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Original Article

Beta-amyloid toxicity modifier genes and the risk of Alzheimer's disease

Samantha L Rosenthal[1], Xingbin Wang[1], F Yesim Demirci[1], Michael M Barmada[1], Mary Ganguli[2,4,5], Oscar L Lopez[3,4], M Ilyas Kamboh[1,2,3,5]

[1]Department of Human Genetics, University Pittsburgh, Pittsburgh, PA, USA; [2]Department of Psychiatry, University of Pittsburgh, Pittsburgh, PA, USA; [3]Alzheimer's Disease Research Center, University of Pittsburgh, Pittsburgh, PA, USA; [4)]Department of Neurology, University of Pittsburgh, Pittsburgh, PA, USA; [5]Department of Epidemiology, University of Pittsburgh, PA, USA.

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Abstract: Late-onset Alzheimer's disease (LOAD) is a complex and multifactorial disease. So far ten loci have been identified for LOAD, including *APOE, PICALM, CLU, BIN1*, *CD2AP, CR1, CD33, EPHA1, ABCA7*, and *MS4A4A/MS4A6E*, but they explain about 50% of the genetic risk and thus additional risk genes need to be identified. Amyloid beta (Aβ) plaques develop in the brains of LOAD patients and are considered to be a pathological hallmark of this disease. Recently 12 new Aβ toxicity modifier genes (*ADSSL1, PICALM, SH3KBP1, XRN1, SNX8, PPP2R5C, FBXL2, MAP2K4, SYNJ1, RABGEF1, POMT2,* and *XPO1*) have been identified that potentially play a role in LOAD risk. In this study, we have examined the association of 222 SNPs in these 12 candidate genes with LOAD risk in 1291 LOAD cases and 958 cognitively normal controls. Single site and haplotype analyses were performed using PLINK. Following adjustment for *APOE* genotype, age, sex, and principal components, we found single nucleotide polymorphisms (SNPs) in *PPP2R5C, PICALM, SH3KBP1, XRN1,* and *SNX8* that showed significant association with risk of LOAD. The top SNP was located in intron 3 of *PPP2R5C* (P=0.009017), followed by an intron 19 SNP in *PICALM* (P=0.0102). Haplotype analysis revealed significant associations in *ADSSL1, PICALM, PPP2R5C, SNX8*, and *SH3KBP1* genes. Our data indicate that genetic variation in these new candidate genes affects the risk of LOAD. Further investigation of these genes, including additional replication in other case-control samples and functional studies to elucidate the pathways by which they affect Aβ, are necessary to determine the degree of involvement these genes have for LOAD risk.

Keywords: Late-onset Alzheimer's disease (LOAD), risk genes, SNPs, *ADSSL1, PICALM, SH3KBP1, XRN1, SNX8, PPP2R5C, FBXL2, MAP2K4, SYNJ1, RABGEF1, POMT2, XPO1,*

Introduction

Alzheimer's disease (AD) is a devastating neurodegenerative disease, affecting an estimated 5.3 million people aged 65 and older in the United States [1]. Characterized by a classic combination of both intracellular and extracellular pathologies, neurofibrillary tangles (NFTs) of hyperphosphorylated tau protein within neurons and accumulation of β-amyloid (Aβ) senile plaques in the brain, AD results in progressive memory loss and cognitive impairment [2]. Although there is still debate whether Aβ or NFTs are the cause or consequence of the disease, evidence suggest that Aβ acts upstream of NFTs [3, 4] and thus is an important contributor to the initiation of AD. The role of Aβ in the rare familial form of early onset AD (EOAD) is well established where disease-associated mutations in three genes, amyloid precursor protein (*APP*), and *presenilin 1* and *2* (*PSEN1, PSEN2*), are associated with elevated levels of Aβ 42 or Aβ 42/40 [5]. However, the role of Aβ in the common and multifactorial late onset form of AD (LOAD) is not well defined. Thus far genome-wide association studies (GWASs) have identified ten susceptibility loci for LOAD, including *APOE, CLU, CR1, PICALM, BIN1, CD2AP, CD33, EPHA1, ABCA7* and *MS4A4/MS4A6E* [6-10]. With the exception of *APOE* that affects Aβ deposition and clearance in the brain [2], the role of other nine known loci in Aβ metabolism is not clear.

Recently, Treusch *et al*. [11] modeled Aβ toxicity in yeast and identified forty hits, twelve of which

were found to be human homologs, including eight Aβ toxicity suppressor (*ADSSLI*, *PICALM, SH3KBP1, PPP2R5C, FBXL2, SYNJ1, RABGEF1,* and *XPO1*) and four Aβ toxicity enhancer genes (*XRN1, SNX8, MAP2K4,* and *POMT2*) whose relationship to Aβ was previously unknown. One of these human homologs is a recently identified gene for LOAD (*PICALM*), and two of them (*SH3KBP1* and *SYNJ1*) interact with two additional known genes for LOAD (*BIN1* and *CD2AP*, respectively). Recently, we have reported the association of *PICALM, BIN1* and *CD2AP* gene variation with LOAD risk [12]. In this study we have comprehensively examined the association of 222 single-nucleotide polymorphisms (SNPs) in the twelve Aβ toxicity modifier genes with LOAD risk in a large case-control sample.

Materials and Methods

Samples

A total of 2,440 Caucasian American subjects, including 1,440 LOAD cases (mean age-at-onset 72.6 ± 6.4 years, 66% women, 24% autopsy-confirmed) and 1,000 controls (mean age 74.07 ± 6.20 years, 60% women) were recruited with informed consent. LOAD cases were selected from University of Pittsburgh Alzheimer's Disease Research Center (ADRC), and controls, aged 60 and older, were cognitively normal individuals recruited from the same geographic region as the cases. All cases met the National Institute of Neurological and Communication Disorders and Stroke (NINCDS)/ Alzheimer's Disease and Related Disorders Association (ADRDA) criteria for probable or definite AD, and were evaluated by the University of Pittsburgh ADRC's standard protocol, including medical history, general medical and neurological examination, psychiatric interview, neurophysiological testing and MRI scan. The study was approved by the University of Pittsburgh Internal Review Board.

Genotyping

The Illumina Omni1-Quad chip was used to genotype all samples. Following standard quality control and exclusion criteria, 2,249 subjects (1,291 LOAD cases and 958 controls) were included in the final analysis as described elsewhere [12]. There were a total of 222 SNPs present on the Illumina chip in the 12 candidate genes examined (*ADSSL1, PICALM, SH3KBP1, XRN1, SNX8, PPP2R5C, FBXL2, MAP2K4, SYNJ1, RABGEF1, POMT2* and *XPO1*).

Single locus analysis

Association of 222 SNPs located in 12 new Aβ toxicity modifier genes was tested using logistic regression under an additive model adjusting for age, sex, and the first four principal components as covariates using PLINK [13]. Further adjustment was made for *APOE* genotype following initial association test.

Haplotype Analysis

Haplotype analysis within each gene was performed using a sliding-windows approach with *haplo.glm* function in the Haplo.Stats R package (version 1.5.5). The global p-value measures significance of the entire set of haplotypes for the locus subset. In the analysis, we included 4 SNPs per window. Only SNPs with allele frequencies of 0.01 and higher in the pooled case-control sample were included in the analysis. Since the *SH3KBP1* gene is located on the X chromosome, we performed haplotype analysis separately in males and females.

Results

Single locus analysis

Of the 222 SNPs tested, 21 SNPs in 5 genes showed nominal significant associations with AD risk ($P<0.05$). Following *APOE* adjustment, 14 SNPs in 5 genes—*PPP2R5C, PICALM, SH3KBP1, XRN1,* and *SNX8* remained significant at $\alpha=0.05$. The most significant SNP, rs1746595 ($P=9.01E-03$), was located in intron 3 of *PPP2R5C*, followed by rs10501602 ($P=1.04E-02$) in intron 19 of *PICALM*. Interestingly, a SNP located in *PICALM* (rs10792820) become more significant following *APOE* adjustment. Despite these findings, none of these SNPs remained significant after correcting for gene-based multiple comparisons. The strongest associations for each gene pre- and post-*APOE* adjustment are displayed in **Table 1**. Results for all loci tested can be found in Supplementary Table 1.

Haplotype analysis

Five of the 12 genes examined (*ADSSL1, PICALM, PPP2R5C, SNX8,* and *SH3KBP1*) showed

Table 1. Most significant SNP for each gene tested in single site analysis

Gene	Chr[1]	SNP	A1[2]	OR[3]	P-unadjusted[4]	*APOE* adj.-P[5]
XPO1	2	rs10186325	C	1.088	0.1896	0.132
XRN1	3	rs1351965	A	1.186	0.01117	0.01861
FBXL2	3	rs6777187	A	1.076	0.2848	0.7143
FBXL2	3	rs13087731	G	0.9511	0.4493	0.308
SNX8	7	rs2286206	A	1.554	0.01335	0.09287
SNX8	7	rs10249052	A	1.167	0.02036	0.04795
RABGEF1	7	rs4717322	A	1.151	0.1076	0.2701
RABGEF1	7	GA006396	G	0.8145	0.2057	0.1767
PICALM	11	rs10501602	G	0.7217	0.0006709	0.01037
PPP2R5C	14	rs1746595	G	1.235	0.004142	0.009017
POMT2	14	rs2363640	A	0.8732	0.07975	0.08041
ADSSL1	14	rs4983382	G	0.9188	0.2467	0.222
MAP2K4	17	rs28921114	I	1.498	0.1387	0.1342
SYNJ1	21	rs2833930	A	0.9047	0.1407	0.05831
SH3KBP1	X	rs12013533	G	0.7977	0.006109	0.01496

[1]Chromosome location; [2]Effect allele; [3]Odds ratio; [4]Unadjusted P-value; [5]P value adjusted for *APOE* genotype

significant haplotype window associations with LOAD (**Figure 1;** Supplementary Table 2). The most significant association in this sample was for *ADSSL1/*SNPs rs11160818 - rs4983382- rs35590716 - rs34672588 (*P*=3.72E-03). The next significant association was observed with *PPP2R5C/*SNPs rs1677999 - rs1741140 - rs2749907 - rs16779919 (*P*=5.10E-03). *PICALM* and *SNX8* yielded significant effects as well, each containing three significant associations. For *SH3KBP1*, we observed six significant associations in males only, with the most significant association being in a window containing SNPs: rs16981251- rs4630061- rs11795873- rs11094775 (*P*=7.82E-03). The 7 genes showing no significant windows in the haplotype analysis are illustrated in The 7 genes showing no significant windows in the haplotype analysis are illustrated in The 7 genes showing no significant windows in the haplotype analysis are illustrated in **Figure 2**.

Discussion

Our data indicate that genetic variation in 6 of the 12 recently described Aβ toxicity modifier genes affects the risk of LOAD at a nominal *P*<0.05. Since these are biological candidate genes for LOAD, we consider *P*<0.05 to be an indication of potential real association that should be followed by comprehensive resequencing of these genes to find functional variants. One of these Aβ toxicity modifier genes, *PICALM*, has been repeatedly implicated as a risk locus for LOAD in other studies [7, 9, 10, 12, 14, 15], and we have replicated similar findings. In our sample, *PICALM* contained four SNPs (rs10501602, rs694011, rs609903, rs10792820) with a significant association following *APOE* adjustment, as well as three adjacent windows with significant haplotypes. While its exact function in AD pathogenesis is unclear, it has been suggested that *PICALM* plays a role in the processing of amyloid precursor protein (APP), the precursor to both amyloidogenic oligomers and non-pathogenic peptides [16]. More recent work has suggested a more specific role as a suppressor of Aβ toxicity rather than a mediator of Aβ production [11]. Our identification of *PICALM*'s association with LOAD risk in both single and multi-site analysis compliments the many other findings regarding its role in AD.

PPP2R5C (*B56γ-PP2A*) also showed significant association in both single locus and haplotype analyses. The only SNP (rs1746595) in this gene that showed significant association was also the most significant SNP in our sample (*P*=9.017E-03). Interestingly, neither of the significant windows from haplotype analysis for this gene contained this putative SNP. A member of a group of phosphoprotein phosphatase genes, *PPP2R5C* is largely recognized as a tumor suppressor gene [17, 18]. Investigation of its role in LOAD has been minimal despite its

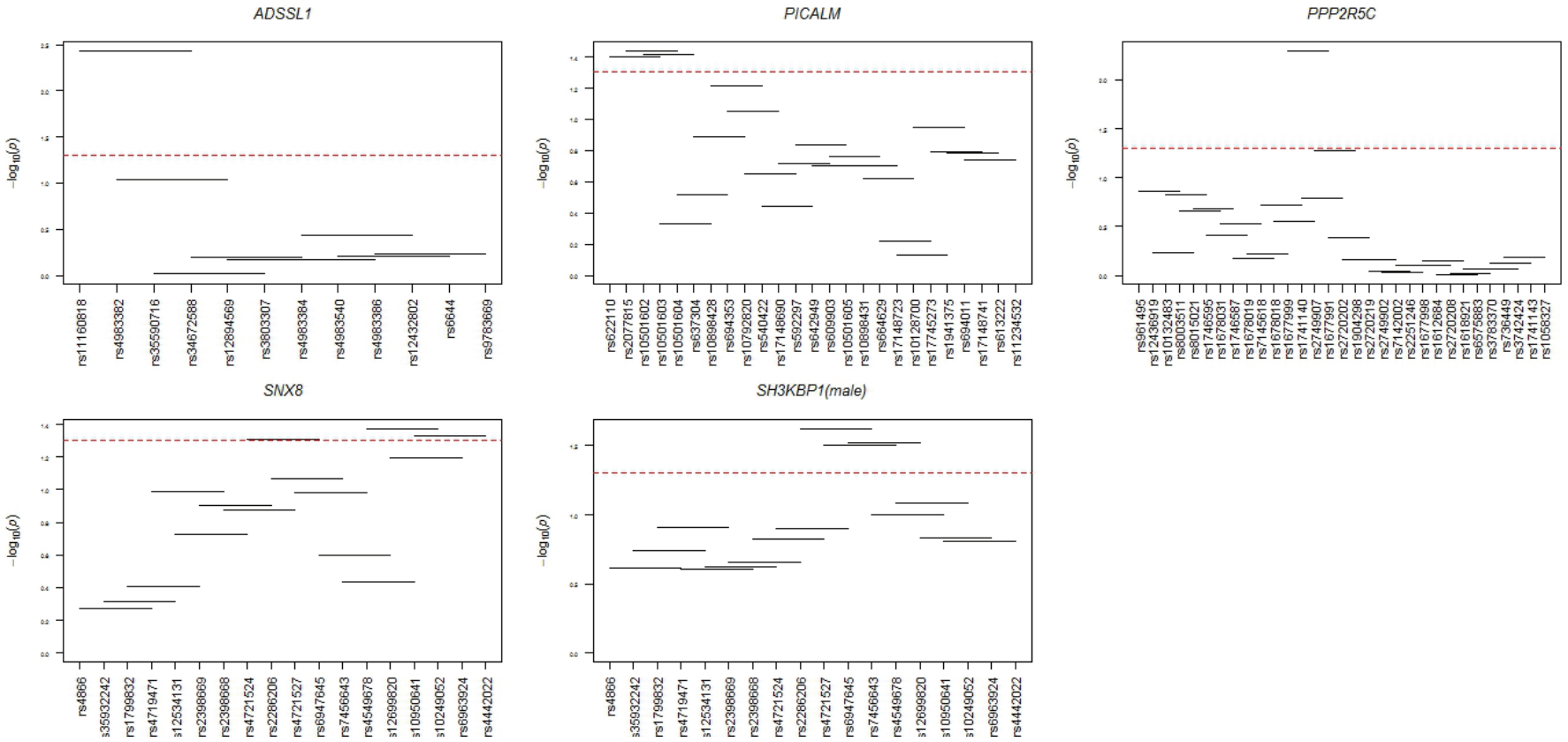

Figure 1. Haplotype windows for genes containing significant windows. Lines represent the window tested, with the corresponding SNP rs numbers along the horizontal axis and global p-value on the vertical axis. Significant associations fall above the reference line (dotted) at $-\log_{10}(0.05)= 1.3$.

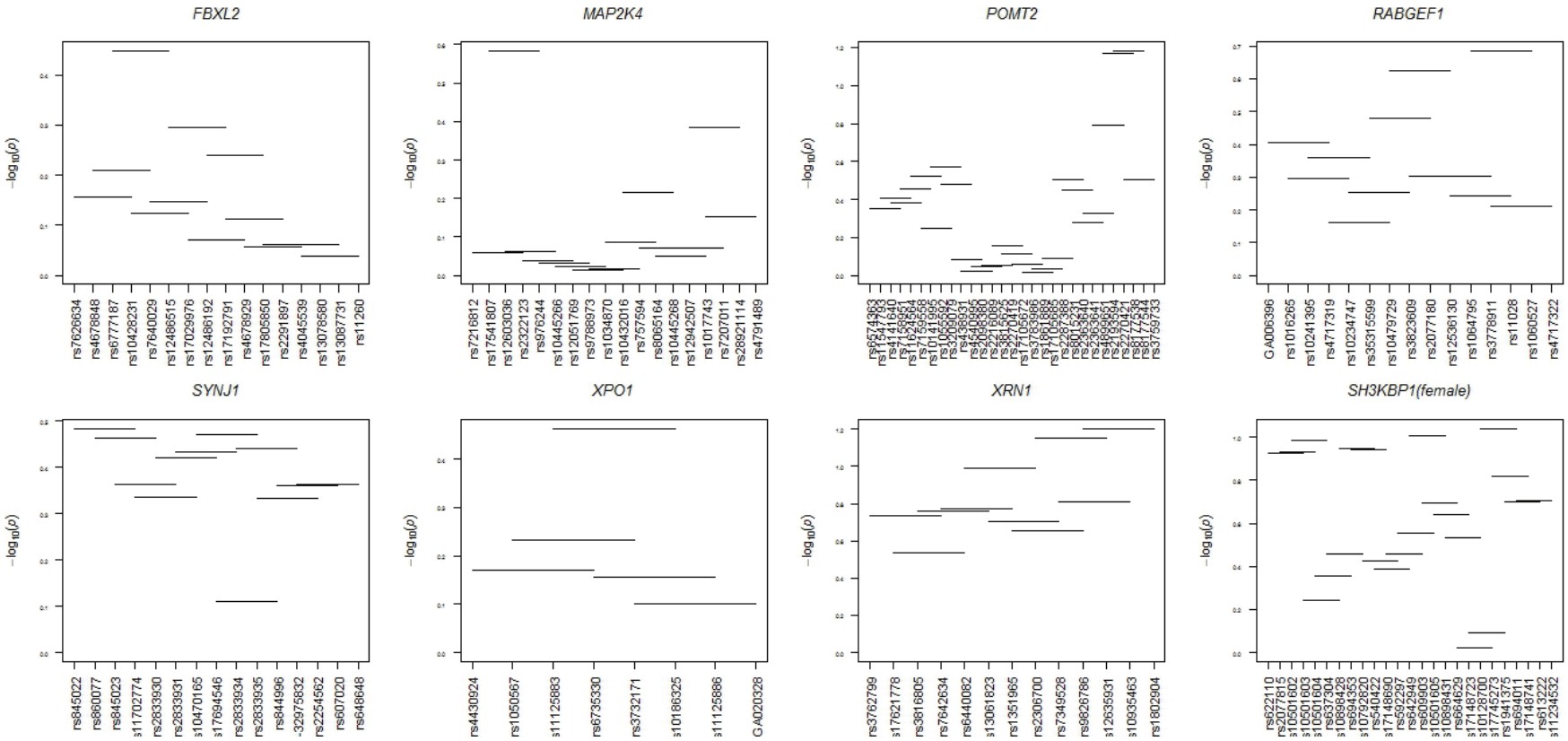

Figure 2. Haplotype windows for genes containing no significant windows. Lines represent the window tested, with the corresponding SNP rs numbers along the horizontal axis and global p-value on the vertical axis.

detection as a possible risk locus in a few previous studies [4], specifically with regard to abnormal Tau protein [19]. Combined with our findings and those of Treusch, more work concerning the role of *PPP2R5C* and its fellow phosphoprotein phosphatases in AD should be undertaken.

SNX8 and *XRN1* have been identified as Aβ toxicity enhancers [11]. *XRN1* contained four *APOE*-adjusted significant SNPs (rs1351965, rs13061823, rs6440082, rs3816805), however, we did not identify any significant windows for haplotype analysis. *SNX8* showed significant associations for both analyses, with a single significant SNP (rs10249052) and three significant windows, two of which contained the suggestive SNP from single locus analysis. Though no mechanism has been proposed to explain how these genes elevate the toxicity of Aβ, the role of *SNX8* in endosomal content sorting [20] fits well with the implication of clathrin-mediated endocytosis (CME) in LOAD risk [11, 21].

ADSSL1 is an intracellular protein responsible for catalyzing the first step of *de novo* biosynthesis of AMP [22, 23] and its genetic variation has been shown to affect AD neuropathology and episodic memory [11]. While this gene lacked significance in our single locus analysis, it possessed the most significant window in haplotype analysis (P=3.724E-03), suggesting that it may be relevant to LOAD risk. *SH3KBP1* (*CIN85)* has been implicated in clathrin-mediated endocytosis (CME) of epidermal growth factor receptor (EGFR) [24] and is a member of Src family kinases that can phosphorylate Tau to produce the second pathological hallmark of LOAD, NFTs [19]. In this study we found both single and multi-locus associations in this gene, further confirming its possible role in LOAD.

Previously, genetic variation in *XPO1* has been reported to be associated with AD in a family-based sample [11]. However, we did not find significant associations in *XPO1* in our case-control sample. Likewise, we did not find associations in 5 additional genes (*FBXL2, RABGEF1, MAP2K4, POMT2,* and *SYNJ1*). The lack of association with these 6 genes does not mean they are not relevant to LOAD risk. LOAD is a multifactorial disease with a number of genes that potentially affect its development and severity. Given this complexity, it is quite plausible that our sample did not contain enough individuals who possessed the causative alleles in these genes. Additionally, our study used only genotyped SNPs in our data set. It is possible that the functional variants affecting Aβ toxicity in these genes were not genotyped in our samples or were not in linkage disequilibrium with the genotyped variants.

Further investigation of these genes, including additional replication in other case-control samples, resequencing, and functional studies to elucidate the pathways by which they affect Aβ toxicity, are necessary to determine the degree of involvement these genes have for LOAD risk. Similar findings would suggest potential therapies that seek to increase expression of genes identified as suppressors of Aβ toxicity or to downregulate production of proteins that enhance Aβ toxicity. However, targeted therapies such as these cannot begin development until the mechanisms of AD are better understood.

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Please address correspondence to: M. Ilyas Kamboh, PhD, Department of Human Genetics, Graduate School of Public Health University of Pittsburgh, Pittsburgh, PA 15161, USA. Telephone: 412-624-3066; Fax: 412-624-3020; E-mail: kamboh@pitt.edu

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Supplementary Table 1. Single locus analysis results for all 222 SNPs tested

Gene	Chr[1]	SNP	A1[2]	OR[3]	P-unadjusted[4]	*APOE* adj.-P[5]
XPO1	2	rs10186325	C	1.088	0.1896	0.132
XPO1	2	rs6735330	A	0.8912	0.1901	0.2817
XPO1	2	rs3732171	G	1.083	0.2139	0.146
XPO1	2	rs4430924	A	1.057	0.3888	0.2238
XPO1	2	rs1050567	A	1.081	0.4273	0.5072
XPO1	2	rs11125886	G	0.8806	0.4482	0.664
XPO1	2	GA020328	A	0.9605	0.5278	0.4122
XPO1	2	rs11125883	C	0.9801	0.7569	0.4837
FBXL2	3	rs6777187	A	1.076	0.2848	0.7143
FBXL2	3	rs12486192	A	1.075	0.3011	0.7498
FBXL2	3	rs13078580	G	0.9178	0.3772	0.8279
FBXL2	3	rs17029976	A	1.076	0.4181	0.6195
FBXL2	3	rs13087731	G	0.9511	0.4493	0.308
FBXL2	3	rs17192791	A	1.185	0.4796	0.8741
FBXL2	3	rs2291897	A	1.055	0.5215	0.9214
FBXL2	3	rs7626634	G	1.045	0.6331	0.8882
FBXL2	3	rs4678929	C	1.041	0.6364	0.9386
FBXL2	3	rs4045539	C	1.039	0.6434	0.9521
FBXL2	3	rs10428231	G	1.046	0.666	0.7717
FBXL2	3	rs17805850	A	1.046	0.6665	0.7774
FBXL2	3	rs12486515	A	1.035	0.7429	0.8865
FBXL2	3	rs4678848	G	1.033	0.7603	0.9422
FBXL2	3	rs11260	A	1.072	0.7956	0.747
FBXL2	3	rs7640029	A	1.016	0.8131	0.8039
XRN1	3	rs1351965	A	1.186	0.01117	0.01861
XRN1	3	rs13061823	G	1.149	0.0271	0.03655
XRN1	3	rs6440082	G	1.148	0.02747	0.03821
XRN1	3	rs3816805	A	1.146	0.03006	0.04431
XRN1	3	rs9826786	A	1.126	0.0624	0.09096
XRN1	3	rs3762799	G	0.898	0.08623	0.05194
XRN1	3	rs1802904	G	0.8939	0.2035	0.3483
XRN1	3	rs10935463	G	0.9384	0.3121	0.1967
XRN1	3	rs12635931	G	0.9269	0.3957	0.49
XRN1	3	rs7349528	G	0.9569	0.5536	0.3518
XRN1	3	rs7642634	G	0.9495	0.5738	0.9038
XRN1	3	rs17621778	G	1.084	0.7441	0.8626
XRN1	3	rs2306700	A	0.9753	0.7819	0.892
RABGEF1	7	rs4717322	A	1.151	0.1076	0.2701
RABGEF1	7	GA006396	G	0.8145	0.2057	0.1767
RABGEF1	7	rs12536130	A	0.8397	0.2776	0.2333
RABGEF1	7	rs3778911	G	0.8398	0.2781	0.2319
RABGEF1	7	rs35315599	A	0.9079	0.2896	0.2689

RABGEF1	7	rs4717319	A	0.9412	0.3331	0.4708
RABGEF1	7	rs2077180	G	0.9345	0.432	0.5984
RABGEF1	7	rs10234747	G	1.076	0.4422	0.3444
RABGEF1	7	rs1064795	A	1.071	0.4695	0.3711
RABGEF1	7	rs11028	G	0.9528	0.4772	0.505
RABGEF1	7	rs3823609	A	1.068	0.4867	0.3973
RABGEF1	7	rs10241395	A	1.039	0.6849	0.5526
RABGEF1	7	rs1060527	C	1.039	0.6849	0.5575
RABGEF1	7	rs1016265	A	1.02	0.7488	0.9475
RABGEF1	7	rs10479729	A	0.9895	0.902	0.9741
SNX8	7	rs2286206	A	1.554	0.01335	0.09287
SNX8	7	rs10249052	A	1.167	0.02036	0.04795
SNX8	7	rs4721524	G	1.296	0.1272	0.4121
SNX8	7	rs2398669	A	1.264	0.1727	0.518
SNX8	7	rs4719471	A	1.248	0.1921	0.6109
SNX8	7	rs4549678	A	0.9275	0.2375	0.3081
SNX8	7	rs12699820	A	1.065	0.335	0.4085
SNX8	7	rs4442022	G	0.9438	0.3884	0.7482
SNX8	7	rs12534131	A	1.045	0.4999	0.7426
SNX8	7	rs6963924	A	0.9569	0.5125	0.9266
SNX8	7	rs35932242	A	0.8151	0.5237	0.4023
SNX8	7	rs4866	A	0.8678	0.6062	0.9885
SNX8	7	rs2398668	A	1.033	0.6228	0.8276
SNX8	7	rs4721527	A	1.024	0.7137	0.9141
SNX8	7	rs7456643	G	0.9732	0.7282	0.8393
SNX8	7	rs10950641	A	0.9578	0.7681	0.7876
SNX8	7	rs6947645	A	0.9829	0.7897	0.7963
SNX8	7	rs1799832	A	0.9843	0.8407	0.8745
PICALM	11	rs10501602	G	0.7217	0.0006709	0.01037
PICALM	11	rs694011	A	0.839	0.008218	0.01608
PICALM	11	rs609903	A	0.8465	0.01206	0.01908
PICALM	11	rs10792820	C	1.146	0.05884	0.03251
PICALM	11	rs613222	C	1.114	0.08479	0.05787
PICALM	11	rs664629	G	0.9127	0.1468	0.2939
PICALM	11	rs10501604	A	1.123	0.1557	0.07547
PICALM	11	rs11234532	A	1.135	0.1862	0.2551
PICALM	11	rs642949	G	1.065	0.3254	0.1782
PICALM	11	rs622110	A	1.071	0.3262	0.4306
PICALM	11	rs1941375	G	1.063	0.376	0.4144
PICALM	11	rs10501603	G	1.068	0.3894	0.6031
PICALM	11	rs10898428	A	0.8963	0.41	0.2053
PICALM	11	rs10898431	A	1.057	0.4528	0.7721
PICALM	11	rs694353	A	1.046	0.477	0.9891
PICALM	11	rs540422	A	1.042	0.5127	0.9739
PICALM	11	rs592297	G	0.955	0.5601	0.3125

PICALM	11	rs10128700	A	1.045	0.5698	0.8103
PICALM	11	rs17745273	G	1.044	0.5737	0.818
PICALM	11	rs10501605	G	1.043	0.5874	0.8181
PICALM	11	rs637304	A	0.9719	0.7183	0.4618
PICALM	11	rs2077815	G	0.9806	0.8017	0.5064
PICALM	11	rs17148741	A	0.9659	0.875	0.7259
PICALM	11	rs17148690	G	1.022	0.9223	0.994
PICALM	11	rs17148723	G	0.9943	0.9799	0.8922
ADSSL1	14	rs4983382	G	0.9188	0.2467	0.222
ADSSL1	14	rs4983540	A	1.064	0.4315	0.577
ADSSL1	14	rs6644	G	1.048	0.4525	0.6044
ADSSL1	14	rs11160818	A	0.9383	0.4749	0.2603
ADSSL1	14	rs3803307	G	1.042	0.5123	0.6585
ADSSL1	14	rs4983386	A	1.041	0.5173	0.6717
ADSSL1	14	rs4983384	A	0.9584	0.5291	0.4718
ADSSL1	14	rs12894569	A	1.062	0.531	0.6716
ADSSL1	14	rs9783669	A	1.07	0.5704	0.663
ADSSL1	14	rs35590716	A	1.054	0.5824	0.7838
ADSSL1	14	rs12432802	A	1.062	0.6344	0.7922
ADSSL1	14	rs34672588	A	1.021	0.7449	0.9351
POMT2	14	rs2363640	A	0.8732	0.07975	0.08041
POMT2	14	rs2270421	A	1.094	0.1864	0.1798
POMT2	14	rs2363641	G	1.09	0.1888	0.1688
POMT2	14	rs438931	A	0.8859	0.1996	0.2085
POMT2	14	rs1055592	A	1.103	0.2014	0.1983
POMT2	14	rs4141640	G	0.9105	0.2385	0.4576
POMT2	14	rs8015231	C	1.109	0.2543	0.2371
POMT2	14	rs10141995	A	1.173	0.2867	0.3166
POMT2	14	rs2193594	G	1.073	0.2937	0.2865
POMT2	14	rs6574363	A	1.163	0.3101	0.3579
POMT2	14	rs8177538	G	0.8942	0.3119	0.3936
POMT2	14	rs3209079	A	0.925	0.3315	0.5562
POMT2	14	rs3815625	A	0.9431	0.4595	0.7288
POMT2	14	rs2270419	G	0.9449	0.4741	0.739
POMT2	14	rs11547793	G	1.049	0.5185	0.4702
POMT2	14	rs4540995	G	0.9546	0.6392	0.2892
POMT2	14	rs2098380	G	1.03	0.6433	0.9483
POMT2	14	rs8177544	A	0.9311	0.6552	0.6006
POMT2	14	rs1861889	A	1.045	0.7104	0.9941
POMT2	14	rs3759733	A	1.024	0.7117	0.7028
POMT2	14	rs4899651	A	1.02	0.7862	0.8779
POMT2	14	rs2216089	A	0.9858	0.8193	0.7985
POMT2	14	rs11624564	G	1.014	0.827	0.4847
POMT2	14	rs7158951	G	0.9864	0.8275	0.7683
POMT2	14	rs3783986	A	1.01	0.8807	0.8536

POMT2	14	rs17105685	A	1.01	0.8997	0.9872
POMT2	14	rs7159558	G	0.9938	0.9218	0.6689
POMT2	14	rs17105672	A	0.9943	0.9308	0.8031
POMT2	14	rs2287388	A	1	0.9976	0.8958
PPP2R5C	14	rs1746595	G	1.235	0.004142	0.009017
PPP2R5C	14	rs1678031	A	1.27	0.04928	0.06185
PPP2R5C	14	rs1741140	A	1.158	0.1368	0.2106
PPP2R5C	14	rs1746587	G	1.152	0.1383	0.07324
PPP2R5C	14	rs1741143	A	1.167	0.1566	0.2385
PPP2R5C	14	rs1058327	G	1.154	0.165	0.1931
PPP2R5C	14	rs12436919	A	0.8663	0.1997	0.4091
PPP2R5C	14	rs1678018	G	1.17	0.2832	0.4172
PPP2R5C	14	rs1618921	A	1.105	0.3148	0.3171
PPP2R5C	14	rs1677999	G	0.9331	0.3332	0.2778
PPP2R5C	14	rs3783370	A	0.9062	0.3704	0.2212
PPP2R5C	14	rs3742424	C	0.9025	0.3756	0.1744
PPP2R5C	14	rs736449	A	0.9284	0.483	0.3647
PPP2R5C	14	rs2749902	G	1.063	0.5264	0.5519
PPP2R5C	14	rs2720219	G	1.051	0.5352	0.8475
PPP2R5C	14	rs1612684	A	1.048	0.545	0.7333
PPP2R5C	14	rs1677991	G	1.047	0.5469	0.9285
PPP2R5C	14	rs10132483	G	1.053	0.6029	0.3632
PPP2R5C	14	rs2251246	A	1.049	0.6091	0.6046
PPP2R5C	14	rs2720208	G	1.03	0.6893	0.9306
PPP2R5C	14	rs1904298	A	1.051	0.693	0.9957
PPP2R5C	14	rs8003511	A	1.039	0.7011	0.4559
PPP2R5C	14	rs7145618	G	0.954	0.7121	0.8657
PPP2R5C	14	rs2720202	G	1.033	0.7245	0.9784
PPP2R5C	14	rs8015021	A	1.032	0.77	0.3977
PPP2R5C	14	rs1678019	G	0.98	0.7732	0.9625
PPP2R5C	14	rs1677998	A	0.9656	0.7879	0.9977
PPP2R5C	14	rs2749907	A	0.9827	0.8029	0.7234
PPP2R5C	14	rs7142002	G	1.031	0.8187	0.6298
PPP2R5C	14	rs961495	G	0.9833	0.8344	0.6537
PPP2R5C	14	rs6575883	G	1.002	0.9856	0.6059
MAP2K4	17	rs28921114	I	1.498	0.1387	0.1342
MAP2K4	17	rs10445266	G	0.9293	0.244	0.6917
MAP2K4	17	rs10432016	A	0.933	0.2718	0.6777
MAP2K4	17	rs12942507	A	1.073	0.2895	0.5588
MAP2K4	17	rs976244	G	0.931	0.3335	0.7225
MAP2K4	17	rs9788973	A	0.9412	0.3364	0.8473
MAP2K4	17	rs7216812	A	1.058	0.376	0.803
MAP2K4	17	rs1034870	C	0.9372	0.3807	0.8049
MAP2K4	17	rs10445268	A	0.9442	0.4024	0.6801
MAP2K4	17	rs7207011	G	0.8628	0.4173	0.5393

MAP2K4	17	rs1017743	A	1.043	0.5403	0.5554
MAP2K4	17	rs17541807	G	0.9651	0.5866	0.8125
MAP2K4	17	rs12051769	G	0.9716	0.6889	0.9164
MAP2K4	17	rs757594	G	0.9716	0.6891	0.9465
MAP2K4	17	rs4791489	A	1.025	0.6991	0.9116
MAP2K4	17	rs12603036	A	1.04	0.7021	0.7012
MAP2K4	17	rs8065164	G	1.023	0.7304	0.6713
MAP2K4	17	rs2322123	G	0.9809	0.788	0.8942
SYNJ1	21	rs2833930	A	0.9047	0.1407	0.05831
SYNJ1	21	rs2254562	G	0.9146	0.1897	0.08072
SYNJ1	21	rs845023	G	1.18	0.2102	0.1171
SYNJ1	21	rs10470165	G	1.165	0.2447	0.1362
SYNJ1	21	rs860077	C	1.074	0.2501	0.3
SYNJ1	21	rs2833935	G	1.072	0.2535	0.2133
SYNJ1	21	rs2833931	A	0.9347	0.2683	0.2057
SYNJ1	21	SNP21-32975832	T	1.153	0.2784	0.1629
SYNJ1	21	rs11702774	A	0.9304	0.3306	0.1335
SYNJ1	21	rs2833934	A	0.8542	0.3497	0.358
SYNJ1	21	rs648648	A	1.089	0.3785	0.1837
SYNJ1	21	rs607020	A	1.042	0.4989	0.4749
SYNJ1	21	rs845022	A	1.041	0.5113	0.4842
SYNJ1	21	rs17694546	A	1.009	0.9447	0.4732
SYNJ1	21	rs844996	G	1.007	0.9455	0.8656
SH3KBP1	X	rs12013533	G	0.7977	0.006109	0.01496
SH3KBP1	X	rs1017874	A	0.7876	0.01772	0.04958
SH3KBP1	X	rs6629352	G	0.8188	0.01957	0.05905
SH3KBP1	X	rs6527933	C	0.826	0.02229	0.0292
SH3KBP1	X	rs10127144	G	0.8282	0.0278	0.05364
SH3KBP1	X	rs16981251	G	0.8277	0.02933	0.0665
SH3KBP1	X	rs5955826	A	0.8321	0.0342	0.07057
SH3KBP1	X	rs7062445	G	0.8372	0.04156	0.05499
SH3KBP1	X	rs4630061	G	0.8252	0.05452	0.0455
SH3KBP1	X	rs5955812	G	0.859	0.0621	0.06608
SH3KBP1	X	rs6527940	A	0.8347	0.06729	0.05181
SH3KBP1	X	rs7888444	A	0.8254	0.07836	0.09562
SH3KBP1	X	rs16981279	C	0.8389	0.1017	0.1275
SH3KBP1	X	rs11094775	A	0.8511	0.1049	0.09655
SH3KBP1	X	rs900686	A	0.8505	0.1075	0.0873
SH3KBP1	X	rs7889157	C	0.8614	0.1555	0.1782
SH3KBP1	X	rs16981266	G	0.8743	0.1694	0.1562
SH3KBP1	X	rs4825317	G	0.883	0.2375	0.3003
SH3KBP1	X	rs11796420	A	1.198	0.2627	0.3501
SH3KBP1	X	rs5955819	A	0.9043	0.3657	0.4975
SH3KBP1	X	rs11795873	G	1.061	0.3879	0.6763
SH3KBP1	X	rs5909133	G	0.9905	0.9404	0.9418

[1]Chromosome location; [2] Effect allele; [3]Odds ratio; [4]Unadjusted P-value; [5]*APOE* adjusted P-value

Supplementary Table 2. Significant windows in five genes in haplotype analysis

Gene	Window[1]	Haplotype	Control Frequency	Case Frequency	Total Frequency	Global P[2]
SNX8	rs4549678	AAAA	0.001967849	0.005011279	0.004045297	0.042122
(15)[3]	rs12699820	AAAG	NA	0.001320437	0.000589227	
	rs10950641	AAGA	0.025940599	0.027085454	0.02631246	
	rs10249052	AAGG	0.031026958	0.02187551	0.025965494	
		ACAA	NA	2.84E-10	7.49E-12	
		ACAG	NA	1.27E-10	2.82E-10	
		ACGA	0.003308397	0.005871904	0.004719863	
		ACGG	0.373038034	0.348636043	0.359024728	
		GAAA	0.044447955	0.03936929	0.041324651	
		GAAG	0.000643274	3.43E-10	0.000316542	
		GAGA	0.211471931	0.251248349	0.234466017	
		GAGG	0.011561002	0.008191831	0.009505745	
		GCAG	NA	NA	2.52E-13	
		GCGA	0.008792288	0.009136419	0.009051677	
		GCGG	0.287801714	0.282253483	0.284678298	
	rs10950641	AAAG	0.004873169	0.003484862	0.004081811	0.047033
	rs10249052	AAGA	0.041483774	0.04112434	0.041295962	
	rs6963924	AGAG	0.000693093	0.000506895	0.00047377	
	rs4442022	AGGA	2.64E-08	0.000586101	0.000422255	
		GAAA	0.000526522	NA	1.39E-09	
		GAAG	0.00837652	0.012893169	0.010926271	
		GAGA	0.238963073	0.278087463	0.261627069	
		GAGG	0.001705961	0.002132861	0.00198885	
		GGAA	9.45E-11	0.000781038	0.000672245	
		GGAG	0.289288525	0.277454098	0.282645367	
		GGGA	0.410047352	0.380810492	0.392954264	
		GGGG	0.004041985	0.00213868	0.002912134	
	rs4721524	AAGA	NA	0.001551279	0.000895151	0.049016
	rs2286206	AAGG	NA	1.66E-10	1.17E-10	
	rs4721527	AGAA	3.88E-10	0.000493691	0.000287401	
	rs6947645	AGAG	0.362181986	0.368034236	0.365563037	

		AGGA	0.391962421	0.377118468	0.383432833	
		AGGG	0.215062273	0.211748878	0.213138608	
		GAGG	0.030793319	0.040661951	0.036444584	
		GGAG	NA	3.44E-09	2.10E-09	
		GGGG	NA	0.000391493	0.000238384	
PICALM	rs2077815	AAAA	0.165970772	0.178931061	0.173410405	0.036627
(22)	rs10501602	AAAG	0.286319737	0.293931393	0.290680662	
	rs10501603	AAGG	0.212943632	0.226181115	0.220542347	
	rs10501604	AGAG	0.134655532	0.104984177	0.117633241	
		AGGG	NA	1.40E-07	1.16E-07	
		GAAG	0.200110326	0.194837144	0.197091797	
		GGAG	NA	0.00113497	0.000641432	
		GGGG	NA	8.72E-11	6.19E-12	
	rs10501602	AAAG	0.165970772	0.178931061	0.173410405	0.038324
	rs10501603	AAGA	0.194154488	0.188048902	0.190651631	
	rs10501604	AAGG	0.292275575	0.300719618	0.297120797	
	rs540422	AGGG	0.212943632	0.226181132	0.220542378	
		GAGA	NA	0.000564576	0.000322135	
		GAGG	0.134655532	0.105554588	0.117952568	
		GGGA	NA	2.91E-11	3.77E-13	
		GGGG	NA	1.23E-07	8.52E-08	
	rs622110	AAAA	0.262526096	0.271882262	0.267896843	0.039749
	rs2077815	GAAA	0.189711167	0.20083557	0.196092084	
	rs10501602	GAAG	0.212943632	0.226181119	0.220542343	
	rs10501603	GAGA	0.134655532	0.105128799	0.117713741	
		GAGG	NA	1.36E-07	1.21E-07	
		GGAA	0.200163572	0.194981762	0.197193942	
		GGGA	NA	0.000990353	0.000560927	
PPP2R5C	rs1677999	AAAG	0.063391664	0.064507676	0.064008472	0.005107
(28)	rs1741140	AAGA	NA	1.40E-10	1.39E-10	
	rs2749907	AGAA	0.034341792	0.032584991	0.033403633	
	rs1677991	AGAG	0.014844765	0.006825857	0.010207884	

		AGGA	0.620119275	0.629882955	0.625750132	
		AGGG	0.001331486	0.001171362	0.001200625	
		GAAG	0.036295183	0.044682219	0.041135104	
		GAGA	NA	0.000415063	0.000236593	
		GGAA	0.040807906	0.021516368	0.029611797	
		GGAG	0.056312378	0.071556012	0.065132879	
		GGGA	0.109532697	0.111211203	0.110539311	
		GGGG	0.023022854	0.015646296	0.01877357	
ADSSL1	rs11160818	AAGG	0.002949317	0.001600814	0.002238167	0.003724
(9)	rs4983382	AGAA	9.32E-08	0.000738023	0.00064964	
	rs35590716	AGGA	0.110873113	0.106567255	0.1082767	
	rs34672588	AGGG	0.028310888	0.026531381	0.02722083	
		GAAA	0.113778612	0.117949668	0.11606806	
		GAGA	0.129372836	0.123813999	0.126047563	
		GAGG	0.506171054	0.523753859	0.516592627	
		GGAA	NA	0.000147006	8.41E-07	
		GGGA	0.089057792	0.095284265	0.092977537	
		GGGG	0.019486293	0.003497369	0.009928036	
SH3KBP1-males	rs16981251	AAAA	0.001519772	0.006277048	0.004299646	0.007823
(19)	rs4630061	AAAG	0.496120256	0.459794796	0.475190379	
	rs11795873	AAGG	0.28596621	0.375912941	0.337784912	
	rs11094775	AGAG	NA	0.004249524	0.00244524	
		GAAA	0.004162117	0.0041841	0.004134558	
		GAGA	1.18E-08	NA	5.50E-11	
		GAGG	0.058822544	0.046090529	0.051482072	
		GGAA	0.1505681	0.096233412	0.11927664	
		GGAG	0.002840991	0.00478491	0.003995133	
		GGGG	NA	0.002472739	0.001391422	
	rs4630061	AAAA	0.002841063	0.004184631	0.003614743	0.009882
	rs11795873	AAAC	0.002840839	0.006276151	0.0048194	
	rs11094775	AAGC	0.495993753	0.45966633	0.475055004	
	rs900686	AGAC	6.97E-08	NA	8.46E-11	
		AGGC	0.344915184	0.422132302	0.38940242	

	GAAA	0.150568028	0.096233779	0.1192767	
	GAGA	NA	0.0041841	0.002409762	
	GAGC	0.002841063	0.004857865	0.004039601	
rs7062445	AAAA	0.498896655	0.465796895	0.479827672	0.010463
rs16981251	AAAG	0.282353345	0.372054332	0.334017814	
rs4630061	AAGA	NA	0.004198983	0.00241502	
rs11795873	AGAA	NA	0.00209205	0.001205028	
	AGAG	NA	0.00209205	0.001209165	
	GAAG	0.002840909	0.0041841	0.003614667	
	GGAA	0.002917515	0.00209205	0.002449046	
	GGAG	0.059582485	0.043947937	0.050568174	
	GGGA	0.153409091	0.101367898	0.123463165	
	GGGG	NA	0.002173705	0.001230249	
rs7888444	ACGC	0.130681818	0.082635983	0.103012048	0.01372
rs16981279	CAAA	0.865056818	0.89958159	0.884939759	
rs4825317	CAGC	NA	0.012552301	0.007228916	
rs7889157	CCGC	0.004261364	0.005230126	0.004819277	
rs11795873	AAAG	0.153354978	0.10041841	0.122855881	0.013747
rs11094775	AACA	5.18E-08	0.0041841	0.003012123	
rs900686	AACG	0.001474567	0.00209205	0.001842839	
rs16981266	AGAG	NA	0.0041841	0.002409713	
	AGCA	0.497419054	0.459287111	0.474874265	
	AGCG	0.002840909	0.005230125	0.004216867	
	GACA	0.001420403	NA	1.37E-10	
	GGCA	0.343490037	0.424604102	0.39078831	
	GGCG	NA	1.74E-10	2.02E-11	
rs16981279	AAAA	0.019887477	0.014646082	0.016868915	0.041451
rs4825317	AAAG	0.845169341	0.884935508	0.868070844	
rs7889157	AGCA	NA	0.0041841	0.002409639	
rs1017874	AGCG	NA	0.008368201	0.004819277	
	CAAA	1.57E-10	NA	4.67E-12	
	CGCA	0.130589038	0.083680278	0.103565348	
	CGCG	0.004354143	0.004185831	0.004265977	

[1]Four SNPs represented in the haplotype window; [2]P value for association of all haplotypes at corresponding four SNPs tested; [3]Number of windows tested in gene.