MAYO CLINIC LABORATORIES

Test Definition: MINT

Molecular Interpretation

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 & Interpretive

Clinical Information
Erythrocytosis (ie, increased red blood cell [RBC] mass or polycythemia) may be primary, due to an intrinsic defect of bone marrow stem cells (ie, polycythemia vera), 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, kidney 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 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.

Table. Genes Associated with Hereditary Erythrocytosis

Gene	Inheritance	Serum EPO	p50
JAK2 V617F	Acquired	Decreased	Normal
JAK2 exon 12	Acquired	Decreased	Normal
EPOR	Dominant	Decreased	Normal
PHD2/*EGLN1*	Dominant	Normal level	Normal
BPGM	Recessive	Normal level	Decreased
Beta Globin	Dominant	Normal level to increased	Decreased
Alpha Globin	Dominant	Normal level to increased	Decreased
HIF2A/*EPAS1*	Dominant	Normal level to increased	Normal
VHL	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 proteasomal 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;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;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;148(6):844-852
5. Maran J, Prchal J. Polycythemia and oxygen sensing. Pathologie Biologie. 2004;52:280-284
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7. Merchant SH, Oliveira JL, Hoyer JD, Viswanatha DS. Erythrocytosis. In: His ED, ed. Hematopathology. 2nd ed. Elsevier Saunders; 2012:22-723
8. Zhuang Z, Yang C, Lorenzo F, et al. Somatic *HIF2A* gain-of-function mutations in paraganglioma with polycythemia. N Engl J Med. 2012;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;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;91(4):507-512
11. Tarade D, Robinson CM, Lee JE, Ohh M. HIF-2alpha-pVHL complex reveals broad genotype-phenotype correlations in HIF-2aalpha-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. doi:10.1002/ajh.2515)
13. Oliveira JL. Algorithmic evaluation of hereditary erythrocytosis: Pathways and caveats. Int J Lab Hematol. 2019;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) Performed

Monday through Friday

Report Available

10 to 25 days

Performing Laboratory Location

Mayo Clinic Laboratories - Rochester Main Campus

Fees & 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 account representative. 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