Genetics of Stuttering

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Stuttering has a genetic cause

• The **identical twin** of a person who stutters is more more likely than a **non-identical twin** to also stutter.

• Studies on **adopted children** indicate that the environment does not have a big role.

• Stuttering often **runs in families** – but not in a simple way.
Stuttering has a genetic cause

- Stuttering is a **neurodevelopmental** disorder – it results when the brain develops in a slightly different way to usual.

- We want to understand the **connections** between DNA, brain development and stuttering.
How DNA works

Cheek cells in saliva

Nucleus

0.1 mm
How DNA works

- **23 pairs of chromosomes**: 1-22 and X/Y.
- One of each pair from each parent.
How DNA works

- The human genome contains **3 billion letters**.
- One copy of the genome is inherited from each parent.

Four types of ‘letter’

A T C G
How DNA works

- A gene is made up of thousands of DNA letters.
- Genes are coded instructions to make proteins.
- In the genetic code: 3 letters of DNA = 1 letter of protein
How DNA works

DNA
ATGGGGGCAAACCGGGAAACGGCAGCGCCTTCTTGTGGAACCATTGGAAGCCCAT

Protein
M G Q P G N G S A F L L A P N G S H

Folding

Unique shape ➔ Unique function
How DNA works

- Proteins are the **molecular machines** that make your body work.
- Humans have **20,000 kinds of protein**.
- Each one has a **unique shape** that determines **what it does**.
How DNA works

ATGGGGCAACCGGGGAACGGCAGCGCCTTCTTTGCTGGCACCACCCAAATGGAAGCCAT

Green fluorescent protein
How DNA works

ATGGGGCAACCCGGGT AACGGCAGCGCCTTCTTGCTGGCACCCAATGGAAGCCAT

variant

Green fluorescent protein
New variants appear in every generation – this is how evolution works.

Any two unrelated people are genetically 99.9% identical.

This means millions of differences.

Genetic variation makes us all different.
Genetic variation

**Common variants**
- arose many thousands of years ago
- found in many people

**Rare variants**
- arose more recently
- still limited to one population, one family, or even one person
Looking for genes related to stuttering

- Aim to find a variant present in people who stutter – but not those who don’t.
Looking for genes related to stuttering

• Aim to find a variant present in people who stutter – but not those who don’t.
• But there are **3 billion letters** of DNA – a **needle in a haystack**.
Looking for genes related to stuttering

- We can **make the haystack smaller** using our knowledge of the way DNA is inherited.
Looking for genes related to stuttering

Chromosome parts are shuffled during reproduction

Mother

Father

sperm

egg

Child
Looking for genes related to stuttering

- The chromosome parts are **shuffled differently** in every egg/sperm.
Looking for genes related to stuttering

Family members who stutter

Family members who don’t stutter

• What DNA is shared by individuals who stutter but not by individuals who don’t?
Looking for genes related to stuttering

- Several studies performed for stuttering – usually with disappointing results.
- Much smaller haystack – but still millions of letters of DNA.
Looking for genes related to stuttering

- Large **consanguineous** families (from Pakistan).
- Reduced amount of **genetic variation**.
- **Relevant** variants are easier to find.
Looking for genes related to stuttering

- **Linked region** on chromosome 12.
- Contains 87 genes – 45 genes in the middle were **fully sequenced**.
The first genes involved in stuttering

- Many variants were found within these 45 genes.
- But most are common in the Pakistani population.
- A rare variant was found in the gene GNPTAB.

<table>
<thead>
<tr>
<th></th>
<th>DNA</th>
<th>Protein</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Normal</strong></td>
<td>GNPTAB</td>
<td>TGCAGGAATGG</td>
</tr>
<tr>
<td><strong>Variant</strong></td>
<td>GNPTAB</td>
<td>TGCAGAAATGG</td>
</tr>
</tbody>
</table>
- Variant arose 14,000 years ago in south Asia – also found in other Pakistani individuals who stutter.
- Different variants in GNPTAB were found in people of both Asian and European ancestry who stutter.
The first genes involved in stuttering
The first genes involved in stuttering

- Lysosome
- Nucleus
- Mitochondrion
- Endoplasmic reticulum
- Golgi apparatus
The first genes involved in stuttering

Lysosomes are the recycling centre for the cell.

1. Old molecules are sent to the lysosome

2. Molecules are broken down into building blocks

3. Building blocks are sent back out of the lysosome

4. Building blocks are used to make new molecules
2. Molecules are broken down into building blocks

Lysosomes are the recycling centre for the cell.

- The lysosome uses **enzymes** to break down molecules.
- The enzymes are made **outside** the lysosome and must be **targeted for delivery** to the lysosome.
The first genes involved in stuttering

• **GNPTAB** puts an **address label** on enzymes to make sure they are delivered to the lysosome.
The first genes involved in stuttering

- **GNPTAB** is not the only protein required to put on the address label.
- **GNPTG** and **NAGPA** are also required.
- Variants in **all three genes** have been found in people who stutter.
The first genes involved in stuttering

- If any of these proteins is **missing**, enzymes are **not delivered** to the lysosome.
The first genes involved in stuttering

Without enzymes, old molecules **build up** inside the lysosome.

This causes **mucolipidosis** – a severe disorder affecting skeleton, heart and brain development.
The first genes involved in stuttering

- The variants found in people who stutter mean the proteins are not missing, just altered – so people who stutter have no symptoms of mucolipidosis.
The first genes involved in stuttering

- The involvement of lysosomal targeting genes in stuttering is unexpected.
- We don’t know why variants lead specifically to stuttering when the altered proteins are found in cells all over the body.
- The brain is more easily damaged than other organs.
- More research is needed to find out how variants affect brain cells and brain development.
- Mice engineered to carry these variants would be informative.
These genes are not the end of the story

- Only a **small proportion** of people who stutter have variants in these genes – there must be **other genes** yet to be discovered.
- Variants are also found in people who **do not stutter** – we need experiments to find out **which variants affect protein function**.
- Carrying one of these variants does not mean an individual will definitely stutter – it just **increases the risk**.

Why is it so complicated?

2. Genes and environment.
3. Randomness.
Combinations of variants

- Characteristics result from **combinations of variants** affecting **multiple genes**.
Combinations of variants

Light eye colour variants

Dark eye colour variants
Some variants **matter more** than others.
Combinations of variants

What this means for the genetics of stuttering

• The risk of developing stuttering may be determined by variants in several different genes, acting together.

• This is difficult to study - but we can begin by looking at variants which have the strongest effects.
Genes and environment

There is no ‘nature versus nurture’

The environment is **meaningless if there’s no DNA** in it.

DNA determines our **responses to the environment**.

DNA guides organisms to **shape their own environment**.
Genes and environment
Genes and environment

What this means for the genetics of stuttering

• We can’t **correct** the errors in brain development that lead to stuttering.
• But the brain is **adaptable** – early intervention might help the brain find **alternative routes** to fluent speech.
• Environmental influences **during brain development** could be important.
Randomness
You are not a microscopic worm

C. elegans

959 cells, 302 neurons
Brains are like fingerprints – even identical twins have different ones.

What this means for the genetics of stuttering

• Random events in brain development may influence whether or not someone who is genetically ‘at risk’ actually develops a stutter.
• Collecting DNA from Dutch children who stutter and their parents.

• Test for variants in the lysosomal targeting genes.

• In the future: look at additional genes of interest and try to discover new genes related to stuttering.

• Collaboration with Bert Bast and Marie-Christine Franken, Erasmuc MC.
The road ahead

- An **explanation** for stuttering in individual children.

- **Prediction** of which children are likely to develop a stutter, and of response to therapy.

- Understanding the **differences in brain development** that lead to stuttering.

- New avenues for **therapies**.