



Fact sheet: Genetic testing

The Genetic Basis of Childhood Apraxia of Speech

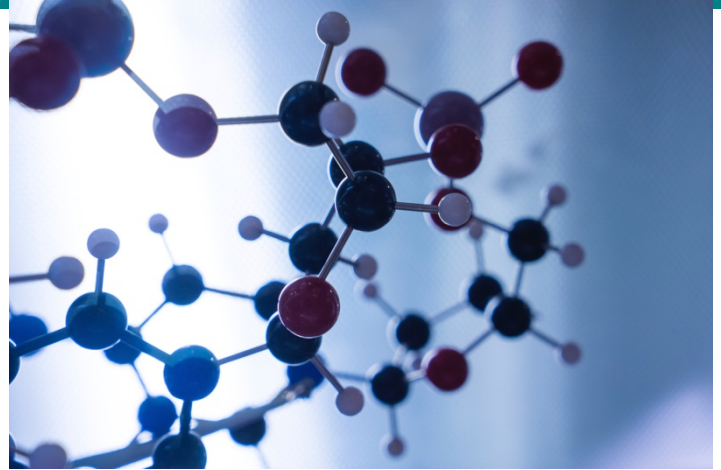
Around 1 in 3 children with childhood apraxia of speech (CAS) have a genetic cause for their condition.

New genetic technologies now enable rapid and relatively cost-efficient genetic testing. This has led to the discovery of many new genetic changes associated with CAS.

Our bodies contain a structure called DNA, which is like the instruction book that tells the cells in our bodies how to function. DNA is tightly packaged into structures called *chromosomes*. There are particular sections of our DNA that correspond to different parts of our bodies, for example, the brain, eyes, or heart. Each of these parts of our DNA is called a *gene* - we have over 20,000 genes which help our bodies to function.

There are many genetic changes in each person, which are like spelling changes in their DNA. Most of these genetic changes do not change how the gene works in the body. Sometimes, there can be a genetic change which alters the way the gene works in the body, including in genes that affect speech and language. For approximately 1 in 3 children with CAS, there is a genetic change in a gene or chromosome which is associated with their CAS.

For the other 2 in 3 children with CAS, a small percentage have damage to the brain from a neurological lesion or stroke which leads to CAS. The remaining children have idiopathic CAS, where the origin of their CAS is unknown. Children with idiopathic CAS do not have observable neurological abnormalities or easily detected genetic conditions. Most children with CAS still fall under this category, which is often challenging for parents as there is no known cause.



Types of genetic changes

There are three types of genetic changes that can be associated with CAS.

1. **Single gene changes (variants):** This is where just one gene on a chromosome is altered. Some gene variants are passed down through families (inherited). Importantly however, *de novo* variants seem more common in children with CAS - this is where a gene variant has occurred in a child in the family for the first time rather than being inherited. There have been over 30 single genes or 'monogenic' conditions shown to cause CAS (e.g., *FOXP2*-related speech and language disorder; *CDK13*-related disorder; *SETBP1*-haploinsufficiency disorder, (see <https://www.geneticsofspeech.org.au>).
2. **Copy number variations (CNVs):** CNVs are essentially small or large extra or missing pieces of chromosomes (deletions, duplications, or rearrangements). These variations typically involve more than one single gene. All humans carry CNVs, and many are not related to any obvious health or medical concerns. For some, these CNVs do cause health or medical conditions, including CAS. Examples include 16p11.2 deletion and Koolen de Vries syndrome.



3. **Other genetic syndromes:** CAS can sometimes occur as part of a broader genetic (e.g. Fragile X, Down syndrome, Klinefelter syndrome, Noonan's syndrome), metabolic (e.g. galactosaemia), or mitochondrial disorder. Metabolic and mitochondrial disorders are also typically genetic conditions, and children with these conditions also typically experience co-occurring neurodevelopmental disorders as well as additional health concerns. There are quite a few disorders in which CAS can arise, but that does not mean that all children with these disorders also have CAS. For example, not all children with galactosemia have a speech problem, and out of those children, only some have CAS.

Genetic causes of CAS

Most genetic causes of CAS are associated with other neurodevelopmental conditions such as gross and fine motor impairments, learning difficulties or intellectual disability, global developmental delays, epilepsy, autism spectrum disorder (ASD), and/or attention deficit hyperactivity disorder (ADHD). That is, few genes or CNV syndromes are associated with CAS in isolation. Rather, these gene pathways are responsible for supporting early brain development and when the pathways are altered, they may be associated with CAS and broader neurodevelopmental conditions. Increasingly, informed in part by genetic research, we realise that CAS is often accompanied by other neurodevelopmental conditions and when this is the case, it has been suggested that genetic testing should be pursued.

Why pursue genetic testing for CAS?

Families may choose to pursue genetic testing for their child with CAS for many reasons, including:

- **Diagnosis:** The primary purpose of genetic testing is to determine whether there is a genetic cause for CAS. Provision of a genetic diagnosis and understanding more about the cause of CAS is helpful for some families who have been on a diagnostic journey to try and understand why their child has CAS.
- **Prognosis:** Some genetic diagnoses are well studied and are known to be associated with other health or neurodevelopmental conditions. This knowledge allows the family and treating

health professionals to be better informed and provide support tailored to this knowledge.

- **Future family planning:** In some cases, the results provide information about recurrence risk. That is, to understand the chances of future children having the same condition. This would be determined by the type of genetic change, if any, detected via testing.
- **Guiding interventions:** Into the future, specific treatments targeting gene pathways, such as drugs, may become available. Yet, this sort of targeted therapy is thought to be many decades away at this time. Hence for the moment, a genetic diagnosis will not alter your child's management of CAS. Although one could argue that having a genetic diagnosis means your child's CAS is less tractable, i.e., more challenging to resolve with therapy. Hence one may suggest that more intensive therapy is required in the early years to try and make the optimal gains possible for a child with CAS associated with a genetic diagnosis.
- **Support:** Some genetic diagnoses have a related support group to connect, advocate for, and educate individuals living with these conditions and their families. Some families may find it helpful to connect with others who have a similar lived experience, or to access more specific resources and services related to their genetic diagnosis, if available.

Genetic testing pathway

The *Speech Apraxia and Genetics clinic* offers a genetic testing pathway for children with CAS. Most commonly, saliva samples can be used to complete the genetic analysis. The genetic testing pathway is conducted in 3 stages:

1. **Chromosomal microarray:** A microarray tests for missing or extra pieces in a person's chromosomes (i.e., CNVs related to CAS). It is a clinical test, and the first stage of genetic testing for the clinic. Results are usually available in 4-6 weeks.



2. **Clinical whole exome sequencing:** Whole exome sequencing involves reading the full set of a person's DNA, which is then analysed by bioinformaticians. This tests for any single gene changes which may be related to CAS. This is a clinical test, and results are typically available in 5-6 months.
3. **Research whole exome sequencing:** If no genetic changes related to CAS are identified in the first two stages of genetic testing, your child's data continues to be analysed using new methods and technologies. This is ongoing for the duration of the study, and can take years. We will contact you if a genetic change related to CAS is identified for your child. We cannot guarantee there will be a genetic finding for all children.

Possible outcomes of genetic testing

There are three main outcomes of genetic testing:

1. A **genetic change** is identified, which explains the cause of CAS in a child.
2. **No genetic change** is identified, meaning the cause of CAS is still unknown.
3. A genetic **variant of uncertain significance** is identified, which means that there is not enough evidence to determine whether or not the genetic change is causing CAS for a child.

In cases where no genetic change is identified, or a genetic variant of uncertain significance is identified, our research team continues to analyse the child's DNA as new technologies and analysis methods become available.

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