PACS1 Related Syndrome

https://www.ncbi.nlm.nih.gov/books/NBK559434/

SummaryClinical characteristics.PACS1 neurodevelopmental disorder (PACS1-NDD) is characterized by mild-to-severe neurodevelopmental delays. Language skills are more severely affected than motor skills. Hypotonia is reported in about a third of individuals and is noted to improve over time. Approximately 60% of individuals are ambulatory. Feeding difficulty is common, with 25% requiring gastrostomy tube to maintain appropriate caloric intake. Other common features include constipation, seizures, behavioral issues, congenital heart anomalies, short stature, and microcephaly. Common facial features include hypertelorism, downslanting palpebral fissures, bulbous nasal tip, low-set and simple ears, smooth philtrum, wide mouth with downturned corners, thin upper vermilion, and wide-spaced teeth. To date approximately 35 individuals with PACS1-NDD have been reported.Diagnosis/testing.The diagnosis of PACS1-NDD is established in a proband with a heterozygous pathogenic variant in PACS1 identified by molecular genetic testing.Management.Treatment: Standard treatment for feeding issues, constipation, seizures, behavioral issues, cardiac anomalies, vision issues, and renal anomalies.Surveillance: Monitor for growth and nutrition issues, constipation, seizures, and behavioral issues. Monitor closure of septal defects as per cardiologist; monitor renal function if renal malformation is present as per nephrologist.Agents/circumstances to avoid: Known seizure triggers.Genetic counseling.PACS1-NDD is an autosomal dominant disorder. All individuals reported to date have the disorder as the result of a de novo pathogenic variant. If the PACS1 pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be 1% because of the theoretic possibility of parental germline mosaicism. Prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

Clinical characteristics.PACS1 neurodevelopmental disorder (PACS1-NDD) is characterized by mild-to-severe neurodevelopmental delays. Language skills are more severely affected than motor

skills. Hypotonia is reported in about a third of individuals and is noted to improve over time. Approximately 60% of individuals are ambulatory. Feeding difficulty is common, with 25% requiring gastrostomy tube to maintain appropriate caloric intake. Other common features include constipation, seizures, behavioral issues, congenital heart anomalies, short stature, and microcephaly. Common facial features include hypertelorism, downslanting palpebral fissures, bulbous nasal tip, low-set and simple ears, smooth philtrum, wide mouth with downturned corners, thin upper vermilion, and wide-spaced teeth. To date approximately 35 individuals with PACS1-NDD have been reported.

Diagnosis/testing.The diagnosis of PACS1-NDD is established in a proband with a heterozygous pathogenic variant in PACS1 identified by molecular genetic testing.

Management.Treatment: Standard treatment for feeding issues, constipation, seizures, behavioral issues, cardiac anomalies, vision issues, and renal anomalies.Surveillance: Monitor for growth and nutrition issues, constipation, seizures, and behavioral issues. Monitor closure of septal defects as per cardiologist; monitor renal function if renal malformation is present as per nephrologist.Agents/circumstances to avoid: Known seizure triggers.

Genetic counseling.PACS1-NDD is an autosomal dominant disorder. All individuals reported to date have the disorder as the result of a de novo pathogenic variant. If the PACS1 pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be 1% because of the theoretic possibility of parental germline mosaicism. Prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

DiagnosisSuggestive FindingsPACS1-NDD should be considered in individuals with the following clinical findings:Developmental delay and/or intellectual disability that are typically moderate, although range includes mild to severe delaysHypotoniaFeeding difficultiesEpilepsy (partial and

tonic seizures reported, often with early or infantile onset; well-controlled by medication)Behavioral features (e.g., autism spectrum disorder, temper tantrums, aggression); overall friendly disposition in individuals of all agesCharacteristic facial features (e.g., hypertelorism, downslanting palpebral fissures, bulbous nasal tip, low-set and simple ears, smooth philtrum, wide mouth with downturned corners, thin upper vermilion, and wide-spaced teeth)Congenital heart anomalies (e.g., atrial septal defect, ventral septal defect, patent ductus arteriosus)Establishing the DiagnosisThe diagnosis of PACS1-NDD is established in a proband with a heterozygous pathogenic (or likely pathogenic) variant in PACS1 by molecular genetic testing (see Table 1). Identification of a heterozygous PACS1 variant of uncertain significance does not establish or rule out a diagnosis of PACS1-NDD.Note: 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.Molecular genetic testing in a child with developmental delay or an older individual with intellectual disability typically begins with chromosomal microarray analysis (CMA). If CMA is not diagnostic, the next step is typically either a multigene panel or exome sequencing.Note: (1) Single-gene testing (sequence analysis of PACS1) is rarely useful and typically NOT recommended. (2) Since PACS1-NDD likely occurs through a gain-of-function or dominant-negative mechanism and large intragenic deletion or duplication has not been reported, testing for intragenic deletions or duplications is unlikely to identify a disease-causing variant.An intellectual disability (ID) multigene panel that includes PACS1 and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition in a person with a nondiagnostic CMA while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. 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. Of note, given the rarity of PACS1-NDD, some panels for ID may not include this gene. (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 an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.Comprehensive genomic testing does not require the clinician to determine which gene(s) are likely involved. Exome sequencing is most commonly used and yields results similar to an ID multigene panel with the additional advantage that exome sequencing includes genes recently identified as causing ID whereas some multigene panels may not. If exome sequencing is not diagnostic, exome array (when clinically available) may be considered to detect (multi)exon deletions or duplications that cannot be detected by exome sequencing. Note: To date, such variants have not been identified as a cause of PACS1-NDD. Genome sequencing is also possible.For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.Table 1. Molecular Genetic Testing Used in PACS1 Neurodevelopmental DisorderView in own windowGene 1MethodProportion of Probands with a Pathogenic Variant 2 Detectable by Method

PACS1

Sequence analysis 3~35/35 4Gene-targeted deletion/duplication analysis 5None reported 61. 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. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]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. Since PACS1-NDD likely occurs through a gain-of-function or dominant-negative mechanism and large intragenic deletion or duplication has not been reported, testing for intragenic deletions or duplication is unlikely to identify a disease-causing variant.

Suggestive FindingsPACS1-NDD should be considered in individuals with the following clinical findings:Developmental delay and/or intellectual disability that are typically moderate, although range includes mild to severe delaysHypotoniaFeeding difficultiesEpilepsy (partial and tonic seizures reported, often with early or infantile onset; well-controlled by medication)Behavioral features (e.g., autism spectrum disorder, temper tantrums, aggression); overall friendly disposition in individuals of all agesCharacteristic facial features (e.g., hypertelorism, downslanting palpebral fissures, bulbous nasal tip, low-set and simple ears, smooth philtrum, wide mouth with downturned corners, thin upper vermilion, and wide-spaced teeth)Congenital heart anomalies (e.g., atrial septal defect, ventral septal defect, patent ductus arteriosus)

Developmental delay and/or intellectual disability that are typically moderate, although range includes mild to severe delays

Hypotonia

Feeding difficulties

Epilepsy (partial and tonic seizures reported, often with early or infantile onset; well-controlled by medication)

Behavioral features (e.g., autism spectrum disorder, temper tantrums, aggression); overall friendly disposition in individuals of all ages

Characteristic facial features (e.g., hypertelorism, downslanting palpebral fissures, bulbous nasal tip, low-set and simple ears, smooth philtrum, wide mouth with downturned corners, thin upper vermilion, and wide-spaced teeth)

Congenital heart anomalies (e.g., atrial septal defect, ventral septal defect, patent ductus arteriosus)

Establishing the DiagnosisThe diagnosis of PACS1-NDD is established in a proband with a heterozygous pathogenic (or likely pathogenic) variant in PACS1 by molecular genetic testing (see Table 1). Identification of a heterozygous PACS1 variant of uncertain significance does not establish or rule out a diagnosis of PACS1-NDD.Note: 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.Molecular genetic testing in a child with developmental delay or an older individual with intellectual disability typically begins with chromosomal microarray analysis (CMA). If CMA is not diagnostic, the next step is typically either a multigene panel or exome sequencing.Note: (1) Single-gene testing (sequence analysis of PACS1) is rarely useful and typically NOT recommended. (2) Since PACS1-NDD likely occurs through a gain-of-function or dominant-negative mechanism and large intragenic deletion or duplication has not been reported, testing for intragenic deletions or duplications is unlikely to identify a disease-causing variant.An intellectual disability (ID) multigene panel that includes PACS1 and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition in a person with a nondiagnostic CMA while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. 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. Of note, given the rarity of PACS1-NDD, some panels for ID may not include this

gene. (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 an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.Comprehensive genomic testing does not require the clinician to determine which gene(s) are likely involved. Exome sequencing is most commonly used and yields results similar to an ID multigene panel with the additional advantage that exome sequencing includes genes recently identified as causing ID whereas some multigene panels may not. If exome sequencing is not diagnostic, exome array (when clinically available) may be considered to detect (multi)exon deletions or duplications that cannot be detected by exome sequencing. Note: To date, such variants have not been identified as a cause of PACS1-NDD. Genome sequencing is also possible.For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.Table 1. Molecular Genetic Testing Used in PACS1 Neurodevelopmental DisorderView in own windowGene 1MethodProportion of Probands with a Pathogenic Variant 2 Detectable by Method

PACS1

Sequence analysis 3~35/35 4Gene-targeted deletion/duplication analysis 5None reported 61. 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. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]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. Since PACS1-NDD likely occurs through a gain-of-function or dominant-negative mechanism and large intragenic deletion or duplication has not been reported, testing for intragenic deletions or duplication is unlikely to identify a disease-causing variant.

Table 1. Molecular Genetic Testing Used in PACS1 Neurodevelopmental DisorderView in own windowGene 1MethodProportion of Probands with a Pathogenic Variant 2 Detectable by Method

PACS1

Sequence analysis 3~35/35 4Gene-targeted deletion/duplication analysis 5None reported 61. 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. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]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. Since PACS1-NDD likely occurs through a gain-of-function or dominant-negative mechanism and large intragenic deletion or duplication has not been reported, testing for intragenic deletions or duplication is unlikely to identify a disease-causing variant.

Molecular Genetic Testing Used in PACS1 Neurodevelopmental Disorder

Gene 1MethodProportion of Probands with a Pathogenic Variant 2 Detectable by

Method

PACS1

Sequence analysis 3~35/35 4Gene-targeted deletion/duplication analysis 5None reported 6

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. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]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. Since PACS1-NDD likely occurs through a gain-of-function or dominant-negative mechanism and large intragenic deletion or duplication has not been reported, testing for intragenic deletions or duplication is unlikely to identify a disease-causing variant.

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. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]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. Since PACS1-NDD likely occurs through a gain-of-function or dominant-negative mechanism and large intragenic deletion or duplication has not been reported, testing for intragenic deletions or duplication is unlikely to identify a disease-causing variant.

See Table A. Genes and Databases for chromosome locus and protein.

See Molecular Genetics for information on variants detected in this gene.

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.

Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]

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.

Since PACS1-NDD likely occurs through a gain-of-function or dominant-negative mechanism and large intragenic deletion or duplication has not been reported, testing for intragenic deletions or duplication is unlikely to identify a disease-causing variant.

Clinical CharacteristicsClinical DescriptionTo date, approximately 35 individuals with PACS1 neurodevelopmental disorder (PACS1-NDD) have been described in the literature [Schuurs-Hoeijmakers et al 2012, Chad et al 2015, Gadzicki et al 2015, Schuurs-Hoeijmakers et al 2016, Stern et al 2017, Martinez-Monseny et al 2018, Miyake et al 2018, Pefkianaki et al 2018, Dutta 2019, Hoshino et al 2019]. The following description of the phenotypic features associated with this condition is based on these reports.Table 2. Select Features of PACS1 Neurodevelopmental DisorderView in own windowFeatureProportion of Persons w/FeatureComment

DD/ID

35/35

Moderate impairment in mostLanguage skills more severely affected than motor skills

Feeding/

GI issues

20-22/35Gastroesophageal reflux & constipation are most common manifestations.

Seizures

20/35

Partial & tonic seizuresInfantile seizures reported

Characteristic

behavioral

features

18/35Autism spectrum disorder present in ~25%-30%

Dysmorphic

facial features

35/35Hypertelorism, downslanting palpebral fissures, bulbous nasal tip, low-set & simple ears, smooth philtrum, wide mouth w/downturned corners, thin upper vermilion (w/a "wavy" profile), wide-spaced teeth

Congenital heart anomalies

15/35Atrial septal defects &/or ventricular septal defects in ~40%

Brain MRI

findings

13/20Hypoplasia or partial agenesis of the cerebellar vermis is most common finding

Ocular

anomalies

11/35Coloboma of the iris, retina, &/or optic nerve, myopia, strabismus, nystagmusDD = developmental delay; GI = gastrointestinal; ID = intellectual disabilityDevelopmental delay and/or intellectual disability was reported in all individuals [Chad et al 2015, Schuurs-Hoeijmakers et al 2016, Stern et al 2017, Martinez-Monseny et al 2018, Miyake et al 2018, Pefkianaki et al 2018, Dutta 2019, Hoshino et al 2019]. Most had moderate delays, with a range of mild-to-severe delay and/or disability reported. Hypotonia was reported in about a third of individuals and was noted to improve over time. Approximately 60% of individuals are ambulatory, with onset of walking between age two and four years [Schuurs-Hoeijmakers et al 2016, Martinez-Monseny et al 2018, Pefkianaki et al 2018, Hoshino et al 2019]. Clumsiness and unsteady gait are reported. Regression in walking with frequent falls was noted in one individual. Two individuals use ambulatory assistive devices; one individual occasionally used a wheelchair from age ten years, and one individual required a walker from age 11 years, as a result of ataxia and a crouching gait [Schuurs-Hoeijmakers et al 2016]. Development of contractures has not been reported.Language skills are universally affected, and more severely affected than motor skills. Most individuals develop verbal language, with several

beginning to speak in their second year of life [Schuurs-Hoeijmakers et al 2016]. Two reported individuals started speaking in their third year of life [Schuurs-Hoeijmakers et al 2012, Gadzicki et al 2015]; one had meaningful words at age one year eight months and two-word sentences at age five years [Hoshino et al 2019], and one started using sentences at age eight years and was reading at age 11 years [Schuurs-Hoeijmakers et al 2016]. Seven out of 32 individuals were nonverbal at the time of evaluation, at ages two, three, four, six, ten, 11, and 20 years, respectively [Schuurs-Hoeijmakers et al 2016, Pefkianaki et al 2018, Hoshino et al 2019]. Stern et al [2017] reported that four of eight individuals were unable to speak more than a few words within the first three years of life. Three individuals were reported to have dysarthria [Stern et al 2017]. Of the individuals reported to be nonverbal, one was able to use sign language, picture exchange cards, and an iPad communication application [Schuurs-Hoeijmakers et al 2016], and one was unable to use sign language but able to use a communication board and demonstrated good receptive language skills [Pefkianaki et al 2018]. No individuals were reported to lose verbal skills.Feeding difficulties / gastrointestinal issues. Poor weight gain and poor suck have been reported; oral aversion and a preference for soft foods were also reported. Difficulty with eating solid foods and poor weight gain may continue into adolescence and adulthood. Six of 27 individuals required a gastrostomy tube to maintain appropriate caloric intake [Schuurs-Hoeijmakers et al 2016, Stern et al 2017]. Constipation and reflux have been reported in several individuals. Delayed stomach emptying was reported in one individual.Epilepsy. Seizures are present in about 50%-60% of reported individuals [Schuurs-Hoeijmakers et al 2016, Stern et al 2017, Martinez-Monseny et al 2018, Miyake et al 2018, Pefkianaki et al 2018, Dutta 2019, Hoshino et al 2019]. Seizure types have included partial and tonic seizures. Seizure onset has been reported as young as day two of life [Schuurs-Hoeijmakers et al 2012]. Seizures in individuals with PACS1-NDD have been well controlled by anti-seizure medication [Schuurs-Hoeijmakers et al 2016].Behavior. Autism spectrum disorder occurs in about 25% to 30% of individuals. Temper tantrums and aggression are frequently reported, as is oral aversion and a preference for soft foods. Many individuals with PACS1-NDD, of all ages, are noted to have a happy, friendly disposition.Facial features. All reported individuals have

dysmorphic facial features [Chad et al 2015, Gadzicki et al 2015, Schuurs-Hoeijmakers et al 2016, Stern et al 2017, Martinez-Monseny et al 2018, Miyake et al 2018, Pefkianaki et al 2018, Dutta 2019, Hoshino et al 2019]. The most common features include: hypertelorism, downslanting palpebral fissures, bulbous nasal tip, low-set and simple ears, smooth philtrum, wide mouth with downturned corners, thin upper vermilion (with a "wavy" profile), and wide-spaced teeth.Congenital heart anomalies were reported in about 45% of individuals [Schuurs-Hoeijmakers et al 2016, Stern et al 2017, Martinez-Monseny et al 2018, Hoshino et al 2019]. About 40% of individuals have an atrial septal defect and/or ventral septal defect. Additional cardiac defects include bicuspid aortic valve in two individuals [Schuurs-Hoeijmakers et al 2016, Martinez-Monseny et al 2018], dysplastic aortic and pulmonary valves [Schuurs-Hoeijmakers et al 2016], and dilatation of pulmonary artery in one individual each [Stern et al 2017]. Additional cardiac findings have included patent ductus arteriosus and patent foramen ovale.Growth. Abnormal height and weight measurements have been reported in 50%-60% of individuals. Approximately 40% of individuals have short stature and/or low weight [Schuurs-Hoeijmakers et al 2012, Chad et al 2015, Gadzicki et al 2015, Schuurs-Hoeijmakers et al 2016, Stern et al 2017, Pefkianaki et al 2018, Martinez-Monseny et al 2018, Miyake et al 2018, Hoshino et al 2019]; 5%-10% of these individuals are affected from birth, while 20% develop growth deficiency during childhood. Frequently, both weight and height are below average, although weight is more frequently affected than height. One individual with birth weight and length below the 10th centile had normal growth by age five years [Stern et al 2017]. Approximately 20% of individuals have microcephaly (7/33) [Schuurs-Hoeijmakers et al 2016, Miyake et al 2018, Dutta 2019]. Limited information is available regarding the onset of microcephaly, but Stern et al [2017] reported one individual with small head circumference (defined as <10th centile) at birth and also at age five years, one individual with small head circumference at birth and normal head circumference at age five years, and one individual with a normal head circumference at birth but a small head circumference at age 19 months.Two individuals were greater than the 90th percentile for weight and/or length at birth, but had normal growth parameters at age three years and age 17 years [Stern et al 2017]. One individual with PACS1-NDD had sustained overgrowth and

macrocephaly [Martinez-Monseny et al 2018].Neuroimaging. Brain abnormalities have been identified in about 65% of individuals who have had imaging. The most frequent findings involve the cerebellar vermis (hypoplasia and partial agenesis). Additional findings include mild colpocephaly, ventriculomegaly/hydrocephalus ex vacuo, thin corpus callosum, frontal cortical dysplasia, paucity of cerebral white matter, mild delay in myelination, and hyperintensity of periventricular white matter.Ocular anomalies. Coloboma of the iris, retina, and/or optic nerve was reported in 5/35 individuals, with three of five individuals reported to have bilateral coloboma [Schuurs-Hoeijmakers et al 2016, Pefkianaki et al 2018, Dutta 2019, Hoshino et al 2019]. Other ocular abnormalities reported include myopia, strabismus, and nystagmus.

Other

Genitourinary abnormalities. Cryptorchidism has been reported in several males. Duplex kidney and hydronephrosis were reported in two individuals. Incontinence, renal agenesis, end-stage renal disease, urinary reflux, testicular microlithiasis, hypospadias and chordee, and bicornate uterus were each reported in one individual.Musculoskeletal features. Minor skeletal differences of the hands and feet are frequently reported, including clinodactyly or camptodactyly of the fifth fingers, tapered fingers, syndactyly, high plantar arch, pes planus, and broad great toe. Scoliosis occurred in three individuals [Author, personal communication]. Vertebral anomalies and pectus excavatum were each identified in one individual.Immunologic abnormalities have included frequent infections (3/33), leukopenia (1/33), neutropenia (1/33), and low immunoglobin levels (1/33) [Schuurs-Hoeijmakers et al 2016].Hearing loss. One individual had mild-to-moderate hearing loss of unknown type [Schuurs-Hoeijmakers et al 2016].Prognosis. It is unknown whether life span in individuals with PACS1-NDD is normal. One reported individual was alive at age 21 years [Schuurs-Hoeijmakers et al 2016], demonstrating that survival into adulthood is possible.Genotype-Phenotype CorrelationsNo genotype-phenotype correlations have been identified.PenetranceTo date, penetrance appears to be 100%.PrevalencePrevalence is currently unknown. Approximately 35 individuals with PACS1-NDD have been reported in the literature.

Clinical DescriptionTo date, approximately 35 individuals with PACS1 neurodevelopmental disorder (PACS1-NDD) have been described in the literature [Schuurs-Hoeijmakers et al 2012, Chad et al 2015, Gadzicki et al 2015, Schuurs-Hoeijmakers et al 2016, Stern et al 2017, Martinez-Monseny et al 2018, Miyake et al 2018, Pefkianaki et al 2018, Dutta 2019, Hoshino et al 2019]. The following description of the phenotypic features associated with this condition is based on these reports.Table 2. Select Features of PACS1 Neurodevelopmental DisorderView in own windowFeatureProportion of Persons w/FeatureComment

DD/ID

35/35

Moderate impairment in mostLanguage skills more severely affected than motor skills

Feeding/

GI issues

20-22/35Gastroesophageal reflux & constipation are most common manifestations.

Seizures

20/35

Partial & tonic seizuresInfantile seizures reported

Characteristic

behavioral

features

18/35Autism spectrum disorder present in ~25%-30%

Dysmorphic

facial features

35/35Hypertelorism, downslanting palpebral fissures, bulbous nasal tip, low-set & simple ears, smooth philtrum, wide mouth w/downturned corners, thin upper vermilion (w/a "wavy" profile), wide-spaced teeth

Congenital heart anomalies

15/35Atrial septal defects &/or ventricular septal defects in ~40%

Brain MRI

findings

13/20Hypoplasia or partial agenesis of the cerebellar vermis is most common finding

Ocular

anomalies

11/35Coloboma of the iris, retina, &/or optic nerve, myopia, strabismus, nystagmusDD = developmental delay; GI = gastrointestinal; ID = intellectual disabilityDevelopmental delay and/or intellectual disability was reported in all individuals [Chad et al 2015, Schuurs-Hoeijmakers et al 2016, Stern et al 2017, Martinez-Monseny et al 2018, Miyake et al 2018, Pefkianaki et al 2018, Dutta 2019, Hoshino et al 2019]. Most had moderate delays, with a range of mild-to-severe delay and/or disability reported. Hypotonia was reported in about a third of individuals and was noted to improve over time. Approximately 60% of individuals are ambulatory, with onset of walking between age two and four years [Schuurs-Hoeijmakers et al 2016, Martinez-Monseny et al 2018, Pefkianaki et al 2018, Hoshino et al 2019]. Clumsiness and unsteady gait are reported. Regression in walking with frequent falls was noted in one individual. Two individuals use ambulatory assistive devices; one individual occasionally used a wheelchair from age ten years, and one individual required a walker from age 11 years, as a result of ataxia and a crouching gait [Schuurs-Hoeijmakers et al 2016]. Development of contractures has not been reported.Language skills are universally affected, and more severely affected than motor skills. Most individuals develop verbal language, with several

beginning to speak in their second year of life [Schuurs-Hoeijmakers et al 2016]. Two reported individuals started speaking in their third year of life [Schuurs-Hoeijmakers et al 2012, Gadzicki et al 2015]; one had meaningful words at age one year eight months and two-word sentences at age five years [Hoshino et al 2019], and one started using sentences at age eight years and was reading at age 11 years [Schuurs-Hoeijmakers et al 2016]. Seven out of 32 individuals were nonverbal at the time of evaluation, at ages two, three, four, six, ten, 11, and 20 years, respectively [Schuurs-Hoeijmakers et al 2016, Pefkianaki et al 2018, Hoshino et al 2019]. Stern et al [2017] reported that four of eight individuals were unable to speak more than a few words within the first three years of life. Three individuals were reported to have dysarthria [Stern et al 2017]. Of the individuals reported to be nonverbal, one was able to use sign language, picture exchange cards, and an iPad communication application [Schuurs-Hoeijmakers et al 2016], and one was unable to use sign language but able to use a communication board and demonstrated good receptive language skills [Pefkianaki et al 2018]. No individuals were reported to lose verbal skills.Feeding difficulties / gastrointestinal issues. Poor weight gain and poor suck have been reported; oral aversion and a preference for soft foods were also reported. Difficulty with eating solid foods and poor weight gain may continue into adolescence and adulthood. Six of 27 individuals required a gastrostomy tube to maintain appropriate caloric intake [Schuurs-Hoeijmakers et al 2016, Stern et al 2017]. Constipation and reflux have been reported in several individuals. Delayed stomach emptying was reported in one individual.Epilepsy. Seizures are present in about 50%-60% of reported individuals [Schuurs-Hoeijmakers et al 2016, Stern et al 2017, Martinez-Monseny et al 2018, Miyake et al 2018, Pefkianaki et al 2018, Dutta 2019, Hoshino et al 2019]. Seizure types have included partial and tonic seizures. Seizure onset has been reported as young as day two of life [Schuurs-Hoeijmakers et al 2012]. Seizures in individuals with PACS1-NDD have been well controlled by anti-seizure medication [Schuurs-Hoeijmakers et al 2016].Behavior. Autism spectrum disorder occurs in about 25% to 30% of individuals. Temper tantrums and aggression are frequently reported, as is oral aversion and a preference for soft foods. Many individuals with PACS1-NDD, of all ages, are noted to have a happy, friendly disposition.Facial features. All reported individuals have

dysmorphic facial features [Chad et al 2015, Gadzicki et al 2015, Schuurs-Hoeijmakers et al 2016, Stern et al 2017, Martinez-Monseny et al 2018, Miyake et al 2018, Pefkianaki et al 2018, Dutta 2019, Hoshino et al 2019]. The most common features include: hypertelorism, downslanting palpebral fissures, bulbous nasal tip, low-set and simple ears, smooth philtrum, wide mouth with downturned corners, thin upper vermilion (with a "wavy" profile), and wide-spaced teeth.Congenital heart anomalies were reported in about 45% of individuals [Schuurs-Hoeijmakers et al 2016, Stern et al 2017, Martinez-Monseny et al 2018, Hoshino et al 2019]. About 40% of individuals have an atrial septal defect and/or ventral septal defect. Additional cardiac defects include bicuspid aortic valve in two individuals [Schuurs-Hoeijmakers et al 2016, Martinez-Monseny et al 2018], dysplastic aortic and pulmonary valves [Schuurs-Hoeijmakers et al 2016], and dilatation of pulmonary artery in one individual each [Stern et al 2017]. Additional cardiac findings have included patent ductus arteriosus and patent foramen ovale.Growth. Abnormal height and weight measurements have been reported in 50%-60% of individuals. Approximately 40% of individuals have short stature and/or low weight [Schuurs-Hoeijmakers et al 2012, Chad et al 2015, Gadzicki et al 2015, Schuurs-Hoeijmakers et al 2016, Stern et al 2017, Pefkianaki et al 2018, Martinez-Monseny et al 2018, Miyake et al 2018, Hoshino et al 2019]; 5%-10% of these individuals are affected from birth, while 20% develop growth deficiency during childhood. Frequently, both weight and height are below average, although weight is more frequently affected than height. One individual with birth weight and length below the 10th centile had normal growth by age five years [Stern et al 2017]. Approximately 20% of individuals have microcephaly (7/33) [Schuurs-Hoeijmakers et al 2016, Miyake et al 2018, Dutta 2019]. Limited information is available regarding the onset of microcephaly, but Stern et al [2017] reported one individual with small head circumference (defined as <10th centile) at birth and also at age five years, one individual with small head circumference at birth and normal head circumference at age five years, and one individual with a normal head circumference at birth but a small head circumference at age 19 months.Two individuals were greater than the 90th percentile for weight and/or length at birth, but had normal growth parameters at age three years and age 17 years [Stern et al 2017]. One individual with PACS1-NDD had sustained overgrowth and

macrocephaly [Martinez-Monseny et al 2018].Neuroimaging. Brain abnormalities have been identified in about 65% of individuals who have had imaging. The most frequent findings involve the cerebellar vermis (hypoplasia and partial agenesis). Additional findings include mild colpocephaly, ventriculomegaly/hydrocephalus ex vacuo, thin corpus callosum, frontal cortical dysplasia, paucity of cerebral white matter, mild delay in myelination, and hyperintensity of periventricular white matter.Ocular anomalies. Coloboma of the iris, retina, and/or optic nerve was reported in 5/35 individuals, with three of five individuals reported to have bilateral coloboma [Schuurs-Hoeijmakers et al 2016, Pefkianaki et al 2018, Dutta 2019, Hoshino et al 2019]. Other ocular abnormalities reported include myopia, strabismus, and nystagmus.

Other

Genitourinary abnormalities. Cryptorchidism has been reported in several males. Duplex kidney and hydronephrosis were reported in two individuals. Incontinence, renal agenesis, end-stage renal disease, urinary reflux, testicular microlithiasis, hypospadias and chordee, and bicornate uterus were each reported in one individual.Musculoskeletal features. Minor skeletal differences of the hands and feet are frequently reported, including clinodactyly or camptodactyly of the fifth fingers, tapered fingers, syndactyly, high plantar arch, pes planus, and broad great toe. Scoliosis occurred in three individuals [Author, personal communication]. Vertebral anomalies and pectus excavatum were each identified in one individual.Immunologic abnormalities have included frequent infections (3/33), leukopenia (1/33), neutropenia (1/33), and low immunoglobin levels (1/33) [Schuurs-Hoeijmakers et al 2016].Hearing loss. One individual had mild-to-moderate hearing loss of unknown type [Schuurs-Hoeijmakers et al 2016].Prognosis. It is unknown whether life span in individuals with PACS1-NDD is normal. One reported individual was alive at age 21 years [Schuurs-Hoeijmakers et al 2016], demonstrating that survival into adulthood is possible.

Table 2. Select Features of PACS1 Neurodevelopmental DisorderView in own windowFeatureProportion of Persons w/FeatureComment

DD/ID

35/35

Moderate impairment in mostLanguage skills more severely affected than motor skills

Feeding/

GI issues

20-22/35Gastroesophageal reflux & constipation are most common manifestations.

Seizures

20/35

Partial & tonic seizuresInfantile seizures reported

Characteristic

behavioral

features

18/35Autism spectrum disorder present in ~25%-30%

Dysmorphic

facial features

35/35Hypertelorism, downslanting palpebral fissures, bulbous nasal tip, low-set & simple ears, smooth philtrum, wide mouth w/downturned corners, thin upper vermilion (w/a "wavy" profile), wide-spaced teeth

Congenital heart anomalies

15/35Atrial septal defects &/or ventricular septal defects in ~40%

Brain MRI

findings

13/20Hypoplasia or partial agenesis of the cerebellar vermis is most common finding

Ocular

anomalies

11/35Coloboma of the iris, retina, &/or optic nerve, myopia, strabismus, nystagmusDD =

developmental delay; GI = gastrointestinal; ID = intellectual disability

Select Features of PACS1 Neurodevelopmental Disorder

FeatureProportion of Persons w/FeatureComment

DD/ID

35/35

Moderate impairment in mostLanguage skills more severely affected than motor skills

Feeding/

GI issues

20-22/35Gastroesophageal reflux & constipation are most common manifestations.

Seizures

20/35

Partial & tonic seizuresInfantile seizures reported

Characteristic

behavioral

features

18/35Autism spectrum disorder present in ~25%-30%

Dysmorphic

facial features

35/35Hypertelorism, downslanting palpebral fissures, bulbous nasal tip, low-set & simple ears, smooth philtrum, wide mouth w/downturned corners, thin upper vermilion (w/a "wavy" profile), wide-spaced teeth

Congenital heart anomalies

15/35Atrial septal defects &/or ventricular septal defects in ~40%

Brain MRI

findings

13/20Hypoplasia or partial agenesis of the cerebellar vermis is most common finding

Ocular

anomalies

11/35Coloboma of the iris, retina, &/or optic nerve, myopia, strabismus, nystagmus

Moderate impairment in most

Language skills more severely affected than motor skills

Partial & tonic seizures

Infantile seizures reported

DD = developmental delay; GI = gastrointestinal; ID = intellectual disability

DD = developmental delay; GI = gastrointestinal; ID = intellectual disability

DD = developmental delay; GI = gastrointestinal; ID = intellectual disability

Genitourinary abnormalities. Cryptorchidism has been reported in several males. Duplex kidney and hydronephrosis were reported in two individuals. Incontinence, renal agenesis, end-stage renal disease, urinary reflux, testicular microlithiasis, hypospadias and chordee, and bicornate uterus were each reported in one individual.

Musculoskeletal features. Minor skeletal differences of the hands and feet are frequently reported, including clinodactyly or camptodactyly of the fifth fingers, tapered fingers, syndactyly, high plantar arch, pes planus, and broad great toe. Scoliosis occurred in three individuals [Author, personal communication]. Vertebral anomalies and pectus excavatum were each identified in one individual.

Immunologic abnormalities have included frequent infections (3/33), leukopenia (1/33), neutropenia (1/33), and low immunoglobin levels (1/33) [Schuurs-Hoeijmakers et al 2016].

Hearing loss. One individual had mild-to-moderate hearing loss of unknown type [Schuurs-Hoeijmakers et al 2016].

Prognosis. It is unknown whether life span in individuals with PACS1-NDD is normal. One reported individual was alive at age 21 years [Schuurs-Hoeijmakers et al 2016], demonstrating that survival into adulthood is possible.

Genotype-Phenotype CorrelationsNo genotype-phenotype correlations have been identified.

PenetranceTo date, penetrance appears to be 100%.

PrevalencePrevalence is currently unknown. Approximately 35 individuals with PACS1-NDD have been reported in the literature.

Genetically Related (Allelic) DisordersNo phenotypes other than those discussed in this GeneReview are known to be associated with germline pathogenic variants in PACS1.

Differential DiagnosisBecause the phenotypic features associated with PACS1 neurodevelopmental disorder are not sufficient to diagnose this condition, all disorders with intellectual disability without other distinctive findings should be considered in the differential diagnosis. See OMIM Autosomal Dominant, Autosomal Recessive, Nonsyndromic X-Linked, and Syndromic X-Linked Intellectual Developmental Disorder Phenotypic Series.

ManagementEvaluations Following Initial DiagnosisTo establish the extent of disease and needs in an individual diagnosed with PACS1 neurodevelopmental disorder (PACS1-NDD), the evaluations summarized in Table 3 (if not performed as part of the evaluation that led to the diagnosis) are recommended.Table 3. Recommended Evaluations Following Initial Diagnosis in Individuals with PACS1 Neurodevelopmental DisorderView in own windowSystem/ConcernEvaluationComment
Development
Developmental assessment
To incl motor, adaptive, cognitive, & speech/language evalEval for early intervention / special education

Feeding issues /

Gastrointestinal manifestations

Gastroenterology / nutrition / feeding team eval

To incl eval of aspiration risk & nutritional statusConsider eval for gastric tube placement in those w/severe feeding/growth issues or aspiration risk.Additional eval may be needed for constipation symptoms.

Neurologic

Neurologic evalConsider EEG if seizures are a concern.

Psychiatric /

Behavioral

Neuropsychiatric evalIndividuals age >12 mos: screen for behavior concerns incl features of autism spectrum disorder

Cardiovascular

EchocardiogramTo evaluate for structural heart defects

Eyes

Ophthalmologic evalTo assess for ↓ vision, abnormal ocular movement, strabismus, or other anomalies

Genitourinary

Renal ultrasoundTo evaluate for renal anomalies

Genetic counseling

By genetics professionals 1To inform affected persons & their families re nature, MOI, & implications of PACS1-NDD to facilitate medical & personal decision making

Family support

& resources

Assess need for:

Community or online resources such as Parent to Parent;Social work involvement for parental support;Home nursing referral.MOI = mode of inheritance1. Medical geneticist, certified genetic counselor, certified advanced genetic nurseTreatment of ManifestationsTable 4. Treatment of Manifestations in Individuals with PACS1 Neurodevelopmental DisorderView in own windowManifestation/ConcernTreatmentConsiderations/Other

DD/ID

See Developmental Delay / Intellectual Disability Management Issues.

Poor weight

gain

Feeding therapyGastrostomy tube placement may be required for persistent feeding issues.

Feeding eval &/or radiographic swallowing study if clinical signs or symptoms of dysphagia

Bowel

dysfunction

Stool softeners, prokinetics, osmotic agents, or laxatives as needed for constipation

Epilepsy

Standardized treatment w/ASMs by experienced child neurologist

Many ASMs may be effective; none demonstrated effective specifically for this disorder.Education of parents/caregivers 1

Behavior

See Social/Behavioral Concerns.

Cardiac

anomalies

Treatment per cardiologist

Abnormal vision

&/or strabismus

Standard treatment(s) per ophthalmologist

Renal anomalies

Treatment per nephrologist &/or urologist

Family/

Community

Ensure appropriate social work involvement to connect families w/local resources, respite, & support.Coordinate care to manage multiple subspecialty appointments, equipment, medications, & supplies.

Consider involvement in adaptive sports or Special Olympics.ASM = anti-seizure medication; DD = developmental delay; ID = intellectual disability1. Education of parents/caregivers regarding common seizure presentations is appropriate. For information on non-medical interventions and coping strategies for children diagnosed with epilepsy, see Epilepsy Foundation Toolbox.Developmental Delay / Intellectual Disability Management IssuesThe 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.Ages 0-3 years. Referral to an early intervention program is recommended for access to occupational, physical, speech, and feeding therapy as well as infant mental health services, special educators, and sensory impairment specialists. In the US, early intervention is a federally funded program available in all states that provides in-home services to target individual therapy needs.Ages 3-5 years. In the US, developmental preschool through the local public school district is recommended. Before placement, an evaluation is made to determine needed services and

therapies and an individualized education plan (IEP) is developed for those who qualify based on established motor, language, social, or cognitive delay. The early intervention program typically assists with this transition. Developmental preschool is center based; for children too medically unstable to attend, home-based services are provided.All ages. Consultation with a developmental pediatrician is recommended to ensure the involvement of appropriate community, state, and educational agencies (US) and to support parents in maximizing quality of life. Some issues to consider:IEP services:An IEP provides specially designed instruction and related services to children who qualify.IEP services will be reviewed annually to determine whether any changes are needed.Special education law requires that children participating in an IEP be in the least restrictive environment feasible at school and included in general education as much as possible, when and where appropriate.Vision consultants should be a part of the child's IEP team to support access to academic material.PT, OT, and speech services will be provided in the IEP to the extent that the need affects the child's access to academic material. Beyond that, private supportive therapies based on the affected individual's needs may be considered. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.As a child enters the teen years, a transition plan should be discussed and incorporated in the IEP. For those receiving IEP services, the public school district is required to provide services until age 21.A 504 plan (Section 504: a US federal statute that prohibits discrimination based on disability) can be considered for those who require accommodations or modifications such as front-of-class seating, assistive technology devices, classroom scribes, extra time between classes, modified assignments, and enlarged text.Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a US 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., contractures, scoliosis, hip dislocation).Consider use of durable medical equipment and positioning devices as needed (e.g., wheelchairs, walkers, bath chairs, orthotics, adaptive strollers).Fine motor dysfunction. Occupational therapy is recommended for difficulty with fine motor skills that affect adaptive function such as feeding, grooming, dressing, and writing.Oral motor dysfunction. Assessment should be carried out at each visit and clinical feeding evaluations and/or radiographic swallowing studies should be obtained for choking/gagging during feeds, poor weight gain, frequent respiratory illnesses, or feeding refusal that is not otherwise explained. Assuming that the child is safe to eat by mouth, feeding therapy (typically by an occupational or speech therapist) is recommended to help improve coordination or sensory-related feeding issues. Feeds can be thickened or chilled for safety. When feeding dysfunction is severe, an NG-tube or G-tube may be necessary.Communication issues. Consider evaluation for alternative means of communication (e.g., augmentative and alternative communication [AAC]) for individuals who have expressive language difficulties. An AAC evaluation can be completed by a speech-language pathologist who has expertise in the area. The evaluation will consider cognitive abilities and sensory impairment to determine the most appropriate form of communication. AAC devices can range from low-tech, such as picture exchange communication, to high-tech, such as voice-generating devices. Contrary to popular belief, AAC devices do not hinder verbal development of speech, but rather support optimal speech and language development.Social/Behavioral ConcernsChildren may qualify for and benefit from interventions used in treatment of autism spectrum disorder, including applied behavior analysis (ABA). ABA therapy is targeted to the individual child's behavioral, social, and adaptive strengths and weaknesses and is typically performed one on one with a board-certified behavior analyst.Consultation with a developmental pediatrician may be helpful in guiding parents through appropriate behavior management strategies or providing prescription medications, such as medication used to treat attention-deficit/hyperactivity disorder, when necessary.Concerns about serious aggressive or destructive behavior can be addressed by a pediatric psychiatrist.SurveillanceTable 5. Recommended Surveillance for Individuals with PACS1 Neurodevelopmental DisorderView in own

windowSystem/ConcernEvaluationFrequency

Development

Monitor developmental progress & educational needs.At each visit

Feeding

Measurement of growth parametersEval of nutritional status & safety of oral intake

Gastrointestinal

Monitor for constipation.

Respiratory

Monitor for evidence of aspiration, respiratory insufficiency.

Neurologic

Monitor those w/seizures as clinically indicated.Assess for new manifestations incl seizures, changes in tone, movement disorders

Psychiatric/

Behavioral

Behavioral assessment for anxiety, attention, & aggressive or self-injurious behavior

Cardiovascular

Monitor closure of septal defects by echo if present & not repaired.Annually or per cardiologist

Genitourinary

Monitor renal function if renal malformation is present.Annually or per nephrologist

Miscellaneous/

Other

Assess family need for social work support (e.g., palliative/respite care, home nursing, other local resources) & care coordination.At each visitAgents/Circumstances to AvoidIndividuals with PACS1-NDD should avoid any known seizure triggers (e.g., sleep deprivation, alcohol use, missed medications).Evaluation of Relatives at RiskSee Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.Therapies Under InvestigationSearch 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.

Evaluations Following Initial DiagnosisTo establish the extent of disease and needs in an individual diagnosed with PACS1 neurodevelopmental disorder (PACS1-NDD), the evaluations summarized in Table 3 (if not performed as part of the evaluation that led to the diagnosis) are recommended.Table 3. Recommended Evaluations Following Initial Diagnosis in Individuals with PACS1 Neurodevelopmental DisorderView in own windowSystem/ConcernEvaluationComment

Development

Developmental assessment

To incl motor, adaptive, cognitive, & speech/language evalEval for early intervention / special education

Feeding issues /

Gastrointestinal manifestations

Gastroenterology / nutrition / feeding team eval

To incl eval of aspiration risk & nutritional statusConsider eval for gastric tube placement in those w/severe feeding/growth issues or aspiration risk.Additional eval may be needed for constipation symptoms.

Neurologic

Neurologic evalConsider EEG if seizures are a concern.

Psychiatric /

Behavioral

Neuropsychiatric evalIndividuals age >12 mos: screen for behavior concerns incl features of autism spectrum disorder

Cardiovascular

EchocardiogramTo evaluate for structural heart defects

Eyes

Ophthalmologic evalTo assess for ↓ vision, abnormal ocular movement, strabismus, or other anomalies

Genitourinary

Renal ultrasoundTo evaluate for renal anomalies

Genetic counseling

By genetics professionals 1To inform affected persons & their families re nature, MOI, & implications of PACS1-NDD to facilitate medical & personal decision making

Family support

& resources

Assess need for:

Community or online resources such as Parent to Parent;Social work involvement for parental support;Home nursing referral.MOI = mode of inheritance1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Table 3. Recommended Evaluations Following Initial Diagnosis in Individuals with PACS1 Neurodevelopmental DisorderView in own windowSystem/ConcernEvaluationComment

Development

Developmental assessment

To incl motor, adaptive, cognitive, & speech/language evalEval for early intervention / special education

Feeding issues /

Gastrointestinal manifestations

Gastroenterology / nutrition / feeding team eval

To incl eval of aspiration risk & nutritional statusConsider eval for gastric tube placement in those w/severe feeding/growth issues or aspiration risk.Additional eval may be needed for constipation symptoms.

Neurologic

Neurologic evalConsider EEG if seizures are a concern.

Psychiatric /

Behavioral

Neuropsychiatric evalIndividuals age >12 mos: screen for behavior concerns incl features of autism spectrum disorder

Cardiovascular

EchocardiogramTo evaluate for structural heart defects

Eyes

Ophthalmologic evalTo assess for ↓ vision, abnormal ocular movement, strabismus, or other anomalies

Genitourinary

Renal ultrasoundTo evaluate for renal anomalies

Genetic counseling

By genetics professionals 1To inform affected persons & their families re nature, MOI, & implications of PACS1-NDD to facilitate medical & personal decision making

Family support

& resources

Assess need for:

Community or online resources such as Parent to Parent;Social work involvement for parental support;Home nursing referral.MOI = mode of inheritance1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Recommended Evaluations Following Initial Diagnosis in Individuals with PACS1 Neurodevelopmental Disorder

System/ConcernEvaluationComment

Development

Developmental assessment

To incl motor, adaptive, cognitive, & speech/language evalEval for early intervention / special education

Feeding issues /

Gastrointestinal manifestations

Gastroenterology / nutrition / feeding team eval

To incl eval of aspiration risk & nutritional statusConsider eval for gastric tube placement in those w/severe feeding/growth issues or aspiration risk.Additional eval may be needed for constipation symptoms.

Neurologic

Neurologic evalConsider EEG if seizures are a concern.

Psychiatric /

Behavioral

Neuropsychiatric evalIndividuals age >12 mos: screen for behavior concerns incl features of autism spectrum disorder

Cardiovascular

EchocardiogramTo evaluate for structural heart defects

Eyes

Ophthalmologic evalTo assess for ↓ vision, abnormal ocular movement, strabismus, or other anomalies

Genitourinary

Renal ultrasoundTo evaluate for renal anomalies

Genetic counseling

By genetics professionals 1To inform affected persons & their families re nature, MOI, & implications of PACS1-NDD to facilitate medical & personal decision making

Family support

& resources

Assess need for:

Community or online resources such as Parent to Parent;Social work involvement for parental support;Home nursing referral.

To incl motor, adaptive, cognitive, & speech/language eval

Eval for early intervention / special education

To incl eval of aspiration risk & nutritional status

Consider eval for gastric tube placement in those w/severe feeding/growth issues or aspiration risk.

Additional eval may be needed for constipation symptoms.

Community or online resources such as Parent to Parent;

Social work involvement for parental support;

Home nursing referral.

MOI = mode of inheritance1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

MOI = mode of inheritance1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

MOI = mode of inheritance

Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of ManifestationsTable 4. Treatment of Manifestations in Individuals with PACS1 Neurodevelopmental DisorderView in own windowManifestation/ConcernTreatmentConsiderations/Other

DD/ID

See Developmental Delay / Intellectual Disability Management Issues.

Poor weight

gain

Feeding therapyGastrostomy tube placement may be required for persistent feeding issues.

Feeding eval &/or radiographic swallowing study if clinical signs or symptoms of dysphagia

Bowel

dysfunction

Stool softeners, prokinetics, osmotic agents, or laxatives as needed for constipation

Epilepsy

Standardized treatment w/ASMs by experienced child neurologist

Many ASMs may be effective; none demonstrated effective specifically for this disorder.Education of parents/caregivers 1

Behavior

See Social/Behavioral Concerns.

Cardiac

anomalies

Treatment per cardiologist

Abnormal vision

&/or strabismus

Standard treatment(s) per ophthalmologist

Renal anomalies

Treatment per nephrologist &/or urologist

Family/

Community

Ensure appropriate social work involvement to connect families w/local resources, respite, & support.Coordinate care to manage multiple subspecialty appointments, equipment, medications, & supplies.

Consider involvement in adaptive sports or Special Olympics.ASM = anti-seizure medication; DD = developmental delay; ID = intellectual disability1. Education of parents/caregivers regarding common seizure presentations is appropriate. For information on non-medical interventions and coping strategies for children diagnosed with epilepsy, see Epilepsy Foundation Toolbox.Developmental Delay / Intellectual Disability Management IssuesThe 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.Ages 0-3 years. Referral to an early intervention program is recommended for access to occupational, physical, speech, and feeding therapy as well as infant mental health services, special educators, and sensory impairment specialists. In the US, early intervention is a federally funded program available in all states that provides in-home services to target individual therapy needs.Ages 3-5 years. In the US, developmental preschool through the local public school district is recommended. Before placement, an evaluation is made to determine needed services and therapies and an individualized education plan (IEP) is developed for those who qualify based on established motor, language, social, or cognitive delay. The early intervention program typically assists with this transition. Developmental preschool is center based; for children too medically unstable to attend, home-based services are provided.All ages. Consultation with a developmental pediatrician is recommended to ensure the involvement of appropriate community, state, and

educational agencies (US) and to support parents in maximizing quality of life. Some issues to consider:IEP services:An IEP provides specially designed instruction and related services to children who qualify.IEP services will be reviewed annually to determine whether any changes are needed.Special education law requires that children participating in an IEP be in the least restrictive environment feasible at school and included in general education as much as possible, when and where appropriate.Vision consultants should be a part of the child's IEP team to support access to academic material.PT, OT, and speech services will be provided in the IEP to the extent that the need affects the child's access to academic material. Beyond that, private supportive therapies based on the affected individual's needs may be considered. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.As a child enters the teen years, a transition plan should be discussed and incorporated in the IEP. For those receiving IEP services, the public school district is required to provide services until age 21.A 504 plan (Section 504: a US federal statute that prohibits discrimination based on disability) can be considered for those who require accommodations or modifications such as front-of-class seating, assistive technology devices, classroom scribes, extra time between classes, modified assignments, and enlarged text.Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a US 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., contractures, scoliosis, hip dislocation).Consider use of durable medical equipment and positioning devices as needed (e.g., wheelchairs, walkers, bath chairs, orthotics, adaptive strollers).Fine motor dysfunction. Occupational therapy is recommended for difficulty with fine motor skills that affect adaptive function such as feeding, grooming, dressing, and writing.Oral motor dysfunction. Assessment should be carried out at each visit and clinical feeding

evaluations and/or radiographic swallowing studies should be obtained for choking/gagging during feeds, poor weight gain, frequent respiratory illnesses, or feeding refusal that is not otherwise explained. Assuming that the child is safe to eat by mouth, feeding therapy (typically by an occupational or speech therapist) is recommended to help improve coordination or sensory-related feeding issues. Feeds can be thickened or chilled for safety. When feeding dysfunction is severe, an NG-tube or G-tube may be necessary.Communication issues. Consider evaluation for alternative means of communication (e.g., augmentative and alternative communication [AAC]) for individuals who have expressive language difficulties. An AAC evaluation can be completed by a speech-language pathologist who has expertise in the area. The evaluation will consider cognitive abilities and sensory impairment to determine the most appropriate form of communication. AAC devices can range from low-tech, such as picture exchange communication, to high-tech, such as voice-generating devices. Contrary to popular belief, AAC devices do not hinder verbal development of speech, but rather support optimal speech and language development.Social/Behavioral ConcernsChildren may qualify for and benefit from interventions used in treatment of autism spectrum disorder, including applied behavior analysis (ABA). ABA therapy is targeted to the individual child's behavioral, social, and adaptive strengths and weaknesses and is typically performed one on one with a board-certified behavior analyst.Consultation with a developmental pediatrician may be helpful in guiding parents through appropriate behavior management strategies or providing prescription medications, such as medication used to treat attention-deficit/hyperactivity disorder, when necessary.Concerns about serious aggressive or destructive behavior can be addressed by a pediatric psychiatrist.

Table 4. Treatment of Manifestations in Individuals with PACS1 Neurodevelopmental DisorderView in own windowManifestation/ConcernTreatmentConsiderations/Other

DD/ID

See Developmental Delay / Intellectual Disability Management Issues.

Poor weight

gain

Feeding therapyGastrostomy tube placement may be required for persistent feeding issues.

Feeding eval &/or radiographic swallowing study if clinical signs or symptoms of dysphagia

Bowel

dysfunction

Stool softeners, prokinetics, osmotic agents, or laxatives as needed for constipation

Epilepsy

Standardized treatment w/ASMs by experienced child neurologist

Many ASMs may be effective; none demonstrated effective specifically for this disorder.Education of parents/caregivers 1

Behavior

See Social/Behavioral Concerns.

Cardiac

anomalies

Treatment per cardiologist

Abnormal vision

&/or strabismus

Standard treatment(s) per ophthalmologist

Renal anomalies

Treatment per nephrologist &/or urologist

Family/

Community

Ensure appropriate social work involvement to connect families w/local resources, respite, & support.Coordinate care to manage multiple subspecialty appointments, equipment, medications, & supplies.

Consider involvement in adaptive sports or Special Olympics.ASM = anti-seizure medication; DD = developmental delay; ID = intellectual disability1. Education of parents/caregivers regarding common seizure presentations is appropriate. For information on non-medical interventions and coping strategies for children diagnosed with epilepsy, see Epilepsy Foundation Toolbox.

Treatment of Manifestations in Individuals with PACS1 Neurodevelopmental Disorder

Manifestation/ConcernTreatmentConsiderations/Other

DD/ID

See Developmental Delay / Intellectual Disability Management Issues.

Poor weight

gain

Feeding therapyGastrostomy tube placement may be required for persistent feeding issues.

Feeding eval &/or radiographic swallowing study if clinical signs or symptoms of dysphagia

Bowel

dysfunction

Stool softeners, prokinetics, osmotic agents, or laxatives as needed for constipation

Epilepsy

Standardized treatment w/ASMs by experienced child neurologist

Many ASMs may be effective; none demonstrated effective specifically for this disorder.Education of parents/caregivers 1

Behavior

See Social/Behavioral Concerns.

Cardiac

anomalies

Treatment per cardiologist

Abnormal vision

&/or strabismus

Standard treatment(s) per ophthalmologist

Renal anomalies

Treatment per nephrologist &/or urologist

Family/

Community

Ensure appropriate social work involvement to connect families w/local resources, respite, & support.Coordinate care to manage multiple subspecialty appointments, equipment, medications, & supplies.

Consider involvement in adaptive sports or Special Olympics.

Feeding therapy

Gastrostomy tube placement may be required for persistent feeding issues.

Many ASMs may be effective; none demonstrated effective specifically for this disorder.

Education of parents/caregivers 1

Ensure appropriate social work involvement to connect families w/local resources, respite, & support.

Coordinate care to manage multiple subspecialty appointments, equipment, medications, & supplies.

ASM = anti-seizure medication; DD = developmental delay; ID = intellectual disability1. Education of parents/caregivers regarding common seizure presentations is appropriate. For information on non-medical interventions and coping strategies for children diagnosed with epilepsy, see Epilepsy Foundation Toolbox.

ASM = anti-seizure medication; DD = developmental delay; ID = intellectual disability1. Education of parents/caregivers regarding common seizure presentations is appropriate. For information on non-medical interventions and coping strategies for children diagnosed with epilepsy, see Epilepsy Foundation Toolbox.

ASM = anti-seizure medication; DD = developmental delay; ID = intellectual disability

Education of parents/caregivers regarding common seizure presentations is appropriate. For information on non-medical interventions and coping strategies for children diagnosed with epilepsy, see Epilepsy Foundation Toolbox.

Developmental Delay / Intellectual Disability Management IssuesThe 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.Ages 0-3 years. Referral to an early intervention program is recommended for access to occupational, physical, speech, and feeding therapy as well as infant mental health services, special educators, and sensory impairment specialists. In the US, early intervention is a federally funded program available in all states that provides in-home services to target individual therapy needs.Ages 3-5 years. In the US, developmental preschool through the local public school district is recommended. Before placement, an evaluation is made to determine needed services and therapies and an individualized education plan (IEP) is developed for those who qualify based on established motor, language, social, or cognitive delay. The early intervention program typically assists with this transition. Developmental preschool is center based; for children too medically unstable to attend, home-based services are provided.All ages. Consultation with a developmental pediatrician is recommended to ensure the involvement of appropriate community, state, and educational agencies (US) and to support parents in maximizing quality of life. Some issues to consider:IEP services:An IEP provides specially designed instruction and related services to children who qualify.IEP services will be reviewed annually to determine whether any changes are needed.Special education law requires that children participating in an IEP be in the least restrictive environment feasible at school and included in general education as much as possible, when and where appropriate.Vision consultants should be a part of the child's IEP team to support access to academic material.PT, OT, and speech services will be provided in the IEP to the extent that the need affects the child's access to academic material. Beyond that, private supportive therapies based on the affected individual's needs may be considered. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.As a child enters the teen years, a transition plan should be discussed and incorporated in the IEP. For those receiving IEP services, the public school district is required to provide services until age 21.A 504 plan (Section 504: a US

federal statute that prohibits discrimination based on disability) can be considered for those who require accommodations or modifications such as front-of-class seating, assistive technology devices, classroom scribes, extra time between classes, modified assignments, and enlarged text.Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a US 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.

IEP services:

An IEP provides specially designed instruction and related services to children who qualify.

IEP services will be reviewed annually to determine whether any changes are needed.

Special education law requires that children participating in an IEP be in the least restrictive environment feasible at school and included in general education as much as possible, when and where appropriate.

Vision consultants should be a part of the child's IEP team to support access to academic material.

PT, OT, and speech services will be provided in the IEP to the extent that the need affects the child's access to academic material. Beyond that, private supportive therapies based on the affected individual's needs may be considered. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.

As a child enters the teen years, a transition plan should be discussed and incorporated in the IEP.

For those receiving IEP services, the public school district is required to provide services until age 21.

A 504 plan (Section 504: a US federal statute that prohibits discrimination based on disability) can be considered for those who require accommodations or modifications such as front-of-class seating, assistive technology devices, classroom scribes, extra time between classes, modified assignments, and enlarged text.

Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a US 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., contractures, scoliosis, hip dislocation).Consider use of durable medical equipment and positioning devices as needed (e.g., wheelchairs, walkers, bath chairs, orthotics, adaptive strollers).Fine motor dysfunction. Occupational therapy is recommended for difficulty with fine motor skills that affect adaptive function such as feeding, grooming, dressing, and writing.Oral motor dysfunction. Assessment should be carried out at each visit and clinical feeding evaluations and/or radiographic swallowing studies should be obtained for choking/gagging during feeds, poor weight gain, frequent respiratory illnesses, or feeding refusal that is not otherwise explained. Assuming that the child is safe to eat by mouth, feeding therapy (typically by an occupational or speech therapist) is recommended to help improve coordination or sensory-related

feeding issues. Feeds can be thickened or chilled for safety. When feeding dysfunction is severe, an NG-tube or G-tube may be necessary.Communication issues. Consider evaluation for alternative means of communication (e.g., augmentative and alternative communication [AAC]) for individuals who have expressive language difficulties. An AAC evaluation can be completed by a speech-language pathologist who has expertise in the area. The evaluation will consider cognitive abilities and sensory impairment to determine the most appropriate form of communication. AAC devices can range from low-tech, such as picture exchange communication, to high-tech, such as voice-generating devices. Contrary to popular belief, AAC devices do not hinder verbal development of speech, but rather support optimal speech and language development.

Physical therapy is recommended to maximize mobility and to reduce the risk for later-onset orthopedic complications (e.g., contractures, scoliosis, hip dislocation).

Consider use of durable medical equipment and positioning devices as needed (e.g., wheelchairs, walkers, bath chairs, orthotics, adaptive strollers).

Social/Behavioral ConcernsChildren may qualify for and benefit from interventions used in treatment of autism spectrum disorder, including applied behavior analysis (ABA). ABA therapy is targeted to the individual child's behavioral, social, and adaptive strengths and weaknesses and is typically performed one on one with a board-certified behavior analyst.Consultation with a developmental pediatrician may be helpful in guiding parents through appropriate behavior management strategies or providing prescription medications, such as medication used to treat attention-deficit/hyperactivity disorder, when necessary.Concerns about serious aggressive or destructive behavior can be addressed by a pediatric psychiatrist.

SurveillanceTable 5. Recommended Surveillance for Individuals with PACS1 Neurodevelopmental DisorderView in own windowSystem/ConcernEvaluationFrequency

Development

Monitor developmental progress & educational needs.At each visit

Feeding

Measurement of growth parametersEval of nutritional status & safety of oral intake

Gastrointestinal

Monitor for constipation.

Respiratory

Monitor for evidence of aspiration, respiratory insufficiency.

Neurologic

Monitor those w/seizures as clinically indicated.Assess for new manifestations incl seizures, changes in tone, movement disorders

Psychiatric/

Behavioral

Behavioral assessment for anxiety, attention, & aggressive or self-injurious behavior

Cardiovascular

Monitor closure of septal defects by echo if present & not repaired.Annually or per cardiologist

Genitourinary

Monitor renal function if renal malformation is present.Annually or per nephrologist

Miscellaneous/

Other

Assess family need for social work support (e.g., palliative/respite care, home nursing, other local

resources) & care coordination.At each visit

Table 5. Recommended Surveillance for Individuals with PACS1 Neurodevelopmental DisorderView in own windowSystem/ConcernEvaluationFrequency

Development

Monitor developmental progress & educational needs.At each visit

Feeding

Measurement of growth parametersEval of nutritional status & safety of oral intake

Gastrointestinal

Monitor for constipation.

Respiratory

Monitor for evidence of aspiration, respiratory insufficiency.

Neurologic

Monitor those w/seizures as clinically indicated.Assess for new manifestations incl seizures, changes in tone, movement disorders

Psychiatric/

Behavioral

Behavioral assessment for anxiety, attention, & aggressive or self-injurious behavior

Cardiovascular

Monitor closure of septal defects by echo if present & not repaired.Annually or per cardiologist

Genitourinary

Monitor renal function if renal malformation is present.Annually or per nephrologist

Miscellaneous/

Other

Assess family need for social work support (e.g., palliative/respite care, home nursing, other local resources) & care coordination.At each visit

Recommended Surveillance for Individuals with PACS1 Neurodevelopmental Disorder

System/ConcernEvaluationFrequency

Development

Monitor developmental progress & educational needs.At each visit

Feeding

Measurement of growth parametersEval of nutritional status & safety of oral intake

Gastrointestinal

Monitor for constipation.

Respiratory

Monitor for evidence of aspiration, respiratory insufficiency.

Neurologic

Monitor those w/seizures as clinically indicated.Assess for new manifestations incl seizures, changes in tone, movement disorders

Psychiatric/

Behavioral

Behavioral assessment for anxiety, attention, & aggressive or self-injurious behavior

Cardiovascular

Monitor closure of septal defects by echo if present & not repaired.Annually or per cardiologist

Genitourinary

Monitor renal function if renal malformation is present.Annually or per nephrologist

Miscellaneous/

Other

Assess family need for social work support (e.g., palliative/respite care, home nursing, other local resources) & care coordination.At each visit

Measurement of growth parameters

Eval of nutritional status & safety of oral intake

Monitor those w/seizures as clinically indicated.

Assess for new manifestations incl seizures, changes in tone, movement disorders

Agents/Circumstances to AvoidIndividuals with PACS1-NDD should avoid any known seizure triggers (e.g., sleep deprivation, alcohol use, missed medications).

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

Therapies Under InvestigationSearch 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 InheritancePACS1 neurodevelopmental disorder (PACS1-NDD) is an autosomal dominant disorder typically caused by a de novo pathogenic variant.Risk to Family Members

Parents of a proband

All of the 31 probands with PACS1-NDD reported in the literature whose parents have undergone molecular genetic testing have had the disorder as a result of a de novo PACS1 pathogenic variant.Molecular genetic testing is recommended for the parents of a proband with an apparent de novo pathogenic variant.If the PACS1 pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the pathogenic variant most likely occurred de novo in the proband. Another possible explanation is that the proband inherited a pathogenic variant from a parent with germline mosaicism. Although theoretically possible, no instances of parental mosaicism have been reported to date.Theoretically, if the parent is the individual in whom the PACS1 pathogenic variant first occurred, the parent may have somatic and germline mosaicism for the variant and may be mildly/minimally affected.Sibs of a proband. The risk to sibs of the proband depends on the genetic status of the proband's parents: if the PACS1 pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be 1% because of the theoretic possibility of parental germline mosaicism [Rahbari et al 2016].Offspring of a proband. Individuals with a PACS1-NDD are

not known to reproduce due to their neurodevelopmental disability; however, many are not yet of reproductive age.Other family members. Given that all probands with PACS1-NDD reported to date have the disorder as a result of a de novo

PACS1 pathogenic variant, 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 TestingRisk to future pregnancies is presumed to be low as the proband most likely has a de novo PACS1 pathogenic variant. There is, however, a recurrence risk (~1%) to sibs based on the theoretic possibility of parental germline mosaicism [Rahbari et al 2016]. Given this risk, prenatal testing and preimplantation genetic testing may be considered.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.

Mode of InheritancePACS1 neurodevelopmental disorder (PACS1-NDD) is an autosomal dominant disorder typically caused by a de novo pathogenic variant.

Risk to Family Members

Parents of a proband

All of the 31 probands with PACS1-NDD reported in the literature whose parents have undergone molecular genetic testing have had the disorder as a result of a de novo

PACS1 pathogenic variant.Molecular genetic testing is recommended for the parents of a proband with an apparent de novo pathogenic variant.If the PACS1 pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the pathogenic variant most likely

occurred de novo in the proband. Another possible explanation is that the proband inherited a pathogenic variant from a parent with germline mosaicism. Although theoretically possible, no instances of parental mosaicism have been reported to date.Theoretically, if the parent is the individual in whom the PACS1 pathogenic variant first occurred, the parent may have somatic and germline mosaicism for the variant and may be mildly/minimally affected.Sibs of a proband. The risk to sibs of the proband depends on the genetic status of the proband's parents: if the PACS1 pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be 1% because of the theoretic possibility of parental germline mosaicism [Rahbari et al 2016].Offspring of a proband. Individuals with a PACS1-NDD are not known to reproduce due to their neurodevelopmental disability; however, many are not yet of reproductive age.Other family members. Given that all probands with PACS1-NDD reported to date have the disorder as a result of a de novo
PACS1 pathogenic variant, the risk to other family members is presumed to be low.

All of the 31 probands with PACS1-NDD reported in the literature whose parents have undergone molecular genetic testing have had the disorder as a result of a de novo
PACS1 pathogenic variant.

Molecular genetic testing is recommended for the parents of a proband with an apparent de novo pathogenic variant.

If the PACS1 pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the pathogenic variant most likely occurred de novo in the proband. Another possible explanation is that the proband inherited a pathogenic variant from a parent with germline mosaicism. Although theoretically possible, no instances of parental mosaicism have been reported to date.

Theoretically, if the parent is the individual in whom the PACS1 pathogenic variant first occurred, the parent may have somatic and germline mosaicism for the variant and may be mildly/minimally affected.

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.

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 TestingRisk to future pregnancies is presumed to be low as the proband most likely has a de novo PACS1 pathogenic variant. There is, however, a recurrence risk (~1%) to sibs based on the theoretic possibility of parental germline mosaicism [Rahbari et al 2016]. Given this risk, prenatal testing and preimplantation genetic testing may be considered.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.

PACS1 Foundation

The PACS1 syndrome research foundation is a private foundation dedicated to finding a therapeutic that would alleviate the symptoms of PACS1 Syndrome (also known as Schuurs-Hoeijmakers Syndrome) as quickly as possible.

www.pacs1foundation.org

PACS1 Smiles – Support Organization

PO Box 2058Sandwhich MA 02563

www.pacs1smiles.org

Unique: Understanding Rare Chromosome and Gene Disorders

United KingdomPhone: +44 (0) 1883 723356Email: info@rarechromo.org

www.rarechromo.org

Simons Searchlight Registry

Simons Searchlight aims to further the understanding of rare genetic neurodevelopmental disorders.

Phone: 855-329-5638Fax: 570-214-7327Email: coordinator@simonssearchlight.org

www.simonssearchlight.org

PACS1 Foundation

The PACS1 syndrome research foundation is a private foundation dedicated to finding a therapeutic that would alleviate the symptoms of PACS1 Syndrome (also known as Schuurs-Hoeijmakers Syndrome) as quickly as possible.

www.pacs1foundation.org

PACS1 Smiles – Support Organization

PO Box 2058

Sandwhich MA 02563

www.pacs1smiles.org

Unique: Understanding Rare Chromosome and Gene Disorders

United Kingdom

Phone: +44 (0) 1883 723356

Email: info@rarechromo.org

www.rarechromo.org

Simons Searchlight Registry

Simons Searchlight aims to further the understanding of rare genetic neurodevelopmental disorders.

Phone: 855-329-5638

Fax: 570-214-7327

Email: coordinator@simonssearchlight.org

www.simonssearchlight.org

Molecular GeneticsInformation in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.Table A.PACS1 Neurodevelopmental Disorder: Genes and DatabasesView in own windowGeneChromosome LocusProteinHGMDClinVar

PACS1

11q13.1-q13.2

Phosphofurin acidic cluster sorting protein 1

PACS1

PACS1

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 PACS1 Neurodevelopmental Disorder (View All in OMIM) View in own window

607492PHOSPHOFURIN ACIDIC CLUSTER SORTING PROTEIN 1; PACS1

615009SCHUURS-HOEIJMAKERS SYNDROME; SHMSMolecular PathogenesisPACS1 encodes PACS1, a trans-golgi-membrane traffic regulator [Schuurs-Hoeijmakers et al 2012] involved in directing protein cargo and cranial-neural-crest cell migration. Expression is upregulated during embryonic brain development, with low expression after birth.An R196RKRY CK2-binding motif is critical to PACS1 autoregulation [Schuurs-Hoeijmakers et al 2012]. Disease-associated variants occur at p.Arg203 in the furin(cargo)-binding domain, directly adjacent to the CK2-binding motif and may affect interaction with cargo. The introduction of the p.Arg203Trp pathogenic variant led to protein-trafficking defects, cellular aggregates, and abolishment of normal PACS1 function [Schuurs-Hoeijmakers et al 2012, Schuurs-Hoeijmakers et al 2016]. The craniofacial phenotype of PACS1 neurodevelopmental disorder is suggested to be a result of impairment in the specification and migration of cranial-neural-crest cells.Mechanism of disease causation. Recurrent disease-associated variants in the same codon, c.608G>A and c.607C>T, as well as studies in zebrafish, suggest either a dominant-negative or gain-of-function disease mechanism [Schuurs-Hoeijmakers et al 2012, Miyake et al 2018].Identification of several individuals with the same de novo variant suggests positive selection for the c.607C>T variant during spermatogenesis, similar to positive selection for FGFR3 pathogenic variants [Schuurs-Hoeijmakers et al 2016]. The c.608G>A variant did occur on the paternal chromosome [Miyake et al 2018]. Data are insufficient at this time to comment on paternal age effects.Table 6. Notable PACS1 Pathogenic VariantsView in own windowReference SequencesDNA Nucleotide ChangePredicted Protein ChangeComment [Reference]

NM_018026.3

NP_060496.2

c.607C>Tp.Arg203TrpCommon pathogenic variant in PACS1 [Schuurs-Hoeijmakers et al 2016]; 1 of the most common recurrent missense variants identified in individuals w/neurodevelopmental disorders [Kaplanis et al 2019]c.608G>Ap.Arg203Gln1 individual w/this pathogenic variant reported [Miyake et al 2018]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.

Table A.PACS1 Neurodevelopmental Disorder: Genes and DatabasesView in own windowGeneChromosome LocusProteinHGMDClinVar

PACS1

11q13.1-q13.2

Phosphofurin acidic cluster sorting protein 1

PACS1

PACS1

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.

PACS1 Neurodevelopmental Disorder: Genes and Databases

GeneChromosome LocusProteinHGMDClinVar

PACS1

11q13.1-q13.2

Phosphofurin acidic cluster sorting protein 1

PACS1

PACS1

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.

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.

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 PACS1 Neurodevelopmental Disorder (View All in OMIM) View in own window

607492PHOSPHOFURIN ACIDIC CLUSTER SORTING PROTEIN 1; PACS1

615009SCHUURS-HOEIJMAKERS SYNDROME; SHMS

OMIM Entries for PACS1 Neurodevelopmental Disorder (View All in OMIM)

607492PHOSPHOFURIN ACIDIC CLUSTER SORTING PROTEIN 1; PACS1

615009SCHUURS-HOEIJMAKERS SYNDROME; SHMS

Molecular PathogenesisPACS1 encodes PACS1, a trans-golgi-membrane traffic regulator [Schuurs-Hoeijmakers et al 2012] involved in directing protein cargo and cranial-neural-crest cell migration. Expression is upregulated during embryonic brain development, with low expression after birth.An R196RKRY CK2-binding motif is critical to PACS1 autoregulation [Schuurs-Hoeijmakers et al 2012]. Disease-associated variants occur at p.Arg203 in the furin(cargo)-binding domain, directly adjacent to the CK2-binding motif and may affect interaction with cargo. The introduction of the p.Arg203Trp pathogenic variant led to protein-trafficking defects, cellular aggregates, and abolishment of normal PACS1 function [Schuurs-Hoeijmakers et al 2012, Schuurs-Hoeijmakers et al 2016]. The craniofacial phenotype of PACS1 neurodevelopmental disorder is suggested to be a result of impairment in the specification and migration of cranial-neural-crest cells.Mechanism of disease causation. Recurrent disease-associated variants in the same codon, c.608G>A and c.607C>T, as well as studies in zebrafish, suggest either a dominant-negative or gain-of-function disease mechanism [Schuurs-Hoeijmakers et al 2012, Miyake et al 2018].Identification of several individuals with the same de novo variant suggests positive selection for the c.607C>T variant during spermatogenesis, similar to positive selection for FGFR3 pathogenic variants [Schuurs-Hoeijmakers et al 2016]. The c.608G>A variant did occur on the paternal chromosome [Miyake et al 2018]. Data are insufficient at this time to comment on paternal age effects.Table 6. Notable PACS1 Pathogenic VariantsView in own windowReference SequencesDNA Nucleotide ChangePredicted Protein ChangeComment [Reference]

NM_018026.3

NP_060496.2

c.607C>Tp.Arg203TrpCommon pathogenic variant in PACS1 [Schuurs-Hoeijmakers et al 2016]; 1 of the most common recurrent missense variants identified in individuals w/neurodevelopmental disorders [Kaplanis et al 2019]c.608G>Ap.Arg203Gln1 individual w/this pathogenic variant reported [Miyake et al 2018]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.

Table 6. Notable PACS1 Pathogenic VariantsView in own windowReference SequencesDNA Nucleotide ChangePredicted Protein ChangeComment [Reference]

NM_018026.3

NP_060496.2

c.607C>Tp.Arg203TrpCommon pathogenic variant in PACS1 [Schuurs-Hoeijmakers et al 2016]; 1 of the most common recurrent missense variants identified in individuals w/neurodevelopmental disorders [Kaplanis et al 2019]c.608G>Ap.Arg203Gln1 individual w/this pathogenic variant reported [Miyake et al 2018]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.

Notable PACS1 Pathogenic Variants

Reference SequencesDNA Nucleotide ChangePredicted Protein ChangeComment [Reference]

NM_018026.3

NP_060496.2

c.607C>Tp.Arg203TrpCommon pathogenic variant in PACS1 [Schuurs-Hoeijmakers et al 2016]; 1 of the most common recurrent missense variants identified in individuals w/neurodevelopmental disorders [Kaplanis et al 2019]c.608G>Ap.Arg203Gln1 individual w/this pathogenic variant reported [Miyake et al 2018]

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.

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.

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.

Chapter NotesRevision History16 July 2020 (sw) Review posted live30 March 2020 (wc) Original submission

Revision History16 July 2020 (sw) Review posted live30 March 2020 (wc) Original submission

16 July 2020 (sw) Review posted live

30 March 2020 (wc) Original submission

ReferencesLiterature CitedChad L, Chung B HY, Marshall CR, Merico D, Babul-Hirji R, Stavropoulos DJ, Chitayat D. Global developmental delay and characteristic facial features

associated with PACS1 gene mutation – report of two cases. J Med Genet. 2015;52 Suppl 1:A1.Dutta AK. Schuurs-Hoeijmakers syndrome in a patient from India. Am J Med Genet Part A. 2019;179:522–4. [PubMed: 30690871]Gadzicki D, Döcker D, Schubach M, Menzel M, Schmorl B, Stellmer F, Biskup S, Bartholdi D. Expanding the phenotype of a recurrent de novo variant in PACS1 causing intellectual disability. Clin Genet. 2015;88:300–2. [PubMed: 25522177]Hoshino Y, Enokizono T, Imagawa K, Tanaka R, Suzuki H, Fukushima H, Arai J, Sumazaki R, Uehara T, Takenouchi T, Kosaki K. Schuurs-Hoeijmakers syndrome in two patients from Japan. Am J Med Genet Part A. 2019;179:341–3. [PubMed: 30588754]Kaplanis J, Akawi N, Gallone G, McRae JF, Prigmore E, Wright CF, Fitzpatrick DR, Firth HV, Barrett JC, Hurles ME. Deciphering Developmental Disorders study. Exome-wide assessment of the functional impact and pathogenicity of multinucleotide mutations. Genome Res. 2019;29:1047–56. [PMC free article: PMC6633265] [PubMed: 31227601]Martinez-Monseny A, Bolasell M, Arjona C, Martorell L, Yubero D, Arsmtrong J, Maynou J, Fernandez G, del Carmen Salgado M, Palau F, Serrano M. Mutation of PACS1: the milder end of the spectrum. Clin Dysmorphol. 2018;27:148–50. [PubMed: 30113927]Miyake N, Ozasa S, Mabe H, Kimura S, Shiina M, Imagawa E, Miyatake S, Nakashima M, Mizuguchi T, Takata A, Ogata K, Matsumoto N. A novel missense mutation affecting the same amino acid as the recurrent PACS1 mutation in Schuurs-Hoeijmakers syndrome. Clinical Genet. 2018;93:929–30. [PubMed: 28975623]Pefkianaki M, Schneider A, Capasso JE, Wasserman B, Bardakjian T, Levin AV. Ocular manifestations of PACS1 mutation. J AAPOS. 2018;22:323–5. [PubMed: 29550517]Rahbari R, Wuster A, Lindsay SJ, Hardwick RJ, Alexandrov LB, Turki SA, Dominiczak A, Morris A, Porteous D, Smith B, Stratton MR, Hurles ME, et al. Timing, rates and spectra of human germline mutation. Nat Genet. 2016;48:126–33. [PMC free article: PMC4731925] [PubMed: 26656846]Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17:405–24. [PMC free article: PMC4544753]

[PubMed: 25741868]Schuurs-Hoeijmakers J HM, Landsverk ML, Foulds N, Kukolich MK, Gavrilova RH, Greville-Heygate S, Hanson-Kahn A, Bernstein JA, Glass J, Chitayat D, Burrow TA, Husami A, Collins K, Wusik K, van der Aa N, Kooy F, Tatton Brown K, Gadzicki D, Kini U, Alvarez S, Fernández-Jaén A, McGehee F, Selby K, Tarailo-Graovac M, Van Allen M, van Karnebeek C DM, Stavropoulos DJ, Marshall CR, Merico D, Gregor A, Zweier C, Hopkin RJ, Wing-Yiu Chu Y, Chung B HY, de Vries B BA, Devriendt K, Hurles ME, Brunner HG. DDD study. Clinical delineation of the PACS1-related syndrome—report on 19 patients. Am J Med Genet. 2016;170:670–5. [PubMed: 26842493]Schuurs-Hoeijmakers J HM, Oh EC, Vissers L. ELM, Swinkels M EM, Gilissen C, Willemsen MA, Holvoet M, Steehouwer M, Veltman JA, de Vries B BA, van Bokhoven H, de Brouwer A PM, Katsanis N, Devriendt K, Brunner HG. Recurrent de novo mutations in PACS1 cause defective cranial-neural-crest migration and define a recognizable intellectual-disability syndrome. Am J Hum Genet. 2012;91:1122–7. [PMC free article: PMC3516611] [PubMed: 23159249]Stenson PD, Mort M, Ball EV, Chapman M, Evans K, Azevedo L, Hayden M, Heywood S, Millar DS, Phillips AD, Cooper DN. The Human Gene Mutation Database (HGMD®): optimizing its use in a clinical diagnostic or research setting. Hum Genet. 2020;139:1197–207. [PMC free article: PMC7497289] [PubMed: 32596782]Stern D, Cho MT, Chikarmane R, Willaert R, Retterer K, Kendall F, Deardorff M, Hopkins S, Bedoukian E, Slavotinek A, Schrier Vergano S, Spangler B, McDonald M, McConkie-Rosell A, Burton BK, Kim KH, Oundjian N, Kronn D, Chandy N, Baskin B, Guillen Sacoto MJ, Wentzensen IM, McLaughlin HM, McKnight D, Chung WK. Association of the missense variant p.Arg203Trp in PACS1 as a cause of intellectual disability and seizures. Clin Genet. 2017;92:221–3. [PMC free article: PMC5513756] [PubMed: 28111752]

Literature CitedChad L, Chung B HY, Marshall CR, Merico D, Babul-Hirji R, Stavropoulos DJ, Chitayat D. Global developmental delay and characteristic facial features associated with PACS1 gene mutation – report of two cases. J Med Genet. 2015;52 Suppl 1:A1.Dutta AK. Schuurs-Hoeijmakers syndrome in a patient from India. Am J Med Genet Part A.

2019;179:522–4. [PubMed: 30690871]Gadzicki D, Döcker D, Schubach M, Menzel M, Schmorl B, Stellmer F, Biskup S, Bartholdi D. Expanding the phenotype of a recurrent de novo variant in PACS1 causing intellectual disability. Clin Genet. 2015;88:300–2. [PubMed: 25522177]Hoshino Y, Enokizono T, Imagawa K, Tanaka R, Suzuki H, Fukushima H, Arai J, Sumazaki R, Uehara T, Takenouchi T, Kosaki K. Schuurs-Hoeijmakers syndrome in two patients from Japan. Am J Med Genet Part A. 2019;179:341–3. [PubMed: 30588754]Kaplanis J, Akawi N, Gallone G, McRae JF, Prigmore E, Wright CF, Fitzpatrick DR, Firth HV, Barrett JC, Hurles ME. Deciphering Developmental Disorders study. Exome-wide assessment of the functional impact and pathogenicity of multinucleotide mutations. Genome Res. 2019;29:1047–56. [PMC free article: PMC6633265] [PubMed: 31227601]Martinez-Monseny A, Bolasell M, Arjona C, Martorell L, Yubero D, Arsmtrong J, Maynou J, Fernandez G, del Carmen Salgado M, Palau F, Serrano M. Mutation of PACS1: the milder end of the spectrum. Clin Dysmorphol. 2018;27:148–50. [PubMed: 30113927]Miyake N, Ozasa S, Mabe H, Kimura S, Shiina M, Imagawa E, Miyatake S, Nakashima M, Mizuguchi T, Takata A, Ogata K, Matsumoto N. A novel missense mutation affecting the same amino acid as the recurrent PACS1 mutation in Schuurs-Hoeijmakers syndrome. Clinical Genet. 2018;93:929–30. [PubMed: 28975623]Pefkianaki M, Schneider A, Capasso JE, Wasserman B, Bardakjian T, Levin AV. Ocular manifestations of PACS1 mutation. J AAPOS. 2018;22:323–5. [PubMed: 29550517]Rahbari R, Wuster A, Lindsay SJ, Hardwick RJ, Alexandrov LB, Turki SA, Dominiczak A, Morris A, Porteous D, Smith B, Stratton MR, Hurles ME, et al. Timing, rates and spectra of human germline mutation. Nat Genet. 2016;48:126–33. [PMC free article: PMC4731925] [PubMed: 26656846]Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17:405–24. [PMC free article: PMC4544753] [PubMed: 25741868]Schuurs-Hoeijmakers J HM, Landsverk ML, Foulds N, Kukolich MK, Gavrilova RH, Greville-Heygate S, Hanson-Kahn A, Bernstein JA, Glass J, Chitayat D, Burrow TA, Husami A,

Collins K, Wusik K, van der Aa N, Kooy F, Tatton Brown K, Gadzicki D, Kini U, Alvarez S, Fernández-Jaén A, McGehee F, Selby K, Tarailo-Graovac M, Van Allen M, van Karnebeek C DM, Stavropoulos DJ, Marshall CR, Merico D, Gregor A, Zweier C, Hopkin RJ, Wing-Yiu Chu Y, Chung B HY, de Vries B BA, Devriendt K, Hurles ME, Brunner HG. DDD study. Clinical delineation of the PACS1-related syndrome—report on 19 patients. Am J Med Genet. 2016;170:670–5. [PubMed: 26842493]Schuurs-Hoeijmakers J HM, Oh EC, Vissers L. ELM, Swinkels M EM, Gilissen C, Willemsen MA, Holvoet M, Steehouwer M, Veltman JA, de Vries B BA, van Bokhoven H, de Brouwer A PM, Katsanis N, Devriendt K, Brunner HG. Recurrent de novo mutations in PACS1 cause defective cranial-neural-crest migration and define a recognizable intellectual-disability syndrome. Am J Hum Genet. 2012;91:1122–7. [PMC free article: PMC3516611] [PubMed: 23159249]Stenson PD, Mort M, Ball EV, Chapman M, Evans K, Azevedo L, Hayden M, Heywood S, Millar DS, Phillips AD, Cooper DN. The Human Gene Mutation Database (HGMD®): optimizing its use in a clinical diagnostic or research setting. Hum Genet. 2020;139:1197–207. [PMC free article: PMC7497289] [PubMed: 32596782]Stern D, Cho MT, Chikarmane R, Willaert R, Retterer K, Kendall F, Deardorff M, Hopkins S, Bedoukian E, Slavotinek A, Schrier Vergano S, Spangler B, McDonald M, McConkie-Rosell A, Burton BK, Kim KH, Oundjian N, Kronn D, Chandy N, Baskin B, Guillen Sacoto MJ, Wentzensen IM, McLaughlin HM, McKnight D, Chung WK. Association of the missense variant p.Arg203Trp in PACS1 as a cause of intellectual disability and seizures. Clin Genet. 2017;92:221–3. [PMC free article: PMC5513756] [PubMed: 28111752]

Chad L, Chung B HY, Marshall CR, Merico D, Babul-Hirji R, Stavropoulos DJ, Chitayat D. Global developmental delay and characteristic facial features associated with PACS1 gene mutation – report of two cases. J Med Genet. 2015;52 Suppl 1:A1.

Dutta AK. Schuurs-Hoeijmakers syndrome in a patient from India. Am J Med Genet Part A. 2019;179:522–4. [PubMed: 30690871]

Gadzicki D, Döcker D, Schubach M, Menzel M, Schmorl B, Stellmer F, Biskup S, Bartholdi D. Expanding the phenotype of a recurrent de novo variant in PACS1 causing intellectual disability. Clin Genet. 2015;88:300–2. [PubMed: 25522177]

Hoshino Y, Enokizono T, Imagawa K, Tanaka R, Suzuki H, Fukushima H, Arai J, Sumazaki R, Uehara T, Takenouchi T, Kosaki K. Schuurs-Hoeijmakers syndrome in two patients from Japan. Am J Med Genet Part A. 2019;179:341–3. [PubMed: 30588754]

Kaplanis J, Akawi N, Gallone G, McRae JF, Prigmore E, Wright CF, Fitzpatrick DR, Firth HV, Barrett JC, Hurles ME. Deciphering Developmental Disorders study. Exome-wide assessment of the functional impact and pathogenicity of multinucleotide mutations. Genome Res. 2019;29:1047–56. [PMC free article: PMC6633265] [PubMed: 31227601]

Martinez-Monseny A, Bolasell M, Arjona C, Martorell L, Yubero D, Arsmtrong J, Maynou J, Fernandez G, del Carmen Salgado M, Palau F, Serrano M. Mutation of PACS1: the milder end of the spectrum. Clin Dysmorphol. 2018;27:148–50. [PubMed: 30113927]

Miyake N, Ozasa S, Mabe H, Kimura S, Shiina M, Imagawa E, Miyatake S, Nakashima M, Mizuguchi T, Takata A, Ogata K, Matsumoto N. A novel missense mutation affecting the same amino acid as the recurrent PACS1 mutation in Schuurs-Hoeijmakers syndrome. Clinical Genet. 2018;93:929–30. [PubMed: 28975623]

Pefkianaki M, Schneider A, Capasso JE, Wasserman B, Bardakjian T, Levin AV. Ocular manifestations of PACS1 mutation. J AAPOS. 2018;22:323–5. [PubMed: 29550517]

Rahbari R, Wuster A, Lindsay SJ, Hardwick RJ, Alexandrov LB, Turki SA, Dominiczak A, Morris A,

Porteous D, Smith B, Stratton MR, Hurles ME, et al. Timing, rates and spectra of human germline mutation. Nat Genet. 2016;48:126–33. [PMC free article: PMC4731925] [PubMed: 26656846]

Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17:405–24. [PMC free article: PMC4544753] [PubMed: 25741868]

Schuurs-Hoeijmakers J HM, Landsverk ML, Foulds N, Kukolich MK, Gavrilova RH, Greville-Heygate S, Hanson-Kahn A, Bernstein JA, Glass J, Chitayat D, Burrow TA, Husami A, Collins K, Wusik K, van der Aa N, Kooy F, Tatton Brown K, Gadzicki D, Kini U, Alvarez S, Fernández-Jaén A, McGehee F, Selby K, Tarailo-Graovac M, Van Allen M, van Karnebeek C DM, Stavropoulos DJ, Marshall CR, Merico D, Gregor A, Zweier C, Hopkin RJ, Wing-Yiu Chu Y, Chung B HY, de Vries B BA, Devriendt K, Hurles ME, Brunner HG. DDD study. Clinical delineation of the PACS1-related syndrome—report on 19 patients. Am J Med Genet. 2016;170:670–5. [PubMed: 26842493]

Schuurs-Hoeijmakers J HM, Oh EC, Vissers L. ELM, Swinkels M EM, Gilissen C, Willemsen MA, Holvoet M, Steehouwer M, Veltman JA, de Vries B BA, van Bokhoven H, de Brouwer A PM, Katsanis N, Devriendt K, Brunner HG. Recurrent de novo mutations in PACS1 cause defective cranial-neural-crest migration and define a recognizable intellectual-disability syndrome. Am J Hum Genet. 2012;91:1122–7. [PMC free article: PMC3516611] [PubMed: 23159249]

Stenson PD, Mort M, Ball EV, Chapman M, Evans K, Azevedo L, Hayden M, Heywood S, Millar DS, Phillips AD, Cooper DN. The Human Gene Mutation Database (HGMD®): optimizing its use in

a clinical diagnostic or research setting. Hum Genet. 2020;139:1197–207. [PMC free article: PMC7497289] [PubMed: 32596782]

Stern D, Cho MT, Chikarmane R, Willaert R, Retterer K, Kendall F, Deardorff M, Hopkins S, Bedoukian E, Slavotinek A, Schrier Vergano S, Spangler B, McDonald M, McConkie-Rosell A, Burton BK, Kim KH, Oundjian N, Kronn D, Chandy N, Baskin B, Guillen Sacoto MJ, Wentzensen IM, McLaughlin HM, McKnight D, Chung WK. Association of the missense variant p.Arg203Trp in PACS1 as a cause of intellectual disability and seizures. Clin Genet. 2017;92:221–3. [PMC free article: PMC5513756] [PubMed: 28111752]