

ABSTRACT

Beta-Secretase is a transmembrane aspartic protease that cleaves the amyloid precursor protein (APP) to generate amyloid beta peptide ($A\beta$) that is believed to be responsible for the Alzheimer's disease (AD). Beta-Secretases include BACE1 and BACE2 which are close homologues, sharing 61.5% similarity and 45% identity at the amino acid level. BACE1 is responsible for generating amyloid plaques in Alzheimer's disease through cleaving $A\beta$ peptides from the amyloid precursor protein, however, the fragments of $A\beta$ produced by BACE2-cleaved have not been observed in senile plaques in AD. The early onset of dementia in patients with Down's syndrome is believed to be associated with BACE2, and it is believed to be greatly expressed in breast cancers. Although the structure of BACE1 and BACE2 are very similar, there are some important differences between their sequences and structure which made their function different with each other. In this study, I compared the conservation pattern of BACE1 and BACE2 throughout species and identified their active site by using evolutionary trace method. By using this method we can rank the functional significance of amino acids in the protein structure and also imply some data about the protein sequence-structure-function relationship. The result of this study identified that, in BACE1 and BACE2 structures, most of the conserved residues are located in the ligand binding site which are the key functionally residues for their activities. The other few conserved residues are more or less randomly localized in the rest of the structure. Also it was observed that, the structure of BACE1 and BACE2 reveals differences in some active site residues which may be of interest for the design of selective BACE1 or BACE2 inhibitors.

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LIST OF ABBREVIATIONS

AD	Alzheimer's Disease
APP	Amyloid Precursor Protein
A β	Amyloid Peptide
α -Secretases	Alpha Secretase
β -Secretases	Beta Secretase
γ -Secretases	Gamma Secretase
BACE1	Beta amyloid cleaving enzymes 1
BACE2	Beta amyloid cleaving enzymes 2
ET	Evolutionary Trace Method
BLAST	Basic Local Alignment Search Tool
MSA	Multiple Sequence Alignment
PDB	Protein Data Bank
3D	Three Dimensional