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Peters Plus Syndrome

Saskia AJ Lesnik Oberstein, MD, PhD,[1] Claudia AL Ruivenkamp, PhD,[2] and Raoul C Hennekam, MD, PhD[3]

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Summary

Clinical characteristics

Peters plus syndrome is characterized by anterior chamber eye anomalies, short limbs with broad distal extremities, characteristic facial features, cleft lip/palate, and variable developmental delay / intellectual disability. The most common anterior chamber defect is Peters' anomaly, consisting of central corneal clouding, thinning of the posterior cornea, and iridocorneal adhesions. Cataracts and glaucoma are common. Developmental delay is observed in about 80% of children; intellectual disability can range from mild to severe.

Diagnosis/testing

The diagnosis of Peters plus syndrome is a clinical diagnosis that can be confirmed by identification of biallelic *B3GLCT* pathogenic variants on molecular genetic testing.

Management

Treatment of manifestations: Consideration of corneal transplantation (penetrating keratoplasty) for severe bilateral corneal opacification before age three to six months to prevent amblyopia; consideration of simple separation of iridocorneal adhesions in mild cases; management of amblyopia by a pediatric ophthalmologist; surgical/medical intervention for glaucoma as needed; developmental/educational interventions as needed.

Surveillance: Assessment by a pediatric ophthalmologist every three months in infancy and childhood or as indicated later on to monitor for glaucoma and amblyopia; regular developmental assessments.

Agents/circumstances to avoid: Agents that increase risk of glaucoma (e.g., corticosteroids).

Author Affiliations: 1 Clinical Geneticist, Department of Clinical Genetics Leiden University Medical Center Leiden, The Netherlands; Email: lesnik@lumc.nl. 2 Molecular Geneticist, Department of Clinical Genetics Leiden University Medical Center Leiden, The Netherlands; Email: c.ruivenkamp@lumc.nl. 3 Department of Pediatrics Academic Medical Center Amsterdam, The Netherlands; Email: r.c.hennekam@amc.uva.nl.

Genetic counseling

Peters plus syndrome is inherited in an autosomal recessive manner. The parents of an affected child are obligate heterozygotes (i.e., carriers of one *B3GLCT* pathogenic variant). Heterozygotes (carriers) are asymptomatic. At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. There is an increased chance for miscarriages and second- and third-trimester fetal loss of affected fetuses. Carrier testing for at-risk family members and prenatal diagnosis for pregnancies at increased risk are possible once the pathogenic variants have been identified in an affected family member.

Diagnosis

Suggestive Findings

Peters plus syndrome **should be suspected** in individuals with anterior chamber anomalies of the eye (usually bilateral but in some cases unilateral), with or without any of the following:

- Short limbs with broad distal extremities
- Characteristic facial features including an exaggerated Cupid's bow of the upper lip, short palpebral fissures, and ear anomalies
- Cleft lip/palate
- Variable developmental delay / intellectual disability

Establishing the Diagnosis

The diagnosis of Peters plus syndrome **can be established** clinically in a proband with the above Suggestive Findings. The diagnosis can be confirmed by identification of biallelic pathogenic variants in *B3GLCT* on molecular genetic testing (see Table 1):

- **Single-gene testing.** Sequence analysis of *B3GLCT* is performed first and followed by gene-targeted deletion/duplication analysis if only one or no pathogenic variant is found.
- **A multigene panel** that includes *B3GLCT* and other genes of interest (see Differential Diagnosis) may also be considered. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*; thus, clinicians need to determine which multigene panel is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.
- **More comprehensive genomic testing** (when available) including exome sequencing and genome sequencing may be considered. Such testing may provide or suggest a diagnosis not previously considered (e.g., mutation of a different gene or genes that results in a similar clinical presentation).

  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 Peters Plus Syndrome

Gene [1]	Method	Proportion of Probands with Pathogenic Variants [2] Detectable by Method
B3GLCT	Sequence analysis [3]	35% [4]-100% [5, 6]
	Gene-targeted deletion/duplication analysis [7]	4 individuals [8]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results click here.
4. Nine of 26 affected individuals tested, as identified by the Laboratory of Diagnostic Genome Analysis, Leiden, The Netherlands. Note: This is a clinically heterogeneous group.
5. Twenty of 20 affected individuals tested, as identified by Lesnik Oberstein et al [2006]. This cohort is clinically well described.
6. Most affected individuals tested to date are homozygous for a splice site pathogenic variant in intron 8 (c.660+1G>A) [Lesnik Oberstein et al 2006]. However, several other loss-of-function variants have been identified, including pathogenic missense variants located in the putative catalytic domain of the enzyme.
7. 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.
8. Lesnik Oberstein et al [2006] described two brothers with a ~1.5-Mb contiguous gene deletion on their maternal allele that included *B3GLCT*. The proximal deletion breakpoint is between exons 7 and 8 of *B3GLCT*; the distal breakpoint is between exons 13 and 14 of *BRCA2*. Haldeman-Englert et al [2009] also reported a large deletion including all of *B3GLCT*. The paternal allele harbored a pathogenic single-nucleotide variant. Within the Laboratory of Diagnostic Genome Analysis, Leiden, The Netherlands, a heterozygous deletion of only exon 7 was identified; the other allele harbored the common intron 8 splice site pathogenic variant [Author, personal communication].

Clinical Characteristics

Clinical Description

Peters plus syndrome is characterized by anterior chamber eye anomalies, short limbs with broad distal extremities, variable developmental delay / intellectual disability, typical facial features, and cleft lip/palate. Unless otherwise stated, the following description of clinical findings is based on the reports of Maillette de Buy Wenniger-Prick & Hennekam [2002] and Lesnik Oberstein et al [2006].

Eyes. The most common anterior chamber defect is Peters' anomaly, consisting of central corneal clouding, thinning of the posterior cornea, and iridocorneal adhesions. Peters' anomaly may be classified as type I, a mild form, or type II, a more severe form associated with lens abnormalities including cataracts, congenital glaucoma, and a poorer visual prognosis [Yang et al 2004, Zaidman et al 2007]. The eye involvement is usually, but not always, bilateral.

Cataracts and glaucoma can subsequently develop later in life.

Other, often unspecified anterior chamber defects have been reported, such as mild mesenchymal dysgenesis [Hennekam et al 1993]. Less expressed symptoms have included iris coloboma. Variation in ocular symptoms may be extensive within a single family, and even a single individual may have Peters anomaly of one eye and iris coloboma or another less marked mesenchymal dysgenesis of the other eye. Minor anterior chamber anomalies may not be associated with visual impairment.

Growth. Growth deficiency with rhizomelic limb shortening has been invariably present in all reported cases to date. Growth restriction begins prenatally, but birth length is not always below the third percentile.

Growth hormone deficiency with good response to growth hormone replacement therapy has been reported in some children [Maillette de Buy Wenniger-Prick & Hennekam 2002, Lee & Lee 2004].

Adult height range is 128-151 cm in females and 141-155 cm in males.

Development. Developmental delay is observed in 78%-83% of children. Intellectual disability typically ranges from mild to severe, although adults with normal cognitive functioning have been reported. Several affected individuals have been diagnosed with classic autism.

A behavioral phenotype has not been well delineated thus far.

Facial features. Typical facial features include a prominent forehead, short palpebral fissures, a long philtrum, and an exaggerated Cupid's bow of the vermillion of the upper lip. The facial phenotype does not appear to evolve significantly over time.

Cleft lip is present in 45% of individuals and cleft palate in 33%.

Ear anomalies, including preauricular pits, are seen in more than one third of affected individuals. A broad neck occurs in approximately 75% of individuals.

Associated findings

- Congenital heart defects (≤33% of individuals), including atrial septal defect, ventricular septal defect, subvalvular aortic stenosis, pulmonary stenosis, and bicuspid pulmonary valve
- Genitourinary anomalies (10%-19%) including hydronephrosis, renal and ureteral duplication, renal underdevelopment with oligomeganephroma, multicystic dysplastic kidney [Boog et al 2005], and glomerulocystic kidneys. A single individual with sexual ambiguity has been published [Siala et al 2013] but no *B3GALTL* pathogenic variants could be detected, and the diagnosis remains uncertain in this individual.
- Structural brain malformations include hypoplasia or agenesis of the corpus callosum, hydrocephalus [Krause et al 1969, Frydman et al 1991], Dandy-Walker malformation and encephalocele [Schoner et al 2013], and an underdeveloped cerebellum with microcephaly; reported in two children suspected of having Peters plus syndrome
- Congenital hypothyroidism; reported in two children with features suggestive of Peters plus syndrome and subsequently described in another affected individual [Kosaki et al 2006]
- Conductive hearing loss; variably present in association with cleft palate but not otherwise a major feature

Prenatal complications. The clinical spectrum appears to include nonviable conceptuses. Several authors have observed an increased rate of miscarriage and stillbirth among mothers of affected children [van Schooneveld et al 1984, Hennekam et al 1993, Thompson et al 1993]. Published prenatal data suggest that 37% of couples with a child with Peters plus syndrome have recurrent (≥2) miscarriages and/or stillbirths.

Polyhydramnios occurred in 18.6% of pregnancies of affected children.

Mortality. Death in early infancy from cardiac failure or undetermined causes has been reported [de Almeida et al 1991, Frydman et al 1991, Lacombe et al 1994].

Genotype-Phenotype Correlations

No genotype-phenotype correlation has yet been demonstrated.

Nomenclature

Alternate terms for Peters plus syndrome have included Krause-Kivlin syndrome and Krause-van Schooneveld-Kivlin syndrome.

Alternate spellings of Peters plus syndrome include: Peters-plus syndrome, Peters'-plus syndrome, Peters' plus syndrome.

Prevalence

The prevalence of Peters plus syndrome is unknown. About 100 affected individuals of diverse ethnic background have been reported in the literature.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with pathogenic variants in *B3GLCT*.

Differential Diagnosis

The differential diagnosis of Peters plus syndrome comprises other conditions with short stature and limb shortening, including the following:

- Isolated Peters' anomaly (OMIM 604229), which can be inherited in an autosomal dominant or autosomal recessive manner or can occur in simplex cases (i.e., a single occurrence in a family) in which the mode of inheritance is unknown. It has been reported in association with mutation of the following genes: *CYP1B1*, *FOXC1*, *PAX6*, *FOXE3*, *NDP*, *SLC4A11*, *HCCS*, *PITX2*, and *PITX3*.
- Cornelia de Lange syndrome
- Smith-Lemli-Opitz syndrome
- Autosomal dominant Robinow syndrome
- *ROR2*-related Robinow syndrome
- Fetal alcohol syndrome (FAS). FAS can also be associated with similar facial features and anterior chamber eye anomalies, including Peters' anomaly.
- Rieger syndrome (OMIM 180500)
- SHORT syndrome (*s*hort stature, *h*yperextensibility, *h*ernia, *o*cular depression, *R*ieger anomaly, *t*eething delay)
- Walker-Warburg syndrome
- Chromosome imbalances such as a 6p25 microdeletion [Maclean et al 2005] and 8q21.11 microdeletion [Happ et al 2016]
- Associated with variants in mendelian acting genes such as *FLNA* and *TFAP2A* [Weh et al 2014]

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with Peters plus syndrome, the following evaluations are recommended if they have not already been completed:

- Complete ophthalmologic assessment including ocular ultrasonography for characterization of the eye anomaly and an assessment for associated ocular defects
- Growth hormone stimulation testing to address the possibility of a treatable cause of growth delay in those affected individuals in whom increased height would improve quality of life
- For neonates or infants, referral to an infant development program for appropriate developmental assessment
- Echocardiography for congenital heart malformations
- Abdominal ultrasound examination for renal anomalies

- Cranial imaging with head ultrasound examination or CT scan/MRI for hydrocephalus and/or structural brain abnormalities if neurologic symptoms are present
- Thyroid function testing in all infants who have not undergone newborn screening for congenital hypothyroidism
- Hearing assessment in a child with cleft palate or speech delay
- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

Eye. Potential preservation of vision in the affected eye(s) often requires surgery. For severe bilateral corneal opacification consideration of corneal transplantation (penetrating keratoplasty) is suggested before age three to six months to prevent amblyopia; in mild cases simple separation of iridocorneal adhesions may suffice [Traboulsi 2006]. A retrospective review of long-term outcome following penetrating keratoplasty before age 18 months in type I Peters' anomaly revealed a visual acuity of 20/400 or better in two thirds of treated persons, and no individuals with phthisis bulbi or visual acuity reduced to light perception only [Zaidman et al 2007]. However, a much poorer outcome with visual acuity in the better eye being ≤0.05 in half of the patients with Peters anomaly has been reported [Reichl et al 2018]. No results of similar studies in a large series of individuals with Peters plus syndrome are available.

Management of amblyopia by a pediatric ophthalmologist is recommended for optimal visual outcome.

Congenital glaucoma in association with Peters' anomaly is more difficult to treat than primary infantile glaucoma. Surgery and medical management result in adequate intraocular pressure in only 32%, and associated ophthalmologic issues such as amblyopia or postoperative complications contribute to poor visual results in long-term outcome studies [Yang et al 2004].

Development. Children diagnosed as neonates or infants should be referred to an infant development program for appropriate developmental interventions.

Other. Additional management is symptomatic and expectant.

Surveillance

The following are appropriate:

- Assessment by a pediatric ophthalmologist every three months or as indicated to monitor for glaucoma and amblyopia
- Regular developmental assessments

Agents/Circumstances to Avoid

Agents that increase risk of glaucoma (e.g., corticosteroids) are to be avoided.

Evaluation of Relatives at Risk

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

Therapies Under Investigation

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

Genetic Counseling

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

Mode of Inheritance

Peters plus syndrome is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected child are obligate heterozygotes (i.e., carriers of one *B3GLCT* pathogenic variant).
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.

  There is an increased chance for miscarriages and second- and third-trimester fetal loss of affected fetuses. Therefore, at birth the risk to a sib of a proband of being affected is less than 25%.

- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. The offspring of an individual with Peters plus syndrome are obligate heterozygotes (carriers) for a *B3GLCT* pathogenic variant.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of a *B3GLCT* pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *B3GLCT* pathogenic variants in the family.

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk, clarification of carrier status, 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 young adults who are affected, are carriers, or are at risk of being carriers.

Prenatal Testing and Preimplantation Genetic Testing

Once the *B3GLCT* pathogenic variants have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for Peters plus syndrome are possible.

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.

- **American Cleft Palate-Craniofacial Association**
  Phone: 919-933-9044
  acpa-cpf.org
- **Foundation Fighting Blindness**
  7168 Columbia Gateway Drive
  Suite 100
  Columbia MD 21046
  Phone: 800-683-5555 (toll-free); 800-683-5551 (toll-free TDD); 410-423-0600
  Email: info@fightblindness.org
  www.fightingblindness.org
- **MAGIC Foundation**
  Phone: 800-362-4423
  Email: contactus@magicfoundation.org
  www.magicfoundation.org
- **National Eye Institute**
  Phone: 301-496-5248
  Email: 2020@nei.nih.gov
  Low Vision
- **Orphanet Directory of Patient Organisations**
  Peters plus syndrome

Molecular Genetics

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

Table A. Peters Plus Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
B3GLCT	13q12.3	Beta-1,3-glucosyltransferase	Beta 1, 3-GALactosylTransferase-Like (B3GALTL) @ LOVD	B3GLCT	B3GLCT

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 Peters Plus Syndrome (View All in OMIM)

261540	PETERS-PLUS SYNDROME; PTRPLS
610308	BETA-3-GLUCOSYLTRANSFERASE; B3GLCT

Gene structure. *B3GLCT,* the β1,3-galactosyltransferase-like gene, contains 15 exons and covers 132 kb. It is expressed in a broad range of human tissues, with tissue-specific regulation. At least two transcripts of 4.2 kb and 3.4 kb are produced [Heinonen et al 2003]. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. To date, 21 different pathogenic variants have been reported (see also Table A, **Locus Specific**); eight of these are splice site variants, including the c.660+1G>A single-nucleotide variant (the most frequently identified variant in persons with Peters plus syndrome). In addition, four deletions, two frameshift variants, three nonsense variants, and four missense variants located in the putative catalytic domain are known.

Table 2. *B3GLCT* Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.347+5G>A	—	NM_194318.3 NP_919299.3
c.660+1G>A	—	
c.1098T>A	p.Tyr366Ter	

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.

Normal gene product. *B3GLCT* encodes B3GLCT (also referred to as β3Glc-T), a 498-amino acid-containing transmembrane protein. It has a short N-terminal tail, a transmembrane region, a "stem" region, and a C-terminal catalytic domain. B3GLCT functions as a glycosyltransferase in a specific O-glycosylation step. It contributes to the elongation of O-fucosylglycan, specifically on TSR (thrombospondin type repeat) domains; i.e., it adds a glucose in a β1,3 linkage to a fucose in TSR [Kozma et al 2006, Sato et al 2006]. The human genome encodes approximately 100 TSR-containing proteins that perform a variety of important biologic functions, including regulation of the coagulation system and cell and axon guidance.

Abnormal gene product. Biallelic pathogenic loss-of-function variants in *B3GLCT* are associated with Peters plus syndrome. All pathogenic variants identified to date are expected to reduce or abolish the function of the protein.

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Chapter Notes

Author History

Gudrun Aubertin, MD, MSc; Children's & Women's Health Centre of British Columbia (2007-2014)
Raoul C Hennekam, MD, PhD (2014-present)
Marjolein Kriek, MD, PhD; Leiden University Medical Center (2011-2014)
Saskia AJ Lesnik Oberstein, MD, PhD (2007-present)
Claudia AL Ruivenkamp, PhD (2017-present)
Martine van Belzen, PhD; Leiden University Medical Center (2014-2017)
Marjan M Weiss, MD, PhD; Leiden University Medical Center (2007-2011)

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