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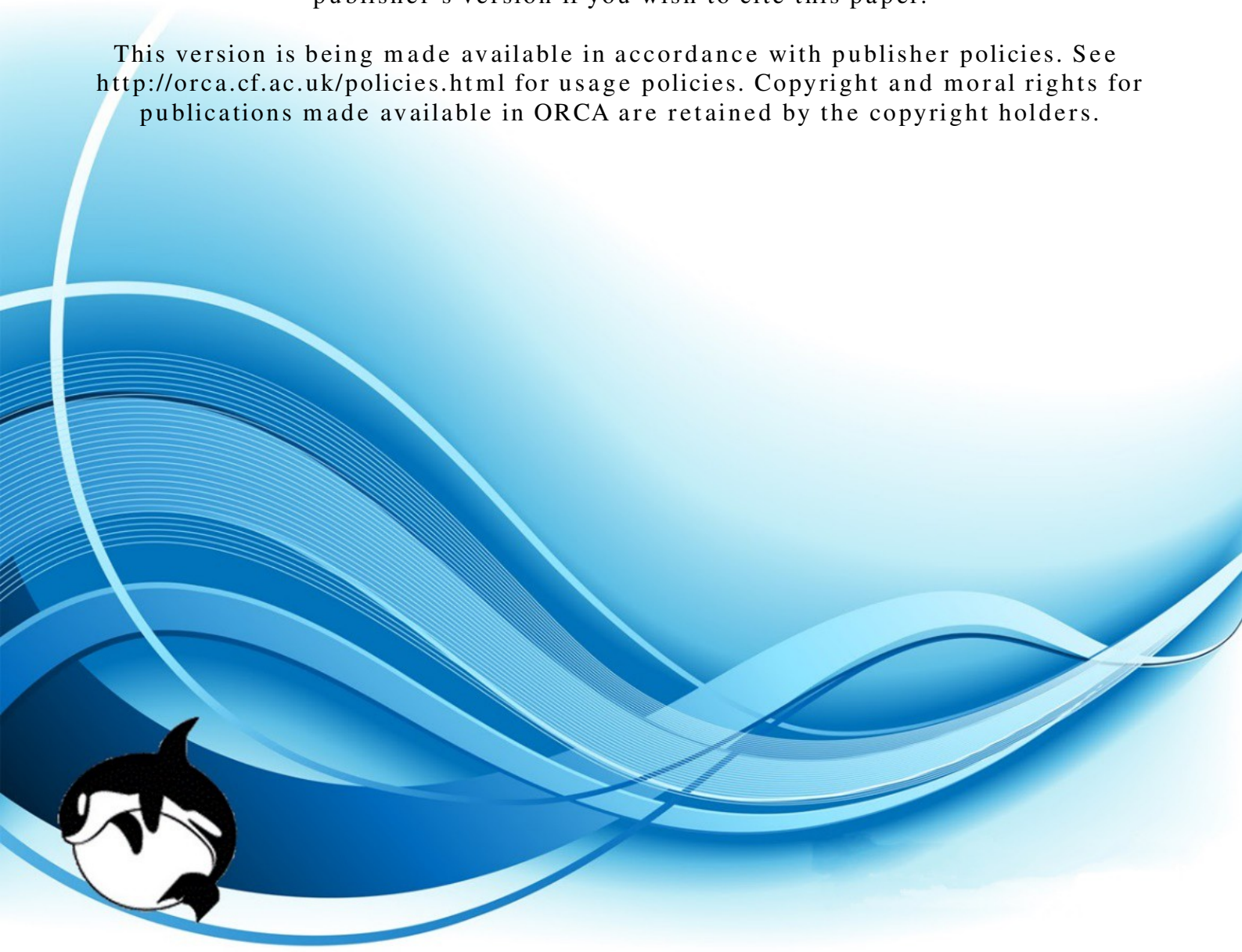

Alzheimer's disease and type 2 diabetes: shared genetic susceptibility?

John Hardy[1,2], Bart de Strooper[1,3,4], Valentina Escott-Price[5]

A PubMed search with the terms "diabetes and Alzheimer's disease" yields nearly 9,000 articles, suggesting an established link between the two common conditions. However, although Alzheimer's disease (AD) has been characterised as "type 3 diabetes" (1), no clear link has been demonstrated (2), so we decided to assess whether there was any shared genetic risk between the two conditions. A detailed description of our methodology is provided in the appendix.

The genetic correlation between the two traits shows no evidence for a shared genetic risk between diabetes and AD (r_g=-0.058, (SE=0.04), p=0.155 between T2D (3) and AD (4) and r_g=0.02 (SE=0.06), p=0.728 between T2D (3) and AD (5), the former despite the large proportion (74.8%) of shared samples from the UK Biobank). We found four regional correlations, after Bonferroni correction for the number of the genomic regions (N=2081) from the input genome partition file. Only one correlation in the region on chromosome 2 was positive (chr2:43309247-44048346, see also *THADA* gene in Table 1), other three (chr14:90075441-92098486, chr22:44317416-44818986, chr8:95810772-96533604) were negative.

When we selected significant SNPs from one GWAS and Bonferroni corrected (study-wise) the corresponding SNPs from the other GWAS, then six AD significant loci were significant in diabetes, but with opposite direction of the association (Table 2). Out of T2D genome-wide significant loci, five loci were significant in AD, but only two in the same direction of association (*THADA* (chr 2) and *PLEKHA1* (chr 10)) (Table 1). *THADA* however has never reached genome-wide significance for AD. This and the positive *local* genetic correlation may indicate that the locus is pleiotropic, however we are hesitant to speculate without further evidence. *PLEKHA1* was reported as AD genome-wide significant gene in (4) for the first time,

when combining the discovery and the replication datasets. Overall, eight loci appear in both tables, but six (*HLA-DQB1, JAZF1, NDUFAF6, CELF1/SPI1, DOC2A, ACE*) show opposite directions of effect.

None of the 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). Out of 2147 significant SNPs found in GWAS in AD (4), 25% were also nominally significant in GWAS in type 2 diabetes. Limiting the analysis to AD GWAS index SNPs, which have also shown nominal replication in diabetes (N SNPs= 19), only 7 of them had the same direction of effects (appendix, Supplemental Table 1). All SNPs from the *APOE* region had opposite directions of effects between AD and type 2 diabetes. Out of 5881 GWAS significant T2D SNPs, 23.6% were also nominally significant in AD (4). Of them, looking at independent (index) SNPs only, 23 out 43 (53%) had opposite direction of effects (appendix, Supplemental Table 2). In particular, all SNPs from the *MHC* region were in the opposite direction. A similar pattern of associations' directionality was observed when comparing T2D with AD GWAS without shared samples from the UK Biobank (5), see appendix, Supplemental Table 3.

We also investigated genetic overlap by assessing whether polygenic risk score for type 2 diabetes had any association with pathologically confirmed AD. The polygenic risk score was not significantly associated with AD in the pathology confirmed sample of 1011 cases and 583 controls for all p-value thresholds, with PRS association p-value ranging from p=0.01 (B_{PRS}=-0.137 (SE=0.05)) when combining independent the 161 diabetes GWAS significant SNPs, till p=0.0048 (B=-0.149 (SE=0.053)), combining 65,788 independent T2D SNPs with p<0.5 (see appendix, Supplemental Table 4).

In thid well-powered approach, we have failed to find convincing evidence for a genetic overlap between AD and type 2 diabetes. Although a shared genetic aetiology has been reported (6), in fact that study found that 57.3% of the shared SNPs have divergent risk alleles in the two diseases, similar to our findings. Alternative explanations for the widely assumed association between the two diseases must exist. The first explanation is that the 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 factors, such as a sedentary lifestyle. In either case, the implication of the lack of association is that treatment strategies aimed at alleviating diabetes are unlikely to have a direct effect on the incidence of AD and the second is that it is unlikely to be fruitful to assess insulin resistance pathways as candidate pathways for AD pathogenesis.

Conflict of interest:

VEP and JH declare no conflict of interests. BDS has no direct conflict of interests with the results reported in this manuscript. He has however consulted for several major drug companies and is scientific founder of Augustin TX and Muna TX. He has a small amount of shares in Muna TX.

Data sharing statement:

The results in this paper are based upon publicly available data. The GWAS summary statistics for T2D (3) is available at https://cnsgenomics.com/content/data; AD (4) is available https://www.ebi.ac.uk/gwas/studies/GCST90027158; AD (5) is available at https://www.niagads.org/datasets/ng00075; the individual level genotype data for pathology confirmed sample is available via www.niagads.org.

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Table 1. Comparison of index AD GWAS significant SNPs (4) with T2D SNPs (3) which replicate after study-wise Bonferroni correction. SNPs in bold have the same direction of the effect size. SNPs in italic are in the region with significant SNPs after the study-wise Bonferroni correction.

					AD			T2D			
SNP	CHR	BP (b37)	A1	A2	B	SE	P	B	SE	P	Map
rs660895	6	32577380	G	A	-0.073	0.010	1.8E-12	0.078	0.009	1.0E-18	
rs67250450	7	28174986	C	T	-0.056	0.010	2.0E-08	0.056	0.009	2.6E-09	
rs4734295	8	96000919	G	A	0.049	0.008	2.0E-09	-0.023	0.007	0.002	*NL*
rs2293579	11	47440758	A	G	0.055	0.008	2.3E-11	-0.016	0.008	0.031	*CEL*
rs12325539	16	30033633	C	T	-0.057	0.008	1.2E-11	0.037	0.008	4.6E-06	*D*
rs4311	17	61560763	T	C	-0.066	0.008	6.9E-16	0.029	0.008	0.0002	

Table 2. Comparison of index T2D GWAS significant SNPs (3) with AD SNPs (4) which replicate after study-wise Bonferroni correction. SNPs in bold have the same direction of the effect size. SNPs in italic are in the region with significant SNPs after the study-wise Bonferroni correction.

					T2D			AD			
SNP	CHR	BP (b37)	A1	A2	B	SE	P	B	SE	P	
rs17334919	2	43707385	T	C	-0.140	0.013	6.7E-28	-0.065	0.014	2.5E-06	
rs1063355	6	32627714	T	G	-0.071	0.008	3.7E-19	0.029	0.008	0.0004	
rs849135	7	28196413	G	A	0.100	0.007	1.0E-43	-0.023	0.008	0.005	
rs7845219	8	95937502	C	T	-0.042	0.007	4.5E-09	0.046	0.008	1.7E-08	*ND*
rs2421016	10	124167512	T	C	-0.046	0.007	1.5E-10	-0.038	0.008	3.3E-06	

Appendix.

Contents

1. GWAS data sets

We used the latest GWAS summary statistics for type 2 diabetes (T2D) (62,892 T2D cases and 596,424 controls of European ancestry (1) and tested for genetic correlation with two Alzheimer's disease (AD) GWAS: first (2) with sample size 21,982 AD cases, and 41,944 cognitively normal controls, and second , the latest AD GWAS (3) with 39,106 clinically diagnosed AD cases, 46,828 proxy cases and 401,577 controls of European ancestry.

2. GWAS data analysis

MungeSumstats R package was used to harmonise the summary statistics data. As T2D contains the UK Biobank data we ought to use AD GWAS with (3) and without (2) UK Biobank participants. We run genetic correlation analysis with LDScore regression (4) and with SUPERGNOVA approach (5) (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 $p \leq 5x10^{-8}$) 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 pair with the most GWAS associated SNP (which could be a proxy to the reported index GWAS significant SNP).

3. Polygenic Risk Scores

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) (9, 10). Prior to PRS calculation, the data was LD pruned, whilst keeping the most associated SNP in (r^2=0.1 in 1MB window).

Supplemental Table 1. Comparison of index AD GWAS significant SNPs (3) with T2D SNPs (1) which replicate at nominal significance level (p=0.05). SNPs in bold have the same direction of the effect size. SNPs in italic are in the region with significant SNPs after the study-wise Bonferroni correction.

					AD			T2D			
SNP	CHR	BP (b37)	A1	A2	B	SE	P	B	SE	P	Mapped gene
rs74490912	2	127846321	C	A	-0.106	0.010	2.8E-24	0.020	0.010	0.048	*BIN1*
rs875394	4	11011598	T	G	0.075	0.014	2.9E-08	-0.027	0.014	0.050	*CLNK/HS3ST1*
rs55695634	5	86299471	T	C	0.074	0.010	2.1E-13	-0.020	0.010	0.042	*COX7C*
rs660895	*6*	*32577380*	*G*	*A*	*-0.073*	*0.010*	*1.8E-12*	*0.078*	*0.009*	*1.0E-18*	*HLA*
rs67250450	*7*	*28174986*	*C*	*T*	*-0.056*	*0.010*	*2.0E-08*	*0.056*	*0.009*	*2.6E-09*	*JAZF1*
rs6971558	**7**	**100079857**	**A**	**T**	**-0.071**	**0.009**	**1.0E-15**	**-0.018**	**0.009**	**0.033**	***ZCWPW1/NYAP1***
rs4734295	*8*	*96000919*	*G*	*A*	*0.049*	*0.008*	*2.0E-09*	*-0.023*	*0.007*	*0.002*	*NDUFAF6*
rs2293579	*11*	*47440758*	*A*	*G*	*0.055*	*0.008*	*2.3E-11*	*-0.016*	*0.008*	*0.031*	*CELF1/SPI1*
rs1582763	**11**	**60021948**	**A**	**G**	**-0.086**	**0.008**	**1.7E-24**	**-0.018**	**0.008**	**0.026**	***MS4A***
rs527162	**11**	**85715736**	**C**	**T**	**-0.095**	**0.010**	**2.6E-20**	**-0.021**	**0.010**	**0.035**	***PICALM***
rs11218343	**11**	**121435587**	**C**	**T**	**-0.165**	**0.021**	**1.0E-14**	**-0.071**	**0.020**	**0.0005**	***SORL1***
rs36026988	**14**	**92938382**	**C**	**T**	**-0.071**	**0.010**	**6.5E-13**	**-0.020**	**0.009**	**0.037**	***SLC24A4***
rs7179399	**15**	**59165527**	**T**	**C**	**-0.048**	**0.009**	**3.4E-08**	**-0.017**	**0.008**	**0.039**	***ADAM10***
rs12325539	*16*	*30033633*	*C*	*T*	*-0.057*	*0.008*	*1.2E-11*	*0.037*	*0.008*	*4.6E-06*	*DOC2A*
rs17763086	17	43905481	G	T	-0.053	0.010	4.2E-08	0.018	0.009	0.041	*CRHR1*
rs4311	*17*	*61560763*	*T*	*C*	*-0.066*	*0.008*	*6.9E-16*	*0.029*	*0.008*	*0.0002*	*ACE*
rs440277	19	45361224	A	G	-0.132	0.009	2.5E-44	0.023	0.008	0.0076	*APOE*
rs718022	20	55003465	A	G	-0.114	0.015	9.2E-15	0.030	0.015	0.045	*CASS4*
rs2830510	**21**	**28161146**	**C**	**T**	**0.049**	**0.009**	**3.6E-08**	**0.017**	**0.008**	**0.033**	***ADAMTS1***

Supplemental Table 2. Comparison of index T2D GWAS significant SNPs (1) with AD SNPs (3) which replicate at nominal significance level (p=0.05). SNPs in bold have the same direction of the effect size. SNPs in italic are in the region with significant SNPs after the study-wise Bonferroni correction.

					T2D			AD			
SNP	CHR	BP (b37)	A1	A2	B	SE	P	B	SE	P	Mapped gene
rs12037222	**1**	**40064961**	**A**	**G**	**0.060**	**0.009**	**1.5E-12**	**0.020**	**0.010**	**0.036**	***MACF1***
rs12088739	**1**	**51506886**	**G**	**A**	**-0.088**	**0.013**	**9.8E-12**	**-0.040**	**0.014**	**0.004**	***MIR4421***
rs340883	1	214145706	T	C	0.051	0.007	1.2E-12	-0.019	0.008	0.020	*PROX1-AS1*
rs11127491	2	646145	T	C	-0.060	0.010	7.3E-10	0.021	0.011	0.045	*TMEM18*
rs780094	2	27741237	T	C	-0.069	0.007	5.2E-21	0.018	0.008	0.032	*GCKR*
rs17334919	***2***	***43707385***	***T***	***C***	***-0.140***	***0.013***	***6.7E-28***	***-0.065***	***0.014***	***2.5E-06***	***THADA***
rs243015	2	60588871	G	A	0.050	0.008	2.4E-11	-0.030	0.009	0.0005	*MIR4432HG*
rs840967	**2**	**65701757**	**C**	**A**	**0.050**	**0.008**	**5.4E-10**	**0.018**	**0.008**	**0.031**	***CEP68***
rs10929976	2	161147528	T	C	-0.056	0.009	2.3E-10	0.018	0.009	0.048	*RBMS1*
rs1899951	**3**	**12394840**	**T**	**C**	**-0.112**	**0.011**	**1.6E-24**	**-0.034**	**0.013**	**0.007**	***PPARG***
rs17361324	**3**	**123131254**	**T**	**C**	**-0.082**	**0.008**	**3.1E-23**	**-0.020**	**0.010**	**0.036**	***ADCY5***
rs11925227	3	170766618	A	G	-0.053	0.010	2.3E-08	0.029	0.011	0.006	*TNIK*
rs4689393	**4**	**6287241**	**T**	**C**	**-0.082**	**0.007**	**3.4E-28**	**-0.016**	**0.008**	**0.048**	***WFS1***
rs735949	4	185716232	C	T	-0.071	0.011	1.9E-11	0.026	0.012	0.024	*ACSL1*
rs3900856	**5**	**55833892**	**A**	**G**	**0.114**	**0.019**	**7.4E-10**	**0.048**	**0.020**	**0.018**	***C5orf67***
rs7756992	6	20679709	G	A	0.130	0.008	6.0E-62	-0.021	0.009	0.022	*CDKAL1*
rs1063355	*6*	*32627714*	*T*	*G*	*-0.071*	*0.008*	*3.7E-19*	*0.029*	*0.008*	*0.0004*	*HLA-DQB1*
rs853974	**6**	**127068983**	**T**	**C**	**0.060**	**0.009**	**7.9E-12**	**0.021**	**0.009**	**0.021**	***RPS4XP9***
rs849135	*7*	*28196413*	*G*	*A*	*0.100*	*0.007*	*1.0E-43*	*-0.023*	*0.008*	*0.005*	*JAZF1*
rs11774915	8	9188762	T	C	0.050	0.009	8.7E-09	-0.023	0.009	0.009	*LOC157273(TNKS)*
rs1073913	8	10611708	A	C	0.045	0.008	6.2E-09	-0.017	0.008	0.046	*PINX1*

rs17411031	8	19852310	G	C	-0.045	0.008	3.0E-08	0.022	0.009	0.018	*LPL*
rs2725370	**8**	**30852826**	**T**	**C**	**0.050**	**0.009**	**3.7E-09**	**0.021**	**0.009**	**0.017**	***PURG***
rs7845219	*8*	*95937502*	*C*	*T*	*-0.042*	*0.007*	*4.5E-09*	*0.046*	*0.008*	*1.7E-08*	*NDUFAF6/TP53INP1*
rs1333051	**9**	**22136489**	**T**	**A**	**-0.149**	**0.011**	**1.3E-41**	**-0.029**	**0.012**	**0.013**	***CDKN2B-AS1***
rs2488075	**10**	**94490174**	**C**	**T**	**0.083**	**0.007**	**5.1E-30**	**0.016**	**0.008**	**0.050**	***HHEX***
rs10128255	10	114742835	G	A	-0.109	0.008	6.5E-47	0.018	0.009	0.037	*TCF7L2*
rs2421016	***10***	***124167512***	***T***	***C***	***-0.046***	***0.007***	***1.5E-10***	***-0.038***	***0.008***	***3.3E-06***	***PLEKHA1***
rs5215	**11**	**17408630**	**C**	**T**	**0.068**	**0.007**	**2.1E-20**	**0.017**	**0.008**	**0.040**	***KCNJ11***
rs7929543	**11**	**49351026**	**C**	**A**	**0.083**	**0.014**	**2.2E-09**	**0.036**	**0.015**	**0.014**	***TYRL***
rs1157343	**11**	**72429141**	**A**	**G**	**-0.048**	**0.008**	**2.7E-10**	**-0.018**	**0.009**	**0.035**	***ARAP1***
rs1355064	11	92797691	G	A	0.061	0.010	1.6E-10	-0.020	0.010	0.049	*MTNR1B*
rs2650000	12	121388962	A	C	0.054	0.008	8.4E-13	-0.018	0.009	0.037	*OASL*
rs825476	**12**	**124568456**	**C**	**T**	**-0.052**	**0.007**	**6.8E-13**	**-0.019**	**0.008**	**0.018**	***ZNF664/FAM101A***
rs11635117	**15**	**64112732**	**A**	**C**	**0.044**	**0.007**	**5.5E-10**	**0.018**	**0.008**	**0.032**	***USP3/HERC1***
rs12910825	**15**	**91511260**	**G**	**A**	**0.052**	**0.007**	**2.2E-12**	**0.029**	**0.008**	**0.0006**	***PRC1***
rs7206790	16	53797908	G	C	0.080	0.007	3.4E-27	-0.017	0.008	0.041	*FTO*
rs8081417	17	3902650	A	T	0.053	0.008	2.8E-10	-0.019	0.009	0.036	*ZZEF1*
rs6963	17	40731597	A	T	0.050	0.009	5.4E-09	0.031	0.009	0.0007	*STAT3/RETREG3*
rs594398	17	46957696	G	C	-0.054	0.008	1.1E-11	0.017	0.008	0.032	*UBE2Z*
rs12970134	18	57884750	A	G	0.056	0.008	5.3E-12	-0.020	0.009	0.029	*MC4R*
rs73001065	**19**	**19460541**	**C**	**G**	**0.101**	**0.015**	**1.1E-11**	**0.035**	**0.017**	**0.042**	***SUGP1 /MAU2***
rs4823182	22	44377442	G	A	0.048	0.008	3.4E-10	-0.019	0.009	0.027	*SAMM50*

Supplemental Table 3. Comparison of index T2D GWAS significant SNPs (1) with AD SNPs (2) which replicate at nominal significance level (p=0.05). SNPs in bold have the same direction of the effect size.

					T2D			AD			Mapped
SNP	CHR	BP (b37)	A1	A2	B	SE	P	B_AD	SE_AD	P_AD	gene
rs636083	**1**	**39821681**	**C**	**T**	**0.049**	**0.008**	**2.6E-10**	**0.032**	**0.016**	**0.040**	***MACF1***
rs17106184	**1**	**50909985**	**A**	**G**	**-0.078**	**0.013**	**6.8E-10**	**-0.054**	**0.024**	**0.026**	***FAF1***
rs7529073	1	214147889	C	T	-0.050	0.007	4.6E-12	0.035	0.014	0.013	*RPS6KC1*
rs1367173	**2**	**43449385**	**T**	**C**	**-0.111**	**0.011**	**1.7E-22**	**-0.049**	**0.022**	**0.027**	***HAAO***
rs7559813	**2**	**65278023**	**T**	**C**	**-0.052**	**0.009**	**9.3E-09**	**-0.035**	**0.016**	**0.034**	***SLC1A4***
rs9860730	**3**	**64701146**	**G**	**A**	**-0.057**	**0.008**	**2.8E-13**	**-0.039**	**0.015**	**0.012**	***ADAMTS9***
rs9844972	3	150097635	C	G	0.096	0.015	1.0E-10	-0.066	0.029	0.021	*PFN2*
rs1374910	**3**	**185531661**	**T**	**C**	**0.111**	**0.015**	**7.1E-14**	**0.059**	**0.030**	**0.045**	***IGF2BP2***
rs17086692	4	53134293	T	G	-0.047	0.008	2.5E-08	0.036	0.015	0.020	*SPATA18*
rs71624138	5	55870395	A	G	0.076	0.012	3.1E-10	0.047	0.023	0.041	*C5orf67*
rs4712540	6	20763171	G	A	-0.079	0.007	1.4E-27	0.030	0.014	0.037	*CDKAL1*
rs3095304	6	31092767	T	C	-0.060	0.011	2.1E-08	0.044	0.019	0.020	*CDSN*
rs1591805	**6**	**126717064**	**G**	**A**	**0.047**	**0.008**	**1.6E-09**	**0.033**	**0.014**	**0.023**	***CENPW***
rs2246012	**6**	**131898208**	**C**	**T**	**0.053**	**0.009**	**2.4E-08**	**0.040**	**0.020**	**0.043**	***MED23***
rs622217	6	160766770	C	T	-0.049	0.008	3.1E-10	0.030	0.014	0.034	*SLC22A2*
rs2191348	**7**	**15064255**	**G**	**T**	**-0.065**	**0.007**	**3.4E-19**	**-0.032**	**0.014**	**0.025**	***DGKB***
rs849135	7	28196413	G	A	0.100	0.007	1.0E-43	-0.044	0.014	0.002	*JAZF1*
rs7845219	8	95937502	C	T	-0.042	0.007	4.5E-09	0.046	0.014	0.001	*NDUFAF6*
rs3802177	**8**	**118185025**	**A**	**G**	**-0.122**	**0.008**	**2.3E-52**	**-0.035**	**0.016**	**0.026**	***SLC30A8***
rs7030641	**9**	**22054040**	**C**	**T**	**-0.062**	**0.007**	**3.6E-17**	**-0.034**	**0.015**	**0.026**	***CDKN2B***
rs290483	**10**	**114915214**	**G**	**T**	**-0.065**	**0.008**	**8.2E-18**	**-0.030**	**0.015**	**0.047**	***TCF7L2***

rs10510109	**10**	**124120457**	**T**	**G**	**-0.046**	**0.008**	**3.9E-09**	**-0.050**	**0.014**	**0.0004**	***BTBD16***
rs2074311	**11**	**17421860**	**A**	**G**	**0.055**	**0.007**	**6.8E-14**	**0.032**	**0.014**	**0.025**	***ABCC8***
rs11040291	**11**	**49248150**	**T**	**C**	**0.077**	**0.014**	**3.6E-08**	**0.070**	**0.026**	**0.007**	***FOLH1***
rs4275659	**12**	**123447928**	**T**	**C**	**-0.044**	**0.008**	**2.0E-08**	**-0.046**	**0.016**	**0.003**	***ABCB9***
rs17804744	13	80700707	C	T	-0.058	0.010	5.6E-09	0.039	0.018	0.033	*NDFIP2*
rs7183842	15	90400030	G	A	0.054	0.009	5.0E-10	-0.034	0.016	0.039	*C15orf38-AP3S2*
rs4783819	**16**	**53816647**	**G**	**C**	**-0.069**	**0.008**	**2.8E-20**	**-0.032**	**0.015**	**0.029**	***FTO***
rs77258096	16	75243772	A	C	-0.117	0.013	1.8E-18	0.057	0.024	0.016	*CTRB2*
rs2927311	16	81531230	G	C	-0.052	0.010	5.3E-08	0.046	0.017	0.007	*CMIP*
rs8081417	17	3902650	A	T	0.053	0.008	2.8E-10	-0.041	0.016	0.008	*ATP2A3*
rs2278524	17	4081975	A	G	0.058	0.008	3.0E-12	-0.037	0.016	0.019	*ANKFY1*
rs12941356	17	17716531	A	G	0.044	0.008	5.3E-08	-0.030	0.015	0.037	*SREBF1*
rs302864	17	56757584	A	G	0.071	0.013	2.5E-08	-0.056	0.026	0.033	*AC011195.2*
rs12970134	18	57884750	A	G	0.056	0.008	5.3E-12	-0.038	0.016	0.019	*PMAIP1*
rs12973258	**19**	**19488718**	**C**	**T**	**0.053**	**0.010**	**4.9E-08**	**0.037**	**0.019**	**0.048**	***MAU2***
rs10404527	19	46160703	A	G	0.057	0.009	4.6E-11	-0.033	0.016	0.042	*EML2*
rs6066138	**20**	**45594711**	**A**	**G**	**-0.049**	**0.008**	**1.9E-09**	**-0.033**	**0.016**	**0.041**	***EYA2***
rs7286205	22	30475154	A	G	-0.073	0.013	1.9E-08	0.056	0.026	0.033	*MTMR3*

Supplemental Table 4. T2D PRS (Polygenic risk score) prediction of AD case/control status in independent sample of pathology confirmed AD cases and controls.

P_T*	NSNPs	B	SE	P**
5e-8	161	-0.137	0.053	0.010
1e-7	181	-0.113	0.053	0.032
1e-5	426	-0.105	0.053	0.047
1e-4	861	-0.104	0.053	0.048
0.001	2222	-0.141	0.053	0.008
0.05	18153	-0.135	0.053	0.011
0.1	27374	-0.150	0.053	0.005
0.5	65788	-0.149	0.053	0.005

* P-value threshold for SNPs selection from the T2D GWAS.

**The analyses were performed with logistic regression adjusting for age at death, sex and 10 principal components.

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