Supplementary Material

Rare versus common variants in pharmacogenetics: *SLCO1B1* variation and methotrexate disposition

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Clinical data

Total XIIIB included consolidation therapy of two weekly doses of methotrexate (2 g/m^2 over 2 hours, followed by leucovorin) and 6-mercaptopurine (75 mg/m^2 per night for 2 weeks) (1, 2). Subsequent therapy included identical methotrexate and 6-mercaptopurine doses administered every 8 weeks up to 1 year. Total XV included four doses of methotrexate during consolidation, each given over 24 hours with dosage adjusted to achieve a steady-state plasma concentration of 33 μM (low-risk arm) or 65 μM (standard/high-risk arm) (3). Clearance was estimated on the basis of three to four methotrexate plasma concentrations per course up to 48 hours from the start of infusion. Clearance was estimated ($CL = k_e \times V$) using a two-compartmental linear pharmacokinetic model and a Bayesian approach, via ADAPT software (University of Southern California, Los Angeles, CA), as described (4). Population priors, mean (variance), were 9.0 L/m^2 (22.1) for V_c, 0.70 $hours^{-1}$ (0.05) for K_e, 0.08 $hours^{-1}$ (0.002) for K_{cp}, and 0.11 $hours^{-1}$ (0.000014) for K_{pc} as described (4). The average methotrexate clearance per patient across courses was calculated using all available courses.

Sequencing strategy

Genotypes using GeneChip Human Mapping 500K Array sets or the Genome-Wide Human SNP Array 6.0 (Affymetrix, Santa Clara, CA) were generated and calls made as described (4). The rs4149056 SNP was genotyped as described (4). Four *SLCO1B1* SNPs typed on Affymetrix arrays were verified by genotyping samples using the Illumina Golden Gate platform (the SNP Center, Johns Hopkins University); genotype concordance between the Affymetrix SNP array and the Golden Gate platform was high (>99%). Sanger sequencing of *SLCO1B1* exons 10 – 15 was performed (Agencourt, Beverly, MA); SNPs were excluded for quality scores less than 90 and call rates below 95% (20 SNPs excluded). Based on full sequencing of exons 10 – 15 in the entire cohort, we verified that all SNPs whose genotypes were associated with methotrexate

clearance ($p<0.05$) would have been identified had we sequenced only the patients whose methotrexate clearance was in the top and bottom decile (Supplementary Figure 3). Thus, patients with the highest and lowest methotrexate clearance (n=32 each) were selected for Sanger sequencing of exons 1 – 9 (St. Jude Children's Research Hospital's Hartwell Center for Bioinformatics and Biotechnology, HWC). Twenty-four SNPs were identified in 64 patients (32 high clearance, 32 low clearance) with call rates greater than 90%. Altogether, deep sequencing of DNA from children with ALL yielded 32 SNPs that had not been previously reported, exhibiting MAFs of 0.07% to 1.4%. The 24 SNPs found in exons 1-9, and all other NS SNPs previously reported, were genotyped using either the Sequenom MassARRAY technology (Washington University's Human Genetics Division Genotyping Core) or using single base extension on the Applied Biosystems 3730xl Genetic Analyzer (St. Jude Children's Research Hospital's HWC). SNPs were excluded if the call rate was less than 90%. All rare SNPs (MAF<1%) were verified using Sanger Sequencing (St. Jude Children's Research Hospital's HWC). The method used for genotyping each SNP is detailed in Supplementary Table 1.

Description of functional prediction algorithms

We used four prediction algorithms (SIFT (5), PMUT (6), SNPS3D (7), and Polyphen2 (8)) to categorize NS SNPs into damaging or tolerated groups. PMUT score of pathological, SNPS3D score of deleterious, SIFT score of damaging, and PolyPhen2 score of probably damaging or possibly damaging were all considered damaging (Supplementary Table 2). All other predictions were considered tolerated. The SNPs were categorized as damaging if they were predicted to be damaging by three or four of the algorithms (n=7), while the other NS SNPs were included in the tolerated group (Table 2, main text).

Assignment of ancestry using STRUCTURE

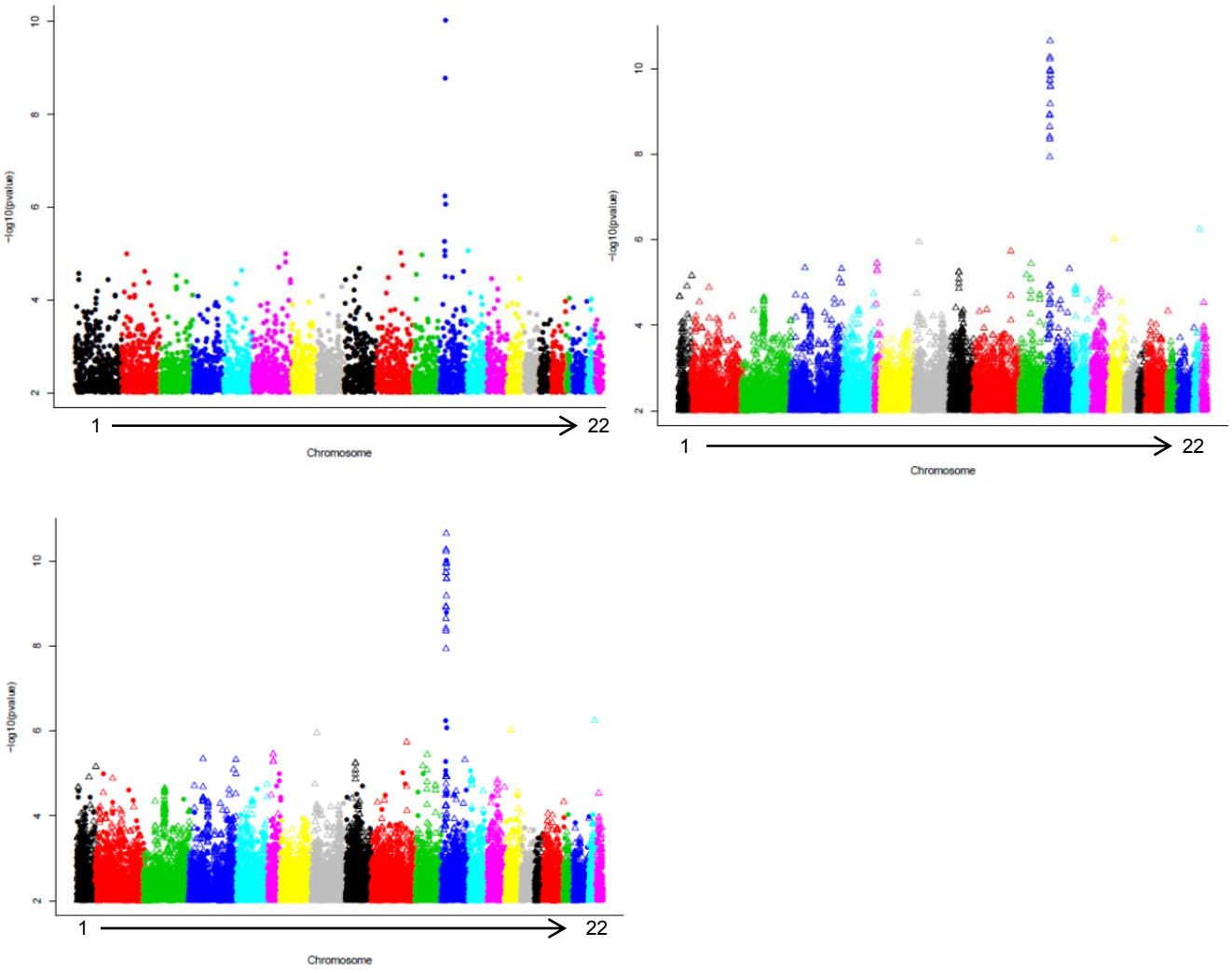
The genetic ancestry estimates were determined by applying STRUCTURE (9) (version 2.2.3) to 3,000 randomly chosen SNPs, a procedure that was repeated 10 times on 10 separate sets of 3,000 SNPs, and the final ancestry was the average of the 10 estimates. HapMap (10) samples from descendants of Northern Europeans (CEU, N=90), West Africans (YRI, N=90), and East Asians (CHB/JPT, N=90) and Native Americans (11) (NA, N=105) were used as ancestral reference populations representing European, African, East Asian, and NA ancestry, respectively. Ancestries were defined as previously described (12). For purposes of assigning patients to their primary ancestral group, patients were classified as European ancestry if they had >90% CEU ancestry, those classified as African ancestry had >80% YRI ancestry, those classified as Asian ancestry had >90% CHB/JPT ancestry, those classified as Native American ancestry had >10% NA ancestry (this corresponded to the majority of patients who self-identified as “Hispanic” (12)), and those classified as “Other” did not fit in any of the aforementioned groups.

Imputation

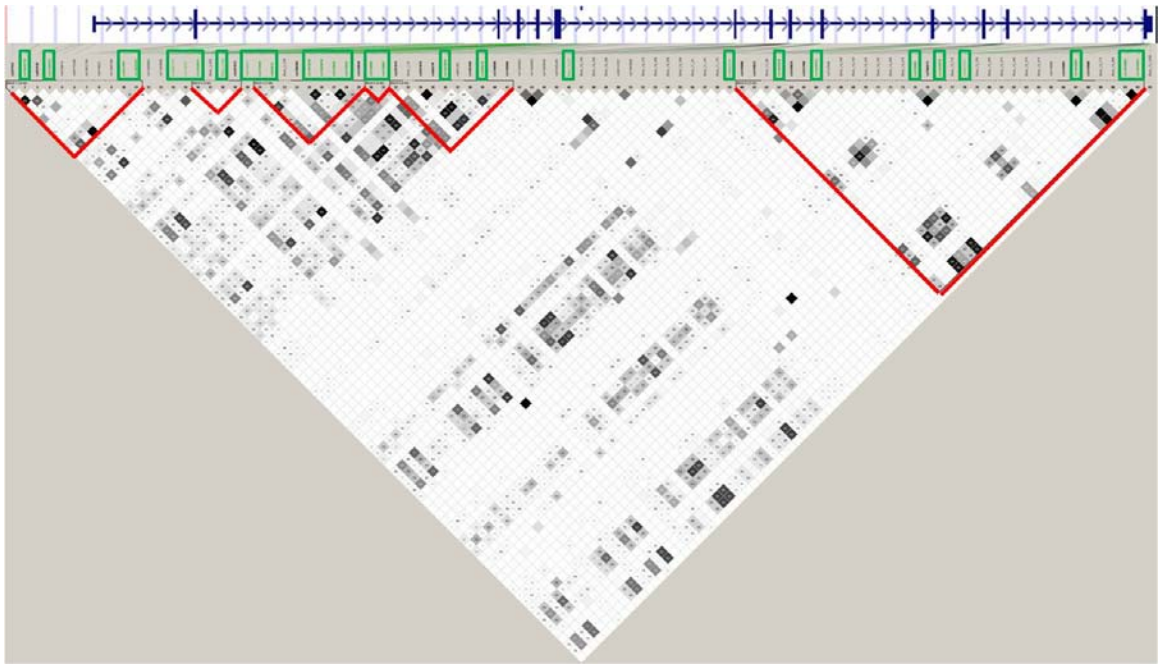
The imputation was done on each ancestral group independently using MACH1.0 (13). In each ancestral group, the genotypes in each chromosome were imputed independently. For European ancestry patients, the reference was 57 CEU samples from the 1000 genomes project (14); for African ancestry patients, the reference was 56 YRI samples from the 1000 genomes project; for Asian ancestry patients, the reference was 59 JPTCHB samples from the 1000 genomes project and for Native American ancestry or “other” patients, the reference was SNPs found in all three ancestries (CEU + YRI + JPTCHB, 172 samples from the 1000 genomes project). For each imputed SNP, the estimated probability that an average imputed genotype will match an experimental genotype had to be at least 95%.

Methotrexate uptake assay

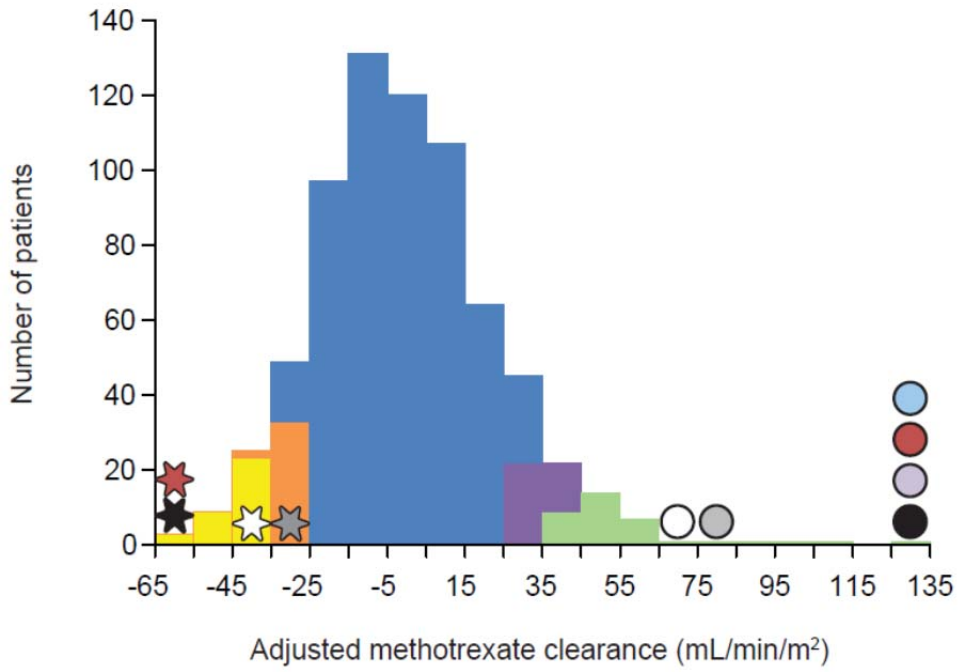
SLCO1B1-expressing HEK 293 cells were grown in Dulbecco's modified Eagle's medium (DMEM) with 10% fetal bovine serum (FBS) and supplemented with 15 µg/ml blasticidin, and 100 µg/mL hygromycin B to maintain the stable cells. *SLCO1B1* transcript expression was confirmed by real-time PCR. Methotrexate was purchased from Sigma Aldrich (St Louis, MO, USA), and [^{3}H]methotrexate (26-38 Ci/mmol) was purchased from Moravek (Brea, CA, USA). Approximately 85,000 cells were plated per well in 12-well plates containing 1 mL media. The next day, media was replaced with media supplemented with 1 µg/mL tetracycline to induce the expression of SLCO1B1. Methotrexate uptake was performed 48 hours after induction. Cells were washed with 1 mL warm PBS, and were incubated for 8 min at 37°C with 750 µL preheated serum-free media containing a mixture of unlabeled and radioactively labeled methotrexate (total concentration, 30 µM). Next, cells were washed twice with 1 mL ice-cold PBS before harvesting and lysing. Samples were analyzed for total radioactivity using an LS 6000IC scintillation counter (Beckman Coulter, Fullerton, CA). Total protein concentrations were measured using Pierce BCA Protein Assay Kit (Thermo Scientific, Rockford, IL). Drug uptake was adjusted to total protein concentration.



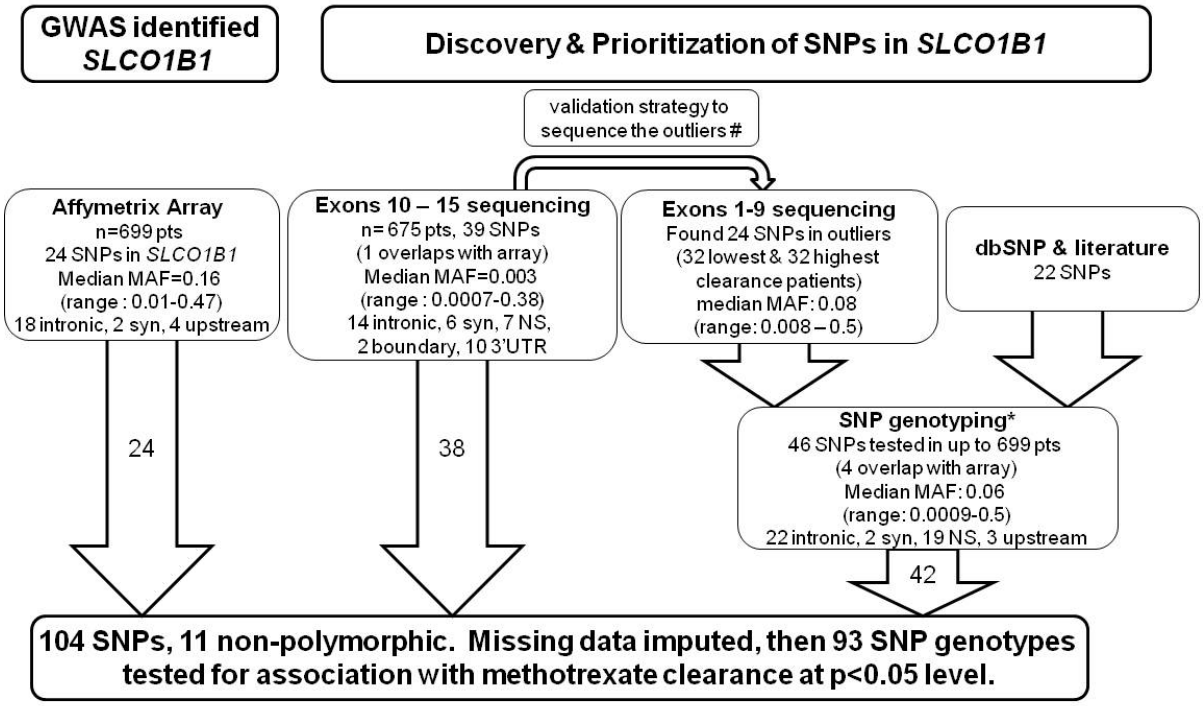
Supplementary Figure 1. After updating the original GWAS based on SNPs typed using the Affymetrix arrays (upper left, circles, 482,252 SNPs) with SNPs imputed based on 1000 Genomes Project (14) (upper right, triangles, 5.8 million SNPs) and the combined typed and imputed SNPs, only SNPs in the *SLCO1B1* gene (chromosome 12) reached genome-wide significance ($p<10^{-7}$).



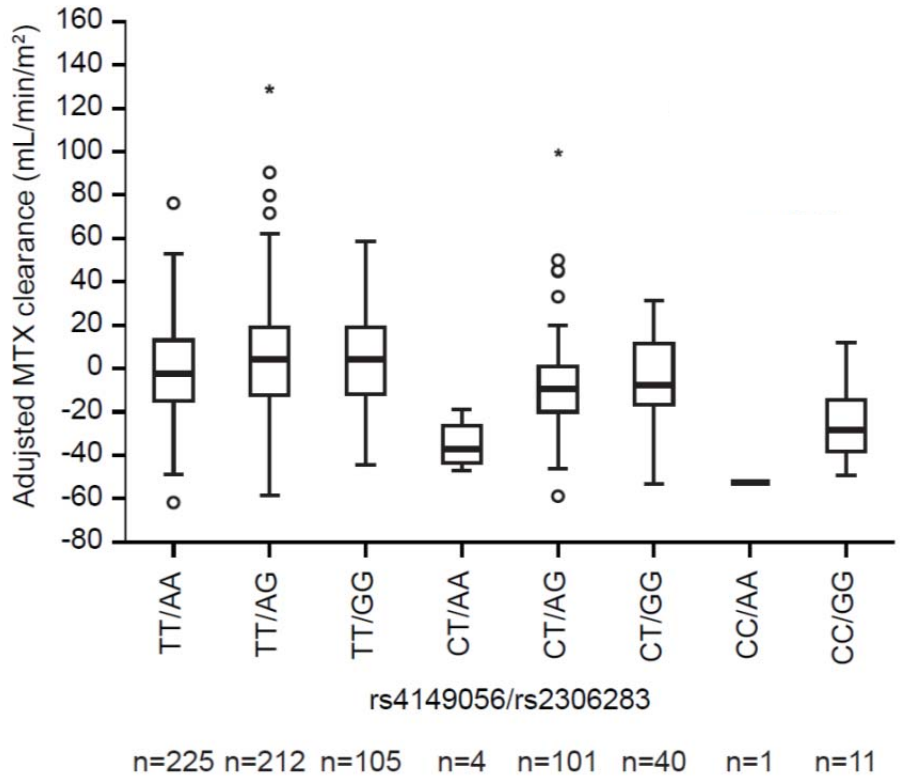
Supplementary Figure 2. Multiple LD blocks in *SLCO1B1* harbor SNPs that are related to methotrexate clearance at the $p < 0.05$ level (indicated in green). White: $R^2=0$; no evidence of LD; Shades of gray= $0 < R^2 < 1$; Black: $R^2=1$; strong evidence of LD. LD blocks are indicated in red. The exons are indicated at the top in blue.



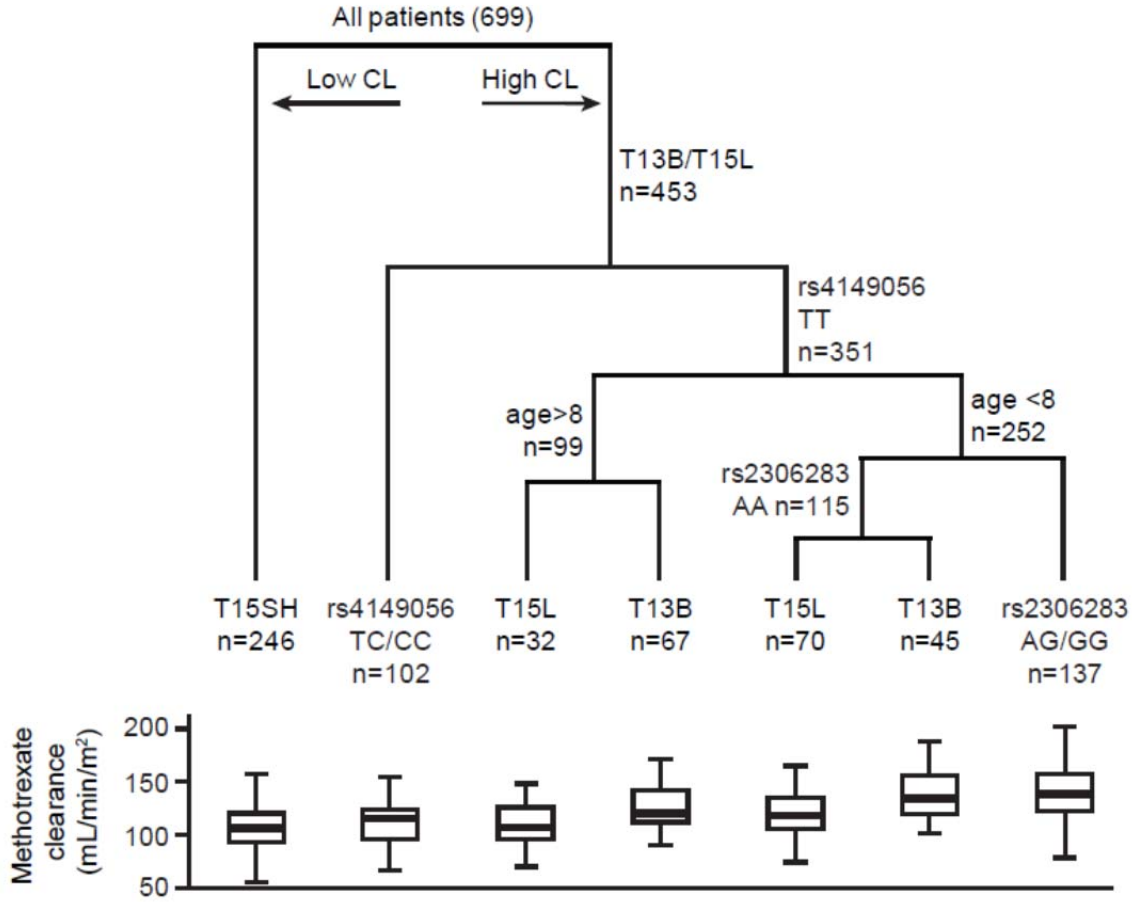
Supplementary Figure 3. Testing the strategy of sequencing phenotypic outliers to identify important SNPs. To test whether a strategy of sequencing only the phenotypic outliers would identify all important SNPs, we evaluated whether all of the SNPs we discovered in exons 10-15 that had $p < 0.05$ for their association with methotrexate clearance (discovered via sequencing the entire population) would have been discovered had we instead only sequenced the outliers (i.e., the top and bottom 10th percentile for clearance). For the 10 SNPs in exons 10-15 that had $p < 0.05$ for associations with methotrexate clearance (indicated by stars and circles), 9 fell within the extreme right (95th percentile for clearance) and left (5th percentile for clearance) of the population frequency histogram for clearance; one intronic SNP was within the lowest 10th percentile for clearance. Therefore, for discovery of SNPs in the remainder of the gene (exons 1-9), we sequenced only the outliers for SNP discovery and then tested all of the discovered SNPs in the entire patient cohort for their association with methotrexate clearance. Stars indicate SNPs in/around exons 10-15 related to lower methotrexate clearance, depicted in the most extreme bin they were found: rs79661732: gray, rs59502379: white, rs4149081: black, and rs11045879: red. Circles indicate SNPs in/around exons 10 – 15 related to higher clearance: rs11045870: gray, rs11045872: black, rs34671512: white, rs11045891: pink, rs11045892: blue, and rs11045893: red. The patients with the lowest 5% of clearance are depicted in yellow, lowest 10% in orange, highest 5% in green, and highest 10% in purple.



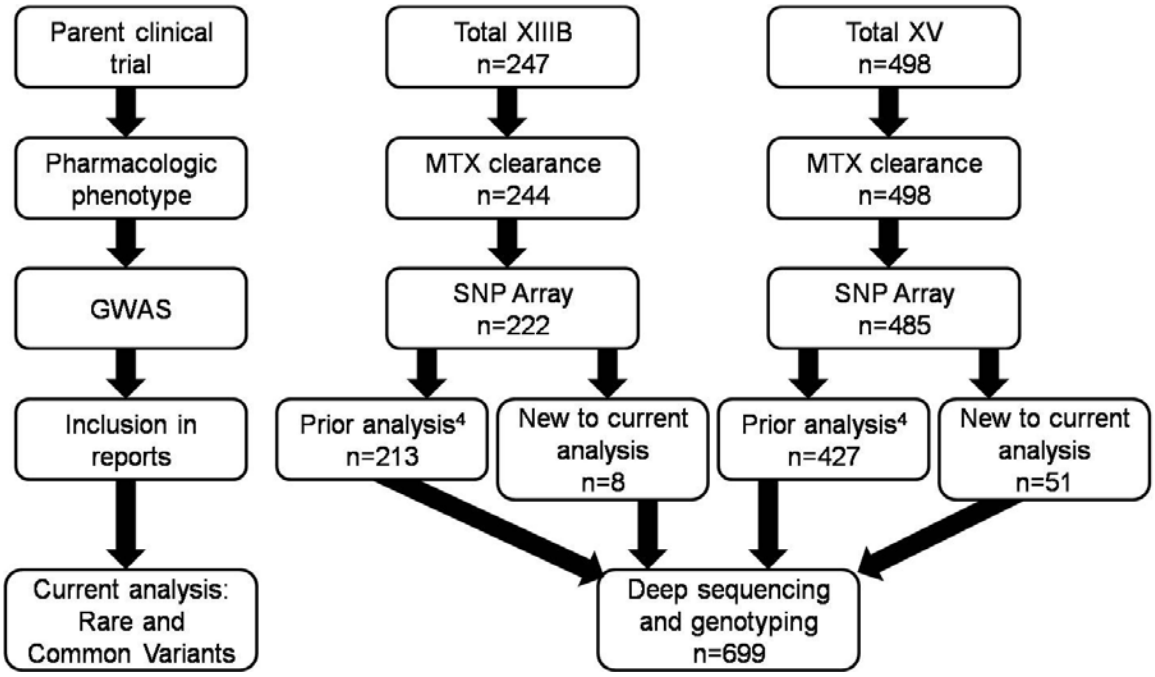
Supplementary Figure 4. SNP discovery & prioritization. GWAS done on 699 patient samples via the Affymetrix 500K and SNP 6.0 arrays included 24 *SLCO1B1* SNPs. Exons 10 – 15 were sequenced in 675 patients, in whom 38 additional SNPs were discovered. Exons 1 – 9 were sequenced in the methotrexate clearance extremes (as described in Supplementary Figure 3), and SNPs discovered by this method and any other reported NS SNP were genotyped (references in Supplementary Table 1). In sum, 104 SNPs were genotyped, and 93 were polymorphic in our patients. *Confirmation of 37 rare SNPs with MAF<2% in 87 patients.



Supplementary Figure 5. Epistasis between rs4149056 and rs2306283. *SLCO1B1* genotypes at rs2306283 (the G allele, right of slash) are significantly related to methotrexate clearance after adjustment for the rs4149056 C allele using a general linear model (p=0.34 before adjustment, $p=2.4 \times 10^{-5}$ after adjustment for rs4149056, Supplementary Table 2). Boxes represent 25^{th} – 75^{th} percentiles, median is represented by a horizontal line, error bars represent the non-outlier range, circles represent outliers and asterisks represent extremes.



Supplementary Figure 6. Classification and regression tree (CART) analysis. All clinical variables (age, gender, ancestry, and treatment arm) and all 93 SNPs were included and the ANOVA procedure as implemented in the R package (rpart). Parameters were optimized to best discriminate all 699 patients on the basis of methotrexate clearance. Boxes represent 25^{th} – 75^{th} percentiles, median is represented by a horizontal line, error bars represent the non-outlier range.



Supplementary Figure 7. Patients included in the current analysis were treated on two different clinical trials (Total XIIIB and Total XV). Methotrexate (MTX) clearance was calculated for each patient after doses of 2 to 5 g/m^2. Affymetrix 500K or 6.0 SNP arrays were run on patient DNA when available, and were included in the prior (4) and current reports.

Supplementary Table 1. Genotyping methods and MAF by SNP

	SNP ID	Position	Source	Type	Function	Method	Major /minor	MAF all pts	in/exclude
1	rs327543	21166718	dbSNP	Upstream		Sequenom Mass Array	C/A	0.095	include
2	rs11045776	21169459	dbSNP	Upstream		Affymetrix Array	A/G	0.22	include
3	rs852549	21173156	dbSNP	Upstream		Affymetrix Array	G/T	0.091	include
4	rs17328763	21173837	dbSNP	Upstream		Illumina Golden Gate	T/C	0.15	include
5	rs4149014	21174220	(15)	Upstream		Affymetrix Array	T/G	0.020	include
6	rs59710386	21175277	dbSNP	Upstream		Sequenom Mass Array	A/C	0.033	include
7	rs12812795	21185596	dbSNP	intron		ABI single base extension	T/A	0.051	include
8	rs11557087	21185803	dbSNP	NS		Sequenom Mass Array	A/G	0	exclude-not polymorphic
9	rs4149021	21186052	dbSNP	intron		ABI single base extension	G/A	0.008	include
10	rs11045784	21186062	dbSNP	intron		Sequenom Mass Array	A/T	0.007	include
11	rs2417955	21187742	dbSNP	intron		Affymetrix Array	A/T	0.47	include
12	rs11045787	21191269	dbSNP	intron		Affymetrix Array	T/G	0.15	include
13	rs11045802	21203587	dbSNP	intron		Affymetrix Array	T/G	0.067	include
14	rs11045808	21209956	dbSNP	intron		Affymetrix Array	C/G	0.11	include
15	rs10841753	21212637	dbSNP	intron		Affymetrix Array	T/C	0.18	include
16	rs7139376	21212696	dbSNP	intron		Affymetrix Array	C/T	0.13	include
17	rs11045813	21213323	dbSNP	intron		Illumina Golden Gate	G/A	0.13	include
18	Exon_3_602	21216935		NS	damaging	Sequenom Mass Array	C/T	0.0009*	include
19	Exon_3_560	21216977		NS	damaging	Sequenom Mass Array	G/A	0.0009*	include
20	rs56101265	21216983	dbSNP	NS		Sequenom Mass Array	T/C	0	exclude-not polymorphic
21	rs2291073	21217081	dbSNP	intron		Sequenom Mass Array	T/G	0.15	include
22	rs56061388	21218796	dbSNP	NS		Sequenom Mass Array	T/C	0	exclude-not polymorphic
23	rs4149037	21219478	dbSNP	intron		Sequenom Mass Array	A/G	0.066	include
24	rs4149040	21219691	dbSNP	intron		Illumina Golden Gate	G/C	0.45	include
25	rs964615	21220691	dbSNP	intron		Sequenom Mass Array	C/T	0.13	include
26	Exon_5_130	21220911		intron		Sequenom Mass Array	A/G	0.0009*	include
27	rs2306283	21221005	(16-45)	NS	tolerated	Sequenom Mass Array	A/G	0.44	include
28	rs11045818	21221028	(18, 34, 35, 43)	Syn		Affymetrix Array	G/A	0.13	include
29	rs2306282	21221069	dbSNP	NS		Sequenom Mass Array	A/G	0	exclude-not polymorphic
30	rs11045819	21221080	(18, 32, 34, 35, 43, 46-49)	NS	tolerated	ABI single base extension	C/A	0.13	include
31	rs72559745	21221084	dbSNP	NS		Sequenom Mass Array	A/G	0	exclude-not polymorphic
32	rs4149044	21221263	dbSNP	intron		Sequenom Mass Array	A/T	0.27	include
33	rs4149045	21221287	dbSNP	intron		Sequenom Mass Array	G/A	0.27	include
34	rs4149046	21221289	dbSNP	intron		Sequenom Mass Array	G/A	0.40	include
35	rs4149056	21222816	(4, 16, 18-30, 32-38, 40-46, 49-80)	NS	damaging	Illumina Golden Gate	T/C	0.12	include
36	rs4149057	21222866	(18, 34, 39, 43, 81)	Syn		Sanger sequencing & imputation	C/T	0.48	include
37	rs72559746	21222873	dbSNP	NS		ABI single base extension	A/C	0	exclude-not polymorphic
38	rs2291075	21222892	(18, 34, 35, 39, 43)	Syn		Affymetrix Array	C/T	0.40	include

	SNP ID	Position	Source	Type	Function	Method	Major /minor	MAF all pts	in/exclude
39	rs61760244	21222903	dbSNP	NS		Sequenom Mass Array	G/A	0	exclude-not polymorphic
40	Exon_7_51	21223158		NS	tolerated	Sequenom Mass Array	A/G	0.005	include
41	rs2291076	21223254	dbSNP	intron		Affymetrix Array	T/C	0.39	include
42	rs999278	21224918	dbSNP	intron		Affymetrix Array	A/C	0.39	include
43	rs11045825	21225277	dbSNP	intron		Sequenom Mass Array	T/C	0.14	include
44	rs991262	21225481	dbSNP	intron		Affymetrix Array	G/A	0.037	include
45	rs1463565	21226648	dbSNP	intron		Affymetrix Array	C/G	0.40	include
46	rs2900476	21227330	dbSNP	intron		Illumina Golden Gate	T/C	0.25	include
47	rs2100996	21229464	dbSNP	intron		Sequenom Mass Array	G/A	0.44	include
48	rs1120964	21230957	dbSNP	intron		ABI single base extension	C/T	0.062	include
49	rs11045852	21241152	dbSNP	NS	tolerated	Sequenom Mass Array	A/G	0.006	include
50	rs11045853	21241177	dbSNP	NS	damaging	Sequenom Mass Array	G/A	0.003	include
51	rs11045854	21241301	dbSNP	Syn		ABI single base extension	G/A	0.005	include
52	rs4603354	21244745	dbSNP	NS		Sequenom Mass Array	C/T	0	exclude-not polymorphic
53	rs72559747	21244772	dbSNP	NS		Sequenom Mass Array	C/G	0	exclude-not polymorphic
54	rs55901008	21244796	dbSNP	NS		Sequenom Mass Array	T/C	0	exclude-not polymorphic
55	rs57040246	21244824	(18)	Syn		Sequenom Mass Array	C/T	0.013	include
56	rs79661732	21246557	dbSNP	intron		Sanger sequencing	T/C	0.006	include
57	Exon_10_198	21246663		intron		Sanger sequencing	G/T	0.0008*	include
58	Exon_10_205	21246670		intron		Sanger sequencing	A/G	0.0008*	include
59	Exon_10_289	21246754		NS	damaging	Sanger sequencing	T/G	0.002	include
60	rs59113707	21246756	dbSNP	NS	tolerated	Sanger sequencing	C/G	0.008	include
61	rs11045859	21246804	dbSNP	Syn		Sanger sequencing	G/A	0.017	include
62	Exon_10_378	21246843		Syn		Sanger sequencing	C/G	0.0008*	include
63	Exon_10_400	21246865		NS	damaging	Sanger sequencing	G/A	0.0008*	include
64	Exon_10_550	21247015		intron		Sanger sequencing	T/A	0.0008*	include
65	Exon_10_569	21247034		intron		Sanger sequencing	G/A	0.0008*	include
66	rs61760248	21249994	dbSNP	intron		Sanger sequencing	C/T	0.003	include
67	rs75563002	21250050	dbSNP	boundary		Sanger sequencing	G/C	0.007	include
68	rs71581991	21250055	dbSNP	boundary		Sanger sequencing	T/C	0.002	include
69	rs59502379	21250200	(18, 34, 35)	NS	damaging	Sanger sequencing	G/C	0.004	include
70	rs4149069	21260593	dbSNP	intron		Affymetrix Array	G/C	0.46	include
71	rs4149072	21261252	dbSNP	intron		Sanger sequencing	G/A	0.068	include
72	Exon_12_98	21261255		intron		Sanger sequencing	A/G	0.0008*	include
73	rs11045870	21262342	dbSNP	intron		Illumina Golden Gate	G/A	0.15	include
74	rs4149076	21262411	dbSNP	intron		Affymetrix Array	T/C	0.31	include
75	rs2417968	21263396	dbSNP	intron		ABI single base extension	C/G	0.43	include
76	rs11045872	21263611	dbSNP	intron		Illumina Golden Gate	A/G	0.15	include
77	Exon13_66542	21266542	UCSF	NS		Illumina Golden Gate	A/T	0	exclude-not polymorphic
78	rs7137959	21268725	dbSNP	intron		Affymetrix Array	G/A	0.009	include
79	Exon_14_180	21268969		Syn		Sanger sequencing	G/A	0.0008*	include
80	Exon_14_195	21268984		Syn		Sanger sequencing	C/G	0.0008*	include
81	Exon_14_324	21269113		intron		Sanger sequencing	A/G	0.0008*	include
82	Exon_14_331	21269120		intron		Sanger sequencing	A/C	0.0008*	include

	SNP ID	Position	Source	Type	Function	Method	Major /minor	MAF all pts	in/exclude
83	rs72655362	21269189	dbSNP	intron		Sanger sequencing	G/A	0.012	include
84	rs71581942	21269259	dbSNP	intron		Sanger sequencing	A/C	0.0008*	include
85	rs4149081	21269288	(4, 82)	intron		Illumina Golden Gate	G/A	0.16	include
86	rs7966613	21270899	dbSNP	intron		Affymetrix Array	A/G	0.32	include
87	rs11045879	21273886	(4, 82)	intron		Illumina Golden Gate	T/C	0.16	include
88	Exon_15_135	21283231		Syn		Sanger sequencing	A/G	0.0007*	include
89	rs34671512	21283243	(18, 34, 35, 43, 83)	NS	tolerated	Sanger sequencing	A/C	0.038	include
90	Exon_15_250	21283346		NS	tolerated	Sanger sequencing	C/T	0.0008*	include
91	Exon_15_263	21283359		NS	tolerated	Sanger sequencing	C/T	0.0008*	include
92	Exon_15_313	21283409		UTR3		Sanger sequencing	T/G	0.0008*	include
93	rs71581985	21283436	dbSNP	UTR3		Sanger sequencing	T/G	0.005	include
94	rs72655363	21283472	dbSNP	UTR3		Sanger sequencing	C/T	0.004	include
95	rs74064260	21283511	dbSNP	UTR3		Sanger sequencing	G/C	0.003	include
96	rs4149085	21283557	dbSNP	UTR3		Sanger sequencing	T/C	0.008	include
97	rs4149087	21283829	dbSNP	UTR3		Sanger sequencing	T/G	0.37	include
98	rs11045891	21283839	dbSNP	UTR3		Sanger sequencing	A/C	0.14	include
99	rs4149088	21283853	dbSNP	UTR3		Sanger sequencing	A/G	0.38	include
100	rs71581986	21283871		UTR3		Sanger sequencing	T/C	0.002	include
101	rs61760249	21283965		UTR3		Sanger sequencing	G/A	0.014	include
102	rs11045892	21284061	dbSNP	intron		Illumina Golden Gate	A/G	0.15	include
103	rs11045893	21284086	dbSNP	intron		Sanger sequencing	T/C	0.15	include
104	Exon_15_1038	21284134		intron		Sanger sequencing	C/T	0.004	include

Supplementary Table 1. Genotyping methods and MAF. SNP ID: dbSNP rsID or if novel, exon and contig location. Position: hg18 position on chromosome 12. Source: source for prior information about each SNP (UCSF refers to http://pharmacogenetics.ucsf.edu/cgi-bin/Gene.py?hgncSymbol=SLCO1B1); others include publications citing the SNP. Type: upstream, intron, NS: non-synonymous, syn: synonymous, boundary: intron/exon boundary, UTR3: 3' untranslated region. Function: NS damaging or tolerated, based on prediction algorithms (see Table 2). Method: Sanger sequencing, Illumina Golden Gate, Affymetrix Array (500K or SNP 6.0), ABI single base extension, Sequenom Mass Array. Major/minor: Major allele, minor allele. MAF all pts: minor allele frequency among all 699 patients, asterisks indicate singletons. In/exclude: SNPs included or excluded based on being non-polymorphic in the patient population.

Supplementary Table 2: P-values for associations of SNP genotypes with methotrexate clearance, after adjusting for age, gender, ancestry and treatment arm.

	SNP ID	p-value all pts	p-value adj for T521C	Euro p-value	African p-value	Native American p-value	Effect size	Effect size SE	Multivar. model
1	rs327543	0.44	0.11	0.25	0.69	0.20	1.1	2.4	no
2	rs11045776	0.013	0.017	0.005	0.63	0.71	3.6	1.5	no
3	rs852549	0.52	0.008	0.57	0.25	0.16	1.7	2.3	yes
4	rs17328763	0.001	0.004	0.003	0.44	0.81	6.1	1.7	no
5	rs4149014	0.94	0.94	0.73	0.44	0.33	0.5	5.1	no
6	rs59710386	0.43	0.010	0.22	0.76	0.0002	-2.8	3.6	no
7	rs12812795	0.64	0.50	0.95	0.50	0.72	-1.4	3.2	no
8	rs11557087	NA	NA	NA	NA	NA	NA	NA	no
9	rs4149021	0.13	0.58	0.41	NA	NA	-13.4	8.1	no
10	rs11045784	0.72	0.72	0.50	0.34	NA	-2.2	7.0	no
11	rs2417955	0.008	0.0004	0.009	0.81	0.63	3.8	1.4	no
12	rs11045787	0.001	0.005	0.004	0.44	0.89	5.9	1.7	no
13	rs11045802	0.26	0.24	0.073	0.094	0.55	1.5	2.6	no
14	rs11045808	0.80	0.82	0.20	0.76	0.70	-1.3	2.0	no
15	rs10841753	$1.7x10^{-6}$	$9.2x10^{-5}$	$5.7x10^{-5}$	0.61	0.069	8.1	1.6	no
16	rs7139376	0.047	0.003	0.080	0.68	0.47	-3.5	1.8	no
17	rs11045813	$1.9x10^{-7}$	$1.8x10^{-5}$	$1.5x10^{-5}$	0.23	0.054	9.5	1.9	no
18	Exon_3_602	0.072	0.049	NA	NA	NA	-41.4	23.3	yes
19	Exon_3_560	0.013	0.006	0.016	NA	NA	-62.1	23.2	yes
20	rs56101265	NA	NA	NA	NA	NA	NA	NA	no
21	rs2291073	0.080	0.23	0.063	0.56	0.97	2.3	1.9	no
22	rs56061388	NA	NA	NA	NA	NA	NA	NA	no
23	rs4149037	0.026	0.032	0.042	0.84	0.20	4.4	2.6	no
24	rs4149040	0.014	$1.5x10^{-7}$	0.10	0.31	0.33	2.9	1.3	no
25	rs964615	0.017	0.0007	0.064	0.23	0.39	-4.4	1.8	no
26	Exon_5_130	0.37	0.34	NA	0.31	NA	22.2	23.4	yes
27	rs2306283	0.34	$2.4x10^{-5}$	0.45	0.63	NA	1.7	1.3	yes
28	rs11045818	$2.6x10^{-7}$	$2.5x10^{-5}$	$5.4x10^{-6}$	0.33	0.28	9.9	1.8	no
29	rs2306282	NA	NA	NA	NA	NA	NA	NA	no
30	rs11045819	$5.6x10^{-6}$	0.0003	0.0001	0.21	0.28	9.8	1.8	no
31	rs72559745	NA	NA	NA	NA	NA	NA	NA	no
32	rs4149044	0.038	0.20	0.021	0.86	0.69	-3.6	1.5	no
33	rs4149045	0.069	0.14	0.030	0.89	0.69	-3.6	1.5	no
34	rs4149046	0.22	0.008	0.47	0.82	0.74	-1.0	1.3	no
35	rs4149056	$7.8x10^{-11}$	NA	$7.8x10^{-10}$	0.32	0.20	-12	1.9	yes
36	rs4149057	$6.5x10^{-6}$	0.10	$4.4x10^{-6}$	0.23	0.33	-6.1	1.3	yes
37	rs72559746	NA	NA	NA	NA	NA	NA	NA	no
38	rs2291075	0.44	$7.5x10^{-6}$	0.74	0.42	0.78	1.0	1.3	no
39	rs61760244	NA	NA	NA	NA	NA	NA	NA	no
40	Exon_7_51	0.65	0.68	NA	0.62	NA	5.6	9.7	no
41	rs2291076	0.54	0.057	0.38	0.98	0.79	0.8	1.3	no
42	rs999278	0.48	0.075	0.37	0.45	0.73	0.9	1.3	no

	SNP ID	p-value all pts	p-value adj for T521C	Euro p-value	African p-value	Native American p-value	Effect size	Effect size SE	Multivar. model
43	rs11045825	$4.9x10^{-7}$	$5.3x10^{-5}$	$2.8x10^{-5}$	0.21	0.021	9.5	1.8	no
44	rs991262	0.59	0.49	0.56	0.69	0.91	-1.6	3.4	no
45	rs1463565	0.39	0.11	0.26	0.52	0.74	1.2	1.3	no
46	rs2900476	0.0004	0.21	0.0006	0.54	0.48	-5.6	1.5	no
47	rs2100996	0.48	0.022	0.24	0.37	0.31	0.9	1.3	no
48	rs1120964	0.13	0.21	0.60	0.92	0.051	3.7	2.7	no
49	rs11045852	0.75	0.68	NA	0.75	NA	-1.8	8.9	no
50	rs11045853	0.25	0.20	NA	0.68	NA	-11.3	11.8	yes
51	rs11045854	0.977	0.926	0.230	0.578	0.96	-0.5	8.8	no
52	rs4603354	NA	NA	NA	NA	NA	NA	NA	no
53	rs72559747	NA	NA	NA	NA	NA	NA	NA	no
54	rs55901008	NA	NA	NA	NA	NA	NA	NA	no
55	rs57040246	0.45	0.36	0.59	0.33	0.89	5.1	6.0	no
56	rs79661732	0.061	0.063	NA	0.047	NA	-18.2	8.4	no
57	Exon_10_198	0.50	0.58	0.49	NA	NA	16.0	23.3	no
58	Exon_10_205	0.38	0.45	0.38	NA	NA	21.0	23.3	no
59	Exon_10_289	0.45	0.31	NA	NA	0.47	-12.8	16.9	yes
60	rs59113707	0.91	0.91	NA	0.58	0.017	0.3	6.9	no
61	rs11045859	0.67	0.74	0.49	0.81	0.017	2.1	5.1	no
62	Exon_10_378	0.81	0.83	NA	0.83	NA	7.4	23.3	no
63	Exon_10_400	0.55	0.43	NA	NA	0.51	-13.1	23.3	yes
64	Exon_10_550	0.86	0.97	0.87	NA	NA	5.2	23.3	no
65	Exon_10_569	0.96	0.83	0.93	NA	NA	-0.5	23.2	no
66	rs61760248	0.68	0.91	0.53	NA	0.77	5.9	11.6	no
67	rs75563002	0.68	0.62	NA	0.76	0.063	0.4	7.8	no
68	rs71581991	0.30	0.48	0.33	NA	NA	-15.2	13.5	no
69	rs59502379	0.031	0.025	NA	0.043	NA	-21.5	9.7	yes
70	rs4149069	0.79	0.0004	0.65	0.86	0.80	0.3	1.3	no
71	rs4149072	0.73	0.95	0.74	0.42	0.77	1.0	2.4	no
72	Exon_12_98	0.21	0.26	NA	NA	0.41	31.2	23.3	no
73	rs11045870	$1.9x10^{-6}$	0.0002	$2.3x10^{-5}$	0.33	0.15	8.4	1.8	no
74	rs4149076	0.15	0.017	0.39	0.37	0.68	-2.2	1.4	no
75	rs2417968	0.92	0.0009	0.56	0.21	0.93	0.1	1.3	no
76	rs11045872	$8.5x10^{-7}$	$6.7x10^{-5}$	$2.4x10^{-6}$	0.38	0.49	8.3	1.7	no
77	Exon13_66542	NA	NA	NA	NA	NA	NA	NA	no
78	rs7137959	0.34	0.28	NA	0.29	0.38	-6.7	6.8	no
79	Exon_14_180	0.081	0.057	NA	NA	NA	-32.3	22.9	no
80	Exon_14_195	0.68	0.99	NA	NA	NA	-9.5	23.3	no
81	Exon_14_324	0.54	0.45	NA	NA	NA	-14.3	23.3	no
82	Exon_14_331	0.37	1.00	0.40	NA	NA	-22.9	23.2	no
83	rs72655362	0.11	0.091	NA	0.20	NA	12.0	6.5	no
84	rs71581942	0.52	0.79	0.51	NA	NA	-15.4	23.3	no
85	rs4149081	$4.6x10^{-11}$	0.033	$1.6x10^{-9}$	0.12	0.26	-11.2	1.7	yes
86	rs7966613	0.31	0.005	0.53	0.86	0.95	-1.9	1.3	no
87	rs11045879	$3.3x10^{-11}$	0.031	$1.5x10^{-9}$	0.085	0.28	-11.2	1.7	no
88	Exon_15_135	0.46	0.71	NA	NA	NA	-17.3	23.3	no

	SNP ID	p-value all pts	p-value adj for T521C	Euro p-value	African p-value	Native American p-value	Effect size	Effect size SE	Multivar. model
89	rs34671512	0.011	0.028	0.034	0.085	0.42	9.0	3.2	no
90	Exon_15_250	0.42	0.65	0.40	NA	NA	-17.9	23.3	no
91	Exon_15_263	0.22	0.19	NA	NA	NA	30.0	24.9	no
92	Exon_15_313	0.50	0.59	0.48	NA	NA	15.7	23.3	no
93	rs71581985	0.86	0.85	0.93	NA	NA	1.9	9.6	no
94	rs72655363	0.57	0.30	NA	0.93	NA	6.5	10.7	no
95	rs74064260	0.38	0.39	NA	0.33	NA	10.4	11.8	no
96	rs4149085	0.28	0.21	NA	0.61	0.46	-9.0	8.2	no
97	rs4149087	0.16	0.11	0.50	0.17	0.31	-2.0	1.3	no
98	rs11045891	$8.4x10^{-7}$	$6.7x10^{-5}$	$2.9x10^{-6}$	0.18	0.66	8.6	1.8	no
99	rs4149088	0.14	0.10	0.46	0.17	0.33	-2.0	1.3	no
100	rs71581986	0.30	0.61	0.33	NA	NA	-17.6	16.4	no
101	rs61760249	0.31	0.12	0.54	0.081	0.88	-5.4	5.4	no
102	rs11045892	$4.6x10^{-7}$	$3.6x10^{-5}$	$4.9x10^{-6}$	0.083	0.47	8.7	1.7	no
103	rs11045893	$2.6x10^{-7}$	$2.2x10^{-5}$	$2.9x10^{-6}$	0.027	0.65	8.7	1.7	no
104	Exon_15_1038	0.14	0.064	0.15	NA	NA	-17.6	11.6	no

Supplementary Table 2. P-values for associations of SNP genotypes with methotrexate clearance, after adjusting for age, gender, ancestry and treatment arm. SNP ID: dbSNP rsID or if novel, exon and contig location. P-value all pts: univariate (one SNP) p-value calculated analyzing all patients. P-value adj for T521C: univariate p-value (for each SNP) calculated analyzing all patients, after adjustment for rs4149056 (T521C) genotype. Euro p-value: univariate p-value calculated analyzing 459 patients with primarily European ancestry. African p-value: univariate p-value calculated analyzing 113 patients with primarily African ancestry. Native American p-value: univariate p-value calculated analyzing 87 patients with > 10% Native American ancestry. P-value is not presented for Asians (n=7) and "others" because of the small sample size (n=33). Effect size: effect size indicating the change in methotrexate clearance with each copy of the minor allele ($mL/min/m^2$). Effect size SE: standard error of the effect size ($mL/min/m^2$). Multivar. model: indicates whether the SNP was ultimately included in the multivariate model (including all SNPs and other covariates) predicting interpatient variation in methotrexate clearance, as described in Figure 3 of the main manuscript. NA, not applicable.

Supplementary Table 3. SNP details: HWE & minor allele frequency by ancestry

	SNP ID	HWE p-value	Major /minor	MAF all pts	MAF category	MAF Euro	MAF African	MAF Asian	MAF Nat. Am.
1	rs327543	1.00	C/A	0.095	common	0.068	0.22	0.20	0.021
2	rs11045776	0.69	A/G	0.22	common	0.23	0.16	0.50	0.20
3	rs852549	0.40	G/T	0.091	common	0.061	0.24	0.14	0.045
4	rs17328763	0.43	T/C	0.15	common	0.18	0.031	0	0.15
5	rs4149014	1.00	T/G	0.020	low freq	0.001	0.058	0.43	0.017
6	rs59710386	0.57	A/C	0.033	low freq	0.042	0.005	0	0.010
7	rs12812795	0.38	T/A	0.051	common	0.061	0.010	0	0.083
8	rs11557087	1.00	A/G	0		0	0	0	0
9	rs4149021	1.00	G/A	0.008	rare	0.009	0	0.10	0
10	rs11045784	1.00	A/T	0.007	rare	0.003	0.027	0	0
11	rs2417955	0.48	A/T	0.47	common	0.38	0.88	0.64	0.39
12	rs11045787	0.11	T/G	0.15	common	0.18	0.031	0	0.13
13	rs11045802	0.56	T/G	0.067	common	0.086	0.005	0.07	0.051
14	rs11045808	1.00	C/G	0.11	common	0.078	0.18	0.36	0.15
15	rs10841753	0.75	T/C	0.18	common	0.18	0.17	0.36	0.21
16	rs7139376	0.68	C/T	0.13	common	0.13	0.16	0	0.11
17	rs11045813	0.48	G/A	0.13	common	0.16	0.037	0	0.11
18	Exon_3_602	1.00	C/T	0.0009	rare	0	0	0	0
19	Exon_3_560	1.00	G/A	0.0009	rare	0.001	0	0	0
20	rs56101265	1.00	T/C	0		0	0	0	0
21	rs2291073	1.00	T/G	0.15	common	0.082	0.49	0.38	0.096
22	rs56061388	1.00	T/C	0		0	0	0	0
23	rs4149037	1.00	A/G	0.066	common	0.027	0.19	0.36	0.090
24	rs4149040	0.55	G/C	0.45	common	0.38	0.72	0.71	0.44
25	rs964615	0.83	C/T	0.13	common	0.12	0.16	0	0.11
26	Exon_5_130	1.00	A/G	0.0009	rare	0	0.005	0	0
27	rs2306283	0.92	A/G	0.44	common	0.37	0.77	0.75	0.50
28	rs11045818	0.47	G/A	0.13	common	0.15	0.040	0	0.12
29	rs2306282	1.00	A/G	0		0	0	0	0
30	rs11045819	0.33	C/A	0.13	common	0.14	0.071	0	0.14
31	rs72559745	1.00	A/G	0		0	0	0	0
32	rs4149044	0.75	A/T	0.27	common	0.20	0.50	0.40	0.22
33	rs4149045	0.75	G/A	0.27	common	0.20	0.50	0.40	0.22
34	rs4149046	0.92	G/A	0.40	common	0.49	0.077	0.20	0.46
35	rs4149056	0.71	T/C	0.12	common	0.15	0.014	0	0.13
36	rs4149057	0.77	C/T	0.48	common	0.38	0.85	0.71	0.44
37	rs72559746	1.00	A/C	0		0	0	0	0
38	rs2291075	0.69	C/T	0.40	common	0.38	0.51	0.36	0.35
39	rs61760244	1.00	G/A	0		0	0	0	0
40	Exon_7_51	1.00	A/G	0.005	rare	0	0.028	0	0
41	rs2291076	0.85	T/C	0.39	common	0.46	0.085	0.29	0.42
42	rs999278	0.64	A/C	0.39	common	0.46	0.12	0.29	0.43
43	rs11045825	0.47	T/C	0.14	common	0.15	0.067	0	0.14
44	rs991262	1.00	G/A	0.037	low freq	0.049	0.009	0	0.023
45	rs1463565	0.71	C/G	0.40	common	0.47	0.13	0.36	0.43

	SNP ID	HWE p-value	Major /minor	MAF all pts	MAF category	MAF Euro	MAF African	MAF Asian	MAF Nat. Am.
46	rs2900476	1.00	T/C	0.25	common	0.21	0.43	0.36	0.20
47	rs2100996	0.35	G/A	0.44	common	0.51	0.13	0.20	0.51
48	rs1120964	1.00	C/T	0.062	common	0.028	0.17	0.40	0.065
49	rs11045852	1.00	A/G	0.006	rare	0	0.028	0	0
50	rs11045853	1.00	G/A	0.003	rare	0	0.014	0	0
51	rs11045854	1.00	G/A	0.005	rare	0	0.027	0.015	0
52	rs4603354	1.00	C/T	0		0	0	0	0
53	rs72559747	1.00	C/G	0		0	0	0	0
54	rs55901008	1.00	T/C	0		0	0	0	0
55	rs57040246	1.00	C/T	0.013	low freq	0.001	0.055	0	0.021
56	rs79661732	1.00	T/C	0.006	rare	0	0.024	0	0
57	Exon_10_198	1.00	G/T	0.0008	rare	0.001	0	0	0
58	Exon_10_205	1.00	A/G	0.0008	rare	0.001	0	0	0
59	Exon_10_289	1.00	T/G	0.002	rare	0	0	0	0.013
60	rs59113707	1.00	C/G	0.008	rare	0	0.038	0	0.013
61	rs11045859	1.00	G/A	0.017	low freq	0.001	0.080	0	0.013
62	Exon_10_378	1.00	C/G	0.0008	rare	0	0.005	0	0
63	Exon_10_400	1.00	G/A	0.0008	rare	0	0	0	0.006
64	Exon_10_550	1.00	T/A	0.0008	rare	0.001	0	0	0
65	Exon_10_569	1.00	G/A	0.0008	rare	0.001	0	0	0
66	rs61760248	1.00	C/T	0.003	rare	0.004	0	0	0.006
67	rs75563002	1.00	G/C	0.007	rare	0	0.031	0	0.006
68	rs71581991	1.00	T/C	0.002	rare	0.003	0	0	0
69	rs59502379	1.00	G/C	0.004	rare	0	0.027	0	0
70	rs4149069	0.15	G/C	0.46	common	0.42	0.60	0.71	0.43
71	rs4149072	0.50	G/A	0.068	common	0.040	0.16	0.40	0.075
72	Exon_12_98	1.00	A/G	0.0008	rare	0	0	0	0.006
73	rs11045870	0.63	G/A	0.15	common	0.17	0.071	0	0.14
74	rs4149076	0.92	T/C	0.31	common	0.33	0.22	0.36	0.31
75	rs2417968	0.63	C/G	0.43	common	0.41	0.47	0.71	0.42
76	rs11045872	0.34	A/G	0.15	common	0.17	0.071	0	0.14
77	Exon13_66542	1.00	A/T	0		0	0	0	0
78	rs7137959	1.00	G/A	0.009	rare	0	0.053	0	0.006
79	Exon_14_180	1.00	G/A	0.0008	rare	0	0	0	0
80	Exon_14_195	1.00	C/G	0.0008	rare	0	0	0	0
81	Exon_14_324	1.00	A/G	0.0008	rare	0	0	0	0
82	Exon_14_331	1.00	A/C	0.0008	rare	0.001	0	0	0
83	rs72655362	1.00	G/A	0.012	low freq	0	0.063	0	0
84	rs71581942	1.00	A/C	0.0008	rare	0.001	0	0	0
85	rs4149081	0.47	G/A	0.16	common	0.15	0.15	0.36	0.18
86	rs7966613	0.83	A/G	0.32	common	0.32	0.29	0.36	0.33
87	rs11045879	0.48	T/C	0.16	common	0.16	0.16	0.36	0.18
88	Exon_15_135	1.00	A/G	0.0007	rare	0	0	0	0
89	rs34671512	0.12	A/C	0.038	low freq	0.037	0.056	0	0.006
90	Exon_15_250	1.00	C/T	0.0008	rare	0.001	0	0	0
91	Exon_15_263	1.00	C/T	0.0008	rare	0	0	0.08	0
92	Exon_15_313	1.00	T/G	0.0008	rare	0.001	0	0	0

	SNP ID	HWE p-value	Major /minor	MAF all pts	MAF category	MAF Euro	MAF African	MAF Asian	MAF Nat. Am.
93	rs71581985	1.00	T/G	0.005	rare	0.006	0	0	0
94	rs72655363	1.00	C/T	0.004	rare	0	0.019	0.08	0
95	rs74064260	1.00	G/C	0.003	rare	0	0.018	0	0
96	rs4149085	1.00	T/C	0.008	rare	0	0.009	0.33	0.012
97	rs4149087	0.54	T/G	0.37	common	0.38	0.32	0.71	0.39
98	rs11045891	0.40	A/C	0.14	common	0.18	0.041	0	0.16
99	rs4149088	0.76	A/G	0.38	common	0.38	0.32	0.71	0.40
100	rs71581986	1.00	T/C	0.002	rare	0.002	0	0	0
101	rs61760249	1.00	G/A	0.014	low freq	0.017	0.009	0	0.012
102	rs11045892	0.52	A/G	0.15	common	0.18	0.076	0	0.14
103	rs11045893	0.40	T/C	0.15	common	0.18	0.080	0	0.16
104	Exon_15_1038	1.00	C/T	0.004	rare	0.005	0	0	0

Supplementary Table 3. SNP details: HWE & minor allele frequency by ancestry. SNP ID: dbSNP rsID or if novel, exon and contig location. HWE p-value: Hardy-Weinberg Equilibrium p-value in patients with primarily European ancestry. Major/minor: Major allele, minor allele. MAF all pts: minor allele frequency among all 699 patients. MAF category: common: MAF>5%; low freq: MAF 1-5%; rare: MAF<1%. MAF Euro: minor allele frequency in 459 patients with primarily European ancestry (ancestry determined by STRUCTURE). MAF African: minor allele frequency in 113 patients with primarily African ancestry. MAF Asian: minor allele frequency in 7 Asian patients. MAF Nat. Am.: minor allele frequency in 87 patients with > 10% Native American ancestry.

Supplementary Table 4. Associations of SNPs with methotrexate clearance from analysis stratified based on accounting for the rs4149056 genotype

	SNP ID	TT effect size	TT SE of effect size	p-value in TT pts	TC/CC effect size	TC/CC SE of effect size	p-value in TC/CC pts	adj. effect size (all pts)	SE of adj. effect size (all pts)	adjusted p-value for all patients	rs4149056 interaction p-value
1	rs327543	1.6	3.4	0.65	10	3.9	0.008	6.1	2.58	0.11	0.15
2	rs11045776	4.6	2.0	0.024	4.9	3.6	0.17	4.2	1.75	0.017	0.84
3	rs852549	2.9	3.3	0.38	10	3.8	0.008	6.5	2.48	0.008	0.20
4	rs17328763	6.3	2.3	0.0060	7.8	3.9	0.046	6.3	1.95	0.004	0.89
5	rs4149014	0.41	5.3	0.94	NA	NA	NA	0.34	5.2	0.94	0.91
6	rs59710386	5.1	15	0.73	8.0	4.1	0.052	9.5	4.02	0.01	0.59
7	rs12812795	-1.9	3.6	0.60	1.1	6.7	0.87	-1.8	3.14	0.5	0.77
8	rs11557087	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
9	rs4149021	-12	17	0.45	-1.9	9.0	0.83	-4.3	7.97	0.58	0.76
10	rs11045784	-4.3	8.6	0.62	-5.2	22	0.82	-3.5	7.91	0.72	0.81
11	rs2417955	5.2	2.3	0.024	13	4.0	0.0009	7.0	1.97	0.0004	0.09
12	rs11045787	6.3	2.3	0.0060	7.8	3.9	0.046	6.3	1.95	0.005	0.89
13	rs11045802	2.9	3.1	0.35	-0.36	4.9	0.94	1.8	2.57	0.24	0.61
14	rs11045808	0.30	2.6	0.91	-6.6	4.5	0.14	-0.52	2.2	0.82	0.41
15	rs10841753	7.4	2.0	0.00030	9.7	4.3	0.025	7.5	1.81	$9.2x10^{-5}$	0.74
16	rs7139376	-4.3	2.2	0.055	-3.4	5.0	0.50	-4.5	2	0.003	0.97
17	rs11045813	8.2	2.3	0.00041	10	4.6	0.025	8.3	2.04	$1.8x10^{-5}$	0.81
18	Exon_3_602	-44	23	0.053	NA	NA	NA	-44	22.6	0.049	NA
19	Exon_3_560	-65	23	0.0047	NA	NA	NA	-66	22.5	0.006	NA
20	rs56101265	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
21	rs2291073	2.7	2.4	0.26	-3.4	5.7	0.55	1.7	2.23	0.23	0.34
22	rs56061388	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
23	rs4149037	3.9	3.0	0.20	6.4	8.2	0.44	4.2	2.8	0.032	0.77
24	rs4149040	9.1	2.1	$2.1x10^{-5}$	11	5.4	0.040	9.4	1.95	$1.5x10^{-7}$	0.66
25	rs964615	-5.5	2.2	0.014	-3.2	5.1	0.53	-5.5	2.02	0.0007	0.77
26	Exon_5_130	22	23	0.34	NA	NA	NA	23	22.7	0.34	NA
27	rs2306283	8.3	2.1	0.00011	36	9.8	0.0004	9.2	2.05	$2.4x10^{-5}$	0.08
28	rs11045818	8.3	2.3	0.00031	13	4.7	0.009	8.7	2.04	$2.5x10^{-5}$	0.55
29	rs2306282	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
30	rs11045819	8.3	2.2	0.00021	12	4.8	0.012	8.6	2	0.0003	0.55
31	rs72559745	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
32	rs4149044	2.9	2.4	0.23	6.6	5.0	0.19	4.0	2.13	0.2	0.44
33	rs4149045	2.5	2.4	0.30	6.6	5.0	0.19	3.6	2.14	0.14	0.40
34	rs4149046	-2.1	2.4	0.38	-1.9	3.7	0.60	-2.6	2.01	0.008	0.81
35	rs4149056	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
36	rs4149057	-3.3	2.2	0.14	NA	NA	NA	-3.0	2.19	0.1	0.80
37	rs72559746	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
38	rs2291075	8.5	2.0	$2.3x10^{-5}$	NA	NA	NA	8.7	1.95	$7.5x10^{-6}$	NA
39	rs61760244	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

	SNP ID	TT effect size	TT SE of effect size	p-value in TT pts	TC/CC effect size	TC/CC SE of effect size	p-value in TC/CC pts	adj. effect size (all pts)	SE of adj. effect size (all pts)	adjusted p-value for all patients	rs4149056 interaction p-value
40	Exon_7_51	4.8	9.5	0.62	NA	NA	NA	4.9	9.42	0.68	NA
41	rs2291076	-1.9	2.4	0.43	0.50	3.6	0.89	-1.9	2	0.057	0.62
43	rs11045825	7.8	2.2	0.00052	13	4.7	0.009	8.3	2.01	$5.3x10^{-5}$	0.48
44	rs991262	-4.2	3.9	0.29	6.1	6.4	0.34	-1.7	3.35	0.49	0.20
45	rs1463565	-0.5	2.4	0.83	-0.27	3.6	0.94	-1.2	1.97	0.11	0.98
46	rs2900476	1.8	2.6	0.47	38	22	0.088	2.8	2.41	0.21	0.20
47	rs2100996	-2.1	2.5	0.41	1.3	3.6	0.73	-1.7	2.05	0.022	0.54
48	rs1120964	2.5	3.0	0.41	2.8	9.1	0.76	2.6	2.82	0.21	0.87
49	rs11045852	-2.8	8.8	0.75	NA	NA	NA	-2.2	8.68	0.68	NA
50	rs11045853	-14	12	0.24	NA	NA	NA	-12	11.4	0.2	NA
51	rs11045854	-1.8	8.6	0.83	NA	NA	NA	-1.2	8.51	0.89	NA
52	rs4603354	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
53	rs72559747	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
54	rs55901008	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
55	rs57040246	9.5	6.3	0.13	-25	17	0.15	5.4	5.83	0.36	0.07
56	rs79661732	-21	8.8	0.016	5.8	23	0.80	-17	8.11	0.063	0.32
57	Exon_10_198	12	23	0.62	NA	NA	NA	12	22.6	0.58	NA
58	Exon_10_205	16	23	0.50	NA	NA	NA	17	22.6	0.45	NA
59	Exon_10_289	-16	17	0.35	NA	NA	NA	-17	16.4	0.31	NA
60	rs59113707	4.9	7.3	0.50	-27	20	0.17	1.1	6.69	0.91	0.14
61	rs11045859	4.2	5.2	0.42	-25	17	0.15	2.1	4.92	0.74	0.11
62	Exon_10_378	9.0	23	0.70	NA	NA	NA	6.5	22.7	0.83	NA
63	Exon_10_400	-17	23	0.46	NA	NA	NA	-18	22.7	0.43	NA
64	Exon_10_550	3.7	23	0.87	NA	NA	NA	1.4	22.6	0.97	NA
65	Exon_10_569	-3.6	23	0.88	NA	NA	NA	-5.1	22.6	0.83	NA
66	rs61760248	1.7	12	0.89	NA	NA	NA	1.2	11.3	0.91	NA
67	rs75563002	6.3	8.3	0.45	-28	21	0.18	1.6	7.57	0.62	0.15
68	rs71581991	-35	23	0.13	7.4	16	0.64	-10.0	13.1	0.48	0.21
69	rs59502379	-22	9.6	0.024	NA	NA	NA	-22	9.43	0.025	NA
70	rs4149069	6.9	2.1	0.0010	35	22	0.12	7.2	2.03	0.0004	0.42
71	rs4149072	0.11	2.8	0.97	3.9	7.3	0.59	0.71	2.59	0.95	0.66
72	Exon_12_98	29	23	0.21	NA	NA	NA	27	22.6	0.26	NA
73	rs11045870	6.8	2.2	0.0017	11	4.5	0.018	7.2	1.94	0.0002	0.57
74	rs4149076	3.2	2.0	0.12	16	13	0.24	3.5	1.94	0.017	0.72
75	rs2417968	6.3	2.0	0.0020	35	22	0.12	6.6	1.97	0.0009	0.40
76	rs11045872	6.9	2.2	0.0016	11	4.5	0.018	7.2	1.94	$6.7x10^{-5}$	0.57
77	Exon13_66542	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
78	rs7137959	-7.2	6.7	0.28	NA	NA	NA	-7.3	6.58	0.28	NA
79	Exon_14_180	-36	22	0.11	NA	NA	NA	-36	22.2	0.057	NA
80	Exon_14_195	NA	NA	NA	0.74	22	0.97	-0.44	22.6	0.99	NA
81	Exon_14_324	-17	23	0.47	NA	NA	NA	-17	22.6	0.45	NA
82	Exon_14_331	NA	NA	NA	-9.3	22	0.67	-0.34	22.8	1	NA

	SNP ID	TT effect size	TT SE of effect size	p-value in TT pts	TC/CC effect size	TC/CC SE of effect size	p-value in TC/CC pts	adj. effect size (all pts)	SE of adj. effect size (all pts)	adjusted p-value for all patients	rs4149056 interaction p-value
83	rs72655362	12	6.6	0.072	19	25	0.44	12	6.29	0.091	0.76
84	rs71581942	NA	NA	NA	-12	22	0.58	-6.3	22.6	0.79	NA
85	rs4149081	-8.9	3.6	0.014	22	12	0.053	-4.9	3.17	0.033	0.09
86	rs7966613	4.1	2.0	0.039	16	13	0.24	4.4	1.93	0.005	0.77
87	rs11045879	-8.9	3.6	0.014	22	12	0.053	-4.9	3.17	0.031	0.09
88	Exon_15_135	NA	NA	NA	-13	22	0.58	-8.5	22.7	0.71	NA
89	rs34671512	8.6	3.6	0.019	-2.0	9.3	0.83	7.4	3.34	0.028	0.43
90	Exon_15_250	NA	NA	NA	-15	22	0.51	-10	22.6	0.65	NA
91	Exon_15_263	29	24	0.23	NA	NA	NA	31	24.1	0.19	NA
92	Exon_15_313	12	23	0.62	NA	NA	NA	12	22.6	0.59	NA
93	rs71581985	-2.7	9.4	0.77	NA	NA	NA	-1.9	9.28	0.85	NA
94	rs72655363	4.6	11	0.66	NA	NA	NA	6.4	10.4	0.3	0.30
95	rs74064260	10	12	0.38	NA	NA	NA	10	11.4	0.39	NA
96	rs4149085	-9.7	9.4	0.30	NA	NA	NA	-9.9	9.25	0.21	0.38
97	rs4149087	3.2	2.0	0.11	-6.0	9.2	0.51	2.9	1.91	0.11	0.36
98	rs11045891	7.8	2.2	0.00052	10	4.4	0.022	7.8	1.98	$6.7x10^{-5}$	0.78
99	rs4149088	3.2	2.0	0.11	-3.0	10	0.76	3.0	1.91	0.1	0.49
100	rs71581986	NA	NA	NA	-3.6	16	0.82	-8.6	16	0.61	NA
101	rs61760249	-6.7	5.5	0.22	-38	22	0.088	-8.3	5.26	0.12	0.31
102	rs11045892	7.9	2.2	0.00027	10	4.4	0.022	7.9	1.93	$3.6x10^{-5}$	0.80
103	rs11045893	7.9	2.2	0.00027	10	4.4	0.022	7.9	1.93	$2.2x10^{-5}$	0.80
104	Exon_15_1038	-21	11	0.066	NA	NA	NA	-21	11.3	0.064	NA

Supplementary Table 4. Stratified analysis based on rs4149056 genotype.
TT effect size: effect size for the association of the given SNP genotype (in each row) in those patients who are homozygous for the rs4149056 TT genotype. The effect size is parameterized in methotrexate clearance units of mL/min/m^2. TT SE of effect size: standard error of effect size (mL/min/m^2) in patients with the TT genotype at rs4149056. p-value in TT pts: p-value for the association of the given SNP in each row with methotrexate clearance in only patients with the rs4149056 TT genotype. TC/CC effect size: effect size for the association of the given SNP genotype (in each row) in those patients with rs4149056 TC or CC genotypes, in mL/min/m^2. TC/CC SE of effect size: standard error of effect size (mL/min/m^2) in patients with the TC or CC genotype at rs4149056. p-value in TC/CC pts: p-value for the association of the given SNP in each row with methotrexate clearance only in patients with the rs4149056 TC or CC genotype. adj effect size (all pts): effect size for the association of the given SNP in each row with methotrexate clearance in all patients (mL/min/m^2), adjusting for rs4149056 as a covariate. SE of adj effect size (all pts): standard error of the effect size in all patients (mL/min/m^2), adjusting for rs4149056 as a covariate.

Adjusted p-value for all pts: p-value in all patients, adjusting for rs4149056 as a covariate.
rs4149056 interaction p-value: p-value of the interaction between each SNP and rs4149056.
NA, not applicable: SNP is not polymorphic in that population.

Supplementary Table 5: Results of 4 prediction algorithms for functional effect of NS SNPs

SNP ID	AA Sub	PMUT	PMUT score	PMUT reliability	SNPs3D	SNPs3D score	SIFT	SIFT Score	PolyPhen2	PolyPhen2 score
Exon_3_602	R57W	Pathological	0.8685	7	deleterious	-3.08	Damaging	0	Probably Damaging	1
Exon_3_560	G71R	Pathological	0.6052	2	deleterious	-2.2	Damaging	0	Probably Damaging	1
rs2306283	N130D	Neutral	0.108	7	non-deleterious	2.04	Tolerated	0.7	Benign	0.001
rs11045819	P155T	Neutral	0.127	7	non-deleterious	0.98	Tolerated	0.41	Benign	0.143
rs4149056	V174A	Neutral	0.1556	6	deleterious	-1.49	Damaging	0.01	Probably Damaging	0.997
Exon_7_51	I222V	Neutral	0.022	9	non-deleterious	0.48	Tolerated	0.33	Benign	0.18
rs11045852	I245V	Neutral	0.0267	9	non-deleterious	0.23	Tolerated	0.16	Benign	0
rs11045853	R253Q	Pathological	0.5224	0	deleterious	-1.31	Tolerated	0.17	Probably Damaging	1
Exon_10_289	F400V	Neutral	0.489	0	deleterious	-1.34	Damaging	0.01	Possibly Damaging	0.757
rs59113707	F400L	Neutral	0.3452	3	non-deleterious	0.37	Damaging	0.02	Benign	0.061
Exon_10_400	G437R	Pathological	0.7173	4	deleterious	-1.84	Damaging	0	Probably Damaging	1
rs59502379	G488A	Neutral	0.4915	0	deleterious	-1.96	Damaging	0	Probably Damaging	0.999
rs34671512	L643F	Neutral	0.2262	5	non-deleterious	0.04	Tolerated	0.28	Benign	0.004
Exon_15_250	H678Y	Pathological	0.7694	5	non-deleterious	0.59	Tolerated	0.35	Benign	0.001
Exon_15_263	S682F	Pathological	0.8892	7	NA	NA	Tolerated	0.06	Possibly Damaging	0.83

Supplementary Table 5. Results of 4 prediction algorithms for functional effect of NS SNPs. Default settings were used for each algorithm. AA sub, amino acid substitution. PMUT (6) score of pathological, SNPS3D (7) score of deleterious, SIFT (5) score of damaging, and PolyPhen2 (8) score of probably damaging or possibly damaging were all considered damaging. All other predictions were considered tolerated. PMUT scores 0-0.5 are considered neutral, 0.5 – 1 are considered pathological. The reliability index is scored from 0 – 9, with scores >5 considered reliable. SNPS3D categorized SNPs as deleterious if the score was below zero, and non-deleterious if the score was above zero. SNPs3D did not score Exon_15_263 because it did not have enough sequence information at that location. SIFT categorized SNPs as damaging if the score was less than 0.05, and tolerated if the score was above 0.05. Polyphen2 scored SNPs as benign if the score was less than 0.15, possibly damaging for scores between 0.15 and 0.84 , and probably damaging if the score was greater than 0.85.

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