The PURA Syndrome Foundation

The PURA Syndrome Foundation is a globally focused charitable organisation. The Foundation supports and educates patients and their families, providing a global community. This community provides a place of belonging to those who may otherwise feel isolated by rare disease, enriches the medical research being completed and educates those outside the community about the condition.

Our mission is to serve, educate and fund research for families coping with the effects of PURA syndrome.

Our values are:
• Respect – everyone is valued
• Community – everyone belongs
• Teamwork – Foundation, families, clinicians and researchers as one
• Continuity – plans for future growth and change
• Responsibility – ethics and governance

Our biggest annual event is a conference where the families of patients with PURA syndrome can convene, support each other and share resources. Families also hear from medical researchers who are working to understand PURA syndrome. Bringing the families and researchers together at this event, increases understanding and knowledge for research. This in turn, enhances the quality of life for patients and their families.

President’s Message

Hello, and welcome.
I am Dominic Spadafore, and I serve as the President of the PURA Syndrome Foundation. The Foundation is here to help support and educate our families as well as support and advance research into PURA syndrome. Thank you for visiting us. There is a lot of information here to support both families of PURA syndrome and their clinicians. We also have a Foundation Facebook page. Please join it to receive regular updates on events and research, register with us through our parent liaisons to receive our regular e-mail updates, and check back here for blog postings and other updates and announcements that you may find helpful.

Please contact Dominic via email at d.spadafore@pura-syndrome.org

Contacting the Foundation

The foundation has parent liaisons that assist and support PURA families. To make contact with the Foundation and/or the private parents group, please email one of the board members below.

USA: Kerry Hildring
Please contact her via email at k.hildring@pura-syndrome.org

EU and other countries: Ceciel van Hoeckel
Please contact her via email at c.vanhoeckel@pura-syndrome.org

(Ceciel can correspond in English, Dutch, German, Italian, Spanish, French)
The PURA Syndrome Global Research Network

The PURA Syndrome Foundation supports the PURA Syndrome Global Research Network, a global network of medical researchers. The Global Research Network coordinates PURA syndrome research, the development of the PURA Syndrome Global Patient Registry and Global PURA Biobank. Research members assist the Foundation in educating families, institutions and clinicians about PURA syndrome.

Research relating to PURA syndrome can broadly be divided into four areas:
- Clinical Phenotype and Natural Histories Study – Clinical study to find an accurate description of the disorder
- Basic Research including Functional Studies - Basic science, including studying how the gene works
- Translational Research – Animal and cellular models
- ‘Cross-cutting’ research - Working with other conditions

Members of the Global Research Network also support the Foundation through various medical committees including:
- Grant Advisory Committee
- Registry Advisory Committee
- Biobank Advisory Committee

The Global Research Network supports the yearly PURA Syndrome Global Conference. Members of the Global Research Network attend to present research updates and educate families about PURA syndrome. Researchers also spend time reviewing existing research projects as well as planning new research to be commenced.

Contact with the Global Research Network is made through the PURA Syndrome Foundation Research Liaison, Mel Anderson m.anderson@pura-syndrome.org
What is PURA syndrome?

PURA syndrome is a rare genetic disorder. The PURA gene is located on the long arm of chromosome 5 (at position 5q31.3). 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 whole gene 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 has a number of different roles. It encodes for a protein, pur-alpha, that is expressed in all tissues, including the brain, muscle, heart, and blood. The protein has a number of different roles in the human cell, including regulatory functions in DNA replication, transcription and translation of mRNA, and is known to be particularly important in brain development. This is why problems with the PURA gene are primarily associated with a neurodevelopmental disorder.

Additional information for clinicians can be located at the [PURA Gene Review PURA-Related Neurodevelopmental Disorders](https://www.ncbi.nlm.nih.gov/books/NBK426063/)

Differential diagnosis

Disorders with similar characteristics are:
- Central Hypoventilation syndrome [OMIM209880]
- Spinal Muscular Atrophy [OMIM253300])
- Myotonic Dystrophy [OMIM160900]
- Prader Willi syndrome [OMIM176270]
- Angelman syndrome [OMIM105830]
- Rett syndrome [OMIM312750]
- Pitt-Hopkins syndrome (OMIM610954)
- Metabolic conditions / disorders

Most common features of PURA syndrome

All patients with PURA syndrome who have been identified to date, have at least a moderate to severe degree of learning disability and developmental delay. Other typical features include:
- Seizures and seizure-like abnormal movements
- Hypotonia (Low muscle tone)
- Feeding difficulties
- Respiratory problems (including obstructive and central apneas)
- Hypersomnolence (excessive sleepiness)
- Constipation
- Abnormal vision
- Temperature instability
- Excessive hiccups
- Orthopedic issues including hip dysplasia and scoliosis
- Endocrine disorders such as Vitamin D deficiency
How many people have this condition?
PURA syndrome is a rare condition, first described in the medical literature in 2014. To date, just over 250 individuals have been reported with this condition, both adults and children. 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.

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 almost all of the 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

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

Moving (gross motor and fine motor)
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. Many individuals have poor fine motor skills.

Speech
The vast majority of individuals with PURA syndrome do not develop meaningful speech. Those who do develop speech may achieve single words, short phrases or rarely basic sentences. 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 and eye gaze devices, may be of benefit to some children.
**Learning**
All individuals that we know of have moderate to profound learning disability and require specialist support with learning.

**Behaviour**
Individuals with PURA syndrome typically have behaviour in keeping with their overall degree of developmental delay.

**Medical concerns**

**Low muscle tone**
Low muscle tone (hypotonia) is most obvious in the newborn period and may persist throughout childhood and adulthood. 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 many children, feeding difficulties may persist. Excessive drooling has been observed in many individuals, as has severe constipation (requiring the use of laxatives).

**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). Due to this, many children undergo overnight sleep assessment studies. Tracheostomies (an opening in the neck to put in a tube to help breathing) have been required by some individuals.

**Seizures and 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 tonic-clonic seizures are most common. In some cases, seizures have proved extremely difficult to manage with standard anti-epileptic drugs. Non seizure movements can include dystonia (muscular spasm) and dyskinesia (involuntary movement).

**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.

**Temperature instability**
Temperature instability (hypothermia) has been seen, particularly in the newborn period.
Hormones and reduced bone density
A diverse range of endocrine issues have been reported. Reduced bone density (known as osteoporosis) has been identified in a number of individuals. Problems in maintaining a normal level of vitamin D, which is important in regulating bone density, are not uncommon. Thyroid hormone and cortisol issues have also been reported. Hormonal issues at puberty need to be further investigated.

Structural malformation
Although not frequently reported, there have reported cases of malformation of urogenital (urinary and genital organs), heart and skeletal systems. This has included kidney stones in some cases.

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.

What is “5q31.3 deletion syndrome including PURA” 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 can remove 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, 8 patients have been described in medical literature to have 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.
Management recommendations

The treatments for PURA syndrome are directed toward the specific symptoms that are apparent in each individual. Treatment will require the coordinated efforts of a multidisciplinary team, ideally with the involvement of a neurologist, geneticist, paediatrician, respiratory physician, ophthalmologist and orthopaedic specialist.

Epilepsy, present in over half of the PURA syndrome cases, can be very difficult to manage effectively. Whilst some individuals have responded well to specific anti-epileptic drugs, refractory (drug resistant) seizures are common. Therefore, further research into seizure causes and management is required.

At diagnosis

- Developmental assessment
- Feeding management and constipation assessment, if necessary
- Respiratory studies, if necessary
- EEG (measurement of brain’s electrical activity), if seizures are suspected
- Brain imaging with MRI, if indicated
- Eye check
- Consider ultrasound scans of heart and kidneys to exclude structural abnormalities
- Vitamin D measurement
- Bone density assessment, if any specific concerns

After diagnosis

- Long term follow up by a developmental paediatrician
- Monitoring for constipation
- Monitoring for musculoskeletal complications including hip dysplasia and scoliosis
- Sleep study if apnoea suspected
- Speech and language support
- Physiotherapy, and occupational therapy as needed
- Regular eyesight checks may be recommended
- EEG (measurement of brain’s electrical activity), if seizures are suspected