# *EPOR* Sequencing of Exons 7 and 8 for Primary Familial or Congenital Polycythemia

## Indications for Ordering

- Confirm a diagnosis of primary familial or congenital polycythemia (PFCP)
- Distinguish inherited polycythemia from acquired polycythemia (eg, polycythemia vera)
- Test at-risk relatives for a known familial *EPOR* mutation

## Test Description

Sequencing of exons 7 and 8 of the *EPOR* gene

## Tests to Consider

**Primary test**

*EPOR* Mutation Detection by Sequencing 2007914

- Preferred test for confirming PFCP

**Related test**

Erythropoietin 0050227

- Initial screening test for evaluation of polycythemia
- Determine eligibility for erythropoietin therapy in anemia due to chronic renal failure

## Disease Overview

**Alternative disease names** – benign familial erythrocytosis, hereditary polycythemia/erythrocytosis, congenital polycythemia/erythrocytosis

**Incidence** – rare

**Symptoms**

- Headaches
- Dizziness
- Epistaxis
- Exertional dyspnea
- Thrombotic and hemorrhagic events have been reported
- Increased risk of cardiovascular events
- Symptoms present at birth or in multiple family members
- No progression to leukemia

**Physiology**

- Caused by intrinsic abnormalities of the hematopoietic progenitors
  - Leads to overproduction of red bloods cells (RBCs) without elevated erythropoietin (EPO) levels

**Diagnosis**

- Increased hematocrit
  - No leukocytosis
  - No thrombocytosis
- EPO concentration (serum) – low
- Hemoglobin-oxygen dissociation curve – normal
- In vitro hypersensitivity of erythroid progenitors to EPO
- Exclusion of acquired polycythemia

## Genetics

**Gene** – *EPOR*

**Inheritance** – primarily autosomal dominant; can be de novo

**Penetrance** – variable

- Some patients with *EPOR* mutations do not have polycythemia
  - Suggests that other genetic modifiers or epigenetic factors may influence the phenotype

**Structure/function**

- Codes for EPO receptor
  - Located on erythroid progenitor cells
- Eight exons
  - Exons 7 and 8 code for the C-terminal cytoplasmic domain of EPO receptor
    - Down-regulates signal transduction leading to erythropoiesis

**Mutations**

- Frameshift and truncating mutations in exons 7 and 8 inhibit negative feedback function
  - Causes hypersensitivity to EPO

## Test Interpretation

**Sensitivity/specificity**

- Clinical sensitivity – 10-20% in patients with PFCP
- Analytical sensitivity/specificity – 99%

**Results**

- Positive – PFCP diagnosis confirmed
- Negative – PFCP diagnosis less likely but not excluded
- Inconclusive – gene variant detected, but whether variant is benign or pathogenic is unclear

**Limitations**

- Mutations in other locations within *EPOR* or in other genes will not be detected
- Results must be interpreted within clinical context and with other relevant data
- Results should not be used to diagnose malignancy
- Rare diagnostic errors may occur due to primer-site mutations