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Investigating the role of rare coding variability in Mendelian dementia genes (*APP*, *PSEN1*, *PSEN2*, *GRN*, *MAPT*, and *PRNP*) in late-onset Alzheimer's disease

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ABSTRACT

The overlapping clinical and neuropathologic features between late-onset apparently sporadic Alzheimer's disease (LOAD), familial Alzheimer's disease (FAD), and other neurodegenerative dementias (frontotemporal dementia, corticobasal degeneration, progressive supranuclear palsy, and Creutzfeldt-Jakob disease) raise the question of whether shared genetic risk factors may explain the similar phenotype among these disparate disorders. To investigate this intriguing hypothesis, we analyzed rare coding variability in 6 Mendelian dementia genes (*APP*, *PSEN1*, *PSEN2*, *GRN*, *MAPT*, and *PRNP*), in 141 LOAD patients and 179 elderly controls, neuropathologically proven, from the UK. In our cohort, 14 LOAD cases (10%) and 11 controls (6%) carry at least 1 rare variant in the genes studied. We report a novel variant in *PSEN1* (p.I168T) and a rare variant in *PSEN2* (p.A237V), absent in controls and both likely pathogenic. Our findings support previous studies, suggesting that (1) rare coding variability in *PSEN1* and *PSEN2* may influence the susceptibility for LOAD and (2) *GRN*, *MAPT*, and *PRNP* are not major contributors to LOAD. Thus, genetic screening is pivotal for the clinical differential diagnosis of these neurodegenerative dementias.

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1. Introduction

Alzheimer's disease (AD) (OMIM #104310) is the most common cause of progressive dementia in the elderly individuals. Aging and genetic factors play a pivotal role for the disease development. AD incidence increases exponentially from the age of 65 years (1.5% affected) to 80 years and older (30% affected). Twin studies have shown that AD heritability ranges between 60% and 80% (Bergem et al., 1997; Gatz et al., 2006; Raiha et al., 1996). Fully penetrant mutations in amyloid precursor protein (*APP*) and presenilins (*PSEN1* and *PSEN2*) are known to cause familial autosomal dominant AD. The *APOE* ε4 allele is the main risk factor for apparently sporadic AD. In the last 5 years, genome-wide association studies (GWASs) identified several loci, harboring common variants with low risk effect size (OR: 1.2–1.5) (Harold et al., 2009; Hollingworth

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et al., 2011; Lambert et al., 2009; Lambert et al., 2013; Naj et al., 2011; Seshadri et al., 2010).

Recently, next generation sequencing has led to enormous progress in AD genetics, with the discovery of 2 rare significant risk factors, mapping to *TREM2* (p.R47H) and *PLD3* (p.V232M), and a very rare protective variant in *APP* (p.A637T) (Cruchaga et al., 2013; Guerreiro et al., 2013; Jonsson et al., 2012). In addition, *C9orf72* repeat expansion has been reported in a few patients with clinical AD (Majounie et al., 2012).

The overlapping clinical and neuropathologic features between AD and other neurodegenerative dementias (frontotemporal dementia [FTD], corticobasal degeneration [CBD], progressive supranuclear palsy [PSP], and Creutzfeldt-Jakob disease [CJD]) lead to a misdiagnosis in 17%–30% of AD cases (Beach et al., 2012). This raises the question of whether genetic risk factors relevant in such dementias may play a role in late-onset Alzheimer's disease (LOAD). GWASs have shown that common noncoding variability in Mendelian dementia genes (*APP*, *PSEN1*, *PSEN2*, *MAPT*, *GRN*, and *PRNP*) does not influence susceptibility to AD. By contrast, a growing body of evidence highlighted the significant role of rare coding variants in *PSEN1* in LOAD (Benitez et al., 2013; Cruchaga et al., 2012). Thus, to test the hypothesis that rare coding variability in genes relevant for familial Alzheimer's disease (FAD) and other types of dementia (*APP*, *PSEN1*, *PSEN2*, *MAPT*, *GRN*, and *PRNP*) may underlie LOAD pathogenesis, we have analyzed exome sequencing data, in a British cohort composed of 141 LOAD cases without any apparent family history and 179 elderly controls autopsy proven.

2. Methods

2.1. Cases and controls

Our cohort was composed of 141 independent LOAD (age at onset ≥65 years) cases and 179 elderly (>60 years) unrelated controls, neuropathologically confirmed. These patients were referred as apparently sporadic LOAD cases.

All the patients and controls were Caucasian, mostly from the UK (London, Manchester, Nottingham, and Edinburgh) and to a lesser extent from North America. The average age at diagnosis was 76.7 years (range 65–97 years) for the LOAD patients and the mean age of ascertainment was 78 years (range 60–102 years) for the controls (Table 1).

Written informed consent was obtained for each individual and the study was approved by the appropriate institutional review boards.

2.2. Exome sequencing

Library preparation for next-generation sequencing was performed according to the NimbleGen (Roche NimbleGen v2) and TruSeq (Illumina) sample-preparation protocols. DNA libraries were then hybridized to exome-capture probes with NimbleGen SeqCap EZ Human Exome Library, version 2.0 (Roche NimbleGen) or TruSeq (Illumina). Each capture method covers the *APP*, *PSEN1*, *PSEN2*, *GRN*, *MAPT*, and *PRNP* loci. Exome-enriched libraries were sequenced on the Illumina HiSeq 2000 using 2 × 100 bp paired end read cycles.

2.3. Bioinformatics

Sequence alignment and variant calling were performed against the reference human genome (UCSC hg19). Paired end sequence reads (2 × 100 bp paired end read cycles) were aligned using the Burrows-Wheeler aligner (Li and Durbin, 2009). Format conversion and indexing were performed with Picard (www.picard.sourceforge.net/index.shtml). The Genome Analysis Toolkit was used to recalibrate base quality scores, perform local realignments around indels and to call and filter the variants (McKenna et al., 2010). VCFtools was used to annotate gene information for the remaining novel variants. We used ANNOVAR software to annotate the variants (Wang et al., 2010). Variants were checked against established databases (1000 Genomes Project and dbSNP v.134). The protein coding effects of variants were predicted using SIFT, Polyphen2, and SeattleSeq Annotation (gvs.gs.washington.edu/SeattleSeqAnnotation). All variants within the coding regions of *APP*, *PSEN1*, *PSEN2*, *MAPT*, *GRN*, and *PRNP* were annotated for both cases and controls.

2.4. Sanger sequencing

All rare variants identified by whole exome sequencing in the candidate genes were validated by Sanger sequencing.

Primers for exons harboring rare variants were designed in Primer3 (http://bioinfo.ut.ee/primer3-0.4.0/) using UCSC (http://genome.ucsc.edu/) reference sequences NM_000484.3 (*APP*), NM_000021.3 (*PSEN1*), NM_000447.2 (*PSEN2*), NM_001123066.3 (*MAPT*), NM_002087.2 (*GRN*), and NM_000311.3 (*PRNP*).

Purified sequences were analyzed on an ABI 3730 DNA Analyzer (Applied Biosystems, CA, USA) and electropherograms were visualized in Sequencher software (version 4.2 Gene Codes Corporation, MI, USA).

2.5. Apoe genotyping

APOE genotypes comprising the *APOE* ε2, ε3, and ε4 alleles were assayed using the TaqMan method (Applied Biosystems Inc [ABI], Foster City, CA, USA). SNP-specific primers and probes were designed by ABI (TaqMan genotyping assays).

3. Results

We identified 226 variants (nonsynonymous, synonymous, intronic, and UTRs) and 18 indels (coding and intronic) in the genes studied. Of these, we analyzed the 18 rare coding variants (minor allele frequency <1%), 1 splice-site mutation (*MAPT* c.115–2A>T), 1 low frequency and 1 common coding polymorphisms in *PRNP*: a 24 bp deletion (rs138688873) and the p.M129V (rs1799990), respectively. In our cohort, 14 LOAD cases (10%) and 11 controls (6%) carry at least one of these rare variants (Table 2). We detected 5 novel variants: 3 present in cases (*APP* p.Y538H, *PSEN1* p.I168T, and *MAPT* c.115-2A>T) and 2 in controls (*MAPT* p.G200E and *PRNP* p.M134V).

PRNP and *APP* harbor an higher relative proportion of rare coding variants in controls (1.3/Kb and 1.2/Kb, respectively), compared to cases (0/Kb and 0.4/Kb, respectively), thus, suggesting that rare coding variability in these genes may be well tolerated (Table 3). On

Table 1
Cohort

Cohort	n	Diagnosis	Sequencing strategy	Age (y) mean ± SD (range)	Male (%)	*APOE* e4+ (%)
LOAD CASES	141	Clinical and neuropathologic	Exome sequencing	76.7 (65–97)	42	62
CONTROLS	179	Clinical and neuropathologic	Exome sequencing	78 (60–102)	55	40.7

Key: LOAD, late-onset Alzheimer's disease; SD, standard deviation.

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