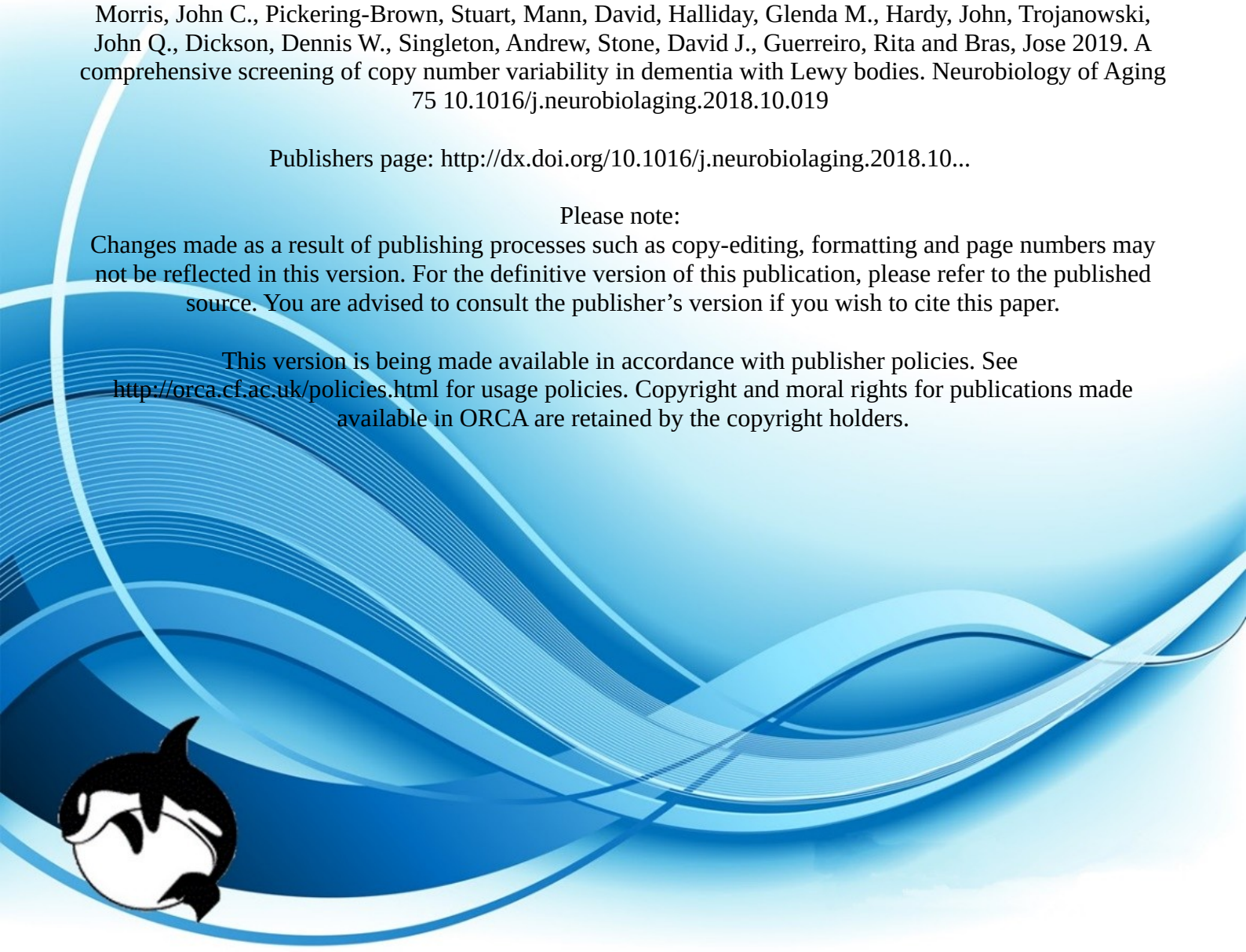

A comprehensive screening of copy-number variability in dementia with Lewy bodies

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Abstract

The role of genetic variability in dementia with Lewy bodies (DLB) is now indisputable, however data regarding copy number variation (CNV) in this disease has been lacking. Here, we used whole-genome genotyping of 1,454 DLB cases and 1,525 controls to assess copy number variability. We used two algorithms to confidently detect CNVs, performed a case-control association analysis, screened for candidate CNVs previously associated with DLB-related diseases, and performed a candidate gene approach to fully explore the data. We identified five CNV regions with a significant genome-wide association to DLB, two of these were only present in cases and absent from publicly available databases: one of the regions overlapped *LAPTM4B*, a known lysosomal protein; whilst the other overlapped the *NME1* locus and *SPAG9*. We also identified DLB cases presenting CNVs in genes previously associated with DLB or related neurodegenerative diseases, namely *SNCA* and *MAPT*. To our knowledge, this is the first study reporting genome-wide CNVs in a large DLB cohort.

Keywords

Dementia with Lewy bodies; Copy number variants; *MAPT*; *SNCA*; Genome-wide

1. Introduction

Dementia with Lewy bodies (DLB) is a common and complex form of dementia and its diagnosis can often be complicated by phenotypic similarities with Alzheimer's disease (AD), Parkinson's disease (PD) or even Frontotemporal dementia (FTD) (Claassen et al., 2008; Heidebrink, 2002). A more accurate DLB diagnosis is usually obtained by integrating clinical and pathological data from brain autopsy (McKeith et al., 2017).

Genetic studies in DLB have been limited, certainly in comparison with studies on AD or PD, for a number of reasons, most notably because DLB has not been historically considered a genetic disease, given the lack of multiplex kindreds where the disease segregates. Additionally, large cohorts of patients are difficult to collect given the frequency of the disease and the rate of misdiagnosis. Despite this, recent studies have conclusively shown that there is a role for genetics in the etiology of DLB (Bras et al., 2014; Guerreiro et al., 2018, 2016; Nalls et al., 2013). Exome sequencing studies have been performed in small cohorts; as have case studies and Sanger sequencing of specific target genes (Clark et al., 2009; Keogh et al., 2016; Koide et al., 2002; Ohtake et al., 2004). Copy number variants (CNVs) have not been assessed thus far in DLB, particularly in an unbiased manner and at a genome-wide level.

CNVs have been widely studied in a number of neurological conditions, particularly in developmental phenotypes such as schizophrenia (SCZ) and autism (Glessner et al., 2009; Marshall et al., 2017; McCarthy et al., 2009) where several microdeletions and microduplications have been found to be associated with both diseases (Bassett et al., 2017; Cook et al., 1997; McCarthy et al., 2009; Stefansson et al., 2008; Weiss et al., 2008). In these phenotypes CNVs play a prominent role in the disease genetic architecture.

Several studies have analyzed CNVs in AD, where *APP* duplications have been unequivocally shown to cause disease (Delabar et al., 1987; Ghani et al., 2012; Swaminathan et al., 2012, 2011; Zheng et al., 2015, 2014). In PD, pathogenic CNVs are also known to occur in *SNCA* and *PARK2* (Chartier-Harlin et al., 2004; Ibáñez et al., 2004; Lesage et al., 2008; Waters and Miller, 1994). Together, these data show that CNVs are an important mutational event in neurological conditions.

Here, we report the first genome-wide analysis of CNVs in DLB in a large cohort of patients, many of which with neuropathology diagnoses of DLB. We performed a case-control association study that was complemented by discovery stage analyses guided by candidate genes and CNVs previously reported as being associated with DLB-related neurodegenerative diseases.

2. Materials and Methods

2.1. Sample selection

A total of 1,454 patients diagnosed with DLB and of European ancestry were selected for this study. Diagnosis of DLB was made according to clinical or pathological criteria (McKeith et al., 2005). Briefly, these included 298 clinically diagnosed and 1,156 neuropathologically diagnosed cases. Detailed sample and processing information has been described previously (Guerreiro et al., 2018). Data from 1,525 control samples was obtained from The Genetic Architecture of Smoking and Smoking Cessation study (phs000404.v1.p1) publicly available at the database of Genotypes and Phenotypes (https://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs000404.v1.p1.) **Supplementary Figure 1** shows an overview of the study design, different QC steps and analyses performed.

2.2. Genotyping, quality control and CNV calling

Seven hundred and fifty four DLB samples were genotyped on HumanOmni2.5Exome-8 v1.0.B Illumina arrays, and 700 DLB samples were genotyped using Infinium OmniExpress-24 v1.2.A1 Illumina arrays (Illumina, Inc., CA, USA). Control samples were genotyped on HumanOmni2.5-4 v1.D arrays (Illumina, Inc., CA, USA). Intensity files were analysed using GenomeStudio v2011.1 software (Illumina, Inc., CA, USA) along with the respective manufacturer's cluster files. Quality control (QC) procedures were performed in GenomeStudio (GS) prior to CNV analysis as described by Jarick and colleagues (Jarick et al., 2014). In short, samples with call rates lower than 0.97 were filtered out. SNP statistics were re-calculated following visual inspection of B allele frequency (BAF) and Log R ratio (LRR) plots. SNPs with GenTrain Scores below 0.7 were excluded. Lastly, samples

with substantial cryptic relatedness scores (PI_HAT >0.1) were removed, as previously described (Guerreiro et al., 2018).

CNV calls were generated using two different algorithms: cnvPartition v2.3.0 (Illumina, Inc). and PennCNV v1.0.4 (Wang et al., 2007). CNV calling based on cnvPartition was performed by GS with default parameters. For PennCNV, probe positions, LRR and BAF values for samples that passed QC procedures were exported from GS. Population frequency of the B allele (PFB) files were calculated for each array separately. All Smoking Cessation samples were used to generate CNVs in cnvPartition and PennCNV, but only a subset of the best performing 700 samples was used for the compilation of the PFB file in PennCNV to match the number of samples used for cases. PennCNV GC-model files were then created based on these PFBs. Lastly, CNVs were inferred by PennCNV using the hidden Markov model (HMM) and the GC-model for wave adjustment. Calls for the X chromosome were generated separately. Chromosomes Y, MT and XY were not analyzed.

2.3. CNV quality control and analysis

To improve the quality of CNVs, only calls generated by both algorithms were kept, while calls made by a single algorithm or calls of opposing type (for example, assigned as a deletion by one algorithm and as duplication by the other) were discarded. Adjacent CNVs were merged if the length of the sequence between them was smaller than 50% of the length of the larger CNV. CNVs were excluded if they were overlapping telomeres, centromeres, known segmental duplications, the immunoglobulin or the T cell receptor loci. Samples having LRR SD > 0.28, BAF drift > 0.002, Waviness Factor (WF) > 0.04, or having more CNV calls than 3*SD + median were excluded (Marshall et al., 2017; Need et al., 2009).

To identify potentially pathogenic CNVs, we analyzed CNVs spanning known genes. We used the Database of Genomic Variants (DGV) (http://dgv.tcag.ca/dgv/app/home, accessed November 2017) to determine the population frequency of CNVs (MacDonald et al., 2014). This information was complemented with the frequency from clinical samples available in DECIPHER v9.18 (https://decipher.sanger.ac.uk/, accessed November 2017).

2.4 Case-control association analysis

Case-control association analysis was implemented using ParseCNV (Glessner et al., 2013). Standard ParseCNV quality metrics were used to filter out low quality results. CNVs that were genome-wide significant (p-value < $5x10^{-4}$ as suggested by (Glessner et al., 2013)), had a minimum length of 50 kb, and passed visual inspection in GS were selected for further analyses.

2.5. Candidate CNVs approach

CNVs previously described in AD (Ghani et al., 2012; Heinzen et al., 2010; Swaminathan et al., 2012, 2011; Zheng et al., 2015, 2014), PD (Bademci et al., 2010; Liu et al., 2013; Mok et al., 2016; Pankratz et al., 2011) and FTD (Gijselinck et al., 2008) were specifically investigated in these data (**Supplementary Table 1**). This analysis was performed in the complete set of CNV results after QC, disregarding the filters used for the case-control association analysis performed by ParseCNV.

2.6. Candidate genes approach

CNVs located in known AD, PD, FTD and DLB genes were also assessed (Brás et al., 2015; Guerreiro et al., 2018, 2015, 2013; Jansen et al., 2015; Keogh et al., 2016; Koide et al., 2002; Ohtake et al., 2004; Saitoh et al., 1995). **Supplementary Table 2** lists all genes studied using this approach.

3. Results

3.1. CNV calling and QC steps

After QC steps at the GS level, a total of 2,819 samples (1,294 cases and 1,525 controls) remained for further analyses. From the 754 DLB samples genotyped with HumanOmni2.5 arrays, 616 (81.7%) samples were kept and from the 2,567,845 probes in this array, 2,496,600 (97.2%) passed quality control. Six hundred and seventy-eight (96.9%) samples of the 700 samples genotyped with OmniExpress arrays passed quality control and from the 713,599 probes available in this chip, 698,680 (97.9%) probes remained. All controls from the Smoking Cessation database had good

quality genotypes (call rate > 0.97) and, consequently, no samples were excluded, and 2,390,384 (97.8%) of the 2,443,177 probes were kept.

After combining the results obtained by the two CNV calling algorithms (cnvPartition and PennCNV), excluding samples due to their relatedness and performing the PennCNV QC steps on the LRR and BAF values and number of calls, a final number of 2,615 individuals (1,187 DLB cases and 1,428 control samples) and 80,416 CNVs were analysed.

3.2. Case-control association analysis

Of the 494 CNV regions (CNVR) resulting from the ParseCNV analysis, only 5 passed QC checks and were statistically significant (**Table 1**). Of these, two of the regions were not present in our control population or in public databases: a deletion overlapping *LAPTM4B* ($p=6.29x10^{-7}$) and a CNVR overlapping *SPAG9-NME1-NME2* ($p=2.72x10^{-4}$) (**Figure 1**).

3.3. Candidate CNVs approach

Five CNVs previously associated with DLB-related neurodegenerative diseases were found in DLB patients (**Table 1**). Two of these were present in the control group with a higher frequency than in the patients' group, and the remaining three are described in public databases and are detailed next. The duplication identified on chromosome 12 overlapping *DDX11* and *OVOS2* has a frequency tenfold higher in DGV than in the DLB cohort. The 16p11.2 microduplication found in one DLB patient, has a frequency of $1.69x10^{-4}$ in the DECIPHER database but does not occur in any control samples or in the DGV database. One of the CNVs that was previously significantly associated with AD locates at chr8:2792874-4852328 and overlaps *CSMD1* (Swaminathan et al., 2011). At this locus, we identified over 100 CNVs in cases and controls. Therefore, in **Table 1**, we only report the shorter interval that showed suggestive significance in the case-control association analysis.

3.4. Candidate genes approach

We investigated CNVs in genes known to be associated with diseases that are related to DLB (**Supplementary Table 2**) and identified a total of 8 CNVs (**Table 1**). These included one duplication in *APP* occurring in a clinically diagnosed case. This large duplication is not present in the databases or in the control cohort. Two samples were found to carry duplications spanning *MAPT,* and one neuropathologically diagnosed patient was found to carry a *SNCA* duplication (**Figure 2**). *PARK2* was found to have many copy number losses and gains in controls (n=28) and cases (n=13) but none as homozygous. A duplication including *CHCHD10* was also identified in a neuropathologically diagnosed DLB patient.

4. Discussion

We performed a systematic analysis of CNVs in a large cohort of DLB patients using three main approaches. The first of these approaches was a case-control association analysis which resulted in five significant CNVRs that have not been previously described as associated with the disease. The most significant result from this analysis was a deletion spanning a lysosome-associated transmembrane protein, *LAPTM4B*. Intraneuronal alpha-synuclein clearance likely occurs through a variety of mechanisms in order to maintain protein homeostasis. However, recent data has highlighted the importance of lysosomal pathways for degradation of this protein (Webb et al., 2003). While we cannot directly link this CNV to the development of DLB in these cases, it is interesting that a lysosomal enzyme is the top hit in our association analysis, given the prominent role of the lysosome in Lewy body diseases. Interestingly, a member of the same protein family, *LAPTM5,* was one of the top hits for incidental DLB in a recent network analysis study (Santpere et al., 2017).

Also associated with DLB and absent from publicly available databases was a deletion overlapping the *NME1* locus. *NME1* is involved in purine metabolism, which has been reported to be disrupted in AD, PD and Creutzfeldt–Jakob disease. *NME1* mRNA was also found to be reduced in these diseases (Ansoleaga et al., 2016, 2015; Garcia-Esparcia et al., 2015). Here, we identified a deletion

at the 3'-end *NME1* which could be consistent with a reduced expression of the gene in DLB, although this was not tested in the present study.

Using a candidate gene approach where we analyzed genes known to have a role in DLB and DLB-related diseases we identified several CNVRs of interest. The hallmark of DLB at autopsy is the accumulation of alpha-synuclein protein within neurons and their processes, termed Lewy bodies and Lewy neurites (Spillantini et al., 1997). Variants in the *SNCA* gene, which encodes alpha-synuclein, have been previously associated with the risk of developing DLB (Bras et al., 2014; Guerreiro et al., 2018). In addition to point mutations, CNVs including *SNCA* are known to cause PD, and over the past years evidence suggested that this gene may also be duplicated in DLB. Nishioka and colleagues identified a PD family with a duplication spanning all of *SNCA* and *MMRN1* where the proband was later neuropathologically diagnosed as DLB (Nishioka et al., 2006b; Obi et al., 2008). Four neuropathologically diagnosed DLB cases presented a large duplication from *DSPP* to *PDLIM5* including *SNCA*, three of these were heterozygous and one was homozygous (Ikeuchi et al., 2008). A duplication in *SNCA* was also described in a probable DLB patient in a study with 99 cases (Meeus et al., 2012). Here, we add to this body of evidence, by identifying another patient neuropathologically diagnosed with DLB carrying a *SNCA* duplication. In our DLB cohort this duplication shows a similar frequency to that provided by DGV. This frequency in DGV results from two entries in the database. When looking in more detail at these entries, they are associated with the same Human Genome Diversity Project (HGDP) sample from Cambodia (HGDP00721). Given that information for each HGDP samples is limited to sex of the individual, population and geographic origin, it is possible this sample originated from a PD or DLB patient; or from an asymptomatic carrier, as these have previously been reported, with *SNCA* multiplications having particular low penetrance levels in Asian populations (Ahn et al., 2008; Nishioka et al., 2006a). It is also possible the duplication reported is an artifact caused by the creation or passage of the lymphoblast cell lines used to extract DNA (Simon-Sanchez et al., 2007).

We also identified one heterozygous duplication encompassing *CHCHD10*, a gene previously shown to cause FTD. However, given that *CHCHD10* FTD-associated mutations are loss-of-function (Perrone et al., 2017), it is unlikely that a duplication of the gene would be pathogenic.

GABRB3 is a gamma-aminobutyric acid (GABA) receptor that was reported as associated with DLB in a recent GWAS, but that did not survive independent replication (Guerreiro et al., 2018). However, loss of GABA receptors could underlie the typical visual hallucinations in DLB (Khundakar et al., 2016), and, because of this, we specifically looked at CNVs in *GABRB3,* and identified a duplication in one case. It is tempting to speculate that, given the GWAS discovery results, the fact that GABA receptors neurotransmission is altered in DLB (Santpere et al., 2017), and the CNV detected here, genetic variability in GABA receptors may in fact modulate risk for DLB.

We identified two clinically diagnosed DLB samples with *MAPT* duplications (**Figure 3**). *MAPT* was not found to be significantly associated with DLB in recent GWAS (Bras et al., 2014; Guerreiro et al., 2018), but the *MAPT* H1 haplotype was previously described as a possible risk factor for DLB (Cervera-Carles et al., 2016; Labbé et al., 2016). Previous studies of small cohorts of FTD patients have not revealed causative *MAPT* duplications (Lladó et al., 2007; Skoglund et al., 2009) but the screening of French FTD patients including multiplex families led to the identification of an heterozygous partial deletion of *MAPT* (Rovelet-Lecrux et al., 2009) and of a 17q21.31 microduplication in an atypical FTD case (Rovelet-Lecrux et al., 2010). More recently, *MAPT* duplications were shown to increase expression of *MAPT* mRNA and were found to cause tangle pathology without Aβ deposition in probable AD patients (Le Guennec et al., 2017).

PARK2 homozygous CNVs are the most common copy-number cause of PD, accounting for more than 50% of all pathogenic mutations in the gene and more frequently affecting the region between exons 2 and 7 (Hedrich et al., 2004; Kim et al., 2012). Our results showed no significant differences between DLB cases and controls, similar to the findings by Kay and colleagues in PD (Kay et al., 2010). Additionally, we did not find any homozygous *PARK2* CNVs suggesting that CNVs in this gene do not play a causative role in DLB.

APP duplications are known to cause AD (Delabar et al., 1987; Ghani et al., 2012; Swaminathan et al., 2012, 2011; Zheng et al., 2015, 2014). The sample carrying an *APP* duplication in our cohort has a clinical diagnosis of DLB without neuropathological confirmation - it is therefore possible this is an AD case misdiagnosed as DLB. However, there have been reports in the literature of DLB cases associated with *APP* duplications. For example, in a French family presenting with a diverse phenotype, *APP* duplication was associated with DLB confirmed by neuropathological findings (Guyant-Marechal et al., 2008). Similarly, one case with Lewy body-variant AD was reported in a multigenerational dementia family from the Netherlands (Sleegers et al., 2006). DLB cases frequently present Aβ pathology at autopsy (Hepp et al., 2016), and it has been suggested that Aβ accumulation can trigger Lewy body disease (Masliah et al., 2001).

There are two main limitations in this study: first, this is a relatively small-sized cohort, which means we cannot confidently assess associations of CNVs with low effect sizes on disease; second, we did not perform independent replication of these findings, which precludes us from establishing definite associations or causes of disease. Despite these limitations we report on the first systematic analysis of CNVs in a large cohort of DLB patients, using well-established analytical practices. We identify potential disease causing CNVs as well as potential novel candidate genes for DLB.

Disclosure statement

The authors have no actual or potential conflicts of interest.

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Figures captions

Figure 1. Schematic representation of CNVs.

Schematic representation of statistically significant CNVs resulting from the case-control analysis that were not found in controls or publicly available databases. CNVs overlapping *LAPTM4B* in **A**; and *SPAG9/NME1* in **B**. Known transcripts are represented at the bottom of each panel. Passing QC SNPs used for the CNV calling are depicted by colour according to the genotyping array (red: OmniExpress, blue: Omni2.5M, green: Omni2.5M for controls). CNVs (duplications) are depicted as bars above the genes. The grey shadow area represents the associated region that is genome-wide significant.

Figure 2. Duplication identified at the *SNCA* locus.

Log R ratio and B allele frequency plots of the CNV identified in the *SNCA* locus. Each point represents a SNP according to location in chromosome 4 (position on X axis). The genomic duplication is indicated by an increase in log R ratio and B allele frequency clusters outside the expected values of 1 (B/B), 0.5 (A/B), and 0 (A/A). Genes are represented at the bottom as black bars. SNPs inside the CNV region are represented in red, SNPs outside the CNV region are represented in blue, and SNPs in *SNCA* are represented in green.

Figure 3. Duplications identified at the *MAPT* locus.

Log R ratio and B allele frequency plots of the CNVs identified at the *MAPT* locus in two clinically diagnosed DLB cases. Each point represents a SNP according to location in chromosome 17 (position on X axis). The genomic duplication is indicated by an increase in log R ratio and B allele frequency clusters outside the expected values of 1 (B/B), 0.5 (A/B), and 0 (A/A). Genes are represented at the bottom as black bars. SNPs inside the CNV regions are represented in red, SNPs outside the CNV regions are represented in blue, and SNPs in *MAPT* are represented in green.

Tables

Table 1 Results from the three types of analyses performed

Genes	Location	CNV	p-value	Cases (Neuro*)	Controls	Cases frequency	Controls frequency	DGV frequency	DECIPHER frequency
Case-control association analysis									
ADGRG7,TFG	chr3:100357671-100439759	Gain	$8.93x10^{-5}$	21 (18)	13	$1.77x10^{-2}$	$9.10x10^{-3}$	$1.43x10^{-2}$	$2.09x10^{-2}$
PDZD2	chr5:32101400-32106628	Gain	$2.94x10^{-6}$	14 (12)	0	$1.18x10^{-2}$	0	$3.00x10^{-4}$	$1.69x10^{-4}$
LAPTM4B	chr8:98755434-98800334	Loss	$6.29x10^{-7}$	12 (6)	0	$1.01x10^{-2}$	0	0	0
MSR1	chr8:15948235-16021468	Loss	$1.20x10^{-4}$	13 (7)	4	$1.10x10^{-2}$	$2.80x10^{-3}$	$4.30x10^{-3}$	$7.10x10^{-3}$
NME1,NME1-NME2,SPAG9	chr17:49177096-49231786	Loss	$2.72x10^{-4}$	9 (4)	0	$7.58x10^{-3}$	0	0	0
Candidate CNVs approach									
CSMD1	chr8:4,033,908-4,126,540	Loss	$2.89x10^{-2\#}$	3 (2)	0	$2.53x10^{-3}$	0	$3.00x10^{-4}$	0
DDX11,OVOS2	chr12:31,249,834-31,407,303	Gain	$1.41x10^{-2\#}$	4 (2)	0	$3.37x10^{-3}$	0	$4.61x10^{-2}$	0
CYFIP1,GOLGA8I,NIPA1,NIPA2,TUBGCP5, WHAMML1	chr15:22,750,305-23,272,733	Gain	na	5 (5)	8	$4.21x10^{-3}$	$5.60x10^{-3}$	$2.50x10^{-3}$	$1.86x10^{-3}$
CHRNA7,OTUD7A	chr15:31,932,865-32,515,849	Loss or Gain	na	6 (5)	13	$5.05x10^{-3}$	$9.10x10^{-3}$	$6.90x10^{-3}$	$8.79x10^{-3}$
ASPHD1,BOLA2,C16orf54,CDIPT,CDIPT-AS1, KIF22,MAZ,MVP,PAGR1,PRRT2,QPRT,SEZ6L2, SPN,ZG16	chr16:29,595,483-29,912,902	Gain	na	1 (1)	0	$8.42x10^{-4}$	0	0	$1.69x10^{-4}$
Candidate genes approach									
***DNAJC6**,LEPR,LEPROT*	chr1:65,854,556-65,955,725	Gain	na	1 (0)	1	$8.42x10^{-4}$	$7.00x10^{-4}$	$1.72x10^{-4}$	$2.53x10^{-3}$
***SNCA**,SNCA-AS1,GPRIN3,MMRN1,CCSER1*	chr4:90,035,549-91,420,358	Gain	na	1 (1)	0	$8.42x10^{-4}$	0	$6.42x10^{-4}$	0
PARK2	chr6:161,601,162-163,259,260	Loss or Gain	na	13 (8)	28	$1.10x10^{-2}$	$1.96x10^{-2}$	$2.30x10^{-3}$	$1.69x10^{-1}$
***GABRB3**,GABRA5 ,GABRG3*	chr15:26,996,126-27,220,713	Gain	na	1 (1)	0	$8.42x10^{-4}$	0	0	$1.18x10^{-3}$
***MAPT**,CRHR1,KANSL1,KANSL1-AS1, MAPT-AS1,MAPT-IT1,SPPL2C,STH*	chr17:43,661,362-44,345,063	Gain	na	2 (0)	0	$1.68x10^{-3}$	0	$1.03x10^{-4}$	$1.18x10^{-3}$
***APP**,ADAMTS1,ADAMTS5,ATP5J,CYYR1, CYYR1-AS1,GABPA,JAM2,MRPL39*	chr21:25,063,840-28,522,487	Gain	na	1 (0)	0	$8.42x10^{-4}$	0	0	0
***CHCHD10**,ADORA2A,ADORA2A-AS1,C22orf15, CABIN1,CES5AP1,DDT,DDTL,DERL3,DRICH1,G GT1,GGT5,GSTT1,GSTT1-AS1,GSTT2,GSTT2B, GSTTP1,GSTTP2,GUCD1,GUSBP11,IGLL1, LRRC75B,MIF,MIF-AS1,MMP11,POM121L9P, RGL4,SLC2A11,SMARCB1,SNRPD3,SPECC1L, SUSD2,UPB1,VPREB3, ZDHHC8P1,ZNF70*	chr22:23,690,325-25,011,417	Gain	na	1 (1)	0	$8.42x10^{-4}$	0	$6.00x10^{-4}$	$1.18x10^{-3}$
***CYP2D6**,NDUFA6-AS1*	chr22:42,522,613-42,531,210	Loss or Gain	na	1 (1)	4	$8.42x10^{-4}$	$2.80x10^{-3}$	$2.20x10^{-1}$	$3.00x10^{-2}$

CNVs identified as significantly associated with DLB in the case-control association analyses and CNVs identified using the candidate CNVs and genes approaches.

All genomic coordinates are for the genome assembly hg19. * Neuropathological diagnosis; na – not applicable; p-value - these were calculated including all cases (not only neuropathologically confirmed cases) # – p-values resulting from the case-control association analysis.

5. References

Ahn, T.-B., Kim, S.Y., Kim, J.Y., Park, S.-S., Lee, D.S., Min, H.J., Kim, Y.K., Kim, S.E., Kim, J.-M., Kim, H.-J., Cho, J., Jeon, B.S., 2008. alpha-Synuclein gene duplication is present in sporadic Parkinson disease. Neurology 70, 43–49.

Ansoleaga, B., Garcia-Esparcia, P., Llorens, F., Hernández-Ortega, K., Carmona Tech, M., Antonio Del Rio, J., Zerr, I., Ferrer, I., 2016. Altered Mitochondria, Protein Synthesis Machinery, and Purine Metabolism Are Molecular Contributors to the Pathogenesis of Creutzfeldt-Jakob Disease. J. Neuropathol. Exp. Neurol. https://doi.org/10.1093/jnen/nlw048

Ansoleaga, B., Jové, M., Schlüter, A., Garcia-Esparcia, P., Moreno, J., Pujol, A., Pamplona, R., Portero-Otín, M., Ferrer, I., 2015. Deregulation of purine metabolism in Alzheimer's disease. Neurobiol. Aging 36, 68–80.

Bademci, G., Edwards, T.L., Torres, A.L., Scott, W.K., Züchner, S., Martin, E.R., Vance, J.M., Wang, L., 2010. A rare novel deletion of the tyrosine hydroxylase gene in Parkinson disease. Hum. Mutat. 31, E1767–71.

Bassett, A.S., Lowther, C., Merico, D., Costain, G., Chow, E.W.C., van Amelsvoort, T., McDonald-McGinn, D., Gur, R.E., Swillen, A., Van den Bree, M., Murphy, K., Gothelf, D., Bearden, C.E., Eliez, S., Kates, W., Philip, N., Sashi, V., Campbell, L., Vorstman, J., Cubells, J., Repetto, G.M., Simon, T., Boot, E., Heung, T., Evers, R., Vingerhoets, C., van Duin, E., Zackai, E., Vergaelen, E., Devriendt, K., Vermeesch, J.R., Owen, M., Murphy, C., Michaelovosky, E., Kushan, L., Schneider, M., Fremont, W., Busa, T., Hooper, S., McCabe, K., Duijff, S., Isaev, K., Pellecchia, G., Wei, J., Gazzellone, M.J., Scherer, S.W., Emanuel, B.S., Guo, T., Morrow, B.E., Marshall, C.R., International 22q11.2DS Brain and Behavior Consortium, 2017. Rare Genome-Wide Copy Number Variation and Expression of Schizophrenia in 22q11.2 Deletion Syndrome. Am. J. Psychiatry 174, 1054–1063.

Bras, J., Guerreiro, R., Darwent, L., Parkkinen, L., Ansorge, O., Escott-Price, V., Hernandez, D.G., Nalls, M.A., Clark, L.N., Honig, L.S., Marder, K., Van Der Flier, W.M., Lemstra, A., Scheltens, P., Rogaeva, E., St George-Hyslop, P., Londos, E., Zetterberg, H., Ortega-Cubero, S., Pastor, P., Ferman, T.J., Graff-Radford, N.R., Ross, O.A., Barber, I., Braae, A., Brown, K., Morgan, K., Maetzler, W., Berg, D., Troakes, C., Al-Sarraj, S., Lashley, T., Compta, Y., Revesz, T., Lees, A., Cairns, N., Halliday, G.M., Mann, D., Pickering-Brown, S., Dickson, D.W., Singleton, A., Hardy, J., 2014. Genetic analysis implicates APOE, SNCA and suggests lysosomal dysfunction in the etiology of dementia with Lewy bodies. Hum. Mol. Genet. 23, 6139–6146.

Brás, J., Guerreiro, R., Hardy, J., 2015. SnapShot: Genetics of Parkinson's disease. Cell 160, 570–570.e1.

Cervera-Carles, L., Pagonabarraga, J., Pascual-Sedano, B., Pastor, P., Campolongo, A., Fortea, J., Blesa, R., Alcolea, D., Morenas-Rodríguez, E., Sala, I., Lleó, A., Kulisevsky, J., Clarimón, J., 2016. Copy number variation analysis of the 17q21.31 region and its role in neurodegenerative diseases. Am. J. Med. Genet. B Neuropsychiatr. Genet. 171B, 175–180.

Chartier-Harlin, M.-C., Kachergus, J., Roumier, C., Mouroux, V., Douay, X., Lincoln, S., Levecque, C., Larvor, L., Andrieux, J., Hulihan, M., Waucquier, N., Defebvre, L., Amouyel, P., Farrer, M., Destée, A., 2004. Alpha-synuclein locus duplication as a cause of familial Parkinson's disease. Lancet 364, 1167–1169.

Claassen, D.O., Parisi, J.E., Giannini, C., Boeve, B.F., Dickson, D.W., Josephs, K.A., 2008. Frontotemporal dementia mimicking dementia with Lewy bodies. Cogn. Behav. Neurol. 21, 157–163.

Clark, L.N., Kartsaklis, L.A., Wolf Gilbert, R., Dorado, B., Ross, B.M., Kisselev, S., Verbitsky, M., Mejia-Santana, H., Cote, L.J., Andrews, H., Vonsattel, J.-P., Fahn, S., Mayeux, R., Honig, L.S., Marder, K., 2009. Association of glucocerebrosidase mutations with dementia with lewy bodies. Arch. Neurol. 66, 578–583.

Cook, E.H., Jr, Lindgren, V., Leventhal, B.L., Courchesne, R., Lincoln, A., Shulman, C., Lord, C., Courchesne, E., 1997. Autism or atypical autism in maternally but not paternally derived

proximal 15q duplication. Am. J. Hum. Genet. 60, 928–934.
Delabar, J.M., Goldgaber, D., Lamour, Y., Nicole, A., Huret, J.L., de Grouchy, J., Brown, P., Gajdusek, D.C., Sinet, P.M., 1987. Beta amyloid gene duplication in Alzheimer's disease and karyotypically normal Down syndrome. Science 235, 1390–1392.
Garcia-Esparcia, P., Hernández-Ortega, K., Ansoleaga, B., Carmona, M., Ferrer, I., 2015. Purine metabolism gene deregulation in Parkinson's disease. Neuropathol. Appl. Neurobiol. 41, 926–940.
Ghani, M., Pinto, D., Lee, J.H., Grinberg, Y., Sato, C., Moreno, D., Scherer, S.W., Mayeux, R., St George-Hyslop, P., Rogaeva, E., 2012. Genome-wide survey of large rare copy number variants in Alzheimer's disease among Caribbean hispanics. G3 2, 71–78.
Gijselinck, I., van der Zee, J., Engelborghs, S., Goossens, D., Peeters, K., Mattheijssens, M., Corsmit, E., Del-Favero, J., De Deyn, P.P., Van Broeckhoven, C., Cruts, M., 2008. Progranulin locus deletion in frontotemporal dementia. Hum. Mutat. 29, 53–58.
Glessner, J.T., Li, J., Hakonarson, H., 2013. ParseCNV integrative copy number variation association software with quality tracking. Nucleic Acids Res. 41, e64.
Glessner, J.T., Wang, K., Cai, G., Korvatska, O., Kim, C.E., Wood, S., Zhang, H., Estes, A., Brune, C.W., Bradfield, J.P., Imielinski, M., Frackelton, E.C., Reichert, J., Crawford, E.L., Munson, J., Sleiman, P.M.A., Chiavacci, R., Annaiah, K., Thomas, K., Hou, C., Glaberson, W., Flory, J., Otieno, F., Garris, M., Soorya, L., Klei, L., Piven, J., Meyer, K.J., Anagnostou, E., Sakurai, T., Game, R.M., Rudd, D.S., Zurawiecki, D., McDougle, C.J., Davis, L.K., Miller, J., Posey, D.J., Michaels, S., Kolevzon, A., Silverman, J.M., Bernier, R., Levy, S.E., Schultz, R.T., Dawson, G., Owley, T., McMahon, W.M., Wassink, T.H., Sweeney, J.A., Nurnberger, J.I., Coon, H., Sutcliffe, J.S., Minshew, N.J., Grant, S.F.A., Bucan, M., Cook, E.H., Buxbaum, J.D., Devlin, B., Schellenberg, G.D., Hakonarson, H., 2009. Autism genome-wide copy number variation reveals ubiquitin and neuronal genes. Nature 459, 569–573.
Guerreiro, R., Brás, J., Hardy, J., 2015. SnapShot: Genetics of ALS and FTD. Cell 160, 798.e1.
Guerreiro, R., Brás, J., Hardy, J., 2013. SnapShot: genetics of Alzheimer's disease. Cell 155, 968–968.e1.
Guerreiro, R., Escott-Price, V., Darwent, L., Parkkinen, L., Ansorge, O., Hernandez, D.G., Nalls, M.A., Clark, L., Honig, L., Marder, K., van der Flier, W., Holstege, H., Louwersheimer, E., Lemstra, A., Scheltens, P., Rogaeva, E., St George-Hyslop, P., Londos, E., Zetterberg, H., Ortega-Cubero, S., Pastor, P., Ferman, T.J., Graff-Radford, N.R., Ross, O.A., Barber, I., Braae, A., Brown, K., Morgan, K., Maetzler, W., Berg, D., Troakes, C., Al-Sarraj, S., Lashley, T., Compta, Y., Revesz, T., Lees, A., Cairns, N.J., Halliday, G.M., Mann, D., Pickering-Brown, S., Powell, J., Lunnon, K., Lupton, M.K., International Parkinson's Disease Genomics Consortium (IPDGC), Dickson, D., Hardy, J., Singleton, A., Bras, J., 2016. Genome-wide analysis of genetic correlation in dementia with Lewy bodies, Parkinson's and Alzheimer's diseases. Neurobiol. Aging 38, 214.e7–214.e10.
Guerreiro, R., Ross, O.A., Kun-Rodrigues, C., Hernandez, D.G., Orme, T., Eicher, J.D., Shepherd, C.E., Parkkinen, L., Darwent, L., Heckman, M.G., Scholz, S.W., Troncoso, J.C., Pletnikova, O., Ansorge, O., Clarimon, J., Lleo, A., Morenas-Rodriguez, E., Clark, L., Honig, L.S., Marder, K., Lemstra, A., Rogaeva, E., St George-Hyslop, P., Londos, E., Zetterberg, H., Barber, I., Braae, A., Brown, K., Morgan, K., Troakes, C., Al-Sarraj, S., Lashley, T., Holton, J., Compta, Y., Van Deerlin, V., Serrano, G.E., Beach, T.G., Lesage, S., Galasko, D., Masliah, E., Santana, I., Pastor, P., Diez-Fairen, M., Aguilar, M., Tienari, P.J., Myllykangas, L., Oinas, M., Revesz, T., Lees, A., Boeve, B.F., Petersen, R.C., Ferman, T.J., Escott-Price, V., Graff-Radford, N., Cairns, N.J., Morris, J.C., Pickering-Brown, S., Mann, D., Halliday, G.M., Hardy, J., Trojanowski, J.Q., Dickson, D.W., Singleton, A., Stone, D.J., Bras, J., 2018. Investigating the genetic architecture of dementia with Lewy bodies: a two-stage genome-wide association study. Lancet Neurol. 17, 64–74.
Guyant-Marechal, I., Berger, E., Laquerrière, A., Rovelet-Lecrux, A., Viennet, G., Frebourg, T., Rumbach, L., Campion, D., Hannequin, D., 2008. Intrafamilial diversity of phenotype associated with app duplication. Neurology 71, 1925–1926.
Hedrich, K., Eskelson, C., Wilmot, B., Marder, K., Harris, J., Garrels, J., Meija-Santana, H., Vieregge, P., Jacobs, H., Bressman, S.B., Lang, A.E., Kann, M., Abbruzzese, G., Martinelli, P.,

Schwinger, E., Ozelius, L.J., Pramstaller, P.P., Klein, C., Kramer, P., 2004. Distribution, type, and origin of Parkin mutations: review and case studies. Mov. Disord. 19, 1146–1157.
Heidebrink, J.L., 2002. Is dementia with Lewy bodies the second most common cause of dementia? J. Geriatr. Psychiatry Neurol. 15, 182–187.
Heinzen, E.L., Need, A.C., Hayden, K.M., Chiba-Falek, O., Roses, A.D., Strittmatter, W.J., Burke, J.R., Hulette, C.M., Welsh-Bohmer, K.A., Goldstein, D.B., 2010. Genome-wide scan of copy number variation in late-onset Alzheimer's disease. J. Alzheimers. Dis. 19, 69–77.
Hepp, D.H., Vergoossen, D.L.E., Huisman, E., Lemstra, A.W., Netherlands Brain Bank, Berendse, H.W., Rozemuller, A.J., Foncke, E.M.J., van de Berg, W.D.J., 2016. Distribution and Load of Amyloid-β Pathology in Parkinson Disease and Dementia with Lewy Bodies. J. Neuropathol. Exp. Neurol. 75, 936–945.
Ibáñez, P., Bonnet, A.-M., Débarges, B., Lohmann, E., Tison, F., Pollak, P., Agid, Y., Dürr, A., Brice, A., 2004. Causal relation between alpha-synuclein gene duplication and familial Parkinson's disease. Lancet 364, 1169–1171.
Ikeuchi, T., Kakita, A., Shiga, A., Kasuga, K., Kaneko, H., Tan, C.-F., Idezuka, J., Wakabayashi, K., Onodera, O., Iwatsubo, T., Nishizawa, M., Takahashi, H., Ishikawa, A., 2008. Patients homozygous and heterozygous for SNCA duplication in a family with parkinsonism and dementia. Arch. Neurol. 65, 514–519.
Jansen, I.E., Bras, J.M., Lesage, S., Schulte, C., Gibbs, J.R., Nalls, M.A., Brice, A., Wood, N.W., Morris, H., Hardy, J.A., Singleton, A.B., Gasser, T., Heutink, P., Sharma, M., IPDGC, 2015. CHCHD2 and Parkinson's disease. Lancet Neurol. 14, 678–679.
Jarick, I., Volckmar, A.-L., Pütter, C., Pechlivanis, S., Nguyen, T.T., Dauvermann, M.R., Beck, S., Albayrak, Ö., Scherag, S., Gilsbach, S., Cichon, S., Hoffmann, P., Degenhardt, F., Nöthen, M.M., Schreiber, S., Wichmann, H.-E., Jöckel, K.-H., Heinrich, J., Tiesler, C.M.T., Faraone, S.V., Walitza, S., Sinzig, J., Freitag, C., Meyer, J., Herpertz-Dahlmann, B., Lehmkuhl, G., Renner, T.J., Warnke, A., Romanos, M., Lesch, K.-P., Reif, A., Schimmelmann, B.G., Hebebrand, J., Scherag, A., Hinney, A., 2014. Genome-wide analysis of rare copy number variations reveals PARK2 as a candidate gene for attention-deficit/hyperactivity disorder. Mol. Psychiatry 19, 115–121.
Kay, D.M., Stevens, C.F., Hamza, T.H., Montimurro, J.S., Zabetian, C.P., Factor, S.A., Samii, A., Griffith, A., Roberts, J.W., Molho, E.S., Higgins, D.S., Gancher, S., Moses, L., Zareparsi, S., Poorkaj, P., Bird, T., Nutt, J., Schellenberg, G.D., Payami, H., 2010. A comprehensive analysis of deletions, multiplications, and copy number variations in PARK2. Neurology 75, 1189–1194.
Keogh, M.J., Kurzawa-Akanbi, M., Griffin, H., Douroudis, K., Ayers, K.L., Hussein, R.I., Hudson, G., Pyle, A., Cordell, H.J., Attems, J., McKeith, I.G., O'Brien, J.T., Burn, D.J., Morris, C.M., Thomas, A.J., Chinnery, P.F., 2016. Exome sequencing in dementia with Lewy bodies. Transl. Psychiatry 6, e728.
Khundakar, A.A., Hanson, P.S., Erskine, D., Lax, N.Z., Roscamp, J., Karyka, E., Tsefou, E., Singh, P., Cockell, S.J., Gribben, A., Ramsay, L., Blain, P.G., Mosimann, U.P., Lett, D.J., Elstner, M., Turnbull, D.M., Xiang, C.C., Brownstein, M.J., O'Brien, J.T., Taylor, J.-P., Attems, J., Thomas, A.J., McKeith, I.G., Morris, C.M., 2016. Analysis of primary visual cortex in dementia with Lewy bodies indicates GABAergic involvement associated with recurrent complex visual hallucinations. Acta Neuropathol Commun 4, 66.
Kim, S.Y., Seong, M.W., Jeon, B.S., Kim, S.Y., Ko, H.S., Kim, J.Y., Park, S.S., 2012. Phase analysis identifies compound heterozygous deletions of the PARK2 gene in patients with early-onset Parkinson disease. Clin. Genet. 82, 77–82.
Koide, T., Ohtake, H., Nakajima, T., Furukawa, H., Sakai, K., Kamei, H., Makifuchi, T., Fukuhara, N., 2002. A patient with dementia with Lewy bodies and codon 232 mutation of PRNP. Neurology 59, 1619–1621.
Labbé, C., Heckman, M.G., Lorenzo-Betancor, O., Soto-Ortolaza, A.I., Walton, R.L., Murray, M.E., Allen, M., Uitti, R.J., Wszolek, Z.K., Smith, G.E., Kantarci, K., Knopman, D.S., Lowe, V.J., Jack, C.R., Jr, Ertekin-Taner, N., Hassan, A., Savica, R., Petersen, R.C., Parisi, J.E., Maraganore, D.M., Graff-Radford, N.R., Ferman, T.J., Boeve, B.F., Dickson, D.W., Ross, O.A., 2016. MAPT haplotype H1G is associated with increased risk of dementia with Lewy bodies. Alzheimers. Dement. 12, 1297–1304.

Le Guennec, K., Quenez, O., Nicolas, G., Wallon, D., Rousseau, S., Richard, A.-C., Alexander, J., Paschou, P., Charbonnier, C., Bellenguez, C., Grenier-Boley, B., Lechner, D., Bihoreau, M.-T., Olaso, R., Boland, A., Meyer, V., Deleuze, J.-F., Amouyel, P., Munter, H.M., Bourque, G., Lathrop, M., Frebourg, T., Redon, R., Letenneur, L., Dartigues, J.-F., Martinaud, O., Kalev, O., Mehrabian, S., Traykov, L., Ströbel, T., Le Ber, I., Caroppo, P., Epelbaum, S., Jonveaux, T., Pasquier, F., Rollin-Sillaire, A., Génin, E., Guyant-Maréchal, L., Kovacs, G.G., Lambert, J.-C., Hannequin, D., Campion, D., Rovelet-Lecrux, A., 2017. 17q21.31 duplication causes prominent tau-related dementia with increased MAPT expression. Mol. Psychiatry 22, 1119–1125.

Lesage, S., Lohmann, E., Tison, F., Durif, F., Dürr, A., Brice, A., French Parkinson's Disease Genetics Study Group, 2008. Rare heterozygous parkin variants in French early-onset Parkinson disease patients and controls. J. Med. Genet. 45, 43–46.

Liu, X., Cheng, R., Ye, X., Verbitsky, M., Kisselev, S., Mejia-Santana, H., Louis, E., Cote, L., Andrews, H., Waters, C., Ford, B., Fahn, S., Marder, K., Lee, J., Clark, L., 2013. Increased Rate of Sporadic and Recurrent Rare Genic Copy Number Variants in Parkinson's Disease Among Ashkenazi Jews. Mol Genet Genomic Med 1, 142–154.

Lladó, A., Rodríguez-Santiago, B., Antonell, A., Sánchez-Valle, R., Molinuevo, J.L., Reñé, R., Pérez-Jurado, L.A., 2007. MAPT gene duplications are not a cause of frontotemporal lobar degeneration. Neurosci. Lett. 424, 61–65.

MacDonald, J.R., Ziman, R., Yuen, R.K.C., Feuk, L., Scherer, S.W., 2014. The Database of Genomic Variants: a curated collection of structural variation in the human genome. Nucleic Acids Res. 42, D986–92.

Marshall, C.R., Howrigan, D.P., Merico, D., Thiruvahindrapuram, B., Wu, W., Greer, D.S., Antaki, D., Shetty, A., Holmans, P.A., Pinto, D., Gujral, M., Brandler, W.M., Malhotra, D., Wang, Z., Fajarado, K.V.F., Maile, M.S., Ripke, S., Agartz, I., Albus, M., Alexander, M., Amin, F., Atkins, J., Bacanu, S.A., Belliveau, R.A., Jr, Bergen, S.E., Bertalan, M., Bevilacqua, E., Bigdeli, T.B., Black, D.W., Bruggeman, R., Buccola, N.G., Buckner, R.L., Bulik-Sullivan, B., Byerley, W., Cahn, W., Cai, G., Cairns, M.J., Campion, D., Cantor, R.M., Carr, V.J., Carrera, N., Catts, S.V., Chambert, K.D., Cheng, W., Cloninger, C.R., Cohen, D., Cormican, P., Craddock, N., Crespo-Facorro, B., Crowley, J.J., Curtis, D., Davidson, M., Davis, K.L., Degenhardt, F., Del Favero, J., DeLisi, L.E., Dikeos, D., Dinan, T., Djurovic, S., Donohoe, G., Drapeau, E., Duan, J., Dudbridge, F., Eichhammer, P., Eriksson, J., Escott-Price, V., Essioux, L., Fanous, A.H., Farh, K.-H., Farrell, M.S., Frank, J., Franke, L., Freedman, R., Freimer, N.B., Friedman, J.I., Forstner, A.J., Fromer, M., Genovese, G., Georgieva, L., Gershon, E.S., Giegling, I., Giusti-Rodríguez, P., Godard, S., Goldstein, J.I., Gratten, J., de Haan, L., Hamshere, M.L., Hansen, M., Hansen, T., Haroutunian, V., Hartmann, A.M., Henskens, F.A., Herms, S., Hirschhorn, J.N., Hoffmann, P., Hofman, A., Huang, H., Ikeda, M., Joa, I., Kähler, A.K., Kahn, R.S., Kalaydjieva, L., Karjalainen, J., Kavanagh, D., Keller, M.C., Kelly, B.J., Kennedy, J.L., Kim, Y., Knowles, J.A., Konte, B., Laurent, C., Lee, P., Lee, S.H., Legge, S.E., Lerer, B., Levy, D.L., Liang, K.-Y., Lieberman, J., Lönnqvist, J., Loughland, C.M., Magnusson, P.K.E., Maher, B.S., Maier, W., Mallet, J., Mattheisen, M., Mattingsdal, M., McCarley, R.W., McDonald, C., McIntosh, A.M., Meier, S., Meijer, C.J., Melle, I., Mesholam-Gately, R.I., Metspalu, A., Michie, P.T., Milani, L., Milanova, V., Mokrab, Y., Morris, D.W., Müller-Myhsok, B., Murphy, K.C., Murray, R.M., Myin-Germeys, I., Nenadic, I., Nertney, D.A., Nestadt, G., Nicodemus, K.K., Nisenbaum, L., Nordin, A., O'Callaghan, E., O'Dushlaine, C., Oh, S.-Y., Olincy, A., Olsen, L., O'Neill, F.A., Van Os, J., Pantelis, C., Papadimitriou, G.N., Parkhomenko, E., Pato, M.T., Paunio, T., Psychosis Endophenotypes International Consortium, Perkins, D.O., Pers, T.H., Pietiläinen, O., Pimm, J., Pocklington, A.J., Powell, J., Price, A., Pulver, A.E., Purcell, S.M., Quested, D., Rasmussen, H.B., Reichenberg, A., Reimers, M.A., Richards, A.L., Roffman, J.L., Roussos, P., Ruderfer, D.M., Salomaa, V., Sanders, A.R., Savitz, A., Schall, U., Schulze, T.G., Schwab, S.G., Scolnick, E.M., Scott, R.J., Seidman, L.J., Shi, J., Silverman, J.M., Smoller, J.W., Söderman, E., Spencer, C.C.A., Stahl, E.A., Strengman, E., Strohmaier, J., Stroup, T.S., Suvisaari, J., Svrakic, D.M., Szatkiewicz, J.P., Thirumalai, S., Tooney, P.A., Veijola, J., Visscher, P.M., Waddington, J., Walsh, D., Webb, B.T., Weiser, M., Wildenauer, D.B., Williams, N.M., Williams, S., Witt, S.H., Wolen, A.R., Wormley, B.K., Wray, N.R., Wu, J.Q., Zai, C.C., Adolfsson, R., Andreassen, O.A., Blackwood, D.H.R., Bramon, E., Buxbaum, J.D., Cichon, S., Collier, D.A.,

Corvin, A., Daly, M.J., Darvasi, A., Domenici, E., Esko, T., Gejman, P.V., Gill, M., Gurling, H., Hultman, C.M., Iwata, N., Jablensky, A.V., Jönsson, E.G., Kendler, K.S., Kirov, G., Knight, J., Levinson, D.F., Li, Q.S., McCarroll, S.A., McQuillin, A., Moran, J.L., Mowry, B.J., Nöthen, M.M., Ophoff, R.A., Owen, M.J., Palotie, A., Pato, C.N., Petryshen, T.L., Posthuma, D., Rietschel, M., Riley, B.P., Rujescu, D., Sklar, P., St Clair, D., Walters, J.T.R., Werge, T., Sullivan, P.F., O'Donovan, M.C., Scherer, S.W., Neale, B.M., Sebat, J., CNV and Schizophrenia Working Groups of the Psychiatric Genomics Consortium, 2017. Contribution of copy number variants to schizophrenia from a genome-wide study of 41,321 subjects. Nat. Genet. 49, 27–35.

Masliah, E., Rockenstein, E., Veinbergs, I., Sagara, Y., Mallory, M., Hashimoto, M., Mucke, L., 2001. β-Amyloid peptides enhance α-synuclein accumulation and neuronal deficits in a transgenic mouse model linking Alzheimer's disease and Parkinson's disease. Proc. Natl. Acad. Sci. U. S. A. 98, 12245–12250.

McCarthy, S.E., Makarov, V., Kirov, G., Addington, A.M., McClellan, J., Yoon, S., Perkins, D.O., Dickel, D.E., Kusenda, M., Krastoshevsky, O., Krause, V., Kumar, R.A., Grozeva, D., Malhotra, D., Walsh, T., Zackai, E.H., Kaplan, P., Ganesh, J., Krantz, I.D., Spinner, N.B., Roccanova, P., Bhandari, A., Pavon, K., Lakshmi, B., Leotta, A., Kendall, J., Lee, Y.-H., Vacic, V., Gary, S., Iakoucheva, L.M., Crow, T.J., Christian, S.L., Lieberman, J.A., Stroup, T.S., Lehtimäki, T., Puura, K., Haldeman-Englert, C., Pearl, J., Goodell, M., Willour, V.L., Derosse, P., Steele, J., Kassem, L., Wolff, J., Chitkara, N., McMahon, F.J., Malhotra, A.K., Potash, J.B., Schulze, T.G., Nöthen, M.M., Cichon, S., Rietschel, M., Leibenluft, E., Kustanovich, V., Lajonchere, C.M., Sutcliffe, J.S., Skuse, D., Gill, M., Gallagher, L., Mendell, N.R., Wellcome Trust Case Control Consortium, Craddock, N., Owen, M.J., O'Donovan, M.C., Shaikh, T.H., Susser, E., Delisi, L.E., Sullivan, P.F., Deutsch, C.K., Rapoport, J., Levy, D.L., King, M.-C., Sebat, J., 2009. Microduplications of 16p11.2 are associated with schizophrenia. Nat. Genet. 41, 1223–1227.

McKeith, I.G., Boeve, B.F., Dickson, D.W., Halliday, G., Taylor, J.-P., Weintraub, D., Aarsland, D., Galvin, J., Attems, J., Ballard, C.G., Bayston, A., Beach, T.G., Blanc, F., Bohnen, N., Bonanni, L., Bras, J., Brundin, P., Burn, D., Chen-Plotkin, A., Duda, J.E., El-Agnaf, O., Feldman, H., Ferman, T.J., Ffytche, D., Fujishiro, H., Galasko, D., Goldman, J.G., Gomperts, S.N., Graff-Radford, N.R., Honig, L.S., Iranzo, A., Kantarci, K., Kaufer, D., Kukull, W., Lee, V.M.Y., Leverenz, J.B., Lewis, S., Lippa, C., Lunde, A., Masellis, M., Masliah, E., McLean, P., Mollenhauer, B., Montine, T.J., Moreno, E., Mori, E., Murray, M., O'Brien, J.T., Orimo, S., Postuma, R.B., Ramaswamy, S., Ross, O.A., Salmon, D.P., Singleton, A., Taylor, A., Thomas, A., Tiraboschi, P., Toledo, J.B., Trojanowski, J.Q., Tsuang, D., Walker, Z., Yamada, M., Kosaka, K., 2017. Diagnosis and management of dementia with Lewy bodies: Fourth consensus report of the DLB Consortium. Neurology 89, 88–100.

McKeith, I.G., Dickson, D.W., Lowe, J., Emre, M., O'Brien, J.T., Feldman, H., Cummings, J., Duda, J.E., Lippa, C., Perry, E.K., Aarsland, D., Arai, H., Ballard, C.G., Boeve, B., Burn, D.J., Costa, D., Del Ser, T., Dubois, B., Galasko, D., Gauthier, S., Goetz, C.G., Gomez-Tortosa, E., Halliday, G., Hansen, L.A., Hardy, J., Iwatsubo, T., Kalaria, R.N., Kaufer, D., Kenny, R.A., Korczyn, A., Kosaka, K., Lee, V.M.Y., Lees, A., Litvan, I., Londos, E., Lopez, O.L., Minoshima, S., Mizuno, Y., Molina, J.A., Mukaetova-Ladinska, E.B., Pasquier, F., Perry, R.H., Schulz, J.B., Trojanowski, J.Q., Yamada, M., Consortium on DLB, 2005. Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. Neurology 65, 1863–1872.

Meeus, B., Verstraeten, A., Crosiers, D., Engelborghs, S., Van den Broeck, M., Mattheijssens, M., Peeters, K., Corsmit, E., Elinck, E., Pickut, B., Vandenberghe, R., Cras, P., De Deyn, P.P., Van Broeckhoven, C., Theuns, J., 2012. DLB and PDD: a role for mutations in dementia and Parkinson disease genes? Neurobiol. Aging 33, 629.e5–629.e18.

Mok, K.Y., Sheerin, U., Simón-Sánchez, J., Salaka, A., Chester, L., Escott-Price, V., Mantripragada, K., Doherty, K.M., Noyce, A.J., Mencacci, N.E., Lubbe, S.J., International Parkinson's Disease Genomics Consortium (IPDGC), Williams-Gray, C.H., Barker, R.A., van Dijk, K.D., Berendse, H.W., Heutink, P., Corvol, J.-C., Cormier, F., Lesage, S., Brice, A., Brockmann, K., Schulte, C., Gasser, T., Foltynie, T., Limousin, P., Morrison, K.E., Clarke, C.E., Sawcer, S., Warner, T.T., Lees, A.J., Morris, H.R., Nalls, M.A., Singleton, A.B., Hardy, J., Abramov, A.Y., Plagnol, V., Williams, N.M., Wood, N.W., 2016. Deletions at 22q11.2 in idiopathic Parkinson's disease: a combined analysis of genome-wide association data. Lancet Neurol. 15, 585–596.

Nalls, M.A., Duran, R., Lopez, G., Kurzawa-Akanbi, M., McKeith, I.G., Chinnery, P.F., Morris, C.M., Theuns, J., Crosiers, D., Cras, P., Engelborghs, S., De Deyn, P.P., Van Broeckhoven, C., Mann, D.M.A., Snowden, J., Pickering-Brown, S., Halliwell, N., Davidson, Y., Gibbons, L., Harris, J., Sheerin, U.-M., Bras, J., Hardy, J., Clark, L., Marder, K., Honig, L.S., Berg, D., Maetzler, W., Brockmann, K., Gasser, T., Novellino, F., Quattrone, A., Annesi, G., De Marco, E.V., Rogaeva, E., Masellis, M., Black, S.E., Bilbao, J.M., Foroud, T., Ghetti, B., Nichols, W.C., Pankratz, N., Halliday, G., Lesage, S., Klebe, S., Durr, A., Duyckaerts, C., Brice, A., Giasson, B.I., Trojanowski, J.Q., Hurtig, H.I., Tayebi, N., Landazabal, C., Knight, M.A., Keller, M., Singleton, A.B., Wolfsberg, T.G., Sidransky, E., 2013. A multicenter study of glucocerebrosidase mutations in dementia with Lewy bodies. JAMA Neurol. 70, 727–735.

Need, A.C., Ge, D., Weale, M.E., Maia, J., Feng, S., Heinzen, E.L., Shianna, K.V., Yoon, W., Kasperaviciūte, D., Gennarelli, M., Strittmatter, W.J., Bonvicini, C., Rossi, G., Jayathilake, K., Cola, P.A., McEvoy, J.P., Keefe, R.S.E., Fisher, E.M.C., St Jean, P.L., Giegling, I., Hartmann, A.M., Möller, H.-J., Ruppert, A., Fraser, G., Crombie, C., Middleton, L.T., St Clair, D., Roses, A.D., Muglia, P., Francks, C., Rujescu, D., Meltzer, H.Y., Goldstein, D.B., 2009. A genome-wide investigation of SNPs and CNVs in schizophrenia. PLoS Genet. 5, e1000373.

Nishioka, K., Hayashi, S., Farrer, M.J., Singleton, A.B., Yoshino, H., Imai, H., Kitami, T., Sato, K., Kuroda, R., Tomiyama, H., Mizoguchi, K., Murata, M., Toda, T., Imoto, I., Inazawa, J., Mizuno, Y., Hattori, N., 2006a. Clinical heterogeneity of alpha-synuclein gene duplication in Parkinson's disease. Ann. Neurol. 59, 298–309.

Nishioka, K., Hayashi, S., Farrer, M.J., Singleton, A.B., Yoshino, H., Imai, H., Kitami, T., Sato, K., Kuroda, R., Tomiyama, H., Others, 2006b. Clinical heterogeneity of α-synuclein gene duplication in Parkinson's disease. Ann. Neurol. 59, 298–309.

Obi, T., Nishioka, K., Ross, O.A., Terada, T., Yamazaki, K., Sugiura, A., Takanashi, M., Mizoguchi, K., Mori, H., Mizuno, Y., Hattori, N., 2008. Clinicopathologic study of a SNCA gene duplication patient with Parkinson disease and dementia. Neurology 70, 238–241.

Ohtake, H., Limprasert, P., Fan, Y., Onodera, O., Kakita, A., Takahashi, H., Bonner, L.T., Tsuang, D.W., Murray, I.V.J., Lee, V.M.-Y., Trojanowski, J.Q., Ishikawa, A., Idezuka, J., Murata, M., Toda, T., Bird, T.D., Leverenz, J.B., Tsuji, S., La Spada, A.R., 2004. Beta-synuclein gene alterations in dementia with Lewy bodies. Neurology 63, 805–811.

Pankratz, N., Dumitriu, A., Hetrick, K.N., Sun, M., Latourelle, J.C., Wilk, J.B., Halter, C., Doheny, K.F., Gusella, J.F., Nichols, W.C., Myers, R.H., Foroud, T., DeStefano, A.L., PSG-PROGENI and GenePD Investigators, Coordinators and Molecular Genetic Laboratories, 2011. Copy number variation in familial Parkinson disease. PLoS One 6, e20988.

Perrone, F., Nguyen, H.P., Van Mossevelde, S., Moisse, M., Sieben, A., Santens, P., De Bleecker, J., Vandenbulcke, M., Engelborghs, S., Baets, J., Cras, P., Vandenberghe, R., De Jonghe, P., De Deyn, P.P., Martin, J.-J., Van Damme, P., Van Broeckhoven, C., van der Zee, J., Belgian Neurology consortium, 2017. Investigating the role of ALS genes CHCHD10 and TUBA4A in Belgian FTD-ALS spectrum patients. Neurobiol. Aging 51, 177.e9–177.e16.

Rovelet-Lecrux, A., Hannequin, D., Guillin, O., Legallic, S., Jurici, S., Wallon, D., Frebourg, T., Campion, D., 2010. Frontotemporal dementia phenotype associated with MAPT gene duplication. J. Alzheimers. Dis. 21, 897–902.

Rovelet-Lecrux, A., Lecourtois, M., Thomas-Anterion, C., Le Ber, I., Brice, A., Frebourg, T., Hannequin, D., Campion, D., 2009. Partial deletion of the MAPT gene: a novel mechanism of FTDP-17. Hum. Mutat. 30, E591–602.

Saitoh, T., Xia, Y., Chen, X., Masliah, E., Galasko, D., Shults, C., Thal, L.J., Hansen, L.A., Katzman, R., 1995. The CYP2D6B mutant allele is overrepresented in the Lewy body variant of Alzheimer's disease. Ann. Neurol. 37, 110–112.

Santpere, G., Garcia-Esparcia, P., Andres-Benito, P., Lorente-Galdos, B., Navarro, A., Ferrer, I., 2017. Transcriptional network analysis in frontal cortex in Lewy body diseases with focus on dementia with Lewy bodies. Brain Pathol. https://doi.org/10.1111/bpa.12511

Simon-Sanchez, J., Scholz, S., Fung, H.-C., Matarin, M., Hernandez, D., Gibbs, J.R., Britton, A., de Vrieze, F.W., Peckham, E., Gwinn-Hardy, K., Crawley, A., Keen, J.C., Nash, J., Borgaonkar, D., Hardy, J., Singleton, A., 2007. Genome-wide SNP assay reveals structural genomic variation, extended homozygosity and cell-line induced alterations in normal individuals. Hum. Mol.

Genet. 16, 1–14.
Skoglund, L., Ingvast, S., Matsui, T., Freeman, S.H., Frosch, M.P., Brundin, R., Giedraitis, V., Growdon, J.H., Hyman, B.T., Lannfelt, L., Ingelsson, M., Glaser, A., 2009. No evidence of PGRN or MAPT gene dosage alterations in a collection of patients with frontotemporal lobar degeneration. Dement. Geriatr. Cogn. Disord. 28, 471–475.
Sleegers, K., Brouwers, N., Gijselinck, I., Theuns, J., Goossens, D., Wauters, J., Del-Favero, J., Cruts, M., van Duijn, C.M., Van Broeckhoven, C., 2006. APP duplication is sufficient to cause early onset Alzheimer's dementia with cerebral amyloid angiopathy. Brain 129, 2977–2983.
Spillantini, M.G., Schmidt, M.L., Lee, V.M., Trojanowski, J.Q., Jakes, R., Goedert, M., 1997. Alpha-synuclein in Lewy bodies. Nature 388, 839–840.
Stefansson, H., Rujescu, D., Cichon, S., Pietiläinen, O.P.H., Ingason, A., Steinberg, S., Fossdal, R., Sigurdsson, E., Sigmundsson, T., Buizer-Voskamp, J.E., Hansen, T., Jakobsen, K.D., Muglia, P., Francks, C., Matthews, P.M., Gylfason, A., Halldorsson, B.V., Gudbjartsson, D., Thorgeirsson, T.E., Sigurdsson, A., Jonasdottir, A., Jonasdottir, A., Bjornsson, A., Mattiasdottir, S., Blondal, T., Haraldsson, M., Magnusdottir, B.B., Giegling, I., Möller, H.-J., Hartmann, A., Shianna, K.V., Ge, D., Need, A.C., Crombie, C., Fraser, G., Walker, N., Lonnqvist, J., Suvisaari, J., Tuulio-Henriksson, A., Paunio, T., Toulopoulou, T., Bramon, E., Di Forti, M., Murray, R., Ruggeri, M., Vassos, E., Tosato, S., Walshe, M., Li, T., Vasilescu, C., Mühleisen, T.W., Wang, A.G., Ullum, H., Djurovic, S., Melle, I., Olesen, J., Kiemeney, L.A., Franke, B., GROUP, Sabatti, C., Freimer, N.B., Gulcher, J.R., Thorsteinsdottir, U., Kong, A., Andreassen, O.A., Ophoff, R.A., Georgi, A., Rietschel, M., Werge, T., Petursson, H., Goldstein, D.B., Nöthen, M.M., Peltonen, L., Collier, D.A., St Clair, D., Stefansson, K., 2008. Large recurrent microdeletions associated with schizophrenia. Nature 455, 232–236.
Swaminathan, S., Kim, S., Shen, L., Risacher, S.L., Foroud, T., Pankratz, N., Potkin, S.G., Huentelman, M.J., Craig, D.W., Weiner, M.W., Saykin, A.J., The Alzheimer's Disease Neuroimaging Initiative Adni, 2011. Genomic Copy Number Analysis in Alzheimer's Disease and Mild Cognitive Impairment: An ADNI Study. Int. J. Alzheimers. Dis. 2011, 729478.
Swaminathan, S., Shen, L., Kim, S., Inlow, M., West, J.D., Faber, K.M., Foroud, T., Mayeux, R., Saykin, A.J., Alzheimer's Disease Neuroimaging Initiative, NIA-LOAD/NCRAD Family Study Group, 2012. Analysis of copy number variation in Alzheimer's disease: the NIALOAD/ NCRAD Family Study. Curr. Alzheimer Res. 9, 801–814.
Wang, K., Li, M., Hadley, D., Liu, R., Glessner, J., Grant, S.F.A., Hakonarson, H., Bucan, M., 2007. PennCNV: an integrated hidden Markov model designed for high-resolution copy number variation detection in whole-genome SNP genotyping data. Genome Res. 17, 1665–1674.
Waters, C.H., Miller, C.A., 1994. Autosomal dominant Lewy body parkinsonism in a four-generation family. Ann. Neurol. 35, 59–64.
Webb, J.L., Ravikumar, B., Atkins, J., Skepper, J.N., Rubinsztein, D.C., 2003. Alpha-Synuclein is degraded by both autophagy and the proteasome. J. Biol. Chem. 278, 25009–25013.
Weiss, L.A., Shen, Y., Korn, J.M., Arking, D.E., Miller, D.T., Fossdal, R., Saemundsen, E., Stefansson, H., Ferreira, M.A.R., Green, T., Platt, O.S., Ruderfer, D.M., Walsh, C.A., Altshuler, D., Chakravarti, A., Tanzi, R.E., Stefansson, K., Santangelo, S.L., Gusella, J.F., Sklar, P., Wu, B.-L., Daly, M.J., Autism Consortium, 2008. Association between microdeletion and microduplication at 16p11.2 and autism. N. Engl. J. Med. 358, 667–675.
Zheng, X., Demirci, F.Y., Barmada, M.M., Richardson, G.A., Lopez, O.L., Sweet, R.A., Kamboh, M.I., Feingold, E., 2015. Genome-wide copy-number variation study of psychosis in Alzheimer's disease. Transl. Psychiatry 5, e574.
Zheng, X., Demirci, F.Y., Barmada, M.M., Richardson, G.A., Lopez, O.L., Sweet, R.A., Kamboh, M.I., Feingold, E., 2014. A rare duplication on chromosome 16p11.2 is identified in patients with psychosis in Alzheimer's disease. PLoS One 9, e111462.

A comprehensive screening of copy-number variability in dementia with Lewy bodies

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18 - UK Dementia Research Institute at UCL, London UK, Department of Molecular Neuroscience, UCL Institute of Neurology, London, UK and Clinical Neurochemistry Laboratory, Institute of Neuroscience and Physiology, Sahlgrenska Academy at the University of Gothenburg, Molndal, Sweden

19 - Human Genetics, School of Life Sciences, Queens Medical Centre, University of Nottingham, Nottingham, UK

20 - Department of Basic and Clinical Neuroscience and Institute of Psychiatry, Psychology and Neuroscience, Kings College London, London, UK

21 - Queen Square Brain Bank, Department of Molecular Neuroscience, UCL Institute of Neurology, London, UK

22 - Queen Square Brain Bank, Department of Molecular Neuroscience, UCL Institute of Neurology, London, UK and Movement Disorders Unit, Neurology Service, Clinical Neuroscience Institute (ICN), Hospital Clinic, University of Barcelona, IDIBAPS, Barcelona, Spain

23 - Department of Pathology and Laboratory Medicine, Center for Neurodegenerative Disease Research, Perelman School of Medicine at the University of Pennsylvania, 3600 Spruce Street, Philadelphia, USA

24 - Banner Sun Health Research Institute, 10515 W Santa Fe Drive, Sun City, AZ 85351, USA

25 - Inserm U1127, CNRS UMR7225, Sorbonne Universites, UPMC Univ Paris 06, UMR and S1127, Institut du Cerveau et de la Moelle epiniere, Paris, France

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27 - Department of Neurosciences, University of California, San Diego, La Jolla, CA, United States; Department of Pathology, University of California, San Diego, La Jolla, CA, United States

28 - Neurology Service, University of Coimbra Hospital, Coimbra, Portugal

29 - Memory Unit, Department of Neurology, University Hospital Mutua de Terrassa, University of Barcelona, and Fundacio de Docencia I Recerca Mutua de Terrassa, Terrassa, Barcelona, Spain. Centro de Investigacion Biomedica en Red Enfermedades Neurdegenerativas (CIBERNED), Madrid, Spain

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31 - Department of Pathology, Haartman Institute, University of Helsinki and HUSLAB

32 - Department of Neuropathology and Neurosurgery, Helsinki University Hospital and University of Helsinki, Helsinki, Finland

33 - Neurology Department, Mayo Clinic, Rochester, MN, USA

34 - Department of Psychiatry and Department of Psychology, Mayo Clinic, Jacksonville, FL, USA

35 - MRC Centre for Neuropsychiatric Genetics and Genomics, School of Medicine, Cardiff University, Cardiff, UK

36 - Department of Neurology, Mayo Clinic, Jacksonville, FL, USA

37 - Knight Alzheimers Disease Research Center, Department of Neurology, Washington University School of Medicine, Saint Louis, MO, USA

38 - Institute of Brain, Behaviour and Mental Health, Faculty of Medical and Human Sciences, University of Manchester, Manchester, UK

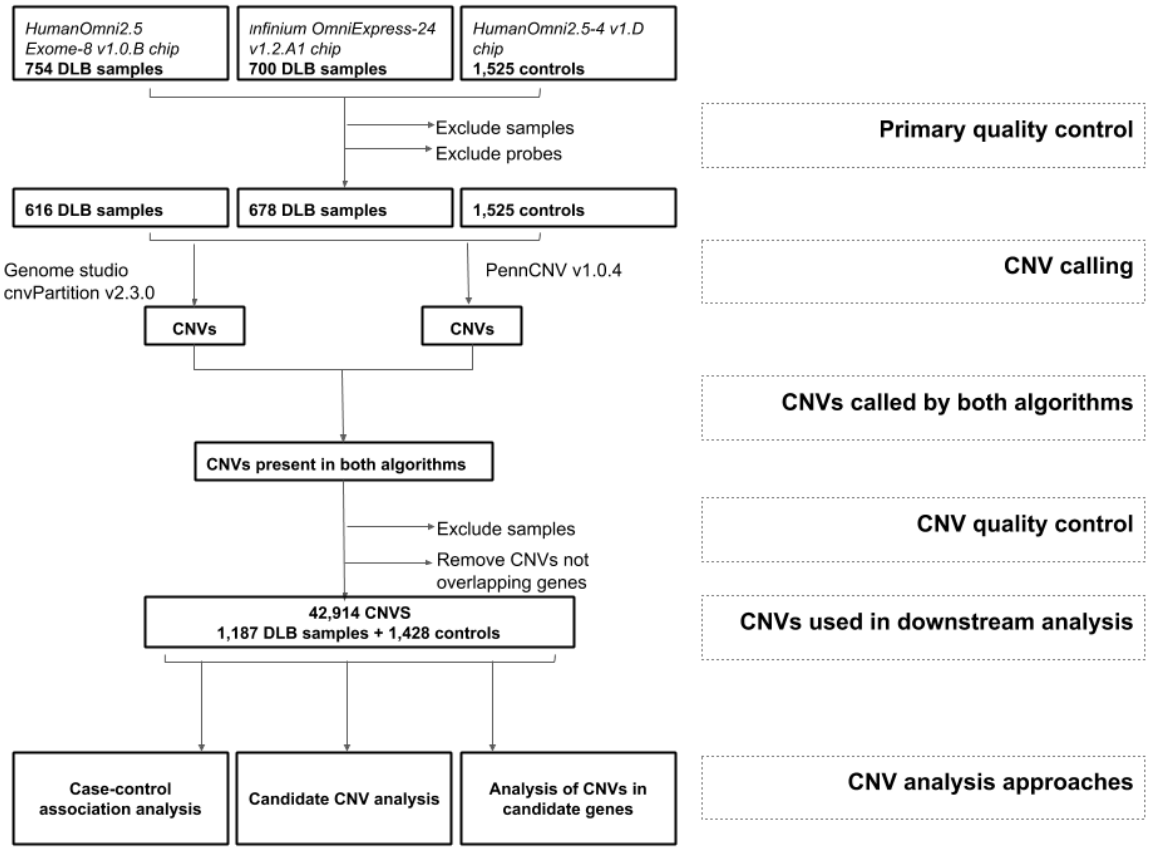
39 - Neuroscience Research Australia, Sydney, Australia and School of Medical Sciences, Faculty of Medicine, University of New South Wales,Sydney, Australia

40 - Brain and Mind Centre, Sydney Medical School, The University of Sydney, Sydney, Australia

41 - Genetics and Pharmacogenomics, Merck Research Laboratories, West Point, Pennsylvania, USA

42 - Department of Medical Sciences and Institute of Biomedicine, iBiMED, University of Aveiro, 3810-193 Aveiro, Portugal

Supplementary Figure 1. Study overview.



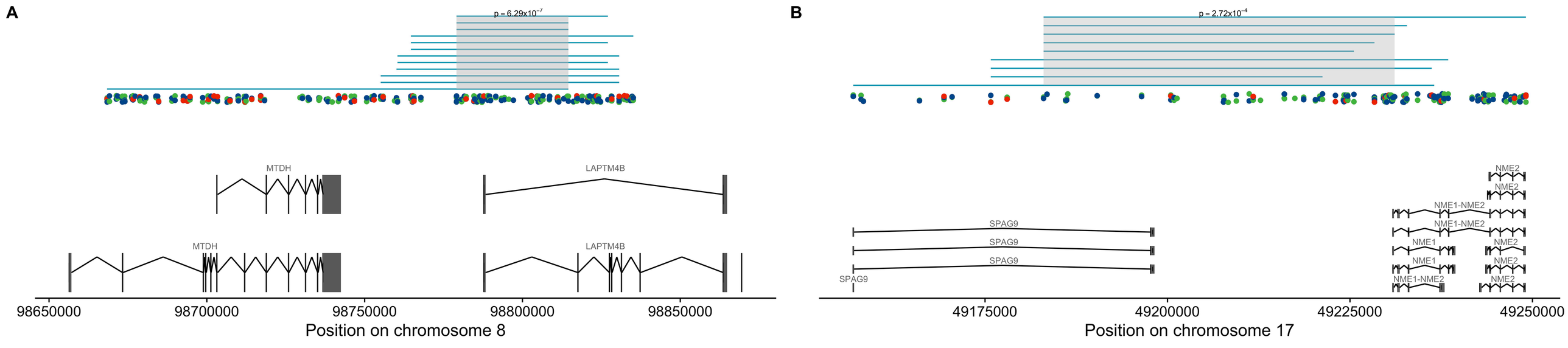
Overview of methods, quality control steps, samples and different analyses performed in this study.

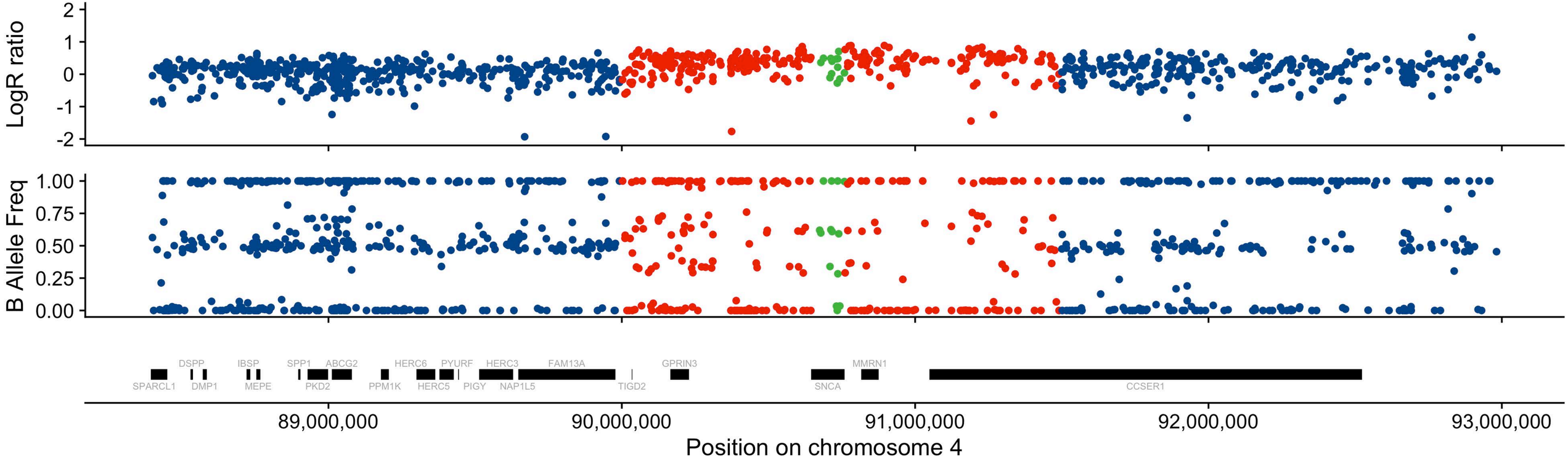
Supplementary Table 1. CNVs previously associated with AD, PD and FTD studied in the candidate CNVs approach.

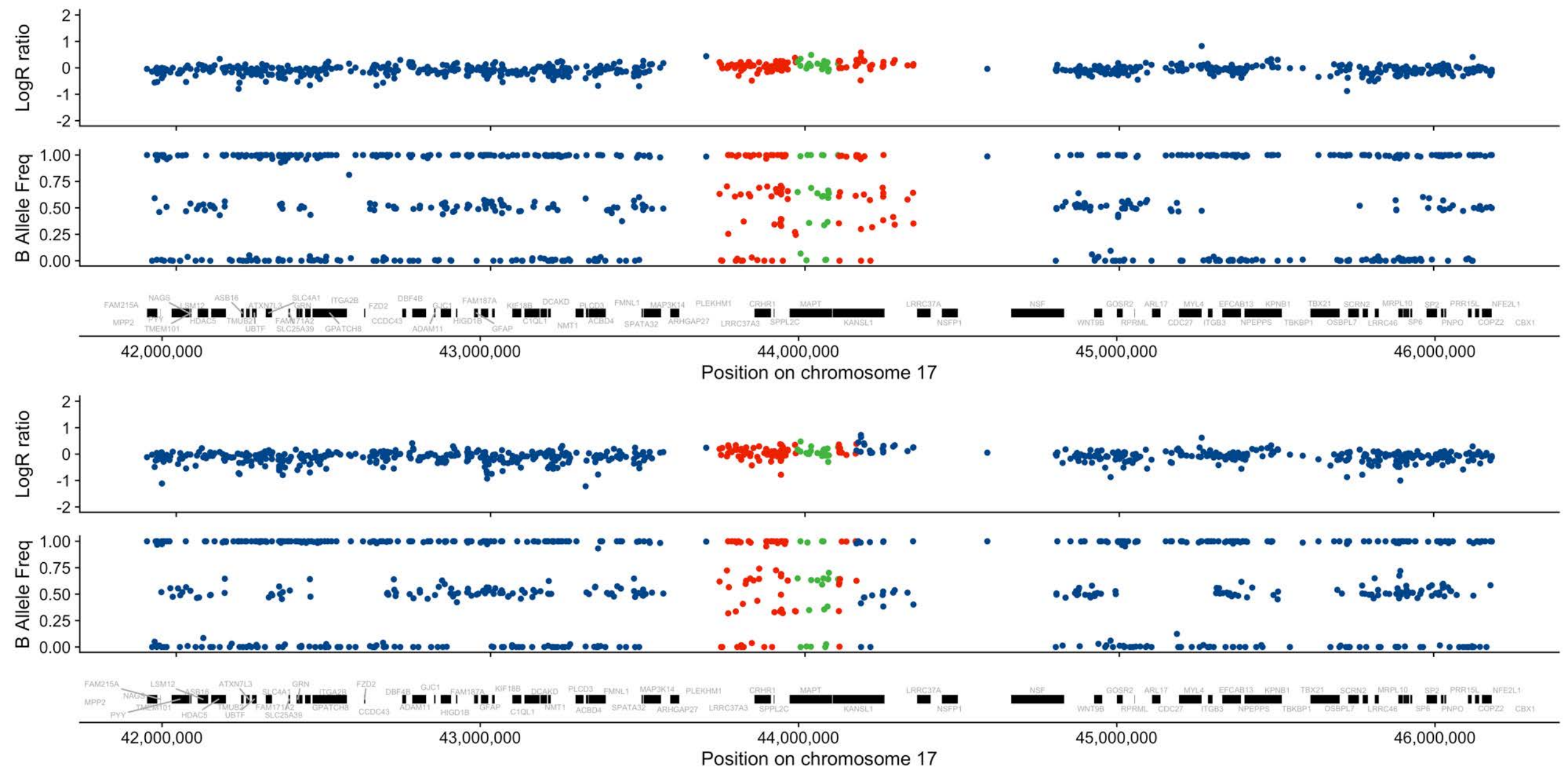
AD		
15q11.2	Ghani et al., 2012	*CYFIP1,NIPA1,NIPA2,TUBGCP5, WHAMML1*
15q13.3	Heinzen et al., 2010	*CHRNA7*
APC2	Zheng et al., 2015	
chr16:29,554,843-30,105,652	Zheng et al., 2014	*ASPHD1,ALDOA,BOLA2,C16orf54, C16orf92,CDIPT,CDIPT-AS1,DOC2A, FAM57B,HIRIP3,INO80E,KCTD13,KIF22, MAZ,MVP,PAGR1,PPP4C,PRRT2, QPRT,SEZ6L2,SPN,TAOK2,TBX6, TMEM219,YPEL,ZG16*
CHRFAM7A	Swaminathan et al., 2011	
CNTLN	Zheng et al., 2015	
CSMD1	Swaminathan et al., 2011	
HLA-DRA	Swaminathan et al., 2012	
HNRNPCL1	Swaminathan et al., 2011	
JAG2	Zheng et al., 2015	
SET	Zheng et al., 2015	
ZFPM1	Zheng et al., 2015	
PD		
22q11.2	Mok et al., 2016	
DOCK5	Pankratz et al., 2011	
OVOS2	Liu et al., 2013	
TH	Bademci et al., 2010	
USP32	Pankratz et al., 2011	
FTD		
RUNDC3A	Gijselinck et al., 2008	
SLC25A39	Gijselinck et al., 2008	

Supplementary Table 2. Genes previously associated with DLB-related diseases and studied in the candidate genes approach.

AD						
APP	PSEN1	PSEN2	APOE	TREM2	CLU	PICALM
CR1	BIN1	MS4A6A	MS4A4E	CD33	ABCA7	CD2AP
EPHA1	HLA-DRB5	HLA-DRB1	SORL1	PTK2B	SLC24A4	ZCWPW1
CELF1	FERMT2	CASS4	INPP5D	MEF2C	NME8	
PD						
SNCA	PARK2	PINK1	PARK7/DJ-1	LRRK2	PLA2G6	FBXO7
VPS35	ATP13A2	DNAJC6	SYNJ1	GBA	MAPT	RAB7L1
BST1	GAK	ACMSD	STK39	SYT11	FGF20	STX1B
GPNMB	SIPA1L2	INPP5F	MIR4697HG	GCH1	VPS13C	DDRGK1
MCCC1	SCARB2	CCDC62	RIT2	SREBF1		
FTD						
GRN	CHMP2B	HNRNPA1	HNRNPA2B1	SQSTM1	OPTN	CHCHD10
VCP	SIGMAR1	PRKAR1B	TMEM106B	UBQLN2	ATXN2	
DLB						
CNTN1	CYP2D6	EIF4G1	BCL7C/STX1B	GABRB3	GIGYF2	PRNP
SNCB	SOX17					
Additional genes						
ANG	CCNF	CSF1R	CSF1R	CTSC	CYLD	DCTN1
FUS	GLE1	ITM2B	MATR3	NEK1	NOTCH3	PFN1
PNPLA6	RAB38	SERPINI1	SERPINI1	SOD1	TAF15	TARDBP
TBK1	TIA1	TUBA4A	TYROBP	VAPB		


A
p = 6.29x10−7
MTDH
LAPTM4B
MTDH
LAPTM4B
98650000
98700000
98750000
98800000
98850000
Position on chromosome 8
B
p = 2.72x10−4
SPAG9
SPAG9
SPAG9
SPAG9
NME2
NME2
NME1-NME2
NME1-NME2
NME1
NME2
NME1
NME2
NME1-NME2
NME2
49175000
49200000
49225000
49250000
Position on chromosome 17


LogR ratio
2
1
0
-1
-2
B Allele Freq
1.00
0.75
0.50
0.25
0.00
DSPP
IBSP
SPP1
ABCG2
HERC6
PYURF
HERC3
FAM13A
GPRIN3
MMRN1
SPARCL1
DMP1
MEPE
PKD2
PPM1K
HERC5
PIGY
NAP1L5
TIGD2
SNCA
CCSER1
89,000,000
90,000,000
91,000,000
92,000,000
93,000,000
Position on chromosome 4


LogR ratio
2
1
0
-1
-2
B Allele Freq
1.00
0.75
0.50
0.25
0.00
FAM215A
NAGS
LSM12
ASB16
ATXN7L3
SLC4A1
GRN
ITGA2B
FZD2
DBF4B
GJC1
FAM187A
KIF18B
DCAKD
PLCD3
FMNL1
MAP3K14
PLEKHM1
CRHR1
MAPT
LRRC37A
NSF
GOSR2
ARL17
MYL4
EFCAB13
KPNB1
TBX21
SCRN2
MRPL10
SP2
PRR15L
NFE2L1
MPP2
PYY
HDAC5
TMUB2
FAM171A2
CCDC43
HIGD1B
C1QL1
ACBD4
SPATA32
ARHGAP27
LRRC37A3
SPPL2C
KANSL1
NSFP1
WNT9B
RPRML
CDC27
ITGB3
NPEPPS
TBKBP1
OSBPL7
LRRC46
SP6
PNPO
COPZ2
CBX1
TMEM101
UBTF
SLC25A39
GPATCH8
ADAM11
GFAP
NMT1
42,000,000
43,000,000
44,000,000
45,000,000
46,000,000
Position on chromosome 17