Supplementary Information

Common variants near *ATM* are associated with glycemic response to metformin in type 2 diabetes

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SUPPLEMENTARY TABLES

Supplementary Table 1

Baseline characteristics of discovery (GoDARTS) and replication Cohorts (GoDARTS and UKPDS). Data are mean ± SD.

Variable	Discovery GoDARTS (1024)	Replication 1 GoDARTS (1783)	Replication 2 UKPDS (1113)
Age	62.8±9.8	61.0±11.7	57.5±9.6
Male Percentage	54.9%	57.7%	53.2%
BMI	31.5±5.7	31.9±5.9	30.2±5.9
Baseline A1c	8.94±1.38	8.95±1.37	8.43±1.93
Adherence	82.9±16.1	82.3±16.1	NA
Creatinine Clearance	89.1±31.3	96.7±37.4	95.9±34.0
Responder Percentage	53.7%	51.4%	35.2%
Monotherapy Percentage	67.3%	72.4%	25.5%

Supplementary Table 2

SNPs associated with metformin response in logistic regression analysis (with p-value <10^{-4}). 'EffAllele' (effective allele) is based on the dbSNP plus strand coding; 'Gene' covers any gene within 50kb vicinity of the SNP

CHR	SNP	POSITION	EffAllele	OR	P	Gene
1	rs12128858	34496515	C	0.5071	2.01E-05	*C1orf94*
1	rs7533876	102883521	A	0.5062	5.17E-06	
1	rs41404544	110944334	C	0.4341	5.58E-05	*KCNA2*
1	rs265128	215683383	A	0.5853	8.31E-05	*GPATCH2*
2	rs737447	44959521	G	1.798	3.29E-05	
2	rs4952726	44961125	C	1.793	3.73E-05	
2	rs13420376	144288475	T	1.898	1.37E-05	*ARHGAP15*
3	rs41521446	2808324	G	0.6114	5.22E-05	*CNTN4*
3	rs1963348	64190295	A	0.6701	8.94E-05	*PRICKLE2*
3	rs3911778	64205473	A	0.6678	8.03E-05	*PRICKLE2*
3	rs7613991	69845276	T	0.6787	4.72E-05	*MITF*
3	rs9853615	135002671	G	1.56	6.85E-06	*TF SRPRB RAB6B*
3	rs1464937	135019345	C	1.493	4.99E-05	*TF SRPRB RAB6B*
3	rs12637089	141370658	T	0.5363	7.30E-05	*CLSTN2*
4	rs10007566	24677262	T	0.637	3.39E-06	*LGI2*
5	rs4701486	25563999	G	0.6456	4.83E-05	
5	rs3843467	55892132	T	1.606	9.91E-05	
5	rs13187208	121014320	A	0.5283	4.76E-05	
6	rs10485258	154155102	T	1.556	8.74E-05	
7	rs4540325	4718366	T	0.6288	2.04E-06	*FOXK1*
7	rs2214096	95521055	G	1.561	6.28E-05	*DYNC1I1*
8	rs17741463	73163435	A	1.563	6.61E-05	*TRPA1*
8	rs1713669	96027813	G	0.6773	4.29E-05	*TP53INP1*
8	rs527234	96032974	G	0.6761	4.27E-05	*TP53INP1*
9	rs2274526	263233	C	0.6423	6.08E-05	*DOCK8*
9	rs10966249	2415127	T	1.493	4.78E-05	
9	rs7039085	2417960	A	1.511	5.72E-05	
9	rs2210396	2419859	C	1.502	6.71E-05	
9	rs2376118	2420189	G	1.514	5.93E-05	
9	rs16925655	7235728	T	0.4234	2.94E-06	
9	rs1928206	7265202	G	0.6011	2.64E-05	
9	rs16925783	7278704	A	0.4526	1.23E-05	
9	rs1008981	10536814	C	0.548	5.04E-06	*PTPRD*
9	rs957252	26049028	A	1.547	1.17E-05	
9	rs9406901	26052582	A	1.52	5.22E-05	
9	rs10984415	120923988	A	1.761	6.82E-05	*DBC1*
9	rs230150	120986331	C	1.756	2.66E-05	*DBC1*
9	rs230089	120995897	A	1.749	2.12E-05	*DBC1*
10	rs4750058	11508447	A	1.486	6.11E-05	*USP6NL*
10	rs7096907	19066847	T	0.5964	5.73E-05	
10	rs10763188	56681358	T	1.553	6.68E-05	
10	rs17123393	109565848	T	0.3917	3.96E-05	
11	rs875973	45083359	C	1.458	9.29E-05	*PRDM11*
11	rs12787445	107539334	G	1.604	8.81E-07	*ACAT1 NPAT*
11	rs6589007	107545314	A	1.635	2.69E-07	*ACAT1 NPAT*
11	rs2083707	107571340	A	1.589	1.80E-06	*ACAT1 NPAT ATM*
11	rs609557	107589723	G	1.632	2.47E-07	*NPAT ATM*
11	rs228606	107593057	T	0.6773	5.07E-05	*NPAT ATM*

Supplementary Table 2 (continued)

CHR	SNP	POSITION	EffAllele	OR	P	Gene
11	rs183460	107595920	A	1.631	2.98E-07	*NPAT ATM*
11	rs228591	107602543	A	1.632	2.65E-07	*NPAT ATM*
11	rs618499	107654049	A	1.585	1.49E-06	*ATM*
11	rs624366	107659307	G	1.648	1.69E-07	*ATM*
11	rs645485	107674073	A	1.638	2.37E-07	*ATM*
11	rs673281	107687279	G	1.579	1.95E-06	*ATM*
11	rs227073	107717902	G	1.622	4.06E-07	*ATM C11orf65*
11	rs227075	107723406	T	1.582	1.73E-06	*ATM C11orf65*
11	rs419716	107726309	A	1.633	2.85E-07	*ATM C11orf65*
11	rs227041	107728011	C	1.633	2.85E-07	*ATM C11orf65*
11	rs664143	107730871	A	1.582	1.73E-06	*ATM C11orf65*
11	rs652541	107731235	A	1.594	1.23E-06	*ATM C11orf65*
11	rs573890	107756573	C	1.625	3.90E-07	*ATM C11orf65*
11	rs227077	107758462	C	1.63	3.35E-07	*ATM C11orf65*
11	rs7931930	107773496	G	1.635	2.78E-07	*ATM C11orf65*
11	rs11212617	107788371	C	1.646	1.92E-07	*ATM C11orf65*
11	rs3765632	107858228	A	1.546	5.50E-06	*C11orf65 KDELC2 EXPH5*
11	rs11212676	107866788	A	0.6798	6.66E-05	*C11orf65 KDELC2 EXPH5*
11	rs893279	107870392	T	0.6864	9.68E-05	*C11orf65 KDELC2 EXPH5*
13	rs1328673	46513595	T	1.507	7.13E-05	
13	rs2039095	46516635	C	0.6871	9.83E-05	
13	rs9562700	46518957	A	0.6812	4.98E-05	
13	rs11148026	46538811	A	0.6746	4.11E-05	
13	rs1469595	46538887	A	0.6746	4.11E-05	
13	rs9595590	46540197	A	0.6746	4.11E-05	
13	rs7994733	46541595	C	1.503	8.40E-05	
13	rs1431768	46567351	A	1.501	8.37E-05	
13	rs9540636	65571144	T	0.6652	4.32E-05	
13	rs9540668	65623234	G	0.6759	6.74E-05	
15	rs2113931	59896761	A	0.5719	5.22E-05	*VPS13C*
16	rs4500723	51259514	T	1.499	4.08E-05	
16	rs4386133	51264345	A	1.467	8.04E-05	
16	rs12932515	51270048	T	1.474	8.91E-05	
16	rs11642888	51359637	C	1.47	5.96E-05	
16	rs7196680	51359682	C	1.461	7.78E-05	
17	rs9303683	30560283	A	0.6838	6.38E-05	*UNC45B AMAC1 SLFN5*
17	rs1383541	30563938	C	0.6549	8.67E-06	*UNC45B AMAC1 SLFN5*
17	rs11080325	30587822	A	0.6796	7.66E-05	*UNC45B AMAC1 SLFN5*
17	rs11653010	30589462	G	0.6812	8.52E-05	*UNC45B AMAC1 SLFN5*
18	rs1626048	3333266	A	2.016	5.53E-05	
18	rs1662830	3335173	G	2.037	4.76E-05	
18	rs9965202	75208922	C	0.5622	1.71E-05	*ATP9B NFATC1*
18	rs12604865	75211701	G	0.5612	1.83E-05	*ATP9B NFATC1*
18	rs6506757	75212528	T	0.5621	1.94E-05	*ATP9B NFATC1*

Supplementary Table 3

Full metformin glycaemic response models. The 95% confidence intervals of the Beta or Odds Ratio (OR) are shown in square brackets. The variables are coded as:

(1) the outcome is Treatment A1c in linear model
(2) the outcome is achieving treatment A1c<=7% (case) in logistic model
(3) genotype is coded as the dosage of the minor allele
(4) adherence is coded in 10%
(5) creatinine CLR is coded in 10mL/min/1.73m^2
(6) group is coded as 1 for monotherapy group and 0 for dual therapy group
(7) time to baseline is coded in months
(8) dose is coded in 300mg

Supplementary Table 3a. The GWA cohort of 1024 GoDARTS patients

	Linear Model		Logistic Model	
	Beta	p	OR	p
rs11212617	**-0.18 [-0.26,-0.10]**	**1.8E-05**	**1.64 [1.37,1.99]**	**1.9E-07**
Baseline A1C	0.28 [0.23,0.32]	8.7E-33	0.69 [0.62,0.76]	3.3E-12
Adherence	-0.11 [-0.14,-0.07]	2.7E-8	1.18 [1.09,1.26]	4.3E-05
Creatinine CLR	0.04 [0.02,0.06]	2.3E-04	0.92[0.87,0.96]	0.0005
Group	-0.22 [-0.35,-0.09]	0.0011	1.97[1.47,2.64]	6.5E-06
Dose	-0.02 [-0.06,0.01]	0.18	0.99[0.96,1.02]	0.96
Baseline Gap	0.08 [0.006,0.14]	0.03	0.92[0.80,1.06]	0.23

Supplementary Table 3b. The first replication cohort of 1783 GoDARTS patients

	Linear Model		Logistic Model	
	Beta	p	OR	p
rs11212617	**-0.07 [-0.13,-0.01]**	**0.022**	**1.21 [1.05,1.38]**	**0.007**
Baseline A1C	0.20 [0.16,0.23]	2.7E-30	0.74 [0.69,0.80]	4.6E-14
Adherence	-0.11 [-0.14,-0.08]	2.6E-15	1.2 [1.14,1.26]	8.0E-10
Creatinine CLR	0.03 [0.01,0.04]	1.4E-05	0.95[0.92,0.98]	0.0003
Group	-0.32 [-0.43,-0.22]	6.5E-10	1.97[1.57,2.48]	3.8E-09
Dose	-0.03 [-0.06,-0.01]	0.02	1.01[0.98,1.04]	0.95
Baseline Gap	0.05 [-0.006,0.10]	0.09	0.90[0.79,1.03]	0.13

Supplementary Table 3c. The second replication cohort of 1113 UKPDS patients

	Linear Model		Logistic Model	
	Beta	p	OR	p
rs609261	**-0.12 [-0.22,-0.02]**	**0.021**	**1.37 [1.10,1.72]**	**0.0057**
Baseline A1C	0.50 [0.46,0.54]	4E-101	0.43 [0.39,0.49]	6.9E-45
Baseline Gap	-0.032[-0.03,-0.01]	5.5E-6	1.08 [1.03,1.14]	8.4E-4
Group	-0.93 [-1.13,-0.73]	8.2E-19	3.19[2.10,4.82]	4.2E-8
Treatment Gap	-0.01[-0.03,0.01]	0.214	1.01[0.97,1.06]	0.55
Creatinine CLR	0.05 [0.03,0.07]	1.6E-5	0.90[0.85,0.95]	1.0E-4

Supplementary Table 4

Logistic regression analysis of metformin response split by treatment group (monotherapy or dual therapy). The 95% confidence intervals of the Odds Ratio (OR) are shown in square brackets. The variables are coded as:

(1) the outcome is achieving treatment A1c<=7% (case)
(2) genotype is coded as the dosage of the minor allele
(3) adherence is coded in 10%
(4) creatinine CLR is coded in 10mL/min/1.73m^2
(5) time to baseline is coded in months
(6) dose is coded in 300mg

Supplementary Table 4a. The GWA cohort of 1024 GoDARTS patients

	Monotherapy (n=689)		Dual therapy (n=335)	
	OR	p	OR	p
rs11212617	**1.63 [1.29,2.06]**	**3.7E-05**	**1.71 [1.24,2.36]**	**0.001**
Baseline A1C	0.66 [0.58,0.75]	1.7E-10	0.75 [0.62,0.91]	0.003
Adherence	1.18 [1.08,1.28]	6.0E-04	1.20 [1.03,1.40]	0.02
Creatinine CLR	0.93[0.87,0.98]	0.008	0.89[0.82,0.98]	0.02
Dose	0.99[0.93,1.07]	0.88	1.0[0.87,1.15]	0.95
Baseline Gap	0.95[0.87,1.10]	0.12	1.0[0.78,1.27]	0.98

Supplementary Table 4b The first replication cohort of 1783 GoDARTS patients

	Monotherapy (n=1291)		Dual therapy (n=492)	
	OR	p	OR	p
rs11212617	**1.29 [1.10,1.51]**	**0.002**	**1.05 [0.81,1.36]**	**0.70**
Baseline A1C	0.79 [0.72,0.86]	6.9E-08	0.60 [0.50,0.72]	2.8E-08
Adherence	1.20 [1.11,1.29]	1.3E-06	1.28 [1.12,1.46]	2.3E-04
Creatinine CLR	0.95[0.92,0.98]	0.001	0.94[0.88,1.01]	0.09
Dose	0.98[0.91,1.04]	0.52	1.05[0.94,1.18]	0.38
Baseline Gap	0.95[0.82,1.10]	0.51	0.81[0.64,1.02]	0.08

Supplementary Table 4c The second replication cohort of 1113 UKPDS

	Monotherapy (n=284)		Dual therapy (n=829)	
	OR	p	OR	p
rs609261	**1.82 [1.20,2.78]**	**0.005**	**1.23 [0.94,1.62]**	**0.13**
Baseline A1C	0.53 [0.43,0.65]	1.2E-09	0.39 [0.34,0.46]	3E-36
Baseline Gap	1.18 [1.03,1.35]	0.02	1.07 [1.02,1.12]	0.007
Treatment Gap	0.99[0.92,1.08]	0.92	1.02[0.97,1.07]	0.41
Creatinine CLR	0.83[0.75,0.90]	3.3E-5	0.94[0.88,1.01]	0.09

Supplementary Table 5

Association between rs11212617 and baseline characteristics in the Go-DARTS controls. The A allele was the reference allele. *These variables were log transformed.

Phenotype	Beta	N	p
LDL	-0.02671	6148	0.1186
Cholesterol	-0.01793	6148	0.3428
Triglycerides	0.00182	6148	0.8921
HDL	0.009234	6148	0.268
Creatinine	-0.1364	6148	0.7004
DBP	-0.1241	6148	0.4979
SBP	0.04596	6148	0.8966
Weight	-0.1744	6148	0.528
BMI	-0.07395	6148	0.377
Height	0.05636	6148	0.7474
A1C	-0.003857	6148	0.5882
Adiponectin*	0.02	2422	0.2555
Leptin*	0.0006	2422	0.9525
F-Insulin*	-0.04174	1806	**0.0485**
Homab*	-0.02116	1806	0.1317
Homas*	0.0418	1806	**0.0474**
F-Glucose*	-0.009783	1806	0.9525

Supplementary Table 6
Bioinformatic exploration of the functionality of rs11212617 and its proxies.

All the 98 SNPs with strong linkage disequilibrium (r^2 >0.8 according to the HapMap CEU panel as indicated by the column rsquare in the table) to rs11212617 at the associated locus are listed in the table. SNPs were mapped to the genomic sequence with UCSC database checking their regulation potential, predicted transcription factor binding sites, CpG islands, predicted microRNA target sites, validated enhancer, promoter and cross species conservative sites.

In addition, none of the SNPs was identified as potential *cis* regulator in the three published eQTL genome wide association studies of liver, cortex and lymphocytes[1-3]. The observed association could not be explained by the only common copy number polymorphism in the region as it is not in linkage disequilibrium with rs11212617 (r^2 = 0.05) according to the HapMap CEU panel[4].

snpsym	chro	position	ingene	coding	rsquare	conservation	regulation
rs4754298	11	107528494			0.979		
rs6589006	11	107536505	*NPAT*	intron	0.99		
rs12787445	11	107539334	*NPAT*	intron	0.952		
rs6589007	11	107545314	*NPAT*	intron	0.99		
rs2070661	11	107549198	*NPAT*	exon7*	0.958		
rs11212538	11	107551166	*NPAT*	intron	0.934		
rs1850730	11	107556322	*NPAT*	intron	0.99		
rs4623864	11	107556510	*NPAT*	intron	0.99		
rs4753833	11	107562640	*NPAT*	intron	0.99		
rs7118967	11	107563066	*NPAT*	intron	0.957	Yes	
rs3781868	11	107564779	*NPAT*	intron	0.987		
rs2056267	11	107567018	*NPAT*	intron	0.99		
rs11212546	11	107570145	*NPAT*	intron	0.99		
rs2083707	11	107571340	*NPAT*	intron	0.925		
rs1607476	11	107580371	*NPAT*	intron	0.99		
rs4754305	11	107581122	*NPAT*	intron	0.99		
rs11605442	11	107583067	*NPAT*	intron	0.973		
rs11212551	11	107583903	*NPAT*	intron	0.99		
rs609557	11	107589723	*NPAT*	intron	0.99		
rs183459	11	107594407	*NPAT*	intron	0.958		
rs183460	11	107595920	*NPAT*	intron	0.984		
rs228589	11	107598418	*NPAT*	intron	0.987		Yes[§]
rs228590	11	107601351	*ATM*	intron	0.99		
rs228591	11	107602543	*ATM*	intron	0.987		
rs641605	11	107607129	*ATM*	intron	1		
rs623860	11	107611992	*ATM*	intron	0.971		
rs228599	11	107612870	*ATM*	intron	1		
rs600931	11	107622545	*ATM*	intron	1		
rs599406	11	107623444	*ATM*	intron	1		
rs694376	11	107624258	*ATM*	intron	0.904		
rs599164	11	107625649	*ATM*	intron	1		
rs228592	11	107628399	*ATM*	intron	1		
rs672655	11	107634867	*ATM*	intron	1		
rs627418	11	107636435	*ATM*	intron	0.971		
rs664677	11	107648392	*ATM*	intron	0.971		
rs618499	11	107654049	*ATM*	intron	0.959		

Supplementary Table 6 (continued 1)

snpsym	chro	position	ingene	coding	rsquare	conservation	regulation
rs4987982	11	107656479	*ATM*	intron	1		
rs1003624	11	107657855	*ATM*	intron	1		
rs624366	11	107659307	*ATM*	intron	0.997		
rs654005	11	107660607	*ATM*	intron	1		
rs592955	11	107661683	*ATM*	intron	0.906		
rs609261	11	107663344	*ATM*	intron	1		
rs645485	11	107674073	*ATM*	intron	0.987		
rs619972	11	107674829	*ATM*	intron	1		
rs599558	11	107682748	*ATM*	intron	1		
rs660429	11	107686721	*ATM*	intron	1		
rs673281	11	107687279	*ATM*	intron	0.965		
rs620613	11	107690688	*ATM*	intron	1		
rs595747	11	107699283	*ATM*	intron	0.968		
rs662218	11	107699738	*ATM*	intron	1		
rs662578	11	107699767	*ATM*	intron	1		
rs609655	11	107709463	*ATM*	intron	0.965		
rs227061	11	107710539	*ATM*	intron	1		
rs227062	11	107710593	*ATM*	intron	1		
rs227064	11	107712603	*ATM*	intron	0.965		
rs227068	11	107715319	*ATM*	intron	1		
rs227070	11	107716622	*ATM*	intron	0.965		
rs227072	11	107717303	*ATM*	intron	1		
rs227073	11	107717902	*ATM*	intron	0.997		
rs227074	11	107720305	*ATM*	intron	1		
rs172896	11	107722259	*ATM*	intron	1		
rs227075	11	107723406	*ATM*	intron	0.959		
rs425538	11	107724549	*ATM*	intron	0.968		
rs419716	11	107726309	*ATM*	intron	0.997		
rs374443	11	107726875	*ATM*	intron	1		
rs227041	11	107728011	*ATM*	intron	0.997		
rs227040	11	107728601	*ATM*	intron	0.997		
rs664143	11	107730871	*ATM*	intron	0.965		
rs652541	11	107731235	*ATM*	intron	0.962		Yes
rs227053	11	107732065	*ATM*	intron	1		
rs227092	11	107741993	*ATM*	3UTR	0.993		
rs4585	11	107744838	*ATM*	3UTR†	1		
rs652311	11	107745279			1		
rs227087	11	107749324			1		
rs186595	11	107756421			1		
rs573890	11	107756573			0.99		
rs227077	11	107758462			0.997		
rs10789659	11	107761038	*C11orf65*	intron	1		
rs113995	11	107762047	*C11orf65*	intron	1		Yes
rs227055	11	107766471	*C11orf65*	intron	0.965		
rs172894	11	107767300	*C11orf65*	intron	0.971		
rs227056	11	107767607	*C11orf65*	intron	0.997		
rs186593	11	107767649	*C11orf65*	intron	0.959		
rs227058	11	107770423	*C11orf65*	intron	1		
rs172895	11	107771086	*C11orf65*	intron	1		
rs7931930	11	107773496	*C11orf65*	intron	1		
rs9667658	11	107781301	*C11orf65*	intron	1		

Supplementary Table 6 (continued 2)

snpsym	chro	position	ingene	coding	rsquare	conservation	regulation
rs2356801	11	107787209	*C11orf65*	intron	1		
rs11212617	11	107788371	*C11orf65*	intron	1		
rs10890834	11	107791653	*C11orf65*	intron	1		
rs1583598	11	107811199	*C11orf65*	intron	0.968		
rs6589019	11	107830171	*C11orf65*	intron	0.873		
rs4754324	11	107830658	*C11orf65*	intron	0.965		
rs7942014	11	107831384	*C11orf65*	intron	0.965		
rs5023001	11	107840748	*C11orf65*	intron	0.956		
rs3901851	11	107857545	*KDELC2*	intron	0.949		
rs3765632	11	107858228	*KDELC2*	intron	0.919		
rs2118309	11	107872663	*KDELC2*	intron	0.956		

Columns 'ingene' and 'coding' indicate whether a SNP is in the gene transcript and whether it is in the exon, intron or UTR region of the transcript. Column 'conservation' indicates whether a SNP is in genomic region conserved across vertebrate species. Column 'regulation' indicates whether a SNP is in predicted regulatory elements.

*rs2070661 is a non-synonymous SNP in gene *NPAT* however no functional change is predicted according to SIFT, PolyPhen and PANTHER.

[§]SNP rs228589, which is in intron 1 of the *NPAT* gene, is in a predicted promoter of *ATM*, hence having the potential to affect the transcription of *ATM*[5, 6].

[†]Studies have shown that addition of poly A tails to mRNA transcripts requires not only the consensus polyadenylation signal AATAAA, but also sequences located 10 – 30bp downstream, termed the GU-rich element[7]. Deletion of these sequences have a profound effect on the efficiency of polyadenylation[8]. The sequence of the DCE is somewhat variable, but is usually UG rich, and the actual cleavage site is commonly preceded by a CA dinucleotide[9]. Variant rs4585 lies 24bp downstream of an alternative polyadenylation site within the *ATM* transcript. This is within the region that is predicted to contain its DCE. Eight of the nucleotides immediately prior to rs4584 are U or G, and the SNP itself is preceded by a CA dinucleotide. This raises the possibility that rs4585 may influence the polyadenylation dynamics, and thus the stability, of *ATM* transcripts utilising this polyadenylation site.

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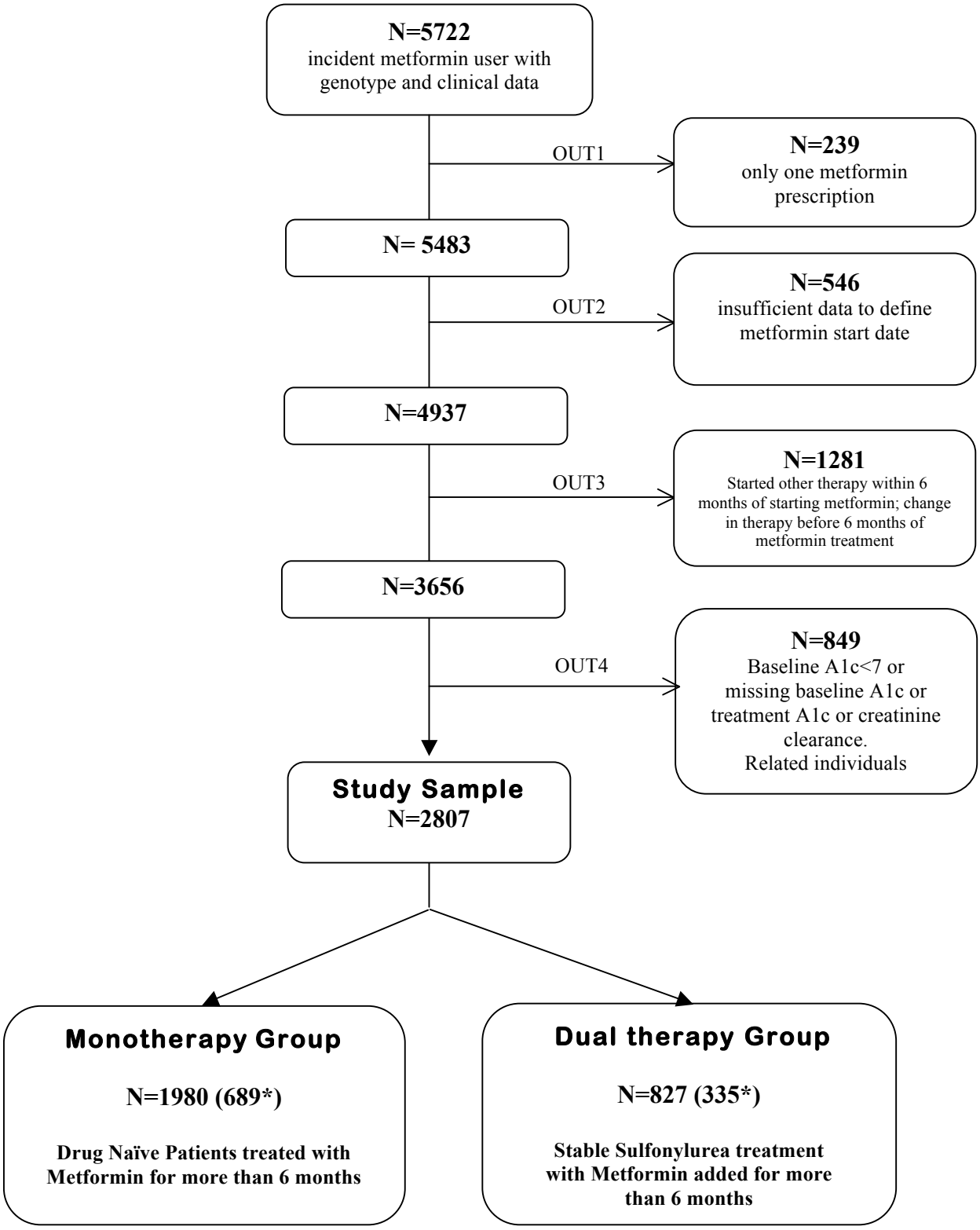
SUPPLEMENTARY FIGURES

Supplementary figure 1.

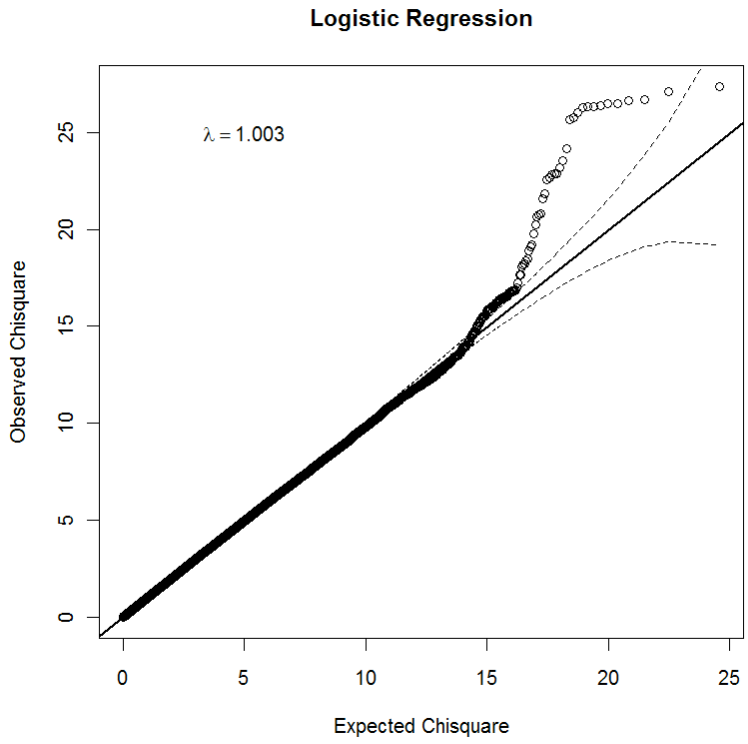
Sample Ascertainment Flow Chart. There was no difference by rs1121617 genotype at each selection/exclusion stage in the definition of the discovery cohort consistent with there being no effect of genotype on metformin tolerability



* number of patients in GWA

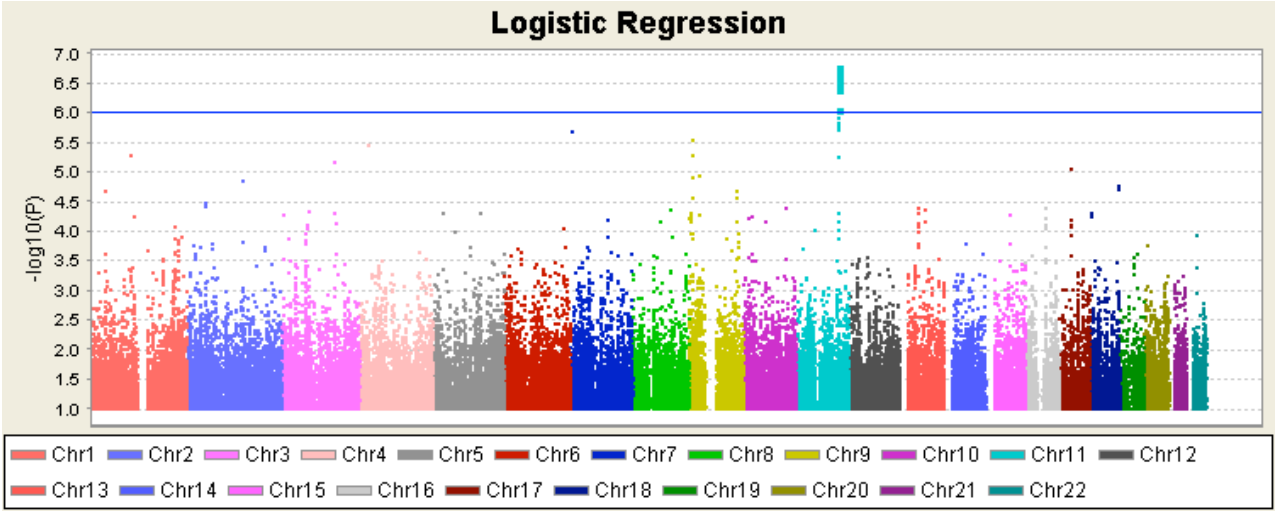
Supplementary Figure 2

Quantile-Quantile plots. The genomic control "inflation factor" lambda=1.003 for logistic regression. The dashed lines are 95% confidence interval



Supplementary Figure 3

Manhattan plot of single marker association test in the 1024 GoDARTS patients



SUPPLEMENTARY NOTES

Sample Ascertainment and Covariates

Inclusion criteria. As shown in the supplementary Figure 1, patients had to fulfill the following criteria to be included in the current study:

1. A pre-treatment HbA1c must be measured within 6 months prior to starting metformin and must be greater than 7% and less than 14%.
2. No new treatment should be started or stopped within 6 months prior to or after metformin start
3. Metformin treatment should continue for at least 6 months
4. At least one HbA1c measurement must be recorded whilst on metformin and within 18 months of commencing metformin.

Covariates. Age, sex and weight were used to derive the creatinine clearance so were not included separately in the models. The covariates that were used in both the logistic and linear regression analyses were defined as follows:

1) *Baseline HbA1c:* The baseline HbA1c value closest to starting metformin, and within the time period six months before and seven days after starting metformin.
2) *Baseline Gap:* The number of days between the baseline HbA1c and start of metformin was used to account for the unobserved deterioration of glycaemia between the HbA1c measure and intitiation of metformin
3) *Drug Adherence*: Adherence was estimated as
   Adherence = sum (days covered by each prescription)/ days in the study period in which the days covered by a prescription was calculated by dividing the dispensing quantity by daily dose; if one prescription covered a time period beyond next prescription start, the extra days were not taken over to the calculation for next prescription.
4) *Daily Dose*: The average daily dose during the 3 months prior to the minimum HbA1c was achieved
5) *Creatinine Clearance*: The creatinine clearance rate was calculated using the Cockcroft-Gault equation as
   *GFR = (140-age) * (weight in kg) * (0.85 if female) / (72 * creatinine in mg/dL)*

in which weight and serum creatinine concentration were the average of measurements from two years either side of the index date; age was at index date.

General Model. The general Metformin drug response outcome model was:

outcome ~ baseline HbA1c + adherence + daily dose + Creatinine Clearance + baseline gap + treatment group + genotype

GWAS Genotyping and Quality Control

DNA samples. Genomic DNA for all cases was shipped to the Sanger Institute, Cambridge. Where there was sufficient DNA, quality was validated using the Sequenom iPLEX assay designed to genotype four gender SNPs and 26 SNPs present on the Illumina Beadchips. DNA concentrations were quantified using a PicoGreen assay (Invitrogen) and an aliquot assayed by agarose gel electrophoresis. A DNA sample was considered to pass quality control if the DNA concentration was greater than or equal to 50 ng/μl, the DNA was not degraded, the gender assignment from the iPLEX assay matched that provided in the patient data manifest and genotypes were obtained for at least two thirds of the SNPs on the iPLEX.

Genotyping. Samples were genotyped at Affymetrix's service laboratory on the Genome-Wide Human SNP Array 6.0. For all samples passing Affymetrix's laboratory quality control, raw intensities were renormalized within collections using CelQuantileNorm. These normalized intensities were used to call genotypes with an updated version of the Chiamo software adapted for Affymetrix 6.0 SNP data.

By Individual QC. Genotype data quality control was via the protocol that was established for the WTCCC2 studies[1]. A few refinements to the conventional fixed-threshold based quality control have been made to obtain the more powerful sets of samples and SNPs for subsequent GWA analysis. For all individuals, we explicitly modelled the data as a mixture of 'normal' and 'outlier' individuals for each of ancestry, missing data and heterozygosity, and sex assignment. We fitted each model in a Bayesian framework and excluded individuals whose posterior probability of belonging to the outlier class was above 0.5. This approach replaces the traditional concept of fixed exclusion thresholds for parameters such as call rate, heterozygosity and ancestry.

Relatedness. To assess relatedness among study individuals, we compared each individual with the 100 individuals they were most closely related to (on the basis of genome-wide levels of allele sharing) and used a hidden Markov model (HMM) to decide, at each position in their genome, whether the two individuals shared 0, 1 or 2 chromosomes identical by descent (IBD). This allowed a more refined assessment of the relatedness between individuals than genome-wide sharing statistics (for example, parent-child relationships can be distinguished from those of siblings). Individuals were removed from the study iteratively to ensure there was no pair of individuals with IBD>= 5%. Within each pair of putatively related individuals, the individual with more missing genotypes was removed.

By SNP QC. For each SNP, we considered a measure of the (Fisher) information carried by the genotype calls for the underlying allele frequency. This will decrease as the number of individuals with low posterior probabilities for the most likely call increases, and it can be considered a more refined measure of both missing data and minor allele frequency. The measure is calculated automatically by the program SNPtest. SNPs were removed if this information measure was below 0.98 or if the estimated minor allele frequency was below 0.01%. SNPs that significantly deviated from Hardy Weinberg Equilibrium ($p<1x10^{-6}$) were also removed and the final data set consisted of 705,125 autosomal SNPs.

Concordance. Part of the current GWA sample was used as replication cohort in the WTCCC1 T2D case control study[2]. The overlapping genotyping is on a maximum number of 116 SNPs by 1779 individuals, depending on whether the SNP was taken into the second stage of the WTCCC1 replication. A total number of 457 discrepancies out of 163391 informative comparisons were observed, which gives a concordance rate of 99.73% between the two studies. Individuals with more than 10% discordance were removed from the current study.

rs11212617 Association with Quantitative Glycaemic Traits.

We requested unpublished summary statistics for the top SNPs of interest from meta-analyses of GWAS datasets, conducted by the Meta-Analyses of Glucose and Insulin-related traits Consortium (MAGIC) to identify genetic determinants of quantitative glycaemic traits in non-diabetic individuals. The published fasting trait meta-analysis included 20 cohorts with available fasting glucose and insulin

measurements and GWAS data, for a total of 35,914-38,237 individuals (depending on the SNP and the trait); participating cohorts are listed in the online supplement to ref 3. The unpublished HbA_{1C} meta-analysis includes 23 cohorts with available HbA_{1C} measurements and GWAS data, for a total of 36,099 subjects (35,841 with valid genotypes for these SNPs). For the latter, cohorts include: B58C-WTCCC (n=1,428), BLSA (n=490), DGI (n=480), EPIC cancer cases (n=957), EPIC cohort (n=1,911), Fenland (n=1,378), Framingham (n=1,996), KORA F3 (n=1,644), Lolipop (n=770), SardiNIA (n=3,346), 1958BC-T1DGC (n=2,501), ARIC (n=6,777), Croatia (n=659), deCODE (n=342), DESIR (n=731), GenomeEUtwin (n=568), HEALTH2000 (n=1,205), KORA_S4 (n=1,814), NTRNESDA (n=1,452), ORCADES (n=651), PROCARDIS (n=831), SHIP (n=3,538) and Sorbs (n=630). All participants were non-diabetic adults of European ancestry from Europe or the United States. Local research ethics committees approved all studies and all participants gave informed consent. In each study HbA_{1C} was measured from whole blood with NGSP-certified methods; details on insulin measurement are listed in the supplementary material to ref.[31]. SNPs were either directly genotyped or imputed from the HapMap CEU phase 2 reference panel using the software programs MACH or IMPUTE. QC metrics were applied to genotyped (Hardy-Weinberg equilibrium $P < 10^{-4}$ or 10^{-6} and call-rate <0.90 or 0.95) and imputed (observed-by-expected variance ratio [r2.hat] <0.3 in MACH, or proper-info <0.4 in IMPUTE) SNPs. In each cohort, a linear regression model was fitted using natural log transformed fasting insulin or HOMA-IR, or untransformed HbA_{1C} as the dependent variable to evaluate the additive effect of genotyped and imputed SNPs, adjusting for age, sex, study-site (when applicable) and family structure if present. Regression estimates for each SNP were combined across studies in each meta-analysis using a fixed effect inverse-variance approach, as implemented in the METAL software.

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