Variation in the Glucose Transporter gene SLC2A2 is associated with glycaemic response to metformin

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Supplementary Tables

Supplementary Table 1. Second-stage replication with the UKPDS and meta-analysis. Two multiple linear regression models of HbA1c reduction with (shaded) or without (non-shaded) adjustment for baseline HbA1c were used to evaluate the replication. Only rs8192675 showed nominally significant replication in the model without baseline adjustment.

SNP	Gene	Allele	GWAS Screening and First-Stage Replication					Second-Stage Replication					Meta-analysis up to the Second Stage					Rep
				Adjusted		Non-Adjusted			Adjusted		Non-Adjusted			Adjusted		Non-Adjusted		
			N	BETA	P	BETA	P	N	BETA	P	BETA	P	N	BETA	P	BETA	P	
rs3013105	LRRC38	C	2294	0.105	0.000272	0.114	0.006599	1156	-0.002	0.9671	-0.058	0.386	3450	0.083	0.00123	0.066	0.064009	-+
rs41404544	KCNA2	C	2704	-0.218	8.81E-05	-0.188	0.02003	1177	-0.166	0.1465	-0.096	0.481	3881	-0.208	3.12E-05	-0.164	0.018231	--
rs34053484	ALCAM	C	2701	-0.144	7.37E-08	-0.187	1.49E-06	1166	0.057	0.3196	0.105	0.127	3867	-0.108	7.35E-06	-0.117	5.55E-04	+-
rs1828652	PLSCR4	T	2298	0.082	0.004901	0.082	0.05232	1125	-0.024	0.6746	-0.059	0.3773	3423	0.060	0.021366	0.042	0.245015	-+
rs8192675	**SLC2A2**	**C**	**2296**	**0.131**	**4.68E-05**	**0.224**	**1.42E-06**	**1160**	**0.112**	**0.06138**	**0.167**	**0.02022**	**3456**	**0.127**	**7.58E-06**	**0.207**	**1.04E-07**	**++**
rs1011691	LOC401134	G	2635	0.107	0.000296	0.110	0.01005	1190	0.037	0.5619	0.047	0.5366	3825	0.094	4.09E-04	0.095	0.010775	++
rs6867983	C5orf67	T	2296	0.135	0.000842	0.226	0.000102	1170	0.074	0.3429	0.071	0.4423	3466	0.122	6.66E-04	0.182	2.13E-04	++
rs3843467	C5orf67	T	2301	0.116	0.000945	0.191	0.000158	1183	0.039	0.5647	0.065	0.4196	3484	0.100	0.001356	0.156	2.77E-04	++
rs9497852	SAMD5	G	2298	-0.118	0.007368	-0.037	0.5569	1163	0.118	0.1562	0.102	0.3058	3461	-0.066	0.087231	0.003	0.954565	+-
rs11231159	EML3/MTA2	T	2299	-0.139	0.001986	-0.192	0.003022	1205	0.018	0.8321	0.016	0.8729	3504	-0.104	0.008516	-0.131	0.016024	+-
rs1957572	RAD51B	C	2684	0.140	0.003691	0.117	0.09534	1205	0.031	0.7606	0.054	0.6546	3889	0.120	0.005879	0.101	0.095527	++
rs4787778	HS3ST4	G	2709	-0.113	3.83E-05	-0.115	0.003801	1006	0.072	0.1872	0.110	0.08865	3715	-0.075	0.002022	-0.053	0.117235	+-

Supplementary Table 2. MetGen cohorts

Cohort	Ethnicity	Citation (PUBMED)	Number Subjects	Genotyping				Clinical Covariates			Description of Cohort
				Platform	C-frequency	Call Rate	HWE-p	Adherence	EGFR/Creatinine Clearance	Treatment Group	
ACCORD	European American	18539917	172	Array	25%	100%	NA	N	Y	Y	Randomised trial of intensive (target A1c 6%) vs conventional (A1c 7-8%)
DCS	European	22453232	748	TaqMan	29%	100%	0.92	N	Y	Y	Population, observational, EMR-linked
GoDARTS	European	21186350	3103	Array & Taqman	27%	100%	0.08	Y	Y	Y	Population, observational, EMR-linked
RIGA	European	22735389	74	Taqman	20%	99%	0.72	N	Y	N	Retrospective pharmacogenetic study
Rotterdam	European	19228809	325	Array	30%	100%	NA	Y	Y	Y	Population, observational, EMR-linked
Kosice	European	22882994	148	Taqman	28%	100%	0.88	Y	Y	N	Retrospective pharmacogenetic study
UKPDS	European	9742977	1223	Taqman	30%	82%	0.12	N	Y	Y	RCT, metformin and sulfonylureas
Sarajevo	European	NA	88	Taqman	35%	100%	0.48	N	Y	N	Population, observational, prospective
PMT1-EU	European American	24853734, 21956618, 23267855	292	Array	30%	100%	NA	N	Y	Y	Population, observational, EMR-linked
PMT2-EU[2]	European American	21565264, 26092716, 26092718	4384	Array	29%	100%	NA	Y	Y	Y	Population, observational, EMR-linked
PMT1-AF[1]	African American	NA	732	Array	68%	100%	NA	N	Y	Y	Population, observational, EMR-linked
PMT2-AF[2]	African American	21903159	369	Array	70%	100%	NA	Y	Y	Y	Population, observational, EMR-linked
PMT2-AS[2]	Asian American	21903159	627	Array	31%	100%	NA	Y	Y	Y	Population, observational, EMR-linked

Supplementary Table 2. MetGen cohorts (Continued)

PMT2-LA[2]	Latino	21903159	743	Array	24%	100%	NA	Y	Y	Y	Population, observational, EMR-linked
SAPPHIRE[3]	African American	24937318	95	Array	75%	100%	0.40	Y	Y	N	Population, observational, EMR-linked
DPP	European American	20682687	1502	Array	30%	100%	0.31	Y	Y	Y	IGT randomised to metformin or intensive exercise and followed up to incident diabetes
HOME	European	19307526	163	Taqman	29%	100%	0.17	Y	Y	N	RCT, metformin and insulin

Note[1]: Participants from PMT1-AF cohort were collected from Kaiser Permanente at Northern California and South East Georgia. This is a funded project to the Pharmacogenomics of Membrane Transporters (PMT) by the National Institute of Health (NIH) Pharmacogenomics Research Network (PGRN). The goal of the study was to identify genetic determinants of response to metformin in African Americans. This is a cohort study where the participants are African American adult with Type 2 diabetes on metformin with baseline HbA1c and treatment HbA1c and was identified through EMR. The identified participants were called back for blood samples for genotyping using Illumina OmniExpressExome Chip. For this replication study in multi-ethnic cohort, we imputed rs8192675 using IMPUTE2 and 1000 Genome Phase I.

Note[2]: As described in the Method section, participants from the PMT2 cohort were selected from the Genetic Epidemiology Research on Adult Health and Aging (GERA) cohort, a subsample of the Kaiser Permanente Research Program on Genes, Environment, and Health (RPEGH). The criteria for selecting the participants from GERA cohort have been described previously (24853734, 21956618, 23267855). A detailed description of the cohort and study design can also be found in dbGAP (dbGaP Study Accession: phs000674.v1.p1). Genotyping of the different ethnic groups in PMT2 were performed using the methods described in the publication provided in the table. We imputed rs8192675 using IMPUTE2 and 1000 Genome Phase I.

Note[3]: This cohort was established as an asthma pharmacogenomics study. However, by virtue of detailed medical record data on this cohort, metformin treatment and response could also be assessed. The methods for determining metformin exposure and response in this patient population have been described elsewhere (24921653).

URL: PGRN, http://dbts.ucsf.edu/pgrn-cgm/projects.php?page=endocrinology

Supplementary Table 3. Association between rs8192675 and alternative measures of metformin efficacy in MetGen. In HOME study of patients using metformin as add on treatment to insulin, the outcome of the change in daily dose of insulin (unit) was modelled in linear regression. In the DPP study of metformin prevention in pre-diabetes patients, the outcome of diabetes incidence was modelled with proportional hazard Cox regression.

Study	Allele	N	Effect Size	95% CI	P
HOME	C	163	0.08	[-0.02,0.18]	0.286
DPP	C	511	0.97	[0.72,1.31]	0.832

Supplementary Table 4. Pharmacogenetic impact of rs8192675 on glycaemic response to metformin in participants of non-European ancestries. The frequency and the effect size estimates were all reported for the C-allele. HbA1c was measured in percentage.

Ethnic groups	n	Frequency	Baseline Adjusted			Baseline Non-Adjusted		
			Beta	SE	p	Beta	SE	p
PMT2-AS (Asian American)	627	31%	0.12	0.049	0.014	0.124	0.093	0.186
PMT2-LA (Latino)	743	24%	0.114	0.06	0.059	0.14	0.102	0.168
PMT2-AF (African American)	369	68%	0.037	0.093	0.694	0.238	0.165	0.15
PMT1-AF (African American)	732	70%	0.031	0.047	0.499	0.183	0.11	0.096
SAPPHIRE (African American)	95	75%	-0.027	0.190	0.887	0.024	0.251	0.924
Combined	2566	--	0.077	0.028	0.006	0.150	0.054	0.005

Supplementary Table 5. Association between rs8192675 and response to sulfonylureas in patients with type 2 diabetes. The upper table shows the additive allelic effect (standard error) of the C-allele on HbA1c level or HbA1c reduction in each of the three cohorts. HbA1c was measured in percentage. The lower table shows the fixed-effect inverse-variance–weighted meta-analysis.

	n	Baseline HbA1c	On-treatment HbA1c	HbA1c Reduction	Baseline Adjusted HbA1c Reduction
GoDARTS	1859	0.10 (0.05)	0.02 (0.04)	0.08 (0.05)	0 (0.04)
UKPDS	387	0.15 (0.09)	0.43 (0.11)	-0.27 (0.12)	-0.39 (0.10)
DCS	408	0.36 (0.11)	0.21 (0.08)	0.15 (0.13)	-0.16 (0.08)
Combined Effect	2654	0.15 (0.04)	0.09 (0.03)	0.04 (0.05)	-0.06 (0.03)
Combined P-value	--	3.1E-04	0.006	0.44	0.04
Meta-Phet	--	0.12	6.2E-4	0.02	6.1E-4

Supplementary Table 6. Pharmacogenetic impact of rs8192675 after adjusting for BMI.
The percentage of obese patients is 54.8% in MetGen cohorts where BMI data are available. BMI adjusted analyses from the Rotterdam and PMT1-EU studies are not available. BMI data are only partially available for the PMT2-EU samples.

Study	#Obese	#Total	Baseline adjusted		Baseline non-adjusted	
			Beta	SE	Beta	SE
ACCORD	116	172	-0.034	0.114	-0.037	0.064
DCS	357	748	0.040	0.039	0.207	0.075
GoDARTS	1727	3103	0.112	0.027	0.200	0.040
Kosice	85	148	0.107	0.097	0.161	0.135
PMT2-EU	1367	2353	0.072	0.025	0.179	0.045
RIGA	73	74	-0.363	0.140	-0.267	0.370
Sarajevo	50	88	0.051	0.111	-0.164	0.188
UKPDS	557	1223	0.138	0.060	0.200	0.071
Meta-analysis	**4332**	**7909**	**0.078**	**0.015**	**0.155**	**0.024**

Supplementary Table 7. Association between rs8192675 and *SLC2A2* expression in other tissues. Following the evidence that rs8192675 is a genomewide cis-eQTL for *SLC2A2*, we examined whether the variant (or its proxies) are associated with *SLC2A2* expression in other tissues. A significance threshold of p<0.05 was used to draw supportive evidence. The GTEx data were based on data release V6. The direction of effect refers to the C-allele at rs8192675 or its linked alleles at the proxy SNPs (NS: not significant).

Tissue	P	Direction of Effect	n	Source
Cells - Transformed fibroblasts	0.0006	LOW	271	GTEx
Liver	0.13	NS	97	GTEx
Pancreas	0.74	NS	149	GTEx
Pituitary	0.92	NS	87	GTEx
Small Intestine - Terminal Ileum	0.9	NS	77	GTEx
Testis	0.98	NS	157	GTEx
Whole Blood	0.23	NS	338	GTEx
Islet	0.003	LOW	118	PMID: 26624892
Intestine	0.007	LOW	173	PMID: 23474282
Kidney	0.03	LOW	44	MetGen data

Supplementary Table 8. Association between rs8192675 and *SLC2A2* expression in the liver. Within four liver eQTL data sets, linear regression was used to model *SLC2A2* expression levels with adjustment of relevant covariates. Results from the four liver datasets were combined by meta-analysis. *SLC2A2* expression level was determined using microarray and only include patients of European ancestry. The data was coded such that a negative beta means that as the number of minor C-allele increases there is decrease in *SLC2A2* expression.

Dataset	n	Expression	Genotyping	P-value	Corrected P-value	Beta	PMID
Set 1	149	Illumina Human Whole Genome-6 v2.0 Expression BeadChip (NCBI GEO accession: GSE39036)	HumanHap300-Duo v2.0 Genotyping BeadChip (NCBI GEO accession: GSE32504)	0.013	0.211	-0.23	22006096
Set 2	168	Agilent-014850 Whole Human Genome 4x44K gene expression (NCBI GEO accession: GSE25935)	Illumina Human610-Quad v1.0 BeadChip (NCBI GEO accession: GSE26105)	1.6x10-4	0.014	-0.19	21637794
Set 3	326	Agilent Technologies (NCBI GEO accession: GSE9588)	Affymetrix GeneChip Human Mapping 500k genotyping microarray	0.175	0.627	-0.05	18462017
Set 4	583	Agilent Technologies (NCBI GEO accession: GSE9588)	HumanHap 650Y	3.2E-10	1.3E-8	-0.19	Unpublished
Meta	1226			1.1E-13	4.2E-12		

Supplementary Table 9. Primers used to clone the genomic region (chr3:170724251-170727543) encompass the *SLC2A2* variant, rs8192675 (chr3:170724883).

Primer	Note
Forward (+ strand): GCTCGCTAGCCTCGAGGCAACCAGATAGAATAATAC	The genomic region cloned into XhoI and BglII digested pGL4.23 using the Infusion HD cloning system (Clontech). The underlined region is the digestion site for XhoI and BglII.
Reverse (+ strand): CGCCGAGGCCAGATCTGGTTCTCGTCCATGGCAATG	

Supplementary Notes

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