

Genome-wide association scan in HIV-1 infected individuals identifies a variant in the *C20orf151/Cables2* gene region influencing disease course



Daniëlle van Manen¹, Neeltje A. Kootstra¹, Brigitte Boeser-Nunnink¹, Judith Burger¹, Ruben van 't Slot², Angélique B. van 't Wout¹, and Hanneke Schuitemaker¹

¹Dept Experimental Immunology, Landsteiner Laboratory Sanquin Research at the Academic Medical Center, Amsterdam, The Netherlands ²Complex Genetics Section, Department of Biomedical Genetics, University Medical Center Utrecht

d.vanmanen@amc.uva.nl

Background

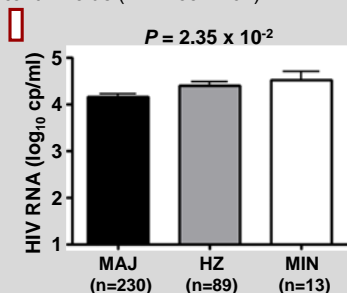
- AIDS develops typically within 7-11 years after infection, but occasionally very rapid disease progression (<2 years) or virtually no disease progression may occur.
- Until now, several host genetic factors have been implicated in the rate of HIV-1 disease progression. Among these are certain human leukocyte antigen (HLA) alleles and the CCR5 Δ32 allele. However, all host genetic factors in AIDS pathogenesis known to date explain variation in clinical course of HIV infection in only a minority of individuals.
- The identification of novel susceptibility alleles in HIV-1 infection or disease progression, will provide new opportunities for disease treatment, prevention and the development of vaccines.

Methods

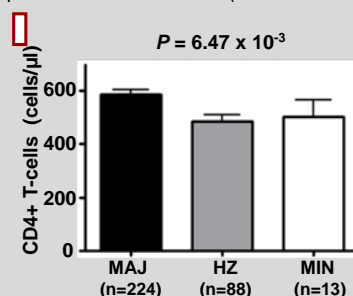
- To reveal additional host genetic factors, we designed a genome-wide association (GWA) study in 335 participants of the Amsterdam Cohort Studies on HIV infection and AIDS (ACS) in homosexual men with an accurately imputed seroconversion date.
- For the combined analysis we analyzed 120 additional individuals, namely participants of the ACS on HIV and AIDS among drug users (DU).
- We genotyped samples with Illumina's Infinium HumanHap300 BeadChip, which assays 317,503 single nucleotide polymorphisms (SNPs).
- The association of SNP genotypes with the clinical course of HIV-1 infection was tested in Kaplan-Meier analyses with AIDS-related death as an endpoint.

Results I:

- The viral load (VL) at set-point is considered to be established 18-24 months post seroconversion and is highly predictive for the clinical course of infection
- Interestingly, the SNP identified in our study was also associated with VL set-point in the ACS of homosexual men, although not with a genome-wide significant P -value ($P = 2.35 \times 10^{-2}$).

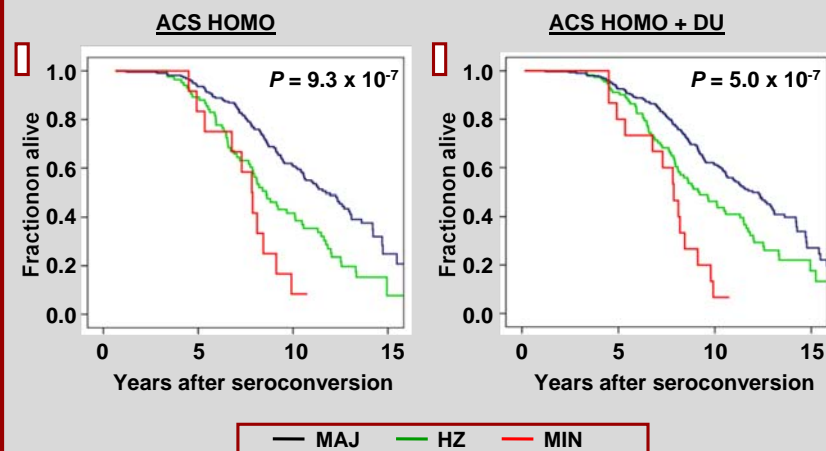


- In addition, the minor allele of *C20orf151/Cables2* rs1570023 correlated with a lower CD4+ T-cell count at set-point in these individuals ($P = 6.47 \times 10^{-3}$).



Results I:

- The top 10 SNPs -all located on different chromosomes- had P -values approaching genome-wide significance. Permutation testing was applied to the complete data set to determine statistical significance when performing multiple correlated tests.
- This revealed that a SNP on chromosome 20, in the *C20orf151/Cables2* gene region, was indeed genome wide significantly associated with time to AIDS-related death in the ACS of homosexual men (Log Rank P -value 9.3×10^{-7}).



- The association of this SNP with disease progression could be confirmed in combined analysis of the ACS of homosexual men and the ACS of HIV-1 infected drug-users (DU) comprising 120 individuals with documented seroconversion dates. When the two cohorts were joined an even stronger association with time to AIDS-related death was seen ($P = 5.0 \times 10^{-7}$).

Allele frequency distribution for the chromosome 20 SNP in both the homosexual participants and the drug users.

Gene	ACS HOMO			ACS HOMO+IVDU						
	MAJ	HZ	MIN	Major allele	Minor allele	MAJ	HZ	MIN	Major allele	Minor allele
<i>C20orf151/</i>	231	91	13	82.5%	17.5%	316	123	16	83.0%	17.0%
<i>Cables2</i>	69.0%	27.2%	3.9%	82.5%	17.5%	69.5%	27.0%	3.5%	83.0%	17.0%

Conclusions:

- A SNP on chromosome 20, in the *C20orf151/Cables2* gene region, was significantly associated with the clinical course of HIV-1 infection.
- C20orf151* is an open reading frame with an unknown function until now. *Cables2* (Cdk5 and Abl enzyme substrate 2), also known as *ik3-2*, is established as a proapoptotic factor involved in both p53-mediated apoptosis and p53-independent cell death pathways. Obviously, the exact mechanism by which the here identified SNP, or the gene region it tags, influences disease progression remains to be established.
- Currently we are trying to replicate these findings in another seroconversion cohort, with participants from whom also long-term follow-up data is available.
- This finding emphasizes the importance of studying human genetic variations as a tool to find new host factors that may influence infectious diseases course.