

## **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 rare CNVs in genes previously associated with DLB or related neurodegenerative diseases, such as *SNCA*, *APP* and *MAPT*. To our knowledge, this is the first study reporting genome-wide CNVs in a large DLB cohort. These results provide preliminary evidence for the contribution of CNVs in DLB risk.

## 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 neurodegenerative disease 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; Peuralinna et al., 2015). Exome sequencing studies have been performed in small cohorts; as have case studies and Sanger sequencing of specific target genes (Clark et al., 2009; Geiger et al., 2016; 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 (100-600kb) 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 analysed 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*, *PARK2*, *PINK1* and *PARK7* (Bonifati et al., 2003; Chartier-Harlin et al., 2004; Ibáñez et al., 2004; Lesage et

al., 2008; Marongiu et al., 2007; 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](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. Chromosome Y SNPs were not analysed.

### 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 (Mok et al., 2016). CNVs were excluded if they were overlapping telomeres, centromeres, known segmental duplications, the immunoglobulin or 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  $3 \times SD + \text{median}$  were excluded (Marshall et al., 2017; Need et al., 2009).

To identify potentially pathogenic CNVs, we analysed 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 ( $p\text{-value} < 5 \times 10^{-4}$  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 on 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. All samples carrying CNVs were confirmed to be of European/North American ancestry by merging their data with that of 1000Genomes.

### 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: the deletion overlapping *LAPTM4B* ( $p=6.29 \times 10^{-7}$ ) and the one overlapping *SPAG9-NME1-NME2* ( $p=2.72 \times 10^{-4}$ ) (**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 patient 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  $1.69 \times 10^{-4}$  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). *CSMD1* has frequent deletions and duplications spanning the whole gene as reported in DGV. Our results agree with this: at this locus, we identified over 100 deletions in cases and controls. One region in

the gene has a deletion in 3 cases and in no controls and this CNV showed a suggestive significance in our DLB case-control association analysis. Therefore we only report this shorter region in **Table 1**.

### 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 DLB subjects 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 were homozygous. A duplication including *CHCHD10* was also identified in a neuropathologically diagnosed DLB patient. No CNVs were identified in *GBA*, the gene presenting the strongest association with DLB.

## 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). 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). 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. In fact, a strong GWAS hit for DLB is *GBA*, a gene involved in lysosomal lipid storage disorders.

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 of *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 analysed genes known to have a role in DLB and DLB-related diseases we identified several CNVs of potential 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 has 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. However, the frequency reported in DGV results from two entries in that database. When looking in more detail at these two entries, they are actually duplicated entries from 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 particularly 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 and/or Amyotrophic Lateral Sclerosis (Zhang et al., 2015). However, given that disease associated *CHCHD10* mutations are loss-of-function (Perrone et al., 2017), it is not clear, whether a duplication of the gene would be pathogenic.

*GABRB3* is a gamma-aminobutyric acid (GABA) receptor that was reported to be associated with DLB in a recent GWAS, but 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. Given the GWAS results mentioned above, the CNV detected here and the fact that GABA receptor neurotransmission is altered in DLB (Santpere et al., 2017), it is tempting to speculate that 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) and is a well-known genetic risk factor for PD. 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 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 A $\beta$  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 in the frequency of heterozygous CNVs overlapping *PARK2* 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 A $\beta$  pathology at autopsy (Hepp et al., 2016), and it has been suggested that A $\beta$  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 identified potential disease causing CNVs as well as potential novel candidate genes for DLB. Despite this, our results suggest that it is unlikely that CNVs play a significant role in the pathogenesis of DLB.

## **Disclosure statement**

The authors have no actual or potential conflicts of interest.

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## Figures captions

**Figure 1. 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.**

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.

## **Supplementary Figure**

### **Supplementary Figure 1. Study overview.**

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

## **Supplementary Tables**

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

List of CNVs analysed in the candidate CNVs approach, respective references and genes.

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

List of the genes analysed in the candidate genes approach.

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