FACTS ABOUT HEALTH CONDITIONS

CAUSED BY CHANGES IN THE *HUWE1* GENE

This fact sheet contains information about the possible impact of a change (variant) in the *HUWE1* 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 *HUWE1* gene. These changes were identified by a genomic (DNA) test. It does not provide information about conditions caused by chromosome duplications that involve the *HUWE1* gene that in general cause a mild intellectual disability in males only. This fact sheet does not relate to cancers that are due to acquired variants in the *HUWE1* gene (changes that occur after a person is born).

Key points

- A change in the *HUWE1* gene will usually cause a moderate to severe developmental delay in males. Other signs and symptoms can occur, and may include short stature and vision problems. The effect is much more varied in females
- Changes (variants) in the *HUWE1* gene that cause health problems may be inherited from a mother or may be a new *('de novo')* change in a child. This means that future children may also have this variant. 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 *HUWE1* gene. Support is available from a number of different organisations and services

Other names this condition may be referred to as:

- *HUWE1*-related disorder
- Turner-type X-linked intellectual disability

Known to cause Juberg Marsidi syndrome and Brooks syndrome

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 *HUWE1* gene

Genes contain instructions that tell our body how to grow, develop and function. *HUWE1* is a **gene** that acts to "fine tune" the levels of other critical genes in the brain. This in turn controls the activity of proteins that are essential for brain growth and function.

The *HUWE1* gene is found on the X chromosome. Usually *HUWE1*-related conditions are caused by a single spelling variation in the gene (called a **variant**), which means the message is not read or received properly.

In some individuals with *HUWE1*-related conditions, the change in the gene is inherited from the mother. The mother may be mildly affected or not show any signs of the condition. A change in the *HUWE1* gene may also occur when a baby is conceived (a new or *'de novo'* change), and is not seen in the parents.

HUWE1-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. *HUWE1*-related conditions are very rare, with less than 50 cases being reported in the medical literature.

What could a change in the *HUWE1* gene mean for my child?

A change in the *HUWE1* 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. Males with a *HUWE1* variant usually have a severe developmental delay, though children with milder symptoms have been reported. Children are usually slow to walk and speak, and some never learn these skills. Many children are of normal size when they are born, but tend to grow more slowly and end up shorter than other children of the same age. They may also have a different head size than other children (most often a smaller head size [microcephaly]).

In some children, the range of movement in the large joints (hips, shoulders, elbows and knees) gradually becomes reduced (large joint restriction), which makes it harder for them to move around. Seizures are seen in some children, as well as problems with sleeping. Most children are described as being friendly, however some develop behavioural issues. Common facial features include deeper set eyes, a broad nasal tip, low-set cupped ears and a broad mouth with a thin upper lip. Symptoms in females can be variable, and are sometimes as severe as in males.

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 months 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. The table on the next page describes males with *HUWE1* variants. Females may also carry a *HUWE1* variant, but in many cases show no symptoms at all.

Possible health problems (% of boys affected)	Management
Developmental delay/intellectual disability (>90%), including low muscle tone (hypotonia [70%])	Early intervention, including speech therapy, occupational therapy and physiotherapy
Challenging behaviours, e.g., poor impulse control and aggression (unknown frequency)	Diagnosis and management by clinician as appropriate
Attention-deficit/hyperactivity disorder (ADD/ADHD) (50%)	Diagnosis and management by paediatrician as appropriate
Short stature after birth (70%)	Measurement of the child's height at least once each year. Consider screening for hypothyroidism and growth hormone deficiency
Genital structural differences (20%)	If the opening of the tube that lets urine out of the body (urethra) is underneath rather than at the end of the penis (hypospadias), a surgical consultation is required If the testicles cannot be felt (palpated), a surgical consultation is required
Brain structural malformations/ developmental differences of brain (uncommon)	Brain MRI if clinically indicated. Does not usually require any specific treatment
Seizures (epilepsy) (30%)	Investigations and management as directed by paediatrician
Joining of the bones in the skull too early (craniosynostosis), seen in children with specific variants (e.g. Arg110 [~50% of children with this variant])	Monitor head growth and shape If craniosynostosis is found, consultation with a craniofacial specialist may be required
Problems with sleeping (disorders of sleep [25%])	Review by paediatrician, consider referral to sleep physician if severe symptoms
Large joint restriction without general increased muscle tone (30%)	Orthopaedics/physiotherapy and rehabilitation/occupational therapy, including stretching to help avoid fixed tightness of the muscles (contractures) and falls. May increase with age
Visual (eyesight) problems/ vision loss (60%)	A squint (strabismus) may require patching or glasses Long- or near-sightedness (refractive error) may require glasses

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 *HUWE1*-related condition. You can make these connections through:

- Social media (e.g. closed Facebook groups such as the **HUWE1 gene** group)
- 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 *HUWE1*-related conditions

You can find further information about *HUWE1*-related conditions by following the links below.

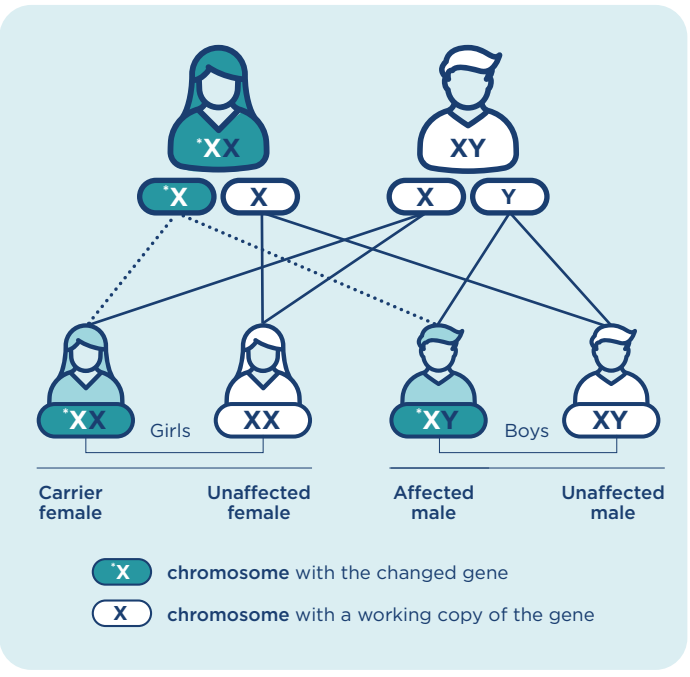
- National Organization for Rare Disorders (NORD): **Juberg-Marsidi syndrome**
- Genetic and Rare Diseases Information Center (GARD): **Juberg Marsidi syndrome**

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 can be passed from a parent to their child. Since the *HUWE1* gene is on the X chromosome, *HUWE1*-related conditions are known as **X-linked** conditions. Females who are genetic carriers of the condition will have one X chromosome with a *HUWE1* variant, and the other X chromosome has a 'backup' working copy of the gene. Female carriers may not show any signs or symptoms of the condition. Males have only one X chromosome (with the variant), and no second working copy of the *HUWE1* gene to act as a backup. So the effect of the variant is usually more obvious in boys than girls.

Female members of the same family (e.g. aunties, nieces or female cousins on the mother's side) may show few or no symptoms even though they may carry a *HUWE1* variant in their DNA. The diagram below shows what can happen when a female who is carrying a *HUWE1* variant has children. The genetic 'carrier' may pass the variant on to her children, who could then have a *HUWE1*-related 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. Even if the same variant was not found in the mother, it is still possible to have another child with the same condition. The chance of this happening is ~4%.

Genetic carrier testing can tell us who is a carrier of a *HUWE1* variant. Women who are found to be carriers are encouraged to see their local genetics service to:

- Discuss concerns about the possibility of having a child with *HUWE1*-related condition
- Discuss options available for genetic testing around a future pregnancy
- Find out what this may mean for other family members, who may then consider genetic counselling and/or genetic testing.

You can also speak with your GP about options for **reproductive genetic carrier screening**, a genetic test that looks for changes in many different genes.

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 'HUWE1'.

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