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Loss of function mutations in dipeptidyl peptidase 6 in Alzheimer disease and Frontotemporal dementia: a novel pathway in neurodegeneration

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Molecular genetic studies have contributed importantly to our current knowledge of the pathogenesis of neurodegenerative dementia such as Alzheimer disease (AD) and frontotemporal dementia (FTD). Yet the genetic underpinnings still remain to be completely disclosed, as proven by the missing genetic etiology in families as well as patients with very young age at onset and/or positive family history. In a previous genome-wide linkage study on an autosomal dominant AD family, we identified a genetic locus of 5.44 Mb at chromosome 7q36, but the underlying disease-linked mutation remained to be identified (Rademakers et al. Am J Hum Genet. 2005; 77 643–52). The rationale of the current study is the reinvestigation of the unresolved linkage locus. Whole genome sequencing (WGS) was performed on 4 patients from the pedigree. This led to the identification of a genomic inversion of ~ 4Mbon the disease haplotype with the distal breakpoint in intron 1 of dipeptidyl peptidase 6 (DPP6) and the proximal breakpoint outside the linked locus in an intergenic region. DPP6 is mostly expressed in brain where it modulates the expression and the function of the potassium channel Kv4.2, regulating synaptic excitability. Massive parallel DPP6 re-sequencing was performed in both Belgian AD (n = 335) and FTD (n = 453) patients as well as control individuals (n = 755). This revealed a significant enrichment of rare variants in the FTD cohort (23/453, 5.08%) compared to control individuals (13/755, 1.72%; SKAT-O p-value = 0.001, relative risk (RR) = 3.0, 95% confidence interval (CI) = 1.51–5.95). In the smaller AD cohort, we observed a non-significant trend in the same direction (RR = 2.1, 95% CI = 0.95–43.63; SKAT-O p-value 0.15). Expression studies on brain tissue of mutation carriers showed a decreased expression of DPP6 transcript (p-value = 0.0096), which was further confirmed on protein level. A decreased Kv4.2 protein expression was also detected in patient carriers when compared to control individuals. Electrophysiology studies in Xenopus laevis oocytes showed a significant negative effect (p-value < 0.05) on Kv4.2 gating properties when the channel was co-expressed with protein truncating loss-of-function (LoF) variants, identified only in patients. In this study, we identified a chromosomal inversion on the 7q36 genomic locus segregating with the disease, thus explaining the linkage signal previously detected in the family. This inversion is predicted to lead to LoF of DPP6 by detaching the first coding exon from the gene. Additional premature protein truncating LoF variants were also identified only in patients. We suggest that LoF variants in DPP6 may lead to synaptic hyperexcitability, thus providing genetic support to the emerging concept of brain network activity alteration as an early event in the neurodegenerative process.