A MISSENSE MUTATION IN CALHM1 FOUND IN AN EARLY ONSET ALZHEIMER´S DISEASE PATIENT ALTERS CALCIUM HOMEOSTASIS AND APP PROCESSING

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Introduction: Ca\(^{2+}\) homeostasis dysregulation may play an important role in the pathogenesis of Alzheimer’s disease (AD). Recently, a nonsynonimous genetic polymorphism (p.P86L) of the Ca\(^{2+}\) homeostasis modulator gene, CALHM1, has been shown to alter Ca\(^{2+}\) permeability, increase amyloid-\(\beta\) peptide (A\(\beta\)) levels, and the risk of late-onset AD.

Aims: To test if mutations within CALHM1 gene could lead to an early-onset form of AD.

Methods: CALHM1 coding regions was sequenced in 98 early onset AD (EOAD) patients without mutations in the amyloid precursor protein (APP) and presenilin genes. Total human A\(\beta\) was measured by ELISA in the conditioned medium of HEK cells stably expressing the Swedish APP mutation. Electrophysiological alterations were also analyzed before and 24 hours after calcium add-back.

Results: We found a novel mutation (p.G330D) in an EOAD patient, that was absent in 637 healthy controls. The mutation had profound effects on calcium homeostasis and APP processing. It also reduced Ca\(^{2+}\) permeability, and increased extracellular A\(\beta\) levels by enhancing the \(\beta\)-secretase cleavage of APP. The p.P86L polymorphism had intermediate effects between the wild-type and the p.G330D-mutated protein.

Conclusions: Our data indicate that rare genetic variants in CALHM1 may result in Ca\(^{2+}\) dysregulation and enhanced amyloidogenic processing of APP. We propose that these disturbances may be relevant pathophysiological processes in EOAD.