KIAA1462, a coronary artery disease associated gene, is a candidate gene for late onset Alzheimer disease in APOE carriers

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**Introduction**

Alzheimer disease (AD) is a devastating neurodegenerative disease affecting more than five million Americans [1–3]. Symptoms begin late in life and progress over several years ultimately leaving the individual uncommunicative and bedridden. The cause of AD is complex, but the heritable component has been estimated to be as high as 80% [4]. Recent advances have been made in understanding the genetic component of AD, so that much of what we understand about the mechanism of AD we owe to genetics [5]. Investigations of early onset AD identified mutations in PSEN1 [6], PSEN2 [7], and APOE [8,9] as causative. APOE was identified in early candidate gene studies as associated with late onset AD (LOAD) [10], and remains the most replicated association in the 21 genome wide association studies (GWAS) that have been performed to date [5]. In fact, the association of APOE with LOAD still explains more of the population attributable risk than all current non-APOE GWAS findings together [5], underscoring the genetic complexity in this disease. Over 40 different loci have been highlighted in GWAS as LOAD susceptibility loci; only a handful of those have been confirmed by follow-up [5]. Thus, much of the heritability in LOAD remains unexplained.

The association between coronary vascular disease (CVD) and LOAD remains unclear. It has been theorized that atherosclerosis resulting in compromised blood flow to the brain and subsequent oxidative stress and inflammation could contribute to the risk for LOAD [11]. APOE has also been linked to CVD, although this association is controversial [12,13]. It appears, however, that the contribution of APOE to AD pathology is not through enhanced CVD, but through more direct effects on amyloid beta processing and neurotoxicity [14].

In this study, we have used updated genetic linkage data from chromosome 10 in combination with expression data from serial analysis of gene expression to choose a new set of thirteen candidate genes for genetic analysis in late onset Alzheimer disease (LOAD). Results in this study identify the KIAA1462 locus as a candidate locus for LOAD in APOE4 carriers. Two genes exist at this locus, KIAA1462, a gene associated with coronary artery disease, and “rokimi,” encoding an untranslated spliced RNA. The genetic architecture at this locus suggests that the gene product important in this association is either “rokimi,” or a different isoform of KIAA1462 than the isoform that is important in cardiovascular disease. Expression data suggests that isoform f of KIAA1462 is a more attractive candidate for association with LOAD in APOE4 carriers than “rokimi” which had no detectable expression in brain.

**Materials and Methods**

**Study Populations**

All individuals included in this study were Caucasian late-onset AD (LOAD) participants (minimum age at onset (AAO) = 60 years) and related unaffected relatives. LOAD was diagnosed according to the NINCDS-ADRDA criteria [23]. All unaffected individuals had results within the normal range in the Mini-Mental State Examination (MMSE). APOE genotyping was performed using a Taqman allelic discrimination assay on a 7900HT Fast Real-Time PCR System (Life Technologies).
Following informed consent, blood samples were collected from CAP participants at the University of Miami, Vanderbilt with protocols approved by the institutional review board for the Alzheimer Project (CAP), including the University of Miami, Vanderbilt University, the University of California at Los Angeles; and the National Institute of Mental Health repository (NIMH). Written consent was obtained from all participants in agreement with protocols approved by the institutional review board for the CAP participants at the University of Miami, Vanderbilt University, and the University of California at Los Angeles. Following informed consent, blood samples were collected from each individual and genomic DNA was extracted using the Puregene system (Gentra Systems, Minneapolis, MN). Extracted DNA was obtained from the NCRAD and NIMH repositories.

**Gene Selection**

The Serial Analysis of Gene Expression (SAGE) method was used to compare the gene expression levels in the brain tissue from LOAD patients and controls as described elsewhere [23,26]. Candidate genes for analysis in this study were chosen by the convergence of their differential expression data in LOAD brain compared to control brain, and their position under the LOAD linkage peaks as shown in previous linkage studies.

**SNP Selection and Genotyping**

Tagging SNPs were selected using LDSelect with an $r^2$ threshold of 0.8 in the CEU subject data of HapMap Release 21 of phase II of the National Center for Biotechnology Information build 35 assembly. CEU subjects were Utah residents of northern and western European ancestry from the Centre d’Etude du Polymorphisme Humain. The minor allele frequency threshold was 0.05, as exceeded by any Caucasian study population of dbSNP, including CEU.

A total of 384 SNPs on chr10 were genotyped with the use of the midthroughput Sequenom genotyping platform, based on a single-base primer extension reaction coupled with mass spectrometry. The assays were designed using Sequenom SpectroDESIGNER software. Genomic DNA (5 ng) was amplified following the manufacturer recommendations (Sequenom). Single primer extension over the SNP was carried out in a final concentration of 1.25 μM of the extension primer. The extension step followed the manufacturer procedure. The reaction was then desalted by addition of 6 mg of resin followed by 15 min mixing and centrifugation (5000 rpm) to settle the contents of the plate. The extension product was then spotted onto a 384 well spectroCHIP before being flown in the MALDI-TOF mass spectrometer. Data was collected, real time, using SpectroTyper Analyzer, SpectraAQUIRE and SpectroCALLER (Sequenom). DNA samples from cases and controls were randomly sorted, and duplicate samples were implemented across plates for genotyping quality control.

**Statistical Methods**

**Association analysis in family data set.** The allelic association analyses were conducted using the association in the presence of linkage (APL) program [27] and the pedigree disequilibrium test (PDT) [28]. These methods provide valid and robust tests for allelic association in trios and extended families. The Genotype-PDT (GenoPDT) tested genotypic association to the risk of LOAD [29]. Genotype efficiency, Hardy-Weinberg Equilibrium and linkage disequilibrium were checked using Haplovew [30]. Linkage analysis was conducted on families using two-point heterogeneity LOD scores (HLOD) calculated using FASTLINK and HOMOG [31]. Both recessive and dominant models with disease allele frequencies of 0.01 and 0.001, respectively, were analyzed. This approach is robust for detecting linkage signals when the underlying model is unknown or complex [32].

**Reverse Transcriptase PCR and Real Time Quantitative PCR**

Frozen superior frontal cortex samples were obtained from the Harvard Brain Tissue Resource Center from four control and four LOAD brains. RNA was isolated from these samples using TRizol reagent (Invitrogen) and converted to first strand cDNA using the

### Table 1. AD family data details.

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<th>NIMH*</th>
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<td>85</td>
<td>289</td>
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*The ALL column lists the combined totals for all ascertainment sites. Samples were ascertained by the following centers: the NCRAD repository at Indiana University (NCRAD); the Collaborative Alzheimer Project (CAP), including the University of Miami and Vanderbilt University and University of California at Los Angeles; and the National Institute of Mental Health repository (NIMH). DOI:10.1371/journal.pone.0082194.t001
SuperScript® III First-Strand Synthesis System for RT-PCR (Invitrogen). Oligo(dT), random hexamers, and a gene specific primer were all used separately to create first strand synthesis for the \textit{rokimi} putative transcript, while oligo(dT) was used as a first strand synthesis primer for the \textit{KIAA1462} mRNA quantitation. TaqMan probes specific for the junction between exons 2 and 3 (Hs1584907\_m1), between exons 3 and 4 (Hs1584907\_m1), and the 3' UTR (6835–6843 of NM\_020848) were used for quantitative real time PCR. Relative levels of the \textit{KIAA1462} transcript were measured with quantitative real time PCR on an ABI 7900HT.

**Table 2.** Candidate Genes on Chromosome 10 Identified by Genomic Convergence.

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<th>Gene Name</th>
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<th>Size (kb)</th>
<th># of SNPs genotyped</th>
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<td>TMEM10</td>
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<tr>
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<tr>
<td>HLLS</td>
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<tr>
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<td>IFIT3</td>
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<td>FAS</td>
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*Expression ratio is from SAGE data [33].
doi:10.1371/journal.pone.0082194.t002

Figure 1. Allelic association test of candidate gene SNPs in the overall data set. \textit{KIAA1462} and \textit{SORBS1} were associated with LOAD at a p value $<.01$.
doi:10.1371/journal.pone.0082194.g001
Fast Real Time PCR System using Taqman Gene Expression Assays. Absolute quantitation was performed using standard curves based on cDNAs cloned into the pCR4-TOPO vector using the TOPO-TA cloning kit (Invitrogen). Endogenous control assays to housekeeping gene GAPDH or ACTB were run in triplicate. The presence or absence of the rokimi transcript in brain was determined by the presence/absence of an RT-PCR product of the correct size. Two sets of primers were used, primer set 1 (5'-ctcctgcccttcctccatc-3' roki1.for and 5'-ggcacgatcttggctcat-3' roki1.rev) primers set 2 (5'-CACTCCTAGGCGGGGCTCCT-3' roki2.for and 5'-TGCGTACCTCACCGAGGTTTC-3' roki2.rev).

Results
Genomic Convergence Identified Genes and Genotyped SNPs
To identify new candidate genes for Alzheimer disease, linkage data from chromosome 10 was combined with expression data from SAGE analysis. Genes that showed significant differential expression in AD brain in at least two SAGE comparisons [33] and were under previously identified linkage peaks [16,18,34–36] were chosen for further study. Thirteen genes were selected for detailed genetic analysis, and all of these genes have evidence for expression in brain in the Unigene database. Tagging SNPs were chosen from both intronic and exonic regions of the genes, except for PRKG1 where size necessitated limiting SNPs to the exonic regions. The gene description, size, and number of genotyped SNPs are summarized in Table 2.

Association Analysis and Real Time Quantitative PCR of KIAA1462
The allelic association of 384 genotyped SNPs in thirteen genes was analyzed in the overall data set of 441 families containing 1001 affected and 352 unaffected individuals (Table 1). The Genotype-PDT (GenoPDT) results are presented in Figure 1 and the linkage analysis results using two-point heterogeneity LOD scores (HLOD) are presented in Figure 2. Fourteen SNPs in six genes (KIAA1462; MIM #605264, CUL2; MIM #603135, PRKG1; MIM #176894, FAS; MIM #134637, SLC16A12; MIM #611910, 611910, and SORBS1; MIM #605264) showed association with AD at nominal p<0.05. Two of those SNPS, rs2488024 in KIAA1462 and rs10823056 in PRKG1, also had calculated two point LOD scores greater than 1.0.

The Association of KIAA1462 Locus SNPs and LOAD is Restricted to APOE Carriers
GWAS studies have identified KIAA1462 as a novel locus for coronary artery disease [37,38]. The association between non-stroke cardiovascular disease (CVD) and Alzheimer’s disease has been debated, but a recent study reports that CVD increases risk of AD only in carriers of the APOE4 allele (Hazard Ratio 2.39, 95% confidence interval) [39]. From these studies, a model is suggested in which variation in KIAA1462 increases the risk of
coronary artery disease, which in turn increases the risk of LOAD only in APOE4 carriers. To test this model, the genetic analysis of the association between SNPs in KIAA1462 and LOAD was performed again after stratifying the families by APOE status. The APOE status of a family was defined as positive if more than 50% of the family members had the APOE4 allele. By this definition, 279 APOE positive families and 162 APOE negative families were analyzed. When the analysis is stratified by APOE status, the association between KIAA1462 and LOAD is significant almost exclusively in the APOE positive group (Table 3).

### The Association of the KIAA1462 Locus with LOAD in a Publicly Available Genome-wide Dataset

The region of interest was examined for association with LOAD using the dataset assembled by the ADGC (stage 1, 8,309 individuals with LOAD (cases) and 7,366 cognitively normal elders (CNEs) as controls) from eight cohorts and a ninth newly assembled cohort from the 29 National Institute on Aging (NIA)-funded Alzheimer Disease Centers (ADCs) [40]. No significant association with LOAD was seen at this locus in this dataset. Although these data might suggest that KIAA1462 is not associated with LOAD, it is also possible that an association would only be detected after stratification by APOE status or presence of cardiovascular disease in this dataset. Thus a large scale GWAS study cannot exclude that this gene is still important in a subset of LOAD.

### Analysis of the Genomic Structure at the KIAA1462 Locus

While three SNPs in the KIAA1462 locus showed nominal association to AD in a previous study, none of these associations survived multiple testing correction [41]. More recently, other SNPs in the locus were discovered in two GWAS to be strongly associated with coronary artery disease (CAD) (p = 8.78×10⁻¹⁶) [42,37]. When Haploview [30] was used to analyze linkage disequilibrium, the groups of SNPs associated with CAD and LOAD appear to cluster in two different LD blocks, suggesting that they are inherited separately (Figure 3). In addition, when the SNPs from the two studies were overlaid on the genomic structure of the locus using the UCSC genome browser (February 2009 human reference sequence (GRCh37)) [43], the SNPs associated with CAD are more distal than the SNPs associated with LOAD.
The CAD SNPs are clustered over the protein coding exons of *KIAA1462*, while the LOAD SNPs are clustered proximal to the protein coding exons.

*KIAA1462* has seven predicted splice isoforms, four of which have protein coding exons (Aceview) (Figure 4). The isoform b structure, which contains all three coding exons, is conserved in mouse, and the predicted protein is expressed in mouse [42]. The SNPs associated with CAD are more distal than the SNPs associated with LOAD, which are clustered upstream of the predicted start of transcription of *KIAA1462* isoforms a, b, c, and f, and in the introns of isoforms d and e. Another gene, designated “rokimi” in Aceview, was recently identified as a noncoding spliced RNA completely internal to the *KIAA1462* gene, but on the opposite strand of DNA. The sequence of the “rokimi” gene is defined by two GenBank accessions from one cDNA clone from synovial membrane tissue from a patient with rheumatoid arthritis. The SNPs associated with LOAD are also within introns of the “rokimi” gene.

**Analysis of Expression Levels of *KIAA1462* and “rokimi”**

The location of the SNPs associated with LOAD suggests that they might alter the transcription of *KIAA1462* or “rokimi”. The
expression of KIAA1462 was investigated in brain of LOAD and control individuals using real time quantitative PCR. KIAA1462 mRNA was measured in brain samples taken from 14 control and 14 LOAD individuals (Table 4) using TaqMan based real time quantitative PCR. Three TaqMan probes were used individually, one specific for the junction between exons 2 and 3 of isoform b, one specific for the junction between exons 3 and 4 of isoform b, and one in the 3’ untranslated region of isoform b. These probes were designed to measure expression of isoforms a, b, c, and d. KIAA1462 was not significantly differentially expressed in AD brains as compared to controls (data not shown) using any of these probes. In addition, KIAA1462 was not differentially expressed in the brain based on any APOE genotype (data not shown).

The presence of expression of the rokimi gene was examined using RT-PCR. RNA from brain and HeLa cell lines was used to perform RT-PCR with two sets of rokimi primers. Because rokimi appears to be a noncoding RNA and it was unclear if the message would be polyadenylated or not, in addition to oligo(dT) primers for first strand synthesis, random hexamers and a gene specific primer were also used. None of these experimental conditions yielded a PCR product, suggesting that rokimi is not expressed in brain tissue or HeLa cells. We have also examined the KIAA1462/rokimi locus for QTLs using both the eQTL Browser [44] and Aperture, an online tool designed by the William Bush laboratory (http://gwar.mc.vanderbilt.edu/aperture) to provide LocusZoom-style plots for over 28 million eQTL associations. No significant eQTLs were found at this locus.

**Discussion**

Ours is not the first genomic convergence study to investigate KIAA1462 in relation to AD and find similar results. Chapuis et al. selected genes from areas of genetic interest in LOAD, analyzed their expression in LOAD brain compared to controls via custom expression microarrays, and found that KIAA1462 was upregulated approximately 2.5 fold in AD brain [41]. Follow-up examination of eighteen SNPs in KIAA1462 showed that three were associated with AD, including rs2488024, the most strongly associated SNP in our study, and five were associated with age on onset of AD. The significance of the association of these SNPs did not, however, survive multiple correction testing [41].

Polymorphisms in KIAA1462 have also been associated with other diseases and phenotypes. KIAA1462 was one of six loci associated with variation in human recombination rates [45]. Specifically rs2505089 in KIAA1462 was found by GWAS to be associated with maternal recombination rate with a combined p value = 4.42×10^{-7}. In addition, recent reports link KIAA1462 to...
CAD with genome wide significance scores [37,38]. The first study showed association of rs3739998, a nonsynonymous SNP in KIAA1462, with CAD in the German MI Family Study with a combined p value = 1.27 × 10⁻¹¹ [39]. The second study, a meta-analysis of four combined GWAS with subjects from both European and South Asian background, revealed five major loci associated with CAD, including KIAA1462 [p value = 3.87 × 10⁻⁸] [37]. The function of KIAA1462 is unknown, but the protein encoded by isoform b is localized to endothelial cell-cell junctions, and this localization is VE-cadherin dependent [42].

Our results support those from another study examining chromosome 10 variation in LOAD [41]. Taken together, these results bolster the idea that KIAA1462 might play some role in the development of LOAD, although the role would likely be quite small. We can not rule out, however, that this locus is not associated with LOAD, considering that the data associating the locus with late onset AD is modest. The role of KIAA1462 in the genetics of CAD, however, seems much clearer from recent GWAS [37,38]. The association between non-stroke cardiovascular disease (CVD) and Alzheimer’s disease has been debated, but a recent study reports that CVD increases risk of AD only in carriers of the APOE4 allele (Hazard Ratio 2.39, 95% confidence interval) [39]. The present study shows that KIAA1462, which is associated with CVD, is associated with APOE positive LOAD. The discovery of a genetic modifier of CVD that is associated with the APOE4 class of LOAD might explain some of the conflicting results in the literature regarding CVD and LOAD. These results suggest a model in which underlying CAD increases the risk of LOAD only in APOE4 carriers.

Several different lines of evidence suggest that variation in two different gene products at this locus may be responsible for the association with CAD and LOAD respectively. The CAD associated SNP rs3739998, which is a nonsynonymous change in exon 3 of isoform b of KIAA1462 that changes a serine to a threonine, is associated with CAD with a p value of 1.27 × 10⁻¹¹, but is not significantly associated with LOAD in our study. Secondly, the genomic arrangement of the SNPs associated with CAD and LOAD suggests that they are in two different linkage disequilibrium blocks. The more proximal nature of the LOAD associated SNPs suggest that the gene product important in this association is either ‘rokimi’, or a different isoform of KIAA1462 than the isoform that is important in CVD. Since expression of ‘rokimi’ was not detected in brain, it is unlikely that ‘rokimi’ is the gene of interest in LOAD. We also did not see any differential expression of KIAA1462 in LOAD brain, but this could be a result of the methods used. With the three different TaqMan probes used, we would have observed a difference in expression of isoforms a, b, c, and d. Isoform e was not recognized by these probes, and isoform f has alternative polyadenylation sites, therefore some forms of isoform f may not have been detected by these TaqMan assays. Isoform e is represented by one Genbank entry from skeletal muscle. Isoform f is represented by 175 Genbank entries from many tissues, including multiple entries from brain, making isoform f a more attractive candidate for association with LOAD.

Acknowledgments

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Author Contributions

Conceived and designed the experiments: DGM NSB XL JLH. Performed the experiments: PM MJA SLM. Analyzed the data: DGM YB LND SLM. Contributed reagents/materials/analysis tools: SZ GWS JRG MAPV JLH. Wrote the paper: DGM.

References


