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Supplemental Information

Atomistic Insights into Structural Differences between E3 and E4 Isoforms of Apolipoprotein E

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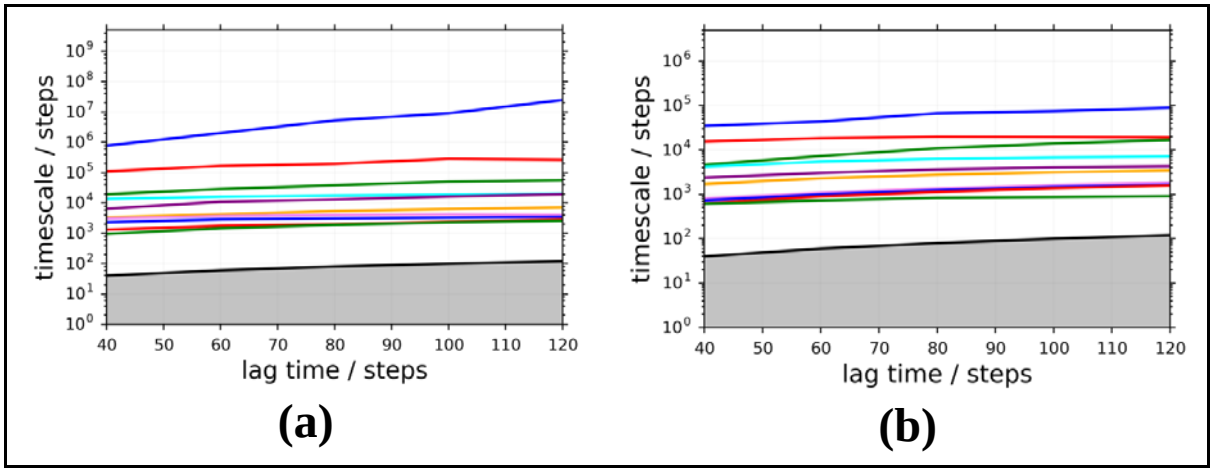


Fig S1. The 10 slowest implied timescales plotted on a log scale as a function of lag time for ApoE isoforms. The trajectory step size is 10 ps. The lag time chosen for all analysis in the main text was 1 ns (100 steps), as the implied time scale leveled off at about 1 ns which ensure the Markovianity of model in (a) ApoE3 and (b) ApoE4.

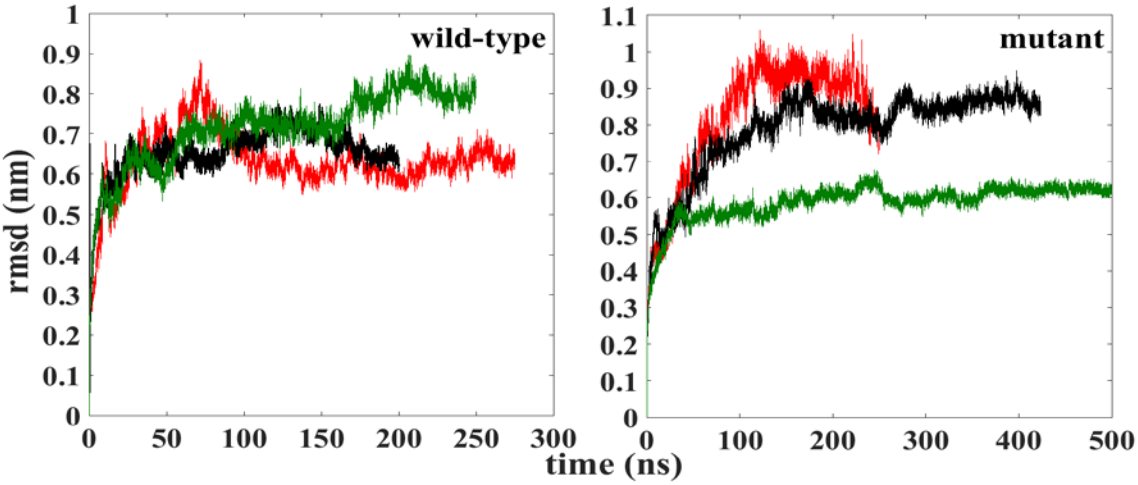


Fig S2. Time evolution plots for RMSD of ApoE3 and ApoE4 (L to R). The three colors indicate three different MD–runs. First 100ns is considered as the equilibration time in each run.

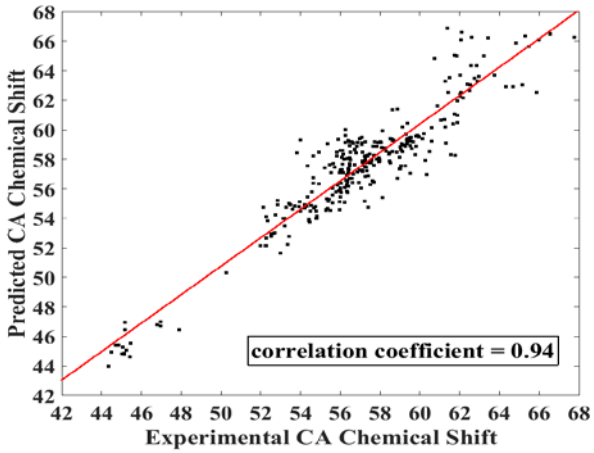


Fig S3. Correlation between the calculated and experimental chemical shift for C-α atoms of ApoE3.

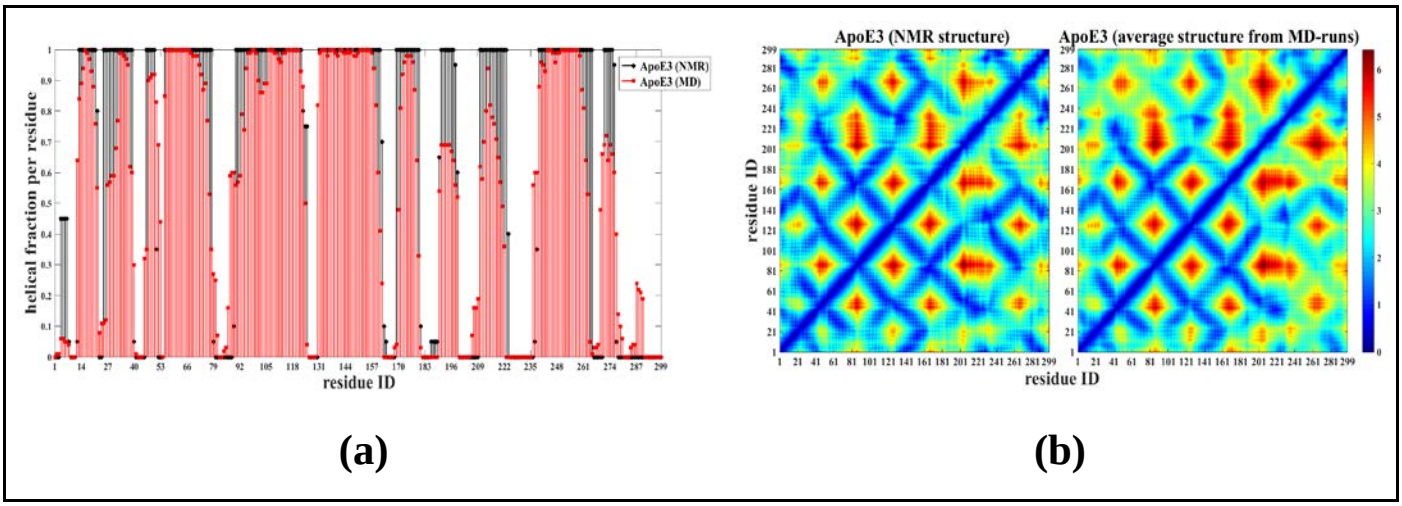
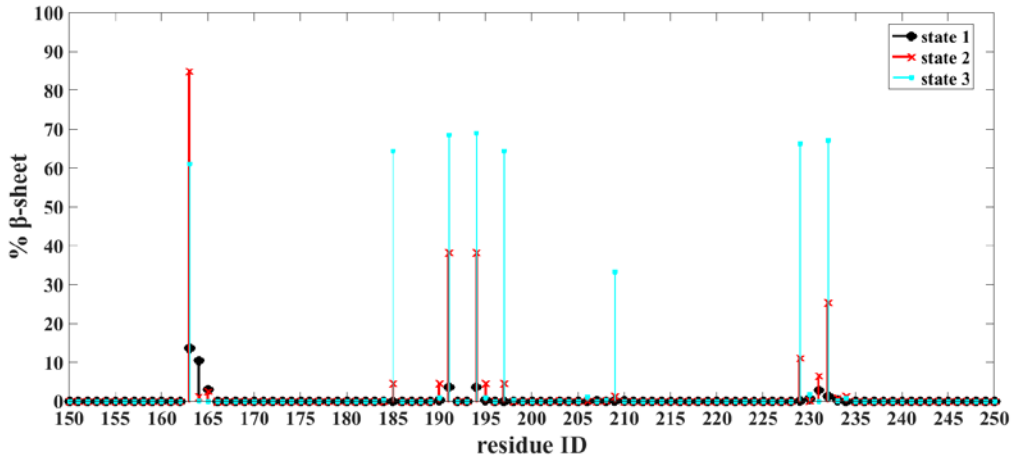
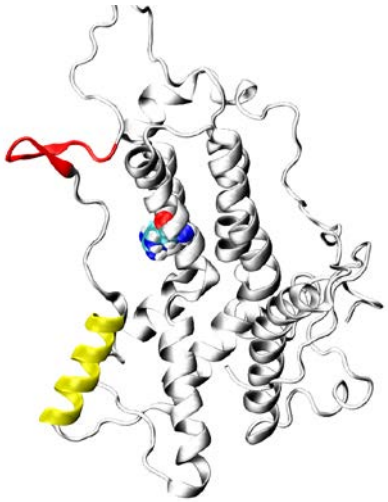


Fig. S4. Difference between ApoE3 NMR structure and MD-run average structure.
(a) Secondary Structure and (b) Contact map plot of ApoE3 NMR ensemble-average structure (black) and MD-run average ApoE3 structure



(a)



(b)

Fig S5. β-sheet content of three ApoE4 macrostates obtained from MSM.
(a) Per residue % β-sheet of ApoE4 macrostates. Residues 190-200 (hinge helix 2 region) have higher β-sheet propensity in macrostate 2 and 3. (b) a snapshot from MD-run of ApoE4 where, this β-sheet formation is visible.

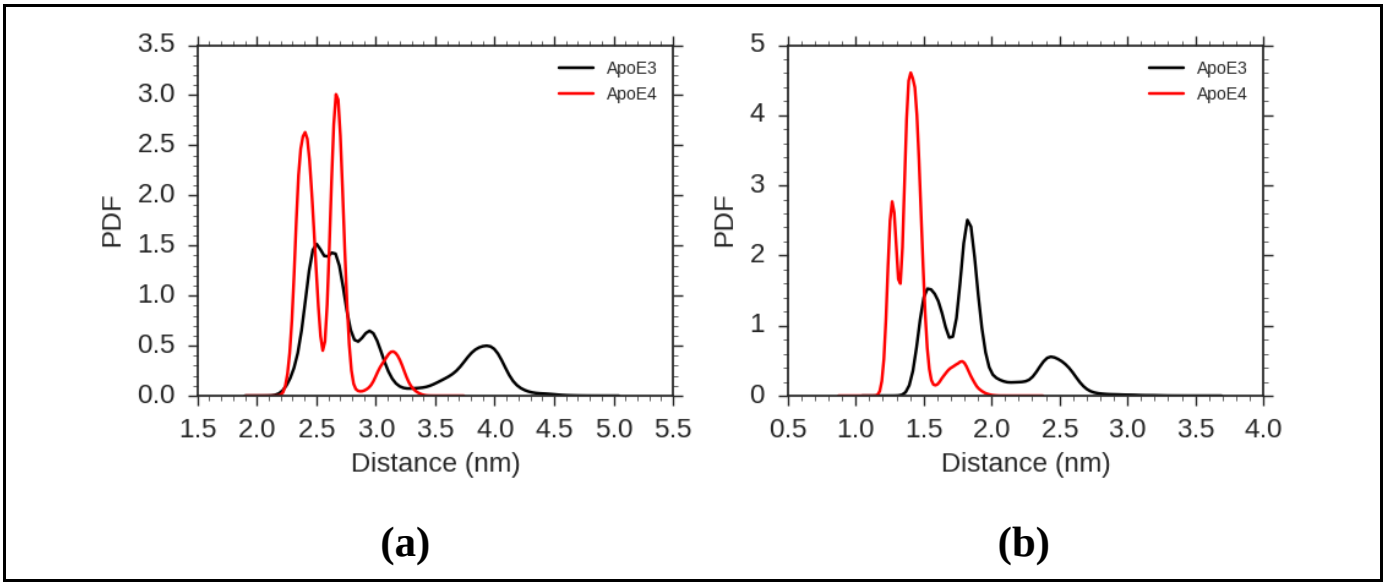


Fig. S6. Proximity of helix C2 to helix 2/helix 4.
Frequency histogram for distances calculated from center of masses of (a) helix 2 and (b) helix 4 of N-terminal domain to center of mass of helix C2

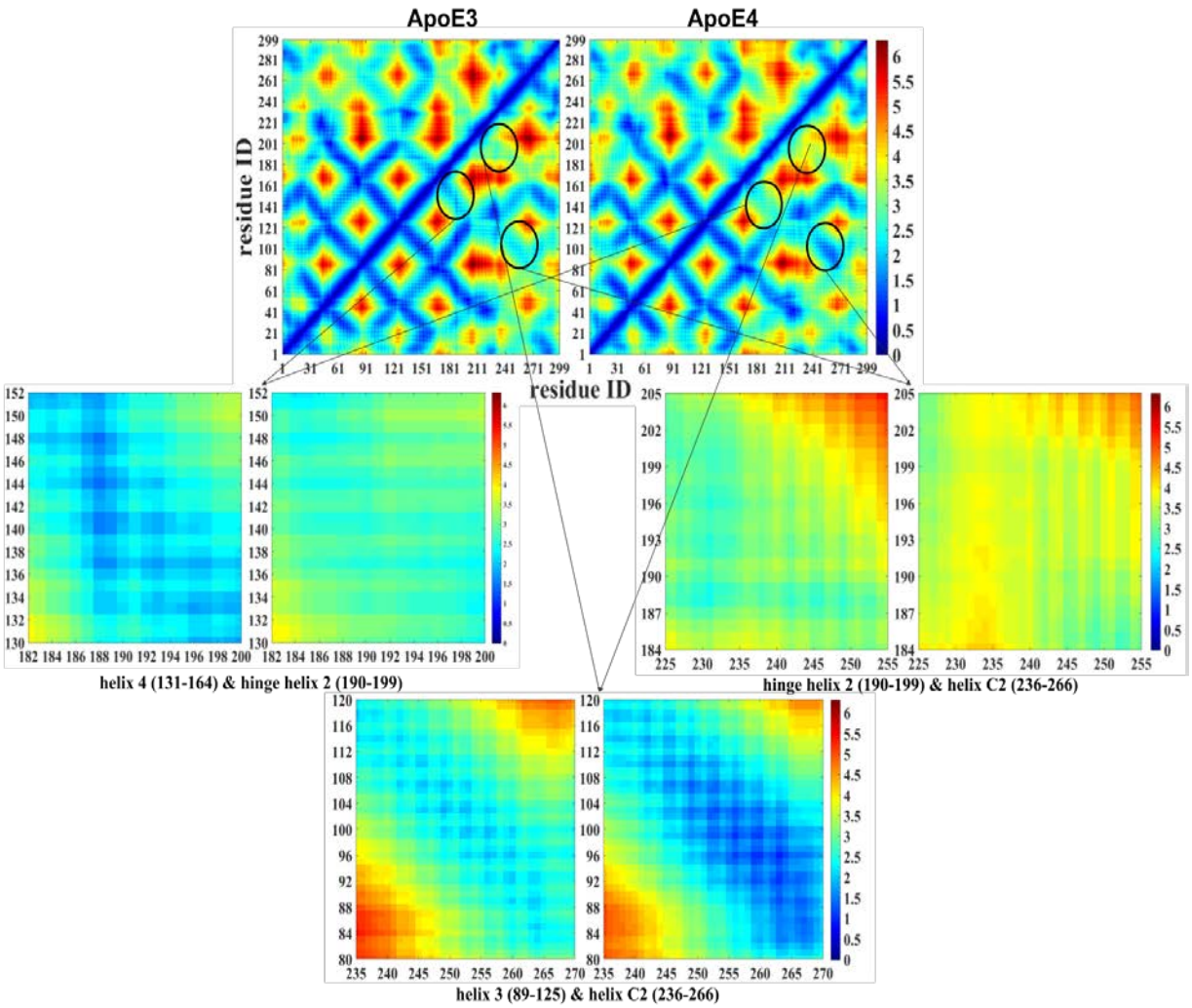


Fig. S7. Contact map plot for ApoE3 and ApoE4

On top is overall contact map for ApoE3 and ApoE4 isoforms obtained on the basis of their respective time-averaged structures. The residues of helix 3 (89-125) and helix C2 (236-266) are far apart in ApoE3, whereas the same region comes in close proximity during MD-run of ApoE4. The helix 4 (residues 131-164) and residues 130-164 (hinge helix 1 and hinge helix 2) are closer in ApoE3 but far apart in ApoE4. The segments forming hinge helix 2 (residues 190-199) and helix C1 (residues 210-223) also are closer in ApoE3 but slightly away from each other in ApoE4.

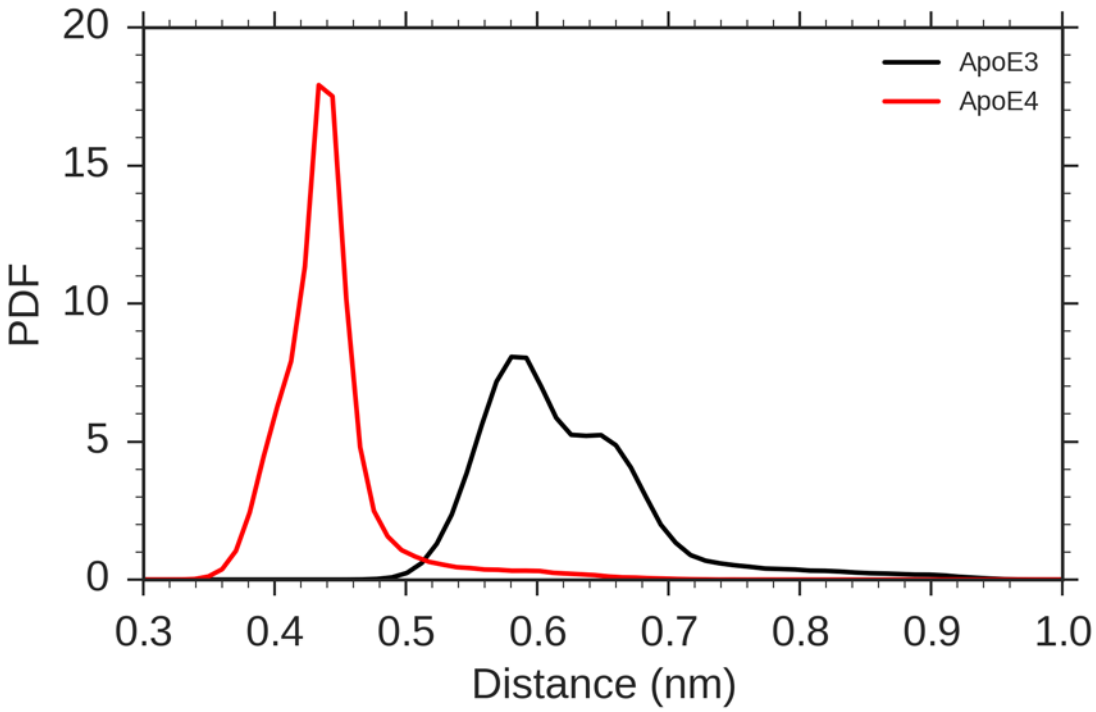
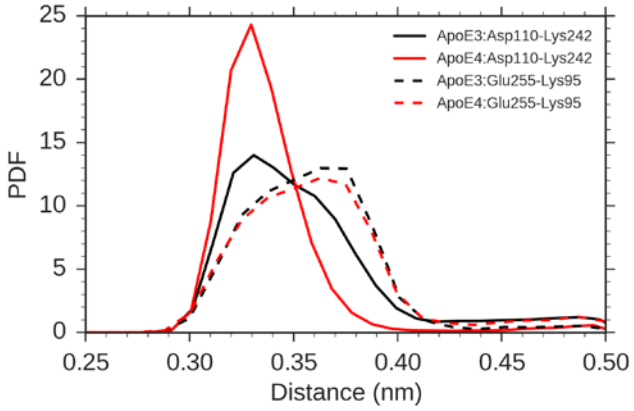


Fig. S8. Distance between residues 112 and 109 of ApoE isoforms (ApoE3 and ApoE4)



Salt-bridge	Mean (std)
ApoE3: Asp110-Lys242	0.357 (0.04)
ApoE4: Asp110-Lys242	0.338 (0.03)
ApoE3: Glu255-Lys95	0.359 (0.03)
ApoE4: Glu255-Lys95	0.363 (0.04)

Fig. S9. Donor...Acceptor distances in salt bridges Lys95-Glu255 and Asp110-Lys242 in ApoE3 and ApoE4.

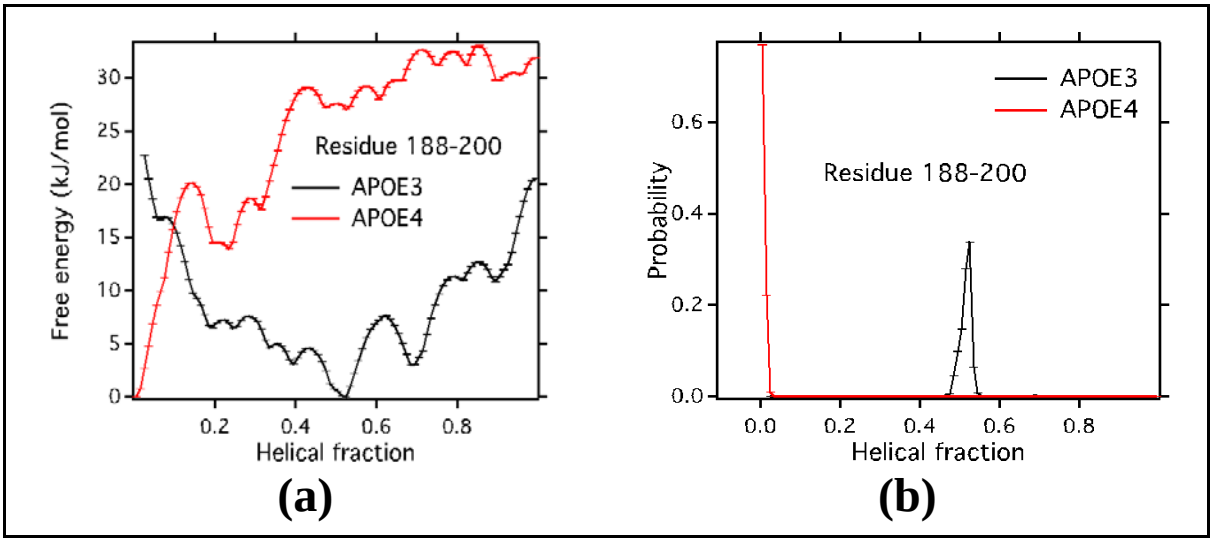


Fig. S10. Comparative free energy profiles of ApoE isoforms
(a) free energy profile for ApoE3 and ApoE4 isoforms. (b) The probability vs. helical fraction plot for ApoE isoforms.

Fig. S11. Sequence of hinge helix 2 and helix 3 of ApoE4

The sequence of hinge helix 2 is:

190 VAL
191 ARG
192 ALA
193 ALA
194 THR
195 VAL
196 GLY
197 SER
198 LEU
199 ALA

The Sequence of helix 3 is

89 THR
90 ARG
91 ALA
92 ARG
93 LEU
94 SER
95 LYS
96 GLU
97 LEU
98 GLN
99 ALA
100 ALA
101 GLN
102 ALA
103 ARG
104 LEU
105 GLY
106 ALA
107 ASP
108 MET
109 GLU (forms salt bridge with 112 ARG)
110 ASP
111 VAL
112 ARG (mutation point)
113 GLY
114 ARG
115 LEU
116 VAL
117 GLN
118 TYR
119 ARG
120 GLY
121 GLU
122 VAL
123 GLN
124 ALA
125 MET

The 112th residue (ARG of ApoE4) is mutation point. The residues 105 GLY and 106 ALA have the lowest (1 kcal/mol) and highest (0 kcal/mol) helical propensities respectively. The residue 107 ASP has low helical propensity of 0.69 kcal/mol whereas 108 MET has comparatively higher helical propensity of 0.24 kcal/mol. This is in-line with our observation that the helix bending occurs at the middle of helix 3 and residue 107 loses it helicity. Also, in ApoE4, 112 ARG forms salt-bridge with 109 GLU, so 112 ARG may not be having close interactions with residues of hinge helix 2, unlike ApoE3, where 112 CYS interacts with 192 ALA and 193 ALA of hinge helix 2.

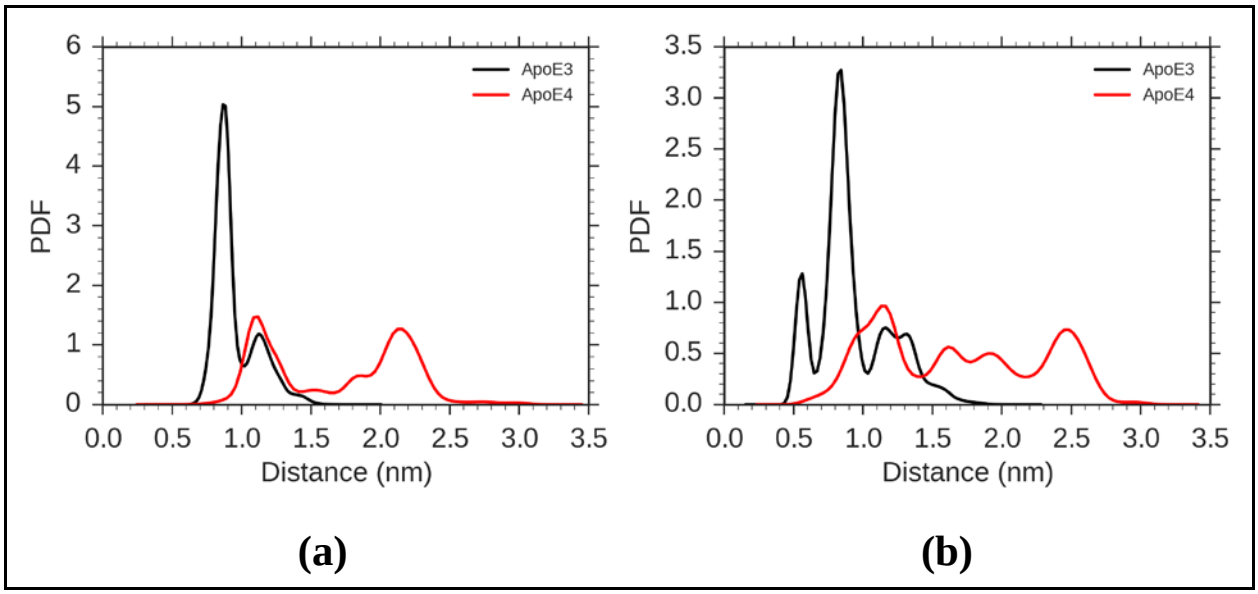


Fig. S12. Frequency distribution of (a) Cys/Arg112-Ala192 and (b)Cys/Arg112-Ala193 distance.