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Primary Familial and Congenital Polycythemia

Synonyms: ECYT1, Familial Erythrocytosis Type 1

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Summary

Clinical characteristics

Primary familial and congenital polycythemia (PFCP) is characterized by isolated erythrocytosis in an individual with a normal-sized spleen and absence of disorders causing secondary erythrocytosis. Clinical manifestations relate to the erythrocytosis and can include plethora, the hyperviscosity syndrome (headache, dizziness, fatigue, lassitude, visual and auditory disturbances, paresthesia, myalgia), altered mental status caused by hypoperfusion and local hypoxia, and arterial and/or venous thromboembolic events. Although the majority of individuals with PFCP have only mild manifestations of hyperviscosity such as dizziness or headache, some affected individuals have had severe and even fatal complications including arterial hypertension, intracerebral hemorrhage, deep vein thrombosis, coronary disease, and myocardial infarction. To date 116 affected individuals from 24 families have been reported.

Diagnosis/testing

The diagnosis of PFCP is established in a proband with isolated erythrocytosis (hemoglobin and hematocrit above the normal reference range when adjusted for age and sex), normal hemoglobin oxygen affinity measured as P_{50}, erythropoietin (EPO) serum level below or in the lower normal range for laboratory-specific reference values, and a family history consistent with autosomal dominant inheritance. The diagnosis of PFCP can be confirmed in 12%-15% of individuals with these findings by detection of a heterozygous pathogenic variant in *EPOR* by molecular genetic testing.

Management

Treatment of manifestations: No management guidelines have been published. While the majority of individuals with PFCP require no regular treatment, some undergo phlebotomy to either treat symptoms of the

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hyperviscosity syndrome or to maintain the hematocrit at an almost normal level. Some patients require antihypertensive therapy. While low-dose aspirin can be considered for the prevention of thromboembolic events, no evidence of efficacy exists.

Prevention of primary manifestations: Maintain good hydration and avoid activities that potentially increase blood viscosity (e.g., mountain climbing, scuba diving, smoking). For those at increased risk for thromboembolic events: take precautions in higher-risk situations such as long-distance airline flights

Surveillance: Regular cardiology assessment including cardiac function (echocardiography) and blood pressure measurement. Life-long assessment for manifestations/severity of hyperviscosity syndrome and investigation of any suspicious clinical events such as thromboembolic complications.

Agents/circumstances to avoid: Dehydration; activities that could increase blood viscosity (mountain climbing, scuba diving, smoking)

Evaluation of relatives at risk: Presymptomatic diagnosis is warranted in relatives at risk in order to identify as early as possible those who would benefit from education about agents and circumstances to avoid including inappropriate treatments.

Genetic counseling

PFCP is inherited in an autosomal dominant manner. Each child of an individual with PFCP has a 50% chance of inheriting the *EPOR* pathogenic variant. Once the *EPOR* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for PFCP are possible; note, however, that molecular genetic test results cannot predict disease onset or severity.

Diagnosis

The consensus recommendations for the diagnosis of absolute erythrocytosis in children established by the Network of Experts on the Molecular Diagnosis of Myeloproliferative Neoplasm (MPN) and MPN-related congenital diseases (MPNr) (MPN & MPNr-Euronet) are mainly based on measurement of serum erythropoietin (EPO) level and hemoglobin oxygen affinity measured as P_{50}. Definitive diagnosis requires identification of a pathogenic variant (or variants) in one of the known genes [Cario et al 2013].

Suggestive Findings

Primary familial and congenital polycythemia (PFCP) **should be suspected** in individuals with the following clinical findings, laboratory findings, and family history.

Clinical findings

- No splenomegaly
- Absence of cardiac, pulmonary, and renal disease causing secondary erythrocytosis

Laboratory findings

- Complete blood count that shows isolated absolute erythrocytosis:
    - Normal platelet and white cell counts, which demonstrate non-involvement of other hematopoietic cell lines and confirm isolated erythrocytosis
    - Hemoglobin and hematocrit in at least two separate blood counts performed at different times that are above the normal reference range (adjusted to age and sex) and confirm absolute erythrocytosis

Note: Absolute erythrocytosis is distinct from: (1) relative erythrocytosis, caused by severe reduction in plasma volume (e.g., due to diuretics or severe diarrhea) and (2) apparent erythrocytosis, caused by arterial hypoxemia (e.g., cigarette smoking, carbon monoxide poisoning, or sleep apnea) (reviewed in McMullin et al [2005]).

- Normal hemoglobin oxygen affinity measured as P_{50} (i.e., the partial pressure of oxygen in the blood at which hemoglobin is 50% saturated)
- Erythropoietin (EPO) serum level that is below or in the lower normal range (based on laboratory-specific reference values), which excludes secondary erythrocytosis associated with an increased serum EPO level (see Differential Diagnosis)

Family history. Other affected relatives in a pattern consistent with autosomal dominant inheritance

Establishing the Diagnosis

The diagnosis of PFCP **can be established** in a proband when:

- Clinical findings alone support the diagnosis (i.e., isolated absolute erythrocytosis, normal P_{50}, EPO serum level below or in the lower normal range, and a positive family history consistent with autosomal dominant inheritance);

  AND/OR

- A heterozygous pathogenic variant in *EPOR* is identified by molecular genetic testing in a proband who represents a simplex case (i.e., a single occurrence in a family) and has some (not all) suggestive findings.

Molecular genetic testing approaches can include **single-gene testing** when clinical findings strongly support the diagnosis of PFCP or use of a **multigene panel** in those with suggestive, but not diagnostic, clinical findings:

- **Single-gene testing.** Sequence analysis identifies a pathogenic *EPOR* variant in 12%-15% of individuals with isolated erythrocytosis and low serum EPO levels [Kralovics & Prchal 2001, Rives et al 2007, Al-Sheikh et al 2008]. Use of deletion/duplication analysis as a next step can be considered; however, to date no *EPOR* deletions or duplications causative of PFCP have been reported.
- **Use of a multigene panel** that includes *EPOR* and the genes causing secondary erythrocytosis (*HBB*, *BPGM*, *VHL*, *EGLN1*, and *EPAS1*) (see Differential Diagnosis) may also be considered, especially for probands who either represent simplex cases (i.e., a single occurrence of PFCP in a family) and/or in whom secondary causes of erythrocytosis have not been excluded. 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 at the most reasonable cost 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.

Table 1. Molecular Genetic Testing Used in Primary Familial Congenital Polycythemia

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
EPOR	Sequence analysis [3]	12%-15% [4]
	Gene-targeted deletion/duplication analysis [5]	None reported to date
Unknown	85%-88% [6]	

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic 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. Kralovics & Prchal [2001], Rives et al [2007], Al-Sheikh et al [2008]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include 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. Because *EPOR* pathogenic variants are found in only 12%-15% of individuals with PFCP, mutation of at least one other yet-to-be-identified gene may also be causative, such as one involved in the EPOR signaling pathway or an erythropoiesis-regulating pathway [Kralovics & Prchal 2001, Jedlickova et al 2003, Bourantas et al 2006]. One possible candidate gene is *SH2B3 (*encoding SH2B adapter protein 3) as germline *SH2B3* pathogenic variants have been detected in several individuals with idiopathic erythrocytosis [McMullin & Cario 2016].

Clinical Characteristics

Clinical Description

Primary familial congenital polycythemia (PFCP) is characterized by isolated erythrocytosis. To date, PFCP caused by inherited pathogenic variants in *EPOR* has been reported in 116 individuals from 24 families [Bento et al 2014]. The little information available on its clinical presentation is derived from case reports and the experience of the authors.

Clinical manifestations of PFCP comprise plethora, arterial and venous thromboembolic events, and symptoms caused by increased blood viscosity leading to hypoperfusion and local hypoxia. The hyperviscosity syndrome is characterized by symptoms including headache, dizziness, fatigue, lassitude, visual and auditory disturbances, paresthesia, and myalgia, and may be associated with altered mental status. Of note, the majority of individuals with PFCP have only mild manifestations with hyperviscosity symptoms such as dizziness or headache.

PFCP has been detected – either by chance or due to symptoms – in several children ages six months to 16 years [Arcasoy et al 1997, Furukawa et al 1997, Percy et al 1998, Petersen et al 2004, Rives et al 2007]. Patient hematocrits ranged from 57% to 63%. Clinical manifestations (present in some, but not all) were usually relatively mild (predominantly chronic headache and plethora) and relieved by phlebotomy (see Management).

In contrast, some affected individuals have had severe and even fatal clinical complications such as arterial hypertension, intracerebral hemorrhage, deep vein thrombosis, coronary disease, and myocardial infarction [Prchal et al 1995, Sokol et al 1995, Kralovics et al 1997, Kralovics et al 1998].

The age at diagnosis and the clinical findings vary even within the same family. The descriptions of reported families/cases are examples of the clinical variability observed in this disorder even within the same family.

One of the first families described with PFCP included four affected individuals in three generations who were subsequently found to be heterozygous for a nonsense *EPOR* pathogenic variant [Prchal et al 1985, Kralovics et al 1998]:

- The proband, who had extensive coronary artery disease and arterial hypertension, died at age 58 years from hemorrhagic stroke.
- Another family member had hypertension and a myocardial infarction at age 40 years.
- The father of a young girl (who initially appeared to be unaffected) had arterial hypertension beginning at age 20 years and one episode of deep vein thrombosis; as a young girl his daughter had a normal blood count but EPO hypersensitivity in erythroid precursor cells (similar to that observed in the 3 other affected family members).

In another family, all three affected individuals were found to have a heterozygous *EPOR* nonsense pathogenic variant [Rives et al 2007]:

- The proband, a 14-year old boy, was diagnosed with erythrocytosis during evaluation by a pediatric endocrinologist for apparent gynecomastia.
- The mother had had confirmed erythrocytosis during childhood and adolescence; at age 27 years her hemoglobin had been 175 g/L. At the time of the diagnosis of the proband, her hemoglobin was normal; however, her low serum ferritin concentration and transferrin saturation suggested that iron deficiency could be the explanation for her normal hematologic findings.
- The brother of the proband had experienced a deep vein thrombosis at age 18 years. Additional hyperviscosity symptoms which occurred intermittently were relieved by phlebotomies.

A large Finnish family with congenital erythrocytosis (including an Olympic medalist in cross-country skiing) was found to have a heterozygous nonsense *EPOR* pathogenic variant [de la Chapelle et al 1993].

In a family heterozygous for an *EPOR* pathogenic variant [Sokol et al 1995]:

- The proband experienced an occipital hemorrhage at age 29 years.
- His two daughters developed asymptomatic erythrocytosis.
- His mother reported headaches and feeling "sluggish," but had not experienced cerebral or coronary vascular accidents.

A pathogenic *EPOR* nonsense variant, predicted to result in the shortest truncated EPOR reported to date, was identified in a woman age 30 years followed since childhood for asymptomatic erythrocytosis of unknown cause. Her hemoglobin was 206 g/L, her hematocrit was 61%, and serum EPO level was low; she did not have splenomegaly [Chauveau et al 2016].

EPOR missense variants of uncertain significance were found in a man age 35 years who required regular phlebotomy and in a person age 52 years with a clinical history of recurrent venous thrombosis but no family history of hematologic disorders [Bento et al 2013, Chauveau et al 2016].

Other laboratory findings. Bone marrow erythroid progenitor colonies exhibit EPO hypersensitivity.

Genotype-Phenotype Correlations

Given the small number of reported affected individuals to date, it has not been possible to identify any genotype-phenotype correlations; however, it is notable that the age at diagnosis and the clinical findings vary even within the same family.

Penetrance

Data are insufficient to draw any conclusions about penetrance.

Prevalence

Primary familial and congenital polycythemia (PFCP) is a rare disorder; the prevalence is not known. To date, PFCP caused by inherited heterozygous pathogenic variant in *EPOR* has been reported in 116 individuals in 24 families [Bento et al 2014].

Genetically Related (Allelic) Disorders

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

Differential Diagnosis

Causes of erythrocytosis to be considered in the differential diagnosis of primary familial and congenital polycythemia (PFCP) include:

- **Acquired primary erythrocytosis** (polycythemia vera due to a somatic *JAK2* pathogenic variant)
- **Secondary erythrocytosis,** which can result from:
  - Events extrinsic to the erythroid compartment (e.g., cardiac or pulmonary insufficiency) which induce hypoxia and increase the production of EPO resulting in erythrocytosis;
  - Inherited variants that result in high oxygen affinity of hemoglobin causing tissue hypoxia, such as:
    - Variants in *HBB* (encoding hemoglobin subunit beta) (OMIM 141900) or *HBA1* (OMIM 141800) and HBA2 (OMIM 141850) (encoding hemoglobin subunit alpha);

      OR
    - Variants in *BPGM* that result in erythrocyte bisphosphoglycerate mutase (2,3- BPG) deficiency (OMIM 222800).
  - Inherited variants in some of the genes encoding oxygen-sensing pathway proteins, such as: *EGLN1*, *EPAS1*, and *VHL* (reviewed in Bento et al [2014]; for diagnostic algorithms see Bento et al [2013] and Cario et al [2013]).

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with primary familial congenital polycythemia (PFCP), the following evaluations are recommended:

- Full blood counts with evaluation of white blood cells and of platelets, if not performed at the time of diagnosis
- Cardiology assessment including cardiac function (echocardiography) and blood pressure measurement. In case of increased blood pressure, perform 24-hour measurement.
- Recording of symptoms of hyperviscosity syndrome and their severity

  Hyperviscosity syndrome symptoms:
  - Headache
  - Dizziness

- Altered mentation, sense of distance
- Visual disturbances
- Tinnitus
- Paresthesia
- Low performance
- Fatigue, lassitude
- Myalgia, muscle weakness

Hyperviscosity syndrome severity:

- Grade 1. Mild; does not interfere with normal activities
- Grade 2. Moderate; interferes with some activities
- Grade 3. Marked to severe; interferes with most or all activities

- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

No management guidelines have been published.

The majority of individuals with PFCP require no regular treatment.

In some individuals with PFCP, antihypertensive treatment and phlebotomies are initiated either:

- When symptoms of the hyperviscosity syndrome are evident;

  OR

- At routine intervals to maintain the hematocrit at an almost normal level.

While low-dose aspirin can be considered for the prevention of thromboembolic events, no evidence of efficacy exists. Of note, at least one individual (a male age 40 yrs) died from myocardial infarction despite regularly performed phlebotomies [Prchal & Sokol 1996].

Hyperviscosity symptoms (See Evaluations Following Initial Diagnosis.)

- Grade 1. Consider aspirin treatment.
- Grade 2. Consider aspirin treatment. In the presence of persistent symptoms perform phlebotomy. In the event of recurrent episodes consider regular phlebotomy to maintain the hematocrit in the age-respective normal range.
- Grade 3. Consider regular phlebotomy to maintain hematocrit in the age-respective normal range. Consider additional aspirin treatment.

Thromboembolic events

- Provide acute treatment according to established practice for the event.
- Evaluate for other thrombophilic risk factors.
- Start regular phlebotomy to maintain hematocrit in the age-respective normal range. Consider additional aspirin treatment in all patients.
- Consider life-long anticoagulation (e.g., heparins, warfarin) when other severe additional risk factors are present or thromboembolic events have recurred.

Prevention of Primary Manifestations

Always maintain good hydration.

Avoid activities that potentially increase blood viscosity (e.g., mountain climbing, scuba diving, smoking).

For those at increased risk for thromboembolic events: take precautions in higher-risk situations such as long-distance airline flights.

Surveillance

The following are appropriate:

- Regular cardiology assessment including cardiac function (echocardiography) and blood pressure measurement. In case of occasionally increased blood pressure, perform 24-hour measurement.
- Regular life-long follow up with investigation of any suspicious clinical events such as thromboembolic complications and symptoms that could be related to hyperviscosity
- Regular life-long follow up to record manifestations of hyperviscosity syndrome and their severity (See Evaluations Following Initial Diagnosis.)

Agents/Circumstances to Avoid

Avoid:

- Dehydration;
- Any activity that would potentially increase blood viscosity.

Evaluation of Relatives at Risk

It is appropriate to evaluate apparently asymptomatic older and younger at-risk relatives of an affected individual in order to identify as early as possible those with PFCP who would benefit from education regarding agents and circumstances to avoid and inappropriate treatments. Evaluations can include the following:

- **If the *EPOR* pathogenic variant in the family is known.** Molecular genetic testing
- **If no pathogenic variant has been identified in the family.** Blood count and serum EPO concentration if hemoglobin and hematocrit are increased

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

Pregnancy Management

No information is available on the management of pregnancy in a woman with PFCP.

Although the only survey of pregnancy in women with congenital erythrocytosis did not include any women with an *EPOR* pathogenic variant, data showed that when treated with low-dose aspirin and phlebotomy to reduce the hematocrit to a suitable level, women with erythrocytosis can have normal pregnancies and give birth to healthy children [McMullin et al 2015].

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.

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

Primary familial congenital polycythemia (PFCP) is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Most individuals diagnosed with PFCP have an affected parent.
- A proband with PFCP may have the disorder as the result of a *de novo EPOR* pathogenic variant. Because simplex cases (i.e., a single occurrence in a family) have not been evaluated sufficiently to determine if the pathogenic variant occurred *de novo*, the proportion of PFCP caused by a *de novo* pathogenic variant is unknown.
- If the *EPOR* pathogenic variant found in the proband cannot be detected in leukocyte DNA of either parent, possible explanations include a *de novo* pathogenic variant in the proband or germline mosaicism in a parent (although no instances of germline mosaicism have been reported, it remains a possibility).
- Recommendations for the evaluation of parents of a proband with an apparent *de novo* pathogenic variant include a complete blood count for determination of hemoglobin and molecular genetic testing for the *EPOR* pathogenic variant identified in the proband.
- The family history of some individuals diagnosed with PFCP may appear to be negative because of failure to recognize the disorder in family members, early death of the parent before the onset of symptoms, or late onset of the disorder in the affected parent. Therefore, an apparently negative family history cannot be confirmed unless appropriate clinical evaluation and/or molecular genetic testing have been performed on the parents of the proband.

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

- If a parent of the proband is affected, the risk to the sibs of inheriting the pathogenic variant is 50%. However, because of the clinical variability observed in this disorder even within the same family, clinical findings and age at diagnosis cannot be predicted in sibs who inherit a pathogenic variant.
- When the parents are clinically unaffected, the risk to the sibs of a proband appears to be low.
- If the *EPOR* pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the risk to sibs is presumed to be slightly greater than that of the general population (though still <1%) because of the theoretic possibility of parental germline mosaicism.

Offspring of a proband. Each child of an individual with PFCP has a 50% chance of inheriting the *EPOR* pathogenic variant.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent is affected, his or her family members may be at risk.

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.

Considerations in families with an apparent *de novo* pathogenic variant. When neither parent of a proband with PFCP has the *EPOR* pathogenic variant or clinical evidence of the disorder, the *EPOR* pathogenic variant is likely *de novo*. However, non-medical explanations including alternate paternity or maternity (e.g., with assisted reproduction) or undisclosed adoption could also be explored.

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 young adults who are affected or at risk.

DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

Prenatal Testing and Preimplantation Genetic Testing

Once the *EPOR* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible. However, because of the clinical variability observed in PFCP even within the same family, molecular genetic test results cannot predict clinical findings or age at diagnosis.

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.

- **National Library of Medicine Genetics Home Reference**
  Familial erythrocytosis
- **European Congenital Erythrocytosis Consortium Registry**
  www.erythrocytosis.org

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. Primary Familial and Congenital Polycythemia: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
EPOR	19p13.2	Erythropoietin receptor	EPOR database	EPOR	EPOR

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 Primary Familial and Congenital Polycythemia (View All in OMIM)

133100	ERYTHROCYTOSIS, FAMILIAL, 1; ECYT1
133171	ERYTHROPOIETIN RECEPTOR; EPOR

Gene structure. *EPOR* comprises eight coding exons. The primary transcript (NM_000121.3) is 2459 nucleotides in length. Alternatively spliced forms of the EPO receptor have been identified, one of which has a truncated cytoplasmic domain. This shorter transcript is expressed at high levels in immature erythroid

progenitor cells. In contrast, the expression of the full-length receptor increases as progenitor cells mature [Nakamura et al 1992]. For a detailed summary of gene and protein information, see Table A, **Gene**.

Variants of uncertain significance. Three *EPOR* missense variants (c.1310G>A, c.1462C>T, c.1460A>G) have been described for which the association with PFCP has not yet been clarified.

- The c.1310G>A variant was described in a male age 35 years who required regular phlebotomy but also in a patient age 52 years with a clinical history of recurrent venous thrombosis, with normal hemoglobin and hematocrit levels and no familial history of hematologic disorders [Bento et al 2013, Chauveau et al 2016].
- The c.1462C>T variant was found in a white male age 42 years with sporadic primary polycythemia and in his non-polycythemic mother [Sokol et al 1994].

Pathogenic variants. To date, about 20 pathogenic variants have been described in association with PFCP with most (if not all) located in exon 8, which encodes the C-terminal negative regulatory domain of the protein. Pathogenic variants are mostly nonsense or frameshift variants (due to small intragenic deletions or insertions) that predict or result in cytoplasmic truncation of the receptor and loss of the C-terminal negative regulatory domain. Of note, not all the mechanisms by which pathogenic variants induce erythrocytosis are fully understood at present.

The founder variant, c.1316G>A, identified in 29 individuals from one Finnish family was predicted to truncate the EPO receptor by 70 amino acids at the C-terminal cytoplasmic domain [de la Chapelle et al 1993]. The same variant was also identified as a *de novo* variant in an English boy [Percy et al 1998].

The pathogenic variant, c.1317G>A, giving rise to the same amino acid substitution (p.Trp439Ter), was also identified as a *de novo* variant in a Spanish newborn [Rives et al 2007].

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

Variant Classification	DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
Uncertain significance	c.1310G>A	p.Arg437His	NM_000121.3 NP_000112.1
	c.1460A>G	p.Asn487Ser	
	c.1462C>T	p.Pro488Ser	
Pathogenic	c.1316G>A	p.Trp439Ter	
	c.1317G>A	p.Trp439Ter	

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. EPOR, a glycoprotein of about 60 kd and 508 amino acids which belongs to the cytokine class I receptor family, is a transmembrane receptor consisting of: an extracellular domain that changes conformation upon EPO binding, a hydrophobic transmembrane domain, and a cytoplasmic domain with eight tyrosine residues, serving as phosphorylation sites for proteins involved in downstream signal transduction [Lacombe & Mayeux 1999].

EPOR dimerization activates cytoplasmic tyrosine Janus kinases 2 (JAK2) activity, enabling phosphorylation of some of the tyrosine residues present in the cytoplasmic domain of EPOR [Lodish et al 1992, Witthuhn et al 1993, Miura et al 1994, Damen & Krystal 1996].

Following phosphorylation of EPOR, a number of other signal transduction proteins also become phosphorylated and initiation of the signal transduction pathways occurs. One such signal transducer and

activator of transcription, the protein STAT5, binds to phosphorylated tyrosine present on the cytoplasmic tail of EPOR and itself becomes phosphorylated at the level of tyrosine residues [Damen et al 1995, Gobert et al 1996].

Phosphorylated STAT5 dissociates from the receptor, dimerizes, and is translocated from the cytoplasm to the nucleus, where it activates the expression of several anti-apoptotic genes in erythroid cells, most notably *BCL2L1,* through a direct binding at the level of STAT5-binding consensus sequences present in the promoter of *BCL2L1.*

These effects of STAT5 on *BCL2L1* activation provide the molecular basis of the anti-apoptotic effects elicited by STAT5 in erythroid cell lines [Nosaka et al 1999, Socolovsky et al 1999, James et al 2005].

Control of intensity and duration of EPO-EPOR signaling is necessary to tightly regulate erythropoiesis. An ubiquitin/proteasome system plays the major role in the control of EPOR signaling. After EPO binding, EPOR is ubiquitinated and the intracellular part is degraded by the proteasome, preventing further signal transduction. The remaining part of the receptor and associated EPO are internalized and degraded by the lysosomes [Meyer et al 2007]. The binding of p85, the regulatory subunit of phosphoinositide 3-kinase (PI3K), to phosphorylated residues Tyr429, Tyr431, or Tyr479, located in the C-terminal site of the cytoplasmic domain of EPOR, plays an important role in EPO-dependent EPOR internalization.

Abnormal gene product. Pathogenic variants in the cytoplasmic portion of EPOR identified in persons with PFCP result in truncated EPORs lacking the cytoplasmic COOH-terminal of the receptor, which contains a negative regulatory domain and is essential in SHP-1 phosphatase binding (a negative regulator of EPOR signaling). The lack of downregulation of EPOR after ligand binding results in increased proliferation rates due to the prolonged activation of JAK2-STAT5 and other signaling cascades and is responsible for the EPO hypersensitivity of erythroid progenitors observed in vitro in persons with PFCP [Huang et al 2010].

Using epidermal growth factor receptor-EPOR chimeras, Gross et al [2014] recently described higher proliferation rates of UT7 cells associated with all *EPOR* pathogenic variants, including missense variants.

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Chapter Notes

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