Pharmacogenetics: global clinical markers

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'Allele frequencies for most polymorphisms show significant differences between populations, and within common population classifications.'

The release of the first working draft of the human genome was quickly followed by the prediction that approximately 1.42 million SNPs would be identified in the human genome [1]. This estimate was rapidly exceeded. Currently, the National Center for Biotechnology Information (NCBI) polymorphism repository dbSNP, has well over 4 million polymorphisms [101]. Endeavours, such as the International HapMap project [102], have provided insights into not only the quantity of polymorphisms, but also the variability in polymorphism frequency between world populations (specifically Europe, Yoruba, Japan and China) [2]. The available data set for pharmacogenetics research will be further expanded with the 1000 Genomes Project [103], which aims to sequence the entire genome of 1000 individuals from multiple populations (chiefly the extended HapMap sample set). This will provide a highly detailed map of polymorphisms that occur at a frequency of 1% or more in the human genome.

The ultimate goal of pharmacogenetics is to define robust markers that can be used in the clinical setting to aid in individualized treatment selection. However, despite the plethora of genetic information at our fingertips the true number of established pharmacogenetic markers ready for integration into clinical practice is remarkably small [3,4], and their usefulness may be geographically limited.

The lack of robust clinical pharmacogenetic markers could be owing to a multitude of reasons, including environmental factors, diet, concurrent medications, sample size, treatment regimen, population variation in allele frequencies and the lack of available sample sets to perform validation analyses.

In addition to the reasons above, commonly published polymorphisms often suffer from contradictory results, making their role in the clinic

unclear. Sometimes this can be clarified by taking a closer look at the studies. For example, conflicting data for *UGT1A1*28*, an FDA approved marker for predicting toxicity in patients receiving the chemotherapy drug irinotecan, can be clarified by including irinotecan dose in the analysis [5]. The polymorphism appears to be a marker for neutropenia in patients receiving high-dose irinotecan, but is a less useful marker for patients receiving low-dose irinotecan.

Another factor involved in the use of *UGT1A1*28* as a clinical marker is the allele frequency difference between populations. Although *UGT1A1*28* is a functional polymorphism and has been associated with irinotecan toxicity in multiple populations [6], the allele frequency is lower in Asian populations (approximately 15% compared with 30–45% in Caucasian and African populations) [7]. Other potentially functional variants in *UGT1A1* (e.g., *UGT1A1*6*) are prevalent in Asian populations and also demonstrate an association with irinotecan toxicity [8]. So although *UGT1A1*28* appears to be a relevant clinical marker for all populations, some information would be missed by screening this alone in every patient. There is still work needed to define a panel of markers for irinotecan toxicity in all populations.

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The differences in *UGT1A1*28* allele frequency highlight a problem with many pharmacogenetic markers. Allele frequencies for most polymorphisms show significant differences between populations [9], and within common population classifications. Significant differences are found for *GSTT1*0* allele frequencies (13–28%) between countries with populations defined as Caucasian [10]. Evidence exists that allele frequencies between African populations can also differ significantly. The Gambia has one of the highest recorded allele

frequencies for *GSTP1* I105V (53%) [11], whereas South Africa has one of the lowest (14%) [12].

Even within countries differences can occur. For example Brazil, which has a highly admixed population, has significant frequency variability for polymorphisms in *N*-acetyltransferase 2 (*NAT2*) [13] and *ABCB1* [14]. Although studies in the USA often stratify the data for European American and African-American patients, this is not frequently performed for analysis in other countries. This could lead to inadequate generalizations regarding allele frequencies in any given country or population classification.

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Another problem resulting from allele frequency variability between populations is the degree of linkage disequilibrium, and consequently haplotype structure can also vary significantly [2,15]. A tagSNP in one population may not be a tagSNP for the same functional variant in a different population. Hence, clinically relevant polymorphisms need to be functional variants, not markers in linkage with a functional variant, as the linkage may breakdown between populations.

The most studied functional polymorphisms in a gene may not be appropriate to screen in every population or ethnic group, or may need to be subsidized with additional polymorphisms within the same gene. Polymorphisms in the genes encoding the enzyme thiopurine methyltransferase (TPMT) can be used to predict severe hematological toxicity from azathioprine drugs. However, the most commonly screened polymorphisms do not include *TPMT**8, which contributes a significant proportion of functional *TPMT* alleles in Mozambique and Cabinda [16]. The functional *CYP2D6**4 allele has been associated with tamoxifen treatment outcome in breast

cancer patients [17] and is prevalent in Caucasian populations (up to 20%) [18]. An FDA advisory committee has recommended altering the tamoxifen package insert to include *CYP2D6* pharmacogenetic information [19]. However, it is still unclear which alleles are the most appropriate to test. *CYP2D6**4 is present at a lower frequency, and even absent from many non-European populations, where other nonfunction alleles, such as *CYP2D6**5, are more prevalent [18,20]. One study has assessed the non-functional alleles *CYP2D6**3, *4, *5 or *6 alleles and determined that patients heterozygous for these alleles have intermediate tamoxifen metabolism levels [21], and patients carrying *CYP2D6**4, *5, *10 or *41 alleles have limited benefit from tamoxifen treatment [22]. A comprehensive study of the effects of *CYP2D6* nonfunctional and reduced function alleles on outcome to tamoxifen therapy including but not limited to *CYP2D6**4 needs to be performed to determine the full effect of *CYP2D6* polymorphisms.

Unfortunately, frequencies of most described functional polymorphisms have not been assessed in multiple populations, and even where some comparison of populations has been performed, it is far from comprehensive [23]. Future studies need to expand to assess multiple populations, and researcher driven input into databases that document worldwide allele frequencies, such as the Allele Frequency Database (ALFRED) [104] and Pharmacogenetics for Every Nation Initiative (PGENI) [105] is essential to build up global profiles of functional polymorphisms. Panels of polymorphisms for each gene can then be constructed that can be screened in any population to identify patients at risk for toxicity and/or lack of efficacy prior to treatment selection.

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