Cytochrome P450 Oxidoreductase Deficiency

Synonyms: POR Deficiency, PORD

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Summary

Clinical characteristics

Cytochrome P450 oxidoreductase deficiency (PORD) is a disorder of steroidogenesis with a broad phenotypic spectrum including cortisol deficiency, altered sex steroid synthesis, disorders of sex development (DSD), and skeletal malformations of the Antley-Bixler syndrome (ABS) phenotype. Cortisol deficiency is usually partial, with some baseline cortisol production but failure to mount an adequate cortisol response in stress. Mild mineralocorticoid excess can be present and causes arterial hypertension, usually presenting in young adulthood. Manifestations of altered sex steroid synthesis include ambiguous genitalia/DSD in both males and females, large ovarian cysts in females, poor masculinization and delayed puberty in males, and maternal virilization during pregnancy with an affected fetus. Skeletal malformations can manifest as craniosynostosis, mid-face retrusion with proptosis and choanal stenosis or atresia, low-set dysplastic ears with stenotic external auditory canals, hydrocephalus, radiohumeral synostosis, neonatal fractures, congenital bowing of the long bones, joint contractures, arachnodactyly, and clubfeet; other anomalies observed include urinary tract anomalies (renal pelvic dilatation, vesicoureteral reflux). Cognitive impairment is of minor concern and likely associated with the severity of malformations; studies of developmental outcomes are lacking.

Diagnosis/testing

The diagnosis of PORD can be established by urinary steroid profiling using gas chromatography / mass spectrometry (GC/MS), which documents combined impairment of 17α-hydroxylase (CYP17A1) and 21-hydroxylase (CYP21A2) enzymatic activity located at key branch points of cortisol, aldosterone, and sex steroid synthesis. Identification of biallelic *POR* pathogenic variants on molecular genetic testing confirms the diagnosis. Molecular genetic testing is desirable for all individuals affected by PORD to confirm the diagnosis, but is mandatory if clinical and laboratory features are inconclusive.

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Management

Treatment of manifestations: Glucocorticoid replacement therapy for cortisol deficiency including stress-dose cover in intercurrent illness; surgery as needed for craniosynostosis, hypospadias, and cryptorchidism in males and clitoromegaly and vaginal hypoplasia in females; dihydrotestosterone treatment has been successful in some males with micropenis; testosterone replacement in males in whom testosterone levels remain relatively low after onset of puberty; females with absent pubertal development may require estrogen replacement therapy; treatment with estradiol to reduce the size of ovarian cysts; endotracheal intubation, nasal stints or tracheotomy, and tracheostomy as needed; physical and occupational therapy for joint contractures and help with fine and gross motor skills.

Prevention of secondary complications: Supplementation with appropriate steroid hormones in individuals who are deficient has helped alleviate adrenal crisis, lack of or poor pubertal development in males and females, sleepiness, and fatigue. Early intervention services may improve the outcome for individuals at risk for developmental delays and learning difficulties.

Surveillance: Evaluations with a specialist tertiary pediatric endocrine service throughout childhood to closely monitor development and adjust steroid supplementation. Periodic formal developmental assessments in centers with expertise and experience in developmental testing.

Evaluation of relatives at risk: It is appropriate to evaluate apparently asymptomatic older and younger sibs of a proband in order to identify as early as possible those who would benefit from initiation of treatment and preventive measures.

Genetic counseling

PORD is inherited in an autosomal recessive manner. 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. Carrier testing for at-risk family members and prenatal genetic testing for pregnancies at increased risk are possible if the *POR* pathogenic variants have been identified in the family. In addition, noninvasive testing of maternal urine steroid excretion by GC/MS can indicate whether the unborn child is affected by PORD from gestational week 12 onwards.

GeneReview Scope

Cytochrome P450 Oxidoreductase Deficiency: Included Phenotypes [1]
• Antley-Bixler syndrome • Congenital adrenal hyperplasia due to apparent combined CYP17A1 and CYP21A2 enzymatic deficiency

For synonyms and outdated names see Nomenclature.
1. For other genetic causes of these phenotypes see Differential Diagnosis.

Diagnosis

Suggestive Findings

Cytochrome P450 oxidoreductase deficiency (PORD) is an autosomal recessive disorder with a broad phenotypic spectrum including skeletal malformations resembling the Antley-Bixler syndrome (ABS) phenotype and abnormalities in adrenal steroid biosynthesis resulting in congenital adrenal hyperplasia (CAH).

Clinical Findings

Skeletal abnormalities. PORD **should be suspected** in individuals with features of ABS. Affected individuals may present with the following congenital craniofacial and skeletal anomalies:

- Midface retrusion
- Craniosynostosis (i.e. brachycephaly or turricephaly)
- Hand and feet malformations (arachnodactyly, clinodactyly, camptodactyly, metacarpal and metatarsal synostoses, wrist deviation, rocker-bottom feet, talipes)
- Large joint synostosis, predominantly radiohumeral or radioulnar synostosis, in severely affected individuals. Other large joints (e.g., knees, ankles) can also be affected.
- Femoral bowing

Ambiguous genitalia at birth. The majority of individuals with PORD have disordered sex development (DSD) and present with ambiguous genitalia at birth. DSD can occur in both sexes:

- Females may present with masculinized genitalia (46,XX DSD; e.g., enlarged clitoris, labial fusion).
- Males can present undermasculinized (46,XY DSD; e.g., hypospadias, micropenis).

Laboratory Findings

Because POR is required for normal enzymatic function at various steps within the cholesterol and steroid synthesis pathways, individuals with PORD exhibit characteristic abnormalities in both sterol and steroid metabolism (see Figures 1, 2, and 3).

Serum steroid abnormalities

- **ACTH** plasma concentration is normal or elevated at baseline.
- **Cortisol** serum concentration is normal or low at baseline, and may not increase as expected following ACTH stimulation.
- **Pregnenolone, progesterone**, **17-OH pregnenolone**, and **17-OH progesterone** serum concentrations are often elevated at baseline and/or after ACTH stimulation.
- **Dehyroepiandrosterone (DHEA)**, **dehydroepiandrosterone sulfate (DHEAS)**, and **androstenedione** serum concentrations are normal or decreased before and/or after ACTH stimulation.
- **Androgen** serum concentration may be low and unresponsive to ACTH or hCG stimulation.

Urinary steroid anomalies detected by gas chromatography / mass spectrometry (GC/MS). Steroid abnormalities in individuals with PORD are consistent with attenuated activity of 21-hydroxylase (encoded by *CYP21A2*) and 17α-hydroxlyase/17,20 lyase activities (encoded by *CYP17A1*) [Krone et al 2012] and are characterized by:

- Increased concentration of pregnenediol (metabolite of pregnenolone) and pregnanediol (metabolite of progesterone);
- Significantly elevated ratio of metabolites associated with:
  - Deficiency of 17α-hydroxylase (5α-tetrahydrocorticosterone, tetrahydrocorticosterone, and 11-dehydro metabolites);
  - Deficiency of 21-hydroxylase (17α-hydroxypregnanolone, pregnanetriol, and pregnanetriolone).

Note: The term "apparent pregnene hydroxylation deficiency (APHD)" refers to individuals with this unique urinary steroid profile [Shackleton & Malunowicz 2003]. Despite sharing common characteristics, steroid profiles vary somewhat among affected individuals, presumably because of differences in how the various *POR* pathogenic variants affect different enzymatic reactions [Pandey et al 2007, Huang et al 2008, Dhir et al 2009, Miller et al 2009].

Evidence of steroid anomalies during pregnancy. Low or undetectable maternal serum unconjugated estriol (uE3) and/or failure of urinary E3 excretion to increase have been noted during pregnancies in which fetuses have PORD [Cragun et al 2004, Shackleton et al 2004]. Prenatal testing for PORD by maternal urinary steroid profiling (GC/MS) has been developed as a sensitive tool to establish the diagnosis in the fetus [Reisch et al 2013] (see Prenatal Testing and Preimplantation Genetic Testing).

Newborn screening for congenital adrenal hyperplasia. In some individuals with PORD, newborn screening for CAH may be positive with moderately elevated serum 17-OH progesterone [Fukami et al 2005]. However, newborn screening does not appear to be sensitive enough to detect all individuals with PORD.

Cholesterol abnormalities. Subtle sterol abnormalities consistent with a partial block in cholesterol synthesis at the level of CYP51 may be present (Figure 3) [Kelley et al 2002, Cragun et al 2004, Fukami et al 2005]. CYP51 catalyzes the conversion of lanosterol into principal intermediates of the distal portion of the cholesterol biosynthesis pathway. Although serum concentrations of cholesterol are grossly normal in individuals with ABS [Fukami et al 2005], lanosterol and dihydrolanosterol accumulate when cells from affected individuals are grown in cholesterol-depleted medium. Sterol profiling of amniotic fluid in an affected pregnancy may reveal di- and trimethylated sterols, but this finding is not unique to PORD [Chevy et al 2005].

Establishing the Diagnosis

The diagnosis of PORD **is established** in a proband with the characteristic urinary steroid profile:

- Increased concentration of metabolites of pregnenolone (pregnenediol) and progesterone (pregnanediol)
- Significantly elevated metabolites associated with:
  - Deficiency of 17α-hydroxylase (5α-tetrahydrocorticosterone, tetrahydrocorticosterone, and 11 dehydrometabolites)
  - Deficiency of 21-hydroxylase (17α-hydroxypregnanolone, pregnanetriol, and pregnanetriolone)

Identification of biallelic pathogenic (or likely pathogenic) variants in *POR* on molecular genetic testing confirms the diagnosis (see Table 1). Molecular genetic testing is desirable for all individuals affected by PORD to confirm the diagnosis, but mandatory if clinical and laboratory features are inconclusive.

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

Molecular testing approaches can include **single-gene testing**, use of a **multigene panel**, and **more comprehensive genomic testing**:

- **Single-gene testing.** Sequence analysis of *POR* 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 *POR* 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
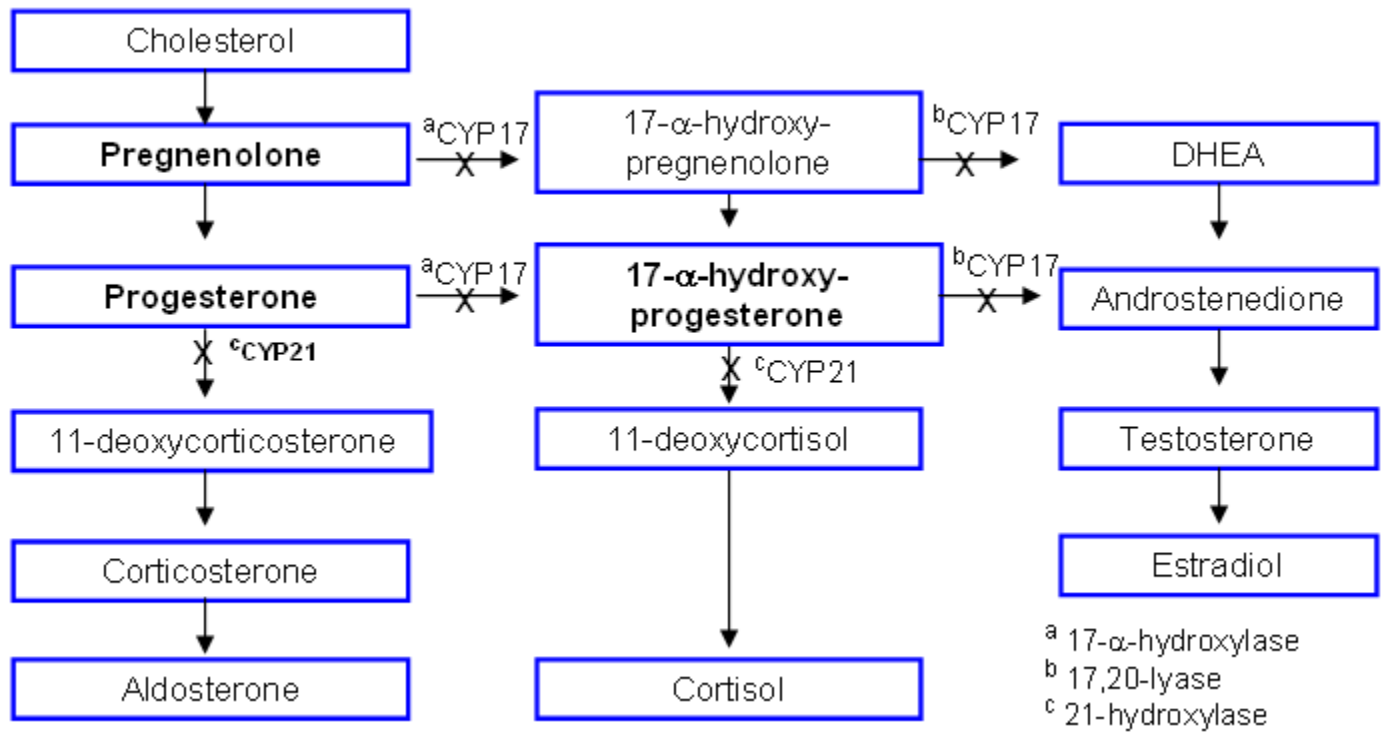
Figure 1. Steroid synthesis

Principal intermediates of steroidogenesis illustrating the location of multiple partial biochemical blocks at steps that rely on cytochrome p450 oxidoreductase. These partial blocks lead to increased serum pregnenolone, progesterone, and 17-alpha-OH-progesterone.

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, mitochondrial 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.
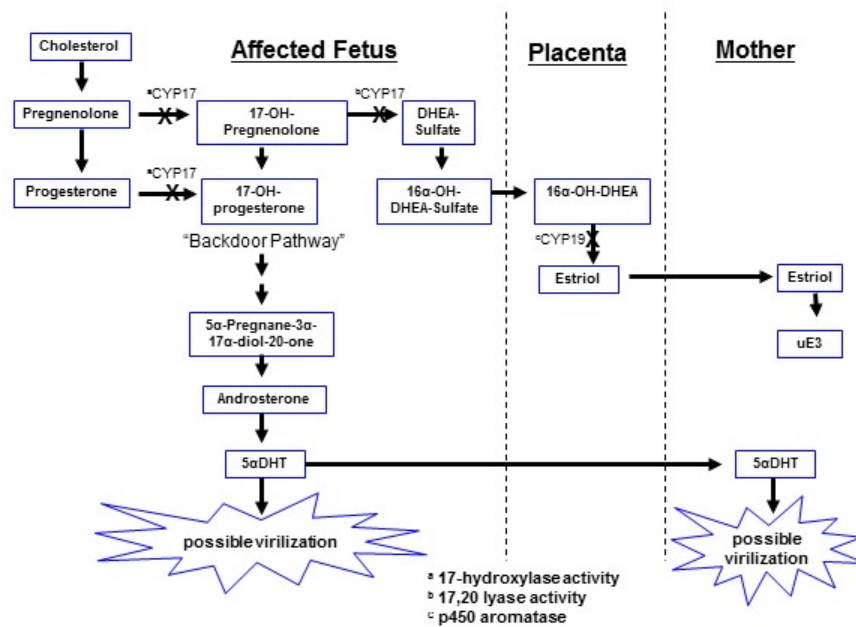
Figure 2. Steroid anomalies and pregnancy

Partial blockages, which occur at each step catalyzed by cytochrome p450 (CYP) dependent enzymes, presumably explain the finding of low maternal serum unconjugated estriol (uE3) during pregnancies with an affected fetus. Impaired aromatization of fetal androgens may also help explain why some mothers experience maternal virilization during pregnancy with an affected fetus. Impaired aromatization of fetal androgens may also contribute to the virilization of affected female infants. The proposed alternative (or "backdoor") pathway of androgen synthesis, which is believed to be active only during fetal life, is also illustrated. This alternative pathway has been proposed as an explanation for ambiguous genitalia present in some affected females. Note: It is unknown if low maternal serum concentration of uE3 is a consistent finding among all individuals with cytochrome P450 oxidoreductase deficiency.
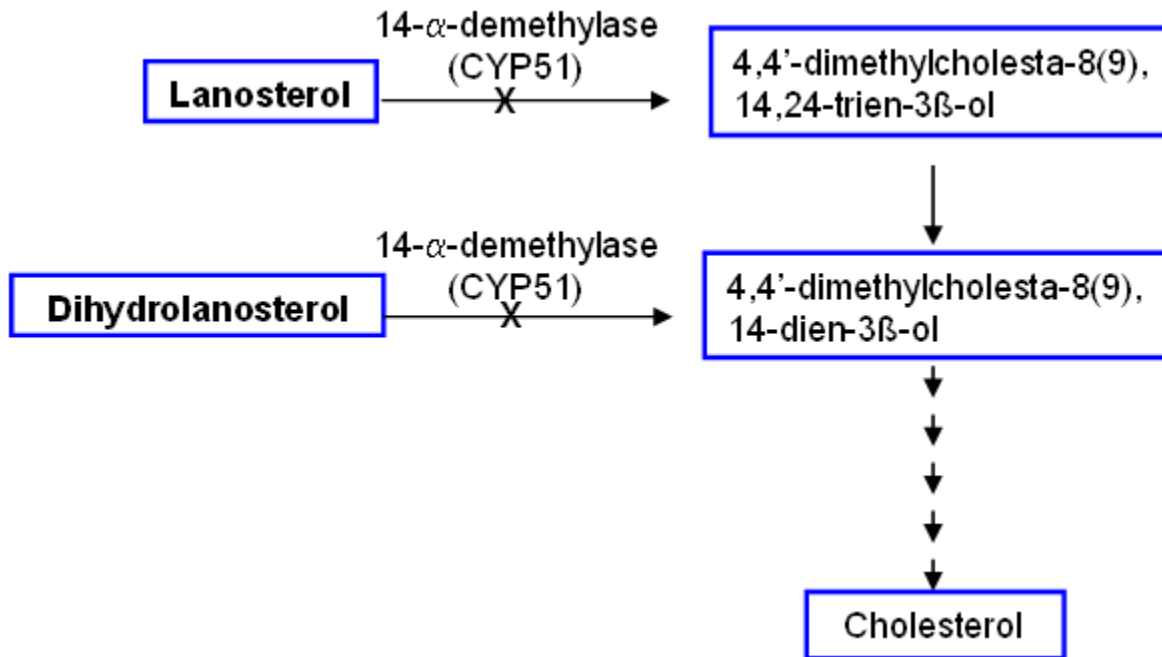
Figure 3. Cholesterol synthesis pathway (distal portion)

Evidence for a partial biochemical block in sterol synthesis at the level of 14- α-demethylase comes from the finding of significantly increased levels of lanosterol and dihydrolanosterol when lymphoblasts are grown in the absence of cholesterol [Kelley et al 2002, Cragun et al 2004, Fukami et al 2005].

Table 1. Molecular Genetic Testing Used in Cytochrome P450 Oxidoreductase Deficiency

Gene [1]	Method	Proportion of Probands with Pathogenic Variants [2] Detectable by Method
POR	Sequence analysis [3]	92% [4]
	Gene-targeted deletion/duplication analysis [5]	2.5% [4]
Unknown [6]	NA	5.5%

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. The results of *POR* molecular genetic testing in 140 individuals with PORD have been reported (see Molecular Genetics). Homozygous or compound heterozygous pathogenic variants were detected by sequence analysis of *POR* in 266 alleles. In seven individuals, a large deletion or insertion was detected on one allele by gene-targeted deletion/duplication analysis [Soneda et al 2011, Krone et al 2012].
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. Affected individuals have been reported with a single pathogenic variant and nearly complete absence of mRNA made from the allele in which no pathogenic variant was found [Fukami et al 2009]. Also reported: a pathogenic variant in a different gene involved in steroidogenesis: a female with a single *POR* pathogenic variant in addition to pathogenic variants in both copies of *CYP21* [Scott et al 2007]; and, as part of a larger PORD cohort, three individuals (5 alleles) in whom a pathogenic sequence variant could not be found following direct sequencing and MLPA [Krone et al 2012].

Clinical Characteristics

Clinical Description

The natural history of cytochrome P450 oxidoreductase deficiency (PORD) varies because it encompasses a wide phenotypic spectrum. However, steroid abnormalities, which occur in all individuals with PORD, can be associated with a number of characteristics.

The summary of clinical characteristics is based on 26 studies on 140 individuals with molecularly confirmed PORD published to date (June 2017).

Cortisol deficiency found in PORD varies, but is present in the majority of individuals.

Based on ACTH stimulation tests, Krone et al [2012] reported severe cortisol deficiency (requiring permanent hydrocortisone replacement) in 43% of individuals, and partial cortisol deficiency (requiring glucocorticoid replacement during stress only) in 40%; no replacement was required in 10% of the cohort.

Mineralocorticoid excess due to inhibition of 17α-hydroxylase activity can result in hypertension, which typically manifests in young adulthood.

Disorders of sex development (DSD) occur in approximately 75% of individuals with molecularly confirmed PORD. DSD can occur in both sexes: 46,XY DSD (e.g., small penis, undescended testes) and 46,XX DSD (e.g., enlarged clitoris, fused and hypoplastic labia). The unusual finding that both sexes can present with DSD (e.g., virilized genitalia in 46,XX and undermasculinized genitalia in 46,XY) was suggested to be caused by the presence of an alternative pathway to dihydrotestosterone [Arlt et al 2004] (see Molecular Genetics). The manifestation of DSD is related to genotype, with some pathogenic variants leading to normal male virilization and 46,XX DSD in girls while other pathogenic variants result in normal female genital appearance and 46,XY DSD in boys (see Genotype-Phenotype Correlations).

Primary amenorrhea was the presenting feature in at least one woman with PORD (milder phenotype) [Scott et al 2007].

Large ovarian cysts with a tendency to spontaneous rupture are present in a number of adolescent and adult females with PORD [Scott et al 2007, Fukami et al 2009, Idkowiak et al 2011].

Poor masculinization and delayed puberty have been reported in some males, but spontaneous progression during puberty has also been observed [Fukami et al 2005, Hershkovitz et al 2008, Idkowiak et al 2011]. Hypospermatogenesis was documented on testicular biopsy in a male with PORD [Fukami et al 2005].

Fertility may be a concern. No reports describe reproduction in individuals with PORD; thus, the prevalence of infertility among individuals with PORD remains uncertain.

Signs of maternal virilization during pregnancy with an affected fetus, including hirsutism, enlargement of the nose and lips, deepening of the voice, and acne, have been reported in women during pregnancies in which fetuses were later found to have PORD [Fukami et al 2009, Krone et al 2012, Reisch et al 2013].

Skeletal abnormalities of the Antley-Bixler syndrome (ABS) phenotype are frequently observed in individuals with PORD. The severity of malformations varies from mild to moderate and severe. Functional studies are currently lacking but individuals with milder skeletal features similar to those in classic ABS probably have moderate PORD. Those with mild PORD tend to have few if any notable physical characteristics. Krone et al have introduced a clinical scoring system rating the severity of the skeletal and craniofacial malformations in PORD (Table 2) [Krone et al 2012], which is useful for systematic assessment of malformations in PORD.

- **Skeletal malformations** occur in approximately 85% of individuals with molecularly confirmed PORD. Elbow ankylosis, often from radiohumeral synostosis, causes fixation of the elbow in a flexed position. Elbow extension may be restricted in the absence of radiohumeral synostosis. Neonatal fractures and congenital bowing of the long bones (especially the femurs) are common. Other common malformations of the limbs include long palms, camptodactyly, other joint contractures, arachnodactyly, clubfeet, irregularly positioned toes, and rocker-bottom feet. Vertebral and rib anomalies, hypoplasia of the scapula, scoliosis, and narrow chest and/or pelvis have been reported. Other skeletal anomalies reported in individuals with PORD include diastases of the radioulnar joint, ulnar deviation of the wrists, marfanoid habitus, flattened metacarpal epiphyses, cubitus valgus, brachymetacarpia, and brachytelephalangy.
- **Craniofacial anomalies.** Craniosynostosis is usually severe and most commonly involves the coronal and lambdoid sutures, resulting in turricephaly; synostosis of other cranial sutures has also been reported. Other craniofacial anomalies include frontal bossing, enlarged anterior fontanelle, severe midface retrusion, choanal stenosis or atresia, short bulbous nose, depressed nasal bridge, narrow mouth, high arched narrow palate, and dysplastic ears that may be low-set with stenotic external auditory canals. In milder forms, the craniofacial features – if present – may not be as easily identified at birth and/or tend to be less severe than those in individuals with severe disease. Although craniosynostosis and/or brachycephaly may be observed, surgical treatment may not require as many procedures. Individuals may have conductive hearing loss.
- **Hydrocephalus** requiring ventriculoperitoneal shunt insertion has been reported in a number of affected individuals [Krone et al 2012].

Table 2. PORD Skeletal Malformation Scoring System Classifying the Major Features of the Antley-Bixler Syndrome Phenotype

Score	Midface Hypoplasia	Craniosynostosis	Hand & Feet Malformations	Large-Joint Synostosis	Femoral Bowing	Additional Malformations
0	None	None	None	None	None	None
1	Mild (low-set ears, pear-shaped nose)	Mild (1 suture affected, e.g. brachycephaly)	1 hand/feet malformation	Extension deficit	Present	1
2	Severe (compressed midface skeletal structure, proptosis)	Severe (≥2 sutures affected, e.g. turricephaly)	2 hand/feet malformations	Fixed synostosis, joint contractures of 1 large joint	Complicated by neonatal fractures	≥2
3	Complicated by choanal stenosis/ atresia	Complicated by hydrocephalus, w/VP-shunt requirement	≥3 hand/feet malformations	Fixed synostosis, joint contractures of several large joints	-	-

Proposed in Krone et al [2012]
The maximum score is 16. A score of 1-4 has been proposed as "mild," 5-8 as "moderate," and >9 as "severe."
VP = ventriculoperitoneal

Associated anomalies, presumably not related to the disruption of sterol or steroid synthesis, are rare in individuals with PORD. These include urinary tract anomalies including several individuals with renal pelvic dilatation and vesicoureteral reflux [Krone et al 2012, Bonamichi et al 2016] and one individual with unilateral renal agenesis [Krone et al 2012]. Gastrointestinal conditions are reported in one individual with PORD who developed severe gastroesophageal reflux and constipation [Williamson et al 2006] and another individual with an anteriorly placed anus [Krone et al 2012]. Other observations include a two vessel umbilical cord in two individuals with PORD; Arnold-Chiari malformation and a frontal capillary hemangioma have each been reported in one individual [Krone et al 2012].

Cognitive function and development. There is a paucity of data on cognitive function and developmental outcomes in individuals with PORD. Developmental delays have been reported in a number of children with PORD, mainly delayed speech and language development and fine motor skills, presumably secondary to conductive hearing loss, skeletal abnormalities, multiple surgical procedures with anesthesia, and prolonged hospitalization with immobility [Williamson et al 2006, Sahakitrungruang et al 2009]. Early and effective management of upper airway obstruction, craniosynostosis, hydrocephalus, and hearing loss appear to be a prerequisite for good cognitive development.

Prognosis is primarily determined by the severity of the skeletal and craniofacial malformations. Stillbirth has been reported in infants with very severe skeletal malformations [Krone et al 2012, Reisch et al 2013]. In individuals with mild to moderate clinical features, the prognosis is guarded in infancy and improves with age. Early death caused by respiratory complications is a concern. However, with careful airway management, many children with ABS survive and the prognosis may be reasonably good. Prospective follow-up studies describing the natural course of PORD are currently lacking.

Genotype-Phenotype Correlations

While individuals with the same pathogenic variants (even sibs) can show phenotypic variations, some commonalities are observed among individuals with the same genotype. The broad phenotypic spectrum of PORD may be caused by the effect of various *POR* pathogenic variants on different enzymatic reactions [Huang et al 2005, Dhir et al 2007, Pandey et al 2007, Huang et al 2008, Burkhard et al 2017].

Three studies report the investigation of genotype-phenotype correlations in larger cohorts of individuals with PORD [Huang et al 2005, Fukami et al 2009, Krone et al 2012]. The observations from these studies include the following.

Skeletal malformations

- The overall reported frequency of skeletal malformations in genetically confirmed PORD is about 85%.
- Homozygotes for p.Arg457His tend to have less severe skeletal abnormalities.
- Compound heterozygosity for p.Arg457His and a severe loss-of-function pathogenic variant on the other allele is associated with a more severe skeletal phenotype.
- Homozygotes for p.Ala287Pro have moderate skeletal malformations.
- Compound heterozygosity for p.Ala287Pro and a severe loss-of-function pathogenic variant on the other allele is associated with a severe skeletal phenotype.

Disorders of sex development (DSD). Homozygosity for either pathogenic variant p.Arg457His or p.Ala287Pro causes 46,XX DSD (virilized females at birth) but undermasculinization occurs less frequently in 46,XY individuals.

Adrenal steroid biosynthesis

- An abnormal urinary steroid pattern has been found in **all** persons with genetically confirmed PORD investigated; however, not all reported patients have had a urinary steroid profile as part of their work-up.
- Adrenal insufficiency is present in most persons with PORD: based on ACTH stimulation tests, Krone et al [2012] reported hydrocortisone replacement in 43%, stress dose cover only in 40%, and no replacement in 10% of his cohort; Fukami et al [2009] found the prevalence of adrenal crisis was increased in individuals with pathogenic variant p.Arg457His combined with a severe loss-of-function pathogenic variant.
- However, a prediction of the overall severity of glucocorticoid deficiency based on genotype is not possible.

Nomenclature

Peterson et al [1985] first reported a male with ambiguous genitalia and apparent combined partial 21-hydroxylase (P450c21, CYP21A2) deficiency and partial 17-hydroxylase (P450c17, CYP17A1) deficiency, and referred to this condition as "mixed oxidase disease" [Peterson et al 1985]. This condition, also known as congenital adrenal hyperplasia due to apparent combined CYP21A1 and CYP17A1 deficiency, has been shown to be caused by biallelic *POR* pathogenic variants [Arlt et al 2004, Flück et al 2004].

Prevalence

The prevalence of PORD has yet to be determined, however it is a very rare condition. Since *POR* pathogenic variants were first reported in 2004, approximately 140 individuals with PORD have been reported in the literature (June 2017).

The most prevalent pathogenic variant in individuals with PORD of Japanese ancestry is p.Arg457His. In individuals of European background with PORD, p.Ala287Pro is the most prevalent pathogenic variant.

Genetically Related (Allelic) Disorders

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

Differential Diagnosis

Congenital adrenal hyperplasia (CAH) is a heterogeneous group of autosomal recessive conditions that result in impaired synthesis of cortisol, mineralocorticoids, and/or sex steroids. Based on this definition, the term CAH can be used to describe cytochrome P450 oxidoreductase deficiency (PORD). PORD and the following etiologies of CAH may be distinguished by differences in urinary steroid profiles, molecular genetic testing, and/or the presence of skeletal anomalies, as skeletal anomalies are never found in other forms of CAH, but may occur in PORD. POR acts as an electron donor to two major steroidogenic enzymes, CYP21A2 and CYP17A1. Therefore, individuals with POR show biochemical features of both 21-hydroxylase and 17α-hydroxylase deficiency.

- **21-hydroxylase deficiency (21-OHD, CYP21A2 deficiency),** the most common form of CAH, is associated with glucocorticoid and, in most cases, mineralocorticoid deficiency as well as with sex steroid excess resulting in masculinization of the external genitalia in females (46,XX DSD). Unlike PORD, 21-OHD is characterized by increased circulating androgens and progressive virilization of females after birth.
- **17α-hydroxylase/17,20-lyase deficiency (CYP17A1 deficiency)** (OMIM 202110) is associated with mineralocorticoid excess, glucocorticoid deficiency and sex steroid deficiency, which is clinically associated with ambiguous genitalia in males (46,XY DSD) and lack of pubertal progression in both sexes. Milder pathogenic variants on the other end of a broad phenotypic spectrum might affect sex steroid production only ("isolated 17,20-lyase deficiency").
- **11β-hydroxylase deficiency** (OMIM 202010) is associated with glucocorticoid deficiency but excess of both mineralocorticoids and sex steroids – therefore, with hypertension and ambiguous genitalia in females (46,XX DSD).
- **3β-hydroxysteroid dehydrogenase deficiency** (OMIM 201810) is associated with glucocorticoid and mineralocorticoid deficiency and leads to ambiguous genitalia in males (46,XY DSD), but in rare cases also in females (46,XX DSD).

Antley-Bixler syndrome (ABS) without genital anomalies or disordered steroidogenesis (OMIM 207410) is characterized by the skeletal features of ABS including craniosynostosis, radioulnar and radiohumeral

synostosis, midface hypoplasia with narrowing of the upper airway, frontal bossing, arachnodactyly and camptodactyly, femoral bowing, irregular positioned toes, and rocker-bottom feet. Pathogenic variants in *FGFR2* are causative. Inheritance is autosomal dominant.

Autosomal dominant craniosynostosis syndromes. Craniosynostosis occurs in the autosomal dominant *FGFR*-related craniosynostosis syndromes that include Pfeiffer syndrome, Crouzon syndrome, Jackson-Weiss syndrome, Apert syndrome, and Beare-Stevenson syndrome (see FGFR-Related Craniosynostosis).

- **Pfeiffer and Crouzon syndromes.** Some individuals with severe *FGFR*-related craniosynostosis have clinical features that overlap ABS. Individuals with *FGFR* pathogenic variants may have more severe proptosis compared to those with PORD. Although common in PORD, a short bulbous nose, low-set and dysplastic ears, arachnodactyly, and rocker-bottom feet are not usually described in *FGFR*-related craniosynostosis syndromes. In Pfeiffer syndrome, limb deformities are part of the spectrum (e.g., broad thumbs and toes, brachydactyly, tarsal fusion). *FGFR1* and *FGFR2* pathogenic variants are causative.
- **Apert syndrome** can usually be distinguished from ABS by the presence of the typical syndactyly. *FGFR2* pathogenic variants are causative.
- **Muenke syndrome** is caused by *FGFR3* pathogenic variant p.Pro250Arg. Muenke syndrome is characterized by uni-or bilateral synostosis of the coronal suture. Deformities of the hand and feet (e.g., broad toes, carpal/tarsal fusions) can be part of the spectrum.
- **Saethre-Chotzen syndrome** is characterized by uni-or bilateral coronal synostosis, facial asymmetry, ptosis, ear anomalies, and syndactyly in some individuals. Pathogenic variants of *TWIST1* are causative.

Cytochrome P450 26B1 (CYP26B1) deficiency (OMIM 614416) is characterized by craniosynostosis, oligodactyly, femoral bowing, radiohumeral synostosis, narrow thorax, and small pelvic bones [Laue et al 2011, Morton et al 2016]. The spectrum of severity in the small number of individuals reported has included perinatal lethal, early infant demise, and a milder phenotype in a female age 22 years, which resembled ABS and Pfeiffer syndrome [Morton et al 2016]. Individuals with cytochrome P450 26B1 deficiency are not reported to have features consistent with abnormal steroid metabolism. Biallelic *CYP26B1* pathogenic variants are causative.

Thanatophoric dysplasia. The combination of femoral bowing and craniosynostosis may be seen in thanatophoric dysplasia, but genital anomalies do not occur in this condition. Unlike ABS, thanatophoric dysplasia is characterized by severe rhizomelia. Brain malformations and severe intellectual disability are also universal features of thanatophoric dysplasia but are not reported as part of PORD [Wang et al 2014, Weaver et al 2014]. Thanatophoric dysplasia is caused by pathogenic variants in *FGFR3* and is inherited in an autosomal dominant manner; the majority of probands have a *de novo* pathogenic variant.

Shprintzen-Goldberg syndrome (SGS) overlaps with PORD skeletal malformations in that both can have camptodactyly, arachnodactyly, femoral bowing, craniosynostosis, and a marfanoid habitus. However, individuals with SGS do not have ambiguous genitalia or the distinctive facial features of PORD. SGS is associated with significant cognitive disability and brain malformations. At least two individuals with PORD without ABS-like malformations were originally classified as having SGS. Pathogenic variants in *SKI* are causative.

Bent-bone dysplasias, which include campomelic dysplasia, kyphomelic dysplasia (OMIM 211350), and Stüve-Wiedemann syndrome (OMIM 601559), are commonly associated with long-bone bowing, primarily of the femora. These conditions are distinguished from PORD by the lack of craniosynostosis or radiohumeral synostosis. Long-bone fractures occur in campomelic dysplasia, but usually after the neonatal period, whereas fractures in PORD usually occur during the neonatal period. Campomelic dysplasia is often associated with abnormal sexual development (e.g., hypospadias to phenotypic female with a 46,XY karyotype) and is caused by pathogenic variants in *SOX9*. Campomelic dysplasia is inherited in an autosomal dominant manner but is most commonly the result of a *de novo* pathogenic variant.

Osteogenesis imperfecta (OI; see *COLA1/2*-Related Osteogenesis Imperfecta) is associated with neonatal fractures, but lacks the characteristic craniofacial, limb, and urogenital anomalies of PORD. Unlike OI, PORD is not associated with osteoporosis or wormian bones.

Teratogen exposure. Early prenatal exposure to oral, high-dose fluconazole has resulted in an ABS-like phenotype in five reported individuals [Aleck & Bartley 1997, Lopez-Rangel & Van Allen 2005]. However, frontal bossing, choanal stenosis/atresia, genital abnormalities, and camptodactyly were not observed. Pregnancy history is important in identifying this exposure.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with PORD, the following evaluations are recommended:

- Evaluations by appropriate specialists in endocrinology, clinical genetics, neurosurgery, otolaryngology, and cardiology
- Assessment for airway problems in individuals with skeletal malformations
- Functional adrenal studies (cosyntropin test) to assess glucocorticoid deficiency, regardless of the presence or absence of genital abnormalities
- Additional studies that may be indicated:
  - Cranial CT scan and/or MRI to determine the degree of craniosynostosis, hydrocephaly, choanal stenosis, and orbital depth
  - Radiographs to identify long-bone fractures and/or bowing, bony synostoses, and/or joint contractures
  - Echocardiogram if a heart defect is suspected
  - Abdominal and pelvic ultrasound examination to identify internal sex organs, detect any renal anomalies, and detect and monitor ovarian cysts in adolescent girls.

Treatment of Manifestations

Cortisol deficiency

- Regular hydrocortisone replacement therapy is indicated if baseline serum cortisol concentrations are low.
- Stress-dose steroids should be provided perioperatively and during times of physiologic stress in individuals in whom cortisol response to ACTH stimulation (cosyntropin test) is below normal [Krone et al 2012].

Genital abnormalities

- Hypospadias and cryptorchidism may be corrected with surgery.
- When clitoromegaly is severe, surgical reduction and plastic reconstruction of the clitoris may be considered.
- Vaginal reconstruction may be performed in females with vaginal hypoplasia.
- Dihydrotestosterone treatment has been successful in some males with micropenis [Fukami et al 2005].
- Testosterone replacement has been initiated in males in whom testosterone levels remained relatively low after onset of puberty [Hershkovitz et al 2008, Idkowiak et al 2011]. Similarly, females with absent pubertal development may require estrogen replacement therapy.

Ovarian cysts. Treatment with estradiol appeared to successfully reduce the size of ovarian cysts in females with PORD [Fukami et al 2009, Idkowiak et al 2011]. Ovarian cysts in females can be a significant problem as they

tend to be large and prone to spontaneous rupture; cases of girls treated with GnRH agonists and potent steroids have been reported [Idkowiak et al 2011].

Craniosynostosis. Treatment for craniosynostosis is similar to that for other syndromes associated with premature fusion of cranial sutures. Although surgical correction can be performed at any age, it is generally believed that earlier surgical correction results in better cognitive outcome.

Airway management is often a primary concern in individuals with ABS as a result of choanal stenosis or atresia, small chest, narrow trachea, and/or shortening of the larynx.

- Endotracheal intubation is often required in the first minutes after delivery.
- Nasal stints or tracheotomy may be required.
- Tracheostomy may be necessary until age three to five years when the pharyngeal encroachment can be corrected.

Hydrocephalus. If present, hydrocephalus may be treated by surgical placement of a ventriculoperitoneal shunt.

Joint contractures and elbow synostosis. Physical and occupational therapy can help individuals with contractures and elbow synostosis develop fine and gross motor skills.

Prevention of Secondary Complications

Supplementation with appropriate steroid hormones in individuals who are deficient has helped alleviate:

- Adrenal crisis
- Lack of or poor pubertal development in males and females
- Sleepiness and fatigue

Early intervention services may improve the outcome for individuals at risk for developmental delays and learning difficulties.

Surveillance

Individuals with PORD should be seen by a specialist tertiary pediatric endocrine service throughout childhood to closely monitor their development and adjust steroid supplementation.

Because of the presence of developmental delays in many individuals with ABS, periodic formal developmental assessments may be indicated. However, interpretation of these assessments may be complicated by the physical limitations of the disorder. Screening evaluations are likely to underestimate cognitive abilities. Therefore, evaluations should be done in centers with expertise and experience in developmental testing.

Evaluation of Relatives at Risk

It is appropriate to evaluate apparently asymptomatic older and younger sibs of a proband in order to identify as early as possible those who would benefit from initiation of treatment and preventive measures. Evaluations can include:

- Molecular genetic testing if the pathogenic variants in the family are known;
- Urinary steroid profiling using gas chromatography / mass spectrometry (GC/MS) can be done if the pathogenic variants in the family are not known. The characteristic urinary steroid profile:
  - Increased coancentration of metabolites of pregnenolone (pregnenediol) and progesterone (pregnanediol)
  - Significantly elevated metabolites associated with:

- Deficiency of 17α-hydroxylase (5α-tetrahydrocorticosterone, tetrahydrocorticosterone, and 11 dehydrometabolites)
- Deficiency of 21-hydroxylase (17α-hydroxypregnanolone, pregnanetriol, and pregnanetriolone)

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

Pregnancy Management

Fertility may be a concern. No reports describe reproduction in individuals with PORD; thus, the prevalence of infertility among individuals with PORD remains uncertain.

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.

Other

Hepatic drug metabolism. NADPH--cytochrome P450 reductase (POR) plays an important role in the metabolism of various drugs and endogenous metabolites/hormones by hepatic microsomal (type 2) P450 cytochromes. Initial studies using bacterially expressed *POR* pathogenic variants and two hepatic P450 enzymes suggest that pathogenic variants in *POR* may alter drug metabolism [Miller et al 2009]. In these studies different pathogenic variants resulted in different effects, ranging from no apparent activity to elevated activity of the hepatic P450 enzymes; these activities were not correlated with their activity in CYP17A1 assays.

In vitro activity assays on major drug-metabolizing enzymes and in vivo investigations to assess the impact of various pathogenic and non-pathogenic variants of *POR* have been performed by various groups [Agrawal et al 2008, Hart & Zhong 2008, Kranendonk et al 2008, Gomes et al 2009, Oneda et al 2009, Agrawal et al 2010, Flück et al 2010, Tomalik-Scharte et al 2010]. For comprehensive reviews on the pharmacogenetics of POR see Pandey & Sproll [2014] and Burkhard et al [2017].

In brief, the different pathogenic variations have different effects on microsomal P450 drug metabolizing enzymes. The common pathogenic variant p.Ala287Pro reduces the activity of the major P450 cytochrome CYP3A4 (which metabolizes ~50% of clinically used drugs) by more than 75% [Nicolo et al 2010]. In vivo cocktail phenotyping in an individual homozygous for the p.Ala287Pro pathogenic variant confirmed altered hepatic detoxification of a variety of drugs due to impaired activity of various hepatic CYP enzymes, including CYP3A4, CYP1A1, CYP2C9, and CYP2D6; the heterozygous mother of this individual also showed impaired activities of CYP1A1 and CYP2C9 [Tomalik-Scharte et al 2010]. In addition, in vitro assays suggest that some variants cause a substrate-specific modulation of CYP3A4 [Agrawal et al 2010].

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

Cytochrome P450 oxidoreductase deficiency (PORD) 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 *POR* pathogenic variant).
- Heterozygotes (carriers) are typically asymptomatic but may have altered hepatic drug metabolism [Tomalik-Scharte et al 2010] (see Management, Other).

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.
- Heterozygotes (carriers) are typically asymptomatic but may have altered hepatic drug metabolism [Tomalik-Scharte et al 2010] (see Management, Other).

Offspring of a proband. The offspring of an individual with PORD would be obligate heterozygotes (carriers) for a pathogenic variant in *POR*. However, no reports describe reproduction in individuals with PORD.

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

Carrier (Heterozygote) Detection

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

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

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 carriers or are at risk of being carriers.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

Maternal serum screening. Low or undetectable levels of maternal serum unconjugated estriol (uE3) have been noted in women carrying a fetus with PORD. Low uE3, however, is not specific and frequently found in other conditions affecting steroid and sterol synthesis, such as Smith-Lemli-Opitz syndrome, STS deficiency, aromatase deficiency, and some forms of severe congenital adrenal hypoplasia.

Maternal urine steroid profiling. PORD can be established by urinary steroid profiling by gas chromatography / mass spectrometry (GC/MS) [Reisch et al 2013]: a distinctive abnormal und uniform steroid profile was observed from week 12 onwards in a prospective study of genetically confirmed fetuses/babies with PORD. Maternal urine shows elevated levels of the pregnenolone metabolite epiallopregnanediol and androgen metabolites of fetal origin with low levels of estriol.

Fetal ultrasound examination. Prenatal diagnosis of PORD by mid-trimester ultrasound examination is possible and would detect skeletal malformations in severely affected fetuses. Fixed flexion of the elbows is an important finding; other supportive findings include bowing of the long bones, midface retrusion, depressed nasal bridge, brachycephaly, and rocker-bottom feet. Individuals with less severe features are unlikely to be identified on ultrasound examination: in a cohort of 20 pregnancies examined, 19 had overt malformations at birth but only five had detectable malformations with fetal ultrasound; the detection of fetal malformations on antenatal ultrasound predicts a very severe phenotype [Reisch et al 2013].

Molecular genetic testing. Once the *POR* pathogenic variants have been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. 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.

- **Congenital Adrenal Hyperplasia Research, Education and Support (CARES) Foundation**
  2414 Morris Ave
  Suite 110
  Union NJ 07083
  Phone: 866-227-3737
  Email: contact@caresfoundation.org
  www.caresfoundation.org

- **Living with CAH**
  CLIMB Congenital Adrenal Hyperplasia Support Group
  www.livingwithcah.com

- **Children's Craniofacial Association**
  Phone: 800-535-3643
  Email: contactCCA@ccakids.com
  www.ccakids.org

- **Face Equality International**
  United Kingdom
  faceequalityinternational.org

- **FACES: National Craniofacial Association**
  Phone: 800-332-2373; 423-266-1632
  Email: info@faces-cranio.org
  www.faces-cranio.org

- **National Institute of Neurological Disorders and Stroke (NINDS)**
  Phone: 800-352-9424
  Craniosynostosis

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. Cytochrome P450 Oxidoreductase Deficiency: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
POR	7q11.23	NADPH--cytochrome P450 reductase	POR database POR @ PharmVar	POR	POR

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 Cytochrome P450 Oxidoreductase Deficiency (View All in OMIM)

124015	CYTOCHROME P450 OXIDOREDUCTASE; POR
201750	ANTLEY-BIXLER SYNDROME WITH GENITAL ANOMALIES AND DISORDERED STEROIDOGENESIS; ABS1
613571	DISORDERED STEROIDOGENESIS DUE TO CYTOCHROME P450 OXIDOREDUCTASE DEFICIENCY

Molecular Pathogenesis

Gene structure. *POR* consists of 16 exons; exon 1 is a non-coding exon upstream of the translation initiation site (NM_000941.2). For a detailed summary of gene and protein information, see Table A, **Gene**.

Benign variants and population genetics. Huang et al [2008] sequenced *POR* in 842 healthy Americans from different ethnic backgrounds (northern European, African, Chinese, and Mexican). Some of the missense variants were associated with decreased catalytic activity during in vitro studies, however the majority maintained more than 40% of wild type activity in most in vitro assays employed. The most common benign sequence variant, NM_000941.2:c.1508C>T (p.Ala503Val), found in 20%-35% of the ethnic groups studied, showed decreased catalytic activity (50%-60%) for CYP17A1, but no decreased activity for CYP1A2 or 2C19 [Miller et al 2009]. Recently, Burkhard et al [2017] reported *POR* variants from the 1000 genomes project.

Pathogenic variants. More than 75 pathogenic variants have been reported in approximately 140 individuals with PORD. They include missense/nonsense variants, splice site variants, small deletions, insertions, and duplications, and large deletions or insertions (see Table 1 and Table A, **Locus Specific** and **HGMD**).

Two pathogenic variants, p.Ala287Pro and p.Arg457His, are common in distinct ethnic groups: p.Ala287Pro accounts for about 40% of pathogenic variants among individuals of European ancestry and p.Arg457His accounts for about 60% of pathogenic variants among individuals of Japanese ancestry, although it is important to note that p.Arg457His has also been reported in individuals of European and African ancestry [Scott & Miller 2008].

Table 3. *POR* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.859G>C	p.Ala287Pro [1]	NM_000941.2
c.1370G>A	p.Arg457His [1]	NP_000932.3

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.

1. See Genotype-Phenotype Correlations.

Normal gene product. NADPH--cytochrome P450 reductase (POR) comprises 680 amino acids and is required for the activity of all 50 of the known human microsomal (type II) P450 enzymes, which play an important role in steroid and sterol synthesis as well as hepatic drug metabolism. POR binds NADPH and accepts a pair of electrons through its FAD moiety. Electrons are then transferred to the FMN moiety and then directly to P450 enzymes.

Abnormal gene product. Expression of recombinant mutated proteins with amino acid substitutions in yeast or bacteria revealed a deficient or reduced capacity for various POR mutants to oxidize cytochrome *c*, NADPH, CYP17A1, CYP21A2, CYP19A1, CYP3A4, CYP2D6, CYP1A2, and CYP2C19 [Arlt et al 2004, Flück et al 2004, Huang et al 2005, Huang et al 2006, Dhir et al 2007, Pandey et al 2007, Kranendonk et al 2008]. The diminished enzyme activity is believed to be caused by the effects of the amino acid substitution on steric conformation, charge, and/or FAD-binding affinity. *POR* pathogenic variants impair the activity of each P450 enzyme to different degrees.

Pathogenic variants that create a premature stop codon are predicted to result in a truncated nonfunctional protein [Adachi et al 2004, Arlt et al 2004, Flück et al 2004, Fukami et al 2005].

A murine knockout of *Por* results in embryonic lethality [Shen et al 2002, Otto et al 2003], while a liver-specific knockout results in a normal morphologic and reproductive phenotype [Gu et al 2003].

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Chapter Notes

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