Whole genome analysis in APOE4 homozygotes identifies the DAB1-RELN pathway in Alzheimer’s disease pathogenesis

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1. Introduction

Genome-wide association studies (GWAS) have led to the identification of many genetic loci influencing the risk of dementia (Hardy and Escott-Price, 2019). However, none of these approach the importance of the APOE locus (Coon et al., 2007) where the APOE-e4 allele has a frequency of ~15% in controls and has a risk ratio of >3 in cases. Other loci with allele frequencies of >1% have risk ratios of <1.4. Recent studies have shown that the APOE genotype is almost solely responsible for amyloid deposition whereas other components of Alzheimer’s disease (AD) genetic risk contribute to the occurrence of dementia in the context of amyloid deposition (Leonenko et al., 2019). Furthermore, neuropathologic studies have shown that clinical diagnoses in Alzheimer series had a diagnostic accuracy of around 80%; this accuracy is implied by analyses comparing the large clinical GWAS with the smaller neuropathologic GWAS, leading to the concern that these larger GWAS are contaminated by other diagnoses. This concern is heightened by the reports of loci for frontotemporal dementia in case series labelled as Alzheimer’s disease in the most recent GWAS for the disorder (Wightman et al., 2021).

With this background, we have undertaken an AD GWAS in individuals who are APOE-e4 homozygotes for 3 reasons. First, because in this group diagnostic accuracy is very high; second, to assess whether in this context there is additional genetic risk at the APOE locus; and third, to assess which previously reported loci are replicated in these cases and whether there are any novel loci we can identify which are dependent on APOE-e4 homozygocity. This study was possible in the UK Biobank (Sudlow et al., 2015) because it has a very large cohort, with a sufficient number (for statistical analyses) of APOE-e4 homozygotes, where many participants are now reaching the age where they are at risk.
Here we report that the APOE allele alone accounts for the AD risk in the LD block on chromosome 19 in the European population. Furthermore, in APOE-e4 homozygotes, we identify AD risk associated with the DAB1 gene that encodes a synapase regulatory protein. Subsequent analyses revealed a gene set association with the DAB1-RELN pathway.

2. Material and methods

2.1. Phenotypes

Individuals from the UK Biobank were considered if they self-reported as white British and were of similar genetic ancestry by principal component analysis (UK Biobank field 22006), were unrelated (kinship coefficient < 0.04) and if they had not withdrawn consent to participate under UK Biobank. Participants were further excluded if they showed excessive missingness or sex chromosome aneuploidy, were outliers for heterozygosity, had mismatching self-reported and inferred sex from genotyping data, and had over 10 putative third-degree relatives. AD definition was derived using ICD-10 codes in hospital and death records. Individuals were coded as cases where dementia in Alzheimer’s disease (ICD-10 code F00) or Alzheimer’s disease (code G30) were present. Controls were defined as those without F00, G30, vascular dementia (F01), dementia in other diseases (F02) and unspecified dementia (F03). APOE status was assigned to each individual, as defined by SNPs rs7412 and rs429358 which are both present on the Affymetrix Axion genotyping array used. After quality control and restriction to APOE-e4 homozygous individuals aged 65 or over, 288 cases and 5,102 controls were included in analysis.

2.2. Genetic quality control

The UK Biobank genetic data from the haplotype reference consortium (HRC), imputed by the UK Biobank (Bycroft et al., 2018), was restricted to biallelic SNPs (minor allele frequency > 0.05) with Hardy-Weinberg equilibrium > 10^-6, INFO>0.4 and posterior probability>0.4. After quality control, 5,349,830 SNPs were included in analysis.

2.3. Analysis

Association analysis using logistic regression was conducted in PLINK2 (Chang et al., 2015) on UK Biobank dosage data using most recently recorded age, sex and the first 15 principal components (field 22009) as covariates.

The significant findings (with the logistic regression) were further tested with Cox proportional-hazards regression (while controlling for the covariates) where the censoring occurred when a participant reported AD, allowing for the fact that some individuals have not reached the age at onset and may develop the disease given time. The code for the risk allele was the same as for the logistic regression.

The enrichment analysis of significant SNPs (at 5% significance level) or for SNPs showing the same direction of the effect (assuming that the chance to have the same direction of effect is 50%) was performed with binom.test() function in R.

The power calculations were performed with qnorm() function in R-statistical package at nominal 5% significance level (unless specified otherwise), where Z-score was estimated as log(OR)/var with the log(OR) as reported in the GWAS. In the Wightman et al. study (Wightman et al., 2021), the largest OR was selected from the reported ORs in the list of contributing studies. The variance estimated as the inverse variance, with allele frequencies in cases and controls (corresponding to the SNP OR), and the sample size as in our study (N cases = 288, N controls = 5,102). Plots of regional associations were created using LocusZoom (Boughton et al., 2021).

Epistasis was defined as deviation from joint 2 SNPs linear effects in the logistic regression model (known as statistical interaction). Significance of the interaction term was assessed using -epistasis option PLINK (Chang et al., 2015), accounting for the same covariates as above. The interaction plots were produced using matplotlib in python (Hunter, 2007). Following results from the GWAS, we assessed SNPs in the DAB1 gene for epistasis. Dab1 encodes a cytoplasmic signaling adaptor that is predominantly expressed in neurons where it acts downstream of the extracellular ligand Reelin to regulate brain lamination during development (Abadescu et al., 2014; Howell et al., 2000, 1999a; Rice et al., 1998). Since Reelin-DAB1 signaling also performs an important role in the adult brain by promoting excitatory synapse maturation (Qu and Weeber, 2007; Ventrutti et al., 2011) and modulating synaptic plasticity, learning and memory (Pujadas et al., 2010; Rogers et al., 2011; Trotter et al., 2013; Weeber et al., 2002), we also explicitly looked at the SNPs associations in the RELN gene (chr7:103,112,231-103,629,963).

2.4. DAB1-RELN pathway analysis

The Reelin ligand and DAB1 adaptor proteins are bridged by 2 partially redundant transmembrane receptors APOER2 (LRP8) and VLDLR (D’Arcangelo et al., 1999; Hiesberger et al., 1999). Reelin binding to its receptors recruits DAB1 to their cytoplasmic tails activating the SRC family kinases, SRC, FYN and YES (Arnaud et al., 2003; Bock and Herz, 2003; Hoe et al., 2006). This leads to the increased tyrosine phosphorylation of DAB1 and the recruitment of additional signaling adaptor proteins that activate 2 key branches of the pathway (Fig. 4). One branch is initiated by the binding of CRK and CRKl to phospho-DAB1, leading to the phosphorylation of C3G (RAPGEF1) and activation of RAPI (RAP1A) (Bailiff et al., 2004; Franco et al., 2011). This leads to the upregulation of N-Cadherin (CDH2) cell-surface expression through engagement with p120 catenin (CTNND) (Jossin and Cooper, 2011). A second branch is regulated by the binding of phosphatidylinositol 3-kinase (PI3K/AKT) to DAB1 leading to the activation of PDK (PDK1, PDK2) and AKT (AKT) ultimately suppressing the activity of the MAPT kinase GSK3 (Bock et al., 2003). In mouse, deficiency of DAB1 has been shown to augment tau-phosphorylation and Stk25 has been implicated in this process (Brich et al., 2003; Matsuuki et al., 2012). Since the signaling complex and the downstream pathways have potential significance in the development of AD, we tested their associated genes for enrichment in AD.

The canonical Reelin-Dab1 signaling pathway has been studied extensively in mouse neurons and brain (Lee and D’Arcangelo, 2016). For analysis, we divided the pathway into 3 sections: (1) the receptor complex, (Reelin, the receptors ApoER2, VLDLR, the adaptor protein DAB1, and the tyrosine kinases SRC, FYN, and YES) (Arnaud et al., 2003; Bock and Herz, 2003; D’Arcangelo et al., 1999; Hiesberger et al., 1999); (2) branch 1 that regulates N-cadherin (CRK, CRKL, C3G, RAP1, P120 catenin, N-cadherin) (Bailiff et al., 2004; Franco et al., 2011; Jossin and Cooper, 2011); and (3) branch 2 that is involved in microtubule-associated protein tau (MAPT) phosphorylation (PI3K, PDK, AKT, GSK3, STK25) (Bock et al., 2003; Brich et al., 2003; Matsuuki et al., 2012). We converted these mouse proteins to the homologous human genes with the BioConductor function in R and the NCBI database (www.ncbi.nlm.nih.gov/) yielding: a) RELN, VLDLR, LRP8, DAB1, SRC, FYN, YES1, b) CRK, CRKL, RAPGEF1, RAPIA, CTNND, CDH2, c) PI3KC3, PDK1, PDK2, GSK3B, AKTI, STK25, MAPT. We tested associations in the DAB1-RELN pathway using individual gene-based tests, and by grouping genes into the 3 candidate
pathways defined above. Gene-based analysis was run by MAGMA using FUMA v1.3.7 (Leeuw et al., 2015; Watanabe et al., 2017) using summary statistics from the GWAS. MAGMA was run using default settings; reported p-values are from a SNP-wise mean model. Competitive setting of MAGMA was used to test the candidate pathways for the enrichment of AD significant genes as compared to the rest of the genome.

3. Results

Total 288 cases and 5,102 controls were analyzed, consisting of 48.6% females in cases and 52.4% in controls, mean age 76.7 in cases and 72.9 in controls. We present the results in the following order: (1) analysis of the APOE locus, (2) analysis of other previously reported GWAS in these cases, (3) identification of the DAB1 locus as a genome wide for disease, and (4) assessment of other loci in the same DAB1–RELN pathway.

3.1. APOE locus

No suggestive variants were identified in the APOE gene or surrounding region (chromosome 19: 44.5–46.5 Mb, as defined previously (Escott-Price et al., 2017)) with the lowest p-value at 0.003 within 1Mb of the APOE gene (Supplementary Fig. S1) in APOE-e4 homozygotes. A logistic regression testing the effect of the APOE locus in all individuals (before restricting to APOE-e4 homozygotes) and adjusting for age, sex and principal components, found the allelic effect of e4 to be OR = 3.91 (3.65–4.18), p = 0 in a logistic regression on AD status. This is similar to the reported OR for the e4-defining SNP in e.g. the Kunkle Stage I genome-wide association analysis (rs419358, OR = 3.33, CI = 3.20–3.45, p = 1.17 × 10−881) (Kunkle et al., 2019). Taking only e4 homozygotes compared to e3 homozygotes gives OR = 14.33 (14.30–16.61), p = 3.45 × 10−274. This is also consistent with previously reported estimates for e4/e4 vs. e3/e3 (OR = 14.49, CI = 11.91–17.64) (Genin et al., 2011).

3.2. Other GWAS hits

Loci previously reported as GWAS for association with Alzheimer’s disease status did not show a strong replication in the current analysis of APOE-e4 homozygotes only (Supplemental Table S1). Though the power to detect the GWAS-reported effect sizes in this sample is not sufficient (see last column of Supplemental Table S1), 4 loci in CD33 (p = 0.004), IQCK (p = 0.009), LILRB2 (p = 0.005) and SORL1 (p = 0.007, MAF=0.04) had the strongest evidence for association in the current analysis and a consistent direction of effect between the current and previous GWAS. Weaker but nominally significant associations with the consistent direction of the effect were also observed in the APH1B (p = 0.024), BNI (p = 0.011), SEC61G (p = 0.015) and SNXI (p = 0.048) genes. In total, 8 out of 77 SNPs (previously reported as genome-wide significant and available in our study), replicated at 0.05 significance level with the same direction of association, which is statistically greater than chance (p = 0.038). In addition, 53/77 (69%) SNPs have same direction of effect in the current analysis and previous GWAS which is greater than expected by chance (p = 0.001).

3.3. Identification of DAB1 as a locus

Multiple novel genome-wide significant intronic SNPs were present in DAB1 (lead SNP: rs112437613, OR = 2.28, CI = 1.73–3.01, p = 5.36 × 10−10; Fig. 1 and Supplemental Fig. S2, Table 1). The minor allele T was associated with disease risk (MAF=6% in non-AD and 12% in AD e4e4-participants of the UK Biobank). To allow for the fact that some individuals might not have reached the age at onset, we fit a survival regression model (adjusting for PCs and sex). The result for the same risk allele (T) remained highly significant (Hazard Ratio=2.27, CI = 1.75–2.95, p = 7.8 × 10−10). The Kaplan–Meier graph (Fig. 2) demonstrates that probability of getting the disease (y-axis) earlier (x-axis) is higher as the number of the risk alleles of rs112437613 SNP increases.

The frequency of this allele is reported 4%–7% in European population cohorts (1000Genomes, TOPMED, GnomAD, Estonian, ALSPAC-UK, TWINSUK, Northern Sweden, see https://genome.ucsc.edu). However, this SNP (and others in LD with it) did not show even a nominal association to AD in recent GWAS that did not preselect for the e4e4 genotype: e.g. a study of 21,982 cases and 41,944 controls the p-values were p=0.5 (Table 1) (Kunkle et al., 2019).

Indeed, in a case/control sample (without screening for the APOE-e4 status), the effect size of this SNP would be OR = 1.016, as the proportion of cases, with both T allele of
rs112437613 and ε4ε4, is 0.016 (=MAF(ε4ε4)2−MAF(rs112437613 in ε4ε4) = 0.362−0.12), where 0.36 is the ε4 allele frequency in cases (Frieden and Garai, 2012), and, similarly, of controls is 0.001. Therefore, the frequencies of the T allele in the overall sample are expected to be 0.061 in cases and 0.06 in controls, and consequently, the power to detect it with the sample size of the (Kunkle et al., 2019) study is close to 0 (~3 × 10−7).

This observation led us to test for an epistatic effect in the whole sample of the UK Biobank aged 65+ (N = 229,748). There was indeed significant epistasis between the 2 loci (interaction effect p = 1.5 × 10−5), whereas the main effect of the T allele (rs112437613) was positive (OR = 1.16, SE = 0.11), but only nominally significant (main effect p = 0.021), providing evidence for cooperation between these 2 loci. The risk allele frequencies in this locus depending on APOE and AD status are shown in Table S2 and the risk of AD, depending on the genotypes at the 2 loci, is shown in Fig. 3. The figure and table clearly show a statistical epistatic effect, where the disease risk is only visible in people with ε4ε4 genotypes.

3.4. Candidate analysis of other loci in the Reelin-DAB1 pathway

Following identification of an epistatic effect in DAB1, we assessed the lead SNP in RELN for statistical interaction. The RELN gene is comprised of 2002 SNPs and the most significantly associated SNP was rs171331137 (chr7:103479651) with OR=1.51 (SE=0.11), p = 2.4 × 10−4 (Supplemental Fig. S5). Similar to DAB1, we tested this SNP for interaction with APOE-ε4 in the whole UK Biobank sample. The interaction term was not significant (p = 0.24), however the pattern of AD risk based on the pair of these markers was similar to DAB1 (Supplemental Fig. S4).

We performed gene-based tests (see “DAB1-RELN pathway analysis” in Methods) on genes in the Reelin-DAB1 pathway which highlighted nominally-significant associations in AKTI, DAB1, PIK3CA, RELN and RAP1A (Table 2). By combining genes into candidate pathways, we also tested whether the receptor complex and the 2 pathway branches contained significantly more AD associated genes as compared with the rest of the genome. We found that they were almost significantly enriched for genes associated to AD in the APOE-ε4 homozygotes (p values 0.061, 0.077, 0.083, for the receptor complex and branches 1 and 2, respectively). The strongest significance was achieved when we combined the receptor complex and the 2 branches of the pathway (p = 0.0061) (Fig. 4).

4. Discussion

4.1. No residual association at the APOE locus

APOE-ε4 is the strongest genetic risk factor for late onset AD. APOE-ε4 carriers have elevated risk for AD and earlier age-at-onset,
with APOE-ε4 homozygotes at the highest risk (Corder et al., 1993; Freudenberg-Hua et al., 2018). Many loci beyond APOE have been reported as associated with disease in increasingly large GWAS and meta-analyses, with over 80 susceptibility loci reported collectively (Andrews et al., 2020; Bellenguez et al., 2022; Wightman et al., 2021). We find no evidence to support the role of additional loci in an extended 2Mb region around APOE in APOE-ε4 homozygotes. This is supported by previous work on risk in the APOE region after adjusting for number of ε4 alleles (Jun et al., 2012; Naj et al., 2011). It is therefore unlikely that variants contribute additional risk to AD in the APOE region in APOE-ε4 homozygotes although association has previously been reported in PVR12 and APOC1 in Chinese samples after adjusting for number of APOE-ε4 alleles (Zhou et al., 2019). Variants around APOE may explain additional variation in risk in populations where polymorphisms are in less pronounced LD with rs429358, and residual variability in APOE-ε3 carriers may still modify risk for the disease (Roses et al., 2009).

4.2. Other established GWAS hits

This study does not have sufficient statistical power to reliably determine whether all the previously reported GWAS hits are associated with disease in APOE-ε4 homozygotes or whether those which do show direct evidence for association (nominal significance) are grouped in any particular pathway.

4.3. Association with DAB1

Putative novel risk SNPs with strong evidence for association were mapped to the DAB1 gene on chromosome 1. Roles for DAB1 and RELN have previously been suggested in AD primarily based on studies in mice (Hoe et al., 2006; Kocherhans et al., 2010; Pujadas et al., 2014; Rice et al., 2013; Rossi et al., 2020) and functional genomic analysis in humans (Gao et al., 2015), but genome-wide association in humans has been lacking. However, it has been shown that the expression of DAB1 and RELN are altered in AD brains (Botella-López et al., 2006; Chin et al., 2007; Muller et al., 2011). DAB1 interacts with Asp-Pro-any residue-Tyr (NPXY) motifs in the cytoplasmic domains of amyloid precursor protein (APP) as it does with similar motifs in the cytoplasmic tails of the Reelin receptors through its N-terminal PTB domain (Howell et al., 1999b; Trommsdorff et al., 1998). The NPXY motif is required for APP internalization and its deletion reduces Aβ production (Perez et al., 1999). DAB1 association with APP has been shown to reduce amyloidogenic processing (Hoe et al., 2006), which suggests it is involved in the intracellular trafficking of APP. Reelin also reduces Aβ production in HEK293 cells that don’t express DAB1 (Rice et al., 2013). In a mouse model of AD, heterozygosity of Reln increases the accumulation of Aβ plaques (Kocherhans et al., 2010), suggesting that the pathway physiologically alters APP cleavage in a manner that would protect against AD. In addition, homozygous loss-of-function in Reln and Dab1 have been shown to augment tau-phosphorylation (Brich et al., 2003). Reelin overexpression reduces abnormal somatodendritic localization of phosphor-Tau, Aβ plaques and synaptic loss in AD model mice (Pujadas et al., 2014; Rossi et al., 2020). Thus there are links between the Reelin-DAB1 pathway and the 2 major pathological features of AD. In this study, both examined branches of the DAB1-RELN pathway had genes with significant association with AD. SNPs near RAP1A were significant; however, it remains to be determined if this branch regulates Aβ phosphor-Tau or another AD related pathology. The other major pathway downstream of Reelin-DAB1 has been associated with tau-phosphorylation and both AKT and PI3K/AKT from this branch were significantly associated with AD.

The dependence of the association between DAB1/RELN and AD on APOE-ε4 homozygosity is intriguing since there are several links between the Reelin pathway and APOE. The Reelin receptors are also APOE receptors and DAB1 binds the NPXY motifs in the cytoplasmic tails of other LDL-superfamily receptors (Howell et al., 1999b; Howell and Herz, 2001; Trommsdorff et al., 1998), such as LDL-receptor related protein 1 that has roles in APOE/Aβ internalization and clearance (Shinohara et al., 2017). Recent studies show that APOE-ε4 reduces recycling of ApoER2 back to the plasma membrane making the cells less responsive to Reelin (Chen et al., 2010) and that Reelin protects against the toxic effects of Aβ.
on synapses (Lane-Donovan et al., 2015). Thus in APOE-ε4 homozygotes, one can imagine a threshold effect with high APOE-ε4 driving a pathological cycle by reducing the effects of DAB1 and RELN signaling including its normal function to reduce Aβ production/toxicity and/or MAPT-phosphorylation. While the effect the SNPs have on the function of DAB1 or other pathway genes remain to be determined, based on previous studies it would seem likely that they cause a partial loss-of-function that is potentially age dependent or cell-type specific in nature and would result in altered expression (eQTL) or splicing (sQTL). More than partial disruption of activity would likely lead to a developmental disorder in the homozygous individuals similar to loss-of-function alleles for Dab1 in mice and RELN in humans and mice (Bar et al., 2003). The significant SNPs identified here fall in intron 2 and are found in 4−7% of the population. Interestingly DAB1 exomic variation is constrained and few variants are more prevalent than 1−2% (GnomAD) suggesting that the identified SNPs do not flag an alteration in the DAB1 coding sequence. DAB1 is alternatively spliced and differentially expressed most notably in a cell-type specific manner (Abadesco et al., 2014; Dhananjaya et al., 2018; Gao and Godbout, 2012; Yano et al., 2016). Alternative splicing has been shown to regulate exons encoding a subset of the phosphorylation sites and a C-terminal exon altering Dab1 functionality in mice. We note that humans have a read through variant of exon 3 that would lead to transcriptional termination 14 residues later (variant 9) that has not been identified in mice. It encodes the first part of the phosphotyrosine binding (PTB) domain residues 37−69, but it is likely to be functionally inert since the PTB domain extends to residue 171 (Howell et al., 1997). With this complexity and the size of the DAB1 gene, over 1 Mb, it could take significant effort to dissect the consequence of the SNPs identified here on gene function and AD.

While the UK Biobank provides a large cohort and contains sufficient APOE-ε4 homozygous individuals for analysis, where AD status is likely to have high diagnostic accuracy, there are several limitations to the current study. First, as a prospective longitudinal cohort, participants in the UK Biobank are relatively young and at point of analysis contained fewer AD cases than are routinely observed in large case-control meta-analyses. Second, this lower sample size meant power was inadequate to replicate associations of previously-reported genome-wide significant loci for AD. Third, the UK Biobank is known to show slight difference from the general UK population (according to the last UK-wide census) with respect to characteristics such as educational attainment, socioeconomic status and gender, and these may limit general applicability of the findings to other populations (Fry et al., 2017).

In conclusion, we find a novel genome-wide significant hit in DAB1 in an APOE-ε4 homozygote AD GWAS. This seems to be a hit only in APOE-ε4 homozygotes. Furthermore, it seems that this association marks a more general importance of the DAB1−RELN pathway in disease pathogenesis. It is not clear why this pathway should be of such importance in APOE-ε4 homozygotes only, but a clue may be that such individuals have particularly dense Aβ pathology and one can imagine that this pathway either has a role in modulating APP processing or in driving tau-phosphorylation in a manner that is dependent on high Aβ levels. This work suggests that DAB1 has a protective role in late onset AD and highlights the importance of resolving the mechanism that likely involves the REELIN-DAB1 pathway for therapeutic development.

**Verification**

The authors verify that the manuscript has not been published previously and is not under consideration for publication elsewhere and will not be published elsewhere, if accepted. Publication is approved by all authors and relevant authorities. A preprint is hosted on medRxiv (DOI: https://doi.org/10.1101/2022.04.28.22274418).

**Data availability**

Data underpinning the findings in this study are available upon successful application to the UK Biobank. Derived data including GWAS summary statistics are openly available at the Cardiff University research portal, at doi:10.17035/d.2022.0216755828.

**Disclosure statement**

The authors report no competing interests.

**CRediT authorship contribution statement**

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**Supplementary materials**

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.neurobiolaging.2022.07.009.

**References**


