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PURA-Related Neurodevelopmental Disorders

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Summary

Clinical characteristics

PURA-related neurodevelopmental disorders include *PURA* syndrome, caused by a heterozygous pathogenic sequence variant in *PURA*, and 5q31.3 deletion syndrome, caused by a 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 issues can include hypotonia, hypothermia, hypersomnolence, feeding difficulties, excessive hiccups, recurrent central and obstructive apneas, epileptic seizures, abnormal nonepileptic 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 with either a heterozygous *PURA* pathogenic sequence variant (90% of affected individuals) or a nonrecurrent 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.

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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 *PURA* pathogenic sequence variant or a 5q31.3 deletion encompassing all or part of *PURA*, are inherited in an autosomal dominant manner. In almost all probands with a *PURA* pathogenic sequence variant the sequence variant is *de novo*; to date, all reported 5q31.3 deletions have been *de novo*. For parents of an 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. However, parents of an affected child may wish to consider prenatal testing or preimplantation genetic testing, as risk may be greater than in the general population owing to the possibility of parental germline mosaicism (estimated empirically at <1%).

GeneReview Scope

PURA-Related Neurodevelopmental Disorders: Included Disorders
• *PURA* syndrome • 5q31.3 deletion syndrome

For synonyms and outdated names see Nomenclature.

Diagnosis

No formal clinical diagnostic criteria have been published for *PURA*-related neurodevelopmental disorders, which comprise *PURA* syndrome (caused by a heterozygous *PURA* pathogenic sequence variant) and 5q31.3 deletion syndrome (caused by a nonrecurrent 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-to-severe intellectual disability, including absent speech
- Seizures
- Abnormal nonepileptic 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 with one of the following genetic findings (see Table 1):

- A heterozygous *PURA* pathogenic (or likely pathogenic) sequence variant (90% of affected individuals)

- Nonrecurrent deletion of 5q31.3 that encompasses all or part of *PURA* (10%)

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) Identification of a heterozygous *PURA* variant of uncertain significance does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include a combination of **genomic testing** (chromosomal microarray analysis, comprehensive genomic sequencing) and **gene-targeted testing** (multigene panel, single-gene testing).

Gene-targeted testing requires the clinician to determine which specific gene(s) are likely involved, whereas 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 multigene panel that includes *PURA* and other genes of interest (see Differential Diagnosis). Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*; thus, clinicians need to determine which multigene panel is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests. For this disorder, a multigene panel that also includes copy number analysis is recommended (see Table 1).

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Chromosomal microarray analysis (CMA) to detect large, nonrecurrent 5q31.3 deletions that include *PURA* which cannot readily be detected by sequence analysis of *PURA*.

Testing to Consider

Comprehensive genomic sequencing (when available) includes exome sequencing and genome sequencing. For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Note: Single-gene testing (sequence analysis of *PURA*, followed by gene-targeted 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]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
PURA	Sequence analysis [3]	71/79 [4]
	Gene-targeted deletion/duplication analysis [5]	Unknown [6]
	CMA [7]	8/79 [8]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. n=11 [Lalani et al 2014], n=4 [Hunt et al 2014], n=6 [Tanaka et al 2015], n=1 [Okamoto et al 2017], n=49 [Author, personal observation]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. No data on detection rate of gene-targeted 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], n=3 [Hosoki et al 2012], n=2 [Brown et al 2013], n=1 [Bonaglia et al 2015]

Clinical Characteristics

Clinical Description

PURA-related neurodevelopmental disorders comprise *PURA* syndrome (caused by a heterozygous *PURA* pathogenic sequence variant) and 5q31.3 deletion syndrome (caused by a nonrecurrent 5q31.3 deletion encompassing all or part of *PURA*). *PURA*-related neurodevelopmental disorders are characterized by moderate-to-severe neurodevelopmental delay; most affected individuals are nonverbal, and many do not achieve independent ambulation.

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

Congenital heart defects, urogenital malformations, skeletal abnormalities, and endocrine disorders occur, but are less common [Hunt et al 2014; Lalani et al 2014; Tanaka et al 2015; Okamoto et al 2017; 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 nonrecurrent 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 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.

Nonepileptic movements that may be seen include dystonia, dyskinesia, and dysconjugate eye movements.

Nonepileptic 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 individuals (42/71).

For the majority of 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 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; Author, personal observation].

Urogenital. In four affected individuals, renal and genital defects including cryptorchidism (3/71), kidney stones (3/71), 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] 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 than variants in the regions that encode PUR I or PUR II repeats (see Molecular Genetics, **Normal gene product**). However, the functional effect at a molecular level is not yet clear and requires further investigation [Hunt et al 2014].

PURA-related neurodevelopmental disorders encompass both *PURA* syndrome and the 5q31.3 deletion syndrome. It has been suggested that *PURA* haploinsufficiency contributes to the neurodevelopmental phenotype of individuals with a 5q31.3 deletion [Brown et al 2013].

The features of individuals with a 5q31.3 deletion that overlap with those of individuals with a *PURA* pathogenic variant include neonatal hypotonia, feeding difficulties, and respiratory difficulties as well as severe intellectual disability and epilepsy [Shimojima et al 2011, Hosoki et al 2012, Brown et al 2013, Bonaglia et al 2015].

Of note, individuals with a deletion that also includes the neighboring gene *NRG2* – as well as those with larger deletions that encompass multiple genes in addition to *PURA* and *NRG2* – show a more severe phenotype (including distinct facial dysmorphisms) than individuals with an intragenic *PURA* 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].

Penetrance

To the authors' knowledge, the 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 31" (OMIM 616158) – is no longer in use.

Prevalence

To date, 71 individuals are known to have *PURA* syndrome [Hunt et al 2014; Lalani et al 2014; Tanaka et al 2015; Okamoto et al 2017; Author, personal observation]. Eight individuals with the 5q31.3 deletion syndrome have been reported.

Based on the study of Hunt et al [2014], the estimated frequency of *PURA* syndrome as a cause of intellectual disability is 3:1,133 (0.3%).

Lalani et al [2014] and Tanaka et al [2015] estimated a higher frequency (0.5%) based on their cohorts of 11:2,117 and 6:1,098, respectively.

Genetically Related (Allelic) Disorders

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

Differential Diagnosis

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

- Congenital central hypoventilation syndrome
- Prader-Willi syndrome
- Lower extremity-predominant autosomal dominant spinal muscular atrophy 1 (OMIM 158600) / distal autosomal recessive spinal muscular atrophy 1 (OMIM 604320)
- Myotonic dystrophy in the newborn (see Myotonic Dystrophy Type 1)
- Neurotransmitter disorder [Pearl et al 2007]
- Rett syndrome
- Pitt-Hopkins syndrome
- Angelman syndrome

See Mental retardation, autosomal dominant: OMIM Phenotypic Series to view genes associated with this phenotype in OMIM.

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

System/Concern	Evaluation	Comment
Cognitive	Developmental assessment	

Table 2. continued from previous page.

System/Concern	Evaluation	Comment
Neurologic	Neurologic eval	
	Brain MRI	Indicated in a child w/a *PURA*-related neurodevelopmental disorder w/seizures &/or hypoventilation &/or abnormal vision or eye movements who has not previously had a brain MRI
	EEG & video EEG	If seizures are suspected
Eyes	Ophthalmology exam	Electrodiagnostic tests may be indicated.
Cardiovascular	Consider echocardiogram	
Respiratory	Assessment of pulmonary function	As needed
Gastrointestinal	• Feeding assessment w/analysis of swallowing & eval for possible aspiration • Assessment for constipation	As needed
Genitourinary	Consider ultrasound of the urinary tract.	
Musculoskeletal	Appropriate radiographs	If hip dysplasia &/or scoliosis is suspected
Endocrine	Assessment of serum vitamin D levels	
	Assessment of bone density	If osteoporosis or osteopenia is suspected
	Eval of anterior pituitary hormones	If necessary
Miscellaneous/ Other	Consultation w/clinical geneticist &/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/Concern	Treatment	Considerations/Other
Cognitive / Developmental delay	See Developmental Delay / Intellectual Disability Educational Issues.	
Seizures	Mgmt by a neurologist	May include video EEG monitoring to help distinguish epileptic from nonepileptic 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; some infants require short periods of intubation & mechanical ventilation, esp during acute illness.	Ambulatory peripheral saturation monitoring may be required.
Congenital heart defect	Mgmt per current practice for specific congenital heart defect	

Table 3. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Frequent aspiration (or high risk of aspiration)	A percutaneous endoscopic gastrostomy tube may be considered.	
Gastroesophageal reflux disease	Medical mgmt; consideration of Nissen fundoplication if medical treatment not sufficient	
Constipation	Routine mgmt	Referral to gastroenterologist may be required in severe cases.
Congenital urogenital defect	Mgmt per current practice for specific urogenital defect	
Scoliosis	Standard mgmt	Progressive neuropathic scoliosis may require spinal fusion.
Osteoporosis/ Oosteopenia	Standard mgmt	
Instability in standing position	Ankle foot orthoses 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 endocrinologist	

Developmental Delay / Intellectual Disability Educational Issues

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

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

Ages 3-5 years. In the US, 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).

Ages 5-21 years

- In the US, 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.

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.

Consideration of private supportive therapies based on the affected individual's needs is recommended. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.

In the US:

- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a public agency that provides services and support to qualified individuals. Eligibility differs by state but is typically determined by diagnosis and/or associated cognitive/adaptive disabilities.
- Families with limited income and resources may also qualify for supplemental security income (SSI) 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 individuals who have difficulty feeding as a result of poor oral motor control.

Communication issues. Consider evaluation for alternative means of communication (e.g., augmentative and alternative communication [AAC] for individuals who have expressive language difficulties.

Surveillance

Table 4. Recommended Surveillance for Individuals with *PURA*-Related Neurodevelopmental Disorders

System/Concern	Evaluation	Frequency/Comment
Cognitive	Monitoring by developmental pediatrician	Long-term
Neurologic	EEG & video EEG monitoring	If seizures suspected
Eyes	Ophthalmologic & vision evals	Routine
Gastrointestinal	Monitoring for dysphagia & constipation	
Musculoskeletal	Monitoring for musculoskeletal complications incl hip dysplasia & scoliosis	

Evaluation of Relatives at Risk

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of 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; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

PURA-related neurodevelopmental disorders, caused by either a heterozygous *PURA* pathogenic sequence variant (*PURA* syndrome) or a 5q31.3 deletion encompassing all or part of *PURA* (5q31.3 deletion syndrome), are inherited in an autosomal dominant manner.

Risk to Family Members

PURA Pathogenic Sequence Variant

Parents of a proband

- In almost all probands with a *PURA* pathogenic sequence variant the sequence variant is *de novo*.
- The exception is a child who inherited a *PURA* pathogenic sequence variant from her unaffected father, who had low-level mosaicism [Author, personal observation].
- Evaluation of parents of a proband with an apparent *de novo* pathogenic variant by molecular genetic testing is recommended.
- If the *PURA* pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the variant is most likely *de novo*; however, parental germline mosaicism is also a possibility.

Sibs of a proband

- The risk to the sibs of the proband depends on the genetic status of the parents.
- Because almost all *PURA* pathogenic sequence variants reported to date have been *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.

Offspring of a 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 individual is 50%.

5q31.3 Deletion Encompassing All or Part of *PURA*

Parents of a proband

- To date, all reported 5q31.3 deletions have been *de novo*.
- Evaluation of the parents by genomic testing that will detect the 5q31.3 deletion identified in the proband is recommended. It is also important to exclude a balanced chromosome rearrangement that may have predisposed to a deletion encompassing 5q31.3 in the proband.

Sibs of a proband. The risk to the sibs of the proband depends on the genetic status of the parents:

- If the 5q31.3 deletion found in the 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.
- If a predisposing balanced chromosome rearrangement is identified in a parent, genetic counseling is important as there may be a significant risk to the sibs of the proband.

Offspring of a 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 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* or inherited from a parent who has low-level 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/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to parents of affected individuals.

Prenatal Testing and Preimplantation Genetic Testing

Risk to future pregnancies is presumed to be low as the familial proband most likely has a *de novo* genetic alteration involving *PURA*. However, couples may wish to consider prenatal testing or preimplantation genetic testing as their risk may be greater than in the general population because of the possibility of parental germline mosaicism.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

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.

- **PURA Syndrome Foundation**
  www.purasyndrome.org
- **American Association on Intellectual and Developmental Disabilities (AAIDD)**
  Phone: 202-387-1968
  aaidd.org
- **CDC - Child Development**
  Phone: 800-232-4636
  Developmental Disability Basics
- **MedlinePlus**
  Intellectual Disability
- **VOR: Speaking out for people with intellectual and developmental disabilities**
  Phone: 877-399-4867
  Email: info@vor.net
  vor.net

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	ClinVar
PURA	5q31.3	Transcriptional activator protein Pur-alpha	PURA	PURA

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for PURA-Related Neurodevelopmental Disorders (View All in OMIM)

600473	PURINE-RICH ELEMENT-BINDING PROTEIN A; PURA
616158	NEURODEVELOPMENTAL DISORDER WITH NEONATAL RESPIRATORY INSUFFICIENCY, HYPOTONIA, AND FEEDING DIFFICULTIES; NEDRIHF

Gene structure. The *PURA* transcript NM_005859.4 has 5,304 nucleotides, a single exon, and a coding sequence of 969 nucleotides.

Pathogenic variants. To date, 61 different *de novo PURA* intragenic sequence variants are known, which include missense, nonsense, frameshift variants, and in-frame deletions [Hunt et al 2014; Lalani et al 2014; Tanaka et al 2015; Okamoto et al 2017; Author, personal observation].

All missense variants occur in regions encoding one of the three PUR repeats (see **Normal gene product**), while truncating pathogenic variants occur throughout the gene [Hunt et al 2014; Lalani et al 2014; Tanaka et al 2015; Okamoto et al 2017; Author, personal observation].

Table 2 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; Lalani et al 2014; Tanaka et al 2015; 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 NP_005850.1
c.596G>C	p.Arg199Pro	
c.697_699delTTC	p.Phe233del	
c.734G>C	p.Arg245Pro	
c.812_814delTCT	p.Phe271del	

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Relationship to 5q31.3 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]. The smallest microdeletion encompassing *PURA* has been reported by Bonaglia et al [2015].

Normal gene product. The 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]. Pur-alpha is a multifunctional

protein that has an important role in normal postnatal brain development in animal models [Khalili et al 2003, Hokkanen et al 2012]. PUR-alpha is a sequence-specific, DNA-/RNA-binding protein with an important role in DNA replication, DNA transcription, mRNA trafficking, and unwindase activity [White et al 2009, Weber et al 2016]. The functionality of Pur-alpha is dependent on three PUR repeat motifs: PUR I, PUR II, and PUR III [Graebsch et al 2009, Weber et al 2016].

Abnormal gene product. Effects of the pathogenic variants at functional levels are not yet clear, but such variants presumably cause functional haploinsufficiency of the protein [Hunt et al 2014].

Chapter Notes

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