Pharmacogenomics and HIV Therapeutics

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AIDS offers perhaps the greatest threat to humans by any infectious disease in history. In response to this challenge, at least 19 distinct antiretroviral agents that target HIV reverse transcriptase, protease, or viral entry have been approved for clinical use. Such a broad armamentarium is critical, given the nature of antiretroviral therapy, which requires the lifelong administration of multiple drugs. Use of these medications greatly reduces AIDS-related mortality [1], but their efficacy is often compromised by their toxicity, viral resistance, and incomplete adherence to treatment, as well as by comorbidities, such as viral hepatitis, diabetes, and cardiovascular disease.

The field of pharmacogenomics strives to understand relationships between human genetic variation and responses to treatment [2–6]. The relevance of pharmacogenomics to HIV therapeutics spans basic science, patient care, and public health disciplines. Laboratory-based investigators use genomic techniques to study viral pathogenesis in the hope of identifying new cellular targets for therapeutic intervention. Standard HIV clinical practice may soon include human genetic testing to help individualize antiretroviral therapy. From a public health perspective, as antiretroviral medications become increasingly available to racially and ethnically diverse populations worldwide, understanding the genetic structures of each population may allow us to anticipate the impact of adverse responses, even in groups that were not represented in drug registration trials.

The potential for human genetic research to identify novel therapeutic targets is highlighted by previous studies of CCR5. This cellular chemokine receptor is required for infectivity of many HIV strains [7–9]. Soon after its role in HIV replication was elucidated, individuals were identified who were highly resistant to HIV infection and lacked functional CCR5 as the result of a 32-bp deletion in the CCR5 gene but were otherwise healthy [10–12]. This experiment of nature suggested that CCR5 inhibitors could be particularly attractive antiretroviral agents, and several CCR5 inhibitors are now being studied in clinical trials. As other cellular factors that restrict HIV replication, such as apolipoprotein B mRNA-editing enzyme, catalytic polypeptide–like 3G (APOBEC3G) [13] and tripartite motif 5a (TRIM5a) [14], are discovered, the identification of naturally occurring variants in these and associated genes that influence the progression of HIV disease may suggest additional new targets for drug development.

Progress in pharmacogenomics requires that accomplished genomic investigators have access to DNA specimens from large, well-characterized patient populations. DNA banks that are associated with clinical trials and cohorts must therefore be established. The Adult AIDS Clinical Trials Group (AACTG), funded by the National Institutes of Health, has created an important repository. Since 1986, the AACTG has enrolled >36,000 individuals into diverse prospective trials that have well-defined entry criteria and on-study evaluations. To establish a usable DNA bank, a group of clinical researchers, genetic investigators, ethicists, statisticians, data managers, regulatory specialists, and community representatives worked in collaboration to develop AACTG Protocol A5128, which allows the use of stored DNA for studies that were not planned when informed consent was provided for other AACTG trials [15].

Since 2001, ∼7500 different participants in these clinical trials—19% female, 51% white, 28% black, and 18% Hispanic—have contributed specimens to the AACTG Human DNA Repository under A5128, and accrual is ongoing. Because its specimens have an average yield of ∼400 µg of extracted DNA, this repository can support an almost unlimited number of projects. One challenge for the identification of genetic associations in cohort studies is to define control groups that share all relevant factors except phenotype [16]. Because most AACTG stud-
ies are randomized, approximately equal numbers of subjects with a given genotype are likely to be assigned to different treatments. The AACTG encourages proposals to utilize this resource for studies relevant to HIV infection and its complications, and a well-established procedure for the consideration of such proposals is in place.

In this issue of the Journal of Infectious Diseases, Tarr et al. describe an association between variant alleles of APOE and APOC3 and protease inhibitor–associated hyperlipidemia in participants in the Swiss HIV Cohort Study [17]. Their study expands the number of putative associations between human genetic variants and responses to antiretroviral therapy.

To date, the most impressive such association regards hypersensitivity to abacavir. Although the drug is generally well tolerated, 5%–9% of whites who receive abacavir experience hypersensitivity reactions that can be life threatening. Two research groups independently reported an association between major histocompatibility complex alleles and hypersensitivity to abacavir [18, 19]. In patients exposed to abacavir in Perth, Australia, the presence of HLA-B*5701, HLA-DR7, and HLA-DQ3 had a positive predictive value of 100% and a negative predictive value of 97% for hypersensitivity [18]. An association between hypersensitivity to abacavir and HLA-B*5701 and HLA-DR7 was confirmed in patients in North America [19]. More-recent analyses have extended this association to include a polymorphism in Hsp70-Hom, a member of the heat shock protein family of chaperonins [20]. In western Australia, the routine screening of patients’ genetic makeup before they are prescribed abacavir has markedly reduced the incidence of hypersensitivity reactions. Such screening is rarely performed in the United States.

The nonnucleoside reverse-transcriptase inhibitor efavirenz is one of the most widely prescribed antiretroviral medications [21, 22], but many recipients of efavirenz experience central nervous system side effects during the initial weeks of therapy [22–24]. Efavirenz is metabolized primarily by hepatic cytochrome P450 (CYP) 2B6 [25], and a large amount of interindividual variability in the amount of CYP2B6 in the liver has been reported [26–29], as have functional differences between genetic variants [28, 30–32]. Specimens from the AACTG Human DNA Repository and associated data from clinical trials were used to show that a CYP2B6 exon 4 polymorphism that occurs more frequently in blacks than in whites is associated with ~3-fold higher plasma concentrations of efavirenz ($P<.0001$) and with increased central nervous system side effects ($P = .036$) [33]. Differences in the frequency of this polymorphism in different populations may explain the lower clearance of efavirenz noted in blacks [34–36]. Additional studies are needed to assess the implications for long-term responses to efavirenz, as well as to nevirapine, which is also metabolized by CYP2B6 [37, 38].

Peripheral fat wasting and central fat deposition often complicate antiretroviral therapy. Independent risk factors for antiretroviral-associated lipoatrophy include white race and prolonged exposure to nucleoside analogues, particularly stavudine [39]. Tumor necrosis factor (TNF)–$\alpha$ has been implicated in the pathogenesis of lipoatrophy [40, 41], and TNF-$\alpha$ expression varies according to race and ethnicity [42]. At least 2 research groups have reported relationships between antiretroviral-associated lipoatrophy and a TNF-$\alpha$ promoter polymorphism that may affect gene expression. In 96 white patients in England, a TNF-$\alpha$ position $-238$ polymorphism was present only in subjects with lipoatrophy ($P = .01$) [43]. Similarly, in 191 white patients in Australia, all of whom had lipoatrophy, this polymorphism was associated with a more-rapid onset of fat wasting ($P = .014$) [44]. Although these findings support a role for TNF-$\alpha$ in the pathogenesis of lipoatrophy, this variant allele may simply be a marker for other genes with which it is linked, such as members of the major histocompatibility complex [42].

Bilirubin is the primary product of heme metabolism. Its efficient elimination requires conjugation with glucuronic acid in a reaction catalyzed by hepatic UDP-glucuronosyltransferase (UGT) 1A1. Approximately 5%–10% of individuals have decreased bilirubin-conjugating activity that is caused by a TA insertion into the UGT1A1 promoter (Gilbert syndrome) [45, 46]. The HIV protease inhibitors indinavir and atazanavir commonly cause unconjugated hyperbilirubinemia by competing with bilirubin for binding to UGT1A1. Although the condition is usually asymptomatic, some patients discontinue treatment with these drugs because of jaundice. In a study of 15 HIV-positive men receiving indinavir, mean increases in serum bilirubin levels were significantly greater in patients with at least 1 Gilbert polymorphism ($P = .012$) [47]. Similarly, of 138 healthy volunteers who participated in phase 1 studies of atazanavir, those homozygous for the Gilbert genotype had significantly higher median total bilirubin levels than did heterozygous or wild-type subjects ($P = .0001$) [48]. Fortunately, not all patients with Gilbert syndrome who receive atazanavir or indinavir experience marked elevations in bilirubin levels.

The HIV protease inhibitors are substrates for P-glycoprotein, the multidrug efflux pump encoded by MDRI [49–54], and a frequent MDRI exon 26 polymorphism has been associated with altered P-glycoprotein expression [55]. P-glycoprotein in the intestine, liver, and kidney is predicted to decrease oral bioavailability of these drugs and enhance their elimination. P-glycoprotein is also present in CD4 T cells [56], and its expression in the brain limits entry of protease inhibitors [51]. Importantly, a provocative report noted an association between the MDRI exon 26 polymorphism, increases in CD4 T cells in response to antiretroviral therapy, and plasma concentrations of efavirenz and nelfinavir [57]. Subsequent stud-
ies, however, have not confirmed these findings [33, 58, 59]. Genetic associations suggested by initial studies are often not confirmed by subsequent analyses [60], and the relevance of MDR1 polymorphisms for HIV therapeutics remains uncertain.

As pharmacogenomics moves from bench to bedside, most genotype-phenotype relationships will reflect the combined influences of multiple genes and polymorphisms. The growing number of identified genetic associations will increase the impetus to make human genetic testing a routine part of HIV clinical care. Prospective clinical trials will ultimately be needed to determine whether the use of human genetic testing to guide the administration of antiretroviral therapy results in an improved response to treatment. Because genetic variants are stable throughout one’s lifetime, genetic testing performed on a single occasion could potentially inform every subsequent treatment decision for a patient, and this makes such an approach to HIV clinical care even more attractive.

References
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