ISNVD
International Society for Neurovascular Disease

9th annual meeting
May 30-31, 2019, University of Ferrara - Italy

Genetic architecture of Meniere disease

Jose Antonio Lopez-Escamez, MD, PhD

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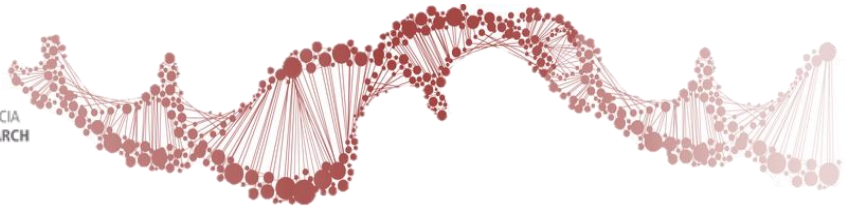

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Consensus Definition of Ménière's Disease

Barany ICVD Committee-AAO-HNS Equilibrium Committee-
EAONO Vertigo Committee-Japan Society for Equilibrium
Research-Korean Balance Society

DEFINITE MENIERE DISEASE	PROBABLE MENIERE DISEASE

AMERICAN ACADEMY OF OTOLARYNGOLOGY–HEAD AND NECK SURGERY

대한평형의학회
The Korean Balance Society

EQUILIBRIUM RESEARCH
日本めまい平衡医学会

EAONO EUROPEAN ACADEMY OF OTOLOGY & NEURO - OTOLOGY

Published in :

- English
- Spanish
- Japanese
- Korean
- Italian
- German

Lopez-Escamez JA, Carey J, Chung W-H, Goebel JA, Magnusson M, Mandalà M, et al. Diagnostic criteria for Menière's disease**. J Vestib Res. 2015** Jan 1;25(1):1–7.

Diagnostic criteria for Ménière's disease

Definite Ménière's disease:

A. Two or more spontaneous episodes of vertigo lasting 20 minutes to 12h
B. Audiometrically documented low to medium frequencies SNHL in the affected ear on at least one occasion before, during or after one of the episodes of vertigo
C. Fluctuating aural symptoms (hearing, tinnitus or fullness) in the affected ear
D. Other causes excluded

Lopez-Escamez JA, Carey J, Chung W-H, Goebel JA, Magnusson M, Mandalà M, et al. Diagnostic criteria for Menière's disease**. J Vestib Res. 2015** Jan 1;25(1):1–7.

Before…

Meniere

Endolymphatic hydrops

Now…

Frejo L et al. Extended phenotype and clinical subgroups in unilateral Meniere disease: A cross-sectional study with cluster analysis. **Clin Otolaryngol. 2017,** 42(6): 1172–80.
Frejo L et al. Clinical Subgroups in Bilateral Meniere Disease. **Front Neurol.2016**;7: 182.

Familial MD 10%

Sporadic MD 90%

> 50 genes with rare mutations

DTNA-FAM136A

DTP-PRKCB

SEMA3D

Incomplete penetrance

Variable expressivity

Unilateral MD

Type 1 Clasic Allergic – triggered 20%

Type 2 Delayed MD

Type 3 Familial MD

Type 4 Migraine

Type 5 Autoimmune MD 12%

Bilateral MD

Type 1 Metachronic

Type 2 Synchronic

Type 3 Familial MD

Type 5 Autoimmune MD

eQTL -17%

Type 4 Migraine

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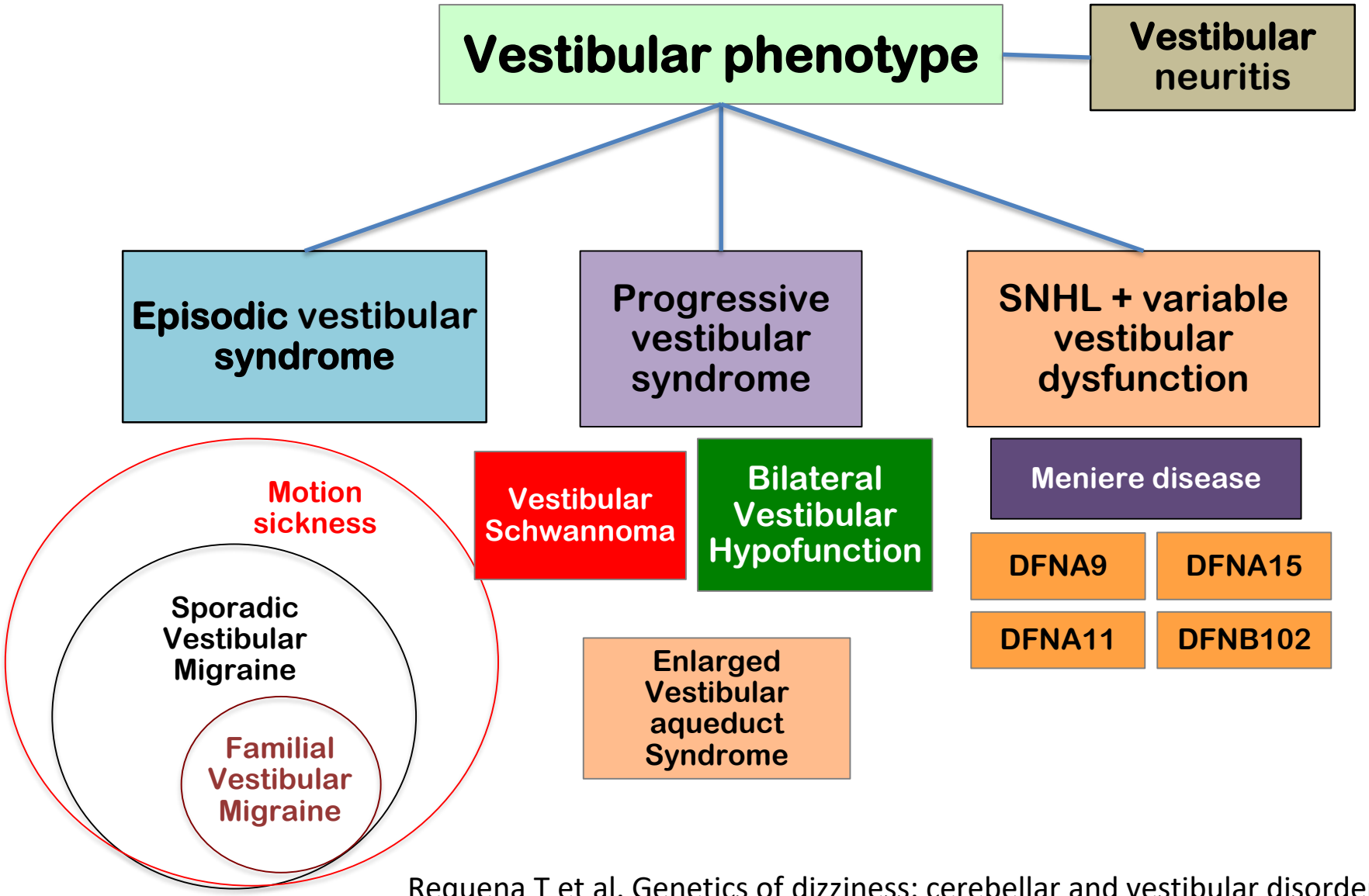
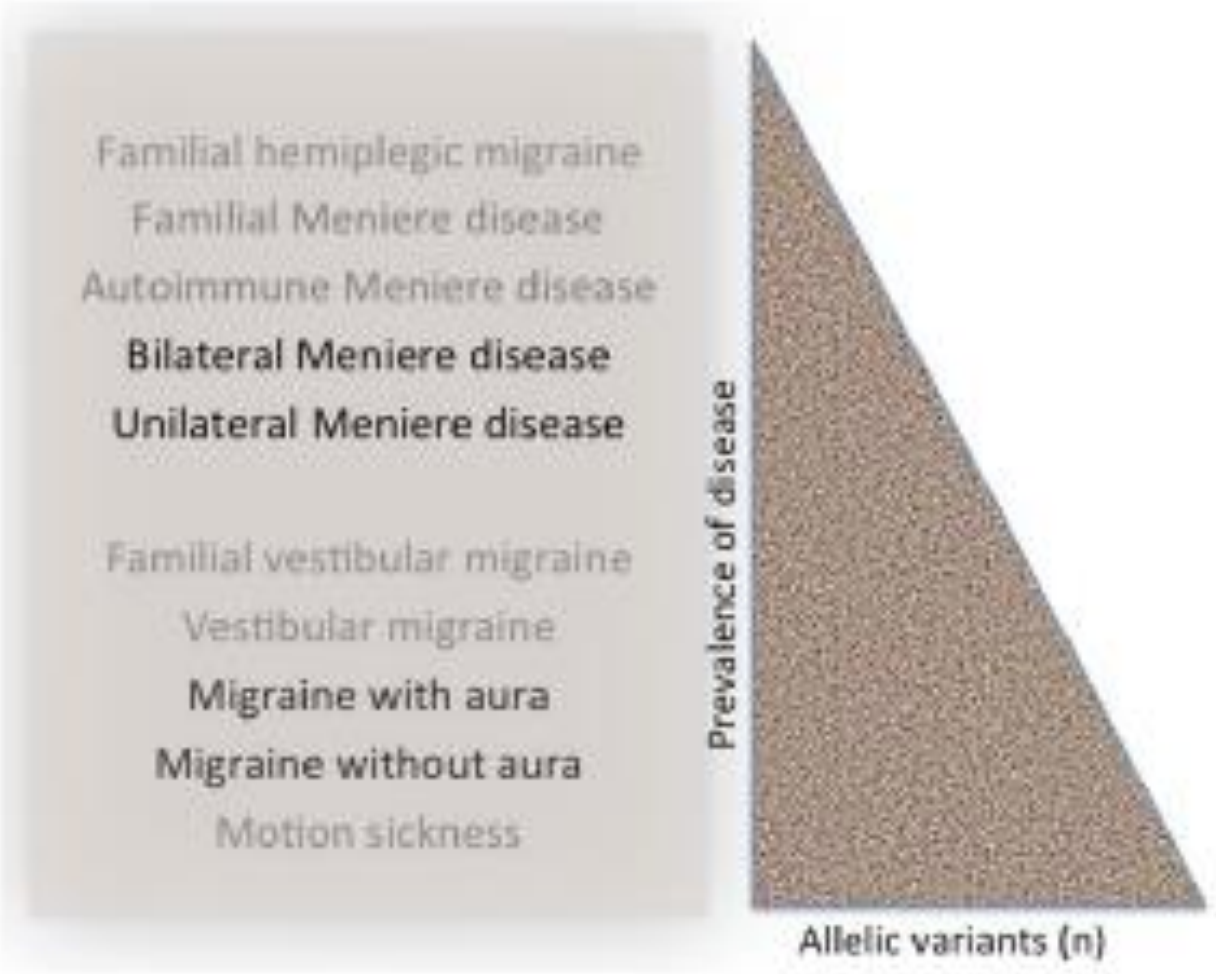
Phenotype = clinical features



Requena T et al. Genetics of dizziness: cerebellar and vestibular disorders. Curr. Opin. Neurol 2014; 27:98-104

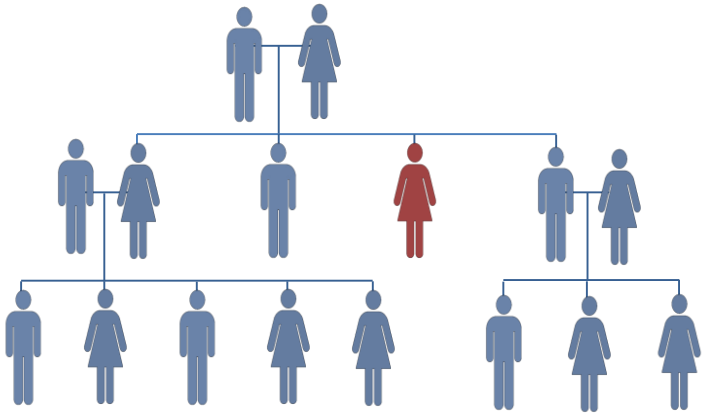
Genome variation and prevalence of disease



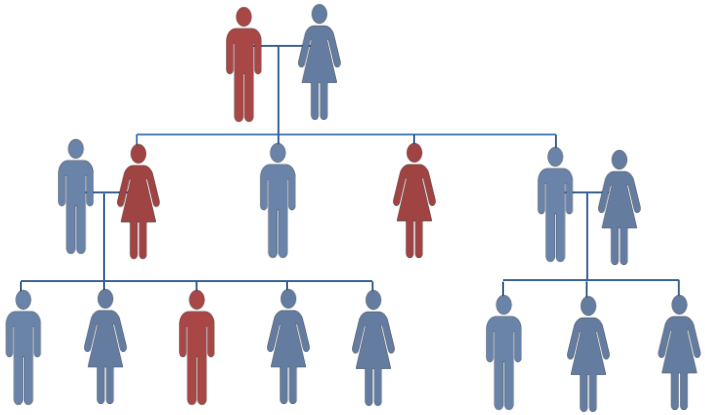
Gallego-Martinez A, Espinosa-Sanchez JM, López-Escámez JA. Genetic contribution to vestibular diseases**. J Neurol 2018** Mar 26;265(S1):29–34.

Familial clustering in MD

Sporadic MD (92%)



Familial MD (8%)

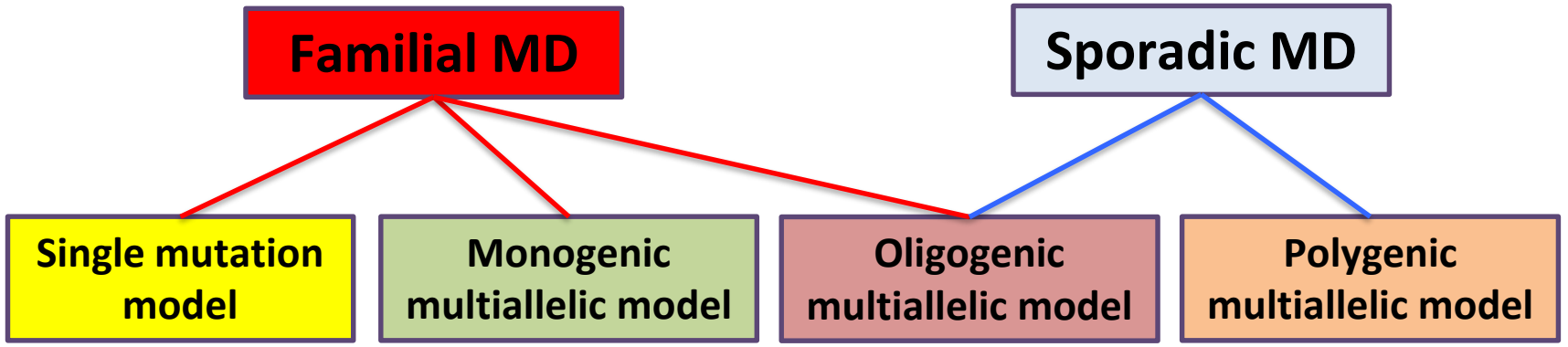


Inheritance

- **Autosomal dominant**
- Autosomal recessive
- Mitochondrial

Requena T Espinosa-Sanchez J, Cabrera S et al. Familial clustering and genetic heterogeneity in Meniere's disease. **Clin Genet 2014**, 85:245-52.

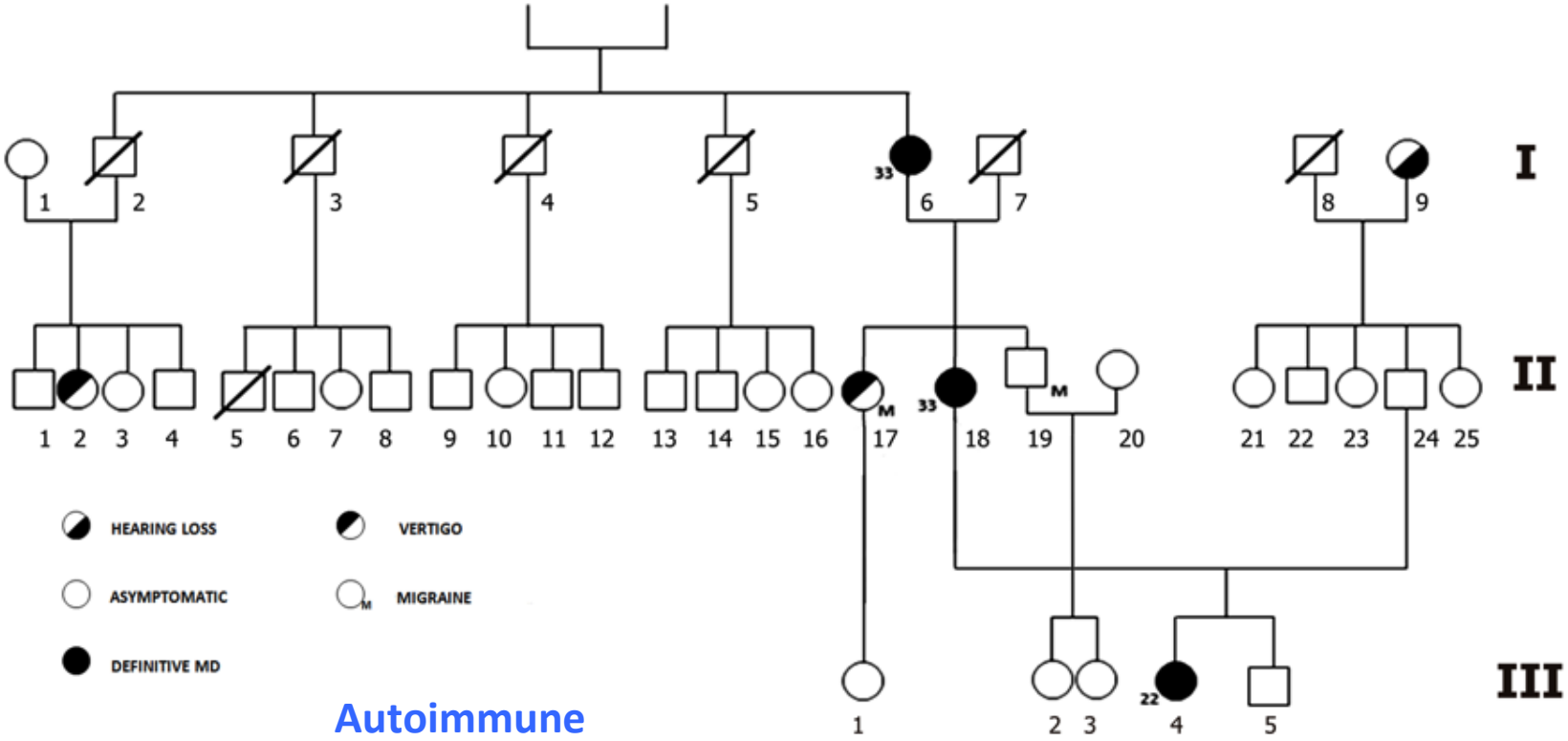
Genetics of Meniere disease



Phenotype in familial MD

1. Clinical heterogeneity
2. Small family size
3. Incomplete penetrance (AD, mito)
4. Variable expressivity

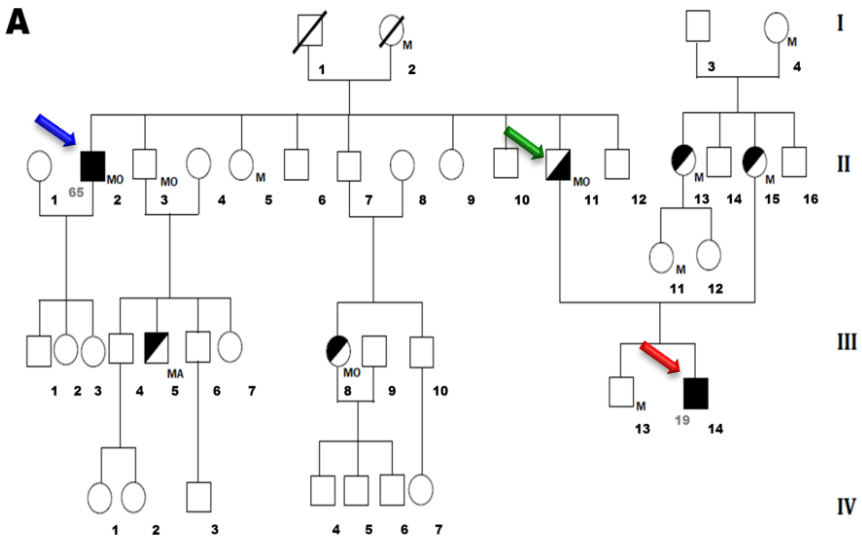
Clinical heterogeneity in families



Autoimmune background

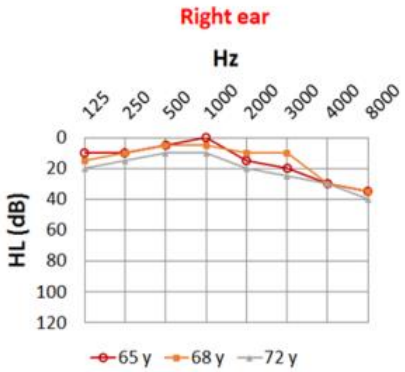
Requena T, Cabrera S, Martín-Sierra C, Price SD, Lysakowski A, Lopez-Escamez JA. Identification of two novel mutations in FAM136A and DTNA genes in autosomal-dominant familial Meniere's disease. **Human Molecular Genetics**. 2015 Feb 14;24(4):1119–26.

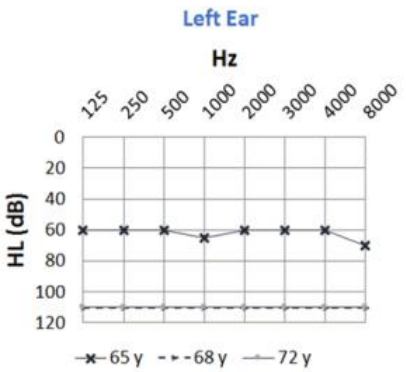
PRKCB family



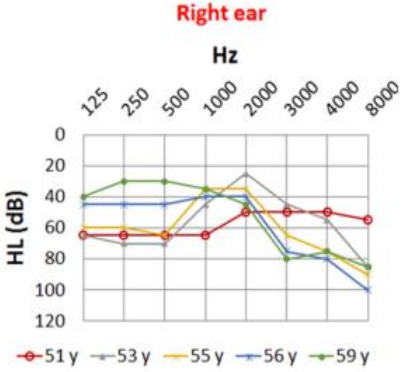
Autoimmune background

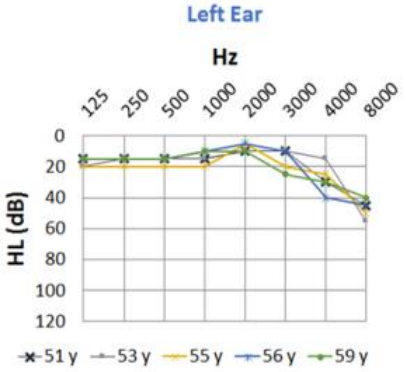
PRKCB segregates low-frequency hearing loss phenotype





II-2





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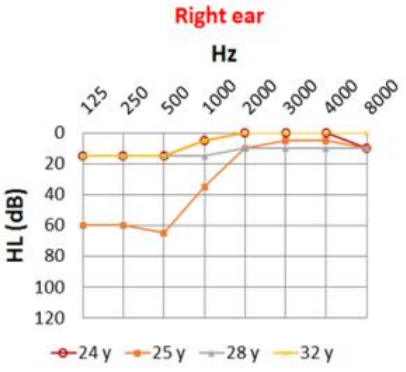
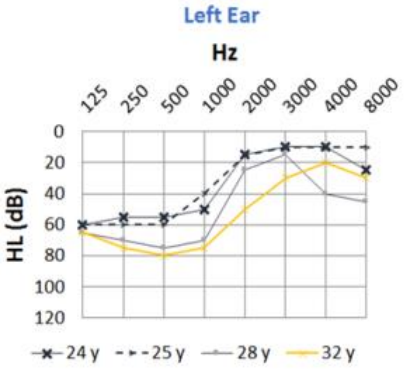
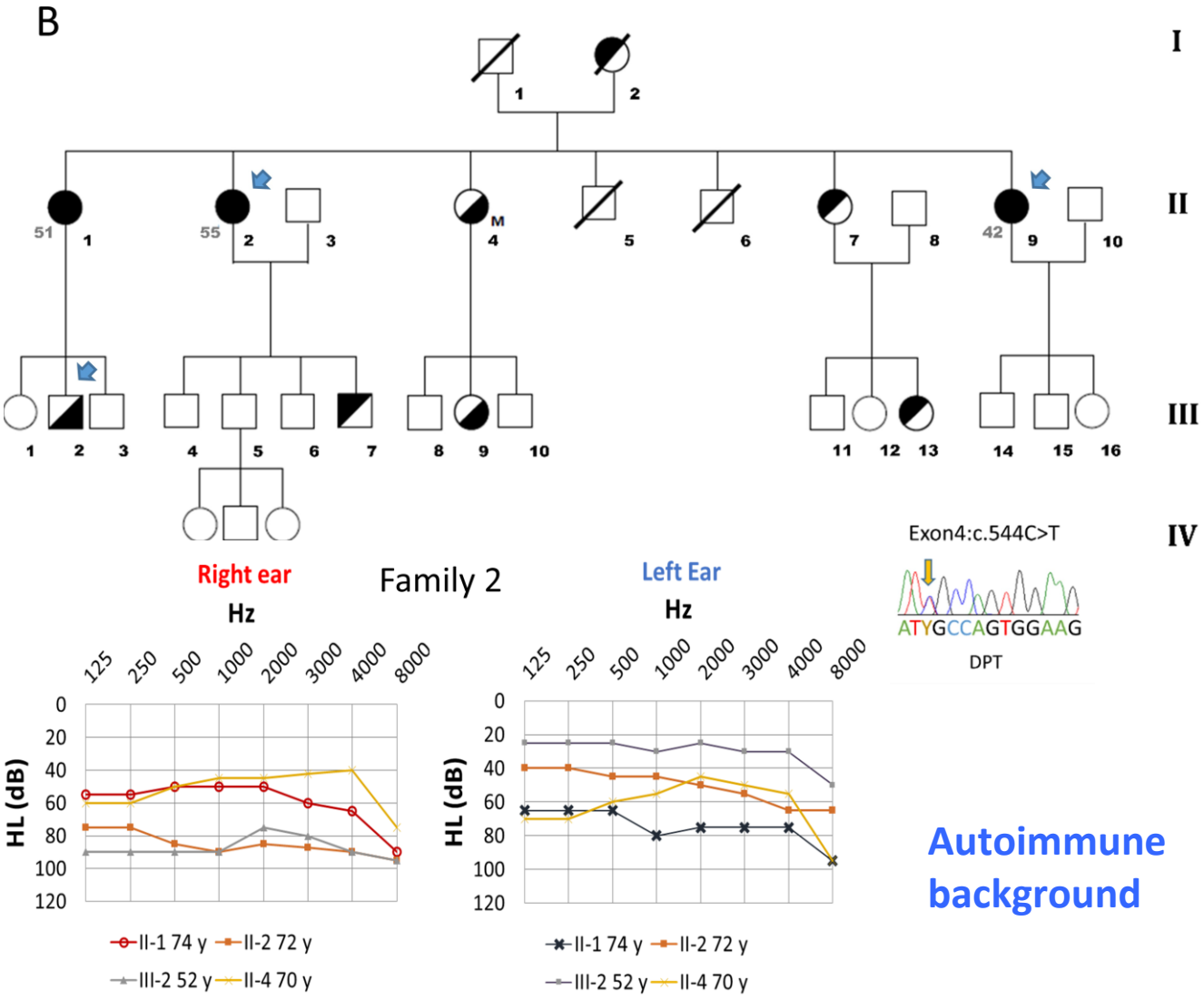




III-14

Variable expressivity

DPT family



Autoimmune background

Martín-Sierra C, Gallego-Martinez A, Requena T et al. Variable expressivity and genetic heterogeneity involving DPT and SEMA3D genes in autosomal dominant familial Meniere's disease. **Eur J Hum Genet** 2017;25(2):200–7.

Exome sequencing studies

6 genes in AD familial Ménière's disease

Gene	Variant	gnomAD MAF	Validation studies	Reference
COCH	Chr14: 25 mutations	low	*Meniere-like HFHL*	Robertson Genomics 1994
DTNA	chr18:32462094G>T	$3.5x10^{-5}$	LCL, novel splice site, rat, drosophila	Requena HMG 2015
FAM136A	chr2:70527974C>T	Not found	LCL, gene expression	Requena HMG 2015
PRKCB	chr16: 23999898 G > T	Not found	Mouse, Rat, in silico	Martin-Sierra HMG 2016
DPT	Chr7: 84642128 C>T	Not found	In silico	Martin-Sierra EJHG 2017
SEMA3D	Chr1: 168665849 C>T	$2.4x10^{-5}$	In silico	Martin-Sierra EJHG 2017

Sporadic Meniere Disease

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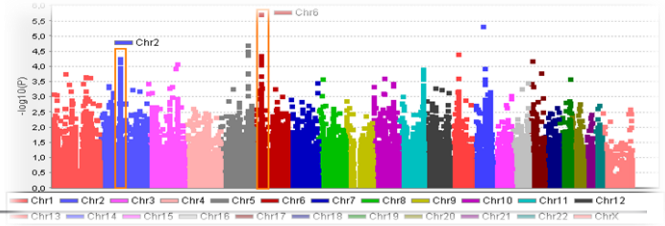
Discovery cohort
681 MD patients (189 bilateral)
735 cc

South european ancestry



SNV					Phase 1 (n = 189 cases; 735 controls)			
Chr.	**Pos.**	**Rs**	**Ref.**	**Alt.**	**RAF_C**	**RAF_N**	**OR (95%)**	***p*-Value**
2	102351615	rs4988957	C	T	0.414	0.358	1.27 (0.99–1.62)	5.24E−02
2	102417980	rs11465670	T	C	0.156	0.093	1.81 (1.29–2.54)	5.02E−04
2	102460685	rs4851589	A	G	0.337	0.279	1.32 (1.02–1.69)	3.35E−02
6	30814225	rs886424	C	T	0.102	0.051	2.11 (1.39–3.21)	3.55E−04
6	31083776	rs9380217	C	T	0.159	0.069	2.55 (1.81–3.58)	3.40E−07
6	31090401	**rs4947296**	T	C	0.164	0.067	2.72 (1.93–3.82)	3.15E−08
6	32082981	rs1150754	C	T	0.117	0.061	2.04 (1.38–3.01)	2.66E−04

Replication cohort
240 bilateral MD patients
895 Iberian controls

SNV					Phase 2 (n = 240 cases; 895 controls)			
Chr.	**Pos.**	**Rs**	**Ref.**	**Alt.**	**RAF_C**	**RAF_N**	**OR (95%)**	***p*-Value**
2	102351615	rs4988957	C	T	0.381	0.355	1.07 (0.93–1.23)	1.88E−01
2	102417980	rs11465670	T	C	0.087	0.083	1.04 (0.73–1.49)	4.41E−01
2	102460685	rs4851589	A	G	0.247	0.258	0.96 (0.79–1.16)	3.61E−01
6	30814225	rs886424	C	T	0.082	0.071	1.14 (0.81–1.62)	2.55E−01
6	31083776	rs9380217	C	T	0.108	0.078	1.43 (1.00–2.06)	5.52E−02
6	31090401	**rs4947296**	T	C	0.108	0.078	1.432 (1.024–2.004)	3.52E−02
6	32082981	rs1150754	C	T	0.089	0.067	1.16 (0.81–1.65)	2.35E−01

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Meta-analysis

429 MD bilateral patients
1630 controls

SNV					Meta-analysis (n = 429 cases; 1,630 controls)			
Chr.	Pos.	Rs	Ref.	Alt.	RAF_C	RAF_N	OR (95%)	p-Value
2	102351615	rs4988957	C	T	0.406	0.351	1.16 (1.05–1.83)	2.91E–03
2	102417980	rs11465670	T	C	0.121	0.087	1.38 (1.10–1.73)	4.52E–03
2	102460685	rs4851589	A	G	0.299	0.267	1.12 (0.99–1.27)	4.53E–02
6	30814225	rs886424	C	T	0.095	0.067	1.41 (1.09–1.83)	7.73E–03
6	31083776	rs9380217	C	T	0.132	0.074	1.854 (1.465–2.347)	2.02E–07
6	31090401	**rs4947296**	T	C	**0.142**	**0.073**	**2.089 (1.661–2.627)**	**1.39E–09**
6	32082981	rs1150754	C	T	0.096	0.071	1.36 (1.05–1.77)	1.34E–02

rs4947296 CC is the risk genotype in bilateral MD

Frejo L, Requena T, Okawa S, Gallego-Martinez A, Martinez-Bueno M, Aran I, et al. Regulation of Fn14 Receptor and NF-κB Underlies Inflammation in Meniere's Disease. **Front Immunol**. 2017;8:1739.

Sporadic Meniere disease

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Panel MDv1: target sequencing 69 genes (N=890)

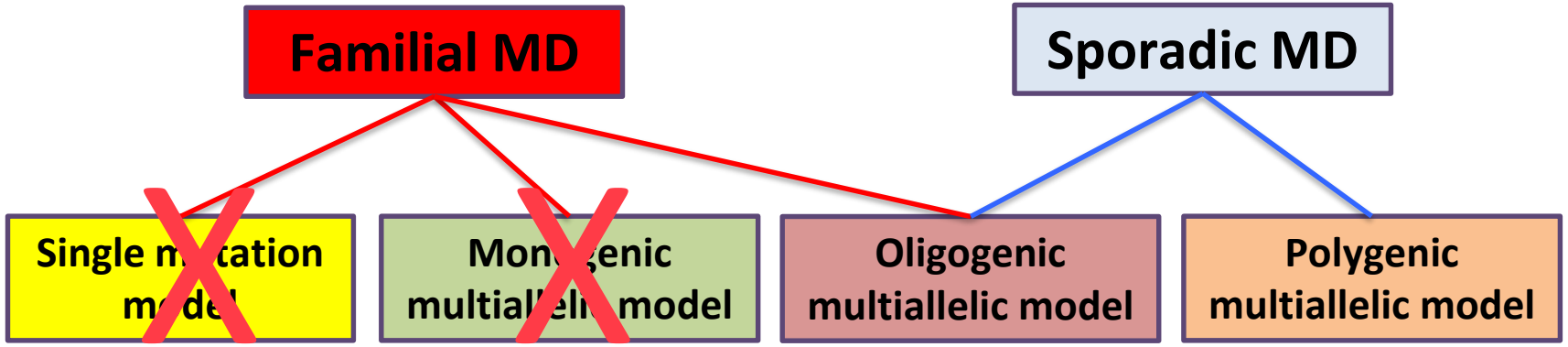
Gen	Localización en el genoma (hg19)	Exón No.	Tamaño (kb)	Gen	Localización en el genoma (hg19)	Exón No.	Tamaño (kb)
ACTG1	chr17:79476947-79479942	3	2666	***MT-ATP8***	chrM:8315-8621	1	307
ADD1	chr4:2845534-2931853	17	13391	*ESPN*	chr1:6484798-6521480	14	5685
ARNT2	chr15:80696642-80890328	21	8996	*EYA4*	chr6:133561686-133853308	23	11034
CCDC50	chr3:191046816-191116509	11	10398	*FAM107B*	chr10:14560506-14816946	21	9203
CEACAM16	chr19:45202371-45214036	7	2583	*FAM136A*	chr2:70523057-70529272	2	3286
CLDN14	chr21:37832869-37948917	8	3653	*GJB2*	chr13:20761554-20767164	2	2709
COCH	chr14:31343691-31364321	11	4442	*GRHL2*	chr8:102504610-102682004	17	7780
DPT	chr1:168664645-168698552	4	2188	*KCNE1*	chr21:35818936-35884623	7	6481
DTNA	chr18:32073204-32471858	30	13821	*KCNE3*	chr11:74165836-74178723	3	3707
POU4F3	chr5:145718537-145720133	2	1382	*KCNJ10*	chr1:160007207-160040101	2	5506
WHRN	chr9:117164310-117267780	14	6942	*KCNQ1*	chr11:2466171-2870390	19	5756
NR3B2	chr14:76776907-76968228	15	5584	*KCNQ4*	chr1:41249634-41306174	16	5783
MT-CO2	chrM:7535-8318	1	784	*MARVELD2*	chr5:68710889-68740207	8	5871
MT-TC	chrM:10008-10453	1	446	*MICA*	chr6:31367511-31384066	6	4618
MT-ND1	chrM:3256-4311	1	1056	*MIF*	chr22:24236141-24237464	2	1309
MT-ATP6	chrM:8476-9256	1	781	*MSRB3*	chr12:65672373-65860737	10	6387
MT-TL1	chrM:3179-3353	1	175	*MYH14*	chr19:50706835-50813852	43	11331
MT-TV	chrM:1550-1718	1	169	*MYO7A*	chr11:76839260-76926336	51	15511
MT-TI	chrM:4212-4380	1	169	*NFKB1*	chr4:103422436-103538509	29	8102
MT-TQ	chrM:4278-4449	1	172	*P2RX2*	chr12:133195316-133199022	7	2939
MT-TM	chrM:4351-4518	1	168	*PNPT1*	chr2:55861148-55921095	24	7916
MT-TW	chrM:5461-5628	1	168	*PRKCB*	chr16:23847250-24231982	20	12059
MT-TA	chrM:5536-5704	1	169	*RDX*	chr11:110045555-110167497	19	7564
MT-TN	chrM:5606-5778	1	173	*SEMA3D*	chr7:84624819-84816221	20	10062
MT-ND3	chrM:5710-5875	1	166	*SLC12A2*	chr5:127419408-127525430	27	13463
MT-TY	chrM:5775-5940	1	166	*SLC26A4*	chr7:107301030-107358304	24	8300
MT-TSI.	chrM:7395-7563	1	169	*THAP1*	chr8:42691767-42698524	4	2868
MT-TD	chrM:7467-7634	1	168	*TJP2*	chr9:71736130-71870174	25	9812
MT-TK	chrM:8244-8413	1	170	*TLR10*	chr4:38773810-38784661	4	4617
MT-TG	chrM:9940-10107	1	168	*TPRN*	chr9:140086019-140098695	3	3277
MT-TR	chrM:10354-10518	1	165	*TRIOBP*	chr22:38092945-38172613	26	15061
MT-TH	chrM:12087-12255	1	169	*USH1C*	chr11:17515392-17566013	29	6576
MT-TS2	chrM:12156-12314	1	159	*USH1G*	chr17:72912126-72919408	3	3868
MT-TL2	chrM:12215-12385	1	171	*WFS1*	chr4:6271526-6305042	8	5313
MT-TT	chrM:15837-16002	1	166				

Burden of missense variants in 12 genes

(only variants reported in Spanish controls)

Gene	Number variants	Percentage variants retained	OR EXAC	p corrected	OR NFE	p corrected	OR CSVS	p corrected
GJB2	6	**80**	0,5 (0,27-0,93)	1.75E-01	**3,2 (2,12-4,83)**	**1.65E-07**	**2,06 (1,33-3,19)**	**6.85E-03**
SEMA3D	2	**50**	1,1 (0,76-1,61)	1.00E+00	0,8 (0,53-1,21)	5.70E-01	**2,67 (1,94-3,68)**	**4.06E-09**
CLDN14	**2**	**50**	4,47 (2,55-7,83)	3.35E-07	**23,18 (13,81-38,9)**	**<1.00E-15**	**4,64 (2,65-8,11)**	**1.49E-07**
SLC26A4	6	**40**	1,18 (0,72-1,93)	1.00E+00	**2,88 (1,89-4,38)**	**4.88E-06**	**2,33 (1,51-3,59)**	**7.37E-04**
NFKB1	3	**30**	1,37 (0,99-1,91)	1.78E-01	1,43 (1,03-1,98)	1.01E-01	**2,73 (2,03-3,66)**	**6.62E-11**
ESRRB	3	**21**	4,41 (3,31-5,89)	<1.00E-15	**3,39 (2,52-4,55)**	**<1.00E-15**	**1,84 (1,33-2,54)**	**6.12E-04**
USH1G	5	**21**	2,51 (1,38-4,56)	1.33E-02	**20,27 (12,06-34,06)**	**<1.00E-15**	**4,67 (2,68-8,17)**	**3.05E-07**
P2RX2	3	14	2,57 (1,93-3,42)	2.61E-10	3,14 (2,38-4,14)	<1.00E-15	2,67 (2,01-3,55)	3.36E-11
RDX	2	12	4,49 (3,59-5,61)	<1.00E-15	2,69 (2,12-3,4)	<1.00E-15	3,33 (2,65-4,2)	<1.00E-15
TPRN	3	12	2,24 (1,7-2,96)	4.37E-08	6,55 (5,1-8,4)	<1.00E-15	2,95 (2,26-3,86)	<1.00E-15
ESPN	2	11	10,69 (9-12,69)	<1.00E-15	10,26 (8,64-12,19)	<1.00E-15	2,01 (1,64-2,46)	1.85E-11
MYH14	3	6	14,44 (10,42-20,03)	<1.00E-15	28,12 (20,38-38,79)	<1.00E-15	5,86 (4,16-8,25)	<1.00E-15

Genetics of Meniere disease



MD is not a monogenic disorder

Gallego-Martinez et al. Excess of Rare Missense Variants in Hearing Loss Genes in Sporadic Meniere Disease. **Front Genet** 2019; 10:76. doi: 10.3389/fgene.2019.00076

MD multiallelic model

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Common cis-regulatory variants and **rare variants** in one or more genes will contribute to the phenotype in MD.

Ind 1= cv a + rv z (gene A)
Ind 2= cv b + rv y (gene B)
Ind 3= cv a + rv x (gene A)
Ind 4= cv b + rv w (gene B)

cv is a common variant
rv is a rare variant

For a given *gene A*, the model could be more complex.

Ind 1= cv a + cv c + rv z
Ind 2= cv b + rv t + rv u

Several **rare variants** will target **driver genes** (*rv z*, *rv x* for gene A; *rv y*, *rv w* for gene B) and **common variants** in these genes will explain variable expressivity of the MD phenotype (**oligogenic multiallelic model**).

Gallego-Martinez et al. Excess of Rare Missense Variants in Hearing Loss Genes in Sporadic Meniere Disease. **Front Genet** 2019; 10:76. doi: 10.3389/fgene.2019.00076

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MINISTERIO DE ECONOMÍA Y COMPETITIVIDAD

Instituto de Salud Carlos III

MARIE CURIE ACTIONS

ESIT

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Meniere Society Grant 2016-17

TINNET

Ménière's Society

ASMES Asociación Síndrome de Ménière España

DIZZYNET

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