Structural and functional analysis of mutations in presenilin-1 protein and its relation with Early-Familiar Alzheimer's disease through bioinformatics and hybrids methods quantum mechanics and molecular mechanics (QM/MM).

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Alzheimer's disease is the most frequent dementia found by researchers as epidemiology in clinical studies, besides this disease is related for two aspects as: the formation of β-amyloid plaques and the neurofibrillary tangles by hyper-phosphorylation of τau protein.(1). The formation of β-amyloid plaques, which are given by the accumulation of the neurotoxic peptide of 40-42 amino acids, which is generated by cleavage of the amyloid precursor protein (PPA) which is mediated by the γ-secretase complex and the active site in presenilin-1 protein (2,3).

The active site of the enzyme γ-secretase is the subunit presenilin-1 (PSEN-1) responsible of final cleavage of substrate peptide precursor of amyloid (PPA), the protein PSEN-1 does not have a complete monocrystal structure (4,5). The prediction of missing fragment was estimated with computational approach from protein structure predictors such as I-Tasser, Phyre2 and Quark, which visualized with a U.C.S.F Chimera software and the positional characterization with the Hidden Markov Models software.

The hypothetical model is helpful to study the mutations effect in the structure of PSEN-1 and the electronic correlation with stochastic method, using quantum mechanics and molecular mechanics in hybrid method with the software spartan14' of wave function. The results indicate that several of the mutations identified have a close relationship with the disease, given that the structural changes are transcendental, such as, change in distance bonding, dihedral angle, potential-potential surfaces and electrostatic map in the alteration of function.

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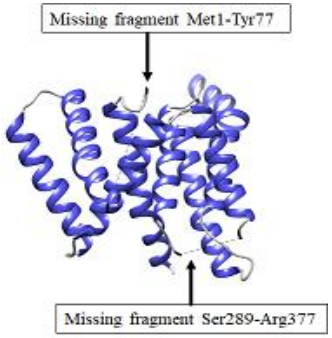

Figure 1. Crystallized structure of subunit PSEN-1 with missing fragments.

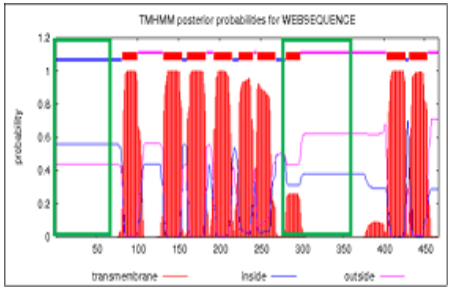

Figure 2. Transmembrane analysis in PSEN-1 with hidden markov model TMHMM.

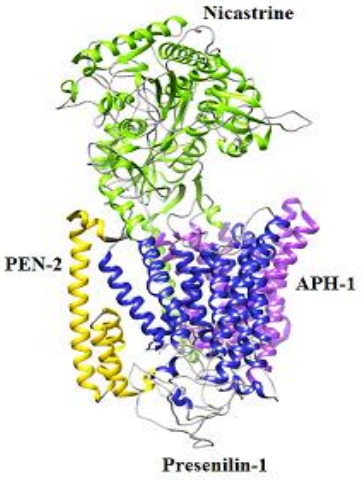

Figure 3. γ-secretase complex with the complete structure of PSEN-1 in hypothetical purpose of subunit of active site.

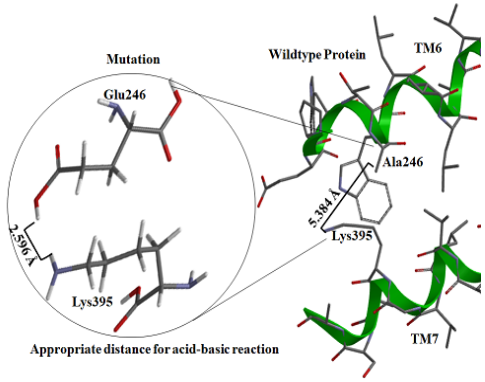

Figure 4. Non covalent interaction of structural analysis of mutation Ala246Glu in PSEN-1