Understanding chromosome disorders

Unique

# PACS1 related syndrome

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# What is PACS1 related syndrome?

## How is it caused?

PACS1 related syndrome is a recently discovered rare genetic condition whose hallmarks are developmental delay/ intellectual disability and a specific facial appearance which is subtle but recognisable. It can be accompanied by various congenital abnormalities. The first two individuals with the PACS1 related syndrome were reported in the medical literature in 2012, and are from the Netherlands and Belgium. To date almost 20 people have been described in the medical literature from countries around the world. About 10 more people have not been formally reported, but their parents are active on the PACS1 Facebook group [*see* back page]. There must be many more individuals in whom the syndrome has not yet been recognised.

PACS1 related syndrome occurs when there is a specific change in the DNA code of the PACS1 gene. This specific change is called c.607C→T (NM_018026.3). DNA consists of four building blocks: A (adenine), C (cytosine), G (guanine), T (thymine). At building block 607 of the PACS1 gene, a cytosine is changed into a thymine.

It is not yet known if other DNA changes in the PACS1 gene give the same disorder, or if they cause a different disorder, or perhaps even no disorder at all.

Genes are instructions for the cells of our body, which have important roles in our growth and development. They are made of DNA and are incorporated along with many other genes into organised structures called chromosomes. The PACS1 gene is on chromosome 11 in band q13.1q13.2 at base pairs 66070454 to 66244747 [hg38 genome assembly]. There is not much knowledge on the function of the PACS1 gene and its relation to the clinical features of people with PACS1 related syndrome. Animal studies suggest a role for PACS1 in the development of craniofacial structure (the facial bones), and can therefore explain some of the facial similarities seen between individuals.

*" It has been extremely helpful to receive a diagnosis as we finally had answers that we were not expecting to get. Although there is little information about the PACS1 mutation available we managed to track down other families around the world. We have been able to share much information with each other and it's invaluable to be able to speak to others who actually know what we are going through."*

## How many people have this condition?

PACS1 related syndrome is a rare condition, and its prevalence has yet to be determined. So far, 19 persons have been recognized in medical literature. However, with the increasing use of the latest 'gene sequencing' technology, it is expected that many more people will be diagnosed with this condition over the next few years (including adults). Two large studies - which are seeking to identify the genetic causes of developmental delay in children - have so far found the c.607C→T change in the PACS1 gene in eight out of 3,133 developmentally delayed children (0.2-0.3%; about 1/400 children with development delay).

## Common features

All children with PACS1 related syndrome who have been diagnosed to date have developmental delay. There is usually a mild to moderate degree of intellectual disability. Language is more severely affected than motor development. Their facial appearance is very similar. Other typical features include:

- Seizures
- Congenital heart defect: atrial septal or ventricular septal defect
- A low muscle tone (hypotonia), most pronounced at a young age
- A variety of eye anomalies
- Oral aversion (reluctance or avoidance of eating/drinking or accepting (specific) sensations in or around the mouth)
- Behavioural problems (autism spectrum disorder, temper tantrums)

These features are not specific for the PACS1 related syndrome. The diagnosis can only be made with a genetic test.

## Development

### Growth

Most babies with PACS1 related syndrome are born with a normal weight. Many children experience difficulties with adapting to solid food (oral aversion). Failure to thrive in infancy is present in some children.

### Sitting, moving, walking

Motor development is delayed, with most children achieving walking between 2 and 3 years of age. There may be a persisting unsteady gait. Some people use a wheelchair for longer distances.

### Speech

Speech is more severely affected than motor development, although the severity of the speech delay varies between individuals. Some children with the syndrome start to talk as early as two years of age. Most will acquire speech later, but some do not develop speech at all. Comprehension can be much better than speaking. One of the adults with the syndrome does not speak, but she can read and communicates via an iPad with a "TouchChat"app. Other devices that may be of benefit are child sign language and picture exchange cards.

### Learning

Children have learning difficulties/ intellectual disability of varying severity. Most children have moderate intellectual disability, but some have mild to moderate or moderate to severe intellectual disability. All need the support of special education. Most individuals are not expected to live fully independently as adults. Parents frequently comment on their child's excellent (visual) memory.

### Behaviour

Most children generally have a friendly and happy disposition. More than half have behavioural problems, which can include autism spectrum disorder, temper tantrums and aggressive behaviour towards themselves or their carers. They profit from a structured day programme. Many parents observe a dislike for loud or sudden noises (hyperacusis). Some children prefer specific sensory stimuli on their face (e.g. covering the face with a scarf).

*" O loves to be helpful. He will happily empty the washing machine, put the plates out for dinner or help to carry the shopping in, and often signs asking to help."*

## Medical concerns

**Epilepsy** Febrile convulsions or seizures are present in more than half of children and adults. Age of onset varies. Most children respond well to anti-epileptic drugs. In some individuals the seizures disappear over time.

**Neuroimaging abnormalities** With cerebral imaging (MRI or CT scan of the brain) a variety of abnormalities can be seen, such as diminished volume of particular parts of the brain, including the cerebellar vermis, and increased volume of the cerebral ventricles. None of these abnormalities is specific for PACS1 syndrome.

**Low muscle tone** Low muscle tone (hypotonia) is usually obvious in the newborn period and may persist throughout childhood. This is likely to contribute to feeding difficulties, delay in reaching motor milestones and flatfoot (pes planus). When initially learning to walk, some children benefit from orthopaedic shoes for support.

**Feeding difficulties/ oral aversion** Feeding difficulties may already be present in the newborn period, but typically become apparent when solid food is introduced. Most children have a strong preference for soft food or certain specific textures. This oral aversion may persist into childhood, adolescence or even adulthood. Oral aversion may contribute to failure to thrive and slender build. A minority of children require gastrostomy feeding (G-tube).

**Heart abnormalities** Congenital heart abnormalities are present in more than half of people. Most common are an atrial septal defect or ventricular septal defect (a gap in the wall of the upper or lower chambers of the heart, resulting in blood flow between the chambers). Patent ductus arteriosus, a failure of the ductus arteriosus to close after birth, is also common.

**Eyes and eyesight** Eye abnormalities are common, but vary in origin and severity. Myopia (short sighted), strabismus (squint) and astigmatism (causing blurred or distorted vision). Some people have nystagmus (involuntary eye movement) and some have a coloboma (a gap in one of the structures of the eye, such as the iris or optic nerve).

**Cryptorchidism** About half of the boys have cryptorchidism, a condition in which the testicles are not located in the scrotum. The testicles are often located in the abdomen, and it needs surgery to position them where they should be. Cryptorchidism is the most common abnormality in male sexual development.

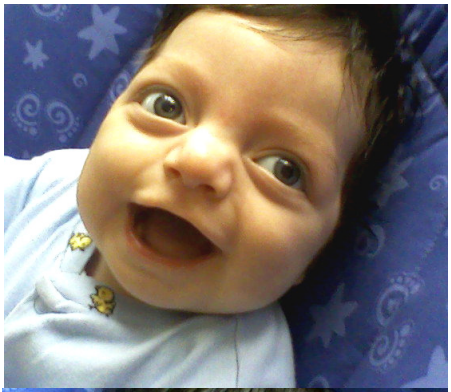
**Constipation** Constipation is present in about half of individuals.

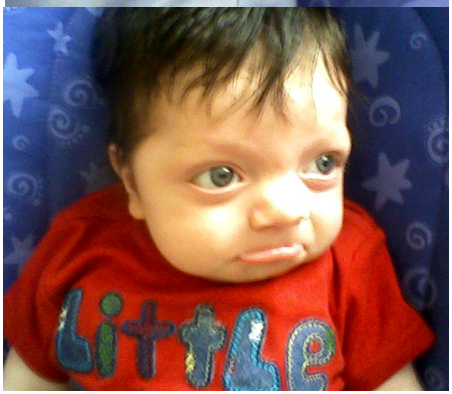
## Management recommendations

A paediatrician should be involved in and coordinate follow-up. Evaluation by a multidisciplinary team can be beneficial (paediatrician, neurologist, speech therapist, dietician).

*Recommended at diagnosis*

- Feeding management & evaluation by dietician, if necessary
- EEG (measurement of the brain's electrical activity), if seizures are suspected
- Brain imaging with MRI, if indicated
- Eye check by ophthalmologist
- Consider ultrasound scans of heart and kidneys to exclude structural abnormalities
- Evaluation for cryptorchidism in boys
- Treatment for constipation, if necessary






*After diagnosis*

- Long term follow up by a developmental paediatrician
- Speech and language support
- Physiotherapy, and occupational therapy as needed
- Regular eyesight checks may be recommended

*" O has an extremely cheeky personality and he loves to play little tricks on people like hiding toys or hiding under his duvet in the morning when he's meant to be getting ready for school! His cheeky smile and giggle helps him to get away with most things.*
*He has a very loving nature, even though he can't speak he will show his affection towards you by a big cuddle, a kiss or stroking your arm or face. He enjoys his routines which usually involves a cuddle before bedtime."*

## Why did this happen?

PACS1 related syndrome develops when a child has the specific mutation in the PACS1 gene. In all families that we know about so far, there is only one affected child and the sequence change in PACS1 occurred out of the blue (this is what you may hear a geneticist referring to as a *'de novo'* change). The parents have normal PACS1 genes. So a new error occurred in the DNA sequence of the gene in the child alone. 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 occasional random, rare changes occur for the first time. New mutations happen naturally and are not due to lifestyle, pregnancy or any other environmental factor.

## Can it happen again?

Most parents of children with the PACS1 related syndrome themselves have the normal DNA code of the PACS1 gene. Provided that neither parent is found to carry the same PACS1 DNA change as their child, the chance of having another child with the same genetic change is very low (less than 1%).

In very rare cases it may happen that parents will have another child with PACS1 related syndrome. The reason is a rare phenomenon called gonadal mosaicism. This is when a parent carries a genetic change, but this change is limited to a small cluster of egg or sperm cells. The genetic change would therefore not be detected on this parent's blood test. Up to now this has not been reported for PACS1 related syndrome. The risk for other family members of having a child with PACS1 related syndrome is not increased and is the same as for anyone else in the population.

If a person with PACS1 related syndrome had offspring, the risk would be 50% for each child of having the syndrome.

Each family situation is different and a clinical genetics specialist can give you specific advice for your family.

*" Parenting a child with additional needs has opened our eyes in many ways. We have had to learn a whole new level of patience, it is extremely challenging and often stressful but also immeasurably rewarding. We have had to learn to communicate with O in ways such as Makaton, reading the noises he makes and body language as he has no speech. But all of this has been worthwhile as we couldn't ask for a more loving, happy and special little boy. We are so proud of everything that he has achieved."*

## Support and Information

**Rare Chromosome Disorder Support Group,**
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Join Unique for family links, information and support.

Unique is a charity without government funding, existing entirely on donations and grants. If you can, please make a donation via our website at www.rarechromo.org Please help us to help you!

www.facebook.com/PACS1Syndrome
www.pacs1.info

www.facebook.com/groups/1521777111380249

Unique lists external message boards and websites in order to be helpful to families looking for information and support. This does not imply that we endorse their content or have any responsibility for it.
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. The text was written by Dr Janneke Schuurs and Professor Han Brunner, Department of Human Genetics, Radboud University Medical centre, Nijmegen, the Netherlands, and the guide was compiled by Unique.

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