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ASSOCIATION OF HIV AND HOST GENETIC VARIANTS IN ANTIRETROVIRAL THERAPY-NAÏVE PERSONS

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BACKGROUND

- HIV-1 genetic diversity allows the virus to **adapt and escape** the host's immune response.
- Certain sections of the host genome **affect the replicative rate of the virus**.
- **The molecular specificity of the interplay** between viral genetic escape and host genomic control **remains poorly understood.**
- We tested **associations** between **viral genetic data** with recently reported (1) **host genetic data** from a demographically diverse cohort of ART naïve HIV+ participants in the START clinical trial (2).

Diverse groups of **HLA alleles possibly impose the selection** on viral genotypes which can **have an effect on viral load** in the context of the host immunotype.

METHODS

- Two 3.6kb amplicons (HIV-1 HXB2 genome: 1,485–5,058 and 5,967–9,517) of viral genomes from baseline (pre-ART) samples of **2,122 HIV+ participants** from **23 countries** across **5 continents** in the START study were sequenced and matched with host genetic data.
- Associations between **HIV-1 amino acid (aa) variants** and **human SNPs/imputed HLA alleles** (described in Ekenberg *et al.* 2019 (1)) were tested with **logistic regression models** adjusting for **age**, **sex** and **genetic structures** in the viral and human population captured by principal component analysis (Fig. 1). Associations were identified using **Bonferroni correction.**
- **Linear regression models** of $\log_{10}$ transformed viral load (VL) adjusting for **age**, **sex** and **genetic structure** were used for HLA allele and HIV aa variant **interaction analysis**.

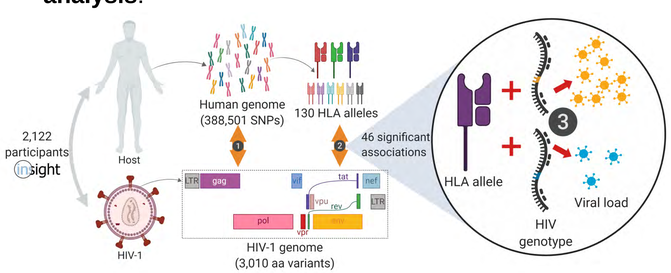

Figure 1. Scheme of performed experiments: (1) association between HIV genome aa variants and host SNPs, (2) association between HIV genome aa variants and host HLA alleles and (3) interaction analysis between VL, HLA alleles and different HIV genotypes.

RESULTS

- **3,010 HIV aa variants** associations with **388,501 host SNPs** were tested. 12 HIV aa variants were associated with 1–512 human SNPs ($p<4.28 \cdot 10^{-11}$). All associated human SNPs were in the **HLA region** (example of the association between Gag242N and human SNPs in Fig. 2); the associations in HIV genome were observed in ***nef* (N=5)**, ***gag* (N=5)** and ***pol* (N=2) genes**.
- For 3,010 HIV aa variants association tests with **130 imputed HLA alleles** were performed. A total of **46 associations** were identified ($p<1.29 \cdot 10^{-7}$); most associations were observed in ***nef* (N=17)** and ***gag* (N=12)** HIV genes (Fig. 3). **31 HIV aa variants** were associated with **33 different HLA alleles** (Fig. 4). Several HLA types were in linkage disequilibrium (LD) while no HIV aa variants were in LD.
- While **Gag242N** HIV aa variant ($b=-0.14$; $p=1.4 \cdot 10^{-3}$) and **B*57:03** HLA allele ($b=-0.59$; $p=1.1 \cdot 10^{-3}$) had a **negative effect on VL**, the **interaction** between **Gag242N** and **B*57:03** ($b=0.58$; $p=6.4 \cdot 10^{-3}$) had a **positive effect on VL** (Fig. 5; left) diluting the Gag242N or B*57:03 effect when they co-exist.
- Similarly, **A*03:01** HLA allele had a **negative effect on VL** ($b=-0.19$; $p= 7.3 \cdot 10^{-3}$) and **Pol432R** HIV aa variant had **no effect on VL** ($p=6.5 \cdot 10^{-1}$) while the **interaction** between **A*03:01** and **Pol432R** had a **positive effect on VL** ($b=0.23$; $p= 5.1 \cdot 10^{-3}$) (Fig. 5; right).

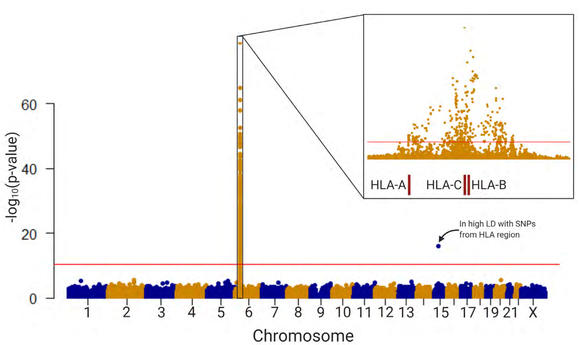

Figure 2. Manhattan plot of the strongest association between HIV aa variant Gag242N and human SNPs.

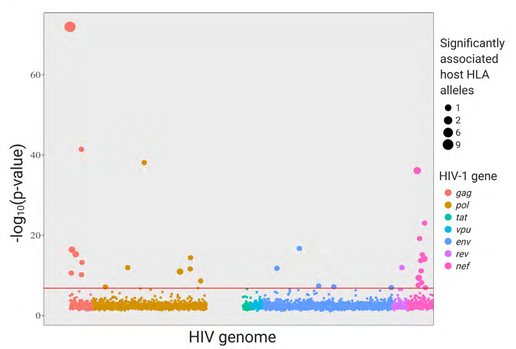

Figure 3. Association between HIV-1 aa variants and human HLA alleles projected on HIV-1 genome with only strongest association for each HIV-1 aa variant.

CONCLUSIONS

- Diverse groups of Class I and Class II human immunotypes possibly impose selection on viral genotypes through viral epitope selection.
- Viral virulence factors cannot be studied and interpreted without the context of the host genetics.

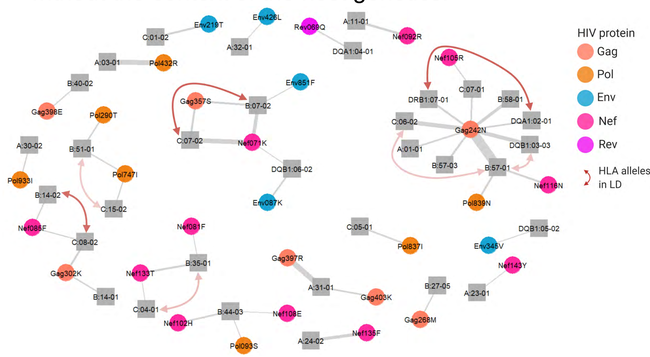

Figure 4. 46 significant associations between host HLA alleles and HIV aa variants; line thickness correspond to the association strength, arrows mark LD between HLA alleles and the opacity marks the strength of LD.

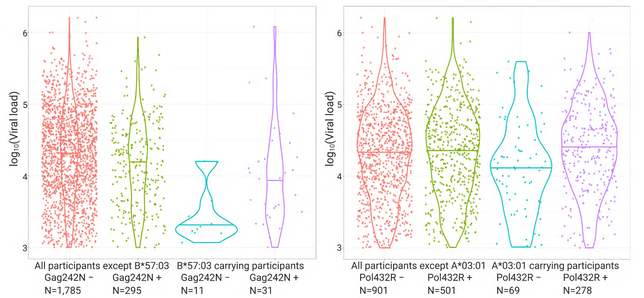

Figure 5. Violin plots of VL in participants carrying B*57:03 (left) or A*03:01 (right) HLA alleles when the associated aa variant (Gag242N or Pol432R) is present or not and the effect of the associated aa variant on the rest of the participants.

REFERENCES

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2. INSIGHT START Study Group. Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection. New England Journal of Medicine 373, 795–807 (2015).

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