FACTS ABOUT HEALTH CONDITIONS

CAUSED BY CHANGES IN THE *TCF4* GENE

This fact sheet contains information about the possible impact of a change (variant) in the *TCF4* gene on your child and family. You can talk about the information in this fact sheet with your paediatrician or GP (family doctor). The links in the fact sheet may help you move forward with family life beyond receiving this rare diagnosis.

This fact sheet relates to health conditions that are due to small variants in the genetic code of the *TCF4* gene. These changes were identified by a genomic (DNA) test.

Key points

- A change (variant) in the *TCF4* gene usually causes developmental delay. When the child is older, they may have moderate-to-severe intellectual disability, may behave differently from other children, and have breathing problems such as episodes of rapid breathing and breath holding
- Less commonly, children may have sleep disturbance, seizures, constipation, near-sightedness, minor skeletal differences and/or show signs of autism
- Variants in the *TCF4* gene that cause health problems are almost always due to a new (*'de novo'*) change in a child. This means that future children are at low risk of having the condition. Genetic counselling before any further pregnancies is recommended
- Supportive management is available
- You and your family are not alone in adjusting to life with the diagnosis of a change in the *TCF4* gene. Support is available from a number of different organisations and services

Other names this condition may be referred to as

- Pitt-Hopkins syndrome (PTHS)

When a rare condition has been diagnosed

For some families, receiving a genetic diagnosis is a relief. Others may feel overwhelmed and sad. It is very common to have a mixture of thoughts and feelings about the news, and your hopes and expectations for the future may shift and change over time.

While experiences may be shared, individuals and families can respond in different ways and have different information and support needs. Many parents describe an ongoing process of adjusting to a different focus and finding ways to celebrate their child's gains made in their own way and time. It is very important to remember that the diagnosis is only one of many things that make your child unique.

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About the *TCF4* gene

Genes contain instructions that tell our body how to grow, develop and function. The *TCF4* **gene** directs the body to make a protein called TCF4 that is important for the usual development and organisation of brain and nerve cells. This protein is critical for the developing baby throughout pregnancy and during early infancy and childhood.

The *TCF4* gene is found on chromosome 18. Usually *TCF4*-related conditions are caused by a single spelling variation in the *TCF4* gene, which means the message is not read or received properly. This in turn means that the TCF4 protein is not made correctly.

In most individuals with *TCF4*-related conditions, the change (**variant**) occurred when the baby was conceived (a new or *'de novo'* variant), and is not seen in the parents. *TCF4*-related conditions are **genetic conditions**. This means that the condition was not caused by anything the mother or father did before the baby was conceived, during pregnancy or birth, or after the baby was born. *TCF4*-related conditions occur very rarely and the actual number of cases in the world is unknown. It is estimated that one in 40,000 children have a *TCF4*-related condition.

What could a change in the *TCF4* gene mean for my child?

A change in the *TCF4* gene can affect children in different ways. Some are more severely affected than others. There may be a range of signs and symptoms even in children with the same genetic variant.

The most common problems are together called Pitt-Hopkins syndrome (PTHS), named after the two doctors who first recognised this condition. The main symptoms are developmental delays, which affect the child's movement and speech. When the child is older they may have intellectual disability, behavioural differences, or breathing problems such as episodes of rapid breathing (hyperventilation) and breath holding. Children may also have common facial features such as deep set eyes, a full lower lip and widely spaced teeth. Other features that are less common include autism spectrum disorder, sleep disturbance, seizures (epilepsy), constipation, near-sightedness and minor differences in the skeleton.

At this point in time, it is not possible to reverse or directly repair this gene change. It is also not possible to accurately predict the level of care your child will require through to adulthood. Your child's individual needs and strengths will become more obvious over time, which will help with planning for the future.

Your child's development may be helped through early use of therapy services such as physiotherapy and treating symptoms if/when they arise. It is likely that many different health professionals will be involved in caring for your child. Your paediatrician or GP will arrange referrals to other health professionals as needed and help with applications for service funding through the **National Disability Insurance Scheme (NDIS)**.

Good communication with the health professionals caring for your child is important to establish common goals, trust and shared responsibility. We encourage you to ask questions and express your concerns as the primary carer for your child.

Management recommendations

As many health or developmental problems are not immediately obvious, your child will need to be checked by their paediatrician at diagnosis and then seen every 6 to 12 months depending on their needs. Sometimes, it may be necessary to be seen more often depending on your child's age and problems. The list on the next page includes many of the common problems, but others may arise. If you have any concerns about your child's health, please speak with your family doctor (GP) or paediatrician.

Possible health problems (% of children affected)	Management
Developmental delay/ intellectual disability (>90%), including unusually low muscle tone (hypotonia [70%])	• Early intervention, including speech therapy, occupational therapy and physiotherapy • Consider a formal developmental assessment before starting school or by school counsellor for school age children • At least yearly checks by GP/paediatrician • Special education programs
Balance problems/ delayed walking (60%)	• Physiotherapy/occupational therapy to help with using medical devices such as wheelchairs, if needed
Speech delay/absent speech (90%)	• Speech therapy to help with language development • Speech aids
Repetitive behaviours, especially of the hands (60%)	• Diagnosis and management by paediatrician as appropriate
Autism spectrum disorder (45%)	• Diagnosis and management by paediatrician as appropriate
Constipation (70%). This can be severe and difficult to treat	• Constipation can be treated with a high fibre diet, adequate fluid intake and/or laxatives • Discussion with paediatrician and consultation with paediatric gastroenterologist if required
Brain structural malformations/ developmental differences of brain (20%)	• Brain MRI if clinically indicated. Most structural problems do not require any specific treatment
Microcephaly/small head size (20%)	• Regular review of height, weight and head size (circumference). No treatment is needed
Seizures (epilepsy) (40%)	• Standard investigations and treatments, including EEG and anti-epileptic medications. Consultation with a paediatric neurologist if seizures are difficult to control • Overnight EEG monitoring is recommended as seizures often occur at night and may not be detected during routine daytime EEG
Disorders of sleep (30%)	• Review by paediatrician, consider referral to sleep physician if severe symptoms
Sleep apnoea (10%)	• Consider a non-urgent sleep study for investigation of possible obstructive sleep apnoea symptoms
Rapid breathing (hyperventilation) and/or breath holding (may occur later in childhood) (40%)	• These episodes are not likely to be harmful, but the family should be aware of these symptoms
Visual (eyesight) problems: **Near-sightedness (50%)** **Astigmatism (25%)** **Squint (40%)**	• Initial review by ophthalmologist for assessment of vision and squint (strabismus) • Yearly eye review by ophthalmologist • A squint (strabismus) may require patching or glasses • Long or near sightedness (refractive error) may require glasses

Detailed management recommendations for healthcare professionals can be found in the **GeneReviews article**.

Resources, support and connecting with others

You may find it helpful to connect with other people who have personal experience of day-to-day life with a child who has a *TCF4*-related condition. You can make these connections through:

- Social media (e.g. closed Facebook groups: Pitt-Hopkins Syndrome New Zealand, Australia, Pitt-Hopkins Research Foundation, Pitt-Hopkins Education and Therapy)
- Umbrella groups (e.g. Genetic Alliance Australia and Rare Voices Australia)
- Condition-specific groups (e.g. Pitt-Hopkins Research Foundation)
- Groups for individuals with common symptoms that may have many different causes (e.g. intellectual disability, hearing loss, autism).

Many organisations (e.g. Carers NSW and Reframing Disability) can also offer general advice and support in caring for a family member with long-term needs.

It is important to know that you are not alone on this journey.

More information about *TCF4*-related conditions

You can find further information about *TCF4*-related conditions by following the links below.

- MedlinePlus: TCF4 gene
- National Organization for Rare Disorders (NORD): Pitt-Hopkins Syndrome
- Genetic and Rare Disease Information Center (GARD): Pitt-Hopkins Syndrome
- Top tips for triaging and treating kids with Pitt Hopkins Syndrome

For more information about genetic conditions and to find your local Clinical Genetics services, visit the NSW Centre for Genetics Education.

Family planning

Genetic conditions may be passed from a parent to their child. Even if the same variant was not found in one of the parents, it is still possible to have another child with the same condition. The chance of this happening is 1–2%.

If you are thinking about having more children, it is recommended that you talk with your local Clinical Genetics service. Some people may choose to have genetic testing before or during a pregnancy. Specialised health professionals such as genetic counsellors can advise you on your options.

You can also speak with your GP about options for reproductive genetic carrier screening. When planning a family, it is best to explore your options before becoming pregnant.

Research, registries and clinical trials

Some people with rare conditions are able to participate in research, which may be of benefit to your child. This may investigate how a particular variant causes health problems or it may be a clinical trial testing new treatments. Sharing information about your child's signs and symptoms through registries such as FaceMatch and IAMRARE can help build further knowledge about this condition.

Information about current clinical trials can be found by searching the international databases ClinicalTrials.gov or EudraCT.

To print more copies of this fact sheet and access links to the underlined topics, go to www.genetics.edu.au and search for 'TCF4'.

This fact sheet should not replace a consultation with a specialist healthcare professional.