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A protective mutation against Alzheimer disease?

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To date, nearly 35.6 million people world wide live with dementia, and the situation is going to get worse by 2050 with 115.4 million cases.[1] In the western world, the prevalence for dementia in people over the age of 60 is greater than 5% and two thirds are due to Alzheimer disease,[2-5] the most common form of dementias.

Alzheimer disease (AD), first described as "presenile dementia" by the German psychiatrist and neuropathologist Alois Alzheimer in 1906,[6] is a devastating disease characterized by progressive cognitive deteriorations, as well as impairments in behavior, language, and visuospatial skills.[7] Furthermore, Alzheimer discovered the presence of intraneuronal tangles and extracellular amyloid plaques in the diseased-damaged brain, the hallmarks of Alzheimer disease.

More specifically, the neuropathological features observed in postmortem AD brains are a selective neuronal and synaptic loss in cortical and subcortical regions, the deposition of extracellular senile plaques, cerebral amyloid angiopathy, and the presence of intracellular neurofibrillary tangles (NFT).[7] The extracellular senile plaques are mostly composed of amyloid-β peptides (Aβ). Aβ is a cleavage product of the amyloid precursor protein (APP), which is sequentially processed by several proteases, the so-called secreatases α, β and γ. The APP cleavage by β-secretase (also known as beta-site APP cleaving enzyme-1 BACE1)[8] produce a soluble form of APP (β-APP_s) and a 99-amino acid C-terminal fragment (C99) that remains anchored in the plasma membrane.[9] In contrast, α-secretase products consist of a 83-amino acid C-terminal fragment (C83) and α-APP_s. Both C-terminal fragments (C99 and C83) are substrates for the γ-secretase complex. Most of the Aβ species produced by the γ-secretase are the 40-amino acid and 42-amino acid peptides, $Aβ_{40}$ and $Aβ_{42}$ respectively. $Aβ_{42}$ is hydrophobe, tends to form fibrils, and represents the major constituent of extracellular depositions in AD brains.

To date, 30 mutations in the gene encoding for APP protein have been described. The majority of these mutations result in an autosomal dominant form of Alzheimer disease with an early onset.[10-12] Mutations that occur near the β– or γ-secreatase cleavage sites result in overproduction of total Aβ, or a shift in the $Aβ_{40}/Aβ_{42}$ ratio toward the longer $Aβ_{42}$ peptide.[13]

In a recent study published in *Nature,* Jonsson et al. have screened the whole genome of 1.795 Icelandders for coding variants of APP, and discovered a new rare mutation in the APP gene that in contrast to previous described mutations may protect against Alzheimer disease.[14] The authors investigated the linkage of the APP variants with the protective effect from Alzheimer disease by screening close relatives of the gene variant carriers. Individuals that have lived to at least age 85 without apparent Alzheimer disease symptoms served as a control group. The results show that substitution of alanine to threonine at position 673 (A673T) was significantly more common in the control group than in Alzheimer patients, suggesting that this mutation might prevent the development of Alzheimer disease. Interestingly, this mutation is located at an important position close to the β-secretase

(BACE1) cleavage site, suggesting a possible interplay with the processing of APP. In order to investigate if the A673T mutation affects the proteolytic cleavage of APP, the authors analyzed the formation of APP fragments by using HEK293T cells transfected with wild-type or mutant APP (APP^{A673T}). The cell supernatant was tested for total APP, β-APP_S and α-APP_S levels by Western Blot. The authors observed that the cleavage of the APP^{A673T} variant by α- and β-secreatase (BACE1) results in a reduced production of β-APP_S compared with wild-type APP. This result was confirmed by quantitative sandwich ELISA assay showing a 50-fold less β-APP_S production in cells expressing the APP^{A673T} variant, with no significant change in α-APP_S. In addition, the production of $Aβ_{40}$ and $Aβ_{42}$ cleavage products resulting from the processing of APP^{A673T} was decreased by 40-fold compared to the wild-type APP.

Interestingly, it was previously shown that substitution of the same alanine at position 673 to a valine (A673V) in contrast increases the risk for Alzheimer disease in homozygote carriers, with the development of amyloid fibrils, possibly by promoting the formation of Aβ.[15] Consistent with this previous observation, the authors demonstrate that the A673T APP mutation reduces BACE1-dependent cleavage of APP, whereas the A673V mutation increases the processing. Finally, using in vitro BACE1 cleavage assay on synthetic APP peptides, the authors show that the APP^{A673T} peptide is 50-fold less processed than the wild-type peptide, supporting the idea that the A673T mutation prevents the cleavage by BACE1. Taken together, the authors demonstrated that alanine at position 673 in the APP protein is critical for amyloidogenic processing of APP by β-secretase (BACE1).

In summary, the authors have identified for the first time a mutation in the gene encoding for APP that prevents the processing of the protein and segregates exclusively with patients who never shown any sign of dementia, suggesting a possible protective role against Alzheimer disease. However, it remains unclear if the absence of any sign of dementia in these patients exclusively relies to the presence of the A673T mutation in APP, or if some other individual-related genetic and social specificities also contribute to the behavior. Reintroducing the APP^{A673T} mutation into rodent will provide an interesting animal model to further investigate the neuronal behavior of this mutation. Moreover, it will provide interesting information about the molecular mechanism by which this mutation might protect from Alzheimer disease. Although the authors have provided compelling evidence that the 673T mutation prevents the processing of APP by BACE1, some details can still not be explained. Hence, one of the major controversies in the APP hypothesis of Alzheimer disease is the amount of Aβ deposits in the brain that does not always correlates with the degree of cognitive impairment that the patient experienced. Indeed, various postmortem reports of patients who never shown any symptoms of dementia have revealed high content of Aβ deposit in the brain.[16] Moreover, besides to be highly expressed in the brain, β-secretase has also been found in a variety of other human tissues,[17-19] and increasing evidence indicates an involvement of BACE1 in the myelination process.[20-23] Hence, it was recently shown a protective effect of Aβ in an experimental autoimmune encephalomyelistis (EAE) model of multiple sclerosis.[24] Considering that the A673T mutant reduces the production of Aβ, it might be interesting to evaluate if a correlation exist between the presence of the mutation and an eventual higher risk to develop some forms of encephalomyelistis.

Overall, the authors have provided important information that definitively contributes to our genetic knowledge of Alzheimer disease, essential for early diagnosis of the disease before the occurrence of the symptoms. Finally, the discovery that a point mutation in the gene encoding for APP, by decreasing the production of Aβ, might produce protective effect against Alzheimer disease is definitively exciting and might ultimately open therapeutic strategies for the development of clinically relevant molecules.

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