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Abstracts

Articles appearing in the February 2021 issue

Can Anti–β-amyloid Monoclonal Antibodies Work in Autosomal Dominant Alzheimer Disease?

The dominant theory of Alzheimer disease (AD) has been that amyloid-β (Aβ) accumulation in the brain is the initial cause of the degeneration leading to cognitive and functional deficits. Autosomal-dominant Alzheimer disease (ADAD), in which pathologic mutations of the amyloid precursor protein (APP) or presenilins (PSENs) genes are known to cause abnormalities of Aβ metabolism, should thus offer perhaps the best opportunity to test anti-Aβ drugs. Two long-term preventive studies (Dominantly Inherited Alzheimer Network Trials Unit Adaptive Prevention Trial [DIAN-TU-APT] and Alzheimer Preventive Initiative–ADAD) were set up to evaluate the efficacy of monoclonal anti-Aβ antibodies (solanezumab, gantenerumab, and crenezumab) in carriers of ADAD, but the results of the DIAN-TU-APT study have shown that neither solanezumab nor gantenerumab slowed cognitive decline in 144 subjects with ADAD followed for 4 years, despite one of the drugs (gantenerumab) significantly affected biomarkers relevant to their intended mechanism of action. Surprisingly, solanezumab significantly accelerated cognitive decline of both asymptomatic and symptomatic subjects. These failures further undermine the Aβ hypothesis and could support the suggestion that ADAD is triggered by accumulation of other APP metabolites, rather than Aβ.

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MAP3K6 Mutations in a Neurovascular Disease Causing Stroke, Cognitive Impairment, and Tremor

Objective To describe a possible novel genetic mechanism for cerebral small vessel disease (cSVD) and stroke.

Methods We studied a Swedish kindred with ischemic stroke and intracerebral hemorrhage, tremor, dysautonomia, and mild cognitive decline. Members were examined clinically, radiologically, and by histopathology. Genetic workup included whole-exome sequencing (WES) and whole-genome sequencing (WGS) and intrafamilial cosegregation analyses.

Results Fifteen family members were examined clinically. Twelve affected individuals had white matter hyperintensities and 1 or more of (1) stroke episodes, (2) clinically silent lacunar ischemic lesions, and (3) cognitive dysfunction. All affected individuals had tremor and/or atactic gait disturbance. Mild symmetric basal ganglia calcifications were seen in 3 affected members. Postmortem examination of 1 affected member showed pathologic alterations in both small and large arteries the brain. Skin biopsies of 3 affected members showed extracellular amorphous deposits within the subepidermal zone, which may represent degenerated arterioles. WES or WGS did not reveal any potentially disease-causing variants in known genes for cSVDs or idiopathic basal ganglia calcification but identified 1 heterozygous variant, NM_004672.4 *MAP3K6* c.322G > A p.(Asp108Asn) that cosegregated with the disease in this large family. *MAP3K6* has known functions in angiogenesis and affects vascular endothelial growth factor expression, which may be implicated in cerebrovascular disease.

Conclusions Our data strongly suggest the *MAP3K6* variant to be causative for this novel disease phenotype, but the absence of functional data and the present lack of additional families with this disease and *MAP3K6* mutations still limit the formal evidence for the variant's pathogenicity.

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