APOL1 Gene Analysis in Chronic Kidney Disease Risk

Disorder also known as: Susceptibility to Focal Segmental Glomerulosclerosis 4 (FSGS4); Susceptibility to Nondiabetic End-stage Renal Disease

Variant List: c.1024A>G, p.Ser342Gly (G1 allele), and c.1164_1169delTTATAA, p.Asn388_Tyr389del (G2 allele) in APOL1

Clinical Features:
The incidence of end-stage renal disease is significantly higher among African Americans than among European Americans.[1,2] This increased risk is largely due to the presence of specific variant alleles in the APOL1 gene. These risk alleles, termed G1 and G2, are relatively prevalent in individuals with African ancestry, and rare in individuals without recent African ancestry[3]. Individuals with two risk alleles have a ten to seventeen-fold higher odds of developing focal segmental glomerulosclerosis type 4 (FSGS4), which presents clinically as proteinuria, nephrotic syndrome, and progressive loss of renal function leading to end-stage renal disease.[3-5] The G1 and G2 risk alleles are also associated with higher rates of kidney disease progression and end-stage renal disease seen in African Americans.[3,6] Additionally, the presence of two risk alleles is associated with a twenty-nine fold higher risk of developing HIV-associated nephropathy[5], an increased risk of sickle cell-associated nephropathy[7], and shortened graft survival of kidney transplants based on the donor's genotype.[8]

Genetics:
The G1 allele comprises two single nucleotide polymorphisms (c.[1024A>G;1152T>G], p.[Ser342Gly;Ile384Met]), however, the risk associated with the G1 allele is considered to be due to only the c.1024A>G, p.Ser342Gly variant.[5] The other polymorphism (c.1152T>G, p.Ile384Met) associated with the G1 allele does not confer an increased risk in isolation and is not analyzed by this test.[9] The G2 allele is a deletion of six nucleotides (c.1164_1169delTTATAA, p.Asn388_Tyr389del) that results in an in-frame deletion of two amino acids. These alleles confer protection against T.b. rhodesiense, which causes trypanosomiasis and the alleles have accordingly risen to high frequencies in Eastern and Southeastern Africa due to positive selection. The G1 and G2 alleles are in complete negative linkage disequilibrium and have not been observed on the same chromosome (in cis). Therefore, if an individual has both the G1 and G2 alleles, it can be assumed that they are on opposite chromosomes (in trans) and no wild-type allele is present.[3]

The risk associated with these alleles is inherited in an autosomal recessive pattern. Individuals who are homozygous or compound heterozygous for the G1 and G2 alleles are at increased risk to develop chronic kidney disease, however, heterozygous carriers (individuals

with only one of these two risk alleles) do not have a significantly higher risk than individuals with two wild-type alleles.[3]

Test Methods:

Using genomic DNA from the submitted specimen, the relevant portion of the requested gene is PCR amplified and capillary sequencing is performed. Bi-directional sequence is assembled, aligned to reference gene sequences based on human genome build GRCh37/UCSC hg19 and analyzed for only the requested variant(s). Sequence alterations are reported according to the Human Genome Variation Society (HGVS) nomenclature guidelines. A homozygous result may be observed and reported if one allele is partially deleted or refractory to amplification.

Test Sensitivity:

The technical sensitivity of this test is estimated to be greater than 99%. This test will not detect variants other than those associated with the G1 and G2 alleles. In large population databases, the G1 and G2 alleles account for about 14% and 23% of APOL1 alleles among individuals with African ancestry, respectively.[10]

References:

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