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A novel Beta synuclein mutation associated with neurodegeneration and beta-amyloid deposition causing dementia

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Background: Beta – synuclein (B-Syn) is a presynaptic protein encoded by the synuclein Beta locus (SNCB) on chromosome 13 and is predominantly expressed in the brain. B-Syn, together with alfa synuclein and gamma synuclein, forms a group of proteins dubbed "synucleins" [1]. Although the physiologic role of B-Syn has not been fully elucidated it has been shown to inhibit alpha synuclein aggregation while recent reports suggest that elevated B-Syn levels in cerobrospinal fluid is an early and specific diagnostic biomarker for Alzheimer's disease [7-12]. Mutations of SNCB previously described (P123H LB and V70M) were associated with clinical and neuropathological diagnosis of Lewy body dementia. [2-3-4-5-6]
We describe here two consanguineous female patients (cousins) carrying a heterozygous variant in the SNCB gene, NM_003085.5: c.382C>G p. (Gln128Glu), not reported in literature and rare in the general population (absent in the gnom AD database). The substitution alters a highly preserved amino acid residue. Both subjects had an early onset cognitive decline (pt 1=56 ys, pt 2=65 ys), in addition patient 1 has familial hypercholesterolemia, macular degeneration and amyloid angiopathy. Both of them show a similar onset of cognitive impairment with memory loss without motor signs. They have a comparable CSF profile typical of AD (A+T+N+) and both of them were positive at florbetaben PET brain scan and neurodegeneration at MR imaging indicative of Alzheimer's disease.

Conclusions: This is the first time for a SNCB mutation associated with diagnosis of Alzheimer Disease (A+T+N+). Although the specific mechanism remains undefined, previous studies and our findings suggest that alterations of beta-synuclein protein might play a role in the pathogenesis of AD clinical phenotypes and that alterations of B-Syn structure or function may play an amyloidogenic role.

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