

**28es Jornades
Federació ACAPPS
de Formació en
Modalitat Oral**



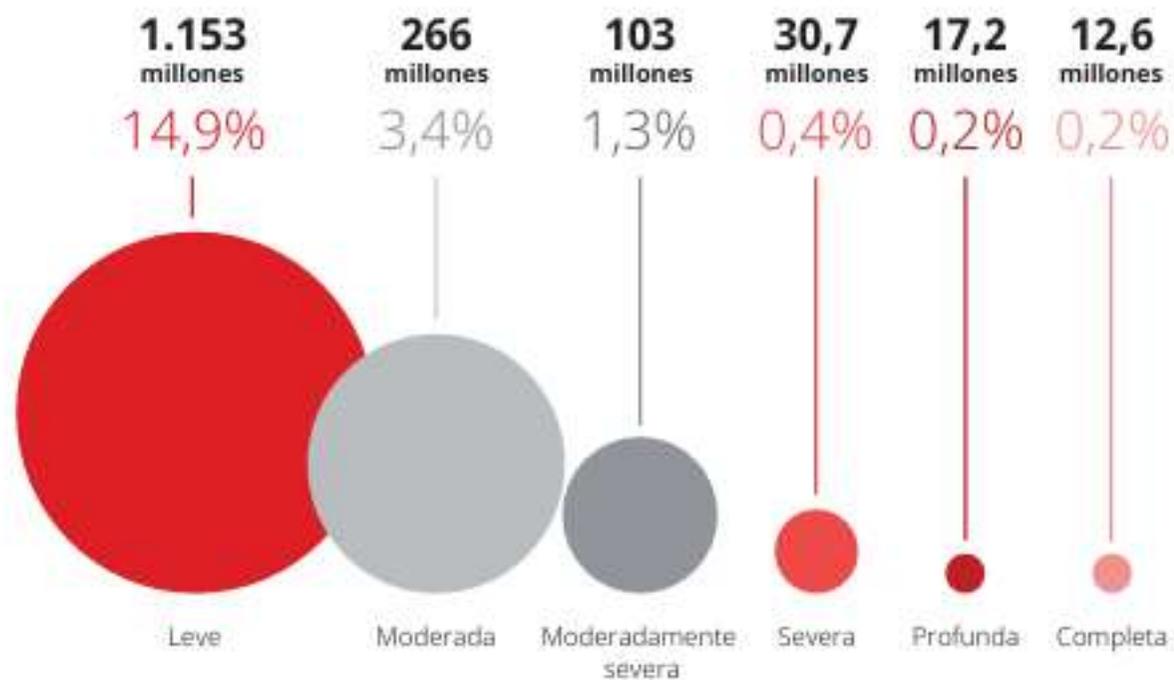
Mesa Redonda

**“Presente y perspectivas de
futuro para el tratamiento
de la sordera”**

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Centro de investigación Biomédica en Red (CIBERER)



1 El 20% de la población mundial padece algún tipo de pérdida auditiva, y en el 5% la pérdida conlleva discapacidad.



A nivel mundial, 1.500 millones de personas viven con pérdida de la audición



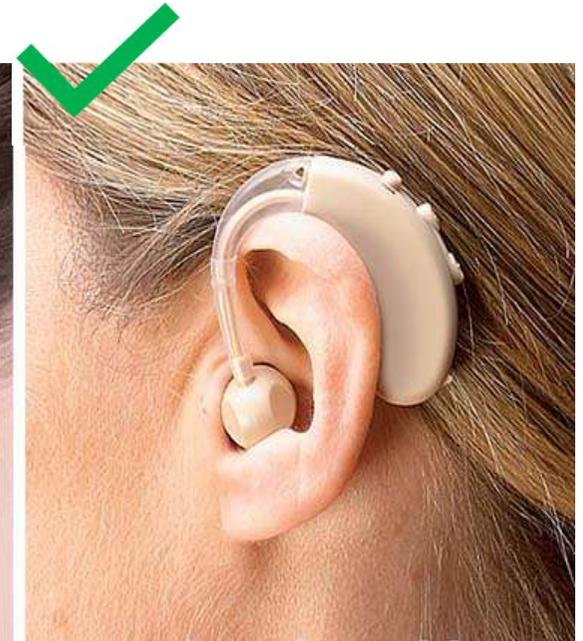
2 La pérdida auditiva dificulta la adquisición del lenguaje, el aprendizaje, el desarrollo profesional, las relaciones sociales y la salud cognitiva durante el envejecimiento.



3 No existe un tratamiento curativo disponible en la actualidad, salvo audífonos e implantes cocleares.



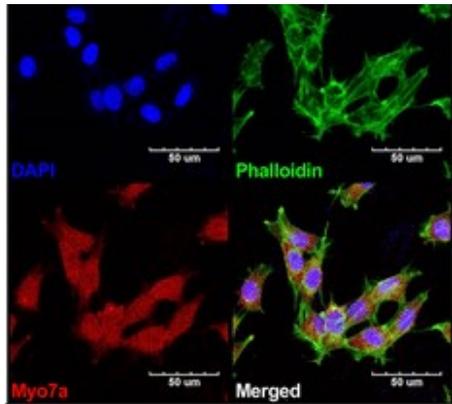
**ECHA 4 GOTAS EN
TU OÍDO Y VOLVERÁS
A ESCUCHAR COMO ANTES
RECUPERA TU AUDICIÓN**



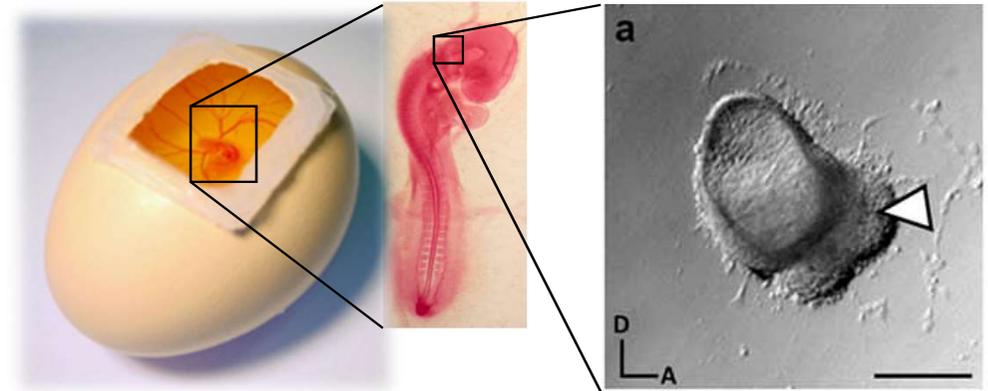


Investigación

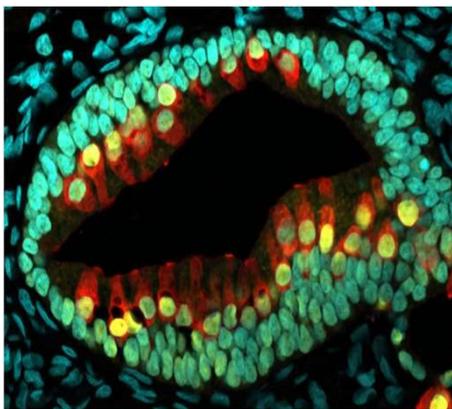
Investigamos con diversos modelos experimentales



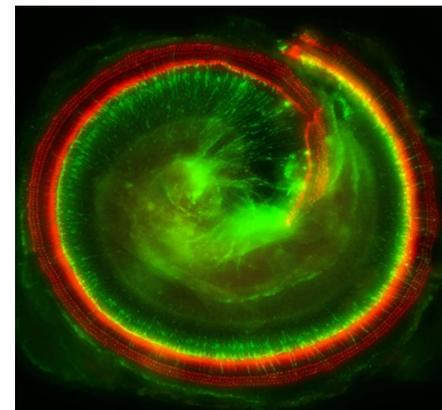
Líneas celulares



Vesícula ótica de embrión de pollo



Organoides



Explantes

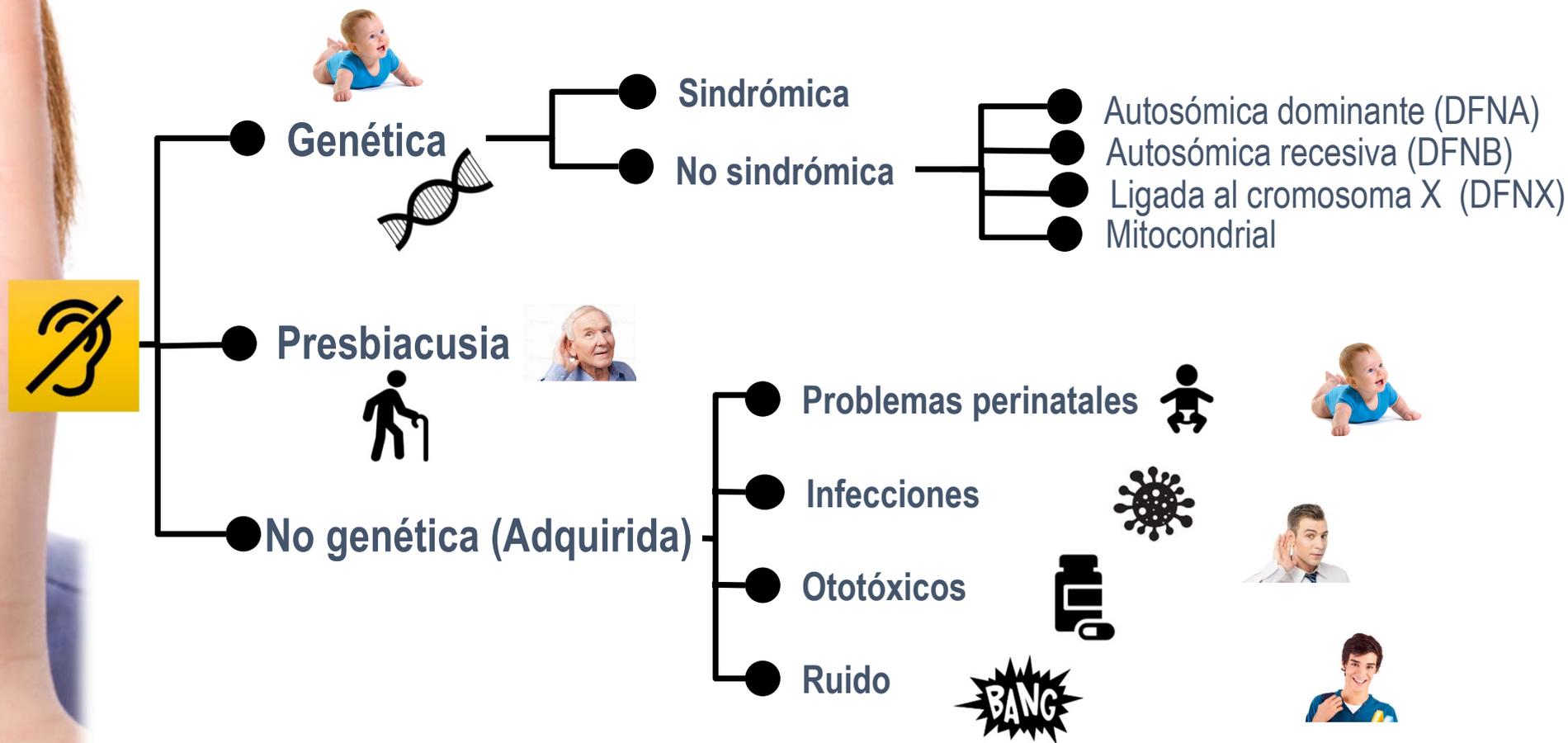


Animales



- ✓ Entender las bases genéticas, moleculares y celulares de la pérdida auditiva
- ✓ Definir nuevas dianas terapéuticas
- ✓ Evaluar la seguridad y eficacia de nuevas estrategias terapéuticas

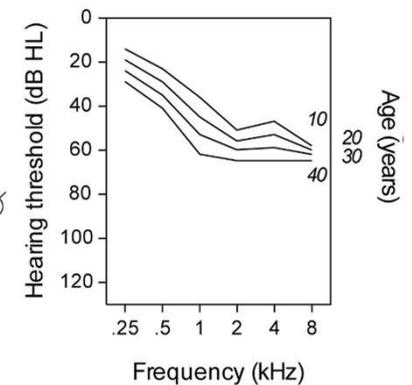
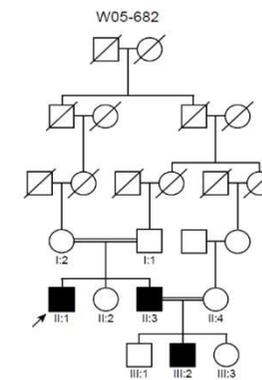
Investigamos muchos tipos de pérdida auditiva





Ejemplo 1: Hipoacusia de origen genético

- Identificación de mutaciones en el gen **MPZL2** en familias con casos de hipoacusia no sindrómica de herencia autosómica recesiva.
- Pacientes con hipoacusia moderada, con más afectación de frecuencias altas, simétrica, de inicio juvenil y progresiva.
- MPZL2 es un gen que codifica para una proteína de adhesión entre células epiteliales, pero **¿cuál es su función en la cóclea?**



Ejemplo 1: Hipoacusia de origen genético

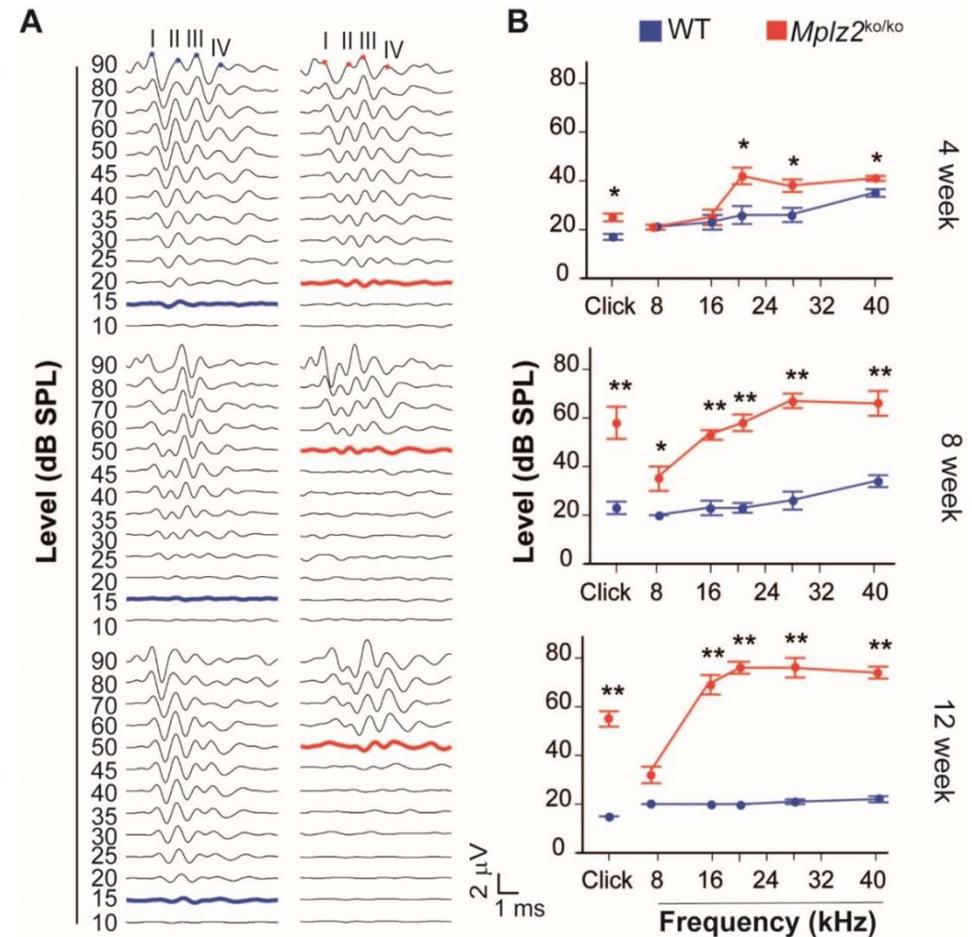
- Generación de un ratón con delección del gen homólogo (*Mpzl2*).



Mpzl2^{tm1.1Jczp/tm1.1Jczp}



- Evaluación auditive → el ratón knockout tiene el mismo tipo de hipoacusia que los pacientes.





Ejemplo 1: Hipoacusia de origen genético

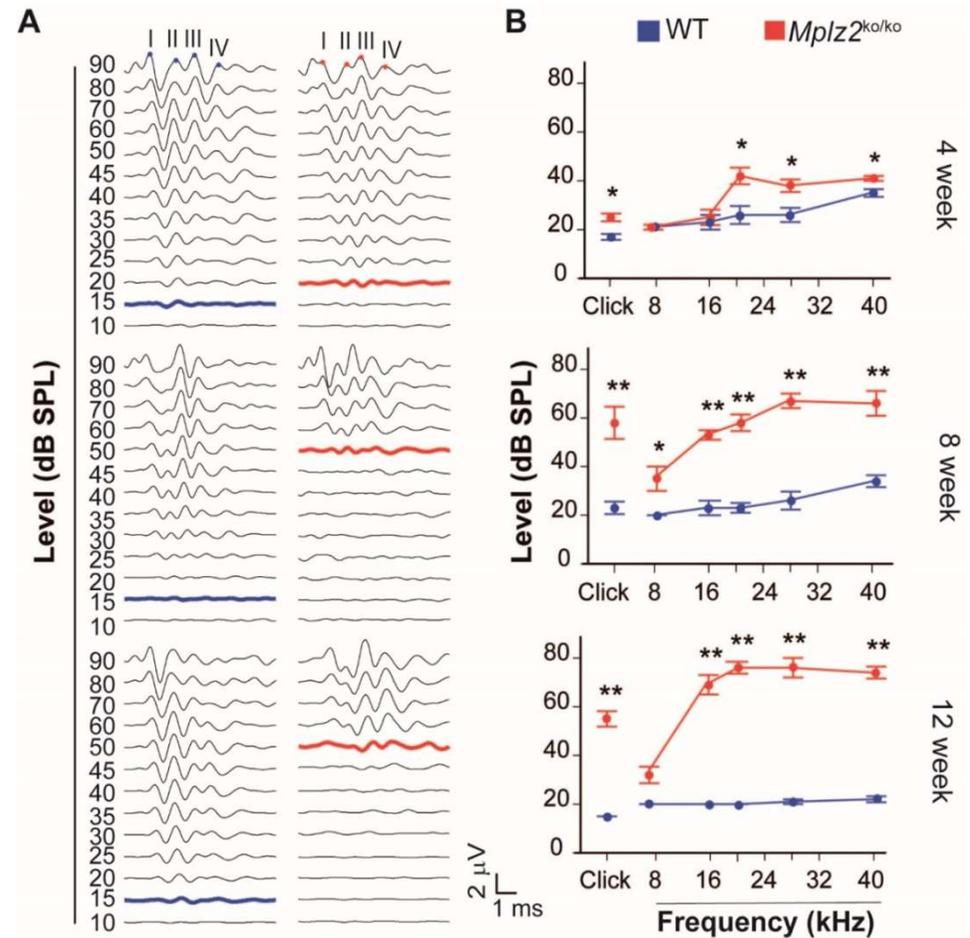
- **Generación del modelo:** ratón con deleción del gen homólogo (*Mpzl2*).



Mpzl2^{tm1.1Jczp/tm1.1Jczp}



- **Evaluación auditiva:** el ratón knockout tiene el mismo tipo de hipoacusia que los pacientes.

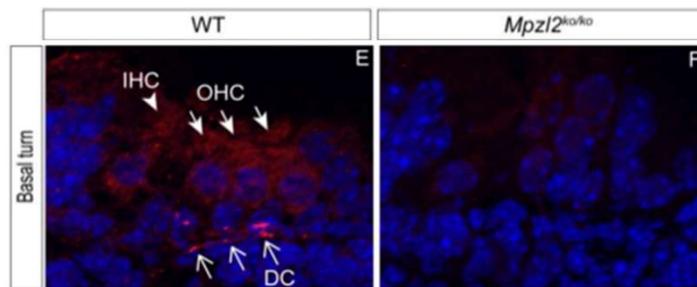




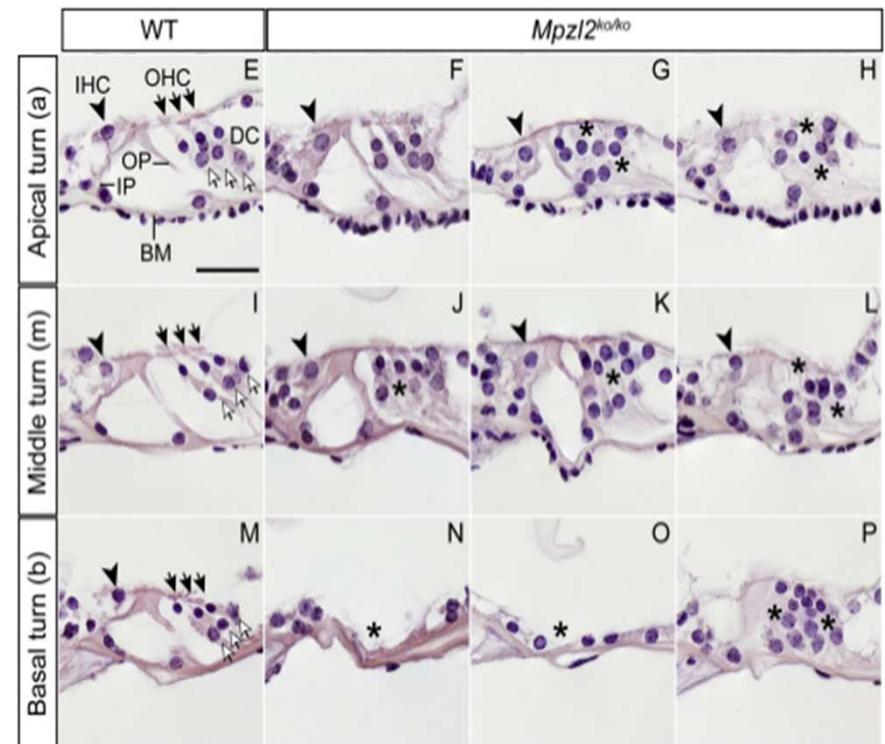
Ejemplo 1: Hipoacusia de origen genético

Evaluación morfológica:

- MPZL2 se expresa en las células de soporte de las células ciliadas externas y no está en el knockout



- El órgano de Corti en el ratón knockout está desorganizado y degenera tempranamente.





Ejemplo 1: Hipoacusia de origen genético



ARTICLE

MPZL2, Encoding the Epithelial Junctional Protein Myelin Protein Zero-like 2, Is Essential for Hearing in Man and Mouse

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In a Dutch consanguineous family with recessively inherited nonsyndromic hearing impairment (HI), homozygosity mapping combined with whole-exome sequencing revealed a *MPZL2* homozygous truncating variant, c.72del (p.Ile24Met*22). By screening a cohort of phenotype-matched subjects and a cohort of HI subjects in whom WES had been performed previously, we identified two additional families with allelic truncating variants of *MPZL2*. Affected individuals demonstrated symmetric, progressive, mild to moderate sensorineural HI. Onset of HI was in the first decade, and high-frequency hearing was more severely affected. There was no vestibular involvement. *MPZL2* encodes myelin protein zero-like 2, an adhesion molecule that mediates epithelial cell-cell interactions in several developing tissues. Involvement of *MPZL2* in hearing was confirmed by audiometric evaluation of *Mpz2*-mutant mice. These displayed early-onset progressive sensorineural HI that was more pronounced in the high frequencies. Histological analysis of adult mutant mice demonstrated an altered organization of outer hair cells and supporting cells and degeneration of the organ of Corti. In addition, we observed mild degeneration of spiral ganglion neurons, and this degeneration was most pronounced at the cochlear base. Although *MPZL2* is known to function in cell adhesion in several tissues, no phenotypes other than HI were found to be associated with *MPZL2* defects. This indicates that *MPZL2* has a unique function in the inner ear. The present study suggests that deleterious variants of *Mpz2*/*MPZL2* affect adhesion of the inner-ear epithelium and result in loss of structural integrity of the organ of Corti and progressive degeneration of hair cells, supporting cells, and spiral ganglion neurons.

Introduction

The identification of genes associated with hereditary nonsyndromic hearing impairment (NSHI) has accelerated in the last decade with the introduction of next-generation sequencing. But despite the fact that currently more than 100 deafness-associated genes are known (Hereditary Hearing Loss Homepage; see Web Resources), more than 60 percent of subjects with hereditary NSHI still cannot be genetically diagnosed.¹⁻³ These individuals and their relatives receive suboptimal care because of insufficient counseling on prognosis and recurrence risk. In addition, syndromic features can be overlooked, or in the opposite case, health-care providers perform unnecessary and costly

tests to screen for additional symptoms that are not present.

Given the number of deafness loci for which the associated gene is not known yet (Hereditary Hearing Loss Homepage), it is estimated that many monogenic forms of NSHI still await identification. Discovery of these NSHI-associated genes will contribute to the full understanding of the complex physiology of hearing. However, the search for genes associated with deafness has become more challenging because most frequently involved genes are already known and those that remain are most likely involved in less than 1 percent of the cases, or even in only one or a few families with NSHI. Also, identification of deleterious variant(s) in a single family in a gene not

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Hereditary Hearing Loss Homepage

- [Home](#)
- [About the HHL Homepage](#)
- [Citing the HHL Homepage](#)
- [Nonsyndromic Hearing Loss](#)
- [Autosomal Dominant](#)
- [Autosomal Recessive](#)
- [Sex-Linked](#)
- [Mitochondrial](#)
- [Auditory Neuropathy](#)
- [Modifiers](#)
- [Otosclerosis](#)
- [Syndromic Hearing Loss](#)
- [Updates Log](#)
- [Useful Links](#)
- [Frequently Asked Questions](#)
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Autosomal Recessive Nonsyndromic Hearing Loss

Locus (OMIM)	Gene (OMIM)	Key Locus References (PubMed)	Key Gene References (PubMed)	Evidence (ClinGen)
DFNB1A	<i>GJB2</i>	Guilford et al., 1994; Scott et al., 1995	Kelsell et al., 1997	Definitive
DFNB1B	<i>GJB6</i>	del Castillo et al., 2002; Pallares-Ruiz et al., 2002	Wich et al., 2010; Abou Tayoun et al., 2016	Refuted
DFNB2	<i>MYO7A</i>	Guilford et al., 1994	Liu et al., 1997; Weil et al., 1997	not reviewed
DFNB3	<i>MYO15A</i>	Friedman et al., 1995; Liang et al., 1998	Wang et al., 1998	Definitive
DFNB4	<i>SLC26A4</i>	Baldwin et al., 1995; Everett et al., 1997	Everett et al., 1997	Definitive
DFNB5	unknown	Fukushima et al., 1995	n/a	n/a
DFNB6	<i>TMC1</i>	Fukushima et al., 1995	Naz et al., 2002	Definitive
DFNB7.11	<i>TMC1</i>	Jain et al., 1995; Scott et al., 1996	Kurima et al., 2002	Definitive
DFNB8.10	<i>TMPRSS3</i>	Veske et al., 1996; Bonnè-Tamir et al., 1996; Berry et al., 2000	Scott et al., 2001	Definitive
DFNB9	<i>OTOF</i>	Chab et al., 1996	Yasunaga et al., 1999	Definitive
DFNB12	<i>CDH23</i>	Chab et al., 1996	Bork et al., 2001	Definitive
DFNB13	unknown	Mustapha et al., 1998; Masmoudi et al., 2004	n/a	n/a
DFNB14	unknown	Mustapha et al., 1998	n/a	n/a
DFNB15/72/95	<i>GIPC3</i> (see note 1)	Chen et al., 1997; Ain et al., 2007; Charizopoulou et al., 2011	Charizopoulou et al., 2011; Rehman et al., 2011	Definitive
DFNB16	<i>STRC</i> (see note 2)	Campbell et al., 1997; Villamar et al., 1999	Verpy et al., 2001	Definitive
DFNB17	unknown	Greinwald et al., 1998; Guo et al., 2004	n/a	n/a
DFNB18A	<i>USH1C</i>	Jain et al., 1998	Verpy et al., 2000	Limited
DFNB18B	<i>OTOF</i>	Scharders et al., 2012	Kurima et al., 2012	Definitive
DFNB20	unknown	Moynihan et al., 1999	n/a	n/a
DFNB21	<i>TECTA</i>	Mustapha et al., 1999	Bork et al., 1999	Definitive
DFNB22	<i>OTOA</i>	Zwaanepoel et al., 2002	Zwaanepoel et al., 2002	Definitive
DFNB23	<i>PCDH15</i>	Ahmed et al., 2003	Ahmed et al., 2003	Limited
DFNB24	<i>RDX</i>	Khan et al., 2007	Khan et al., 2007	Definitive
DFNB25	<i>GRXCR1</i>	Schraders et al., 2010	Schraders et al., 2010	Definitive
DFNB26 (see note 3)	<i>GAB1</i>	Riscuadín et al., 2000	Yousaf et al., 2018	not reviewed

DFNB107	<i>MPZL2</i>	Booth et al., 2018	Booth et al., 2018	Limited
DFNB108	<i>ROR1</i> (see note 9)	Diaz-Horta et al., 2016	Diaz-Horta et al., 2016	Limited
DFNB109	<i>ESRPI</i>	Rohacek et al., 2017	Rohacek et al., 2017	not reviewed
DFNB110	<i>COCH</i>	JanssensdeVarebeke et al., 2018	JanssensdeVarebeke et al., 2018	not reviewed
DFNB111	<i>MPZL2</i>	Wesporp et al., 2018; Bademci et al., 2018	Wesporp et al., 2018	Strong
DFNB113	<i>CEACAM16</i>	Booth et al., 2018	Booth et al., 2018	Strong
DFNB114	<i>GRAP</i>	Li et al., 2019	Li et al., 2019	not reviewed
DFNB115	<i>SPNS2</i>	Ingham et al., 2019	Ingham et al., 2019	not reviewed



Ejemplo 2: Hipoacusia inducida por ruido

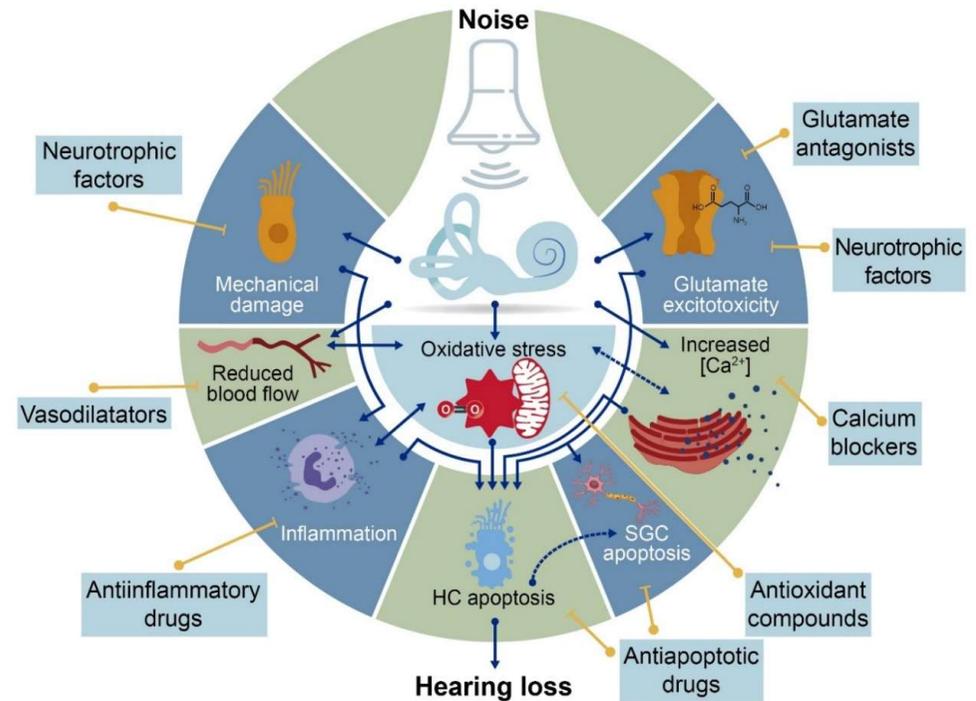
- Es la hipoacusia más frecuente en **adultos**, y la enfermedad profesional más prevalente.
- Aumento del riesgo en **jóvenes** por exposición a ruido recreativo.
- Es una hipoacusia “evitable” si no supera el límite de seguridad **85 dB** durante **8 horas** al día.



Niveles de ruido		dB(A)	
Riesgo	A partir de 75 dB(A) puede haber alteraciones auditivas	105	Concierto
		95	
Saludable		85	Aspiradora
		75	Conversación, TV, música
		65	
Concentración	Evitar sobrepasar los 55 dB(A)	55	Sala de estudio
		45	Dormitorio
Descanso		35	

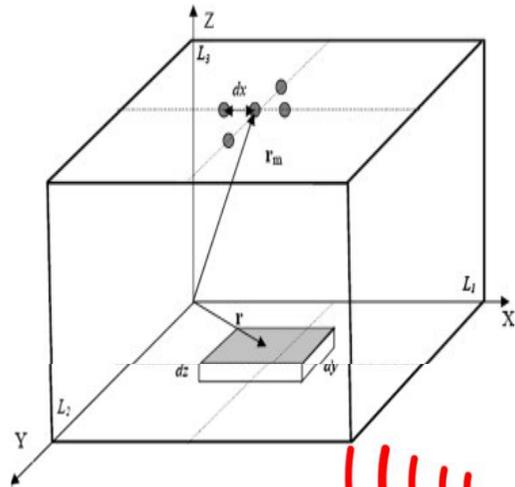
Ejemplo 2: Hipoacusia inducida por ruido

- El ruido desencadena diversos mecanismos que dan lugar a **daños irreversibles** en el oído .
- Se han identificado numerosas dianas terapéuticas a las que dirigir nuevos tratamientos.
- Los ratones se exponen a ruido intenso en cámaras reverberantes.

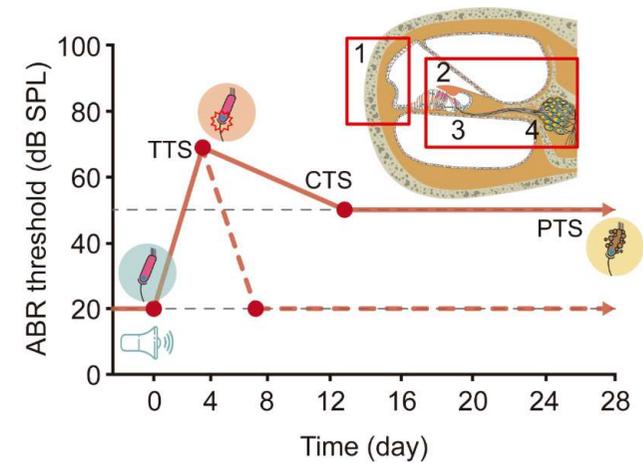




Ejemplo 2: Hipoacusia inducida por ruido



Altas frecuencias
 2-22 kHz
 100-110 dB SPL
 Despiertos
 Individualizados
 Durante 30 minutos



Control

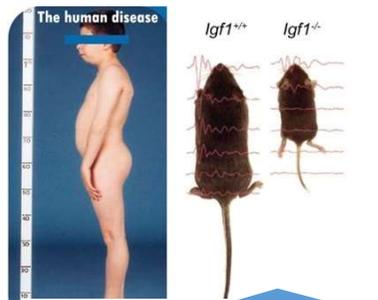


Ruido



Tratamiento

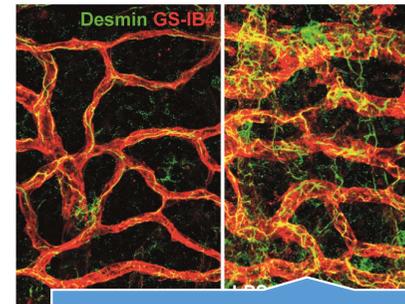
Y otros muchos ejemplos....



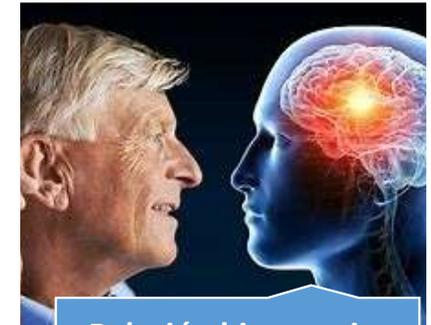
Hipoacusias
sindrómicas (raras)



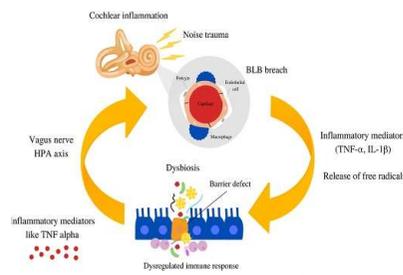
Hipoacusia por
ototoxicidad-cisplatino



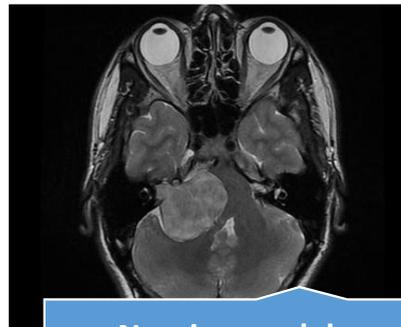
Hipoacusias
autoinflamatorias



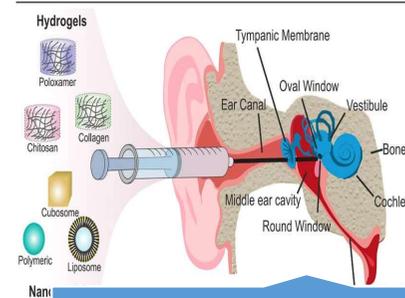
Relación hipoacusia-
deterioro cognitivo



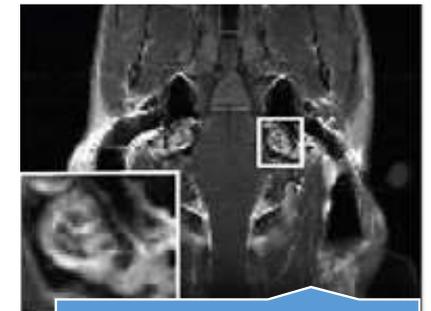
Hipoacusia y
microbiota



Neurinoma del
acústico



Sistemas de
administración



Diagnóstico por
imagen

Miembros actuales

Isabel Varela-Nieto (PI)
Rafael Cediel
Julio Contreras
Ana M Jimenez
José M. Cosgaya
Sandra Franco
Carmen Ruiz
Carmen G^a Montoya
Ludi Blanco

Miembros pasados

Hortensia S. Calderón
Guadalupe Camarero
Ada M. Celaya
Blanca A. Cervantes
Rocío de Iriarte
Yolanda León
Marta Magariños
Raquel Mtnz. Vega
Lourdes R. de la Rosa
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Jing Wang (INSERM)
María R. Aburto (APC Microbiome)

Instituciones

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COST Action Proteocure
COST Action BenBedPhar
FEDER/MICIN PID2020 THEARPY
MULTARGET & VIEW
MINA-Neurotech Alliance CAM
Inflammasome Network
NANOMED CSIC Connection
RER Biomedicine CSIC
Spiral Therapeutics



Gracias

