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Higher frequency of genetic variants conferring increased risk for ADRs for commonly used drugs treating cancer, AIDS and tuberculosis in persons of African descent

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Abstract

There is established clinical evidence for differences in drug response, cure rates and survival outcomes between different ethnic populations, but the causes are poorly understood. Differences in frequencies of functional genetic variants in key drug response and metabolism genes may significantly influence drug response differences in different populations. To assess this, we genotyped 1330 individuals of African (n = 372) and European (n = 958) descent for 4535 single-nucleotide polymorphisms in 350 key drug absorption, distribution, metabolism, elimination and toxicity genes. Important and remarkable differences in the distribution of genetic variants were

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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observed between Africans and Europeans and among the African populations. These could translate into significant differences in drug efficacy and safety profiles, and also in the required dose to achieve the desired therapeutic effect in different populations. Our data points to the need for population-specific genetic variation in personalizing medicine and care.

Keywords

pharmacogenomic diversity; genetic ancestry; drug response; ADRs

INTRODUCTION

Drug response, cure rates and survival outcomes for many diseases have improved significantly over the last few decades, but not all populations have benefited equally from this progress. In particular, there is growing clinical evidence concerning differences in the incidence of adverse drug reactions (ADRs) by population.[1] ADRs represent the fourth leading cause of morbidity and mortality in developed countries, with direct medical costs of US$137–177 billion annually in the USA alone.[2–4] The cost and contribution of ADRs to patient morbidity, hospitalization and mortality in African countries are not known.

Several observations have pointed to the fact that African and Hispanic populations are generally at increased susceptibility to ADRs, and have poorer survival and response rates for many diseases and medications when compared with European and Asian populations.[5,6] For example, the rate of cisplatin-related toxicity has been shown to be significantly higher amongst African Americans compared with western Europeans (47.6% vs 8.3%, P=0.007)[7] The maximum tolerable dose of cisplatin is 40% lower in the South African Black population compared with western countries (25 vs 40 mg m^{-2} per week).[8] The risk and frequency of cardiotoxicity and congestive heart failure (CHF) after anthracycline treatment has been reported to be significantly higher in African compared with European populations (1.7-fold greater relative risk and 7% vs 2.4% frequency, P<0.027, odds ratio = 2.93).[9,10] African ancestry has also been associated with increased likelihood of anthracycline dose reduction, early termination of treatment and decreased survival rates when compared with Europeans.[11] African populations also have poorer survival and response rates,[12] and experience significantly more frequent hematologic toxicities of leukopenia and anemia when compared with Europeans (P<0.006) after treatment with 5-fluorouracil (5-FU).[13]

The causes of these differences are poorly understood but could be due to genetic, clinical and/or environmental factors. The recent identification of the genetic basis of drug response and ADRs for many agents now makes it possible to identify the genetic causes of drug response differences at a population level. In the current study, we tested the hypothesis that the differences in frequencies of genetic variants in key genes involved in drug biotransformation may underlie these differences in ADR rates and response to therapy by population. Studies on pharmacogenomic diversity in African populations are underrepresented in published genomic and pharmacogenomic research and this study begins to address this deficiency.[14–15]

MATERIALS AND METHODS

Study population

Our study population (n = 1330) consisted of individuals of African (n = 372) and European (n = 958) descent. Individuals of African ancestry were drawn from indigenous ethnically, geographically, linguistically and culturally diverse African populations originating from Eastern (Kenya and Tanzania), Central (Cameroon and Chad), Western (Nigeria), Saharan (Sudan),[14] and Southern (South Africa) Africa, recruited via field expeditions (Table 1). Europeans were from North America (Canada) recruited via the Canadian Pharmacogenomics Network for Drug Safety, a multicenter active drug surveillance and pharmcogenomics consortium.[17] All genetic ancestries were self-reported and verified by principal component analysis. All participants were verified for cryptic relatedness using identity by descent estimation, and no duplicates (>99% identity) or related individuals (86–98% identity) were found.

This study was approved by the ethics committees of the universities and institutions participating in the scientific projects of the Canadian Pharmacogenomics Network for Drug Safety and the ethics committee of the University of Pennsylvania. Written informed consent was obtained from all participants or from the parents or legal guardians in case of minors in accordance with the Helsinki Declaration as revised in 2008 (http://www.wma.net/en/30publications/10policies/b3/index.html, accessed 4 March 2013).

Pharmacogenomic assay design and variant clinical annotation

Our assay was designed to genotype for 4535 single-nucleotide polymorphisms (SNPs) in 350 key genes involved in drug biotransformation, drug response and ADRs, and included transporters, enzymes, receptors, ion channels, transcription factors and drug targets. The candidate genes were selected based on their physiological roles in drug absorption, distribution, metabolism, elimination and toxicity. Genetic variations in the absorption, distribution, metabolism, elimination and toxicity genotyping panel were selected to have the maximum set of informative markers to assay the candidate genes. Tagging SNPs were selected by IdSelect algorithm,[18] using data from the International HapMap consortium.[19] Functional SNPs were identified via publicly available databases (PharmGKB, HuGENet, ALFRED) and also from published information about their role in protein structure and/or function. Clinical annotations were curated from PharmGKB,[20] Hiv-pharmacogenomics.org,[21] and published studies[22–26]

Genotyping and quality control

Genomic DNA was extracted from blood, saliva or buccal swab samples using the QIAamp DNA purification system (Qiagen, Toronto, Ontario, Canada) and quantified by Quant-iT PicoGreen assay (Invitrogen, Eugene, OR, USA), according to the manufacturer's protocols. A total of 1330 DNA samples were genotyped using a customized Illumina GoldenGate SNP genotyping assay (Illumina, San Diego, CA, USA). Genotypes were called with the Illumina Genome Studio software package (Illumina). All samples in the study cohort were used to determine cluster boundaries in order to maximize clustering accuracy. The clusters were then evaluated using automated scripts, while the ambiguous ones were evaluated

manually. Twenty samples and 326 SNPs with call rates below 90% were excluded from the analyses (average call rate for included samples = 95.0% and SNPs = 99.8%). Quality control analysis was performed by date of genotyping and by plate to check for systematic errors in the generated data set. No systematic errors were found. After quality control, 1310 samples and 4209 SNPs remained for further analyses.

Statistical analyses

Statistical analyses were performed using SVS/HelixTree 7.6.8 (Golden Helix, Bozeman, MT, USA). Fisher's exact test was used for comparing allele frequencies among populations and an ANOVA F-test was used to explore the pharmacogenomic diversity in African populations. The type-I error rate of 0.05 was used as a significance threshold after Bonferroni correction for 4209 tests.

RESULTS

Pharmacogenomic diversity and population ancestry

Distribution of pharmacogenomic polymorphisms—We compared allele frequencies between African and European populations (Supplementary Table 1). Several variants in the cytochrome P4503A (*CYP3A*) family showed the most significant differences and were more frequent in African compared with European populations: *CYP3A* rs4646450 −90.34% vs 16.77%, *P*=6.93E-274; *CYP3A4* rs2740574 −66.25% vs 3.25%, *P*=3.95E-257; *CYP3A4* rs2242480 −77.59% vs 11.14%, *P*=2.92E-231; *CYP3A4* rs4646437 − 77.73% vs 11.45%, *P*=1.43E-229; *CYP3A5* rs776746 − 74.37% vs 10.13%, *P*=3.60E-221; and *CYP3A* rs6945984 − 76.89% vs 12.72%, *P* = 3.52E-212 (Table 2). Striking differences were also observed for other cytochrome P450 variants and variants in solute carrier and ATP-binding cassette transporters.

Most ADR-associated risk variants or variants associated with poor response or shortened survival rates were more frequent in African populations compared with Europeans (Supplementary Table 2). Specific examples of clinically important differences between African and European populations focusing on cancer, antiretroviral and antimicrobial pharmacogenomics are provided here, while other examples can be found in the Supplementary Material of this manuscript (Supplementary Tables 1–2).

Pharmacogenomic diversity in cancer therapy

Anthracyclines and related substances—*UGT1A6* rs17863783, *ABCC2* rs8187694, *ABCC2* rs8187710, *ABCB1* rs2235047 and *ABCC1* rs4148350 have been associated with the risk of anthracycline-induced cardiotoxicity (ACT) and CHF,[22,23] while *RAC2* rs13058338, *SULT2B1* rs10426377, *CBR1* rs9024 and *HNMT* rs17645700 have been shown to have a protective effect.[22,23] Also, *ABCB1* rs2032582 has been clinically linked to improved survival and response rates,[26] while *CYP2B6* rs3745274 has been associated with decreased tolerance and survival.[27] The distributions of these variants were significantly different between African and European populations (Table 3). *UGT1A6* rs17863783 (12.04% vs 2.78%, *P*=9.75E-15), *ABCC2* rs8187694 (14.29% vs 5.37%, *P*=2.54E-09), *ABCC2* rs8187710 (22.99% vs 5.47%, *P* = 8.87E-31), *ABCB1* rs2235047 (18.21% vs 2.52%,

P=3.84E-36), *ABCC1* rs4148350 (13.48% vs 5.43%, *P*=2.09E-07), *RAC2* rs13058338 (10.92% vs 24.97%, *P*=.09E-12), *SULT2B1* rs10426377 (17.51% vs 27.39%, *P*= 4.66E-04), *CBR1* rs9024 (1.40% vs 12.46%, *P*=1.73E-19), *HNMT* rs17645700 (4.76 vs 20.17, *P*=4.57E-22), *ABCB1* rs2032582 (3.78% vs 45.10%, *P*=1.87E-106) and *CYP2B6* rs3745274 (77.73% vs 24.97%, *P*=4.34E-131). Variants associated with increased risk of ACT and CHF and decreased tolerance and survival were more frequent in African populations, while those associated with protection against ACT and CHF and improved survival and response rates were less frequent.

Cisplatin and platinum compounds—*COMT* rs9332377 has been associated with increased risk of cisplatin-induced hearing loss,[28] *MTR* rs1805087 associated with reduced risk of cisplatin-induced toxicity, *XRCC1* rs25487 associated with decreased risk of severe neutropenia when treated with platinum compounds (cisplatin, carboplatin, oxaliplatin and platinum)[29] and *MTHFR* rs1801133 clinically linked to increased response to platinum compounds.[30] The allele frequencies of these pharmacogenomic variants were significantly different between African and European populations (Table 4). *COMT* rs9332377 (32.68% vs 16.82%, *P*=5.40E-14), *XRCC1* rs25487 (14.85% vs 35.07%, *P*=.37E-22), *MTR* rs1805087 (0.27.17 vs 18.68, *P*=.0142) and *MTHFR* rs1801133 (6.86% vs 34.77%, *P*=. 57E-51). Pharmacogenomic variants associated with increased risk of toxicity related to platinum compounds were more common in African populations, while variants associated with decreased risk were less common. Also, variants associated with improved response to platinum compounds were less frequent in African populations.

Fluororuracil—The majority of 5-FU-induced toxicity are related to the deficiency of dihydropyrimidine dehydrogenase, an enzyme, which metabolizes 5-FU. The common mutations in the dihydropyrimidine dehydrogenase gene—*DPYD* (*DPYD* rs1801265 and *DPYD* rs2297595) have been associated with fluoropyrimidine-related toxicity in cancer patients,[31,32] while *MTHFR* rs1801133 has been linked to improved survival and response rates.[33] The distributions of these mutations were different in African and European populations (Table 5). *DPYD* rs1801265 −48.88% vs 22.19%, *P*=4.46E-35; *DPYD* rs2297595 −19.75% vs 10.19%, *P*=1.30E-06; *MTHFR* rs1801133 −6.86% vs 34.77%, *P*=2.57E-51. Pharmacogenomic variants associated with increased risk of 5-FU-induced toxicity were more frequent in African populations, while MTHFR rs1801133 associated with improved response was less frequent.

Vincristine—Vincristine is a metabolic substrate for CYP3A5. It has been shown that increased risk of vincristine-induced neurotoxicity is associated with low CYP3A5 expression.[34] Therefore, mutations in *CYP3A5* may influence the efficacy and toxicity of vincristine. We explored the distribution of *CYP3A5* mutations in African and European populations. Strikingly significant differences were observed for the following *CYP3A5* polymorphisms: *CYP3A5* rs776746 −74.37% vs 10.13%, *P*=3.60E-221; *CYP3A5* rs10224569 − 28%.37% vs 0.0%, *P*=2.39E-121; *CYP3A5* rs10264272 −22.33% vs 0.32%, *P*=2.44E-83; *CYP3A5* rs10249369 − 21.91% vs 0.58%, *P*=1.02E-75; *CYP3A5* rs41303343 − 7.56% vs 0.10% *P*=2.59E-25; *CYP3A5* rs6956305 −9.10% vs 4.41%, *P*=0.0443)—Table 6. Also, significant differences were observed for *MTHFR* rs1801133 (34.77% vs 6.86%,

P=2.57E-51) and *NOS* rs1799983 (33.80% vs 4.95%, *P*=8.47E-012) that have been associated with other vincristine-related toxicities.[35,36] *CYP3A5* polymorphisms were more frequent in African compared with European populations. In contrast, ADR-associated variants and *ABCB1*13* (3.78% vs 45.10% *P*=1.87E-106) that has been associated with efficacy[26] were less frequent in African populations.

Pharmacogenomic diversity in antiretroviral and antimycobacterial therapy— *CYP2B6* rs28399499 is associated with Nevirapine-induced hepatotoxicity.[21] *CYP2B6* rs3745274 is associated with rifampicin-induced liver injury and with efavirenz-induced lowered HDL levels, hepatotoxicity, neurotoxicity, fatigue and sleep disorders and early termination of treatment.[21] Also, *ABCC2* rs717620, *ABCC2* rs17222723 and *ABCC4* rs1751034 are associated with Tenofovir-induced proximal tubulopathy and kidney tubular dysfunction and *APOE* rs429358 associated with extreme hypertriglyceridemia.[20,21] The allele frequencies of these variants were significantly higher in the African compared with European populations (*CYP2B6* rs28399499 − 5.20% vs 0.052%, *P*=7.04E-17; *CYP2B6* rs3745274 −77.73% vs 24.97%, *P*=4.34E-131; *ABCC2* rs717620 −19.77% vs 3.24%, *P*=4.54E-28; *ABCC2* rs17222723 − 14.29% vs 5.46%, *P*=5.94E-09; *ABCC4* rs1751034 −30.95% vs 17.79%, *P*=4.77E-09; *APOE* rs429358 −24.86% vs 13.27%, *P*=5.75E-08 −Table 7), which would be compatible with increased frequency of ADRs with these drugs.

Pharmacogenomic diversity among African populations

We characterized and compared allele frequencies in five different African populations (Supplementary Tables 3–5). The F-statistics and P-values revealed high pharmacogenomic diversity among African populations. The most clinically relevant diversity was observed for *VKORC1* rs7294 (*P*=8.93E-21), which is associated with warfarin dosage requirement[37] (Table 8). Other top clinically annotated variations include *VKORC1* rs8050894 (*P*=8.92E-07) for warfarin dosage[38] and several cytochrome P450 variants associated with response to immunosuppressive drugs (*CYP2B6* rs2279343 - *P*=.46E-20 for cyclophosphamide-induced mucositis,[39] *CYP2B6* rs8192709 - *P*=.0167 for cyclophosphamide-induced hemorr-hagic cystitis[39] and *CYP3A5* rs776746 - *P*=.14E-09 for cyclospo-rine dosage requirements[20]).

Pharmacogenetic variant frequencies including the frequencies of the CYP enzymes were observed to be remarkably variable within African populations as demonstrated by the following examples (Table 9 and Supplementary Table 3):

Antharcycline—The *UGT1A6*4* haplotype associated with the risk of ACT and clinical heart failure was more frequent among Saharan (18.4%), Southern (12.9%) and Eastern (12.8%) Africans compared with Central (9.9%) and Western (8.8%) Africans.

Cisplatin—*COMT* rs9332377, which is associated with increased risk of cisplatin-induced hearing loss, was less common among Western (20.6%) and Saharan (23.7%) Africans compared with Eastern (35.2%), Southern (33.0%) and Central (32.3%) Africans.

Antiretroviral therapy—*ABCC4* rs1751034 is associated with Tenofovir-induced proximal tubulopathy and kidney tubular dysfunction. This variant is very frequent among Western Africans (44.1%), intermediate among Central (32.5%), Eastern (30.5%) and Southern (29.2%) Africans, and comparatively less frequent in Saharan Africans (23.7%). Also, *CYP2B6* rs28399499, which is associated with Nevirapine-induced hepatotoxicity is rare among Saharan (0.0%), Central (1.2%) and Western (2.9%) Africans, and relatively more common in Southern (8.0%) and Eastern (6.7%) Africans.

DISCUSSION

In this manuscript, we have chosen to focus on antineoplastic, antiretroviral and antimycobacterial commonly used drugs from the WHO Model List of Essential Medicines. Cancer, HIV/AIDS and tuberculosis and their associated ADRs are major public health problems and have become the primary focus in health-care. In general, a higher frequency of genetic variants conferring increased risk to ADRs for different and commonly used antineoplastic, antiretroviral and antituberculosis drugs was evident in African populations.

Anthracyclines are a group of very efficacious chemotherapeutic agents and have been part of the backbone of therapy worldwide including Africa for the treatment of many cancers including leukemia, lymphoma, sarcomas, Wilms' tumor, hepato-blastoma, and uterine, ovarian, lung and breast cancers. They are used to treat over 70% of all childhood malignancies, as well as 50–90% of breast cancer patients each year.[40] Their clinical utility is primarily limited by a highly individually variable, cumulative dose-dependent, cardiac toxicity, manifesting as asymptomatic cardiac dysfunction in up to 57% of treated patients[41,42] and restrictive or dilated cardiomyopathy resulting in CHF in up to 16% of treated patients.[43] African populations are more sensitive to ACT and CHF when compared with Europeans (1.7-fold greater relative risk; frequency −7% vs 2.4%, $P<0.027$, odds ratio = 2.93).[9,10] The enrichment of genetic risk factors for ACT and CHF such as *UGT1A6* rs17863783, *ABCC2* rs8187694, *ABCC2* rs8187710, *ABCB1* rs2235047 and *ABCC1* rs4148350, in African populations suggests that these genetic differences may partially account for the increased sensitivity to ACT and CHF in African populations. Also, the enrichment of pharmacogenetic factors such as *CYP2B6* rs3745274 associated with poor drug tolerance and poor survival rates[27] could contribute to the reported increased likelihood of dose reduction, early termination of treatment and decreased survival rates in African populations.[11]

Cisplatin, carboplatin and oxaliplatin are all platinum compounds that have excellent antineoplastic properties. Cisplatin is the drug of choice for solid tumors including hepatoblastoma, osteosarcoma, neuroblastoma and ovarian, central nervous system, testicular, cervical, lung, bladder, head and neck tumors.[44] Major complications include ototoxicity, nephrotoxicity, neurotoxicity and myelotoxicity. Irreversible hearing loss (ototoxicity) occurs in 10–25% of treated adults, 50% of patients treated with high doses (>400mgm^{-2}) and 41–61% of treated children[45–47] Cisplatin-related toxicity is more frequent in African populations when compared with the European population (47.6% vs 8.3%, $P = 0.007$)[7] Also, the maximum tolerable dose is 40% lower in African populations (25 vs 40 mg m^{-2} per week).[8] In the current study, an overrepresentation of *COMT*

rs9332377 (32.58% vs 16.82%) variants associated with increased risk of hearing loss[28] and a depletion of *XRCC1* rs25487 (14.85% vs 35.07%) associated with protection against cisplatin-induced neutropenia,[29] in African populations, was evident. This correlates with the reported increased frequency of cisplatin-induced toxicity in these populations and suggests that these differences in allele frequency may contribute to the increased ADR rates in these populations.

5-FU is a very effective drug commonly used in the treatment of advanced stage colon cancer and several other types of cancer including, breast, esophageal and stomach cancers. About 30% of 5-FU-treated patients suffer from severe and sometimes deadly toxicity including hematologic toxicities of leukopenia and anemia, myelosuppression, diarrhea, nausea, vomiting, mucositis and dermatitis.[1] Poorer survival and decreased response rates,[12] and more frequent toxicities have been reported in African Americans when compared with Europeans ($P<0.006$).[13] An enrichment of risk factors for dihydropyrimidine dehydrogenase deficiency such as the *DPYD* variants (rs1801265 −48.88% vs 22.19% and rs2297595 −19.75% vs 10.19%) and a decrease in the frequency of *MTHFR* rs1801133 (6.9% vs 34.8%) linked to increased therapeutic response was evident[33] in Africans compared with Europeans. These genetic findings could at least partially explain differences in ADR rates and drug responsiveness between these two populations.

Vincristine is a commonly prescribed vinca alkaloid and is used in the treatment of both hematological and solid malignancies. In the US alone, vincristine is used to treat over 50% of all childhood cancers and ~30 000 adults cancer patients.[34] Vincristine-induced neurotoxicity has been found in 34.8% of Europeans vs 4.8% of African Americans ($P = 0.007$). Europeans have been shown to have a higher average grade of neurotoxicity (2.72 vs 1, $P<0.0001$) and require dose reduction (4% vs 0.1%, $P<0.0001$) and dose omission (1.2% vs 0.1%, $P<0.01$) when compared with African populations.[48] The biotransformation of vincristine is CYP3A5-dependent.[1] The current study found an increased frequency of CYP3A5 polymorphisms in African populations, which correlates with the reported increased in the expression of CYP3A5 in these populations when compared with Europeans (10–30% vs 60–70%).[1,49–51] Increased CYP3A5 expression would increase the clearance of vincristine, thus lowering the concentration of the drug in the body and decrease the risk of vincristine-related toxicity in African populations. This could possibly be a mechanism by which African populations are protected from vincristine-related toxicity.

African populations experience more frequent antiretroviral and antimycobacterial drug-induced toxicities compared with Europeans. The incidence of nevirapine-induced hepatotoxicity is 17% among South Africans Blacks compared with 1–10% in Europeans, while 10% of Africans discontinue efavirenz therapy because of persistent toxicity compared with only 3% of Europeans.[52] Also, 69% of Africans compared with 50% of European patients experience neurotoxicity after initiation of efavirenz therapy.[52] This correlates with an overrepresentation of pharmacogenetic risk variants such as *ABCC2* rs717620, *ABCC2* rs17222723, *ABCC4* rs1751034, *CYP2B6* rs28399499, *CYP2B6* rs3745274, *APOE* rs429358 and *CYP2B6* rs3745274 in Africans compared with Europeans as observed in the current study. *CYP2B6* rs3745274 is also associated with rifampicin-induced liver injury, an important drug used in antituberculous therapy.[20,21] Even though

differences in the incidence between Africans and Europeans are currently not known, this result indicates the possibility of such differences, which should be investigated in the future.

Overall, *CYP3A* variants showed the most significant differences and were more frequent in Africans compared with Europeans. *CYP3A* enzymes are involved in the metabolism of ~40–60% of all drugs.[53] Their expression varies significantly by population, with increased expression of *CYP3A5* in particular reported in African compared with European populations (10%–30% of Europeans vs 60%–70% of Africans).[49–51] This observation is consistent with the observed dramatic enrichment of *CYP3A5* variants in African compared with European populations in the current study. Renbarger has postulated that *CYP3A5* gene region could explain most of the drug response differences by population.[48] Other striking differences were observed with ATP-binding cassette and solute carrier transporters, indicating the additional contribution of other genes. In general, we observed an enrichment of genetic variants, which could underlie an enhanced predisposition to several ADRs and poor response rates in Africans compared with Europeans.

The current study also observed important differences among the African populations, which could translate to significant differences in drug efficacy and safety profiles, and also in the dose required to achieve the desired therapeutic effect in different African populations. This is consistent with the reported highly variable distribution of ABCB1, VKORC1 and CYP enzymes among African populations.[54,55] This pharmacogenomic heterogeneity across different ethnic groups and geographical regions within African populations highlights the challenge faced by regulatory agencies in African countries when assessing new drug applications especially when there is minimal or no data from local clinical trials. Therefore, an important area of focus for improving drug distribution and access in African populations is the development and effective use of pharmacovigilance systems to monitor drug response in treated patients in order to avoid, in particular, serious and permanently disabling ADRs. Also, local trials to assess the frequency of ADRs will be important.

The current study places emphasis on the importance of including different populations in the development of biomarkers for pharmacogenetic testing, clinical practice guidelines, and clinical trials. To the best of our knowledge, it is the largest study of pharmacokinetic and pharmcodynamic genetic markers to dissect the pharmacogenomic variation at the level of individual populations and the first to have included such a large number of individuals recruited from different indigenous African populations. This study clearly demonstrates that clinical trials and safety studies, which are typically done in European populations, cannot be extrapolated to African populations. Furthermore, it also highlights the compounded challenge of population heterogeneity with respect to the delivery of health-care services in Canada and the USA. This type of study can inform clinical practice and clinical trials and is imperative for tailoring therapy towards individual populations. Our study population is not the complete representative sample of all African and European populations, but points to the need for local studies of genetic variants contributing to ADRs within all populations.

We have shown that there are important differences in the distribution of genetic variants in key drug biotransformation genes by population. These could translate to significant differences in drug response and toxicity rates. African populations have a pharmacogenetic enrichment to ADR susceptibility when compared with Europeans, which could explain the increased susceptibility and conferring poorer survival and response rates in these populations. This observation highlights the need for further investment in active drug surveillance systems, which should be central to all health-care systems to ensure each patient achieves maximal therapeutic benefit and minimal toxicity. Even though studies of pharmacogenomic differences among populations predicts the existence of drug response differences by populations, some of which have already being elucidated, a prospective evaluation of the relationship between pharmacogenomic diversity and drug response variability will be warranted to validate these findings. As population diversity, especially in Canada and the USA continues to increase, the need for information on population-specific genetic variation for the implementation of personalized medicine will become more important.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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APPENDIX

THE CANADIAN PHARMACOGENOMICS NETWORK FOR DRUG SAFETY CONSORTIUM

The Canadian Pharmacogenomics Network for Drug Safety Consortium (Participants are arranged geographically by institution across Canada)—**Vancouver, BC, Children's Hospital, Child & Family Research Institute, CMMT, POPi:** Michael Hayden, Bruce Carleton, Colin Ross, Stuart MacLeod, Wyeth Wasserman, Craig Mitton, Anne Smith, Claudette Hildebrand, Lucila Castro Pastrana, Reza Ghannadan, Rod Rassekh, Jonathan

Lim, Fudan Miao, Henk Visscher, Kusala Pussegoda, Folefac Aminkeng, Michelle Higginson, Nasim Massah,Mojgan Yazdanpanah, Johanne Sistonen, Ricardo Jimenez, Adrienne Borrie, Ursula Amstutz, Shevaun Hughes, Kaitlyn Shaw; **Calgary, Alberta Children's Hospital:** Cheri Nijssen-Jordan, David Johnson, Linda Verbeek, Rick Kaczowka, Patti Stevenson, Andrea Hurton; **Edmonton, Stollery Children's Hospital:** Paul Grundy, Kent Stobart, Bev Wilson, Sunil Desai, Maria Spavor, Linda Churcher, Terence Chow; **Winnipeg, Winnipeg Children's Hospital:** Kevin Hall, Nick Honcharik, Sara Israels, Shanna Chan, Byron Garnham, Michelle Staub; **London, London Health Sciences Centre:** Michael Rieder, Becky Malkin; **Hamilton, McMaster Children's Hospital:** Carol Portwine, Amy Cranston; **Toronto, Hospital for Sick Children:** Gideon Koren, Shinya Ito, Paul Nathan, Mark Greenberg, Facundo Garcia Bournissen, Miho Inoue, Sachi Sakaguchi, Toshihiro Tanaka, Hisaki Fujii, Mina Ogawa, Ryoko Ingram, Taro Kamiya & Smita Karande; **Kingston, Kingston General Hospital:** Mariana Silva, Stephanie Willing; **Ottawa, Children's Hospital of Eastern Ontario:** Régis Vaillancourt, Pat Elliott-Miller, Donna Johnston, Herpreet Mankoo, Elaine Wong, Brenda Wilson, Lauren O'Connor; **Health Canada:** Maurica Maher; **Montreal, Hospital Sainte-Justine:** Jean-Francois Bussie`res, Denis Lebel, Pierre Barret, Aure´lie Closon, Eve Coulson; **Montreal Heart Institute:** Marie-Pierre Dube´, Michael Phillips; **McGill University Health Centre-Montreal Children's Hospital:** Nada Jabado, Anelise Espirito Santo, Martine Nagy; **McGill University:** Denise Avard; **Halifax, IWK Health Centre:** Margaret Murray, Darlene Boliver, Marilyn Tiller and Carolanne Osborne.

Table 1

Origin and characteristics of study Population

Population	Country	Ethnic group	Subsistence	Latitude	Longitude	Language family	Language major subgrouping	Sample size
North America	Canada	Europeans	—	—	—	English	Canadian English	958
Central Africa	Cameroon	Fulani	Herder	9	13.5	Niger-Kordofanian	Senegambian	19
		Lemande	Farmer	4.5	11	Niger-Kordofanian	Bantoid	19
		Mada	Farmer	10.8	14.1	Afro-Asiatic	Chadic	19
		Bakola Pygmy	Hunter-gatherer	2.8	10	Niger-Kordofanian	Bantoid	19
	Chad	Bulala	Farmer (with fishing)	13	18	Nilo-Saharan	Central Sudanic	16
Eastern Africa	Kenya	Boni	Hunter-gatherer	—	—	—	—	19
		Borana	Herder	3	38	Afro-Asiatic	Cushitic	19
		Luo	Herder	−0.5	34.5	Nilo-Saharan	Eastern Sudanic	19
		Sengwar	Hunter-gatherer	1	35	Nilo-Saharan	Eastern Sudanic	19
	Tanzania	Datog	Herder	−4.5	35.5	Nilo-Saharan	Eastern Sudanic	19
		Hazda	Hunter-gatherer	−3.5	35.3	Khoesan	Hazda	19
		Iraqw	Mixed farmer	−4	35.5	Afro-Asiatic	Cushitic	19
		Sandawe	Hunter-gatherer	−5.5	35.5	Khoesan	Sendawe	18
Western Africa	Nigeria	Yoruba	Farmer	8	4	Niger-Kordofanian	Defoid	19
Saharan Africa	Sudan	Beja	Herder	21	36	Afro-Asiatic	Cushitic	19
Southern African	South Africa	Tswana/Xhosa/ Venda	Farmers/Miners	—	—	Afrikaans	Afrikaans	91
Study Sample Size								**1330**

Table 2

Pharmacogenomic diversity and genetic ancestry (top 20 ADME gene variants)

Gene	Variant	CHR	Position	Functional annotation	Alleles[a]	MAF—African ancestry	MAF—European ancestry	Bonferroni *P*-value[b,c]
CYP3A	rs4646450	7	99104254	Intron	A/G	0.903	0.168	6.93E-274
CYP2B6	rs34097093	19	46210210	Coding NONSYN R378* (CYP2B6*28)	G/A	0.562	0.002	2.68E-262
CYP3A4	rs2740574	7	99220032	Flanking_5UTR	G/A	0.662	0.033	3.95E-257
GSTA1/2/3/4/5	rs6577	6	52723374	Coding NONSYN E210A	C/A	0.709	0.057	2.51E-250
ABCC1/6	rs246227	16	16043648	Intron	G/A	0.749	0.083	1.06E-244
CYP3A4	rs2242480	7	99199402	Intron	A/G	0.776	0.111	2.92E-231
CYP3A4	rs4646437	7	99203019	Intron	A/G	0.777	0.114	1.43E-229
CYP3A5	rs776746	7	99108475	Intron	A/G	0.744	0.101	3.60E-221
TBXAS1	rs4529	7	139308433	Coding NONSYN L357V	C/G	0.478	0.001	1.49E-219
ABCG2	rs2622610	4	89246566	Intron	A/G	0.689	0.077	2.60E-213
CYP3A	rs6945984	7	99186264	Flanking_3UTR	G/A	0.769	0.127	3.52E-212
SLCO1B3	rs7311358	12	20907027	Coding NONSYN M233I	G/A	0.846	0.193	3.39E-208
CYB5R3	rs137124	22	41345660	Flanking_3UTR	G/A	0.843	0.194	1.29E-206
SLC28A1	rs16974622	15	83265515	Intron	G/A	0.620	0.050	6.25E-203
PPARD	rs6901410	6	35438008	Intron	G/A	0.655	0.073	8.79E-198
ALDH7A1	rs3736171	5	125959275	Flanking_5UTR	A/C	0.768	0.145	9.80E-196
ABCA4	rs3789375	1	94237720	Intron	C/A	0.724	0.116	1.80E-194
PPARD	rs6457816	6	35470826	Intron	G/A	0.657	0.077	2.08E-194
ALDH2	rs2238151	12	110696216	Intron	A/G	0.050	0.658	5.15E-193
CYP27A1	rs6436094	2	219395841	Flanking_3UTR	G/A	0.890	0.262	6.52E-191

Abbreviations: ADME, absorption, distribution, metabolism, elimination and toxicity; CHR, chromosome; MAF, minor allele frequency; SNP, single-nucleotide polymorphism; UTR, untranslated region.

[a] Minor/major.

[b] Corrected *P*-value (4209 SNPs).

[c] Statistics—Fisher's exact test.

Table 3

Pharmacogenomic diversity and response to anthracyclines and related substances

Drug response[a]	Gene	Variant	CHR	Position	Functional annotation	Alleles[b]	African ancestry[c]	European ancestry[c]	Bonferroni *P*-value[d,e]
TOXICITY/ADR Increased risk of cardiotoxicity and heart failure	*UGT1A6*	rs17863783	2	234267016	Coding SYNON V209V	A/C	0.120	0.028	9.75E-15
	ABCC2	rs8187694	10	101585986	Coding NONSYNON	T/A	0.143	0.054	2.54E-09
	ABCC2	rs8187710	10	101601284	Coding NONSYN (C1515Y)	A/G	0.230	0.055	8.87E-31
	ABCB1	rs2235047	7	86976468	Intron	C/A	0.182	0.025	3.84E-36
	ABCC1/6	rs4148350	16	16077978	Intron	A/C	0.135	0.054	2.09E-07
TOXICITY/ADR Decreased risk of cardiotoxicity and heart failure	*RAC2*	rs13058338	22	35962716	Intron	T/A	0.109	0.250	1.09E-12
	SULT2B1	rs10426377	19	53784046	Intron	A/C	0.175	0.274	4.66E-04
	CBR1	rs9024	21	36367183	Flanking_3UTR	A/G	0.014	0.125	1.73E-19
	HNMT	rs17645700	2	138497402	Flanking_3UTR	G/A	0.048	0.202	4.57E-22
DOSAGE Increased likelihood of dose reduction	*CYP2B6*	rs3745274	19	46204681	Coding NONSYN Q172H (CYP2B6*6)	A/C	0.777	0.250	4.34E-131
EFFICACY increased response	*ABCB1*	rs2032582	7	86998554	Coding NONSYNON (ABCB1*13 and ABCB1*2)	A/C	0.038	0.451	1.87E-106

Abbreviations: ADR, adverse drug reaction; CH, chromosome; SNP, single-nucleotide polymorphism; UTR, untranslated region.

[a] Clinical information for relevant pharmacogenomics variants were curated from PharmGKB,[20] and published studies.[22–26]

[b] Alleles = minor allele/major allele.

[c] Variant minor allele frequency (MAF).

[d] Corrected *P*-value (corrected for 4209 SNPs).

[e] Statistical test—Fisher's exact test.

Table 4

Pharmacogenomic diversity and response to cisplatin and platinum compounds

Drug	Drug response[a]	Gene	Variant	CH	Position	Functional annotation	Alleles[b]	African ancestry[c]	European ancestry[c]	Bonferroni *P*-value[d,e]
Cisplatin	TOXICITY/ADR Increased risk of hearing loss (Ototoxicity)	*COMT*	rs9332377	22	18335692	Intron	A/G	0.327	0.168	5.40E-14
	TOXICITY/ADR Decreased risk of severe neutropenia	*XRCC1*	rs25487	19	48747566	Coding NONSYN Q399R	A/G	0.148	0.351	3.37E-22
	TOXICITY/ADR Increased likelihood of drug toxicity	*MTR*	rs1805087	1	235115123	Coding NONSYN D919G	G/A	0.272	0.187	0.0142
	EFFICACY Increased response	*MTHFR*	rs1801133	1	11778965	Coding NONSYN A222V	A/G	0.069	0.348	2.57E-51
Carboplatin	TOXICITY/ADR Decreased risk of severe neutropenia	*XRCC1*	rs25487	19	48747566	Coding NONSYN Q399R	A/G	0.148	0.351	3.37E-22
	EFFICACY Increased response	*MTHFR*	rs1801133	1	11778965	Coding NONSYN A222V	A/G	0.069	0.348	2.57E-51
Oxaliplatin	TOXICITY/ADR Decreased risk of severe neutropenia	*XRCC1*	rs25487	19	48747566	Coding NONSYN Q399R	A/G	0.148	0.351	3.37E-22
	EFFICACY Increased response	*MTHFR*	rs1801133	1	11778965	Coding NONSYN A222V	A/G	0.069	0.348	2.57E-51

Abbreviations: ADR, adverse drug reaction; CH, chromosome; SNP, single-nucleotide polymorphism.

[a] The clinical annotations of the relevant pharmacogenomics variants were curated from PharmGKB[20] and published studies.[28–30,33]

[b] Minor allele/Major allele.

[c] Variant minor allele frequency (MAF).

[d] Corrected *P*-value (corrected for 4209 SNPs).

[e] Statistical test—Fisher's exact test.

Table 5

Pharmacogenomic diversity and response to fluorouracil

Drugs	Drug response[a]	Gene	Variant	CH	Position	Function	Alleles[b]	African ancestry[c]	European ancestry[c]	Bonferroni *P*-value[d,e]
PYRIMIDINE COMPOUNDS Fluorouracil	TOXICITY/ADR Increased risk of middle-severe nausea and vomiting	*DPYD*	rs1801265	1	98121473	Coding NONSYN r29c (DPYD*9A)	G/A	0.489	0.222	4.46E-35
	TOXICITY/ADR Increased risk of severe toxicity	*DPYD*	rs2297595	1	97937679	Coding NONSYN M166V	G/A	0.197	0.102	1.32E-06
	EFFICACY Increased response	*MTHFR*	rs1801133	1	11778965	Coding NONSYN A222V	A/G	0.069	0.348	2.57E-51

Abbreviations: ADR, adverse drug reaction; CH, chromosome; SNP, single-nucleotide polymorphism.

[a] The clinical annotations of the relevant pharmacogenomics variants were curated from PharmGKB[20] and published studies.[31–33,56,57]

[b] Minor allele/Major allele.

[c] Variant minor allele frequency (MAF).

[d] Corrected *P*-value (corrected for 4209 SNPs).

[e] Statistical test—Fisher's exact test.

Table 6

Pharmacogenomic diversity and response to vincristine

Drug response[a]	Gene	Variant	CH	Position	Function	Alleles[b]	African ancestry[c]	European ancestry[c]	Bonferroni *P*-value[d,e]
TOXICITY/ADR Increased risk of drug toxicity	*MTHFR*	rs1801133	1	11778965	Coding NONSYN A222V	A/G	0.069	0.348	2.57E-51
TOXICITY/ADR Decreased IQ	*NOS*	rs1799983	7	150327044	Coding NONSYN D298E	A/C	0.049	0.338	8.47E-012
EFFICACY Improved Response	*ABCB1*	rs2032582	7	86998554	Coding NONSYNON (ABCB1*13 and ABCB1*2)	A/C	0.038	0.451	1.87E-106
DRUG RESPONSE PATHWAY Vincristine main metabolic substrate	*CYP3A5*	rs776746	7	99108475	Intron (CYP3A5*3)	A/G	0.744	0.101	3.60E-221
	CYP3A5	rs10224569	7	99086240	Intron	A/G	0.284	0	2.39E-121
	CYP3A5	rs10264272	7	99100771	Coding SYNON K208K (CYP3A5*6)	A/G	0.223	0.003	2.44E-83
	CYP3A5	rs10249369	7	99084928	Intron	G/A	0.219	0.006	1.02E-75
	CYP3A5	rs41303343	7	99088358	Coding FRAMESHIFT	A/T	0.076	0.001	2.59E-25
	CYP3A5	rs6956305	7	99079246	Flanking_3UTR	G/A	0.091	0.044	0.0443

Abbreviations: ADR, adverse drug reaction; CH, chromosome; IQ, intelligence quotient; SNP, single-nucleotide polymorphism; UTR, untranslated region.

[a] The clinical annotations of the relevant pharmacogenomics variants were curated from PharmGKB[20] and published studies.[26,35,36,49–51]

[b] Minor allele/major allele.

[c] Variant minor allele frequency (MAF).

[d] Corrected *P*-value (corrected for 4209 SNPs).

[e] Statistical test—Fisher's exact test.

Table 7

Pharmacogenomic diversity and response to antiretroviral and antimycobacterial drugs

Drug	Drug response[a]	Gene	Variant	C	Position	Functional annotation	Sq[b]	African ancestry[c]	European ancestry[c]	Bonferroni *P*-value[d]
Nucleoside reverse-transcriptase inhibitors										
Tenofovir	Increased risk of proximal tubulopathy and risk of kidney tubular dysfunction	*ABCC2* *ABCC2*	rs717620 rs17222723	10 10	101532568 101585986	Flanking_5UTR Coding NONSYNON	G/A T/A	0.968 0.143	0.802 0.055	4.54E-28 5.94E-09
	Increased risk of proximal tubulopathy	*ABCC4*	rs1751034	13	94512977	Coding FRAMESHIFT	G/A	0.310	0.178	4.77E-09
Nonnucleoside reverse-transcriptase inhibitors										
Nevirapine	Increased risk of hepatotoxicity	*CYP2B6*	rs28399499	19	46210061	Coding NONSYN I328T (CYP2B6* 16/*18)	G/A	0.052	0.0005	7.04E-17
Efavirenz	Increase in HDL-cholesterol levels	*CYP2B6*	rs3745274	19	46204681	Coding NONSYN Q172H (CYP2B6*6)	A/C	0.777	0.250	4.34E-131
	Increased risk of neurotoxicity, CNS depression and neuropsychiatric disorders	*CYP2B6*	rs3745274	19	46204681	Coding NONSYN Q172H (CYP2B6*6)	A/C	0.777	0.250	4.34E-131
	Increased risk of fatigue and sleep disorder	*CYP2B6*	rs3745274	19	46204681	Coding NONSYN Q172H (CYP2B6*6)	A/C	0.777	0.250	4.34E-131
	Increased risk of hepatotoxicity and drug-induced liver injury	*CYP2B6*	rs3745274	19	46204681	Coding NONSYN Q172H (CYP2B6*6)	A/C	0.777	0.250	4.34E-131
Protease inhibitors										
Ritonavir	Increased risk of extreme hypertriglyceridemia	*APOE*	rs429358	19	50103781	Coding NONSYN C130R	G/A	0.249	0.133	5.75E-08
Antituberculosis therapy										
Rifampicin	Increased risk of hepatotoxicity and drug-induced liver injury (DILI)	*CYP2B6*	rs3745274	19	46204681	Coding NONSYN Q172H (CYP2B6*6)	A/C	0.777	0.250	4.34E-131

Abbreviations: C, chromosome; CNS, central nervous system; DILI, drug-induced liver injury; HDL, high-density lipoprotein; MAF, minor allele frequency

[a] Clinical annotation curated from PharmGKB[20] and http://www.hiv-pharmacogenomics.org.[21]

[b] Sq, sequence (minor/major).

[c] MAF.

[d] *P*-value corrected for 4209.

Table 8

Distribution of clinically associated pharmacogenomic variants in African populations (clinically annotated variants that show significant pharmcogenetic diversity across all African populations)

Associated drugs[b]	Associated[b] response	Gene	Variant	CH	Position	Function	F-statistic[c]	Bonferroni *P*-value[a]
Warfarin	Dosage	*VKORC1*	rs7294	16	31009822	flanking_3UTR	34.655	8.93E-21
Cyclophosphamide	Toxicity/ADR	*CYP2B6*	rs2279343	19	46207103	Coding NONSYN K262R (CYP2B6*6)	34.374	1.46E-20
Cyclosporine	Dosage	*CYP3A5*	rs776746	7	99108475	Intron	17.760	1.14E-09
Warfarin	Dosage	*VKORC1*	rs8050894	16	31012010	Intron	13.714	8.92E-07
Thiotepa	Drug clearance	*GSTP1*	rs1138272	11	67110155	Coding NONSYNON A114V	14.343	3.49E-05
Cisplatin, Cyclophosphamide	Toxicity/ADR	*ERCC1*	rs11615	19	50615493	Coding SYNON N118N	10.730	0.0040
Repaglinide	Plasma concentration	*SLCO1B1*	rs2306283	12	21221005	Coding NONSYNON	8.034	0.0139
Cyclophosphamide	Toxicity/ADR	*CYP2B6*	rs8192709	19	46189114	Coding NONSYNON R22C (CYP2B6*2 and *10)	9.654	0.0167

Abbreviations: ADR, adverse drug reactions; ANOVA, analysis of variance; CH, chromosome; SNP, single-nucleotide polymorphism.

[a] The clinical annotations of the relevant pharmacogenomics variants were curated from PharmGKB,[20] and published studies.

[b] Statistical test = ANOVA F-test.

[c] Corrected *P*-value (corrected for 4209 SNPs).

Table 9

Pharmacogenomic diversity in African populations

Drug	Drug response[a]	Gene	Variant	Functional annotation	Sq[b]	Central Africans	Eastern Africans	Saharan Africans	Southern Africans	Western Africans
Anthracyclines and related substances										
Anthracycline	Increased risk of cardiotoxicity and heart failure	*UGT1A6* *ABCC2* *ABCB1* *ABCC1/6*	rs17863783 rs8187710 rs2235047 rs4148350	Coding SYNON V209V Coding NONSYN (C1515Y) Intron Intron	A/C A/G C/A A/C	0.090 0.213 0.139 0.169	0.128 0.257 0.178 0.122	0.184 0.237 0.211 0.053	0.129 0.200 0.213 0.135	0.088 0.219 0.235 0.176
	Decreased risk of cardiotoxicity and heart failure	*RAC2* *SULT2B1* *CBR1* *HNMT*	rs13058338 rs10426377 rs9024 rs17645700	Intron Intron Flanking_3UTR Flanking_3UTR	T/A A/C A/G G/A	0.108 0.223 0.000 0.066	0.134 0.158 0.013 0.044	0.132 0.211 0.053 0.000	0.079 0.146 0.017 0.056	0.029 0.206 0.029 0.000
	Increased likelihood of dose reduction	*CYP2B6*	rs3745274	Coding NONSYN Q172H (CYP2B6*6)	A/C	0.783	0.748	0.658	0.837	0.824
	Increased response	*ABCB1*	rs2032582	Coding NONSYNON (ABCB1*13 and ABCB1*2)	A/C	0.036	0.034	0.026	0.045	0.059
Platinum compounds										
Cisplatin	Increased risk of hearing loss (ototoxicity)	*COMT*	rs9332377	Intron	A/G	0.323	0.352	0.237	0.330	0.206
	Decreased risk of severe neutropenia	*XRCC1*	rs25487	Coding NONSYN Q399R	A/G	0.193	0.128	0.211	0.135	0.118
	Increased likelihood of drug toxicity	*MTR*	rs1805087	Coding NONSYN D919G	G/A	0.295	0.262	0.132	0.287	0.324
	Increased response	*MTHFR*	rs1801133	Coding NONSYN A222V	A/G	0.048	0.060	0.132	0.090	0.059
Carboplatin	Decreased risk of severe neutropenia	*XRCC1*	rs25487	Coding NONSYN Q399R	A/G	0.193	0.128	0.211	0.135	0.118
	Increased response	*MTHFR*	rs1801133	Coding NONSYN A222V	A/G	0.048	0.060	0.132	0.090	0.059
Oxaliplatin	Decreased risk of severe neutropenia Increased response	*XRCC1* *MTHFR*	rs25487 rs1801133	Coding NONSYN Q399R Coding NONSYN A222V	A/G A/G	0.193 0.048	0.128 0.060	0.211 0.132	0.135 0.090	0.118 0.059
Antimetabolites										
PYRIMIDINE COMPOUNDS Fluorouracil	Increased risk of toxicity of fluoropyrimidine-based chemotherapy	*DPYD* *DPYD*	rs1801265 rs2297595	Coding NONSYN R29C (DPYD*9A,) Coding NONSYN M166V	G/A G/A	0.452 0.253	0.550 0.141	0.579 0.079	0.381 0.275	0.529 0.147

Drug	Drug response[a]	Gene	Variant	Functional annotation	Sq[b]	Central Africans	Eastern Africans	Saharan Africans	Southern Africans	Western Africans
	Increased response	*MTHFR*	rs1801133	Coding NONSYN A222V	A/G	0.048	0.060	0.132	0.090	0.059
Vincristine										
Vincristine	Increased risk of drug toxicity	*MTHFR*	rs1801133	Coding NONSYN A222V	A/G	0.048	0.060	0.132	0.090	0.059
	Improved response	*ABCB1*	rs2032582	Coding NONSYNON (ABCB1*13 and ABCB1*2)	A/C	0.036	0.034	0.026	0.045	0.059
	Vincristine main metabolic substrate	*CYP3A5*	rs776746	Intron (CYP3A5*3)	A/G	0.771	0.799	0.684	0.685	0.500
		CYP3A5 *CYP3A5*	rs10224569 rs10264272	Intron Coding SYNON K208K (CYP3A5*6)	A/G A/G	0.367 0.283	0.260 0.209	0.316 0.289	0.264 0.191	0.147 0.147
		CYP3A5 *CYP3A5* *CYP3A5*	rs10249369 rs41303343 rs6956305	Intron Coding FRAMESHIFT Flanking_3UTR	G/A A/T G/A	0.277 0.036 0.066	0.205 0.111 0.117	0.263 0.079 0.079	0.193 0.062 0.079	0.147 0.029 0.059
Nucleoside reverse-transcriptase inhibitors										
Tenofovir	Increased risk of proximal tubulopathy and risk of kidney tubular dysfunction	*ABCC2* *ABCC2*	rs717620 rs17222723	Flanking_5UTR Coding NONSYNON	G/A T/A	0.957 0.151	0.990 0.138	0.974 0.211	0.944 0.135	0.941 0.118
	Increased risk of proximal tubulopathy	*ABCC4*	rs1751034	Coding FRAMESHIFT	G/A	0.325	0.305	0.237	0.292	0.441
Nonnucleoside reverse-transcriptase inhibitors										
Nevirapine	Increased risk of hepatotoxicity	*CYP2B6*	rs28399499	Coding NONSYN I328T (CYP2B6*16/*18)	G/A	0.012	0.067	0.000	0.080	0.029
Efavirenz	Increase in HDL-cholesterol levels	*CYP2B6*	rs3745274	Coding NONSYN Q172H (CYP2B6*6)	A/C	0.783	0.748	0.658	0.837	0.824
	Increased risk of neurotoxicity, CNS depression and neuropsychiatric disorders	*CYP2B6*	rs3745274	Coding NONSYN Q172H (CYP2B6*6)	A/C	0.783	0.748	0.658	0.837	0.824
	Increased risk of fatigue and sleep disorder	*CYP2B6*	rs3745274	Coding NONSYN Q172H (CYP2B6*6)	A/C	0.783	0.748	0.658	0.837	0.824
	Increased risk of hepatotoxicity and drug-induced liver injury	*CYP2B6*	rs3745274	Coding NONSYN Q172H (CYP2B6*6)	A/C	0.783	0.748	0.658	0.837	0.824
Protease Inhibitors										

Drug	Drug response[a]	Gene	Variant	Functional annotation	Sq[b]	Central Africans	Eastern Africans	Saharan Africans	Southern Africans	Western Africans
Ritonavir	Increased risk of extreme hypertriglyceridemia	*APOE*	rs429358	Coding NONSYN C130R	G/A	0.179	0.284	0.211	0.247	0.324
Antituberculosis therapy										
Rifampicin	Increased risk of hepatotoxicity and drug-induced liver injury	*CYP2B6*	rs3745274	Coding NONSYN Q172H (CYP2B6*6)	A/C	0.783	0.748	0.658	0.837	0.824

Abbreviations: CNS, central nervous system; HDL, high-density lipoprotein; UTR, untranslated region.

[a] Clinical annotation curated from PharmGKB,[20] http://www.hiv-pharmacogenomics.org and published studies.

[b] Sq, sequence (minor/major).