Why did this happen?

In all but one person with *PCGF2* related syndrome reported so far, this happened because of a change in the gene which most likely occurred in making either the egg or the sperm which joined to make that child. In this situation, testing the mother and father of an affected child will show that neither of them have the same gene change. This is called '*de novo*' in genetic terminology.

In one family the variant in the *PCGF2* gene was found to be present in some, but not all, of that individual's mother's cells. This is called 'mosaicism' and happens when a genetic change occurs *after* the egg and sperm have fused to make the embryo. This means that some of the mother's eggs carry the *PCGF2* variant, and that she can be mildly affected by the condition too.

This genetic change in the *PCGF2* gene occurs because the biological process that copies genes each time a cell divides is not perfect. This is not something that happened because of anything that either parent did during the pregnancy or prior to conceiving the child.

Can it happen again?

If both parents have been tested and do not have the *PCGF2* gene variant (i.e. it is *de novo*) then the chance of them having another affected child is very low. The exception to this is if there is 'germline mosaicism'. This is when some eggs or sperm carry the *PCGF2* change, even though this is not detectable in genetic testing from blood. This has not been reported in any families with *PCGF2* related syndrome so far but is a theoretical possibility. If one parent is mosaic for the *PCGF2* genetic change, i.e. the gene variant is present in some but not all of their cells, the possibility of them having another child affected by this condition is higher, up to 50%, or a 1 in 2 chance in each pregnancy.

Families say:

" She is a very happy and loving girl. We have had a few ups and downs but that is not with her being poorly, it was due to finding out about her heart problem a few years back. She loves going out with her friends to McDonalds or Kaspas. When she finished school she went to her school prom, she loved it. "

Management

As *PCGF2* related syndrome is a relatively newly identified and rare condition we are still learning about the best ways to look after those who are affected. Based on what we know to date, once this diagnosis has been made, the following recommendations apply:

- Children should be under the care of a paediatrician to monitor their health and development
- Screening for heart abnormalities and prophylactic medical treatment if indicated
- Screening for hearing impairment
- Monitoring weight gain and providing support for feeding difficulties
- Constipation is a common feature and may need medical treatment
- Dribbling or drooling is a common feature and some children may require treatment
- An educational and healthcare plan should be put in place to ensure the child's needs are adequately addressed in their educational setting
- Involvement of one, or more, of: speech and language therapy, physiotherapy and occupational therapy – depending on the particular issues each child faces

Useful links: Facebook group:
"Our unique Turnpenny-Fry syndrome (PCGF2) families"

Inform Network Support

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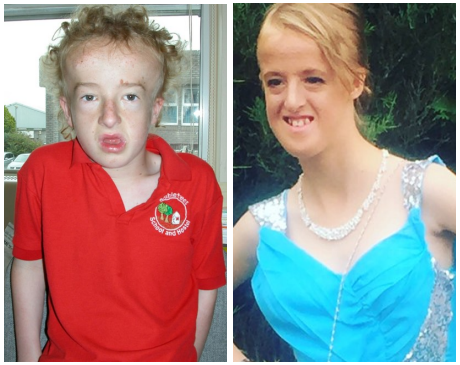
Version 1 (AP) 2019

Rare Chromosome Disorder Support Group
Registered in England and Wales
Charity Number 1110661
Company Number 5460413

Unique
Understanding Chromosome & Gene Disorders

PCGF2 related syndrome



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What is PCGF2 related syndrome?

PCGF2 related syndrome is a very recently described and rare condition (Turnpenny 2018), reported in 13 people worldwide. It is very likely that more people will be diagnosed with this condition with time. The condition is due to DNA changes (variants) in a gene called *PCGF2*. Genes are like the instructions which tell our bodies how to develop, grow and work properly. Each gene is the recipe for a particular protein. *PCGF2* stands for 'polycomb group ring finger 2 protein'. This particular gene has important roles in early development of a baby during pregnancy. It also has an important role in regulating how genes are 'read' in special cells known as stem cells. So far everyone with *PCGF2* related syndrome has been found to have a genetic change at exactly the same position in the *PCGF2* gene. This genetic variant means that one of the protein building blocks (amino acids) in the protein encoded by the *PCGF2* gene is substituted for another. Exactly how and why changing this protein building block causes a problem is not known in detail and further research needs to be undertaken to understand this.

Common features

These are the most common features reported in individuals with *PCGF2* related syndrome. The full spectrum of features are discussed in more detail later.

- Characteristic facial appearance
- Developmental delay or learning disability
- Heart abnormalities
- Skeletal abnormalities

Can this be cured?

The *PCGF2* genetic change is usually present in every cell in an affected person's body, and has had an effect of their development from a very early stage, and we are not able to change this through any specific treatment. Individuals with *PCGF2* related syndrome should have access to supportive therapies to optimise their development; including speech and language therapy, physiotherapy and occupational therapy. Where there are specific issues such as seizures, medication can help to treat this, and cardiovascular problems can be monitored and treated.

Characteristic facial features

Individuals with *PCGF2* related syndrome look similar to each other, such that if you saw them together you might think they were related. Aspects of their facial appearance, which many of the individuals share, include a prominent forehead, long face, small eyes with the appearance of fullness around the eyes, a prominent jaw, and a small mouth sometimes with a tendency to keep their mouth open, and unusually shaped ears. All individuals with *PCGF2* related syndrome share some or all of these facial features, although there is variability from person to person. Recognising this pattern of facial features helps doctors to provide families with this diagnosis.

Developmental delay and learning disability

There is a wide variability in the degree of developmental delay in people with PCGF2 related syndrome.

Physical development

All reported individuals were delayed in achieving the usual developmental milestones. They achieved the ability to sit between 11 and 15 months. All children learnt to walk but this was achieved later than usual (between 18 months and 4.5 years old). The majority of individuals did not have difficulties with coordination but for some this was an issue. Nine children were described as having hypotonia, which means being relatively floppy.

Learning

All individuals are reported to have intellectual disability or developmental delay. In a younger child, developmental delay is often noticeable before they are old enough to enable assessment for intellectual ability. In those with a diagnosis of a learning disability this varied in severity from mild to severe.

Behaviour

There have been diagnoses made of attention deficit hyperactivity disorder (2 individuals), autism spectrum disorder (1 individual), and one child has anxiety requiring treatment with medication. Some individuals have no behaviour problems.

Speech and language

All children had delayed speech development. This ranged from mild speech delay with first words at under 2 years old, to complete absence of speech in a 21-year-old. Some individuals had problems with pronunciation of words.

Heart

Heart anomalies were present in most but not all individuals with this condition (11 out of 13). These included a patent ductus arteriosus (PDA, when a temporary structure in the fetal heart does not close as expected after birth; five individuals), atrial septal defect (ASD, a whole in the wall that separates the two atria (upper chambers) or the heart; three individuals), and widening (or dilatation) of the main blood vessel from the heart, known as the aorta (five individuals). One individual had an irregular heart rhythm known as a supraventricular tachycardia.

Skeleton

Skeletal anomalies in people with *PCGF2* related syndrome include mild changes to the curvature of the spine (known as kyphosis or scoliosis; six individuals), under developed vertebrae (two individuals), and an unusually shaped base of the spine, or sacrum in one individual. Subtle changes in the appearance of fingers or toes were present in four individuals.

Growth

All babies with *PCGF2* related syndrome had a birth weight that was relatively low compared to average. There were concerns about fetal growth during pregnancy for three babies (in medical terminology this is known as 'intrauterine growth retardation', or IUGR). The height and weight of children with *PCGF2* related syndrome has remained relatively low compared to the average for someone of the same age for most children. Nine children experienced feeding difficulties and six children had gastro-oesophageal reflux, which may be contributing factors to poor weight gain. These issues tended to improve as the child grew up, though for some children chronic constipation was a significant problem.

Other symptoms

Additional symptoms identified in children with this condition to date (2019) include conductive hearing impairment (obstructed or altered sound wave transmission) which is often well treated with grommets (draining ear tubes) and/or hearing aids. Two children have had seizures (episodes of unusual electrical activity of the brain) and two had a diaphragmatic hernia (an opening in the muscle that helps us breathe). Families have also mentioned excessive drooling and dribbling.