Development

Physical development

Most children have some mild delay in their physical development. Most would be expected to walk and gain other physical skills albeit slightly behind their peers.

Learning

Almost all children will have mild learning problems. Some may have more significant problems with learning. It is possible that some may have none at all. Some may have very specific areas requiring learning support.

Behaviour

Some children have been reported to have challenging behaviours. These include self-injuring behaviours such as biting and head banging. Temper tantrums and outburst have also been described. Immature behaviour compared to peers is also seen. Some children do not have any behavioural concerns.

Speech

Speech is normally mildly delayed but most children are expected to learn to speak, albeit at a slower rate than their peers.

Growth

Most children and adults will be shorter than average. For some this may be still within the expected range but for others this may be significantly below it. The same is true for head size, which can vary from average to well below the lowest average values.

Very few children with *PUF60*-related developmental disorder have required treatment for hormone deficiencies. If there are concerns regarding slow growth these should be investigated by a paediatrician with expertise in growth/endocrinology. One child has required hormone therapy to help with puberty.

Management recommendations

At diagnosis

- Genetic testing and counselling about the implications of *PUF60*-related developmental disorder and counselling about the implications of Verheij syndrome
- ECG (measurement of heart's electrical activity) and echocardiogram (ultrasound scan of heart) if not already done
- Eye and hearing checks
- Spine X-ray including neck
- Kidney scan if not previously done

After diagnosis

- Long term follow up by a paediatrician (for children)
- Further eye checks may be recommended
- Follow up may be required by heart or kidney doctors if anomalies are detected
- Brain scan (MRI or MRA) if indicated by neurological symptoms or seizures
- Paediatrician to consider referral to endocrinology specialist if slow growth
- Additional support for families as needed to help with behavioural and psychiatric issues that develop

Families say ...

"The photograph on the front page is of our son having fun and being himself with his friends! Our son is a happy, cheeky boy with a fun sense of humour. He enjoys life to the full. He is a special boy who has the support and help of his amazing sisters, supportive family and friends on a daily basis. We all actively encourage him to be the best he can be and believe in himself - you can do it!"

Inform Network Support

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 This booklet was originally compiled in 2017 by Dr Karen Low, Clinical Genetics StR, and reviewed by Dr Sarah Smithson Clinical Geneticist, Department of Clinical Genetics, University Hospitals Bristol NHS Foundation Trust. An update based on medical literature was carried out by Dr Hannah Grimes, ST1 Paediatrics and reviewed by Dr Karen Low, Consultant Clinical Geneticist, in 2024 (CA).

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Understanding Chromosome & Gene Disorders

PUF60-related developmental disorder (Verheij syndrome)

rarechromo.org

This leaflet is designed to help families and healthcare professionals looking after people affected by *PUF60*-related developmental disorder (also known as PUF60-related syndrome or Verheij syndrome). It contains information about the causes of this syndrome, the ways in which it can affect people and suggestions about the help and management that can benefit people with *PUF60*- related developmental disorder. The information in this guide is drawn from clinical experience and cases published in the medical literature.

What is *PUF60*- related developmental disorder?

PUF60- related developmental disorder is a specific set of features that was initially named Verheij syndrome after Dr Verheij, who first described them in a medical journal in 2009 (Verheij 2009, Dauber 2013, El Chehadeh 2016, Low 2017, Santos-Simarro 2017; Toader 2021; Grimes 2023). The features occur when one of a person's two copies of the *PUF60* gene does not function as expected. This is caused by a small change in the genetic code (a pathogenic sequence variant), or a deletion of one of the two *PUF60* genes.

Genes carry the set of instructions that tell the body how to develop, grow and function. They are made of a complex chemical called DNA and are incorporated into organized structures called chromosomes. The *PUF60* gene is located in chromosome 8. *PUF60* plays an important role in a complex process called "splicing", which controls how the genetic code of other genes is translated from an 'instruction' (DNA) into a 'message' (protein), ensuring the correct instructions are assembled in the right way to form a functional protein. When there is a change to the *PUF60* gene this process becomes faulty. This can result in a problem with instructions being translated into messages and can affect many parts of the body. It is not fully understood why this leads to the clinical features associated with *PUF60*-related developmental disorder but research looking into this is underway.

Although a deletion of the gene associated with these features was first described in 2009, a change to the *PUF60* gene sequence, known as a pathogenic variant, was first described in 2013. In 2023, Unique had 26 member families with a *PUF60* variant. The information in this leaflet is based on what we know so far but given the small number of cases it is important to recognize that we are limited in our knowledge.

Common Features

- Short stature and/or a smaller than usual head size (microcephaly)
- Learning difficulties
- Behavioural concerns
- Heart anomalies/conditions
- Anomalies of the kidney
- Eye/visions concerns (including coloboma)
- Anomalies of the skeleton

Is there a difference between people with a *PUF60* deletion and those with a *PUF60* variant?

The *PUF60* gene is located in the long (q) arm of chromosome 8 in a region called q24.3. Genetic test results of people who are missing all or part of one copy of the *PUF60* gene will mention an 8q24.3 deletion or microdeletion. Most people with a deletion/microdeletion that includes *PUF60* will also have other genetic material missing. For this reason, people with a *PUF60* deletion may have more severe developmental delay and learning difficulties than those seen in people with a *PUF60* pathogenic sequence variant.

Why did this happen?

When children are conceived their parents' genetic material is copied in the egg and sperm that makes a new child. The biological copying method is not perfect and occasionally random, rare changes occur in the genetic code of children that are not seen in the DNA of their parents. This type of change, which occurs out of the blue for the first time in a child and is not inherited from a parent, is called "*de novo*".

If someone has *PUF60*- related developmental disorder, they can pass the genetic alteration on to their children. The chance of this happening is 1 in 2 (or 50%) for each child. Girls and boys are equally likely to be affected. This is called autosomal dominant inheritance. However, the vast majority of cases are *de novo* and occur for the first time in the affected child; there has been only one case reported to date of a parent and child both affected with *PUF60*- related developmental disorder,

Can it happen again?

Provided that neither parent is found to carry the same *PUF60* gene change or deletion as their child, the chance of having another child with the same genetic change is considered to be extremely low. Empirically, this risk would be less than 1%.

The reason why there is some residual risk of recurrence is due to a rare phenomenon called 'gonadal mosaicism'. This is when a parent carries a genetic change, but it is limited to only a small number of egg or sperm cells. The genetic change would not, therefore, be detected from this parent's blood test. There is one family in whom two siblings have PUF60-related disorder but testing of parents was not confirmed. For specific advice about the chance of this happening again, it would be ideal to talk to a clinical geneticist or genetic counsellor.

Medical concerns

Children and adults with *PUF60*-related developmental disorder may have health concerns related mainly to their heart. However, in general they are in good health.

Heart

Children may be born with a heart condition(s). Sometimes these can be picked up on scans in pregnancy but not always. The most common anomaly is a hole between two of the chambers of the heart known as a ventricular septal defect (VSD).

Other heart anomalies have also been seen. These include Tetralogy of Fallot (a combination of four different structural changes in the heart), coarctation of the aorta (narrowing of the main artery), pulmonary stenosis (a narrowing of the heart valve between the heart and the blood vessel travelling from the heart to the lungs) and atrioventricular septal defect (AVSD; a hole between all four chambers of the heart).

Kidneys

Children can be born with kidney anomalies and sometimes these can be picked up on scans during pregnancy. These can include a missing kidney (agenesis) or an abnormally shaped kidney such as a duplex kidney or a horseshoe kidney. Anomalies of the kidneys seem to be a less frequently seen feature in the reported children so far.

Eyes

A small proportion of children have a hole in part of the structure of the eye (coloboma). This can be at the front of the eye or the back. More commonly seen are other features such as a squint (strabismus) and either long- or short-sightedness.

Spine and bones

Some people may have problems with the bones in their spine (vertebrae). Occasionally this may require monitoring but often is of little clinical significance. Scoliosis can occur, where there is a sideways curve of the spine. Some children may have subtly unusual hands and feet. An extra digit has been reported in a small number of cases.

Joints

Joint laxity (bendy joints) is very common. In some cases, this can result in joints coming out of their sockets (dislocation), which has been reported in several children in their hips.

Feeding

Feeding concerns, particularly in early infancy, are common but only persist significantly in a small number of children. Behavioural feeding issues such as selective feeding have also been identified in some children with this condition.

Hearing

Some children may have hearing concerns. For some it may be due to a nerve problem (sensorineural), for others it is due to glue ear (fluid build-up behind the eardrum) or a very narrow ear canal (conductive) which can result in blockages of ear wax. We are aware of a small number of children who have anomalies of the shape or position of the external ear.

Facial and physical features

PUF60-related developmental disorder does not cause children to have very clear, shared facial features. Some children may have facial asymmetry, and some may have a thin top lip. Some may have increased facial hair. Some may have skin tags or pits in the face/neck or around the ears.

Nervous system

Most children don't seem to have major neurological concerns. Brain scan anomalies have been reported in a few and a small number have seizures.