Alzheimer Disease Risk
APOE ε4 Risk Allele

Disorder also known as: Dementia

Genotyped variants: APOE ε4 allele: c.[388T>C;526=], p.[C130R;R176=]

Clinical Features:
Alzheimer disease (AD) is a progressive neurodegenerative disorder characterized by dementia that typically begins with subtle and poorly recognized failure of memory, that slowly becomes more severe, eventually leading to incapacitation and death. Common findings include confusion, poor judgment, language disturbance, agitation, withdrawal, and hallucinations.[1] AD is the most common form of dementia, accounting for 60-80% of dementia diagnoses, affecting approximately 10% of individuals over the age of 65 living in the US.[2] Early onset AD (EOAD) typically presents before 65 years of age and late onset AD (LOAD) presents after the age of 65.[1] LOAD accounts for approximately 95% of all AD cases.[3]

Inheritance Pattern/Genetics:
Both early-onset AD (EOAD) and late onset AD (LOAD) are genetically complex and have multifactorial causes.[2] Among numerous genetic risk factors, a variant allele in the Apolipoprotein E (*APOE*) gene has been identified as the strongest risk factor for AD.[2,4] Variant alleles are characterized by the combination of amino acids at residues 130 (aka 112) and 176 (aka 158). Three common *APOE* alleles have been identified and are referred to as *APOE* alleles ε2 (Cys130 and Cys176), ε3 (Cys130 and Arg176), and ε4 (Arg130 and Arg176).[5] Studies have shown that APOE ε4 carriers are at increased risk for developing AD and increased risk for developing the disease at an earlier age.[4,5,6]

Alzheimer disease is an adult onset disorder for which there is currently no specific medical intervention that, if initiated in childhood, would alter the clinical course. Therefore, in accordance with policy and position statements from the American College of Medical Genetics (ACMG)[7,8], American Society of Human Genetics (ASHG)[9], and the American Academy of Pediatrics[8], samples from individuals younger than 18 years of age will not be accepted for this testing.

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.

Test Sensitivity:

One study showed that the presence of one or more APOE ε4 alleles as a test for the pathological diagnosis of Alzheimer's disease had a sensitivity of 65% and a specificity of 68%.[10] However, up to 75% of individuals heterozygous for APOE ε4 do not develop AD during life and up to 50% of people with AD do not carry the high-risk APOE ε4 allele.[5] Multiple lines of evidence show that APOE ε4 status is neither necessary nor sufficient to cause AD, and numerous consensus statements recommend caution in interpretation in the context of clinical care.[7] Only the presence of the APOE ε4 allele (p.[C130R;R176=]) will be reported.

References:

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4. Corder et al. (1993) Science 261 (5123):921-3 (PMID: 8346443)
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8. Ross et al. (2013) Genet. Med. 15 (3):234-45 (PMID: 23429433)
9. Botkin et al. (2015) Am. J. Hum. Genet. 97 (1):6-21 (PMID: 26140447).
10. Mayeux et al. (1998) N. Engl. J. Med. 338 (8):506-11 (PMID: 9468467)