MUTATIONS AT THE NOTCH3 GENE IN THE NORMAL ELDERLY ARE ASSOCIATED WITH CEREBRAL SMALL VESSEL DISEASE

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Introduction: Cerebral small vessel disease (cSVD) detected as white matter lesions (WMLs) and lacunes is highly prevalent in the elderly. It progresses rapidly enhancing the risk for stroke, dementia and depression. Major risk factors are age and hypertension. Its heritability is between 50-73\%. cSVD shows remarkable similarities with CADASIL including MRI presentations, histopathology and clinical correlates. CADASIL is caused by mutations in NOTCH3 gene.

Aims: Test the hypothesis that genetic variations at NOTCH3 are related to the development of cSVD.

Methods: The study cohort was the Austrian Stroke Prevention Study, a community-based, longitudinal cohort study on brain aging. WMLs were scored and their measured cross-sectional and longitudinal. All 33 exons, the promoter and 3'-UTR of NOTCH3 were sequenced in 186 probands with severe cSVD and in 91 probands without. All detected common SNPs were genotyped by real-time PCR in the whole cohort (N=888).

Results: We detected 9 common (MAF>5\%) and 33 rare SNPs (MAF< 5\%). Four common SNPs were associated with presence of WML (p=0.015) and their progression(p=0.05). There were 9 non-synonymous rare SNPs only present in severe WMLs. SIFT analyses and simulation of the protein structure predicted at least 7 of these SNPs is functional.

Conclusions: This is the first study investigating NOTCH3 variations in the normal population. We show that NOTCH3 is highly variable and that both rare and common SNPs may play a role in age-related cSVD. NOTCH3 signaling may therefore represent a common pathway and a therapeutic target in both CADASIL and in age-related cSVD.