

Haptoglobin (HP) Genotyping

TO PREDICT CORONARY ARTERY DISEASE IN PATIENTS WITH DIABETES MELLITUS

Test Highlights

- Diabetes mellitus patients with Hp 2-2 genotype are at a significantly higher risk for cardiovascular disease.
- Preliminary evidence indicates that vitamin E supplementation may be beneficial for diabetic individuals with the Hp 2-2 genotype.

Clinical Background

- Haptoglobin (HP) functions as a hemoglobin-binding protein conserving the iron released following red cell hemolysis, thus preventing kidney damage.
- HP is composed of an alpha and beta chain. The alpha chain is represented by two common alleles (Hp 1 and Hp 2), while the beta chain is identical in all HP types. Hp 2 results from a partial Hp 1 gene duplication and is approximately twice the molecular size of Hp 1.
- Smoking, hypertension, and hyperlipidemia represent cardiovascular risk factors for the general population. Diabetics are known to have a higher risk for cardiovascular disease than non-diabetics. Hp 2 is believed to be an independent source of additional cardiovascular risk in diabetics.
- Since Hp1 is markedly smaller than Hp 2, it enters extravascular areas to reduce hemoglobin-mediated tissue damage at sites of vascular injury. It also functions as a hemoglobin scavenger and antioxidant, protecting tissues against hemoglobin-mediated tissue oxidation. The monocyte/macrophage scavenger receptor, CD163, clears the Hp 1-1-Hb complexes markedly faster than the Hp 2-2-Hb complexes. Additionally, the antioxidant ability of HP for glycosylated hemoglobin is decreased in diabetics. This increases the need to clear glycosylated hemoglobin from the subendothelial space before the hemoglobin can oxidize LDLs into atherogenic LDLs.
- Diabetics with the Hp 2-2 genotype are five times more likely to have cardiovascular disease than those with Hp 1-1. They are also three times more likely to have cardiovascular disease than those with the Hp 2-1 genotype. Therefore, Hp genotype is a predictor of cardiovascular disease in diabetics. In non-diabetics, Hp genotype and cardiovascular disease have not shown the same association.
- Vitamin E does not appear to protect against cardiovascular disease (and may even be detrimental) when provided to the general population or diabetics as a group. Yet preliminary evidence indicates that vitamin E supplementation may be beneficial for diabetic individuals with the Hp 2-2 genotype.
- Diabetics with the Hp 1-1 genotype are at decreased risk for developing microvascular complications, such as nephropathy and retinopathy. Furthermore, restenosis following percutaneous coronary angioplasty is significantly decreased in Hp 1-1 diabetics. A one-year follow-up of diabetics requiring coronary artery stent placements revealed that those with the Hp 1-1 genotype had fewer myocardial infarctions and a decreased need for target vessel revascularization compared to those with Hp 2-1 or Hp 2-2 genotypes.

Epidemiology

- The allele frequencies of Hp 1 and Hp 2 vary greatly throughout the world.
- In Europeans, the Hp 1 and 2 allele frequencies are 40 percent and 60 percent, respectively. Thus, the expected frequency of Hp genotypes for this population include: 16 percent Hp 1-1, 48 percent Hp 2-1, and 36 percent Hp 2-2.
- Rarely, individuals have anaphthoglobinemia, referring to lack of expression of the haptoglobin gene or Hp 0-0 genotype. This condition is present in up to 4 percent of African-Americans and one in 1,000 Caucasians.

Genetics

- The HP gene is located on chromosome 16q22.
- The HP alpha and beta chains are synthesized as a single polypeptide chain that is later cleaved.
- The Hp 2 allele, found only in humans, originated from nonhomologous crossing over of Hp 1. Since Hp 2 resulted from a partial Hp 1 gene duplication, it is approximately twice the molecular size of Hp 1.

Indications for Ordering

- Diabetic patients at risk for cardiovascular disease.
- Diabetic patients considering various cardiovascular treatment options.

Contraindications

Assessment of cardiovascular risk for the general population; no known correlation exists between the Hp genotype and cardiovascular risk in non-diabetics.

Interpretation

- The Hp 2-2 genotype predicts increased risk for cardiovascular disease in diabetics.
- Diabetics with the Hp 1-2 genotype are at intermediate risk for cardiovascular complications.
- Diabetics with the Hp 1-1 genotype are at lowest risk for cardiovascular complications.
- Persons with rare anaphthoglobinemia (Hp 0-0) or hypohaptoglobinemia (Hp 1-0 or Hp 2-0) may be misclassified depending on the cause of lack of gene expression.

Methodology

- Hp 1 and Hp 2 alleles are assayed from extracted DNA by polymerase chain reaction and fluorescent monitoring using hybridization probes.
- Analytical sensitivity and specificity is 99 percent. Rare diagnostic errors may occur due to primer site mutations.

References

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5. Levy AP, et al. Haptoglobin phenotype is an independent risk factor for cardiovascular disease in individuals with diabetes: the strong heart study. *J Am Coll Cardiol* 2002; 40:1984–90.
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Test Information

0040116

Haptoglobin by PCR

For specific collection, transport, and testing information, refer to the ARUP Web site at www.aruplab.com.

For information on test selection, ordering, and interpretation, refer to ARUP Consult® at www.arupconsult.com.