Population-Based Analysis of Alzheimer's Disease Risk Alleles Implicates Genetic Interactions

Supplemental Information

Table S1. Demographic comparison between cases and controls included in the study analysis. The mean age between cases and controls included in the study were significantly different as are the differences in the proportion of females.

	Age		**Gender**			
	Mean	**Standard Deviation**	**Male**	**Female**	***n***	**Proportion of Females**
Cases	80.17	7.24	119	207	326	0.63
Controls	74.34	6.68	894	1199	2093	0.57
n			1013	1406	2419	
p-value	< 2.2e-16					< 0.04

Table S2. Demographic comparison between participants included and excluded in the analysis. The mean age between participants included and those excluded were significantly different, but the proportion of females was not. One possible cause of this difference is that samples excluded for missing genotype data were significantly older than those that were included. This is likely because the majority of DNA samples come from the original buccal swabs. These samples have lower call rates than the blood DNA that was collected at later waves of assessment. As a result, the individuals who were oldest at the start of the study have higher genotype missing rates. This results in the slightly higher age of excluded samples over included samples. However, unless there is a loss of individuals who go on to develop Alzheimer's disease vs. those who remain non-demented this unlikely to bias our results. There is no evidence for such a bias.

	Age		**Gender**			
	Mean	**Standard Deviation**	**Male**	**Female**	***n***	**Proportion of Females**
Included	75.13	6.92	1013	1406	2419	0.58
Excluded	77.33	7.48	1074	1399	2473	0.57
n			2087	2805	4892	
p-value	< 2.2e-16					< 0.29

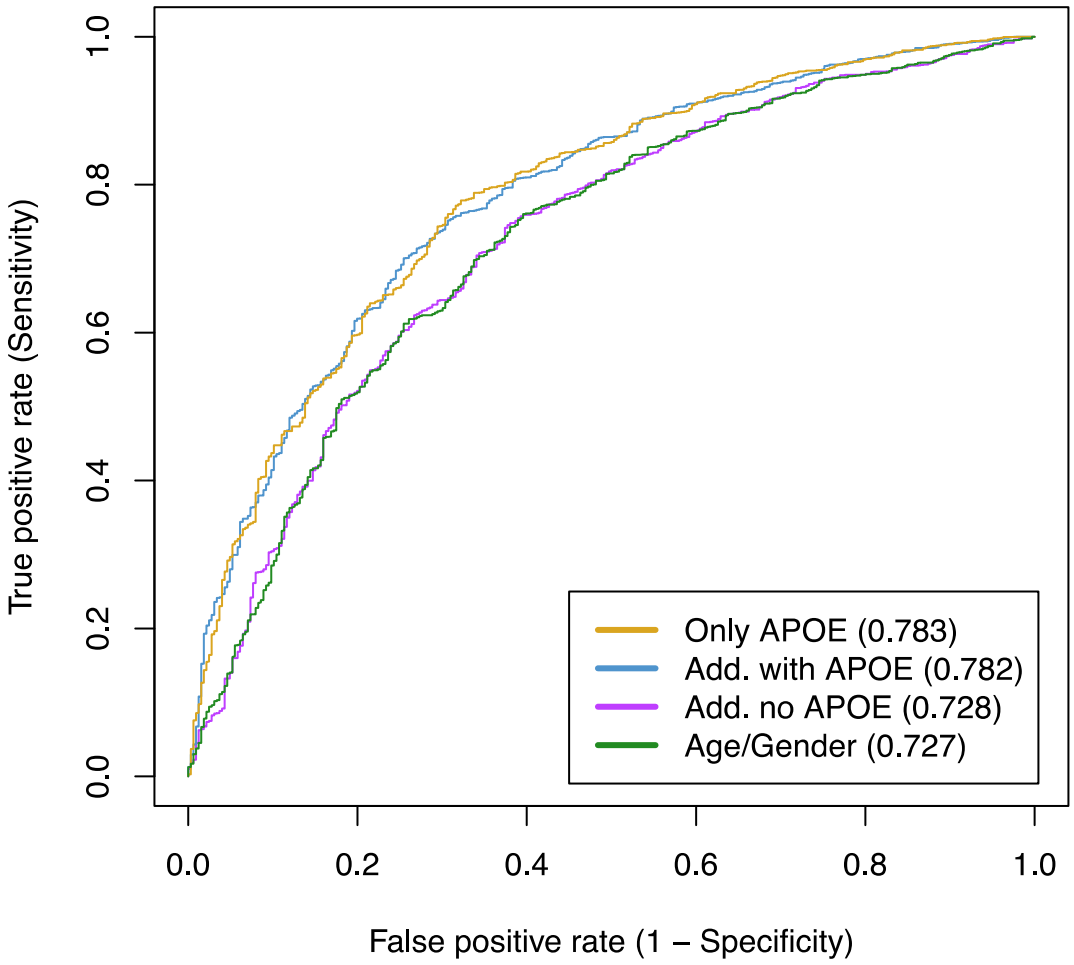

Figure S1. Non-*APOE* late-onset Alzheimer's disease (LOAD) risk loci contributions to LOAD status prediction performance under additive constraints. The non-*APOE* alleles combined with *APOE* did not improve LOAD status prediction performance over *APOE* alone when constrained to an additive model; nor did the non-*APOE* alleles without *APOE* significantly improve LOAD status prediction performance over age and gender alone ($p < 0.2372$). Area under the curve is listed in parentheses within the legend.

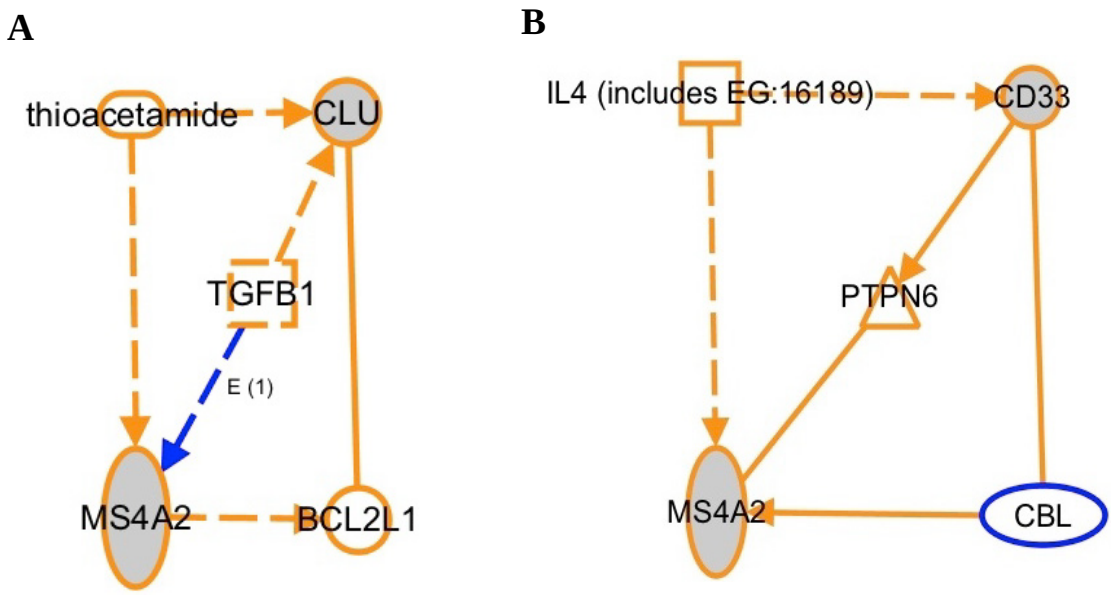

Figure S2. *CLU-MS4A4E* and *CD33-MS4A4E* pathway analysis. Pathway analysis using Ingenuity's IPA demonstrates evidence that both *CLU* and *CD33* interact indirectly with *MS4A2*, a member of the membrane-spanning 4-domain gene family, as is *MS4A4E*. Both thioacetamide and *TGFB1* act indirectly on both *CLU* and *MS4A2* (**A**). *CLU* also binds to *BCL2L1*, which is acted upon by *MS4A2*. Likewise, *CD33* acts on *PTPN6*, which binds to *MS4A2* and *CD33* binds to *CBL*, which then acts on *MS4A2* (**B**). No information regarding *MS4A4E* specifically was available in IPA. An exhaustive legend describing the molecules and interactions are available on Ingenuity's website (http://ingenuity.force.com/ipa/articles/Feature_Description/Legend).