APOE genotyping in Alzheimer's disease

Risk assessment prior to initiating anti-amyloid therapy

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Apolipoprotein E (*APOE*) genotype is a risk factor for adverse effects from new disease-modifying therapies for Alzheimer's disease. The *APOE* ε4 allele is associated with the highest risk, especially when present in two copies in homozygous carriers. *APOE* genotyping is therefore recommended for individual risk assessment prior to treatment with anti-amyloid drugs.

ALZHEIMER'S DISEASE

Alzheimer's disease is the most common cause of dementia in old age and is associated with progressive and irreversible loss of memory and cognitive function. The number of cases is rising rapidly and is projected to continue growing over the coming decades without any progress in treatment and prevention. Most cases of Alzheimer's disease occur in people over 65. The prevalence doubles with about every five years of age, from just over 1% in the age group 65 to 69 to more than 25% in those over 90 years old (1).

PATHOLOGY AND DIAGNOSTICS

The primary hallmark of Alzheimer's disease is the formation of deposits of amyloid-beta in the brain, which disrupt vital neuronal processes and lead to the destruction of nerve cells. The rest of the disease process, like neurofibrillary tau tangles results from an imbalance between amyloid-beta production and clearance (2) (**Fig. 1**).

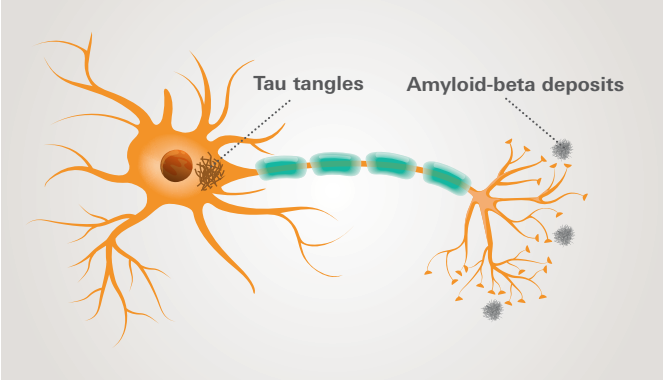

Fig. 1. Graphic illustration of a neuron with amyloid-beta deposits and tau tangles.

> *New disease-modifying therapies can delay disease progression in patients with early-stage Alzheimer's disease*

Early diagnosis of Alzheimer's disease is important for effective therapy management and planning of long-term care and support. Diagnosis of Alzheimer's disease is based on clinical evaluation, imaging methods such as positron emission tomography (PET) and analysis of biomarkers in cerebrospinal fluid (CSF). The most important CSF biomarkers are the amyloid-beta 1-42 to 1-40 ratio, phosphorylated tau and total tau. These markers can be measured, for example, by ELISA or chemiluminescence immunoassay (ChLIA).

NEW ERA OF THERAPY

Although Alzheimer's disease cannot be cured, new disease-modifying therapies can delay disease progression in patients with early-stage Alzheimer's disease (3). Unlike traditional therapies which only relieve symptoms, the novel drugs tackle the underlying cause of the disease. They are based on monoclonal antibodies, which facilitate the removal of amyloid-beta plaques in the brain and thus slow down cognitive and functional decline. To be effective, anti-amyloid therapies must be implemented in the prodromal stage of mild cognitive impairment.

The first drug on the market, aducanumab (Aduhelm® from Biogen), received U.S. FDA approval in 2021 under the accelerated approval pathway. A second drug, lecanemab (Leqembi® from Eisai and Biogen), received traditional U.S. FDA approval in 2023 for treatment of patients in the early stage of Alzheimer's disease with confirmed amyloid

pathology as demonstrated by PET or CSF testing. In late 2024 the European Medicines Agency (EMA) recommended the authorisation of lecanemab in the treatment of mild cognitive impairment or mild dementia in Alzheimer's patients with no or only one copy of the *APOE* ε4 allele (4). The licensing of lecanemab by the United Kingdom's Medicines and Healthcare products Regulatory Agency (MHRA) is similarly restricted to treatment of *APOE* e4 non-carriers and heterozygotes. Lecanemab has further been approved in, for example, Japan, China, South Korea, Hong Kong, Israel and the United Arab Emirates and is under regulatory review in many countries.

Another new drug, donanemab (Kisunla™ from Eli Lilly and Company) was approved by the U.S. FDA in 2024 for treatment of adults with early symptomatic Alzheimer's disease. Many further promising anti-amyloid drugs are in the pipeline.

> *Determination of the APOE genetic variant is recommended prior to initiation of anti-amyloid therapy to assess the risk of negative consequences.*

SIDE EFFECTS OF ANTI-AMYLOID THERAPIES

Anti-amyloid treatments can in some individuals induce side effects which are linked to the *APOE* genotype. The adverse effects include amyloid-related imaging abnormalities (ARIA) with edema and/or effusion (ARIA-E) or hemorrhagic changes (ARIA-H) (2, 5). Although mainly asymptomatic, ARIA may cause additional symptoms such as headache, confusion, visual changes, dizziness, nausea and gait difficulty. A few cases have even been fatal.

There are three clinically relevant *APOE* alleles, which are denoted ε2, ε3 and ε4. Carriers of the ε4 allele have a greater risk of side effects, with homozygous carriers considered at highest risk. The rate of ARIA amounted to 5.4% in ε4 non-carriers, 10.9% in heterozygotes and 32.6% in homozygotes. Rates of symptomatic ARIA were 1.4%, 1.7% and 9.2%, respectively (6).

SIGNIFICANCE OF *APOE* GENOTYPING

Determination of the *APOE* genetic variant is recommended prior to initiation of anti-amyloid therapy to assess the risk of negative consequences. Information about the increased risk of ARIA for ε4 carriers compared to other genotypes can be included in patient management decisions. In patients receiving lecanemab, post-treatment monitoring is directed principally at detecting ARIA, and heightened vigilance for ARIA is recommended in ε4 carriers, especially homozygotes (6). Homozygous ε4 carriers are, however, excluded from treatment with lecanemab by some agencies (e.g. EMA and U.K. MHRA) due to an uncertain level of benefit versus risk.

APOLIPOPROTEIN E

Apolipoprotein E (ApoE) is a lipid transporter which delivers cholesterol and phospholipids throughout the body. ApoE plays a role in Alzheimer's disease by interacting with amyloid-beta and regulating its aggregation and clearance (7). ApoE also contributes to various systems by binding to several receptors on the cell surface which are involved in, for example, neuronal signalling. Three different isoforms of the ApoE protein, E2, E3 and E4, can be produced depending on the allele. These differ in the amino acids at positions 130 and 176 (112 and 158) (8,9) **(Fig. 2)**.

APOE GENETIC VARIANTS

Of the three *APOE* alleles, variant ε3 is the most frequent. ε3/ε3 is considered the normal genotype and is carried, for example, by 63% of the population. The ε4 allele is associated with an increased risk of developing Alzheimer's disease. This variant occurs at frequencies of 21% for the heterozygous ε3/ε4 form, 2% for the combination ε2/ε4, and 2% for the homozygous ε4/ε4 form. The ε2 allele, on the other hand, is neuroprotective for Alzheimer's disease. 11% of the population carry the heterozygous ε2/ε3 form and 1% the homozygous ε2/ε2 form (10).

The ε4 allele is found around three times more frequently in Alzheimer's disease patients than in the cognitively normal population, corresponding to about 38% compared to 14%, respectively (11). In contrast, the ε2 allele occurs in just 3.9% of Alzheimer's patients compared to 7% of cognitively normal persons. Furthermore, the ε4 gene dosage impacts both

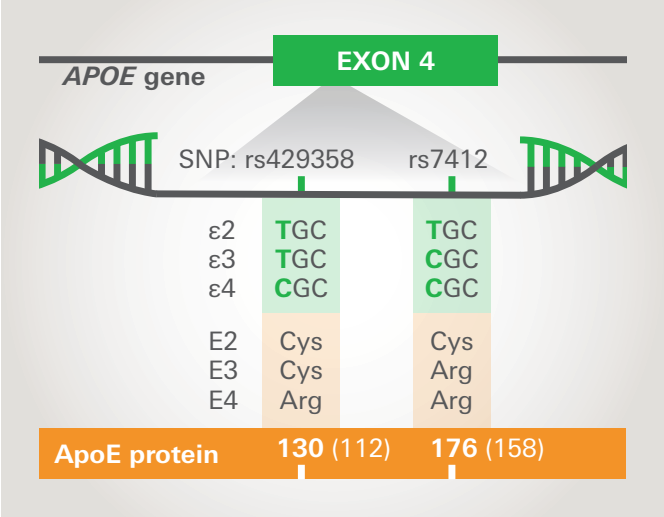

Fig. 2. Scheme of *APOE* gene polymorphism and its effect on amino acid level (according to Zhong et al. 2016 and Harrison et al. 2024).

the disease risk and the age at which late-onset Alzheimer's disease manifests. The relative risk of developing late-onset Alzheimer's disease with respect to the genotype is in ascending order: ε2/ε2, ε2/ε3, ε2/ε4, ε3/ε3, ε3/ε4 and ε4/ε4. The average age of disease onset amounts to 84 years for non-ε4 carriers, 76 years for heterozygote carriers and 68 years for homozygous carriers (12).

PCR-BASED GENOTYPING TEST

A real-time PCR test to determine the *APOE* genotype has been developed by EUROIMMUN (13). The multiplex EURORealTime APOE detects the *APOE* ε2, ε3 and ε4 alleles and deduces the six possible genotypes ε2/ε2, ε2/ε3, ε2/ε4, ε3/ε3, ε3/ε4 and ε4/ε4. Only one reaction is required per patient sample. The test is performed on genomic DNA (gDNA) isolated from EDTA blood samples. The assay processing can be automated on established instruments, and results are evaluated, documented and archived automatically using the software EURORealTime Analysis.

CONCLUSION

APOE genotyping is an important analysis for decision-making on anti-amyloid therapy in patients with Alzheimer's disease. The information gained from *APOE* genetic testing helps clinicians to assess the risk of adverse effects and implement a more personalised approach to anti-amyloid therapy. *APOE* genotyping can also guide design of clinical trials and selection of suitable participants for research on promising future therapeutics.

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