SUPPLEMENTARY DATA

Supplementary Table 1. Use of gastrointestinal medications in metformin intolerant and tolerant patients

Drug Class	BNF code	Intolerant group (n=251)	Tolerant group (n=1915)	*p*
Number of patients treated with GI drugs before metformin commencement				
Compound alginates	1.1.2	10 (4.0%)	54 (2.8%)	0.306
Antispasmodics and other drugs altering gut motility	1.2	4 (1.6%)	22 (1.2%)	0.533
Antidiarrhoeals	1.4	5 (2.0%)	18 (0.9%)	0.176
Antiemetics	4.6	14 (5.6%)	44 (2.3%)	0.003
Number of patients who started treatment with GI drugs after metformin commencement				
Compound alginates	1.1.2	4 (1.6%)	28 (1.5%)	0.782
Antispasmodics and other drugs altering gut motility	1.2	5 (2.0%)	19 (1.0%)	0.187
Antidiarrhoeals	1.4	7 (2.8%)	19 (1.0%)	0.024
Antiemetics	4.6	10 (4.0%)	45 (2.4%)	0.122

Data are presented as numbers of patients (percentages). BNF, British National Formulary.

Supplementary Table 2. Number of patients treated concomitantly with different OCT1 inhibiting drugs in metformin intolerant and tolerant group.

Drug/ Drug Class	Intolerant group (n=251)	Tolerant group (n=1915)	*p*
TCAs	14 (5.6%)	148 (7.7%)	0.223
Citalopram	6 (2.4%)	14 (0.7%)	0.022
PPIs	71 (28.3%)	311 (16.2%)	<0.001
Verapamil	6 (2.4%)	7 (0.4%)	0.002
Diltiazem	16 (6.4%)	90 (4.7%)	0.248
Doxazosin	23 (9.2%)	68 (3.6%)	<0.001
Spironolactone	5 (2.0%)	24 (1.3%)	0.373
Clopidogrel	7 (2.8%)	26 (1.4%)	0.095
Rosiglitazone	4 (1.6%)	24 (1.3%)	0.558
Quinine	11 (4.4%)	45 (2.4%)	0.056
Tramadol	16 (6.4%)	67 (3.5%)	0.026
Codeine*	8 (3.2%)	9 (0.5%)	<0.001

Data are presented as numbers of patients (percentages). TCAs, tricyclic antidepressants; PPIs, proton pump inhibitors. *Codeine was used as an opioid analgesic (BNF code 4.7.2) and a cough suppressant (BNF code 3.9.1), and not as an antimotility drug (BNF code 1.4.2).

SUPPLEMENTARY DATA

Supplementary Table 3. Haplotype analysis of the five functional variants in the OCT1 gene for directly genotyped individuals in the GoDARTS (n=3023)

Haplotype	R61C	C88R	G401S	M420del	G465R	n (%)
H1	R	C	G	M	G	4330 (71.6%)
H2	R	C	G	**del**	G	939 (15.5%)
H3	**C**	C	G	M	G	411 (6.8%)
H4	R	C	G	**del**	**R**	196 (3.2%)
H5	R	C	**S**	M	G	145 (2.4%)
H6	R	**R**	G	**del**	G	25 (0.4%)

Minor alleles are shown in bold.

Supplementary Table 4. Classification of individuals directly genotyped for the five OCT1 SNPs according to the number of deficient OCT1 haplotypes

OCT1 diplotype	Number of subjects		Number of reduced-function alleles
H1/H1	1562	1562 (51.7%)	0
H1/H2	661	1206 (39.9%)	1
H1/H3	277		
H1/H4	145		
H1/H5	107		
H1/H6	16		
H2/H2	72	255 (8.4%)	2
H2/H3	75		
H2/H4	33		
H2/H5	21		
H2/H6	5		
H3/H3	18		
H3/H4	12		
H3/H5	9		
H3/H6	2		
H4/H4	1		
H4/H5	2		
H4/H6	2		
H5/H5	3		

Number of reduced-function alleles in R61C, M420del and G401S is equivalent to the number of haplotypes carrying any of the five variants.

SUPPLEMENTARY DATA

Supplementary Table 5. OCT1 combined genotype frequencies in metformin tolerant and intolerant patients

Number of reduced-function alleles	Intolerant group (n=211)	Tolerant group (n=1729)	p_{add}	p_{dom}	p_{rec}
0	109 (51.7%)	881 (51.0%)	0.191	0.847	<0.001
1	74 (35.1%)	734 (42.5%)			
2	28 (13.3%)	114 (6.6%)			

Data are presented as numbers of subjects (percentages). p_{add}, p_{dom}, and p_{rec} represent significance of test for comparison of combined genotype frequencies between the two groups under the additive, dominant, and recessive model, respectively.

Supplementary Table 6. Conditional logistic regression model of metformin intolerance after matching patients for age and sex

	OR (95% CI)	*p*
Weight	0.99 (0.98-1.00)	0.129
Use of OCT1 inhibiting drugs	1.71 (1.19-2.45)	0.004
Two reduced-function OCT1 alleles	2.41 (1.40-4.17)	0.002

OR, odds ratio for intolerance. Conditional logistic regression analysis included 184 intolerant and 518 tolerant patients.

Supplementary Table 7. Joint effects of OCT1 genotype and OCT1 interacting drugs on intolerance after matching patients for age and sex

	OR (95% CI)	*p*
One or no reduced-function allele carriers not treated with OCT1 inhibiting drugs*	1.00	
One or no reduced-function allele carriers treated with OCT1 inhibiting drugs†	1.68 (1.15-2.46)	0.008
Two reduced-function alleles carriers not treated with OCT1 inhibiting drugs ‡	2.25 (1.03-4.90)	0.042
Two reduced-function alleles carriers treated with OCT1 inhibiting drugs§	4.37 (1.97-9.68)	<0.001

OR, odds ratio for intolerance. Analysis was adjusted for weight.* 82 intolerant and 308 tolerant patients; † 75 intolerant and 178 tolerant patients; ‡ 12 intolerant and 19 tolerant patients; § 15 intolerant and 13 tolerant patients.

Supplementary Table 8. Sensitivity analysis - logistic regression model of metformin intolerance for a subset of directly genotyped patients

	OR (95% CI)	*p*
Age	1.11 (1.07-1.15)	<0.001
Sex (Females vs Males)	1.83 (1.04-3.22)	0.035
Weight	0.99 (0.98-1.01)	0.462
Use of OCT1 inhibiting drugs	1.53 (0.90-2.62)	0.120
Two reduced-function OCT1 alleles	2.99 (1.40-6.38)	0.005

OR, odds ratio for intolerance. Logistic regression analysis included 70 intolerant and 590 tolerant patients.

SUPPLEMENTARY DATA

Supplementary Figure 1. Effects of individual OCT1 inhibiting drugs/drug classes on metformin intolerance risk after matching patients for age and sex. Analysis was adjusted for weight and co-treatment with other OCT1 inhibitors. TCAs, tricyclic antidepressants; PPIs, proton pump inhibitors; OR, odds ratio; LCL, lower confidence limit; UCL, higher confidence limit.