

Overview

Useful For

Interpretation of the hereditary erythrocytosis profile

Testing Algorithm

A molecular interpretation will be provided when HEMP / Hereditary Erythrocytosis Mutations, Whole Blood is ordered.

Method Name

Only orderable as part of a profile. For more information see HEMP / Hereditary Erythrocytosis Mutations, Whole Blood.

Medical Interpretation

NY State Available

Yes

Specimen

Specimen Type

Whole blood

Specimen Stability Information

| Specimen Type | Temperature | Time | Special Container |
|---------------|--------------------------|---------|-------------------|
| Whole blood | Refrigerated (preferred) | 30 days | |
| | Ambient | 14 days | |

Clinical and Interpretive

Clinical Information

Erythrocytosis (ie, increased RBC mass or polycythemia) may be primary, due to an intrinsic defect of bone marrow stem cells (ie, polycythemia vera: PV), or secondary, in response to increased serum erythropoietin (EPO) levels. Secondary erythrocytosis is associated with a number of disorders including chronic lung disease, chronic increase in carbon monoxide (due to smoking), cyanotic heart disease, high-altitude living, renal cysts and tumors, hepatoma, and other EPO-secreting tumors. When these common causes of secondary erythrocytosis are excluded, a heritable cause involving hemoglobin or erythrocyte regulatory mechanisms may be suspected.

Unlike polycythemia vera, hereditary erythrocytosis is not associated with the risk of clonal evolution and should present with isolated erythrocytosis that has been present since birth. A small subset of cases is associated with pheochromocytoma and/or paraganglioma formation. It is caused by variations in several genes and may be inherited in either an autosomal dominant or autosomal recessive manner. A family history of erythrocytosis would be expected in these cases, although it is possible for new variants to arise in an individual.

The genes coding for hemoglobin, beta globin and alpha globin (high-oxygen-affinity hemoglobin variants), hemoglobin-stabilization proteins (2,3 bisphosphoglycerate mutase: *BPGM*), and the erythropoietin receptor, *EPOR*, and oxygen-sensing pathway enzymes (hypoxia-inducible factor: *HIF/EPAS1*, prolyl hydroxylase domain: *PHD2/EGLN1*, and von Hippel Lindau: *VHL*) can result in hereditary erythrocytosis (see Table). High-oxygen-affinity hemoglobin variants and *BPGM* abnormalities result in a decreased p50 result, whereas those affecting *EPOR*, *HIF*, *PHD*, and *VHL* have normal p50 results. The true prevalence of hereditary erythrocytosis-causing variants is unknown. The hemoglobin genes, *HBA1/HBA2* and *HBB* are not assayed in this profile.

Genes Associated with Hereditary Erythrocytosis

| Gene | Inheritance | Serum EPO | p50 |
|---------------------|-------------|---------------------------|-----------|
| <i>JAK2</i> V617F | Acquired | Decreased | Normal |
| <i>JAK2</i> exon 12 | Acquired | Decreased | Normal |
| <i>EPOR</i> | Dominant | Decreased | Normal |
| <i>PHD2/EGLN1</i> | Dominant | Normal level | Normal |
| <i>BPGM</i> | Recessive | Normal level | Decreased |
| Beta Globin | Dominant | Normal level to increased | Decreased |
| Alpha Globin | Dominant | Normal level to increased | Decreased |
| <i>HIF2A/EPAS1</i> | Dominant | Normal level to increased | Normal |
| <i>VHL</i> | Recessive | Normal to increased | Normal |

The oxygen-sensing pathway functions through an enzyme, hypoxia-inducible factor (HIF), which regulates RBC mass. A heterodimer protein comprised of alpha and beta subunits, HIF functions as a marker of depleted oxygen concentration. When present, oxygen becomes a substrate mediating HIF-alpha subunit degradation. In the absence of oxygen, degradation does not take place and the alpha protein component is available to dimerize with a HIF-beta subunit. The heterodimer then induces transcription of many hypoxia response genes including *EPO*, *VEGF*, and *GLUT1*. HIF-alpha is regulated by von Hippel-Lindau (VHL) protein-mediated ubiquitination and proteosomal degradation, which requires prolyl hydroxylation of HIF proline residues. The HIF-alpha subunit is encoded by the *HIF2A* (*EPAS1*) gene. Enzymes important in the hydroxylation of HIF-alpha are the prolyl hydroxylase domain proteins, of which the most significant isoform is PHD2, which is encoded by the *PHD2* (*EGLN1*) gene. Variations resulting in altered HIF-alpha, PHD2, and VHL proteins can lead to clinical erythrocytosis. A small subset of variants, in *PHD2/EGLN1* and *HIF2A/EPAS1*, has also been detected in erythrocytic patients presenting with paragangliomas or pheochromocytomas.

Truncating variants in the *EPOR* gene coding for the erythropoietin receptor can result in erythrocytosis through loss of the negative regulatory cytoplasmic SHP-1 binding domain leading to EPO hypersensitivity. All currently known variants have been localized to exon 8 and are heterozygous truncating variants. *EPOR* variants are associated with decreased EPO levels and normal p50 values (see Table).

Reference Values

Only orderable as part of a profile. For more information see HEMP / Hereditary Erythrocytosis Mutations, Whole Blood.

Interpretation

An interpretive report will be provided and will include specimen information, assay information, and whether the specimen was positive for any variations in the gene. If positive, the variant will be correlated with clinical

significance, if known.

Cautions

No significant cautionary statements

Clinical Reference

1. Patnaik MM, Tefferi A: The complete evaluation of erythrocytosis: congenital and acquired. *Leukemia*. 2009 May;23(5):834-844
2. McMullin MF: The classification and diagnosis of erythrocytosis. *Int J Lab Hematol*. 2008;30:447-459
3. Percy MJ, Lee FS: Familial erythrocytosis: molecular links to red blood cell control. *Haematologica*. 2008 Jul;93(7):963-967
4. Huang LJ, Shen YM, Bulut GB: Advances in understanding the pathogenesis of primary familial and congenital polycythaemia. *Br J Haematol*. 2010 Mar;148(6):844-852
5. Maran J, Prchal J: Polycythemia and oxygen sensing. *Pathologie Biologie*. 2004;52:280-284
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8. Zhuang Z, Yang C, Lorenzo F, et al: Somatic *HIF2A* gain-of-function mutations in paraganglioma with polycythemia. *N Engl J Med*. 2012 Sep 6;367(10):922-930
9. Ladroue C, Carcenac R, Leporrier M, et al: *PHD2* mutation and congenital erythrocytosis with paraganglioma. *N Engl J Med*. 2008 Dec 18;359(25):2685-2692
10. Lorenzo FR, Yang C, Ng Tang Fui M, et al: A novel *EPAS1/HIF2A* germline mutation in congenital polycythemia with paraganglioma. *J Mol Med*. 2013 Apr;91(4):507-512
11. Tarade D, Robinson CM, Lee JE, Ohh M: HIF-2alpha-pVHL complex reveals broad genotype-phenotype correlations in HIF-2alpha-driven disease. *Nat Commun*. 2018;9(1):3359
12. Oliveira JL, Coon LM, Frederick LA, et al: Genotype-phenotype correlation of hereditary erythrocytosis mutations, a single center experience. *Am J Hematol*. 2018 May 23. doi: 10.1002/ajh.2515)
13. Oliveira JL: Algorithmic evaluation of hereditary erythrocytosis: Pathways and caveats. *Int J Lab Hematol*. 2019 May;41 Suppl 1:89-94

Performance

Method Description

A hematologist reviews the laboratory data and an interpretive report is issued.

PDF Report

No

Day(s) and Time(s) Test Performed

Monday through Friday; Varies

Performing Laboratory Location

Rochester

Fees and Codes**Fees**

- Authorized users can sign in to [Test Prices](#) for detailed fee information.
- Clients without access to Test Prices can contact [Customer Service](#) 24 hours a day, seven days a week.
- Prospective clients should contact their Regional Manager. For assistance, contact [Customer Service](#).

Test Classification

Not Applicable

LOINC® Information

| Test ID | Test Order Name | Order LOINC Value |
|---------|--------------------------|-------------------|
| MINT | Molecular Interpretation | 69047-9 |

| Result ID | Test Result Name | Result LOINC Value |
|-----------|--------------------------|--------------------|
| 34648 | Molecular Interpretation | 69047-9 |
| 35000 | Reviewed By | 18771-6 |