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ORIGINAL INVESTIGATION

Shared genetic architecture between metabolic traits and Alzheimer's disease: a large-scale genome-wide cross-trait analysis

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Abstract

A growing number of studies clearly demonstrate a substantial link between metabolic dysfunction and the risk of Alzheimer's disease (AD), especially glucose-related dysfunction; one hypothesis for this comorbidity is the presence of a common genetic etiology. We conducted a large-scale cross-trait GWAS to investigate the genetic overlap between AD and ten metabolic traits. Among all the metabolic traits, fasting glucose, fasting insulin and HDL were found to be genetically associated with AD. Local genetic covariance analysis found that 19q13 region had strong local genetic correlation between AD and T2D ($P = 6.78 \times 10^{-22}$), LDL ($P = 1.74 \times 10^{-253}$) and HDL ($P = 7.94 \times 10^{-18}$). Cross-trait meta-analysis identified 4 loci that were associated with AD and fasting glucose, 3 loci that were associated with AD and fasting insulin, and 20 loci that were associated with AD and HDL ($P_{meta} < 1.6 \times 10^{-8}$, single trait $P < 0.05$). Functional analysis revealed that the shared genes are enriched in amyloid metabolic process, lipoprotein remodeling and other related biological pathways; also in pancreas, liver, blood and other tissues. Our work identifies common genetic architectures shared between AD and fasting glucose, fasting insulin and HDL, and sheds light on molecular mechanisms underlying the association between metabolic dysregulation and AD.

Introduction

Alzheimer's disease (AD) is a progressive and devastating neurodegenerative disorder characterized by impairments of memory, cognitive function, language and behavior (Craft 2009; Vemuri et al. 2017). In 2016, over 44 million people worldwide were estimated to be affected (Alzheimers.net 2016) and by 2050, the prevalence will nearly triple (Brookmeyer et al. 2007). While aging is the major risk factor for the vast majority of cases, susceptibility is also influenced by genetics. During the last decade, 19 loci have been identified for AD, a number of which are related to metabolism. The link between metabolic dysregulation and impaired cognition has recently become clearer, leading some to consider late-onset AD a "metabolic" disease (Craft 2009; Demetrius and Driver 2013; Fabbri et al. 2015; Leoni et al. 2010). Diabetes mellitus, both type 1 (T1D) and type 2 (T2D), increases the risk of AD four-fold. The metabolic syndrome, a clinical entity including abdominal obesity, hypertension, low HDL, hyperglycemia and hypertriglyceridemia (Milionis et al. 2008; Pasinetti and Eberstein 2008), is associated with cognitive decline and structural brain changes such as cortical thinning (Schwarz et al. 2018).

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One hypothesis to account for the link between metabolism and AD is a common genetic etiology. Metabolic traits and AD may have similar clinical or epidemiological risk factors and these risk factors can be originated from the same genetic variants. Specifically, our initial hypothesis was that AD is associated with glucose-related traits, represented by T2D, fasting glucose and fasting insulin. The sharing of multiple risk factors for two complex diseases could be due to an overlap in causal genes and pathways. Thus, grouping the genetic variants common to multiple diseases or traits could provide insight into specific biological processes underlying their comorbidity; in addition, except for population stratification bias which was usually accounted for using principal components of genome-wide association studies (GWAS) data, these shared genetic variants are not likely affected by confounding factors at the phenotypic level, such as diet and other environmental factors. For example, we recently identified 38 loci that shared by asthma and allergic diseases and these loci were found to be enriched in epithelium and immune-related biological process (Zhu et al. 2018b), and we also found 11 loci shared by AD and 5 common cancers (Feng et al. 2017). Genetic factors play a significant role in AD, as evidenced by twin data indicating heritability varying between 58 and 79%, even after accounting for shared environmental influences (Gatz et al. 2006; Pedersen 2010). The co-occurrence of metabolic disorders and AD in the same individual suggests the potential of pleiotropic effects, which may have a substantial genetic contribution. A recent study assessed the genetic causality between AD and metabolic traits (Østergaard et al. 2015). However, no genome-wide study has been conducted to identify the shared genetic loci between AD and metabolic traits and provide biological interpretation of the shared loci. We, therefore, conducted a large-scale cross-trait GWAS analysis to investigate the shared heritability between AD and ten metabolic traits, at both globally whole-genome level and individual variant level.

Methods

Study design, data summary and quality control (QC)

The overall study design is shown in Supplementary Fig. 1. We retrieved summary statistics from publically available GWAS studies, including AD from the International Genomics of Alzheimer's Project (IGAP) consortium ($N = 54,162$), body mass index (BMI) (Locke et al. 2015) ($N = 236,231$) and waist-to-hip ratio (WHR) (Shungin et al. 2015) ($N = 142,762$) from the GIANT Consortium, T2D from the DIAGRAM Consortium (Scott et al. 2017) ($N = 159,208$), fasting glucose ($N = 58,047$) and fasting insulin ($N = 51,750$) from the MAGIC Consortium (Dupuis et al. 2010), and blood lipids [HDL-C ($N = 60,812$), LDL-C ($N = 58,381$), TC ($N = 60,027$), and TG ($N = 62,166$)] from ENGAGE Consortium (Surakka et al. 2015). Details of each of the datasets can be found in Supplementary Table 1.

We applied standardization of GWAS summary data to minimize potential biases due to the different array platforms and QC procedures. First, we used the LiftOver tool to convert any GWAS summary data that have reference genome NCBI36/hg18 to GRCh37/hg19. We further filtered out variants with a minor allele frequency (MAF) < 1%. In this study, we restricted our analysis to autosomal chromosomes.

LD score regression analysis

We conducted post-GWAS genome-wide genetic correlation analysis by LD score regression (LDSC) using all SNPs after merging with HapMap3 SNP excluding the HLA region. LDSC estimates genetic correlation between the true causal effects of two traits (ranging from − 1 to 1) from summary statistics using the fact that the GWAS effect size estimate for each SNP represents the effects of all SNPs in linkage disequilibrium with that SNP. SNPs in a high linkage disequilibrium region would have higher $\chi 2$ statistics than SNPs in a low linkage disequilibrium region, and a similar relationship is observed when single-study test statistics are replaced with the product of the z scores from two studies of traits with some correlation (Bulik-Sullivan et al. 2015a). LDSC applied a self-estimated intercept during the analysis to account for shared subjects between the studies (Bulik-Sullivan et al. 2015b).

Partitioned genetic correlation analysis

To characterize the genetic overlap at the level of functional categories, we estimated genetic correlation between AD and 3 metabolic traits in 11 large genomic functional annotation using partitioned LDSC, where each annotation contains more than 200,000 SNPs that are in common with our GWAS data. These annotations included transcribed region, transcription factor binding sites (TFBS), Super Enhancer, intron, DNaseI digital genomic footprinting (DGF) region, DNase I hypersensitivity sites (DHSs), fetalDHS and histone marks H3K9ac, H3K4me1, H3K4me3, H3K27ac (Finucane et al. 2015). For each annotation, we re-calculated LD scores for SNPs assigned to that particular category and then used the annotation-specific LD scores for estimating the AD-metabolic trait genetic correlation for each partition separately.

Local genetic covariance analysis

To investigate whether there is local genetic correlations between AD and metabolic traits, we performed ρ-HESS (Shi et al. 2017), a method to estimate the local genetic correlation between a pair of traits at each LD-independent region in the genome. Approximately, independent LD blocks with average 1.5 Mb long were used for the calculation of each local genetic heritability and genetic covariance. The traits were included in this analysis based on two criteria: the genome-wide genetic correlation estimate from LDSC analysis is greater than 10%; the summary statistic data are based on 1000 genome imputation to ensure non-zero number of variants in each local region in ρ-HESS; thus, three traits pairs were included in this analysis, AD and T2D, AD and LDL, AD and HDL.

Meta-analysis of fasting glucose and fasting insulin (FG–FINS meta-analysis)

The fasting glucose and fasting insulin GWAS summary statistics were derived from the MAGIC consortium, with a sample size of 58,047 and 51,750, respectively. All participants were adults with European ancestry. Both traits were measured from whole blood, plasma or serum with standard and used for GWAS linear regression model. However, the power of each GWAS trait was limited by their sample size in terms of their genetic correlation with AD. Thus, to boost the power of GWAS for glucose metabolism phenotype, we used inverse-variance-weighted meta-analysis from METAL (Willer et al. 2010) to combine the GWAS summary statistics from fasting glucose and fasting insulin. We flipped the sign of effect estimates of fasting insulin before the meta-analysis to incorporate the known negative biological relationship between insulin and glucose. To account for the genomic inflation due to shared samples where the two GWAS summary statistics were calculated, Z-score output from METAL meta-analysis was further adjusted by dividing the square root of LDSC intercept (1.333) of meta-analysis summary statistics (Bulik-Sullivan et al. 2015b). *P* values were re-calculated based on adjusted Z scores. Thus, the adjusted genomic inflation factor for fasting glucose and fasting insulin meta-analysis result is 1.061.

Cross-trait meta-analysis

After assessing genetic correlations among all traits, we applied cross-trait GWAS meta-analysis using the R package Cross-Phenotype Association (CPASSOC) to combine the association evidence for AD with fasting glucose, fasting insulin and HDL, respectively, at individual variants as exploratory post hoc analysis based on the criteria of both Rg > 10% and $P < 0.05$ from LDSC (Zhu et al. 2015). This method combines effect estimate and standard error of the GWAS summary statistics to test hypothesis of association between the SNP with both traits, for example AD and fasting glucose, or AD and fasting insulin, or AD and HDL. A heterogeneous version of CPASSOC (SHet) was used in this study.

SHet is a cross-phenotype meta-analysis method based on fixed effect model. It can be viewed as the maximum of weighted sum of trait-specific test statistics, which is closely related to a gamma distribution. It is more powerful when there is heterogeneous effect present between studies, which is common in meta-analysis of different phenotypes (Lee et al. 2019; Zhu et al. 2015, 2018a). SHet also uses the sample size for a trait as a weight instead of variance.

We applied PLINK clumping function (parameters: --clump-p1 1.6e-8 --clump-p2 1e-5 --clump-r2 0.2 --clump-kb 500) to determine top loci that are independent of each other, i.e., variants with *P* value less than 1×10^{-5} have r^2 more than 0.2 and less than 500 kb away from the peak will be assigned to that peak's clump. We identified all genes falling within each clump region. A *P* value of 1.6×10^{-8} ($5 \times 10^{-8}/3$) was used as genome-wide significance level for cross-trait meta-analysis to account of 3 meta-analysis testing.

Pathway analysis, tissue enrichment analysis and transcriptome-wide association analysis (TWAS)

To understand the biological insights of the shared genes between 3 trait pairs, AD and fasting glucose, AD and fasting insulin, AD and HDL, we have performed multiple post-GWAS functional analyses using shared genes identified from cross-trait meta-analysis. We used the WebGestalt tool (Zhang et al. 2005) to assess overrepresented enrichment of the identified shared gene set between AD and 3 metabolic traits in the Gene Ontology (GO) biological process functional categories. The Benjamini–Hochberg procedure was used for correcting multiple testing in pathway analysis. The GTEx tissue (Consortium et al. 2017) enrichment analysis was performed based on 30 general tissue types (Watanabe et al. 2017). Integrative transcriptome-wide association analyses were performed using FUSION package based on 44 post-mortal GTEx (version 6) tissues (Consortium et al. 2017) expression weights. To identify association between AD and metabolic traits with gene expressions in specific tissues, we conducted a TWAS using FUSION software package based on 44 post-mortal GTEx (version 6) tissues expression weights (Gusev et al. 2016). Bonferroni correction was applied for each trait's all gene–tissue pairs on TWAS *P* values to account for multiple testing.

Prioritization of candidate genes

We used two methods to prioritize the genes to be discussed among the candidates within the region boundaries from cross-trait meta-analysis. First, we prioritized the genes that are overlapping with TWAS functional analysis. When there is no overlapping genes with TWAS, we review the literature for all genes within the boundaries and then discuss genes/gene families with the most biologically relevance to the traits of interest.

Mendelian Randomization (MR) analysis

We performed MR analysis using MR-PRESSO (Verbanck et al. 2018) between two types of continuous traits (fasting glucose and HDL) and AD since they are genetically correlated. We built the MR instruments based on LD-independent SNPs. We did not include fasting insulin trait because no genome-wide significant SNPs was presented.

Results

Genetic correlation between AD and metabolic traits

We evaluated the genetic correlation of AD and ten metabolic traits using cross-trait LD score regression from both GWASs to estimate their genetic relationship. Fasting glucose and fasting insulin both have substantial magnitude of genetic correlation with AD, though statistical significance was marginal (Rg = 0.169, $P = 0.081$ for fasting glucose; Rg = − 0.196, $P = 0.087$ for fasting insulin). Their genetic correlations with AD were in opposite direction with similar magnitude. We did not observe substantial genetic correlation between AD and obesity traits (BMI and WHR, both Rg < 0.05 and $P > 0.3$), T2D (Rg = 0.106, $P > 0.2$) and other lipid traits (LDL, TC and TG, Rg = 0.104, -0.076, 0.022, respectively, all $P > 0.17$) (Table 1). Considering the well-known inverse direct relationship between glucose and insulin, we carried out cross-trait meta-analysis between FG and FINS to boost GWAS power for glucose regulation effect. This meta-analysis would increase the power to detect genetic effects that increase glucose level via reduction of insulin secretion. We observed that FG–FINS meta-analysis effect has an even greater magnitude of genetic correlation with AD and is statistically significant (Rg = 0.254, $P = 0.016$). We also observed that HDL had a significant genetic correlation with AD (Rg = − 0.137, $P = 0.0436$).

Analysis of partitioned genetic correlation by functional category

In partitioned LDSC analysis, we evaluated the genetic correlation between AD and 3 metabolic traits by 11 functional annotations to pin down specific regions on the genome that may explain more of the genetic effect sharing than others. In this analysis, we found AD and metabolic traits to have a similar genetic correlation pattern.

The genetic correlation suggested various signals but with similar trends in all the regions. Notably, the Rg estimate was negatively correlated between AD and fasting insulin, AD and HDL, among all partitioned categories. We identified intron that had the highest level of genetic correlation between AD and fasting insulin (Rg = − 0.366) (Fig. 1 and Supplementary Table 2), which does not involve in coding of mRNA but might harbor genetic variants related to alternative splicing. In addition, the transcribed region was found to have the highest level of genetic correlation between AD and HDL (Rg= − 0.1471), where this region can transcribe DNA sequence to mRNA.

Table 1 Genetic correlation and SNP-based heritability between AD and metabolic traits

Phenotype 1	Phenotype 2	Rg	Rg_SE	*P* value	H2	H2_SE
Alzheimer's disease	BMI	0.046	0.050	0.358	0.137	0.007
	WHR	0.012	0.073	0.865	0.094	0.006
	T2D	0.106	0.096	0.268	0.077	0.006
	FG	0.169	0.097	0.081	0.099	0.018
	FINS	− 0.196	0.115	0.087	0.069	0.010
	FG–FINS meta-analysis	0.254	0.106	0.016	0.032	0.007
	LDL	0.104	0.077	0.176	0.103	0.038
	HDL	− 0.137	0.068	0.044	0.131	0.027
	TC	− 0.076	0.071	0.286	0.133	0.034
	TG	0.021	0.053	0.680	0.184	0.033

Rg genetic correlation estimate, *SE* standard error of genetic correlation estimate, *BMI* body mass index, *WHR* waist hip rate, *T2D* type 2 diabetes, *FG* fasting glucose, *FINS* fasting insulin, *LDL* low-density lipoprotein, *TC* total cholesterol, *TG* triglyceride

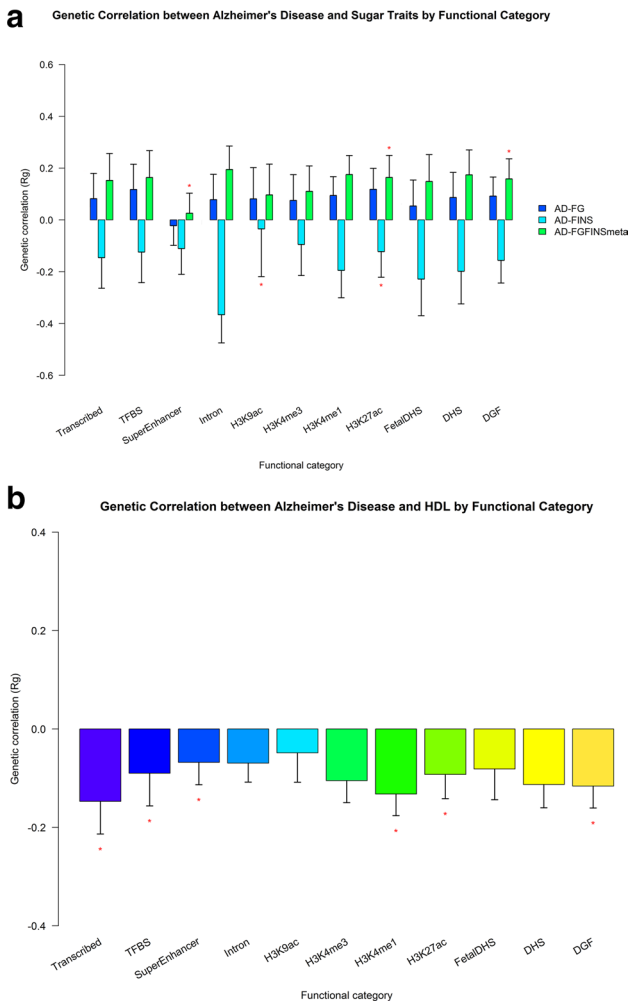

Fig. 1 Partitioned genetic correlation. **a** Genetic correlation between Alzheimer's disease and sugar traits by functional category. **b** Genetic correlation between Alzheimer's disease and HDL by functional category. Vertical axis represents the genetic correlation estimate Rg (standard error) and horizontal axis represents 11 functional categories. Asterisk represents significance ($P<0.05$). *DGF* DNase I digital genomic footprinting, *DHS* DNase I hypersensitivity site, *TFBS* transcription factor binding sites, *AD* Alzheimer's disease, *FG* fasting glucose, *FINS* fasting insulin, *FGFINSmeta* meta-analysis of fasting glucose and fasting insulin

On the contrary, positive genetic correlations were observed among fasting glucose and the FG–FINS meta-analysis in almost all the functional categories for AD. Specifically, we identified that intron had the highest level of genetic correlation between AD and FG–FINS meta-analysis (Rg = 0.1946) (Fig. 1 and Supplementary Table 2).

Local genetic correlation between AD and metabolic traits

Although the genome-wide genetic correlation between AD and some metabolic traits was not significant, we additionally performed ρ-HESS to investigate whether a specific region of genome can be genetically correlated between them. In the analysis among 3 trait pairs (AD–T2D, AD–LDL, AD–HDL), we identified 1 region (chromosome 19: 44,744,108–46,102,697) that showed a strong local genetic correlation between each of the 2 traits ($P=6.78\times10^{-22}$ for AD–T2D, 1.74×10^{-253} for AD–LDL, 7.94×10^{-18} for AD–HDL) (Fig. 2 and Supplementary Table 3–5). This region is known for the *APOE* gene, who serves as a modulator between AD and T2D.

Cross-trait meta-analysis between AD and metabolic traits

We used CPASSOC to perform genome-wide meta-analysis to identify genetic loci that were associated with both AD and metabolic traits (meta-analysis $P<5\times10^{-8}$, and trait-specific $P<0.05$).

AD and fasting glucose

After pruning, we found 4 loci that were associated with both AD and fasting glucose at the genome-wide significance level in the cross-trait meta-analysis (Table 2). The first locus (index SNP: rs10501320, $P_{meta}=2.80\times10^{-16}$) was in close proximity to genes *MADD, ACP2* and *AGBL2*, which was found to play roles in insulin sensitivity (Wagner et al. 2011), lysosome and cerebellar function (van de Bunt et al. 2015) and immune complexes (Zhang et al. 2014). The second loci (index SNP: rs12805422, $P_{meta}=1.57\times10^{-13}$) was mapped to the genes *C11orf94* and *CRY2* which encode for a flavin adenine dinucleotide-binding protein involved in regulating the circadian clock. The third loci (index SNP rs1483121 $P_{meta}=6.10\times10^{-10}$) was in close proximity to an intergenic region closest to the *OR4S1* gene, which is related to G-protein coupled receptor activity and transmembrane signaling receptor activity. In addition, we found that genetic loci represented by rs17747324 ($P_{meta}=4.52\times10^{-9}$) on *TCF7L2* are associated with both AD and fasting glucose after meta-analysis. Notably, *TCF7L2* is a well-known risk gene for diabetes, which exerts a strong inhibitory effect on glucose-induced insulin secretion (Gloyn et al. 2009).

AD and Fasting insulin

A total of three loci were identified after meta-analysis of AD and fasting insulin (Table 3). The first one (index SNP: rs2279590, $P_{meta}=1.14\times10^{-17}$) was mapped on *CLU*, a gene that encodes a secreted chaperone protein involved in basic biological events such as cell death, tumor progression, and neurodegenerative disorders. The second locus represented by rs6656401 ($P_{meta}=3.71\times10^{-15}$) was mapped on *CR1* and *CR2*, genes encoding for membrane protein. The

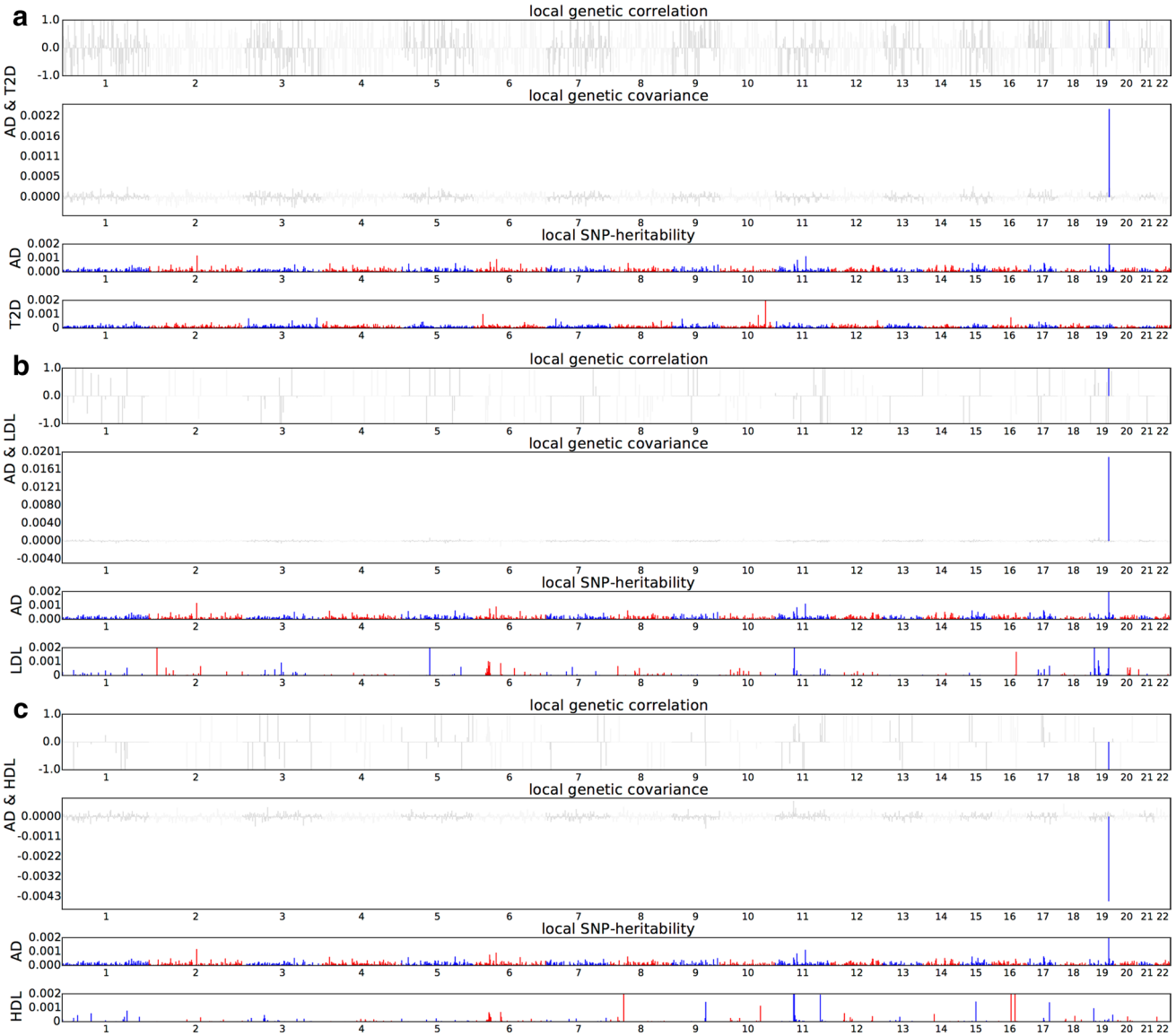

Fig. 2 Local genetic correlation and local SNP-heritability between Alzheimer's disease and T2D (2a), LDL (2b) and HDL (2c), respectively. For each sub-figure, the top part represents local genetic correlation, the middle part represents local genetic covariance, and significant local genetic correlation and covariance after multiple testing correction are highlighted in blue; the bottom part represents local SNP heritability for individual trait

third locus (index SNP: rs4803750, $P_{meta} = 6.54 \times 10^{-13}$) located in close proximity to *BCL3*, which encodes the apolipoprotein J/clusterin, whose polymorphisms have been related to AD susceptibility in published GWAS (Lancaster et al. 2015).

AD and HDL

The cross-phenotype meta-analysis between AD and HDL identified 20 genome-wide significant loci (Supplementary Table 6). The most significant locus is characterized by the *APOE/APOC1* gene (index SNP rs157595, $P_{meta} = 1.21 \times 10^{-97}$). We noticed that this locus was not only significant after meta-analysis, but also reached genome-wide significance in both single trait GWAS of AD ($P = 3.76 \times 10^{-101}$) and HDL ($P = 1.92 \times 10^{-8}$). Among 20 independent loci, eight of them were from 19q13.32 region, which is known for the *APOE/APOC1/APOC2* gene cluster. In addition, *BIN1* on 2q14.3 (index SNP rs6733839, $P_{meta} = 3.19 \times 10^{-25}$) and *CCDC116* on 22q11.21 (index SNP rs5754166, $P_{meta} = 3.61 \times 10^{-12}$) showed moderately strong association with both AD and HDL, which drove the overall significance of the meta-analysis.

Table 2 Cross-trait meta-analysis between AD and fasting glucose ($P_{meta} < 1.6 \times 10^{-8}$; single trait $P < 0.05$)

SNP	CHR	N	Position	AD		Fasting Glucose		CPASSOC P	Genes within clumping region	pQTL
				BETA	P	BETA	P			
rs10501320	11	109	chr11:46,297,631..48009074	8.23×10^{-2}	2.98×10^{-6}	-2.50×10^{-2}	7.11×10^{-13}	2.80×10^{-16}	ACP2,AGBL2,AMBRA1,ARFGAP2,ARHGAP1,ATG13,C1QTNF4,C11orf49,CELF1,CHRM4,CKAP5,CREB3L1,DDB2,DGKZ,F2,FAM180B,FNBP4,HARBI1,KBTBD4,LRP4,LRP4-AS1,MADD, MDK, MIR3160-1, MIR3160-2, MIR4688, MIR5582, MIR6745, MTCH2, MYBPC3, NDUFS3, NR1H3,NUP160,PACSIN3,PSMC3,PTPMT1,PTPRJ,RAPSN,SLC39A13,SNORD67,SPI1,ZNF408	NA
rs12805422	11	27	chr11:45,838,926..45932800	5.62×10^{-2}	3.38×10^{-4}	-2.20×10^{-2}	9.55×10^{-13}	1.57×10^{-13}	C11orf94,CRY2,MAPK8IP1,PEX16	NA
rs1483121	11	1	chr11:48,333,360..48333360	6.65×10^{-2}	2.58×10^{-3}	-2.90×10^{-2}	1.66×10^{-9}	6.10×10^{-10}	Intergenic region, OR4S1*	NA
rs17747324	10	7	chr10:114,752,503..114808902	-4.12×10^{-2}	3.23×10^{-2}	-2.40×10^{-2}	7.50×10^{-10}	4.52×10^{-9}	TCF7L2	Glypican−1, C-type lectin domain family 5 member A, Gastrin-releasing peptide, Interferon gamma receptor 1

SNP Single nucleotide polymorphisms, *HR* chromosome, *AD* Alzheimer's disease, *CPASSOC* cross-phenotype association, *pQTL* genotype–protein associations

Table 3 Cross-trait meta-analysis between AD and fasting insulin ($P_{meta} < 1.6 \times 10^{-8}$; single trait $P < 0.05$)

SNP	CHR	N	Position	AD		Fasting insulin		CPASSOC P	Genes within clumping region	pQTL
				BETA	P	BETA	P			
rs2279590	8	11	chr8:27,422,740..27477509	−0.143	3.75×10^{-17}	7.20×10^{-3}	0.036	1.14×10^{-17}	CLU,MIR6843	Pulmonary surfactant-associated protein C, Tenascin, Protein FAM163A, GDP-fucose protein O-fucosyltransferase 2, Prolargin, Scavenger receptor class A member 5, Protein eva-1 homolog C
rs6656401	1	11	chr1:207,653,395..207804141	0.157	7.73×10^{-15}	-9.60×10^{-3}	0.018	3.71×10^{-15}	CR1,CR2	Polymeric immunoglobulin receptor, Protein S100-A5, Complement decay-accelerating factor
rs4803750	19	2	chr19:45,242,173..45247627	−0.241	9.04×10^{-13}	-1.90×10^{-2}	0.008	6.54×10^{-13}	Intergenic region, BCL3*	Many, see Supplement Table 6

SNP single nucleotide polymorphisms, *CHR* chromosome, *AD* Alzheimer's disease, *CPASSOC* cross-phenotype association, *pQTL* genotype–protein associations

Overlap between cross-trait meta-analysis results and genotype–protein associations (pQTL)

For assisting in further functional annotation, we checked our cross-trait meta-analysis for the three pairs with recent published study pQTL study (Sun et al. 2018). We compared the genomic position of our significant SNP clumps with the pQTL genomic regions for overlap checking (Tables 2, 3 and Supplementary Table 6–8). A total of 23 loci overlap with pQTL regions. Notably, we identified 19q13.32 (known for *APOE*) and 19q13.42 (known for *LILRA3*) regions were associated with many correlated proteins.

Biological pathway, tissue enrichment and TWAS

Pathway analyses were performed to identify biological pathways enriched in shared loci ($P_{meta} < 1.6 \times 10^{-8}$) related to AD and metabolic traits. We found that AD shared amyloid metabolic process pathways with both fasting glucose trait and fasting insulin trait ($FDR < 0.01$), and shared protein lipid remodeling reverse cholesterol transport and sensory perception-related pathways with HDL trait ($FDR < 0.01$) (Supplementary Table 9–11).

The GTEx enrichment analysis identified five independent tissues expression that was significantly enriched (after Benjamini–Hochberg correction) for expression of cross-trait associated genes for each of the three trait pairs, including blood, heart, liver, muscle and pancreas for AD and fasting glucose; blood, liver, pancreas, small intestine and spleen for AD and fasting insulin; blood esophagus, heart, liver and pancreas for AD and HDL (Fig. 3). Among them, the most strongly enriched tissue was part of the hormone and enzyme producing system (pancreas).

To identify association between AD and metabolic traits with gene expressions in specific tissues, we conducted a TWAS in 44 GTEx tissues (Supplementary Table 12–14). We used the Bonferroni correction for each trait's all gene–tissue pairs on TWAS *P* values to account for multiple testing. A total of 33 gene–tissue pairs were significantly associated with AD, 66 gene–tissue pairs with fasting glucose, and 37 gene–tissue pairs with fasting insulin. Specifically, *MADD*, a gene expressed in multiple tissues, such as pituitary, artery and esophagus, was shared by AD ($P_{TWAS} = 2.49 \times 10^{-8}$) and fasting glucose trait ($P_{TWAS} = 4.5 \times 10^{-10}$). Interestingly, *MADD* was also found to be genome-wide significant in AD and fasting glucose cross-trait meta-analysis ($P_{meta} = 2.80 \times 10^{-16}$).

Discussion

To our knowledge, this is the first study to identify genome-wide genetic correlation and shared genetic variants between AD and metabolic traits. Specifically, we found a genetic

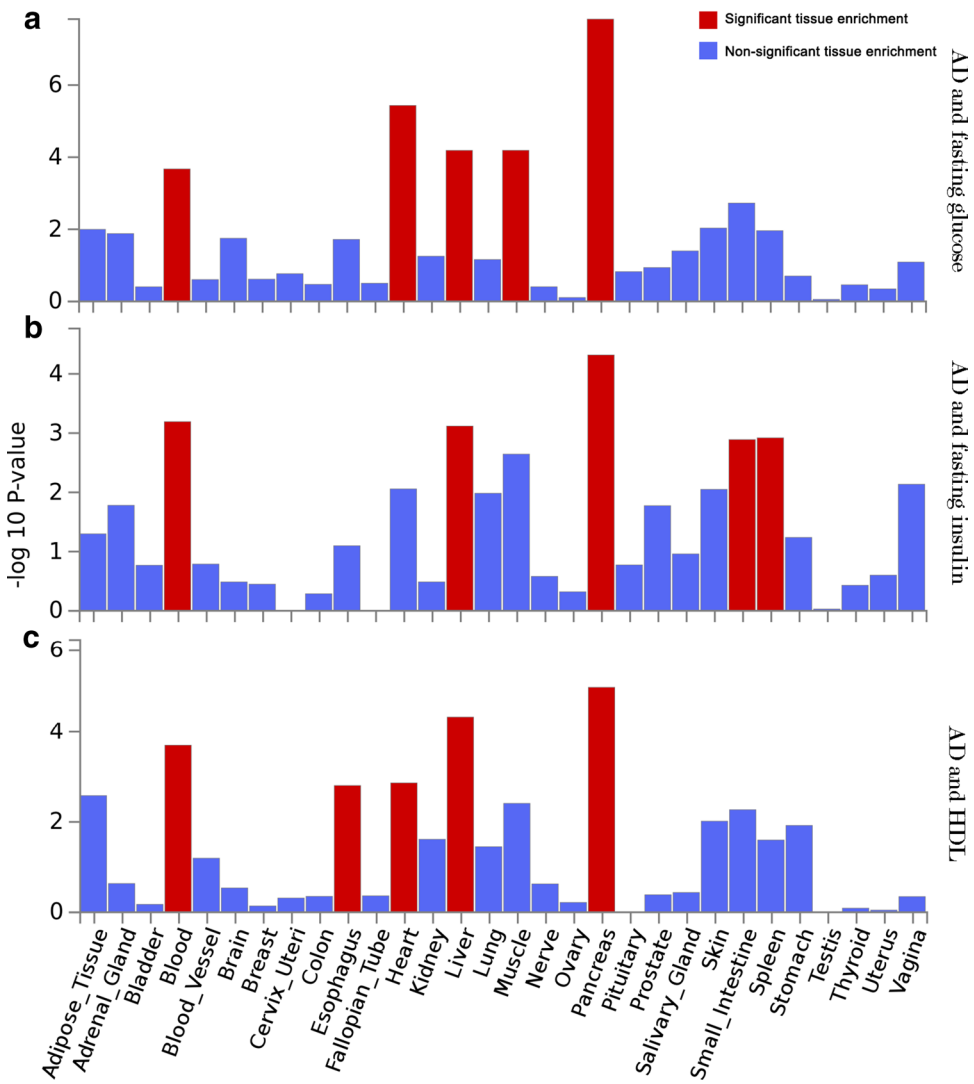

Fig. 3 GTEx tissue enrichment analysis. **a** GTEx tissue enrichment analysis of AD and fasting glucose. **b** GTEx tissue enrichment analysis of AD and fasting insulin. **c** GTEx tissue enrichment analysis of AD and HDL. Red bar represents a significant tissue enrichment after Benjamini–Hochberg correction

correlation between AD and fasting glucose, fasting insulin and HDL. In the LDSC analysis between AD and metabolic traits (Table 1), only FG–FINS meta-analysis and HDL had a statistically significant genetic correlation with AD.

These findings are consistent with the known association between higher glucose levels and cognitive impairment, including AD (Carantoni et al. 2000; Craft et al. 1999; Crane et al. 2013). Previous studies also found that HDL is negatively correlated with AD (Atzmon et al. 2002; Carantoni et al. 2000; Merched et al. 2000). Our findings suggest that the phenotypic correlation between AD and metabolic traits was due to a common genetic predisposition base. However, we did not observe genetic correlation between AD and obesity traits, which suggests that the phenotypic association between AD and BMI may be due to environmental factors, such as lifestyle (Kivipelto et al. 2018). In the analysis of partitioned co-heritability by functional categories, we observed positive genetic correlation between AD and fasting glucose or FG–FINS meta-analysis, and negative genetic correlation between AD and fasting insulin or HDL in different functional categories. We found that the genetic correlation estimates were significant in super enhancer, H3K9ac, H3K27ac and DGF for AD-sugar traits pairs (Fig. 1a); and genetic correlation estimates were significant in transcribed, TFBS, super enhancer, H3K4me1, H3K27ac and DGF in AD–HDL trait pair (Fig. 1b). This indicates the possible role of genetic correlation with respect to these functional categories in the shared genetic etiology of AD and these traits.

With regard to fasting glucose, we found six significant loci related to AD, including the genes *MADD, CRY2 and OR4S1. MADD* has been shown to play a critical role in glucose-induced insulin release as well as AD (Cornes et al. 2014; Huyghe et al. 2013; Lambert et al. 2013; Li et al. 2014). The reduced expression of *MADD* was found to link with declined long-term neuronal viability in late-onset AD (Lambert et al. 2013). With regard to fasting insulin, our results indicated three significant loci related to AD. The top locus is *CLU*, which induces the differentiation of pancreatic

duct cells into insulin-secreting cells (Kim et al. 2006). *CLU* has also been found to be increased in affected cortical areas in AD and is present in amyloid plaques and in the cerebrospinal fluid of patients with ADs (Harold et al. 2009).

Twenty loci were identified from the cross-trait meta-analysis of HDL and AD. Among them, the most significant gene was *APOE*, a well-established risk factor for late-onset AD (Coon et al. 2007; Genin et al. 2011; Green et al. 2009; Schuff et al. 2009). Notably, in the single-trait GWAS analysis, *APOE* also achieved genome-wide significance with HDL level ($P = 1.92 \times 10^{-8}$) (Supplementary Table 6) (Surakka et al. 2015), indicating a potential important pleotropic effect. Recent studies suggest that *APOE* is the major cholesterol carrier in the central nervous system and that *APOE*-containing HDL contributes to the redistribution of cholesterol for cellular remodeling and repair in the brain (Rasmussen 2016; Takahashi et al. 2016).

In local genetic correlation analysis, we also found the *APOE* region to have a strong genetic correlation with both AD and T2D. The presence of *APOE* in T2D cases with AD is associated with increased neurofibrillary tangles, amyloid plaques, and cerebral amyloid angiopathy (Jayaraman and Pike 2014; Peila et al. 2002).

In addition, we also tested SNPs that were identified from our cross-trait meta-analysis in 3 AD-related endophenotypes: hippocampal volume, Alzheimer's disease progression score and cortical amyloid beta load (Scelsi et al. 2018), to see if these SNPs are also nominally significant in these additional 3 GWAS results (Supplementary Table 15). We found rs2279590 was significant in cortical amyloid beta load ($P = 0.0197$) and rs157595 was significant in hippocampal volume ($P = 0.0265$), which may provide additional insight into these shared loci in terms of endophenotypes of AD.

The post-GWAS functional analyses provided biological insights into the shared genes between AD and 3 metabolic traits. The GTEx tissue enrichment analysis identified shared genes enriched in several tissues, such as pancreas, liver and spleen, which are known to play important roles in regulating the hormone and enzyme function. These hormones and enzymes can further impact the glucose and lipid level in the blood or brain (Sridhar et al. 2015). Blood, as a transporting carrier for nutrients, hormones and enzymes, was also found to be enriched in all three trait pairs. From TWAS analysis, we identified 14 significant unique gene–tissue pairs associated with AD, 21 with fasting glucose, and 5 with fasting insulin. Of these, *MADD* was the only gene significantly associated with AD and fasting glucose, exclusively in pituitary tissue; it is also the only shared gene found in both cross-trait meta-analysis and TWAS. *MADD* is known to improve insulin sensitivity, especially proinsulin-to-insulin conversion, for the variant with higher fasting glucose (Wagner et al. 2011). The pituitary plays a central role the endocrine axis because its hormones regulate the function of other endocrine glands. The relationship between diabetes and pituitary function is well known (Arrais and Dib 2006; Chan et al. 2003; Yi et al. 2010), but research has also noted an association between pituitary function and AD (Mrak and Griffin 2005; Pomara et al. 2003). Our results thus supported the hypothesis that the pituitary may link fasting glucose and AD. Even though *MADD* was only found to be significantly associated with AD in pituitary tissue, we found this gene expressed in 4 other tissues in fasting glucose trait, including the tibial artery, the aorta, and the muscularis and mucosa of the esophagus, which showed the importance of vascular and epithelium system in AD and neurodegeneration (Karlsson et al. 2017; Vemuri et al. 2017).

The genetic correlation between AD and metabolic traits may be due to both pleiotropy and causality (Chung et al. 2019). Our MR analysis showed no causal relationship between fasting glucose or HDL and AD after adjusting pleiotropy (Supplementary Table 16). These results further supported our findings that the shared genetic effects between metabolic traits and AD are more likely to be pleiotropic effects, rather than causal etiology or mechanism.

In addition to the genetic contribution to AD and metabolic traits, environmental and behavioral factors also play important role in their comorbidity. The combination of diet and exercise and some drugs that modulate metabolism are a few interventions that have been shown to improve cognition in AD, and currently represent the most hopeful approach to its prevention and treatment (Cheng et al. 2012; Marengoni et al. 2017).

We also acknowledge the limitations of our work. First, our study power is also limited by the sample size of the AD IGAP consortium. A larger sample size AD or its related endophenotypes, such as infarcts, amyloid, tau accumulation and vascular dementia, are needed to identify more novel shared loci between AD and metabolic traits. With the understanding that the power of individual GWAS traits is limited, we seek evidences based on multiple analyses from the genome-wide level, to locus, gene and genetic variant level, where we can take advantage of the benefit of each method. Among these methods, LDSC can be used to determine the genome-wide genetic correlation by aggregating information from all genetic variants but lack of the possibility to pin-point contribution from local regions and individual variants (Bulik-Sullivan et al. 2015b). On the other hand, ρ-HESS can help to narrow down to locally shared heritability (Shi et al. 2017). The TWAS and cross-trait meta-analysis can further investigate genetic overlap on gene and genetic variant level, respectively, which also provide functional interpretation (Gusev et al. 2016; Zhu et al. 2018a). There were two reasons why we did not apply Bonferroni correction for ten traits in this study. Our primary focus is based on glucose-related traits, given the high correlation between

T2D, fasting glucose and fasting insulin; the Bonferroni correction would seem too conservative. Nevertheless, it is still significant after accounting for 2 traits: T2D and FG–FINS analysis ($P < 0.025$). In addition, our study is based on publicly available GWAS summary statistics. Even though we have tried to standardize the data using ImpG summary statistic imputation to the 1000 Genome reference panel, the fasting glucose and fasting insulin summary statistics did not yield good quality imputed data, with only ~ 1.5 million SNPs' imputation quality having a r2pred > 0.6. Thus, we kept original fasting glucose and fasting insulin summary statistics data for downstream analysis, which is based on HapMap 2 imputation. However, the HapMap 2 platform can also provide powerful and accurate results for the entire genome (International HapMap et al. 2007).

Conclusion

In conclusion, our novel genome-wide cross-trait analysis reinforced the idea that AD and disorders of metabolism are connected. Evaluation of the genetic overlap between AD and metabolic traits can be beneficial to understand the shared biological mechanisms underlying this comorbidity. We highlighted the key roles of *APOE* and *MADD* genes played for shared etiology between AD and metabolic traits. More work is needed to fully characterize the heritable component of the metabolic origins of AD.

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Author contributions ZZ, JAD, and LL designed the study. ZZ and XL performed the statistical analysis. ZZ, YL, JAD, and LL wrote the manuscript. All authors helped interpret the data, reviewed and edited the final paper, and approved the submission.

Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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