How common is *HUWE1*-related ID?

HUWE1-related ID is very rare. Currently (2020) less than 50 children with this diagnosis have been reported in the medical literature. The information in this leaflet is based on what we know so far but given the small number of people fully described it is important to recognize that we are limited in our knowledge at present.

Why did this happen?

When a child is conceived, a single set of chromosomes from the mother's egg pairs up with a single set from the father's sperm. When the egg and sperm are made, the parental chromosomes need to be copied so a single set can be placed in each. The biological copying method is not perfect and small changes (known as variants) in the genetic code arise that are not found in the parents (they are known as *de novo*). This happens to all of us but it's only when specific variants occur in important genes that effects on health and development are noticed.

Can it happen again?

Provided that neither parent is found to carry the same *HUWE1* gene variant as their child, the chance of having another child with the same genetic change is considered to be extremely low (less than 1%). There is still a very small risk of recurrence because it is possible that a parent carries the genetic change in a small number of their egg or sperm cells (this is called 'gonadal mosaicism'). Since blood cells do not have the variant, it would not be identified in a genetic test performed on a parent's blood sample. It is also possible for a parent to have some cells in their body carry the variant, whereas others do not, since these cells are not important for growth and function, they are not affected (this is called 'somatic mosaicism').

If a woman is found to carry a pathogenic variant of the *HUWE1* gene, she has a 50% chance of passing it on to each child (unless she has somatic mosaicism). No affected men have been reported to have children of their own so far. Theoretically an affected man would have a 50% risk of passing on the variant to a daughter but not to a son due to the *HUWE1* gene being located on the X chromosome (fathers pass on a Y chromosome to their sons, and an X chromosome to their daughters). For specific advice about the chance of this happening again in your family, it would be ideal to talk to a clinical geneticist or genetic counsellor.

Can *HUWE1*-realted ID be cured?

HUWE1-related ID cannot be cured at the present time however, knowing the diagnosis means that appropriate monitoring and treatment can be put in place.

Families say ...

"Day-to-day he is cheerful and inquisitive. He has a great sense of humour and is very much loved by his brother and sister as well as by all the family. He is non-verbal and can have tricky behaviour but is learning to read basic words, improving his Makaton signing and has started enjoying long walks outdoors!"

Inform Network Support

Rare Chromosome Disorder Support Group,
The Stables, Station Road West, Oxted, Surrey RH8 9EE, UK
Tel: +44(0)1883 723356
email: info@rarechromo.org
www.rarechromo.org

www.huwe1.org
www.facebook.com/groups/huwe1gene
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 This booklet was compiled by Unique (AP) and reviewed by Dr Karen Low, Clinical Genetics consultant, Department of Clinical Genetics, University Hospitals Bristol NHS Foundation Trust.

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Understanding Chromosome & Gene Disorders

HUWE1-related intellectual disability (ID)

rarechromo.org

What is *HUWE1*-related intellectual disability?

HUWE1-related intellectual disability is a recently described genetic condition that is named after the gene responsible - *HUWE1* and the most commonly associated feature - intellectual disability or ID for short.

What causes *HUWE1*-related ID?

HUWE1-related ID occurs when the *HUWE1* gene does not function as expected. This happens when a small change in the gene sequence (the genetic code), known as a pathogenic variant, has a significant effect on its function.

HUWE1 and chromosome X

Our bodies are made up from many different types of cells, most of which contain the same set of chromosomes. Chromosomes are made from very long pieces of DNA, parts of which code for our genes. Genes are instructions that help control our growth, development and how we function.

The HUWE1 gene is located on one of our chromosomes known as the X chromosome, it is located in the short 'p' arm in a region called 11.22 (shaded pink in the image below).

The X chromosome is one of the sex-determining chromosomes, two X chromosomes are usually found in the cells of girls and women (XX), while an X and a Y chromosome are present in the cells of boys and men (XY).

Males only have one X chromosome in each cell, so they have one copy of the *HUWE1* gene. When a boy or man has a pathogenic variant of this gene, he is assumed to be affected.

Females have two copies of the X chromosome and therefore two copies of the *HUWE1* gene. However, one X chromosome is 'switched off' during a natural process called X-inactivation that prevents more than one X chromosome from being fully active in the same cell. When a girl or woman has a pathogenic variant of this gene, the extent to which she is affected, if at all, will depend on which X chromosome is inactivated in important cells, such as those of the developing brain. (Unique publishes a quick read guide to X inactivation freely available at www.rarechromo.org).

Further information associating specific gene variants with different features may become available in the future.

Common Features

Children and adults with *HUWE1*-related ID are often in generally good health and have one or more of the following features in addition to intellectual disability:

- Global developmental delay
- Low muscle tone (hypotonia)
- Few words or absent speech
- Small head (microcephaly)
- Seizures
- Autistic features

Intellectual disability

So far, most males with *HUWE1*-related ID have been found to have severe to profound intellectual disability. Females with a pathogenic variant in HUWE1 will have a variable intellectual ability ranging from no obvious problems to severe or profound. This variability may be related to individual profiles of X-inactivation although studies have not been able to prove this.

Global developmental delay

The majority of children reported so far are significantly delayed in reaching a number of developmental milestones.

Hypotonia and mobility

Hypotonia has been identified in just over half the people with *HUWE1*-related ID to date (2020). Children are often delayed in walking and some children do not achieve this ability.

Speech delay

Almost all children reported in the medical literature with *HUWE1*-related ID have speech delay, just over half have absence of speech (or are able to speak less than 5 words).

Small head (microcephaly)

Microcephaly has been found in about half of the children reported so far, it often happens after birth.

Seizures

Roughly a third of children reported in the medical literature so far, experience or have experienced seizures that were reported to start between 9 months and 13 years of age.

Autistic features

Autistic features have been reported in about half of the children reported so far as have repetitive hand movements (hand stereotypies).

Other features

Short stature and/or small hands and feet have been found in about half of the children described so far. Other less common features that have been reported in a few children with *HUWE1*-related ID include:

- Joint contractures (shortening of joints)
- Increased hair growth
- Hearing loss
- Sleep disorder
- Hyperactivity
- Undescended testis (cryptorchidism)
- Increased muscle tone (hypertonia) of the lower limbs
- Constipation
- Feeding difficulties

Brain MRI results have appeared normal in some children whereas others were found to have structural changes. Eye anomalies include deep set eyes, underdeveloped eyelids or eyelid folds. Squints, long-sightedness, eye ball shape and the retina can also be affected.

Possible facial features include a long face, a broad nasal tip, a short space between the nose and upper lip, a thin upper lip and full lower lip, low set or posteriorly rotated ears.

What is Xp11.22-linked intellectual ID and how is it related to *HUWE1*-related ID?

Xp11.22-linked ID is caused by a small duplication (known as a microduplication) of a stretch of DNA in region p11.22 of chromosome X. This piece of DNA can vary in size but typically includes the *HUWE1* gene. Other genes that may be found in the duplication include *HSD17B10*, *RIBC1* and *SMC1A*. The features of Xp11.22-linked ID are very similar to those of *HUWE1*-related ID, but can vary and may be influenced by the duplication of additional genes. People with an Xp11.22 microduplication that includes *HUWE1* have mild to moderate ID with speech delay.

This leaflet is designed to help families, healthcare professionals and carers looking after people affected by *HUWE1*-related intellectual disability (ID). It contains information about the causes, the ways in which it can affect children and adults, and suggestions about the help and management that may benefit people with this diagnosis. The information in this guide is drawn from clinical experience, information published in the medical literature and families of children who have *HUWE1*-related ID.