No shared genetic susceptibility between Type 2 Diabetes and Alzheimer's disease.

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Abstract

A search of PubMed using the terms "Alzheimer's disease" and "Diabetes" yields nearly 9000 publications and yet no clear mechanistic link between the two conditions has been identified. With this background we assessed whole genome association study (GWAS) data from the latest GWAS for the two syndromes, where each syndrome GWAS contained UK biobank data. These well powered analyses gave no support to common genetic risk. They strongly suggest the two diseases do not share genetic mechanisms and, if there is a relationship it may be that they both be downstream of common environmental influences.

Introduction

A PubMed search "diabetes and Alzheimer's disease" yields nearly 9,000 articles suggesting that a mechanistic link between the two common conditions was established. However, although Alzheimer's disease (AD) has been characterised as "type 3 diabetes" (de la Monte and Wands, 2008) no clear mechanistic link between these two prevalent conditions has been demonstrated (Salas and De Strooper, 2019). Clearly, such a link would be important to understand, especially as type 2 diabetes (T2D) could constitute a modifiable risk factor in the quest to reduce the incidence of dementia (Ngandu et al., 2015).

With this background, primarily using the most recent GWAS for each condition: (Xue et al., 2018) for diabetes and two AD (Kunkle et al., 2019) and (Bellenguez et al., 2022), we decided to assess whether there was any shared genetic risk between the two conditions. If there was a genetic overlap between the diseases it would give mechanistic insight and if there wasn't, it would cast doubt on any purported association or, perhaps, suggest that both conditions were independently downstream of related environmental triggers. Because it is clear that there is substantial misdiagnosis of AD in clinical case series, we repeated the assessment of diabetes induced dementia risk in a comparatively small pathologically confirmed AD case control series.

Methods

We used the latest GWAS summary statistics for T2D (62,892 T2D cases and 596,424 controls of European ancestry (Xue et al., 2018) and tested for genetic correlation with two AD GWAS: first (Kunkle et al., 2019) with sample size 21,982 AD cases, and 41,944 cognitively normal controls), and second , the latest AD GWAS (Bellenguez et al., 2022) with 39,106 clinically diagnosed AD cases and 401,577 controls. As T2D contains the UK Biobank data we ought to use AD GWAS with (Bellenguez et al., 2022) and without (Kunkle et al., 2019) UK Biobank participants. We run genetic correlation analysis with LDScore regression (Bulik-Sullivan et al., 2015) and with SUPERGNOVA approach (Zhang et al., 2021) (the latter reports local genetic correlation). Then we looked at the direct replication of AD GWAS significant SNPs in T2D (and vice versa) at least at the nominal significance level 0.05. When comparing the GWAS significant SNPs we have extracted all SNPs (with $p \leq 10^{-7}$) in one study and matched them with all available SNPs in the other. Then we looked at SNPs which

were significant at 5% level in the second study and reported the best SNP from the second study here. Therefore, if the GWAS index SNP from the first study was not available in the second study, the proxy SNP was reported instead.

Finally, we assessed polygenic risk scores (PRS) generated with SNPs associated with T2D at a range of p-vales thresholds ($5x10^{-8}$, 10^{-7}, 10^{-5}, 10^{-4}, 0.001, 0.05, 0.1 and 0.5) and tested them in an independent sample of AD pathology confirmed cases (N=1011) and controls (N=583) (Corneveaux et al., 2010; Escott-Price et al., 2017). Prior to PRS calculation, the data was LD pruned, whilst keeping the most associated SNP in (r^2=0.1 in 1MB window).

Results

Table 1 shows all the T2D GWAS hits and the significance of their associations with diabetes and with AD and table 2 shows all the AD GWAS hits and the significance of their association with AD and with diabetes. None of the "cross referenced" SNPs are genome wide significant in the other disease and those which are nominally significant are approximately evenly split in terms of the direction of their effect (i.e. there is no evidence for co-association). Thus, there is no evidence that there is shared genetic risk between T2D and dementia (r_g=0.02 (SE=0.06), p=0.728 between T2D and AD (Kunkle et al., 2019), and r_g=0.054 (SE=0.05), p=0.285, T2D and AD (Bellenguez et al., 2022), the latter despite the large proportion (74.8%) of shared samples from the UK Biobank). The only regional significant correlation after correction for the number of the genomic regions from the input genome partition file (N=2081, p=0.009) was found for between T2D and AD (Bellenguez et al., 2022) in the region on chromosome 2 (43309247-44048346, see also *THADA* gene in Table 2). No regional significant correlations were found between T2D and AD (Kunkle et al., 2019).

Out of 882 AD GWAS significant SNPs in (Bellenguez et al., 2022), 252 (28%) were also nominally significant in T2D GWAS. Limiting the analysis to AD GWAS index SNPs, which have also shown nominal replication in T2D (N SNPs= 11), only 5 of them had the same direction of effects (Table 1). All SNPs from the APOE region had opposite directions of effects between AD and T2D. For example, rs2927439 (chr19:45242740) had the risk allele "A" (B=0.1684 (SE=0.01), $p=7.68x10^{-56}$, whereas its effect size was negative in T2D (B=-0.0175 (SE=0.008), p=0.036).

Out of 4592 GWAS significant T2D SNPs, 842 (18%) were also nominally significant in (Bellenguez et al., 2022) AD. Of them, looking at independent (index) SNPs only, 14 out 37 (38%) had opposite direction of effects (Table 2). In particular, all SNPs from the MHC region were in the opposite direction. For example, the most significant SNP for T2D (rs660895, chr6:32577380, *HLA-DRB1*) had risk allele "G" (B=0.078 (SE=0.009), $p=1.0x10^{-18}$), but in AD the risk allele was "A" (B=0.058 (SE=0.0129), $p=2.76x10^{-6}$).
A similar pattern was observed when comparing T2D with (Kunkle et al., 2019) AD GWAS, which is independent of T2D GWAS (see Supplemental Table 1).
THADA gene is strongly associated with T2D, and also is associated with AD (Table 2) with the same direction of effect. This gene however never reached genome-wide significance for AD, and to our knowledge, never was reported for association in AD in functional or candidate gene studies.

Because we have been concerned that clinic-based diagnosis of AD was contaminated with other dementia diagnoses (Beach et al., 2012; Escott-Price et al., 2019), we confirmed this lack of genetic overlap by assessing whether polygenic risk score for T2D had any predictive value for pathologically confirmed AD: it did not. The T2D PRS was slightly negatively significantly associated with AD in the pathology confirmed sample of 1011 cases and 583 controls for all p-value thresholds from $5x10^{-8}$ till 0.5, with PRS association p-value ranging from B_{PRS}=-0.137 (SE=0.05), p=0.01 when combining independent the 161 diabetes GWAS sig. SNPs, till B=-0.149 (SE=0.053), p=0.0048, combining 65,788 independent T2D SNPs with p<0.5 (see Supplemental Table 2).

Discussion

In this well powered study, we have failed to find any evidence for a genetic overlap between AD/dementia and T2D. Although (Hao et al., 2015) reported a shared genetic aetiology underlying Alzheimer's disease and type 2 diabetes, in fact they report that more than 50% (57.3%) of the shared SNPs have divergent risk alleles in the two diseases, similar to our observation reported here. Given this, it is appropriate to consider what are the alternative explanations for the widely assumed and referenced association between the two diseases. The first explanation is that the reported association is simply wrong or is

confounded by the acute effects of diabetes and high glucose concentrations on cognitive performance and the second is that both syndromes are independent downstream events of environmental influences such as a sedentary lifestyle. Since we observed opposite direction of SNPs in the APOE and MHC regions and negative association of the PRS at all p-value thresholds, the only speculation we can offer is that from population genetics point of view, both disorders involve earlier mortality (apart of recent advances in T2D, where this condition can now be managed), ~~therefore to have risk for one genetic condition is sufficient.~~ In either case, the implication of the lack of association is that treatment strategies aimed at alleviating T2D are unlikely to have a direct effect on the incidence of AD and the second is to imply that it is unlikely to be fruitful to assess insulin resistance pathways as candidate pathways for Alzheimer's disease pathogenesis.

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Table 1. Comparison of index AD GWAS significant SNPs (Bellenguez et al., 2022) with T2D SNPs (Xue et al., 2018) which replicate at nominal significance level (p=0.05). SNPs in bold have the same direction of the effect size.

			Alzheimer's Disease				Type 2 Diabetes				
SNP	CHR	BP	Effect allele	B	SE	p-value	Effect allele	B	SE	p-value	Gene
rs74490912	2	127846321	A	0.103	0.012	2.86e-17	C	0.020	0.010	0.048	BIN1
rs2452760	5	86186781	A	0.073	0.011	1.45e-10	A	-0.019	0.009	0.042	COX7C
rs2293579	11	47440758	A	0.060	0.010	7.05e-10	A	-0.016	0.008	0.031	PSMC3/SPI1
rs1582763	**11**	**60021948**	**A**	**-0.091**	**0.010**	**3.64e-20**	**A**	**-0.018**	**0.008**	**0.026**	**MS4A4E**
rs2458500	**11**	**85779310**	**A**	**-0.096**	**0.012**	**3.46e-15**	**A**	**-0.021**	**0.010**	**0.033**	**PICALM**
rs1784920	**11**	**121437571**	**A**	**-0.093**	**0.015**	**1.13e-9**	**A**	**-0.036**	**0.012**	**0.004**	**SORL1**
rs36026988	**14**	**92938382**	**T**	**0.077**	**0.012**	**7.69e-11**	**C**	**-0.020**	**0.009**	**0.037**	**SLC24A4**
rs4311	17	61560763	T	-0.064	0.010	2.44e-11	T	0.029	0.008	0.00021	ACE
rs2927439	19	45242740	A	0.168	0.011	7.68e-56	G	0.018	0.008	0.036	CEACAM16/NECTIN2/BCAM
rs718022	20	55003465	A	-0.124	0.017	9.92e-13	A	0.030	0.015	0.045	CASS4
rs2830510	**21**	**28161146**	**T**	**-0.059**	**0.011**	**1.71e-8**	**C**	**0.017**	**0.008**	**0.033**	**CYYR1**

Table 1. Comparison of index T2D GWAS significant SNPs (Xue et al., 2018) with AD SNPs (Bellenguez et al., 2022) which replicate at nominal significance level (p=0.05). SNPs in bold have the same direction of the effect size.

			Type 2 Diabetes				Alzheimer's disease				
SNP	CHR	BP	Effect allele	B	SE	P	Effect allele	B	SE	P	gene
rs6931514	6	20703952	G	0.131	0.008	2.33E-58	A	0.025	0.011	0.018	CDKAL1
rs1421085	16	53800954	C	0.104	0.007	1.60E-47	T	0.019	0.010	0.046	FTO
rs849135	7	28196413	G	0.100	0.007	1.04E-43	A	0.022	0.010	0.019	JAZF1
rs11774700	8	118220270	C	-0.100	0.008	5.15E-35	T	0.021	0.010	0.049	SLC30A8
rs4458523	4	6289986	T	-0.089	0.007	9.37E-34	T	-0.020	0.010	0.039	WFS1
rs17334919	2	43707385	T	-0.140	0.013	6.69E-28	T	-0.067	0.016	4.21e-05	THADA/ZFP36L2
rs5215	11	17408630	C	0.068	0.007	2.09E-20	T	-0.022	0.010	0.028	KCNJ11/NCR3LG1/ABCC8
rs660895	6	32577380	G	0.078	0.009	1.00E-18	A	0.058	0.012	2.76e-6	HLA-DRB1/HLA-DQB1/TNXB
rs290483	10	114915214	G	-0.065	0.008	8.25E-18	T	0.021	0.010	0.039	TCF7L2
rs340874	1	214159256	T	-0.063	0.007	8.41E-18	T	0.021	0.010	0.026	PROX1/RPS6KC1
rs11187105	10	94384427	T	-0.075	0.009	1.17E-15	T	0.023	0.012	0.048	KIF11/IDE
rs17513135	1	40035686	T	0.062	0.009	2.73E-13	T	0.027	0.011	0.016	PABPC4/BMP8A/MACF1
rs825476	12	124568456	C	-0.052	0.007	6.81E-13	T	0.020	0.010	0.039	AC068790.8/ABCB9
rs12910825	15	91511260	G	0.052	0.007	2.16E-12	A	-0.028	0.010	0.0051	AC068831.7/VPS33B/RCCD1
rs12970134	18	57884750	A	0.056	0.008	5.31E-12	A	-0.025	0.011	0.020	PMAIP1
rs73001065	19	19460541	C	0.101	0.015	1.09E-11	C	0.046	0.020	0.017	MAU2
rs7607886	2	165509579	A	-0.061	0.009	2.21E-11	A	-0.024	0.012	0.034	GRB14
rs243015	2	60588871	G	0.050	0.008	2.42E-11	A	0.038	0.010	0.00015	FANCL
rs12453443	17	36104121	G	-0.052	0.008	5.52E-11	C	-0.024	0.010	0.024	HNF1B
rs7621569	3	12184557	G	-0.080	0.012	8.51E-11	A	0.032	0.015	0.027	SYN2/TIMP4
rs2421016	10	124167512	T	-0.046	0.007	1.48E-10	T	-0.037	0.010	0.00011	PLEKHA1/BTBD16
rs3900856	5	55833892	A	0.114	0.019	7.35E-10	A	0.066	0.023	0.0042	C5orf67

rs11668386	19	19531910	G	0.066	0.011	8.23E-10	A	-0.040	0.015	0.0080	GATAD2A/PBX4
rs2237892	11	2839751	T	-0.096	0.016	8.75E-10	T	-0.040	0.021	0.049	KCNQ1
rs4686388	3	185484257	G	-0.050	0.008	8.94E-10	A	0.020	0.010	0.044	IGF2BP2
rs12075991	1	51252618	C	-0.083	0.014	1.75E-09	T	0.033	0.016	0.045	FAF1/CDKN2C
rs10087241	8	30863722	G	0.048	0.008	2.80E-09	A	-0.022	0.010	0.025	/TEX15
rs7845219	8	95937502	C	-0.042	0.007	4.55E-09	T	-0.041	0.010	1.28E-05	NDUFAF6/TP53INP1
rs10120688	9	22056499	A	0.042	0.007	5.26E-09	A	0.019	0.010	0.043	CDKN2B
rs11774915	8	9188762	T	0.050	0.009	8.73E-09	T	-0.025	0.010	0.015	PPP1R3B
rs16988333	22	30552813	G	-0.075	0.013	9.17E-09	A	-0.039	0.017	0.023	HORMAD2/MTMR3/ASCC2/UQCR10
rs2179642	22	44391588	C	0.048	0.008	1.06E-08	T	0.027	0.010	0.0088	SAMM50/PARVB
rs11040293	11	49260556	T	0.080	0.014	1.61E-08	A	-0.060	0.016	0.0003	FOLH1
rs4696137	4	153518973	G	-0.050	0.009	1.66E-08	A	0.022	0.011	0.047	FBXW7
rs11925227	3	170766618	A	-0.053	0.010	2.25E-08	A	0.034	0.012	0.0069	SLC2A2
rs17320971	17	40546917	G	0.083	0.015	2.85E-08	A	-0.036	0.018	0.040	STAT3/RETREG3/TUBG1
rs4622883	3	152188290	A	0.044	0.008	3.02E-08	A	0.025	0.010	0.0087	MBNL1