GENETICS AND HEARING LOSS

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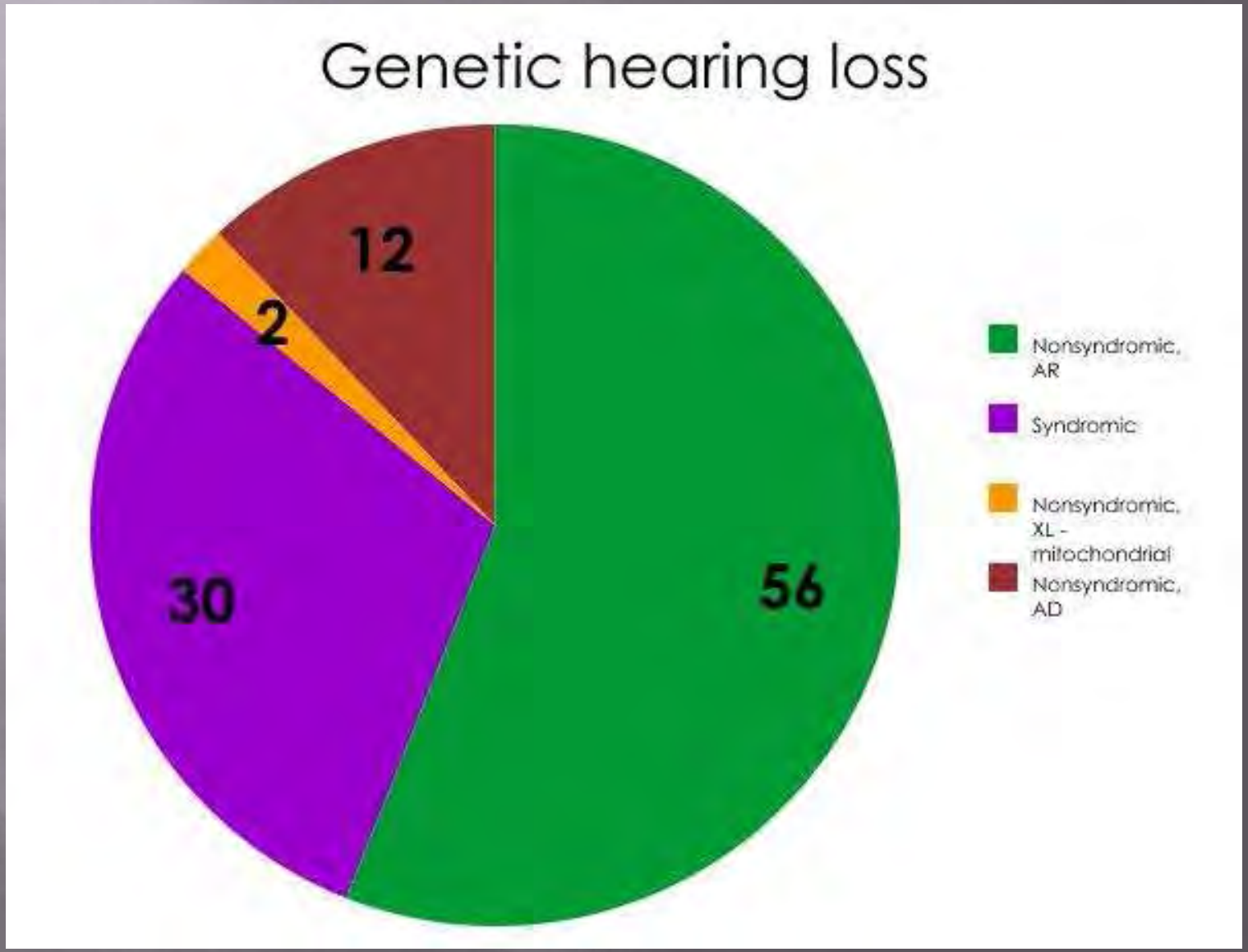
CAUSES OF DEAFNESS:

- 60% of childhood hearing loss is genetic
  - -Syndromic
  - -Nonsyndromic

- 40% of childhood hearing loss is caused by infectious/environmental factors
  - -prenatal infections (CMV, toxoplasmosis ,etc)
  - -meningitis
  - -low birth weight/prematurity
  - -Oto-toxic medications
  - -mechanical ventilation
  - -trauma

60% of deafness is genetic

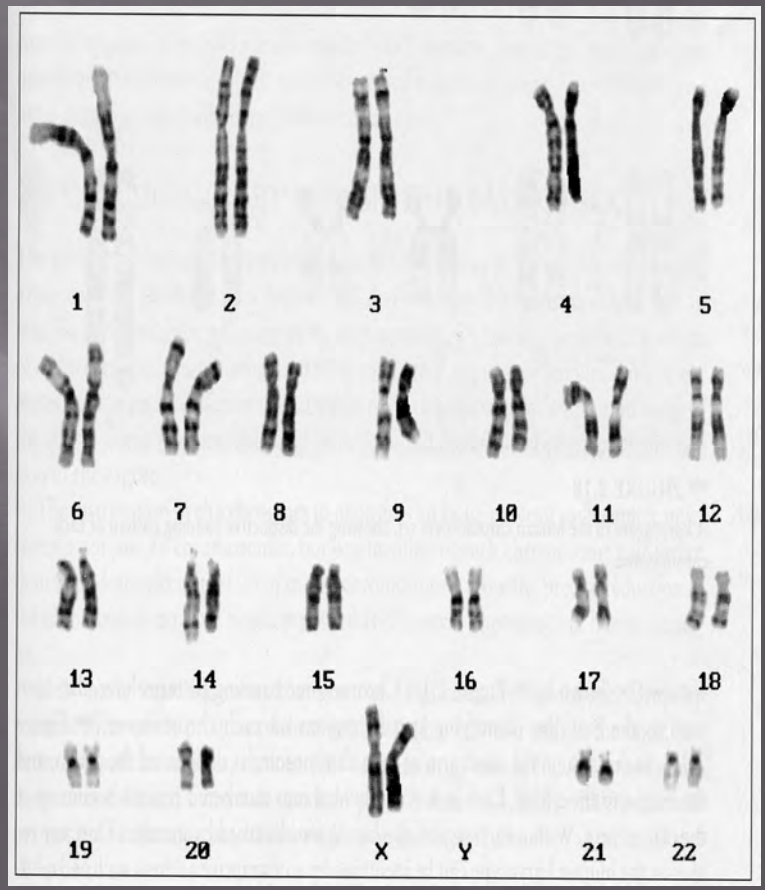


Genetic Hearing Loss

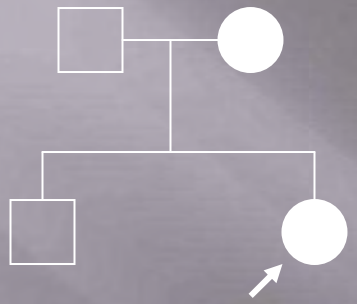
- Nonsyndromic hearing loss
  - Categorized by mode of inheritance:
    - DFN- X-linked deafness (~1%)
    - DFNA - Autosomal dominant deafness (12%)
    - DFNB - Autosomal recessive deafness (56%)
    - Mitochondrially inherited deafness (~1%)
- Syndromic hearing loss
  - 300+ syndromes with deafness as component

Review of Basic Genetics

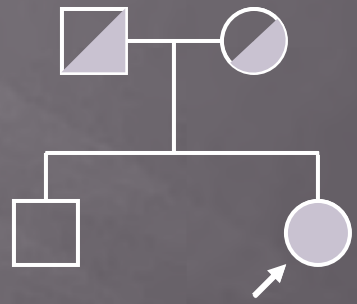
- Chromosomes in every cell
- 23 pairs of chromosomes for total of 46
- One from each pair we inherit from mom and the other from dad
- Chromosomes contain our genes



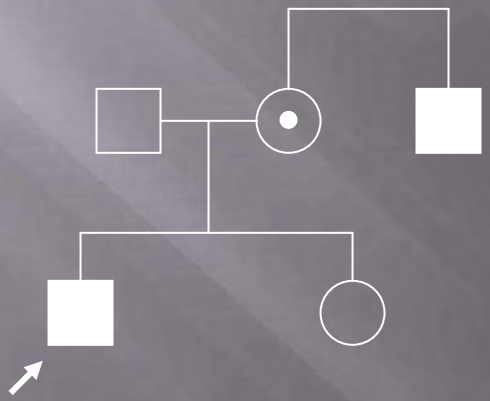
Modes of inheritance for non-syndromic hearing loss



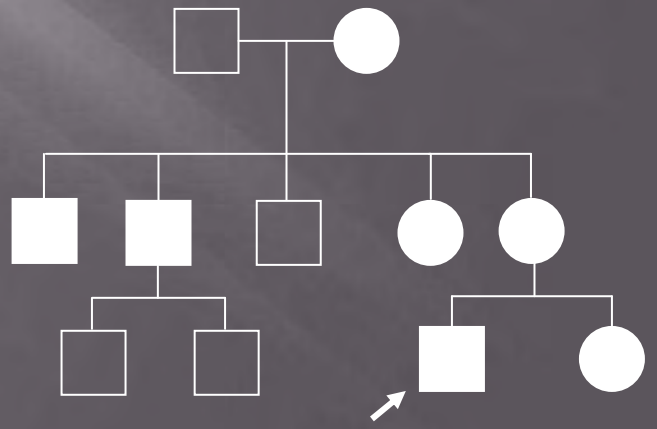
Autosomal Dominant
DFNA – 12%



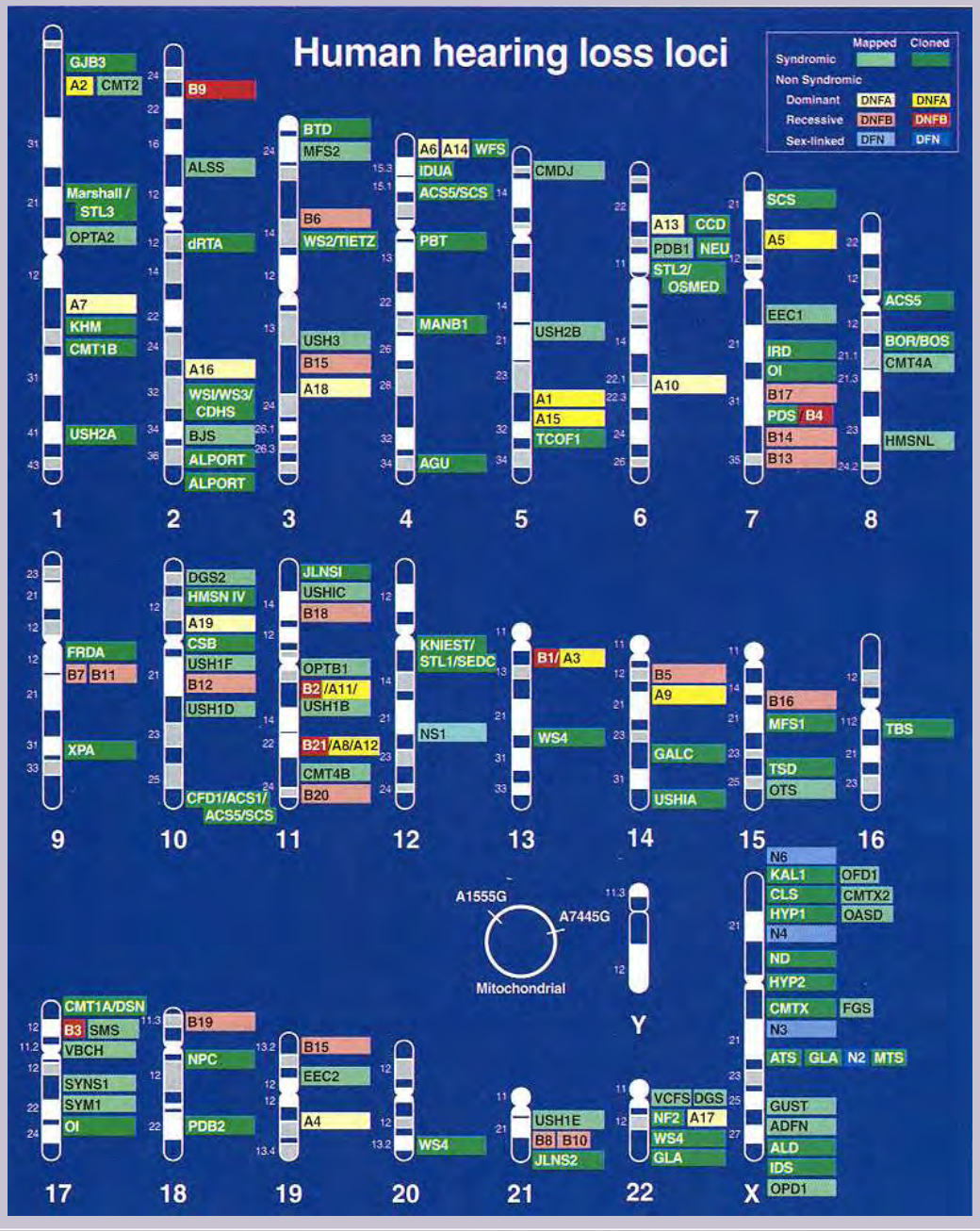
Autosomal Recessive
DFNB – 56%



X-linked
DFN – 1%



Mitochondrial
1%



Why is genetic deafness so common?

There are so many genes associated with hearing loss

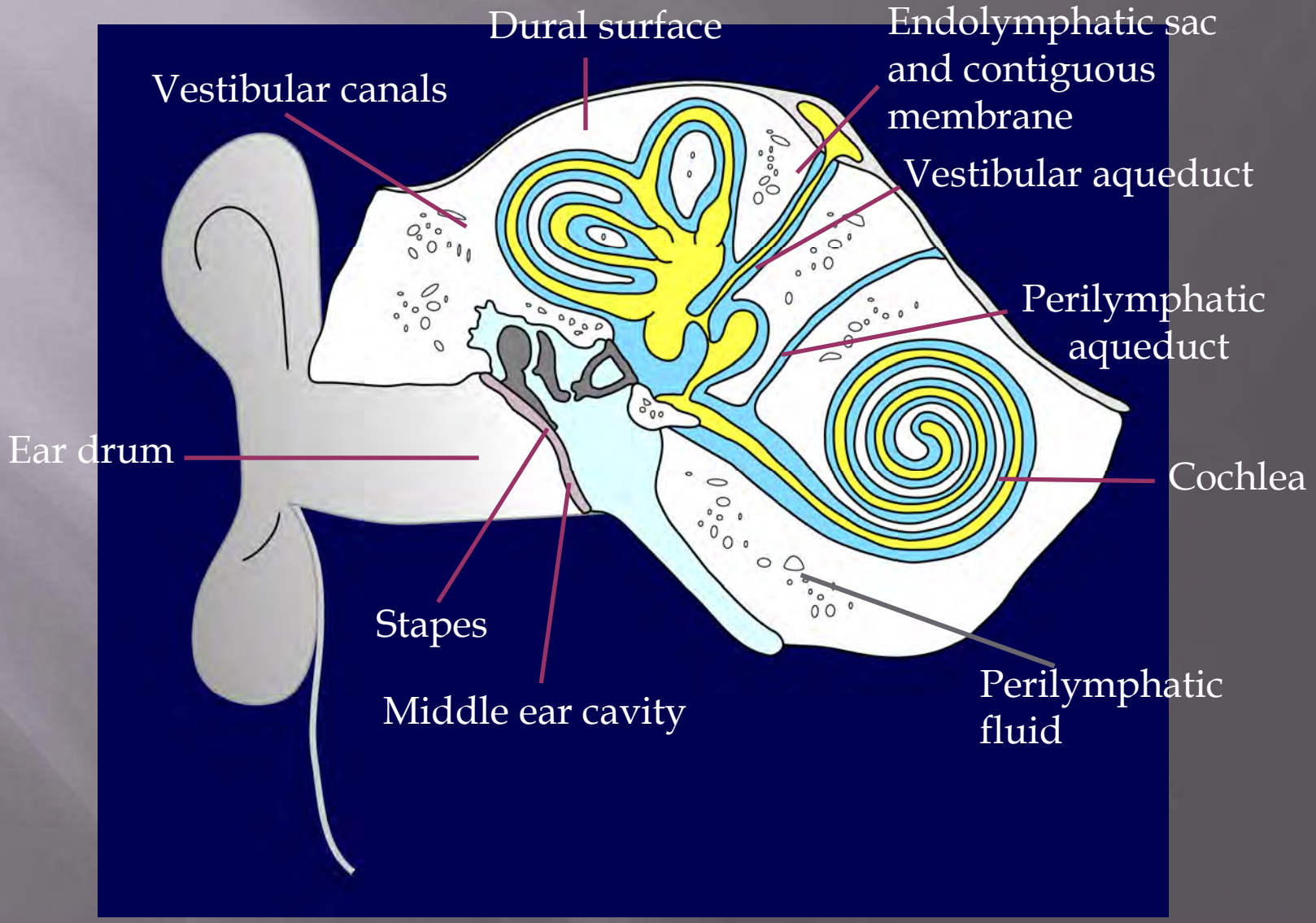
Genetic Evaluation of Deafness

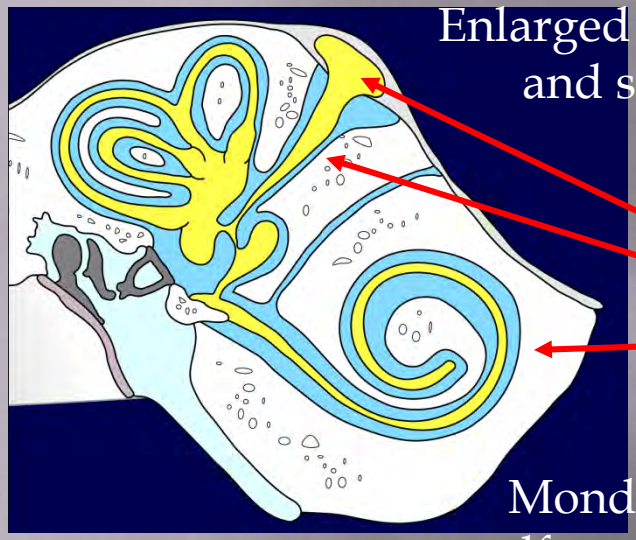
- Complete family history, prenatal and medical history, developmental assessment and physical examination
- Associated testing may include:
  - EKG, audiologic and vestibular testing, ophthalmology exam, X rays, CT/MRI of inner ear

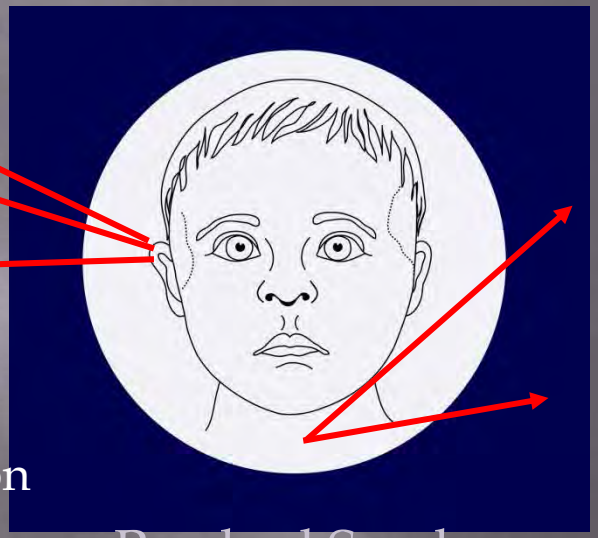
Hearing Loss Syndromes

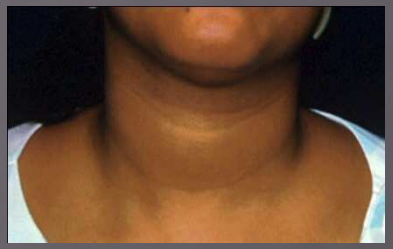
- Account for 20-30% of genetic HL
- >300 syndromes
- Each syndrome is relatively rare
- Syndromes identified by:
  - Physical examination findings
  - Internal ear malformations
  - Physiological traits (e.g., ECG changes)

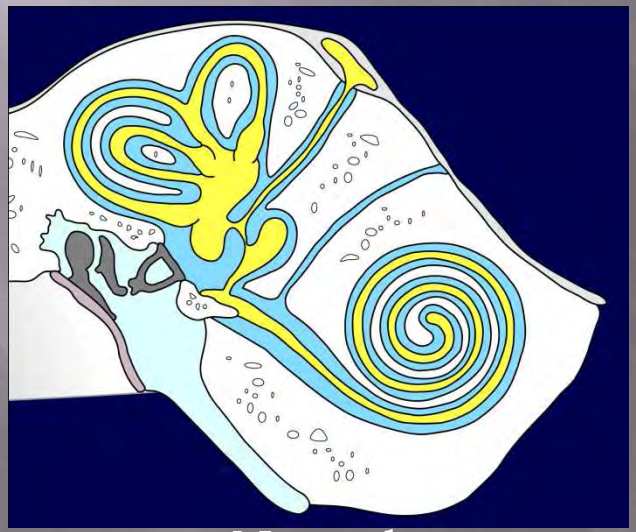
Anatomy Review





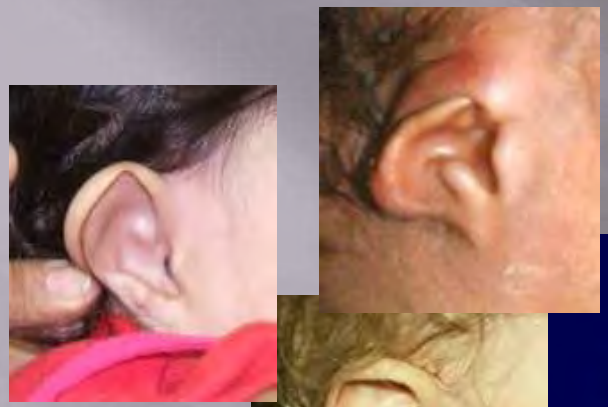


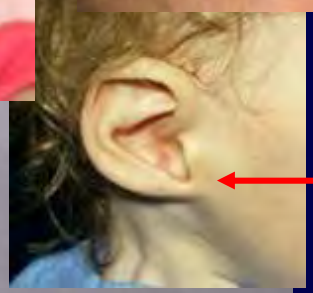


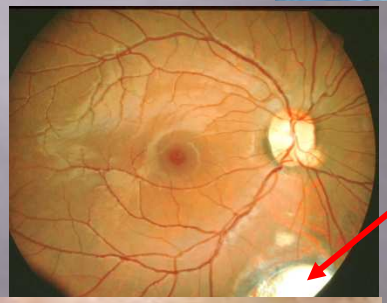


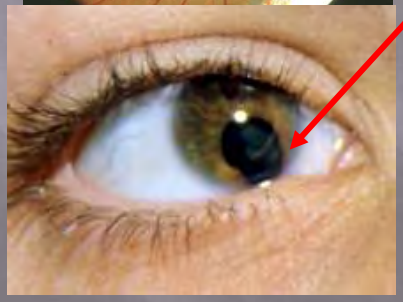
Normal

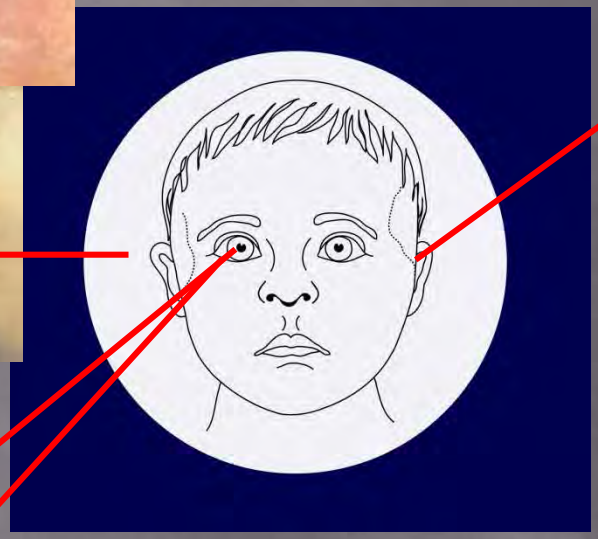
- Pendred Syndrome
  - Hearing loss, usually prelingual
  - Goiter in 2nd decade, most are euthyroid
  - Large vestibular aqueduct and endolymphatic sac
  - Upper 2/3 of cochlea is poorly formed



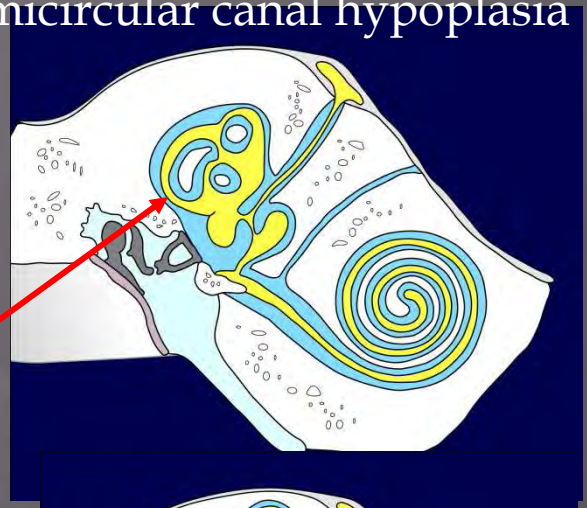


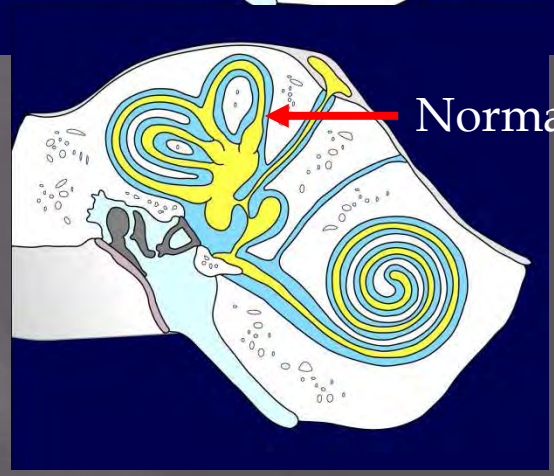






Semicircular canal hypoplasia





Normal

CHARGE Syndrome

Coloboma of the iris or retina

Heart defects

Atresia or stenosis of the choanae

Retarded growth and development

Genital hypoplasia in males

Ear anomalies

Deafness and Pigmentation

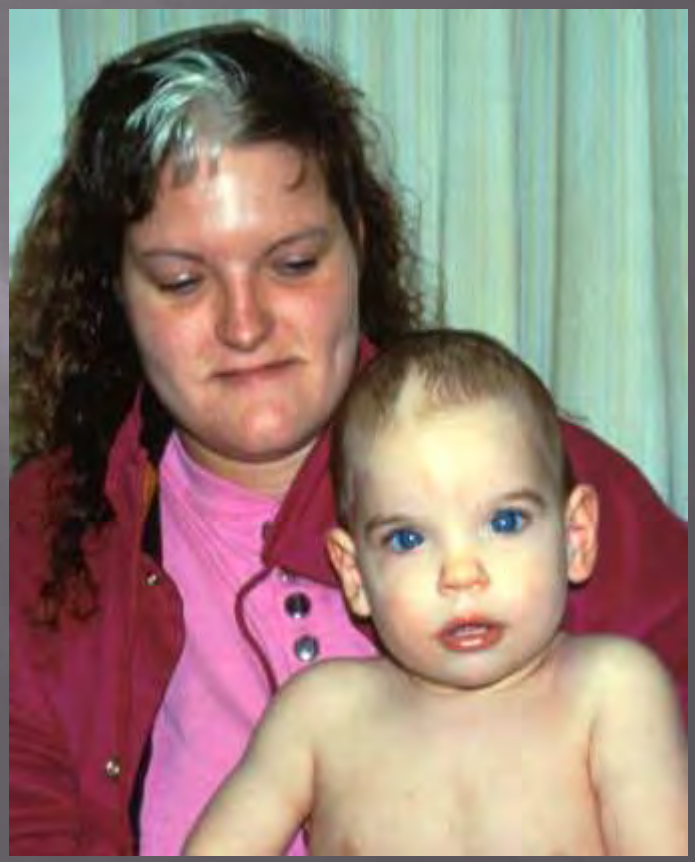
- Neural crest cell migration in early embryonic development is critical to both hearing and pigmentation processes
- Waardenburg syndrome and LEOPARD syndrome both involve defects in pigmentation and hearing loss

Waardenburg syndrome

- Accounts for 2-3% of all congenital deafness
- Several types of Waardenburg syndrome, most common type I
- Autosomal dominant inheritance
- PAX3 (2q35) and MITF (3p1) genes implicated in WS-I and WS-2

Waardenburg syndrome

- White forelock
- Heterochromia irides
- Synophrys
- Telecanthus
- Nl intelligence
- Nl lifespan

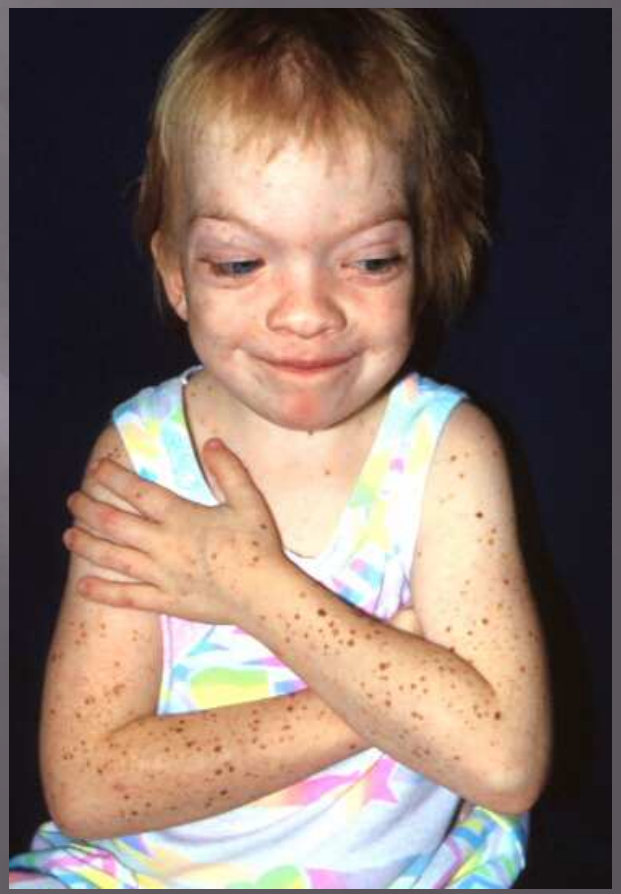


LEOPARD Syndrome

- Autosomal dominant inheritance
- Gene same as gene for Neurofibromatosis type 1 (NF1)

LEOPARD Syndrome

- Lentigenes
- EKG abnormalities
- Ocular hypertelorism
- Pulmonic stenosis
- Abnormal genitalia
- Retarded growth
- Deafness



Retinal Abn. and Deafness

- Retinal abnormalities seen in approx. 10% of deaf population
- Most commonly Retinitis Pigmentosa (RP - progressive night blindness)
- Usher syndrome, Refsum disease are autosomal recessive disorders and Norrie disease is X-linked recessive
- Suggest that all deaf individuals have ophthalmologic evaluations

Usher Syndrome

- Progressive night blindness due to RP
- Sensorineural hearing loss
- Eventual blindness and deafness
- Balance problems
- Multiple different genes can cause

Kidney Problems and Deafness

- Renal problems occur in a significant number of individuals with deafness
- Primarily accounted for by 2 diseases: Alport syndrome and BOR syndrome
- Suggested that all children with hearing loss have evaluation of kidney structure and function

Alport syndrome

- Progressive hearing loss in teen age or early adult years
- Renal problems characterized by hematuria and proteinuria; sometimes leading to end-stage renal failure
- Inherited as X-linked dominant or autosomal recessive trait
- Gene testing available

Cardiac conduction defects and deafness

- Presence of prolonged QT and heart arhythmia is known as “Long QT syndrome”
- When associated with SNHL results in a condition called Jervell-Lange-Nielsen
- JLN is inherited as an autosomal recessive condition, but heterozygotes display long QT intervals
- Genetic testing for JLN is available clinically - genes involved are KVLQT1 and KCNE1

Thyroid disease and deafness

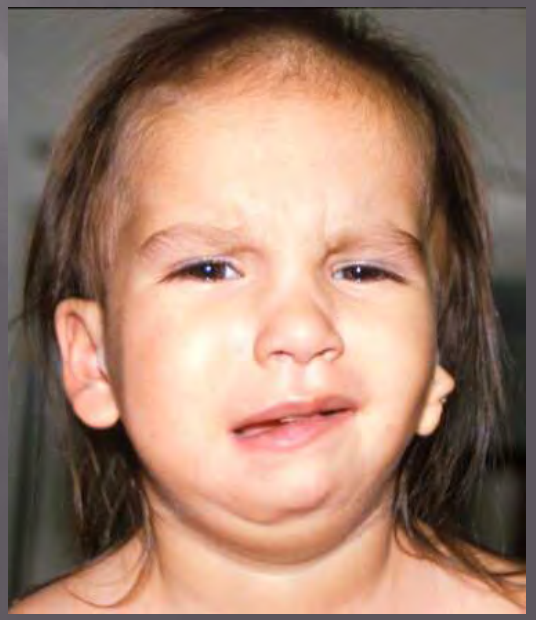
- Goiter/thyroid dysfunction occurs in Pendred syndrome
- Most common genetic cause of deafness, accounting for 5% of deaf individuals
- PDS gene at 7q31 responsible for Pendred syndrome and some nonsyndromic hearing loss (DFNB4)
- Autosomal recessive inheritance

Other syndromes with SNHL

- Hundreds of other genes which result in SNHL with other physical findings
- Some of these conditions are very rare, others common
- Identification of SNHL genes continues at a fast rate, but the utility of genetic testing for many of these conditions is not keeping pace

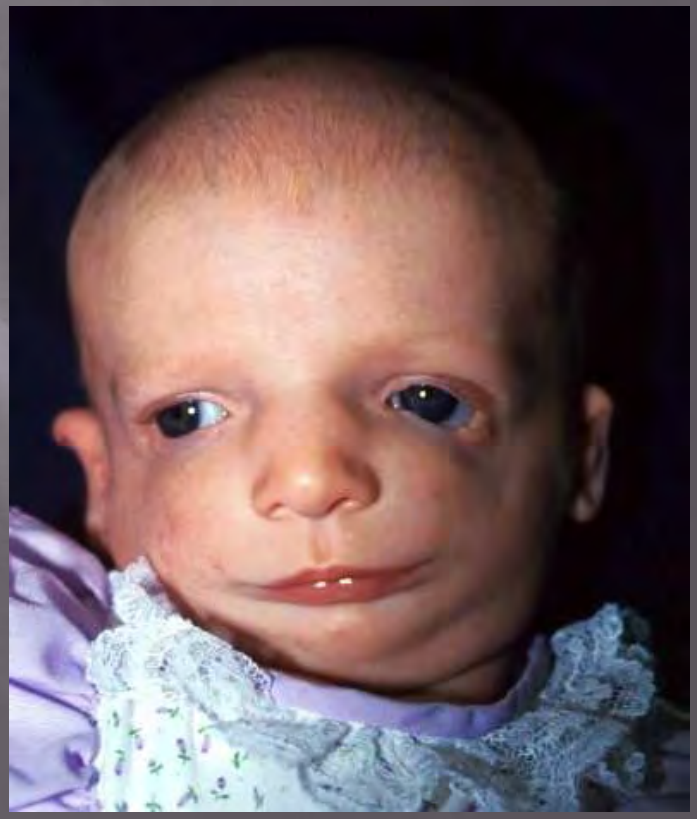
Goldenhar syndrome

- Aka Hemifacial Microsomia
- Features include:
  - facial asymmetry
  - eye abnormalities (epibulbar dermoid)
  - ear malformations
  - vertebral anomalies
- Sporadic inheritance

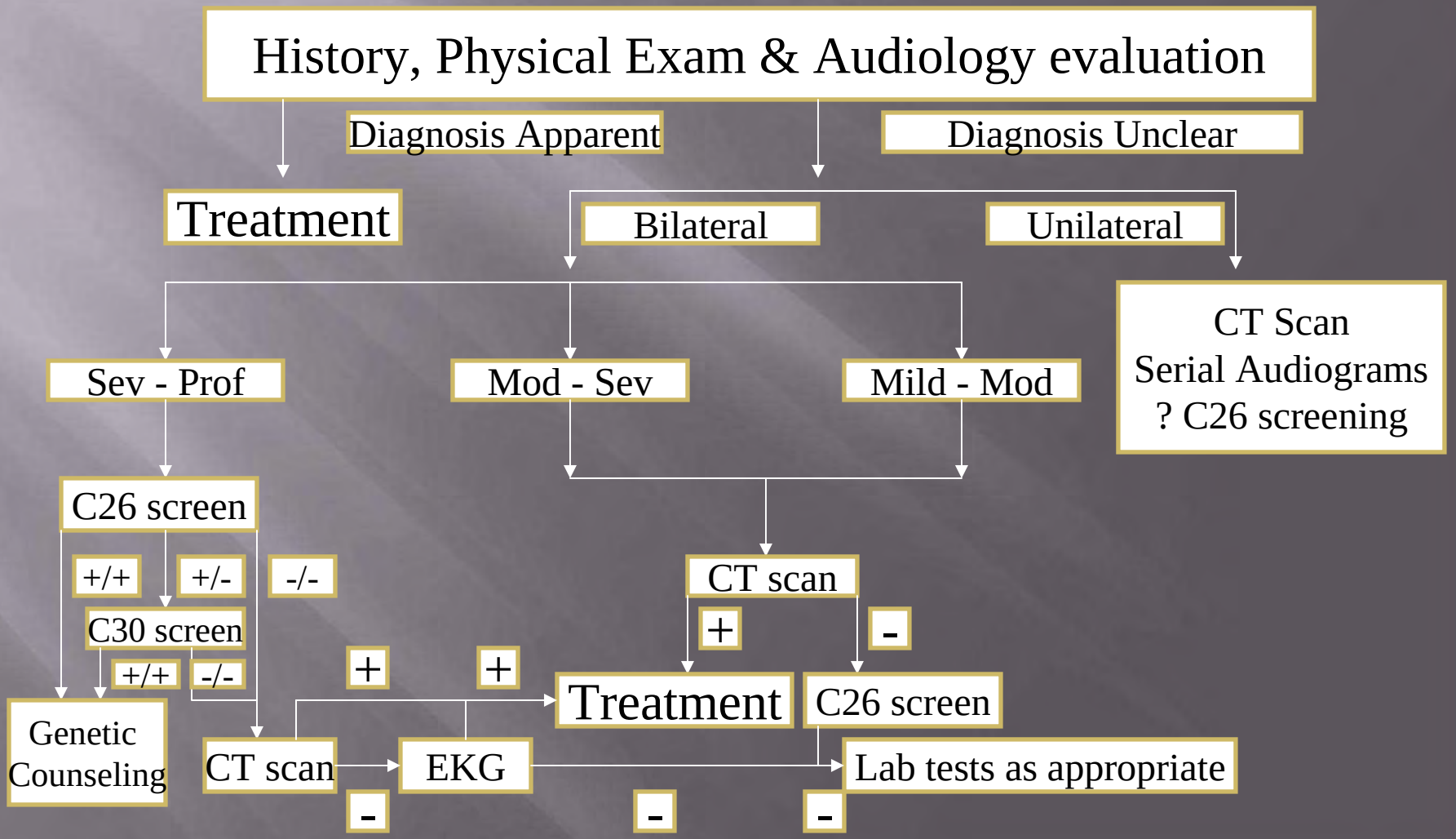


Treacher Collins syndrome

- Features include:
  - downslanting eyes
  - eyelid colobomas
  - dysplastic ears & conductive deafness
  - small chin
  - nl intelligence
- Autosomal dominant inheritance
- Gene testing available



Protocol for evaluation of childhood deafness



Nonsyndromic Hearing loss

- Inherited in autosomal dominant, recessive, X-linked recessive and mitochondrial patterns
- DFN - X-linked (2-3%)
- DFNA - Autosomal dominant (10-20%)
- DFNB - Autosomal recessive (75-80%)
- Mitochondrial (< 1%)

Connexin 26 Prevalence

- Accounts for 10% of all hearing loss
- Accounts for 30% of all sporadic deafness
- Accounts for 50-80% of autosomal recessive hearing loss
- Gene codes a gap junction in the cochlea (GJB2)
- 1/50 US Caucasians carry a mutation

Connexin 26 Clinical Features

- Hearing loss is prelingual
- Hearing loss is non-progressive
- Severity varies both between families and within a given family
- No health or learning problems associated
- Connexin 26 gene is implicated in KID syndrome (keratoderma, ichthyosis, deafness)

Connexin 30

- Gene codes a gap junction in the cochlea (GJB6)
- Mutations can interact with mutations in Connexin 26 to result in recessive hearing loss
- Accounts for 3% of all recessive hearing loss but is much more common in the Spanish population
- May account for deafness in 30-70% of Connexin 26 heterozygotes

Genetic Counseling for NSHL

- Genetic testing is available for only a few of the genes which have currently been identified for NSHL
- At present, genetic counseling very often consists of risk appraisal without the option of DNA testing or prenatal diagnosis by DNA or other methods
- Advances in the field may result in rapid changes to what we are able to offer families

Questions?