Heritability and genetic variance of dementia with Lewy bodies

Rita Guerreiro[1, 2], Valentina Escott-Price[3], Dena G. Hernandez[4, 5], Celia Kun-Rodrigues[1], Owen A. Ross[6], Joao Neto[1, 2], Tatiana Orme[1, 2], Susana Carmona[1, 2], Nadia Dehghani[1, 2], John D. Eicher[7], Claire Shepherd[8], Laura Parkkinen[9], Lee Darwent[2, 1], Michael G. Heckman[10], Sonja W. Scholz[11, 12], Juan C. Troncoso[13], Olga Pletnikova[13], Ted Dawson[12], Liana Rosenthal[12], Olaf Ansorge[9], Jordi Clarimon[14], Alberto Lleo[14], Estrella Morenas-Rodriguez[14], Lorraine Clark[15], Lawrence S Honig[15], Karen Marder[15], Afina Lemstra[16], Ekaterina Rogaeva[17], Peter St. George-Hyslop[17, 18], Elisabet Londos[19], Henrik Zetterberg[20], Imelda Barber[21], Anne Braae[21], Kristelle Brown[21], Kevin Morgan[21], Claire Troakes[22], Safa Al-Sarraj[22], Tammaryn Lashley[23], Janice Holton[23], Yaroslau Compta[23, 24], Vivianna Van Deerlin[25], Geidy E Serrano[26], Thomas G Beach[26], Suzanne Lesage[27], Douglas Galasko[28], Eliezer Masliah[29], Isabel Santana[30], Pau Pastor[31], Monica Diez-Fairen[31], Miquel Aguilar[31], Pentti J. Tienari[32], Liisa Myllykangas[33], Minna Oinas[34], Tamas Revesz[23], Andrew Lees[23], Brad F Boeve[35], Ronald C. Petersen[35], Tanis J Ferman[36], Neill Graff-Radford[37], Nigel J. Cairns[38], John C. Morris[38], Stuart Pickering-Brown[39], David Mann[39], Glenda M. Halliday[40, 41], John Hardy[1], John Q. Trojanowski[25], Dennis W. Dickson[6], Andrew Singleton[4] for the International Parkinson's Disease Genomics Consortium, David J. Stone[42], Jose Bras[1, 2,]*

* Correspondence to: Jose Bras, PhD | UK Dementia Research Institute at UCL, University College London, UK | Email: j.bras@ucl.ac.uk

1 - Department of Neurodegenerative Diseases, UCL Institute of Neurology, London, UK
2 - UK Dementia Research Institute (UK DRI) at UCL, London, UK
3 - MRC Centre for Neuropsychiatric Genetics and Genomics, School of Medicine, Cardiff University, Cardiff, UK
4 - Laboratory of Neurogenetics, National Institutes on Aging, NIH, Bethesda, MD, USA
5 - German Center for Neurodegenerative Diseases (DZNE)-Tubingen
6 - Department of Neuroscience, Mayo Clinic, Jacksonville, FL, USA
7 - Genetics and Pharmacogenomics, Merck Research Laboratories, Boston, MA, USA
8 - Neuroscience Research Australia, Sydney, Australia and School of Medical Sciences, Faculty of Medicine, University of New South Wales, Sydney, Australia
9 - Nuffield Department of Clinical Neurosciences, Oxford Parkinsons Disease Centre, University of Oxford, Oxford, UK
10 - Division of Biomedical Statistics and Informatics, Mayo Clinic, Jacksonville, FL, USA
11 - Neurodegenerative Diseases Research Unit, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, Maryland, USA
12 - Department of Neurology, Johns Hopkins School of Medicine, Baltimore, MD, USA
13 - Department of Pathology (Neuropathology), Johns Hopkins University School of Medicine, Baltimore, MD, USA
14 - Memory Unit, Department of Neurology, IIB Sant Pau, Hospital de la Santa Creu i Sant Pau, Universitat Autonoma de Barcelona, Barcelona, Spain; Centro de Investigacion Biomedica

en Red en Enfermedades Neurodegenerativas (CIBERNED), Instituto de Salud Carlos III, Madrid, Spain
15 - Taub Institute for Alzheimer Disease and the Aging Brain and Department of Pathology and Cell Biology, Columbia University, New York, NY, USA
16 - Department of Neurology and Alzheimer Center, Neuroscience Campus Amsterdam, VU University Medical Center, Amsterdam, the Netherlands
17 - Tanz Centre for Research in Neurodegenerative Diseases and department of Medicine, University of Toronto, Ontario, Canada
18 - Department of Clinical Neurosciences, Cambridge Institute for Medical Research, University of Cambridge, Cambridge, UK
19 - Clinical Memory Research Unit, Institution of Clinical Sciences Malmo, Lund University, Sweden
20 - UK Dementia Research Institute at UCL, London UK, Department of Neurodegenerative Disease, UCL Institute of Neurology, London, UK and Clinical Neurochemistry Laboratory, Institute of Neuroscience and Physiology, Sahlgrenska Academy at the University of Gothenburg, Molndal, Sweden
21 - Human Genetics, School of Life Sciences, Queens Medical Centre, University of Nottingham, Nottingham, UK
22 - Department of Basic and Clinical Neuroscience and Institute of Psychiatry, Psychology and Neuroscience, Kings College London, London, UK
23 - Queen Square Brain Bank, Department of Molecular Neuroscience, UCL Institute of Neurology, London, UK
24 - 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
25 - 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
26 - Banner Sun Health Research Institute, 10515 W Santa Fe Drive, Sun City, AZ 85351, USA
27 - Inserm U1127, CNRS UMR7225, Sorbonne Universites, UPMC Univ Paris 06, UMR and S1127, Institut du Cerveau et de la Moelle epiniere, Paris, France
28 - Department of Neurosciences, University of California, San Diego, La Jolla, CA, United States; Veterans Affairs San Diego Healthcare System, La Jolla, CA, United States
29 - 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
30 - Neurology Service, University of Coimbra Hospital, Coimbra, Portugal
31 - Memory Unit, Department of Neurology, University Hospital Mutua de Terrassa, University of Barcelona, and Fundacion de Docencia I Rercerca Mutua de Terrassa, Terrassa, Barcelona, Spain. Centro de Investigacion Biomedica en Red Enfermedades Neurdegenerativas (CIBERNED), Madrid, Spain
32 - Molecular Neurology, Research Programs Unit, University of Helsinki, Department of Neurology, Helsinki University Hospital, Helsinki, Finland

33 - Department of Pathology, University of Helsinki and Helsinki University Hospital, Helsinki, Finland
34 - Department of Neuropathology and Neurosurgery, Helsinki University Hospital and University of Helsinki, Helsinki, Finland
35 - Neurology Department, Mayo Clinic, Rochester, MN, USA
36 - Department of Psychiatry and Department of Psychology, Mayo Clinic, Jacksonville, FL, USA
37 - Department of Neurology, Mayo Clinic, Jacksonville, FL, USA
38 - Knight Alzheimers Disease Research Center, Department of Neurology, Washington University School of Medicine, Saint Louis, MO, USA
39 - Institute of Brain, Behaviour and Mental Health, Faculty of Medical and Human Sciences, University of Manchester, Manchester, UK
40 - Neuroscience Research Australia, Sydney, Australia and School of Medical Sciences, Faculty of Medicine, University of New South Wales, Sydney, Australia
41 - Brain and Mind Centre, Sydney Medical School, The University of Sydney, Sydney, Australia
42 - Genetics and Pharmacogenomics, Merck Research Laboratories, West Point, Pennsylvania, USA

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 the 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 (X% vs. Y%). We also determine the amount of phenotypic variance in DLB that can be explained by recent polygenic risk scores from both Parkinson's disease (PD) and 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.

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 (1–3), and a recent genome-wide association study (GWAS) identified several risk and candidate variants associated with the disease (4). 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 (5). One of the possible explanations for this issue is that all common SNPs, regardless of their association p-value, contribute to the heritability of complex traits (6–8). 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) (9) and Alzheimer's diseases (AD) (10) 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 (11). This allows us to identify pleiotropic effects between traits that might be apparently unrelated. We have performed a preliminary study of genetic correlation between DLB and both PD and AD (12), 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 (13). 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^2_{SNP}) relates to an allele's independent effect on a phenotype; dominance variance (δ^2_{SNP}) 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 (14).

Here, using data from the first GWAS in DLB that included haplotype reference consortium (HRC)-imputed genotypes (15), 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 (16). Since it has been suggested that heritability estimates may be inflated by non-additive variation (17), 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.

Results

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%; $p=6.8\times10^{-6}$) 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 (Figure 1, Table 1). A traditional approach of analyzing the data only explained X% of the DLB phenotypic variance, we previously reported (ref).

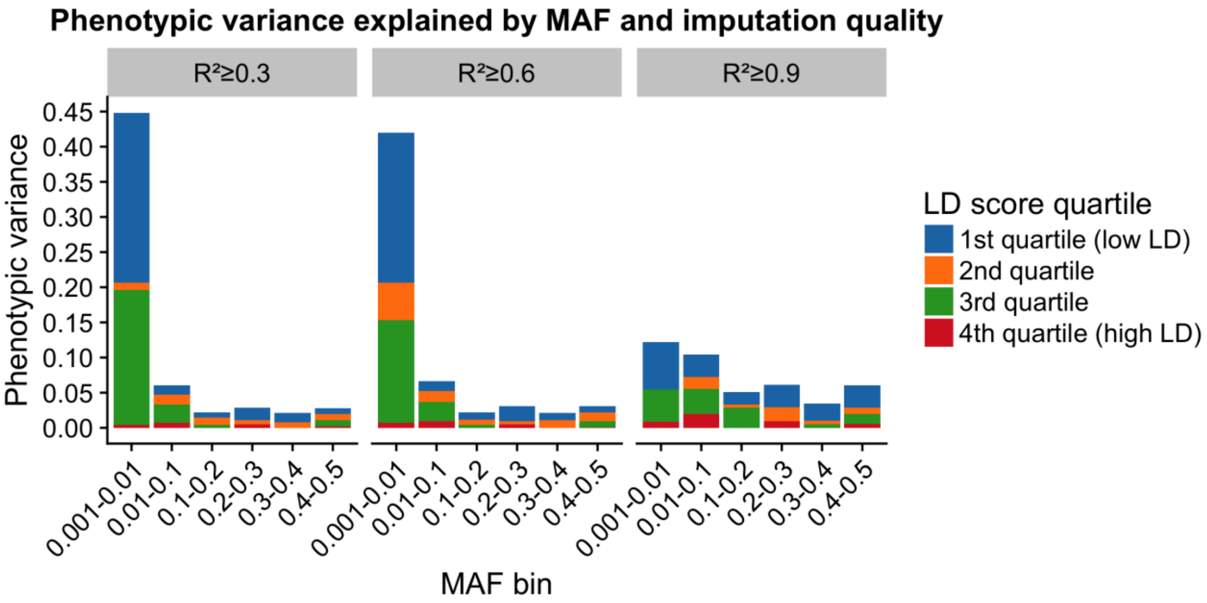


Figure 1: Estimate of the DLB variance explained by HRC-imputed variants by MAF and LD. Segmental LD score increases from the 1st to 4th quartiles. Negative scores are not shown for simplicity but are present in Table 1. The estimates of variance explained are from the GREML-LDMS analyses of fitting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

Table 1: Phenotypic variance explained at varying MAF bins, LD score quartiles and imputation quality

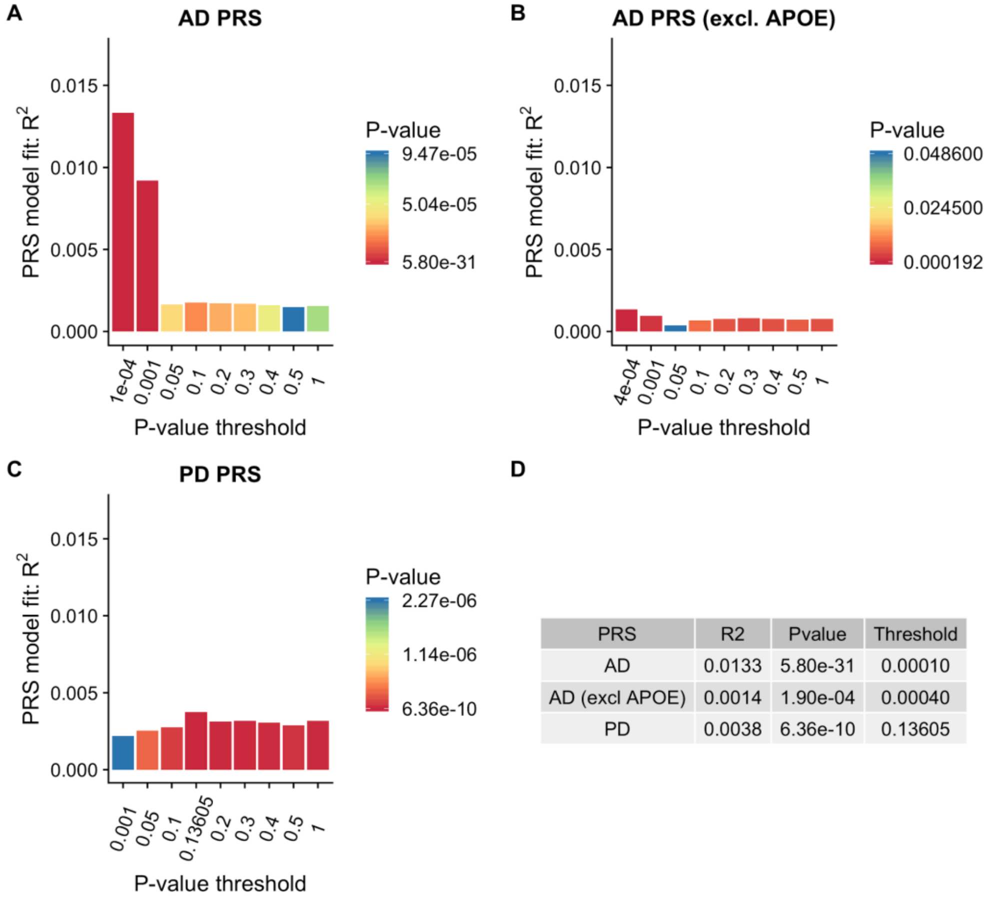
Minor allele frequency bin and LD score quartile	Imputation R^2>=0.3		Imputation R^2>=0.6		Imputation R^2>=0.9	
	Variance	s.e.	Variance	s.e.	Variance	s.e.

MAF 0.001-0.01; LD Score quartile 1	0.242	0.052	0.213	0.053	0.067	0.047
MAF 0.001-0.01; LD Score quartile 2	0.026	0.014	0.053	0.055	0	0.048
MAF 0.001-0.01; LD Score quartile 3	0.018	0.008	0.146	0.057	0.046	0.054
MAF 0.001-0.01; LD Score quartile 4	-0.003	0.005	0.007	0.041	0.009	0.039
MAF 0.01-0.1; LD Score quartile 1	0.011	0.057	0.014	0.014	0.032	0.019
MAF 0.01-0.1; LD Score quartile 2	0.007	0.01	0.016	0.014	0.017	0.017
MAF 0.01-0.1; LD Score quartile 3	0.006	0.007	0.027	0.014	0.036	0.016
MAF 0.01-0.1; LD Score quartile 4	-0.001	0.003	0.01	0.01	0.02	0.012
MAF 0.1-0.2; LD Score quartile 1	0.191	0.057	0.01	0.009	0.018	0.014
MAF 0.1-0.2; LD Score quartile 2	0.007	0.008	0.008	0.007	0.004	0.011
MAF 0.1-0.2; LD Score quartile 3	0	0.006	0.004	0.007	0.028	0.01
MAF 0.1-0.2; LD Score quartile 4	0.008	0.007	-0.005	0.004	-0.014	0.005
MAF 0.2-0.3; LD Score quartile 1	0.005	0.04	0.021	0.009	0.032	0.014
MAF 0.2-0.3; LD Score quartile 2	0.011	0.007	0.004	0.007	0.02	0.011
MAF 0.2-0.3; LD Score quartile 3	0.005	0.004	-0.002	0.006	-0.004	0.008
MAF 0.2-0.3; LD Score quartile 4	0.009	0.006	0.005	0.004	0.009	0.006
MAF 0.3-0.4; LD Score quartile 1	0.013	0.014	0.01	0.008	0.024	0.013
MAF 0.3-0.4; LD Score quartile 2	0.004	0.007	0.011	0.007	0.005	0.01
MAF 0.3-0.4; LD Score quartile 3	0.014	0.007	-0.006	0.005	0.005	0.008
MAF 0.3-0.4; LD Score quartile 4	0.009	0.005	0	0.004	-0.004	0.005
MAF 0.4-0.5; LD Score quartile 1	0.014	0.014	0.009	0.007	0.032	0.012
MAF 0.4-0.5; LD Score quartile 2	-0.005	0.004	0.013	0.006	0.009	0.009
MAF 0.4-0.5; LD Score quartile 3	0.008	0.006	0.009	0.005	0.014	0.008
MAF 0.4-0.5; LD Score quartile 4	0.002	0.003	0	0.003	0.006	0.005
N SNPs	7,818,430		6,568,910		3,027,853	
P-value	6.81E-06		8.11E-05		8.90E-02	
Total phenotypic variance	0.599	0.021	0.579	0.021	0.410	0.028

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-GREMLd. 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^2_{SNP} and δ^2_{SNP} simultaneously. Our results suggest that DLB does not show significant dominance variance with an overall estimate δ^2_{SNP}=-0.05 (s.e. = 0.02).

Polygenic Prediction of Case-Control Status

We applied the PRSs derived from AD and PD data, as well as the AD score excluding the *APOE* locus, to determine if these would discriminate between DLB and controls. The AD score explained 1.5% 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 0.4% of the variance in DLB being explained by that score, a result that was also significant ($p = 6.4 \times 10^{-10}$).



PRS	R2	Pvalue	Threshold
AD	0.0133	5.80e-31	0.00010
AD (excl APOE)	0.0014	1.90e-04	0.00040
PD	0.0038	6.36e-10	0.13605

Figure 2: Proportion of variance of DLB case-control status explained by PRSs from AD (A), AD excluding the *APOE* locus (B) and PD (C). 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.

The bar plots of DLB variance explained by the AD and PD polygenic risk scores are presented in Figure 2. As expected given these results, DLB cases had on average higher polygenic risk scores than control subjects for both PD and AD (Figure 3).

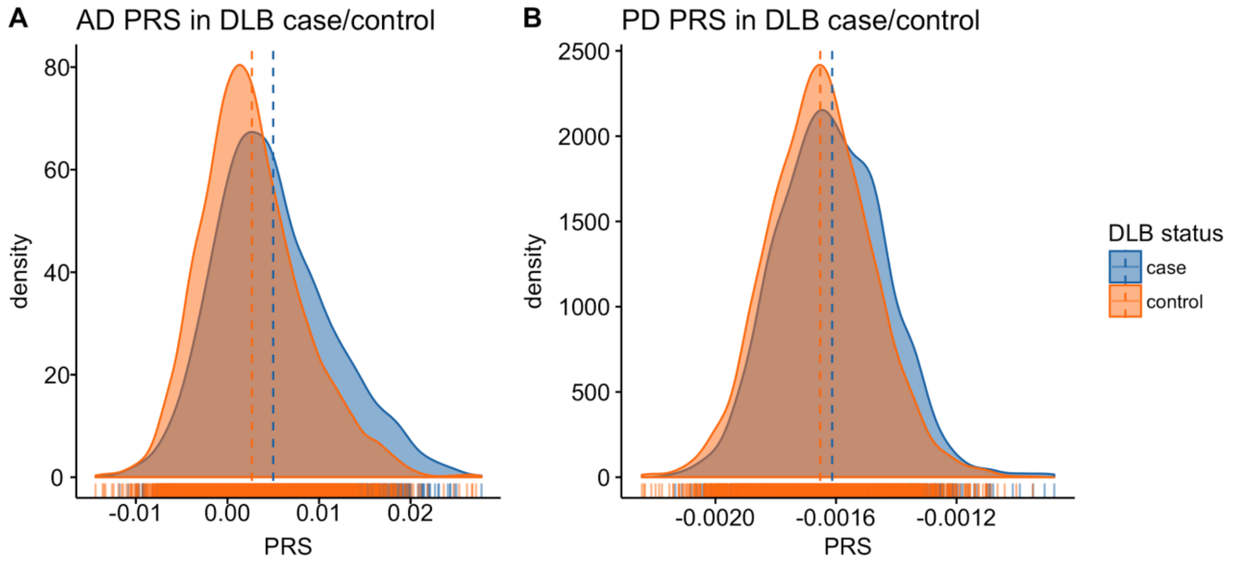


Figure 3: Density distribution of polygenic risk scores (PRSs) from AD and PD in DLB case and control subjects. PRS represents the standardized residuals of PRS after adjustment for the 6 principal components. Blue indicates case subjects; orange indicates case subjects.

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. 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 <0.01 in DLB and tested these in AD and PD (Figure 4).

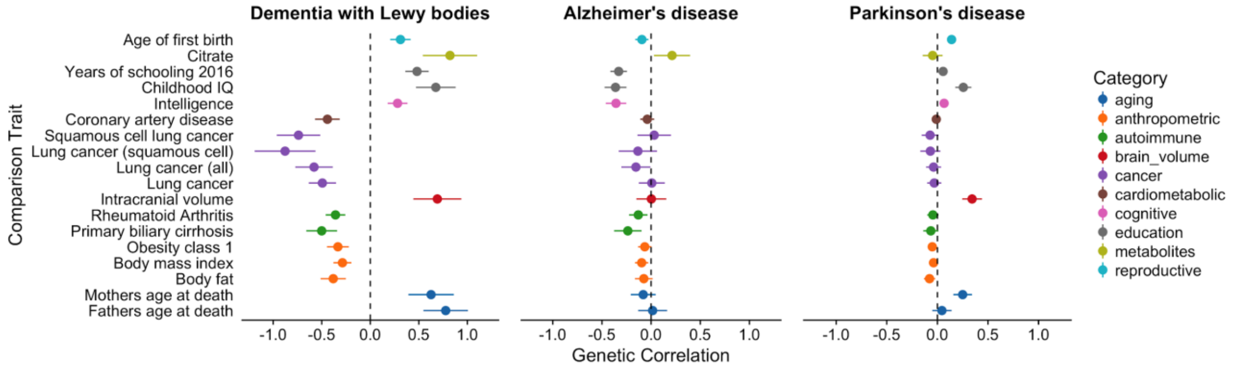


Figure 4: Correlation scores with p-value <0.01 in DLB. Shown are also the scores for those same traits in PD and AD.

The most significant correlation identified between DLB and each of the 235 tested traits was with “Years of schooling” (18) reaching a p-value of 6.32x10^{-5} (Bonferroni corrected p-value=0.015) 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=8.87x10^{-5}; PD: rg=0.05, p-value=0.07) (Figure 4). A positive correlation was also obtained for “Childhood IQ” (19) in DLB and PD, whereas a negative correlation was identified in AD (DLB: 0.68, p-value=0.0009; AD: rg=-0.36, p-value=0.0011; PD: rg=0.25, p-value=0.0013). Similarly, “Intracranial volume” (20) presented a positive correlation with both DLB and PD, but no discernible correlation with AD (DLB: 0.69, p-value=0.0052; AD: rg=-0.003, p-value=0.96; PD: rg=0.34, p-value=0.0005). Conversely, “Citrate” (21) was positively correlated with both DLB and AD, but had no correlation with PD (DLB: 0.82, p-value=0.0033; AD: rg=-0.21, p-value=0.25; PD: rg=-0.05, p-value=0.63).

Table 2: Significant correlation scores (p<0.01) for DLB, AD and PD.

		DLB			AD			PD		
Trait	**Category**	**rg**	**se**	**p-value**	**rg**	**se**	**p-value**	**rg**	**se**	**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

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 (12). 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 (16). 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) (16). 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 as the previous estimate (ref?). 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^2 above 0.5 (15), 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 (14). However, we 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 (10) and PD (9). 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 were predictive of case-control status, although explaining only relatively small proportions of variance (0.4-1.5%). In AD, excluding the *APOE* locus greatly reduced the amount of variance explained in DLB (0.15%), which is in accordance with the strong effect that locus has in the risk of both diseases (ref). 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 (22, 23), 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. It is interesting to note that education scores were positively correlated with DLB, while they have a well-established negative correlation with AD (24, 25). Similar positive correlations have been identified for bipolar disorder and autism spectrum disorders (26), 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 (27). Here, supporting those findings, we identify a positive genetic correlation between both PD and DLB 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 (28) 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 (29). A positive correlation between both DLB and AD with citrate (21) was identified, although this was not the case for PD, where no evidence of correlation was found. Increased citrate is associated with increased levels of oxidative stress (30), 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. This has implications in the statistical power to make novel findings and is reflected in the standard errors of the analyses performed. 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. 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.

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.

Materials and Methods

Sample description

The DLB dataset was previously published (4) and is comprised of 1,216 cases and 3,791 controls, imputed with HRC v1.1 and includes variants with minor allele frequency >= 0.001 and R^2>=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) (31), 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 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 (32).

DLB heritability estimates

We used the GCTA-LDMS method to estimate heritability based on imputed data (16, 33) 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 200kb (with 100kb 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.

DLB dominance variance estimates

To estimate the dominance GRM between pairs of individuals, we used genome-wide imputed SNPs as implemented in GCTA-GREMLd (14). This method calculates the additive and dominance GRMs and fits both GRMs in a mixed linear model to estimate additive and dominance variance simultaneously.

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 aetiology 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 (34). We performed clumping on the target data by retaining the SNP with the smallest p-value from each LD block (excluding SNPs with r2 > 0.1 in 250kb 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.

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 (26, 35). 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 ($p<0.01$), we estimated the correlation of those traits with PD and AD.

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Conflict of Interest Statement

HZ has served at scientific advisory boards for Eli Lilly, Roche Diagnostics, Wave, Samumed and CogRx and has received travel support from Teva.

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Legends to Figures, Tables and, finally, Abbreviations.