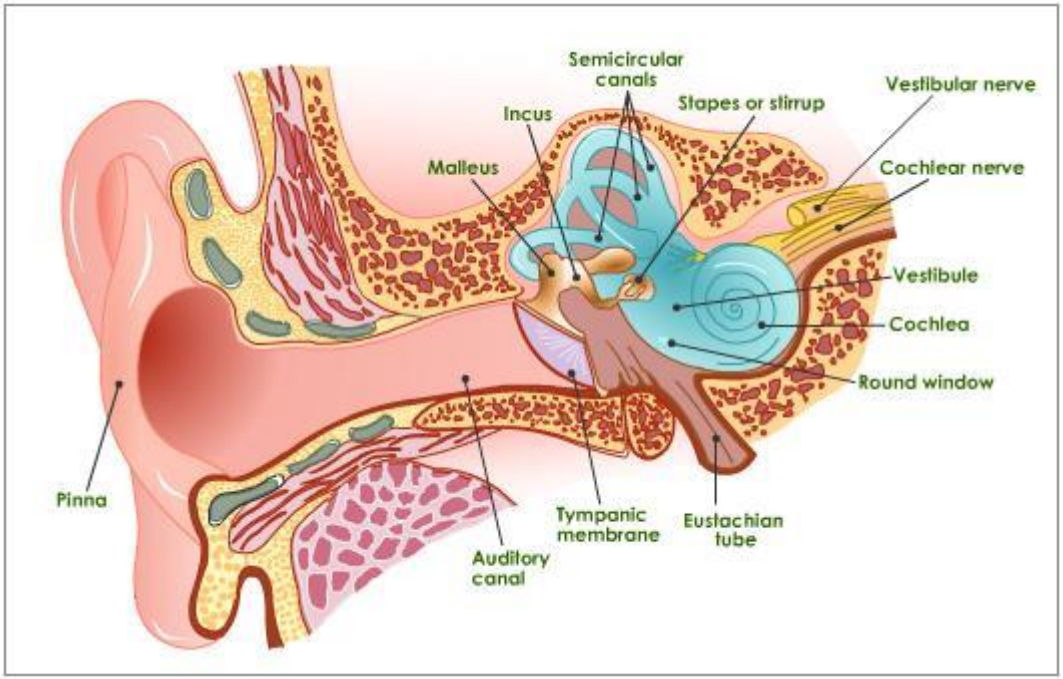
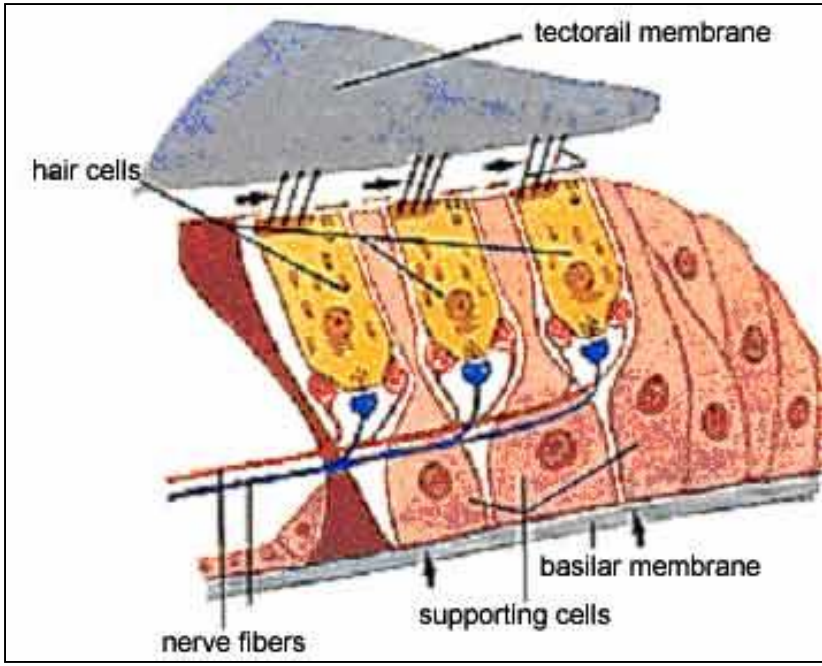
Disorders of Hearing Loss





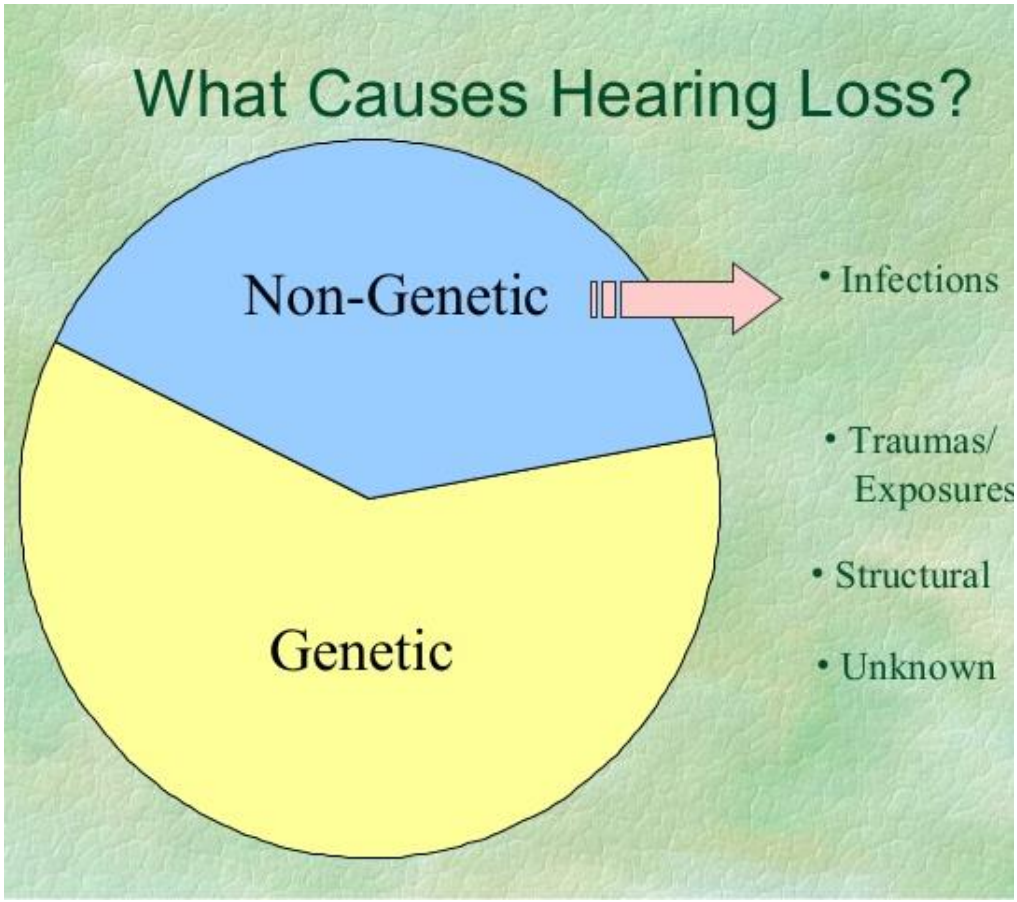
Dr. Bilal Azab

hearing loss affects approximately
17 in 1000 children and adolescents younger than 18 years

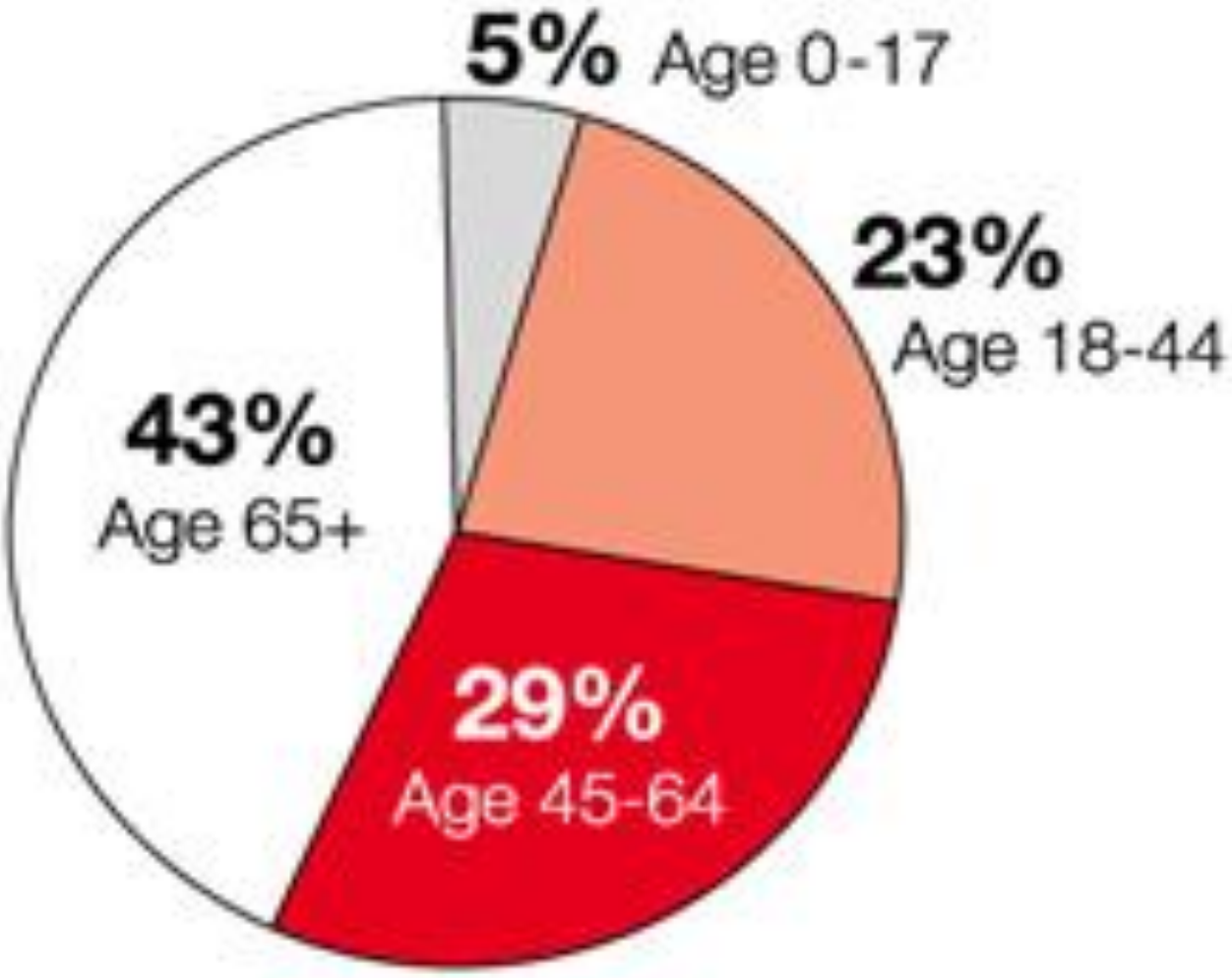
average incidence of hearing loss in neonates in the United States is 1.1 per 1000

prevalence of childhood and adolescent hearing loss was 3.1%, with higher rates in Hispanic Americans and in families with lower incomes

40-50% of all cases of congenital hearing loss are due to nongenetic effects, such as prematurity, postnatal infections, ototoxic drugs, or maternal infection (with cytomegalovirus [CMV] or rubella).



Who has hearing loss?



Source:
http://ihcrp.georgetown.edu/agingsociety/pdfs/hearing.pdf

categories

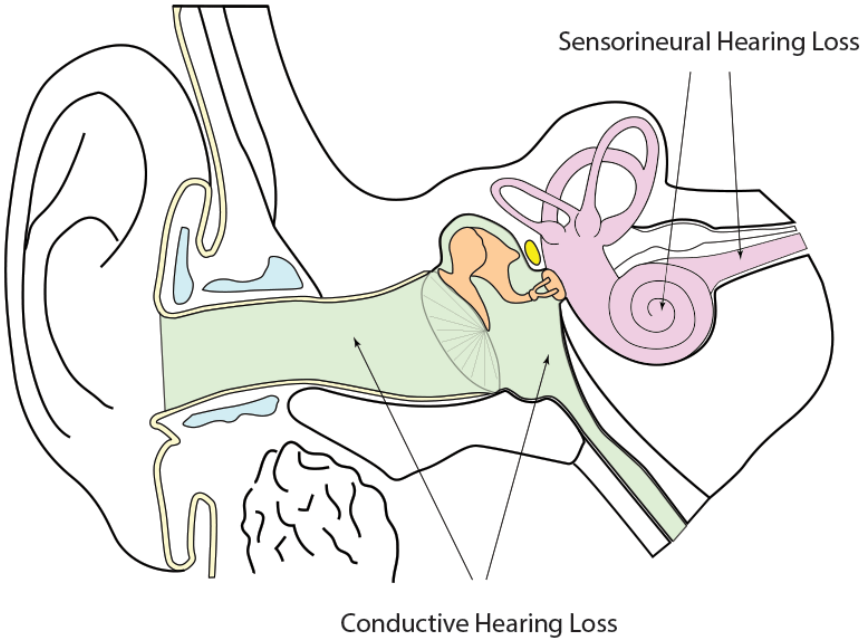
Type:

conductive: abnormalities of the external and/or the ossicles of the middle ear

sensorineural: malfunction of inner ear structures (i.e., cochlea)

Mixed: conductive and sensorineural

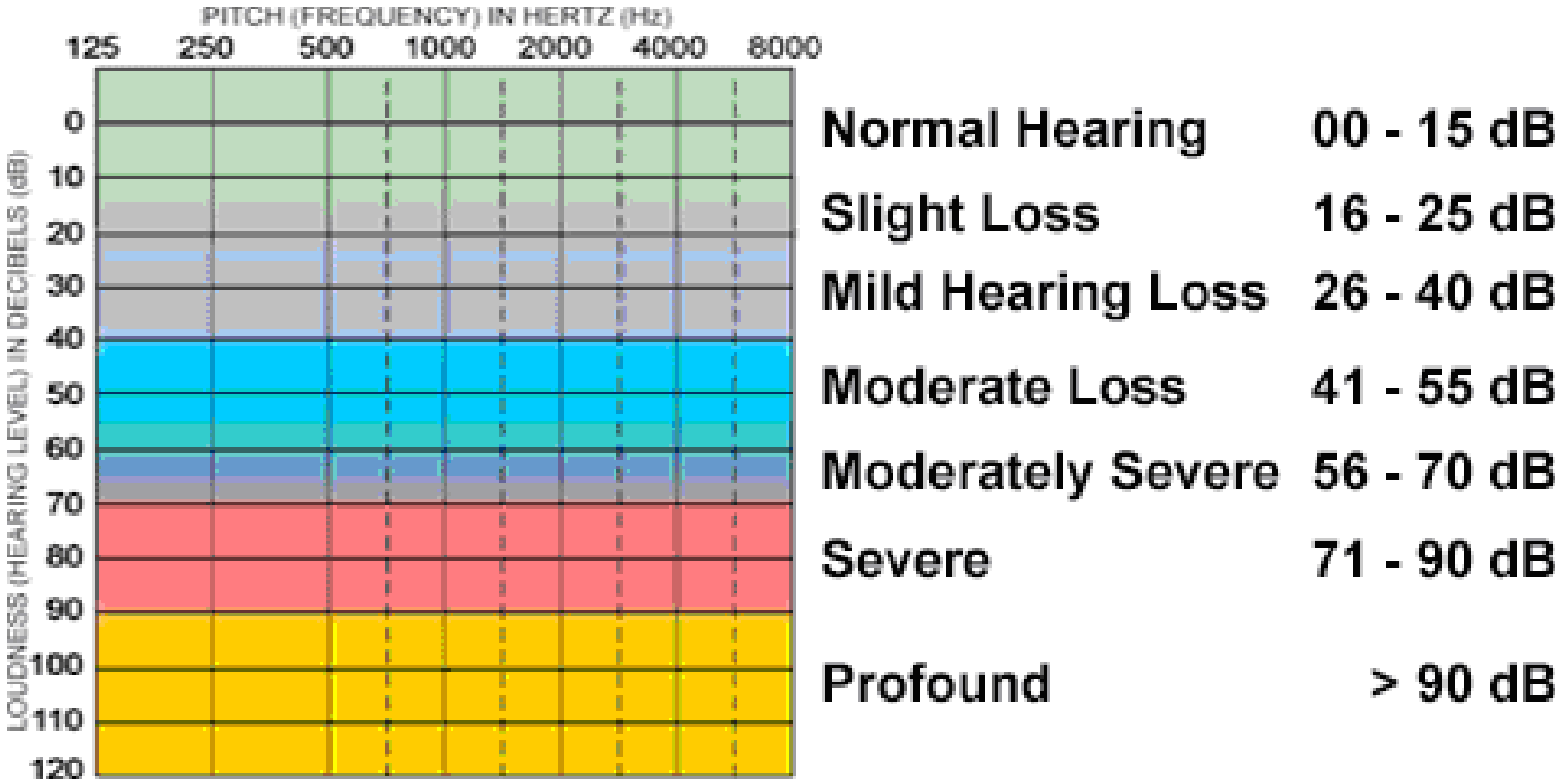
Central auditory dysfunction results from damage or dysfunction at the level of the eighth cranial nerve, auditory brain stem, or cerebral cortex

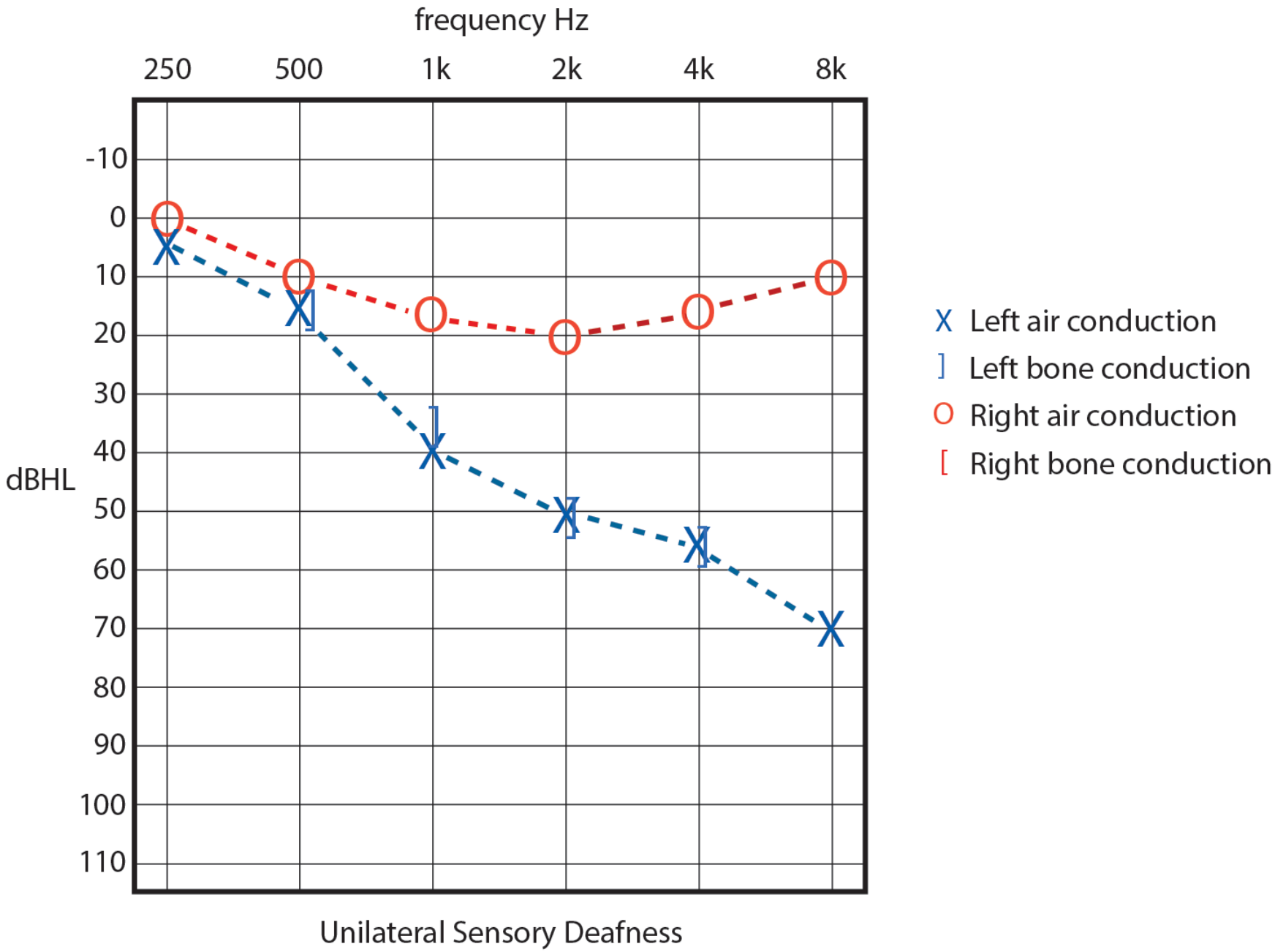


categories

Severity:

- Mild: adults 27-40 dB, children 20-40 dB
- Moderate: 41-55 dB
- Moderately severe: between 56 and 70 dB
- Severe: between 71 and 90 dB
- Profound: 90 dB or greater




frequency Hz
250
500
1k
2k
4k
8k
-10
0
10
20
30
40
50
60
70
80
90
100
110
dBHL
X Left air conduction
] Left bone conduction
O Right air conduction
[Right bone conduction
Unilateral Sensory Deafness

categories

Type:

- conductive: abnormalities of the external and/or the ossicles of the middle ear
- sensorineural: malfunction of inner ear structures (i.e., cochlea)
- Mixed: conductive and sensorineural
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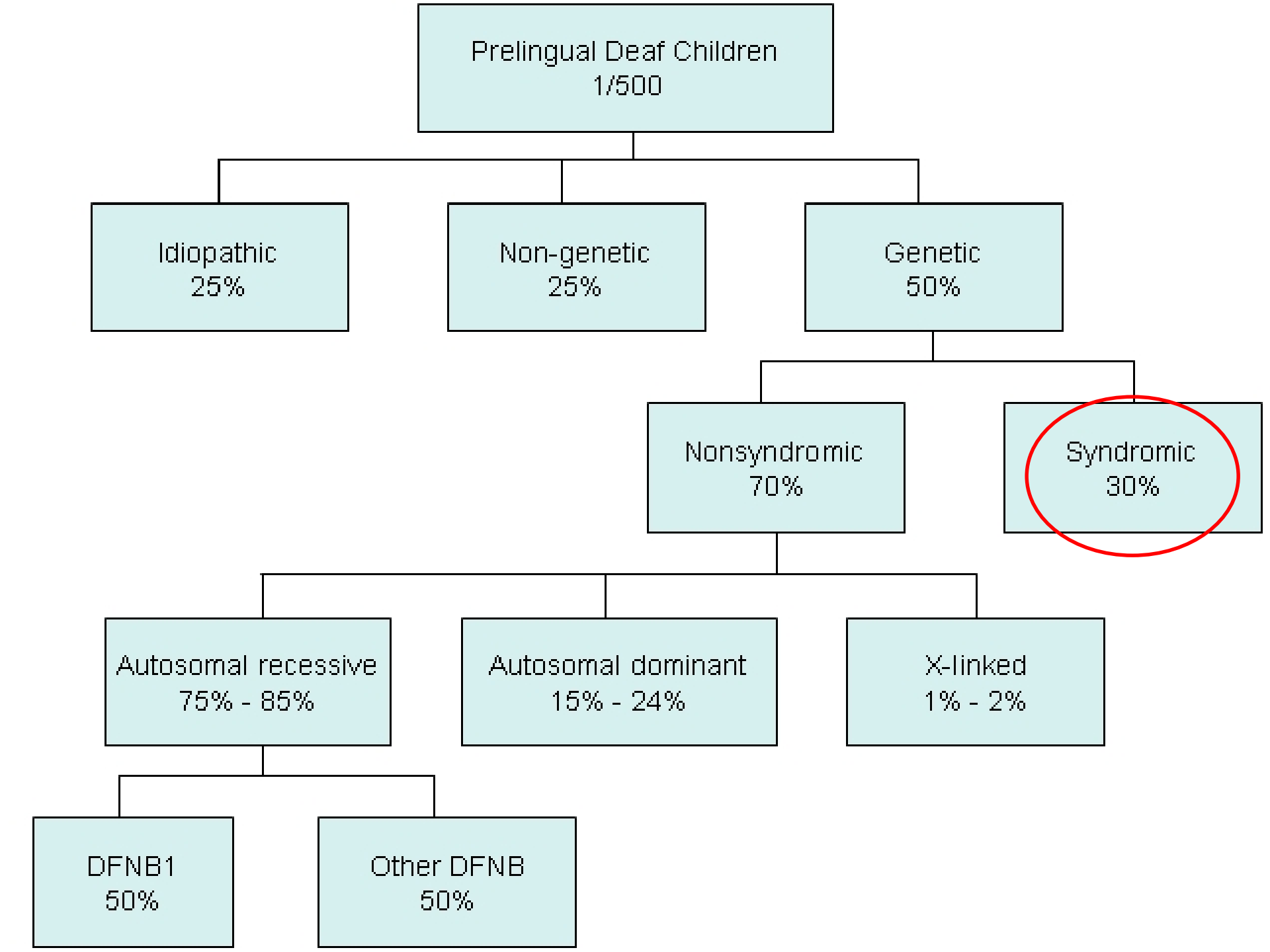
- Profound: 90 dB or greater

Age of onset:

- Pre-lingual: congenital, or in early infancy (before speech develops)
- Post-lingual: occurs after the development of normal speech (more common)

Furthermore, a hearing impairment may exist in only one ear (unilateral) or in both ears (bilateral).


Prelingual Deaf Children
1/500
Idiopathic
25%
Non-genetic
25%
Genetic
50%
Nonsyndromic
70%
Syndromic
30%
Autosomal recessive
75% - 85%
Autosomal dominant
15% - 24%
X-linked
1% - 2%
DFNB1
50%
Other DFNB
50%

Syndromic Hearing Impairment

Over 400 genetic syndromes include hearing loss
30% of prelingual deafness, but its relative contribution to all deafness is much smaller

Autosomal Dominant
Waardenburg syndrome (WS)
Branchiootorenal syndrome (BOR)
Stickler syndrome
Neurofibromatosis 2 (NF2)

Autosomal Recessive
Usher syndrome
Pendred syndrome
Jervell and Lange-Nielsen syndrome
Biotinidase deficiency
Refsum disease

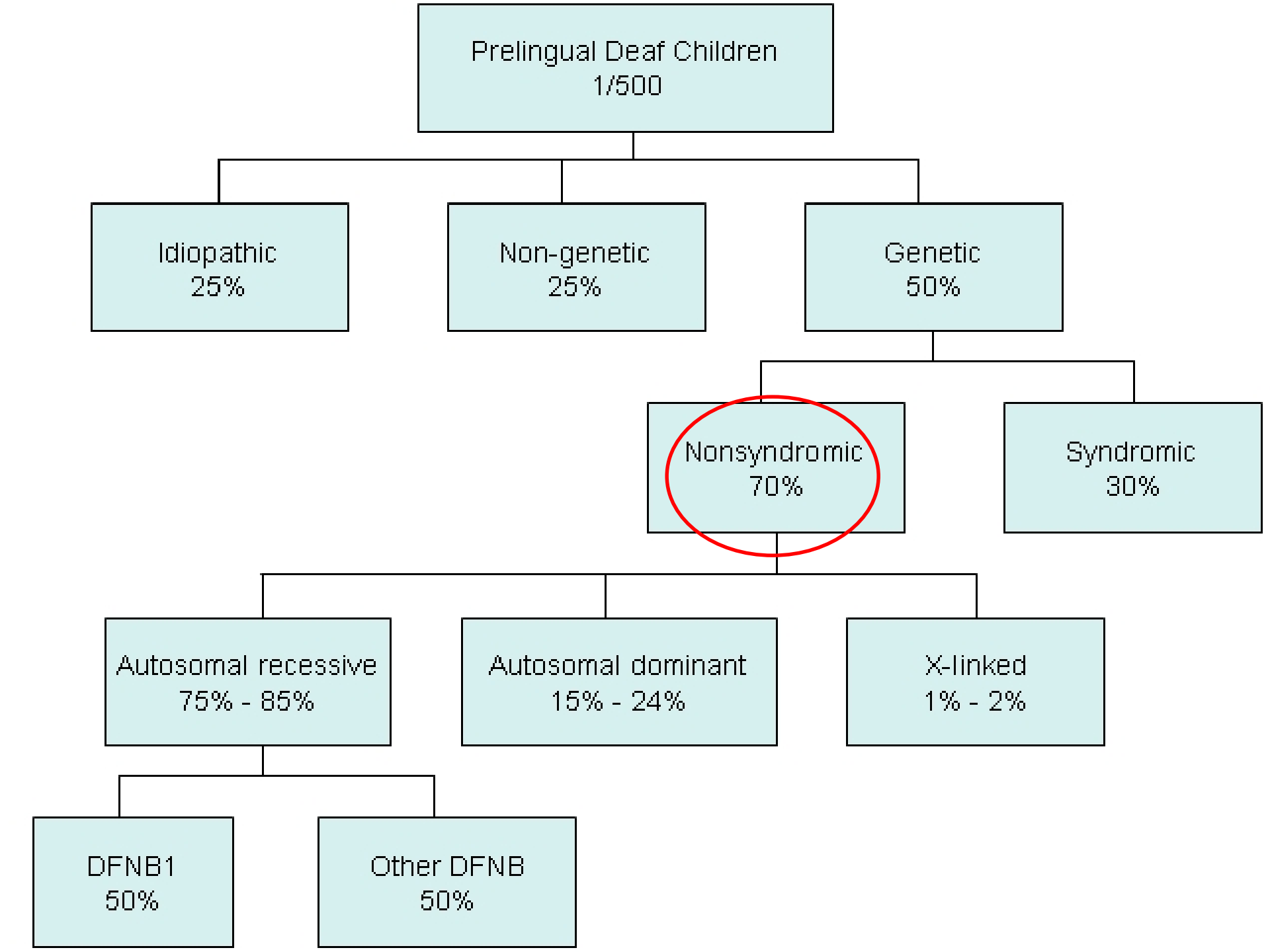
X-Linked Syndromic Hearing Impairment
Alport syndrome
Mohr-Tranebjaerg syndrome (deafness-dystonia-optic atrophy syndrome)

Mitochondrial Syndromic Hearing Impairment

Syndromic Hearing Loss

Syndromes	Gene(s)
Alport	*COL4A5, COL4A3, COL4A4*
Branchio-Oto-Renal	*EYA1*
Jervell and Lange-Nielsen	*KCNQ1, KCNE1/IsK*
Mitochondrial (MELAS/MERRF)	*$tRNA^{leu(UUR)}$, $tRNA^{lys}$*
Neurofibromatosis type II	*NF2*
Norrie	*NDP*
Osteogenesis Imperfecta	*COL1A1, COL1A2*
Pendred	*PDS*
Stickler	*COL2A1, COL11A2, COL11A1*
Tranebjaerg-Mohr (DFN1)	*DDP*
Treacher Collins	*TCOF1*
Usher	*MYO7A, USH1C, CDH23, PCDH15, SANS, USH2A, VLGR1, USH3*
Waardenburg	*PAX3, MITF, SLUG, EDNRB, EDN3, SOX10*

There are currently over 400 syndromes with associated hearing loss.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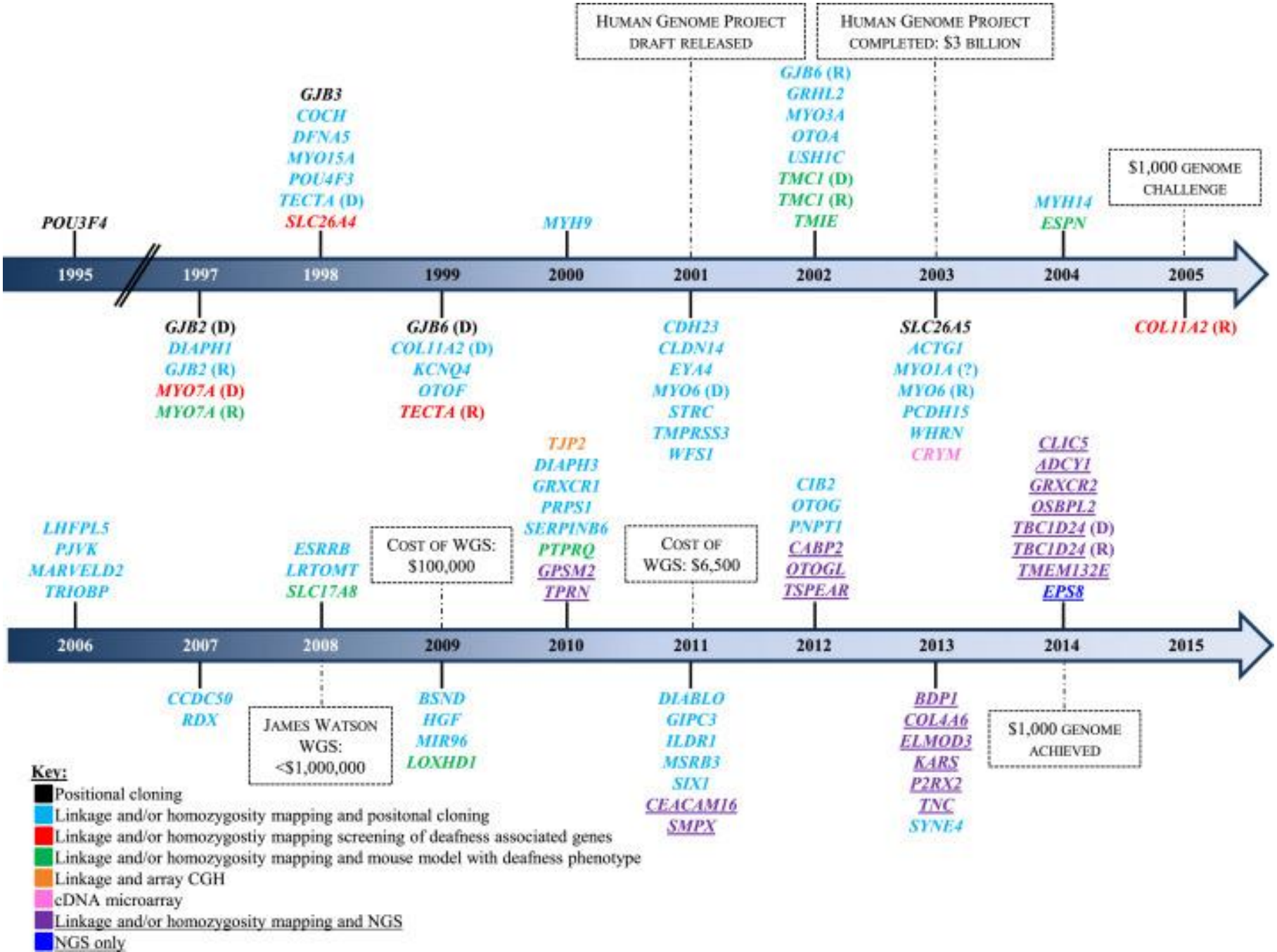
Non-syndromic hearing loss gene identification



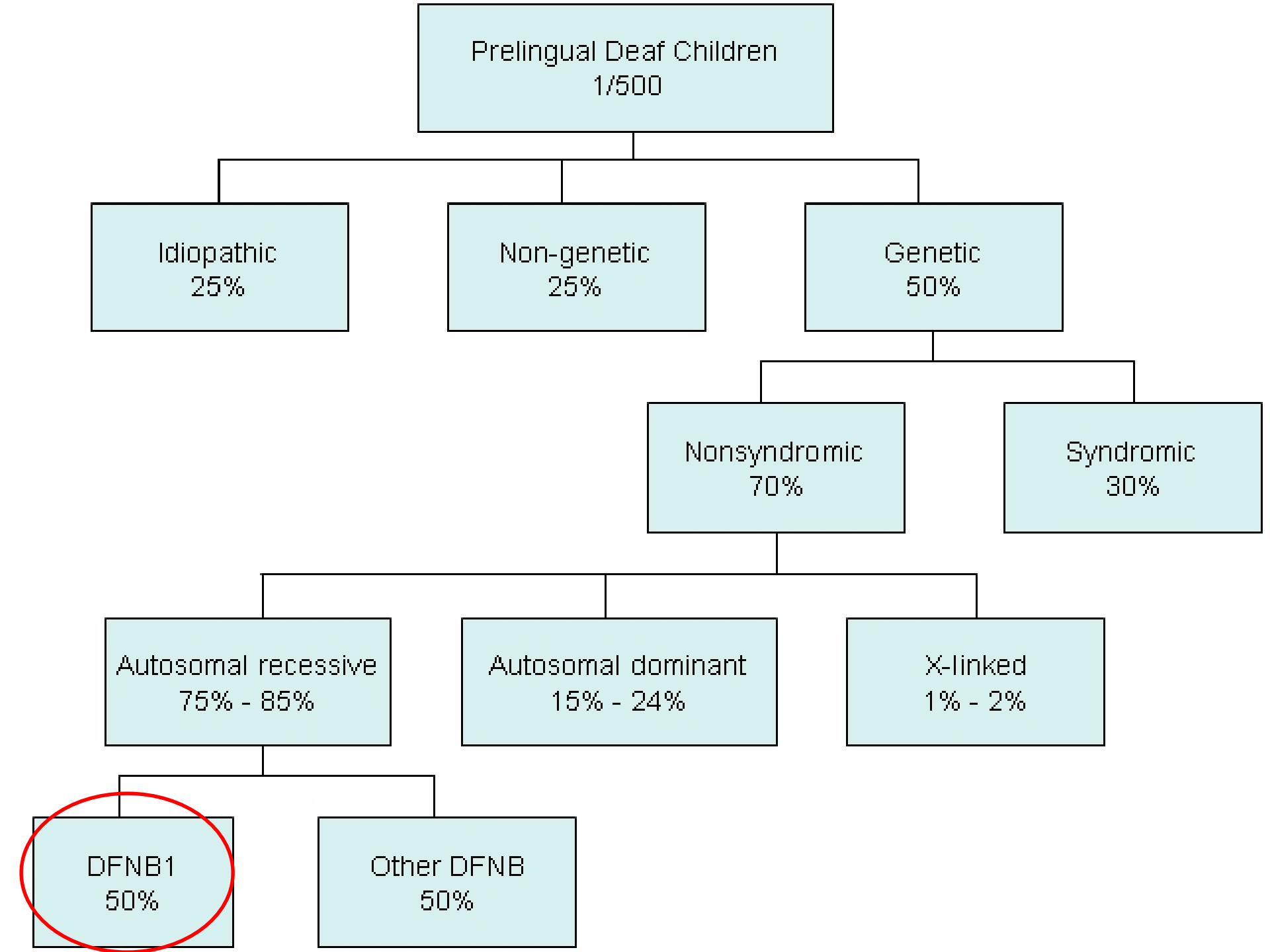
Nonsyndromic Hearing Impairment

AR: DFNB1→ DFNB84
Most autosomal recessive loci cause prelingual severe-to-profound hearing loss.
An exception is DFNB8, in which the hearing impairment is postlingual and rapidly progressive.

AD: DFNA1→ DFNA51
Most autosomal dominant loci cause postlingual hearing impairment
Some exceptions are DFNA3, DFNA8, DFNA12, and DFNA19
No identifiable single gene responsible for the majority of the cases (unlike AR)
Testing include sequence analysis of entire coding region

DFNX1, DFNX2
X-linked nonsyndromic hearing loss can be either pre- or postlingual; one disorder, DFNX3, has mixed hearing loss.

Mitochondrial: MT-RNR1, MT-TS1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Other DFNB
50%

GJB2 & GJB6

Cytogenetic Location: 13q11-q12

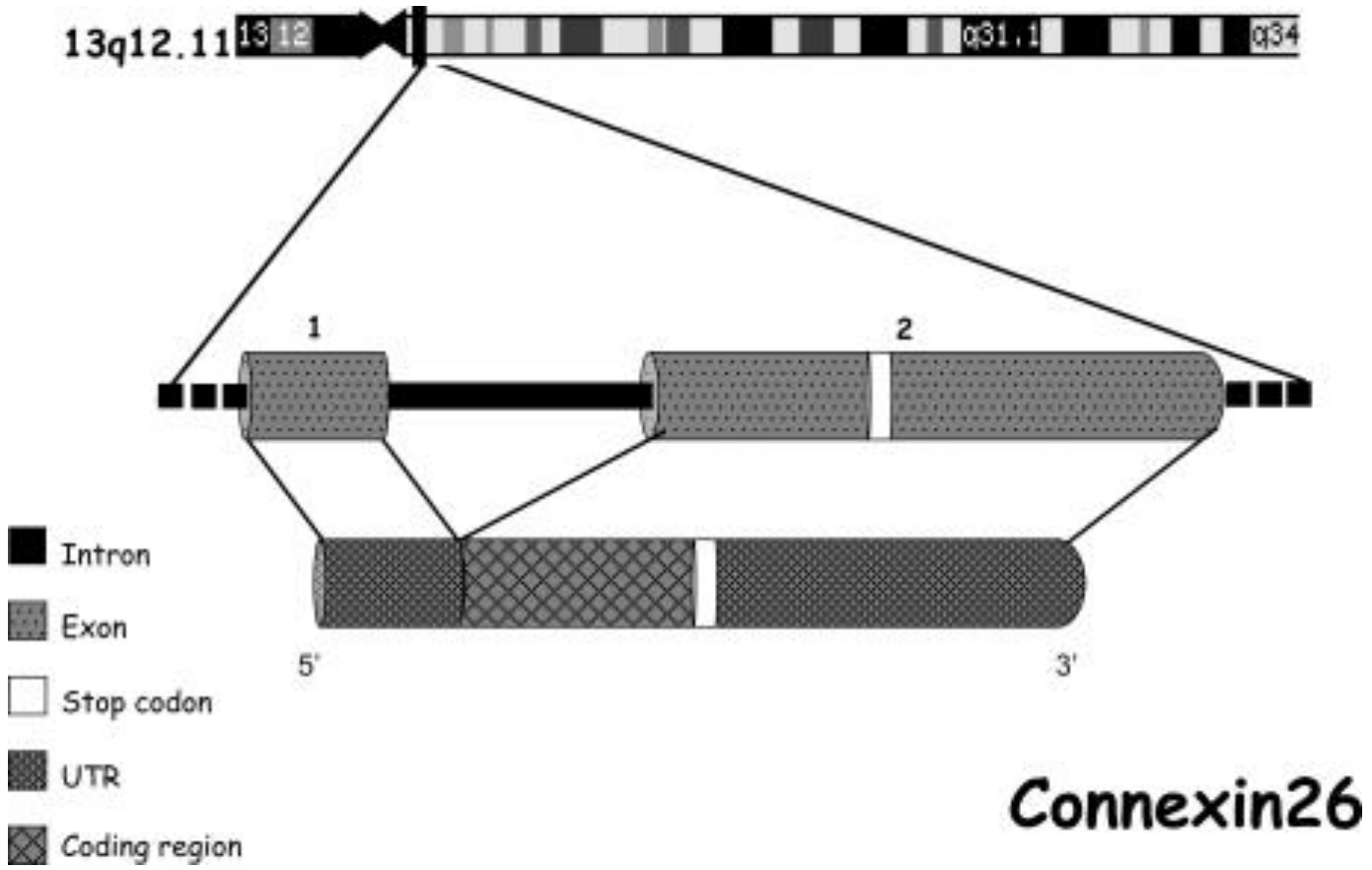
GJB2 encodes: gap junction beta 2 protein, AKA connexin26

connexin 26 form gap junctions between cells that transport potassium ions to maintain its correct level. Other research suggests that connexin 26 is required for the maturation of certain cells in the cochlea.

GJB2 variants cause DFNB1 which is inherited in an autosomal recessive manner.

GJB6 encodes: gap junction beta 6 protein, AKA connexin30

GJB6, participate in causing DFNB1



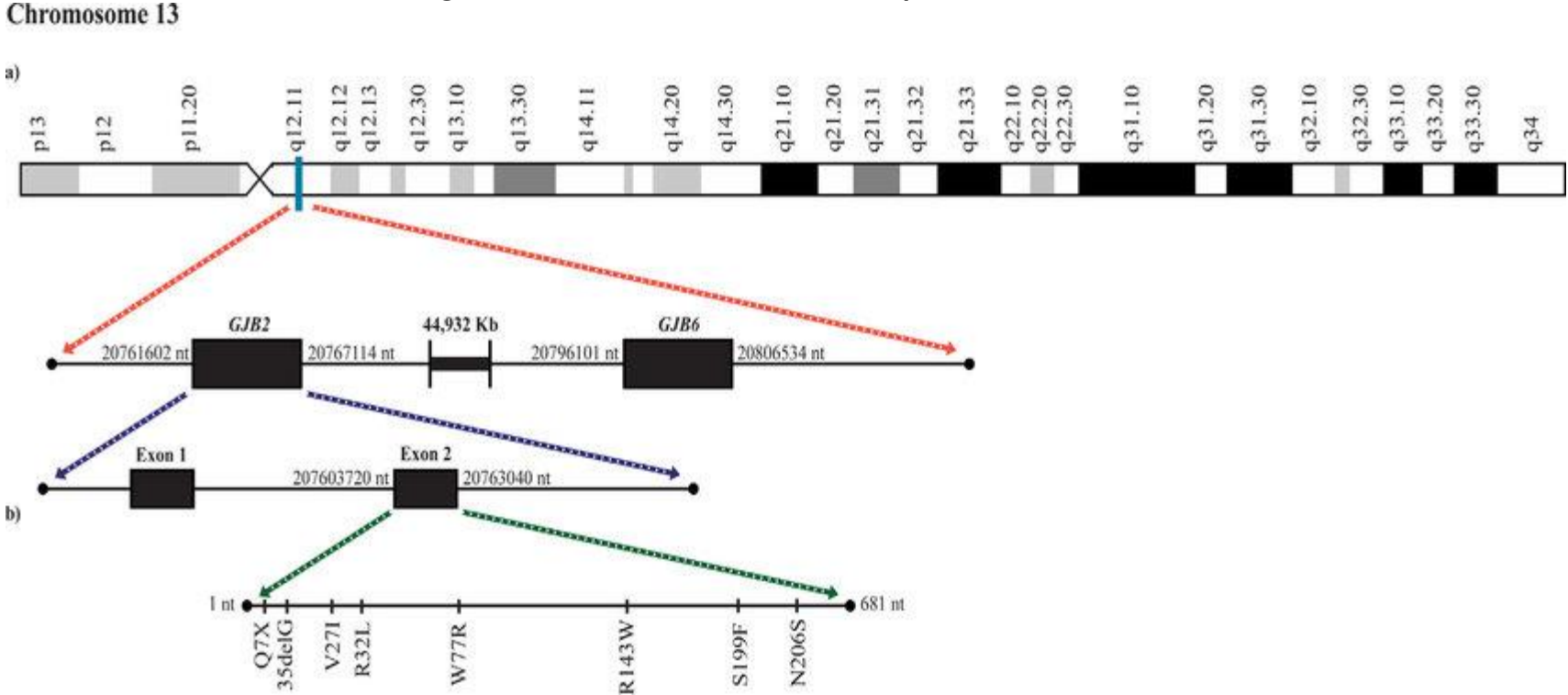
DFNB1

characterized by congenital, non-progressive, mild-to-profound sensorineural hearing impairment. No other associated medical findings are present

50% of AR-NSHL can be attributed to the disorder DFNB1, caused by mutations in the *GJB2* genes and*GJB6* gene.

Approximately 98% of individuals with DFNB1 have two identifiable *GJB2* mutations (i.e., they are homozygotes or compound heterozygotes).

Approximately 2% of individuals with DFNB1 have one identifiable GJB2 mutation and one of two large deletions that include a portion of GJB6



Clinical testing

GJB2

Sequence analysis of the entire coding region detects both mutations in 98% of persons with DFNB1, although mutation screening for DFNB1 is **not** complete unless screening for the splice site mutation (exon 1 of *GJB2*) and the large *GJB6*-containing deletions is included

Targeted mutation analysis. (looking for only one or several specific mutations) is generally **not recommended** because this type of analysis has an ethnic bias:

- c.35delG mutation is most common in populations of northern European ancestry
- c.167delT mutation is most common in the Ashkenazi Jewish population
- c.235delC mutation is most common in the Japanese and Chinese populations

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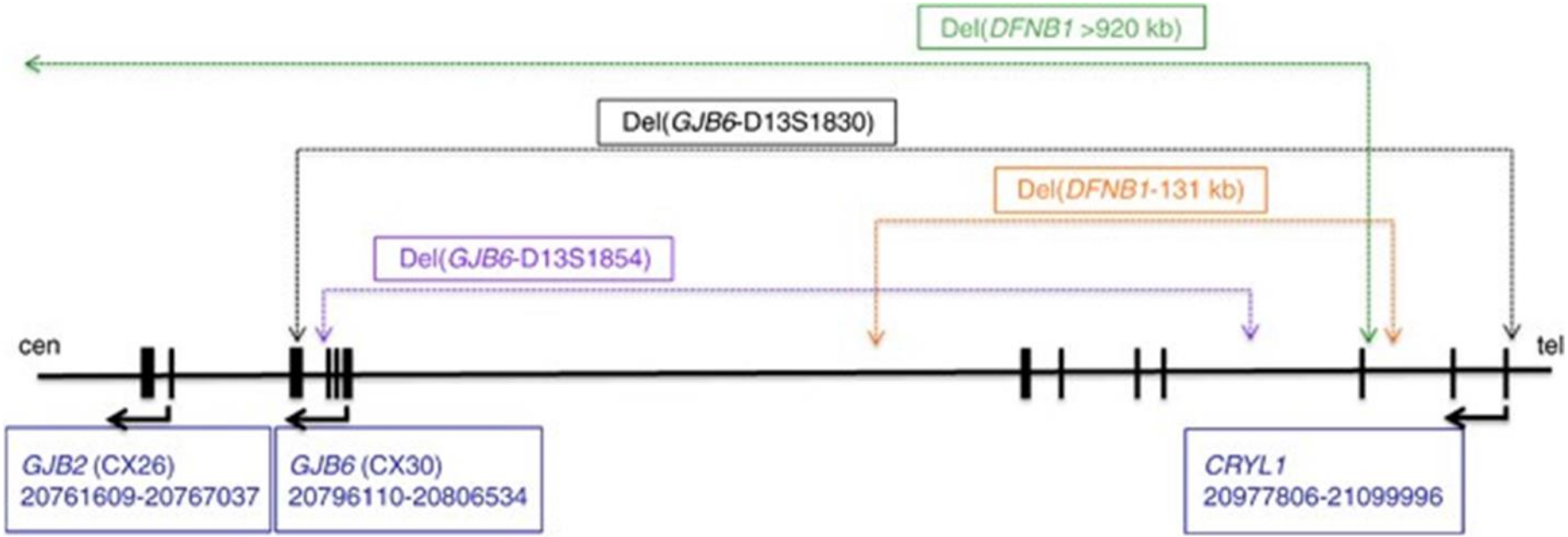
GJB6: Approximately 2% of individuals with DFNB1 have one identifiable *GJB2* mutation and one of two large deletions that include a portion of *GJB6* (i.e., they are double heterozygotes).



Clinical testing

For individuals suspected of having DFNB1:

The first step in diagnosis is sequence analysis of *GJB2* exon 2. If two deafness-causing mutations are identified, the diagnosis of DFNB1 is established.

If one deafness-causing mutation is identified, deletion analysis for *GJB6* deletions is warranted.

Clinical Diagnosis

Pre- or postlingual, mild to profound, progressive sensorineural hearing impairment

No related systemic findings

A family history of nonsyndromic hearing loss consistent with autosomal dominant inheritance

DFNA3

Clinical Diagnosis

Pre- or postlingual, mild to profound, progressive sensorineural hearing impairment

No related systemic findings

A family history of NSHL consistent with autosomal dominant inheritance

Molecular Genetic Testing

GJB2 > 90%, and *GJB6 <10%*

GJB2. Sequence analysis of *GJB2* identifies 100% of the 10 substitution mutations, including p.Trp44Cys, p.Trp44Ser, p.Pro58Ala, p.Arg75Gln,p.Arg75Trp, p.Arg143Gln , p.Met163Leu, p.Asp179Asn, p.Arg184Gln, and p.Cys202Phe
GJB6. A mutation in the *GJB6* gene, p.Thr5Met

Treatment of Manifestations

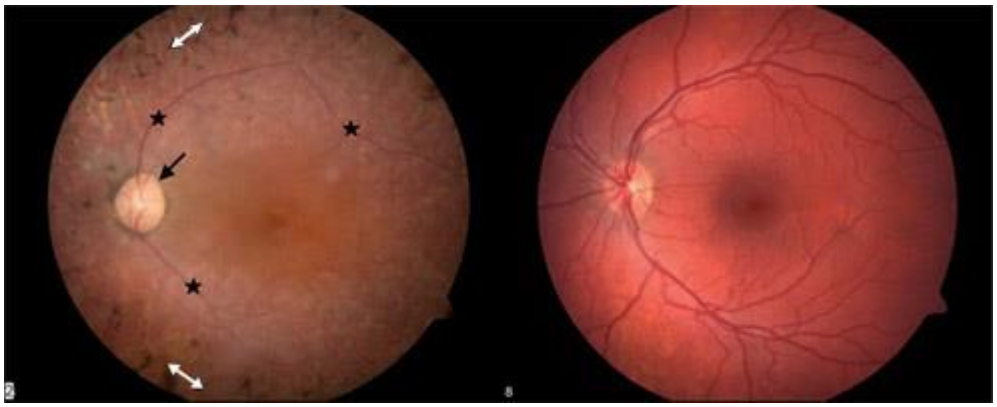
- Fitting with appropriate hearing aids
- Enrollment in an appropriate educational program for the hearing impaired
- Consideration of cochlear implantation, a promising habilitation option for persons with profound deafness

Usher Syndrome

Usher syndrome is the most common condition that affects both hearing and vision.

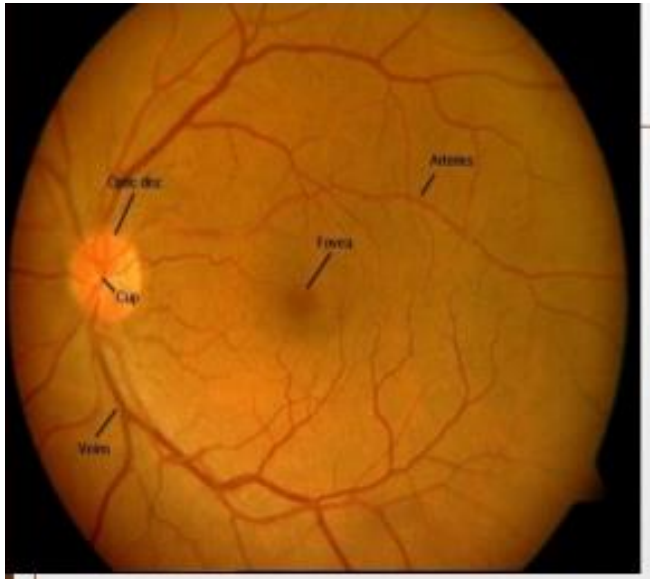
retinitis pigmentosa (RP):
causes night-blindness and a loss of peripheral vision (side vision) through the progressive degeneration of the retina.
the field of vision narrows—a condition known as “tunnel vision”—until only central vision (the ability to see straight ahead) remains.

Many people with Usher syndrome also have severe balance problems.

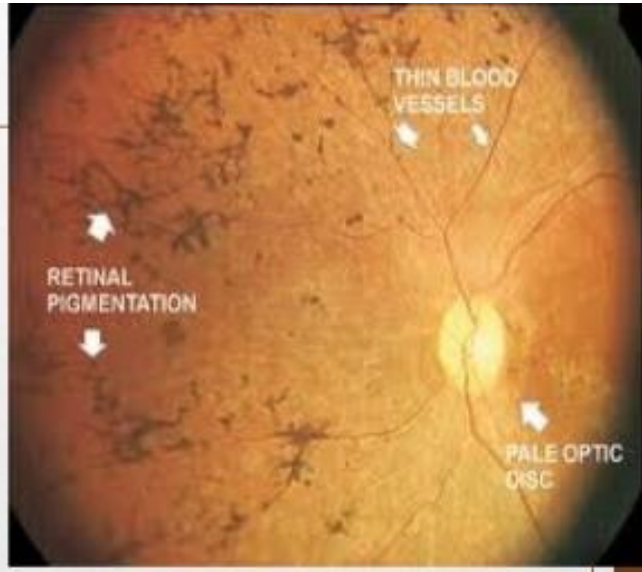


The optic nerve (arrow) looks very pale, the vessels (stars) are very thin and there is characteristic pigment, called bone spicules (double arrows).

Fundus Imaging



NORMAL FUNDUS

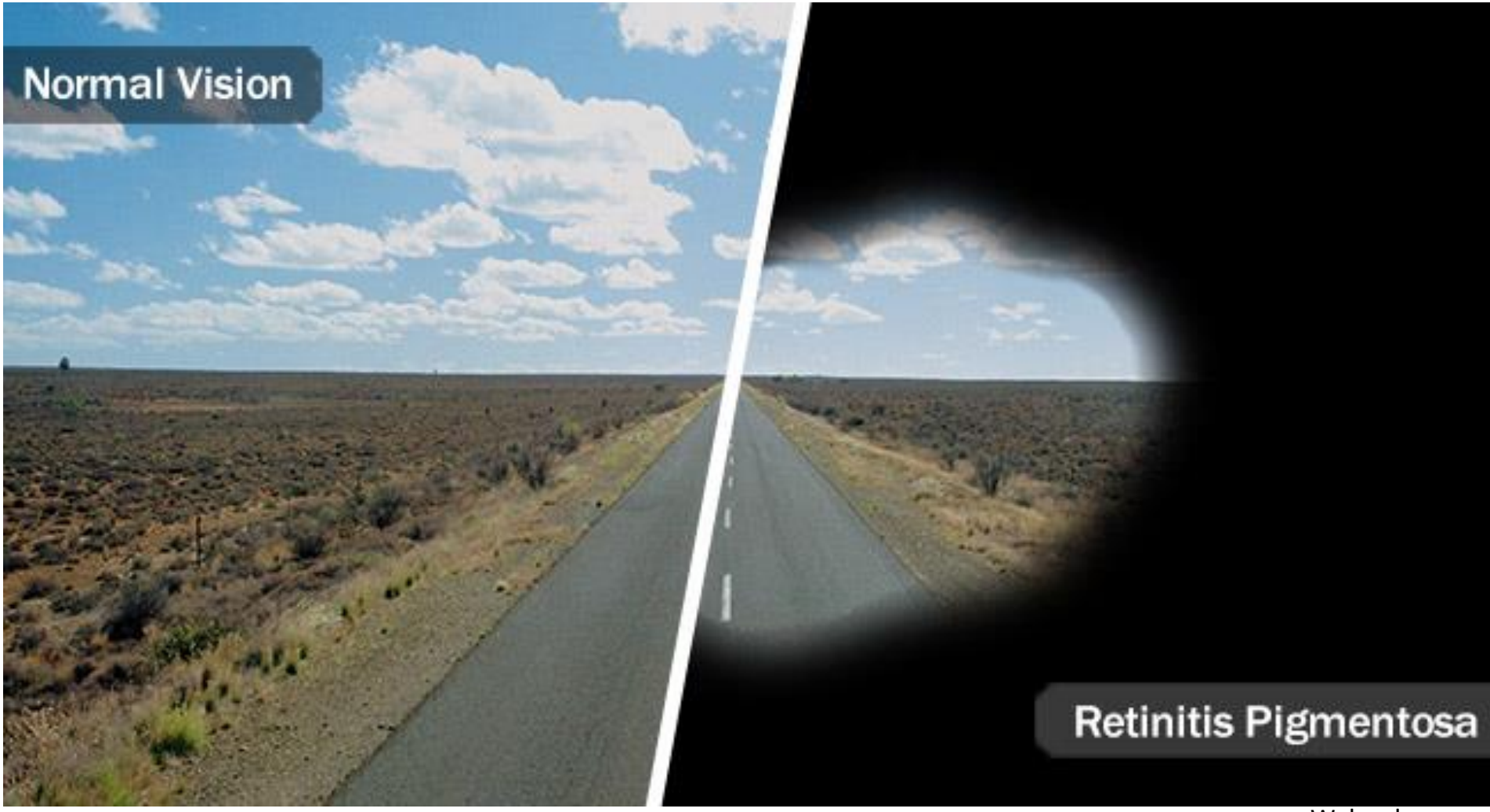


RETINITIS PIGMENTOSA

Retinitis Pigmentosa

Nyctalopia

Wikipedia.org



Webmd.com

prevalence

- The prevalence of Usher syndrome in the general US population has been conservatively estimated at 4.4:100,000 and the carrier frequency may be as high as 1:70

- The prevalence of Usher syndrome in persons of Scandinavian descent has been estimated at around 3.6:100,000

- Usher syndrome has been estimated to be responsible for 3%-6% of all childhood deafness and approximately 50% of all deaf-blindness

Usher Syndrome

(3-6% of childhood deafness)

	Hearing Loss	Vestibular System	Retinitis Pigmentosa
Type I	Congenital profound	Congenital balance problems	Onset pre-puberty
Type II	Congenital mild-severe sloping	Normal	Onset in teens-20s
Type III	Progressive later onset	Progressive balance problems	Variable onset

In the United States, types 1 and 2 account for approximately 90 to 95 percent of all cases of children who have Usher syndrome.

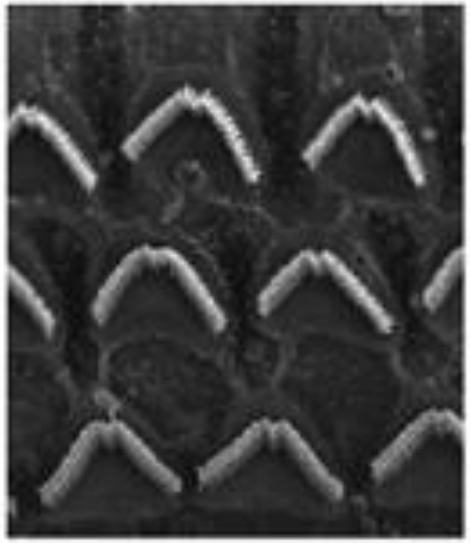
Usher type	Human Gene	Protein
USH1B	*MYO7A*	Myosin VIIA: motor activity; endocytosis
USH1C	*USH1C*	Harmonin: scaffolding
USH1D	*CDH23*	Cadherin 23: cell adhesion
USH1E	*unknown*	
USH1F	*PCDH15*	Protocadherin15: adhesion; signaling
USH1G	*USH1G*	SANS: membrane associated scaffold
USH2A	*USH2A*	Usherin: extracellular matrix domains
USH2C	*GPR98*	G-protein receptor 98: ion exchange, signaling
USH2D	*CIP98*	Whirlin: scaffolding.
USH3A	*CLRN1*	Clarin 1: transmembrane
USH3B	*unknown*	

Usher Type	Locus	Gene	Relative Incidence
USH1A	14q32	unknown	2%
USH1B	11q13.5	*MYO7A*	60%
USH1C	11p15.1	*USH1C*	5%
USH1D	10q	*CDH23*	10%
USH1E	21q	unknown	Rare
USH1F	10q21.1	*PCDH15*	Rare
USH1G	17q24-25	*SANS*	Rare
USH2A	1q41	*USH2A (+51)*	80%
USH2B	3p23-24.2	unknown	Rare
USH2C	5q14.3-q21.3	*VLGR1*	15%
USH3	3q21-q25	*USH3*	100%

Molecular Genetic Testing Used in USH1

Percent of All USH1 [1]	Gene Symbol (Locus Name)	Test Method	Mutations Detected	Mutation Detection Frequency by Gene and Test Method [2]
39%-55%	*MYO7A* (USH1B)	Sequence analysis	Sequence variants [3]	~90% [1, 4]
		Targeted mutation analysis	Panel of targeted known sequence variants [5]	See footnote 5
		Deletion / duplication analysis [6]	Exonic or whole-gene deletions	Unknown
6%-7% [7]	*USH1C* (USH1C)	Sequence analysis	Sequence variants [3]	Unknown
		Deletion / duplication analysis [6]	Exonic or whole-gene deletions	
19%-35%	*CDH23* (USH1D)	Sequence analysis	Sequence variants [3]	~90% [1]
		Deletion / duplication analysis [6, 8]	Exonic or whole-gene deletions	Unknown
Rare	Unknown (USH1E)	Linkage analysis	N/A	N/A
11%-19%	*PCDH15* (USH1F)	Sequence analysis	Sequence variants [3]	Unknown
		Targeted mutation analysis	p.Arg245X	See footnote 10
		Deletion / duplication analysis [6]	Exonic or whole-gene deletions	Unknown
Rare (7%)	*USH1G* (USH1G)	Sequence analysis	Sequence variants [3]	Unknown
Rare	Unknown (USH1H)	Linkage analysis	N/A	N/A

wild type
+/+

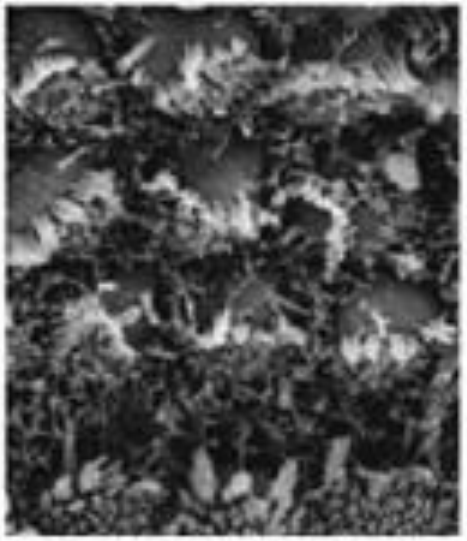


shaker 1
Myo7a^{4626SB}*/Myo7a*^{4626SB}

waltzer
Cdh23^{v}*/Cdh23*^{v}

deaf circler
Ush1C$^{dfcr-2J}$*/Ush1C*$^{dfcr-2J}$

Ames waltzer
Pcdh15^{av}*/Pcdh15*^{av}



Jackson shaker
Ush1g^{js}*/Ush1g*^{js}

Treatment

- Hearing aids: Young children can benefit from early fitting of hearing aids and speech training to normalize language.

- cochlear implantation may be warranted.

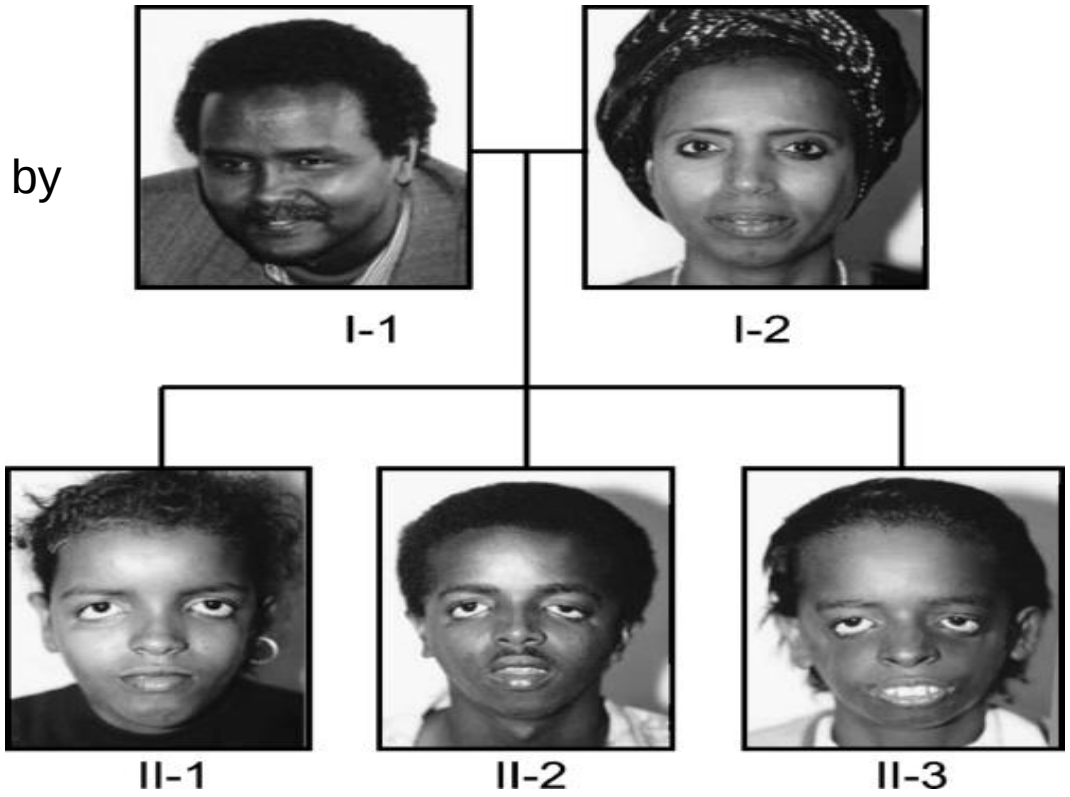
Treacher Collins Syndrome (TCS)

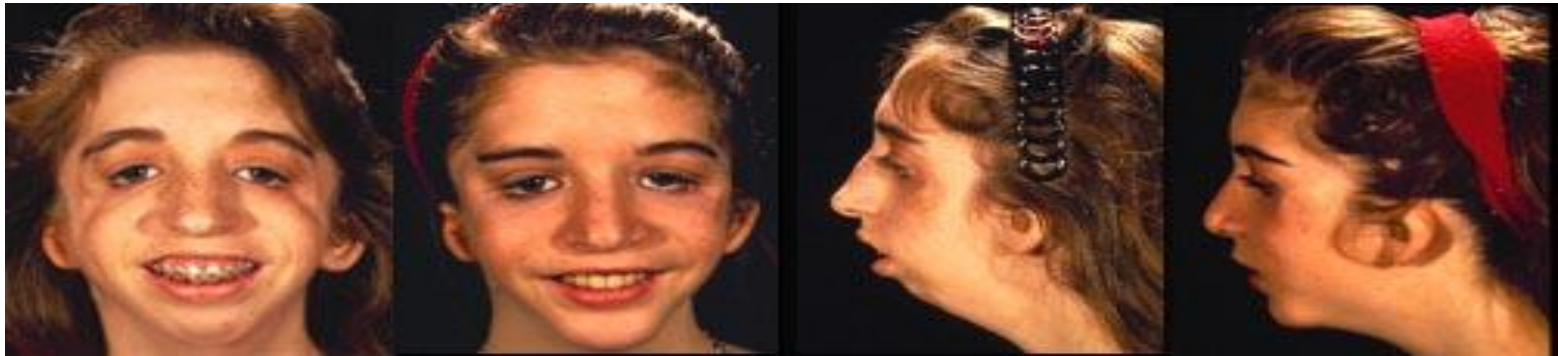
- Autosomal dominant disorder of craniofacial development
- prevalence of 0.2–1/10,000
- More than 60% of cases do not appear to have a previous family history
- **External ear abnormalities** (77%) including absent, small, and malformed ears (microtia) or rotated ears
- **Lower eyelid abnormalities** including the following:
  - Coloboma (notching) (69%)
  - Sparse, partially absent, or totally absent cilia (lashes) (53%)

Variability & Penetrance

Incomplete penetrance

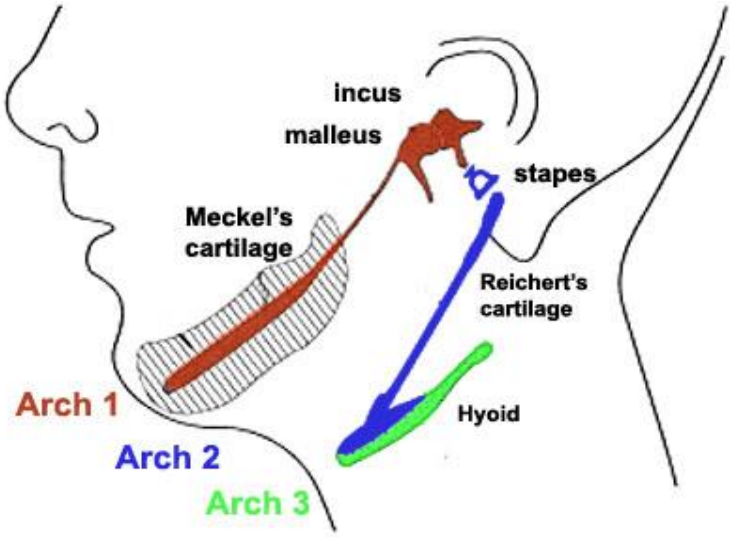
The phenotype cannot be predicted by the genotype



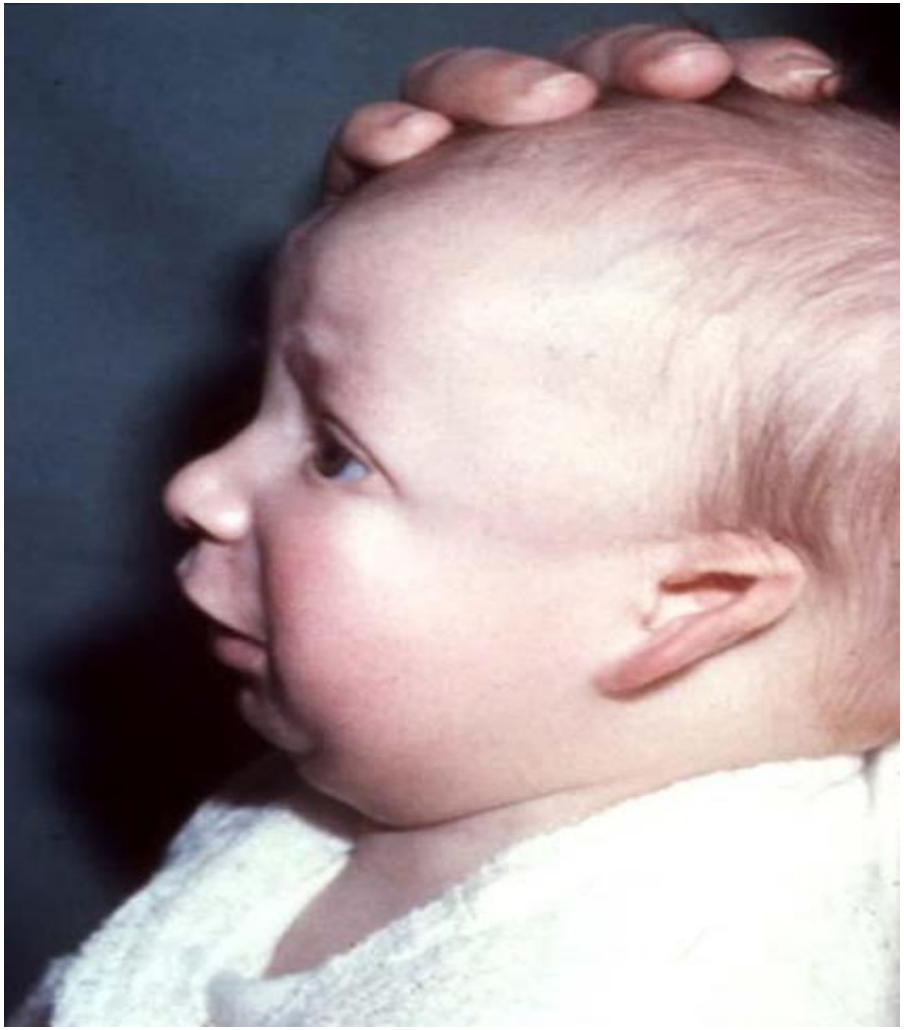


Phenotypes
Ear anomalies

- external ear abnormalities
- external auditory canals atresia
- Impairment of the middle ear ossicles
- 40%-50% of individuals have conductive hearing loss

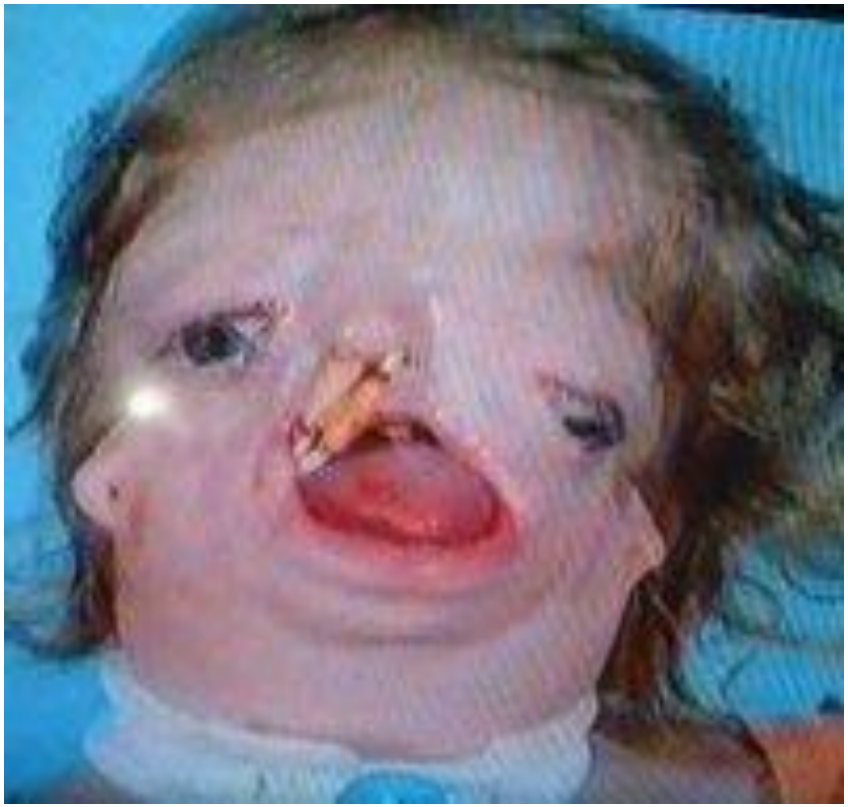


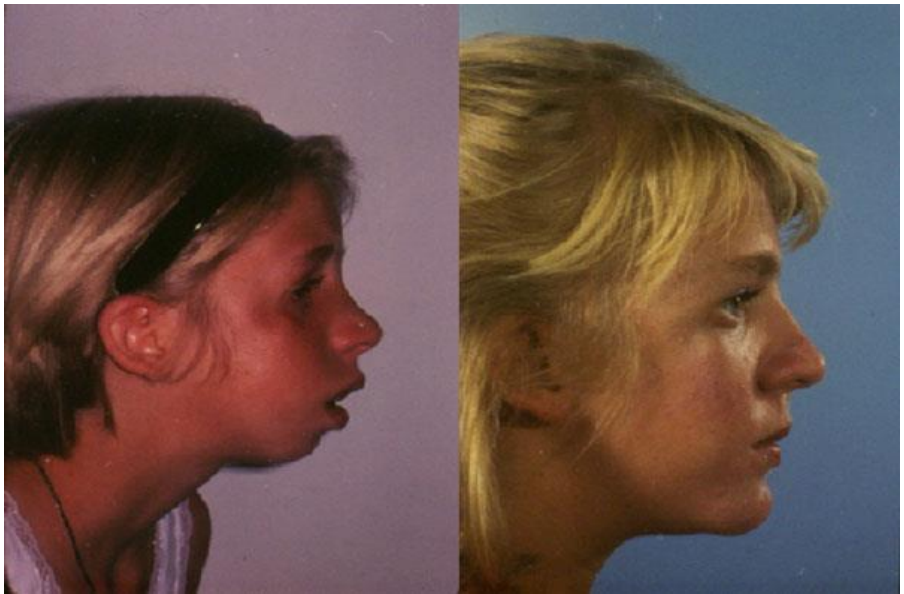
Pharyngeal Arch Structures



Facial anomalies

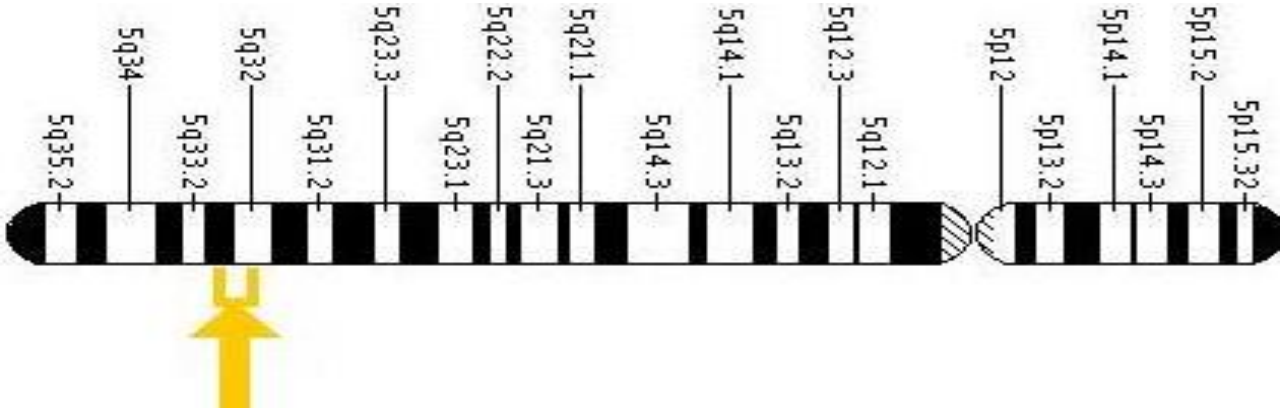
- Palpebral fissures (separation between the upper and lower eyelids)
- coloboma (notching) of the lower eyelid
- Mandible hypoplasia
- Zygomatic complex hypoplasia

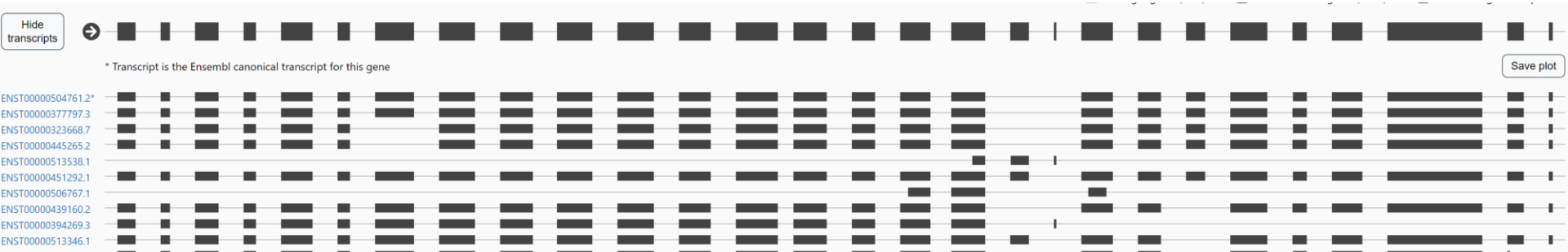




- To date, three genes are known to be involved in TCS:
  - *TCOF1*
  - *POLR1C*
  - *POLR1D*

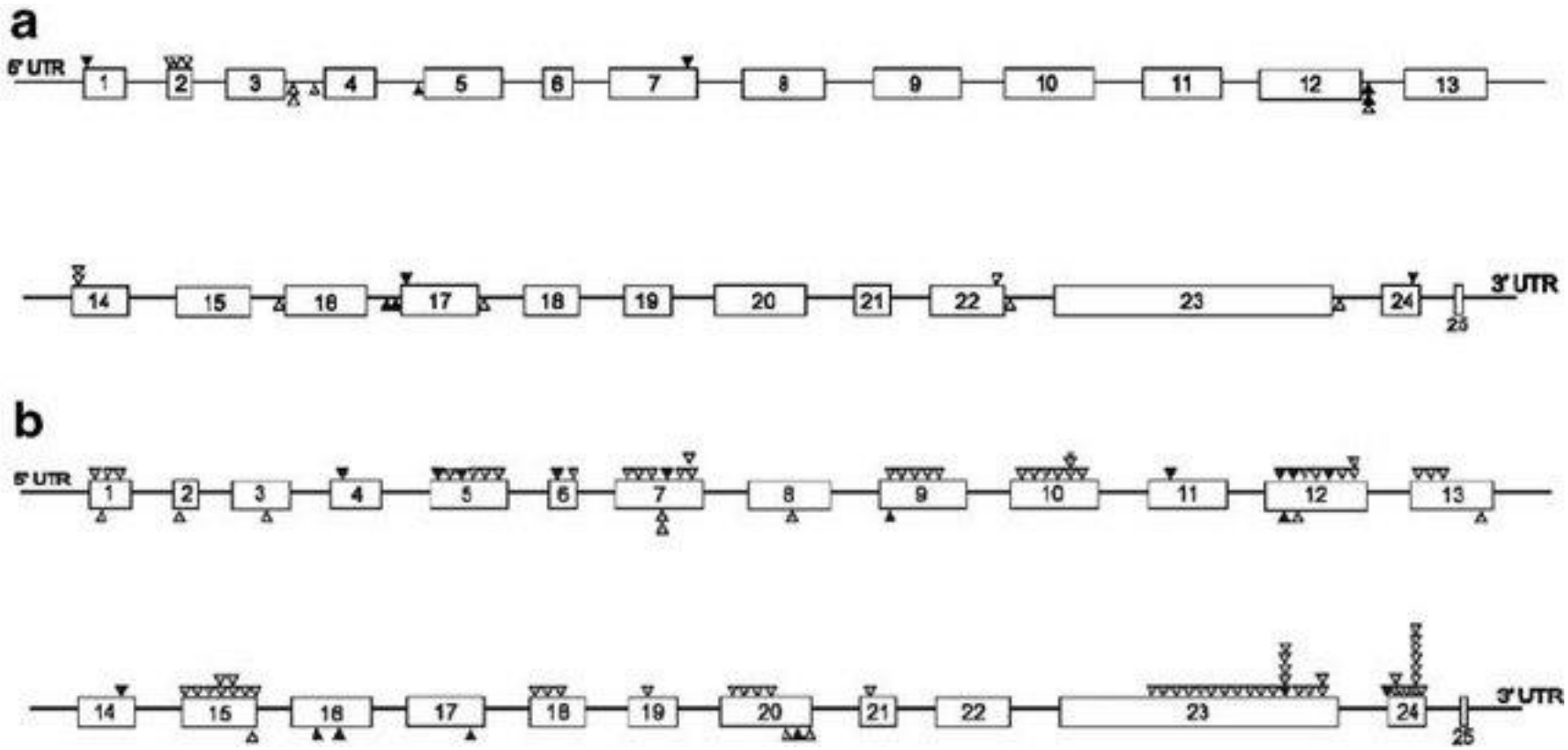
- Pathogenic variants in *TCOF1* are responsible for about 80–85% of TCS cases with typical facial features, whereas *POLR1C* and *POLR1D* are involved in less than 10%

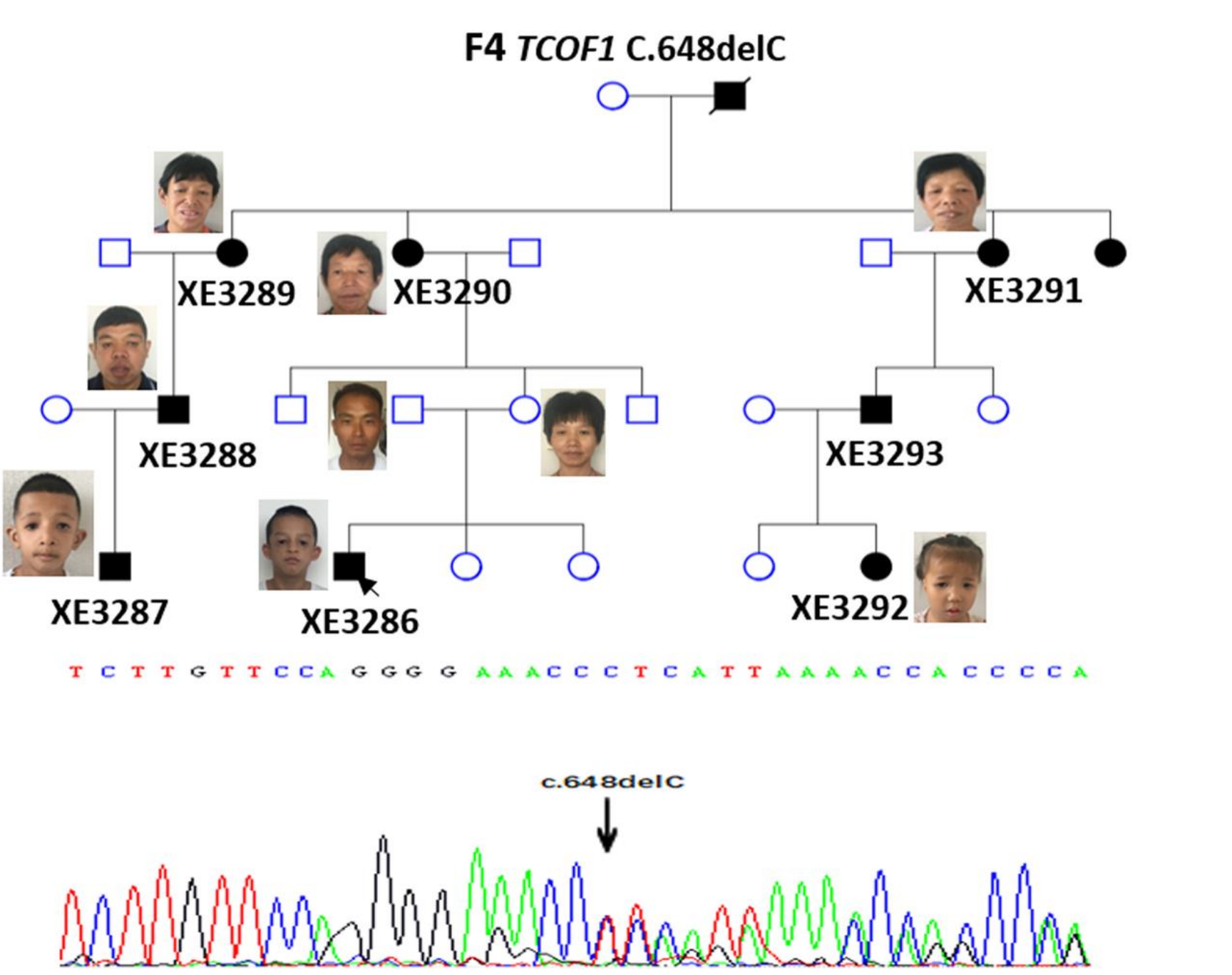




TCOF1 gene

- Affect the craniofacial complex development that arise from NC in the first and the second BA
- About 40% of individuals diagnosed with TCS have an affected parent
- About 60% of probands with TCS have the disorder as the result of a *de novo* gene mutation

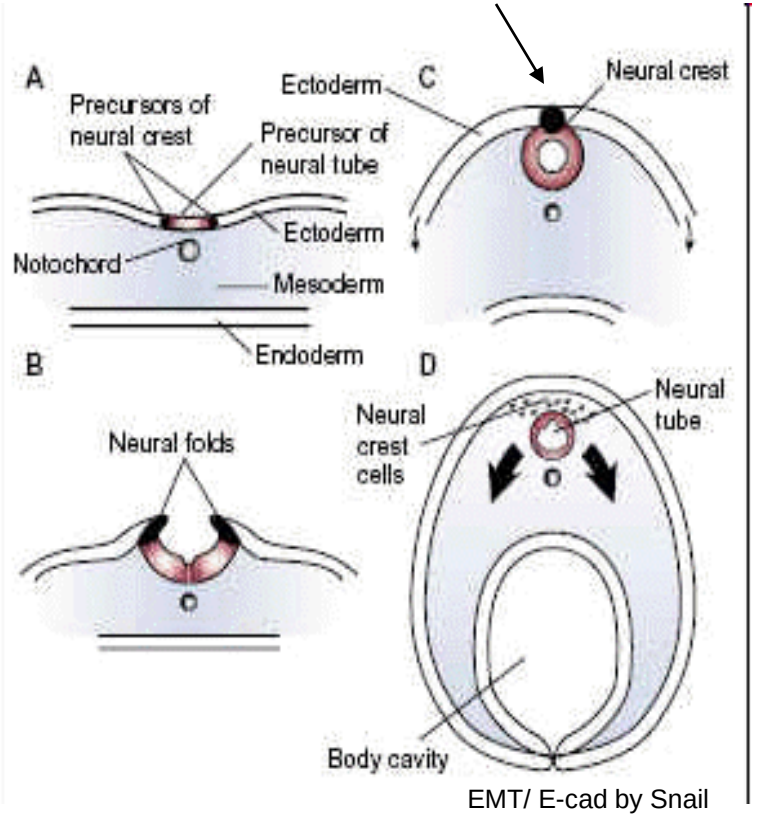




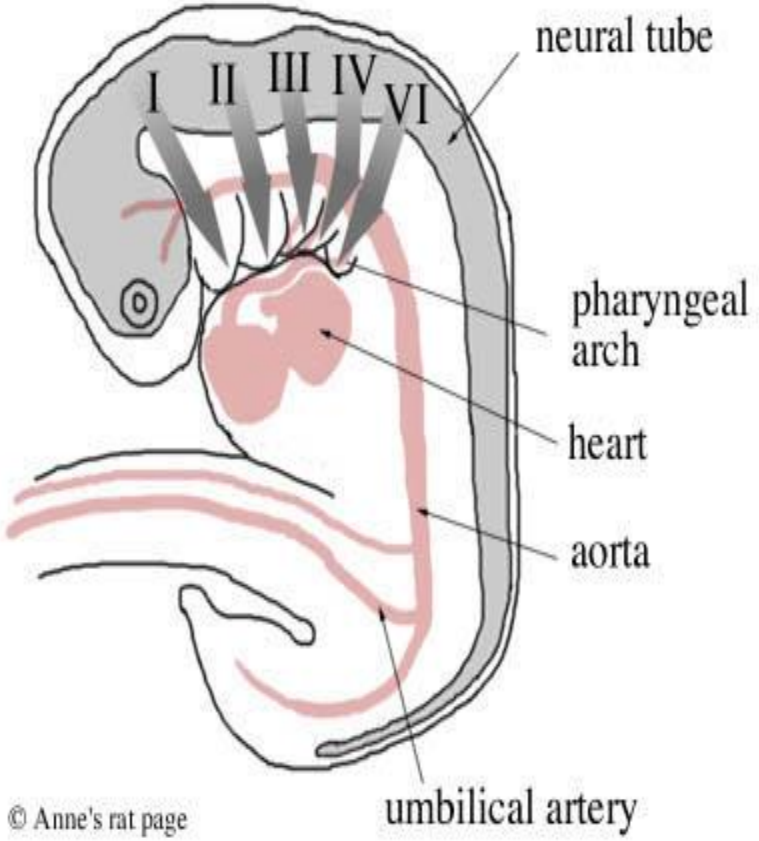
https://ojrd.biomedcentral.com/articles/10.1186/s13023-019-1136-z

The pathogenic *TCOF1* variants can reduce the number of neural crest cells (NCCs), which are needed for craniofacial embryological development

BMP, Wnt and FGF



EMT/ E-cad by Snail



http://missinglink.ucsf.edu/lm/IDS_101_embryology_basics/CoreText.htm