

Genetic effects on HIV disease progression

The controversy surrounding the effect of specific chemokine receptor polymorphisms on HIV disease progression^{1,2} highlights the need for synthesis of the pertinent evidence. It also suggests that large-scale international collaborations^{3,4} are indispensable when it comes to addressing important questions in the field. We propose an international meta-analysis of HIV host genetics.

As an initial effort, we performed a preliminary meta-analysis for the effect of CCR5 and CCR2 genotypes on progression to AIDS among HIV-infected patients. We included published data from ten adult/adolescent cohorts. Among 3,034 patients with known CCR5 genotype, there is an unequivocal protective effect for heterozygotes with the CCR5-Δ 32 compared to CCR5 wild-type individuals (Fig.; fixed effects hazard ratio [HR] 0.69 [95% CI, 0.60–0.78]). Despite no statistically significant heterogeneity between cohorts ($\chi^2 p = 0.25$), the benefit seems slightly larger in 1,520 seroconverters (HR 0.65 [0.54–0.79]) than in 1,514 seroprevalent subjects (HR 0.73 [0.61–0.86]).

The preliminary analysis on CCR2 64I is less conclusive (Fig.) with an overall borderline effect across 2,383 patients with known CCR2 genotype (HR 0.92 [0.81–1.05] for heterozygotes compared with wild-type homozygotes). The cohort results are not significantly heterogeneous (between-study variance = 0), yet evidence for a protective effect seems present among 1,181 seroconverters (HR 0.81 [0.67–0.98]) but not among seroprevalent subjects (HR 1.03 [0.86–1.23]). The available data were insufficient to perform analyses using wild-type homozygotes for both CCR2 and CCR5 as the standard comparison group.

Preliminary analysis of summary viral load data (weighted by size) from six cohorts (Amsterdam, Swiss, Copenhagen, SEROCO, SFHMS, Chicago MACS; $n = 1,429$) shows a 0.35 \log_{10} lower median early viral load in CCR5 heterozygotes than in wild-type homozygotes. The difference seems consistent (range: 0.20, 0.60) across cohorts. For CCR2 64I het-

erozygotes, data from three cohorts (Swiss, SFHMS, Chicago MACS; $n = 737$) suggest a less consistent 0.19 \log_{10} (range: -0.04, 0.50) lower median viral load compared to CCR2 wild-type homozygotes.

Examination of the complex interrelationships between genetic polymorphisms that may affect the outcome of HIV-1 infection requires large numbers of patients to achieve reliable and authoritative conclusions. Isolated efforts are increasingly likely to be inconclusive, with results that diverge simply by chance being labeled "contradictory", and thereby stirring unfruitful debate. More importantly, small numbers cannot address reliably the diversity of effects among different populations and subgroups⁵ (such as racial background or route of infection) and the relationship of polymorphisms with other predictors of disease progression. Finally, to date analyses have not been standardized, making it possible that subtle differences in definitions, patient selection and data analyses will introduce bias.

A large international collaborative meta-analysis of individual patient data with a standardized protocol and advance planning is needed to address these issues. We recently distributed such a protocol to identified cohorts and we invite all other investigators in the field to join this effort. The meta-analysis is sponsored by the HIV/AIDS Collaborative Review Group of the International Cochrane Collaboration⁵. The Col-

laboration's principles of being systematic, all-inclusive and objective should benefit this rapidly growing field. Please contact us for further details. (ji24m@NIH.gov).

JOHN P.A. IOANNIDIS^{1,2}, THOMAS R. O'BRIEN³, PHILIP S. ROSENBERG⁴, DESPINA G. CONTOPOULOS-IOANNIDIS⁵ & JAMES J. GOEDERT³

¹HIV Research Branch, Division of AIDS, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland 20852, USA

²Editorial Board, Collaborative Review Group on HIV infection and AIDS, International Cochrane Collaboration

³Viral Epidemiology Branch and ⁴Biostatistics Branch, DCEG, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20852, USA

⁵Department of Pediatric Infectious Diseases, Children's National Medical Center, Washington, District of Columbia 20010, USA

1. Kostrikis, L.G. *et al.* A chemokine receptor CCR2 allele delays HIV-1 disease progression and is associated with a CCR5 promoter mutation. *Nature Med.* 4, 350–3 (1998).
2. Michael, N.L., *et al.* The role of CCR5 and CCR2 polymorphisms in HIV-1 transmission and disease progression. *Nature Med.* 3, 1160–2 (1997).
3. Stewart, G. Chemokine genes - beating the odds. *Nature Med.* 4, 275–6 (1998).
4. Wrong kind of chemokine research. Editorial. *Nature Med.* 3, 1051 (1997).
5. Lau, J., Ioannidis, J.P.A. & Schmid, C.H. Summing-up evidence: one answer is not always enough. *Lancet* 351, 123–7 (1998).
6. Bero, L. & Rennie, D. The Cochrane Collaboration. *JAMA* 274, 1935–8 (1995).

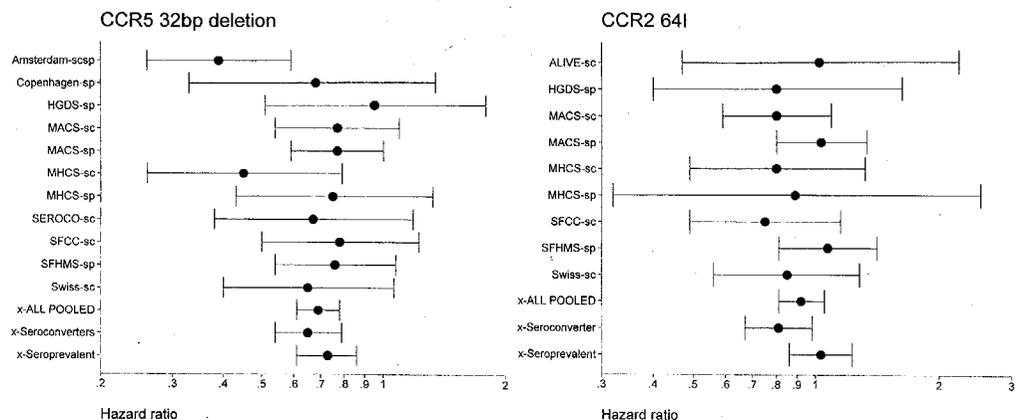


Fig. Preliminary meta-analysis on the effect of CCR5-Δ 32 deletion heterozygosity and CCR2 64I mutation, on the rate of disease progression to AIDS among HIV-infected patients. Whenever different AIDS definitions were specified in a cohort, the 1993 CDC definition was used. Each study and pooled estimates are shown by the point estimate hazard ratio and 95% confidence intervals. The pooled hazard ratios are obtained by fixed effects (weighting each study by the inverse of its variance), but random effects estimates were similar. Non-Caucasians are excluded from all CCR5 data except for 53 patients in the SFHMS. Non-Caucasians were not excluded in CCR2 data except for few patients in the seroprevalent MHCS, MACS and HGDS. sc, seroconverters; sp, seroprevalent (Amsterdam included both). ALIVE, AIDS Link to the Intravenous Experience; HGDS, Hemophilia Growth and Development Study; MACS, Multicenter AIDS Cohort Study; MHCS, Multicenter Hemophilia Cohort Study; SFCC, San Francisco City Clinic Study; SFHMS, San Francisco Men's Health Study.