SUPPLEMENTARY DATA

Supplementary Table S1. Logistic regression model of metformin intolerance.

Variable	OR [CI]	p
Age at ITE (years)	1.04[1.03-1.06]	7.44×10^{-08}
Gender	2.31[1.72-3.10]	2.52×10^{-08}
Weight (kg)	1.00[0.99-1.00]	0.20
Use of metformin transporter inhibiting drugs	1.72[1.26-2.32]	5.17×10^{-04}
rs3889348	1.34[1.09-1.65]	0.005

Gender coded as women vs men. ITE: index intolerance event

Supplementary Table S2. Number of patients treated concomitantly with metformin transporter inhibiting drugs in the intolerant and tolerant groups.

Drug/ Drug Class	Intolerant group (237)	Tolerant group (1128)	p
PPI	58 (24.5%)	156 (13.8%)	<0.001
Codeine	22 (9.3%)	35 (3.1%)	<0.001
TCA	17 (7.2%)	33 (2.93%)	0.003
Tramadol	10 (4.2%)	18 (1.6%)	0.004
Clopidogrel	5 (2.1%)	14 (1.24%)	0.46
Spironolactone	3 (1.3%)	9 (0.8%)	0.75
Verapamil	3 (1.3%)	8 (0.7%)	0.64

Data are presented as numbers of patients (percentages). TCAs, tricyclic antidepressants; PPIs, proton pump inhibitors.

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Supplementary Table S3. Population characteristics by rs3889348 genotype.

	rs3889348 genotype			
	AA (n = 205)	GA (n = 681)	GG (n = 532)	*p*
Age at ITE (years)	61.03 ± 10.50	61.34 ± 10.0	61.94 ± 9.73	0.21
Age at diagnosis (years)	55.97 ± 10.32	56.31 ± 9.67	56.78 ± 9.65	0.27
Gender (women %)	36.6%	42.6%	45.1%	0.11[*]
Weight (kg)	97.21 ± 19.39	92.53 ± 18.22	93.15 ± 19.43	0.06
BMI (kg/m^2)	32.77 ± 6.02	31.89 ± 6.09	31.88 ± 5.96	0.15
Height (m)	1.72 ± 0.10	1.71 ± 0.10	1.71 ± 0.10	0.29
Creatinine (μmol/dL)	80.51 ± 15.57	79.09 ± 16.29	79.90 ± 17.80	0.95
Creatinine clearance (mL/min)	84.75 ± 18.95	84.98 ± 18.55	84.04 ± 20.80	0.52
HbA1c (%)	8.21 ± 1.59	8.18 ± 1.62	8.39 ± 1.75	0.11
Diabetes duration (years)[†]	4 [1.16-7.00]	4 [2.00-7.19]	4 [1.78-7.00]	0.78[‡]
Dose (mg)[†]	1000 (1000-1500)	1000 (1000-1500)	1000 (1000-1500)	1.00[‡]
Drug naïve (%)	44.1%	51.7%	51.4%	0.14[*]
Use of metformin transporter inhibiting drugs (%)	22.4%	27.6%	28.8%	0.27[*]

*chi-square test for independence, ‡kruskal-Wallis one-way analysis of variance, †Median (IQR). ITE: index intolerance event

Supplementary Table S4. Joint effect of *SLC29A4* (PMAT) genotype and metformin transporter inhibiting drugs on metformin intolerance.

	Intolerant/Tolerant	OR [95% CI]	*p*
Carries no risk allele and not treated with metformin transporter inhibiting drugs	15/141	1	---
Carries one risk allele and not treated with metformin transporter inhibiting drugs	67/408	1.52 [0.86-2.88]	0.17
Carries two risk alleles and not treated with metformin transporter inhibiting drugs	60/305	1.76 [1.01-3.35]	0.04
Carries no risk allele and treated with metformin transporter inhibiting drugs	8/37	1.74 [0.64-4.46]	0.25
Carries one risk allele and treated with metformin transporter inhibiting drugs	44/137	2.44 [1.30-4.78]	0.007
Carries two risk alleles and treated with metformin transporter inhibiting drugs	43/100	3.23 [1.71-6.39]	< 0.001

Supplementary Table S5. Joint effects of PMAT genotype and metformin transporter inhibiting drugs on intolerance after matching subjects for age and gender.

	OR (95% CI)	*p*
Weight	0.99[0.98-1.00]	0.08
Use of metformin transporter inhibiting drugs	1.75[1.28-2.38]	<0.001
rs3889348_G	1.26[1.02-1.59]	0.03

**Supplementary Table S6.** Joint effect of *SLC29A4* (PMAT) genotype and metformin transporter inhibiting drugs on metformin intolerance after matching patients for age and gender. 237 cases and 711 controls (1 case ~3 controls).

	Intolerant/Tolerant	OR [95% CI]	*p*
Carries no risk allele and not treated with metformin transporter inhibiting drugs	15/93	-	-
Carries no risk allele and treated with metformin transporter inhibiting drugs	8/18	2.76[0.99-7.38]	0.05
Carries one risk allele and not treated with metformin transporter inhibiting drugs	67/234	1.78[0.99-3.37]	0.06
Carries one risk allele and treated with metformin transporter inhibiting drugs	60/189	1.97[1.09-3.76]	0.03
Carries two risk allele and not treated with metformin transporter inhibiting drugs	44/100	2.73[1.45-5.37]	0.003
Carries two risk alleles and treated with metformin transporter inhibiting drugs	43/77	3.46[1.82-6.88]	<0.001

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Supplementary Figure S1. Boxplot of association between rs3889348 genotype and *SLC29A4* (PMAT) expression in the gut, colon transverse (left side) and terminal ilium of the small intestine (right side).
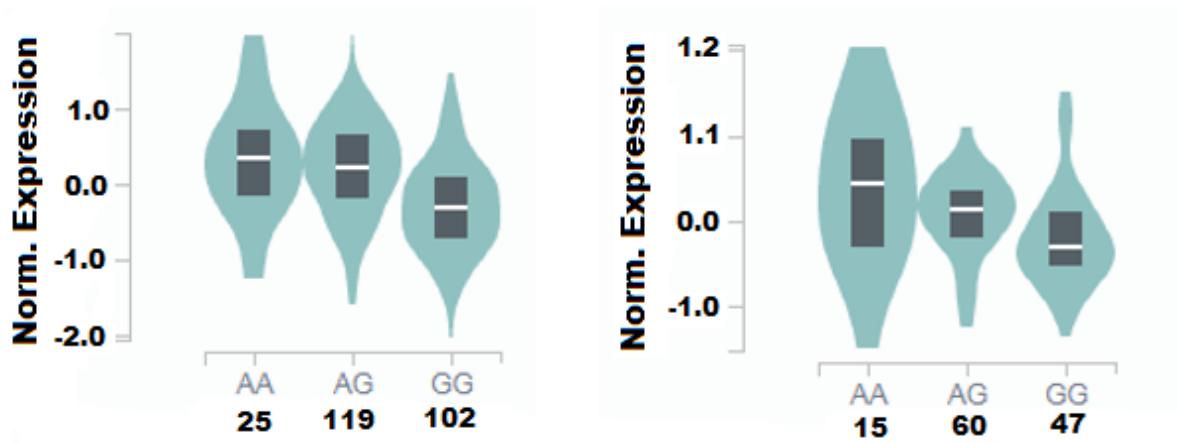
SUPPLEMENTARY DATA

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