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 (e.g., 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 blood 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/specifity
  • Clinical sensitivity – 10-20% in patients with PFCP
  • Analytical sensitivity/specifity – 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 *EPO* 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