MDR1 pharmacogenetics: frequency of the C3435T mutation in exon 26 is significantly influenced by ethnicity.

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Abstract:

P-glycoprotein (PGP), the product of the multidrug resistance gene (MDR1), acts as an energy-dependent efflux pump that exports its substrates out of the cell. PGP expression is an important factor regulating absorption of a wide variety of medications. It has also been associated with intrinsic and acquired cross resistance to a number of structurally unrelated anticancer drugs. A single nucleotide polymorphism (SNP) in exon 26 of the MDR1 gene, C3435T, was recently correlated with PGP protein levels and substrate uptake. Individuals homozygous for the T allele have more than four-fold lower PGP expression compared with CC individuals. As overexpression of PGP has been associated with altered drug absorption, therapy-resistant malignancies, and lower concentrations of HIV-1 protease inhibitors, this SNP may provide a useful approach to individualize therapy. To facilitate clinical application throughout the world, 1280 subjects from 10 different ethnic groups were evaluated for this SNP using the polymerase chain reaction-restriction fragment length polymorphism assay and the genotype and allele frequency for each group were ascertained. Marked differences in genotype and allele frequency were apparent between the African populations and the Caucasian/Asian populations ($P < 0.0001$). The Ghanaian, Kenyan, African American and Sudanese populations studied had frequencies of 83%, 83%, 84% and 73%, respectively, for the C allele. The British Caucasian, Portuguese, South-west Asian, Chinese, Filipino and Saudi populations had lower frequencies of the C allele compared to the African group (48%, 43%, 34%, 53%, 59%, and 55%, respectively). The high frequency of the C allele in the African group implies over expression of PGP and may have important therapeutic and prognostic implications for use of PGP dependent drugs in individuals of African origin. PMID: 11337937 [PubMed - indexed for MEDLINE]