

Electronic Supplementary Information (ESI) to

Effect of Protective Mutation on Structure and Dynamics of APOE: a Molecular Dynamics Simulation Study

Newton A. Ihoeghian,^a Usman L. Abass,^a Ibrahim Imam,^a and Qing Shao^{*a}

Department of Chemical & Material Engineering, University of Kentucky, Lexington, KY, 40506 USA.

E-mail: q.shao@uky.edu

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S1. Statistics for KS Cumulative distribution plot of SASA for lipidation region of the six APOE proteins. (a) total residues, (b) hydrophobic residues, and (c) hydrophilic residues

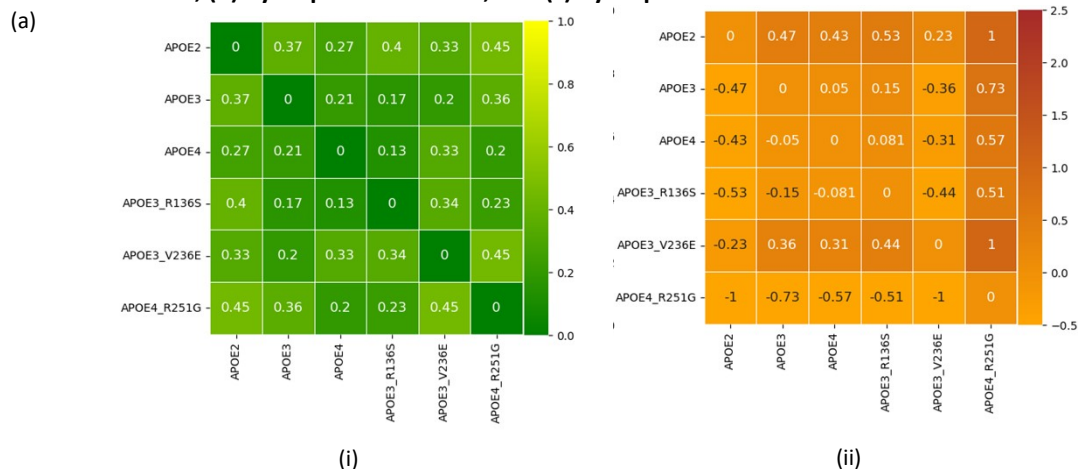


Figure S1.1: Statistics for Total SASA of Lipidation Region (i) KS Test Matrix (ii) Cohen's d matrix

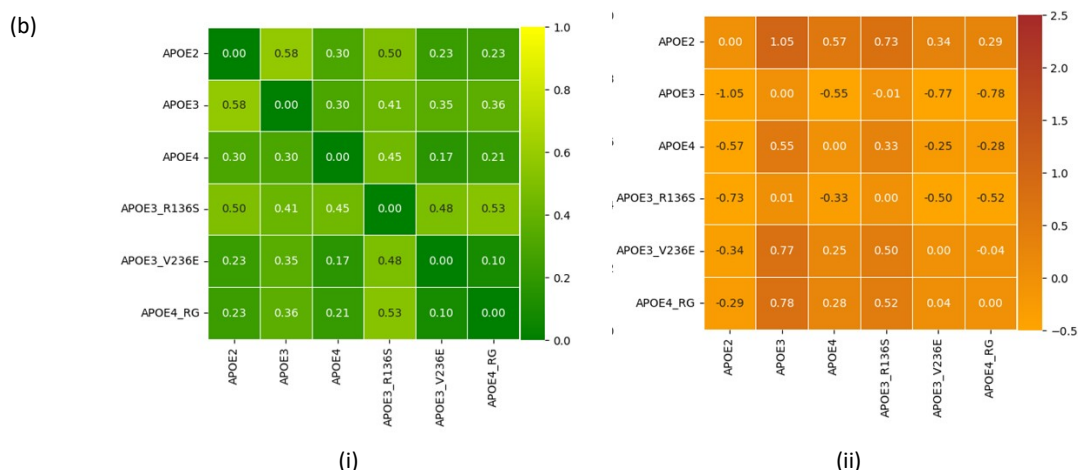


Figure S1.2: Statistics for Hydrophobic SASA of Lipidation Region (i) KS Test Matrix (ii) Cohen's d matrix

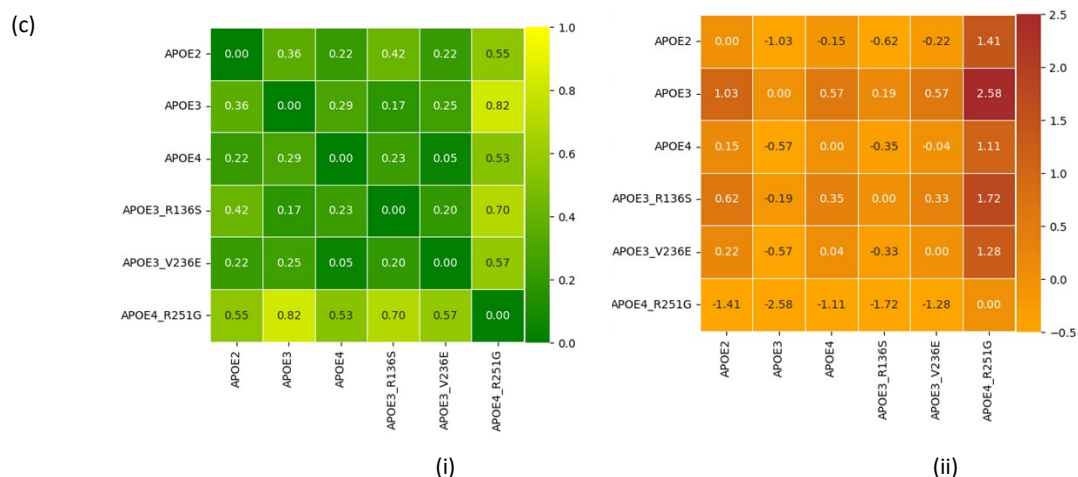


Figure S1.3: Statistics for Hydrophilic SASA of Lipidation Region (i) KS Test Matrix (ii) Cohen's d matrix

S2: Statistics for KS Cumulative distribution plot of SASA for oligomerization region. (a) total residues, (b) hydrophobic residues, and (c) hydrophilic residues

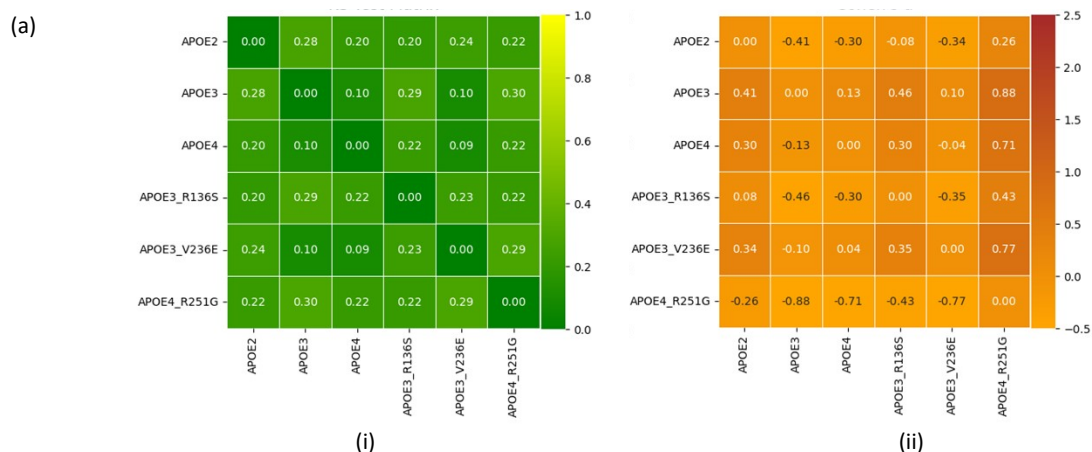


Figure S2.1: Statistics for Total SASA of Oligomerization Region (i) KS Test Matrix (ii) Cohen's d matrix

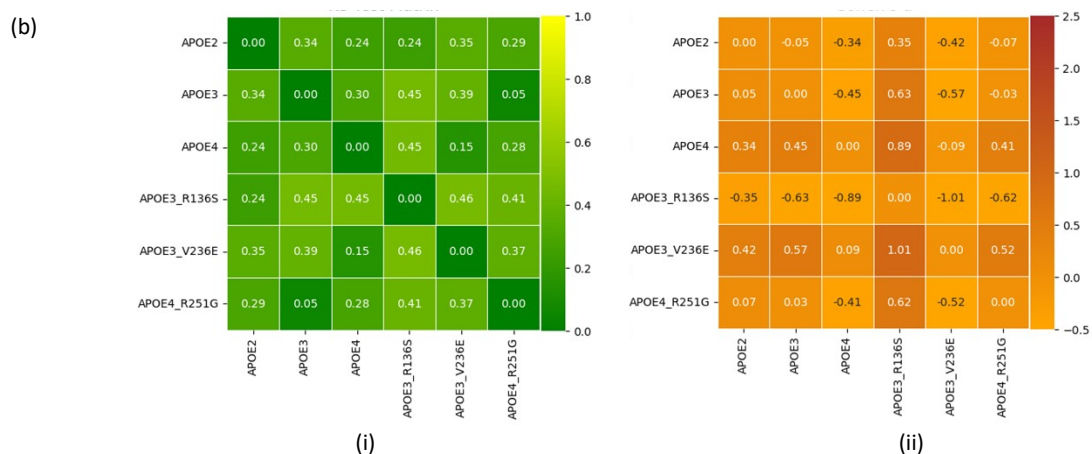


Figure S2.2: Statistics for Hydrophobic SASA of Oligomerization Region (i) KS Test Matrix (ii) Cohen's d matrix

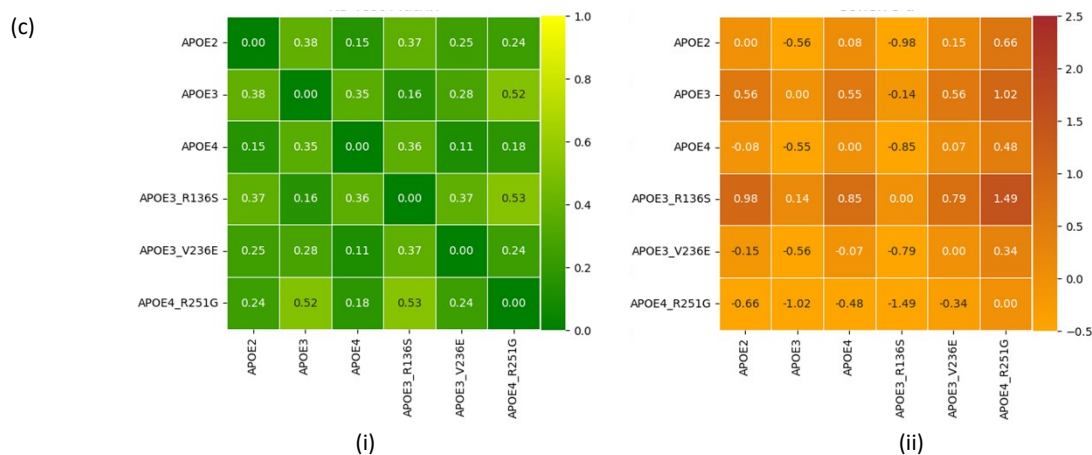


Figure S2.3: Statistics for Hydrophilic SASA of Oligomerization Region (i) KS Test Matrix (ii) Cohen's d matrix

S3. Statistics for KS Cumulative distribution of number of Hydrogen bonds for the Lipidation region (a) lipidation with other residues, (b) within lipidation region, and (c) lipidation region with water molecules

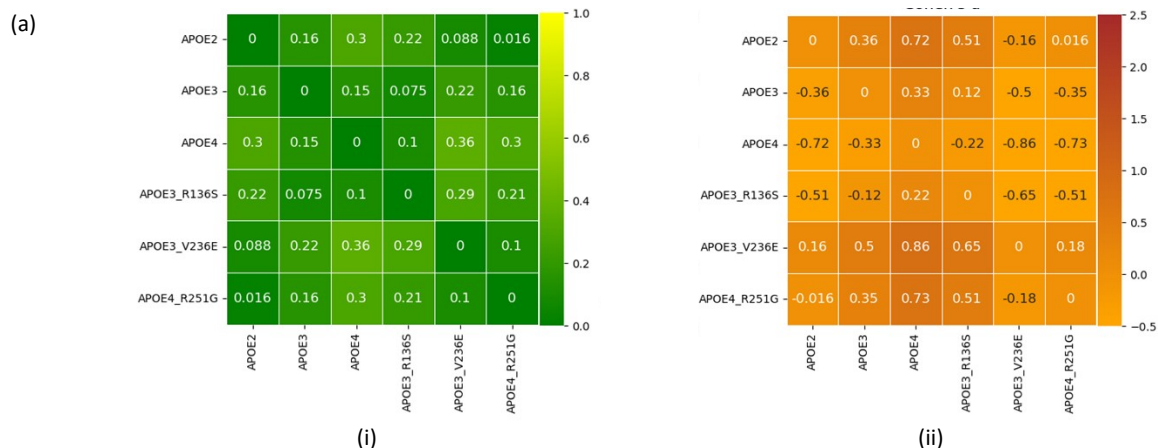


Figure S3.1: Statistics for Hydrogen bonding of lipidation with other residues (i) KS Test Matrix (ii) Cohen's d matrix

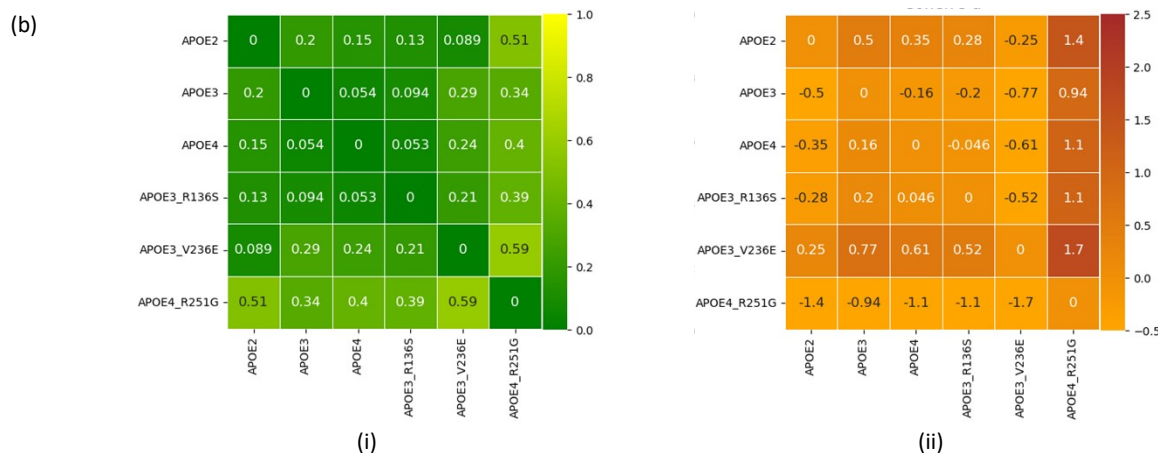


Figure S3.2: Statistics for Hydrogen bonding within lipidation region (i) KS Test Matrix (ii) Cohen's d matrix

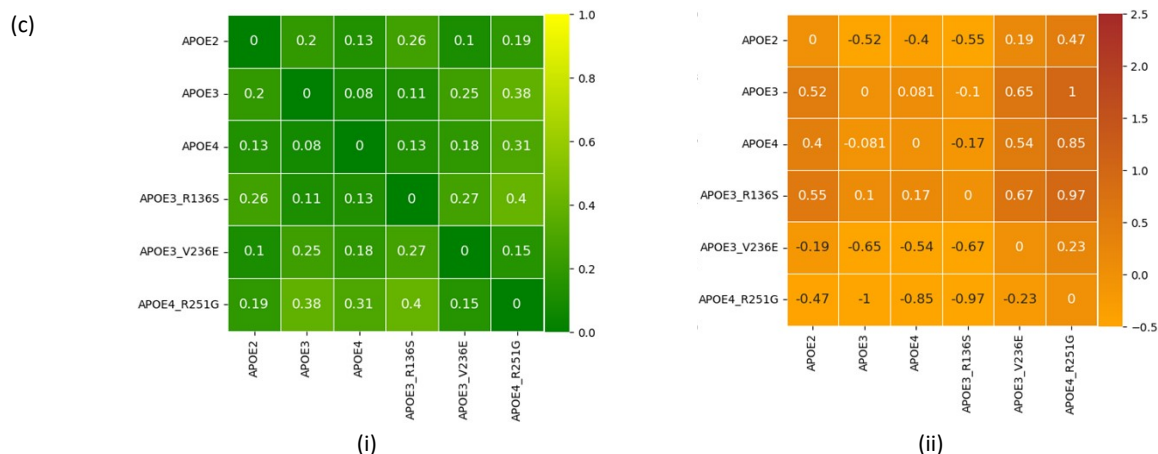


Figure S3.3: Statistics for Hydrogen bonding of Lipidation region with water molecules (i) KS Test Matrix (ii) Cohen's d matrix

S4. Statistics for Cumulative distribution of number of Hydrogen bonds for the Oligomerization region (a) Oligomers with other residues, (b) within oligomerization region, and (c) oligomers with water molecules

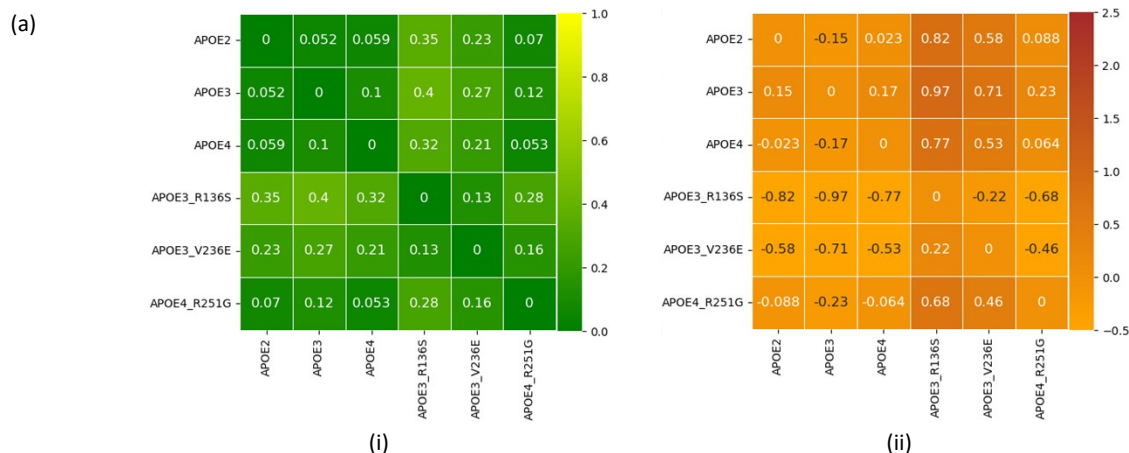


Figure S4.1: Statistics for Hydrogen bonding of Oligomers with other residues (i) KS Test Matrix (ii) Cohen's d matrix

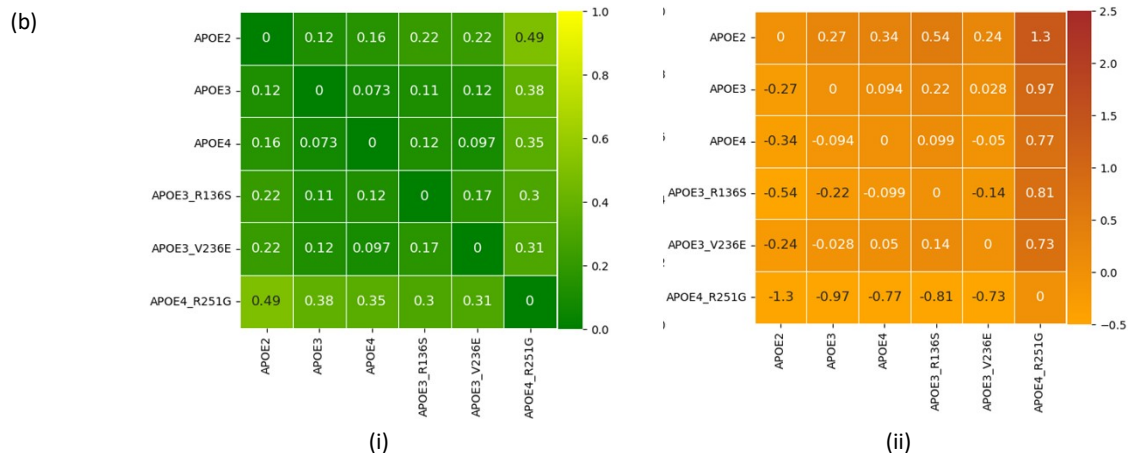


Figure S4.2: Statistics for Hydrogen bonding of residues within oligomerization region (i) KS Test Matrix (ii) Cohen's d matrix

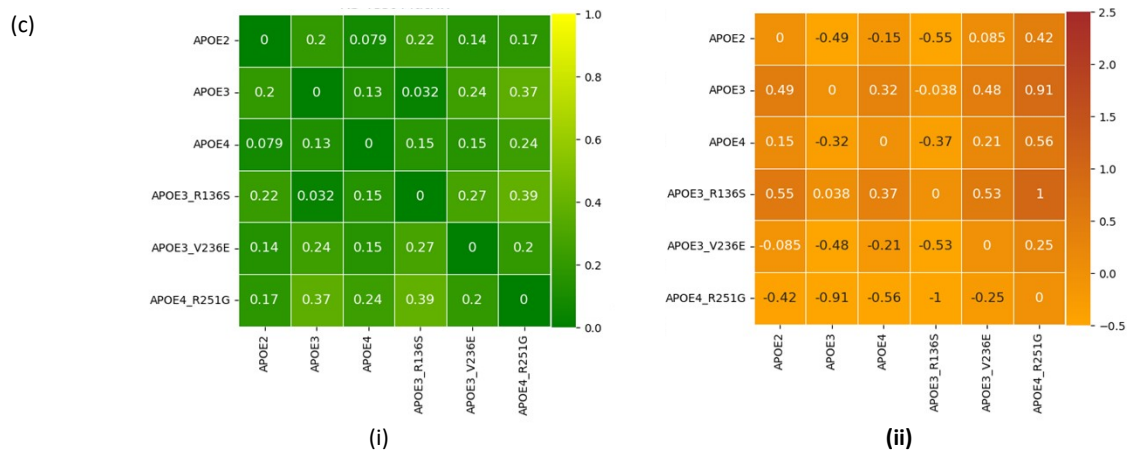


Figure S4.3: Statistics for Hydrogen bonding between Oligomerization region with water molecules (i) KS Test Matrix (ii) Cohen's d matrix

S5: Time-series plot of SASA for lipidation region of the six APOE proteins. (a) total residues (b) hydrophobic residues (c) hydrophilic residues

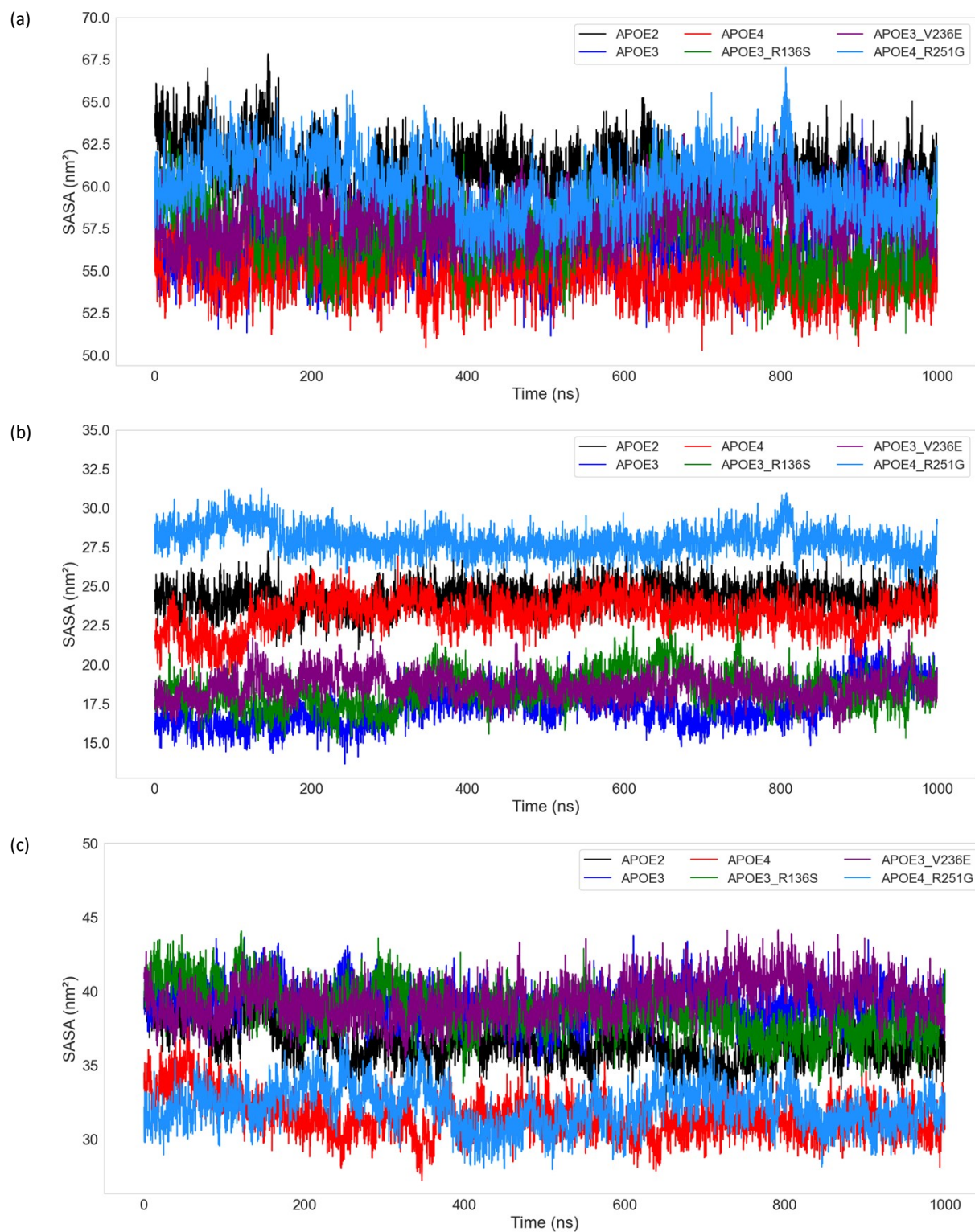
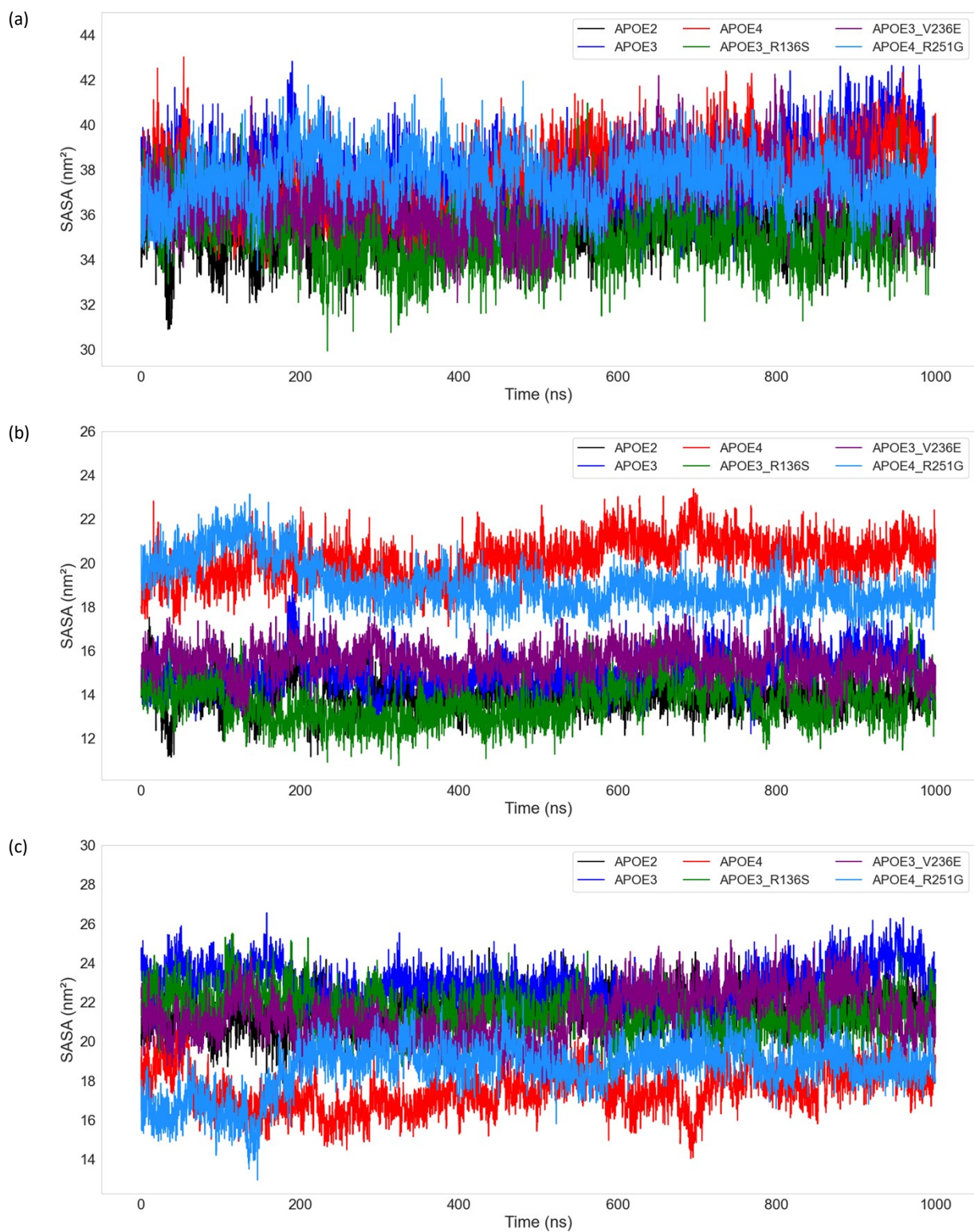


Figure S5: Time-series plot of SASA for lipidation region of the six APOE proteins. (a) total residues (b) hydrophobic residues (c) hydrophilic residues

S6: Time-series plot of SASA for oligomerization region of the six APOE proteins. (a) total residues (b) hydrophobic residues (c) hydrophilic residues



S7: Time-series plot of number of Hydrogen bonds for the Lipidation region for (a) lipidation with other residues, (b) within lipidation region, and (c) lipidation region with water molecules

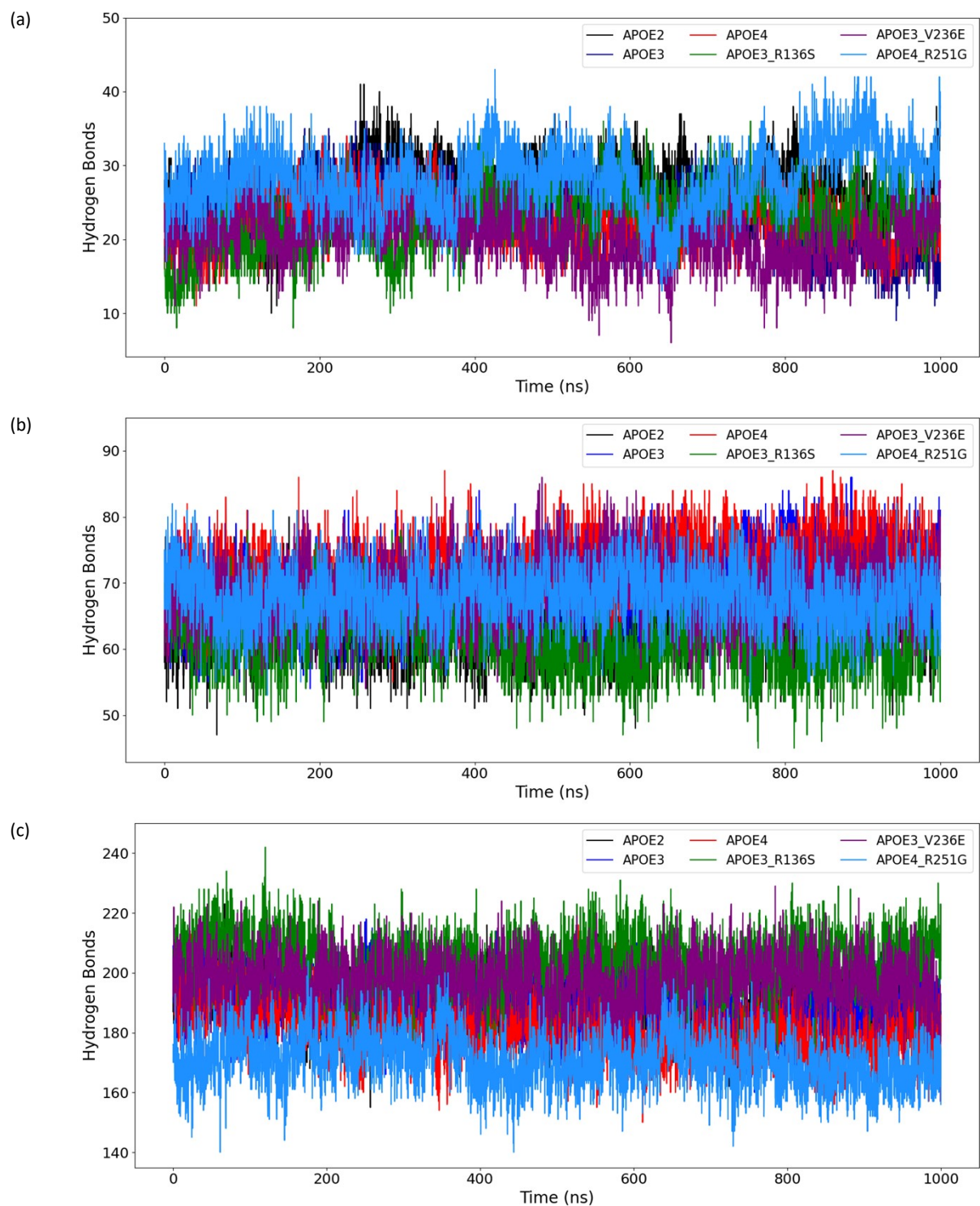


Figure S7: Time-series plot of number of Hydrogen bonds for the Lipidation region for (a) lipidation with other residues, (b) within lipidation region, and (c) lipidation region with water molecules

S8: Time-series plot of number of Hydrogen bonds for the oligomerization region for (a) Oligomers with other residues, (b) within oligomerization region, and (c) oligomers with water molecules

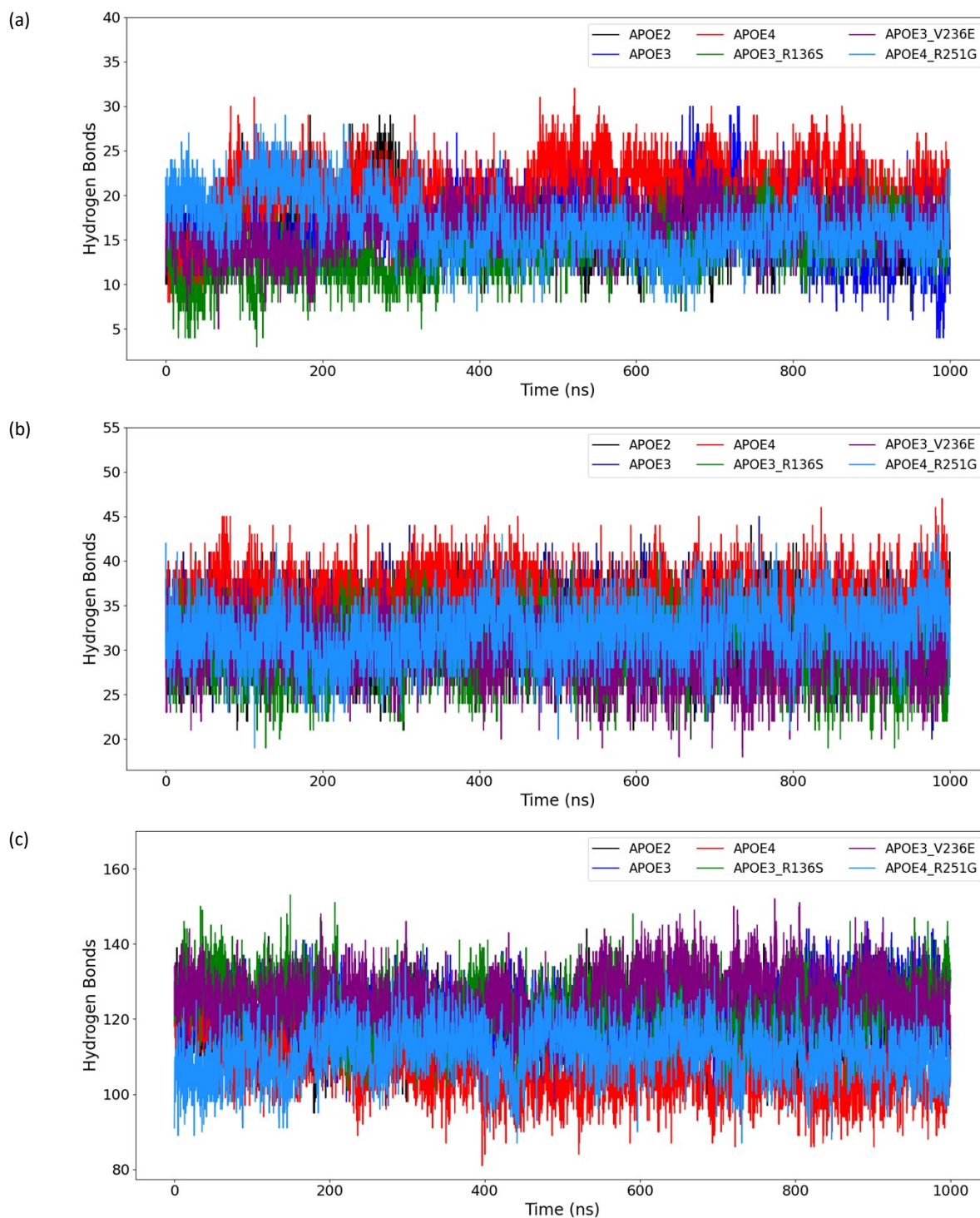


Figure S8: Time-series plot of number of Hydrogen bonds for the oligomerization region for (a) Oligomers with other residues, (b) within oligomerization region, and (c) oligomers with water molecules

S9: Quantification of how mutations restore or shift flexibility toward APOE2/APOE3-like patterns

Table S1: Correlation Analysis and Flexibility Metrics for APOE Isoform and Variant Comparisons by Structural Region

Segment	Residues	Comparison	pearson correlation (r _p)	spearman correlation (r _s)	mean_ref (nm)	mean_test (nm)	Δμ (nm)	%Δ	RMSD	Flexibility Direction
Lipid-only region_192-202	192-202	APOE3_R136S vs APOE2	0.690	0.682	0.572	0.411	-0.162	-28.239	0.165	↓
	192-202	APOE3_R136S vs APOE3	0.772	0.682	0.470	0.411	-0.060	-12.718	0.082	↓
	192-202	APOE3_V236E vs APOE2	0.910	0.964	0.572	0.527	-0.045	-7.828	0.072	↓
	192-202	APOE3_V236E vs APOE3	0.995	0.991	0.470	0.527	0.057	12.108	0.058	↑
	192-202	APOE4 vs APOE2	0.844	0.900	0.572	0.346	-0.226	-39.532	0.229	↓
	192-202	APOE4 vs APOE3	0.923	0.945	0.470	0.346	-0.124	-26.453	0.129	↓
	192-202	APOE4_R251G vs APOE2	0.021	-0.209	0.572	0.460	-0.112	-19.574	0.129	↓
	192-202	APOE4_R251G vs APOE3	-0.239	-0.227	0.470	0.460	-0.010	-2.179	0.107	↓
	192-202	APOE4_R251G vs APOE4	0.004	-0.082	0.346	0.460	0.114	33.005	0.139	↑
Lipid-only region_240-247	240-247	APOE3_R136S vs APOE2	0.297	0.238	0.209	0.369	0.160	76.302	0.161	↑
	240-247	APOE3_R136S vs APOE3	-0.858	-0.833	0.264	0.369	0.105	39.712	0.113	↑
	240-247	APOE3_V236E vs APOE2	0.280	0.262	0.209	0.243	0.034	16.087	0.036	↑
	240-247	APOE3_V236E vs APOE3	0.436	0.619	0.264	0.243	-0.021	-8.006	0.030	↓
	240-247	APOE4 vs APOE2	0.683	0.571	0.209	0.328	0.119	56.663	0.119	↑
	240-247	APOE4 vs APOE3	-0.416	-0.310	0.264	0.328	0.064	24.150	0.071	↑
	240-247	APOE4_R251G vs APOE2	0.536	0.643	0.209	0.251	0.042	19.863	0.043	↑
	240-247	APOE4_R251G vs APOE3	0.207	0.143	0.264	0.251	-0.013	-5.013	0.027	↓
	240-247	APOE4_R251G vs APOE4	-0.029	-0.071	0.328	0.251	-0.077	-23.490	0.079	↓
Overlapping region_248-260	248-260	APOE3_R136S vs APOE2	0.827	0.813	0.262	0.453	0.190	72.540	0.191	↑
	248-260	APOE3_R136S vs APOE3	0.749	0.736	0.258	0.453	0.195	75.663	0.196	↑
	248-260	APOE3_V236E vs APOE2	0.958	0.956	0.262	0.333	0.071	26.996	0.084	↑
	248-260	APOE3_V236E vs APOE3	0.969	0.918	0.258	0.333	0.075	29.294	0.089	↑
	248-260	APOE4 vs APOE2	0.814	0.813	0.262	0.453	0.191	72.809	0.193	↑
	248-260	APOE4 vs APOE3	0.733	0.758	0.258	0.453	0.196	75.937	0.198	↑
	248-260	APOE4_R251G vs APOE2	0.797	0.736	0.262	0.307	0.045	16.998	0.050	↑
	248-260	APOE4_R251G vs APOE3	0.888	0.824	0.258	0.307	0.049	19.116	0.052	↑
	248-260	APOE4_R251G vs APOE4	0.604	0.626	0.453	0.307	-0.146	-32.296	0.151	↓
Overlapping region_265-272	265-272	APOE3_R136S vs APOE2	0.665	0.619	0.315	0.480	0.165	52.367	0.168	↑
	265-272	APOE3_R136S vs APOE3	0.141	0.381	0.399	0.480	0.081	20.323	0.096	↑
	265-272	APOE3_V236E vs APOE2	0.804	0.738	0.315	0.617	0.302	95.754	0.305	↑
	265-272	APOE3_V236E vs APOE3	0.384	0.405	0.399	0.617	0.218	54.586	0.224	↑
	265-272	APOE4 vs APOE2	0.784	0.762	0.315	0.375	0.060	18.975	0.063	↑
	265-272	APOE4 vs APOE3	0.215	0.333	0.399	0.375	-0.024	-6.046	0.049	↓
	265-272	APOE4_R251G vs APOE2	0.745	0.762	0.315	0.344	0.028	9.023	0.032	↑
	265-272	APOE4_R251G vs APOE3	0.054	0.214	0.399	0.344	-0.055	-13.906	0.071	↓
	265-272	APOE4_R251G vs APOE4	0.598	0.619	0.375	0.344	-0.031	-8.365	0.038	↓
Oligomerization region_273-299	273-299	APOE3_R136S vs APOE2	0.314	0.261	0.308	0.422	0.113	36.820	0.133	↑

	273-299	APOE3_R136S vs APOE3	0.090	0.147	0.467	0.422	-0.045	-9.692	0.119	↓
	273-299	APOE3_V236E vs APOE2	0.250	0.189	0.308	0.420	0.112	36.369	0.126	↑
	273-299	APOE3_V236E vs APOE3	-0.576	-0.654	0.467	0.420	-0.047	-9.990	0.139	↓
	273-299	APOE4 vs APOE2	0.790	0.768	0.308	0.386	0.078	25.152	0.086	↑
	273-299	APOE4 vs APOE3	0.558	0.534	0.467	0.386	-0.081	-17.394	0.111	↓
	273-299	APOE4_R251G vs APOE2	0.519	0.515	0.308	0.408	0.100	32.425	0.107	↑
	273-299	APOE4_R251G vs APOE3	0.365	0.384	0.467	0.408	-0.059	-12.593	0.103	↓
	273-299	APOE4_R251G vs APOE4	0.618	0.595	0.386	0.408	0.022	5.811	0.051	↑