

# PURA and 5q31.3 deletion syndrome



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#### What is PURA syndrome and how is it caused?

PURA syndrome is a recently discovered condition. Clinical geneticists tend to refer to it as a neurodevelopmental disorder rather than a syndrome. In this guide, however, the condition is referred to as PURA syndrome.

PURA syndrome occurs when one of a person's two copies of the PURA gene does not function normally. This can be caused by a spelling mistake in the gene or by loss of one copy of the gene (a deletion). Genes are instructions, 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 PURA gene is on chromosome 5. It has a number of different roles, but is known to be particularly important in brain development. This is why problems with the PURA gene are primarily associated with a neurodevelopmental disorder.

#### Most common features

All children with PURA syndrome who have been identified to date have at least a moderate degree of learning disability and developmental delay. Other typical features include:

- Seizures and seizure-like movements
- Low muscle tone at birth and throughout childhood
- Feeding difficulties in the newborn period
- Breathing problems

These features are not specific for a problem with the PURA gene, so the diagnosis can only be made with a genetic test. See also page 6

#### How many people have this condition?

PURA syndrome is a rare condition, first described in the medical literature in 2014. To date, only 15 children have been reported with this condition. 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). One large study - which is seeking to identify the genetic causes of developmental delay in children - has so far found new changes in PURA in three out of 1,133 developmentally delayed children (0.26%; about 1/400).

## What is 5q31.3 deletion syndrome and how is it related to PURA syndrome?

Sometimes deletions can occur, removing a large segment of DNA from a chromosome. Such deletions may remove many adjacent genes. One chromosomal deletion, which removes a single copy of the PURA gene along with neighbouring genes, is the 5q31.3 deletion. For this reason, the 5q31.3 deletion syndrome has overlapping features with PURA syndrome.

To date, seven children have been described with 5q31.3 deletions. All have very similar clinical features, but none has an identical chromosomal deletion. Broadly speaking, children with a 5q31.3 deletion have the same types of problem as are found in PURA syndrome. However, children with a 5q31.3 deletion tend to be more severely affected. A likely explanation for this is that other neighbouring genes included in the 5q31.3 deletion may also be contributory. One gene that is usually included in this deletion and is suspected to have an important role is NRG2.

#### 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 for the first time. Such changes, therefore, cannot be found in a child's parents. In all families that we know about so far, the DNA change in PURA occurred 'out of the blue' in this way (this is what you may hear a geneticist referring to as a de novo change).

#### Can it happen again?

Provided that neither parent is found to carry the same PURA change as their child, the chance of having another child with the same genetic change would be considered extremely low. Empirically, this risk would be considered 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 a small cluster of egg or sperm cells. The genetic change would not, therefore, be detected on this parent's blood test. For specific advice about the chance of this happening again, it would be sensible to speak to a clinical geneticist or genetic counsellor.



#### Development

"I have learned from Aidan that being non-verbal is not the same thing as not being able to communicate, and being non-ambulatory does not prevent him from being independently mobile. We've learned new ways of being in the world with Aidan so that he can live life more fully." age 14

#### Growth

Babies with PURA syndrome are usually born at a normal weight and grow appropriately.

#### Sitting, moving, walking

All children have delayed motor development and most do not achieve independent walking. Those who do manage to walk independently tend to have an unsteady, wide-based gait.

#### Speech

Many children with PURA syndrome do not develop meaningful speech. Those who do develop speech may achieve single words, short phrases or basic sentences.

Some parents have reported good receptive language skills (understanding of spoken language) in non-verbal children with PURA syndrome. Devices to enable and encourage expressive communication, such as symbol-based touch screen communication devices, may be of benefit to some children.



" Sarah has great receptive language skills, but has been unable to say more than the occasional word. With therapists she is now learning to express herself using a PODD communication book and an electronic communication device. She loves to use these devices." age 7

#### Learning

All children that we know of have at least moderate learning disability and require specialist support with learning.

#### Behaviour

Children with PURA syndrome typically have behaviour in keeping with their overall degree of developmental delay.



"Everything about Rylee is special, he gives the best hugs and kisses, and is the happiest little boy I have ever met in my life. He has opened our eyes and heart to a whole new world. He has taught us to love unconditionally." - age 7

"Lucas is the most sweet natured boy you could meet, so loving, with a really cheeky sense of humour to boot. He has made myself and my husband better and stronger people and we are humbled daily by how strong a person he is becoming, dealing daily with problems that would floor most people, and all with a smile on his face. He makes us so proud every day." - age 7



#### Other features noticed by families

Some families have noticed certain features that have not yet been reported in the medical literature by doctors. These include:

- Significant temperature instability in newborn babies
- Hiccups. Several mothers noticed hiccupping in utero (in the womb), and hiccups were common in young babies.

#### Medical concerns

Children with 5q31.3 deletions that include PURA as well as neighbouring genes tend to have more severe problems than children with changes confined to the PURA gene alone.

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, breathing problems and delay in reaching motor milestones.

**Feeding difficulties** Feeding difficulties are typical in newborn babies. Many babies with PURA syndrome ultimately require temporary feeding by nasogastric tube. A minority require gastrostomy feeding because of swallowing problems. In some children, feeding difficulties may persist.

**Breathing problems** Respiratory difficulties are common to most children, and usually become apparent in the newborn period. These may include central apnoea (in which the brain does not control breathing properly) and obstructive sleep apnoea (in which the upper airway becomes blocked due to low muscle tone during sleep). Tracheostomies (an opening in the neck to put in a tube to help breathing) have been required by some children.

Seizures/seizure-like movements Almost all children with PURA syndrome have seizures or seizure-like episodes warranting further investigation at some point in early childhood. Different patterns of seizures have been reported, but myoclonic jerks and generalised tonicclonic seizures are most common. In one child, seizures have proved extremely difficult to manage with standard anti-epileptic drugs.

**Eyes and eyesight** A wide range of eye and eyesight problems have been reported. These include - but are not limited to - short-sightedness, squint, and abnormal eye movements. Most children are affected in some way.

**Hormones** There is some evidence that endocrine dysfunction (especially of the anterior pituitary gland) may represent a less common part of PURA syndrome.

**Reduced bone density** Reduced bone density (known as osteoporosis) has been identified in two children. Problems in maintaining vitamin D levels, which has an important role in regulating bone density, have been identified in one child.

**Heart** One child has been reported with a 'hole in the heart' and another with an abnormally formed heart valve [bicuspid aortic valve].

**Kidney** One child has been reported with a structural abnormality of the kidneys.

**Neuroimaging abnormalities** Some children have abnormal findings on their brain imaging. This can include 'delayed myelination', which refers to a delay in the normal formation of the white matter in the brain and spinal cord.

#### Management recommendations

#### At diagnosis

- Feeding management, if necessary
- Respiratory studies, if necessary
- EEG (measurement of brain's electrical activity), if seizures are suspected
- Eye check
- Consider ultrasound scans of heart and kidneys to exclude structural abnormalities
- Brain imaging with MRI, if indicated

#### 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

"We were told Sarah may never walk, but she thought otherwise. Through hard work, she is learning to use a supportive walker to take steps. She has participated in her first school 'walkathon' with support from her aide. Sarah has an incredible outlook on life. She has the most infectious giggle, a gorgeous smile and a determination to do whatever she sets her mind to. Sarah has a way of inspiring people and making you stop and think about what is truly important in life."



### Support and Information



#### Rare Chromosome Disorder Support Group,

G1, The Stables, Station Road West, Oxted, Surrey RH8 9EE, United Kingdom Tel/Fax: +44(0)1883 723356 info@rarechromo.org | www.rarechromo.org

#### Join Unique for family links, information and support.

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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.

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