

Supplementary file

Hidden Aggregation Hot-Spots on Human Apolipoprotein E: a Structural Study

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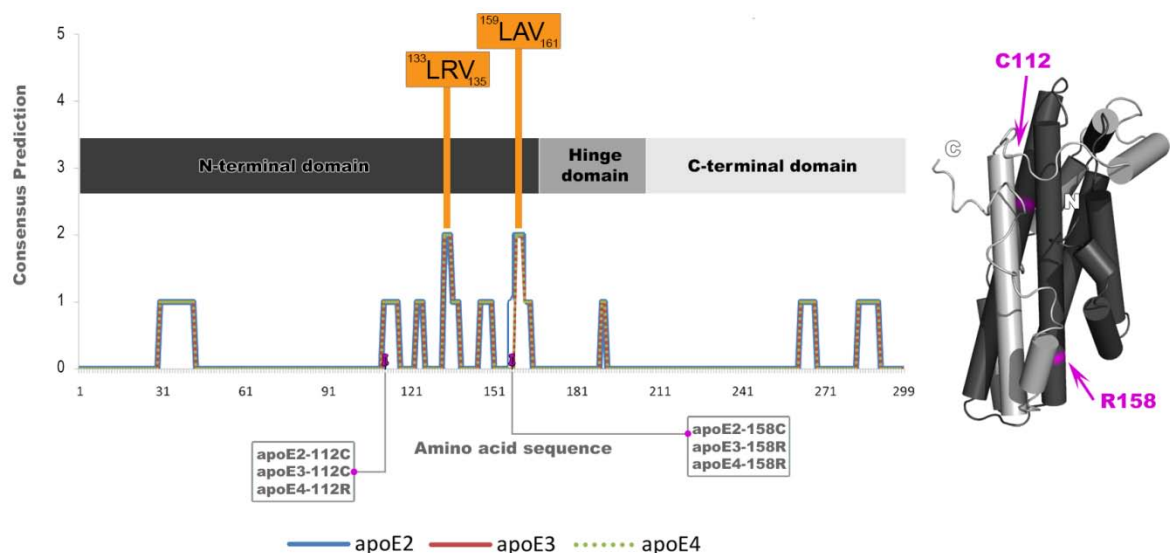


Figure S1. Amyloid propensity histograms of apoE2, apoE3 and apoE4, based on AMYLPRED [1]. Two apoE regions, namely $^{133}\text{LRV}^{135}$ and $^{159}\text{LAV}^{161}$, were recognized as “aggregation-prone” segments (orange boxes). ApoE2 (blue line) has a slightly different profile in comparison to two other isoforms. Residues that differ between isoforms are coloured in magenta on the 3D - NMR structure of apoE.

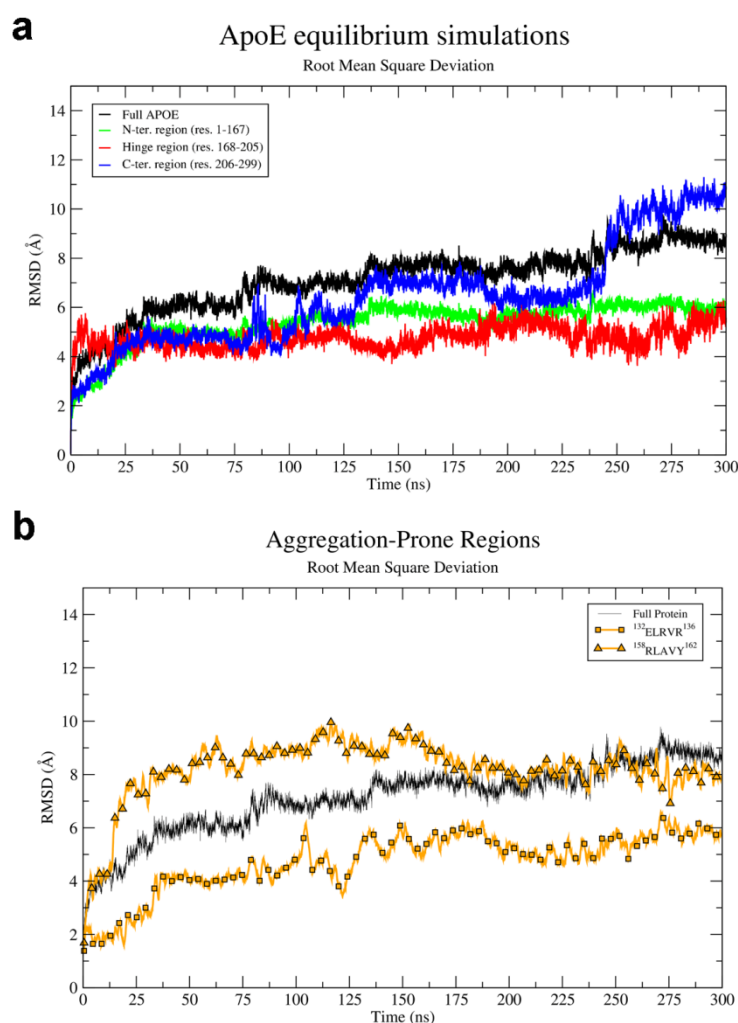


Figure S2. Molecular dynamics simulation diagrams. (a) All three domains are compared with the RMSD of the full-length apoE over time. (N-terminal domain in green, C-terminal domain in blue, hinge domain in red). **(b)** Structural deviations of $^{132}\text{ELRVR}^{136}$ and $^{158}\text{RLAVY}^{162}$ as compared with full-length apoE over 300 ns simulation time. $^{158}\text{RLAVY}^{162}$ exhibits 8 to 10 Å structural fluctuations.

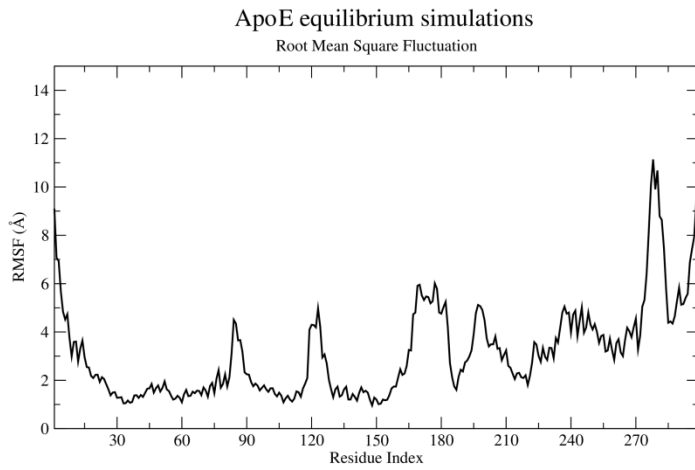


Figure S3. The average RMSF of apoE simulations. C-terminal domain exhibits the highest fluctuation rate (Please refer to the main manuscript for more details).

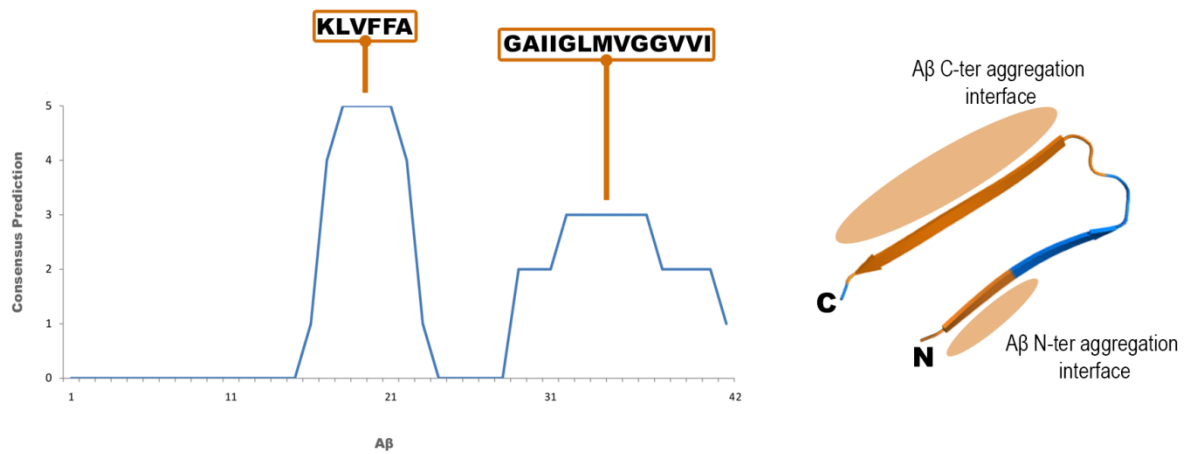


Figure S4. Amyloid propensity histograms of Aβ according to AMYLPRED [1]. Predicted Aβ “aggregation-prone” interfaces (orange) are also represented in the misfolded Aβ form obtained by 2BEG NMR structure [2].

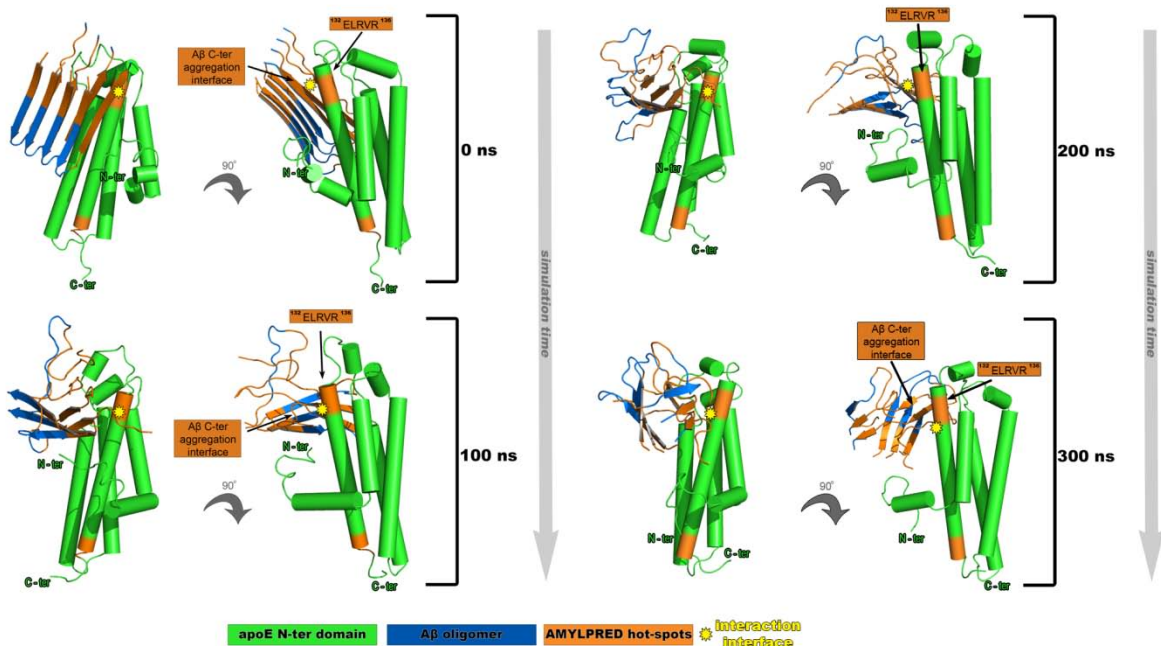


Figure S5. Molecular Dynamics simulations of Aβ-apoE complex for 300 ns. Despite the critical structural rearrangements observed for the Aβ-apoE complex over time, the C-terminal aggregation-prone

epitope of A β anchors the amyloidogenic ¹³²ELRVR¹³⁶ peptide located at the N-terminal apoE domain. (N-terminal apoE domain; green, A β oligomer; navy blue, AMYLPRED hot-spots; orange)

References

1. Frousios, K. K.; Iconomidou, V. A.; Karletidi, C. M.; Hamodrakas, S. J., Amyloidogenic determinants are usually not buried. *BMC structural biology* **2009**, 9, 44.
2. Luhrs, T.; Ritter, C.; Adrian, M.; Riek-Loher, D.; Bohrmann, B.; Dobeli, H.; Schubert, D.; Riek, R., 3D structure of Alzheimer's amyloid-beta(1-42) fibrils. *Proc Natl Acad Sci U S A* **2005**, 102, (48), 17342-7.