***PURA*-Related Neurodevelopmental Disorders**

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**Summary**

**Clinical characteristics.**

***PURA***-related **neurodevelopmental** disorders include ***PURA*** syndrome, caused by a [heterozygous](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/heterozygous/) pathogenic sequence variant in ***PURA***, and 5q31.3 [deletion syndrome](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/deletion-syndrome/), caused by a [genomic](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/genomic/) 5q31.3 deletion encompassing all or part of ***PURA****.* ***PURA***-related **neurodevelopmental** disorders are characterized by moderate to severe **neurodevelopmental** delay with absence of speech in most and lack of independent ambulation in many. Early-onset problems can include hypotonia, hypothermia, hypersomnolence, feeding difficulties, excessive hiccups, recurrent central and obstructive apneas, epileptic seizures, abnormal non-epileptic movements (dystonia, dyskinesia, and dysconjugate eye movements), and abnormal vision. Congenital heart defects, urogenital malformations, skeletal abnormalities, and endocrine disorders occur, but are less common.

**Diagnosis/testing.**

The diagnosis of a ***PURA***-related **neurodevelopmental** disorder is established in a [proband](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/proband/) with either a [heterozygous](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/heterozygous/) ***PURA*** pathogenic sequence variant (90% of [affected](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/affected/) individuals) or a non-[recurrent deletion](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/recurrent-deletion/) of 5q31.3 that encompasses all or part of ***PURA*** (10%).

**Management.**

*Treatment of manifestations:* Ongoing routine care by a multidisciplinary team. Treatment and/or therapy for developmental delays; neurologic findings (hypotonia, seizures, abnormal movements); feeding difficulties; apnea; visual impairment; and malformations of the heart, urogenital tract, and skeleton.

*Surveillance*: Long-term follow up to assess psychomotor development, seizures or suspected seizures, vision, feeding for dysphagia, and musculoskeletal complications (hip dysplasia and scoliosis).

**Genetic counseling.**

***PURA***-related **neurodevelopmental** disorders, caused by either a [heterozygous](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/heterozygous/) ***PURA***pathogenic sequence variant or a 5q31.3 [deletion](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/deletion/) encompassing all or part of ***PURA*** are inherited in an [autosomal dominant](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/autosomal-dominant/) manner. In almost all probands with a ***PURA*** pathogenic sequence variant the sequence variant is [*de novo*](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/de-novo/); to date, all reported 5q31.3 deletions have been *de novo*. For parents of an [affected](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/affected/) child, the risk to future pregnancies is presumed to be low, as a *de novo* genetic alteration involving ***PURA*** is most likely in the [proband](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/proband/). However, parents of an affected child may wish to consider prenatal testing or [preimplantation genetic diagnosis](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/preimplantation-genetic-diagnosis/) as risk may be greater than in the general population owing to the possibility of parental [germline mosaicism](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/germline-mosaicism/) (estimated empirically at <1%).

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***GeneReview* Scope**

| ***PURA*-Related Neurodevelopmental Disorders: Included Disorders** |
| --- |
| * ***PURA*** syndrome * 5q31.3 [deletion syndrome](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/deletion-syndrome/) |

For synonyms and outdated names see [Nomenclature](https://www.ncbi.nlm.nih.gov/books/NBK426063/#pura-dis.Nomenclature).

[Go to:](https://www.ncbi.nlm.nih.gov/books/NBK426063/)

**Diagnosis**

No formal clinical diagnostic criteria have been published for ***PURA***-related **neurodevelopmental** disorders, which comprise ***PURA*** syndrome (caused by a [heterozygous](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/heterozygous/) ***PURA*** pathogenic sequence variant) and 5q31.3 [deletion syndrome](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/deletion-syndrome/) (caused by a non-recurrent 5q31.3 deletion encompassing all or part of ***PURA***).

**Suggestive Findings**

*A****PURA***-related **neurodevelopmental** disorder **should be suspected** in infants and older individuals with the following clinical findings.

**Infants**

* Hypotonia
* Neonatal hypoventilation
* Hypothermia
* Hypersomnolence
* Feeding difficulties, including gastroesophageal reflux disease (GERD)

**Older individuals**

* Hypotonia
* Moderate-severe intellectual disability, including absent speech
* Seizures
* Abnormal non-epileptic movements (e.g., dystonia, dyskinesia, and dysconjugate eye movements)

**Establishing the Diagnosis**

The diagnosis of a ***PURA***-related **neurodevelopmental** disorder **is established** in a [proband](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/proband/) with one of the following genetic findings (see [Table 1](https://www.ncbi.nlm.nih.gov/books/NBK426063/table/pura-dis.T.molecular_genetic_testing_use/?report=objectonly)):

* A [heterozygous](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/heterozygous/) ***PURA*** pathogenic sequence variant (90% of [affected](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/affected/) individuals)
* Non-[recurrent deletion](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/recurrent-deletion/) of 5q31.3 that encompasses all or part of ***PURA*** (10%)

Molecular genetic testing approaches can include a combination of [**genomic**](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/genomic/)**testing** ([chromosomal microarray](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/chromosomal-microarray/)analysis, comprehensive [genome sequencing](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/genome-sequencing/)) and [**gene**](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/gene/)**-targeted testing** ([multi-gene panel](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/multi-gene-panel/) and single-gene testing).

Gene-targeted testing requires the clinician to determine which specific [gene](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/gene/)(s) are likely involved, whereas [genomic](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/genomic/)testing does not. Because the phenotypes of many genetic intellectual disability disorders overlap, most children with a ***PURA***-related **neurodevelopmental** disorder are diagnosed by one of the following.

**Recommended Testing**

**A**[**multi-gene panel**](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/multi-gene-panel/) which includes ***PURA*** and other genes of interest (see Differential Diagnosis). Note: (1) The genes included in the panel and the diagnostic [sensitivity](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/sensitivity/) of the testing used for each gene vary by laboratory and over time. (2) Some multi-gene panels may include genes not associated with the condition discussed in this GeneReview; thus, clinicians need to determine which multi-gene panel provides the best opportunity to identify the genetic cause of the condition at the most reasonable cost while limiting secondary findings. (3) Methods used in a panel may include [sequence analysis](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/sequence-analysis/), [deletion/duplication analysis](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/deletion-duplication-analysis/), and/or other non-sequencing based analyses. For this disorder, a multi-gene panel that also includes copy number analysis is recommended (see [Table 1](https://www.ncbi.nlm.nih.gov/books/NBK426063/table/pura-dis.T.molecular_genetic_testing_use/?report=objectonly)).

For more information on multi-[gene](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/gene/) panels click [here](https://www.ncbi.nlm.nih.gov/books/n/gene/app5/#app5.MultiGene_Panels).

**Chromosomal microarray analysis (CMA**) to detect large, non-recurrent 5q31.3 deletions that include ***PURA*** which cannot readily be detected by [sequence analysis](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/sequence-analysis/) of ***PURA***.

**Testing to Consider**

**Comprehensive**[**genome sequencing**](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/genome-sequencing/) (when available) includes [exome sequencing](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/exome-sequencing/) and genome sequencing. For more information on comprehensive genome sequencing click [here](https://www.ncbi.nlm.nih.gov/books/n/gene/app5/#app5.Comprehensive_Genome_Sequencing).

Note: Single-[gene](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/gene/) testing ([sequence analysis](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/sequence-analysis/) of ***PURA****,* followed by gene-targeted [deletion/duplication analysis](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/deletion-duplication-analysis/)) may be helpful in some circumstances – for example, when clinical suspicion in a neonate is considerable and a rapid diagnosis would be beneficial.

**Table 1.**

Molecular Genetic Testing Used in ***PURA***-related **Neurodevelopmental** Disorders

| **Gene 1** | **Test Method** | **Proportion of Probands with a Pathogenic Variant 2 Detectable by This Method** |
| --- | --- | --- |
| ***PURA*** | Sequence analysis 3 | 71/79 4 |
| Gene-targeted [deletion/duplication analysis](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/deletion-duplication-analysis/) 5 | Unknown 6 |
| CMA 7 | 8/79 8 |

1.

See [Table A. Genes and Databases](https://www.ncbi.nlm.nih.gov/books/NBK426063/#pura-dis.molgen.TA) for [chromosome](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/chromosome/) [locus](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/locus/) and protein.

2.

See [Molecular Genetics](https://www.ncbi.nlm.nih.gov/books/NBK426063/#pura-dis.Molecular_Genetics) for information on allelic variants detected in this [gene](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/gene/).

3.

Sequence analysis detects variants that are benign, likely benign, of [uncertain significance](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/uncertain-significance/), likely pathogenic, or pathogenic. Pathogenic variants may include small intragenic deletions/insertions and [missense](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/missense/), [nonsense](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/nonsense-variant/), and [splice site](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/splice-site/) variants; typically, [exon](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/exon/) or whole-[gene](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/gene/) deletions/duplications are not detected. For issues to consider in interpretation of [sequence analysis](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/sequence-analysis/) results, click [here](https://www.ncbi.nlm.nih.gov/books/n/gene/app2/).

4.

n=11 [[Lalani et al 2014](https://www.ncbi.nlm.nih.gov/books/NBK426063/)], n=4 [[Hunt et al 2014](https://www.ncbi.nlm.nih.gov/books/NBK426063/)], n=6 [[Tanaka et al 2015](https://www.ncbi.nlm.nih.gov/books/NBK426063/)], n=1 [[Okamoto et al 2017](https://www.ncbi.nlm.nih.gov/books/NBK426063/)], n=49 [Author, personal observation]

5.

Gene-targeted [deletion/duplication analysis](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/deletion-duplication-analysis/) detects intragenic deletions or duplications. Methods that may be used include: [quantitative PCR](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/quantitative-pcr/), long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a [gene](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/gene/)-targeted microarray designed to detect single-[exon](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/exon/) deletions or duplications.

6.

No data on detection rate of [gene](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/gene/)-targeted [deletion/duplication analysis](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/deletion-duplication-analysis/) are available.

7.

Chromosomal microarray analysis (CMA) using oligonucleotide arrays or SNP arrays. CMA designs in current clinical use target the 5q31.3 region.

8.

n=2 [[Shimojima et al 2011](https://www.ncbi.nlm.nih.gov/books/NBK426063/)], n=3 [[Hosoki et al 2012](https://www.ncbi.nlm.nih.gov/books/NBK426063/)], n=2 [[Brown et al 2013](https://www.ncbi.nlm.nih.gov/books/NBK426063/)], n=1 [[Bonaglia et al 2015](https://www.ncbi.nlm.nih.gov/books/NBK426063/)]

[Go to:](https://www.ncbi.nlm.nih.gov/books/NBK426063/)

**Clinical Characteristics**

**Clinical Description**

***PURA***-related **neurodevelopmental** disorders comprise ***PURA*** syndrome (caused by a [heterozygous](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/heterozygous/) ***PURA***pathogenic sequence variant) and 5q31.3 [deletion syndrome](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/deletion-syndrome/) (caused by a non-recurrent 5q31.3 deletion encompassing all or part of ***PURA***). ***PURA***-related **neurodevelopmental** disorders are characterized by moderate to severe **neurodevelopmental** delay; most [affected](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/affected/) individuals are nonverbal, and many do not achieve independent ambulation.

Early-onset problems are wide ranging and can include hypotonia, hypothermia, hypersomnolence, feeding difficulties, excessive hiccups, recurrent central and obstructive apneas, epileptic seizures, abnormal non-epileptic movements, and visual problems.

Congenital heart defects, urogenital malformations, skeletal abnormalities, and endocrine disorders occur, but are less common [[Hunt et al 2014](https://www.ncbi.nlm.nih.gov/books/NBK426063/); [Lalani et al 2014](https://www.ncbi.nlm.nih.gov/books/NBK426063/); [Tanaka et al 2015](https://www.ncbi.nlm.nih.gov/books/NBK426063/); [Okamoto et al 2017](https://www.ncbi.nlm.nih.gov/books/NBK426063/); Author, personal observation].

The figures given for the following clinical features are based on observed frequencies in individuals with ***PURA***syndrome. Individuals with 5q31.3 deletions encompassing ***PURA*** have not been included here as they have non-recurrent chromosomal deletions of varying sizes; thus, genetically, they represent a comparatively heterogeneous group.

**Development.** All 71 individuals with ***PURA*** syndrome reported to date have had moderate-to-severe **neurodevelopmental** delay.

Speech is absent in most; however, the use of augmentative and alternative communication aids has proved beneficial in some children. Many children have relatively good receptive language skills and may follow simple instructions, despite having no overt expressive language.

Motor development is delayed, but with variable severity. Some individuals never achieve independent ambulation. In those who do, the age ranges from 22 months to seven years. The gait of [affected](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/affected/) children is typically broad-based.

Many individuals have poor fine-motor skills, which can hinder the use of some types of communication aids.

**Neurologic.** Severe hypotonia and hypersomnolence are common at birth.

Epilepsy has been reported in at least 50% of the individuals (42/71) and usually starts with myoclonic jerks progressing to other seizure types including generalized tonic-clonic seizures, tonic seizures, and epileptic spasms. In some instances, the seizure disorder progresses to the Lennox-Gastaut syndrome.

The age of seizure onset ranges between the neonatal period and 16 years, although most of those who develop epilepsy do so in the first five years, many in infancy.

The seizures are often drug resistant.

Non-epileptic movements that may be seen include dystonia, dyskinesia, and dysconjugate eye movements.

Non-epileptic exaggerated startle response is present in several children.

Nystagmus is present in 17/71 individuals.

MRI findings include the following:

* Delayed myelination or nonspecific subtle white matter hyperintensities, which constitute the most frequently reported brain abnormalities (23/71)
* Excessive extra-axial fluid spaces (7/71)
* Volume loss of the corpus callosum (4/71)
* Cerebellar tonsillar ectopia (1/71)
* Possible cerebral atrophy (1/71)
* Absent septum pellucidum (1/71)

**Ophthalmologic.** Strabismus, Brown syndrome, and exophoria are the most frequently reported abnormalities (21/71).

Early cortical visual impairment (7/71), hypermetropia (6/71), and optic nerve pallor (1/71) have also been reported.

**Respiratory.** Apnea and hypoventilation are present in more than 50% of [affected](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/affected/) individuals (42/71).

For the majority of [affected](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/affected/) individuals, the episodes of apnea and hypoventilation resolve after the first year of life; however, in a minority, apnea may persist or recur during an acute respiratory illness.

Aspiration pneumonia due to hypotonia and dysphagia has been reported.

**Cardiovascular.** Structural heart defects, present in a minority of [affected](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/affected/) individuals, include ventricular septal defect (3/71), persistent foramen ovale (2/71), persistent ductus arteriosus (1/71), pulmonic stenosis (1/71), atrial septal defect (1/71), bicuspid aortic valve (1/71), and aberrant left subclavian artery (1/71). However, it should be borne in mind that these figures may represent an underestimate (particularly of minor cardiac abnormalities that may not be manifesting obvious signs of disease) as not all individuals will have had an echocardiogram as a matter of course.

**Gastrointestinal.** A significant number of neonates have severe feeding difficulties and/or gastroesophageal reflux disease (GERD) (56/71).

Dysphagia often persists throughout life. Drooling is common; however, the cause (either excessive salivation or oromotor dyspraxia/swallowing problems) requires further investigation.

Constipation has been reported in the majority of individuals [[Tanaka et al 2015](https://www.ncbi.nlm.nih.gov/books/NBK426063/); Author, personal observation].

**Urogenital.** In four [affected](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/affected/) individuals, renal and genital defects including cryptorchidism (3/71), kidney stones (3/71), [congenital](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/congenital/) hydronephrosis (2/71), prolapsed uterus (1/71), and urinary reflux (1/71) have been reported.

**Skeletal.** Scoliosis (13/71), hip dysplasia (11/71), and osteoporosis/osteopenia (7/71) are the most frequently reported skeletal abnormalities.

**Endocrine.** Anterior pituitary dysregulation may be within the spectrum of ***PURA***-related **neurodevelopmental**disorders [[Hunt et al 2014](https://www.ncbi.nlm.nih.gov/books/NBK426063/)] based on the following observations:

* Disturbed levels of gonadotropins (2/71) and medical treatment for precocious puberty (3/71)
* A blunted cortisol response (2/71)
* Hypothyroidism (2/71)
* Elevated prolactin levels (1/71)

Although low vitamin D levels (7/71) and anemia and/or low iron levels (4/71) have been reported, the true prevalence may be higher as vitamin D and iron levels are often not measured routinely and deficiency may not be obvious clinically.

**Other**

* Neonatal hypothermia. Difficulties in regulating body temperature in the neonatal period have not yet been reported in the literature, but appear to occur frequently [Author, personal observation].
* Excessive hiccups in utero and in the neonatal period have been observed in a significant proportion of the individuals [Author, personal observation].

**Genotype-Phenotype Correlations**

Current data suggest that ***PURA*** variants in the region encoding the PUR III repeat cause a more severe [phenotype](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/phenotype/)than variants in the regions that encode PUR I or PUR II repeats (see [Molecular Genetics](https://www.ncbi.nlm.nih.gov/books/NBK426063/#pura-dis.Molecular_Genetics), **Normal**[**gene product**](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/gene-product/)). However, the functional effect at a molecular level is not yet clear and requires further investigation [[Hunt et al 2014](https://www.ncbi.nlm.nih.gov/books/NBK426063/)].

***PURA***-related **neurodevelopmental** disorders encompass both ***PURA*** syndrome and the 5q31.3 [deletion syndrome](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/deletion-syndrome/). It has been suggested that ***PURA*** [haploinsufficiency](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/haploinsufficiency/) contributes to the **neurodevelopmental** [phenotype](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/phenotype/) of individuals with a 5q31.3 deletion [[Brown et al 2013](https://www.ncbi.nlm.nih.gov/books/NBK426063/)].

The features of individuals with a 5q31.3 [deletion](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/deletion/) that overlap with those of individuals with a ***PURA*** [pathogenic variant](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/pathogenic-variant/) include: neonatal hypotonia, feeding difficulties, and respiratory difficulties as well as severe intellectual disability and epilepsy [[Shimojima et al 2011](https://www.ncbi.nlm.nih.gov/books/NBK426063/), [Hosoki et al 2012](https://www.ncbi.nlm.nih.gov/books/NBK426063/), [Brown et al 2013](https://www.ncbi.nlm.nih.gov/books/NBK426063/), [Bonaglia et al 2015](https://www.ncbi.nlm.nih.gov/books/NBK426063/)].

Of note, individuals with a [deletion](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/deletion/) that also includes the neighboring [gene](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/gene/) *NRG2* – as well as those with larger deletions that encompass multiple genes in addition to ***PURA*** and *NRG2* – show a more severe [phenotype](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/phenotype/) (including distinct facial dysmorphisms) than individuals with an intragenic ***PURA*** [pathogenic variant](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/pathogenic-variant/). It has been suggested that deletion of *NRG2* contributes to the more severe phenotype observed in individuals with a large 5q31.3 deletion [[Brown et al 2013](https://www.ncbi.nlm.nih.gov/books/NBK426063/)].

**Penetrance**

To the authors’ knowledge, the [penetrance](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/penetrance/) of all intragenic ***PURA*** pathogenic variants and 5q31.3 deletions encompassing ***PURA*** is complete.

**Nomenclature**

The OMIM designation for ***PURA***-related **neurodevelopmental** disorders - “mental retardation, [autosomal dominant](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/autosomal-dominant/)31” (OMIM [616158](http://omim.org/entry/616158)) - is no longer in use.

**Prevalence**

To date, 71 individuals are known to have ***PURA*** syndrome [[Hunt et al 2014](https://www.ncbi.nlm.nih.gov/books/NBK426063/); [Lalani et al 2014](https://www.ncbi.nlm.nih.gov/books/NBK426063/); [Tanaka et al 2015](https://www.ncbi.nlm.nih.gov/books/NBK426063/); [Okamoto et al 2017](https://www.ncbi.nlm.nih.gov/books/NBK426063/); Author, personal observation]. Eight individuals with the 5q31.3 [deletion syndrome](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/deletion-syndrome/) have been reported.

Based on the study of [Hunt et al [2014]](https://www.ncbi.nlm.nih.gov/books/NBK426063/), the estimated frequency of ***PURA*** syndrome as a cause of intellectual disability is 3:1,133 (0.3%).

[Lalani et al [2014]](https://www.ncbi.nlm.nih.gov/books/NBK426063/) and [Tanaka et al [2015]](https://www.ncbi.nlm.nih.gov/books/NBK426063/) estimated a higher frequency (0.5%) based on their cohorts of 11:2,117 and 6:1,098, respectively.

[Go to:](https://www.ncbi.nlm.nih.gov/books/NBK426063/)

**Genetically Related (Allelic) Disorders**

No phenotypes other than those discussed in this *GeneReview* are known to be associated with pathogenic variants in ***PURA***.

[Go to:](https://www.ncbi.nlm.nih.gov/books/NBK426063/)

**Differential Diagnosis**

Disorders in the differential diagnosis of ***PURA***-related **neurodevelopmental** disorders are:

* [Congenital central hypoventilation syndrome](https://www.ncbi.nlm.nih.gov/books/n/gene/ondine/)
* [Prader-Willi syndrome](https://www.ncbi.nlm.nih.gov/books/n/gene/pws/)
* Lower extremity-predominant [autosomal dominant](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/autosomal-dominant/) spinal muscular atrophy 1 (OMIM [158600](http://omim.org/entry/158600)) / distal [autosomal recessive](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/autosomal-recessive/) spinal muscular atrophy 1 (OMIM [604320](http://omim.org/entry/604320))
* Myotonic dystrophy in the newborn (see [Myotonic Dystrophy Type 1](https://www.ncbi.nlm.nih.gov/books/n/gene/myotonic-d/))
* Neurotransmitter disorder [[Pearl et al 2007](https://www.ncbi.nlm.nih.gov/books/NBK426063/)]
* Rett syndrome (see [*MECP2*-Related Disorders](https://www.ncbi.nlm.nih.gov/books/n/gene/rett/))
* [Pitt-Hopkins syndrome](https://www.ncbi.nlm.nih.gov/books/n/gene/pitt-hopkins/)
* [Angelman syndrome](https://www.ncbi.nlm.nih.gov/books/n/gene/angelman/)

See [Mental retardation, autosomal dominant: OMIM Phenotypic Series](https://www.omim.org/phenotypicSeries/PS156200) to view genes associated with this [phenotype](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/phenotype/)in OMIM.

[Go to:](https://www.ncbi.nlm.nih.gov/books/NBK426063/)

**Management**

**Evaluations Following Initial Diagnosis**

To establish the extent of disease and needs in an individual diagnosed with a ***PURA***-related **neurodevelopmental**disorder, the following evaluations are recommended.

**Table 2.**

Recommended Evaluations Following Initial Diagnosis

| **Affected System** | **Evaluation** | **Comment** |
| --- | --- | --- |
| **Cognitive** | Developmental assessment |  |
| **Neurologic** | Neurologic evaluation |  |
| Brain MRI | Indicated in a child w/a ***PURA****-*related **neurodevelopmental**disorder w/seizures and/or hypoventilation and/or abnormal vision or eye movements who has not previously had a brain MRI |
| EEG and video EEG | If seizures are suspected |
| **Eyes** | Ophthalmology examination | Electrodiagnostic tests may be indicated in some cases. |
| **Cardiovascular** | Consider echocardiogram |  |
| **Respiratory** | Assessment of pulmonary function | As needed |
| **Gastrointestinal** | Feeding assessment w/analysis of swallowing & evaluation for possible aspiration | As needed |
| Assessment for constipation |
| **Genitourinary** | Consider ultrasound of the urinary tract |  |
| **Musculoskeletal** | Appropriate radiographs | If hip dysplasia and/or scoliosis is suspected |
| **Endocrine** | Assessment of serum vitamin D levels |  |
| Assessment of bone density | If osteoporosis or osteopenia is suspected |
| Evaluation of anterior pituitary hormones | If necessary |
| **Miscellaneous/other** | Consultation w/a clinical geneticist and/or genetic counselor |  |

**Treatment of Manifestations**

Individuals often benefit when management is provided by a multidisciplinary team including relevant specialists, which may include, but is not limited to, a pediatrician, clinical geneticist, child neurologist, pulmonologist, ophthalmologist, orthopedic surgeon, physiotherapist, occupational therapist, and speech and language therapist.

**Table 3.**

Treatment of Manifestations in Individuals with ***PURA***-Related **Neurodevelopmental** Disorders

| **Manifestation** | **Treatment** | **Considerations/Other** |
| --- | --- | --- |
| Cognitive/developmental delay | See [Global Developmental Disability/ Intellectual Disability Educational Issues](https://www.ncbi.nlm.nih.gov/books/NBK426063/#pura-dis.Global_Developmental_Disability). |  |
| Seizures | Management by a neurologist | May include video EEG monitoring to help distinguish epileptic from non-epileptic events (e.g., dystonia, dyskinesia, dysconjugate eye movements) |
| Vision deficits | Correction of refractive errors; vision support; standard treatment for strabismus & exophoria |  |
| Hypoventilation | Supplementary oxygen (at night) & rarely tracheostomy | Ambulatory peripheral saturation monitoring may be required. |
| Some infants require short periods of intubation & mechanical ventilation, particularly during acute illness. |
| Congenital heart defect | Management as per current practice for the specific [congenital](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/congenital/) heart defect |  |
| Frequent aspiration (or high risk of aspiration) | A percutaneous endoscopic gastrostomy tube may be considered. |  |
| GERD | Medical management; consideration of Nissen fundoplication if medical treatment is not sufficient |  |
| Constipation | Routine management | Referral to a gastroenterologist may be required in severe cases. |
| Congenital urogenital defect | Management as per current practice for the specific urogenital defect |  |
| Scoliosis | Standard management | Progressive neuropathic scoliosis may require spinal fusion. |
| Osteoporosis/osteopenia | Standard management |  |
| Instability in standing position | Ankle foot orthoses (AFO) may improve stability, allowing for better standing & transferring ability. |  |
| Neuropathic hip dysplasia, progressive subluxation, & dislocation | Consideration of hip reconstructions w/varus derotational proximal femoral osteotomies | Generalized joint laxity & continued inability to walk may cause relapsing hip subluxation even after previous femoral osteotomies. |
| Vitamin D deficiency | Vitamin D supplementation |  |
| Anterior pituitary hormone deficiencies | Standard treatment as directed by an endocrinologist |  |

GERD = gastroesophageal reflux disease

The following information represents typical management recommendations for individuals with developmental delay/intellectual disability in the United States; standard recommendations may vary from country to country.

**Global Developmental Disability/ Intellectual Disability Educational Issues**

**For ages 0-3 years.** Referral to an early intervention program is recommended for access to occupational, physical, speech, and feeding therapy. In the United States, early intervention is a nationwide, federally funded program available in all states.

**For ages 3-5 years.** In the United States, developmental preschool through the local public school district is recommended. An evaluation will occur before placement to determine needed services and therapies and will be subsequently written into an individualized education plan (IEP).

**For ages 5-21 years**

* In the United States, an IEP should be developed by the local public school district based on each individual’s level of function. Affected children are permitted to remain in the public school district until age 21.
* Discussion about transition plans including financial, vocation/employment, and medical arrangements should begin at age 12 years. Developmental pediatricians can provide assistance with transition to adulthood.

**For all ages.** Consultation with a developmental pediatrician is recommended to ensure that appropriate community, state, and educational agencies are involved and to support parents in maximizing quality of life. Some issues to consider:

* Private supportive therapies based on the [affected](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/affected/) individual’s needs. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.
* In the United States, enrollment in DDA (Developmental Disabilities Administration) is recommended. DDA is a public agency that provides services and supports to qualified individuals. Eligibility differs by state but is typically determined by diagnosis and/or associated cognitive/adaptive disabilities.
* In the United States, families with limited income and resources may also qualify for supplemental security income for their child with a disability.

**Motor Dysfunction**

**Gross motor dysfunction**

* Physical therapy is recommended to maximize mobility and to reduce the risk for later-onset orthopedic complications (e.g., scoliosis, hip dislocation).
* Consider use of durable medical equipment as needed (e.g., wheelchairs, walkers, bath chairs, orthotics, adaptive strollers).
* For muscle tone abnormalities including dystonia, consider involving appropriate specialists to aid in management of medications or orthopedic procedures.

**Fine motor dysfunction.** Occupational therapy is recommended for difficulty with fine motor skills that affect adaptive function (e.g., feeding, grooming, dressing).

**Oral motor dysfunction.** Assuming that the individual is safe to eat by mouth, feeding therapy (typically from an occupational or speech therapist) is recommended for [affected](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/affected/) individuals who have difficulty feeding due to poor oral motor control.

**Communication issues.** Consider alternative means of communication for individuals who have expressive language difficulties, such as an Augmentative and Alternative Communication (AAC) evaluation.

**Surveillance**

**Table 4.**

Recommended Surveillance for Individuals with ***PURA***-Related **Neurodevelopmental** Disorders

| **Affected System** | **Evaluation** | **Frequency/Comment** |
| --- | --- | --- |
| **Cognitive** | Monitoring by developmental pediatrics | Long-term |
| **Neurologic** | EEG & video EEG monitoring | If seizures are suspected |
| **Eyes** | Ophthalmologic & vision evaluations | Routine |
| **Gastrointestinal** | Monitoring for dysphagia & constipation | Routine |
| **Musculoskeletal** | Monitoring for musculoskeletal complications including hip dysplasia & scoliosis | Routine |

**Evaluation of Relatives at Risk**

See [Genetic Counseling](https://www.ncbi.nlm.nih.gov/books/NBK426063/#pura-dis.Related_Genetic_Counseling_Issu) for issues related to testing of at-risk relatives for [genetic counseling](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/genetic-counseling/) purposes.

**Therapies Under Investigation**

Search [ClinicalTrials.gov](https://clinicaltrials.gov/) for access to information on clinical studies for a wide range of diseases and conditions.

[Go to:](https://www.ncbi.nlm.nih.gov/books/NBK426063/)

**Genetic Counseling**

*Genetic counseling is the process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional*. —ED.

**Mode of Inheritance**

***PURA***-related **neurodevelopmental** disorders, caused by either a [heterozygous](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/heterozygous/) ***PURA*** pathogenic sequence variant (***PURA*** syndrome) or a 5q31.3 [deletion](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/deletion/) encompassing all or part of ***PURA*** (5q31.3 [deletion syndrome](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/deletion-syndrome/)), are inherited in an [autosomal dominant](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/autosomal-dominant/) manner.

**Risk to Family Members – *PURA* Pathogenic Sequence Variant**

**Parents of a**[**proband**](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/proband/)

* In almost all probands with a ***PURA*** pathogenic sequence variant the sequence variant is [*de novo*](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/de-novo/).
* The exception is a child who was found to have inherited a ***PURA*** pathogenic sequence variant from her unaffected father, who had low-level [mosaicism](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/mosaicism/) [Author, personal observation].
* Evaluation of parents of a [proband](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/proband/) with an apparent [*de novo*](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/de-novo/) [pathogenic variant](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/pathogenic-variant/) by [molecular genetic testing](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/molecular-genetic-testing/) is recommended.
* If the ***PURA*** [pathogenic variant](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/pathogenic-variant/) found in the [proband](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/proband/) cannot be detected in leukocyte DNA of either parent, the variant is most likely [*de novo*](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/de-novo/); however, parental [germline mosaicism](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/germline-mosaicism/) is also a possibility.

**Sibs of a**[**proband**](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/proband/)

* The risk to the sibs of the [proband](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/proband/) depends on the genetic status of the parents.
* Because almost all ***PURA*** pathogenic sequence variants reported to date have been [*de novo*](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/de-novo/), the risk to sibs appears to be low (<1%), but greater than that of the general population because of the possibility of parental [germline mosaicism](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/germline-mosaicism/).

**Offspring of a**[**proband**](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/proband/)**.** To date, very few adults have been identified with a ***PURA***-related **neurodevelopmental**disorder. None has had children. However, the theoretic risk to offspring of an [affected](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/affected/) individual is 50%.

**Risk to Family Members – 5q31.3 Deletion Encompassing All or Part of *PURA***

**Parents of a**[**proband**](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/proband/)

* To date, all reported 5q31.3 deletions have been [*de novo*](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/de-novo/).
* Evaluation of the parents by [genomic](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/genomic/) testing that will detect the 5q31.3 [deletion](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/deletion/) identified in the [proband](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/proband/) is recommended. It is also important to exclude a balanced [chromosome](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/chromosome/) rearrangement that may have predisposed to a deletion encompassing 5q31.3 in the proband.

**Sibs of a**[**proband**](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/proband/)**.** The risk to the sibs of the proband depends on the genetic status of the parents:

* If the 5q31.3 [deletion](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/deletion/) found in the [proband](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/proband/) is not identified in one of the parents, the risk to sibs is presumed to be low (<1%) but greater than that of the general population because of the theoretic possibility of parental [germline mosaicism](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/germline-mosaicism/).
* If a predisposing balanced [chromosome](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/chromosome/) rearrangement is identified in a parent, [genetic counseling](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/genetic-counseling/) is important as there may be a significant risk to the sibs of the [proband](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/proband/).

**Offspring of a**[**proband**](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/proband/)**.** To date, very few adults have been identified with a ***PURA***-related **neurodevelopmental**disorder. None has had children. However, the theoretic risk to offspring of an [affected](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/affected/) individual is 50%.

**Other Family Members**

Given that all probands with a ***PURA***-related **neurodevelopmental** disorder reported to date have had a genetic alteration that is either [*de novo*](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/de-novo/) or inherited from a parent who has low-level [mosaicism](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/mosaicism/) [Author, personal observation], the risk to other family members is presumed to be low.

**Related Genetic Counseling Issues**

**Family planning**

* The optimal time for determination of genetic risk and discussion of the availability of prenatal testing is before pregnancy.
* It is appropriate to offer [genetic counseling](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/genetic-counseling/) (including discussion of potential risks to offspring and reproductive options) to parents of [affected](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/affected/) individuals.

**DNA banking** is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of [affected](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/affected/) individuals.

**Prenatal Testing and Preimplantation Genetic Diagnosis**

Risk to future pregnancies is presumed to be low as the [familial](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/familial/) [proband](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/proband/) most likely has a [*de novo*](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/de-novo/) genetic alteration involving ***PURA***. However, couples may wish to consider prenatal testing or [preimplantation genetic diagnosis](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/preimplantation-genetic-diagnosis/) as their risk may be greater than in the general population because of the possibility of parental [germline mosaicism](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/germline-mosaicism/).

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. Although most centers would consider decisions about prenatal testing to be the choice of the parents, discussion of these issues is appropriate.

[Go to:](https://www.ncbi.nlm.nih.gov/books/NBK426063/)

**Resources**

*GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click*[*here*](https://www.ncbi.nlm.nih.gov/books/n/gene/app4/)*.*

* **PURA Syndrome Foundation**

[www.purasyndrome.org](http://www.purasyndrome.org/)

* **American Association on Intellectual and Developmental Disabilities (AAIDD)**

501 3rd Street Northwest

Suite 200

Washington DC 20001

**Phone:** 202-387-1968

**Fax:** 202-387-2193

**Email:** sis@aaidd.org

[www.aaidd.org](http://www.aaidd.org/)

* **Medline Plus**

[Intellectual Disability](http://www.nlm.nih.gov/medlineplus/ency/article/001523.htm)

* **National Center on Birth Defects and Developmental Disabilities**

1600 Clifton Road

MS E-87

Atlanta GA 30333

**Phone:** 800-232-4636 (toll-free); 888-232-6348 (TTY)

**Email:** cdcinfo@cdc.gov

[Intellectual Disability](http://www.cdc.gov/ncbddd/dd/ddmr.htm)

* **VOR: Speaking out for people with intellectual and developmental disabilities**

836 South Arlington Heights Road, #351

Elk Grove Village IL 60007

**Phone:** 877-399-4867

**Fax:** 847-253-0675

**Email:** info@vor.net

[www.vor.net](http://www.vor.net/index.php)

[Go to:](https://www.ncbi.nlm.nih.gov/books/NBK426063/)

**Molecular Genetics**

*Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —*ED.

**Table A.**

**PURA**-Related **Neurodevelopmental** Disorders: Genes and Databases

|  |  |  |  |
| --- | --- | --- | --- |
| **Gene** | **Chromosome Locus** | **Protein** | **HGMD** |
| [***PURA***](https://www.ncbi.nlm.nih.gov/gene/5813) | [5q31​.3](https://www.ncbi.nlm.nih.gov/projects/mapview/maps.cgi?taxid=9606&chr=5&query=PURA&qstr=PURA&maps=snp,genes-r,pheno&zoom=2) | [Transcriptional activator protein Pur-alpha](http://www.uniprot.org/uniprot/Q00577) | [**PURA**](http://www.hgmd.cf.ac.uk/ac/gene.php?gene=PURA%20) |

Data are compiled from the following standard references: gene from [HGNC](http://www.genenames.org/index.html); chromosome locus, locus name, critical region, complementation group from [OMIM](http://www.omim.org/); protein from [UniProt](http://www.uniprot.org/). For a description of databases (Locus Specific, HGMD) to which links are provided, click [here](https://www.ncbi.nlm.nih.gov/books/n/gene/app1/).

**Table B.**

OMIM Entries for **PURA**-Related **Neurodevelopmental** Disorders ([View All in OMIM](https://www.ncbi.nlm.nih.gov/omim/600473,616158))

|  |  |
| --- | --- |
| [600473](https://www.ncbi.nlm.nih.gov/omim/600473) | PURINE-RICH ELEMENT-BINDING PROTEIN A; **PURA** |
| [616158](https://www.ncbi.nlm.nih.gov/omim/616158) | MENTAL RETARDATION, AUTOSOMAL DOMINANT 31; MRD31 |

**Gene structure.** The ***PURA*** transcript [NM\_005859.4](https://www.ncbi.nlm.nih.gov/nuccore/NM_005859.4) has 5304 nucleotides, a single [exon](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/exon/), and a coding sequence of 969 nucleotides.

**Pathogenic variants.** To date, 61 different [*de novo*](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/de-novo/) ***PURA*** intragenic sequence variants are known, which include [missense](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/missense/), [nonsense](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/nonsense-variant/), frameshift variants, and [in-frame](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/in-frame/) deletions [[Hunt et al 2014](https://www.ncbi.nlm.nih.gov/books/NBK426063/); [Lalani et al 2014](https://www.ncbi.nlm.nih.gov/books/NBK426063/); [Tanaka et al 2015](https://www.ncbi.nlm.nih.gov/books/NBK426063/); [Okamoto et al 2017](https://www.ncbi.nlm.nih.gov/books/NBK426063/); Author, personal observation].

All [missense](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/missense/) variants occur in regions encoding one of the three PUR repeats (see **Normal**[**gene product**](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/gene-product/)), while truncating pathogenic variants occur throughout the gene [[Hunt et al 2014](https://www.ncbi.nlm.nih.gov/books/NBK426063/); [Lalani et al 2014](https://www.ncbi.nlm.nih.gov/books/NBK426063/); [Tanaka et al 2015](https://www.ncbi.nlm.nih.gov/books/NBK426063/); [Okamoto et al 2017](https://www.ncbi.nlm.nih.gov/books/NBK426063/); Author, personal observation].

[Table 2](https://www.ncbi.nlm.nih.gov/books/NBK426063/table/pura-dis.T.recommended_evaluations_follo/?report=objectonly) shows five recurrent pathogenic variants: c.697\_699delTTC (7 individuals), c.289A>G (2 individuals), c.812\_814delTCT (2 individuals), c.734G>C (2 individuals) and c.596G>C (2 individuals) [[Hunt et al 2014](https://www.ncbi.nlm.nih.gov/books/NBK426063/); [Lalani et al 2014](https://www.ncbi.nlm.nih.gov/books/NBK426063/); [Tanaka et al 2015](https://www.ncbi.nlm.nih.gov/books/NBK426063/); Author, personal observation].

**Table 5.**

***PURA*** Pathogenic Variants Discussed in This GeneReview

| **DNA Nucleotide Change** | **Predicted Protein Change** | **Reference Sequences** |
| --- | --- | --- |
| c.289A>G | p.Lys97Glu | [NM\_005859​.4](https://www.ncbi.nlm.nih.gov/nuccore/NM_005859.4) [NP\_005850​.1](https://www.ncbi.nlm.nih.gov/protein/NP_005850.1) |
| c.596G>C | p.Arg199Pro |
| c.697\_699delTTC | p.Phe233del |
| c.734G>C | p.Arg245Pro |
| c.812\_814delTCT | p.Phe271del |

Note on variant classification: Variants listed in the table have been provided by the authors. GeneReviews staff have not independently verified the classification of variants.

Note on nomenclature: GeneReviews follows the standard naming conventions of the Human Genome Variation Society ([www​.hgvs.org](http://www.hgvs.org/)). See [Quick Reference](https://www.ncbi.nlm.nih.gov/books/n/gene/app3/) for an explanation of nomenclature.

**Relationship to 5q31.3**[**deletion syndrome**](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/deletion-syndrome/)**.** ***PURA*** is one of three genes located within the critical deleted region associated with the 5q31.3 deletion syndrome [[Brown et al 2013](https://www.ncbi.nlm.nih.gov/books/NBK426063/)]. The smallest microdeletion encompassing ***PURA***has been reported by [Bonaglia et al [2015]](https://www.ncbi.nlm.nih.gov/books/NBK426063/).

**Normal**[**gene product**](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/gene-product/)**.** The [NM\_005859.4](https://www.ncbi.nlm.nih.gov/nuccore/NM_005859.4) transcript encodes a highly conserved 322-amino acid protein, known as purine-rich element-binding protein A (Pur-alpha) [[Lalani et al 2014](https://www.ncbi.nlm.nih.gov/books/NBK426063/)]. Pur-alpha is a multifunctional protein that has an important role in normal postnatal brain development in animal models [[Khalili et al 2003](https://www.ncbi.nlm.nih.gov/books/NBK426063/), [Hokkanen et al 2012](https://www.ncbi.nlm.nih.gov/books/NBK426063/)]. PUR-alpha is a sequence-specific, DNA-/RNA-binding protein with an important role in DNA replication, DNA transcription, [mRNA](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/mrna/) trafficking, and unwindase activity [[White et al 2009](https://www.ncbi.nlm.nih.gov/books/NBK426063/), [Weber et al 2016](https://www.ncbi.nlm.nih.gov/books/NBK426063/)]. The functionality of Pur-alpha is dependent on three PUR repeat motifs: PUR I, PUR II, and PUR III [[Graebsch et al 2009](https://www.ncbi.nlm.nih.gov/books/NBK426063/), [Weber et al 2016](https://www.ncbi.nlm.nih.gov/books/NBK426063/)].

**Abnormal**[**gene product**](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/gene-product/)**.** Effects of the pathogenic variants at functional levels are not yet clear, but such variants presumably cause functional [haploinsufficiency](https://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/haploinsufficiency/) of the protein [[Hunt et al 2014](https://www.ncbi.nlm.nih.gov/books/NBK426063/)].

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