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Linking Alzheimer's disease and type 2 diabetes: Novel shared susceptibility genes detected by cFDR approach

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ABSTRACT

Background: Both type 2 diabetes (T2D) and Alzheimer's disease (AD) occur commonly in the aging populations and T2D has been considered as an important risk factor for AD. The heritability of both diseases is estimated to be over 50%. However, common pleiotropic single-nucleotide polymorphisms (SNPs)/loci have not been well-defined. The aim of this study is to analyze two large public accessible GWAS datasets to identify novel common genetic loci for T2D and/or AD.

Methods and materials: The recently developed novel conditional false discovery rate (cFDR) approach was used to analyze the summary GWAS datasets from International Genomics of Alzheimer's Project (IGAP) and Diabetes Genetics Replication And Meta-analysis (DIAGRAM) to identify novel susceptibility genes for AD and T2D.

Results: We identified 78 SNPs (including 58 novel SNPs) that were associated with AD in Europeans conditional on T2D (cFDR < 0.05). 66 T2D SNPs (including 40 novel SNPs) were identified by conditioning on SNPs association with AD (cFDR < 0.05). A conjunction-cFDR (ccFDR) analysis detected 8 pleiotropic SNPs with a significance threshold of ccFDR < 0.05 for both AD and T2D, of which 5 SNPs (rs6982393, rs4734295, rs7812465, rs10510109, rs2421016) were novel findings. Furthermore, among the 8 SNPs annotated at 6 different genes, 3 corresponding genes *TP53INP1*, *TOMM40* and *C8orf38* were related to mitochondrial dysfunction, critically involved in oxidative stress, which potentially contribute to the etiology of both AD and T2D.

Conclusion: Our study provided evidence for shared genetic loci between T2D and AD in European subjects by using cFDR and ccFDR analyses. These results may provide novel insight into the etiology and potential therapeutic targets of T2D and/or AD.

1. Introduction

Type 2 diabetes (T2D) and Alzheimer's disease (AD) often occur together in the aging individuals and affect a growing number of people. AD is a chronic neurodegenerative disease of the central nervous system, and is characterized by progressive memory loss, cognitive dysfunction and behavior changes. According to the World Alzheimer Report 2015, the number of patients with AD in Europe is expected to increase to 18.6 million in 2050 from 10.5 million in 2015 [1]. T2D is a chronic disease that is defined by early-onset peripheral insulin resistance, and later dysfunction of β-cell and insulin deficiency. The overall prevalence of diabetes mellitus (DM) was 8.5% among 20–79 years old adults in Europe [2].

Recent epidemiological studies have suggested a close relationship between T2D and AD. A cross-sectional study found that patients with T2D were prone to have cognitive dysfunctions among those aged 45–65 years [3]. Another cross-sectional study among Chinese elderly individuals with T2D also showed association of T2D with dementia [4]. A five-year follow-up study suggested that DM individuals had a 65% increase in the risk of AD development compared with non-DM individuals [5]. It has been postulated that the common pathogenesis involving in AD and T2D is multifactorial, including systemic inflammation, insulin resistance, mitochondrial dysfunction and oxidative stress [6,7]. It is well-known that insulin resistance is the key determinant in the pathogenesis of T2D and has been shown to be highly associated with memory loss [8,9]. Hence, AD was proposed to be the type 3 diabetes mellitus [10].

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It has been widely accepted that interactions between hereditary factors and environmental aspects contribute to pathogenesis of both AD and T2D. Heritability is estimated to be over 50% for T2D [11] and up to 79% for AD [12]. Genome-wide association study (GWAS) has led to the discovery of single-nucleotide polymorphisms (SNPs) and genomic loci that contribute to complex traits and diseases, including T2D and AD [13]. Over the last decade, GWASs have successfully identified multiple genomic loci for AD, such as *APOE, CLU,CR1, PICALM, BIN1, ABCA7, MS4A6A, CD33, CD2AP,* and *EPHA1* [14], and also revealed approximately 40 susceptibility loci related to variants in T2D [15]. Recent studies attempted to explore the shared genes or SNPs for AD and T2D using bioinformatic analysis [16] or multiple cutoff p-value criteria [17]. However, only a small portion of estimated susceptibility loci for AD and T2D has been discovered using the above-mentioned approaches.

Conditional false discovery rate (cFDR) is a recently developed method that has been effectively applied to identify previously unsuspected common genetic risk loci for complex diseases [18–22]. cFDR can significantly improve detection of share susceptibility loci in two related phenotypes A and B by focusing on association of genetic variants in the first principal phenotype when conditional on the second and conditional phenotype [18]. In this study, we analyzed two large public accessible GWAS datasets to identify common genetic loci for T2D and/or AD using this novel cFDR method. Our results may provide novel insights into the etiology and potential therapeutic targets of T2D and AD for future studies.

2. Materials and methods

2.1. GWAS datasets

We acquired two GWAS summary statistics from public accessible datasets. The first one is AD GWAS dataset in the form of summary statistic p-values from International Genomics of Alzheimer's Project (IGAP). It consisted of 17,008 AD cases and 37,154 controls in IGAP stage 1, which is from four previously published GWAS datasets on individuals of European ancestry, with genotyped or imputed data of 7,055,881 SNPs [23].

The 2nd dataset is the T2D GWAS dataset in the form of summary statistic p-values from Diabetes Genetics Replication And Meta-analysis (DIAGRAM). It consisted of 12,171 T2DM cases and 56,862 controls in stage 1, which is from 12 previously published GWAS datasets on individuals of European ancestry with genotyped or imputed data at 2,473,441 SNPs [24].

It is necessary to adjust GWAS results with genomic controls [25] in order to make sure that the variance of each SNP are not inflated due to latent population structure. The two GWAS datasets had previously used genomic control by the original authors; hence, it was unnecessary to apply this adjustment again here in our study.

2.2. Data preparation

A total of 2,310,500 common SNPs were identified when we combined the two GWAS summary datasets. The SNP data were pruned according to high correlations of pairs of SNP variants involved by using linkage disequilibrium (LD) measure. The pruning operation process involves a window of 10 SNPs where LD is calculated between each pair of SNPs inside the window. If R [2] value is >0.2 in pairs of SNPs, one of that SNP with smaller minor allele frequency (MAF) will be removed. Along with this initial elimination of SNPs, the process is repeated until no pairs of SNPs in a high LD with the window sliding 5 SNPs forward. The pruning of the dataset used the HapMap 3 CEU reference genotypes. There were 262,661 variants remained for use in our analysis after the pruning process.

After obtaining the pruned dataset, we used an R statistical software (https://www.r-project.org/) to conduct subsequent analyses.

2.3. Statistical analysis

2.3.1. Stratified Q-Q (quantile-quantile) plots for pleiotropic enrichment

The Q-Q plots is a curve graph of the observed distribution of p-values plotted against the expected distribution of p-values under the null. We constructed the Q-Q plots on the basis of difference levels of association significance in the conditional phenotype in order to visualize the enrichment of SNP association compared with that expected under the null hypothesis of no shared genes between the principal and conditional phenotypes. We plot the Q-Q curve for the quantiles of nominal $-\log_{10}(p)$ values for the association of the subset of SNPs that reached each significance threshold in the conditional phenotype. All the nominal p-values were obtained from the GWAS summary datasets. The quantiles of the empirical p-values and the nominal $-\log_{10}(p)$ values are plotted on the x-axis and y-axis respectively. The enrichment of pleiotropic genes was evaluated on the basis of the degree of leftward shift from the expected null line as the principal phenotype successively conditioned on more stringent significance standard in the conditional phenotype.

2.3.2. The calculation of cFDR

The cFDR is an extension of traditional false discovery rate (FDR), which for a set of SNPs, is characterized as the posterior probability of a false positive association. The FDR is given by [26].

$$\mathrm{FDR}(p_i) = \Pr\left(H_o^{(i)} | P_i \le p_i\right) \tag{1}$$

The p-values of association for a trait *i* across all SNPs as realizations of the random variable is defined as P_i, p_i is an instance of this random variable corresponding to a particular SNP. $H_o^{(i)}$ is the null hypothesis that there is no association between a particular variant and trait *i*. Given a set of observed association p-values, the FDR is estimated as the expected quantile of the p-value under the null divided by the observed quantile. Based on the above definition and principle of FDR, the cFDR is logically defined as the posterior probability that a random SNP is null for the principal phenotype given that the observed p-values for both two phenotypes are less than two predetermined cutoffs [26]. Formally, the cFDR is given by [26].

$$cFDR\left(p_i | p_j\right) = \Pr\left(H_o^{(i)} | P_i \le p_i, P_j \le p_j\right) \tag{2}$$

where *pi* is the strength of association for a particular SNP with the principal phenotype, p_j is the strength of association for that same SNP with the conditional phenotype. We followed the development and the steps outlined by Andreassen et al. [19] to compute the cFDR for each variant after obtaining the summary statistics from the pruned dataset. The method used in computing the cFDR is a generalization of the empirical Bayesian approach, which is the way for computing FDR originally developed by Efron et al. [27].

The value of cFDR for each SNP was calculated in the case where T2D is the principal phenotype conditioned on AD (T2D|AD) as well as the reverse (AD|T2D). To assess whether the cFDR method leads to an enrichment of associated SNPs, we restricted the subset of SNPs being tested on the basis of the significance level for the association of each SNP with the conditional phenotype using the following criteria for $-\log10(P) \ge 0$, $-\log10(P) \ge 1$, $-\log10(P) \ge 2$, $-\log10(P) \ge 3$ and $-\log10(P) \ge 4$, corresponding to $P \le 1$, $P \le 0.1$, $P \le 0.01$, $P \le 0.001$ and $P \le 0.0001$, respectively. SNPs with the values of cFDR lower than 0.05 were deemed to be associated with the principal phenotype.

We constructed cFDR Manhattan plots to visualize the localization of genetic loci associated with AD given their association with T2D as well as the reverse (the localization of genetic loci associated with T2D given their association with AD). We plotted all the SNPs with their locations on the chromosomes. Any SNP with a $-\log_{10}(p)$ value > 1.3 (equivalent to $p < 0.05$) was considered to be significantly related with the principal

phenotype given the association for that SNP with the conditional phenotype.

2.3.3. The calculation of ccFDR (conjunction-cFDR)

In order to detect common susceptibility loci for AD and T2D after calculating the values of cFDR for each SNP under T2D|AD and AD|T2D, we computed the ccFDR value, which refers to the probability that a given SNP is null for both two phenotypes when the p-values ≤ the observed p-value [19]. It was calculated as the maximum cFDR value between the two cFDR values (obtained for T2D|AD and AD|T2D respectively) [26]. The ccFDR is given by [26].

$$ccFDR_{i\&j} = \max\left(cFDR_{i|j}, cFDR_{j|i}\right) \quad (3)$$

Any SNPs with the value of $cFDR_{T2D|AD}$ and $cFDR_{AD|T2D}$ are both lower than 0.05 were deemed to be significantly associated with two phenotypes. We also constructed a conjunction-Manhattan plot for illustrating the locations of pleiotropic genetic variants.

2.3.4. Functional annotation and gene enrichment analysis

We performed functional annotation and gene enrichment analysis using the Database for Annotation, Visualization and Integrated Discovery (DAVID) bioinformatics resources for assessing the biological functions of the genes identified by cFDR (https://david.ncifcrf.gov/summary.jsp). Using the DAVID analysis, the relate-genes were annotated and characterized based on the biological processes, cellular components and molecular functions. This analysis provided some supporting evidence for our findings by determining genes that may be functionally associated with T2D and/or AD.

3. Results

3.1. Q-Q plots of T2D SNPs conditional on association with AD and vice versa

To evaluate the pleiotropic enrichment for these two diseases, we constructed conditional Q-Q plots, which provide a visualization of polygenic enrichment for pleiotropic genes. Conditional Q-Q plots for T2D given nominal p-values of association with AD (Fig. 1A) show some enrichment across different levels of significance for AD. The strong enrichment Q-Q plot for AD conditional on T2D p-value is shown in Fig. 1B. The earlier deflections from the null line shows a greater proportion of true associations for the principal disease given the nominal p-value of the conditional disease. Moreover, greater spacing between the lines in conditional Q-Q plots suggests a larger trend with more and/or higher impact of pleiotropic loci shared between the two related-diseases [28].

3.2. AD gene loci identified with cFDR

We identified a total of 78 significant SNPs associated with AD, when conditional on T2D (Table 1), and presented a Manhattan plot for AD (Fig. 2A). These SNPs were mapped to 15 different chromosomes. 33 of those 78 SNPs reached a genome wide significance level of $<5 \times 10^{-8}$ in the original meta-analysis [23], but some of them were not reported before. In our study, 20 SNPs and their corresponding genes have been already known to be associated with AD [29–34]. Furthermore, 58 of the 78 SNPs were identified as novel variants through cFDR which were not reported earlier, and annotated at 58 different genes, of which 34 are novel genes. These SNPs and related genes would not have been discovered without employing the cFDR method in the current analysis. Interestingly, our study first identified some novel genes that may play essential roles in the development of AD. For example, two novel SNPs rs3844143 and rs10898439 are on chromosome 11q13, near the *FNTAP1* gene, also known as the *FNTAL1* gene, which belongs to farnesyltransferase coding genes [35]. Importantly, an earlier

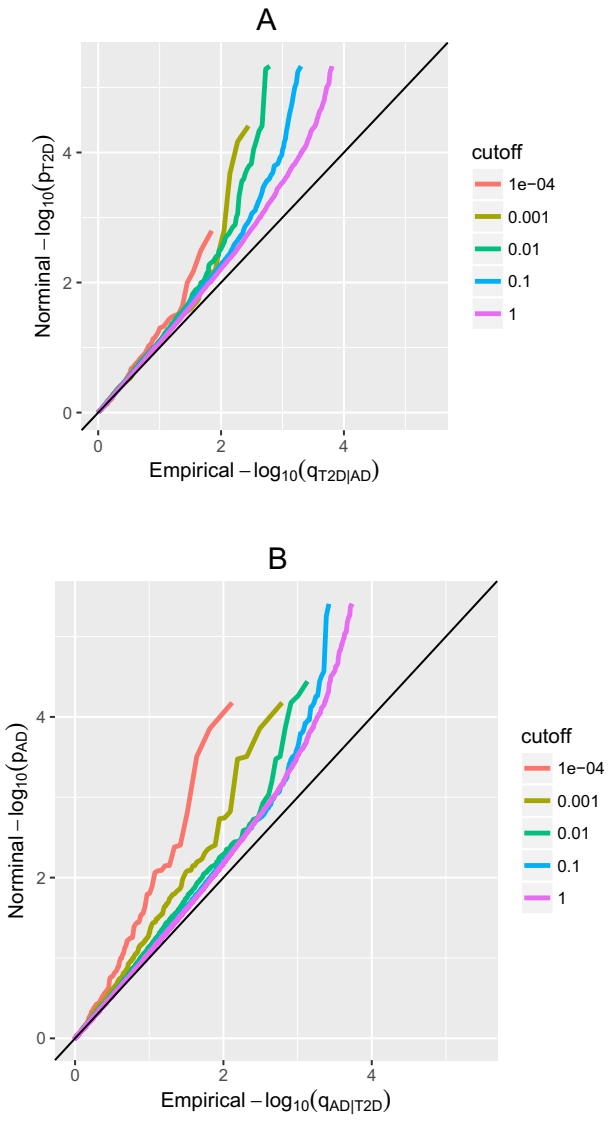

Fig. 1. A): Stratified QQ plots of nominal versus empirical $-\log_{10}$ p-values for T2D as a function of significance of the association with AD; B): Stratified QQ plots of nominal versus empirical $-\log_{10}$ p-values for AD as a function of significance of the association with T2D.

animal study provided evidence that farnesyltransferase participate in the etiopathogenesis of AD due to the progressive decline of levels of amyloid-β (Aβ), neuroinflammation and impairment of cognitive function in APPPS1 mice of deletion of farnesyltransferase [36]. Therefore, our results for the first time provided population level evidence from humans for the significance of farnesyltransferase to the AD etiology and may provide a basis for further exploring the molecular genetic basis of the pathogeny of AD based on functional studies of farnesyltransferase in the future. Detailed descriptions are provided in Table1, which shows location of chromosomes, and neighboring genes as well as cFDR values and p-values for each of the analyzed 78 SNPs. We input corresponding genes of the 78 significant SNPs into DAVID, six genes were enriched in the terms of "CD20-like", four genes in "negative regulation of beta-amyloid formation", three genes in "positive regulation of beta-amyloid formation" (Table 4).

3.3. T2D gene loci identified with cFDR

We identified a total of 66 significant SNPs located on 16 chromosomes [1–12,14,16,17,19] related to T2D with a significance threshold of cFDR < 0.05 (Table 2), and also presented a conditional Manhattan

Table 1
Conditional FDR, AD given loci T2D.

Previously identified AD SNPs and genes					
	SNP	Gene	chr	p-val AD	cFDR AD
1	rs10194375	BIN1	2	3.61e-07	2.60e-03
2	rs7561528	BIN1	2	6.54e-18	2.02e-13
3	rs2516049	HLA-DRB5	6	3.61e-05	3.08e-02
4	rs1316801	CLU	8	1.01e-06	7.00e-03
5	rs11136000	CLU	8	1.72e-16	4.40e-12
6	rs2081547	MS4A4E	11	2.19e-10	1.19e-06
7	rs677909	PICALM	11	8.35e-11	1.32e-06
8	rs3781835	SORL1	11	3.16e-07	2.40e-03
9	rs2276412	SORL1	11	4.68e-07	3.20e-03
10	rs10498633	SLC24A4	14	1.47e-07	1.20e-03
11	rs3764650	ABCA7	19	2.50e-07	1.80e-03
12	rs714948	PVR	19	6.26e-13	4.40e-09
13	rs2927438	BCL3	19	5.69e-29	3.08e-25
14	rs2927477	BCAM	19	4.04e-11	6.14e-07
15	rs1871047	PVRL2	19	2.20e-18	2.48e-14
16	rs6859	PVRL2	19	3.31e-96	2.29e-92
17	rs2075650	TOMM40	19	0	0
18	rs405509	APOE	19	4.35e-73	2.50e-68
19	rs2288911	APOC2	19	6.42e-10	7.63e-06
20	rs7254892	PVRL2	19	1.12e-05	3.31e-02
Newly identified AD SNPs					
	SNP	Gene	chr	p-val AD	cFDR AD
1	rs6668266	CDC73[b] EEF1AL12[b]	1	5.78e-06	3.02e-02
2	rs1887726	CDC73[b] EEF1AL12[b]	1	6.23e-06	3.07e-02
3	rs7550917	CDC73[b] EEF1AL12[b]	1	4.29e-06	2.31e-02
4	rs6715234	MCFD2[b] LOC388948[b]	2	8.82e-06	4.23e-02
5	rs6743470	BIN1[a] CYP27C1[b]	2	7.35e-08	3.00e-04
6	rs2811488	FLJ40473[b] RPN1[b]	3	1.05e-05	3.76e-02
7	rs10022344	ANKRD50[b] FAT4[b]	4	5.44e-05	4.29e-02
8	rs1347143	PFDN1[b]	5	1.17e-05	3.04e-02
9	rs304132	MEF2C[a] LOC729011[b]	5	9.17e-06	3.46e-02
10	rs2184397	CD2AP[a] TNFRSF21[b]	6	5.51e-06	3.07e-02
11	rs12703526	EPHA1[a] TAS2R62P[b]	7	6.91e-08	5.00e-04
12	rs10226151	EPHA1[a] TAS2R62P[b]	7	5.91e-09	4.17e-05
13	rs896854	TP53INP1[a]	8	4.16e-03	4.36e-02
14	rs6982393	TP53INP1[a] C8orf38[a]	8	3.11e-04	1.21e-02
15	rs4734295	TP53INP1[a] C8orf38[a]	8	1.40e-04	7.10e-03
16	rs7812465	C8orf38[a]	8	3.33e-04	1.74e-02
17	rs2582367	CLU[a] SCARA3[b]	8	6.97e-07	2.30e-03
18	rs689266	GTF3C5[b]	9	1.50e-05	4.60e-02
19	rs11257238	LOC439951[b] ECHDC3[b]	10	5.60e-06	1.22e-02
20	rs10510109	BTBD16[b] PLEKHA1[b]	10	6.65e-05	2.60e-03
21	rs2421016	PLEKHA1[b]	10	1.51e-03	3.10e-02
22	rs1286170	MS4A3[a]	11	9.01e-06	2.35e-02
23	rs4939311	MS4A6A[a] MS4A2[a]	11	1.29e-09	4.18e-06
24	rs4939312	MS4A6A[a] MS4A2[a]	11	4.96e-10	2.14e-06
25	rs7935829	MS4A6A[a]	11	1.64e-10	1.01e-06
26	rs4938931	MS4A4A[a] MS4A4E[a]	11	1.54e-10	7.80e-07
27	rs10792263	MS4A4A[a] MS4A6E[a]	11	3.21e-11	1.73e-07
28	rs2044981	MS4A4A[a]	11	3.92e-06	8.90e-03
29	rs2868121	MS4A6E[a]	11	1.92e-06	5.90e-03
30	rs618679	PICALM[a]	11	1.35e-06	8.80e-03

(continued on next page)

Table 1 (*continued*)

Previously identified AD SNPs and genes					
	SNP	Gene	chr	p-val AD	cFDR AD
31	rs2856650	MYBPC3[b]	11	4.07e-06	2.36e-02
32	rs896817	SPI1[b]	11	7.56e-06	2.08e-02
33	rs10838702	SPI1[b] SLC39A13[b]	11	8.98e-06	2.95e-02
34	rs10838709	PSMC3[b]	11	1.56e-05	4.84e-02
35	rs3844143	FNTAL1[b] LOC100130431[b]	11	1.27e-08	1.00e-04
36	rs10898439	FNTAL1[b] LOC100130431[b]	11	2.96e-09	2.73e-05
37	rs10483861	YLPM1[a]	14	YLPM1	5.40e-03
38	rs888417	LTBP2[a] KIAA0317[b]	14	4.09e-06	2.23e-02
39	rs2526378	BZRAP1[b]	17	1.22e-06	1.70e-03
40	rs3737355	L3MBTL4[b]	18	1.07e-05	3.96e-02
41	rs7255066	PVR[a]	19	5.27e-10	6.40e-06
42	rs12150984	CEACAM16[a]	19	2.12e-09	1.13e-05
43	rs1531517	CEACAM16[a] BCL3[a]	19	5.83e-12	4.89e-08
44	rs387976	PVRL2[a]	19	4.39e-12	9.40e-08
45	rs11667640	PVRL2[a]	19	1.12e-09	7.83e-06
46	rs12460985	BLOC1S3[a] EXOC3L2[a]	19	3.21e-08	1.00e-04
47	rs2627641	BLOC1S3[a] EXOC3L2[a]	19	1.26e-13	1.54e-09
48	rs10410003	EXOC3L2[a]	19	3.11e-06	1.67e-02
49	rs8100239	BCL3[a]	19	1.50e-22	3.37e-18
50	rs16979600	CLPTM1[a]	19	4.36e-11	7.52e-07
51	rs7257916	CLPTM1[a]	19		3.53e-08
52	rs17714718	CEACAM22P[b]	19	1.48e-08	8.63e-05
53	rs846848	CEACAM22P[b] LOC147710[b]	19	2.52e-06	1.57e-02
54	rs41334244	NA	19	5.01e-09	5.09e-05
55	rs1560725	SFRS16[b]	19	4.72e-08	4.00e-04
56	rs1469704	GEMIN7[b]	19	1.26e-05	3.99e-02
57	rs16939	DMPK[b]	19	4.64e-05	3.80e-02
58	rs16980051	SYMPK[b]	19	6.61e-06	1.74e-02

The following abbreviations are used: chr, chromosome; T2D, type 2 diabetes; AD, Alzheimer's disease; and cFDR, conditional false discovery rate.
[a] This gene is previously reported to be associated with AD but the SNP is not.
[b] This SNP and gene have neither been reported to be associated with AD.

plot for visualizing the localization of significant SNPs associated with T2D (Fig. 2B). 15 of these SNPs reached a genome wide significance level of $<5 \times 10^{-8}$ in the original meta-analysis [24]. Based on the published literature and our results, 26 SNPs and corresponding genes are associated with T2D and have been previously reported, including those in *PROX1* (rs340835) [37], *IGF2BP2* (rs7651090) [38], *WFS1* (rs734312) [39], *CDKAL1* (rs10946403/rs7741604/rs10484634/rs1012635) [28,40–42], *JAZF1* (rs849135) [43], *KLF14* (rs4731702/rs13234407) [44,45], *TP53INP1* (rs896854) [46], *SLC30A8* (rs11558471) [47], *HHEX* (rs7911264) [48], *ZMIZ1* (rs810517) [49], *IDE/KIF11* (rs6583826) [50], *TCF7L2* (rs4074720/rs7079711/rs290483/rs11196212) [51–54], *HMGA2* (rs2261181) [55], *CHR12* (rs7132840) [56], *FTO* (rs9940128/rs9930506/rs8057044) [51,57], *HNF1B* (rs4430796) [58], *BCAR1* (rs9927309) [59]. Furthermore, 40 SNPs were identified as novel variants for T2D and annotated at 44 different genes, of which 23 genes have been reported to be significantly related with T2D in earlier researches [15,43,60–67], and remaining 21 genes were not previously detected in earlier T2D GWAS studies. With the application of the cFDR method, these SNPs were detected as novel findings. Similarly with AD, some genes were for the first time identified to be associated with T2D, and were found by other studies to have strong effects on regulating blood glucose. For example, SNP rs9267576 (cFDR = 1.39e-02) near *NEU1* gene, which is extremely important for regulating the signaling pathways of energy metabolism and glucose uptake [68], was identified as a novel gene of T2D in our study. Detailed descriptions are provided in Table 2 which shows the location of chromosomes, and neighboring genes as well as cFDR values and p-values for the 66 SNPs significant in the analysis. Furthermore, we input corresponding genes of the 66 significant SNPs into DAVID for the functional term enrichment analysis, some genes are enriched in terms of "pancreas development", "glucose homeostasis" (details given in Table 4).

3.4. Pleiotropic gene loci in AD and T2D identified with ccFDR

We identified 8 SNPs located on three chromosomes (rs896854, rs7812465, rs6982393 and rs4734295 on chr8; rs10510109 and rs2421016 on chr10; rs6859 and rs2075650 on chr19) with ccFDR < 0.05, of which 5 SNPs (rs7812465, rs896854, rs4734295, rs10510109 and rs2421016) are novel findings for both T2D and AD (details given in Table 3), and constructed a "conjunction" Manhattan plot (Fig. 2C). The 8 SNPs annotated at 6 different genes, of which two genes *TP53INP1* and *TOMM40* were identified to be associated with both AD and T2D in previous association studies [50,63,69,70] and *BDBT16* was discovered as a novel gene. Another two genes were only considered as AD susceptibility genes in previous studies but not for T2D: *C8orf38* and *PVRL2* [23,69]. We also provided evidence for the association between AD and another gene *PLEKHA1*, which has been previously reported as T2D susceptibility gene [43]. In all, our results implied that it is feasible to employ the ccFDR to detect the common susceptibility genes in two diseases or traits, and these findings may hint overlapping pathogenesis in AD and T2D.

4. Discussion

Numerous epidemiological studies have shown the close association between AD and T2D. Detecting novel susceptibility loci for AD and T2D

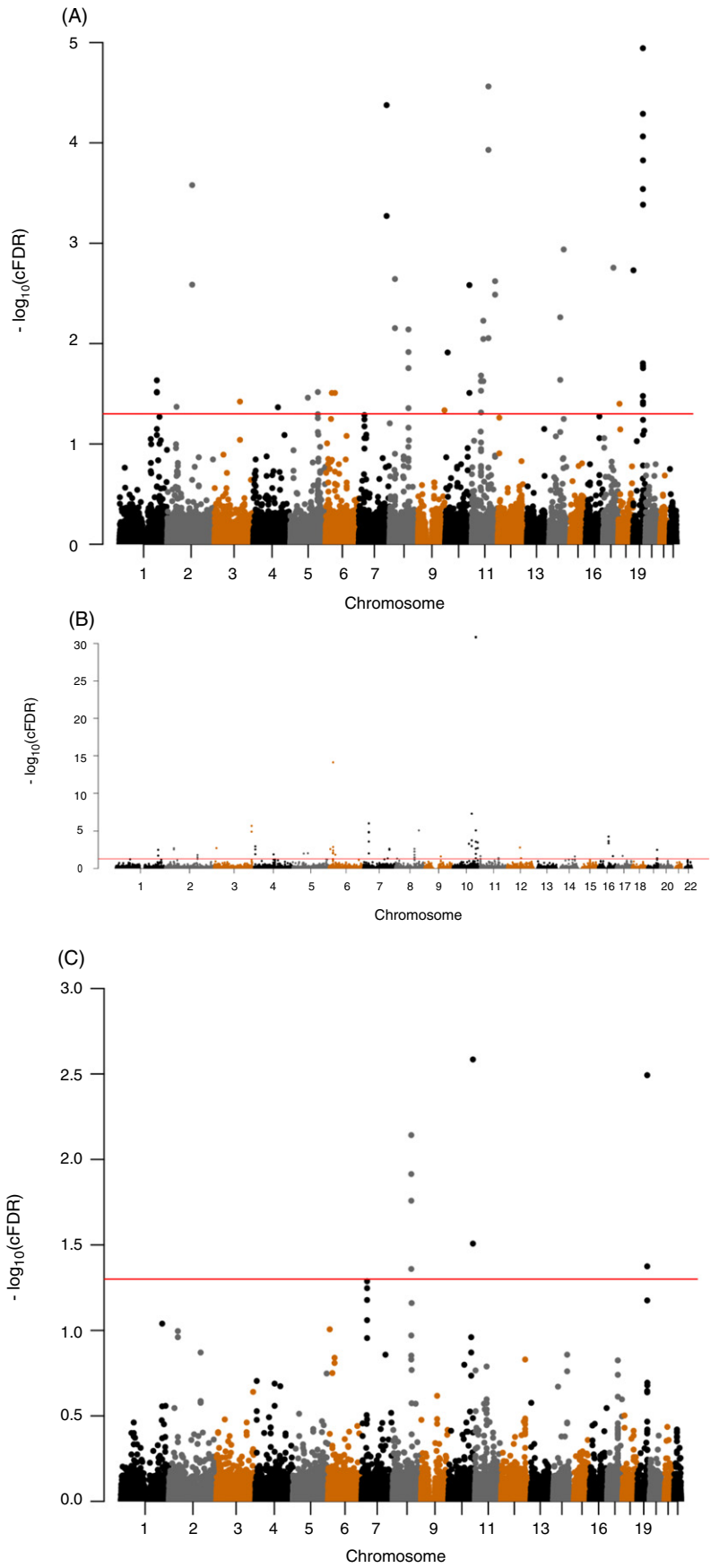

Fig. 2. A) "Conditional Manhattan plot" of conditional −log10 FDR values for AD given T2D (AD|T2D); B) "conditional Manhattan plot" of conditional −log10 FDR values for for T2D given AD (T2D|AD); C) "conjunction Manhattan plot" of conjunction −log10 FDR values for AD and T2D. The red line marking the conditional $-\log_{10}$ FDR value of 1.3 corresponds to a cFDR < 0.05.

Table 2
Conditional FDR;T2D given AD.

Previously identified T2D SNPs and genes					
	SNP	Gene	chr	P val T2D	cFDR T2D
1	rs340835	PROX1	1	1.10e-06	3.10e-03
2	rs7651090	IGF2BP2	3	2.00e-11	2.02e-06
3	rs734312	WFS1	4	3.20e-07	1.10e-03
4	rs10946403	CDKAL1	6	9.00e-20	7.20e-15
5	rs7741604	CDKAL1	6	8.60e-08	1.30e-03
6	rs10484634	CDKAL1	6	9.70e-07	9.70e-03
7	rs1012635	CDKAL1	6	4.00e-07	3.80e-03
8	rs849135	JAZF1	7	3.40e-10	9.35e-07
9	rs4731702	KLF14	7	2.00e-07	2.30e-03
10	rs13234407	KLF14	7	2.90e-07	3.00e-03
11	rs896854	TP53INP1	8	5.20e-06	2.30e-03
12	rs11558471	SLC30A8	8	8.70e-10	8.10e-06
13	rs810517	ZMIZ1	10	2.00e-07	5.00e-04
14	rs6583826	IDE,KIF11	10	6.00e-08	1.00e-03
15	rs7911264	HHEX	10	4.50e-13	4.64e-08
16	rs7079711	TCF7L2	10	2.50e-07	2.20e-03
17	rs4074720	TCF7L2	10	7.80e-37	1.57e-31
18	rs290483	TCF7L2	10	1.60e-04	4.29e-02
19	rs11196192	TCF7L2	10	1.10e-07	3.00e-04
20	rs2261181	HMGA2	12	1.00e-07	1.50e-03
21	rs7132840	CHR12	12	1.30e-05	4.02e-02
22	rs9940128	FTO	16	1.10e-08	2.00e-04
24	rs9930506	FTO	16	2.80e-09	5.36e-05
24	rs8057044	FTO	16	2.70e-08	4.00e-04
25	rs9927309	BCAR1	16	9.00e-06	2.15e-02
26	rs4430796	HNF1B	17	2.40e-06	2.05e-02
Newly identified T2D SNPs					
	SNP	Gene	chr	P val T2D	cFDR T2D
1	rs340883	PROX1[a] LOC643330[b]	1	4.70e-05	1.83e-02
2	rs17030835	THADA[a]	2	1.70e-06	1.90e-03
3	rs7575024	THADA[a]	2	2.60e-06	2.70e-03
4	rs12692585	RBMS1[a] ITGB6[a]	2	2.10e-05	1.57e-02
5	rs7569522	RBMS1[a]	2	2.50e-05	3.00e-02
6	rs2881654	PPARG[a]	3	1.70e-07	1.90e-03
7	rs4481184	IGF2BP2[a]	3	3.20e-10	1.17e-05
8	rs4688982	WFS1[a] LOC285484[b]	4	1.40e-06	2.70e-03
9	rs12510298	UNC5C[b] PDHA2[b]	4	9.90e-06	1.28e-02
10	rs4688983	WFS1[a]	4	5.30e-06	1.21e-02
11	rs3843467	MAP3K1[a] LOC441073[b]	5	2.50e-06	1.02e-02
12	rs6885904	LOC728723[b] LOC100129287[b]	5	1.10e-06	9.10e-03
13	rs9267576	C6orf48[b] NEU1[b]	6	1.70e-05	1.39e-02
14	rs1050226	RREB1[a] SSR1[a]	6	2.70e-06	2.50e-03
15	rs13205786	CDKAL1[a]	6	1.20e-06	9.70e-03
16	rs13200415	CDKAL1[a]	6	7.80e-07	7.80e-03
17	rs4712540	CDKAL1[a]	6	5.80e-06	7.30e-03
18	rs849336	LOC100128081[b]	7	4.80e-09	1.32e-05
19	rs498475	LOC100128081[b]	7	8.80e-09	1.50e-05
20	rs1859351	CADPS2[b]	7	1.60e-04	4.44e-02
21	rs3133780	C8orf37[b] LOC643228[b]	7	1.80e-04	3.25e-02
22	rs1109484	JAZF1[a]	7	1.30e-05	9.30e-03
23	rs10245867	JAZF1[a]	7	2.20e-07	2.00e-04
24	rs17150816	TNKS[a] MSRA[a]	8	1.60e-05	4.70e-02
25	rs11996455	INTS8[a]	8	9.00e-05	3.11e-02
26	rs6982393	TP53INP1[a] C8orf38[b]	8	3.90e-05	5.20e-03
27	rs4734295	TP53INP1[a] C8orf38[b]	8	6.80e-05	5.60e-03
28	rs7812465	C8orf38[b]	8	2.10e-04	1.43e-02
29	rs17198915	CHCHD9[a] KRT18P24[b]	9	3.60e-06	2.36e-02
30	rs2497304	HHEX[a] EXOC6[b]	10	8.50e-09	2.00e-04
31	rs11196212	TCF7L2[a]	10	1.90e-10	8.08e-06
32	rs7077039	TCF7L2[a]	10	1.00e-36	1.05e-31

Table 2 (*continued*)

Previously identified T2D SNPs and genes					
	SNP	Gene	chr	P val T2D	cFDR T2D
33	rs10885414	TCF7L2[a]	10	8.70e-06	1.09e-02
34	rs10510109	BTBD16[b] PLEKHA1[a]	10	2.90e-06	3.00e-04
35	rs2421016	PLEKHA1[a]	10	4.70e-06	1.80e-03
36	rs2283202	KCNQ1[a]	11	9.30e-06	2.17e-02
37	rs271057	MTNR1B[a] SLC36A4[b]	11	6.80e-06	3.94e-02
38	rs1285850	CCDC88C[b] SMEK1[b]	14	3.10e-05	2.39e-02
39	rs2075650	TOMM40[a]	19	3.20e-03	3.20e-03
40	rs6859	PVRL2[b]	19	4.20e-02	4.20e-02

The following abbreviations are used: chr, chromosome; T2D, type 2 diabetes; AD, Alzheimer's disease; and cFDR, conditional false discovery rate.
[a] This gene is previously reported to be associated with T2D but the SNP is not.
[b] This SNP and gene have neither been reported to be associated with T2D.

may point the way to explore the genetic or pathophysiology mechanisms between these two related diseases.

The cFDR, a promising approach for improving the detection of genetic variants of complex diseases based on existing summary GWAS data, was proposed by Andreassen et al. [21]. This method allows to increase effective sample size, and subsequently improve the detection power for true associations for two correlated diseases/traits-related variants which may be unnoticeable in the standard GWAS. It was found that the an increase of at least 15 times the number of non-null SNPs can be identified by using the cFDR method in comparison to the traditional FDR through simulation analysis [19]. The cFDR analyses conducted to date have indeed proven its effectiveness and practicability in discovering genetic variation of many diseases/traits, including schizophrenia, bipolar disorder, cardiovascular disease and blood pressure etc. [19–21]. We also successfully conducted cFDR analyses earlier to detect novel traits for height and femoral neck bone mineral density [26], and for T2D and birth weight [28].

Similar analysis methods in using summary statistics datasets for identifying the genetic loci of complex diseases include GPA (genetic analysis incorporating Pleiotropy and annotation), metaCCA (meta-analysis using canonical correlation analysis) etc. GPA can integrate multiple GWAS summary statistics data and use functional annotations in an attempt to search for novel genetic loci [71]. However, its required functional annotation is currently not perfect, which may be influenced by many confounding factors such as uncertainties of annotations. Compared with cFDR, GPA has not been as widely applied thus far in GWAS summary statistics analyses for diseases or traits. The advantage of metaCCA method is that it can combine GWAS summary statistics for detecting genetic loci underlying multiple (such as 3 or more) complex diseases/traits, and allows analyses of multiple SNPs against multiple traits [72]. The empirical application of metaCCA is also limited currently. Our purpose here is to explore the additional genetic loci of two related-diseases rather than multiple diseases. Hence, employment of cFDR here is appropriate.

In this study, we selected two previously reported publicly available GWAS summary statistical datasets from IGAP and DIAGRAM consortia, and analyzed them using cFDR and ccFDR. 66 T2D susceptibility SNPs, including 40 novel ones were identified through conditioning on polymorphisms associated with AD. We also identified 78 SNPs, including 58 novel SNPs associated with AD, when conditioned on T2D. Furthermore, our ccFDR analysis detected 8 pleiotropic SNPs: two SNPs (rs6859, rs2075650) were recognized as AD-related SNPs before [29], one (rs896854) was previously confirmed to be associated with T2D [46], five (rs6982393, rs4734295, rs7812465, rs10510109, rs2421016) were identified as novel SNPs for both AD and T2D. Based on our results, we demonstrated that cFDR and ccFDR not only confirmed previously reported loci, but also identified novel loci, further reaffirming the effectiveness and feasibility of this recently proposed method.

The significantly common variants for both AD and T2D in 8 SNPs are annotated at 6 different genes (*TP53INP1*, *C8orf38*, *TOMM40*, *BTBD16*, *PLEKHA1* and *PVRL2*). It is noteworthy that *BTBD16* was previously identified to be related with bipolar disorder [73]. The roles of this gene in the pathogenesis of T2D and AD are poorly understood currently and require further clarification. The following two genes, *PLEKHA1* and *PVRL2* were associated with either AD [29] or T2D [43]. *PLEKHA1* is notably associated with the regulation of PI3K, as the signaling pathway of PI3K/Akt plays a vital role in AD [74] and T2D [75]. Another gene, *PVRL2* is expressed in the brain and several neuronal cell lines [76] and is known as a susceptibility gene of AD [29]. This gene is close to the *APOE*, which is a widely acknowledged susceptibility gene for AD [29].

The remaining three significant shared genes (*TP53INP1*, *C8orf38* and *TOMM40*) between AD and T2D are noteworthy. Our results, along with previous studies, have indicated that both *TP53INP1* and *TOMM40* were related to AD [69,70] and T2D [50,63], whereas *C8orf38* was identified

Table 3
ccFDR for AD and T2D.

	SNP	Gene	chr	cFDR.AD	cFDR.T2D	ccFDR
1	rs896854	TP53INP1	8	3.32e-02	2.40e-03	3.32e-02
2	rs6982393	TP53INP1 C8orf38	8	1.21e-02	5.20e-03	1.21e-02
3	rs4734295	TP53INP1 C8orf38	8	5.10e-03	4.40e-03	5.10e-03
4	rs7812465	C8orf38	8	1.66e-02	1.35e-02	1.66e-02
5	rs10510109	BTBD16 PLEKHA1	10	1.50e-03	3.00e-04	1.50e-03
6	rs2421016	PLEKHA1	10	3.10e-03	1.80e-03	3.10e-03
7	rs6859	PVRL2	19	3.80e-92	4.20e-02	4.20e-02
8	rs2075650	TOMM40	19	0	3.20e-03	3.20e-03

The following abbreviations are used: chr, chromosome; T2D, type 2 diabetes; AD, Alzheimer's disease; cFDR, conditional false discovery rate and ccFDR, conditional-conjunction false discovery rate.

Table 4
Functional term enrichment analysis.

Terms	Gene count	P_value	Benjamin
AD genes			
CD20-like	6	1.8E-9	2.1E-7
Negative regulation of beta-amyloid formation	4	1.7E-7	9.2E-5
Positive regulation of beta-amyloid formation	3	1.4E-4	3.8E-2
T2D genes			
pancreas development	4	1.1E-5	5.1E-3
glucose homeostasis	5	5.6E-5	1.3E-2

as a novel gene for T2D. The *TP53INP1* encodes a protein for mediating autophagy-dependent cell death through apoptosis and regulating cellular-extracellular matrix adhesion and cell migration [77], and was expressed by activation via p53, which regulated the oxidative damage response [78]. A study with mice genetically engineered knockout for *TP53INP1* demonstrated that the impaired mitophagy of dysfunctional mitochondria is the main source of the chronic oxidative stress, and may cause insulin resistance and promote the predisposition to T2D [79]. *TOMM40*, translocase of outer mitochondrial membrane 40, is an indispensable part to transfer protein across the mitochondria [80]. Meanwhile, the variation of *TOMM40* could result in mitochondrial dysfunction, which is increasingly recognized to be involved in the pathogenesis of AD [81]. In addition, the age-related memory performance was obviously influenced by *TOMM40* [82]. *C8orf38* (also known as *NDUFAF6*), encodes a protein involved in the assembly of mitochondrial respiratory chain complex I [83]. Interestingly, previous research suggested that the main function of complex I is deemed to participated in the generation of reactive oxygen species (ROS), which in turn might contribute to oxidative stress [84]. In addition, a slight inhibition of the activity of complex I would improve the cognitive function by reducing the level of Aβ and tau phosphorylation in AD animal models [85]. Based on these findings, we speculate that the genetic variants in three genes (*TP53INP1*, *TOMM40*, *C8orf38*) may significantly contribute to the development of these two disorders via oxidative stress and mitochondrial dysfunction.

Mitochondria play critical roles in regulating cell death and survival, metabolism, energy production, and apoptosis. Earlier studies indicated that brain is much more vulnerable when it comes to mitochondrial dysfunction including mitochondrial DNA (mtDNA) mutation, lower activity of mitochondrial respiratory chain complex I-IV, reduced ATP production, and increased ROS [7]. Notably, mitochondrial dysfunction has been proposed to play a crucial role in increasing oxidative stress, which is a noticeable and one of the earliest features in susceptible neurons [86] and also block the insulin cation pathway and induce insulin resistance [87]. Meanwhile, increased mitochondrial electron transport chain gene expression, protein and mtDNA in the brain were associated with AD [88]. More importantly, mitochondrial dysfunction led to AD pathologies, including accumulation of Aβ and abnormal of tau phosphorylation [89]. Strong evidence indicated that mutations of mtDNA negatively regulate mitochondrial function and gene expression, and increased generation of ROS with reduction in ATP production is closely related to T2D [90]. Taken together, the findings in our study highlighted the pleiotropic genes as well as the dysfunction of mitochondria which may play important roles in the pathogenesis of AD and T2D.

The present study has several strengths. First, the study populations were both homogeneous in ethnicity involving only Caucasian populations with a large sample sizes. Second, the study examined the association between T2D-related SNPs in AD patients and AD-related SNPs in T2D. Third, additional analysis was conducted using ccFDR and detected 8 shared pleiotropic susceptibility SNPs in two diseases. Therefore, our results revealed some of the susceptibility genes as potential therapeutic targets in both diseases. However, there are some limitations in our study. First, this study population was Caucasian and further studies may be necessary to determine whether our findings can be replicated in other ethnic patients or they are ethnic-specific. Secondly, we identified the genetic variants significantly associated with the pleiotropic loci of AD or T2D, but the functional mechanisms of these genetic variants in the regulation of the two diseases are largely unclear. Further studies will be helpful to delineate the functions of these genetic variants significantly associated with AD and T2D.

In summary, the present study revealed the common genetic variants for T2D and AD in Caucasians. In addition, cFDR is a promising and powerful tool, for its ability to identify novel loci even without extra significant expense by re-analyzing previous GWAS datasets simultaneously. Further works will be required to fully explore the role of these particular loci in the etiology of T2D and AD to shed light with novel insight into potential therapeutic targets.

The authors declare that they have no conflicts of interest.

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Authors' roles: Study conception, initiation, general design and development and finalization: HW D. Data collection: XF W, YC C, X L, CP Z, LP P, ZX A, JM L, J.G, YF G and RZ. Drafting manuscript: XF W, HW D, DYL. Revising manuscript content: XF W, DY Li, JS and HW D.

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