Development

- Physical development
  Most children have some mild delay in their physical development. However 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. However 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 normal 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.

Management recommendations

At diagnosis
- Genetic testing and counselling about the implications of PUF60 related 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 abnormalities are detected
- Brain scan (MRI or MRA) if indicated by neurological symptoms or seizures

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!”

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This information guide is not a substitute for personal medical advice. Families should consult a medically qualified clinician in all matters relating to genetic diagnosis, management and health. Information on genetic changes is a very fast-moving field and while the information in this guide is believed to be the best available at the time of publication, some facts may later change. Unique does its best to keep abreast of changing information and to review its published guides as needed. This booklet was compiled by Dr Karen Low, Clinical Genetics StR, and reviewed by Dr Dr Sarah Smithson Clinical Geneticist, Department of Clinical Genetics, University Hospitals Bristol NHS Foundation Trust.

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This leaflet is designed to help families and healthcare professionals looking after people affected by PUF60 related 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 syndrome. The information in this guide is drawn from clinical experience and cases published in the medical literature.

**What is PUF60 related syndrome?**
PUF60 related syndrome is a very recently described specific set of features that have not yet been named and are simply referred to by the gene responsible (Dauber 2013, El Chehadeh 2016, Low 2017, Santos-Simarro 2017). The features are caused 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, like a spelling mistake, in one of the two genes. Genes are instructions, which have important roles in our growth and development. They are made of a complex chemical called DNA and are incorporated, along with many other genes, into organized structures called chromosomes. PUF60 is located on chromosome 8. PUF60 plays an important role in how the genetic code of other genes is translated from an ‘instruction’ (DNA) into a ‘message’ (protein). This is because it is involved in a complex process called ‘splicing’ which is where the correct instructions are assembled together in the right way. When a spelling mistake occurs in PUF60 this process becomes faulty which 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 but research looking into this is underway.

This condition was first described in one person in 2013. In 2016 there were about 20 known individuals. This number will increase with the advances in genetic testing but the condition will remain very rare. 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 at present.

**Common Features**
- Short stature and/or a smaller than usual head size
- Learning difficulties
- Heart problems
- Kidney problems
- Eye problems (including coloboma)
- Abnormalities of the skeleton

**Medical concerns**
Children and adults with PUF60 related syndrome may have health problems related mainly to their heart. However in general they are in good health.

- **Heart**
  Children may be born with problems with their heart. Sometimes these can be picked up on scans in pregnancy but not always. The most common problem is a hole between two of the chambers known as a ventriculo-septal defect (VSD).

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

- **Eyes**
  Some people may have problems with the eyes and often these can be picked up on scans in pregnancy. These may include a small area of the eye (coloboma) and this can be at the front of the eye or at the back. More generally they are other features such as a squint and either long or short sightedness.

- **Spine and bones**
  Some children may have problems with their spine (vertebrae). Occasionally this may require monitoring but often is of little clinical significance. Scoliosis can occur. 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) are 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 problems, particularly in early infancy are common but only persist significantly in a small number of children.

- **Hearing**
  Some children may have hearing problems. This seems to be caused by different reasons. For some it may be a nerve problem, for others it is due to glue ear (fluid build-up behind the eardrum) or a very narrow ear canal which can result in blockages of ear wax.

- **Facial and physical features**
  PUF60 related syndrome 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 problems. However brain scan abnormalities have been reported in a few, and a small number have seizures.

**What is 8q24.3 microdeletion syndrome and how is it related to PUF60 related syndrome?**

8q24.3 microdeletion syndrome (Verheij 2009) causes features that are very similar to those seen in PUF60 related syndrome. This is because people with 8q24.3 microdeletion are missing a section of genetic material on chromosome 8 that often includes part of or all of one of the copies of PUF60. However other genetic material is often missing as well. For this reason people with the microdeletion may have more severe developmental delay and learning difficulties than those seen in PUF60 related syndrome.

**Why did this happen?**
At the time of conception of a child, copies of genetic material from each parent in the egg and sperm join together. The biological copying method that makes the eggs and sperm is not perfect and occasionally small changes (spelling mistakes) in the genetic code arise for the first time. If this happens in the PUF60 gene, the child but not the parents, will be affected with the syndrome. Once someone has PUF60 related syndrome, they can pass the gene alteration on to their children and 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 so far there have not been any cases in the medical literature of a parent and child affected with this condition.

**Can it happen again?**
Provided that neither parent is found to carry the same PUF60 gene change 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 ‘genetic 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. For specific advice about the chance of this happening again, it would be ideal to talk to a clinical geneticist or genetic counsellor.

**Eye problems (including coloboma)**

- **Face/neck or around the ears**
  - Asymmetry and some may have a thin top lip.
  - Some may have clear shared facial features.

**Heart problems**

- **Learning difficulties**
  - Include a missing kidney (agenesis) or an abnormally shaped kidney such as a duplex kidney or a horseshoe kidney.
  - Kidney problems seem to be a less frequently seen feature in the reported children so far.

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