Genetics of Hearing Loss: Connexin 26

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**DNA** the molecule of life

**Trillions of cells**

Each cell:
- 46 human chromosomes
- 2 meters of DNA
- 3 billion DNA subunits (the bases: A, T, C, G)
- Approximately 30,000 genes code for proteins that perform most life functions
Gene expression

- Gene expression is the process of decoding the information in DNA and producing the protein encoded by the gene (i.e., the gene product).

- The amino acid sequence of the produced protein depends on the nucleotide sequence in the gene.
Genes contain instructions for making proteins.

Proteins act alone or in complexes to perform many cellular functions.
DNA Sequence Variation in a Gene Can Change the Protein Produced by the Genetic Code

**Gene A from Person 1**

- GCA AGA GAT AAT TGT...
- Protein Products: Ala Arg Asp Asn Cys...

**Gene A from Person 2**

Codon change made no difference in amino acid sequence

- GCG AGA GAT AAT TGT...
- Protein Products: Ala Arg Asp Asn Cys...

**Gene A from Person 3**

Codon change resulted in a different amino acid at position 2

- GCA AAA GAT AAT TGT...
- Protein Products: Ala Lys Asp Asn Cys...

OR
Normal Gene

Types of gene mutations

Beta-globin DNA and amino acid sequence

<table>
<thead>
<tr>
<th>Normal Sequence</th>
<th>Beta-globin protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTG 4 ACT 5 CCT 6 GAG 7 GAG 8 AAG</td>
<td>Leu Thr Pro Glu Glu Lys</td>
</tr>
</tbody>
</table>

Missense Mutation

<table>
<thead>
<tr>
<th>CTG ACT CCT GTG GAG AAG</th>
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<tr>
<td>Leu Thr Pro Val Glu Lys</td>
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</table>

Silent Mutation

<table>
<thead>
<tr>
<th>CTG ACT CCT GAA GAG AAG</th>
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<tbody>
<tr>
<td>Leu Thr Pro Glu Glu Lys</td>
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</table>

Polymorphism

<table>
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<tr>
<th>CTG ACT CCT GAG GGG AAG</th>
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<td>Leu Thr Pro Glu Gly Lys</td>
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Congenital Hearing Loss

- Hereditary hearing loss is divided into syndromic and non-syndromic cases
  - Syndromic = a condition with various symptoms affecting multiple organ systems; non-syndromic = an isolated issue
  - 70% is non-syndromic & 30% is syndromic

- Mode of inheritance for non-syndromic hearing loss:
  - Autosomal recessive in 75%-80% of cases
  - Autosomal dominant in 20%-25% of cases
  - X-linked in less than 2% of cases

- Autosomal recessive non-syndromic hearing loss:
  - Connexin 26 mutations are the most common cause of autosomal recessive, non-syndromic hearing loss
Prelingual Deaf Children
1/1000

Unknown causes
25%

Environmental
25%

Genetic causes
50%

Autosomal Recessive
78% - 85%

Autosomal Dominant
15% - 24%

X-linked
1% - 2%

Mitochondrial
≤1%

30% syndromic
70% non-syndromic

Connexin 26
50%
Human Connexins

- There are 20 different human connexins

- Connexin molecules differ in molecular mass, thus their different names: Cx 26, Cx 30, Cx 32

- Connexin protein molecules join together to form gap junctions

- Gap junctions are channels that connect adjacent cells and allow the rapid movement of small ions and molecules between cells
What are Connexins & Connexons?

- 6 connexin molecules = 1 connexon (hexagonal tube)
- 2 connexons form 1 gap junction
- Gap junctions connect cell membranes in multiple locations across the intracellular space
Connexin 26

- Cx 26 gap junction channels between adjacent cells in the cochlea are essential for potassium recycling

- Potassium ions carry positive electrical current in the cochlea

- The positive electrical current that flows through the hair cells is carried mainly by potassium ions

- Hair cells convert positive electrical/mechanical signals (sound) to electrochemical signals (receptor potential)

- Potassium recycling in cochlea is essential for normal auditory function
Connexin 26 (GJB2) is one of the main proteins involved in potassium (K+) homeostasis in the cochlea of the inner ear. It is found in the supporting cells, fibrocytes of the spiral ligament and in cells of the spiral limbus. [Adapted from Steel, K.P. (1999) Science 285, 1363-1364, with permission.]
Potassium Recycling

Potassium enters hair cells through specialized channels in stereocilia

- as stereocilia are sheared, cation channels open & close
- positive current, carried by potassium, is thus modified by mechanical displacement of the stereocilia
- potassium current modulations mimic the variations in movement produced by sound stimuli, thus encoding properties of sound in the hair cell as an “electrochemical signal” or receptor potential

- Potassium ions pass through Cx26 gap junctions between supporting cells in organ of Corti, through spiral ligament and spiral limbus, and through the stria vascularis to be secreted into the endolymph again
The GJB2 Gene (Cx26) & Hearing

- The GJB2 gene (gap junction beta2) codes for the Connexin 26 protein. GJB2/Cx26 gene mutations produce abnormal Cx26 proteins.

- This results in abnormal gap junctions which disrupt the potassium recycling pathway and therefore cochlear transduction.

- When movement of basilar membrane and hair cell stereocilia is not converted into an electrochemical signal in the hair cell, the transduction process breaks down resulting in hearing loss.
Mutations in Connexin 26

- More than 22 different deafness-causing Cx26 mutations have been found.

- The most common deafness-causing Cx26 mutation is 35delG with a carrier rate of 2.5% of the population.

- Cx26 carriers are not deaf, but two carriers (of the same Cx26 mutation) have a 25% chance of having a deaf child (A double dose of the same mutation = autosomal recessive inheritance of hearing loss).
**Cx26 Gene Locus:**

13q12

13 = chromosome #

q = long arm (the lower arm) of the chromosome

12 = the band along the chromosome where the gene is found


NCBI Genes and Disease website, 2006
The Connexin 26: DNA nucleotide base sequence (a small gene)
**NORMAL GJB2 GENE:**

Nucleotide Base Sequence and & Amino Acid

```
1  4  7  10  13  16  19  22  25  28  31  34  37  40
ATG GAT TGG GGC  ACG CTG CAG ACG ATC CTG GGG GT GTG AAC
```

START  Asp  Trp  Gly  Thr  Leu  Gln  Thr  Ile  Leu  Gly  Gly  Val  Asn

**MUTATION GJB2 GENE: 35delG**

Nucleotide Base Sequence and & Amino Acid

```
1  4  7  10  13  16  19  22  25  28  31  34  37  40
ATG GAT TGG GGC  ACG CTG CAG ACG ATC CTG GGG GT GTG AACTTG TGA ACA
```

START  Asp  Trp  Gly  Thr  Leu  Gln  Thr  Ile  Leu  Gly  Gly  STOP

**Result:** truncated Connexin 26 protein is produced due to the creation of a premature STOP codon
Degree of hearing loss associated with Connexin 26 mutations

- The degree of sensorineural hearing loss associated with Connexin 26 mutations varies from mild to profound
  - Variation in the degree of HL is seen even in people with the same Cx26 mutation (range: mild to severe-to-profound).
  - It is likely that environmental factors and gene interactions both play a role to modify the phenotype of Cx26.

- radiologically normal inner ear
- vestibular system status unclear; research is ongoing
Other Connexin-related causes of hearing loss

- Other Connexins involved in hearing loss include Connexin 32, Connexin 31 and Connexin 30

- Connexin 32 is associated with X-linked Charcot-Marie-Tooth disease:
  - hereditary chronic motor and sensory polyneuropathy
  - distal muscle weakness and atrophy
  - X-linked and is associated with sensorineural hearing loss in some cases

- Connexin 31 is associated with deafness and/or a skin disease
Digenic Inheritance

- **Digenic Inheritance**: genes at 2 different loci (non-allelic genes) can together cause a trait or condition
  - Affected individuals are heterozygous for mutations in 2 different genes
  - **Example**: A mutation in one copy of GBJ2 (connexin 26) and a mutation in one copy of GJB6 (connexin 30) can cause deafness

- **Recessive Inheritance**: in comparison, a condition is inherited in a recessive pattern if mutations occur on both copies of the same gene (allelic), at the same locus on homologous chromosomes.
In Conclusion

- Autosomal recessive deafness is the most common form of genetic hearing loss.

- In the Caucasian population, the 35delG mutation in the Connexin 26 gene is most common cause of autosomal recessive, non-syndromic sensorineural hearing loss; genetic screening is available.

- The facts about Cx26 highlight the need for genetic screening and genetic counseling for hearing-impaired children and their families.
References


