fractures

1199. Paavola, Liisa (2013) Salla disease – rare but diverse : a clinical follow-up study of a Finnish patient sample

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1206. Penttilä, Matti (2013) Duration of untreated psychosis : Association with clinical and social outcomes and brain morphology in schizophrenia

1207. Wikström, Erika (2013) Epidemiology of *Chlamydia trachomatis* infection in Finland during 1983–2009

1208. Jokela, Tiina (2013) Analyses of kidney organogenesis through *in vitro* and *in vivo* approaches : Generation of conditional Wnt4 mouse models and a method for applying inducible Cre-recombination for kidney organ culture

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