

## SHORT REPORT

Further evidence for *LBP-1c/CP2/LSF* association in Alzheimer's disease families

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**Objectives:** Several studies suggested chromosome 12 harbours an Alzheimer's disease (AD) risk factor gene. Significant association of a single nucleotide polymorphism (SNP) in the 3' UTR of transcription factor CP2 (*LBP-1c/CP2/LSF* or *TFCP2*) at 12q13 was reported in three independent case-control studies, but no family based analyses have been performed to date.

**Methods:** Genotypes for three SNPs were generated in two independent AD family samples. A meta-analysis on all published case-control studies was also performed.

**Results:** The A allele of the 3' UTR SNP was associated with increased risk for AD in one sample (odds ratio (OR) 2.1, 95% confidence interval (95% CI) 1.1 to 4.3), but not in the other, possibly due to low power. Haplotype analyses showed that this allele is part of a putative risk-haplotype overtransmitted to affected individuals in one sample and in both samples combined. Meta-analysis of the previously associated 3' UTR SNP showed a trend towards a protective effect of the A allele in AD (OR 0.73, 95% CI 0.5 to 1.1).

**Conclusions:** This is the first study to examine *LBP-1c/CP2/LSF* in AD families, and the fifth to independently show significant association. While our results support a role of this gene in AD pathogenesis, the direction of the effect remains uncertain, possibly indicating linkage disequilibrium with another variant nearby.

Alzheimer's disease (AD) is a neurodegenerative disorder with a complex genetic background. The rare, early onset autosomal dominant forms of AD are caused by mutations in three genes (*APP*, *PSEN1*, and *PSEN2*), all of which lead to an increase in  $\beta$  amyloid protein ( $A\beta$ ) levels in brain.<sup>1</sup> Disease onset is typically before the sixth decade of life, and pathogenic mutations display virtually 100% penetrance. The more common late onset form of AD (that is, with disease onset usually between 60 and 80 years of age) is likely governed by genetic susceptibility factors of smaller effect and greatly reduced penetrance, which are transmitted in a non-Mendelian fashion.<sup>2</sup> The only established risk factor to date is the  $\epsilon 4$  allele of apolipoprotein E (*APOE*) on chromosome 19q13, which is involved in the accumulation and/or clearance of  $A\beta$  in the brain of AD patients.<sup>3</sup> While several dozen papers are published each year claiming or refuting association with additional candidate genes on just about every chromosome, none of these has been unequivocally confirmed.<sup>4</sup>

Since the discovery of *APOE*  $\epsilon 4$ , numerous laboratories worldwide have performed either linkage, or association based, full genome screens in search of other AD predisposing variants. Linkage to chromosome 12 was one of the first major signals to emerge from these efforts. However, while

some studies predominantly observed the strongest findings on the short arm of this chromosome (on 12p13, near 10 Mb)<sup>5–7</sup>, other groups detected more pronounced linkage approximately 40 Mb distal (on 12q13, near 50 Mb).<sup>8,9</sup> To date, it remains unclear whether these signals are caused by the same underlying locus, or are actually the result of two distinct genes. The latter hypothesis is supported by the fact that there is at least one candidate gene in each region that has received independent confirmation—albeit not unequivocally—in at least ten studies:  $\alpha 2$ -macroglobulin (*A2M*) on 12p13, and the lipoprotein receptor related protein-1 (*LRP1*) on 12q13 (reviewed in Bertram and Tanzi<sup>10</sup> and in Saunders *et al*<sup>11</sup>). Other candidates on chromosome 12 reported to be associated with AD include: on 12p13, oxidised lipoprotein receptor-1 (*OLR1*), and on 12q13, transcription factor CP2 (*LBP-1c/CP2/LSF*) and neurotrophin-3 (*NTF3*). Of these, *LBP-1c/CP2/LSF* (also known as *TFCP2*) has received the most consistent support from independent groups with four papers reporting significant association, and thus far no published negative study.<sup>12–15</sup>

*LBP-1c/CP/LSF* encodes a nuclear transcription factor that regulates the expression of *A2M* and glycogen synthase kinase-3 $\beta$  (*GSK3\beta*),<sup>16,17</sup> and also interacts with Fe65,<sup>18</sup> which serves as an adapter molecule for the cytoplasmic domain of  $A\beta$  precursor protein (*APP*), and may also be involved in the regulation of gene expression via interaction with the *APP* intracellular domain (*AICD*).<sup>19</sup> The original paper associating *LBP-1c/CP/LSF* with AD examined three independent case-control series from France, the US, and the UK (table 1).<sup>12</sup> While two of these (France and UK) showed a significant protective effect in carriers of the A allele at a single nucleotide polymorphism (SNP) in the 3' UTR of the gene, the authors detected no significant association in the US sample. Combining all three populations revealed a significantly decreased risk of developing AD in carriers of the A allele *v* the G/G genotype (odds ratio (OR) 0.58, 95% confidence intervals (95% CI) 0.44 to 0.75; table 1). Two subsequent independent case-control studies by Taylor *et al*<sup>13</sup> and Luedeking-Zimmer *et al*<sup>14</sup> replicated the protective effect of the A allele with similar effect sizes (table 1). Finally, a fourth case-control study from Italy also detected a significant association between this SNP and AD.<sup>15</sup> In contrast to the other papers, however, the data of this report suggested an over-representation of the A allele in AD cases *v* controls. To date, there are no published reports investigating the potential role of the *LBP-1c/CP2/LSF* gene in family based AD datasets, which have the advantage of being unbiased in the presence of population admixture. In this study we have examined a total of three SNPs in *LBP-1c/CP2/*

**Abbreviations:** AD, Alzheimer's disease; CAG, Consortium on Alzheimer's Genetics; CLR, conditional logistic regression; LD, linkage disequilibrium; OR, odds ratio; PDT, pedigree disequilibrium test; SNP, single nucleotide polymorphism; 95% CI, 95% confidence interval

**Table 1** Summary of published case-control AD association studies for the 3' UTR SNP in *LBP-1c/CP/LSF*

Study	AD cases		Normal controls		Results	
	Subjects, n (% women)	Onset age, mean (SD)	Subjects, n (% women)	Age, mean (SD)	A allele frequency (AD v CTRL)	OR (95% CI)
Panza <i>et al</i> <sup>5</sup> Italy	166 (63%)	69.4 (10.3)	225 (68%)	71.3 (10.4)	0.06 v 0.02	2.97 (1.33 to 6.66)
Luedecking-Zimmer <i>et al</i> <sup>4</sup> USA	564 (68%)	77.3 (6.4)	523 (66%)	76.8 (6.3)	0.05 v 0.07	0.65 (0.43 to 0.96)
Taylor <i>et al</i> <sup>3</sup> UK	239 (64%)*	81.2 (7.8)	342 (59%)*	82.1 (3.8)	0.05 v 0.08	0.59 (0.35 to 1.00)
Lambert <i>et al</i> <sup>2</sup> All combined	1139 (64.6%)	70.5 (6.6)	1317 (62.5%)	73.4 (9.2)	0.04 v 0.07	0.58 (0.44 to 0.75)
UK	159 (67%)	65.7 (11.1)	205 (51%)	60.8 (11.3)	0.04 v 0.09	0.46 (0.23 to 0.93)
USA	296 (67%)	75.7 (0.2)	462 (67%)	79.2 (9.3)	0.06 v 0.07	0.87 (0.56 to 1.38)
France	684 (63%)	69.4 (8.4)	650 (63%)	73.2 (8.6)	0.04 v 0.07	0.48 (0.33 to 0.70)

Studies are shown in chronological order, with the most recent study listed first. Odds ratios (ORs) and 95% confidence intervals (CI) as reported by authors; some ORs are adjusted for co-variables (like age, gender, and *APOE*  $\epsilon$ 4 status) and might thus vary slightly from the crude ORs presented in fig 1, which were used to calculate summary ORs.

*LSF* in two independent and carefully ascertained and evaluated AD family samples, and provide further support for a significant role of this gene in contributing to overall AD risk.

## METHODS

### Samples

#### The NIMH AD genetics initiative study sample

Subjects were collected following a standardised protocol applying NINCDS/ADRDA criteria for the diagnosis of AD.<sup>20</sup> Over the 10 years that the participating families have been followed, a clinical diagnosis of AD has been confirmed at autopsy in 94% of the cases.<sup>21</sup> The NIMH sample includes 1439 individuals (69% female) from 437 families with at least two affected individuals (994 affected individuals (mean (SD) age of onset 72.4 (7.7) years, range 50–97 years), 411 unaffected individuals, and 34 with unknown phenotype.

#### Consortium on Alzheimer's Genetics (CAG) study sample

Subjects for this second, independently ascertained, AD family sample were collected under the auspices of the Consortium on Alzheimer's Genetics, a collaborative effort of the Massachusetts AD Research Center, the University of California, Los Angeles, the University of California, San Diego, and the University of Rochester Medical Center.<sup>22</sup> NINCDS/ADRDA criteria were used for a clinical diagnosis of AD, and probands were included only if they had at least one unaffected living sibling willing to participate in this study. Unlike the NIMH sample, no affected individual beyond the proband was required; thus, the vast majority of families are not multiplex. Currently, data and specimen collection is completed for 489 individuals (62.6% female) from 217 sibships in which all affected individuals displayed an onset age  $\geq$ 50 years ( $n = 224$  affected individuals (mean (SD) age of onset 71.2 (9.1) years, range 50–89 years),  $n = 265$  unaffected individuals). Most sibships consisted of just one discordant sibpair, but in 41 families there were more than two siblings available.

### Genotyping

Genotypes for a total of three polymorphisms (that is, the original 3' UTR SNP, rs4438107 (~10 kb proximal), and rs10876135 (773 bp distal)) in *LBP-1c/CP/LSF* were generated using fluorescent polarisation detected single base extension (FP-SBE) on a Criterion Analyst AD (Molecular Devices, Sunnyvale, CA). PCR primers were designed to yield a product of approximately 250 bp in length and added to

~10 ng of genomic DNA using individually optimised PCR conditions (sequences available on request). PCR primers and unincorporated dNTPs were degraded by the direct addition of exonuclease I (0.1–0.15 U/rxn) and shrimp alkaline phosphatase (1 U/rxn). The single base extension step was carried out using Thermosequenase (0.4 U/rxn) and the appropriate mix of R110-ddNTP, TAMRA-ddNTP (3 mM), and all four unlabeled ddNTPs (22 or 25  $\mu$ M) to the Exo1/SAP treated PCR product. To assess genotyping quality and ensure consistency of the genotyping calls, ~10% of the samples were randomly duplicated and genotyped twice. For all three SNPs combined, average genotyping efficiency was 97.8%, and the discrepancy rate (based on comparison to blinded duplicated samples) was below 0.3% in both samples.

### Statistical analyses

Single locus and haplotype based tests of association were done in FBAT (v.1.5.3). FBAT uses a generalised score statistic to perform a variety of TDT type tests and despite the true underlying genetic model, FBAT performs best assuming an additive genetic model, which was used here.<sup>23</sup> We used the empirical variance function of the program to account for the presence of linkage in the area<sup>24</sup> (as was suggested by previous studies), and an equal weight offset correction to incorporate genotypes from both affected and unaffected individuals. All analyses were performed on the full NIMH sample, the CAG sample, and on the two samples combined. All single locus analyses were repeated using the pedigree disequilibrium test (PDT)<sup>25,26</sup> to confirm results obtained with FBAT (note that the PDT currently does not accommodate haplotype tests). While both tests compute valid *p* values under the null hypothesis of linkage but no association, the PDT statistic can be less efficient under some circumstances as it only includes discordant sibships and ignores families where only affected siblings are available. Further, to assess the magnitude of any potential effect on disease risk for the 3' UTR SNP, we performed conditional logistic regression (CLR) stratified on family,<sup>27</sup> comparing carriers of the A allele to carriers of the GG genotype. All OR are adjusted for age, gender, and *APOE*  $\epsilon$ 4 allele status. Note that confidence intervals may be too narrow because CLR may slightly underestimate the standard errors when multiple affected and unaffected subjects are included in each family. However, the magnitude of this effect is expected to be small unless genetic effects are very large.<sup>28</sup> Finally, to assess whether families showing association with the 3' UTR SNP in *LBP-1c/CP/LSF* overlap with families associated with the intron 18 deletion in *A2M*,<sup>11</sup> we determined for both polymorphisms which of the NIMH pedigrees showed

transmission of at least two risk alleles to affected individuals (using the Viewstat option in FBAT).

### Haplotype block predictions

Haplotype blocks were estimated using the program Haploview based on the four gamete rule (fourth gamete at 0.02 frequency; see Haploview website for details at <http://www.broad.mit.edu/personal/jcbarret/haploview/index.php>). Haploview was also used for the calculation of pairwise linkage disequilibrium (LD) measures across all three SNPs.

### Meta analysis

Study specific crude ORs and 95% CIs were calculated from the raw data for each of the case-control studies investigating the association between the *LBP-1c/CP/LSF* 3' UTR SNP and AD. The Q statistic, a test for heterogeneity among the study specific ORs, that is distributed approximately as  $\chi^2$  with  $k-1$  degrees of freedom ( $k$  = number of studies),<sup>29</sup> resulted in a  $p$  value  $<0.1$ , suggesting significant between-study heterogeneity. Therefore, to calculate a summary OR for all studies, we used the DerSimonian and Laird<sup>30</sup> random effects model, which utilises weights that incorporate both the within study and between study variance. Note the ORs estimated from the CLR in our family based analyses are adjusted for a number of co-variables (see above), which is why we elected not to combine them with the crude or differently adjusted ORs from the case-control studies. Statistical Analysis System (SAS) was used for the statistical analyses and resulting graphs.

### RESULTS

The results of the single locus and haplotype association analyses are shown in table 2. Allele frequencies, as estimated by FBAT, were very similar for all three SNPs in both samples, and for the 3' UTR SNP are comparable to the previous reports (see legend to table 2). Genotype frequencies for all SNPs were in Hardy-Weinberg equilibrium ( $p>0.90$ ). Testing the 3' UTR SNP in FBAT revealed significant overtransmission of the A allele to affected individuals in the NIMH families ( $p=0.05$ ). This was confirmed using the PDT ( $p=0.04$ ), and resulted in a significant risk increase in carriers of the A allele *v* non-carriers (OR 2.1, 95% CI 1.1 to 4.3) using CLR stratified on family. Due to the low numbers, heterozygous and homozygous A allele carriers could not be examined separately, but all three subjects carrying the A/A genotype were affected (two autopsy confirmed, one clinical AD diagnosis), in accordance with the observation that the A allele confers risk in this sample. While the same allele was also overtransmitted to affected individuals in families of the

CAG sample resulting in a similar effect size estimate as for the NIMH families, this did not reach statistical significance in any of the analyses (OR 2.1, 95% CI 0.5 to 8.5), possibly due to low power in this overall smaller sample. Also, there were no homozygous A allele carriers in these families. However, combining both samples yielded slightly decreased  $p$  values (FBAT = 0.03; PDT = 0.02) and narrower confidence intervals in the effect size estimates (OR 2.1, 95% CI 1.1 to 3.7). In addition to these findings, one of the other two tested SNPs (that is, rs10876135, located 773 bp further 3') also showed significant association in the NIMH but not in the CAG sample ( $p=0.04$  and 0.2, respectively; table 2). All three SNPs showed strong pairwise LD and were estimated to reside within the same haplotype block, which is in good agreement with predictions from the International HapMap Project (<http://www.hapmap.org/>). Thus, all three SNPs were combined in the haplotype analyses which showed evidence for one rare haplotype (H4) being significantly overtransmitted to affected individuals in the NIMH sample ( $p=0.03$ ; table 2). A similar frequency and transmission pattern for this haplotype were observed in the CAG families, although the overtransmission to affected individuals did not reach statistical significance, again possibly due to low power. However, as for the 3' UTR SNP, the association signal of this haplotype was strongest when both samples were combined ( $p=0.01$ ). None of these SNPs showed a significant interaction with *APOE*  $\epsilon 4$ , gender, or onset age in our CLR analyses (data not shown). This is noteworthy because most of the previous studies demonstrating a protective role for the A allele of the 3' UTR SNP were comprised of late onset AD samples. In this study, however, effect size estimates are quite comparable in families of late (OR 1.8 (1.0–3.2)) and early/mixed onset (OR 2.2 (0.7–7.2); combined sample).

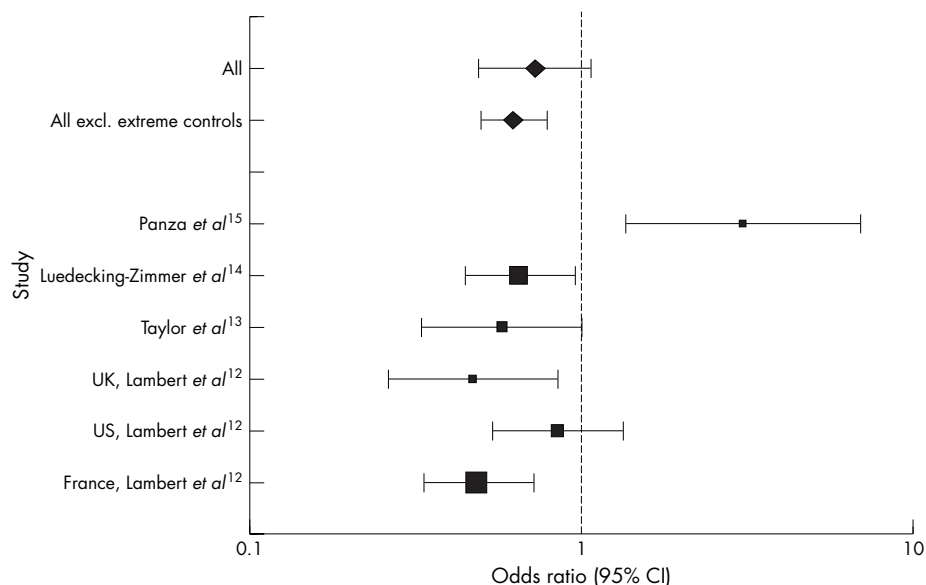
Combining all four previously published case-control studies into one meta-analysis revealed an overall protective effect of the A allele, although this did not reach statistical significance when all six independent case-control series were considered (0.73, 95% CI 0.5 to 1.1; fig 1). Interestingly, allele-frequency estimates across studies were quite similar for the AD cases (ranging from 0.04 to 0.06), but were considerably more variable in the control populations (ranging from 0.02 to 0.09; table 1). In an attempt to reduce this variability, we removed the two populations with the most extreme allele frequency estimates in healthy controls (that is, Panza *et al*<sup>15</sup> and the UK sample from Lambert *et al*<sup>12</sup>) and repeated the analyses. As expected, the resulting summary OR proved somewhat more stable, indicating a significant protective effect across the remaining samples (OR 0.62, 95% CI 0.5 to 0.8; fig 1).

**Table 2** Association analyses of three SNPs in *LBP-1c/CP/LSF* in two independent family samples

	Single locus analyses*			Haplotype analyses†	
	rs4438107	3' UTR	Rs10876135	Allele	z score (p)
<b>FBAT</b>	<b>z score (p)</b>	<b>z score (p)</b>	<b>z score (p)</b>		
NIMH (n=437)	-0.4 (0.7)	1.9 (0.05)	-2.0 (0.04)	H4	2.1 (0.03)
CAG (n=217)	0.5 (0.6)	1.1 (0.3)	1.4 (0.2)	H4	1.3 (0.2)
Combined (n=654)	0 (1)	2.2 (0.03)	-0.9 (0.4)	H4	2.5 (0.01)
<b>PDT</b>	<b><math>\chi^2</math> (p)</b>	<b><math>\chi^2</math> (p)</b>	<b><math>\chi^2</math> (p)</b>		
NIMH (n=437)	0.5 (0.5)	5.1 (0.02)	2.8 (0.09)	-	-
CAG (n=217)	1.2 (0.3)	0.5 (0.5)	1.5 (0.2)	-	-
Combined (n=654)	0 (0.9)	5.5 (0.02)	2.1 (0.15)	-	-

\*Minor allele frequencies in the NIMH (CAG) sample are: rs4438107 (T)=0.46 (0.47), 3' UTR (A)=0.06 (0.07), rs10876135 (T)=0.08 (0.06). z score for minor allele or denoted haplotype allele (positive values indicate overtransmission to affected individuals).

†Haplotype frequencies in the NIMH (CAG) sample are: H1 (C-G-C)=0.51 (0.48), H2 (T-G-C)=0.39 (0.43), H3 (T-G-T)=0.06 (0.04), H4 (C-A-C)=0.04 (0.04). Association statistics are presented for risk associated haplotype (H4) and 1 df.



**Figure 1** Meta-analysis estimating summary ORs of all published case-control association studies for *LBP-1c/CP2/LSF* in AD. The three independent case-control samples described in the study by Lambert *et al*<sup>12</sup> are considered separately. For all samples, crude ORs were determined from published genotype distributions in cases *v* controls; summary ORs are based on these crude ORs. "All" represents the summary OR across all published studies; "All excl extreme controls" represents the summary OR after removing samples with extreme allele frequencies in the control populations (that is, the UK sample in Lambert *et al*<sup>12</sup> and the sample in Panza *et al*<sup>15</sup>). Filled squares represent sample specific crude ORs (sizes of squares are directly proportional to the sample sizes) and filled diamonds summary ORs; lines represent 95% CI. See Methods section for details.

## DISCUSSION

This is the first study to assess the previously reported association between *LBP-1c/CP2/LSF* and AD using family based methods. Examining two independently ascertained and carefully characterised AD family samples, we observed a significant risk effect of the A allele of the 3' UTR SNP in the NIMH families, and a similar but insignificant effect in the smaller CAG dataset. Combining both samples resulted in the same effect size estimate as for the NIMH families alone, with slightly narrower confidence intervals. This could indicate that the A allele is also a risk factor in the CAG families, which possibly remained undetected due to insufficient power. Interestingly, only two of the NIMH families found to be associated with *LBP-1c/CP2/LSF* here also show association with the intron 18 deletion in *A2M* published earlier by our group using the same NIMH dataset,<sup>11</sup> if association is assumed when at least two risk alleles are transmitted (as indicated by the Viewstat function in FBAT; see Methods) to affected individuals for each polymorphism. This suggests that these two genes, which are located ~40 Mb apart on chromosome 12, likely function as independent risk factors.

In addition to the findings with the previously reported 3' UTR SNP, we also detected evidence of association with a nearby second SNP (rs10876135) in the NIMH families. It is interesting that the minor allele (that is, T) of this SNP was undertransmitted to affected individuals, reminiscent of the transmission pattern observed in all but one previous case-control study for the 3' UTR SNP. Overtransmitted alleles for both SNPs were located on a rare haplotype (H4), which was associated with risk for AD in the NIMH sample. A similar overtransmission was found in the CAG sample, although this did not reach statistical significance, possibly due to low power (that is, there were only 17 informative transmissions *v* 30 in the NIMH sample). Taken together, our findings clearly support and extend the previously suggested role of the *LBP-1c/CP2/LSF* gene in AD pathogenesis.

Thus far, only one study has investigated the potential consequences of the 3' UTR SNP on *LBP-1c/CP2/LSF*

expression and protein function.<sup>12</sup> These experiments were somewhat preliminary and revealed that the A allele—which the same authors found to be underrepresented (that is, protective) in their AD cases as compared to controls—had a lower affinity to nuclear proteins in neuroblastoma cells using electrophoresis mobility shift assays, potentially suggesting a decreased function of this nuclear transcription factor. However, when *LBP-1c/CP2/LSF* mRNA expression was compared in lymphocytes from AD cases and controls, the A allele carriers showed no detectable differences. In fact, only the affected G/G carriers showed an overall reduced expression of this gene in cases *v* controls. However, the numbers in these latter experiments were very low (only three A allele carriers in each group) and were only performed in peripheral blood cells. Thus, no inference can be currently drawn from these data regarding any pathophysiological consequences in the brain.

Despite these promising findings, there remains discrepancy with respect to the direction of the potential effect uncovered by the genetic analyses, where two studies now show a risk effect, while three studies favour a protective role for the A allele. There are at least three conceivable scenarios to explain the observed discrepancies across studies. The first possibility is that *LBP-1c/CP2/LSF* is not an AD susceptibility gene, and the previously published reports constitute false-positive findings published on the basis of publication bias. While currently the possibility of publication bias cannot be assessed reliably due to the limited number of studies, this scenario appears unlikely as it is typically only an issue for the first, and usually positive, publication.<sup>31</sup> In AD and other genetically complex diseases, the majority of promising initial findings are followed by a number of non-confirmative studies, which—at least in the past—have mostly outweighed the positive results. However and as mentioned earlier, *LBP-1c/CP2/LSF* has thus far been quite remarkable in that only positive studies have been published following the initial report, our study being no exception. A second explanation for the discrepant findings is that the families driving the association in our analyses (that is, NIMH) were



ascertained based on the presence of at least two AD cases in first degree relatives of the same pedigree, while all previous samples did not specifically consider family history. This could potentially lead to the sampling of genetically distinct populations, that is, samples that are governed by different genetic risk factors and risk alleles. However, the observation that at least one other investigation (by Panza *et al*) also described an over-representation of the A allele in their AD cases as compared to controls, suggests that differences in ascertainment are probably not responsible for the observed differences in allele and genotype distributions across studies. Finally, it is possible that the 3' UTR SNP is not actually pathogenic, but that the observed associations merely reflect LD with another genetic variant nearby. In this case, the—still elusive—*true* disease predisposing variant would have independently occurred on the haplotype background of the major allele in four of the examined case-control populations, while in the sample by Panza *et al* and our study it has arisen coupled with the minor allele. In the former samples the A allele would thus appear as protective (since the actual risk allele is actually in LD with the G allele at the 3' UTR SNP), while in the latter cases it would appear as a risk factor. On the other hand, there could be several independent and rare disease modifying variants within the *LBP-1c* gene, which would have also arisen on different haplotype backgrounds (for example, similar to what is observed for *PSEN1*). Both alternatives are consistent with the analyses provided in this study, which—at least in the families analysed here—favour the existence of risk increasing variant(s) on the H4 background. It is noteworthy that similar observations, that is, significant associations with opposite alleles across different samples and populations, have actually been reported with several other AD candidate genes in the past (for example, *A2M* (recently reviewed in Saunders *et al*<sup>11</sup>), *LRP1*,<sup>32–33</sup> tumour necrosis factor  $\alpha$  (TNFA),<sup>34–35</sup> and butyrylcholinesterase K (BChE-K)<sup>36–37</sup>). If they do not merely represent a collection of varying false-positive findings, these differences could be attributed to the different patterns of LD across populations of different origin and/or differing degrees of population heterogeneity. While we favour this last alternative as the most likely explanation for the observed differences with the 3' UTR SNP, clearly more studies need to be performed on the potential association of this and possibly other polymorphisms in *LBP-1c/CP2/LSF* and AD.

In conclusion, we provide additional and independent evidence suggesting that genetic variants in *LBP-1c/CP2/LSF* significantly alter the risk for developing AD. More studies will need to be performed to further establish this association, and to more definitively assess which variant(s) are actually responsible for the observed effects and how they affect disease pathogenesis.

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## ELECTRONIC-DATABASE INFORMATION



The Haploview website can be found at <http://www.broad.mit.edu/personal/jcbarret/haploview/index.php> and International HapMap Project can be found at <http://www.hapmap.org/>.

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## CORRECTION

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In the paper titled, A new syndrome, congenital extraocular muscle fibrosis with ulnar hand anomalies, maps to chromosome 21qter (*J Med Genet* 2004;**42**:408–15) there are a number of errors. The affiliations and correspondence details were incorrect, the correct details have been listed below:

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In figure 3 the marker D21S1400 should be D21S1440.

On page 413 in the second paragraph, the marker D21S1446 should be D21S1446.