Carboplatin/Taxane-induced gastrointestinal toxicity: a pharmacogenomics study on the SCOTROC1 trial

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Keywords: ovarian cancer, carboplatin/taxane, gastrointestinal toxicity

ABSTRACT

Carboplatin/taxane combination is first-line therapy for ovarian cancer. However, patients can encounter treatment delays, impaired quality of life, even death because of chemotherapy induced gastrointestinal (GI) toxicity. A candidate gene study was conducted to assess potential association of genetic variants with GI toxicity in 808 patients who received carboplatin/taxane in the Scottish Randomized Trial in Ovarian Cancer 1 (SCOTROC1). Patients were randomized into discovery and validation cohorts consisting of 404 patients each. Clinical covariates and genetic variants associated with grade III/IV GI toxicity in discovery cohort were evaluated in replication cohort. Chemotherapy-induced GI toxicity was significantly associated with 7 SNPs in the ATP7B, GSR, VEGFA and SCN10A genes. Patients with risk genotypes were at 1.53 to 18.01 higher odds to develop carboplatin/taxane-induced GI toxicity ($p<0.01$). Variants in the VEGF gene were marginally associated with survival time. Our data provides potential targets for modulation/inhibition of GI toxicity in ovarian cancer patients.

INTRODUCTION

In United States, 21,980 new cases and 14,270 deaths of ovarian cancer were reported in 2014 according to the most recent survey by the American Cancer Society.[1] It ranks fifth as the cause of cancer death in women and over 2 billion dollars are spent every year in the U.S. on its treatment.[2] In combination with surgical cytoreduction, platinum (cisplatin or carboplatin) based chemotherapy in combination with a taxane agent (paclitaxel or docetaxel) is a standard treatment for ovarian cancer.[3, 4] Despite the therapeutic impact of platinum in conjunction with taxane agents in the management of ovarian cancer, 20-30% of patients will face grade III/IV peripheral neuropathy, 30-40% grade IV neutropenia and 20% grade III/IV gastro-intestinal (GI) toxicity.[5] Carboplatin/taxane-induced mucositis, diarrhea and vomiting represent a major GI toxicity that patients encountered in the SCOTROC1 trial, which recruited 1077 ovarian cancer patients to treatment with either docetaxel–carboplatin or paclitaxel–carboplatin.[6] Acute GI toxicity represents a substantial negative impact on patients' quality of life.[7] However, there are no genetic markers that have been shown to be associated with a higher risk of gastrointestinal toxicity after carboplatin/taxane therapy.

In this study, we investigated 1261 selected polymorphisms with described functional effects in 60 genes to identify any genetic variants associated with carboplatin/taxane-induced GI toxicities in ovarian cancer patients. The inclusion criteria of these genes were described previously.[8] The findings of this study provide new biologic insights and potential predictive factors for risk of GI toxicity in ovarian cancer patients receiving carboplatin/taxane-based chemotherapy.

METHODS

Patients. A randomized phase III study, SCOTROC 1, recruited 1077 ovarian cancer patients to treatment with docetaxel–carboplatin (n=539) or with paclitaxel–carboplatin (n=538).[6] Of the 1077 patient samples, 880 samples had germline DNA of sufficient quality for gene chip analysis.[8] The GI-toxicity including mucositis, vomiting, and diarrhea was documented using the National Cancer Institute Common Toxicity Criteria (NCI–CTC, version 2.0). Written informed consent was collected from all patients. Details of SCOTROC1 trial, patients' demographic characteristics and clinical assessments were described previously.[6] Clincal characteristics are displayed in Table 1.

Genotyping. A total of 60 candidate genes (Supplemental table 1) with 1536 SNPs were genotyped with an Illumina GoldenGate custom SNP array (Illumina, San Diego, CA) (Supplemental table 2a) and an additional 33 SNPs not suitable for the Illumina assay were genotyped using pyrosequencing (Biotage, Uppsala, Sweden) (Supplemental table 2b). Specific genotyping methods were described previously.[8]

Quality Control. To ensure high genotyping quality, only SNPs with greater than 90% efficiency for all patients were included in the analysis. Of the 1569 SNPs genotyped, 1303 SNPs passed standards of genotyping efficiency. Of the 1303 SNPs, we evaluated potential deviations from Hardy-Weinberg proportions[9] using a Chi-square test of association with a Bonferroni multiple testing correction for the significance cutoff. A total of 42 SNPs showed significant deviations (after multiple testing correction) and were removed from the subsequent analysis (for a total of 1261 SNPs evaluated). Principle Components Analysis (PCA) was performed on the remaining SNPs to evaluate potential population substructure. As expected given the self-reported ethnicity in the current cohort,

no substructure was observed (data strongly grouped into a single cluster, and eigenvalues from the first three components were not significantly related to toxicity, data not shown). Additionally, only patients with an observed grade of GI toxicity and greater than 90% complete observations for all SNPs were included in the association analysis. 880 patient samples were initially available, and 808 passed completeness standard filters. The patients were randomly assigned into test/discovery and replication/validation cohorts, stratified by case/control status to achieve equal numbers of cases in both sets: 71 cases (grade III/IV GI toxicity) and 333 controls (grade I/II GI toxicity) were included in the testing/discovery set, and 72 cases and 332 controls in the validation/replication set (Figure 1).

Data Analysis. The aim of this study was to discover variants associated with chemotherapy induced GI toxicity rather than building a predictive model, with an emphasis on whether genetic information had influence after accounting for clinical variables. Clinical covariates and genetic variants significantly associated with grade III/IV GI toxicity in the first discovery cohort were evaluated in the second replication cohort. Important clinical covariates significantly associated with the response were selected with step-wise logistic regression to minimize AIC (Akaike's Information Criteria).[10]; selected covariates included pre-treatment ECOG performance status, CA125 response, treatment arm, survival status, and first cycle at which neuropathy was experienced. Single-SNP analyses including important clinical covariates were performed using logistic regression in order to test for association of each SNP with toxicity; no genetic model of inheritance was assumed, and a genotypic model was used that included dummy variables for the SNP genotypes. SNPs with nominal p-values less than 0.05 were evaluated in the validation set. This two-stage analysis identifies SNPs that replicate in independent data, which reduces possible false positive associations. Across both independent replication sets, we calculate a joint

p-value and ascribe statistical significance using permutation testing (repeating the entire variable selection and two-stage approach). A corrected p-value was obtained from this permutation test that can be compared to the usual 5% significance level to account for multiple testing and our two-stage design.

To further reduce potential false positive findings, only the SNPs that met these strict criteria and also were consistent in direction of the risk effect for each genotype (positive vs. negative estimated odds ratio) were considered true replications. Additionally, to further examine the cumulative effect of genetic risk variants, we constructed a genetic risk score equal to the number of independent risk genotypes possessed by each individual, based on the four independent genetic signals (risk genotypes at SNPs in high LD were counted only once). Therefore the genetic risk score could take on values of 0, 1, 2, 3, or 4; because only one individual possessed 4 risk genotypes, the genetic risk score was modeled as an ordinal variable with categories 0, 1, 2, and 3+. This score was examined as an exploratory data analysis, and does not represent a predictive model; the predictive ability of this score should be evaluated in an independent cohort.

We also investigated whether the SNPs significantly associated with GI toxicity were also associated with either overall survival or progression free survival time after controlling for important clinical covariates (ECOG performance status, CA125 response, FIGO stage, histology, presence of neuropathy, bulk of residual disease, and clinical response) using a Cox Proportional Hazards model. All data analysis was performed in the freely-available R-software (http://www.r-project.org/).[11]

RESULTS

SNPs associated with grade III/IV GI toxicity

The regression modeling of the clinical data identified the following variables as covariates for further analysis of the risk of developing grade III/IV GI toxicity: treatment arm, first cycle of grade 2 neuropathy, CA125 response, overall survival, and ECOG status. From the 1261 SNPs that passed quality control standards, 81 SNPs were significant in the test set at the $p<0.05$ level. Of those significant in the test set, 11 were also significant in the validation set. Seven of these SNPs passed further assessment for direction of effect and a genotypic model was selected as the most likely genetic model for all SNPs (Figure 1). These seven SNPs reside in or near four genes: *ATP7B*, *GSR*, *VEGFA*, and *SCN10A* (Table 2). The odds of developing platinum/taxane-induced GI toxicity in patients with risk genotypes ranged from 1.53 to 18.01 times for each risk SNP (corrected $P<0.05$; Table 2). For each SNP, genotype counts by GI toxicity status are displayed for each cohort (Table 3). The independence of each significant SNP from other SNP signals was assessed by evaluating linkage disequilibrium (LD) between the markers (quantified as R^2 values) (Shown in Table 4). Rs1061472 and rs1801249 are both in ATP7B and are in strong LD (R^2=91.78%) and rs6900017, rs879825 and rs9369421 are all in VEGFA and are in strong LD (Table 4); therefore these five SNPs represent only two independent genetic signals.

Genetic Risk Score Analysis

After calculating a risk genotype composite score for each individual (equal to the number of independent risk genotypes that individual carries), a strong association between the number of risk genotypes and GI toxicity was observed (Figure 2A). The number of risk genotypes was associated with a multiplicative increase in the odds of developing GI toxicity, with the odds of developing GI

toxicity estimated to increase by an average of 1.89 for every subsequent risk genotype (p=1.62E-7), although this is only marginally significant after permutation correction (p=0.056). Patients with a composite score of 2 had an estimated odds ratio for GI toxicity of 3.56 (2.21-5.72) compared to individuals with a composite score of 0. The number and percentage of patients in each genetic risk score category by GI toxicity/no toxicity status are presented in Table 5, along with the model odds ratios.

Survival time analysis

Patients with a high risk genotype score (2-3+ risk genotypes) had the same progression free survival (p=0.98) and overall survival (p=0.90) as patients with the lower risk composite score (0-1 risk genotypes) (Figure 2B and 2C, respectively). Additionally, Cox proportional hazards analysis for both survival time and progression-free survival for each individual genotype indicate no association with progression-free or overall survival. The only SNP in association with patient's survival time is *VEGFA* rs9369421, where genotype GG is associated with high risk of GI toxicity (Figure 3). However, the G allele is associated with increased survival; the hazard, or risk of death, for patients with genotype AA (n=685) is 1.58 times higher than patients with either AG or GG genotype (n=120) (p=0.012).

DISCUSSION

In this study, seven SNPs from four genes (*ATP7B, GSR, VEGFA,* and *SCN10A*) were found to be associated with platinum/taxane-induced grade III/IV GI toxicity in ovarian cancer patients. The odds for a patient to develop severe GI toxicity are 18 times higher in *VEGFA* rs879825 GG carriers than A allele carriers. To date, the most promising association between gene variants

and platinum/taxane-induced grade III/IV GI toxicity in ovarian cancer patients was reported in 118 Korean patients that revealed a strong risk with carriage of the *ABCB1* 2677 T or A allele (adjusted odds ratio, 9.74; 95% CI, 1.59–15.85).[12] However, no significant association was found with this variant in our previous small-scale study[13] and was not validated in this study either. Inconsistent results of *ABCB1* 2677G>T/A pharmacogenetics were seen in breast cancer, non-small cell lung cancer and prostate cancer patients receiving platinum/taxane regarding patients' survival time as well.[14-16] *ABCB1* encodes a cross membrane protein named P-glycoprotein (P-gp) that effluxes a wide range of structurally diverse substrates including xenobiotics and endogenous compounds.[17] Substrates can interact with chemotherapy agents which may mask the impact of *ABCB1* variants on the pharmacokinetics of drugs,[18] especially in cancer patients that multiple drugs are administrated concomitantly. This could be a cause of inconsistent findings of *ABCB1* pharmacogenetics in different cancer patients.

Deeken and his colleagues assessed 1256 SNPs in 170 drug metabolism and disposition genes in 74 prostate cancer patients who received either docetaxel and thalidomide, or docetaxel alone.[19] Twenty three genes were common between DMET 1.0 and the 123 genes assessed in our study (Supplemental table 3). *ATP7A* and *CYP2D6* genes were correlated with docetaxel related toxicity in Deeken's study ($p<0.01$). However, this result was not replicated in either our previous small-scale study or the current, expanded study. *ATP7B* gene was identified as a significant marker for carboplatin/taxane-related GI toxicities ($p<0.01$). This effect was not seen in Deeken's study.[19] Different combinations of chemotherapy may mask the genetic effect on drug response and toxicity. Moreover, the same gene or variants may also play a different role in different cancers while the same drug treatment is applied.

The findings of this study provides novel genes that may be correlated with platinum/taxane based therapy, although it remains unclear given that few reports have disclosed an important role of any of the above genes in the metabolism or disposition of either agent. Moreover, the gene variations that are known to be involved in detoxification, disposition and response to carboplatin/taxane, including the 7 genes overlapped in our previous study, were not associated with either toxicity or survival time. Although these genes may play a role in platinum/taxane metabolism pathways directly or indirectly, we can only speculate the mechanism of gene-drug interactions. For instance, the function of rs9825762of *SCN10A* gene was unclear but the rs3594 of glutathione reductase, *GSR,* gene was associated with oxidative stress status of children infected by malaria, which suggested a potential function of this variant. [20] The *ATP7B* (ATPase, Cu++ transporting, beta polypeptide) gene encodes a protein called copper-transporting ATPase 2. This protein is found primarily in the liver and plays a role in transporting copper from the liver to other organs. It is also important for the elimination of excess copper from the body through bile. [21] *ATP7B* gene mutations may cause copper accumulation in tissues. As a result, toxic level of copper could impair the lining of the gastrointestinal tract and trigger nausea and vomiting while chemotherapy was applied. Molecular genetic testing for *ATP7B* mutations is available in clinic, which is applied for diagnosis/prediction of a disease caused by *ATP7B* mutations, Wilson's disease.[22] A study in pre-school kids found that rs6900017 of *VEGFA* gene was associated with their lung function at school age but not at birth which suggested a potential function of *VEGFA* variants in lung development. [23] Although no studies of the function of rs879825 and rs9369421 so far, they are in high linkage disequilibrium with rs6900017 as we found in our study. *VEGFA* also has been identified as the primary tumor angiogenesis factor and targeted by several newly developed agents for patients with metastatic carcinoma. However, these novel *VEGF* targeting agents including bevacizumab,

sorafenib, sunitinib, brivanib and cilengitide have had only modest effect on human cancers.[24] In combination with standard chemotherapy, carboplatin–paclitaxel, and bevacizumab moderately improved progression free survival time in ovarian cancer patients according to two randomized phase III studies, GOG218 and ICON7.[25, 26] Additionally, *VEGFA* gene variants were found to be related to the therapeutic outcome of oxaliplatin based chemotherapy in metastatic colorectal cancer patients.[27] However, these variants were not associated with the GI toxicity of carboplatin based chemotherapy in ovarian cancer patients. In this study, three variants of *VEGFA* gene were found highly correlated with chemotherapy induced GI toxicity which indicated a critical role of *VEGFA* in ovarian cancer patients who received a standard chemotherapy.

In summary, this study is the first step in defining a pharmacogenetics model for platinum/taxane-induced GI toxicity in ovarian cancer patients. Seven SNPs from four genes increased the risk of developing platinum/taxane-induced grade 3-4 GI toxicity, whereas *VEGFA* gene was associated with patients' survival time. Our data suggests new genetic markers associated with platinum/taxane GI toxicity in ovarian cancer patients and the risk may vary between populations because the minor allele frequency of these risk variants are quite different in Caucasian, Asian and African populations. These genetic markers provide potential targets to modulate/inhibit GI toxicity in ovarian cancer patients. Further studies are required to validate these risk factors from *in vitro* models to independent clinic trials in multiple ethnic groups to clarify the potential role they might play in predicting chemotherapy induced GI toxicity and to evaluate the value of these risk variants as therapeutic markers.

CONFLICT OF INTEREST

The authors declared no conflict of interest. None of the funding bodies had a role in the preparation of the manuscript.

ACKNOWLEDGEMENT

This work was partially supported by T32GM081057 from the National Institute of General Medical Sciences and the National Institute of Health. Dr. McLeod is a 1000 Talent Scholar of the People's Republic of China.

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Table 1: Clinical characteristics by cohort.

		Replication Set (N=404)		Discovery Set (N=404)		Total (N=808)	
Variable	Level	N	%	N	%	N	%
FIGO stage	IC	27	6.7%	25	6.2%	52	6.4%
	II	57	14.1%	41	10.1%	98	12.1%
	III	257	63.6%	281	69.6%	538	66.6%
	IV	63	15.6%	57	14.1%	120	14.9%
Tumor grade	Well differentiated	27	6.7%	30	7.4%	57	7.1%
	Moderate	103	25.5%	108	26.7%	211	26.1%
	Poor/undifferentiated	222	55.0%	221	54.7%	443	54.8%
	Unknown	52	12.9%	45	11.1%	97	12.0%
ECOG status	0	142	35.1%	126	31.2%	268	33.2%
	1	211	52.2%	215	53.2%	426	52.7%
	2	51	12.6%	63	15.6%	114	14.1%
CA125 response	No response	59	14.6%	71	17.6%	130	16.1%
	Response	213	52.7%	211	52.2%	424	52.5%
	Not evaluated	132	32.7%	122	30.2%	254	31.4%
Treatment	Paclitaxel/Carboplatin	196	48.5%	204	50.5%	400	49.5%
	Docetaxel/Carboplatin	208	51.5%	200	49.5%	408	50.5%
Worst grade of GI toxicity	0	19	4.7%	18	4.5%	37	4.6%
	1	105	26.0%	107	26.5%	212	26.2%
	2	208	51.5%	208	51.5%	416	51.5%
	3	66	16.3%	64	15.8%	130	16.1%
	4	6	1.5%	7	1.7%	13	1.6%
Worst grade of neuropathy	0	143	35.4%	142	35.1%	285	35.3%
	1	169	41.8%	172	42.6%	341	42.2%
	2	64	15.8%	71	17.6%	135	16.7%
	3	26	6.4%	18	4.5%	44	5.4%
	4	2	0.5%	1	0.2%	3	0.4%
First cycle of grade 2 neuropathy	1	16	4.0%	9	2.2%	25	3.1%
	2	21	5.2%	16	4.0%	37	4.6%
	3	37	9.2%	21	5.2%	58	7.2%

	4	27	6.7%	29	7.2%	56	6.9%
	5	21	5.2%	22	5.4%	43	5.3%
	Censored	282	69.8%	307	76.0%	589	72.9%
Survival status	Alive	252	62.4%	262	64.9%	514	63.6%
	Dead	152	37.6%	142	35.1%	294	36.4%
Median survival time (months)		20.05		20.30		20.24	

Table 2. SNPs significantly associated with significant gastro-intestinal toxicity in the discovery and replication cohorts. Analyses are adjusted for ECOG performance status, CA125 response, treatment arm, survival status, and first cycle at which neuropathy was experienced.

SNP	Gene	Polymorphism	P-value Discovery Set (N=404)	P-value Replication Set (N=404)	Joint P-value	Corrected P-Value (compare to 0.05)	Odds Ratio (N=808)	95% CI (N=808)	Risk Genotype
rs1061472	ATP7B	A->G	0.004	0.031	1.22E-04	0.00111	1.70	(1.02, 2.84)	AA
rs1801249	ATP7B	A->G	0.003	0.032	8.64E-05	0.00081	1.53	(0.93, 2.51)	AA
rs3594	GSR	A->C	0.035	0.030	1.05E-03	0.00848	2.83	(1.45, 5.52)	CC
rs6900017	VEGFA	A->G	0.037	0.040	1.47E-03	0.01162	9.97	(1.85, 53.72)	AA
rs879825	VEGFA	A->G	0.036	0.014	4.97E-04	0.00417	18.01	(2.78, 116.56)	GG
rs9369421	VEGFA	A->G	0.040	0.037	1.47E-03	0.01162	9.91	(1.83, 53.52)	GG
rs9825762	SCN10A	A->G	0.018	0.022	3.90E-04	0.00335	1.90	(0.76, 4.77)	AA

Table 3. Genotype counts by GI toxicity status for each cohort.

		Discovery Set		Validation Set		Total	
SNP	Genotype	Grade I/II	Grade III/IV	Grade I/II	Grade III/IV	Grade I/II	Grade III/IV
rs1061472	AA	54	19	58	21	112	40
rs1061472	AG	177	31	166	24	343	55
rs1061472	GG	93	19	97	24	190	43
rs1801249	AA	52	18	57	20	109	38
rs1801249	AG	172	28	167	23	339	51
rs1801249	GG	106	24	105	28	211	52
rs3594	AA	58	7	56	5	114	12
rs3594	AC	152	27	138	32	290	59
rs3594	CC	114	34	132	35	246	69
rs6900017	AA	2	2	1	1	3	3
rs6900017	AG	41	7	48	13	89	20
rs6900017	GG	286	62	283	58	569	120
rs879825	AA	298	64	293	61	591	125
rs879825	AG	30	4	37	9	67	13
rs879825	GG	1	2	1	1	2	3
rs9369421	AA	287	62	277	59	564	121
rs9369421	AG	44	6	52	12	96	18
rs9369421	GG	2	2	1	1	3	3
rs9825762	AA	189	53	196	53	385	106
rs9825762	AG	124	16	117	15	241	31
rs9825762	GG	20	2	17	4	37	6

Table 4. LD correlation matrix (R^2) for the seven SNPs associated with significant gastro-intestinal toxicity

		rs1061472	**rs1801249**	**rs3594**	**rs6900017**	**rs879825**	**rs9369421**	**rs9825762**
Chr.13	**rs1061472**	1.0000	0.9178	0.0003	0.0045	0.0058	0.0046	0.0003
Chr.13	**rs1801249**	0.9178	1.0000	0.0000	0.0051	0.0060	0.0052	0.0002
Chr.8	**rs3594**	0.0003	0.0000	1.0000	0.0000	0.0001	0.0000	0.0003
Chr.6	**rs6900017**	0.0045	0.0051	0.0000	1.0000	0.7420	0.9706	0.0001
Chr.6	**rs879825**	0.0058	0.0060	0.0001	0.7420	1.0000	0.7724	0.0001
Chr.6	**rs9369421**	0.0046	0.0052	0.0000	0.9706	0.7724	1.0000	0.0000
Chr.3	**rs9825762**	0.0003	0.0002	0.0003	0.0001	0.0001	0.0000	1.0000

Table 5: Frequencies (percentages) of cases and controls in each genetic risk category.

Risk Score	0	1	2	3+	Total
Cases	15 (10%)	54 (38%)	58 (41%)	16 (11%)	143
Controls	148 (22%)	309 (46%)	184 (28%)	24 (4%)	665
Total	163 (20%)	363 (45%)	242 (30%)	40 (5%)	808
Model Odds Ratio	1.0	1.89	3.56	6.71	

Figure 1. Workflow of the data analysis, with processing of the samples shown in gray, and the workflow related to the SNPs shown in black.

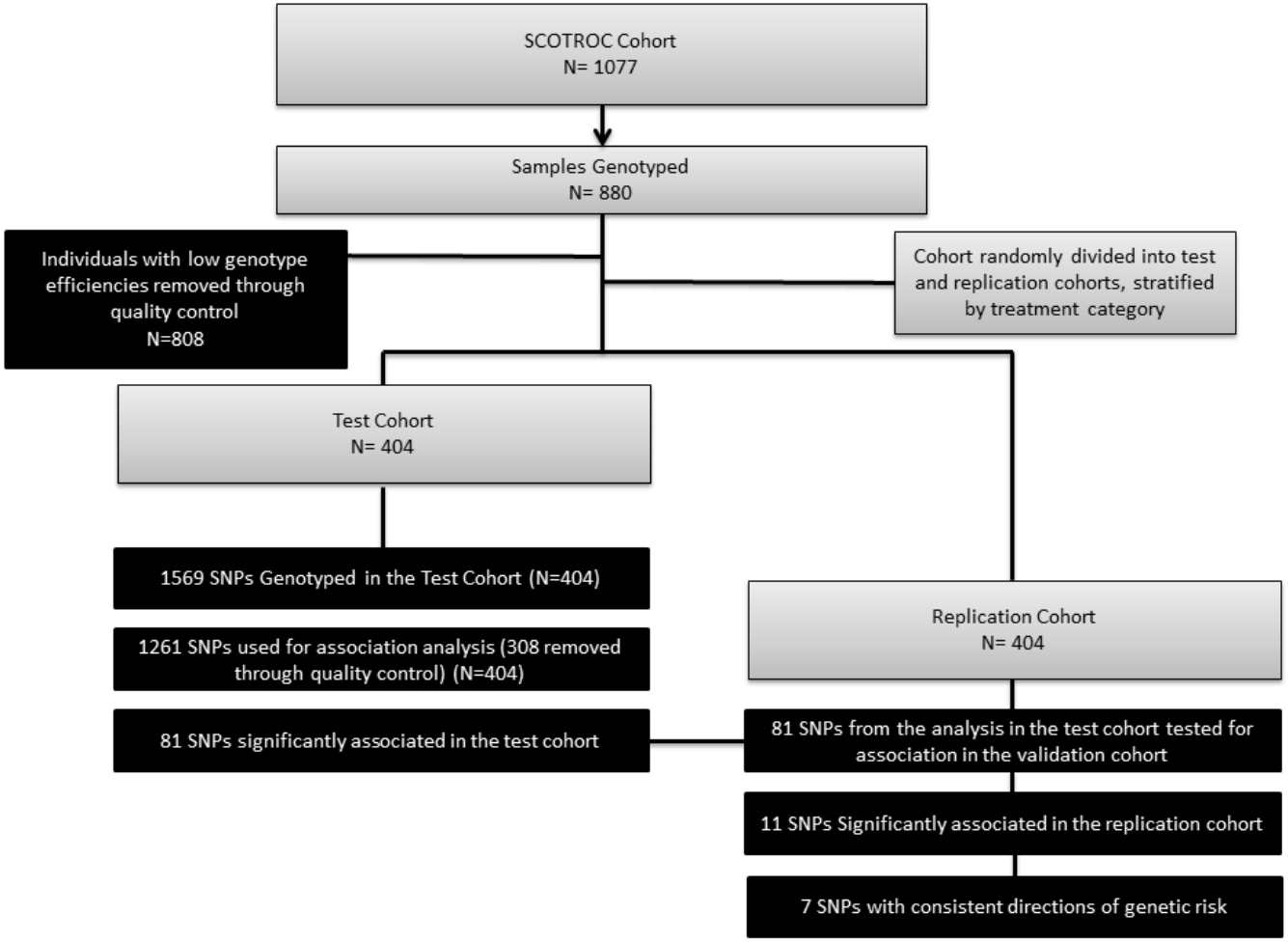


Figure2. (A) Proportion of ovarian cancer cases experiencing GI toxicity by number of risk genotypes. (B) Progression Free Survival Time by number of risk genotypes. (C) Overall Survival Time by number of risk genotypes.

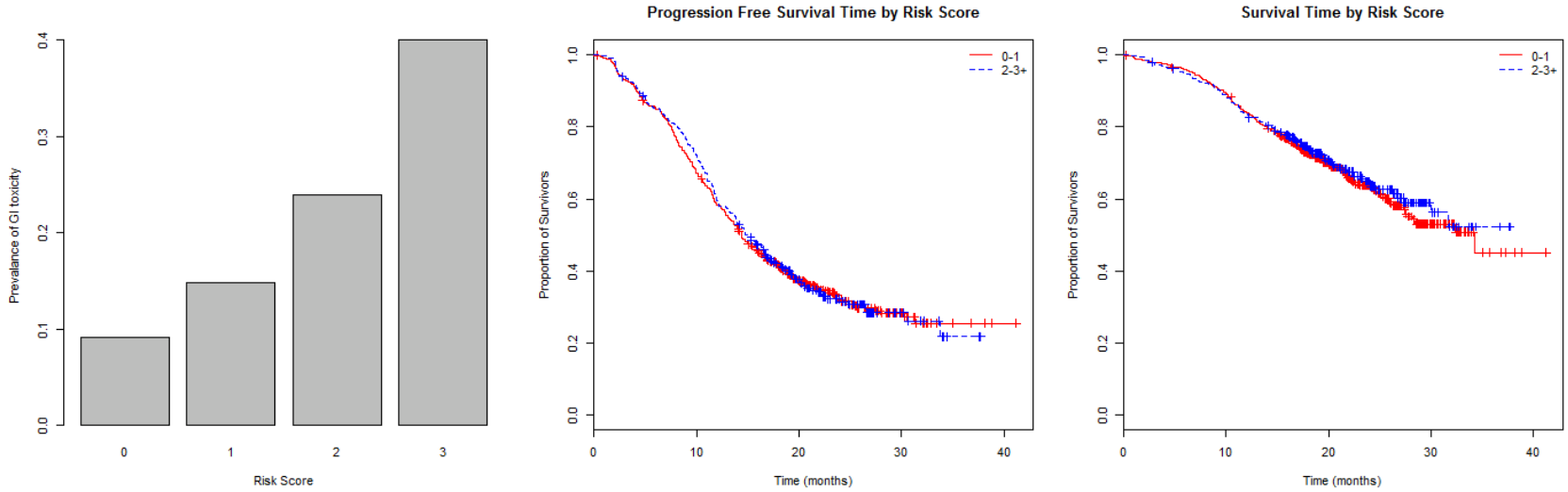
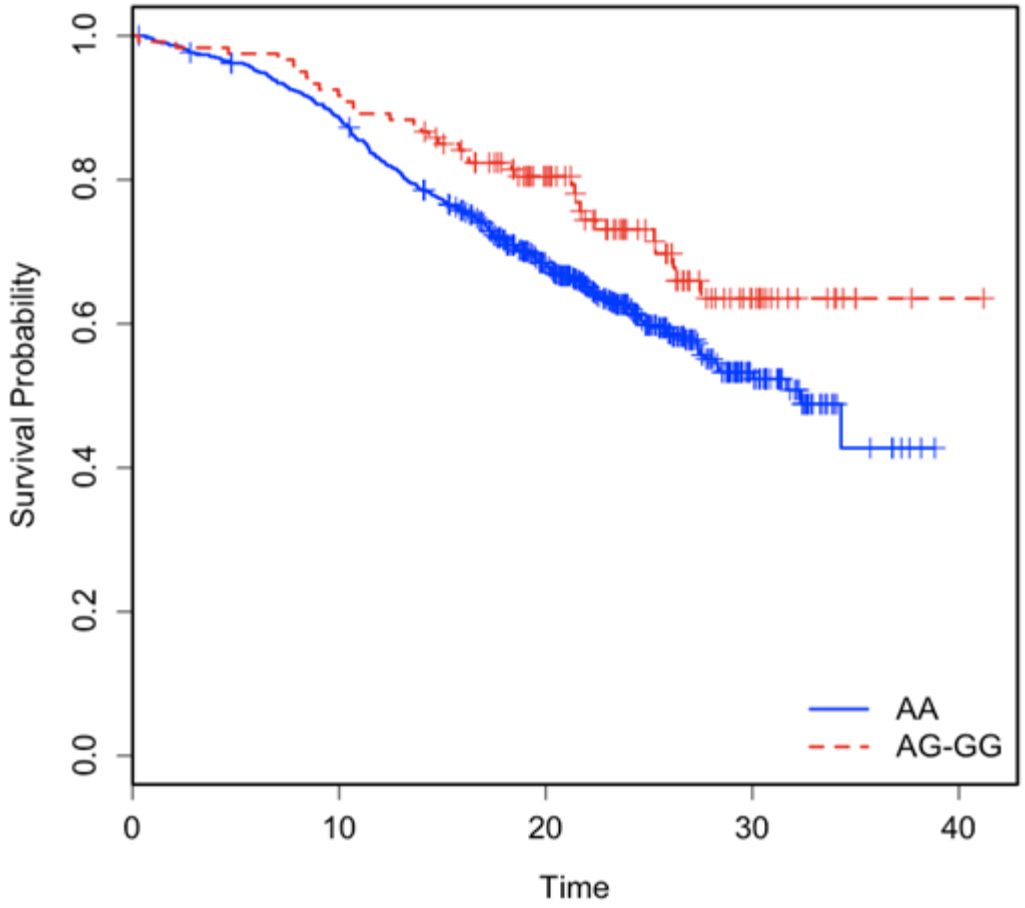


Figure 3. Survival time by rs9369421 genotype. (Kaplan-Meier survival curve, log rank analysis)



Supplementary table 1: 123 genes genotyped in this study

Detoxification	Apoptosis or cell signal	DNA repair or regulation	Disposition	Neuropathies
AKR1B1	AR	ERCC1	ABCA4	ANK3
ALDH1A1	BAX	ERCC2	ABCB1	DST
CYP1B1	BCL2	ERCC5	ABCC1	INA
CYP2C19	BCL2L1	ERCC6	ABCC2	MAP4
CYP2C8	BIRC2	GARS	ABCC5	MAPK1
CYP2C9	BIRC4	MGMT	ABCG2	MAPT
CYP2D6	CAMK2B	MLH1	ATP7A	MFN2
GPX1	CCND1	MTHFR	ATP7B	MPZ
GPX2	CD40LG	PPARA	CACNA2D1	MT1A
GPX4	CD8A	PPARG	CFTR	MT1F
GSR	DCT	RB1	GJB1	NEFH
GSS	DNM2	RBM17	SCN10A	NEFL
GSTA1	EGR2	RRM2	SCN1A	NEFM
GSTM1	EPHA2	TLR4	SCN2A	NFKB1
GSTP1	EPO	VDR	SCN4A	NGFB
PON1	ESR1	XRCC1	SCN7A	NGFR
PON2	GDAP1		SCN8A	NTRK1
PTGS2	HMGB1		SCN9A	OPRK1
SOD1	HSPA5		SCNN1A	OPRM1
TPMT	IL6		SLC11A1	PMP22
UGT1A1	OPRM1		SLC15A2	PNPLA6
XDH	PPP4R1		SLC19A1	PRX
	PPP4R2		SLC22A1	SOX10
	PRKCB1		SLC22A16	SPTAN1
	PRR13		SLC22A2	TRPV1
	RAB7		SLC31A1	TRPV5
	RAMP1		SLC40A1	TRPV6
	TP53		TAP1	
	TUBB3			
	VEGF			
	YARS			

Supplemental Table 2: All SNPs genotyped including a. 1536 SNPs on the Illumina GoldenGate custom SNP array and b. 33 SNPs genotyped by pyrosequencing.

a. SNPs on Illumina GoldenGate custom SNP array

rs3213245	rs4417063	rs885479	rs304729	rs6467897	rs2302236
rs11168286	rs11829863	rs12465675	rs3810366	rs11568820	rs10994148
rs5912559	rs13025009	rs4987786	rs6675934	rs2296147	rs4784701
rs6928818	rs12779378	rs7975319	rs3900008	rs6058391	rs8176036
rs4760650	rs6795970	rs11688164	rs7191944	rs10267099	rs1860545
rs2893389	rs6763876	rs12320663	rs877611	rs304731	rs4558416
rs2228478	rs3746166	rs3213829	rs74915	rs3745202	rs4728502
rs10445337	rs1483000	rs9323457	rs3212363	rs2316776	rs2229107
rs2069829	rs10994162	rs7132324	rs3757985	rs10404348	rs2214102
rs4987849	rs1016860	rs9524489	rs4941716	rs4149578	rs1157511
rs10175267	rs10821662	rs10858075	rs4623700	rs7965281	rs2393602
rs10808299	rs10821683	rs739837	rs10509117	rs7139166	rs11574077
rs3213246	rs11588779	rs4395073	rs2239622	rs10509119	rs2074447
rs3741707	rs11700037	rs2074452	rs8081989	rs2299185	rs4253002
rs4732449	rs11988344	rs2887140	rs10954673	rs1529668	rs17803819
rs3212368	rs13041792	rs7958704	rs1467966	rs3754963	rs4743
rs2893388	rs1381547	rs11971283	rs17564983	rs7100448	rs4150386
rs11720058	rs1381548	rs1805005	rs10486948	rs762562	rs2077360
rs2316777	rs1564483	rs12632942	rs2979687	rs1827208	rs10761450
rs2010963	rs1610095	rs11466103	rs2976427	rs4150383	rs161383
rs4252418	rs1799787	rs13254844	rs2166772	rs3212346	rs17651549
rs1799788	rs2121371	rs744389	rs17634022	rs9524500	rs4148150
rs12664104	rs2126152	rs2074445	rs12423042	rs2005132	rs7232082
rs11988346	rs2156192	rs7965397	rs4858887	rs4252499	rs929351
rs3741708	rs2228527	rs2229920	rs4839435	rs2270836	rs161365
rs2258689	rs2295283	rs10416031	rs10776797	rs11900439	rs38559
rs4252417	rs3114018	rs7136534	rs545331	rs4987859	rs10994171
rs13016251	rs3746165	rs11168290	rs10776798	rs7630989	rs6329
rs3109823	rs4253211	rs12354956	rs2471736	rs928169	rs2970504

rs11720061	rs490317	rs4146585	rs11880613	rs4135301	rs38557
rs2316780	rs4987752	rs460716	rs3744683	rs11672096	rs9668931
rs12048019	rs562859	rs3801739	rs2043332	rs12720464	rs924469
rs675026	rs6678788	rs7921	rs3213244	rs7627568	rs3785930
rs5912558	rs699947	rs11659758	rs9692165	rs10849446	rs4076018
rs7965274	rs873458	rs1948431	rs9915741	rs1990071	rs2671642
rs10821677	rs1800795	rs3212345	rs7374804	rs3759324	rs2239179
rs10821659	rs11614164	rs1540339	rs11466086	rs12944357	rs4252412
rs7965266	rs2298881	rs4150324	rs4076737	rs2336219	rs4253003
rs2893823	rs6087656	rs17563965	rs1012018	rs161375	rs8000418
rs6809264	rs7989652	rs10158276	rs12760036	rs4474385	rs17650901
rs10175360	rs4236480	rs4479290	rs268674	rs2025097	rs8079120
rs2393576	rs12763974	rs11658700	rs4790520	rs11672431	rs10954670
rs11466087	rs17791817	rs4334089	rs8177146	rs11671653	rs238416
rs2278444	rs2435204	rs4858881	rs268662	rs939336	rs11568305
rs12779035	rs1126112	rs11574026	rs16949859	rs9301959	rs4761986
rs4987847	rs10776800	rs12402406	rs9967700	rs2070720	rs10994160
rs11466088	rs7224541	rs10761452	rs1998876	rs3766744	rs2299169
rs2336384	rs231017	rs9895612	rs230938	rs4252535	rs17773227
rs6791171	rs9922409	rs2013775	rs4987665	rs6499850	rs7068231
rs7540561	rs12150576	rs38555	rs2393581	rs9524494	rs1052587
rs13015709	rs4987855	rs12058002	rs3785931	rs7649970	rs2237526
rs16914571	rs17184707	rs12232396	rs3213238	rs17033692	rs10876200
rs4252357	rs9828268	rs599548	rs11712354	rs3805134	rs12302725
rs4657015	rs13306558	rs6747673	rs4676593	rs1800100	rs17156246
rs741071	rs3097112	rs7430439	rs2914879	rs10278483	rs2316782
rs9563078	rs3847987	rs2075572	rs3025000	rs161381	rs2856813
rs3890734	rs4870266	rs9827941	rs4987682	rs4773797	rs7588659
rs4902343	rs16940799	rs6819279	rs2368020	rs6580842	rs2236055
rs11816586	rs4941188	rs17830392	rs4253060	rs11971167	rs2853564
rs12150460	rs7299460	rs4760658	rs879207	rs4148725	rs4150393
rs3769943	rs10821666	rs35588	rs9900655	rs4712138	rs9827945
rs4252372	rs10994198	rs8060203	rs12996930	rs10821660	rs12330440

rs4253012	rs4994970	rs11466075	rs17650771	rs10994182	rs12957119
rs11130152	rs2108373	rs1381109	rs6599250	rs3760239	rs10994174
rs2094258	rs719452	rs2975180	rs6432894	rs4073129	rs3810031
rs10509121	rs11574132	rs2239186	rs8080613	rs4987866	rs3791251
rs16851332	rs17802184	rs6580643	rs10171225	rs11574124	rs4948254
rs7651106	rs7900212	rs7305135	rs12581731	rs2141384	rs510587
rs3745674	rs13447445	rs4252416	rs11924846	rs4987844	rs6599237
rs767059	rs612020	rs17183814	rs1406274	rs6724623	rs3213266
rs2281885	rs12457831	rs3786719	rs7428538	rs10237261	rs4252444
rs4792893	rs3801705	rs17070861	rs2393577	rs179521	rs12357325
rs10221276	rs1132776	rs10994189	rs9561561	rs610231	rs13006006
rs540825	rs4148682	rs7068951	rs11168287	rs3025030	rs4149570
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rs4803817	rs5742912	rs10279911	rs10417071	rs557222	rs600120
rs6591252	rs8077624	rs3798683	rs3744685	rs11466072	rs3024994
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rs9970214	rs11721285	rs11466106	rs13239493	rs11466162	rs1035050
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rs3213282	rs1992294	rs8065080	rs11101137	rs9584233	rs4253200
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rs11574120	rs3759681	rs4150992	rs7372391	rs4792894	rs11102929
rs3782723	rs3782478	rs915927	rs9825762	rs10857502	rs12203621
rs735482	rs1799782	rs1078534	rs4516035	rs873601	rs3785380
rs2239181	rs303803	rs1886087	rs7100478	rs9844644	rs1001362
rs12205732	rs4804523	rs222740	rs7966983	rs10876202	rs11553502
rs7580482	rs17749561	rs3819545	rs3097109	rs16852186	rs2316781
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rs7217945	rs17650579	rs9479756	rs9478506	rs1318345	rs2583118
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rs8078212	rs10821668	rs1047769	rs1163081	rs139879	rs1799971
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rs7520839	rs10233444	rs10821704	rs12606418	rs1505	rs1919179
rs2291957	rs11170558	rs10821708	rs12621853	rs1523519	rs1922076
rs230911	rs1002149	rs10821709	rs12707484	rs1528488	rs1924608
rs9815891	rs1002442	rs10821723	rs12778431	rs1531695	rs1924609
rs2393595	rs1005230	rs10821747	rs12844215	rs1531697	rs1927907
rs3213403	rs1005793	rs10829611	rs12844432	rs1540923	rs1934956
rs6060129	rs1007722	rs10829619	rs12996382	rs1540979	rs1944419
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rs8190893	rs10133054	rs10954664	rs1325611	rs1557044	rs1954134
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rs38556	rs1020853	rs10994199	rs1340655	rs161382	rs1972445
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rs2018836	rs2256327	rs25487	rs316032	rs3810831	rs4426541
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rs2031002	rs2272381	rs2551715	rs3212948	rs3819437	rs4453709
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rs2031527	rs2273684	rs258651	rs3448	rs3825527	rs4480996
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rs2046136	rs2277502	rs2622604	rs348472	rs3924001	rs4529705
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rs2068797	rs2281620	rs2712402	rs37067	rs4129395	rs4633936
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rs2188525	rs2298432	rs2854344	rs3761144	rs4252491	rs4823613
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rs2224780	rs2304014	rs2893022	rs3769931	rs4253042	rs484926
rs2226711	rs2307491	rs2893830	rs3769938	rs4253047	rs4870268
rs222747	rs231018	rs2976441	rs3769949	rs4253073	rs488133
rs2227869	rs2335410	rs2978296	rs3774937	rs4253077	rs4902345

rs2228526	rs2341629	rs2978662	rs3778148	rs4253082	rs4911165
rs2228528	rs2352262	rs2978663	rs3778156	rs4253101	rs4940573
rs2228529	rs2361634	rs3002005	rs3779449	rs4253145	rs4940574
rs2235132	rs2388546	rs3014804	rs3779647	rs4253160	rs4941183
rs2236058	rs2389098	rs3020729	rs3780014	rs4253219	rs4941185
rs2236256	rs2393585	rs3025010	rs3782970	rs4253681	rs4941189
rs2237528	rs2393596	rs3025033	rs3782972	rs4253755	rs4941195
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rs2238833	rs2393607	rs3025042	rs3788205	rs4303728	rs4948255
rs2239185	rs2393609	rs3026645	rs3791253	rs43044	rs4948385
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rs224083	rs2393612	rs303774	rs3793786	rs4310561	rs4948410
rs2241113	rs2393613	rs303802	rs3793854	rs4314511	rs4948412
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rs4986894	rs6087772	rs692995	rs7557805	rs8096471	rs997238
rs4987585	rs6088655	rs6935207	rs7561953	rs8141815	rs998584
rs4987599	rs6121038	rs6935927	rs7562525	rs8177139	rs9990
rs4987613	rs613355	rs6945352	rs7565062	rs8190996	rs17149866
rs4987661	rs614080	rs6952619	rs7570201	rs833060	rs2188528
rs4987702	rs619974	rs6965402	rs757228	rs833069	rs10232449
rs4987721	rs623956	rs6966	rs757343	rs84770	rs1978095
rs4987724	rs6328	rs6968274	rs7574618	rs854555	rs12704366
rs4987736	rs6330	rs6975647	rs757847	rs873457	rs17149850
rs4987746	rs636433	rs6977797	rs758000	rs874742	rs10246878
rs4987757	rs6432885	rs6980031	rs7582791	rs876430	rs4263684
rs4987765	rs6432888	rs699946	rs7586412	rs879825	rs7796247
rs4987768	rs6432916	rs7004754	rs7586794	rs880301	rs2622624
rs4987778	rs644261	rs7072073	rs7590387	rs899968	rs1800130
rs4987801	rs6467882	rs7075820	rs7593452	rs905238	rs1610157
rs4987808	rs6467890	rs7077937	rs7597971	rs910330	rs1800797
rs4987821	rs6472841	rs7087489	rs7600731	rs913930	rs6765101

rs4987825	rs6473797	rs7100767	rs7607896	rs917557	rs4253686
rs4987828	rs6479706	rs714307	rs763448	rs922116	rs4253701
rs4987835	rs6479711	rs720321	rs764481	rs922224	rs4253652
rs4987839	rs648007	rs722204	rs764660	rs9289182	rs5769366
rs4987843	rs6482747	rs7231531	rs766323	rs929416	rs135549
rs4987851	rs6492706	rs7232625	rs7745499	rs929737	rs4253623
rs4987852	rs6506676	rs723685	rs7774038	rs9332216	rs8090926
rs4987869	rs6525485	rs7242402	rs7778344	rs935403	rs10929303
rs4987873	rs6537539	rs726511	rs7790798	rs9357155	rs1573601
rs510769	rs6537860	rs727299	rs7794797	rs9371781	rs6060127
rs511435	rs6599251	rs728539	rs7796947	rs938487	rs6060531
rs520342	rs660756	rs731014	rs7797314	rs9400393	rs6060563
rs5277	rs6616813	rs7320009	rs7800456	rs9474321	rs6060652
rs534561	rs661825	rs7321909	rs7802397	rs947895	rs689466
rs535372	rs6658541	rs732518	rs7804449	rs9479791	rs6900017
rs544093	rs6673287	rs732774	rs7805499	rs949037	rs6900677
rs545238	rs6673867	rs7328751	rs7809256	rs949879	rs6906755
rs557311	rs668394	rs7334764	rs7818511	rs9516418	rs7530686
rs557748	rs671531	rs735883	rs782054	rs9535809	rs754512
rs558948	rs6718242	rs7364220	rs7858741	rs956572	rs754610
rs563649	rs6722462	rs7373373	rs7885634	rs9586002	rs7548209
rs569284	rs6732627	rs740649	rs7889824	rs9610470	rs7991232
rs577306	rs6734499	rs747781	rs7896287	rs9649651	rs8083946
rs5918757	rs6736291	rs749072	rs7902905	rs9649652	rs8084922
rs5958324	rs6738638	rs749174	rs7907557	rs967614	rs8088662
rs5958347	rs6741870	rs752081	rs7907761	rs968340	rs9812515
rs5980747	rs6744911	rs7521	rs7910123	rs971667	rs9829181
rs603965	rs6758728	rs7523086	rs7911934	rs9804190	rs9830721
rs6058381	rs6789471	rs752569	rs7990565	rs9807663	rs9888034

b. SNPs genotyped by pyrosequencing

rs42342	rs1800668	rs657770	rs11407	rs17139614	rs13402540

rs42049	rs904775	rs303817	rs2682560	rs545331	rs13007020
rs11615	rs9936741	rs4764585	rs7597178	rs11707517	rs6756630
rs238403	rs2976433	rs7976804	rs2233913	rs4280575	rs9646772
rs5980747	rs11135835	rs10952540	rs3810660	rs4676590	ATP7A c317
rs1997625	rs600120	rs3025000			

Supplemental Table 3. Genes in common between DMET 1.0 and the 123 genes assessed in this study

ABCB1	*ABCC1*	*ABCC2*	*ABCC5*	*ABCG2*	*ALDH1A1*	*ATP7A*	*ATP7B*	*CYP1B1*	*CYP2C19*	*CYP2C8*
CYP2C9	*CYP2D6*	*GSTA1*	*GSTP1*	*PPARG*	*SLC15A2*	*SLC19A1*	*SLC22A1*	*SLC22A2*	*TPMT*	*UGT1A1*
XDH										