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, CD33, EPHA1, ABCA7, and MS4A44/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
Aβ toxicity modifier genes and the risk of AD

were found to be human homologs, including eight Aβ toxicity suppressor (ADSSL1, 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, neuro-physiological 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 α=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
Aβ toxicity modifier genes and the risk of AD

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

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<th>Gene</th>
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<th>SNP G</th>
<th>A1</th>
<th>OR</th>
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\(^3\text{Chromosome location; }^2\text{Effect allele; }^3\text{Odds ratio; }^4\text{Unadjusted P-value; }^5\text{P value adjusted for APOE genotype}\)

Significant haplotype window associations with LOAD (Figure 1; Supplementary Table 2). The most significant association in this sample was for ADSSL1/SNPs rs11660818 - rs4983382 - rs3590716 - 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 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 complements 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
Aβ toxicity modifier genes and the risk of AD

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.
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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.

Acknowledgements

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References

Secreted amyloid beta-protein similar to that in the senile plaques of Alzheimer’s disease is increased in vivo by the presenilin 1 and 2 and APP mutations linked to familial Alzheimer’s Disease. Nat Med 1996; 2:864-870.


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

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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

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Aβ toxicity modifier genes and the risk of AD

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