GBA and APOE ε4 associate with sporadic dementia with Lewy bodies in European genome wide association study

Arvid Rongve1,2, Aree Witoelar3,4, Agustin Ruiz5, Lavinia Athanasiu3,4, Carla Abdelnour4, Jordi Clarimon6,7, Stefanie Heilmann-Heimbach5,6, Isabel Hernández5, Sonia Moreno-Grau5, Itziar de Rojas5, Estrella Morenas-Rodriguez6,7, Tormod Fladby10,11, Sigrid B. Sando12, Geir Bråthen13, Frédéric Blanc16,15, Olivier Bousiges16, Afina W. Lemstra17,18, Inger van Steenoven17,18, Elisabet Londos19, Ina S. Almdahl11,12, Lene Pålhaugen10,11, Jon A. Eriksen3,4, Srđjan Djurovic6,20,21, Eystein Stordal22,23, Ingvild Saltvedt15,16, Ingun D. Ulstein14,25, Francesco Bettella13, Rahul S. Desikan26, Ane-Victoria Idland27,28,29, Mathias Toft6,30, Lasse Pihlstrøm6,30, Jon Snaedal31, Lluís Tárraga3, Mercé Boada3, Alberto Lleó6,7, Hreinn Stefánsson32, Kári Stefánsson32, Alfredo Ramirez33,34, Dag Aarsland35,36 & Ole A. Andreassen3,4

1Haugesund Hospital, Helse Fonna, Department of Research and Innovation, Haugesund, Norway. 2The University of Bergen, Department of Clinical Medicine (K1), Bergen, Norway. 3NORMENT, KG Jebsen Centre for Psychosis Research, Division of Mental Health and Addiction, Oslo University Hospital, Oslo, Norway. 4Institute of Clinical Medicine, University of Oslo, Oslo, Norway. 5Memory Clinic and Research Center of Fundació ACE, Institut Català de Neurociències Aplicades, Universitat Internacional de Catalunya (UIC), Barcelona, Spain. 6Department of Neurology, JIB Sant Pau, Hospital de la Santa Creu i Sant Pau, Universitat Autònoma de Barcelona, Barcelona, Spain. 7Center for Networked Biomedical Research in Neurodegenerative Diseases (CIBERneuro), Madrid and Barcelona, Spain. 8Institute of Human Genetics, University of Bonn, Bonn, Germany. 9Department of Genomics, Life & Brain Center, University of Bonn, Bonn, Germany. 10Department of Neurology, Akershus University Hospital, Lørenskog, Norway. 11University of Oslo, AHUS Campus, Oslo, Norway. 12Department of Neuromedicine and Movement Science, Norwegian University of Science and Technology, Trondheim, Norway. 13Department of Neurology, St Olav’s Hospital, Trondheim, Norway. 14University Hospital of Strasbourg, CMRR (Memory Resources and Research Centre), Geriatrics Department, Strasbourg, France. 15University of Strasbourg and CNRS, ICube laboratory and FMTS, team IMIS/Neurocrypto, Strasbourg, France. 16University Hospital of Strasbourg, CMRR (Memory Resources and Research Centre), Laboratory of Biochemistry and Molecular Biology, Strasbourg, France. 17Department of Strasbourg and CNRS, Laboratoire de Neurosciences Cognitives et Adaptatives (LNCA), UMR7364, 67000, Strasbourg, France. 18Alzheimercenter & Department of Neurology VU University Medical Center, Amsterdam, the Netherlands. 19Lund University, Skane University Hospital, Institute of Clinical Sciences, Malmö, Sweden. 20Department of Medical Genetics, Oslo University Hospital, Oslo, Norway. 21NORMENT, KG Jebsen Centre for Psychosis Research, Department of Clinical Science, University of Bergen, Bergen, Norway. 22Department of Psychiatry, Namsos Hospital, Namsos, Norway. 23Department of Mental Health, Norwegian University of Science and Technology, Trondheim, Norway. 24Department of Geriatric Psychiatry, Oslo University Hospital, Oslo, Norway. 25Departments of Radiology and Biomedical Imaging, Neurology and Pediatrics, UCSF, San Francisco, USA. 26Oslo Delirium Research Group, Department of Geriatric Medicine, Institute of Clinical Medicine, University of Oslo, Oslo, Norway. 27Research Group for Lifespan Changes in Brain and Cognition, Department of Psychology, University of Oslo, Oslo, Norway. 28Institute of Basic Medical Sciences, University of Oslo, Oslo, Norway. 29Department of Neurology, Oslo University Hospital, Oslo, Norway. 30Landspitali University Hospital, Reykjavik, Iceland. 31DeCODE genetics, Reykjavik, Iceland. 32Division for Neurogenetics and Molecular Psychiatry, Department of Psychiatry and Psychotherapy, Medical Faculty, University of Cologne, 50924, Cologne, Germany. 33Department for Neurodegenerative Diseases and Geriatric Psychiatry, University of Bonn, 53127, Bonn, Germany. 34Institute of Psychiatry, Psychology and Neuroscience, King’s College London, London, UK. 35Center for Age-Related Diseases, Stavanger University Hospital, Stavanger, Norway. Arvid Rongve and Aree Witoelar contributed equally. Correspondence and requests for materials should be addressed to A.R. (email: arvid.rongve@helse-fonna.no) or D.A. (email: daarsland@gmail.com) or O.A.A. (email: ole.andreassen@medisin.uio.no)
Dementia with Lewy Bodies (DLB) is a common neurodegenerative disorder with poor prognosis and mainly unknown pathophysiology. Heritability estimates exceed 30% but few genetic risk variants have been identified. Here we investigated common genetic variants associated with DLB in a large European multisite sample. We performed a genome wide association study in Norwegian and European cohorts of 720 DLB cases and 6490 controls and included 19 top-associated single-nucleotide polymorphisms in an additional cohort of 108 DLB cases and 75545 controls from Iceland. Overall the study included 828 DLB cases and 82035 controls. Variants in the ASH1L/GBA (Chr1q22) and APOE e4 (Chr19) loci were associated with DLB surpassing the genome-wide significance threshold (p < 5 × 10^-8). One additional genetic locus previously linked to psychosis in Alzheimer’s disease, ZFPM1 (Chr16q24.2), showed suggestive association with DLB at p-value < 1 × 10^-4. We report two susceptibility loci for DLB at genome-wide significance, providing insight into etiological factors. These findings highlight the complex relationship between the genetic architecture of DLB and other neurodegenerative disorders.
analyses. Individuals showing high rates of genotyping missingness (above 5%), cryptic relatedness (pairwise Identity-By-Descent PI_HAT above 20%) or genome-wide heterozygosity (outside mean ± 5 SD of the sample) were removed from the analyses. Further, sex-check was performed based on the heterozygosity estimate of X chromosome markers implemented in PLINK.

**Association analysis.** We performed association analysis in two stages. Due to data regulations and ethical approvals regarding data sharing, we performed genome-wide association analyses on Cohorts 1 and 2 independently and combined the results through meta-analysis to obtain Stage 1 results. HRC imputation was not accessible for cohort 1 due to national regulations in Norway. To reduce possible genomic inflation or over-correction, the results from the Stage 1 meta-analysis were corrected for genomic inflation before we performed meta-analysis with Cohort 3 to obtain Stage 2 results.

Genotypes from Cohort 1 samples were imputed onto the European reference haplotypes from the 1000 Genomes Project (GRCh37/hg19 assembly) Phase 3 using MACH (http://www.sph.umich.edu/csg/abecasis/MACH). We excluded variants with MAF lower than 0.01 or R-squared quality metric (INFO) > 0.5. We performed principal component analysis (PCA) on Cohort 1 pre-imputation data using PLINK 1.9 (https://www.cog-genomics.org/plink2) to account for population stratification. The association analysis by logistic regression on dosage data using PLINK 1.9 included gender, age, and the two first principal components as covariates. Genomic inflation factors were calculated as the ratio of the median of the empirically observed distribution of the association chi-square statistic to the expected median.

Genotypes from Cohort 2 samples were imputed onto the GRCh37/hg19 assembly with ShapeIT & Minimac3 using the haplotype reference consortium HRC version r1.1 reference data at the imputation server of the University of Michigan. PCA was done independently for Cohort 2 because there was no relatedness to samples from Cohort 1. Logistic regression was performed using PLINK 1.9 using gender, age and the top two genetic principal components as covariates. The genomic inflation factor was calculated as previously described.

To obtain Stage 1 results, variants from Cohort 1 and Cohort 2 were mapped to each other using GRCh37/ hg19 assembly. All variants with allele discrepancies across cohorts were discarded. We performed meta-analysis of Cohort 1 and Cohort 2 using PLINK 1.9 with fixed effects inverse-variance weighted effect sizes. Biases from different cohorts due to genotype array and imputation procedures are mitigated through correction on the inflation factor. The results were verified using METAL meta-analysis tool (http://csg.sph.umich.edu/abecasis/Metal). To identify independently associated loci, we used FUMA’s SNP2GENE function to define lead SNPs and genomic risk loci. Graphical representations including quantile-quantile plots and Manhattan plots were performed in R using the qqman package (http://cran.r-project.org/web/packages/qqman).

We selected variants with Stage 1 meta-analysis p-value < 1 × 10^-6 for follow up in Cohort 3 (Iceland) and used the same approach described above to meta-analyse the results in Stage 2.

**Functional mapping and annotation (FUMA) of GWAS.** We utilized FUMA to functionally annotate our Stage 1 results. FUMA incorporates 18 biological data repositories such as the Genotype-Tissue Expression (GTeX), the Encyclopedia of DNA Elements (ENCODE), the Roadmap Epigenomics Project and chromatin interaction information. FUMA requires GWAS summary statistics and its outputs include multiple tables and figures containing extensive information on, e.g., functionality of SNPs in genomic risk loci, including protein-altering consequences, gene-expression influences, open-chromatin states as well as three-dimensional (3D) chromatin interactions. Functionally annotated variants are subsequently mapped to prioritized genes based on (i) physical position mapping on the genome, (ii) expression quantitative trait loci (eQTL) mapping and (iii) 3D chromatin interactions (chromatin interaction mapping). Biological information for each prioritized gene is provided to gain insight into previously associated diseases. On top of the single gene level analyses, FUMA also provides information on association overrepresentation in sets of differentially expressed genes (DEG) to identify tissue specificity of prioritized genes. We refer to the details of methods and repositories of FUMA in [21].

**Ethics committee approval.** All cohorts and sites providing samples for this study have local ethics approval for DNA collection and data sharing, and the names of local ethics committees are provided in the in the supplemental materials. In Norway the joint study was approved by the Regional Committees for Medical and Health Research Ethics in Mid Norway.

**Results**

From Cohort 1, we obtained genotypes for 719,755 SNPs and performed imputation to obtain 7,769,477 high-quality variants. We performed association using 478 DLB cases and 1322 controls, see Table 1. After controlling for population stratification using PCA (S. Fig. 1A), the genomic inflation factor Lambda was 1.005 (S. Fig. 2A). We found genome-wide significance on rs2230288 (closest gene GBA, p = 3.77 × 10^-9) and rs429358 (closest gene APOE, p = 3.21 × 10^-9). The regional association plots for this locus is visualized in S. Fig. 3.

To increase the power of our study, we included additional Norwegian population controls in the study, see S. Table 1. Using two principal components (S. Fig. 1B), the addition of population controls increased inflation to a Lambda of 1.244, possibly due to inflation from the additional controls. We verified the inflation using LD Score Regression and found the intercept at 1.2094, consistent with Lambda. Quantile-quantile plots for Cohort 1 before and after genomic correction are given in S. Fig. 2. After correction, the strongest associations in Cohort 1 remain with rs2230288 (p = 1.77 × 10^-10) and rs429358 (p = 4.13 × 10^-9).

We found 45 SNPs associated to DLB at p < 5 × 10^-6 with strong associations in Chromosomes 1 and 19; a summary of our findings from Cohort 1 is given in S. Table 2A.
From Cohort 2, we analysed 7,570,659 successfully imputed variants. The genomic inflation factor Lambda was 1.031. Quantile-quantile plots for Cohort 2 are given in S. Fig. 2. The Cohort 2 study revealed 9 SNPs associated with DLB at p < 5 × 10^{-6}; also with strong associations in Chromosome 19, see S. Table 2B. After individual analyses of discovery Cohorts 1 and 2, we performed a Stage 1 meta-analysis of 6,963,063 variants (898 were discarded due to allele mismatches). The meta-analysis genomic inflation factor Lambda was 0.865, possibly due to overcorrection for the genomic inflation in Cohort 1. We corrected the chi-square statistics of the meta-analysis at fixed ORs, see the quantile-quantile plots in S. Fig. 2. Genome-wide Stage 1 results are visualized as a Manhattan plot of Stage 1 meta-analysis. Manhattan plot of meta-analysis of Cohorts 1 and 2 for genome-wide significant associations to Dementia with Lewy Body (DLB). Genome-wide significant associations to DLB are found in chromosomes 1 (ASH1L/GBA) and 19 (APOE), and a suggestive association to DLB at p < 1 × 10^{-4} is identified at chromosome 16 (ZFPM1). A comprehensive result of Stage 1 is presented in Supplementary Table 2.

After correction, Stage 1 analysis revealed 108 SNPs associated with DLB at p < 5 × 10^{-6} (S. Table 2C). The statistical power of our study is estimated to be 0.085 (MAF = 0.05) to 0.395 (MAF = 0.1) to 0.823 (MAF = 0.2) for SNPs with genomic risk ratio GRR = 1.5 and GRR = 1.2, shown in S. Fig. 4. GRR values were chosen based on ORs of discoveries of earlier DLB studies. We followed up on 18 of these SNPs, which were successfully analysed in an independent sample from Iceland (Cohort 3) and performed a Stage 2 meta-analysis. Because stage 2 meta-analysis included only 18 selected SNPs instead of a genome-wide analysis, this result was not corrected for genomic inflation.

From the Stage 2 meta-analysis, we found two susceptibility regions associated with DLB surpassing genome-wide significance, p < 5 × 10^{-6}. We found APOE ε4 related SNPs at genome-wide significance, represented by rs429358 (OR = 2.28, p = 6.15 × 10^{-17}, see Table 1 for details). A regional association plot of the APOE locus from Stage 1 meta-analysis is presented in S. Fig. 5A. From a recent large study, we found that this SNP is identical to the reported top hit (OR = 2.40, p = 1.05 × 10^{-46}) in Guerreiro et al. We also discovered a DLB-associated locus on Chromosome 1, represented by rs12734374 (closest gene: ASH1L, OR = 4.31, p = 1.33 × 10^{-5}, see Table 1 and regional association plots in S. Fig. 5B). This SNP is located in the same genomic region of rs2230288, the strongest hit in Cohort 1 which was not successfully imputed in Cohort 2, but had implicated GBA. Furthermore, in another study, we found that rs12734374 is in high LD (R^2 = 0.79) with a GBA hit, rs35749011 (OR = 2.27, p = 6.57 × 10^{-18}) in Guerreiro et al. Both our APOE and ASH1L/GBA hits provide genome-wide significant confirmations of the findings from Guerreiro et al.

Furthermore, we investigated SNPs with a suggestive association to DLB. From the Stage 1 meta-analysis, we noted 9 SNPs at p < 1 × 10^{-4} in chromosome 16, represented by rs12926163 (closest gene ZFPM1, OR = 1.68, p = 1.45 × 10^{-7}). These SNPs were not successfully analysed in the Icelandic cohort, and therefore we present only the Stage 1 result of this locus in Table 1 and S. Fig. 5C.

Next, we analysed specific gene signals reported previously in DLB for their significance under locus-wide Bonferroni correction for each gene. Due to the small SNP coverage in the Stage 2 analysis, we used results from Stage 1. We extracted variant information for SNCA (GRCh37hg19 chr4:90,645,250-90,759,466), SCARB2 (chr4:77,079,886-77,155,689), MAPT (chr17:43,971,748-44,105,700) and CNTN1 (chr12:41,086,244-41,466,220) with upstream and downstream flanking of 200kB. Regional plots of these candidate genes are shown in S. Fig. 5D–G.

Among the 1509 successfully imputed SNPs in the SNCA locus, the strongest association was with rs2301135 (chr4:90,758,389, p = 5.68 × 10^{-5}, OR = 1.40, minor allele C) and remained nearly significant after correction (threshold p < 3.3 × 10^{-4}) using conservative multiple test assumptions of independent SNPs. In the SCARB2 locus, the strongest association among the 1600 SNPS was with rs34216031 (chr4:76,971,832, OR = 1.63, p = 1.37 × 10^{-2}), but its significance did not survive correction (threshold p < 3.1 × 10^{-3}). In the MAPT locus, 694 SNPs passed quality checks. Among these, the strongest association was with rs1652003 (chr17:44,132,659, OR = 0.75, p = 1.89 × 10^{-2}) but did not withstand correction (threshold p < 7.2 × 10^{-3}). Of note, coverage of MAPT is relatively poor in our genotyping and imputation procedure, see S. Fig. 5E. In the CNTN1 locus, the strongest association was with rs56260639 (chr12:41122583, OR = 0.50, p = 1.17 × 10^{-2}). Despite the strong OR, this association did not remain significant after correction (threshold p < 2.1 × 10^{-3}).

Finally, we investigated the potential biological roles of the resulting list of genes in brain disorders. For this, we performed functional analysis with FUMA GWAS. We summarized the independent genomic risk loci from...
Stage 1 with suggestive association \( p < 1 \times 10^{-6} \) in S. Fig. 6. The strongest associations were close to \( APOE \) in Chromosome 19 and distributed in a relatively small region spanning only 41kB and 4 genes. The significant associations in Chromosome 1, within the large haplOBloc containing \( GBA \), spanned 1.2MB and up to 64 genes (see S. Fig. 6). We computed gene-based P-value test for protein-coding genes by mapping SNPs to genes if SNPs were located within the genes. The chromosome 1 genes (\( GBA \)) did not surpass the significance threshold (S. Fig. 7), but the chromosome 19 genes (\( APOE, APOC1, TOMM40 \)) remained significant. We also found significant results applying the gene-based test to the gene on chromosome 16 (\( ZFPM1 \)), which was suggestive at the single variant level. Using MAGMA tissue expression analysis, we found the strongest expression in whole blood, substantia nigra and spinal cord cervical level c-1. (S. Fig. 8).

FUMA prioritized 65 genes (S. Table 3, S. Fig. 9) for further functional analyses; see Methods on how genes are prioritized. Of note, in Chromosome 1, \( GBA \) was prioritized based on eQTL analysis (S. Fig. 9), further strengthening the case that our top hit implicated not only \( ASH1L \) but also \( GBA \). From the set of 65 genes, we looked up tissue specific expression patterns based on GTEx v6 RNA-seq data. These are visualized as a heatmap in S. Fig. 10. Relative to other genes, we found \( APOE \) highly expressed in all tissues (S. Fig. 10A). \( ASH1L \) and \( GBA \) are moderately expressed and \( ZFPM1 \) has a lower gene expression relative to other genes in all tissues. Next, we looked at the tissue specificity for each gene. We found \( APOE \) with moderately higher expression in brain tissue (S. Fig. 10B), while \( ASH1L, GBA \) and \( ZFPM1 \) are not specific to brain tissues. Notably, we found higher expression in brain tissues for \( PAQR6, CHRN82, SYT11 \) and \( APOC1 \) and conversely we found lower expression for \( PVRL2, LMNA \) and \( SHC1 \) (S. Fig. 10B).

Besides the single gene level analyses, we also identified tissue specificity of prioritized genes by looking at overrepresentation in sets of differentially expressed genes (DEG), see S. Fig. 11. DEG for each tissue was calculated in FUMA. We found the spinal cord cervical level c-1 and amygdala being two of the top five tissues with the most DEG, however, none passed Bonferroni corrected significance. The finding of the spinal cord cervical level c-1 is consistent with the MAGMA analysis.

**Discussion**

We performed a genome-wide association study based on 828 clinically diagnosed DLB cases and a large sample of 82035 controls. We confirmed the \( APOE \) ε4 allele and a locus close to \( ASH1L \) and \( GBA \) (Chr1q22) as significantly associated with DLB. Furthermore, we nominate a novel genetic locus near \( ZFPM1 \) as suggestively associated with DLB. Taken together with recent findings from another DLB GWAS\(^{13}\), the current results firmly establish \( APOE \) ε4, \( SNCA \) and \( GBA \) as robust risk loci for DLB, which implicate novel disease mechanisms to be followed up in experimental studies.

The top-hit SNP at the 1q22 locus is located within the large haplobloc containing \( GBA \) (glucocerebrosidase gene), also recently identified by Guerreiro et al.\(^{13}\). We note that the strongest association was in SNPs with relatively high LD (\( D' \geq 0.66 \)) with \( rs2230288 \), referred to in the literature as the \( APOE \) ε4 allele and a locus close to \( ASH1L \) and \( GBA \) (Chr1q22) as significantly associated with DLB. Furthermore, we nominate a novel genetic locus near \( ZFPM1 \) as suggestively associated with DLB. Taken together with recent findings from another DLB GWAS\(^{13}\), the current results firmly establish \( APOE \) ε4, \( SNCA \) and \( GBA \) as robust risk loci for DLB, which implicate novel disease mechanisms to be followed up in experimental studies.

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**Table 1.** Genetic loci with significant and suggestive associations with DLB at meta-analysis Stage 1 and Stage 2. CHR:BP: Chromosome and Base pair location based on Build 37, Assembly Hg19. Allele (min/maj): Minor and major alleles; MAF: Minor Allele Frequency (on European 1000 G), Cohort 1 and Cohort 2. Gene: Nearest gene within 500 kB; OR, P: case-control odds-ratio and association P-values from Stage 1 combining Cohorts 1 and 2, and Stage 2 Meta-analysis combining Cohorts 1, 2 and 3.

| SNP         | CHR:BP     | Allele (min/maj) | MAF (1KG) | MAF Cohort 1 | MAF Cohort 2 | Gene       | Meta Stage 1 | Meta Stage 2 |
|-------------|------------|-----------------|-----------|--------------|--------------|------------|--------------|--------------|
| rs429358    | 19:45411941| C/T             | 0.155     | 0.143        | 0.153        | \( APOE \) ε4 | 2.79         | 2.00e-14     |
| rs12734374  | 1:155388851| T/A             | 0.023     | 0.022        | 0.012        | \( ASH1L/GBA \) | 4.29         | 4.29e-09     |
| rs1926163   | 16:88572056| C/T             | 0.311     | 0.252        | 0.323        | \( ZFPM1 \) | 1.68         | 1.45e-07     |

We and others have previously reported \( APOE \) (\( Apolipoprotein E \)) ε4 (Chr19q13.32) as an important genetic risk factor for DLB. Guerreiro et al. found the locus highly significant\(^{13}\), and we reported an OR for carriers of one copy of the \( APOE \) ε4 allele to be 2.9 for developing DLB and 4.2 for developing AD. For carriers of two copies of the \( APOE \) ε4 alleles the OR for developing DLB increased to 5.9 while the OR for developing AD was as high as 15.2\(^{14}\). Bras and colleagues have reported \( APOE \) as the strongest associated risk gene in both clinically...
and neuropathologically diagnosed DLB cases, and this was confirmed in an expanded cohort from the same group recently. Guerreiro et al. estimated the DLB SNP-heritability based on the Illumina Neuro-X content to be 31%, with APOE accounting for about 9%.

APOE ε4 has also been found to increase the risk of dementia in pure alpha-synucleinopathies in a study where its frequency was 38% in pathologically diagnosed pure AD, 40.6% in the mixed AD and DLB group, 31.9% in pure DLB, 19.1% in Parkinson’s Disease Dementia (PDD) and 7.2% among healthy controls. In another AD GWAS, Lewy body pathology in the brain was associated with APOE variants. Most cases with clinically diagnosed DLB will contain both Lewy bodies and AD pathology in the brain.

SNCA (synuclein alpha) is the strongest associated risk gene in PD and encodes α-synuclein, which is a major constituent of Lewy bodies, pathological hallmark for both DLB and PD/PDD. Accumulation of α-synuclein aggregates have been found to create synaptic dysfunction in DLB. The top associated variant in our data (rs2301135) is in LD with the SNCA′ variants. Most cases with clinically diagnosed DLB will contain both Lewy bodies and AD pathology in the brain.

Meta-analysis of PD GWAS (r-squared 0.98 and D′ 1.0 with rs894280 in 1000 genomes European population) and the secondary signal from a large meta-analysis of PD GWAS (r-squared 0.98 and D′ 1.0 with rs7681154). Both p-value and effect size of the SNCA association observed here are equivalent to those found in the similarly sized DLB study by Bras et al., and despite falling short of genome wide significance, we interpret this result as supportive for an SNCA association in DLB. Deviations from other studies with respect to the strongest SNP at the locus could well arise if key SNPs are not well imputed across all cohorts.

Together, the identified genetic loci could be involved in a common neurobiological disease pathway in DLB. The normal degradation of α-synuclein is highly dependent on lysosomal function and glucocerebrosidase is an important enzyme in this degradation. Impaired function of glucocerebrosidase due to coding variants like E326K will slow down the degradation of α-synuclein thus increasing the concentration of toxic oligomers and thereby driving the pathological process in DLB. Inhibition of lysosomal enzymes also results in Aβ accumulation and aggregation. The apolipoproteins accelerate neuronal Aβ uptake, lysosomal trafficking and degradation in an isoform-dependent manner with apolipoprotein E3 more efficiently facilitating Aβ trafficking and degradation than apolipoprotein E4, a risk factor for AD and DLB, thus linking both GBA, APOE and SNCA.

The present findings of genetic loci suggestively associated with DLB indicate interesting pathological mechanisms. The chromosome 16 locus associated with DLB at p = 1.45 × 10⁻⁷ implicates ZFPM1 (Zinc finger protein, FOG family member 1), which is expressed in human hematopoietic tissues and in the cerebellum and is involved in erythroid differentiation. In one study of AD and psychosis, duplications in this gene were associated with psychosis in AD, a symptom highly relevant in DLB, were visual hallucinations and related delusions are core symptoms of the disease. Our findings suggest other putative molecular mechanisms in DLB.

CNTN1 (contactin 1) is a glycosylphosphatidylinositol anchored neuronal membrane protein that functions as a cell-adhesion molecule with important roles in axonal function. It is located near the LRKK2 locus and was associated to PD and reported as a suggestive hit in the largest GWAS of DLB to date. We found no significant hits under correction in our study. Further, we found no genome-wide significant associations with MAPT (microtubule associated protein tau), the gene encoding tau, in our study. However, this gene was poorly covered in our genotyping and imputation procedure. MAPT is the second strongest associated risk gene in PD and is associated also with AD. It exists on two different haplotypes, H1 and H2. H1P has been associated with Parkinson’s disease with dementia, whereas H1C has been associated with Alzheimer’s disease. Thus, MAPT would be a plausible candidate gene also for DLB due to clinical and likely genetic overlap with AD and PD beyond APOE. The negative finding suggests that the role of MAPT variability might represent a genetic difference between DLB and PD, but this hypothesis needs to be further tested in larger cohorts, preferentially including both DLB and PD samples.

All cases included in our study were clinically diagnosed with common sporadic and late onset type of DLB. Cases solely diagnosed based on pathology might not always fulfil clinical diagnostic criteria during life, and therefore might include cases of PD and even early onset PD developing dementia in late stages. The clinically diagnosed DLB cases included in our study might therefore have a purer, less PD-like genetic profile than studies based on brain bank cases, a possible explanation for why we do not find the previously PD-associated risk loci like MAPT in our analysis. Diagnosing DLB clinically is challenging both because of the clinical heterogeneity and the overlapping AD pathology masking typical DLB core symptoms in many cases. Although diagnostic procedures differed among centres, nearly all centres are academic dementia research centres with high-level clinical expertise on DLB and used standardized and established procedures, including, in a subset of patients, biomarkers. Thus, we believe diagnoses were as accurate as can be achieved in a clinical setting, although pathological confirmation was available only in a subset. The clinical diagnostic criteria for probable DLB have been found to have high specificity and this was confirmed in a pathological study in one of the samples included in this study. We therefore argue that only few cases with other diagnoses like AD can have been erroneously included in this sample. Adding biomarkers like (123)FP-CIT-SPECT to the diagnostic procedure could increase diagnostic precision in DLB. AD-pathology could be detected by PET or CSF-biomarkers of amyloid and tau deposition. The recently published revised diagnostic criteria for DLB are slightly different from the previous. Whether this will impact on the genetic architecture of DLB cohorts is not known, however.

There are few other large cohorts diagnosed with DLB with well characterized patients, and although this is one of the largest studies in DLB to date – sample size is still small for a hypothesis-free GWAS approach. Consequently, we only had statistical power to detect signals with large effect sizes, such as APOE and GBA. We anticipate that GWAS with larger samples will detect more common genetic risk loci associated with DLB with effect sizes comparable to the vast majority of AD and PD GWAS loci. Current evidence further indicates that rare variants contribute significantly to the disorder, suggesting next generation sequencing approaches will also be important to further characterize the genetic architecture of DLB.
DLB is increasingly recognized as a specific clinical diagnosis distinct from AD and PD both clinically and genetically, and has a poor prognosis with no approved treatment. To detect more of the genetic risk loci contributing to DLB pathogenesis new methods like Bayesian statistics may prove useful. This notwithstanding, larger samples obtainable through international collaboration are needed in a future GWAS of DLB. We therefore plan to collaborate to increase sample size in a next step to increase the power to detect more common genetic variants with small effects associated with the risk of development of DLB.

Data Availability
Genotype datasets from the Norwegian DemGene network generated and analysed during the current study are not publicly available due to compliance to privacy. Summary statistics are available from the corresponding author on reasonable request.

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Author Contributions

Arvid Rongve collected samples, initiated and planned the study, organized recruitment of cohorts, wrote the first draft and updated the manuscript based on input from all co-authors. Aree Wittoelor conducted biostatistical analyses in Cohort 1 and combined analyses, and wrote the manuscript. Dag Aarsland and Ole A. Andreassen organized and planned the study, coordinated and supervised the work, and wrote the manuscript. Agustín Ruiz did the biostatistical analyses in Cohort 2 and helped with writing the manuscript. Francesco Bettella and Jon A. Eriksen were involved in genotype quality control and parts of biostatistical analyses. Lavinia Athanasiu was involved in genotyping and data collection. Kari Stefansson and Hreinn Stefansson genotyped Cohort 1 and provided cohort 3 samples. Stefanie Heilmann-Heimbach did the genotyping of Cohort 2. Lasse Pihlstrom collected samples and contributed to writing the manuscript. Carla Abdelnour and Jordi Clarimon, Isabel Hernández, Sonia Moreno-Grau, Itziar de Rojas, Estrella Morenas-Rodriguez, Sigrid B. Sando, Geir Bråthen, Frédéric Blanc, Olivier Bousiges, Afina W. Lemstra, Inger van Steenoven, Elisabet Londos, Ina S. Almdahl, Lene Pålhaugen, Srdjan Djurovic, Eystein Stordal, Ingvild Saltvedt, Ingun D. Ulstein, Ane-Victoria Idland, Mathias Toft, Jon Snaedal, Lluís Tarraga, Mercè Boada, Alberto Lleó and Alfredo Ramirez all organized and collected samples at different study sites. Tormod Fladby planned the study and coordinated Norwegian sites, and together with Rahul Desikan provided input to interpretation of the results. All co-authors read and approved the paper.

Additional Information

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Competing Interests: Arvid Rongve, Aree Wittoelor, Agustín Ruiz, Lavinia Athanasiu, Carla Abdelnour, Jordi Clarimon, Stefanie Heilmann-Heimbach, Isabel Hernández, Sonia Moreno-Grau, Itziar de Rojas, Estrella Morenas-Rodriguez, Tormod Fladby, Sigrid B. Sando, Geir Bråthen, Frédéric Blanc, Olivier Bousiges, Afina W. Lemstra, Inger van Steenoven, Elisabet Londos, Ina S. Almdahl, Lene Pålhaugen, Jon A. Eriksen, Srdjan Djurovic, Eystein Stordal, Ingvild Saltvedt, Ingun D. Ulstein, Francesco Bettella, Rahul S. Desikan, Ane-Victoria Idland, Mathias Toft, Jon Snaedal, Lluís Tarraga, Mercè Boada, Alberto Lleó and Alfredo Ramirez declare no competing interests. Kari Stefansson and Hreinn Stefansson are employees of deCODE Genetics, Iceland. Ole A. Andreassen has received speaker’s honorarium from Lundbeck and has a pending patent for biostatistical genetic methodology. Dr Aarsland has received research support and/or honoraria from Astra-Zeneca, H. Lundbeck, Novartis Pharmaceuticals and GE Health, and served as paid consultant for H. Lundbeck, Eisai, Heptares, Srafoi, Mentis Cura. Dag Aarsland is a Royal Society Wolfson Research Merit Award Holder and would like to thank the Wolfson Foundation and the Royal Society for their support.

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