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Genome-Wide Association Studies of Chemotherapeutic Toxicities: Genomics of Inequality

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Abstract

With an estimated global population of cancer survivors exceeding 32 million and growing, there is a heightened awareness of the long-term toxicities resulting from cancer treatments and their impact on quality of life. Unexplained heterogeneity in the persistence and development of toxicities, as well as an incomplete understanding of their mechanisms have generated a growing need for the identification of predictive pharmacogenomic markers. Early studies addressing this need used a candidate gene approach; however, over the last decade, unbiased and comprehensive genome-wide association studies (GWAS) have provided markers of phenotypic risk and potential targets to explore the mechanistic and regulatory pathways of biological functions associated with chemotherapeutic toxicity. In this review, we provide the current status of GWAS of chemotherapeutic toxicities with an emphasis on examining the ancestral diversity of the representative cohorts within these studies. Persistent calls to incorporate both ancestrally diverse and/or admixed populations into genomic efforts resulted in a recent rise in the number of studies utilizing cohorts of East Asian descent; however, few pharmacogenomic studies to date include cohorts of African, Indigenous American, Southwest Asian, and admixed populations. Through comprehensively evaluating sample size, composition by ancestry, genome-wide significant variants, and population-specific minor allele frequencies as reported by HapMap/dbSNP using NCBI PubMed, and the NHGRI-EBI GWAS Catalog, we illustrate allele frequencies and effect sizes tend to vary among individuals of differing ancestries. In an era of Personalized Medicine, the lack of diversity in genome-wide studies of anticancer agent toxicity may contribute to the health disparity gap.

Keywords

GWAS; toxicity; anticancer agent; ethnic differences

Introduction

Over 1.5 million new cancer cases are diagnosed in the United States every year with overall five-year survival rates approaching two thirds of all diagnoses (1). Patients diagnosed at less than twenty years of age exhibit even higher five-year survival rates at roughly 80% (1). The

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total number of cancer survivors world-wide has increased over 33% between 2002 and 2013, from an estimated 24.2 million survivors to over 32 million (2–4). The growing population of survivors has led to a growing awareness of the debilitating long-term toxicities of chemotherapy. Toxicities often drastically alter a patient's quality of life and exhibit comorbidities, including cardiovascular and endocrine-related diseases (5,6). Toxicities can be life-long, and their permanence can have a dramatic impact on a patient's physical and psychological wellbeing. In a study of 1,713 diverse childhood cancer survivors, 48–65% displayed impaired pulmonary functions, hearing loss, endocrine dysfunction, cardiac disorders, and neurocognitive impairments at a median of 25 years after diagnosis (7–9). Neurocognitive disorders and hearing loss, although not typically life threatening, can be particularly disruptive to quality of life. For instance, cisplatin-related hearing loss in children impedes speech and language development with irreversible effects (10). Inadequate understanding of underlying mechanisms and inter-patient variability represent major obstacles facing clinical actionability. In the era of genome-wide association studies (GWAS), pharmacogenomic studies aim to address variability in drug response and/or toxicity and suggest plausible mechanisms for phenotypic variation. Genetic predictors of adverse effects allow for the alteration of regimens and doses according to the patient's genetic susceptibilities, providing a personalized approach to mitigating toxicities. Besides moving medicine into a more preventative paradigm, they also reveal toxicological etiology (11–13). In this review, we address some lessons learned from GWAS of adverse effects of chemotherapy, focusing on findings pertaining to pharmacoethnicity. By comprehensively evaluating the literature, we reveal stark disparities in population representation despite numerous calls to include more diverse cohorts (14–16). These disparities could contribute to widening gaps in health outcomes.

GWAS of Anticancer Agent Toxicity

The basic principle of genetic studies is to statistically associate genetic variants to a particular phenotype. Early studies exploring the genetic contribution to chemotherapeutic toxicities relied heavily upon candidate gene approaches, associating polymorphisms in genes encoding known drug metabolizing enzymes, DNA repair pathways, receptors, and transporters (17–23). Though candidate gene studies successfully identified clinically applicable variants associated with chemotherapeutic toxicities, they lack the ability to identify risk loci outside of already well studied pathways (24). The advent of GWAS allowed researchers to detect novel associations while avoiding variant ascertainment bias, with a downside of an incurred burden of multiple hypothesis testing (i.e. >1 million independent tests). Thus, statistical significance can only be achieved with considerable sample and effect sizes, and false positives are likely without the careful accounting of confounding variables and stringent criteria. Confounders such as inter-population differences in toxicity, differing minor allele frequencies (MAF), and haplotype/linkage disequilibrium (LD) structures all compromise the accuracy of estimates across populations (25). Informative variants in one group may therefore not be useful in another. Ancestral heterogeneity can be accounted for with various methods, including sample exclusion. However, the inclusion of ancestrally diverse participants in GWAS is necessary to gain broader insights into genetic architectures and to capitalize on genomic variation.

Ancestral differences in prevalence of chemotherapeutic toxicities

Inter-population differences in incidence and severity of adverse reactions to chemotherapeutic treatment have been observed (26). Bevacizumab, an anti-angiogenic monoclonal antibody targeting vascular endothelial growth factor A (VEGFA), has several documented population discrepancies in toxicities. Among 4,308 lung cancer patients, East Asian populations were found more likely to develop bevacizumab-induced thromboembolism (RR = 3.65) and severe bleeding (RR = 2.17), and were less susceptible to proteinuria (RR = 0.43) compared to others (27). Two studies have shown increased susceptibility of African Americans to bevacizumab-related hypertension; one showing a 1.6-fold increase in bevacizumab-induced hypertension (14), and a second showing bevacizumab-induced exacerbation of pre-existing hypertension disproportionately affecting African Americans (28). The former study included a GWAS of bevacizumab-induced hypertension which excluded the African American sample during quality control to avoid confounding population substructure (29).

Cancer patients are at a 4–7 fold increase for venous thromboembolism (VTE) compared to the general populace (30,31), making it a leading cause of mortality. VTE can manifest as a direct result of cancer via the aberrant activation of pro-coagulatory pathways (32,33), or due to chemotherapy-mediated complications (34,35). Among 1,295 acute lymphocytic leukemia and acute myeloid leukemia patients, African Americans were more likely to develop VTE (33.3% vs. 20.3%; P = 0.04) (36). Increased rates of VTE in African Americans has also been reported in the general population (37).

Peripheral neuropathy is the most common non-hematologic toxicity associated with chemotherapy (38). One study showed African Americans were roughly twice as likely as European Americans to have dose reductions due to taxane-induced peripheral neuropathy (39). Some rare variants in the Charcot-Marie-Tooth gene SET binding factor 2 (*SBF2*) increase the frequency of paclitaxel-induced peripheral neuropathy in African Americans (23). Conversely, patients of European descent are more likely to develop vincristine-induced neurotoxicity than African Americans, partially due to allelic differences in the gene coding cytochrome P450 enzyme 3A5 (40,41).

Higher rates of toxicities have been observed in East Asian populations compared to European and North American populations that frequently lead to dose-limiting restrictions (42,43). Some rates of toxicity remain higher in East Asians despite dose titration (44). Rates of neutropenia among patients treated with cisplatin, docetaxel, and 5-FU remained twice as high (19% vs. 8%) in Japanese individuals, despite an 80% dose reduction compared to US counterparts, with no significant change in overall response or survival (45,46). A retrospective study of breast cancer from five international centers found East Asian participants to be twice as likely to experience hematological toxicities from equivalent FEC100 (fluorouracil, epirubicin, cyclophosphamide) treatment compared to patients of European and African ancestry (32% vs. 16% and 10% respectively; P < 0.05) (47).

Cisplatin-induced ototoxicity affects up to 80% of treated adults with severe/profound hearing loss in 18%, and over 60% of children (10,48). Hearing loss rates as high as 77% have been observed in an adult Japanese cohort (49), and a single South African study reported rates of over 55% (50) suggesting the prevalence of drug-induced ototoxicity may not be uniform across ancestry, although different study methodologies make comparisons less straightforward.

Higher rates of therapeutic toxicities could be attributed to pharmacokinetic mechanisms such as metabolism and/or, clearance as well as pharmacodynamics, and genetic studies often obscure the distinction. A hypothetical example would be a membrane drug transporter expressed in both the renal epithelium and neuronal tissue. In the kidneys, it might excrete the drug into the collecting duct and be considered to have pharmacokinetic functions. In the neuron, it might mitigate neurotoxicity by lowering intracellular drug concentration and therefore be considered to play a pharmacodynamic role. Accounting for variability in drug pharmacokinetics is paramount to provide accurate estimates of drug exposure, an increasingly prominent necessity in pharmacogenomic studies (51). Large GWAS of anticancer agent toxicities in diverse, well-characterized cohorts could resolve many ambiguities and partition trait heritability to specific chromosomal regions and biological pathways (11,51). Several GWAS of chemotherapeutic toxicities have been conducted in recent years, and we have queried them using databases to make inferences about pharmacoethnic differences.

Literature Query

We utilized two publically available databases to assess total peer-reviewed pharmacogenomic anticancer agent toxicity GWAS: MEDLINE (PubMed) and the GWAS Catalog, a continuously curated database of all published English-language GWAS under the partnership of the European Bioinformatics Institute and the US National Human Genome Research Institute [https://www.ebi.ac.uk/gwas/home]. A diagram of the query is presented in Figure 1. Animal and cell based studies, review articles, and candidate gene studies were excluded in subsequent filtering. All three searches were performed on March 3, 2017. We additionally queried minor allele frequencies (MAF) of important SNPs based on HapMap via dbSNP at the National Center for Biotechnology Information [www.ncbi.nlm.nih.gov/projects/SNP/]. We used Yoruban (YRI), Han Chinese (HCB), and European American (CEU) populations as representatives of African, East Asian, and European populations respectively.

Results

In Table 1 we list 28 GWAS of anticancer agent that were performed, 17 of which included at least one replication set (22,29,39,52–77). Of the discovery studies, 22 were ancestrally homogeneous. Any number of non-specific ancestral descriptors in a single manuscript including white and black are used. Often, the term African is used in reference to admixed individuals from North America and the term Asian is used without population or region specificity. These observations are consistent with a study performed by Panofsky and Bliss

that found ambiguity in ethnic descriptors among geneticists including the tendency to use both racially based terms and geographic descriptors of populations (78).

Two studies used diverse replication cohorts after beginning with a homogenous discovery set (57,64). Additionally, only two studies maintained a similar degree of diversity in the discovery and replication panels (65,77). We compared inter-ethnic differences in significant GWAS findings and observed that several studies found associations to variants with differing MAF among African, East Asian and European populations. We observed seventeen polymorphisms that reached genome-wide significance and had a fixed allele in at least one of the three populations (Table 2).

Of note was a particular SNP from a Korean study (in bold) associated with thiopurine-induced myelosuppression (leukopenia) (52). The coding SNP (rs79206939 p.A134T) in the Fat mass and obesity-associated protein alpha-ketoglutarate dependent dioxygenase gene (*FTO*) was revealed in a study designed to explore genetic risk factors outside of the thiopurine methyltransferase (*TPMT*) variants. The variant was found in 9% of patients exhibiting thiopurine-induce leukopenia, and only 1.5% of unaffected patients treated with thiopurine ($p = 1.3\times10^{-3}$). SNPs in *TPMT* have been implicated in thiopurine toxicities in European populations but failed to replicate in East Asian populations (47). The failed replication is likely a product of low MAF in East Asian populations (20). Similarly, the variant in *FTO* associated with thiopurine-induced myelosuppression has an MAF of 3% in East Asian populations (5.1% in the Korean discovery cohort), but is fixed as the non-risk allele in European and African populations (Table 2).

However, the majority of common variants are shared across populations (79), suggesting that many GWAS findings may be applicable across populations. For instance, a finding by the Cancer and Leukemia Group B (CALGB) Alliance trials (56) in which a SNP in FYVE, RhoGEF and PH domain containing 4 (*FGD4*) met significance criteria for association with peripheral neuropathy in a Caucasian discovery sample ($p = 3 \times 10^{-6}$) and was replicated in two independent cohorts: a European cohort ($p = 0.01$) and an African cohort ($p = 0.007$). This study highlights the possibility of consistent SNP effects across ancestries. However, despite broadly shared common variation, inter-population divergences in allele frequencies do exist, as do differences in LD driven by population specific demographic histories (79,80). As such, GWAS results cannot be automatically assumed to be broadly applicable across all populations (15).

A few mechanisms exist to explain ancestral differences in SNP-phenotype association. Most simply, a site could be polymorphic with a toxicity-associated allele in one population and be monomorphic (or have very low MAF) in another. Another explanation follows from the presumption that many SNPs do not exert effects themselves but rather tag proximal causal variants in LD with the detected variant. Different ancestral backgrounds have different LD structures, and therefore a common SNP that falls within a haplotype block containing causal variants in one population might not tag for those same variants in another. While it is safe to assume that high-penetrance causal alleles (i.e. loss-of-function alleles from nonsense mutations) will exert their effects regardless of genetic background, more nuanced causal explanations behind the associations between common variants and

complex, polygenic phenotypes might reveal genetic background-dependent SNP effects. These effects might therefore be manifest only in individuals with a certain genetic background. Whether ancestral differences in phenotypic associations are predominantly due to differing MAFs, differing LD structures around causal loci, or more complex differences in the causal pathway of the association is unclear, although these explanations are not mutually exclusive (15, 79–81).

Disparities in GWAS Population Representation

Four of the ten toxicities investigated by GWAS were represented by a single study (29,64,65,72), and only one of those four studies incorporated participants of non-European descent (Figure 2A) (65). Of the 28 total studies, 16 utilized cohorts of entirely European descent, compared to 6 that were entirely East Asian, and 6 studies with diverse cohorts (Figure 2B). There were no studies composed entirely of individuals of African descent. Additionally, within the 6 diverse/multi-ancestral studies, half of all participants were of European descent (5817/11861 in discovery sets) (Table 1).

We evaluated population representation by tallying the ancestry of participants in each study. We found that 70.8% of GWAS participants were of European descent compared to 14.9% from East Asian descent, 6.6% from Hispanic/Native American ancestry, 3.7% from African descent, and 3.9% from all other ancestries. A single Japanese study was noted to represent more than half of the participants from all East Asian discovery cohorts (Figure 2C) (63). Four diverse studies included participants of Hispanic ancestry with one including 1,238 Hispanic individuals in the discovery and replication sets [>10% Native American ancestry as assessed by STRUCTURE] (77). Unfortunately, it was not always apparent which studies may have categorized participants of Hispanic ancestry as European.

Paucity of African Sampling

Sub-Saharan African participants are woefully under-represented, with 920 participants in discovery cohorts and only 1240 (discovery and replication) out of 33,112 total participants, or 3.7% (39,56,57,65,74,77). This may be an artifact of the trend to use currently available phase III clinical trial data-sets, which have tended to use non-diverse cohorts of European descent [<15% non-white participants in Cancer Trials Support Unit (CTSU) and CALGB combined] (82). The paucity of participants of African descent in anticancer agent toxicity GWAS is particularly unfortunate as Sub-Saharan African populations are among those with the highest genetic diversity, and least LD of extant human populations world-wide (83). Such diversity could be highly valuable in the application of fine-mapping in diverse trans-ethnic cohorts, and analyzing a greater numbers of variants could lead to associations with novel pathways (84). Additionally, the majority of participants of African ancestry in these studies are admixed individuals from North America. Admixed African Americans are individuals who share European, African, and in some cases, Native American ancestry. African Americans are not equivalent to Sub-Saharan African populations, nor do they share the same degree of genetic diversity (85).

The pharmacogenetics community has consciously and appropriately avoided using multi-ethnicity or admixed populations in GWAS to avoid false-positive associations (86,87). However, by limiting participants of African descent to admixed and migrant populations from relatively few North American and Western European locales, studies may be restricting associations to limited haplotypes that may be specific to the historical demographics of migrants to these regions. Appropriate statistical methods can be used to address spurious associations when including admixed populations by accounting for ancestry in imputation and regression (87–90). Including diverse participants in cohorts can increase power in GWAS (91), and the proper incorporation of these improved statistical models mitigates confounding due to admixture (92). Although admixed participants lead to greater genetic diversity overall, they cannot be considered a comprehensive solution to the lack of African participants in GWAS. Additional hurdles must be overcome to expand ancestral diversity within GWAS and leverage the genetic diversity that is unique to humans in the African continent, home to more than 15% of the world's population and a greater proportion of the total human genetic diversity (83,93). It is therefore imperative to undertake bigger efforts to include African populations in future pharmacogenomic anticancer toxicity GWAS as well as in other GWAS.

Pharmacogenomic Challenges

Although associations in pharmacogenomic GWAS tend to have greater effect sizes than traditional disease-associated GWAS (94), several factors have added to challenges that are not as common in traditional GWAS. Most obvious is limited sample sizes of anticancer agent toxicity GWAS; cases and controls in pharmacogenomic studies correspond to patients treated with a specific agent and therefore represent a smaller pool of potential participants than that of typical common diseases. This makes large phase III clinical trials of anticancer agents good resources given the large participation and adequate data collection of dosages, phenotypes, and demographics. However and as stated, the utilization of these readily available datasets may come at the cost of ancestral diversity. "Nonwhite" participants are less likely to consent to pharmacogenomic studies [OR = 0.50, 95% CI = 0.43 to 0.57, $P < .001$], and participation in pharmacogenomics suffers overall (both "white" and "nonwhite" participants) as racial diversity increases at institutions (82).

Of the 28 studies evaluated, we found that the mean sample size of the GWAS dataset was 879 individuals (including both cases and controls), with a median of 490. The largest study included 5,185 (77), while the smallest study utilized only 144 participants (60). Studies with such small sample sizes are greatly underpowered, leading to a limited ability to detect variants with moderate to low effect sizes (95–97). However, studies with small sample sizes can still provide meaningful insight and do not require ancestrally homogeneous cohorts if proper methods are implemented. For instance, researchers from St. Jude Children's Research Hospital investigating the association of glucocorticoid treatment and osteonecrosis in a diverse panel of childhood acute lymphoblastic leukemia patients identified many potential gene candidates despite analyzing only 400 cases (65). This highlights the importance of mining biological data from available resources to maximize GWAS utility.

Another challenge lies in evaluating toxicity phenotypes. Most are not quantitative. Myelosuppression and ototoxicity represent exceptions; however the degree of myelosuppression could be missed based on the frequency of measurement. Ototoxicity requires audiometry by a hearing specialist. Toxicities can occur at various times during or after treatment and are sometimes subject to a physician's best judgment rather than objectively quantifiable means. Unless great care is taken when characterizing participants, such challenges could lead to case-control assignment errors. Furthermore, treatments vary in regimens and doses, and toxicities often lead to dose reduction or treatment termination. The standard of care varies by malignancy type and subtype, which can differentially contribute to manifestations of toxicities. Secondary interventional therapeutics are common among cancer patients. Variability can be observed across geographical regions, institutions, and patient characteristics. Such clinical heterogeneity confounds analyses unless rigorous care is taken during data collection and analysis. A number of studies evaluated in this review displayed heterogeneity of agents within a class, multiple primary agents, or multiple toxic drugs (55,63,68,72,73,76,77). Problems with accurately assessing phenotype and clinical heterogeneity are particularly troublesome when choosing and properly applying replication sets. Replicating the findings of a GWAS requires great care in matching both phenotype criteria and demographics of the subjects being used (98,99). This can also exacerbate problems with the inclusion of diversity in GWAS, as replication sets are typically chosen to reflect the demographics of the discovery set as closely as possible in the hopes of maximizing the probability of replicating observed effects.

These challenges have likely contributed to the scarcity of anticancer agent toxicity GWAS and the limited sample sizes. Disparities in the availability of resources required to overcome these challenges unfortunately exacerbate the insufficient diversity among these studies. Furthermore, the history and wealth of phase III clinical data, and early failures to address potential false positives when utilizing diverse or admixed panels in GWAS have also contributed to the lack of diversity in the relatively few studies that have been performed to date.

Conclusion

We have shown that pharmacogenomic anticancer agent toxicity GWAS suffer from a lack of diversity in the populations studied. A number of strategies to garner greater diversity in GWAS have been suggested in recent years. Institutional changes such as prioritizing funding of non-European and ancestrally diverse studies, and incorporating the importance of utilizing under-represented populations in training programs have been proposed (16). Other recommendations include initiating dialog in under-represented communities, developing educational programs to increase awareness, and employing more strategic means of recruitment (100).

Several barriers exist with regards to ancestral disparities in the realm of biological research and medical care. These barriers include, but are not limited to socio-economic disadvantages, access to care, and geographical proximity to institutions of academic medicine. Fortunately, the incorporation of GWAS has now spread well beyond the initial confines of large academic centers in North America and Europe and has led to several

recent studies in China, Japan, and Korea, expanding upon much needed data from East Asian populations. Despite representing the second most studied population after Europeans, East Asians are still proportionally underrepresented. While it is promising that researchers are attempting to include diversity in cohorts, there is a great need to further increase diversity while making a concerted effort to initiate studies including diverse panels on the African continent itself.

Representatives of other populations are almost non-existent in current pharmacogenomic studies of anticancer agent toxicities. It is essential to leverage genetic diversity by including all ancestries in future studies. Existing disparities pose challenges in the implementation of genetic studies that could logically lead to widening health outcome gaps, creating a vicious cycle of inequality. We support making significant efforts to include diverse panels of participants to maximize the potential of discovering associated variants. Further efforts need to be implemented to develop better statistical and computational models to estimate risk in diverse populations, potentially utilizing local chromosomal ancestry (101), fine-scale mapping using multi-ethnic cohorts (84), and incorporating functional data into traditional GWAS (102). We also echo the call to increase the number of non-European studies and biobanks, multi-institute consortia and multisite studies that serve to increase genetic diversity (16,100,103). Finally, it is essential that efforts be made to perform large-scale GWAS in diverse populations across the globe, not merely cities in North America and Western Europe. The long-term persistence of a lack of diversity in GWAS could perpetuate disparities in outcomes.

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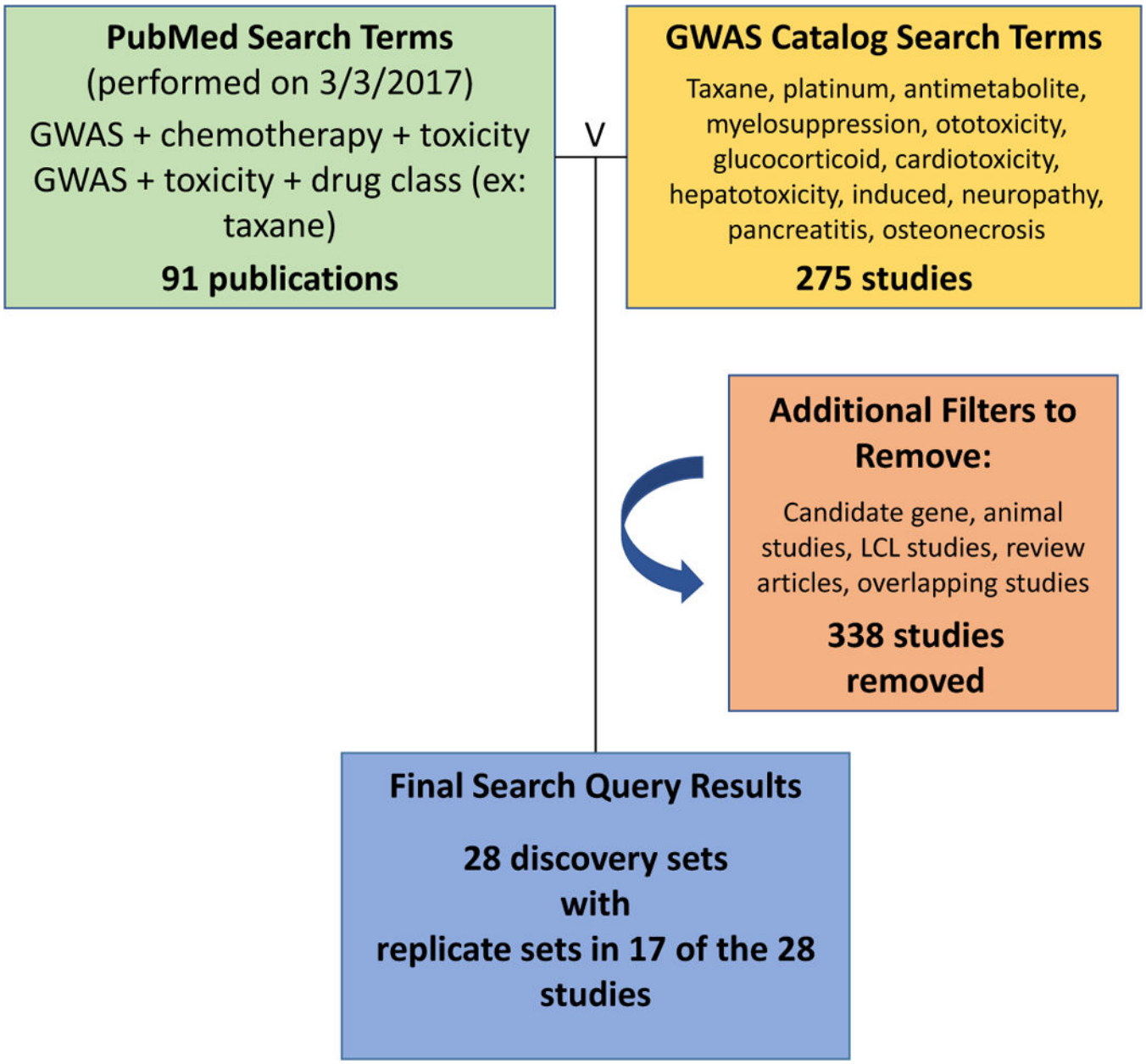

Figure 1. Literature search of all current pharmacogenomic anticancer chemotherapeutic induced toxicity GWAS

Filters were designed to maximize initial results using PubMed [www.ncbi.nlm.nih.gov/pubmed] and the NHGRI-EBI GWAS Catalog [www.ebi.ac.uk/gwas/], followed by removing all candidate gene studies, studies of non-anticancer drugs, animal models, lymphoblastoid cell-line based GWAS and review articles. Numbers in blue boxes indicate initial query results; −338 indicates the studies that did not pass filtering criteria. The final result was 28 non-overlapping discovery studies with 17 studies including at least one replication set. Note: Search terms that yielded no results were excluded.

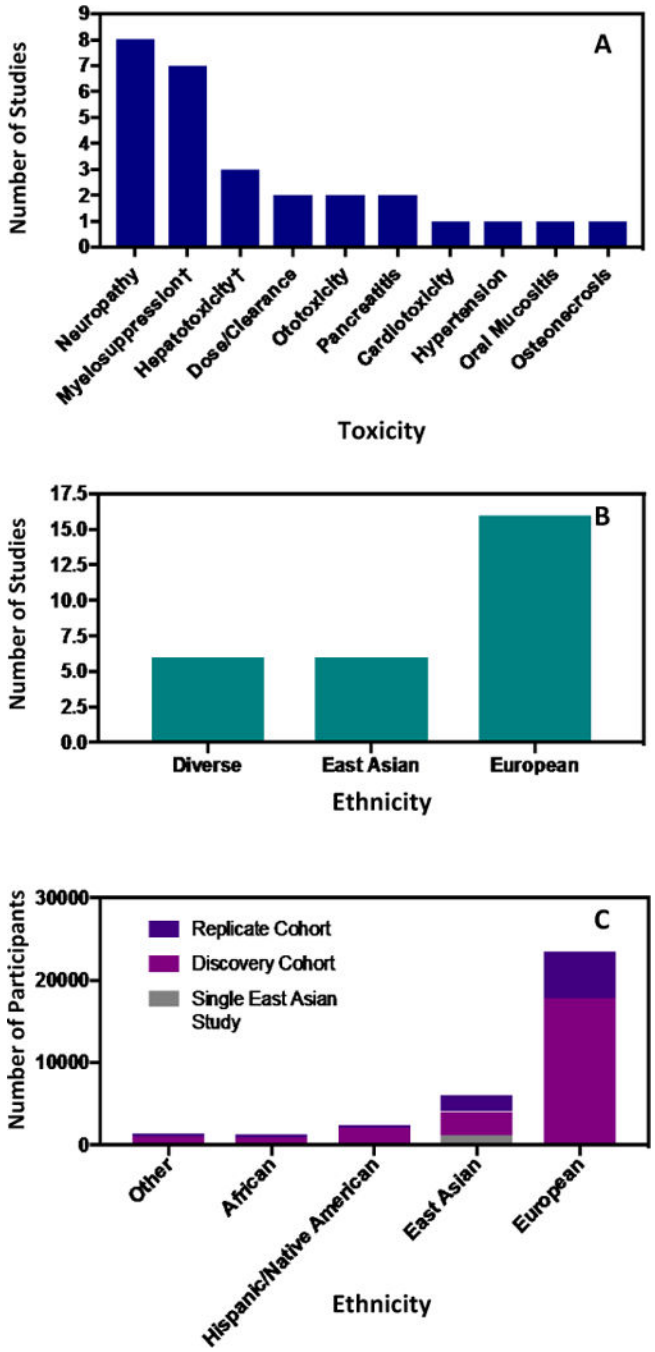

Figure 2. GWAS studies of Chemotherapeutic Toxicity

(A) Breakdown of toxicities from GWAS of anticancer agent toxicity studies. 15 of the 28 (54%) studies investigated myelosuppression and neuropathy. Associations to cardiotoxicity, hypertension, pancreatitis, and oral mucositis are all based on single European studies lending to potential population-based bias among these toxicities. Of the four toxicities represented by a single GWAS, only two of the studies investigating osteonecrosis and pancreatitis used broadly diverse panels of participants. († indicates a single cohort that was used to evaluate two separate toxicities.) (B) Breakdown of 28 studies by ancestry. Half of

participants within the five multi-ancestral studies were of European descent (>49%), and more than 85% of all participants were either entirely of European descent, or entirely of East Asian descent. (C) Population based breakdown of participants in GWAS of pharmacogenomic anticancer agent toxicity with further breakdown into replication and discovery cohorts. More than half of the participants from the East Asian discovery GWAS come from a single Japanese study.

Table 1
List of Genome Wide Association Studies of Chemotherapeutic Toxicity

Query Results by Study

Drug	Toxicity	Study Population ($n_{discovery}$){$n_{by\ population}$}[$n_{replicate}$]*	Reference
methotrexate	myelosuppression	Diverse (1279){806 EA; 58 AA; 22 EAS; 266 HIS; 127 OTH}	(56)
cisplatin	myelosuppression	East Asian (333)[876]	(53) †
carbo + paclitaxel	myelosuppression	Japanese (1154)	(63)
5-FU + FOLFOX	myelosuppression	European (221)[791]	(55)
thiopurine	myelosuppression	European (175)	(54)
thiopurine	myelosuppression	Korean (331)[767]	(52)
anthracycline (epirubicin)	myelosuppression	Japanese (318)	(70)
paclitaxel	neuropathy	European American (144)	(60)
paclitaxel	neuropathy	European (1303)	(59)
paclitaxel	neuropathy	European American (855)[154 EA; 117 AA]	(57)
paclitaxel/docetaxel	neuropathy	Diverse (1570){1357 EA; 213 AA}[789 EA; 90 AA; 56 OTH]	(39)
docetaxel	neuropathy	European American (623)	(58)
alkyloid (vincristine)	neuropathy	Diverse (341){209 EA; 43 AFR; 2 EAS; 44 HIS; 23 OTH}	(74)
platinating (combination)	neuropathy	Korean (366)	(73)
bortezomib	neuropathy	European (469)[114]	(76)
antibody (lapatinib)	hepatotoxicity	Diverse American (366){222 EA; 144 OTH}[144 EA; 31 OTH]	(71)
antibody (lapatinib)	hepatotoxicity	European American (844)[45]	(69)
cisplatin/carboplatin	hepatotoxicity	East Asian (329)[375]	(61) †
cisplatin	ototoxicity	European American (511)	(75)
cisplatin	ototoxicity	European American (238)[68]	(62)
mercaptopurine	dose tolerance	European American (657)[371]	(67)
bevacizumab	hypertension	European (824)[149]	(29)
anthracycline	cardiotoxicity	European American (280)[diverse: 176]	(64)
mercaptopurine	pancreatitis	European (2207)[2122]	(66)
asparaginase	pancreatitis	Diverse American (5185){3069 EA; 350 AA; 99 EAS; 1667 OTH}[213 diverse]	(77)
glucocorticoid	osteonecrosis	Diverse American (2285){EA:1275; AA:139; EAS:48; other:823}[670]	(65)
antimetabolite (methotrexate)	GI toxicity and clearance	European (434)[206]	(68)
alkyloid (melphalan)	oral mucositis	European American (972)	(72)

* Replicate is in reference to any study that performs a second association study in another cohort within a given study. Abbreviations: 5-FU (fluorouracil); FOLFOX (folinic acid, fluorouracil, oxaliplatin combination); carb (carboplatin); GI (gastro intestinal); EA (European American); AA (African American); EAS (East Asian); HIS (Hispanic); OTH (other);

† (Same cohort, separate evaluations).

Table 2

Minor Allele Frequency of GWAS significant variants associated with chemotherapeutic toxicity.

	Associated non-uniform variants by ancestry					MAF by Population (HapMap)			
Drug (Class)	**SNP**	**Toxicity**	**Study Population**	**Gene**	**Location (GRCh38.p7)**	**HCB**	**YRI**	**CEU**	**Reference**
thiopurine (antimetabolite)	rs79206939	myelosuppression	East Asian (Korea)	*FTO*	16:53826140	2.8*	0	0	(52)
5-FU/FOLFOX	rs16857540	myelosuppression	European (Spain)	*NLGN1*	3:174182785	0	37.2	15.3	(55)
cis/carboplatin	rs2838566	hepatotoxicity	East Asian (China)	intergenic	21:44468699	7.1	33	0	(61)
paclitaxel + epi. (taxane)	rs9501929	neuropathy	European (USA)	*TUBB2A*	6:3157620	0	28.6	4.7	(59)
epi/doxo (anthracyclin)	rs229774	cardiotoxicity	diverse (Canada)	*RARG*	14:83435125	0	11.1	6.6	(64)
melphalan (alkylating)	rs1469167	oral mucositis	European (USA)	*ALDH1A1*	9:72942091	0	31.4	2.7	(72)
epirubicin (anthracyclin)	rs4149639	myelosuppression	East Asian (Japan)	*TNFRSF1A*	12:6332835	11.4	22	0	(63)
docetaxel (taxane)	rs3747851	myelosuppression	East Asian (Japan)	DAB2IP	9:121758981	0	15.1	0.4	(63)
docetaxel (taxane)	rs875858	neuropathy	European (USA)	*VAC14*	16:70741552	0	0	7.5	(58)
paclitaxel (taxane)	rs17348202	neuropathy	European (USA)	*EPHA4*	2:221207458	0	17.7	5.8	(60)
glucocorticoid	rs2229288	osteonecrosis	diverse (USA)	*ZFHX3*	16:72794405	0	0	0.5	(65)
mercaptopurine	rs116855232	dose tolerance	diverse (USA)	*NUDT15*	13:48045719	9.5	0	0.2	(67)
cisplatin	rs62283056	ototoxicity	European (USA)	*WFS1*	4: 6274903	0.3	17.6	22.9	(75)
melphalan (alkylating)	rs1426765	oral mucositis	European (USA)	intergenic	3:25976116	0	0.8	14.4	(72)
melphalan (alkylating)	rs6804277	oral mucositis	European (USA)	intergenic	3:25977271	0	10	12	(72)
melphalan (alkylating)	rs1940228	oral mucositis	European (USA)	intergenic	11:103004647	0	6.1	1.7	(72)
melphalan (alkylating)	rs948695	oral mucositis	European (USA)	intergenic	11:102990584	0	32.2	1.7	(72)
oxaliplatin (platinum)	rs10486003	neuropathy	East Asian (Korea)	intergenic	7:97600466	23.3	0	10.2	(73)

Abbreviations: SNP (single nucleotide polymorphism); MAF (minor allele frequency); HCB (Han Chinese in Beijing, China); YRI (Yorubans in Ibadan, Nigeria); CEU (CEPH collection Europeans in Utah, United States of America); PMID# (PubMed Identification number); 5-FU (fluorouracil); FOLFOX (folinic acid, fluorouracil, oxaliplatin combination); epi (epirubicin), doxo (doxorubicin).

*Minor Allele Frequency as reported by ExAc (http://exac.broadinstitute.org/); note that HapMap MAF is absent, and a MAF of 5.1% was observed in the Korean cohort used in the cited study.