



Stanford - South Africa

Biomedical Informatics Program



Pharmacogenomics and HIV

Caroline F. Thorn, Ph.D.
thorn@helix.stanford.edu



Overview

- Host vs Viral genome
- CCR5 genotype and infection
- Hypersensitivity to abacavir
- Drug transporters
- Drug-drug interaction
- Lipid alterations



Host vs Viral genome

- Drug therapy for HIV, like antimicrobial and antiparasite therapies, targets differences between virus and host metabolism
- Classes of drugs include reverse transcriptase inhibitors both non-nucleoside (NNRTI) and nucleoside analogue, and protease inhibitors
- HAART - highly active anti-retroviral therapy, reverse transcriptase inhibitors plus protease inhibitors



Host vs Viral genome

- Drug responses can be influenced by host genome but also by virus genome
- Eg. Host may have SNP associated with higher PK of drug, leading to lower plasma drug concentrations and higher viral load
- Eg. Virus may manipulate transcription of transporter genes to increase drug efflux



Host vs Viral genome

- Viral genome - see HIV Drug resistance DB
- Host genome -
 - CCR5 genotype and infection
 - Hypersensitivity to abacavir
 - Drug transporters
 - Drug-drug interaction
 - Lipid alterations

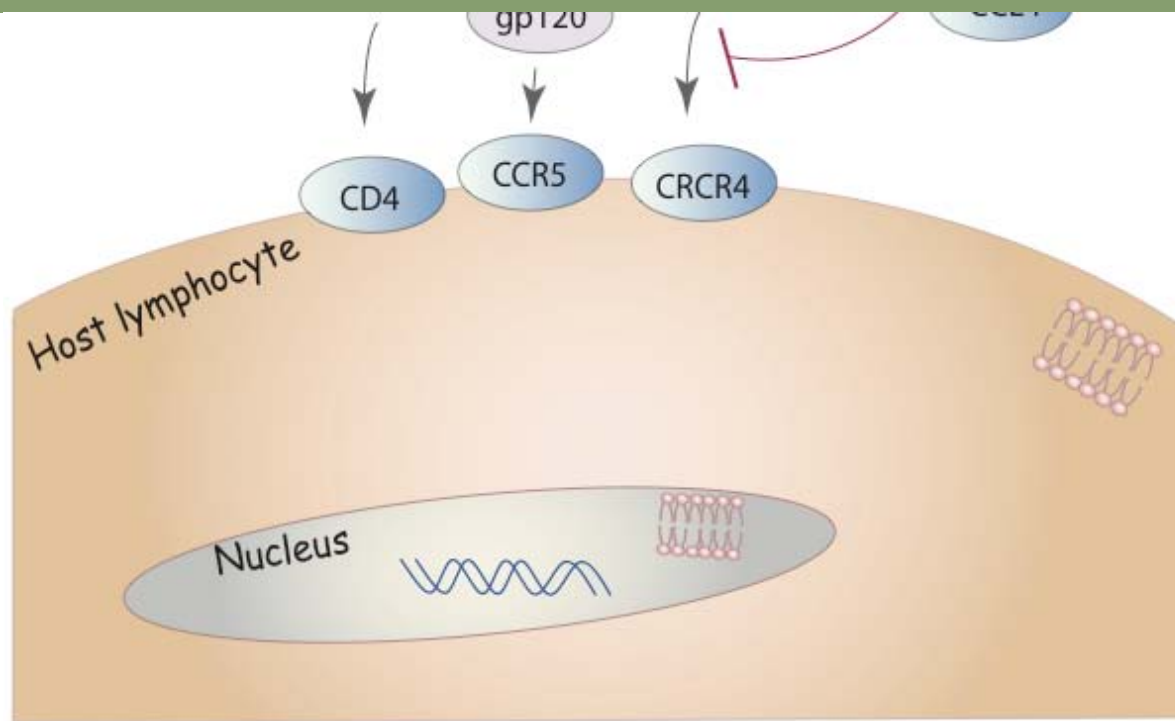


CCR5 and infection

- HIV gp120 binds to CD4 to gain entry to cell
- CCR5 is cell surface chemokine receptor
- Virus also binds to CCR5 or CXCR4 coreceptor
- Once inside virus integrates into genome and replicates
- Polymorphism in coreceptors can effect infection



CCR5 and infection



CCR5 and infection

J Virol. 2005 Sep;79(18):11677-84.

[Related Articles, Links](#)

Full text article at
jvi.asm.org

Combined effect of CCR5-Delta32 heterozygosity and the CCR5 promoter polymorphism -2459 A/G on CCR5 expression and resistance to human immunodeficiency virus type 1 transmission.

[Hladik F](#), [Liu H](#), [Speelmon E](#), [Livingston-Rosanoff D](#), [Wilson S](#), [Sakchalathorn P](#), [Hwangbo Y](#), [Greene B](#), [Zhu T](#), [McElrath MJ](#).

- High risk exposed caucasian individuals compared to low risk caucasian controls, showed enrichment of haplotype of CCR5
- CCR5 haplotype correlated with decreased expression in isolated lymphocytes and monocytes



CCR5 and infection

AIDS. 2000 Mar 10;14(4):449-51.

[Related Articles, Links](#)



Allelic frequencies of host genetic variants influencing susceptibility to HIV-1 infection and disease in South African populations.

[Williamson C](#), [Loubser SA](#), [Brice B](#), [Joubert G](#), [Smit T](#), [Thomas R](#), [Visagie M](#), [Cooper M](#), [van der Ryst E](#).

SAIMR Virology, Department of Medical Microbiology, University of Cape Town, Observatory, South Africa.

OBJECTIVES: Limited information is available on the prevalence in African populations of host genetic polymorphisms conferring resistance to HIV-1 infection and disease. The objective of this study was to determine the allelic frequencies in South African populations of the chemokine receptor gene variants CCR5delta32, CCR5m303 and CCR2b-641 and the CXCR4 ligand gene variant SDF1-3'A. **METHOD:** Cross-sectional study to determine the prevalence of these gene variants in South African subjects of African and European descent. **RESULTS:** The CCR5delta32 genetic variant is rare in individuals of African origin, having an allelic frequency of 0.1% (n = 1247) compared with 9.8% (n = 144) in Caucasians. The CCR5m303 mutation was not detected in Africans (n = 687), whereas an allelic frequency of 0.9% (n = 145) was identified in Caucasians. The frequency of CCR2b-641 allele was 13.1% (n = 180) in Africans, which was significantly higher than the 7.2% (n = 146) detected in Caucasians. Finally the allelic frequency of the SDF1-3'A gene variant was only 1.0% (n = 198) in Africans compared with 19.8% (n = 145) in Caucasians. **CONCLUSIONS:** These results indicate that genetic polymorphisms conferring resistance to HIV-1 infection are rare in the South African Black population. Except for the CCR2b-641 gene variant, individuals of African origin also had a much lower prevalence of genetic variants associated with prolonged disease progression.

PMID: 10770549 [PubMed - indexed for MEDLINE]

- Frequency of the CCR5 variants is much lower in this South African population
- What does this mean for design of anti-infectives?
- What does this mean for therapy to increase time to progression



Host genome

- CCR5 genotype and infection
- Hypersensitivity to abacavir
- Drug transporters
- Drug-drug interaction
- Lipid alterations



Hypersensitivity to abacavir

- Abacavir is a nucleoside reverse transcriptase inhibitor, NRTI
- Hypersensitivity occurs in around 5% of patients
- Rash (mild), anaphylaxis (severe), leads to discontinuation of treatment



Hypersensitivity to abacavir

Pharmacogenomics. 2004 Mar;5(2):203-11.

[Related Articles, Links](#)



Association of genetic variations in HLA-B region with hypersensitivity to abacavir in some, but not all, populations.

[Hughes AR](#), [Mosteller M](#), [Bansal AT](#), [Davies K](#), [Haneline SA](#), [Lai EH](#), [Nangle K](#), [Scott T](#), [Spreen WR](#), [Warren LL](#), [Roses AD](#); [CNA30027 Study Team](#); [CNA30032 Study Team](#).

- HLA-B*5701 associated with hypersensitivity in White and Hispanic subjects
- TNF α -308A associated with hypersensitivity in Black or African American subjects (but small sample size)



Host genome

- CCR5 genotype and infection
- Hypersensitivity to abacavir
- Drug transporters
- Drug-drug interaction
- Lipid alterations



Drug transporters and HIV

THE LANCET


Volume 359, Issue 9300, 5 January 2002, Pages 30-36

[doi:10.1016/S0140-6736\(02\)07276-8](https://doi.org/10.1016/S0140-6736(02)07276-8)  Cite or Link Using DOI

Copyright © 2002 Elsevier Ltd All rights reserved.

Articles

Response to antiretroviral treatment in HIV-1-infected individuals with allelic variants of the multidrug resistance transporter 1: a pharmacogenetics study

Jacques Fellay MD^a, Catia Marzolini PhrmaD^b, Emma R Meaden BScⁱ, David J Back PhDⁱ, Thierry Buclin MD^b, Jean-Philippe Chave PhD^g, Laurent A Decosterd PhD^b, Hansjakob Furrer MD^e, Milos Opravil MD^f, ProfGiuseppe Pantaleo MD^c, Dorota Retelska PhD^a, Lidia Ruiz PhD^j, Alfred H Schinkel PhD^k, Pietro Vernazza MD^h, Chin B Eap PhD^d, Amalio Telenti^a,  and for the Swiss HIV Cohort Study

- ABCB1 C3435T predicts immune recovery after treatment with antiretrovirals (some on efavirenz, nelfinavir plus nucleoside analogue reverse transcriptase inhibitors)

This Document

► Abstract

- [Full Text + Links](#)
- [PDF \(112 K\)](#)

Actions

- [E-mail Article](#)



Drug transporters and HIV

- But as we already know ABCB1 is highly polymorphic and 3435 SNP has different frequency in different populations



ABCB1 C3435T

ELSEVIER
FULL-TEXT ARTICLE

Frequency of C3435T polymorphism of MDR1 gene in African people.

[Schaeffeler E](#), [Eichelbaum M](#), [Brinkmann U](#), [Penger A](#), [Asante-Poku S](#), [Zanger UM](#), [Schwab M](#).

The variability of P-glycoprotein expression between individuals is linked to a C3435T polymorphism of the human MDR1 gene. Concentration of P-glycoprotein in intestinal epithelial cells and in a subset of lymphoid cells is substantially lower in people with the T/T genotype than those with the C/C genotype. We compared allele frequencies of the C3435T polymorphism in random samples of west African, African American, white, and Japanese people. We recorded a significantly higher frequency of the C/C genotype in West Africans and African Americans (142 of 172 [83%] and 25 of 41 [61%], respectively), than in white people (139 of 537 [26%]) ($p < 0.0001$). These findings could affect use of drugs that are P-glycoprotein substrates (such as HIV-1 protease inhibitors and ciclosporin) in African populations.

- 3435C associated with higher intestinal expression
- Higher frequency of CC in west Africans
- More efficient drug export in africans? So lower plasma concentrations?



Host genome

- CCR5 genotype and infection
- Hypersensitivity to abacavir
- Drug transporters
- Drug-drug interaction
- Lipid alterations



Drug-drug interactions and HIV

- HIV patients are on many drugs concurrently
- May also need treatment for opportunistic infections, TB
- Any pharmacogenomic effects in drug metabolizing enzymes and transporters may then become even more important if these systems being hit with several drugs at once



Lipid alterations and HIV drugs

- Protease inhibitor treatment associated with lipodystrophy – loss of body fat but elevation of total cholesterol, triglycerides and insulin resistance
- Common side effect ~25%



Lipid alterations and HIV drugs

- SREBP-1c pathway may be involved
- Can SNPs in SREBP-1c gene, or others in pathways predict development of lipodystrophy?

AIDS. 2002 Aug 16;16(12):1587-94.

[Related Articles, Link](#)



Indinavir inhibits sterol-regulatory element-binding protein-1c-dependent lipoprotein lipase and fatty acid synthase gene activations.

[Miserez AR](#), [Muller PY](#), [Spaniol V](#).



Summary

- Genetic variation is important in design of both prevention of HIV infection and drugs to prevent HIV progression
- Variation in drug metabolizing enzymes and drug transporters may be even more significant in context of multiple drugs
- Long term side effects of antiretroviral therapy important



References

- Response to antiretroviral treatment in HIV-1-infected individuals with allelic variants of the multidrug resistance transporter 1: a pharmacogenetics study. Fellay J, Marzolini C, Meaden ER, Back DJ, Buclin T, Chave JP, Decosterd LA, Furrer H, Opravil M, Pantaleo G, Retelska D, Ruiz L, Schinkel AH, Vernazza P, Eap CB, Telenti A; Swiss HIV Cohort Study. Lancet. 2002 Jan 5;359(9300):30-6. [PMID: 11809184](#)
- Allelic frequencies of host genetic variants influencing susceptibility to HIV-1 infection and disease in South African populations. Williamson C, Loubser SA, Brice B, Joubert G, Smit T, Thomas R, Visagie M, Cooper M, van der Ryst E. AIDS. 2000 Mar 10;14(4):449-51. [PMID: 10770549](#)

