JORNADAS ANDALUZAS
SALUD INVESTIGA
28 de noviembre | Málaga

SESIÓN 2
ALIANZAS CIENTÍFICAS EN LA I+i EN SALUD

Red COST TINNET: Tinnitus heterogeneity

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Genyo CENTRO PFIZER-UNIVERSIDAD DE GRANADA-JUNTA DE ANDALUCÍA DE GENÓMICA E INVESTIGACIÓN ONCOLÓGICA
ibs.GRANADA INSTITUTO DE INVESTIGACIÓN BIOSANITARIA
GOBIERNO DE ESPAÑA
MINISTERIO DE CIENCIA E INNOVACIÓN
UNIÓN EUROPEA FONDO EUROPEO DE DESARROLLO REGIONAL
"Una manera de hacer Europa"

Investigación biomédica = co-laborar

Trabajo en equipo = *Networking*

Estrategia de trabajo= combinar *expertise*

- **Investigadores**
- **Asociaciones de pacientes**
- **Entidades públicas**
- **Empresas privadas**

Idea behind TINNET: heterogeneity

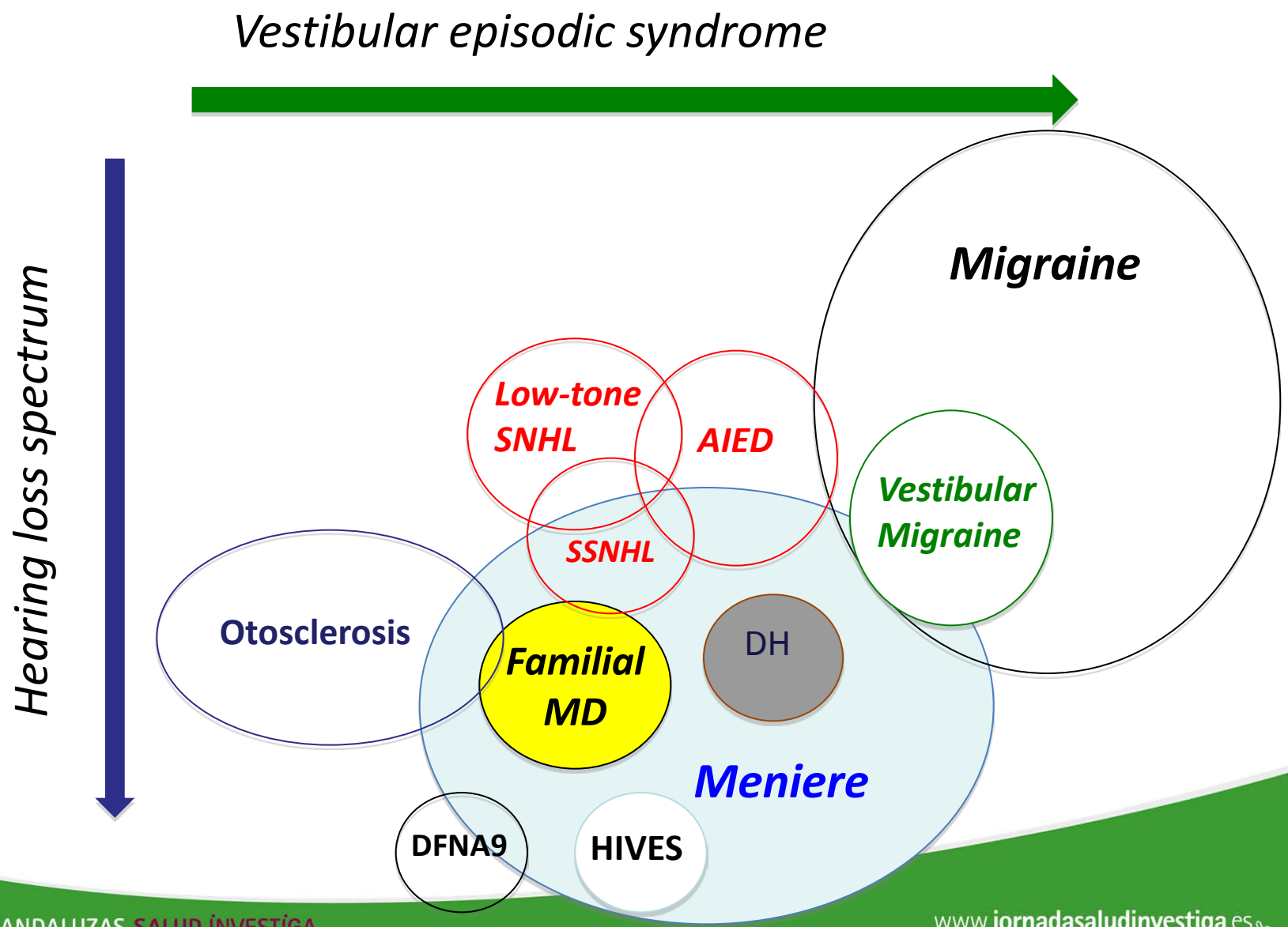
Idea behind TINNET: heterogeneity

Idea behind TINNET: heterogeneity

Evidence of heterogeneity

1. Patients groups differ on distinct symptoms AND symptoms are associated
2. Group definition has a logical sense: group response differs to clinical treatment
3. Within a patient group treatment outcome is similar
4. Noisy data, large variability
5. Variable expressivity

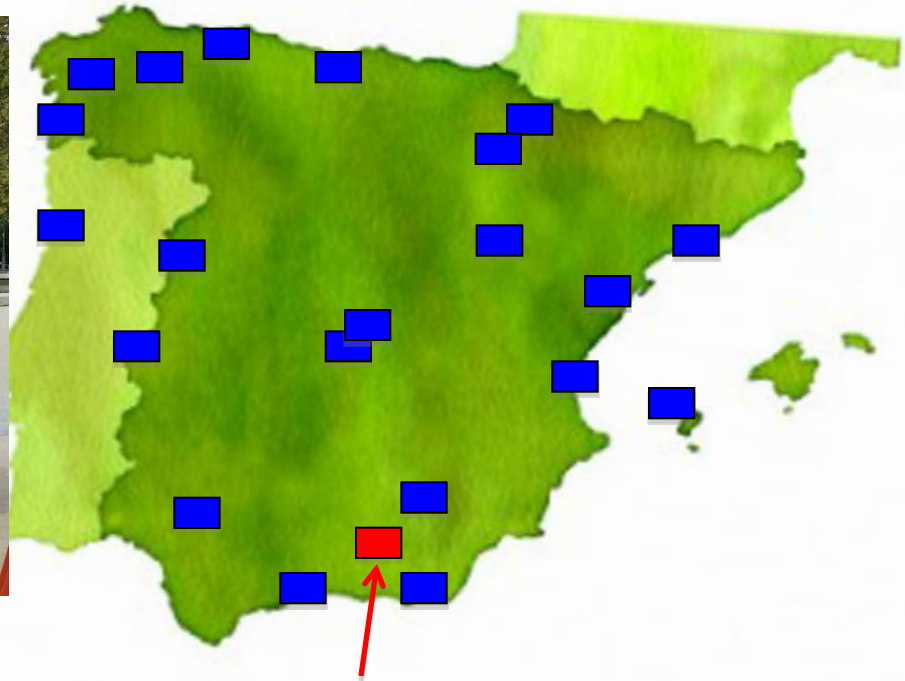
Clinical heterogeneity in Ménière disease



Meniere's disease Consortium (MeDiC): network for study of Meniere's disease

25 hospitals in Spain, 2 Portugal and 2 Italy

>2000 patients: DNA + clinical data



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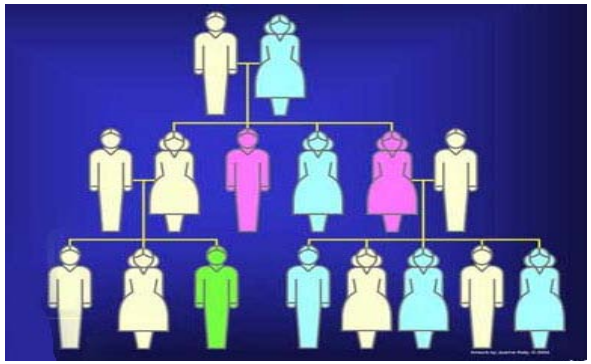
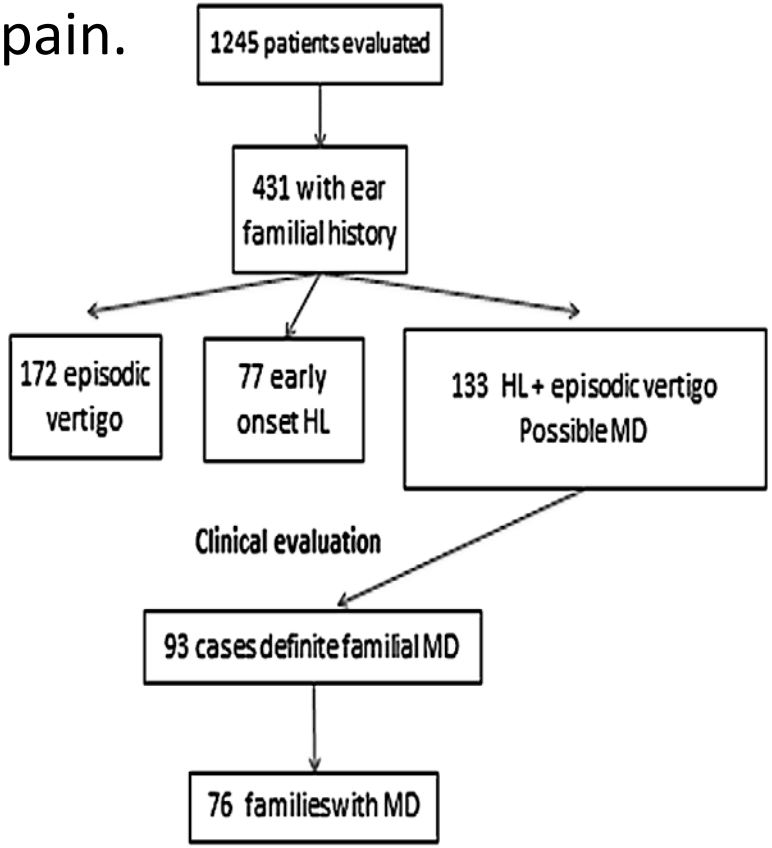
Familial Meniere's disease: the Spanish cohort (N=1245)

- FMD is found in 8% of cases in Spain.
- Genetic heterogeneity
  - **Autosomal dominant (AD)** with incomplete penetrance.
  - Autosomal recessive?
  - Mitochondrial inheritance?





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

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.

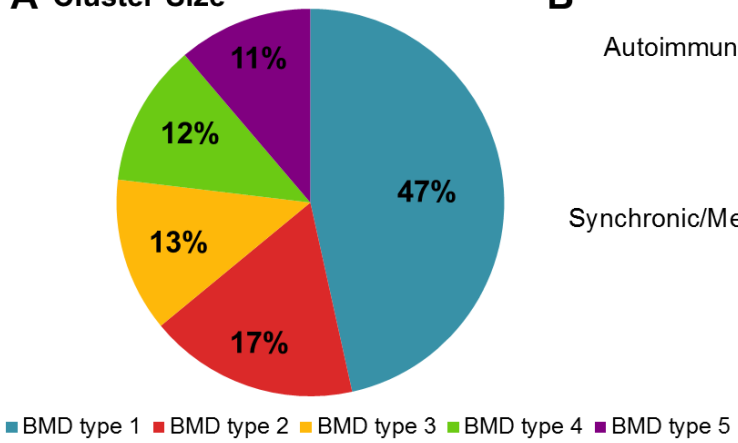
Diagnostic criteria for Ménière's disease

Definite Ménière's disease:

A. Two or more spontaneous episodes of vertigo lasting 20 minutes to 12h
B. Audiometrically documented low to middle 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

Clinical variants in bilateral Ménière disease

A Cluster Size



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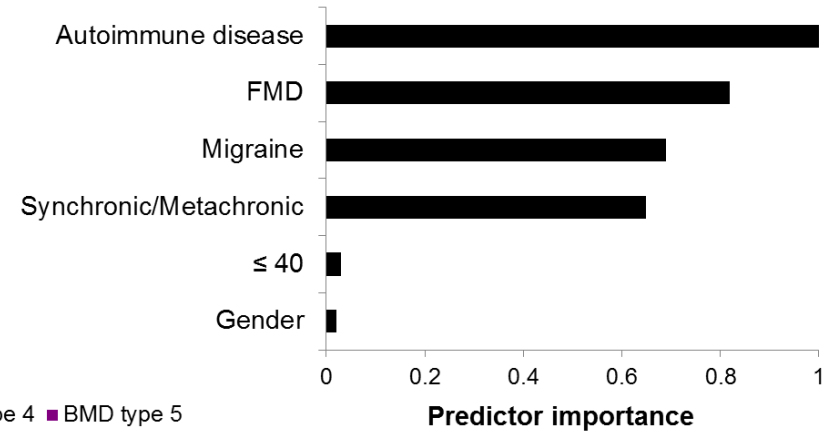
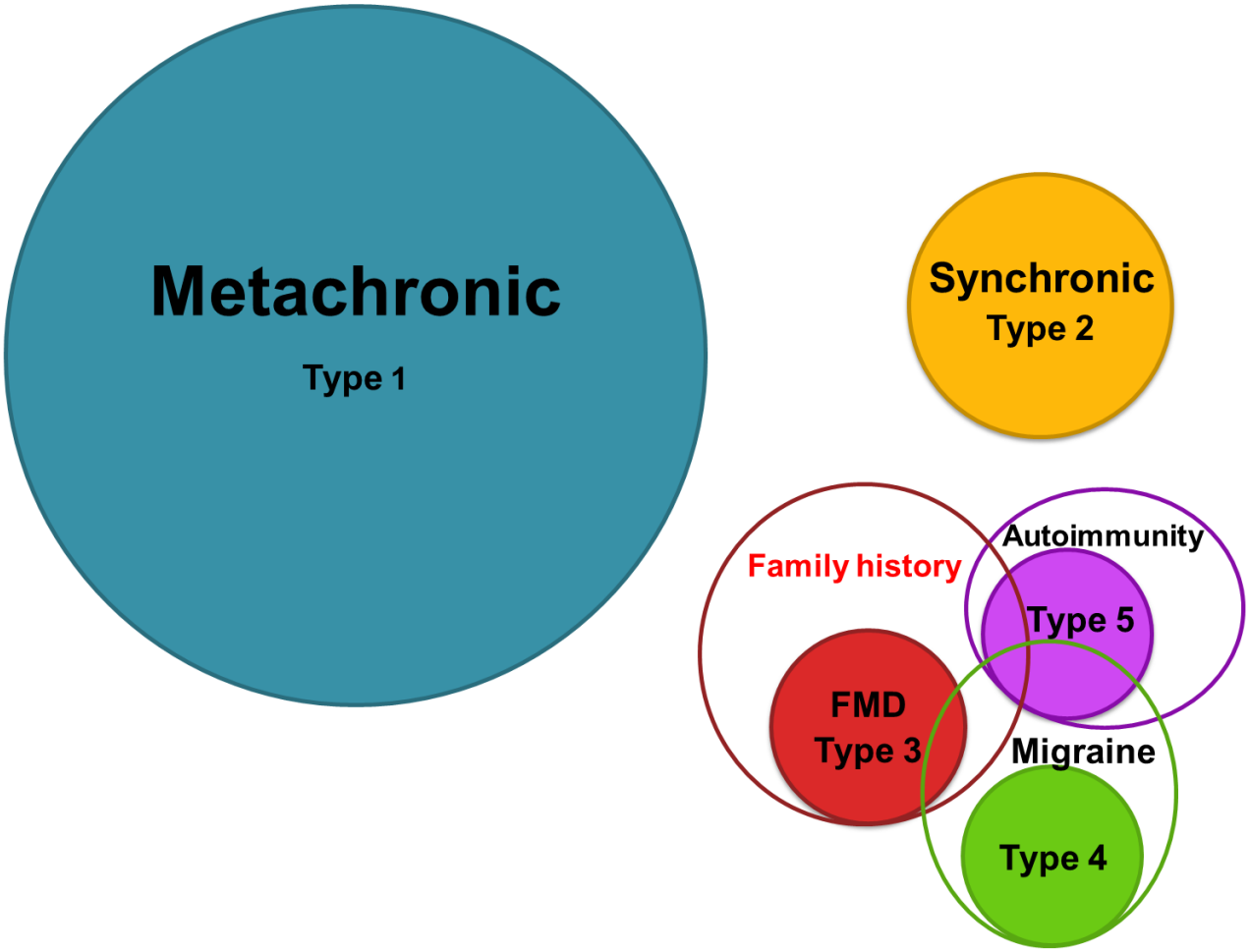


C

VARIABLES	BMD type 1	BMD type 2	BMD type 3	BMD type 4	BMD type 5
N, (%)	141 (46.5)	53 (17.5)	39 (12.9)	36 (11.9)	34 (11.2)
METACHRONIC HL (%)	100	0	82.1	77.8	61.8
SYNCHRONIC HL (%)	0	100	17.9	22.2	38.2
MIGRAINE (%)	0	0	17.9	100	38.2
AUTOIMMUNE DISEASE (%)	0	0	0	0	100
FMD (%)	0	0	100	0	29.4
SMD (%)	100	100	0	100	70.6

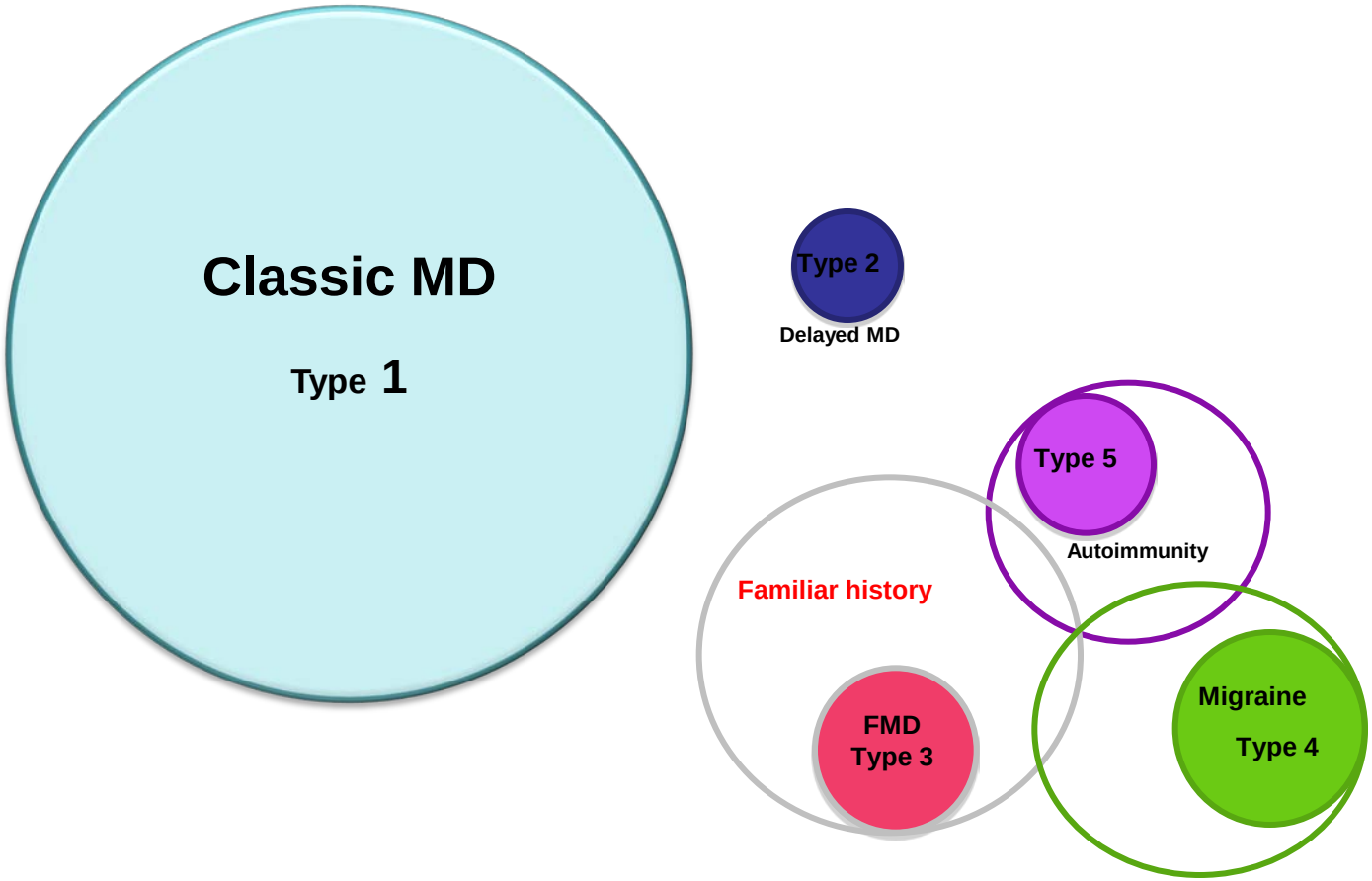
Frejo L et al. Clinical subgroups in bilateral Meniere disease. Front Neurol 2016

Extended phenotype in bilateral MD



Frejo L et al. Clinical subgroups in bilateral Meniere disease. **Front Neurol 2016**

Clinical variants in unilateral Ménière disease



Frejo L et al. Extended phenotype and clinical subgroups in unilateral Meniere disease: a cross-sectional study with cluster analysis (submitted).

Better understanding of Meniere's disease

Familial MD 10%

Sporadic MD

> 50 genes with rare mutations

DTNA-FAM136A

DTP-PRKCB

SEMA3D

Incomplete penetrance

Variable expressivity

Unilateral MD

Type 1 Clasic Allergic –triggered ??

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 6p21.33

Type 4 Migraine

Better understanding tinnitus heterogeneity (TINNET) BM1306

http://tinnet.tinnitusresearch.net/

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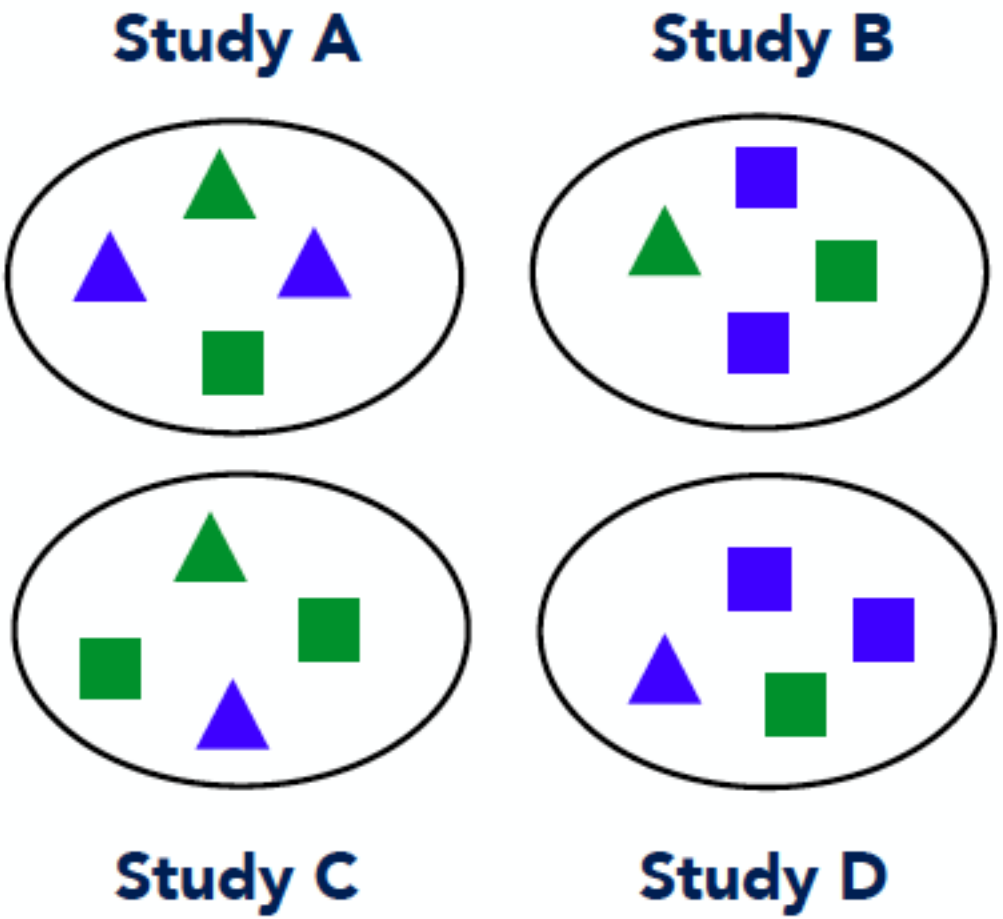
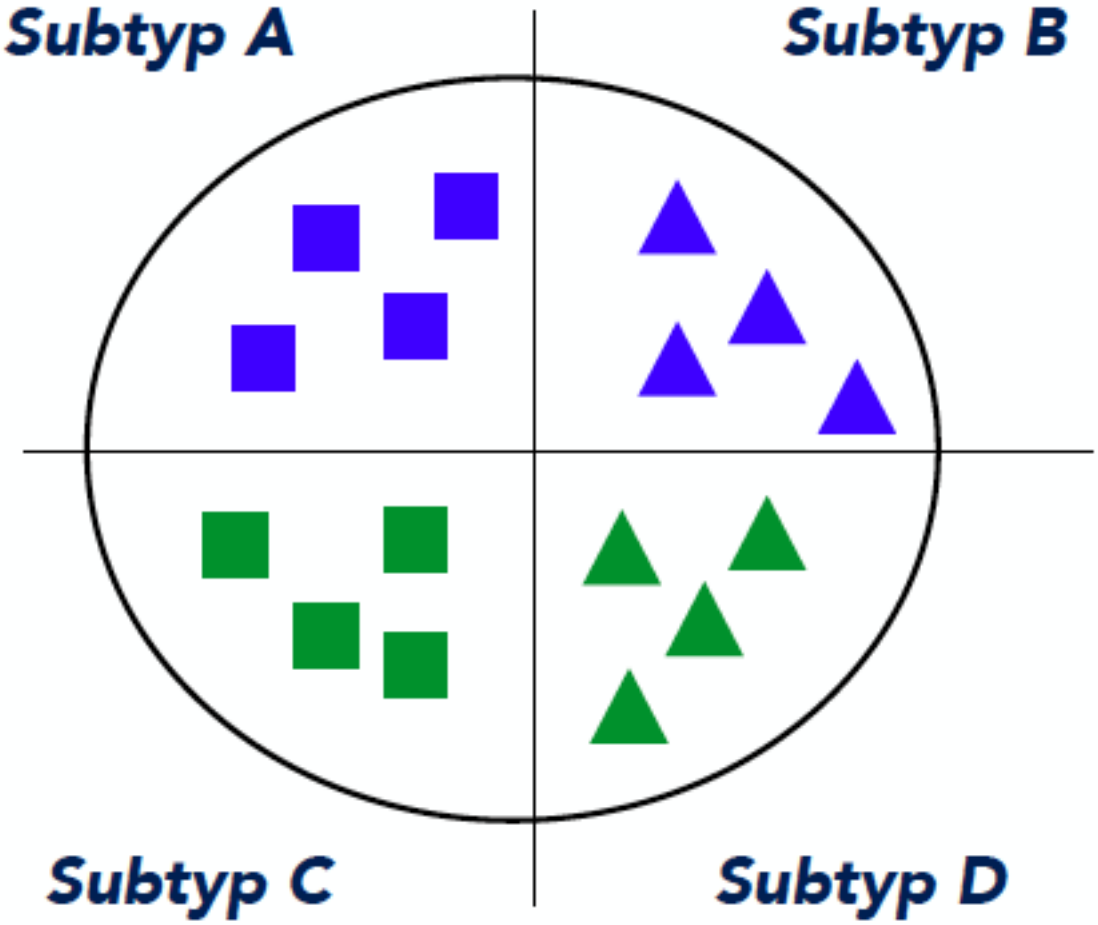
TINNET

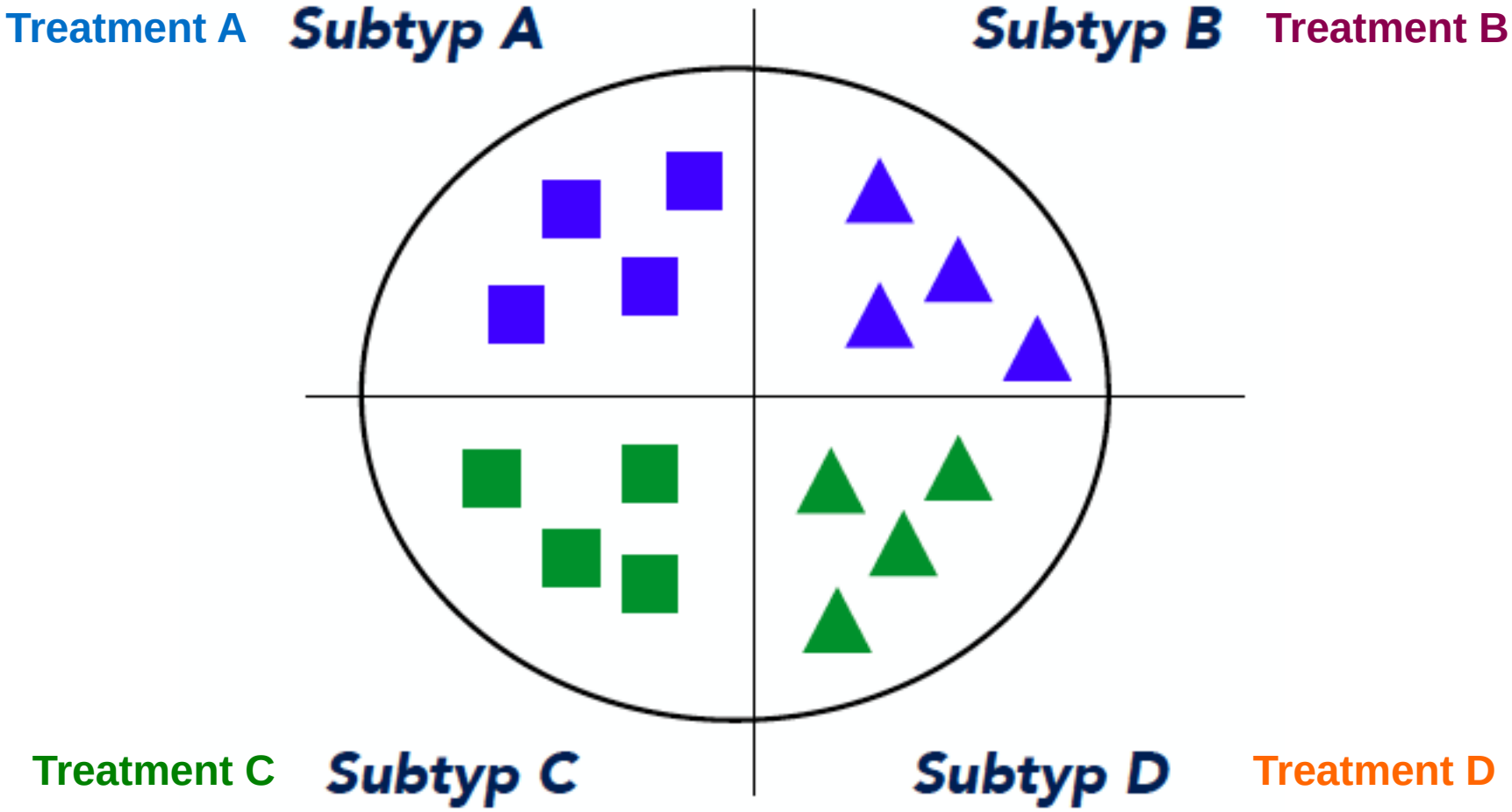
Tinnitus: no effective treatment in RCT



Tinnitus: no effective treatment in RCT



Tinnitus: no effective treatment in RCT



TINNET
Better understanding tinnitus heterogeneity

STRUCTURE

- WG1: Clinical
- WG2: Data Base
- WG3: Neuroimaging
- WG4: Genetics
- WG5: Outcome Measures

OBJECTIVES

(1) **Clinical and audiological** assessment of tinnitus patients according to common standards

(2) Data management in a **central database** and identification of subtype candidates

(3) Developing **standards for neuroimaging studies** and probing the neurobiological entity of the defined subtypes by large-scale analyses of neuroimaging data

(4) Identifying the **involvement of genetic factors** in the pathogenesis of the different subtypes of tinnitus

(5) Development of **standards for outcome measurements** in clinical trials

TINNET
Better understanding tinnitus heterogeneity

STRUCTURE

	Members	Chairs
WG1: Clinical	87	Rilana Cima, Haúla Haider
WG2: Data Base	33	Berthold Langguth, Michael Landgrebe
WG3: Neuroimaging	54	Pim van Dijk, Sven Vanneste
WG4: Genetics	21	Antonio Lopez-Escamez, Christopher Cederoth
WG5: Outcome Measures	43	Deborah Hall, Alain Londero

TINNET
Better understanding tinnitus heterogeneity

TINNET

TINNET key persons

29 European Countries
> 200 members

Chair, Vice-Chair	Winfried Schlee, Tobias Kleinjung
WG1	Rilana Cima, Haúla Haider
WG2	Berthold Langguth, Michael Landgrebe
WG3	Pim van Dijk, Sven Vanneste
WG4	Antonio Lopez-Escamez, Christopher Cederoth
WG5	Deborah Hall, Alain Londero
STSM Coordinator	Malgorzata Wrzosek
Dissemination Manager	Martin Meyer
Promoter for gender balance and equality	Tobias Kleinjung
Grant Holder	Berthold Langguth
Task Force (TF) Animal Research	Christopher Cederroth, Arnaud Norena
TF Patients' organizations	Isabel Diges
TF Companies	David Baguley
TF EU Grant Proposals	Dimitrios Kikidis

TINNET
Better understanding tinnitus heterogeneity

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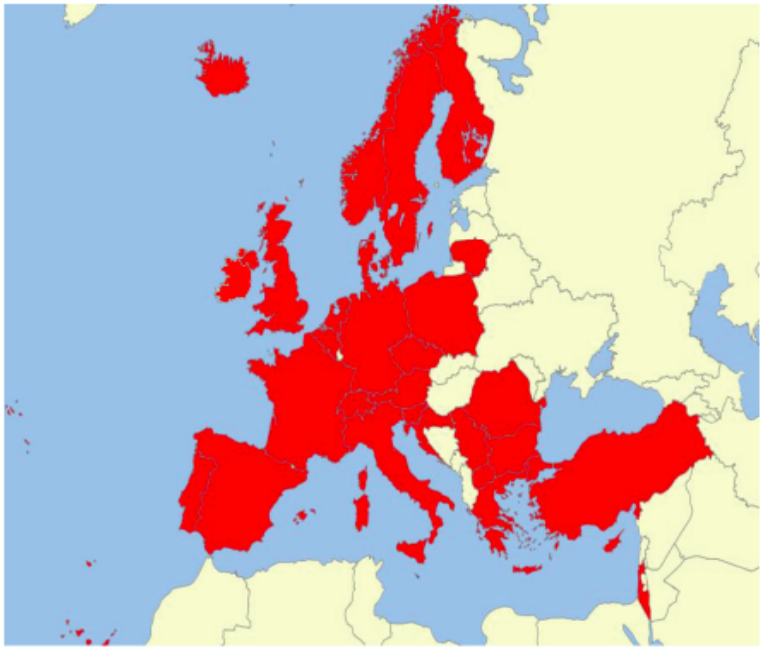
Funding by COST

almost only for travel costs



29 European Countries
> 200 members

Our „tools“:

1) **Meetings**
   Workgroup meetings, Management Committee, Workshops
2) **Short-Term Scientific Missions (STSM)**
   (Young) scientists visit a lab in another country
3) **Training schools**
   mostly for young scientists
4) **Dissemination activities**
   open access publication fees (if authors are from 3 different countries)

Project duration: 4/2014 - 4/2018

TINNET
Better understanding tinnitus heterogeneity

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If TINNET is just a European project - it will fail.

OBJECTIVES

(1) **Clinical and audiological** assessment of tinnitus patients according to common standards

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(4) Identifying the **involvement of genetic factors** in the pathogenesis of the different subtypes of tinnitus

(5) Development of **standards for outcome measurements** in clinical trials

TINNET
Better understanding tinnitus heterogeneity

frontiers Research Topics

Towards an Understanding of Tinnitus Heterogeneity

Edited by: Peyman Adjamian, Jianxin Bao, Christopher R. Cederroth, Rilana Cima, Silvano Gallus, Deborah Hall, Berthold Langguth, Tobias Kleinjung, Jose Antonio Lopez Escamez, Birgit Mazurek, Martin Meyer, Antonello Moriotti, Arnaud Norena, Heidi Olze, Thomas Probst, Rüdiger Pryss, Manfred Reichert, Winfried Schlee, Grant Searchfield, Raj Shekhawat, Bård Støve, Pim Van Dijk, Sven Vanneste, Nathan Weisz.

Submission deadlines:
Manuscript: 15th October 2016

Participating journals:
Spanning all relevant journals in the Frontiers in series, including *Frontiers in Aging Neuroscience, Frontiers in Neuroscience, Frontiers in Behavioral Neuroscience, Frontiers in Integrative Neuroscience, Frontiers in Neurology - Neuropharmacology, Frontiers in Public Health – Epidemiology, Frontiers in Psychiatry, Frontiers in Psychology, Frontiers in Genetics, Frontiers in Pharmacology*

TINNET Genetics WG4

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Low evidence on tinnitus heritability

- Prevalence chronic tinnitus 10-30%
- Age-dependent increase
- No data for ethnic differences
- No twins studies
- Genetic studies are underpowered, no replicated
- Case-control design based in candidate gene approach

TINNET Genetics WG4

Evidences on tinnitus heritability

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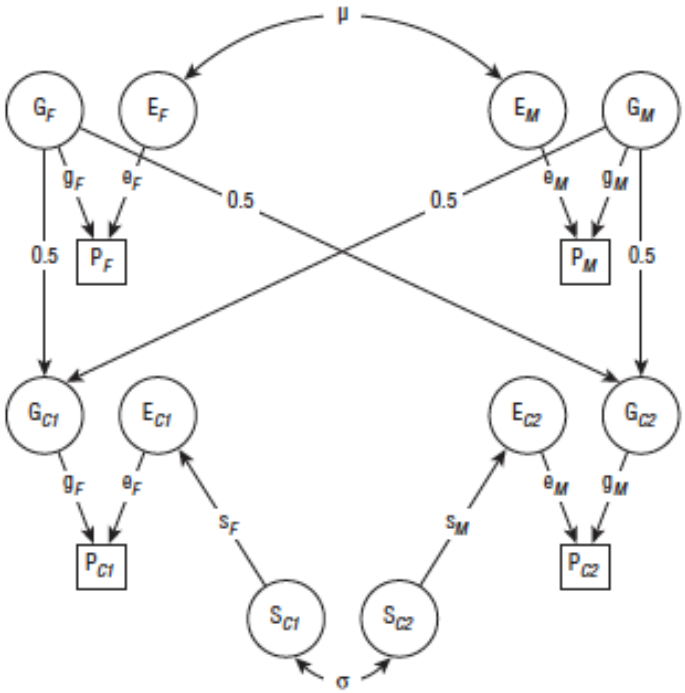
Familial aggregation studies

Norway N=28066

- Low heritability 0.11
- Environmental effect in sibling only in men

European N=981 (198 families)

- Low heritability 0.15
- Higher prevalence in men 21%

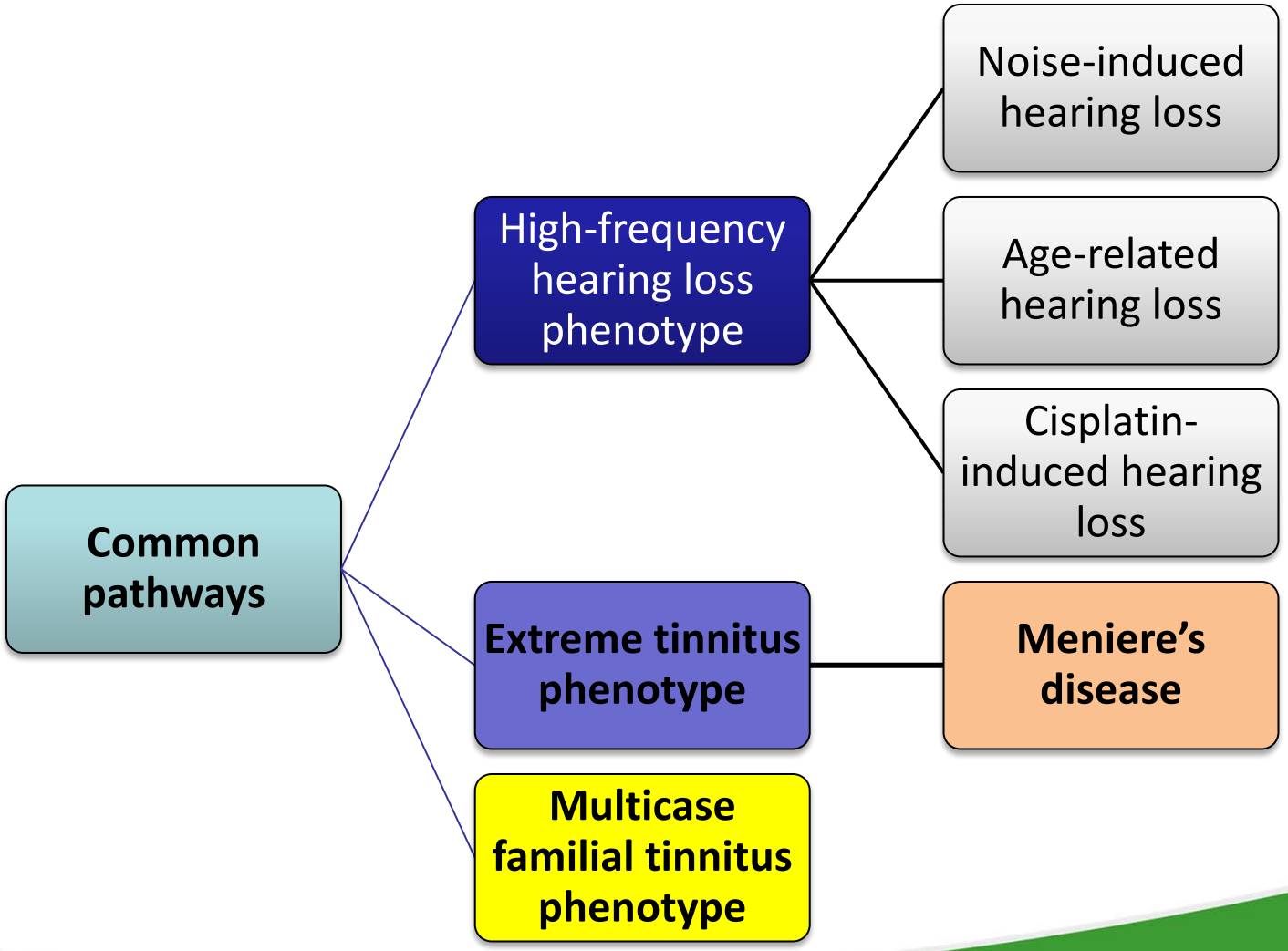


Tinnitus is a **symptom** described in a **heterogeneous group of diseases** and the heritability could differ substantially **depending on the underlying disease**

Kvestad E, Czajkowski N, Engdahl B, Hoffman HJ, Tambs K. Low heritability of tinnitus: results from the second Nord-Trøndelag health study. Arch Otolaryngol Head Neck Surg. 2010 Feb;136(2):178–82.

TINNET Genetics WG4

Strategy for tinnitus phenotyping



TINNET Genetics WG4

Strategy for genetic studies on tinnitus

1. Twin studies: Swedish twin cohort >60000 twins
2. Multicase families with tinnitus phenotype
3. Extreme tinnitus phenotype in Meniere disease
4. Identification of common genes and pathways
5. Molecular diagnosis and drug development

Lopez-Escamez JA, Bibas T, Cima RFF, Van de Heyning P, Knipper M, Mazurek B, et al. Genetics of Tinnitus: An Emerging Area for Molecular Diagnosis and Drug Development. Front Neurosci. 2016 Aug 19;10(41):129.

Otology & Neurotology Group CTS495- Genomics of vestibular disorders

Genomics of vestibular disorders Lab at Granada

- Juan Manuel Espinosa
- Teresa Requena
- Lidia Frejo
- Alvaro Gallego
- Alejandra Estepa
- Juan Antonio Zarza

Meniere disease, a set of rare disorders

Contact: antonio.lopezescamez@genyo.es

#ALEscamez