Genome-wide meta-analysis identifies variants associated with platinating agent susceptibility across populations

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Platinating agents are used in the treatment of many cancers, yet they can induce toxicities and resistance that limit their utility. Using previously published and additional world population panels of diverse ancestry totaling 608 lymphoblastoid cell lines (LCLs), we performed meta-analyses of over 3 million single-nucleotide polymorphisms (SNPs) for both carboplatin- and cisplatin-induced cytotoxicity. The most significant SNP in the carboplatin meta-analysis is located in an intron of NBAS (neuroblastoma amplified sequence; $P = 5.1 \times 10^{-7}$). The most significant SNP in the cisplatin meta-analysis is upstream of KRT16P2 ($P = 5.8 \times 10^{-7}$). We also show that cisplatin-susceptibility SNPs are enriched for carboplatin-susceptibility SNPs. Most of the variants that associate with platinum-induced cytotoxicity are polymorphic across multiple world populations; therefore, they could be tested in follow-up studies in diverse clinical populations. Seven genes previously implicated in platinating agent response, including BCL2 (B-cell CLL/lymphoma 2), GSTM1 (glutathione S-transferase mu 1), GSTT1, ERCC2 and ERCC6, were also implicated in our meta-analyses.

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Introduction

Platinum compounds comprise a class of chemotherapeutic agents that are used worldwide as essential components of many anticancer treatment regimens. In particular, carboplatin and cisplatin are commonly used to treat cancers such as lung, head and neck, colorectal, testicular, ovarian, cervical and relapsed lymphoma.1–6 Intrastrand and interstrand crosslinks are thought to be the covalent cytotoxic lesions introduced onto DNA by platinating agents.4 Both agents are associated with particular toxicities, predominantly myelosuppression for carboplatin and nephrotoxicity, and ototoxicity for cisplatin.4,7,8 However, there are currently no reliable means to identify patients at high risk for developing significant platinum-related toxicities, nor means to predict anti-tumor response. Heterogeneity in sensitivity is consistent with a role for genetic variation in explaining differences in response and toxicity to platinating agents. The similar mechanisms of action of carboplatin and cisplatin could suggest that the same genetic variants might contribute to platinum response. However, different predominant toxicities could mean the two drugs also have independent variants involved in susceptibility to each drug.
Candidate gene investigations of cisplatin-related ototoxicity, focusing on the role of genetic variants in GSTM3, GSTPI, mitochondrial DNA or megalin were inconclusive, possibly due to the use of single gene approaches and small patient cohorts. Another analysis focused on pathways associated with reactive oxygen species induction, were restricted to glutathione S-transferase (GST) genotypes, and identified variants in GSTP1 and GSTM1 as risk factors for ototoxicity in cisplatin-treated testicular cancer survivors. Ross et al. tested variants in 220 drug-metabolism genes in children for association with cisplatin-induced hearing loss, and found variants in methyltransferase genes (COMT and TPMT) with large 8- to 16-fold risks. A recent genome-wide association (GWA) study in non-small cell lung cancer patients receiving platinum treatment identified a single-nucleotide polymorphism (SNP) in CMKLR1 associated with overall survival, but it was not significant after multiple testing correction.

Patient populations of adequate size treated with the same chemotherapeutic dosage regimen are rare, making GWA studies of chemotherapeutic response in clinical settings challenging. To avoid confounders such as comorbidities, concomitant medications and diet, lymphoblastoid cell line (LCL) models have been developed as useful discovery tools in germline genetic studies of chemotherapeutic susceptibility. Recently, some SNPs associated with chemotherapeutic susceptibility in LCL studies have been replicated in patient populations by associating with phenotypes like tumor response and overall survival, demonstrating the potential utility of this model.

Several GWA studies using LCLs from different population panels of the International HapMap Project have been performed to find variants and genes associated with platinum cytotoxicity. Previous studies identified variants associated with carboplatin and cisplatin cytotoxicity, which also associated with gene expression in the initial (phase I/II) YRI (Yoruba from Ibadan, Nigeria) and CEU (Northern and Western European ancestry from Utah) HapMap panels. Taking an innovative approach that considered cytotoxicity-associated SNPs in cell lines derived from the population most sensitive to platinating agents (ASN, Japanese from Tokyo and Han Chinese from Beijing), O’Donnell et al. then identified those that replicated in a combined YRI and CEU population. Although each of these studies found suggestive variants associated with platinating agent response, the top findings did not always replicate when examined in additional populations.

In this study, our goal was to identify variants that associate with platinating agent-induced cytotoxicity across populations. We believe that, once validated, such cross-population variants could be used to identify individuals who are likely to be sensitive or resistant to carboplatin and/or cisplatin regardless of genetic ancestry. In addition to the population panels mentioned in the studies above, we collected platinating agent cytotoxicity data from the HapMap phase III YRI, CEU, ASW (African ancestry from the Southwestern United States) and CHD (Chinese ancestry from Denver, Colorado) panels. Using a meta-analysis approach, we combined the results of GWA studies for carboplatin- or cisplatin-induced cytotoxicity in each of the seven population panels. We identified SNPs associated with each of the two drug phenotypes and an enrichment of carboplatin-associated SNPs in the top cisplatin-associated SNPs. Most of the identified SNPs were common in all the seven panels, but several were specific to a population class. Seven genes previously implicated in platinating response through candidate studies were also implicated in our meta-analyses.

Materials and methods

Lymphoblastoid cell lines

International HapMap Project LCLs from the seven panels were purchased from the Coriell Institute for Medical Research (Camden, NJ, USA). The panels included 176 individuals from the Yoruba in Ibadan, Nigeria (YRI1/2 (HAPMAPPT03) and YRI3 (HAPMAPPT04), 83 individuals of African ancestry from the Southwestern United States (ASW (HAPMAPPT07)), 85 individuals of Han Chinese ancestry from Denver, Colorado (CHD (HAPMAPV11)), 90 Japanese from Tokyo and Han Chinese from Beijing (ASN (HAPMAPPT02)) and 174 Utah residents with Northern and Western European ancestry (CEU1/2 (HAPMAPPT01) and CEU3 (HAPMAPPT06)) for which genotype data is available (HapMap r27). Family structure of the panels is indicated in Table 1. Cell lines were maintained in RPMI 1640 (Mediatech, Herndon, VA, USA) supplemented with 15%

Table 1 Characteristics and mean responses to carboplatin and cisplatin of the HapMap panels included in the meta-analyses

|          | YRI1/2 | YRI3 | ASW | CHD | ASN | CEU1/2 | CEU3 |
|----------|--------|------|-----|-----|-----|--------|------|
| N        | 90     | 86   | 83  | 85  | 90  | 90     | 84   |
| Family structure | 30 trios | 27 trios, 1 duo, 3 singletons | 10 trios, 20 duos, 13 singletons | Unrelated | Unrelated | 30 trios | 22 trios, 5 duos, 8 singletons |
| Carboplatin IC50 (μM) | 30.0 (17.4) | 36.8 (14.1) | 20.1 (7.1) | 25.1 (23.7) | 19.7 (8.2) | 24.5 (13.9) | 28.2 (14.0) |
| Cisplatin IC50 (μM)  | 8.3 (6.5) | 10.2 (6.1) | 4.6 (4.1) | 6.7 (11.5) | 4.5 (3.7) | 7.8 (8.5) | 8.1 (5.6) |

Abbreviations: YRI, Yoruba from Ibadan, Nigeria; ASW, African ancestry from the Southwestern United States; CHD, Chinese ancestry from Denver; ASN, Japanese from Tokyo and Chinese from Beijing; CEU, Northern and Western European ancestry from Utah.

*Mean (s.d.).
fetal bovine serum (HyClone Laboratories, Logan, UT, USA) and 1% L-glutamine (Invitrogen, Carlsbad, CA, USA). Cell lines were diluted three times per week at a concentration of 3.5 × 10^6 cells/ml and incubated at 37 °C with 5% CO_2 and 95% humidity.

**Cytotoxicity assays**

Cells were treated with carboplatin\(^2\) and cisplatin\(^1\) as previously described. The concentration required to inhibit 50% of cell growth (IC\(_{50}\)) was calculated for each carboplatin- and cisplatin-treated cell line. All IC\(_{50}\) values were either log_2- or rank-transformed to normality (\textit{muttrans} function in the \texttt{GenABEL} R library) before statistical modeling. If the log_2-transformed data was not consistent with normality (Shapiro–Wilk test \(P<0.05\)), the phenotype was rank-transformed to normality. The ASW phenotypes were rank-transformed; the phenotypes from the other panels were log_2-transformed.

**GWA analyses of individual panels**

GWA studies of carboplatin- and cisplatin-induced cytotoxicity were performed on each of the seven panels individually. Studies of carboplatin- and cisplatin-susceptibility in the YRI1/2,\(^{17,18}\) CEU1/2\(^1\) and ASN\(^2\) panels have been previously published. To increase genome coverage of YRI3 and CEU3 (HapMap r27), ungenotyped makers were imputed using the BEAGLE software, using YRI1/2 and CEU1/2 (HapMap r22) as reference, respectively.\(^{29}\) BEAGLE imputes ungenotyped markers for parent–offspring trios by modeling the family structure in the analysis. To measure the accuracy of the imputation at each SNP locus, \(R^2\) was calculated as described, following 100 imputations of the data.\(^{29}\) Imputed SNP genotypes with \(R^2>0.80\) were carried through the rest of the analysis. For YRI1/2, YRI3, CEU1/2 and CEU3, greater than 2 million SNPs (minor allele frequency (MAF) > 0.05) within the panel, no Mendelian errors and in Hardy–Weinberg equilibrium (\(P>0.001\)) were tested for association with carboplatin log_2(IC\(_{50}\)) and cisplatin log_2(IC\(_{50}\)), using the quantitative trait disequilibrium test total association model.\(^{30}\)

To control for population structure in the admixed ASW population (HapMap r27), local ancestry at each genotyped SNP locus was estimated using the HAPMIX software.\(^{31}\) Phased genotypes from the YRI1/2 and CEU1/2 populations were used as the two parental populations to estimate the ancestry of the ASW population. For each individual, the algorithm estimated the number of CEU chromosomes (0–2) at each SNP locus. To increase genome coverage of the ASW, ungenotyped makers were imputed using the BEAGLE software,\(^{29}\) using both YRI1/2 and CEU1/2 as reference populations. Local ancestry for each imputed SNP was inferred by using the predicted number of CEU chromosomes from nearest genotyped SNP. GWA studies in the ASW population were performed between carboplatin and cisplatin IC\(_{50}\) phenotypes rank transformed to normality and greater than 2 million SNPs using the quantitative trait disequilibrium test total association model.\(^{30}\) Local ancestry (continuous predicted number of CEU chromosomes at each locus) was included as a covariate in the model for each drug.

To increase genome coverage of the CHD (HapMap r27), ungenotyped makers were imputed using the MaCH software with the ASW population (HapMap r27) as reference.\(^{32}\) Imputed SNP genotypes with \(R^2>0.80\) were carried through the rest of the analysis. For CHD and ASN, PLINK software was used to test greater than 2 million SNPs (MAF > 0.05, and in Hardy–Weinberg equilibrium (\(P>0.001\))) for linear association with carboplatin log_2(IC\(_{50}\)) and cisplatin log_2(IC\(_{50}\)).\(^{13}\)

Genomic control lambda (\(\lambda_{GC}\)) values\(^{34}\) were calculated for the GWA study of each population panel–drug phenotype combination. Studies with \(\lambda_{GC}\) values greater than 1 were corrected for residual inflation of the test statistic by dividing the observed test statistic at each SNP by the \(\lambda_{GC}\),\(^{34}\) and then the corresponding \(P\)-values were carried through the meta-analyses.

**Meta-analysis of seven GWA studies**

To determine which SNPs associate with carboplatin- and cisplatin-induced cytotoxicity across populations, we performed a meta-analysis to combine the results of the individual GWA studies from the seven panels. We used the software METAL, which combines SNP \(P\)-values across studies, taking into account a study-specific weight (sample size) and direction of effect (positive or negative beta).\(^{28}\) This approach converted the direction of effect and \(P\)-value observed in each study into a signed \(Z\)-score, such that very negative \(Z\)-scores indicate a small \(P\)-value and an allele associated with lower IC\(_{50}\) whereas large positive \(Z\)-scores indicate a small \(P\)-value and an allele associated with higher IC\(_{50}\). \(Z\)-scores for each SNP were combined across studies in a weighted sum, with weights proportional to the square-root of the sample size for each study.\(^{28}\) Q–Q plots of the corresponding \(P\)-values are shown in Supplementary Figure S1. Gene region plots of top SNPs were made with LocusZoom.\(^{35}\)

**Results**

**Population panel characteristics**

Carboplatin- and cisplatin-induced cytotoxicity was measured in 608 LCLs from seven HapMap panels. The panels included YRI1/2,\(^{17,18}\) YRI3, ASW, CHD, ASN\(^2\), CEU1/2,\(^{18,36}\) and CEU3. Percent survival data at several concentrations (0–80 \(\mu\)M carboplatin or 0–20 \(\mu\)M cisplatin) were used to calculate the IC\(_{50}\) for each cell line and drug. Table 1 displays the means and s.d. of carboplatin and cisplatin IC\(_{50}\) for each panel. For both drugs, the IC\(_{50}\) values are in the range of the plasma platinum concentrations observed in patients after treatment. The mean IC\(_{50}\) values ranged from 19.7–36.8 \(\mu\)M (7.3–13.7 \(\mu\)g ml\(^{-1}\)) for carboplatin and 4.5–10.2 \(\mu\)M (1.4–3.1 \(\mu\)g ml\(^{-1}\)) for cisplatin in the LCL panels. In previous pharmacokinetic studies, plasma concentrations of platinum a few hours after administration ranged from 5–20 \(\mu\)g ml\(^{-1}\) in patients treated with

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carboplatin, and from 1–10 μg ml⁻¹ in patients treated with cisplatin.

Meta-analysis reveals SNPs associated with platinating agent cytotoxicity

GWA studies of carboplatin- and cisplatin-induced cytotoxicity were performed in each of the seven panels individually. Each study tested 2–2.5 million genotyped or imputed SNPs for association with carboplatin IC₅₀ or cisplatin IC₅₀. To determine which SNPs associate with carboplatin IC₅₀ or cisplatin IC₅₀ across populations, we performed a meta-analysis to combine the results of the individual GWA studies from the seven panels. Some SNPs are unique to a particular panel or subset of panels, and therefore, ~3 million SNPs were tested in the meta-analysis. At the suggestive threshold of P < 10⁻⁴, 322 SNPs associated with carboplatin IC₅₀ and 334 SNPs with cisplatin IC₅₀ (Figure 1, Supplementary Table S1). Most of the SNPs at this threshold were common (MAF > 0.05) in all the seven HapMap panels (Figure 2).

The most significant SNP in the carboplatin IC₅₀ meta-analysis was rs7572081, which is located in an intron of NBAS (neuroblastoma amplified sequence; Supplementary Table S1, P = 5.1 × 10⁻⁷). The most significant SNP in the cisplatin IC₅₀ meta-analysis was rs7210837 (Supplementary Table S1, P = 5.8 × 10⁻⁷). The most significant missense SNP in the meta-analyses was rs244903, which associated with carboplatin IC₅₀ and is located in the first exon of RARS (P = 5.4 × 10⁻⁴, Figure 3).

Cisplatin-associated SNPs are enriched for carboplatin-associated SNPs

To compare the top SNP associations for the two drug phenotypes, we examined the Z-score distributions of the top cisplatin IC₅₀ SNPs at various thresholds in the carboplatin IC₅₀ meta-analysis results and vice versa (Figure 4). We verified that the directions of effect of the top SNPs are the same between the two drugs. That is, when the minor allele of a particular SNP is associated with increased resistance to carboplatin, the minor allele is also associated with increased resistance to cisplatin. Therefore, cisplatin-associated SNPs are enriched for carboplatin-associated SNPs, and common genetically mediated mechanisms may influence the effect of both the chemically related drugs. The Pearson correlation between carboplatin IC₅₀ and cisplatin IC₅₀ varied across HapMap panels (YRI1/2 = 0.84, YRI3 = 0.75, ASW = 0.67, CHD = 0.82, ASN = 0.76, CEU1/2 = 0.58, CEU3 = 0.60).

Genes previously implicated in platinating agent cytotoxicity replicated by meta-analysis

We compiled a list of 41 genes previously implicated in platinating agent response (Supplementary Table S2). This list contained the genes that make up the PharmGKB platinum pathway, the two methyltransferases found associated with cisplatin-induced hearing loss, and several genes from a review of platinating agents. None of the top SNPs (P < 10⁻⁴) from both the carboplatin and cisplatin meta-analyses were

![Figure 1](link-to-figure1) Meta-analysis results of seven genome-wide association (GWA) studies of platinum-induced cytotoxicity. Each point represents a single-nucleotide polymorphism (SNP). Horizontal lines are at the suggestive significance threshold of P = 10⁻⁴ and the genome-wide significance threshold of P = 5 × 10⁻⁸.

![Figure 2](link-to-figure2) Population class distribution of the top meta-analysis hits. The number of single-nucleotide polymorphisms (SNPs) with a meta-P-value < 10⁻⁴ that have a minor allele frequency (MAF) > 0.05 in each population panel included in the listed population classes. Most (50.3% for carboplatin and 45.5% for cisplatin) of the top SNPs (P < 10⁻⁴) were present in all the seven panels. For the vast majority of these SNPs present in all the seven panels, the direction of effect was the same for either 7/7 or 6/7 panels (98.1% for carboplatin, 96.7% for cisplatin). SNPs not included in this bar chart were present in a subset of panels not included as one of the listed population classes.
located within these 41 genes. However, 28 of the 41 genes are expressed in LCLs and seven of these 28 genes were expression targets of top meta-analysis SNP expression quantitative trait loci (eQTLs) (Supplementary Table S2).

Included in these seven genes are BCL2 and GSTM1, which are both targeted by YRI1/2 eQTLs from the same region of chromosome 14 that also associate with both carboplatin and cisplatin IC50 (Figure 5). Also included in the previously implicated genes are GSTTI, ERCC6 and ERCC2. rs2191934 is associated with cisplatin IC50 (meta-

Discussion

We performed a meta-analysis of the results of GWA studies for carboplatin- and cisplatin-induced cytotoxicity in the seven HapMap panels that included a total of 608 LCLs. We identified 322 SNPs that associate with carboplatin IC50 and 334 SNPs that associate with cisplatin IC50 at the suggestive threshold of \( P < 10^{-4} \). About half of the identified SNPs were common in all the seven panels. By the nature of the meta-analysis, this indicates that the allelic relationship with IC50 was the same in most, if not all, of the populations. Therefore, if these variants are confirmed in clinical cohorts, they could be used to predict chemotherapeutic response in individuals from most world populations. However, several SNPs were specific to a population class and therefore were not interrogated in as many individuals. For these population-specific SNPs, additional cell lines from the appropriate population are needed to confirm these findings.

We identified an enrichment of carboplatin-associated SNPs in the top cisplatin-associated SNPs. This is somewhat expected given that the phenotypes are correlated. The correlation between carboplatin and cisplatin IC50 within a HapMap panel ranges from 0.58 in CEU1/2 to 0.84 in YRI1/2. Both carboplatin and cisplatin are platinating agents that act through the formation of intrastrand and interstrand DNA crosslinks, which result in DNA strand breaks leading to cell death. Our results support that common genetic mechanisms may influence the effects of both drugs. However, there are also likely unique genetic mechanisms contributing to the different clinical toxicities observed.
between the two drugs. Although findings in LCL studies have been replicated by associating with patient phenotypes like tumor response and overall survival,\textsuperscript{21,22} studies testing top LCL findings for association with patient toxicity phenotypes are also needed to fully understand the utility of the LCL model.

Several genes connected to top SNPs associated with platinum susceptibility have been implicated in tumorigenesis. For instance, the most significant SNP in the carboplatin IC\textsubscript{50} meta-analysis, rs7572081, is located in an intron of \textit{NBAS}. Carboplatin is often used in neuroblastoma treatment regimens,\textsuperscript{44,45} and increased \textit{NBAS} expression has been associated with poorer outcome in patients greater than 18 months old.\textsuperscript{46} The most significant missense SNP in the meta-analyses was rs244903, which associated with carboplatin IC\textsubscript{50} and is located in the first exon of \textit{RARS} (arginyl-tRNA synthetase). As \textit{RARS} is necessary for protein synthesis,\textsuperscript{47} it has been recognized as a potential chemotherapeutic drug target.\textsuperscript{47} The \textit{RARS} SNP is also an eQTL associated with the expression of five genes in YRI1/2, including \textit{NOL1} and \textit{CCNG2}.\textsuperscript{43} Reduced expression of \textit{NOL1}, also known as p120, reduced cell growth in the human breast cancer line MCF-7.\textsuperscript{48} \textit{CCNG2} is a negative regulator of cell cycle progression and decreased expression of the gene has been observed in oral cancers.\textsuperscript{49}

Seven genes previously implicated in platinating response out of 28 tested were also implicated in our meta-analyses. These genes included \textit{BCL2} and \textit{GSTM1}, which are both targeted by eQTLs located in the same region of chromosome 14 that also associate with both carboplatin and cisplatin IC\textsubscript{50}. Inhibition of apoptosis by increased \textit{BCL2} expression has been shown to lead to cisplatin resistance.\textsuperscript{50} Here, the opposite effect was observed, the eQTL minor alleles associated with decreased \textit{BCL2} expression\textsuperscript{42} and increased IC\textsubscript{50}. Further studies are necessary to elucidate how \textit{BCL2} may be functioning in LCLs in response to platinating agents. \textit{GSTM1} is an enzyme that contributes to the detoxification of platinating agents.\textsuperscript{41} Here, alleles associated with increased \textit{GSTM1} expression\textsuperscript{42} were also associated with increased IC\textsubscript{50}. Correlations have been observed between high levels of the related protein GSTP1 and cisplatin resistance in colon, lung adenocarcinoma and glioblastoma tumor cell lines; however, results in other studies are inconsistent.\textsuperscript{4}

\textit{GSTT1}, another glutathione S-transferase, was also implicated in our meta-analysis. rs2191934 associated with cisplatin IC\textsubscript{50} and the expression of \textit{GSTT1} and \textit{ERCC6}.\textsuperscript{41} \textit{GSTT1} is an enzyme that contributes to the detoxification of platinating agents.\textsuperscript{41} Here, alleles associated with increased \textit{GSTT1} expression\textsuperscript{13} were also associated with increased IC\textsubscript{50}. Correlations have been observed between high levels of the related protein GSTP1 and cisplatin resistance in colon, lung adenocarcinoma and glioblastoma tumor cell lines; however, results in other studies are inconsistent.\textsuperscript{4}

\textit{ERCC2} and \textit{ERCC6} are components of the platinum pathway involved in nucleotide excision repair.\textsuperscript{41} Platinating agent DNA adduct repair occurs primarily through nucleotide excision repair.\textsuperscript{4} Here, alleles associated with increased expression of \textit{ERCC2} and \textit{ERCC6} were also associated with cisplatin resistance (increased IC\textsubscript{50}). Cisplatin resistance is correlated with the increased expression of several nucleotide excision repair genes in ovarian cancer, \textit{XPA} and \textit{ERCC1} were shown to have increased expression in tumors of patients resistant to platinum treatment.\textsuperscript{51,52} Similarly, a study of gastric cancer patients showed a correlation between cisplatin resistance and \textit{ERCC1} levels.\textsuperscript{53} The observation that numerous candidate genes are not replicated here is not necessarily surprising, as our unbiased
GWA approach might not be expected to identify prior candidate genes, as it makes no assumption that these are the most important. In addition, some of the SNPs within candidate genes have a MAF < 0.05 and therefore would not be tested in this model.

One previous study from our laboratory identified six SNPs that contribute to cisplatin-induced cytotoxicity through their effects on the expression of eight genes in the combined CEU1/2 and YRI1/2 population. Although not one of our top findings, one of these six SNPs remained associated with cisplatin IC₅₀ when the additional panels were added in the current study (rs2136241, meta- P = 6.9 × 10⁻⁴). This SNP was present and the direction of effect was the same in all seven HapMap panels. The association signal for the other five SNPs was lost, due to discordant directions of effect when the additional panels were added. The previous study examined 176 individuals, so power to detect associations was limited. Another study from our group identified cytotoxicity-associated SNPs in cell lines derived from the population most sensitive to platiniting agents (ASN, n = 90) and showed that 13 of the SNPs also associated with either carboplatin or cisplatin IC₅₀ in a combined CEU1/2 and YRI1/2 population (n = 106).³⁵ One of these SNPs, rs6691275, remained associated with carboplatin IC₅₀ in the current study (meta- P = 3.1 × 10⁻⁴) and the direction of effect was the same in six of the seven
tested HapMap panels. The association signal for the other 12 SNPs was lost, due to discordant directions of effect when the additional panels were added, again likely due to limited power in the initial study. However, the direction of effect was the same in the two panels of Asian ancestry (ASN, CHD) for 10 of the 13 SNPs, indicating the SNPs could associate with cytotoxicity in a population-specific manner.

Our results show that many genes and variants may be involved in cellular response to platting agents. As most of the variants that associate with platinum-induced cytotoxicity are polymorphic across multiple world populations (African, Asian, European), they can be tested in follow-up studies in both LCL and tumor cell line panels from multiple populations, or in diverse clinical populations. Our cell line models allow us to select the most promising SNPs for testing in clinical studies. We plan to clinically validate cytotoxicity-associated variants in a cohort of patients treated with carboplatin or cisplatin to determine their roles in patient response and toxicity.

Conflict of interest
The authors declare no conflict of interest.

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