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Conformational Study of Alzheimer's A β Wild Type Peptide and Flemish Mutant

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Using replica exchange Molecular Dynamics simulations of A β peptide, we compare the ensembles of monomer configurations of the Flemish (A21G) familial Alzheimer's disease mutant the wild type (WT) sequence. Our simulations start from random conformations. We find that similarities between the Flemish and WT A β peptide in terms of the random coil like structure. At room temperature in implicit solvent, the A β_{1-39} monomer does not adopt a unique folded conformation but adopts one of the several low energy structures, with the U-shape configurations that are strongly amphipathic. No beta content is observed which therefore seems to be a product of oligomerization and aggregation.

1 Introduction

Alzheimer's disease (AD) is a neurological disorder, affecting approximately 12.5 and 47.2% of the population in the United States over the ages 65 and 85, respectively. Formation of amyloid fibrils is the hallmark of Alzheimer's disease. These A β peptides are released from proteolytic cleavage of the amyloid precursor protein (APP) as A β_{39} or A β_{42} residue sequence with unknown function. Many familial Alzheimer's disease mutants of the APP protein are external to the A β peptide sequence, and thus influence A β processing, but some set of mutations which cluster near amino acid positions 21 through 23 in the amyloid β peptide possibly changes peptide biochemistry¹. Some well studied point mutations are Flemish (A21G), Arctic(E22G), Italian (E22K), Dutch(E22Q), Iowa(D23N) and double Dutch/Iowa mutants². Despite point mutations near 21/22 region, these mutations show strong differences in the kinetics of the formation of fibril assemblies as compared to wild type A β peptide and in vitro studies have found that A21G (Flemish) mutations slower aggregation kinetic as compared to WT A β and E22G (Arctic) mutations. Hence, this distinction is important for understanding the mechanism of amyloid assembly and critical for correctly assigning the identity of NMR cross peak resonances in 2D structural analysis of A β , where it has been assumed that the peptide is monomer. Thus the present study focus on the effect of mutation (A21G) on the monomer structure of A β_{39} Wild Type(WT) by performing molecular dynamics simulations.

2 Material and Methods

The peptide A β originally consists of 42 amino-acid residues: [Asp-Ala-Glu-Phe-Arg-His-Asp-Ser-Gly-Tyr-Glu-Val-His-His-Gln-Lys-Leu-Val-Phe-Phe-Ala-Glu-Asp-Val-Gly-Ser-Asn-Lys-Gly-Ala-Ile-Ile-Gly-Leu-Met-Val-Gly-Gly-Val-Val-Ala-Ala], which is usually expressed as A β . Replica exchange Molecular Dynamics (MD) and canonical MD

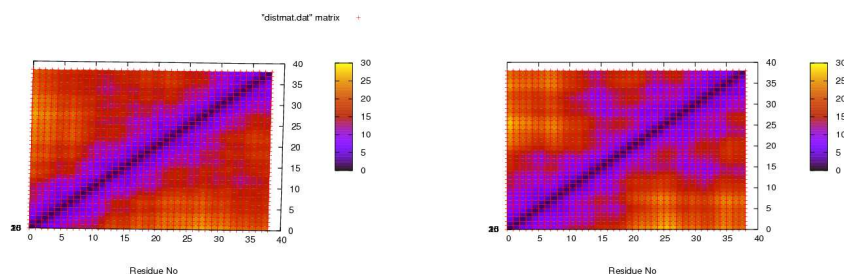


Figure 1. Contact map for $C\alpha$ - $C\alpha$ for WT and Flemish mutant.

simulations are carried out with the AMBER9 program, using all atom force field ff99. The effect of solvation is approximated by a generalized Born solvent implicit solvent model, with random starting geometry. Sixteen replicas are simulated at temperatures range of 200 K to 640 K and periodically swapped between neighboring temperatures. Exchange attempts are made after every 0.02ps of simulation. High temperature simulation segments facilitate the crossing of the energy barriers while the low temperature ones explore in detail energy minima^{3,4}. The Shake algorithm is used to constraint all bond lengths. In the canonical simulation, temperature is set by velocity reassignment from a Maxwell-Boltzmann distribution at 291 K and maintained at that temperature by using a Langevin thermostat. About 5,000 steps of minimization is followed by an initial equilibration run.

3 Results and Discussion

In order to probe the structure of $A\beta_{39}$ monomer we have performed multiple replica-exchange and regular canonical molecular dynamics (at $T=291K$) simulations starting with different initial configuration of flemish mutant and WT $A\beta$ peptide. Replica exchange molecular dynamics simulations results indicate that each replicas perform a random walk in temperatures ladder, allowing the replicas to escape local minima. As a consequence, reliable physical quantities are calculated over the whole range of temperatures.

At room temperature, the WT $A\beta$ monomer does not have a unique folded conformation but adopts one of the several low energy structures. The root mean square displacement based clustering analysis⁵ shows that the ensemble at 291K consists of three clusters differ little in their average potential energies (cluster A: 946.09(4) kcal/mol, cluster B: 962.59(2) kcal/mol, cluster C: 949.10 (2) kcal/mol, data for WT $A\beta$ peptide)⁶. All three cluster also share as a common theme the U-shape of the configurations that are strongly amphipathic. The longer arm is made mostly from hydrophilic and charged amino acid residues while the shorter arm is formed exclusively hydrophobic branched residues. However, no beta content is observed in both WT and flemish mutant (1.4%), which therefore seems to be a product of oligomerization and aggregation. A more thorough analysis reveals differences between the various clusters. Cluster A, is a random coil structure with turn around Ala21-Asn27 and appears with a frequency of 58 % in WT $A\beta$ peptide and

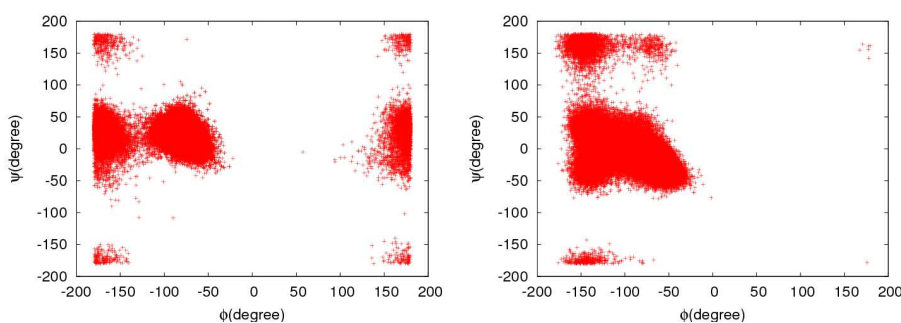


Figure 2. Ramachandran Plot for residue Ala21 and Gly21 in WT and Flemish mutant.

30% in Flemish mutant. We observe that the turn around residues 21-28 is conserved, however having lower probability in Flemish mutant as compared to WT, with turn stabilized by hydrophobic interactions between Val24 and Asn27, Gly25 and Lys28 and electrostatic interactions between Lys28 and Glu22 in WT peptide. The region Leu17-Ala21 in WT A β has a well defined structure and shows considerably smaller structural fluctuations than rest of the peptide, which is consistent with NMR studies^{7,8} that suggest a defined structure around central hydrophobic region and indicates that this region is critical for fibril formation. Configurations of cluster B also shows a random coil like structure with a turn around Val12-Leu17. This cluster appears with a frequency of 29% in WT and 31% in Flemish mutant. In these configurations we observe in WT the salt bridges between residue Asp23-Lys28/16 that have been reported in various experiments as controlling the aggregation rate of A β ⁹. Finally, 13% of configurations are rich in helicity and form cluster C present only in WT A β peptide. Configurations in this cluster are similar to the structure that was determined in a 40% TFE/water solution.¹⁰

In Flemish mutant, Ala21Gly we observe another cluster populated with 39% that has turn shifted from Glu22-Lys28 region to 16-23 region. Gly at position 21 might diminish the N-terminal *beta* strand integrity in amyloid fibril by shifting the turn region, resulting into qualitatively different behavior in the structural integrity of the protofibril. In order to further quantify the variation of the turn region, we calculated the intramolecular distance between N atom of the Lys28 and carbonyl oxygen of Glu22 (distance around 10Å) and various other hydrophobic interaction between Val24 and Asn27, Gly25 and Lys28 (distance around 8Å) present in WT A β peptide, as expected the interactions stabilizing the turn region around 21-28 are not present in this cluster.

Fig. 1 shows the intramolecular C α -C α contact map for Flemish mutant, indicates more populated interactions around region 16-23 as compared to WT A β peptide. However the RMSD plot of the C β A β ₃₀ WT and Flemish mutant displays that similar trend with radius of gyration around 10Å for both the peptides, indicating similar size or end to end distance C α distances for both the monomer. The Ramachandran plot of residues Ala21 in WT and Gly21 in Flemish mutant (Fig. 2) also explores essentially the same the favored regions of ϕ, ψ , indicating no much effect on the flexibility of the monomer around this region. The mean percentage of α -helix, turn and β contents for all the residues in both A β peptide, percentage of beta strand is 1.2% and 35-40% for α helix in Flemish mutant, however no

change in the secondary structure content observed around residue Ala21 and Gly21 in both WT and Flemish mutant.

We found that the region around 17-21 which is conserved in WT A β was not well conserved in Flemish mutant. Even the new cluster lacks the native interactions present in WT A β peptide around the turn region, with some new interactions not specific to native. In native A β peptide the lactam bridge between Asp23 and Lys 28 increases the fibrillogenesis rate by three orders of magnitude, however this bridge is disrupted in Flemish mutant which might explain the possible role of this mutant on slowing the aggregation kinetics of A β peptide and further stabilizing the monomer structure.

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References

1. Goedert, M. and M.G. Spillantini. *Science* **134**,777-781 (2006).
2. Christian Haass and Harald Steiner *Nature Neuroscience* **9**, 859-860 (2001).
3. U. H. E. Hansmann, *Chem. Phys. Lett.* **281**, 140-150 (1997).
4. Y. Sugita, and Y. Okamoto, *Chem. Phys. Lett.* **314**, 141-151 (1999).
5. Michael Feig, John Karanicolas, Charles L. Brooks III, *Journal of Molecular Graphics and Modeling* **22**, 377-395 (2004).
6. Priya Anand, F.S. Nandel and U.H.E. Hansmann *J. Chem. Phys.* **128**, 165102-06 (2008).
7. R. Riek, P. Guntert, H. Dobeli, B. Wipf, and Wu Trich, K., *Eur. J. Biochem.* **268**, 5930-5936 (2001).
8. S. Zhang, K. Iwata, M. J. Lachenmann, J. W. Peng, S. Li, E. R. Stimson, Y. A. Lu, A. M. Felix, J. E. Maggio, and J. P. Lee, *J. Struct. Biol.* **130**, 130-141 (2000).
9. K. L. Sciarretta, D. L. Gordan, A. T. Petkova, R. Tycko, and S. C. Meredith, *Biochemistry*, **44**, 6003-6014 (2005).
10. P. E. Fraser, J. T. Nguyen, W. K. Surewicz, and D. A. Kirschner, *Biophys. J.* **60**, 1190-1201 (1991).