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Mitochondrial pathway polygenic risk scores are associated with Alzheimer's Disease

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ABSTRACT

Genetic, animal and epidemiological studies involving biomolecular and clinical endophenotypes implicate mitochondrial dysfunction in Alzheimer's disease (AD) pathogenesis. Polygenic risk scores (PRS) provide a novel approach to assess biological pathway-associated disease risk by combining the effects of variation at multiple, functionally related genes. We investigated the associations of PRS for genes involved in 12 mitochondrial pathways (pathway-PRS) with AD in 854 participants from Alzheimer's Disease Neuroimaging Initiative. Pathway-PRS for the nuclear-encoded mitochondrial genome (OR: 1.99 [95% CI: 1.70, 2.35]) and three mitochondrial pathways is significantly associated with increased AD risk: (i) response to oxidative stress (OR: 2.01 [95% CI: 1.71, 2.38]); (ii) mitochondrial transport (OR: 1.81 [95% CI: 1.55, 2.13]); (iii) hallmark oxidative phosphorylation (OR: 1.22 [95% CI: 1.06, 1.40]. Therapeutic approaches targeting these pathways may have the potential for modifying AD pathogenesis. Further investigation is required to establish a causal role for these pathways in AD pathology.

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1. Introduction

Alzheimer's disease (AD) is a debilitating neurological condition characterized by memory deficits, cognitive and behavioural impairment (Huang and Mucke, 2012) affecting more than 43.8 million people worldwide (Nichols et al., 2019). The classical neuropathological hallmarks of AD are the accumulation of amyloid-β peptides into extracellular neuritic plaques and hyperphosphorylated tau into intracellular neurofibrillary tangles in isocortical, subcortical and memory-associated regions of the brain (Thal et al., 2002). The substantial attempts to develop drugs based on the role of amyloid-β and tau in AD pathogenesis have led to limited success in identifying disease-modifying therapies (Cummings et al., 2018). This lack of success has led to the exploration of other potential causal mechanisms such as mitochondrial dysfunction.

Mitochondria are intracellular organelles involved in producing energy-carrying ATP molecules through oxidative phosphorylation (OXPHOS) and other cellular processes, including calcium homeostasis, response to oxidative stress (OXSTRESS) and apoptosis (Cuperfain et al., 2018). Each mitochondrion possesses its own ~16.5 kb circular genome (mtDNA) encoding 37 genes (2 ribosomal RNA genes, 22 tRNA genes, and 13 protein-coding genes). There are a further ~1,158 genes in the nuclear genome (nDNA) that also encode proteins involved in mitochondrial function, known as nuclear-encoded mitochondrial genes (nMT-genes; or collectively nMT-DNA) (Calvo et al., 2016).

The mitochondrial cascade hypothesis of AD pathogenesis was first described in 2004 (Swerdlow and Khan, 2004a). Briefly, baseline mitochondrial function is genetically determined and declines

Abbreviations: nMT-DNA, nuclear-encoded mitochondrial genome; nMT-genes, nuclear-encoded mitochondrial genes; OXPHOS, Oxidative phosphorylation; OXSTRESS, Response to oxidative stress; PRS, Polygenic risk scores; Pathway-PRS, Pathway polygenic risk scores.

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with age due to environmental and lifestyle factors (Swerdlow and Khan, 2004a). This declining mitochondrial function is either the primary event initiating Aβ- or tau-induced toxicity (primary mitochondrial cascade) or a by-product of the amyloid cascade (secondary mitochondrial cascade) that results in AD pathology (Swerdlow, 2018).

This hypothesis is supported by several lines of evidence. Early epidemiological studies reported a 3-9 fold higher AD risk associated with maternal AD history (possibly associated with maternally-inherited mtDNA) compared with paternal or no AD family history (Edland et al., 1996). Altered mitochondrial structures and bioenergetics (Hirai et al., 2001), reduced glucose utilization and functional deficits in several mitochondrial enzymes have been observed in AD brains (Swerdlow and Khan, 2004b). In transgenic *APP* mutant mice, upregulated compensatory mitochondrial mechanisms precede rather than follow amyloid-β plaque deposition and behavioural changes (Reddy et al., 2004). Cell culture studies demonstrate inhibition of mitochondrial COX enzyme activity (Gabuzda et al., 1994), and increased mitochondrial-generated reactive oxygen species (ROS) (Leuner et al., 2012) shift AβPP processing towards the amyloidogenic pathway.

Several mitochondrial pathways are dysregulated or dysfunctional in AD. ATP production is reduced due to OXPHOS dysfunction (Biffi et al., 2014), mitochondrial transport is interrupted (Devi et al., 2006; Manczak and Reddy, 2012b), oxidative stress is increased (Wang et al., 2014), cellular apoptotic pathways are upregulated (Jia et al., 2015), intracellular neuronal calcium levels are increased, calcium buffering mechanisms are dysregulated (Jadiya et al., 2019), mitochondrial fission is increased and fusion decreased (Manczak and Reddy, 2012a), mitophagy is defective (Fang, 2019), and mitochondrial membrane potential (m$\Delta\Psi$) is reduced (Pérez et al., 2018). However, the molecular and genetic mechanisms through which the mitochondria mediate, initiate or contribute to AD-related pathology remain unknown and highly debated.

Individually, most variants in the nuclear-encoded mitochondrial genome (nMT-DNA) have sub-threshold ($p > 10^{-8}$) effects on AD risk (Kunkle et al., 2019a) in genome-wide association studies (GWAS). Greater predictive power is obtained by investigating the combined effect of multiple SNPs as polygenic risk scores (PRS), which can be weighted by their GWAS effect sizes (Choi et al., 2020; Escott-Price et al., 2015). PRSs can also be composed of genetic variants in multiple genes associated with the same biological pathway, forming a pathway-PRS. Taking this approach, we recently demonstrated that PRS composed of sub-threshold variants in nMT-genes is significantly associated with AD (Andrews et al., 2020).

In this study, we use a pathway-based approach, constructing PRSs for sets of genes that encode components of mitochondrial pathways, to investigate their association with AD in a biologically informative way.

2. Methods

2.1. Alzheimer's disease neuroimaging initiative

This study used data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) (Weiner et al., 2017), last accessed on 28 April 2019 ($n = 2175$). ADNI is a longitudinal study launched in 2004 with the objective of validating amyloid phenotyping, characterizing AD-associated biomarkers, and understanding the genetic underpinnings of AD to inform clinical trial design. ADNI's AD diagnostic criteria are based on both clinical assessments and neurophysiological tests (Weiner et al., 2017). A case-control study design was employed based on diagnosis at last assessment for each participant.

Participants were excluded if they had any of the following: (i) missing diagnoses ($n = 33$), (ii) diagnosis of mild cognitive impairment (MCI) but not AD ($n = 558$), (iii) missing *APOE* genotype ($n = 44$) or missing genome-wide sequencing data ($n = 517$). Only participants with self-reported 'non-Hispanic white' ancestry were included in the study to avoid bias due to population stratification, resulting in the exclusion of 169 additional samples. The final study sample included 854 participants (CN = 355, AD = 499).

2.2. Genotype data

Genotype data was obtained from the ADNI database (http://adni.loni.usc.edu). Details of the collection, curation, processing and quality-control of ADNI data are described in detail elsewhere (Saykin et al., 2015; Weiner et al., 2017). Briefly, nDNA was extracted from whole blood and genotyped on Illumina GWAS arrays for ADNI1 (Illumina Human 610-Quad BeadChip), ADNI GO/2 participants (Illumina HumanOmniExpress BeadChip), and ADNI3 participants (Illumina Infinium Global Screening Array v2) (Weiner et al., 2017). *APOE* genotyping of the two SNPs (rs429358, rs7412) that distinguish the $\varepsilon 2$, $\varepsilon 3$, and $\varepsilon 4$ alleles was performed separately for all individuals, and quality controlled (Saykin et al., 2015). Missing genotype information was imputed on the Michigan Impute server using MiniMac3 and HRC Reference panel (MAF $> 1\%$, r2 > 0.3).

Standard GWAS quality control (Marees et al., 2018) of ADNI genotype data included removing: (i) individuals with SNP missingness $> 5\%$, (ii) SNPs with sample missingness $> 5\%$, (iii) SNPs with MAF $< 1\%$; (iv) ambiguous SNPs, (v) duplicate SNPs, (vi) individuals ± 3 SD from the mean sample heterozygosity rate (indicative of sample contamination or inbreeding), (vii) SNPs deviating from Hardy-Weinberg equilibrium (HWE) $p < 10^{-6}$ for cognitively normal controls and $p < 10^{-10}$ for MCI and AD cases (indicative of possible genotyping errors), (viii) discordance between reported and genetic sex; (ix) cryptic sample relatedness (pi-hat threshold 0.18752) using KING (Manichaikul et al., 2010); and (x) samples of non-European ancestry (± 6 SD from 1000 genomes EUR population mean on 10 PCs).

Principal component analysis (PCA) (Price et al., 2006) was performed using plink version 1.90 beta to obtain eigenvalues and eigenvectors. A scree plot was generated using eigenvalues and the elbow method was used to determine that the first 3 principal components (PCs) explained >90% of the variance due to genetic ancestry. These first 3 PCs were used as covariates in the regression model to correct for residual population stratification (see section 2.4).

2.3. Polygenic risk profiling

We constructed three whole-genome AD PRSs and 12 mitochondrial pathway-specific PRSs (Table 2) for each ADNI participant using the 'standard weighted allele' method implemented in PRSice2 and PRSet (Choi and O'Reilly, 2019) for the whole-genome and specific mitochondrial pathway gene sets, respectively.

SNPs were weighted by their GWAS effect sizes from the International Genomics of Alzheimer's Project (IGAP; GWAS Catalog Study ID: GCST007511) (Kunkle et al., 2019a). We retained GWAS SNPs with a p-value threshold (P_T) ≤ 0.5 for computing the PRS. This threshold provided a good model fit for our data (see Appendix C) and is supported by published evidence as the optimum threshold for estimating AD PRSs using common variants (Escott-Price et al., 2015). Linkage disequilibrium (LD) clumping was performed for the whole genome (250 kb window, r2 < 0.1) using

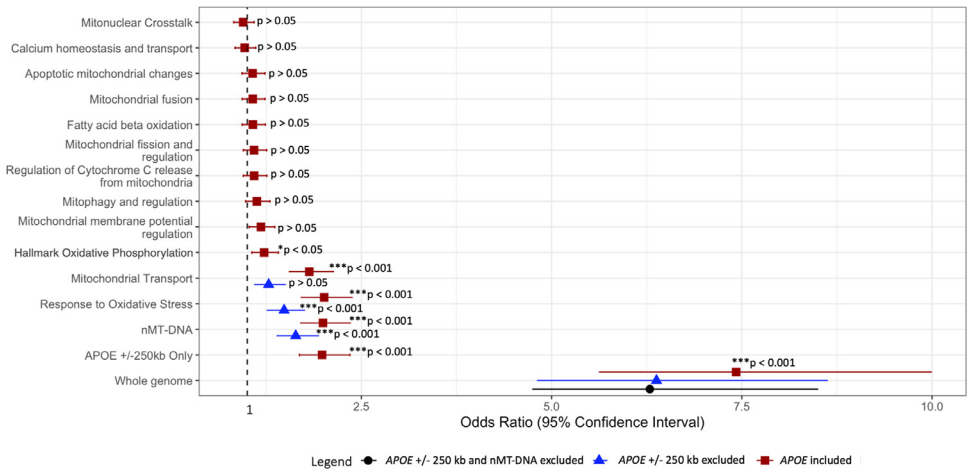

Fig. 1. Odds Ratio estimates (95% Confidence intervals) for polygenic risk scores regressed with AD diagnosis. Significance of Competitive p-values reported here, are interpreted as follows: * $p < 0.05$ (significant); ** $p < 0.01$ (very significant); *** $p < 0.001$ (highly significant). Red squares denote the inclusion of variants in the APOE region, blue triangles denote exclusion of the APOE ± 250 kb region, and the black circle denotes exclusion of the APOE ± 250 kb region and the complete nuclear-encoded mitochondrial genome (nMT-DNA).

PRSice-2 (Choi and O'Reilly, 2019). Set-based LD clumping was performed using PRSet (Choi and O'Reilly, 2019) for pathway-specific polygenic risk scores to retain SNPs in the gene-set regions only (250 kb window, r2 < 0.1).

We omitted loci on sex chromosomes and in the major histocompatibility complex (MHC: 28.47 Mb–33.44 Mb, Chr6, GRCh37 (NCBI GRCh37, 2019)) because estimation of polygenic risk scores in these regions is difficult due to their genomic complexity, i.e. mis-mapping of reads due to high sequence homology between X and Y chromosomes, and high polymorphic diversity in the MHC region (Choi et al., 2020; Dawkins and Lloyd, 2019). As a result, 40 X-linked nMT-genes (Appendix A) and 5 nMT-genes in the MHC region (Appendix B) were excluded.

2.3.1. Whole-genome polygenic risk scores

Whole-genome PRS was estimated in three ways: (i) Whole-genome, i.e., for all included

SNPs; (ii) Excluding *APOE* gene ± 250 kb (19:45409011 – 45412650 on GRCh37), to assess effects that are independent of the known AD-risk alleles of the *APOE* and *TOMM40* genes (Yu et al., 2007); and (iii) Excluding the *APOE* gene ± 250 kb region and nMT-genes, to provide a baseline for estimating nMT-gene-specific effects. Polygenic risk score for *APOE* ± 250 kb region alone was also calculated including SNPs lying within the *APOE* gene and 250 kb high LD window on either side.

2.3.2. Mitochondrial pathway-specific polygenic risk scores

Mitochondrial pathway-specific PRSs were constructed for (i) 12 mitochondrial pathways represented by genesets obtained from the Molecular signatures database (MsigDB) (Liberzon, 2014) (Table 2) and (ii) the nMT-DNA geneset (comprising all nMT-genes) obtained from Mitocarta 2.0 (Calvo et al., 2016). Information about the curation and selection of these pathway genesets is detailed in Appendix D. These genesets were not limited to nMT-genes and include all nuclear genes known to influence or to be involved in mitochondrial function (Appendix E). Only the SNPs in introns and exons defined by GRCh37 gene boundaries (NCBI GRCh37, 2019) were included for PRS calculation.

The association of *TOMM40* with increased AD risk is confounded by its high LD with the *APOE* (Roses et al., 2016). Therefore, for the nMT-DNA and mitochondrial transport genesets, 2 PRSs were calculated, one that included *TOMM40* and thus the confounding effect of *APOE*, and one that excluded *TOMM40* and thus excluding both the direct effect of *TOMM40* and the confounding effect of *APOE*. All polygenic risk scores were standardized to z-scores with respect to the sample mean. A normal PRS distribution was obtained for all genomic regions and pathways assessed here. PRS distribution curves and summary statistics are reported in Appendix J.

2.3.3. Variance explained by mitochondrial pathway-specific polygenic risk scores

The amount of phenotypic variance explained by the genetic contribution of each mitochondrial pathway (represented by the pseudo-r2 metric (Lee et al., 2012)) was calculated using PRSet. Genotypic variance explained by each pathway-PRS was calculated as the additive sum of genetic variance explained by each SNP within genes of that pathway. Results are reported in Appendix F.

2.4. Statistical analysis

2.4.1. Association testing

Differences in the demographic characteristics of AD cases and CN controls were assessed via one-way ANOVA for continuous variables (age, years of education, Mini Mental State Examination (MMSE) score) and Fisher's exact test for categorical variables (gender, *APOE* genotype). 1-way ANOVA was also performed to assess if there were significant differences in the mean whole-genome PRS and nMT-DNA PRS between the 2 diagnostic groups.

To evaluate the effect of pathway-PRS on AD, a multivariable logistic regression model was run for AD cases vs. CN controls. Age, sex, years of education, *APOE* $\varepsilon 4$ copy number (0, 1, 2), ADNI cohort (1/2/GO/3), and the first three principal components were included as covariates.

A replication study was performed in a small independent ADNI cohort (n = 375, CN = 229, AD = 146). These samples were obtained from ADNI1 (n = 10), ADNI2 (n = 198) and ADNI3 (n = 167) and have no overlap with the original target sample. Demographics of this cohort and results from the pathway-PRS analysis are reported in Appendix H.

A fixed-effects meta-analysis of the results from association testing of target cohort (Table 3, Fig. 1) and replication cohort (Appendix H) was performed using the R package 'metafor' (Viechtbauer, 2010). These results are reported in Appendix I.

The association between pathway-PRS and four AD endophenotypes was also investigated in a larger cohort (n = 1065, CN = 235,

Table 1
Demographics of ADNI participants ($n = 854$) included in this study

	Diagnosis		SMD[c]	p-value[c]
	CN	AD		
Number of individuals (N)	355	499		
Age (M (SD) years)[b]	79.45 (6.82)	78.41 (7.63)	0.143	$p < 0.05$
Male (%)[a]	192 (22.4)	295 (34.5)	0.102	$p > 0.05$
Education (M (SD) years)[b]	16.39 (2.60)	15.51 (2.89)	0.321	$p < 0.001$
APOE genotype (N (%))[a]				$p < 0.001$
$\varepsilon 2+$	47 (5.5)	26 (3.0)	0.284	
$\varepsilon 3/\ \varepsilon 3$	219 (25.6)	161 (18.8)	0.708	
$\varepsilon 4+$	91 (10.6)	325 (38.0)	0.898	
MMSE (M (SD))[b]	28.93 (1.38)	19.77 (6.09)	2.074	$p < 0.001$
Whole-genome PRS (M (SD))[b]	-0.47 (1.02)	0.34 (0.84)	0.864	$p < 0.001$
nMT-DNA PRS (M (SD))[b]	-0.35 (0.94)	0.25 (0.97)	0.626	$p < 0.001$

APOE, Apolipoprotein E; CN, Cognitively Normal; AD, Alzheimer's Disease; PRS, Polygenic Risk Score; nMT-DNA, nuclear-encoded mitochondrial DNA.

[a] *Number of individuals (N) and percentage of cohort (%) have been reported for gender and APOE genotypes.*

[b] *Mean (M) ± standard deviation (SD) have been reported for age, education, MMSE (mini-mental state examination score), whole-genome PRS, and nMT-DNA PRS.*

[c] *One-way ANOVA was performed for continuous variables (age, years of education, MMSE score, whole-genome PRS, and nMT-DNA PRS) and Fisher's exact test for categorical variables (gender, APOE genotypes). SMD (standardized mean difference) and p-values have been reported.*

AD = 463, MCI = 367). 2 cerebrospinal (CSF) biomarkers - amyloid beta ($n = 619$) and tau levels ($n = 718$), and 2 global cognition scores – ADAS Cog-score ($n = 1062$) and mPACCdigit ($n = 1065$) were examined. Samples sizes for each endophenotype analysis reduced due to missing data. A multivariable linear regression model was run with age, sex, years of education, *APOE* $\varepsilon 4$ copy number (0, 1, 2), ADNI cohort (1/2/GO/3), and first three principal components included as covariates. Demographic statistics and results are reported in Appendix K.

All statistical analyses were performed in R 3.4.4.

2.4.2. Multiple testing burden correction

p-value significance was calculated after correcting for multiple testing burden using two methods (a) False Discovery Rate (FDR < 0.05) using the Benjamini-Hochberg procedure (Benjamini and Hochberg, 1995) embedded within p.adjust() R function, and (b) competitive empirical *p*-value approach using PRSice and PRSet (Choi and O'Reilly, 2019) to compare the outcome of adjusted p-value significance for each pathway using both methods.

A competitive *p*-value (*Competitive – p*) was obtained for each pathway-PRS as:

$$Competitive - P = \frac{\sum_{n=1}^{N} I\ (Pnull < Pobserved) + 1}{N + 1}$$

where *Pobserved* is the probability of the observed difference between cases and controls for each pathway-PRS, *Pnull* is obtained for SNPs randomly selected from the background exome in numbers (N) equivalent to those in the pathway-PRSs.

PRSet randomly generates hypothetical 'control' pathway gene sets with a similar number of SNPs as the target pathway, then randomly shuffles samples' phenotype (case/control diagnosis) and runs the regression model to obtain a null *p*-value. This is repeated over 10000 permutations to generate a *Pnull* distribution curve, against which the observed p-value of association for that pathway is compared, to determine the *p*-value significance. This approach ensures that a higher *p*-value significance is not simply a consequence of greater number of SNPs in a pathway, since the *p*-value of the target pathway is assessed against a null *p*-value distribution generated from hypothetical pathways with the same number of SNPs chosen randomly from the background genome. Pathways yielding both significant FDR-adjusted and competitive *p*-values were deemed as overall significant, while those with inconsistent *p*-value significance were regarded as tentative results.

3. Results

3.1. Research cohort

Descriptive statistics for ADNI participants ($n = 854$; CN = 355, AD = 499) are presented in (Table 1). There are significant differences between the CN and AD groups for years of education, *APOE* genotype, and MMSE score. The mean whole-genome PRS and complete nMT-DNA PRS are also significantly different between groups, with AD cases having a higher mean PRS than CN controls.

3.2. Polygenic scores of the whole nuclear genome and AD risk

The whole-genome PRS is significantly associated with AD, with a 1 SD increase in the PRS associated with AD (OR: 7.40 [95% CI: 5.60, 9.97]). These results remain highly significant even after (i) exclusion of *APOE* region ±250kb (OR: 6.37 [95% CI: 4.81, 8.62]) and (ii) exclusion of both *APOE* region ±250kb and nMT-genes (OR: 6.29 [95% CI: 4.75, 8.49]) (Fig.1). The OR decreases when these gene regions are excluded, but the confidence intervals largely overlap (Fig.1). These ORs are substantially greater than the OR for *APOE* ±250kb region alone (OR: 1.96 [95% CI: 1.66, 2.33).

3.3. Polygenic scores of nMT-DNA and mitochondrial pathways and AD risk

The nMT-DNA PRS is significantly associated with AD (OR: 1.99 [95% CI: 1.70, 2.35]). In the pathway analyses, 3 mitochondrial pathways are significantly associated with AD: (i) OXSTRESS (OR: 2.01 [95% CI: 1.71, 2.38]); (ii) mitochondrial transport (OR: 1.81 [95% CI: 1.55, 2.13]); and (iii) hallmark oxidative phosphorylation (OR: 1.22 [95% CI: 1.06, 1.40]; Fig.1). For the mt$\Delta\Psi$ regulation pathway (OR: 1.18 [95% CI: 1.02, 1.36]), the FDR-adjusted p-value is nominally significant ($p_{FDR} < 0.05$), however the competitive p-value is not significant ($p_{competitive} > 0.05$).

Table 2
Genomic regions and pathway genesets for which polygenic risk scores were calculated

Polygenic Risk Score	Total genes[a]	nMT-genes[a]	SNPs[b]
Whole nuclear genome	18463	1158	515164
Whole nuclear genome (excluding APOE ± 250 kb)	18298	1156	515058
Whole nuclear genome (excluding APOE ±250kb and nMT-DNA[b])	17142	0	83066
nMT-DNA[c]	1158	1158	13992
Response to Oxidative Stress	352	60	5803
Hallmark Oxidative Phosphorylation	245	211	2399
Mitochondrial Transport	179	107	2394
Apoptotic mitochondrial changes	58	25	922
Mitochondrial membrane potential regulation	54	21	1124
Mitonuclear crosstalk	38	0	1061
Mitochondrial fission and regulation	24	13	652
Fatty acid beta-oxidation	21	14	211
Calcium homeostasis and transport	19	7	402
Mitochondrial fusion	19	11	262
Mitophagy and regulation	171	24	3401

APOE, Apolipoprotein E.
[a] *Total number of nuclear genes and nuclear-encoded mitochondrial genes (nMT-genes) in each geneset have been reported.*
[b] *Total number of SNPs included for polygenic risk score calculation for each pathway are reported.*
[c] *nMT-DNA comprises of the complete geneset of nuclear-encoded mitochondrial genome.*

Table 3
Significant associations of polygenic risk scores for different genomic regions or pathways with Alzheimer's Disease

Genomic region/ pathway	Including *APOE* region				Excluding *APOE* (±250 kb window)			
	Beta[a]	SE[b]	FDR-adjusted *p*-value[b]	Competitive *p*-value	Beta[a]	SE[b]	FDR-adjusted *p*-value[c]	Competitive p-value[c]
Whole-genome	13.69	0.14	9.27×10^{-34}	1.00×10^{-4}	12.44	0.14	9.94×10^{-34}	1.00×10^{-4}
APOE +/- 250 kb region[c]	8.05	0.08	2.33×10^{-15}	1.00×10^{-4}	N/A	N/A	N/A	N/A
nMT-DNA[d]	8.37	0.08	3.89×10^{-9}	1.00×10^{-4}	5.91	0.08	1.65×10^{-8}	1.00×10^{-4}
Response to oxidative stress[d]	8.32	0.08	3.71×10^{-6}	1.00×10^{-4}	4.75	0.08	7.51×10^{-6}	1.00×10^{-4}
Mitochondrial transport[d]	7.40	0.08	6.01×10^{-3}	1.00×10^{-4}	3.13	0.07	4.62×10^{-3}	1.56×10^{-1}
Hallmark oxidative phosphorylation	2.77	0.07	1.18×10^{-2}	2.15×10^{-2}	-	-	-	-
Mitochondrial membrane potential regulation	2.28	0.07	4.24×10^{-1}	2.42×10^{-2}	-	-	-	-
Mitophagy and regulation	1.64	0.07	1.72×10^{-1}	1.99×10^{-2}	-	-	-	-
Regulation of cytochrome C release from mitochondria	1.20	0.07	3.33×10^{-1}	5.42×10^{-2}	-	-	-	-
Mitochondrial fission and regulation	1.20	0.07	3.33×10^{-1}	5.59×10^{-1}	-	-	-	-
Apoptotic mitochondrial changes	0.95	0.07	4.02×10^{-1}	8.96×10^{-1}	-	-	-	-
Mitochondrial fusion	0.98	0.07	4.02×10^{-1}	9.99×10^{-1}	-	-	-	-
Fatty acid beta-oxidation	0.99	0.07	4.02×10^{-1}	9.95×10^{-1}	-	-	-	-
Calcium homeostasis and transport	-0.47	0.07	6.66×10^{-1}	9.99×10^{-1}	-	-	-	-
Mitonuclear crosstalk	-0.76	0.07	4.97×10^{-1}	9.97×10^{-1}	-	-	-	-

APOE, Apolipoprotein E. nMT-DNA represents the complete nuclear-encoded mitochondrial geneset.
[a] *Beta denotes beta estimates from multivariate regression between pathway-PRS and diagnosis.*
[b] *Standard errors (SE), FDR-adjusted p-value, and competitive p-value of association are reported.*
[c] *APOE +/- 250 kb region includes APOE gene and 250 kb window on either side.*
[d] *Apart from the whole-genome, only 3 pathway genesets (nMT-DNA, Response to oxidative stress, and Mitochondrial transport) included genes lying within the APOE +/- 250 kb region, therefore only these pathways were tested for association with AD after excluding the APOE +/- 250 kb region, to reduce multiple testing burden. Hence, p-values are NA for all other pathway genesets.*

The associations of nMT-DNA PRS (OR: 1.63 [95% CI: 1.39, 1.93]) and OXSTRESS (OR: 1.48 [95% CI: 1.26, 1.75]) pathways remains significant even after exclusion of the *APOE* ±250kb region (Table.3). For the Mitochondrial transport pathway-PRS (OR: 1.23 [95% CI: 1.03, 1.48]), the FDR-adjusted *p*-value remains significant ($p_{FDR} < 0.01$), but the competitive *p*-value becomes non-significant ($p_{competitive} > 0.05$) on *APOE* ±250kb exclusion. Omission of the *APOE* ±250kb region was not necessary for the other pathways because they do not contain genes within this region.

The results from the replication study (reported in Appendix H) showed that the nMT-DNA PRS is significantly associated with AD (OR: 1.65 [95% CI: 1.30, 2.13]). In the pathway analyses, 2 mitochondrial pathways are significantly associated with AD: (i) OXSTRESS (OR: 1.62 [95% CI: 1.28, 2.06]) and (ii) mitochondrial transport (OR: 2.02 [95% CI: 1.58, 2.64]; Appendix H). Whole-genome PRS is significantly associated with AD, with a 1 SD increase in the PRS associated with higher AD risk (OR: 5.41 [95% CI: 4.93, 6.14]), and remains highly significant even after the exclusion of *APOE* ±250kb region (OR: 4.84 [95% CI: 4.36, 5.57]).

The results from fixed-effects meta-analysis of both target and replication studies (reported in Appendix I) showed that the nMT-DNA PRS is significantly associated with AD (OR: 1.88 [95% CI: 1.64, 2.15]). In the pathway analyses, four mitochondrial pathways are significantly associated with AD: (i) OXSTRESS (OR: 1.87 [95% CI: 1.63, 2.14]), (ii) mitochondrial transport (OR: 1.87 [95% CI: 1.63, 2.14]), (iii) hallmark oxidative phosphorylation (OR: 1.19 [95% CI: 1.05, 1.34]), and (iv) mitochondrial membrane potential regulation (OR: 1.15 [95% CI: 1.02, 1.30]). Even after the exclusion of *APOE* ±250kb region, nMT-DNA (OR: 1.51 [95% CI: 1.31, 1.73]), OXSTRESS (OR: 1.36 [95% CI: 1.19, 1.56]), and mitochondrial transport path-

way (OR: 1.24 [95% Cl: 1.09, 1.42]) remain significant. Furthermore, the whole-genome PRS is significantly associated with AD, with a 1 SD increase in the PRS associated with higher AD risk (OR: 6.61 [95% Cl: 5.26, 8.30]), and remains highly significant even after the exclusion of *APOE* ±250kb region (OR: 5.76 [95% Cl: 4.57, 7.25]).

We found statistically significant associations between some pathway-PRS and AD endophenotypes. These results are reported and briefly described in Appendix K.

The highest amount of AD phenotypic variance in the model was explained by collective genetic variation of the whole-genome (∼30%) followed by the OXSTRESS pathway (∼8%). The variance explained by nMT-DNA, mitochondrial transport, and OXPHOS pathway-PRS was 7%, 5%, and 1.5% respectively (see Appendix F). Although the variance explained by each mitochondrial pathway is small, it highlights the contribution of their genetic variation to the AD phenotype.

4. Discussion

In this study, we investigated the association of AD polygenic risk scores composed of genetic variants located within genes associated with known mitochondrial pathways with AD risk. We found that pathway-PRS composed of the complete nuclear-encoded mitochondrial genome and genes involved in (i) response to oxidative stress, (ii) mitochondrial transport, and (iii) hallmark oxidative phosphorylation were associated with increased AD risk. The results obtained by the pathway-based approach used here suggest that SNPs in nMT-genes and other nuclear genes involved in mitochondrial pathways significantly contribute to AD risk, suggesting therapeutic potential in targeting them.

Previous multi-omics studies support the role of mitochondrial pathways in AD. For instance, (Mostafavi et al. (2018) built molecular networks using modules of co-expressed genes associated with AD and its endophenotypes. They found three modules enriched for gene ontology categories related to mitochondria showing a positive correlation with histopathological β-amyloid burden, cognitive decline, and clinical diagnosis of AD (Mostafavi et al., 2018). Similarly, (Johnson et al. (2020) conducted a co-expression network analysis of AD brains and found that protein co-expression families involved in mitochondrial metabolism strongly correlated with AD, and showed the strongest differences by case status (Johnson et al., 2020).

Two studies performed proteomic profiling of AD brain tissues and cerebrospinal biomarkers and found modules of co-expressed proteins strongly linked to mitochondrial metabolism (Higginbotham et al., 2020; Muraoka et al., 2020). In parallel, (Ryu et al., 2021) demonstrated that neural cell cultures differentiated from LOAD patient-derived pluripotent stem cells show multiple mitochondrial bioenergetic alterations, such as lower mitochondrial mass, reduced glucose uptake, low NAD levels, and overcompensation by OXPHOS upregulation (Ryu et al., 2021). Collectively, these studies suggest that higher baseline genetic susceptibility conferred by mitochondrial pathway-associated polygenic risk results in lifelong altered and inefficient mitochondrial bioenergetics. Through progressive homeostatic imbalances, environmental influences with aging and accumulation of mutations, this may exacerbate mitochondrial dysfunction, thereby predisposing higher AD risk.

Our results add to accumulating evidence from genetic, clinical, model cell and animal studies supporting the involvement of these mitochondrial pathways and nMT-genes in AD. We found that a 1 SD increase in the OXPHOS pathway-PRS is associated with 1.22 times increased likelihood of developing AD. The importance of OXPHOS pathway in generating ATP-energy to support the high cellular energy demand in the brain and the body is well-established (Cuperfain et al., 2018). Reduced ATP production due to mitochondrial OXPHOS dysfunction activates a cascade of events leading to neural cell death observed in AD-associated neurodegeneration (Biffi et al., 2014). Importantly, dysregulation of gene networks and gene regulation can also facilitate OXPHOS dysfunction, as demonstrated for *PTCD1* using knock-out and cell-culture models (Fleck et al., 2019; Pa et al., 2019).

We found that a 1 SD increase in the mitochondrial transport pathway-PRS is associated with 1.81 times increased likelihood of developing AD. Disruption of mitochondrial transport can lead to defective communication with the nucleus and other cytosolic components. Current evidence indicates that defective mitochondrial transport in AD is primarily due to Aβ- and tau-interactions blocking mitochondrial channels such as TOMM40 (Devi et al., 2006), TIM23 (Devi et al., 2006), TOMM22 (Hu et al., 2018), and VDAC1 (Manczak and Reddy, 2012b). Hence, mitochondrial transport dysfunction may be a secondary effect of Aβ and tau toxicity. The contribution of *TOMM40*-specific effects to mitochondrial transport pathway-PRS is difficult to delineate due to confounding from its high LD with *APOE* (Roses et al., 2016).

We found that a 1SD increase in the OXSTRESS pathway-PRS is associated with 2.01 times increased likelihood of developing AD. The OXSTRESS pathway, which, when upregulated, activates the eIF2α/ATF4 axis increasing expression of stress response genes (Michel et al., 2015), is strongly associated with AD pathology and causes calcium dyshomeostasis, loss of mt$\Delta\Psi$, high mutation rates, interrupted gene transcription and regulation due to high ROS-mediated cellular damage (Wang et al., 2014). The OXSTRESS geneset contains the *APOE* gene. Increasing evidence suggests that the *APOE* genotype influences mitochondrial stress-related processes in an APOE isoform-specific manner (Dose et al., 2016). Therefore, SNPs from the *APOE* gene would have contributed to the higher pathway-PRS and AD association.

Finally, we found that a 1 SD increase in the mt$\Delta\Psi$ regulation pathway-PRS is associated with 1.18 times increased likelihood of developing AD. However, while this of mt$\Delta\Psi$ was significant after FDR correction, it non-significant after applying permutation testing, therefore the results for this pathway are interpreted with caution.

In the replication analysis of a small independent ADNI cohort, we obtained significant results for the whole-genome (with and without exclusion of *APOE* +/-250 kb), nMT-DNA, OXSTRESS, and mitochondrial transport, thus validating these results. Due to the small sample size (n = 375, CN = 229, AD = 146), we had insufficient power to detect a significant association for mitochondrial membrane potential regulation pathway, and nMT-DNA and mitochondrial transport after *APOE* +/-250 kb exclusion. The fixed-effects meta-analysis of target and replication studies showed similar results as the target study (reported in Appendix I).

Moderate to high heritability of late-onset AD (LOAD) is indicated by SNP (∼53%) (Ridge et al., 2016) and twin studies (∼60% –80%) (Gatz et al., 2006). *APOE* is the strongest known genetic predictor of LOAD risk, explaining up to 13% of the phenotypic variance (Ridge et al., 2016). GWAS have identified multiple GWS non-APOE loci which explain up to 33% of AD phenotypic variance (Ridge et al., 2016) and have been implicated in multiple pathways (Karch and Goate, 2015). This could explain our result that the OR estimates for AD risk slightly decrease yet remain significant after the exclusion of *APOE* region (±250 kb window) from the whole-genome PRS (Fig.1). The exclusion of *APOE* ±250kb and nMT-DNA from whole-genome PRS was an attempt to estimate baseline nMT-gene-specific effects. It results in a slightly smaller yet significant OR with large overlapping intervals with whole-genome PRS. We

found that beta estimates are not significantly different between 'whole-genome PRS excluding *APOE* ±250kb' and 'whole-genome excluding *APOE* ±250kb and nMT-DNA'. Possibly because the nMT-DNA explains a much smaller proportion of phenotypic variance compared to the high genome-wide contribution even after *APOE* exclusion.

Our result for the OR estimate of *APOE* +/- 250kb region PRS is slightly smaller yet comparable to those reported in a recent systematic review of *APOE* ORs ranging between 2.07 (95% CI: 1.67 –2.56) - 4.87 (95% CI: 4.22 –5.63) (Stocker et al., 2018). ADNI's smaller sample size and differing cohort characteristics may have contributed to a slightly smaller OR. Additionally, previous studies only calculated OR for the *APOE* ε4 allele, while we calculated a PRS for *APOE* gene region, which will include protective SNPs with negative effect sizes that contributed to a lower OR compared to the *APOE* ε4 allele alone.

The nMT-DNA, mitochondrial transport, and OXSTRESS genesets contain genes located in the *APOE* ±250 kb region (Kunkle et al., 2019b). Interestingly, the OR estimates for nMT-DNA and OXSTRESS pathways are similar to the estimate for the APOE ±250kb region. Yet, the association of nMT-DNA and OXSTRESS pathway-PRS with AD remains significant even after the exclusion of the *APOE* ±250 kb region. Thus, re-emphasising the contribution of non-*APOE* genes in conferring substantial polygenic risk of these pathway genesets. However, the competitive *p*-value for mitochondrial transport is not significant after the exclusion of *APOE* ±250 kb region, which includes the *TOMM40* gene. This result may reflect the known high risk of *APOE/TOMM40* loci (Roses et al., 2016). Because of high LD, the contributions of these two loci to PRS cannot be separated. Exclusion of the region may, therefore, result from either removal of a real effect of *TOMM40* variation or removal of a confounding effect of *APOE* variation.

These results should be interpreted in conjunction with some study limitations. First, the ADNI cohort is relatively small, and our results require replication in a larger independent cohort. Second, only participants of European ancestry were included, therefore these results may not be generalizable to other ancestrally diverse populations. Third, our analysis was conducted using the ADNI clinical diagnostic criteria for AD which did not include biomarker assessment. This can result in heterogeneity in clinical diagnosis due to concomitant or alternative neuropathology's that can lead to clinical phenotypes that are analogous to AD. Future studies should consider the reassessment of AD diagnoses by integrating biomarkers data. Finally, our pathway-PRS may underestimate of true genetic risk conferred by mitochondrial pathways. We could not include mtDNA SNPs previously implicated with AD risk (Hahn and Zuryn, 2019) since large-scale AD GWAS for mtDNA variants are currently unavailable.

The primary strength of this study is the pathway-driven, biologically informed approach to polygenic risk scoring. The pathway-PRS OR estimates presented in this paper are comparable to those previously reported for high-risk single GWS variants (Kunkle et al., 2019b). This is because pathway-PRS effectively capture the cumulative small effects of sub-threshold variants within genes involved in mitochondrial pathways. This results in a larger combined effect size and hence higher statistical power to detect association with AD than association testing of GWS variants individually.

Future research may benefit by (a) performing out-of-sample validations and replication in larger datasets to challenge overfit prediction models and to validate the findings of this study; (b) investigating the association between the pathway-PRS and AD endophenotypes or within the A/T/N research framework (Dubois et al., 2021); (c) incorporating functional annotation of intronic and exonic gene regions or AD-associated intergenic eQTLs to calculate PRS; and (d) assessing the clinical utility of pathway-PRS for patient risk stratification to guide prevention and early treatment.

5. Conclusion

In conclusion, this study demonstrated that the genetic variation within the OXPHOS, mitochondrial transport, and OXSTRESS pathways captured by pathway-PRS significantly influences AD risk. These findings contribute to the growing evidence of a mitochondrial role in AD and suggest these pathways as potential targets in ameliorating AD pathogenesis. However, it remains to be determined if mitochondrial dysfunction is the primary cause of AD pathogenesis. Further investigations are required to validate and establish the causal role of nMT-genes and pathways in AD pathology.

Disclosure statement

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Conceptualisation and design of study: SJA, DP, Acquisition of data: SJA, Analysis and/or interpretation of data: DP, SJA, TWM, Drafting of the manuscript: DP, Revising the manuscript critically for important intellectual content: SJA, DP, JP, RHS, SE, Approval of the version of the manuscript to be published: SJA, DP, TWM, JP, RHS, SE.

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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.2021.08.005.

Appendix

Appendices A-K provided.

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