FACTS ABOUT HEALTH CONDITIONS
CAUSED BY CHANGES IN THE *ITPR1* GENE

This fact sheet contains information about the possible impact of a change (variant) in the *ITPR1* 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 this 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 *ITPR1* gene. These changes were identified by a genomic (DNA) test.

Key points

- Several distinct conditions may be caused by changes in the *ITPR1* gene
- The condition and how it is passed down (inherited) depends on the type of change in the gene. This change may be inherited from one or both parent(s) or may be a new (*'de novo'*) change in a child. This means that future children may also have an *ITPR1*-related condition. Genetic counselling before any further pregnancies is recommended
- Children with changes in the genetic code of the *ITPR1* gene are usually slower than other babies to develop movement skills, have low muscle tone and may be unsteady when walking
- Children may or may not have development delay/intellectual disability.
- The symptoms usually remain stable throughout life, with some people improving over time
- Supportive management is available
- You and your family are not alone in adjusting to life with the diagnosis of a change in the *ITPR1* gene. Support is available from a number of different organisations and services

Conditions that may be caused by changes in this gene include:

- Spinocerebellar ataxia 29 (SCA29)
- Gillespie syndrome (aniridia-cerebellar ataxia-intellectual disability)
- Spinocerebellar ataxia 15 (SCA15)
- Autosomal dominant congenital progressive cerebellar ataxia

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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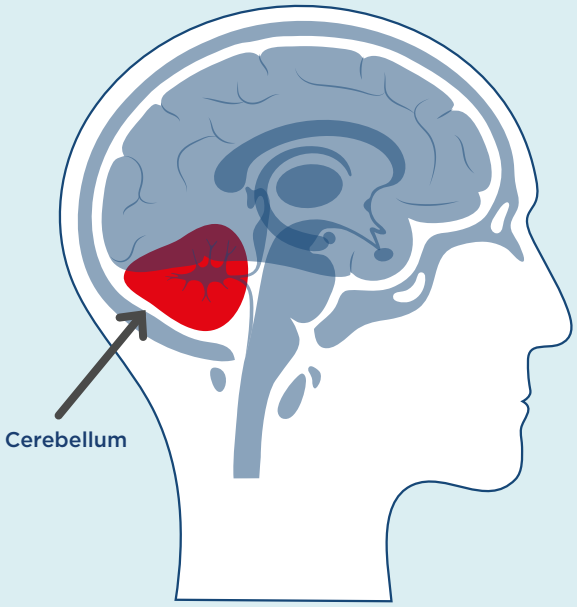
About the *ITPR1* gene

Genes contain instructions that tell our body how to grow, develop and function. *ITPR1* is a **gene** that tells the body to make a special type of protein called the type 1 inositol 1,4,5-trisphosphate (IP3) receptor. This receptor helps to control how our body distributes calcium.

The *ITPR1* gene is very active in a part of the brain known as the cerebellum. The cerebellum is found at the lower back of the brain (see figure below). It combines signals from the eyes, muscles and ears with commands from our brain to control balance, movement and coordination (how our muscles work together). The cerebellum also plays a role in speaking and learning. Changes (**variants**) in the *ITPR1* gene can mean that the cerebellum does not grow to its full size (hypoplasia) or the cerebellum may reduce in size after it is fully grown (atrophy).

Figure: Location of the cerebellum in the brain



The *ITPR1* gene is found on chromosome 3. Usually, *ITPR1*-related conditions are caused by a single spelling variation in the gene, which means the message is not read or received properly.

Sometimes, a section within the gene is missing (a deletion). *ITPR1* gene variants can cause different conditions, described below, depending on how the variant affects the normal function of the gene.

Spinocerebellar ataxia 29 (SCA29)
The most common *ITPR1*-related condition is known as congenital non-progressive cerebellar **ataxia** (spinocerebellar ataxia 29 [SCA29]). People with ataxia have trouble controlling their muscles or voluntary movements, such as walking or picking things up. Children with SCA29 usually have mild developmental delay.

SCA29 is usually inherited in an **autosomal dominant** manner. This means that an affected child only needs to have a variant in one copy of their *ITPR1* gene. This variant may have been passed down (inherited) from a parent or occurred for the first time when the baby was conceived (a new or *'de novo'* variant) and is not seen in the parents.

Gillespie syndrome
Children with Gillespie syndrome also have spinocerebellar ataxia and developmental delay/ intellectual disability. They may also have problems with their eyes.

Gillespie syndrome can be inherited in an **autosomal recessive** or autosomal dominant manner. Autosomal recessive Gillespie syndrome occurs when a child has inherited an *ITPR1* gene variant from each parent. The parents are usually unaffected carriers, which means they carry this gene change without being aware of it. Most of the autosomal dominant gene changes are seen as a new variant in the child.

Spinocerebellar ataxia 15 (SCA15)
Spinocerebellar ataxia 15 (SCA15) occurs when the entire *ITPR1* gene is missing (deleted). Affected individuals usually have a cerebellar ataxia that starts when they are adults and slowly gets worse. People with SCA15 do not usually have an intellectual disability. People with SCA15 usually inherit the condition in an autosomal dominant pattern from an affected parent.

ITPR1-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. *ITPR1*-related conditions are rare.

What could a change in the *ITPR1* gene mean for my child?

A change in the *ITPR1* 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 main symptoms are unsteady walking (gait ataxia) with mild developmental delay or learning difficulty. Walking is often delayed, however the ataxia usually does not worsen over time (non-progressive). Children often have low muscle tone (hypotonia) and are slow to reach their developmental milestones, including big movements (gross motor), small movements (fine motor) and speech. Learning ability varies, ranging from normal intelligence to moderate intellectual disability, with the majority having a mild disability. This can vary even between affected individuals within the same family.

Some changes in the brain (cerebellar hypoplasia/atrophy) can be seen using medical imaging. Cerebellar hypoplasia may not be seen the first time imaging studies are done but can develop later in life. Ataxia improves over time in some adults. Other variable symptoms affecting the nervous system (neurological symptoms) include speech difficulty (dysarthria), abnormal eye movements (nystagmus or oculomotor apraxia), squint (strabismus) and shaking hands (tremor).

Individuals with Gillespie syndrome may have cerebellar ataxia that does not worsen over time (non-progressive) and intellectual disability. Many children with Gillespie syndrome have a condition called aniridia, in which the coloured part of the eye, the iris, does not fully develop. As aniridia develops before the baby is born, children with a normal eye examination will not go on to develop aniridia later in life.

At this point in time, it is not possible to reverse or directly repair this gene variant. 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 you 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 year or more often if needed. 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 (60–85%), including difficulty/delayed walking (>90%) and low muscle tone (hypotonia) (40–80%)	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
Balance problems/gait ataxia (95–100%)	Regular monitoring Physiotherapy, occupational therapy
Speech delay (90%) and difficulty in forming sounds (dysarthria)	Speech therapy to help with language development
Visual (eyesight) problems/vision loss (>50%)	Initial review by ophthalmologist for assessment of vision, squint (strabismus), unusual horizontal eye movements (nystagmus) and developmental eye abnormalities such as aniridia Yearly eye review by ophthalmologist if visual problems are identified Treatment for aniridia involves regular eye examinations and corrective lenses when necessary A squint (strabismus) may require patching or glasses
Brain structural malformations, typically underdevelopment of the cerebellum (70%)	Cerebellar symptoms such as ataxia do not usually correlate with brain imaging findings. Imaging is not usually required. Structural changes do not usually require any specific treatment

Detailed management recommendations on SCA15 for healthcare professionals can be found at **GeneReviews**.

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 an *ITPR1*-related condition. You can make these connections through:

- Social media (e.g. closed Facebook groups such as **The Gillespie band, children affected by Gillespie Syndrome)**
- Umbrella groups (e.g. **Genetic Alliance Australia** and **Rare Voices Australia**)
- Condition-specific groups
- 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 *ITPR1*-related conditions

You can find further information about *ITPR1*-related conditions by following the links below.

- MedlinePlus: **ITPR1 gene** and **Gillespie Syndrome**
- Genetic and Rare Disease Information Center (GARD): **Spinocerebellar ataxia 29**

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 are sometimes passed from a parent to their child. The different ways the genetic variant may be passed down (inherited) are described with each specific condition earlier in this fact sheet. Parents who are carrying an *ITPR1* variant may not have any signs of an *ITPR1*-related condition, so it is important that both parents are tested for the variant. 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.

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 **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 'ITPR1'.

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