

test, test , Test, Test

DOB/AGE:03/16/48 70 yrs

Gender:Male

Accession: 10280638

Collected: 05/14/2018

Released: 05/22/2018 07:18

MTHFR Genotyping Report

Source of Collection: Saliva

Specimen Received: Blood

Gene Test	SNP Ref ID	Result	Interpretation
MTHFR-677	rs1801133	C/T	Heterozygous for C677T polymorphism
MTHFR-1298	rs1801131	A/C	Heterozygous for A1298C polymorphism

Approximate MTHFR Enzyme Activity (%)¹: 48

The MTHFR (methylene tetrahydrofolate reductase) gene produces an enzyme that helps in processing folate and regulating homocysteine levels in the body. Folate is a critical nutrient involved in methylation, DNA synthesis and amino acid metabolism.² Impaired folate metabolism due to MTHFR enzyme inactivity, or a low folate level, results in elevated plasma homocysteine.³ Homocysteine is an amino acid synthesized by the body through demethylation of methionine. In the presence of adequate B-vitamins, homocysteine is either irreversibly degraded to cysteine or it is re-methylated back to methionine, an essential amino acid.⁴ An elevated homocysteine level is known to be an independent risk factor for ischemic stroke, thrombotic and cardiovascular diseases.^{5,6} Folate, vitamin B6 or vitamin B12 are all necessary for the proper conversion of homocysteine into methionine. A deficiency in any of these vitamins can cause homocysteine levels to rise. Two single nucleotide variants known to affect MTHFR function are C677T (a change from cytosine to thymine at position 677 within the gene) and the A1298C mutation (a change from adenine to cytosine at position 1298 within the gene).^{1,6,7} It is not uncommon for some individuals to have both MTHFR variants. Clinical relevance for hyperhomocysteinemia is associated with homozygosity for C677T or A1298C variant alleles and the compound heterozygous state (presence of both heterozygous genotypes C677T/ A1298C). In general, these genotypes produce MTHFR enzyme with reduced function and activity. In addition to vascular health, defects in folate metabolism due to dietary factors or MTHFR mutations may contribute to the pathophysiology of neural tube defects and a variety of malignancies.^{1,8} Also, a strong association between MTHFR variants and methotrexate toxicity has been reported.⁹ Methotrexate, a drug used in treatment of cancer and autoimmune diseases, is a structural analogue of folate that interferes with folate metabolism and leads to depletion of cellular folate. MTHFR gene variants associated with reduced enzyme function and hyperhomocysteinemia may affect methotrexate sensitivity and contribute to toxicity.⁹ MTHFR genotyping may support methotrexate dose adjustment and limitation/discontinuation of therapy in affected individuals.

References:

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APOE Genotyping by PCR*

SNPrs429358 C/T

SNPrs7412 C/C

APOE Genotype: e3/e4

The APOE gene codes for the protein Apolipoprotein E (ApoE), one of the lipoproteins involved in lipid transport. Like all genes, every individual has two copies of APOE, a maternal allele and a paternal allele. There are three common variants of the gene: APOE-e2, APOE-e3, and APOE-e4, distinguished by the presence of different amino acids (arginine vs. cysteine) at positions 112 and 158 of the ApoE protein. The e3 allele is most common (about 78% allele frequency) followed by e4 and e2 (about 14% and 8% allele frequencies, respectively).¹

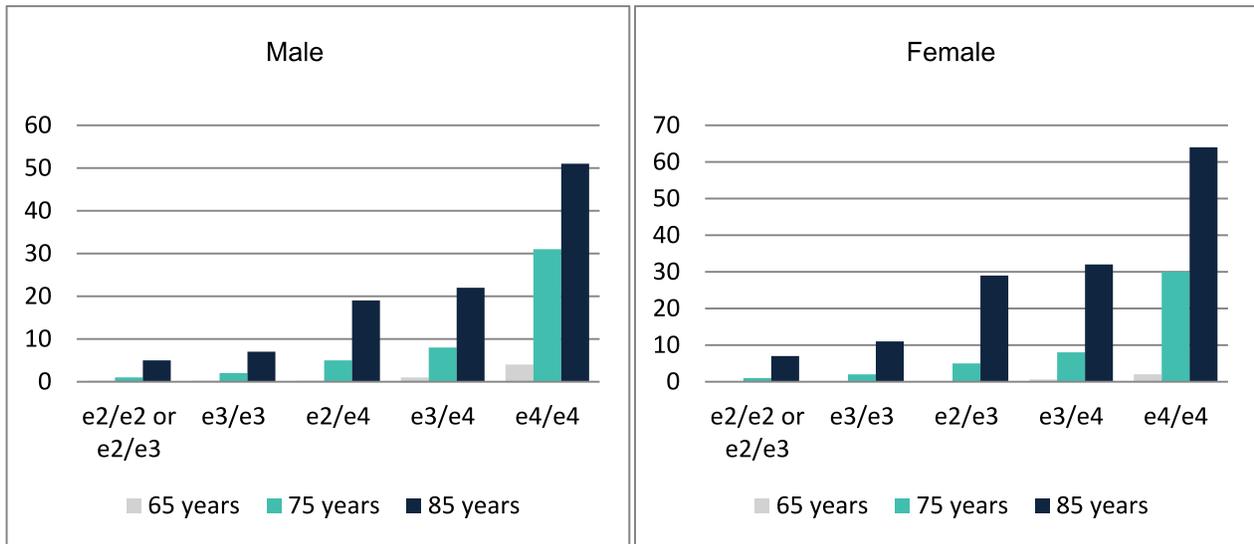
There is a significant association between APOE genotype and risk for Alzheimer's disease. This was first demonstrated over 20 years ago² and has been confirmed in numerous subsequent studies. Compared to the most common genotype (e3/e3), the presence of a single APOE-e4 allele (e3/e4) increases an individual's risk for Alzheimer's disease about 3- to 4-fold, and the presence of two e4 alleles (e4/e4) increases the risk about 12-fold,³ although some studies have indicated an even higher risk for e4/e4 individuals.^{4,5} These risk levels are based on studies in which APOE genotype is considered independently. Recent studies have revealed additional genetic factors that modify the risk, but in all studies APOE is the most powerful genetic factor⁶ (apart from the rare "familial" Alzheimer's disease mutations in PS1, PS2 or APP, which are associated with autosomal dominant early-onset Alzheimer's disease, a rare subtype of the disease). APOE-e4 is often described as a risk factor only for "late-onset" Alzheimer's disease (the most common type, with onset at 65 years of age or older), but in fact it is also a risk factor for sporadic early-onset Alzheimer's disease (onset before age 65, which is much less common).^{3,7-8} In contrast to the e4 allele, the e2 allele is associated with reduced risk for Alzheimer's disease. The provided table and graph show approximate lifetime risks for Alzheimer's disease at various ages based on APOE genotype. Note that these risk figures account only for APOE genotype, without consideration of other genetic, medical or lifestyle factors that modify the risk for an individual.

It is important to note that although APOE genotype is a powerful genetic risk factor for Alzheimer's disease, the test itself is not diagnostic of the disease. Having a high-risk genotype does not guarantee development of the disease, and having a low-risk genotype does not exclude the possibility of the disease. Furthermore, as noted above, other factors modify the risk, including both genetic and non-genetic factors. In particular, many lifestyle factors (e.g. diet, sleep quality, smoking status, education, mental activity, etc.) have a significant impact on risk for both Alzheimer's disease and other forms of dementia independent of APOE status.⁹⁻¹⁶

APOE genotype is also associated with serum lipid status and cardiovascular disease risk. APOE-e4 is associated with increased plasma LDL levels and increased risk for coronary artery disease in a dose-dependent manner (two e4 alleles are associated with higher risk than a single allele).¹⁷ The presence of an e2 allele is generally associated with reduced plasma LDL and reduced risk of coronary artery disease,¹⁷ although a small percentage of patients with an APOE-e2/e2 genotype develop the rare hyperlipidemia disorder type III hyperlipoproteinemia (dysbetalipoproteinemia).¹⁸

* Performed by nucleic acid amplification and melting curve analysis of tagged oligomers targeting nucleotides 388 (SNP rs429358) and 526 (SNP rs7412) at Northwest Pathology, Bellingham, WA (CLIA #50D1017935). Rare variants of APOE may not be detected. If rare alleles are suspected, phenotyping by isoelectric focusing may be indicated. Diagnostic errors can occur due to rare sequence variations. This test was developed and its performance characteristics determined by Northwest Pathology, P.S. It has not been cleared or approved by the U.S. Food and Drug Administration. The FDA has determined that such clearance or approval is not necessary.

Lifetime Risk(%) for Alzheimer's disease by Age and ApoE Genotype*



Age	Gender	e2/e2 or e2/e3	e3/e3	e2/e4	e3/e4	e4/e4
65	Male	0.2%	0.2%	0.2%	1%	4%
65	Female	0.1%	0.2%	0.2%	0.6%	2%
75	Male	1%	2%	5%	8%	31%
75	Female	1%	2%	5%	8%	30%
85	Male	5%	7%	19%	22%	51%
85	Female	7%	11%	29%	32%	64%

* Adapted from Genin et al.⁵ Listed rates are the average of Rochester and PAQUID incidence rates. Figures are rounded for simplicity and 95% confidence intervals are not shown. Please see original publication for complete details.

References:

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