What's Genetics got to do with it?

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Text **GENETICS18** to **22333** once to join

Learning points

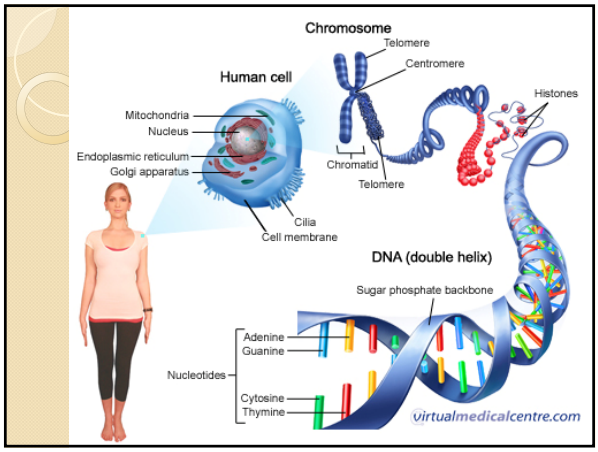
- Genetic changes in our DNA
- Syndromes that cause delayed speech acquisition or hearing loss
- Is it important to know if speech delay hearing loss is genetic or acquired?

Reflection

Imagine yourself as a parent of a 6 month old child who has just been diagnosed with hearing loss and seizures. Your child just had skull surgery. The physician is now recommending genetic testing.

What are your concerns?

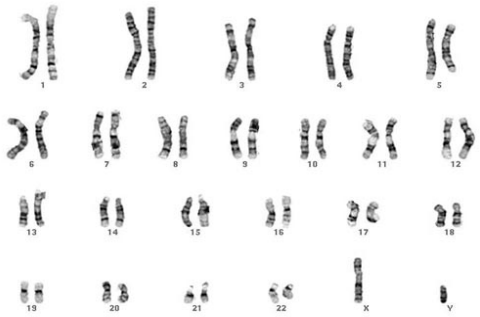
What are your expectations?



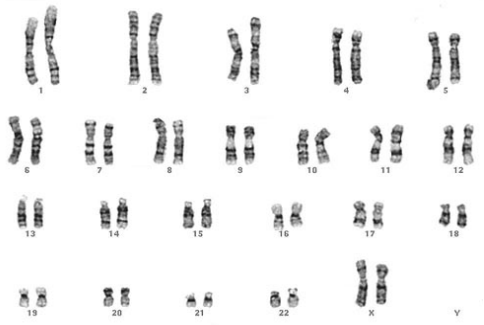
Chromosomes in one cell

(under the microscope)

Male Chromosome 46, XY



Female Chromosomes 46, XX



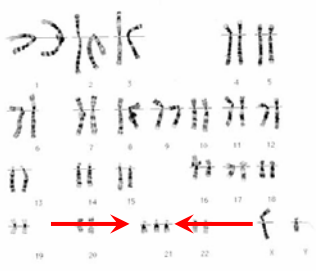
TEST
High Resolution Chromosomes

- Detects large chromosomal changes
- Easy test
- Inexpensive

What does this Child Have?

Source: http://articles.complexchild.com/jan2011/00264.html

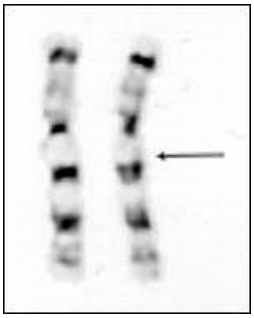
Down Syndrome- Trisomy 21



•Incidence ~1/ 800 babies born

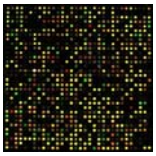
•Incidence increases with mom's age

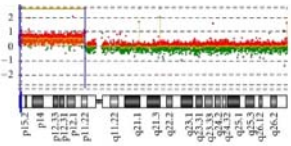
Microdeletion/Microduplication Syndromes



TEST
Chromosome Microarray (CMA)

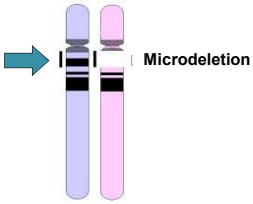
- Detects microdeletions or microduplications
- Variants of unknown significance
- **Informed consent**

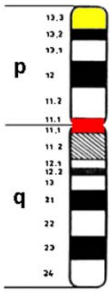




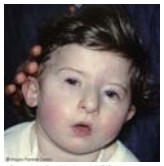
Chromosome structure

- p- short arm (petite)
- q- long arm





22q11 Deletion syndrome



Source: https://en.wikipedia.org/wiki/DiGeorge_syndrome

- Heart defects
- Feeding difficulties
- Kidney problems
- Hearing loss
- Cognitive and speech delay
- Behavioral, emotional, and psychiatric differences(ADHD, autism, anxiety, etc.)
- Older Names include: DiGeorge syndrome (DGS), velo-cardio-facial syndrome (VCFS), conotruncal anomaly face syndrome (CTAF), Opitz G/BBB syndrome, CATCH-22 and Cayler cardiofacial syndrome.

William syndrome (7q11.23 deletion)

- Characteristic facial appearance
- Heart and blood vessel problems
- Low birth-weight / low weight gain
- Feeding problems
- Dental abnormalities
- **Hyperacusis**
- Overly friendly (cocktail) personality
- Developmental delay, learning disabilities and attention deficit

Source: https://williams-syndrome.org/what-is-williams-syndrome

7q11.23 duplication syndrome

- significant expressive speech and language delays
- receptive language often stronger than expressive
- behavioral concerns such as social phobias and separation anxiety
- possible oppositional defiance disorder
- sometimes misdiagnosed as on autism spectrum.

16p12.2 Microdeletion

- developmental delay
- delayed speech
- intellectual disability that ranges from mild to profound
- weak muscle tone (hypotonia)
- slow growth resulting in short stature
- an usually small head (microcephaly)
- malformations of the heart
- recurrent seizures (epilepsy)
- psychiatric and behavioral problems

16p12.2 Microdeletion continued

Sometimes…

- hearing loss
- an opening in the lip (cleft lip) with or without an opening in the roof of the mouth (cleft palate)
- dental abnormalities
- malformed kidneys
- genital abnormalities in males

TEST

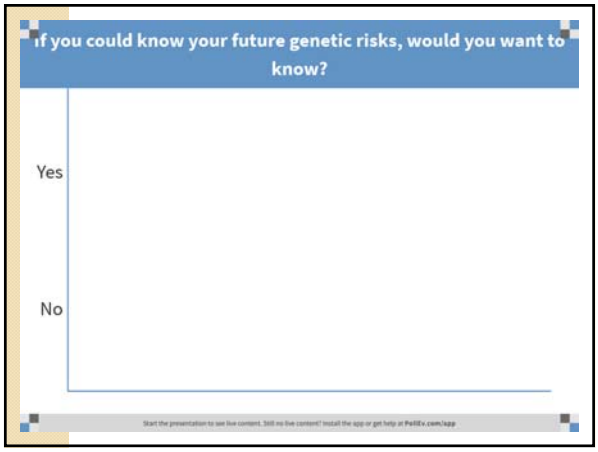
Single Gene(s) Analysis

- Specify gene(s) of interest
- Available in panels

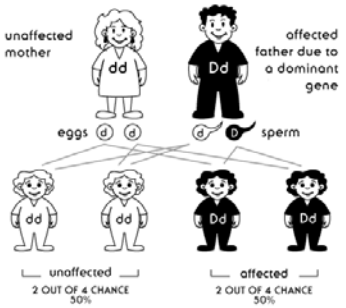
TEST

Whole Exome Sequencing (WES)

- Method
- Results are expansive
- Wait for results
- Informed consent – Parents are tested!



Dominant Inheritance



Autosomal Dominant Inheritance

- If one copy has a mutation then you get the disease
- We see it being passed down through the generations from parent to child to grandchild
- Does not SKIP a generation
- Both boys and girls are affected
- Chance of passing it on is ~ 50%

Mowat-Wilson syndrome

- unusually small head (microcephaly)
- intellectual disability ranging from moderate to severe
- delayed development of motor skills
- Speech is absent or severely impaired
  - affected people may learn to speak only a few words
  - many with this condition can understand others' speech and some use sign language to communicate
  - if speech develops, it is delayed until mid-childhood or later

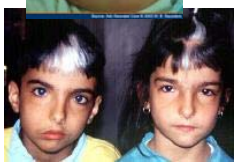
AD HL Nonsyndromic

- No single prominent causative gene
- *DIAPH1, KCNQ4, GJB3, GJB2, GJB6, MYH14, DFNA5, WFS1, TECTA, COCH, EYA4, MYO7A, COL11A2, POU4F3, MYH9, ACTG1, MYO6, SIX1, SLC17A8, TFCP2L3, TMC1, DSPP, P2RX2, CCDC50, MYO1A, MIR96, TJP2, FAM189A*
- **Phenotype:** Most progressive and onset postlingual, varying ages at presentation.

AD HL Syndromes

Waardenburg syndrome (WS)

- 4 subtypes-WS I, WS II, WS III, and WS IV. *PAX3, MITF EDNRB, EDN3, SOX10*
- **Phenotype:** varying degrees SNHL and pigmentary abnormalities of the skin, hair, and eyes.



Source: https://emedicine.medscape.com/article/950277-overview

Other AD HL Syndromes

- **Branchiootorenal disorder spectrum (BOR):** conductive, sensorineural, or mixed hearing loss, branchial cleft abnormalities (i.e. preauricular pits), malformations of external ear, renal anomalies.
- **Neurofibromatosis 2 (NF2):** hearing loss, usually in the third decade, secondary to bilateral vestibular schwannomas. Balance dysfunction and tinnitus.

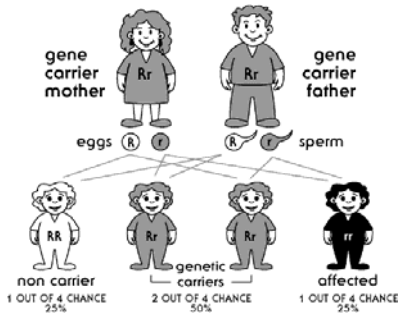
Other AD HL Syndromes

- **Stickler syndrome:** progressive sensorineural and/or conductive hearing loss, cleft palate, and spondyloepiphyseal dysplasia, precocious arthritis, high incidence of retinal detachment due to severe myopia.
  - Interfamilial variability

Source: https://medicalpictures.net/stickler-syndrome-pictures/

Autosomal Recessive Inheritance

(both parents carriers)



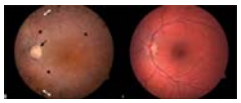
Autosomal Recessive Inheritance

- Parents generally not affected
- Can be male or female
- If parents are related, there is a higher risk of these conditions
- Individuals with only one changed copy are carriers
- Tend to see multiple affected siblings, but may not have family history
- Ethnicities

AR HL Nonsyndromic

- Connexin 26 (*GJB2*)
- *GJB6, MYO7A, MYO15, SLC26A4, TMIE, TMC1, TMPRSS3, OTOF, CDH23, STRC, USH1C, TECTA, OTOA, PCDH15, RDX, GRXCR1, TRIOBP, CLDN14, MYO3A, DFNB31, GPSM2, ESRRB, ESPN, MYO6, HGF, MARVELD2, COL11A2, PJVK, SLC26A5, LRTOMT, LHFPL5, BSND, SYNE4, LOXHD1, TPRN, and PTPRQ*
- **Phenotype:** most severe to profound stable hearing loss; some moderate and progressive hearing loss.

AR HL Syndromes



Usher syndrome

- **Phenotype:** SNHL and retinitis pigmentosa
  - Type I - congenital severe-to-profound SNHL, abnormal vestibular dysfunction
  - Type II - congenital mild-to-severe SNHL (mild to moderate in the low frequencies and severe to profound in the higher frequencies) and normal vestibular function
  - Type III - progressive hearing loss and deterioration of vestibular function

Other AR HL Syndromes

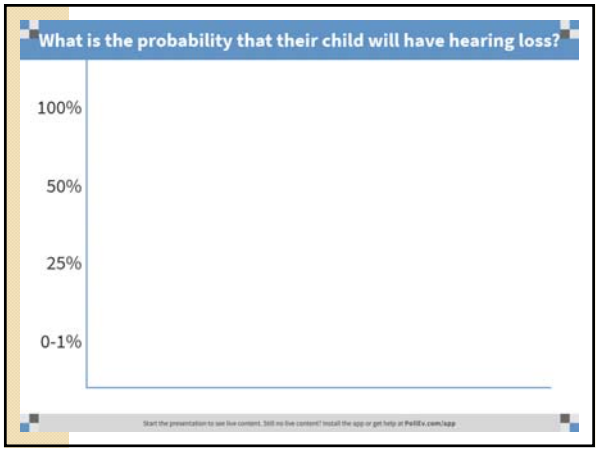
- **Pendred syndrome:** congenital SNHL, (severe-to-profound) and thyroid goiter, develops in puberty or adulthood.
- **Jervell and Lange-Nielsen syndrome:** congenital profound SNHL, Long QT syndrome (syncopal episodes and may have sudden death

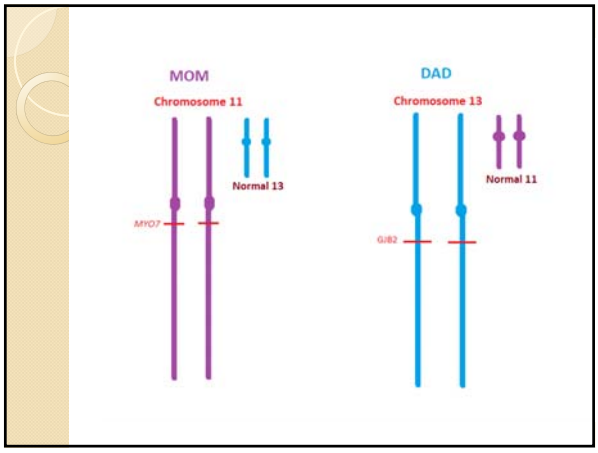
Other AR HL Syndromes

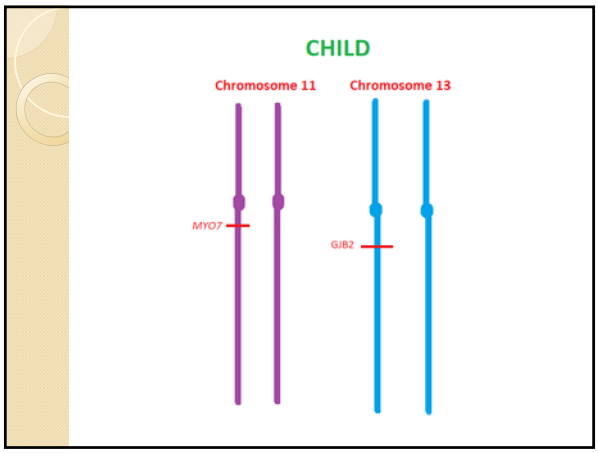
- **Biotinidase deficiency:** Some degree of SNHL; cutaneous features (skin rash, alopecia), hypotonia, seizures, developmental delay.
  - TREATMENT
- **Refsum disease:** early retinitis pigmentosa, anosmia, caused by faulty phytanic acid metabolism. Severe progressive SNHL, ataxia and ichthyosis.
  - TREATMENT

Check-in

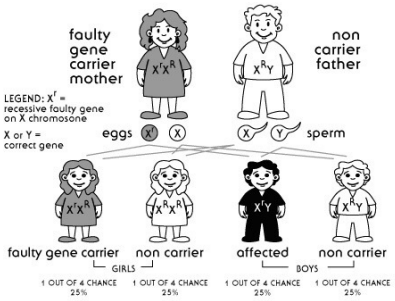
A young couple seeks genetic counseling before conceiving a child. The prospective mother is diagnosed with Usher Syndrome, confirmed with genetic testing showing loss of function in both *MYO7A* alleles. She has profound hearing loss, present since birth. The prospective father also has profound hearing loss. His genetic test results revealed a mutation in both *GJB2* alleles. They want to know the probability of their child having hearing loss of any kind.



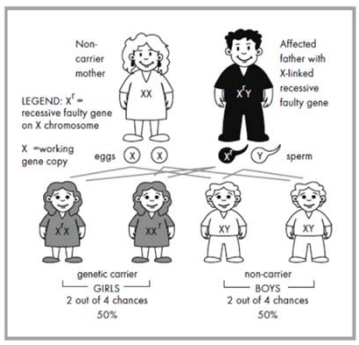




X-linked Recessive - Maternal



X-linked Recessive - Paternal



Mucopolysaccharidosis type II (Hunter syndrome)

Source: https://mpssociety.org/learn/diseases/mps-ii/

- At birth, individuals are typical

At ~2 years:

- Vocal cords also enlarge causing a deep, hoarse voice
- large head (macrocephaly) and a buildup of fluid in the brain (hydrocephalus)
- **develop hearing loss** and recurrent ear infections
- develop heart valve problems that cause the heart to become enlarged and heart failure.
- grow steadily until about age 5, and then growth slows and they develop short stature
- developmental and speech delay with regression

X-linked HL Nonsyndromic

- *PRPS1, POU3F4, SMPX*
- **Phenotype:** progressive mixed conductive-sensorineural hearing loss, mild to profound.
- 4 subtypes, categorized by the mutated gene: DFNX1, DFNX2, DFNX3, DFNX4.

X-linked HL syndromes

- **Alport syndrome:** varying severity progressive SNHL (usually after age 10), progressive glomerulonephritis (progressing to renal failure), various ophthalmologic problems.
- **Mohr-Tranebjaerg syndrome (deafness-dystonia-optic atrophy syndrome):** SNHL hearing loss (pre and post-lingual), impaired vision, dystonia or ataxia in teens, fractures, and intellectual disability.

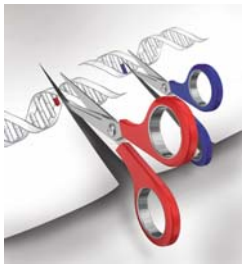
Why is knowing the genetic cause important?

Treatments

- Disease specific
- Enzyme Replacement Therapy
- Targeted protein expression
- Mutation specific Gene Therapies
  - Exon skipping with Duchenne Muscular Dystrophy

CRISPR

- Targeted gene editing
- Applications
- Update



Rare Diseases and Genetics in Healthcare

- Physicians are no longer the specialists
- Technology is changing daily
- "Today's best practice is tomorrow's malpractice"
- Know your resources
- New treatments

Thanks for Staying Awake!