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Genetics and Hearing (Part 1)
Presented in partnership with Salus University

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Course Description:

- This course will address basic concepts of genetics and its relation to syndromic and non-syndromic hearing losses. Additionally, hereditary syndromes and birth defects associated with hearing impairments will be reviewed.
Learning Outcomes:

As a result of this course, participants will be able to:

1) Define the basics of genetics, pedigrees and modes of inheritance.
2) Identify genetic and chromosomal defects.
3) Identify a variety of syndromic and nonsyndromic hearing losses.

Lecture Outline

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Gallaudet Genetics

Special thanks to Genetics Program at Gallaudet University (Summer Faculty Training Program on Genetics):

- Dr. Kathleen Armos
- Sarah Burton, M.S.
- Dr. Arti Pandya

Genetics for Audiologists

An Academic and Professional Necessity
History of Genetics

- 1859: Darwin Published *On the Origin of Species*,
- 1865: Mendel’s Peas

**Genetic Terms:**

The term gene: Danish botanist Wilhelm Johannsen used the word gene to describe the Mendelian units of heredity. The word traced from the Greek word genos, meaning "birth".

Definition of Genetics:
The science of heredity and inherited variations.
Gene: Fundamental unit of heredity (e.g.: GJB2)

Genes are the smallest unit of heredity. Each chromosome includes thousands of genes.

Locus: Position of a gene on the chromosome

Locus Name: DFNA#, DFNB#, DFN#

Protein: Protein encoded is determined by the gene (e.g.: connexin 26)

Mutation: Changes in the genes

Phenotype: The observable traits or characteristics of an organism (vs genotype)

Allele: One form of a gene

Heterozygous: having 2 different alleles

Homozygous: having 2 identical alleles

Heterogeneity: A phenotype may be the result of various genotypes or environmental events

Phenocopy: Environmentally caused trait which mimics a genetically inherited trait.

Pleiotropy: One gene (or a pair of genes) causes multiple phenotypic effects in the body
Pleiotropy (e.g., Marfan Syndrome)

Deafness is a Heterogeneous Condition!
**Cell and Cell Divisions**

- Lipid bi-layer plasma membrane
- Proteins of the cell membrane
- Channels of the cell membrane
- Nucleus
- Mitochondrion
- Smooth endoplasmic reticulum
- Golgi apparatus
- Lysosomes
- Ribosomes

**What a cell is made of?**

- Lipid bi-layer plasma membrane
- Proteins of the cell membrane
- Channels of the cell membrane
- Nucleus
- Mitochondrion
- Smooth endoplasmic reticulum
- Golgi apparatus
- Lysosomes
- Ribosomes

https://en.wikipedia.org/wiki/Plant_cell

https://www.flickr.com/photos/ajc1/11820433176
Mitochondria

This part of a cell is surrounded by a double membrane with a series of folds called cristae. Contains its own DNA. It is a power generator for the cell.

https://en.wikipedia.org/wiki/Eukaryote

Chromosome Structure

- Centromere
- Chromatids
- Telomeres

https://commons.wikimedia.org/wiki/File:Chromosome.gif
Chromosomal Structure and Karyotypes

Number of Genes:
Currently for Humans: 20,000
Common Sources of Cells for Chromosomal Studies

- Fetal skin cells – amniocentesis
- Fetal chorionic villi cells – CVS
- Lymphocytes

Human Karyotype

Normal Karyotype

https://commons.wikimedia.org/wiki/File:Karyotype_(normal).jpg

https://commons.wikimedia.org/wiki/File:Cell_free_fetal_DNA_migrating_into_maternal_bloodstream.jpg
Acrocentric Chromosomes include #13, 14, 15, 21, 22

Normal Karyotype

https://commons.wikimedia.org/wiki/File:Karyotype_(normal).jpg

Classes of Molecules:

1. Lipids
2. Proteins
3. Carbohydrates
4. Nucleic acids

https://commons.wikimedia.org/wiki/File:Porin.png
Cell Divisions

- Mitosis
- Meiosis

Mitosis

[Diagram of mitosis process]

https://eu.m.wikipedia.org/wiki/Fitxategi:Major_events_in_mitosis.svg
Meiosis

Further info can be retrieved from:

Genetic Symbols and Pedigree

Note the symbols for identical and non-identical twins.

Genetic Symbols and Pedigree

[Diagram of a pedigree chart showing male, female, affected male, affected female, deceased male, and deceased female symbols.]


Numbering of Chromosome Bands

Cytogenetic Banding Nomenclature

[Diagram showing chromosome 3 with p-arm and q-arm bands, and descriptions of regions called 3p22, 3p22.1, and 3p21.]

https://en.wikipedia.org/wiki/Locus_(genetics)#/media/File:Cytogenetic_Banding_Nomenclature.png
Schematic diagram of chromosomes known as an idiogram, or ideogram, showing the arms and bands of chromosomes. The Nomenclature of chromosomes are designed and promoted by International System for Cytogenetic Nomenclature (ISCN).


Connexin Deafness, Connexin 26 (Cx26), GJB2 gene, DFN B1
Locus: 13q12.11

A Sample Chromosome (Deafness, Otosclerosis, RP, ...)

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DNA and RNA
DNA and RNA

- Gene Expression requires:
  - DNA Transcription to RNA
  - RNA Translation to Proteins
  - Proteins initiate cell division and cell death
  - One of the many functions of proteins is to activate promoter regions of DNA and activate gene transcription.
  - For example a protein called myosin 7 is expressed in the cochlear hair cells, therefore it will be essential for the hair cell regeneration.

Fig 2, Parker 2011

Modes of Inheritance and Role of Mendel

Mendel studied pea plants and published his work of eight years in 1865. He showed that:

1. Genes are inherited in pairs
2. One gene from each parent
Laws of Heredity (Mendel 1865):

1. Law of Segregation
2. Law of Independent Assortment
3. Law of Dominance

- Law of Segregation – Parents gene pairs are separated so only one copy of each gene is transmitted to the sex cell; The child will inherit one gene from each parent.
- Law of Independent Assortment – Genes for different traits are not passed together so inheritance of one trait is not concomitant with inheritance of a trait from a separate gene.
- Law of Dominance – With two different copies of a gene, the gene will express the form that is dominant. (from: Kathleen Arnos, 2003)
Modes of Inheritance Patterns

Traditional Modes:
1. Autosomal Dominant
2. Autosomal Recessive
3. X-linked
4. Y-Linked

AD: Autosomal Dominant

- Only one copy of the gene needed to produce phenotype
- Statistically speaking 50% of offspring will have the trait if one parent has the trait.
- Male and female have the same prevalence
- Autosomal dominant inheritance may skip generations due to reduced genetic penetrance
- Trait that does not appear in the family tree may be a new mutation of a disorder
Waardenburg’s Syndrome: an Autosomal Dominant Disorder

Heterochromia iridum

https://en.wikipedia.org/wiki/Heterochromia_iridum

https://upload.wikimedia.org/wikipedia/commons/9/9f/Waardenburg2.jpg
AR: Autosomal Recessive

- The offspring must inherit two copies of the gene
- Statistically speaking there is 25% chance of affected child when both parents are carriers of the gene
- Male and female have equal prevalence
- Prevalence increases with consanguinity

Usher Syndrome: an Autosomal Recessive Condition

Unaffected "Carrier" Father
Unaffected "Carrier" Mother
Unaffected 1 in 4 chance
Affected 1 in 4 chance

X-linked inheritance (Sex-linked, X-Linked Recessive)

- No father to son transmission
- Males have more prevalence than females
- 50% of sons of a carrier mother will be affected.
- 50% of daughters of a carrier mother will be carriers.
- All daughters of an affected male will be carriers
Hemophilia is usually an X linked disorder

Y-Linked Inheritance

50 million base pairs

Legend
- Female
- Male
- Male w/ Y linked trait
Non-Traditional Modes of Inheritance

- Mitochondrial Inheritance
- Imprinting
- Modifier Gene
- Uniparental Disomy

Mitochondrial Inheritance

- Mitochondria has its own DNA.
- It contains a circular DNA
Mitochondrial Inheritance

- In this mode of inheritance the genes are passed only from mother to child in cytoplasm of egg
- Affected fathers cannot pass the trait
- All children of an affected mother will be affected
- Males and females have equal prevalence

Here is a pedigree example of a mitochondrial inheritance
Mitochondrial Inheritance

- One of the hallmarks of Mitochondrial Inheritance is that affected fathers cannot pass the gene or trait to their offspring.

Non Traditional Mode of Inheritance

- Imprinting is a condition where for some genes, the copy inherited from the mother functions differently from the copy inherited from the father.
- Examples include Angelman Syndrome and Prader-Willi Syndrome.
Chromosomal Defects and Abnormalities

Chromosomal Defects

- **22q11 Deletion Syndrome** have the following features:
  Congenital Heart Disease, Palatal abnormalities and Velopharyngeal Incompetence
22q11 Deletion Syndrome

- Includes Shprintzen syndrome, DiGeorge syndrome, velocardiofacial syndrome, etc.
- Congenital heart disease in 74%
- Palatal abnormalities (particularly Velopharyngeal incompetence and cleft palate) in 69%
- Learning difficulties in 70-90%

https://www.nature.com/articles/nrdp201571

Common Chromosomal Trisomy includes Trisomy 13, Trisomy 18 and Trisomy 21

https://commons.wikimedia.org/wiki/File:Trisomia_18.jpg
Kleinfelter Syndrome (XXY)


Recognition of Syndromic and Non-Syndromic Hearing Losses

https://commons.wikimedia.org/wiki/File:Pitt-rogers-danks_syndrome.jpg
Syndromic and Non-Syndromic Hearing Losses

- Hearing losses can be divided into idiopathic, genetic and those due to environmental factors such as diseases and accidents. Genetic hearing losses are divided into syndromic and non-syndromic hearing losses. One third of the childhood genetic hearing loss is associated with a syndrome and two thirds are non syndromic. More than seventy five percent of the genetic hearing losses are Autosomal recessive, while around twenty percent are autosomal dominant and less than five percent are x-linked, y-linked or mitochondrial.

International System for Cytogenetic Nomenclature (ISCN).

Nomenclature for Deafness Genes:
DFNA#, DFNB#, DFN#
Apert Syndrome

https://en.wikipedia.org/wiki/Apert_syndrome

A variety of Syndromes can be associated with hearing loss. Current estimate is more than 300!

Connexin 26 Deafness is the Most Common Form of Non-Syndromic Hearing Loss

- The first published description of a gene for non-syndromic deafness.

Summary

What we have learned so far:
1. Genetic terminology
2. Chromosomal structure and chromosomal defects
3. DNA to RNA transcription and RNA translation to Proteins
4. Syndromic vs non-syndromic hearing loss
We will continue with:
Genetics and Hearing Part 2

Q and A.

Thank you!