Investigating the role of rare coding variability in Mendelian dementia genes (\textit{APP}, \textit{PSEN1}, \textit{PSEN2}, \textit{GRN}, \textit{MAPT}, and \textit{PRNP}) in late-onset Alzheimer’s disease

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\textsuperscript{1}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 (\textit{APP}, \textit{PSEN1}, \textit{PSEN2}, \textit{GRN}, \textit{MAPT}, and \textit{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 \textit{PSEN1} (p.I168T) and a rare variant in \textit{PSEN2} (p.A237V), absent in controls and both likely pathogenic. Our findings support previous studies, suggesting that (1) rare coding variability in \textit{PSEN1} and \textit{PSEN2} may influence the susceptibility for LOAD and (2) \textit{GRN}, \textit{MAPT}, and \textit{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 (\textit{APP}) and presenilins (\textit{PSEN1} and \textit{PSEN2}) are known to cause familial autosomal dominant AD. The \textit{APOE} e4 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 et al., 2009; et al., 2010).
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 PPD2 (p.V232M), and a very rare protective variant in APP (p.A637T) (Cruchaga et al., 2013; Guerrero 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 $\geq$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 x 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 x 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://bioinfot.ee/primer3-0.4.0/) using UCSC (http://genome.ucsc.edu/) reference sequences NM_000484.3 (APP), NM_0000213 (PSEN1), NM_0004472 (PSEN2), NM_00123066.3 (MAPT), NM_0020872 (GRN), and NM_0003113 (PRNP).

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

2.5. ApoE genotyping

APOE genotypes comprising the APOE $\epsilon 2$, $\epsilon 3$, and $\epsilon 4$ 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 (non-synonymous, 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 (rs135868873) 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.1168T, 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 (0.0/Kb and 0.4/Kb, respectively), thus, suggesting that rare coding variability in these genes may be well tolerated (Table 3). On
<table>
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<tr>
<th>Variant interpretation</th>
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<th>Position</th>
<th>Nucleotide change</th>
<th>Aa change</th>
<th>Minor allele status</th>
<th>SIFT/Polyphen</th>
<th>LOAD cases (n = 141)</th>
<th>Comment</th>
<th>CONTROLS (n = 179)</th>
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<td>p.A201V</td>
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<td>rs149995579</td>
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<td>c.1612T&gt;C</td>
<td>p.Y538H</td>
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<td>possibly-damaging</td>
<td>1 (0.7)</td>
<td>69y-77y</td>
<td>T/C</td>
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<td>p.E599K</td>
<td>A</td>
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<td>p.R62C</td>
<td>T</td>
<td>rs150400387</td>
<td>possibly-damaging</td>
<td>1 (0.7)</td>
<td>83y-91y</td>
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<td>C/T</td>
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<td>A/C</td>
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<td>frameshift</td>
<td>T</td>
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<td>81y-89y</td>
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<td>p.Y224G</td>
<td>G</td>
<td>rs141120474</td>
<td>possibly-damaging</td>
<td>2 (1.4)</td>
<td>74y-82y; 85y-</td>
<td>T/G</td>
</tr>
<tr>
<td></td>
<td>PRNP</td>
<td>20:4680266</td>
<td>c.400A&gt;G</td>
<td>p.G200E</td>
<td>G</td>
<td>rs76375268</td>
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<td>2 (1.4)</td>
<td>74y-82y; 75y-</td>
</tr>
<tr>
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<td>c.599G&gt;A</td>
<td>p.G200E</td>
<td>G</td>
<td>rs76375268</td>
<td>possibly-damaging</td>
<td>0 - -</td>
<td>-</td>
<td>-</td>
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<td><strong>LIKELY LOW FREQUENCY AND COMMON BENIGN POLYMORPHISMS</strong></td>
<td>PRNP</td>
<td>20:4680904-4680118</td>
<td>delACAGCC TCTAGTGG TGCTGTCG</td>
<td>2 (1.4)</td>
<td>80y-88y; 76y-83y</td>
<td>delACAGCC TCTAGTGG TGCTGTCG</td>
<td>possibly-damaging</td>
<td>64 (45)</td>
<td>-</td>
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<td>c.385A&gt;G</td>
<td>p.M129V</td>
<td>G</td>
<td>rs1799990</td>
<td>tolerated</td>
<td>64 (45)</td>
<td>-</td>
<td>-</td>
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</table>

Rare variants in causative genes for the monogenic forms of neurodegenerative dementias (AD, FTD, PSP, CBD, CJD): amyloid precursor protein, APP (NM_000484.3); presenilins 1 and 2, PSEN1 (NM_000213) and PSEN2 (NM_000447.2); progranulin, GRN (NM_0002087.2); microtubule associated protein Tau, MAPT (NM_001123066.3); prion protein, PRNP (NM_000311.3). Key: AD, Alzheimer's disease; AAD, age at death; AO, age at onset; CJD, Creutzfeldt-Jakob disease; FAD, familial Alzheimer's disease; FTD, frontotemporal dementia; PSP, progressive supranuclear palsy; Aa, amino acid.

* Classification based on the algorithm proposed by Guerreiro et al., 2010a.
the other hand, no controls carry any rare variant in PSEN1, suggesting that an amino acid change in PS1 is frequently pathogenic.

In our LOAD cohort, we identified a total of 9 rare coding variants in APP, PSEN1, PSEN2, MAPT, GRN, and PRNP; absent in controls. Of these, 2 are likely to be pathogenic, one in PSEN1 (p.I168T) and the other in PSEN2 (p.A237V). In contrast, the variants detected in APP, GRN, MAPT, and PRNP are likely tolerated polymorphisms.

Several lines of evidence suggest that p.I168T in PSEN1 is a deleterious change. First, it clusters in the third transmembrane domain (TM3), on the alpha helix surface, where all the known pathogenic variants have been reported (alpha-helix rule) (Hardy and Crock, 2001). Second, a 4 bp inframe deletion (g.38798_38800delTAT, ΔI167; ΔI168) has already been described in a British family with early-onset Alzheimer’s disease (Jassens et al., 2003). The patient carrying this variant (PSEN1 p.I168T) was diagnosed at 86 years of age, heterozygous for APOE ε4 allele (ε2ε4), presented an advanced Alzheimer’s disease (Braak V), and did not report any positive family history.

The PSEN2 p.A237V has been only recently reported by the ClinSeq pilot study (Biesecker et al., 2009) and is likely to be a functional variant with a probable deleterious effect. It clusters on the alpha helix surface of the fifth transmembrane domain (TM5), corresponds to a conserved residue among different species and in PSEN1 (p.A231), where 2 causative mutations (p.A231V and p.A231T) have been described in a Dutch, French and Canadian family (Campion et al., 1999; Cruts et al., 1998; Rogaeva et al., 2001). The patient carrying the p.A237V variant was diagnosed at 87 years, homozygous for APOE ε3 allele, and did not refer any positive family history of AD.

The other variants detected in our cohort in PSEN2 (p.R62C, p.R62H, p.S130L, and p.D439A) do not cluster in any TM domain. In addition, the p.S130L and p.D439A have been found also controls. GRN harbors 4 missense mutations (p.A324T, p.R432C, p.R433W, and p.A582T), 2 of which have only been detected in cases (p.R432C and p.R433W). Although the p.R432C variant has been already associated with familial FTLD and clinical AD (Brouwers et al., 2010a; Cruchaga et al., 2012; Shankaran et al., 2008), its pathogenic role remains unclear. By contrast, the p.R433W has been reported as a nonpathogenic variant (www.molgendatabase).

The variants detected in MAPT (c.115-2A>T, p.V224G, p.G213R and p.G200E) cluster outside the microtubule binding domain, where most of the pathogenic mutations have been reported up to date (www.molgendatabase). The c.115-2A>T is predicted to alter Tau exon 7 splicing, introducing a nonsense codon within exon 11. We have not detected any difference in exon 7 and in MAPT expression between the splice-site mutation carrier and the other cases and controls. Thus, these findings suggest that c.115-2A>T is not disease related (Supplementary data).

The MAPT p.G213R has been found in 2 cases and is absent from the controls. It has been described as possibly damaging by in silico predictions and clusters close to a pivotal phosphorylation site (S214) for the serum and glucocorticoid inducible kinase 1 (SGK1). SGK1 controls neurite outgrowth by depolarizing the microtubules through the serine phosphorylation at codon 214 (Yang et al., 2006).

Two cases and no controls carry a 24 bp deletion in the PRNP open reading frame (rs138688873), between the repeat 3 (R3) and repeat 4 (R4). This octapeptide deletion (rs138688873) has been described as a risk factor for neurodegenerative diseases with some controversy (Palmer et al., 1993; Perry et al., 1995). Furthermore, although these 2 patients were homozygous for PRNP p.M129M, a common polymorphism and risk factor for sporadic Creutzfeldt-Jakob disease (sCJD) (Palmer et al., 1991), p.M129M was not significantly associated with AD in this study (p-value = 0.22, OR = 0.75). Thus, suggesting this common variant may be a benign polymorphism.

Finally, we report a significant association between APOE ε4 allele and LOAD in our cohort (p-value = 0.0002, OR = 2.4). Nevertheless, we have not detected any enrichment for the APOE ε4 allele among the patients carrying rare variants in APP, PSEN1, PSEN2, GRN, MAPT, and PRNP (only 6 of 14 LOAD carriers [42%] carry at least one APOE ε4 allele). By contrast, APOE ε2 allele did not present a significantly higher frequency in controls compared to cases (p-value = 0.3, OR = 0.68).

4. Discussion

In this study, we tested the hypothesis that the significant phenotypic overlap between sporadic LOAD and other neurodegenerative dementias (FAD, FTD, PSP, CBD, and CJD) may be explained by a common genetic background. Thus, we screened 6 Mendelian dementia genes (APP, PSEN1, PSEN2, MAPT, GRN, and PRNP) aiming to establish whether rare coding variability in these genes is responsible for an appreciable portion of the LOAD risk.

In our LOAD cohort, we found a novel rare variant in PSEN1 (p.I168T) and a rare variant in PSEN2 (p.A237V). These variants are likely pathogenic: (1) both cluster in TM domains, on the alpha helix surface; (2) the literature already reported in the same (PSEN1 p.I168) or homologous residue (PSEN2 p.A237 and PSEN1 p.A231) causative mutations for FAD; and (3) the PSEN1 p.I168T and PSEN2 p.A237V are classified as possible pathogenic, following the algorithm proposed by Guerreiro et al. (2010a). The other variants detected in our LOAD cases are likely to be tolerated. First, they have already been described as benign polymorphisms (PSEN2 p.R62H; PRNP rs138688873 and GRN p.R433W) (Guerreiro et al., 2010a; Palmer et al., 1993; www.molgendatabase). Second, they cluster outside the reported pathogenic domains (APP p.A201V, p.Y538H, p.V562I, p.E599K; PSEN2 p.R62C, p.R62H, p.S130L, p.D439A; MAPT p.V224G, p.G213R and p.G200E). Third, they do not alter the gene expression (MAPT c.115-2A>T).

Finally, despite the functional consequence of GRN p.R433C, the effect of a decreased GRN secretion in AD pathogenesis remains controversial. GRN pathogenic mutations act through a messenger RNA nonsense-mediate decay, interfering with GRN expression and generally are loss of function mutations (LoF) (stop-gain, frameshift mutations, and deletions). The only exception to this rule is represented by the pathogenic missense mutations which cluster in the GRN signal peptide domain (GRN p.A9D) (www.molgendatabase). Thus, we suggest, in concert with previous studies (Guerreiro et al., 2010b), that GRN missense mutations mapping outside the signal peptide domain are likely to be well tolerated.

In conclusion, our findings support recent studies, suggesting that rare coding variability in PSEN1 and PSEN2 contributes to susceptibility for apparently sporadic LOAD. Therefore, sporadic LOAD and FAD may be influenced by the same genes and thus pathogenic mechanisms. On the contrary, rare coding variants in MAPT, GRN, and PRNP are not major players in the development of LOAD and other familial cases of FTD and AD.
LOAD. Thus, genetic screening is fundamental for the differential diagnosis of these disparate neurodegenerative dementias.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.neurobiolaging.2014.06.002.

References


