

Sana Amanat¹, Jose Antonio Lopez-Escamez^{1,2}

¹ Otolaryngology & Neurotology Group CTS495, Department of Genomic Medicine, GENyO - Centre for Genomics and Oncological Research – Pfizer/University of Granada/ Junta de Andalucía, PTS, Granada, Spain

² Department of Otolaryngology, Instituto de Investigación Biosanitaria ibs. GRANADA, Hospital Universitario Virgen de las Nieves, Universidad de Granada, Granada, Spain

What is tinnitus?

Tinnitus is the perception of sound when no external sound exists but you hear it. Perception means the way you regard or interpret this sound. Tinnitus affects more than 15% of the general population and is more common in older adults compared to younger adults. Tinnitus patients also exhibit some associated factors including hearing loss, migraine, sleep disorders, discomfort, distress, anxiety and depression^{1,2}.

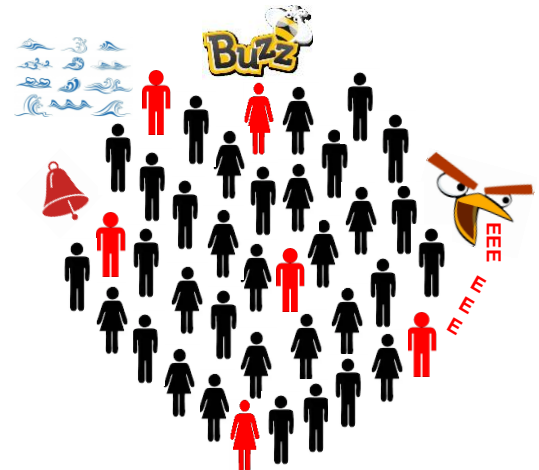


Figure 1: Black icon shows controls (*patients without tinnitus*) and red indicates tinnitus patients with different perception of sound.

"You are not alone in the struggles of life. Entire cosmos is with you. It evolves through the way you face and overcome challenges of life. Use everything in your advantage." **Amit Ray**

Tinnitus can take various forms such as ringing, beeping, humming, buzzing or hissing in the ear and varies from person to person, see Figure 1. It could affect one ear (unilateral) or both (bilateral)². It can be sporadic if you are the only one with tinnitus in the family, or familial if other family members are also affected e.g. parents or siblings. See Figures 2 and 3 to get an idea if your tinnitus is inherited or not.

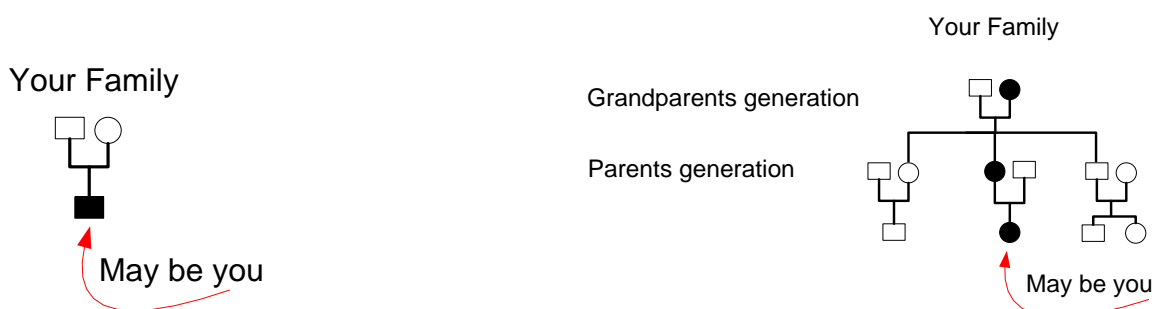
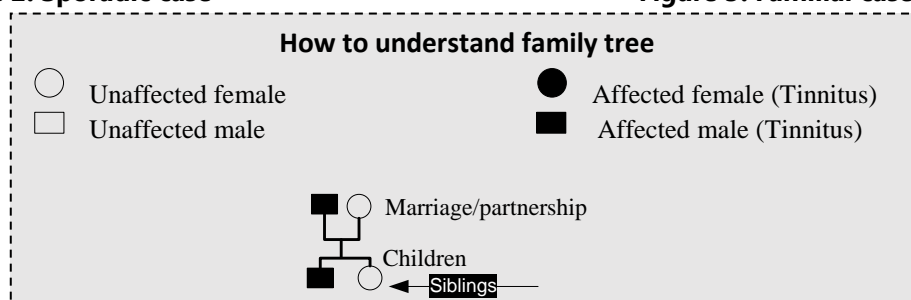


Figure 2. Sporadic case

Figure 3. Familial case



Classification of tinnitus:

Tinnitus can be classified as objective and subjective tinnitus³. Objective tinnitus can be heard by an observer, maybe using a stethoscope. Subjective tinnitus is the most common form of tinnitus, but unfortunately only you can hear it. Almost 95%⁴ of tinnitus cases have subjective tinnitus. Other than this, the detailed information on tinnitus flowchart for patient management is provided by Tinnitus Research Initiative (TRI)⁵.

How tinnitus is generated?

There are many hypotheses on tinnitus mechanisms or how tinnitus is generated, such as:

1. Tinnitus might be generated due to a turbulent flow of blood in jugular vein or muscle contraction in the head⁶.
2. The damaged cochlea hair cells and their synapses at the cochlear nerve in the inner ear can also cause tinnitus. These damaged hair cells randomly move and generate signals which are interpreted by the brain as sound; then you hear tinnitus⁶. Some people, however, without damaged hair cells also have tinnitus. So, this is not the only cause of tinnitus.
3. A reorganisation of synaptic networks in the brain has been observed in most tinnitus patients. The loss of peripheral input produces an increase of the gain in the auditory pathway that became independent of hearing loss.

Tinnitus in Meniere's disease

Meniere's is a rare and complex disorder characterised by episodes of vertigo, sensorineural hearing loss, tinnitus or aural fullness. Vertigo attacks are associated with unilateral low frequency hearing loss, tinnitus and aural fullness. It can be unilateral or bilateral⁷. Tinnitus in Meniere's is well described by a low pitch narrow band of noise and it is reported as a troublesome symptom by most of the Meniere's patients. However, Meniere's can be with or without tinnitus and the major hypothesis involved is the damaged hair cells in inner ear. There are several factors associated with the pathophysiology of Meniere's disease⁸; some of them are shown in Figure 4.

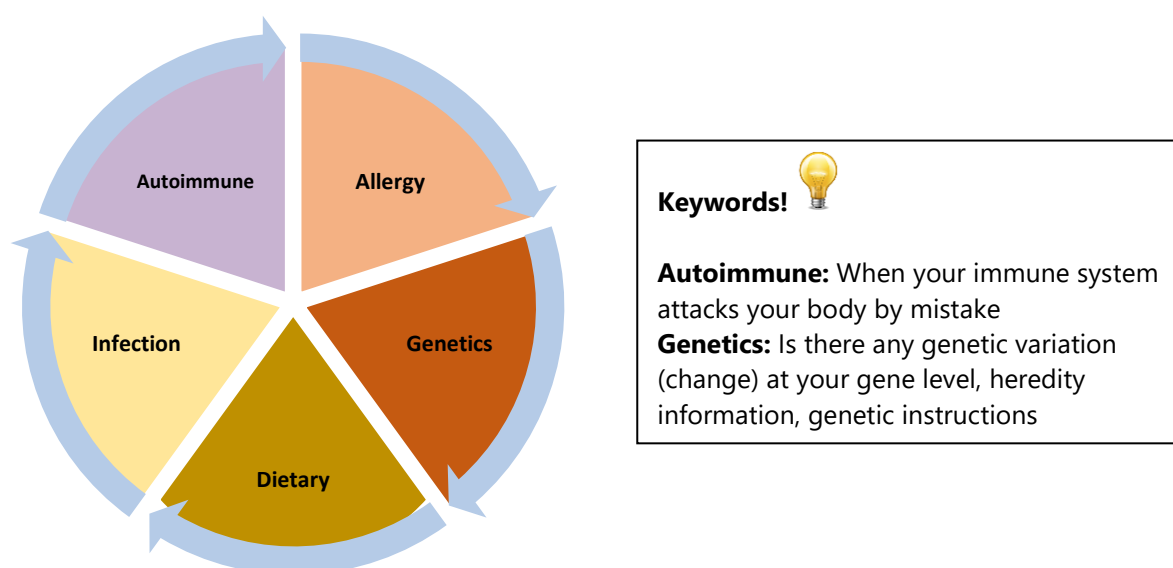


Figure 4: Some factors involved in Meniere's



Is tinnitus associated with other diseases?

Tinnitus can also occur together with other diseases⁸ as shown in Figure 5. It is said that tinnitus is also associated with autism in terms of hallucination (individuals hear unrealistic or superficial voices), but very limited information is available on it.

This means tinnitus and Meniere's both have a heterogeneous (diverse) nature and the careful selection of patients is very important in terms of severity level, age of onset and family history etc.

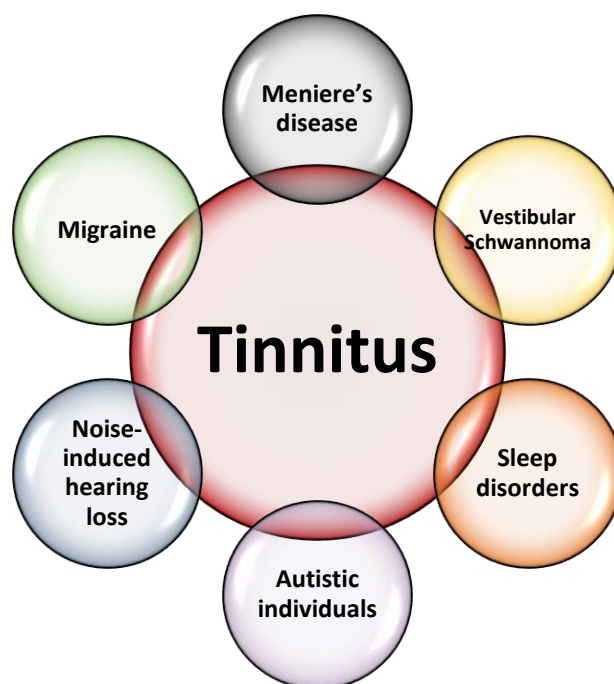


Figure 5: Tinnitus with other conditions

A pinch of new information!

Do you know there are some genetic factors associated with tinnitus and Meniere's?

Meniere's is a complex disorder which means there is more than one gene involved and also some environmental factors which play an important role⁷. The field of genetics is not new and many researchers have been working to identify the underlying genetic cause of tinnitus and Meniere's. Meniere Disease Consortium (MediC)⁹ has defined five clinical subgroups of patients for unilateral and bilateral Meniere's. Due to this clinical heterogeneity it is very difficult to investigate your DNA sequences (genetic information in your DNA) to know if a particular type of change has occurred in your DNA or not? This change could be the deletion of useful information or the addition of harmful information in your DNA. Maybe this change in your DNA has contributed to tinnitus/Meniere's. This small change in your DNA which makes you different from a control could be inherited from your affected parents. The inherited pattern in Meniere's is not very clear due to the complex and heterogeneous nature of this condition.



Let's consider your DNA contains four different types of genetic instructions A,G,T,C and these letters have some biological meanings. Don't worry, if you are not familiar with biological terms. Just assume, these instructions contain very important information used to regulate (for growth and function) your body. Here are a few examples on what your genetic information looks like and what kind of change might happen at your DNA level.

Example 1: Change/Substitution of information

Control	AAAGTGTATATGCTC
	↓
Tinnitus/Meniere's case	AAAGTTTATATGCTC

Example 2: Addition of harmful information

Control	AAAGTGTATATGCTC
	↙
Tinnitus/Meniere's case	AAAGTGGGTTTCTTATATGCTC

Example 3: Deletion of useful information

Control	AAAGTGTATATGCTC
	⏟
Tinnitus/Meniere's case	AAA - - -TATATGCTC

There are several genetic studies which have investigated the genetic susceptibility to tinnitus/Meniere's and evidenced the heritability in different populations. In 2015, a study was performed on Spanish family with a female Meniere's case in three consecutive generations. This research team found two novel mutations (change in DNA sequence) in this family and evidenced the genetic heritability¹⁰.

Two years later, Swedish twin cohorts were recruited for a study and found that there is heritability to bilateral tinnitus in both sexes. But when they selected bilateral tinnitus cases with an age less than 40 years; there was an observed increase in heritability from 41% to 62% in female cases, and that was incredible¹.

In 2019, some researchers investigated if there is some environmental factor or genetic susceptibility involved in tinnitus? For this study, they recruited Swedish-born adoptees, adoptive parents and biological parents for research. From this study the researchers found that both environmental and genetic factors, associated with the transmission of tinnitus, contributed to tinnitus heritability¹¹.



What could be done for your tinnitus?

There are few suggestions recommended by the NHS for tinnitus, such as:

1. Sound therapy known as tinnitus retraining therapy that might be helpful for tinnitus cases.
2. Cognitive behaviour therapy could play an important role to reduce the anxiety that tinnitus causes you and maybe you start thinking differently (a bit positive) for your tinnitus.
3. Through tinnitus counselling sessions you can know more about tinnitus and can identify the way to deal with tinnitus.

For more information about prevention and treatment for tinnitus you may also wish to visit the following websites:

- NHS <https://www.nhs.uk/conditions/tinnitus/>
- British Tinnitus Association <https://www.tinnitus.org.uk/>

How genetic studies would be helpful?

Many patients hope their GP/ENT specialist will offer them medication for their tinnitus.

Unfortunately, to-date effective drugs are not available for tinnitus and the need for such a drug is increasing day by day.

These genetic studies would be helpful for drug development by providing different molecular targets such as genetic variant information in a particular gene.¹²

What are we doing for you?

The European School for Interdisciplinary Tinnitus Research (ESIT) started 15 different projects in 2017, with the aim to improve the situation of more than 42 million European tinnitus patients. Under the ESIT projects, the scientists are developing new treatment solutions for tinnitus including genetic studies. One of the ESIT projects is dedicated for tinnitus in Meniere's patients under Otology & Neurotology- Genomics of vestibular disorders group, GENyO, Granada, Spain. This research group has been actively working on vestibular disorders since 2005.



References:

1. Maas IL, Brüggemann P, Requena T, et al. Genetic susceptibility to bilateral tinnitus in a Swedish twin cohort. *Genet Med*. 2017;19(9):1007-1012. doi:10.1038/gim.2017.4
2. Vona B, Nanda I, Shehata-Dieler W, Haaf T. Genetics of tinnitus: Still in its infancy. *Front Neurosci*. 2017. doi:10.3389/fnins.2017.00236
3. Ueberfuhr MA, Wiegrebe L, Krause E, Gürkov R, Drexl M. Tinnitus in normal-hearing participants after exposure to intense low-frequency sound and in Ménière's disease patients. *Front Neurol*. 2017;7(JAN):1-11. doi:10.3389/fneur.2016.00239
4. Fournier P, Cuvillier AF, Gallego S, et al. A New Method for Assessing Masking and Residual Inhibition of Tinnitus. *Trends Hear*. 2018;22:1-19. doi:10.1177/2331216518769996
5. Tinnitus Research Initiative (TRI) <https://www.tinnitusresearch.net/index.php/for-clinicians/diagnostic-flowchart>.
6. Møller AR. Pathophysiology of tinnitus. *Otolaryngol Clin North Am*. 2003;36(2):249-266. doi:10.1016/S0030-6665(02)00170-6
7. Lopez- JA, Carey J, Chung H, et al. Diagnostic criteria for Menière ' s disease. (Icvd):1-15.
8. Møller AR, Langguth B, DeRidder D, Kleinjung T, editors. Textbook of tinnitus. *Springer Science & Business Media*; 2010 Nov 16.
9. Frejo L, Soto-Varela A, Santos-Perez S, et al. Clinical subgroups in bilateral meniere disease. *Front Neurol*. 2016;7(OCT):1-10. doi:10.3389/fneur.2016.00182
10. 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. *Hum Mol Genet*. 2015;24(4):1119-1126. doi:10.1093/hmg/ddu524
11. Cederroth CR, Pirouzifard M, Trpchevska N, et al. Association of Genetic vs Environmental Factors in Swedish Adoptees with Clinically Significant Tinnitus. *JAMA Otolaryngol - Head Neck Surg*. 2019;145(3):222-229. doi:10.1001/jamaoto.2018.3852
12. Lopez-Escamez JA, Bibas T, Cima RFF, et al. Genetics of tinnitus: An emerging area for molecular diagnosis and drug development. *Front Neurosci*. 2016;10(AUG):1-13. doi:10.3389/fnins.2016.00377



Contact the Ménière's Society for information and support

01306 876883

info@menieres.org.uk

menieres.org.uk

About the Meniere's Society: The Ménière's Society is the only UK registered charity dedicated solely to supporting people with vestibular disorders causing dizziness and imbalance. We have over 30 years' experience providing information to those affected by these conditions and those who care for them, health professionals and the general public. Our work also raises awareness of the huge impact these distressing and debilitating conditions have on people's day to day lives. The Ménière's Society funds vital research in the field and is pleased to have invested over £1million into research to-date. For more information about our work, please visit <https://www.menieres.org.uk/>

Disclaimer: The Ménière's Society recommends that you always consult your GP, consultant or therapist for professional guidance before you begin, change, temporarily suspend or discontinue any treatment, medication, exercise or diet. The Society cannot advise on individual cases nor accept any liability resulting from the use of any treatments referred to in this information sheet. Information correct at time of publication.

This factsheet may be printed, photocopied, downloaded or distributed free of charge provided the Meniere's Society is properly credited and no profit gained from its use. Permission to reproduce in any other way must be obtained from the Meniere's Society. For further information or additional copies of our factsheets, please contact us (details below).

© Meniere's Society 2019

Registered charity number 297246



Ménière's Society The Rookery, Surrey Hills Business Park, Wotton, Dorking, Surrey RH5 6QT

+44 (0) 1306 876 883 | info@menieres.org.uk | www.menieres.org.uk | RCN 297246

Follow us: Facebook: facebook.com/menieressociety | Twitter: @menieressociety | Instagram: menieressociety