

Possible Ethnic-Specific HIV Antiretroviral Resistance?

By Rebecca Hersher

HIV resistance varies considerably across populations and is at least partially attributable to genetics. The multi-drug resistance transporter (MDR-1) gene, which codes for the p-glycoprotein, contains a single nucleotide polymorphism (SNP) that varies widely and is correlated in part to ethnicity. A landmark study by Fellay et al. showed a marked difference in drug concentration and CD4 count in patients with the C3435T polymorphism. Patients with

glycoprotein (PGP) and decreased resistance while the CC genotype leads to an increased resistance. Interestingly, subsequent studies found the rate of TT genotype distribution in various ethnic populations to vary greatly for the C3435T polymorphism (2). African populations were found to have dramatically lower instance of the TT genotype than East Asian and Caucasian populations. Assuming that the C3435T SNP is as strong a predictor as Fellay et al. demonstrated, this would mean that there is a dramatic variance in antiretroviral resistance depending on ethnicity.

The study published recently by Swaminathan et al. has increased available data on ethnicity as a genotypic predictor of antiretroviral resistance by providing results for an Indian cross-sectional population, but has also raised questions about the correlation between antiretroviral resistance and the C3435T polymorphism. The study was conducted on a population of 179 individuals, 126 HIV infected and 53 healthy, from South India. The percentages of the TT, CT, and CC genotypes, respectively, were 78 (44%), 74 (41%), and 27 (14%), the highest rate of TT genotype of any population studied thus far (Figure 1). Contrary to Fellay, Swaminathan found the distribution of the TT polymorphism to be similar in healthy and HIV infected subjects and was not correlated to non-genetic risk factors.

Swaminathan et al. also tested for effects of the C3435T polymorphism on antiretroviral resistance using the same two antiretroviral drugs tested by Fellay et al, nelfinavir (55 patients) and efavirenz (71 patients). Plasma concentration for the drug was measured after treatment to look for a difference in drug efficacy in the three different genotypes. Again contrary to the results published by Fellay et al, there was no appreciable difference in drug plasma concentration, suggesting that MDR-1 polymorphism at C3435T does not govern drug resistance.

Similar results have been observed with re-

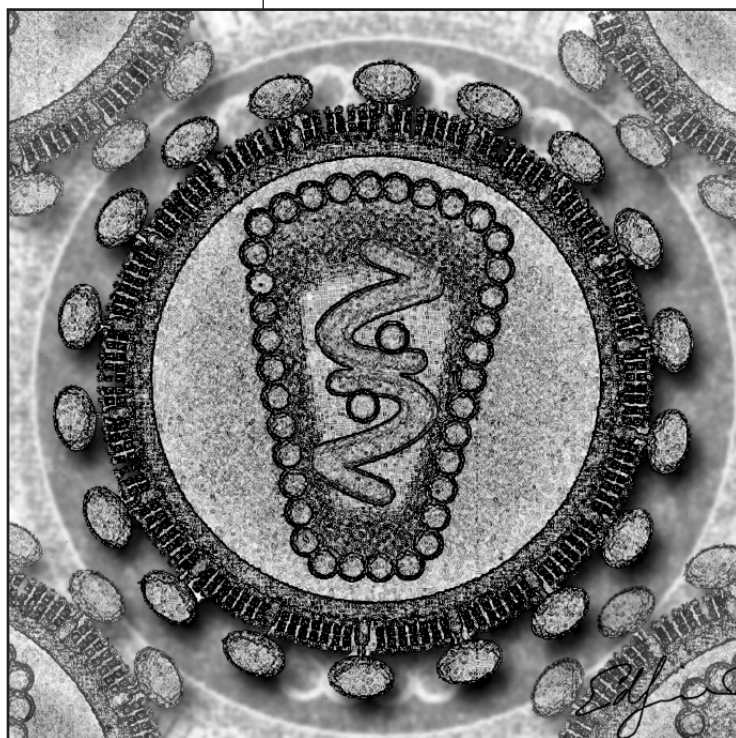


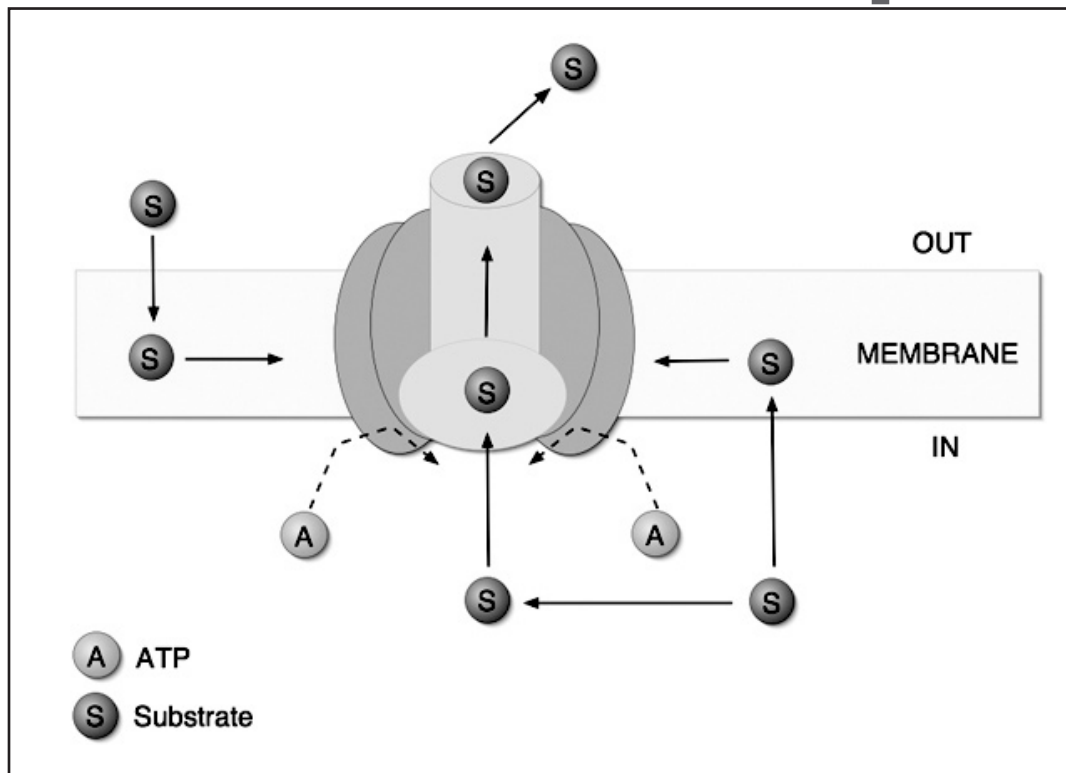
Figure 1. An artist's depiction of the cross section of a human immunodeficiency virus (HIV).

the CT genotype fell in the 50th percentile for drug concentration while those with the mutation fell well above and below at the 30th (TT) and 75th (CC) (1).

This established a correlation between the MDR-1 SNP and conferred resistance to antiretroviral treatment in populations based on the instance of genotypes in that population. Fellay et al. thus showed that the TT genotype leads to a decrease in the transcription of p-

spect to the effects of the C3435T polymorphism on drug resistance in other studies, calling into question whether the correlation observed by Fellay et al. is in fact reproducible with certainty. Solas et al. showed in a 2007 paper that there was little or no correlation between drug resistance and MDR-1 polymorphism using a protease inhibitor, Indinavir, as the test drug (3). Torti et al. showed similar results for an Italian subpopulation in which the only predicting factor for drug resistance was homosexuality and was independent of polymorphism (4). It remains to be determined whether the antiretroviral resistance observed by Fellay et al. was conclusively caused by the C3435T polymorphism, but the studies by Swaminathan, Solas, and Torti has made clear that the rate of polymorphism varies widely by ethnicity and may have implications for genetically specific treatment of HIV in the future. **H**

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Population Ethnicity	% TT genotype ¹ (C3435T)
Caucasian	21-32%
African	1-7%
Chinese	22%
Japanese	20%
Filipino	17%
South Indian	44%

Figure 2. Diagram depicting P-glycoprotein, the protein coded by the MDR-1 gene. P-glycoprotein, which spans the cell membrane, has a central portion that serves as a channel through which toxic chemicals can be pumped from within the cell back into the environment. These toxic chemicals come in contact with the protein either via the cell membrane or directly from the cell interior. The process is powered by ATP molecules.

References:

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