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Comprehensive Evaluation of the Contribution of X Chromosome Genes to Platinum Sensitivity

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Abstract

Utilizing a genome-wide gene expression dataset generated from Affymetrix GeneChip[®] Human Exon 1.0ST array, we comprehensively surveyed the role of 322 X chromosome gene expression traits on cellular sensitivity to cisplatin and carboplatin. We identified 31 and 17 X chromosome genes whose expression levels are significantly correlated (after multiple testing correction) with sensitivity to carboplatin and cisplatin, respectively, in the combined HapMap CEU and YRI populations (false discovery rate, FDR<0.05). Of those, 14 overlap for both cisplatin and carboplatin. Employing an independent gene expression quantification method, the Illumina Sentrix Human-6 Expression BeadChip, measured on the same HapMap cell lines, we found that 4 and 2 of these genes are significantly associated with carboplatin and cisplatin sensitivity respectively in both analyses. Two genes, *CTPS2* and *DLG3*, were identified by both genome-wide gene expression analyses as correlated with cellular sensitivity to both platinating agents. The expression of *DLG3* gene was also found to correlate with cellular sensitivity to platinating agents in NCI60 cancer cell lines. In addition, we evaluated the role of X chromosome gene expression to the observed differences in sensitivity to the platinum agents between CEU and YRI derived cell lines. Of the 34 distinct genes significantly correlated with either carboplatin or cisplatin sensitivity, 14 are differentially expressed (defined as p<0.05) between CEU and YRI. Thus, sex chromosome genes play a role in cellular sensitivity to platinating agents and differences in the expression level of these genes are an important source of variation that should be included in comprehensive pharmacogenomic studies.

Keywords

platinum agents; X chromosome gene expression; population differences

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Introduction

Despite the fact that gene expression has long been recognized to contribute to drug sensitivity (1), little is known regarding the expression of sex chromosome genes for their role in drug response. Furthermore, gender differences in drug sensitivity are observed both in cell lines (2) and in patients (3). Our previous studies have revealed *in vitro* inter-individual differences in platinum drug response, prompting us to evaluate whether sex chromosome genes may perhaps play a unique role in the transcriptome in governing inter-individual drug response. Indeed, genes on the sex chromosomes have been relatively understudied in relation to drug sensitivity (4,5). In this study, we systematically evaluated the role of X chromosome genes in predicting platinum sensitivity.

Materials and Methods

In vitro cellular sensitivity to platinating agents

Fifty-seven unrelated HapMap CEU (Utah residents with ancestry from northern and western Europe), 59 unrelated YRI (Yoruba in Ibadan, Nigeria) and 90 unrelated ASN (Han Chinese in Beijing and Japanese in Tokyo) lymphoblastoid cell lines (LCLs) were purchased from Coriell Institute for Medical Research (Camden, NJ) (6) between 2001 and 2007. One advantage of the use of these cell lines is that extensive whole-genome genotype information is publicly available to the scientific community, which allows us to perform genotyping assays on randomly selected cell lines for randomly selected SNPs to authenticate the cell lines. This genotyping assay is routinely carried out in our Pharmacogenomic of Anticancer Agent Research (PAAR) cell line and genotyping core; furthermore, the cell lines have been the subject of extensive genetic studies (6). Cell line maintenance has been reported previously (2). Cells were treated with increasing concentrations of cisplatin or carboplatin for 48 and 72 h, respectively. Cell growth inhibition was assessed using the alamarBlue™ assay (BioSource International Inc., Camarillo, CA) (2). IC₅₀ (the drug concentration required to inhibit 50% of cell growth) was determined by curve fitting of percent cell survival against drug concentration.

X chromosome gene expression

Our lab previously evaluated global baseline gene expression on 87 CEU and 89 YRI LCLs using the Affymetrix GeneChip® Human Exon 1.0 ST array (Affymetrix exon array) (7). We excluded from analysis all Affymetrix exon array probes that contain more than one known polymorphism to eliminate spurious associations due to hybridization artifacts (8). The Affymetrix gene expression data have been deposited into GEO (9) (Accession No: GSE9703). Three hundred and twenty two X chromosome transcript clusters/genes interrogated on the Affymetrix array and defined as expressed in LCLs (average normalized expression intensity greater than 5.34) were included in this study. In addition, baseline genome-wide gene expression data have been generated on 210 HapMap LCLs (including the CEU, YRI and ASN samples used in this study) using Illumina Sentrix Human-6 Expression BeadChip version 1 (Illumina array) (10). We downloaded these data from the Gene Expression Omnibus (GEO) database (Series Accession Number GSE6536). The probe intensities derived from 461 X chromosome genes (represented by 562 probes) were evaluated and compared to the Affymetrix exon array findings. From this comparison, we found 190 X chromosome genes are interrogated on both platforms.

Evaluating the relationship between X chromosome gene expression and platinum sensitivity

Linear regression was used to evaluate the role of X chromosome baseline gene expression levels in predicting sensitivity to carboplatin and cisplatin across populations. A schematic

diagram of the study is illustrated in Figure 1. We utilized the Affymetrix exon array data for discovery and the Illumina array data to check robustness of the results. First, platinum IC₅₀ values for all samples were log₂ transformed to achieve approximate normality. Separate linear models were estimated within each population with transformed platinum IC₅₀ values as the dependent variable and normalized expression intensities and an indicator of gender as independent variables. Subsequently, a meta-analysis was performed combining the individual p-values obtained for each X chromosome gene from the two populations to generate a cross-population p-value for each gene expression/platinum sensitivity correlation. Fisher's method was used to combine p-values. Cisplatin and carboplatin data were analyzed separately. For multiple testing correction, FDRs were calculated using the q-value package in R (11). An FDR of < 0.05 was used as the statistical significance cutoff. The significant findings for cisplatin and carboplatin generated using the Affymetrix exon array data were compared and genes in the overlap were identified. We then evaluated, using Illumina array data, these gene candidates found in the overlap.

The same analysis was performed using gene expression measurements, assayed by the Illumina array. For this platform we used HapMap CEU, YRI and ASN populations. As in the Affymetrix exon array, we conducted a meta-analysis in the combined populations. P values less than 0.05 from the meta-analysis for cisplatin and carboplatin, evaluated separately, were identified.

In addition, to determine whether our results are confounded by X inactivation, we compared the expression levels of the identified genes between males and females within each population using Student's t-tests.

Candidate gene expression evaluation in NCI-60 datasets

To explore the relevance of our findings in tumors, we examined the degree of correlation between candidate X chromosome gene expression and cellular susceptibility to cisplatin and carboplatin using NCI60 tumor cell lines. We downloaded the NCI-60 microarray expression and GI₅₀ datasets (released in March, 2007) from the DTP/NCI Molecular Target Databases (12,13). These datasets are comprised of gene expression data on untreated NCI-60 cell lines using different microarray platforms along with GI₅₀ data. Linear regression was performed between the expression of a gene of interest and log₁₀ carboplatin GI₅₀. p<0.05 was considered statistically significant.

Regulatory variation and X chromosome gene expression

Previous studies in our laboratory have shown that platinum response-associated single nucleotide polymorphisms (SNPs) are enriched for expression quantitative trait loci (eQTLs) (14), suggesting the role of genetic variation in drug sensitivity and gene expression. Using the SCAN database (8), which hosts our genome-wide SNP and gene expression association data, we searched for evidence that eQTLs may be regulating these X chromosome genes that are significantly correlated with platinum sensitivity. The thirty-four genes (Table 1) whose expression levels are significantly correlated (q-value<0.05) with either carboplatin or cisplatin sensitivity were evaluated in the SCAN database. SNP-expression correlations that met the p<10⁻⁴ cutoff were reported. Of these, the associations between SNP genotype and platinum sensitivity were also evaluated to arrive at candidate SNPs whose genotypes met the p<10⁻⁴ threshold with both gene expression and cellular sensitivity to platinum.

Evaluating the contribution of X chromosome genes to the observed population differences in platinum sensitivity

We have previously reported significant *in vitro* differences among HapMap populations in cellular sensitivity to carboplatin and cisplatin (2,15). In this study, we tested the 34 genes

listed in Table 1 for differential expression between the CEU and YRI samples using a two tailed t-test. Raw $p < 0.05$ was used as cutoff. In addition, we compared the minor allele frequency (MAF) in the two populations of any eQTLs for the differentially expressed X chromosome genes.

Results

Inter-individual cellular sensitivity differences to platinum agents

Large inter-individual variations in sensitivity to platinum agents were observed among unrelated samples obtained from the three HapMap populations. As shown previously, there were 32.5-, 17.4- and 19.9-fold variation for cisplatin IC_{50} ; and 8.8-, 12- and 5.2-fold variation for carboplatin IC_{50} in the CEU, YRI and ASN samples, respectively (2,15).

X chromosome gene expression levels correlate with cellular sensitivity to platinum agents

Through a meta-analysis in the combined CEU and YRI samples (q -value <0.05) using the gene expression dataset from the Affymetrix exon array, we identified 31 and 17 X chromosome genes whose expression levels are significantly correlated with cellular sensitivity to carboplatin and cisplatin, respectively (Table 1). Fourteen of these genes are significantly correlated with both carboplatin and cisplatin sensitivity. For confirmation, using an independent gene expression quantification method (Illumina array), 8 of the 14 genes were found to be interrogated on the Illumina array. Four (*CD99L2*, *STS*, *DLG3*, and *CTPS2*) and three (*DLG3*, *FAM3A*, and *CTPS2*) of the 8 were found to correlate with carboplatin and cisplatin sensitivity, respectively, using a meta-analysis in the combined CEU, YRI and ASN samples ($p < 0.05$). Two X chromosome genes, *CTPS2* and *DLG3*, were found to correlate with both carboplatin and cisplatin sensitivity using both Affymetrix exon array and Illumina array data. Specifically, the increased expression of both genes is correlated with increased sensitivity to the two platinum agents studied (Figure 2).

Furthermore, we examined the correlation between the expression of *CTPS2* and *DLG3*, and cisplatin and carboplatin GI_{50} s in the NCI60 cancer cell lines. *DLG3* expression was found to significantly correlate with carboplatin GI_{50} in all 60 cancer cell lines ($p < 0.05$). This finding was confirmed by multiple gene expression arrays including Affymetrix U95 and U133.

Genetic variation may be regulating X chromosome genes whose expression correlates with platinum sensitivity

Using the SCAN database, we identified 36 and 57 eQTLs (at $p < 10^{-4}$) in CEU and YRI respectively, which predict the expression of the X chromosome genes that have been shown to be significantly associated (q -value <0.05) with either of the platinating agents (from Table 1). These SNPs, which are associated with baseline gene expression of 11 and 15 such X chromosome genes in CEU and YRI respectively, have genotypes that also associated with carboplatin or cisplatin sensitivity (meeting the $p < 10^{-4}$ cutoff). In CEU, 6 such eQTLs (rs11001716, rs11001720, rs7087332, rs7099295, rs4503472 and rs1865644), located in the intronic region of the *C10orf11* gene on chromosome 10, are associated with carboplatin sensitivity and predict two X chromosome genes (*GRPR* and *CDKL5*) with expression levels that themselves show significant platinum associations (q -value <0.05). In YRI, 3 such eQTLs are associated with both carboplatin and cisplatin sensitivity and are targeting X chromosome genes (rs1595273 and *CD99L2*; rs9686286 and *GLA* and *PIGA*; rs9749439 and *PIGA*) with expression levels showing significant platinum associations (q -value <0.05). These findings provide strong evidence that the effect of the expression of X chromosome genes on platinum sensitivity may in part be mediated by genetic variants.

X chromosome gene expression patterns may in part explain population differences in response to platinating agents

Population differences, observed *in vitro*, in susceptibility to carboplatin and cisplatin were previously reported in HapMap YRI and ASN samples (15) as well as between CEU and YRI for carboplatin (2). After establishing the role of X chromosome gene expression in platinum sensitivity, we further evaluated whether sex chromosome gene expression patterns, especially on the X chromosome, contribute to the observed population differences in platinum sensitivity. Of the 34 genes (Table 1) whose expression levels are significantly correlated with sensitivity to either platinum (q -value <0.05), 14 genes showed evidence of differential expression between the CEU and YRI samples ($p<0.05$. Affymetrix exon array data). Nine (*CD99L2*, *CLIC2*, *DLG3*, *CNKS2*, *CXorf21*, *PIM2*, *ATP6AP2*, *GPR174*, and *MIDI1P1*) and seven (*CD99L2*, *CLIC2*, *DLG3*, *PIM2*, *ATP6AP2*, *GPR174*, and *MIDI1P1*) of these 14 genes also meet the $p<0.05$ cutoff with carboplatin and cisplatin sensitivity, respectively, in the separate CEU and YRI populations with concordant effect direction.

Furthermore, we identified 24 eQTLs that predict (at the $p<10^{-4}$ level) the expression of at least one of the differentially expressed X chromosome genes found to be important in platinum sensitivity (q -value <0.05). The majority of these SNPs show variation in allele frequencies in the CEU and YRI populations. As an example, one gene, *CD99L2*, is differentially expressed between the CEU and YRI samples ($p=0.01$). This gene's expression is significantly correlated with both carboplatin and cisplatin sensitivity in both populations ($p=0.002$ and <0.0001 for carboplatin in CEU and YRI, respectively; $p<0.0001$ and $=0.0003$ for cisplatin in CEU and YRI, respectively; Figure 3A, 3B). Furthermore, an eQTL (rs1595273), whose genotype meets $p<10^{-4}$ with the expression of *CD99L2* is also associated with carboplatin and cisplatin sensitivity in YRI ($p=7\times 10^{-5}$ and 1×10^{-4} ; Figure 3C, 3D). Interestingly, consistent with the observed difference in expression between the two populations, rs1595273 has MAF of 0.43 and 0.31 in CEU and YRI, respectively.

A comparison of the expression levels between males and females in *CTPS2*, *DLG3* and *CD99L2* shows that the correlation between expression and drug sensitivity is not driven by the phenomenon of X inactivation ($P>0.2$ between females and males).

Discussion

Studies involving platinating agent sensitivity with X chromosome genes have been conducted on a single gene, or gene product. To date, there have been no comprehensive studies to explore the importance of X chromosome genes in predicting platinum sensitivity. Taking advantage of genome-wide gene expression array datasets, our study comprehensively explored the role of the expression of X chromosome genes in predicting platinum sensitivity. We identified 31 and 17 X chromosome genes whose expression levels are significantly correlated with carboplatin and cisplatin sensitivity in the combined HapMap CEU and YRI populations, 14 of which were found to be in the overlap between the two platinating agents evaluated in this study. Utilizing an independent expression quantification method (Illumina array), measured on the same HapMap cell lines, we found overlap with 4 and 2 of these genes, respectively. Two X chromosome genes were identified by both genome-wide gene expression analyses to be correlated with sensitivity to both platinating agents.

One interesting gene from our findings, *CTPS2*, encodes cytidine 5'-triphosphate (CTP) synthase II (16), the rate-limiting enzyme in the synthesis of cytosine nucleotides, which plays an important role in various metabolic processes and provide the precursors necessary for the synthesis of RNA and DNA. It has been shown that cancer cells that exhibit increased cell proliferation also exhibit an increased activity of *CTPS2*. Furthermore, our

laboratory has reported a significant positive correlation between cellular sensitivity to platinating agents and cellular growth rate (17). Thus, it is plausible that increased *CTPS2* gene expression leads to increased cellular proliferation, which in turn leads to increased platinum sensitivity.

Another novel gene, *DLG3*, encoding human neuroendocrine Dlg (NE-Dlg), is located within the 1.8-Mb dystonia-parkinsonism region at Xq13.1 (18). It also directly interacts with the colorectal tumor suppressor adenomatous polyposis coli (APC) and negatively regulates cell proliferation (19). In fact, overexpression of *DLG3* in proliferating cells induces growth suppression and impairment of cell adhesive ability. Indeed, we observed significant correlation between *DLG3* expression and platinum sensitivity in a set of 60 NCI60 cancer cell lines: the higher the expression of this gene, the less sensitivity a tumor cell shows to carboplatin treatment. As mentioned earlier, we have described a positive correlation between cellular proliferation and platinum sensitivity (17). This supports our finding in NCI60 cell lines that *DLG3*'s effect on platinum sensitivity may be mediated by its effects on cellular proliferation.. Further evaluation of the mechanism underlying the observed relationship between *DLG3* expression and platinum sensitivity is warranted.

Previously, we observed *in vitro* population differences in sensitivity to platinum agents (9,20,21) that could be the result of transcription-level, epigenetic, posttranscriptional, and posttranslational effects; however, we hypothesized that differential gene expression may have a key role in the observed population differences. In this study, we chose to focus on X chromosome genes for their potential contribution to the observed population differences in cellular sensitivity to platinating agents. Of the 34 X chromosome genes whose expression levels are significantly correlated with platinum sensitivity, 14 are differentially expressed between the CEU and YRI samples. Furthermore, we also identified a set of eQTLs that predict the expression of the differentially expressed X chromosome genes and showed expected MAF variation between CEU and YRI. Whether these population differences in platinum sensitivity observed *in vitro* are recapitulated in clinical settings is not definitively established (22) but closer inspection of the available clinical data on ethnically-divergent chemotherapy outcomes may deserve increased attention based upon our findings.

There have been some reports of cisplatin effect on the expression of an X-linked inhibitor of apoptosis protein, XIAP, as a key determinant in chemosensitivity in various cancer cell lines (4,5). Interestingly, *XIAP*, did not show significant correlation with either cisplatin or carboplatin sensitivity in our samples ($p=0.17$, 0.19 in CEU; 0.92 and 0.31 in YRI, for cisplatin and carboplatin, respectively). However, the majority of studies on XIAP and other platinum-implicated genes have been done after platinum therapy, suggesting that perhaps platinum-induced gene expression changes in *XIAP* are important in mediating alterations in platinum sensitivity (4,5). Since our study evaluated baseline gene expression, it is not surprising that we did not find a correlation between *XIAP* expression and platinum sensitivity.

Our study has several recognized limitations. In comparing the independent gene expression quantification methods (the Illumina versus the Affymetrix array), it is well-known that the chromosomal coverage of these two platforms is different. For example, we evaluated 322 X chromosome genes using the Affymetrix exon array while 562 probes (representing 461 genes) were evaluated on the Illumina array with 190 overlap. Only 8 of the 14 genes identified using the Affymetrix exon array to be associated with sensitivity to cisplatin and carboplatin are interrogated on the Illumina array. Therefore, some important X chromosome genes may still be identified by one platform but not validated by the other. However, the X chromosome genes whose expression levels were shown to be important for

platinum sensitivity across two different expression platforms constitute findings that are robust.

In summary, the current study demonstrates the importance of the expression of X chromosome genes in cellular sensitivity to platinum agents. This study raises a critical, but neglected, perspective on the relationship between the X chromosome and drug response. Our work shows that sex chromosome gene expression differences may be an important source of variation that should be included in comprehensive studies of pharmacogenomics.

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The abbreviations used are

EBV	Epstein-Barr Virus
IC₅₀	the concentration required to inhibit 50% of cell growth
CEU	Centre d'Etude du Polymorphisme Humain (CEPH) Utah residents with northern and western European ancestry
YRI	Yoruba people from Ibadan, Nigeria
ASN	Han Chinese in Beijing and Japanese in Tokyo

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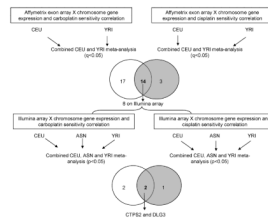


Figure 1. Schematic diagram of the study. The top venn diagram shows the number of X chromosome genes whose expression significantly correlated with either carboplatin (left circle) or cisplatin (right circle) sensitivity ($q < 0.05$). The number shown in the overlap region of the venn diagram represents the number of X chromosome genes whose expression significantly correlated with sensitivity to both platinum. When evaluating these 14 genes on Illumina array via meta-analysis, 4 (2+2) also correlated with carboplatin sensitivity (left circle) and 3 (1+2) correlated with cisplatin sensitivity (right circle). CEU = Caucasian; YRI = Yoruba people from Ibadan, Nigeria; ASN= Asian.

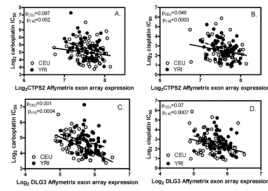


Figure 2.

The correlation between the expression of *CTPS2* or *DLG3* and cellular sensitivity to platinum in CEU and YRI. Affymetric exon array expression data are presented. *CTPS2* (A, B) and *DLG3* (C, D) expression levels are significantly correlated with both carboplatin (A, C) and cisplatin (B, D) sensitivity.

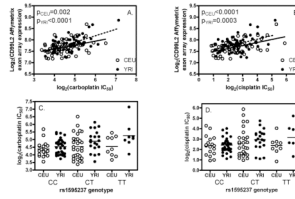


Figure 3.

The relationship between the expression of *CD99L2*, *rs1595237* genotype and cellular sensitivity to platinum in CEU and YRI. Affymetrix exon array expression data are presented. *CD99L2* expression level is significantly correlated with carboplatin (A) and cisplatin (B) in both CEU and YRI populations. *rs1595237* genotype, which predicts the expression of *CD99L2*, meets the $p < 10^{-4}$ cutoff with carboplatin (C) and cisplatin (D) sensitivity in YRI ($p = 7 \times 10^{-5}$ and 1×10^{-4}).

X chromosome genes whose expression are significantly correlated with either carboplatin or cisplatin sensitivity in the CEU and the CEU and YRI samples.

Table 1

gene name	transcript cluster ID	Affymetrix														
		combined CEU and YRI						CEU						YRI		
		meta p values		meat q values		p values		q values		p values		q values		q values		
carboplatin	cisplatin	carboplatin	cisplatin	carboplatin	cisplatin	carboplatin	cisplatin	carboplatin	cisplatin	carboplatin	cisplatin	carboplatin	cisplatin	carboplatin	cisplatin	
CD99L2 *	4025771	1.70E-08	4.20E-09	2.73E-06	9.02E-07	6.23E-04	2.37E-06	1.24E-06	7.55E-05							
GPR174 *	3982612	4.05E-07	7.01E-06	3.25E-05	7.54E-04	1.78E-05	1.15E-03	1.22E-03	3.91E-04							
STS *	3967689	6.29E-06	2.85E-05	2.69E-04	1.53E-03	8.89E-06	8.16E-05	4.50E-02	2.48E-02							
DLG3 *	3980643	6.70E-06	5.50E-04	2.69E-04	1.31E-02	1.11E-03	7.34E-02	3.85E-04	6.88E-04							
MID1IP1 *	3974098	2.24E-05	1.12E-05	7.19E-04	8.00E-04	1.35E-01	1.36E-02	1.16E-05	5.42E-05							
CLIC2	4027769	3.40E-05	4.24E-03	9.11E-04	5.06E-02	2.60E-05	2.07E-03	9.39E-02	2.38E-01							
GRPR	3970024	1.00E-04	8.04E-03	2.30E-03	6.66E-02	1.03E-02	1.26E-02	7.67E-04	8.10E-02							
TMEM164 *	3987029	1.19E-04	1.75E-03	2.39E-03	2.35E-02	1.06E-03	2.29E-03	8.92E-03	7.96E-02							
ACSL4 *	4017810	3.89E-04	2.64E-04	6.94E-03	7.43E-03	4.27E-04	6.12E-04	8.08E-02	3.69E-02							
MAP3K15 *	4001850	5.44E-04	1.39E-04	7.35E-03	5.99E-03	1.97E-01	2.74E-02	2.53E-04	4.10E-04							
FAM3A *	4027387	5.37E-04	9.10E-04	7.35E-03	1.78E-02	1.58E-01	6.52E-02	3.11E-04	1.35E-03							
WWC3	3968397	5.49E-04	3.28E-02	7.35E-03	1.43E-01	5.21E-04	8.38E-02	9.67E-02	6.26E-02							
CLCN5 *	3977299	9.02E-04	8.41E-04	1.04E-02	1.78E-02	1.57E-02	6.82E-03	5.54E-03	1.18E-02							
CDKL5	3970642	8.49E-04	6.05E-02	1.04E-02	1.86E-01	2.55E-02	3.04E-01	3.19E-03	3.61E-02							
PIA1	4011464	1.18E-03	6.54E-03	1.26E-02	6.52E-02	2.60E-04	2.87E-02	4.50E-01	2.81E-02							
CTPS2 *	4000839	1.73E-03	1.71E-04	1.40E-02	6.13E-03	9.71E-02	4.78E-02	1.86E-03	2.94E-04							
ATP6AP2 *	3974556	1.46E-03	1.07E-03	1.40E-02	1.83E-02	2.18E-02	8.03E-03	6.83E-03	1.32E-02							
CNKSR2	3971219	1.72E-03	1.95E-02	1.40E-02	1.22E-01	5.34E-02	3.36E-01	3.34E-03	8.46E-03							
MED12	3980758	1.65E-03	3.64E-02	1.40E-02	1.51E-01	2.44E-04	1.18E-02	6.97E-01	5.04E-01							
GDI1	3996404	1.74E-03	1.38E-01	1.40E-02	2.90E-01	3.68E-03	8.71E-02	4.92E-02	3.52E-01							
SILC9A7	4006841	2.65E-03	4.92E-02	2.03E-02	1.75E-01	1.61E-01	8.77E-01	1.80E-03	9.74E-03							
MAGEH1	3978760	3.25E-03	6.15E-02	2.38E-02	1.86E-01	4.99E-01	3.98E-01	7.32E-04	2.81E-02							

gene name	transcript cluster ID	Affymetrix															
		combined CEU and YRI							CEU							YRI	
		meta p values		meat q values		p values			q values		p values		q values		p values		q values
carboplatin	cisplatin	carboplatin	cisplatin	carboplatin	cisplatin	carboplatin	cisplatin	carboplatin	cisplatin	carboplatin	cisplatin	carboplatin	cisplatin	carboplatin	cisplatin	carboplatin	cisplatin
GPC4	4022370	5.00E-03	8.06E-03	3.50E-02	6.66E-02	1.56E-02	1.35E-02	3.81E-02	3.81E-02	1.35E-02	1.35E-02	3.81E-02	3.81E-02	3.81E-02	3.81E-02	7.59E-02	7.59E-02
TSC22D3 *	4017381	5.84E-03	1.11E-03	3.87E-02	1.83E-02	2.54E-02	2.28E-01	2.79E-02	2.79E-02	2.54E-02	2.28E-01	2.79E-02	2.79E-02	2.79E-02	4.79E-04	4.79E-04	
EDA2R *	4011096	6.02E-03	3.03E-03	3.87E-02	3.83E-02	1.12E-03	7.24E-04	6.51E-01	6.51E-01	1.12E-03	7.24E-04	6.51E-01	6.51E-01	6.51E-01	4.64E-01	4.64E-01	
PIM2	4007617	6.61E-03	2.86E-02	4.08E-02	1.43E-01	8.22E-01	1.41E-01	9.91E-04	9.91E-04	8.22E-01	1.41E-01	9.91E-04	9.91E-04	9.91E-04	3.16E-02	3.16E-02	
PDZD11	4011637	7.11E-03	1.48E-01	4.23E-02	2.97E-01	6.13E-02	3.29E-01	1.44E-02	1.44E-02	6.13E-02	3.29E-01	1.44E-02	1.44E-02	1.44E-02	1.03E-01	1.03E-01	
Cxorf21	4003895	7.65E-03	2.83E-01	4.39E-02	3.88E-01	2.63E-03	8.27E-02	3.66E-01	3.66E-01	2.63E-03	8.27E-02	3.66E-01	3.66E-01	3.66E-01	9.73E-01	9.73E-01	
OFD1	3969455	8.62E-03	7.52E-03	4.53E-02	6.66E-02	2.42E-01	1.50E-01	4.56E-03	4.56E-03	2.42E-01	1.50E-01	4.56E-03	4.56E-03	4.56E-03	6.28E-03	6.28E-03	
CFP	4007164	8.26E-03	1.56E-01	4.53E-02	2.99E-01	1.75E-03	5.47E-02	6.01E-01	6.01E-01	1.75E-03	5.47E-02	6.01E-01	6.01E-01	6.01E-01	6.58E-01	6.58E-01	
LOC170082	3969396	8.75E-03	1.72E-01	4.53E-02	3.03E-01	6.34E-01	7.81E-01	1.77E-03	1.77E-03	6.34E-01	7.81E-01	1.77E-03	1.77E-03	1.77E-03	5.26E-02	5.26E-02	
PIGA	4000512	1.10E-02	2.76E-04	5.04E-02	7.43E-03	2.10E-02	1.79E-03	6.95E-02	6.95E-02	2.10E-02	1.79E-03	6.95E-02	6.95E-02	6.95E-02	1.33E-02	1.33E-02	
GLA	4015763	2.27E-02	1.52E-03	7.36E-02	2.34E-02	2.45E-02	1.67E-03	1.39E-01	1.39E-01	2.45E-02	1.67E-03	1.39E-01	1.39E-01	1.39E-01	9.33E-02	9.33E-02	
PGK1	3982462	1.10E-01	1.67E-03	1.91E-01	2.35E-02	4.09E-02	2.50E-04	5.67E-01	5.67E-01	4.09E-02	2.50E-04	5.67E-01	5.67E-01	5.67E-01	6.89E-01	6.89E-01	

* represents the 14 genes whose expression levels are significantly correlated with both carboplatin and cisplatin sensitivity (q-value<0.05) after a meta-analysis in the combined CEU and YRI samples, based on Affymetrix exon array data.

Bold: indicates that the gene expression level is correlated with sensitivity to both platinum agents (q-value<0.05) from a meta-analysis using the Affymetrix exon array data and is correlated with sensitivity to both platinum agents (p<0.05) from a meta-analysis (in the combined CEU, YRI and ASN data) using the Illumina array.

NA: not available.

CEU = Caucasian; YRI = Yoruba people from Ibadan, Nigeria; ASN= Asian.

Table 2

Illumina											
combined CEU, YRI and ASN				CEU		YRI		ASN			
meta p values		meta q values		p values		p values		p values			
carboplatin	cisplatin	carboplatin	cisplatin	carboplatin	cisplatin	carboplatin	cisplatin	carboplatin	cisplatin		
1.91E-03	5.42E-02	4.65E-02	1.91E-01	9.03E-02	3.46E-01	2.69E-03	6.61E-02	1.19E-01	9.01E-02		
NA	NA	NA	NA	NA	NA	NA	NA	NA	NA		
4.45E-03	7.84E-02	7.08E-02	2.04E-01	3.04E-04	3.94E-02	3.47E-01	2.48E-01	7.72E-01	3.53E-01		
8.87E-04	9.31E-03	3.76E-02	8.65E-02	2.45E-02	2.72E-01	4.71E-03	1.47E-03	9.95E-02	5.11E-01		
NA	NA	NA	NA	NA	NA	NA	NA	NA	NA		
6.09E-01	7.42E-01	5.96E-01	5.03E-01	1.47E-01	4.45E-01	9.69E-01	8.67E-01	7.39E-01	4.48E-01		
5.58E-01	4.50E-01	5.74E-01	4.29E-01	3.90E-01	1.93E-01	4.38E-01	3.47E-01	5.08E-01	8.33E-01		
NA	NA	NA	NA	NA	NA	NA	NA	NA	NA		
1.39E-01	1.78E-01	3.31E-01	3.13E-01	5.06E-02	2.80E-01	5.85E-01	3.51E-01	2.67E-01	1.17E-01		
NA	NA	NA	NA	NA	NA	NA	NA	NA	NA		
1.13E-01	4.03E-03	3.07E-01	6.55E-02	7.78E-01	4.91E-01	7.64E-02	2.13E-01	9.81E-02	6.88E-04		
NA	NA	NA	NA	NA	NA	NA	NA	NA	NA		
7.98E-02	4.84E-01	2.79E-01	4.46E-01	4.15E-02	9.86E-01	1.65E-01	1.33E-01	5.16E-01	4.91E-01		
8.65E-01	6.64E-01	6.91E-01	4.90E-01	5.40E-01	6.43E-01	7.58E-01	5.67E-01	6.88E-01	3.54E-01		
7.77E-02	7.46E-02	2.74E-01	2.04E-01	1.99E-01	4.82E-01	1.44E-01	5.49E-02	1.18E-01	1.21E-01		
8.92E-03	5.76E-03	9.25E-02	7.03E-02	1.05E-01	3.15E-02	2.33E-02	3.63E-02	7.94E-02	9.80E-02		
5.30E-01	6.64E-01	5.57E-01	4.90E-01	7.65E-01	4.97E-01	1.04E-01	2.99E-01	9.75E-01	8.69E-01		
NA	NA	NA	NA	NA	NA	NA	NA	NA	NA		
NA	NA	NA	NA	NA	NA	NA	NA	NA	NA		
9.85E-02	4.95E-02	2.87E-01	1.91E-01	1.24E-01	1.24E-01	7.71E-02	3.99E-01	4.99E-01	3.66E-02		
5.79E-01	8.05E-01	5.77E-01	5.12E-01	9.77E-01	5.47E-01	1.14E-01	6.77E-01	8.41E-01	5.94E-01		
1.14E-02	6.02E-02	1.06E-01	1.93E-01	2.11E-02	3.80E-01	4.27E-02	9.97E-02	2.94E-01	6.28E-02		
2.69E-02	1.94E-01	1.70E-01	3.26E-01	3.28E-02	4.59E-01	6.49E-01	6.89E-02	3.76E-02	4.18E-01		
NA	NA	NA	NA	NA	NA	NA	NA	NA	NA		
NA	NA	NA	NA	NA	NA	NA	NA	NA	NA		

Illumina													
combined CEU, YRI and ASN				CEU		YRI		ASN					
meta p values		meta q values		p values		p values		p values					
carboplatin	cisplatin	carboplatin	cisplatin	carboplatin	cisplatin	carboplatin	cisplatin	carboplatin	cisplatin				
8.86E-02	2.27E-01	2.84E-01	3.43E-01	5.64E-01	5.91E-01	3.08E-02	3.09E-01	2.36E-01	9.28E-02				
NA	NA	NA	NA	NA	NA	NA	NA	NA	NA				
NA	NA	NA	NA	NA	NA	NA	NA	NA	NA				
1.05E-01	3.40E-01	2.99E-01	3.91E-01	7.80E-01	9.45E-01	2.19E-02	5.74E-02	3.08E-01	6.15E-01				
NA	NA	NA	NA	NA	NA	NA	NA	NA	NA				
NA	NA	NA	NA	NA	NA	NA	NA	NA	NA				
2.96E-01	7.84E-01	4.52E-01	5.07E-01	6.17E-02	4.32E-01	7.88E-01	6.86E-01	5.41E-01	6.83E-01				
2.52E-01	1.08E-01	4.21E-01	2.40E-01	2.29E-01	8.02E-02	9.27E-02	1.53E-01	9.45E-01	4.46E-01				
3.71E-01	1.70E-01	4.97E-01	3.03E-01	4.73E-02	1.73E-02	8.55E-01	8.27E-01	9.67E-01	7.53E-01				