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Polymorphisms in *LMNA* and near a *SERPINA* gene cluster are associated with cognitive function in older people

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Abstract

A recent genome-wide association (GWA) study of late-onset Alzheimer's disease (LOAD) identified 15 novel single nucleotide polymorphisms (SNPs) independent of ApoE. We hypothesized that variants associated with LOAD are also associated with poor cognitive function in elderly populations. We measured additive associations between the five most strongly associated LOAD SNPs and grouped Mini Mental State Examination (MMSE) scores. Variants were genotyped in respondents (mean age 79yrs) from the Oxford Healthy Aging project (OHAP) and other sites of the MRC Cognitive Function and Aging Study (MRC-CFAS). In adjusted ordinal logistic models, two variants were associated with poorer cognitive function: rs11622883 (OR=1.14, 95%CI: 1.01 to 1.28, p=0.040) and rs505058 (OR=1.29, 95% CI: 1.02 to 1.64, p=0.036). These SNPs are close to a *SERPINA* gene cluster and within *LMNA* respectively. The mechanisms underlying the associations with cognitive impairment and LOAD require further elucidation, but both genes are interesting candidates for involvement in age-related cognitive impairment.

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Keywords

Late-onset Alzheimer's disease; dementia; cognitive function; cognitive impairment; gene; single nucleotide polymorphism; *ApoE*; *LMNA*

1. Introduction

Late-onset Alzheimer's disease (LOAD) is a common condition characterised by degenerative brain changes in later life, and is believed to have a substantial genetic component ([Farrer et al., 1991]). Several studies have attempted to identify the gene variants contributing to increased risk of the disease, but thusfar only one variant, *ApoE ε4*, has been fully validated ([Bennett et al., 1995], [Blacker et al., 1997], [Coon et al., 2007], [Rubinsztein and Easton, 1999]). However, the *ApoE* haplotype only explains about 7–15% of the heritability of LOAD ([Bennett et al., 1995], [Daw et al., 2000], [Farrer et al., 1991], [Rao et al., 1996], [Slooter et al., 1998]).

While LOAD represents the extreme of cognitive impairment, there is evidence for a moderate genetic component in the full range of cognitive abilities seen in the elderly populations. Estimates for the heritability of general cognitive function in older people range from 26% – 62% ([McClearn et al., 1997], [McGue and Christensen, 2001]). Even the relatively simple Mini Mental State Examination (MMSE) test for cognitive function shows a heritability of 60% in elderly twins ([Swan et al., 1990]).

Several genetic association or linkage studies aiming to identify new markers for LOAD or cognitive decline have been performed ([Baune et al., 2008], [Harris et al., 2007], [Seshadri et al., 2007], [Yaffe et al., 2007]). The largest recent GWA study ([Grupe et al., 2007]) tested over 17,000 SNPs, the majority of which were putative functional variants. Associations were tested across a tiered set of five samples, including a total of 1808 LOAD cases and 2062 healthy controls. Three variants on chromosome 19, in linkage disequilibrium with the *ApoE* locus, reached genome-wide significance. An additional 15 independent SNPs were identified at $p<5\times10^{-5}$ across the five sets of samples, providing suggestive evidence of association with LOAD, although these did not reach genome-wide significance.

In our study we aimed to examine associations between the five most strongly associated new LOAD SNPs suggested by the GWA study ([Grupe et al., 2007]) and cognitive function in a population-based study of older people.

2. Methods

2.1 Study Populations

The samples were drawn from the population based MRC Cognitive Function and Aging Study (MRC CFAS, www.cfas.ac.uk). This is a six site cohort study based in geographically defined sites in Cambridgeshire, North Wales, Newcastle, Nottingham, Oxford and Liverpool, all in the United Kingdom. The first five of these sites used identical methodology for sampling and interviewing, with common instruments and training. We therefore included data from these first five sites in our analyses, including the Oxford site (also called the Oxford Healthy Aging Project `OHAP'). A baseline screening interview containing the MMSE was followed by a more intensive diagnostic interview in 20% of the sample, with over-representation of those who were cognitively impaired. This was repeated at a two year follow-up. During a six year follow-up, a sub-sample of all those who had had more detailed assessment was re-interviewed. All participants were of white, European descent.

2.2. Blood Collection & Genotyping

In the OHAP site, all respondents taking part at the two year incidence re-screen (excluding the sub-group who had been assessed in more detail at baseline) were asked to donate blood samples. In the four other MRC-CFAS sites, blood samples were requested from the intensively interviewed sub-samples, which were weighted to over-represent those with impaired cognition (from the prevalence and two year incidence assessment interviews).

DNA samples from 1566 OHAP respondents and 1202 other site respondents were available for genotyping (pooled n=2768). Genotyping in both studies was carried out using a TaqMan PCR assay with specific probes designed by Applied Biosystems and automated genotype calling using Klustercaller software (KBioscience). Five variants were genotyped: rs3745833 (*GALP*), rs1554948 (*TNK1*), rs11622883 (*SERPINA13/GSC*), rs8192708 (*PCK1*) and rs505058 (*LMNA*). Call rates for these SNPs were close to 95% for both studies. There were no significant deviations from Hardy-Weinberg equilibrium (P>0.01) in either study dataset or within the pooled sample. *ApoE* genotypes have been previously described in these four sites ([Yip et al., 2002])

2.3. Phenotyping

Cognitive function was measured using the clinical version of the MMSE ([Brayne et al., 2006]). MMSE scores can range from 0 to 30, with higher scores reflecting better cognitive function. MMSE scores within both populations were highly skewed, with large proportions of the sample scoring at the upper end of the range. We therefore grouped scores into four categories reflecting widely used cut-points as follows: group 1 (scores 26–30), 2 (22–25), 3 (18–21) and 4 (0–17), where group 4 included those with the poorest cognitive function

2.4. Statistical Analysis

Ordered logistic regression models were used to estimate associations between the number of LOAD risk alleles (0, 1, 2) present for each SNP and MMSE group. The ordinal odds ratio (OR) results from these models estimate the relative odds of the risk group being in an outcome group one level higher than the comparison risk group. Significance levels were computed using the `two sided' convention, which is conservative given that we were testing for associations in the same direction as in the Grupe et al. (2007) LOAD GWA. Models were adjusted for age, sex and years of education. Allele frequencies were checked using a Hardy-Weinberg Equilibrium test with the `gtab' function. All the analyses were carried out using STATA SE 9.2.

2.5. Ethics approval

The phenotype data collection and analysis for all MRC-CFAS sites is covered by the MREC ethics approval, as is the blood collection for the sites other than Oxford (Cambridgeshire Committee ref 99/5/22). The OHAP blood collection was carried out at the incidence screen and received local ethical approval in Oxford. The current analysis and genotyping were approved by the PMCD ethics committee.

3. Results

OHAP respondents were slightly younger (77.9 vs 79.9 years) and had higher MMSE scores compared to the rest of MRC-CFAS (Table 1). The numbers of respondents in each SNP allele and MMSE group are presented in Table 2.

In ordered logistic regression models, adjusted for age, sex, years of education and study (Table 3), there were significant associations between the LOAD risk allele and poor cognitive function for both the *SERPINA*-cluster adjacent SNP (OR=1.14, 95% CI: 1.01–1.28, p=0.040)

and the *LMNA* SNP (OR=1.29, 95% CI: 1.02–1.64, p=0.036). Thus the LOAD associated risk alleles of rs505058 and rs11622883 were associated with poorer cognitive function in our elderly population samples, and these effects were in the same direction as expected from Grupe et al. (2007) study. There was no association between *ApoE* status and either rs505058 (correlation coefficient r=0.0016) or rs11622883 (r=0.0044) genotype.

4. Discussion

Cognitive function in old age is a moderately heritable trait, but previously only the *ApoE* genotype was clearly proven to be associated with cognitive function in the general older population. In this study we have examined the five most promising new polymorphisms identified in a recent genome-wide study of LOAD. In our analysis covering 2768 older people from population representative cohorts, we have shown that two of the five implicated polymorphisms are associated with poorer cognitive function, assessed by grouped MMSE scores.

The synonymous polymorphism rs505058 is located in exon 7 of the *LMNA* gene, which encodes the protein Lamin A/C. The lamin family of proteins interact to make up the 2-dimensional matrix of the nuclear lamina, situated adjacent to the inner nuclear membrane ([Moir and Spann, 2001]). During mitosis the lamina matrix is reversibly deconstructed due to protein phosphorylation and thus the structure is thought to be involved in nuclear stability, chromatin structure and also gene expression ([Bridger et al., 2007], [Moir and Spann, 2001]). Mutations in the gene lead to numerous diseases including forms of Muscular Dystrophy ([Raffaele Di Barletta et al., 2000]), Cardiomyopathy ([Araujo-Vilar et al., 2007]) and Familial Lipodystrophy ([Cao and Hegele, 2000]). In addition, *LMNA* mutations are implicated in Hutchinson-Gilford progeria syndrome ([Denecke et al., 2006]), a rare disorder with a phenotype resembling accelerated aging beginning in childhood. ([Huang et al., 2007]) observed that cellular over-expression of *LMNA* causes an accelerated rate of telomere loss and decreased replicative lifespan in fibroblasts. This is supported by experimental evidence that the gene is inactivated in certain malignancies ([Agrelo et al., 2005]) due to its tumour suppressor-like characteristics, which are hypothesised to decrease tissue proliferation and repair ([Sharpless and DePinho, 2007]) Together, this evidence indicates a possible role for *LMNA* mutations in aging phenotypes via mutant protein forms, overexpression of wild-type *LMNA* or via beneficial tumour-suppression actions. Additionally the rs505058 rare allele has recently been associated with late-onset Diabetes in a large-scale study ([Duesing et al., 2008]), providing further evidence that the gene is involved in general aging processes.

The rs11622883 SNP is not an intragenic variant but is situated near a *SERPINA* gene cluster, closest to *SERPINA13*. The common role of serpins is in peptidase inhibition, but some serpins can act in distinctly different roles. For example, Maspin is considered to be a tumour suppressor ([Shams et al., 2006]) and plays a vital role in the prevention of metastasis in breast and prostate cancers ([Schaefer and Zhang, 2003]). Interestingly, the *INK4/ARF* locus, which controls both the p53 and Rb tumour suppression pathways, is also linked to aging phenotypes ([Sharpless and DePinho, 2007]). In addition *GSC* is the nearest 3' gene within the region surrounding rs11622883, and is a homeobox transcription factor. The mouse homolog of *GSC* is involved in craniofacial development ([Boucher et al., 2000]) but interestingly the human gene has been linked to cancer, being overexpressed in a majority of human breast tumours ([Hartwell et al., 2006]).

The results of genetic association studies should only be considered robust if they are replicated in independent populations. Strengths of association for the rs11622883 and rs505058 SNPs were near study wide significance in the Grupe et al. (2007) GWA study (p = 0.000094 and 0.0002 respectively). As cognitive impairment is the principal feature of LOAD, the prior

probability of these polymorphisms being associated with cognition was relatively high. Our findings are consistent with the Grupe et al. (2007) study and are therefore likely to be robust. Further work is required to identify the significance of these associations in independent populations.

The MMSE score is a simple but well validated marker of cognitive function, used widely in clinical practice. The MMSE score shows moderate heritability ([Swan et al., 1990]), which makes it a potentially useful measure for exploring the effects of common genetic variants. Scores are typically skewed, with most respondents scoring in the normal functioning end of the scale: our grouping of scores into the four well established clinical groupings should have provided a valid outcome measure reflecting poor cognitive function.

Data in all CFAS sites were collected using an identical study protocol, but the DNA samples were collected at different follow-up waves: in OHAP around three years into the study, and in the four other sites during the sixth year follow-up. Differences in cognitive function between Oxford and the other sites may reflect differences in the selection of respondents asked to donate blood specimens (See Methods). Despite the differences in the proportions of cognitively intact and impaired groups included in the various weighted subsamples, the entire aging population is reflected in the two sample sets.

The Grupe et al. (2007) GWA showed that the *LMNA* and *SERPINA* associated SNPs were independent of *ApoE* status. In our study, there was no correlation between *ApoE* and SNP status for both rs505058 (r=0.0016) and rs11622883 (r=0.0044). However the association of the *SERPINA* associated SNP with poor cognitive function was no longer significant following adjustment for *ApoE* status (OR=1.11, 95% CI: 0.98–1.27, p=0.110), whereas the *LMNA* associated SNP was found to be robust against this adjustment (OR=1.33, 95% CI: 1.03, 1.72, p=0.03). The effect on rs11622883 is likely to be due to lack of power rather than a real effect, as the estimate of effect size for this SNP and the p-value were only marginally changed, but this finding requires further study in larger populations.

Having identified these new variants, future work should aim to clarify the mechanisms of action of the implicated genes. Understanding of these mechanisms of action should reveal elements of the aetiology of cerebral damage with aging and LOAD. It is likely that several more markers associated with cognitive impairment will emerge from subsequent genome-wide studies, and combined effects will need to be estimated.

Polymorphisms in *LMNA* and near the *SERPINA* gene cluster are associated with cognitive function in the studied older population samples. Given the high prior probability of associations with LOAD it is likely these findings are robust, but further replication is needed. Mechanisms of action remain unclear but *LMNA* has been implicated in an accelerated aging phenotype of progeria.

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Table 1

Summary characteristics by study population.

Measure	Oxford (OHAP)	*4 CFAS sites* Mean (s.d.) or n (%)	Pooled
Number Genotyped	1566	1202	2768
Age (Years)	77.9 (6.5)	79.9 (6.9)	78.8 (6.7)
Women	924 (59.0)	691 (57.5)	1615 (58.4)
MMSE Category (score grouping)			
1 (26–30)	1110 (70.9)	581 (49.9)	1691 (62.1)
2 (22–25)	339 (21.6)	303 (26.0)	642 (23.6)
3 (18–21)	77 (4.9)	131 (11.2)	208 (7.6)
4 (0–17)	30 (1.9)	150 (12.9)	180 (6.6)
Education (Years)			
Less than 10	742 (47.8)	843 (70.5)	1585 (57.7)
Less than 14	1331 (85.8)	1159 (96.9)	2490 (90.6)

Table 2

Population distribution by genotype and grouped MMSE scores.

		Mmse 4pt Score			
SNP	**Genotype**	**1 (26–30)**	**2 (22–25)**	**3 (18–21)**	**4 (0–17)**
rs3745833 n **row %** (95% CI)	*GG*	635	254	80	73
		60.9	**24.4**	**7.7**	**7.0**
		(57.9–63.9)	(21.9–27.0)	(6.2–9.5)	(5.6–8.7)
	GC	708	281	94	87
		60.5	**24.0**	**8.0**	**7.4**
		(57.7–63.3)	(21.7–26.6)	(6.6–9.7)	(6.1–9.0)
	CC	214	74	22	17
		65.4	**22.6**	**6.7**	**5.2**
		(60.1–70.4)	(18.4–27.5)	(4.5–10.0)	(3.3–8.2)
rs1554948 n **row %** (95% CI)	*AA*	301	134	35	39
		59.1	**26.3**	**6.9**	**7.7**
		(54.8–63.3)	(22.7–30.3)	(5.0–9.4)	(5.6–10.3)
	AT	683	252	83	80
		62.2	**23.0**	**7.6**	**7.3**
		(59.3–65.0)	(20.6–25.5)	(6.1–9.3)	(5.9–9.0)
	TT	384	142	54	53
		60.7	**22.4**	**8.5**	**8.4**
		(56.8–64.4)	(19.4–25.9)	(6.6–11.0)	(6.5–10.8)
rs11622883 n **row %** (95% CI)	*AA*	292	105	31	28
		64.0	**23.0**	**6.8**	**6.1**
		(59.5–68.3)	(19.4–27.1)	(4.8–9.5)	(4.3–8.8)
	AT	782	291	101	87
		62.0	**23.1**	**8.0**	**6.9**
		(59.3–64.7)	(20.8–25.5)	(6.6–9.6)	(5.6–8.4)
	TT	476	209	63	59
		59.0	**25.9**	**7.8**	**7.3**
		(55.6–62.3)	(23.0–29.0)	(6.1–9.9)	(5.7–9.3)

		Mmse 4pt Score			
SNP	**Genotype**	**1 (26–30)**	**2 (22–25)**	**3 (18–21)**	**4 (0–17)**
rs8192708 n **row %** (95% CI)	AA	1175	468	157	139
		60.6	**24.1**	**8.1**	7.2%
		(58.4–62.8)	(22.3–26.1)	(7.0–9.4)	(6.1–8.4)
	AG	330	125	35	34
		63.0	**23.9**	**6.7**	**6.5**
		(58.8–67.0)	(20.4–27.7)	(4.8–9.2)	(4.7–8.9)
	GG	24	4	4	3
		68.6	**11.4**	**11.4**	**8.6**
		(51.7–81.7)	(4.4–26.8)	(4.4–26.8)	(2.8–23.5)
rs5050558 n **row %** (95% CI)	AA	1360	536	164	153
		61.5	**24.2**	**7.4**	**6.9**
		(59.4–63.5)	(22.5–26.1)	(6.4–8.6)	(5.9–8.0)
	AG	175	61	29	20
		61.4	**21.4**	**10.2**	**7.0**
		(55.6–66.9)	(17.0–26.6)	(7.2–14.3)	(4.6–10.6)
	GG	3	4	4	2
		23.1	**30.8**	**30.8**	**15.4**
		(7.6–52.2)	(12.0–59.1	(12.0–59.1)	(3.9–45.1)

Table 3

Odds Ratios for LOAD risk alleles against lower grouped MMSE scores.

		OHAP			CFAS			Pooled		
SNP	**Nearest Gene(s)**	**Risk Allele[c] (Freq.)**	**Odds Ratio[a] (95% CI)**	**p-value**	**Risk Allele[c] (Freq.)**	**Odds Ratio[a] (95% CI)**	**p-value**	**Risk Allele[c] (Freq.)**	**Odds Ratio[b] (95% CI)**	**p-value**
rs3745833	*GALP*	C (0.36)	0.99 (0.83–1.19)	0.944	C (0.35)	0.85 (0.72–1.01)	0.069	C (0.36)	0.91 (0.80–1.03)	0.124
rs1554948	*TNK1*	T (0.52)	0.82 (0.67–1.00)	0.057	T (0.52)	1.07 (0.91–1.25)	0.414	T (0.52)	0.97 (0.86–1.10)	0.636
rs11622883	*SERPINA/GSC*	T (0.57)	1.15 (0.96–1.37)	0.136	T (0.57)	1.15 (0.97–1.35)	0.115	T (0.57)	1.14 (1.01–1.28)	0.040*
rs8192708	*PCK1*	G (0.13)	0.90 (0.69–1.18)	0.454	G(0.11)	0.99 (0.76–1.28)	0.922	G (0.12)	0.93 (0.77–1.12)	0.434
rs505058	*LMNA*	G (0.06)	1.68 (1.18–2.38)	0.004	G (0.07)	1.06 (0.77–1.46)	0.736	G (0.06)	1.29 (1.02–1.64)	0.036*

[a] Ordinal logistic regression models adjusted for age, sex and years of education.

[b] Ordinal logistic regression models adjusted for age, sex and years of education and study.

[c] Allele associated with increased risk of LOAD.