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Association Studies Testing for Risk for Late-Onset Alzheimer's Disease With Common Variants in the β-Amyloid Precursor Protein (APP)

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Linkage studies have suggested a susceptibility locus for late-onset Alzheimer's disease (LOAD) on chromosome 21. A functional candidate gene in this region is the β-amyloid precursor protein (APP) gene. Previously, coding mutations in APP have been associated with early onset Alzheimer's Disease (EOAD). Three copies of APP are associated with AD pathology in Down's syndrome and in EOAD, suggesting that overexpression of APP may be a risk factor for LOAD. Although APP is a strong functional and positional candidate, to date there has been no thorough investigation using a dense map of SNPs across the APP gene. In order to investigate the role of common variation in the APP gene in the risk of LOAD, we genotyped 44 SNPs, spanning 300 kb spanning the entire gene, in a large case-control series of 738 AD cases and 657 healthy controls. The SNPs showed no association in genotypic or allelic tests, even after stratification for presence or absence of the *APOE 4* allele. Haplotype analysis also failed to reveal significant association with any common haplotypes. These results suggest that common variation in the APP gene is not a significant risk factor for LOAD. However, we cannot rule out the possibility that multiple rare variants that increase APP expression or Aβ production might influence the risk for LOAD.

KEY WORDS: single nucleotide polymorphism (SNP); association analysis; β-amyloid precursor protein (APP); Alzheimer's disease (AD)

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INTRODUCTION

Linkage studies have provided evidence for a susceptibility locus for late-onset Alzheimer's disease (LOAD) on chromosome 21 [Myers et al., 2002; Olson et al., 2002; Blacker et al., 2003]. In the study of Myers et al. [2002] the linkage on chromosome 21 was observed only in the subgroup of affected sibling pairs without an *APOE ε4* allele. Consistent with this observation Olson et al. [2002] reported that the linkage was largely observed in families with a later age of onset. A functional candidate gene in this region of chromosome 21 is the β-amyloid precursor protein (APP) gene. Previously, coding mutations in APP have been associated with early onset Alzheimer's Disease (EOAD) [Goate et al., 1991]. Complete or partial trisomy of chromosome 21 leads to Down Syndrome, including AD pathology only when the APP gene is present in three copies, suggesting that overexpression of APP may be a risk factor for LOAD [Rumble et al., 1989; Prasher et al., 1998]. APP locus duplication in trisomy 21 leads to elevated levels of circulating Aβ peptide [Schupf et al., 2001] and to premature accumulation of Aβ in amyloid plaques in the brain [Wisniewski et al., 1985; Kida et al., 1995], a process that likely contributes to the observed lower age of onset of AD in people with Down syndrome [Hyman, 1992; Zigman et al., 1996]. A recent study has reported that duplication of the APP locus is associated with a familial disorder characterized by dementia and cerebral amyloid angiopathy (CAA) [Rovelet-Lecrux et al., 2006]. Together these observations suggest that variability in APP expression could influence risk for late-onset AD, especially in individuals with concurrent CAA.

Surprisingly, only a few studies have examined the role of APP as a risk factor for LOAD. In 1999, one study examined segregation of two APP polymorphisms in a series of sib pairs with LOAD and the APP gene could not be ruled out as a risk locus in those without an *APOE ε4* allele [Wavrant-De Vrieze et al., 1999]. A second report tested single nucleotide polymorphisms (SNPs) in the promoter region of APP for their association with LOAD in a population of African American and Caribbean Hispanic ethnicity [Athan et al., 2002]. The most significant association was found with a G/C promoter polymorphism at position +37 relative to the transcription start site in patients lacking the *APOE ε4* allele. Two other promoter polymorphisms have also been reported to influence risk for LOAD by changing expression levels [Lahiri et al., 2005]. Recently, a study identified three rare variants in AD patients, which, in vitro, showed a nearly twofold neuron-

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specific increase in APP transcriptional activity [Theuns et al., 2006]. Lastly, a polymorphic tetra nucleotide repeat site found in intron 7 of the APP gene did not exhibit association with LOAD [Li et al., 1998].

Although APP is a strong functional and positional candidate, to date there has been no investigation using a dense map of SNPs across the entire gene. In order to thoroughly investigate the role of APP in the risk for LOAD, we genotyped 44 SNPs, spanning 300 kb in and around the *APP* gene, in a large case-control series, which consisted of 738 AD cases and 657 healthy controls.

MATERIALS AND METHODS

Clinical Samples

The SNPs were genotyped in a Caucasian LOAD case-control series from the WashU-ADRC and a case-control series generated by selecting one case per family from our genetic linkage sample [Myers et al., 2002] and matching them to an equal number of ethnically matched non-demented elderly controls, who were also recruited by the WashU-ADRC. For the cases a clinical diagnosis of probable or definite dementia of the Alzheimer's type was made using the NINCDS-ADRDA or similar criteria with a minimum age of onset of 60 years [Morris et al., 1997]. Non-demented controls were at least 60 years old when screened for dementia by clinical interview of the subject and a knowledgeable collateral source [Cacchione et al., 2003]. In the combined case-control series there were 738 cases and 657 controls. The cases have an average age-of-onset of 75 ± 6.9 years (range 58–99 years) while average age at last assessment for the controls is 77.1 ± 8.9 years (range 60–104 years). The controls are 60% women and the cases are 70% women. The case-control series had the expected *APOE ε4* allele distribution. Using the program STRUCTURE, we found no evidence of population stratification among the WashU-ADRC case control data set [Li et al., 2004].

SNP Selection and Genotyping

Forty-four SNPs were chosen either from the International Haplotyping Project (Hap Map) database (http://www.hapmap.org), dbSNP (NCBI) (http://www.ncbi.nlm.nih.gov) or because they had been used in previous association studies of APP. SNPs were selected in order to tag the major haplotypes present in each haplotype block spanning the APP gene. We also did some fine mapping in regions of introns 2 and 3 due to initial significant associations with single SNPs. Most of the SNPs (40/44) had a MAF>0.1. The SNPs were genotyped using two methods: Pyrosequencing technology™ and Sequenom technology™. APOE genotyping was performed following the protocol on the Pyrosequencing™ website (http://www.pyrosequencing.com/pages/assay_register_clin_gen.html).

Statistical Analysis

Chi square tests were used to test for deviation from Hardy–Weinberg equilibrium and to test for allelic association. A Fisher's exact test was used for the genotypic tests and to stratify for presence or absence of the *APOE4 ε4* allele. Odds ratios and 95% confidence intervals were calculated for allelic associations and haplotypes. Linkage disequilibrium (LD) analysis was carried out on a pair-wise basis for all the SNPs in the control sample using the Haploview program (http://www.broad.mit.edu/mpg/haploview/index.php).

Haplotype Analysis

A number of studies have shown that placing individual SNPs into the context of a haplotype increases biological information [Balciuniene et al., 2002; Knoblauch et al., 2002; Van Eerdewegh et al., 2002]. Placing haplotypes into their evolutionary context also increases biological information [Templeton et al., 2005]. Haplotype analysis using tagging SNPs was computed using the program COCAphase [Dudbridge, 2003]. Because some rare haplotypes within several haplotype blocks showed evidence of association in the tag SNP analysis we performed a second more detailed analysis, which tests for association across branches of the haplotype network to determine whether the rare haplotypes showing association in the tag SNP analysis were in the same regions of the haplotype network. In order to minimize error in estimating haplotype phase and the haplotype network, SNPs in APP were divided into five groups based on LD patterns (Fig. 1) and a preliminary sliding window haplotype analysis

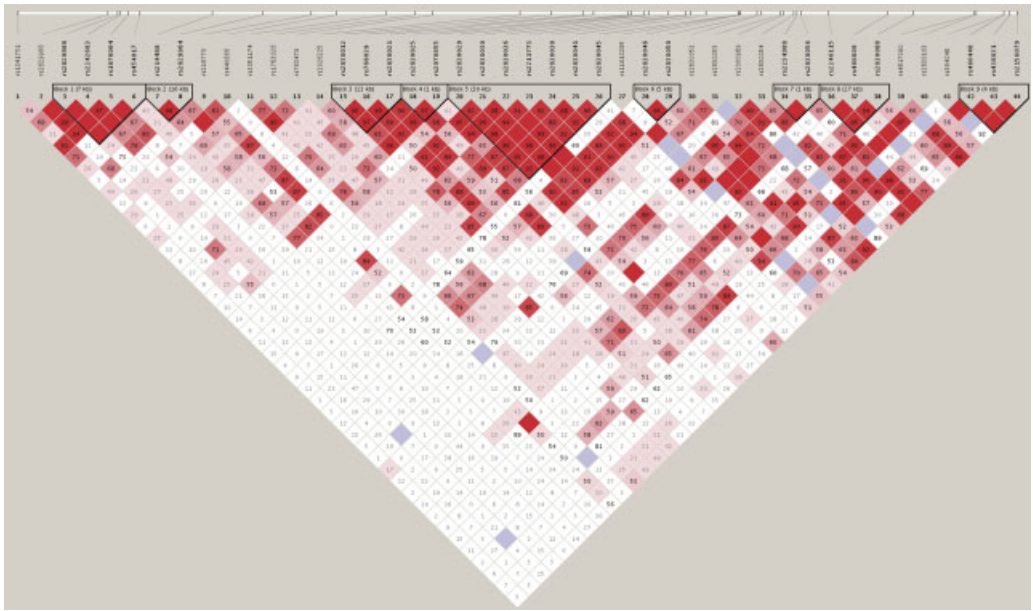

Fig. 1. LD map of the 44 APP SNPs used in this study. The LD was computed using Haploview.

(data not shown). Haplotypes for each group were estimated using the software PHASE [Stephens et al., 2001; Stephens and Donnelly, 2003]. Individuals, for which the best inference of the haplotype pair had a probability of lower than 80%, were removed from the analysis. A set of 95% plausible haplotype trees was then estimated using statistical parsimony in the program TCS [Clement et al., 2000]. Association with LOAD was tested using nested clade analysis [Templeton et al., 2000].

RESULTS

We tested 44 SNPs (Table I), which tag the major haplotypes in 9 LD blocks spanning the entire APP gene region (300 kb) (Fig. 1). To maximize power to detect association, we combined the two samples for our statistical analysis, giving us a dataset of over 730 AD cases and 650 healthy controls.

None of the individual SNPs showed association when analyzed in allelic or genotypic tests (data not shown). We also stratified for absence or presence of the *APOE* e4 allele because the original linkage signal on chromosome 21 was observed in sibling pairs without an APOE ϵ4 allele. Several SNPs were significant when the sample was stratified by the presence or absence of the APOE e4 allele (Table II). However, the significant results were in the *APOE ϵ4* positive subset not the individuals without an *APOE ϵ4* allele as might have been predicted from the linkage results. None of these results survive correction for multiple testing.

We genotyped four SNPs in the 5′ UTR and putative promoter region of APP, including one SNP reported to influence risk for LOAD in the study of Lahiri et al. [2005]. None of these SNPs showed association with LOAD.

To determine whether there are SNPs that may be associated but not genotyped and that may be in LD with specific haplotypes we performed haplotype analysis using the tagging SNPs from each block (Table III). We used this information and the D′ between the SNPs (Fig. 1) to select blocks and test them with the program TCS. We failed to detect evidence for association in the groups including SNPs 1–8, 9–18, 27–35, and 36–44 (Table I). In the region including SNPs

TABLE I. SNPs in APP and Their Locations

	SNP ID	Chromosome position	Distance spanned (bp)	Position	Block in Hapmap[a]
1	rs1041731	26,146,914		3′ UTR	
2	rs2829966	26,176,065	29,151	Intron 17	1
3	rs2829968	26,179,169	2,151	Intron 17	2
4	rs2242683	26,180,016	847	Intron 17	2
5	rs1876064	26,182,682	2,666	Intron 17	2
6	rs454017	26,186,455	3,773	Intron 16	2
7	rs214488	26,209,795	7,271	Intron 13	
8	rs2829984	26,226,123	16,328	Intron 13	
9	rs216773	26,241,805	15,682	Intron 13	
10	rs440666	26,250,046	8,241	Intron 11	
11	rs2051174	26,260,108	10,062	Intron 11	
12	rs1783026	26,275,436	15,328	Intron 9	3
13	rs762479	26,281,147	5,711	Intron 8	
14	rs2026225	26,309,441	28,294	Intron 6	4
15	rs2830012	26,319,478	9,623	Intron 5	5
16	rs768039	26,329,891	10,413	Intron 5	5
17	rs2830021	26,333,127	3,236	Intron 5	5
18	rs2830025	26,344,266	11,139	Intron 5	5
19	rs2070655	26,345,431	1,165	Intron 4	5
20	rs2830029	26,349,463	1,733	Intron 3	6
21	rs2830030	26,351,042	915	Intron 3	6
22	rs2830036	26,357,396	6,354	Intron 3	6
23	rs2211773	26,363,078	5,682	Intron 3	6
24	rs2830038	26,364,467	1,389	Intron 3	6
25	rs2830041	26,369,533	4,012	Intron 3	6
26	rs2830045	26,380,280	10,747	Intron 3	6
27	rs11910285	26,380,317	37	Intron 3	6
28	rs2830046	26,380,577	260	Intron 3	6
29	rs2830050	26,386,141	5,564	Intron 2	7
30	rs2830052	26,387,468	1,327	Intron 2	7
31	rs2830053	26,393,582	6,114	Intron 2	7
32	rs2000989	26,394,664	1,082	Intron 2	7
33	rs2830054	26,397,975	3,311	Intron 2	7
34	rs2234988	26,398,958	983	Intron 2	7
35	rs2830056	26,400,220	1,262	Intron 2	7
36	rs2246115	26,409,179	5,965	Intron 1	7
37	rs466609	26,428,188	19,009	Intron 1	7
38	rs2830088	26,436,611	8,423	Intron 1	
39	rs4817090	26,456,132	19,521	Intron 1	
40	rs2830103	26,456,976	844	Intron 1	
41	rs364048	26,465,912	8,936	5′ UTR	
42	rs466448	26,465,979	67	5′ UTR	
43	rs438031	26,467,875	1,896	5′ UTR	
44	rs2156079	26,470,201	2,326	5′ UTR	

[a]Block in Hapmap when the study was started.

TABLE II. Results Stratified for Presence or Absence of the APOE ϵ 4 Allele

	Genotypic tests			Allelic tests		
SNP	All data	Apoe4neg	Apoe4pos	All data	Apoe4neg	Apoe4pos
rs1041731	0.70	0.76	0.99	0.48	0.55	0.93
rs2829966	0.49	0.22	0.88	0.59	0.28	0.66
rs2829968	0.56	0.88	0.96	0.40	0.94	0.77
rs2242683	0.71	0.71	0.72	0.57	0.50	0.48
rs1876064	0.76	1.00	0.81	0.81	0.93	0.54
rs454017	0.30	0.50	0.81	0.23	0.37	0.99
rs214488	0.74	0.49	0.91	0.44	0.23	0.64
rs2829984	0.41	0.62	0.76	0.35	0.46	0.41
rs216773	0.33	0.67	0.76	0.20	0.44	0.33
rs440666	0.18	0.56	0.28	1.00	0.55	0.67
rs2051174	0.41	0.55	0.48	0.43	0.25	0.79
rs1783026	0.42	0.81	0.97	0.74	0.86	0.88
rs762479	0.20	0.53	0.11	0.21	0.53	0.05
rs2026225	0.13	0.90	0.10	0.08	0.86	0.07
rs2830012	0.16	0.98	0.19	0.09	0.90	0.08
rs768039	0.70	0.38	0.65	0.49	0.85	0.45
rs2830021	0.70	0.91	0.93	0.77	0.76	0.75
rs2830025	0.68	0.74	0.47	0.81	0.58	0.31
rs2070655	0.71	0.26	0.88	0.41	0.19	0.72
rs2830029	0.86	0.69	0.64	0.91	0.67	0.64
rs2830030	0.57	0.15	0.48	0.38	0.05	0.29
rs2830036	0.66	0.16	0.44	0.50	0.05	0.26
rs2211773	0.65	0.54	0.66	0.84	0.70	0.92
rs2830038	0.89	0.31	0.28	0.79	0.12	0.22
rs2830041	0.76	0.66	0.67	0.47	0.35	0.39
rs2830045	0.98	0.32	0.76	0.85	0.15	0.49
rs11910285	0.70	0.14	0.18	0.45	0.37	0.29
rs2830046	0.36	0.61	0.01	0.27	0.48	0.01
rs2830050	0.20	0.56	0.04	0.11	0.66	0.03
rs2830052	0.13	0.49	0.34	0.07	0.42	0.18
rs2830053	0.23	0.23	0.63	0.09	0.08	0.63
rs2000989	0.39	1.00	0.55	0.24	0.97	0.17
rs2830054	0.44	0.65	0.61	0.36	0.36	0.35
rs2234988	0.38	0.78	0.97	0.96	0.92	0.83
rs2830056	0.14	0.38	0.06	0.06	0.13	0.37
rs2246115	0.41	0.22	0.41	0.18	0.06	1.00
rs466609	0.06	0.02	0.88	0.08	0.02	0.77
rs2830088	0.76	0.87	0.04	0.51	0.88	0.07
rs4817090	0.98	0.98	0.86	0.94	0.83	0.95
rs2830103	0.92	0.40	0.03	0.85	0.53	0.02
rs364048	0.28	0.57	0.10	0.23	0.50	0.06
rs466448	0.26	0.18	0.32	0.14	0.45	0.52
rs438031	0.31	0.54	0.23	0.13	0.23	0.91
rs2156079	0.52	0.52	0.42	0.26	0.85	0.28

15–26 a small group of haplotypes (approximately 4% in frequency) was significantly associated with increased risk for disease. However, the *P*-value of 0.02 does not survive a Bonferroni correction for the 17 tests performed in the analysis of that region. Upon inspection of the haplotype network, 33 of the 44 SNPs we tested were inferred to be subject to recurrent mutation. Recurrent mutation (homoplasy) has previously been shown to result in false negative associations [Templeton et al., 2005] and is thus a cause for concern in the genetic analysis of complex disorders. We have observed evidence of

TABLE III. Haplotypes Calculated Using the Tagging SNPs From Hapmap

Block	SNPs in the haplotype	global *P*-value
1	rs2829966	0.590
2	rs2829968, rs2242683, rs1876064, rs454017, rs214488	0.960
3	rs1783026	0.736
4	rs2026225	0.077
5	rs2830012, rs768039, rs2830021, rs2830025, rs2070655	0.128
6	rs2830029, rs2830030, rs2830036, rs2211773, rs2830038, rs2830041, rs2830045, rs11910285, rs2830046	0.052
7	rs2830050, rs2830052, rs2830053, rs2000989, rs2830054, rs2234988, rs2830056, rs2246115, rs466609	0.015

See also Table I.

homoplasy in several other candidate genes in the course of our studies on the genetics of LOAD [Nowotny et al., 2005; Grupe et al., 2006].

CONCLUSIONS

APP is a strong functional and positional candidate for a LOAD risk factor. Not only is APP mutated or duplicated in FAD but mutations in other FAD genes lead to altered APP metabolism [Pastor and Goate, 2004]. Second, studies in Down syndrome indicate that the AD neuropathology results from three copies of the APP gene because DS patients who are trisomic for regions that do not include the APP gene do not develop AD pathology. Linkage studies in LOAD have also reported evidence for a LOAD locus on chromosome 21, particularly in *APOE ϵ4* negative sib pairs. Together these observations suggest that even moderate variation in APP expression levels (<twofold) could result in an increased risk for LOAD.

In this study we have attempted to systematically evaluate the APP gene as a risk factor for LOAD in a large series of unrelated cases and controls of Caucasian origin. We have genotyped 44 common SNPs, which span the entire gene. This study also includes several SNPs, which were reported by others to be associated with risk for LOAD. We observed no evidence for association with LOAD for either single SNPs or haplotypes in the unstratified sample and only weak evidence of association in the *APOE ϵ4* positive subset of cases and controls. These results are somewhat surprising given the evidence in other sporadic and familial neurodegenerative diseases. For example, several studies have reported an association between promoter variation in α-synuclein and sporadic PD [Farrer et al., 2001; Chiba-Falek and Nussbaum, 2003]. Similarly, variation in the prion protein gene is associated with familial and sporadic Creutzfeldt-Jakob disease [Prusiner, 1998] and variation in the microtubule associated protein tau gene is associated with both familial and sporadic tauopathies [Singleton et al., 2004].

A caveat to our study is that our selection criteria for LOAD cases may have inadvertently excluded individuals who are most likely to carry a risk factor in the APP gene. Families that carry a duplication of the APP locus exhibit both dementia and hemorrhagic strokes with neuropathological evidence of plaques and tangles as well as CAA [Rovelet-Lecrux et al., 2006]. Studies in transgenic animals have also reported that higher levels of Aβ, rather than changes in Aβ ratios are associated with CAA [Herzig et al., 2004]. These observations suggest that higher levels of APP expression would be associated with both DAT and hemorrhagic strokes. Since a stroke within 5 years prior to the onset of dementia, is an exclusion criteria at the WashU-ADRC, it is possible that we have excluded individuals most likely to carry a LOAD risk factor in the APP gene from our AD case series.

A second caveat to our study is that it was designed to test whether common variation in APP explains any risk for AD. We cannot rule out the possibility that multiple rare variants in APP, that increase APP expression or Aβ production, might influence the risk for LOAD since this type of association would not be detected by a method that relies on LD. Indeed the recent report of rare variants in AD cases that modulate APP expression in vitro does support this possibility [Theuns et al., 2006]. In addition, although we genotyped 44 SNPs in APP, our results show that there are still regions of low LD in the gene (Fig. 1). This number of SNPs is therefore not sufficient to exclude APP as a risk factor for LOAD. To resolve this issue a higher density of SNPs will be required to be genotyped in a larger case-control sample than ours. This goal makes it difficult for an individual study and can only be reached in a community effort.

In summary, this is the largest and most comprehensive analysis of the APP gene as a risk factor for LOAD reported to date. In contrast to other neurodegenerative disorders we failed to detect evidence for association between sporadic AD using common SNPs from a gene associated with the familial form of the disorder.

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