





TINNITUS

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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).

"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 ifyou 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.



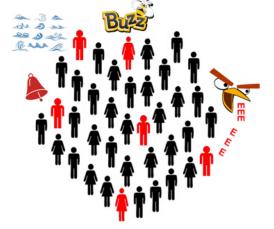
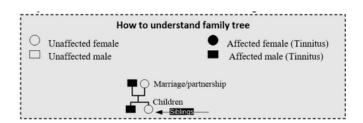


Figure 1. Black icon shows controls (patients without tinnitus) and red indicates tinnitus patients with different perception of sound.



Figure 2. Sporadic Case

Figure 3. Familial Case



CLASSIFICATION OF TINNITUS

Tinnitus can be classified as objective and subjective tinnitus (3). 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).

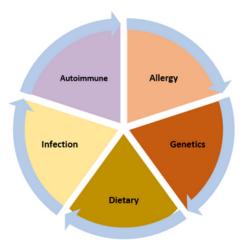
HOW TINNITUS IS GENERATED

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 head (6).
- 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 tinnitus (6). 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.

Ménière'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 bilateral (7). Tinnitus in Ménière's is well described by a low pitch narrow band of noise and it is reported as a troublesome symptom by most of the Ménière's patients. However, Ménière'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 Ménière's disease (8); some of them are shown in Figure 4.



Keywords

Autoimmune: When your immune system attacks your body by mistake.



Genetics: Is there any genetic variation (change) at your gene level, heredity information, genetic instructions.

Figure 4: Some factors involved in Meniere's

IS TINNITUS ASSOCIATED WITH OTHER DISEASES?

Tinnitus can also occur together with other diseases (8) 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 Ménière'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.

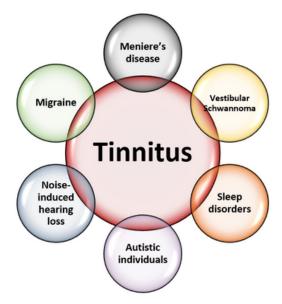


Figure 5: Tinnitus with other conditions

DO YOU KNOW THERE ARE SOME GENETIC FACTORS ASSOCIATED WITH TINNITUS AND MENIERE'S?

Ménière's is a complex disorder which means there is more than one gene involved and also some environmental factors which play an important role (7). The field of genetics is not new and many researchers have been working to identify the underlying genetic cause of tinnitus and Ménière's. Ménière's Disease Consortium (MediC) (9) has defined five clinical subgroups of patients for unilateral and

bilateral Ménière'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/Ménière'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 Ménière'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/Substituion of informaton	Control	AAAGTGTATATGCTC
	Tinnitus/Meniere's case	AAAGTTTATATGCTC
Example 2: Addition of harmful information	Control Tinnitus/Meniere's case	AAAGTGGGTTTCTTATATGCTC
Example 3: Deletion of useful information	Control Tinnitus/Meniere's case	AAAGTGTATATGCTC

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 heritability (10).

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 incredible (1).

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 heritability 11.

WHAT COULD BE DONE FOR YOUR TINNITUS?

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

- Sound therapy known as tinnitus retraining therapy that might be helpful for tinnitus cases.
- 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.
- Through tinnitus counselling sessions you can know more about tinnitus and can identify the way to deal with tinnitus.

Further information about prevention and treatment for tinnitus can be found online:

- NHS https://www.nhs.uk/conditions/tinnitus/
- Tinnitus UK 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. (lcvd):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

DISCLAIMER

This information does not replace medical advice.

The Ménière's Society recommends you always consult your GP, consultant, therapist or other medical professional 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.

To the best of our knowledge, information correct at time of publication.

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ABOUT THE MENIERE'S SOCIETY

We're here to help people with inner ear (vestibular) disorders. We provide essential support and information to enable people to cope positively and get the right diagnosis. We are a voice for sufferers within the medical community and raise awareness for greater public understanding. We work towards a brighter future through investment in vital medical research.

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Ménière's Society

for dizziness and balance disorders