

## Heritability and genetic variance of dementia with Lewy bodies

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## ABSTRACT

Recent large-scale genetic studies have allowed for the first glimpse of the effects of common genetic variability in dementia with Lewy bodies (DLB), identifying risk variants with appreciable effect sizes. However, it is currently well established that a substantial portion of the genetic heritable component of complex traits is not captured by genome-wide significant SNPs. To overcome this issue, we have estimated the proportion of phenotypic variance explained by genetic variability (SNP heritability) in DLB using a method that is unbiased by allele frequency or linkage disequilibrium properties of the underlying variants. This shows that the heritability of DLB is nearly twice as high as previous estimates based on common variants only (31% vs 59.9%). We also determine the amount of phenotypic variance in DLB that can be explained by recent polygenic risk scores from either Parkinson's disease (PD) or Alzheimer's disease (AD), and show that, despite being highly significant, they explain a low amount of variance. Additionally, to identify pleiotropic events that might improve our understanding of the disease, we performed genetic correlation analyses of DLB with over 200 diseases and biomedically relevant traits. Our data shows that DLB has a positive correlation with education phenotypes, which is opposite to what occurs in AD. Overall, our data suggests that novel genetic risk factors for DLB should be identified by larger GWAS and these are likely to be independent from known AD and PD risk variants.

## 1. Introduction

Recent studies have highlighted the role of genetics in the common, but often underappreciated, form of dementia that is dementia with Lewy bodies (DLB). Associations with *GBA*, *APOE* and *SNCA* have all been reproducibly reported by independent groups (Bras et al., 2014; Hardy et al., 1994; Nalls et al., 2013), and a recent genome-wide association study (GWAS) identified several risk and candidate variants associated with the disease (Guerreiro et al., 2018). However, GWAS significant single nucleotide polymorphisms (SNPs) often explain only a small proportion of the total heritability estimated (usually from family-based studies) for a given trait, which results in the 'missing heritability' issue (Manolio et al., 2009). One of the possible explanations for this issue is that, for complex diseases, SNPs with small effect sizes and well below genome-wide statistical significance account for most of the heritability of those traits (Boyle et al., 2017; Lee et al., 2011; Yang et al., 2013). However, given that each individual associated marker explains only a small proportion of the genetic variation with little predictive power, methods have been developed to test disorder prediction by summarizing variation across many loci (regardless of association *p*-values) into quantitative scores. One such approach is the generation of polygenic risk scores (PRSs). PRSs have been successfully applied to Parkinson's (PD) (Escott-Price et al., 2015a) and Alzheimer's diseases (AD) (Escott-Price et al., 2015b) and their usefulness will continue to increase as discovery datasets are augmented.

A separate, but related, concept is that of genetic correlation of traits. Here, what is estimated is the genetic covariance between traits that is tagged by common genome-wide SNPs (Lee et al., 2012). This allows us to identify pleiotropic effects between traits that might be unrelated by any other measurement. We have performed a preliminary

study of genetic correlation between DLB and both PD and AD (Guerreiro et al., 2016), however performing similar analyses with other (even apparently unrelated) traits might provide novel insights for the underlying pathobiology of disease and perhaps for treatments across diseases.

The phenotypic variance of most complex human traits combines the genetic with the environmental variance (Mackay, 2001). While the effects of the environment are difficult to ascertain given their complexity and lack of adequate measurements, we are able to determine the genetic variance more accurately. Classically, genetic variance has been partitioned into sources of variation due to additive, dominance and epistatic effects. Additive genetic variance ( $h_{SNP}^2$ ) relates to an allele's independent effect on a phenotype; dominance variance ( $\delta_{SNP}^2$ ) refers to the effect on a phenotype caused by interactions between alternative alleles at a specific locus; epistatic variance refers to the interaction between different alleles in different loci. Most available cohorts for studies of human biology and disease are still underpowered to identify epistatic events, however, additive and dominance variance can be estimated from standard genome-wide genotyping data (Zhu et al., 2015).

Here, using data from the first GWAS in DLB that included haplotype reference consortium (HRC)-imputed genotypes (McCarthy et al., 2016), we have estimated the total heritability of this disease. We used a method (GCTA-LDMS) that is unbiased regardless of the minor allele frequency (MAF) and linkage disequilibrium (LD) properties of variants and thus greatly improves on previous estimates (Yang et al., 2015). Since it has been suggested that heritability estimates may be inflated by non-additive variation (Eichler et al., 2010), we have also estimated the dominance genetic variation in DLB. Additionally, to measure the proportion of variance explained by PRSs from PD and AD in a large

DLB cohort, we measured the ability of PRS to discriminate case from control subjects. Lastly, to attempt to derive novel biological insights from unrelated traits, we have performed pairwise genetic correlation analysis of DLB with 235 phenotypes, including cognitive, anthropometric and education traits.

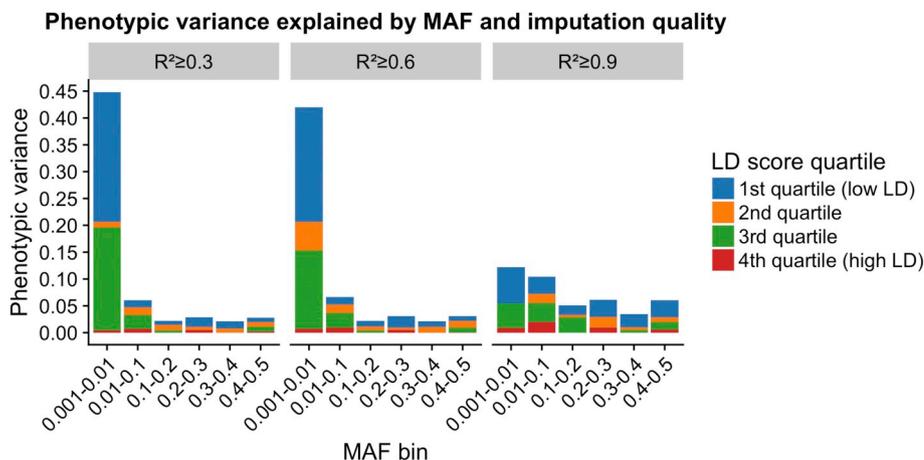
## 2. Materials and methods

### 2.1. Sample description

The DLB dataset was previously published (Guerreiro et al., 2018) and is comprised of 1216 cases and 3791 controls matched for ancestry, imputed with HRC v1.1 and includes variants with minor allele frequency  $\geq 0.001$  and  $R^2 \geq 0.3$ , for a total number of 18.4 million variants (median  $R^2 = 0.92$ ). We used AD summary statistics from the International Genomics of Alzheimer's Project (IGAP) (Lambert et al., 2013), which is a large two-stage study based upon genome-wide association studies (GWAS) on individuals of European ancestry. In stage 1, IGAP used genotyped and imputed data on 7,055,881 single nucleotide polymorphisms (SNPs) to meta-analyse four previously-published GWAS datasets consisting of 17,008 Alzheimer's disease cases and 37,154 controls (the European Alzheimer's disease Initiative – EADI the Alzheimer's disease Genetics Consortium – ADGC, the Cohorts for Heart and Aging Research in Genomic Epidemiology consortium – CHARGE, the Genetic and Environmental Risk in AD consortium – GERAD). PD summary statistics were derived from the International Parkinson's Disease Genomics Consortium (IPDGC) previously published data and included 13,708 cases and 95,282 controls (Nalls et al., 2014).

### 2.2. DLB heritability estimates

We used the GCTA-LDMS method to estimate heritability based on imputed data (Yang et al., 2015; Yang et al., 2011) using an imputation quality above 0.3 and a disease prevalence of 0.1%. This method considers the LD-bias that occurs in the SNP-based estimates and is unbiased regardless of the properties of the underlying variants. We calculated segment-based LD scores using a segment length of 200 kb (with 100 kb overlap between two adjacent segments), which were used to stratify the SNPs into quartiles. We then estimated the genetic relationship matrix (GRM) for each sample using the SNPs in each quartile separately and further stratified by minor allele frequency bins (0.001–0.01, 0.01–0.1, 0.1–0.2, 0.2–0.3, 0.3–0.4, 0.4–0.5). Lastly, we performed restricted maximum likelihood (REML) analysis using the multiple GRMs.



**Fig. 1.** Estimate of the DLB variance explained by HRC-imputed variants by MAF and LD. Segmental LD score increases from the 1st to 4th quartiles. Negative scores are not shown for simplicity but are present in Supplementary Table 1. The estimates of variance explained are from the GREML-LDMS analyses of fitting all the 24 genetic components simultaneously.

### 2.3. DLB dominance variance estimates

To estimate the dominance GRM between pairs of individuals, we used genome-wide imputed SNPs as implemented in GCTA-GREMLd (Zhu et al., 2015). This method calculates the additive and dominance GRMs and fits both GRMs in a mixed linear model to estimate additive and dominance variance simultaneously.

### 2.4. PRS analyses

Determining the polygenic risk of a given phenotype and applying it to another trait is an approach that allows to determine shared genetic etiology between traits. We calculated PRSs on the base phenotypes (PD and AD), using GWAS summary statistics, and used these as predictors of the target phenotype (DLB) in a regression test. To construct and apply the PRSs we used PRSice v2.1 (Euesden et al., 2015). We performed clumping on the target data by retaining the SNP with the smallest  $p$ -value from each LD block (excluding SNPs with  $r^2 > 0.1$  in 250 kb windows). Each allele was weighted by its effect-size as estimated in the respective study (for PD and AD). Association of PRSs with case-control status was performed with logistic regression, and Nagelkerke's pseudo- $R^2$  was calculated to measure the proportion of variance explained.

### 2.5. Genetic correlation analysis

To estimate the genetic correlation between DLB and other complex traits and diseases, we used a method based on LD score regression and implemented in the online web utility LDHub v1.9.0 (Bulik-Sullivan et al., 2015; Zheng et al., 2017). The LD score regression method uses summary statistics from the DLB GWAS and the other available traits, calculates the cross-product of test statistics at each SNP, and then regresses the cross-product on the LD score. After identifying the most significant correlations for DLB ( $p < .01$ ), we estimated the correlation of those traits with PD and AD.

## 3. Results

### 3.1. Quantifying the genetic heritability of DLB

We applied the GREML-LDMS approach to estimate the proportion of phenotypic variance explained by the HRC-imputed variants for DLB. Results from this approach showed that imputed variants with  $R^2$  greater than or equal to 0.3 and frequency above 0.1% explained 59.9% (s.e. = 2.1%;  $p = 6.8 \times 10^{-6}$ ) of phenotypic variance for DLB. Lower frequency variants explained a large proportion of the phenotypic variance in DLB. This pattern was maintained for the higher quality

imputed variants as well (Fig. 1, Supplementary Table 1).

To determine if non-additive variance in DLB would explain a subset of the total disease heritability, we calculated the disease dominance variance as implemented in the tool GCTA-GREML. This method uses genome-wide data to estimate the additive and dominance genetic relationship matrices (GRMs) and fits both GRMs in a mixed linear model to estimate  $h_{SNP}^2$  and  $\delta_{SNP}^2$  simultaneously. Our results suggest that DLB does not show significant dominance variance with an overall estimate  $\delta_{SNP}^2 = -0.05$  (s.e. = 0.02).

### 3.2. Polygenic prediction of case-control status

We applied the PRSs derived from AD and PD data to determine if these would discriminate between DLB and controls. The AD score explained 1.33% of the variance (Nagelkerke's pseudo- $R^2$ ) and was highly significant ( $p = 5.8 \times 10^{-31}$ ). Performing the same analysis while excluding the *APOE* locus brought the estimate down to 0.14%, while reaching only nominal significance. Using the PD polygenic risk score, we obtained an estimate of 0.37% of the variance in DLB being explained by that score, a result that was also significant ( $p = 6.4 \times 10^{-10}$ ). Interestingly, removing the *GBA* locus resulted in only a small reduction in the variance explained by the PD PRS (0.36%,  $p = 1.23 \times 10^{-9}$ ) at the best  $p$ -value threshold.

The bar plots of DLB variance explained by the AD and PD polygenic risk scores are presented in Fig. 2.

### 3.3. Unbiased genetic correlation

To test whether DLB has a shared genetic etiology with any of 235 other diseases or biomedical relevant traits, we used LD score regression as implemented in LDHub (<http://ldsc.broadinstitute.org/ldhub/>). This method estimates the degree to which genetic risk factors are shared between pairs of diseases or traits, although it should be noted that it does not inform regarding how this shared genetic etiology arises. We selected the correlations with a  $p$ -value < .01 in DLB and tested these in AD and PD (Fig. 3).

The most significant correlation identified, and the only surpassing Bonferroni correction, between DLB and each of the 235 tested traits was with “Years of schooling” (Okbay et al., 2016) reaching a  $p$ -value of  $6.32 \times 10^{-5}$  (Bonferroni corrected  $p$ -value = .015) and a correlation estimate (rg) of 0.48 (s.e. = 0.12) (Table 2). Interestingly, these scores were found to be in the opposite direction in AD, but in the same direction in PD (AD: rg = -0.33,  $p$ -value =  $8.87 \times 10^{-5}$ ; PD: rg = 0.05,  $p$ -value = .07) (Fig. 3). A positive correlation was also obtained for “Childhood IQ” (Benyamin et al., 2014) in DLB and PD, whereas a negative correlation was identified in AD (DLB: 0.68,  $p$ -value = .0009; AD: rg = -0.36,  $p$ -value = .0011; PD: rg = 0.25,  $p$ -value = .0013). Similarly, “Intracranial volume” (Hibar et al., 2015) presented a positive correlation with both DLB and PD, but no discernible correlation with AD (DLB: 0.69,  $p$ -value = .0052; AD: rg = -0.003,  $p$ -value = .96; PD: rg = 0.34,  $p$ -value = .0005). Conversely, “Citrate” (Kettunen et al., 2016) was positively correlated with both DLB and AD, but had no

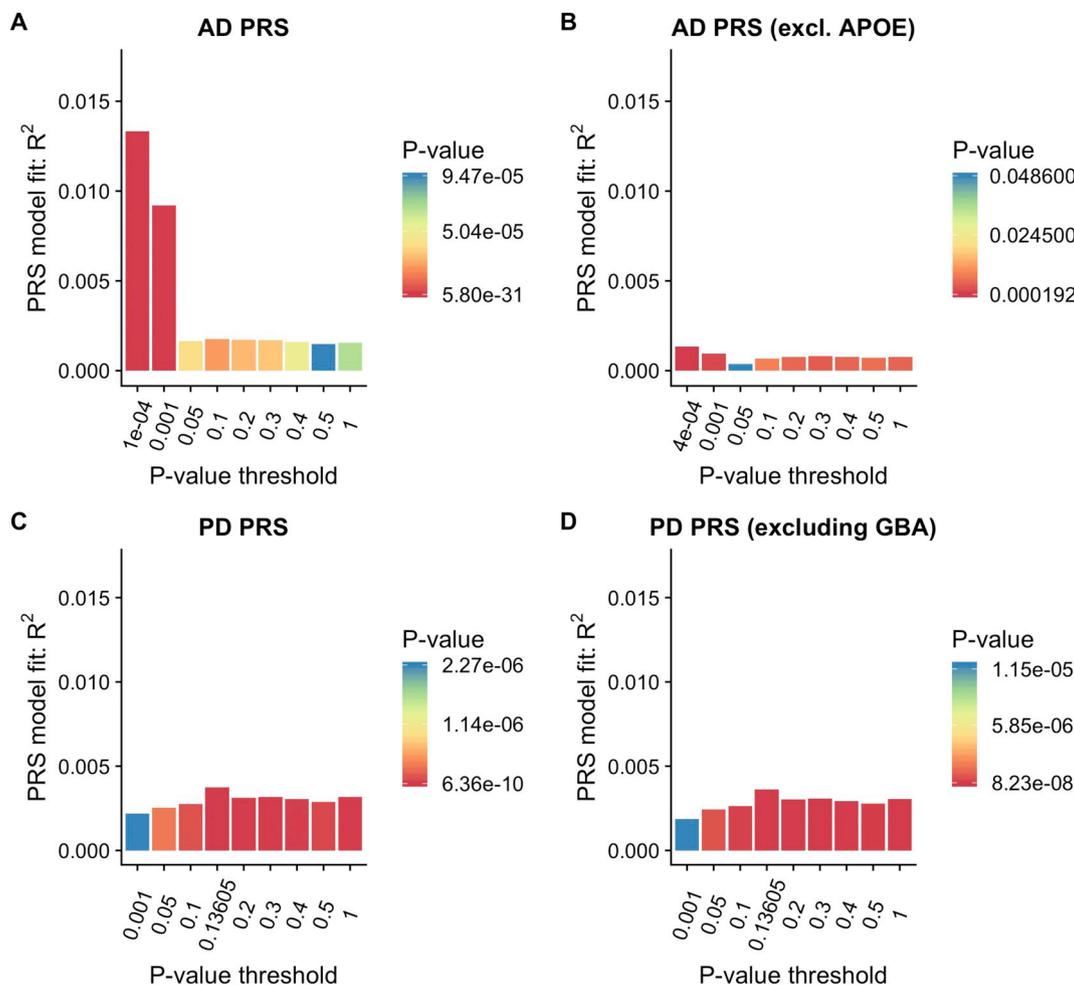


Fig. 2. Proportion of variance of DLB case-control status explained by PRSs from AD (A), AD excluding the *APOE* locus (B), PD (C) and PD excluding the *GBA* locus (D). The bars represent PRSs calculated for 9 subsets of markers at different  $p$ -value thresholds in the original GWAS publications. Best scores for each PRS are presented in (D).  $R^2$ : Nagelkerke's pseudo- $R^2$ ; Threshold:  $P$ -value threshold in original GWAS.

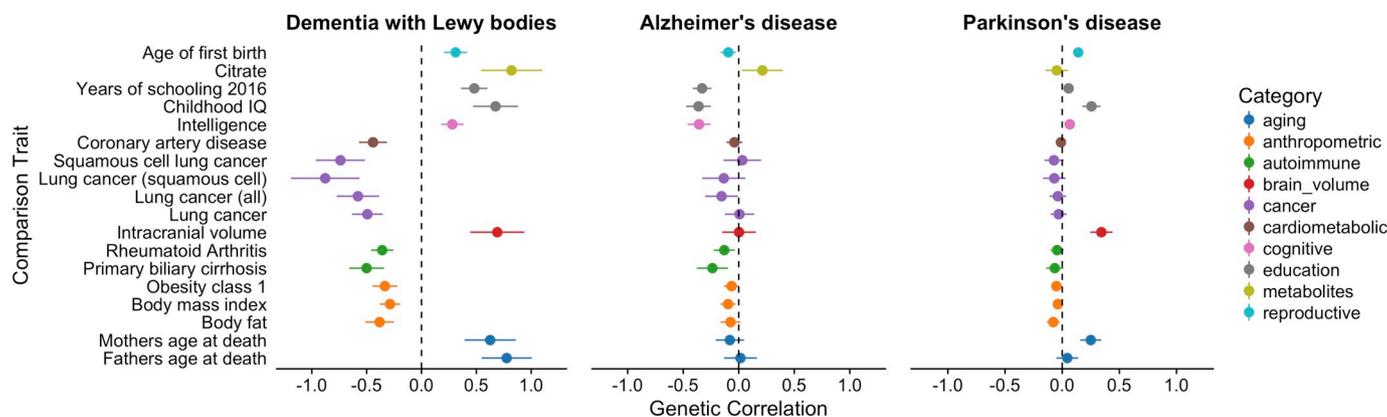


Fig. 3. Correlation scores with p-value < .01 in DLB. Shown are also the scores for those same traits in PD and AD.

correlation with PD (DLB: 0.82, p-value = .0033; AD: rg = -0.21, p-value = .25; PD: rg = -0.05, p-value = .63) (Table 1).

4. Discussion

With this study we provide more accurate estimates of genetic heritability for DLB, quantify the variance explained by AD and PD polygenic risk and estimate pleiotropy between DLB and over 200 diseases and biomedical relevant traits.

Previous heritability estimates for DLB were calculated based on a smaller cohort genotyped at a relatively smaller number of sites and using GCTA's GREML-SC (based on a single genetic relationship matrix). These earlier studies provided an estimate of 31% heritability for this disease (Guerreiro et al., 2016). It is now recognised that GREML-SC may, under certain circumstances (such as causal variants being enriched in regions with higher or lower LD than average or if the causal variants had a different MAF spectrum than the variants sampled), be biased (Yang et al., 2015). Because of this, we used a recently developed approach that corrects for the LD bias in the estimated SNP-based heritability and that is unbiased regardless of the properties (e.g.

MAF and LD) of the underlying causal variants (GCTA GREML-LDMS) (Yang et al., 2015). We applied this tool to a larger cohort, that was imputed with the most recent imputation panel, providing more detailed genetic information. Using this approach we estimated that all HRC-imputed variants with MAF > 0.001 explained 59.9% (s.e = 2.1%) of phenotypic variance for DLB, which is nearly double the previous estimate (Guerreiro et al., 2016). Our results also show that a large proportion of the variance is explained by variants with lower frequency (MAFs from 0.001 to 0.01). Given that the current version of HRC allows for imputation of variants with frequencies as low as 0.0005 and aggregate R<sup>2</sup> above 0.5 (McCarthy et al., 2016), this indicates that performing GWAS in DLB with increased sample sizes will allow us to identify novel loci involved in conferring risk for disease without the need for large-scale whole-genome sequencing.

One of the explanations for the common issue of “missing heritability” is that non-additive heritability (such as dominance variance or epistatic variance) represents a substantial component of a trait's total heritable genetic component. Our results suggest that dominance variance has a negligible effect on the genetic heritability of DLB, in line with findings from 79 unrelated traits (Zhu et al., 2015). However, we

Table 1 Significant genetic correlations for DLB, PD and AD.

Trait	Category	DLB			AD			PD		
		rg	s.e.	p-value	rg	s.e.	p-value	rg	s.e.	p-value
Fathers age at death; PMID:27015805	Aging	0.777	0.230	0.001						
Mothers age at death; PMID:27015805	Aging	0.626	0.234	0.007				0.250	0.092	0.007
Body fat; PMID:26833246	Anthropometric	-0.382	0.130	0.003						
Body mass index; PMID:20935630	Anthropometric	-0.287	0.093	0.002						
Height; Females at age 10 and males at age 12; PMID:23449627	Anthropometric				-0.282	0.107	0.008			
Obesity class 1; PMID:23563607	Anthropometric	-0.334	0.113	0.003						
Primary biliary cirrhosis; PMID:26394269	Autoimmune	-0.501	0.159	0.002						
Rheumatoid Arthritis; PMID:24390342	Autoimmune	-0.358	0.101	0.000						
ICV; PMID:25607358	Brain_volume	0.691	0.247	0.005				0.343	0.098	0.001
Mean Accumbens; PMID:25607358	Brain_volume							0.402	0.143	0.005
Mean Caudate; PMID:25607358	Brain_volume							0.266	0.075	0.000
Mean Putamen; PMID:25607358	Brain_volume							0.251	0.082	0.002
Lung cancer; PMID:27488534	Cancer	-0.493	0.141	0.001						
Lung cancer (all); PMID:24880342	Cancer	-0.579	0.193	0.003						
Lung cancer (squamous cell); PMID:24880342	Cancer	-0.878	0.313	0.005						
Squamous cell lung cancer; PMID:27488534	Cancer	-0.739	0.224	0.001						
Coronary artery disease; PMID:26343387	Cardiometabolic	-0.442	0.128	0.001						
Intelligence; PMID:28530673	Cognitive	0.281	0.102	0.006	-0.357	0.104	0.001			
Childhood IQ; PMID:23358156	Education	0.675	0.204	0.001	-0.362	0.111	0.001	0.256	0.080	0.001
College completion; PMID:23722424	Education				-0.364	0.100	0.000			
Years of schooling (proxy cognitive performance); PMID:25201988	Education				-0.300	0.081	0.000	0.138	0.048	0.004
Years of schooling 2013; PMID:23722424	Education				-0.290	0.092	0.002	0.137	0.048	0.005
Years of schooling 2016; PMID:27225129	Education	0.481	0.120	0.000	-0.330	0.084	0.000			
Citrate; PMID:27005778	Metabolites	0.821	0.280	0.003						
Isoleucine; PMID:27005778	Metabolites				-0.547	0.208	0.009			
Age of first birth; PMID:27798627	Reproductive	0.311	0.105	0.003				0.140	0.042	0.001

cannot exclude that epistatic variance plays a role in DLB, given that our cohort is underpowered to detect epistatic events.

Recently, there has been growing interest in the use of PRSs as a way to perform risk prediction in various diseases and these have successfully been applied to AD (Escott-Price et al., 2015b) and PD (Escott-Price et al., 2015a). To determine how much of the phenotypic variance in our DLB cohort can be caused by AD and PD known genetic risk factors, we used PRSs from recent GWAS from each of these diseases. In both cases scores explained only relatively small proportions of variance (0.37–1.33%). In AD, excluding the *APOE* locus greatly reduced the amount of variance explained in DLB (0.14%), which is in accordance with the strong effect that locus has in the risk of both diseases (Guerreiro et al., 2018; Lambert et al., 2013). Conversely, excluding the *GBA* locus in PD had only a modest effect, which likely results from the lower frequency in the general population of the variants that comprised this signal compared to *APOE*. Since the amount of variance explained by each of the PRS is relatively small, this adds to the growing body of evidence that suggests that, genetically, DLB is a unique condition and not simply a mix of PD and AD risk factors. These data also confirm the polygenic nature of DLB as well as quantify the amount of variance that polygenic risk from each of those diseases accounts for in DLB.

Given the large number of pleiotropic events that are being identified for a variety of diseases and traits (Guerreiro et al., 2014; Visscher et al., 2017), finding correlated conditions opens the door to a better understanding of disease pathobiology and perhaps may even suggest novel therapeutic targets. Assessing the genetic correlation of DLB with over 200 diseases and traits showed correlations that were in the same direction of those seen in PD while others were in the same direction as in AD. Due to the relatively small sample size in our cohort, the only correlation surpassing Bonferroni correction was for “Years of schooling”. It is interesting to note that these scores were positively correlated with DLB, while they have a well-established negative correlation with AD (Barnes and Yaffe, 2011; Norton et al., 2014). Similar positive correlations have been identified for bipolar disorder and autism spectrum disorders (Bulik-Sullivan et al., 2015), as well as for PD in the present data. Also in PD, there is evidence for the presence of increased intracranial volumes when compared to controls (Krabbe et al., 2005). Here, supporting those findings, we identify a positive genetic correlation between both PD and DLB (although not statistically significant) with intracranial volume, whereas in AD no evidence for genetic correlation was identified. Interestingly, the anthropometric characteristics obesity, body mass index (BMI) and body fat were negatively correlated with all 3 diseases. For BMI and PD, recent Mendelian randomization results have shown a negative effect (Noyce et al., 2017) which our results replicate and suggest they extend to both AD and DLB. A similar finding was obtained for cancer traits, where lung cancer showed a general negative correlation with the three traits. This agrees with transcriptomic studies that showed that the cancer gene expression profile is almost an opposite mirror image to that of neurodegenerative disease (Aramillo Irizar et al., 2018). A positive correlation between both DLB and AD with citrate (Kettunen et al., 2016) was identified, although this was not the case for PD, where no evidence of correlation was found. Increased plasma levels of citrate have been shown to be associated with increased levels of oxidative stress (Convertini et al., 2016), making it tempting to speculate that in AD and DLB oxidative stress may be involved in the neurodegenerative processes, while in PD it may be more akin to a consequence.

We note several limitations in our study. First, the DLB dataset, despite being the largest to date, is relatively small when compared to other recently published GWAS in PD or AD. This is reflected in a lower statistical power to identify novel associations; while the recent PD and AD GWAS were sufficiently powered to detect variants with effects as low as 1.4 and frequencies of only 1%, at this frequency, the DLB dataset is only sufficiently powered to detect variants with large effects of 3 and above. The lower statistical power is also reflected in the standard

errors of the analyses performed in this work. We are underpowered to detect rare variants and certainly rare variants with small effect sizes. Second, we are unable to provide definitive biological mechanisms underlying the genetic correlations identified. This means that it is possible that for some of the correlations observed, what we are seeing are proxy effects and not direct correlations. Lastly, this study focused on individuals of European/North American descent. It is likely that studies of populations of different ancestries will reveal not only novel loci, but perhaps also novel pleiotropic effects, which could improve our understanding of the pathobiology of DLB.

## 5. Conclusion

In summary, we provide updated estimates of the genetic heritability of DLB and show that dominance variance is not a substantial part of the heritability of this disease. We quantify the amount of phenotypic variance in DLB that can be attributed to PD and AD polygenic risk scores and show that this is relatively small. Lastly, we estimate genetic correlations between DLB and over 200 diseases and medically relevant traits, shedding light into the complex relationship between DLB and both PD and AD.

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## Conflict of interest statement

The authors report no conflicts of interest for this work.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.nbd.2019.04.004>.

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