Sensorion

UNDERSTANDING **GENE THERAPY FOR HEARING** IN 10 **QUESTIONS**

SUMMARY

Looking for a definition? Look in the glossary, page 15.

1 WHAT IS A **GENE** ?

WHAT ROLE DOES IT **PLAY** ?

Genes are located in chromosomes. Their main role is to provide the instructions needed to make the proteins required for our body to develop and function. They make up our genetic heritage, which is unique to each of us and is passed on by our parents.

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Most of our body's genetic information is stored in **23 pairs of chromosomes** inside the nucleus of our cells. For each pair, there is one chromosome of paternal origin and one of maternal origin. **Each chromosome is made up of genetic material called DNA** (deoxyribonucleic acid).

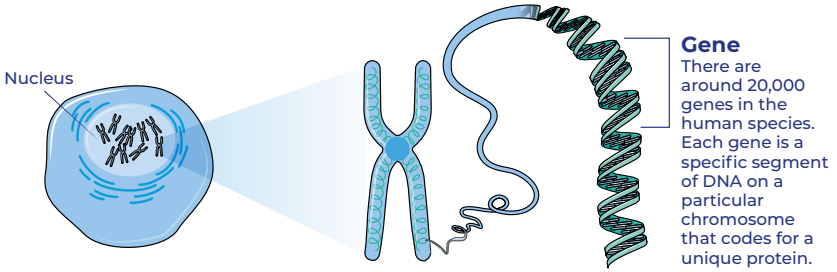
The DNA present in all our cells is the language used to code genetic instructions. **Specific sections of DNA are called genes.** These genes control a large proportion of our body's biological functions and constitute the functional unit of heredity (transmission and expression of one or more character traits from parent to child).

Each gene consists of a code that the cell will transform into a protein at a certain point in its life and in certain cells. This is the translation of the genetic code.

We produce tens of thousands of proteins in this way. Each protein has its own biological role (antibodies, eye color etc.). Certain changes in the genetic code (abnormalities in the genes) make it impossible for cells to produce a protein, or result in the creation of a non-functional protein. This genetic defect is then the cause of a disease. This genetic disease may be present at birth (congenital) or manifest itself later in life.

A genetic anomaly does not always lead to disease. Certain errors in the manufacturing of proteins can go completely unnoticed or only be expressed as a function of the environment which plays an important role in gene expression.

Chromosome, DNA, gene: the genetic code

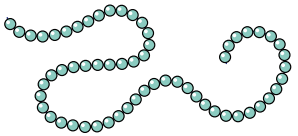


Cell
There are over 70,000 billion cells in the human species. It is the basic unit of every human being.

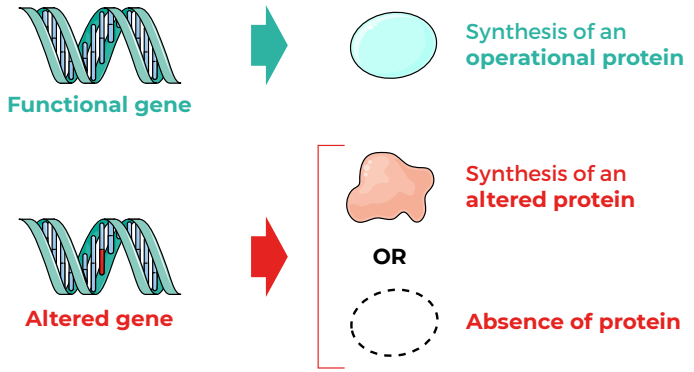
Chromosome
46 chromosomes in each cell (23 pairs, including one sexual pair: XX in women and XY in men).

DNA
Shaped like a double helix, the DNA molecule contains our genes.

Protein
Proteins are encoded (produced) by genes and each have a clearly defined role in the functioning of the human body.



Gene



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2 WHAT CAUSES **CONGENITAL DEAFNESS** (DEAFNESS PRESENT AT BIRTH)?

Nearly 80% of deafness detected at birth or in early childhood is genetic in origin.

To date, more than 150 genes have been identified. Hearing loss results when any of these genes are altered.

The most frequently found are the *GJB2* and *STRC* genes, which enable protein production in the cochlea.

The other causes of congenital deafness (less than 20%) are generally:

- Infections occurring during pregnancy;
- Complications arising at the time of delivery;
- Exposure to certain drugs or toxic products during pregnancy.

The vast majority of children who experience a genetic cause for their hearing loss do not present **any major health problems** and the hearing loss is an isolated condition.

In most cases, despite a genetic cause, there is no family history of deafness.

3 WHAT IS THE CAUSE OF MY CHILD'S **DFNB9** CONGENITAL DEAFNESS?

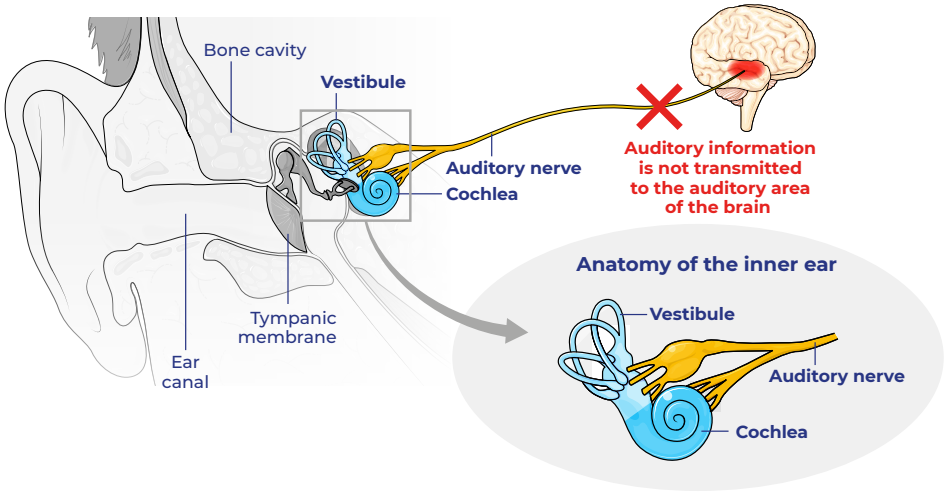
DFNB9 congenital deafness is due to changes in the *OTOF* gene, leading to an alteration in the transmission of sound information between the cells of the inner ear and the brain.
This rare genetic deafness affects between 3% to 8% of children born deaf, and affects both boys and girls.

An **alteration in the *OTOF*** gene results in the **absence or inadequate production** of a protein called **Otoferlin** by the inner hair cells of the cochlea. This protein is essential for the transmission of information to the brain via the auditory nerve connected to the cochlea. The cochlea is the part of the inner ear that converts sound into electrical signals that can be sent to the brain.

In the absence of Otoferlin, the sound information will reach the inner ear (cochlea) but will not be transferred to the auditory nerve.

DFNB9 hearing loss can vary in severity, but is most often **severe to profound and affects both ears.**

In children with congenital deafness DFNB9



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4 HOW IS DFNB9 CONGENITAL DEAFNESS TRANSMITTED?

The alteration in the *OTOF* gene (responsible for the production of the Otoferlin protein, essential for the transmission of sound information) is inherited by both the father and the mother: this is known as autosomal recessive inheritance.

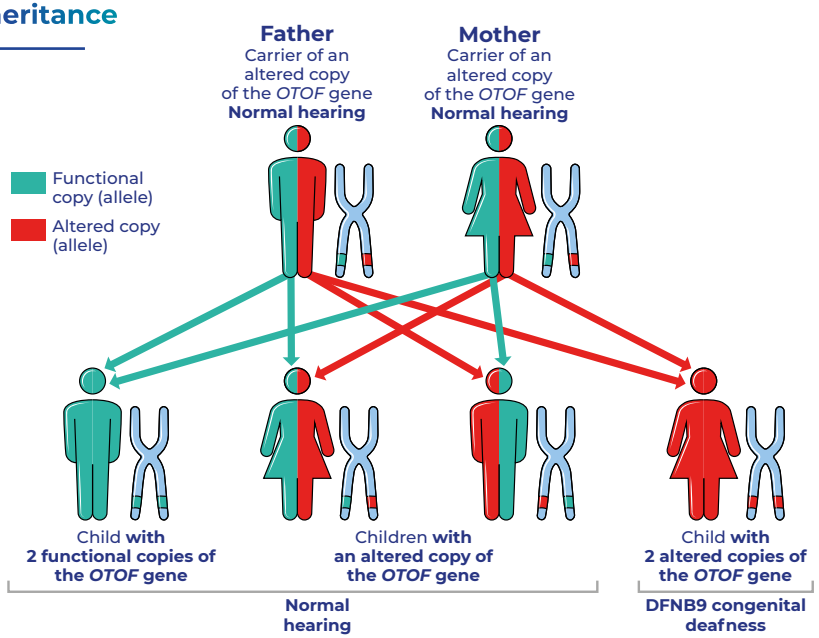
Each gene in our cells has two copies, one from our mother and one from our father. These two copies of the same gene, known as **alleles,** are usually different: **one of paternal origin and the other of maternal origin.**

In the case of DFNB9 congenital deafness, both parents pass on an altered copy of the *OTOF* gene to their child (boy or girl).

Parents who have an altered copy and a functional copy of the *OTOF* gene have normal hearing.

A child, boy or girl, who has received two altered copies of the *OTOF* gene (one passed on by the father and the other by the mother) usually has severe to profound deafness affecting both ears.

Autosomal recessive inheritance



5 WHAT IS GENE THERAPY AND HOW DOES IT WORK?

Gene therapy is a technique that involves introducing genetic material, as a drug, into cells to treat certain diseases with a predetermined genetic cause.
This innovative technique involves replacing altered DNA with functional DNA to compensate for the dysfunction of the associated gene.

Most gene therapies currently available in humans involve the **delivery of a functional gene to compensate for the altered gene responsible for the disease.**

To do this, the 'fonctional gene' is delivered directly to the cells concerned to **enable production of the missing protein.**

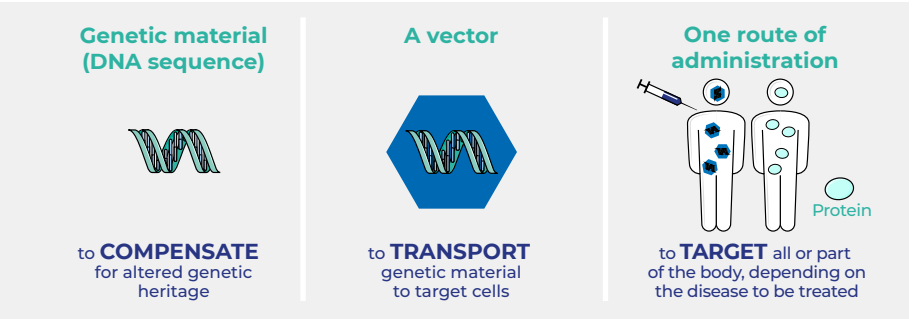
This new genetic material enters the cell nucleus using a specific transporter, called a vector.

The vectors traditionally used are derived from viruses that have been rendered harmless and have retained their ability to penetrate cells easily.

Today, gene therapy drugs are the subject of numerous clinical trials for a range of diseases, including cancer, blood disorders and neurodegenerative diseases.

In general, gene therapy drugs are **indicated for diseases for which a genetic origin has been demonstrated, and administered in hospital by a specialist doctor.**

In practice: gene therapy



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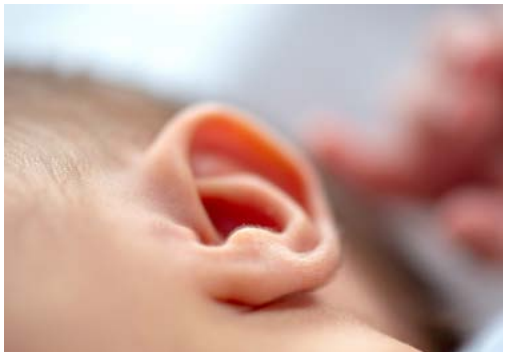
6 WHAT TYPE OF CONGENITAL DEAFNESS **CAN BE TREATED BY GENE THERAPY,** AND HOW?

Current clinical trials are evaluating the principle of gene therapy for a single type of deafness linked to alterations in the *OTOF* gene (responsible for making the Otoferlin protein), known as DFNB9 congenital deafness.



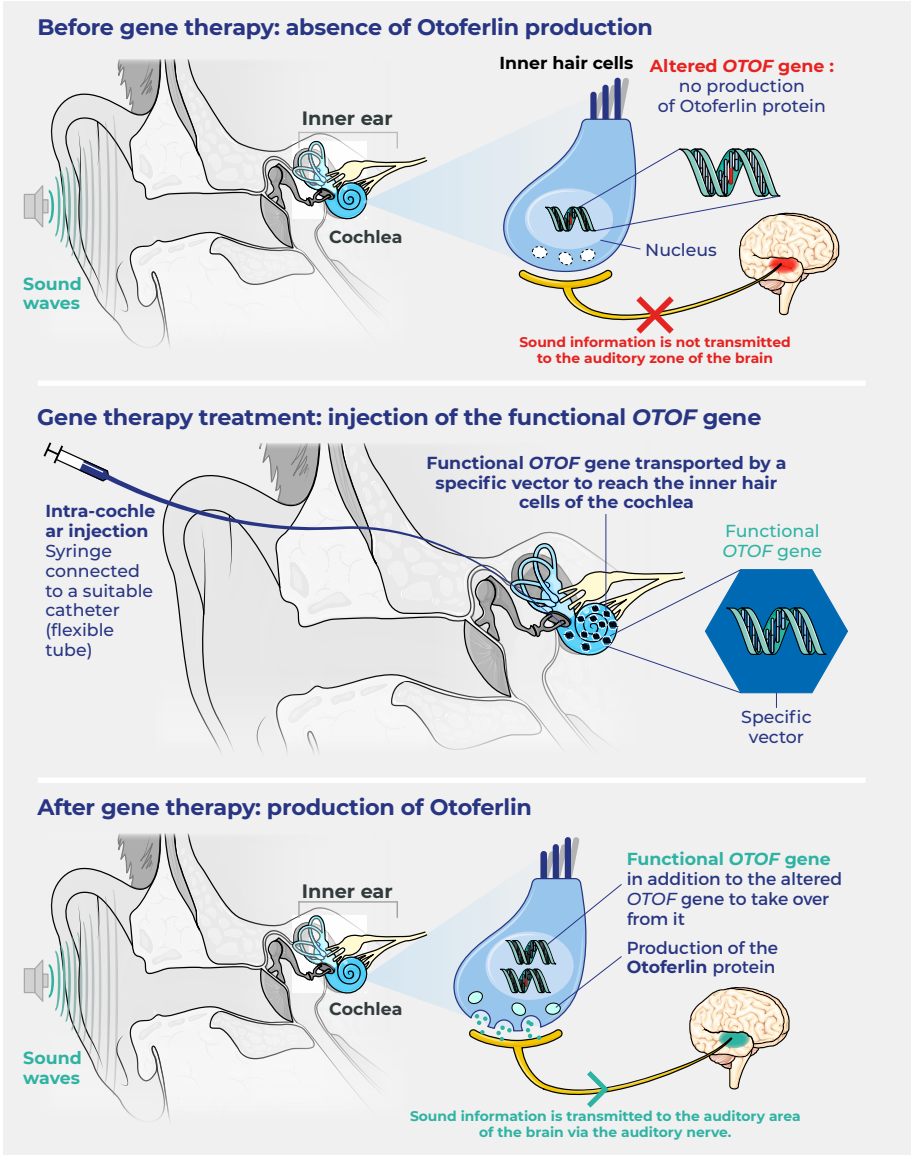
A DNA sequence containing the **functional *OTOF* or 'drug gene'** is introduced **into a vector,** a kind of 'transporter' designed to **deliver it specifically to the nucleus of the inner hair cells** of the cochlea.

This 'medicinal gene' will, in a way, **take over from the altered *OTOF* gene** and enable the inner hair cells to **regain their ability to transmit sound information to the brain.**

The gene therapy drug is administered by **a single intra-cochlear injection during surgery.** This procedure is similar to that used to insert a cochlear implant.

Evaluation of the efficacy and safety profile of this new gene therapy could then enable the development of other gene therapies targeting different genes responsible for other types of deafness.

Gene therapy applied to DFNB9 congenital deafness: steps and principles



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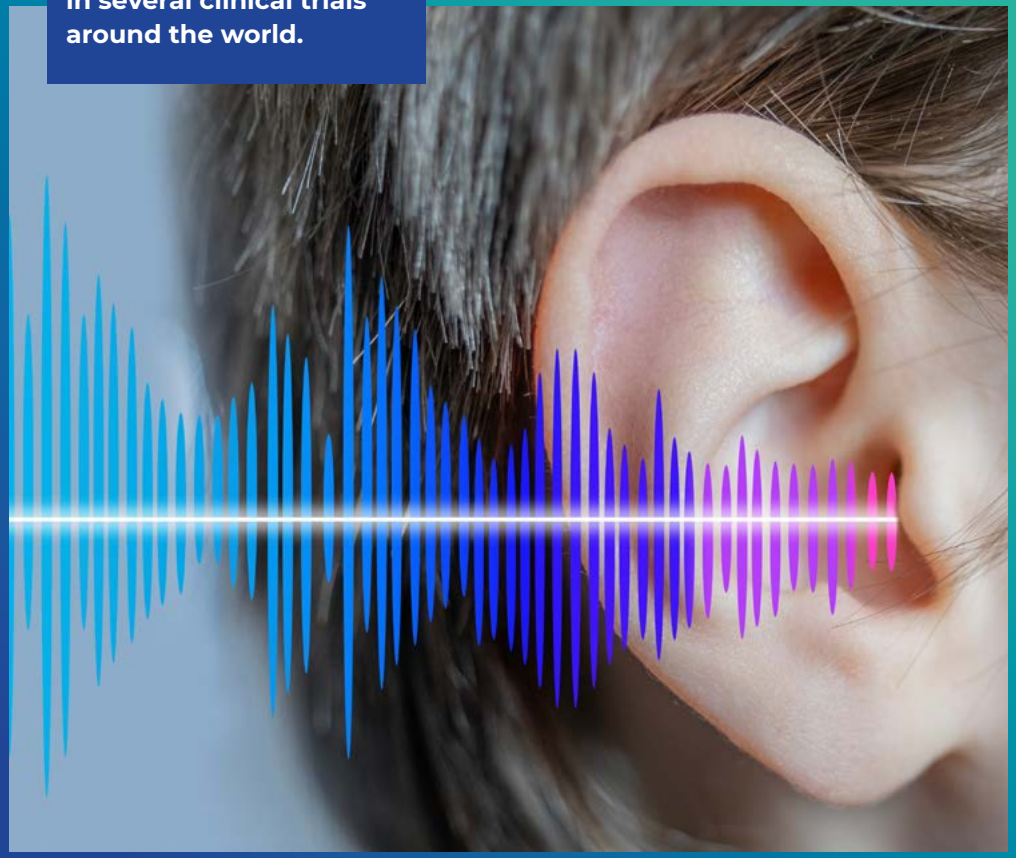
WHAT ARE **THE BENEFITS** OF GENE THERAPY FOR DFNB9 DEAFNESS?

Gene therapy applied to DFNB9 severe to profound deafness is currently being evaluated in several clinical trials around the world.

Administered early in life, this treatment may provide children the improvement in hearing they need to develop speech and language without the use of other technology.



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WHAT ARE **THE RISKS** ASSOCIATED WITH GENE THERAPY TO TREAT DFNB9 CONGENITAL DEAFNESS?

Gene therapy for severe to profound DFNB9 congenital deafness is currently being evaluated in various clinical trials around the world. This treatment is therefore not yet available in the form of a drug that can be offered as an alternative to your child by a specialist hospital doctor. The aim of these clinical trials is to evaluate safety and efficacy in children with severe to profound DFNB9 hearing loss according to strict rules.

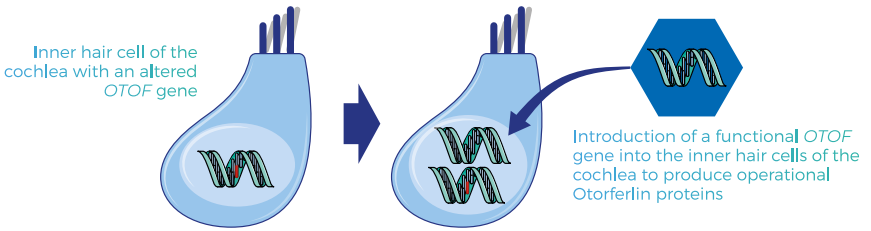
It is possible that the gene therapies applied to DFNB9 deafness currently being studied may not work or may cause unexpected side effects.

Gene therapy clinical trials are f**ollowed up in patients for several years after treatment,** in order to monitor the long-term effects (positive and negative), which remain unknown.

In gene therapy applied to DNFB9 deafness, the new functional gene or 'drug gene' does not repair the altered *OTOF* gene at the origin of this deafness. Its role is to **compensate for the defective function,** thereby enabling auditory information to circulate to the brain.

The gene therapy drug does not become part of the genetic code and is therefore **not passed on to descendants.** Nonetheless, the existing altered gene can still be passed on to future generations.

Gene therapy applied to DFNB9 deafness



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9 HOW LONG DOES THE EFFECT OF GENE THERAPY FOR DFNB9 CONGENITAL DEAFNESS LAST?

The gene therapies currently being developed for severe to profound congenital deafness associated with DFNB9 have been developed to improve hearing after a single injection and provide a long-term benefit, possibly for life.

Long-term monitoring of patients who have benefited from this type of therapy will reveal more about how long the treatment **actually lasts.**

10 CAN MY CHILD BENEFIT FROM **GENE THERAPY** AFTER A COCHLEAR IMPLANT?

According to current medical knowledge, gene therapy to treat severe to profound DFNB9 congenital deafness is not indicated on a previously implanted ear.

If the gene therapy given to your child doesn't provide enough benefit, your doctor will talk with you about how a cochlear implant could help your child in the future.

GLOSSARY

ALLELE

An allele is one of several possible versions of the same gene. Each gene has two alleles: one copy from the mother, the other copy from the father.

CELL

The cell is the basic unit of each human being and contains its DNA. It produces energy and uses it to keep the body running. Humans have more than 70,000 billion cells.

CHROMOSOME

A chromosome, the carrier of genetic information, is made up of DNA, which is in condensed form. It is present in the nucleus of our cells. Humans have 23 pairs of chromosomes (22 pairs of autosomes and 1 pair of sex chromosomes).

COCHLEA

The cochlea is the part of the inner ear responsible for hearing. This small, spiral-shaped organ transforms auditory information into nerve impulses that can be understood by the brain, enabling us to perceive sounds.

DFNB9

DFNB9 congenital deafness is an autosomal recessive form of isolated deafness associated with mutations in the *OTOF* gene.

- DFN: is an abbreviation of *'deafness'*
- B: indicates autosomal recessive inheritance
- 9: designates the chronological order of gene discovery among the genes responsible for isolated deafness

DNA

DNA (deoxyribonucleic acid) is a double-helix molecule found in the nucleus of the body's cells. It carries our genes.

GENE

Zones of DNA containing the information (instructions) needed by the cell to make proteins.

INNER HAIR CELL

Inner hair cells are tiny, specialized cells located in the cochlea, a part of the inner ear. They play a crucial role in our ability to hear as each one is tuned to detect different pitches or frequencies of sound and transmit the information to the nerve allowing the brain to process and understand.

OTOFERLIN

Otoferlin is a protein that plays a major role in the transmission of sound information between the inner hair cells of the cochlea and the nerve endings in the inner ear. Without this protein, sound information will reach the inner ear but will not be transmitted to the auditory nerve.

PROTEIN

Proteins are an assembly of amino acids. They are encoded by genes, and each has a well-defined role in the functioning of the human body (immunity, digestion, hormones, enzymes, etc.).

VECTOR

A vector or *'transporter'* is used to efficiently transport genetic material (a functional gene) into cells. There are two types used in gene therapy: a viral vector that has been rendered harmless (inactivated) or a synthetic vector.

TO FIND OUT MORE

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- https://www.ern-cranio.eu
- https://www.fondationpourlaudition.org
- https://www.genethon.com
- https://www.genetique-medicale.fr
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