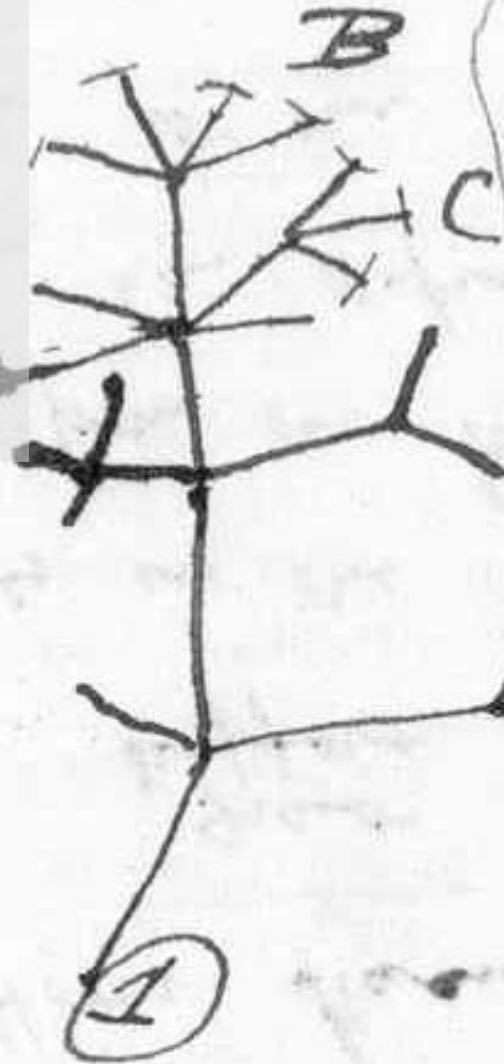


What Have We Learned from the Study of HIV Susceptibility and Treatment

Amalio TELENTI
Institute of Medical Microbiology
CHUV – UNIL, Lausanne
www.chuv.ch/imul
And Ragon Institute, Boston

I think



Do you think it is possible to have many species in one place (as in the case of the HIV virus)?

living in the same place

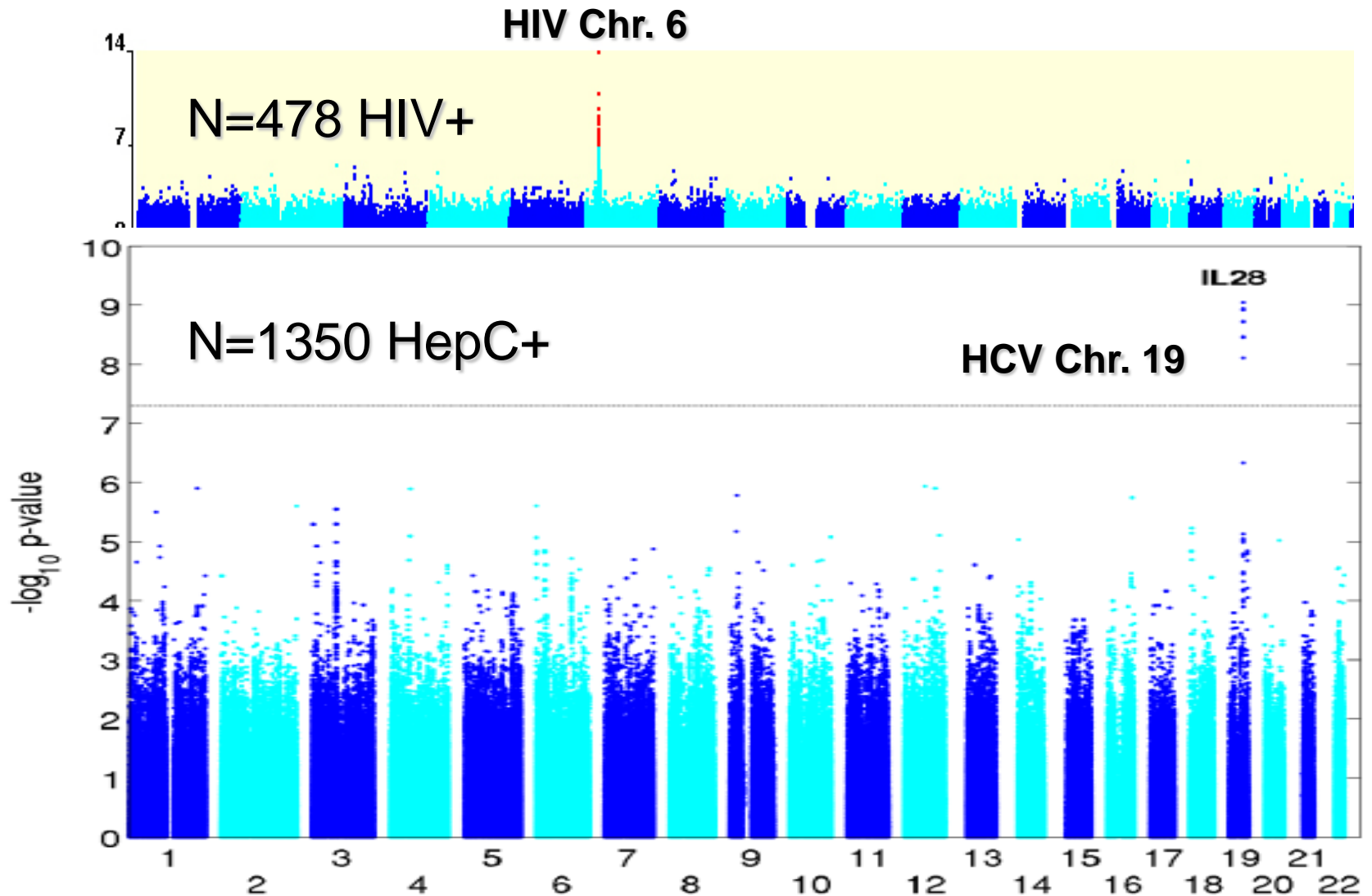
Can you see from the phylogenetic tree that the HIV virus is a very recent species?



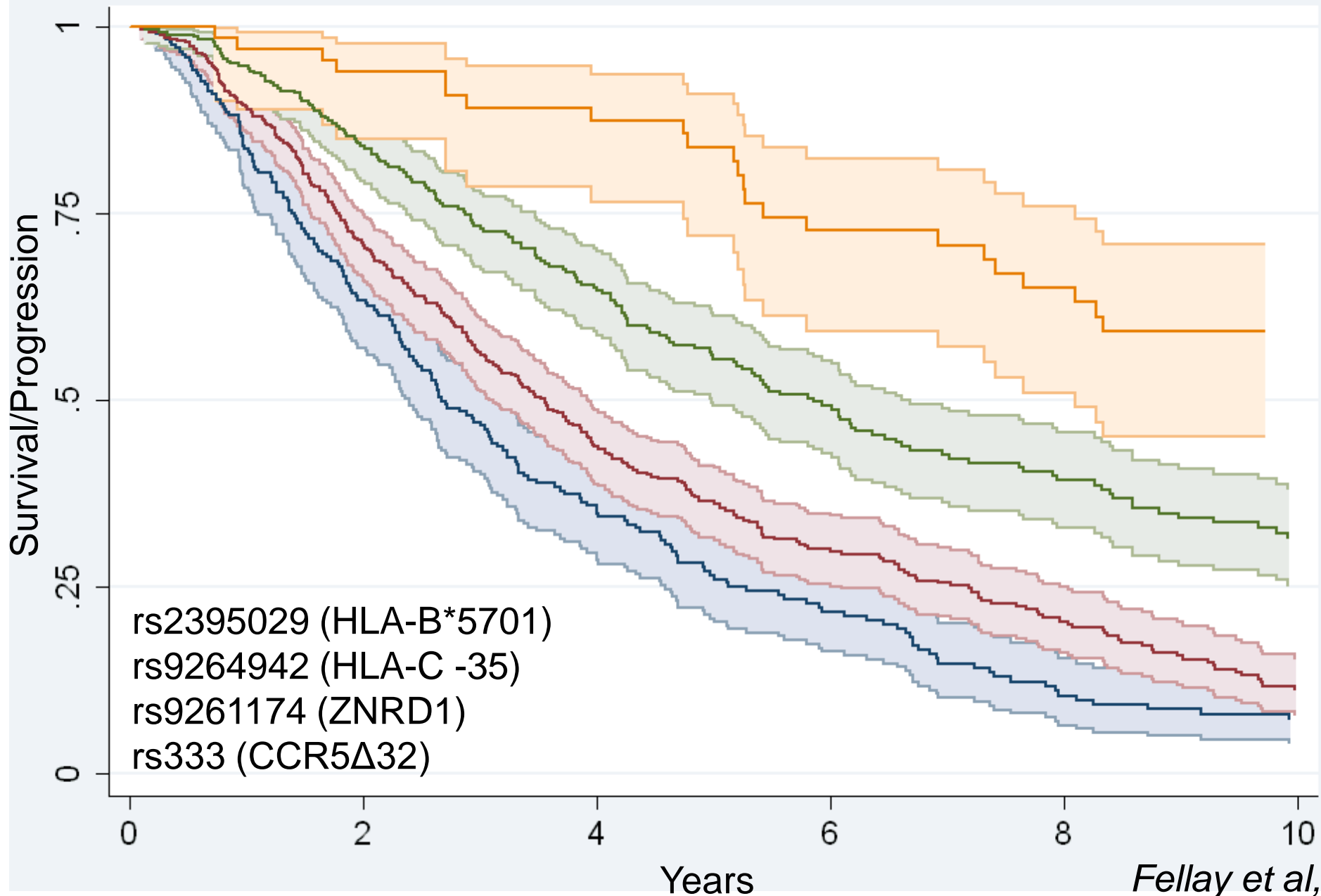
- Strong association signals
- Co-evolution and positive selective pressure.
- Possibility to create « perturbed » research settings and integrate datasets.

#1 - Exploiting differences among pathogens

Chromosomal location of locus of susceptibility to HIV-1 and to Hepatitis C



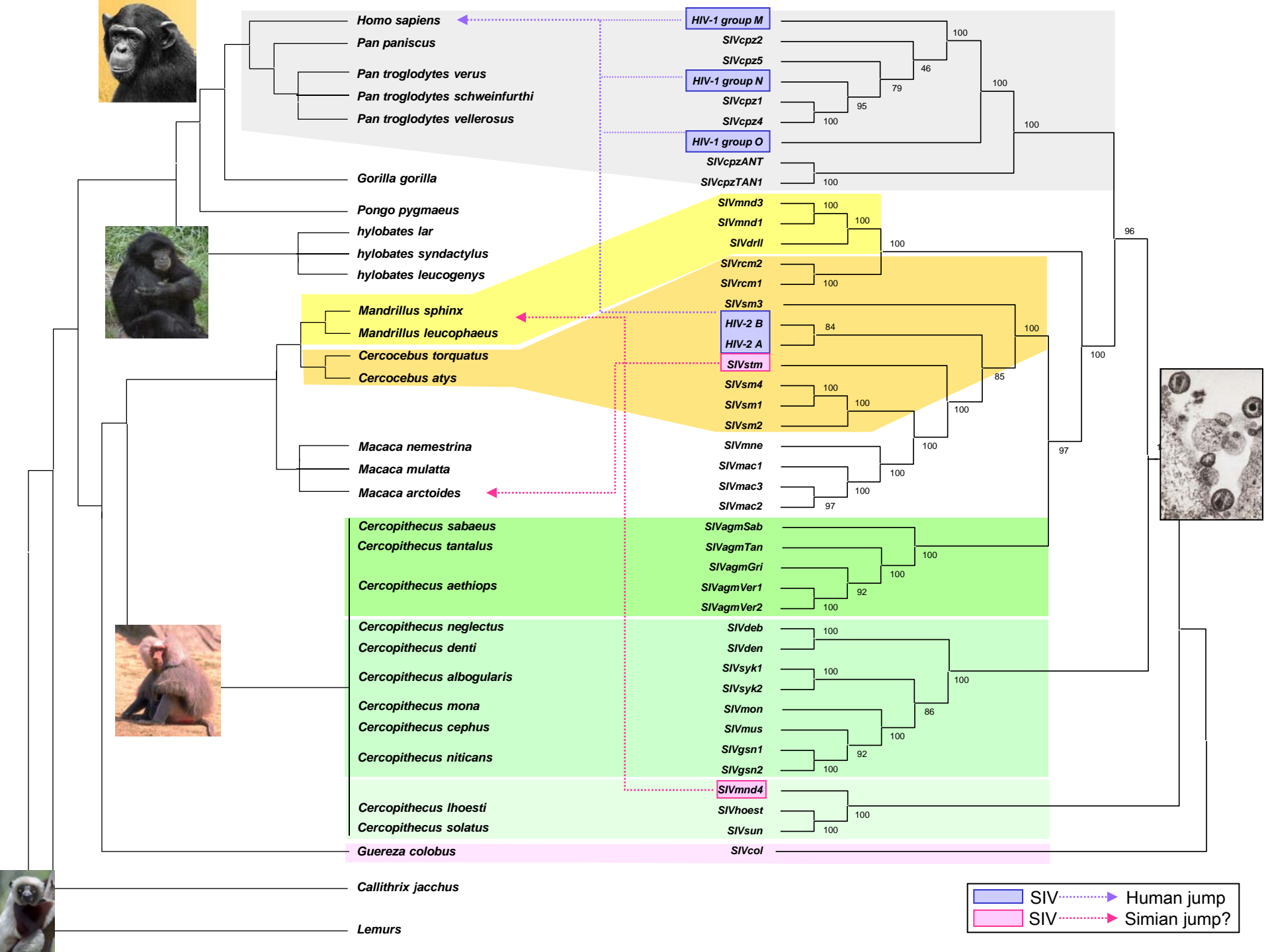
Additive genetic score



GWAS Results

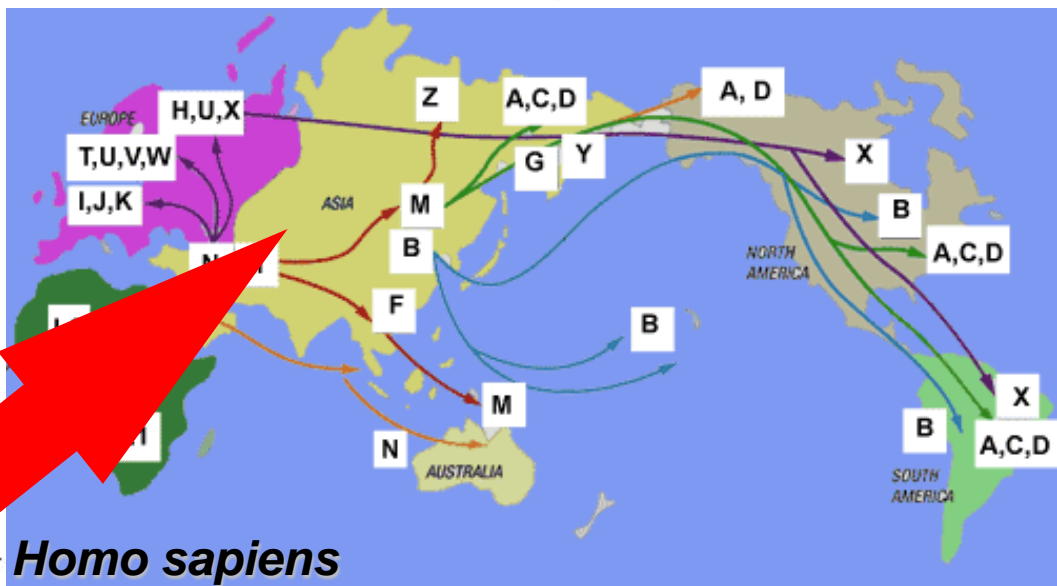
- We have reached experimental power conditions to identify most common human (Caucasian) variation influencing susceptibility to HIV
- We can now explain 22% of population variance by genetics, population effects, gender and age.
- Clear and profoundly different signals for various pathogens (n=2).

#2 - Exploiting evolutionary trajectory

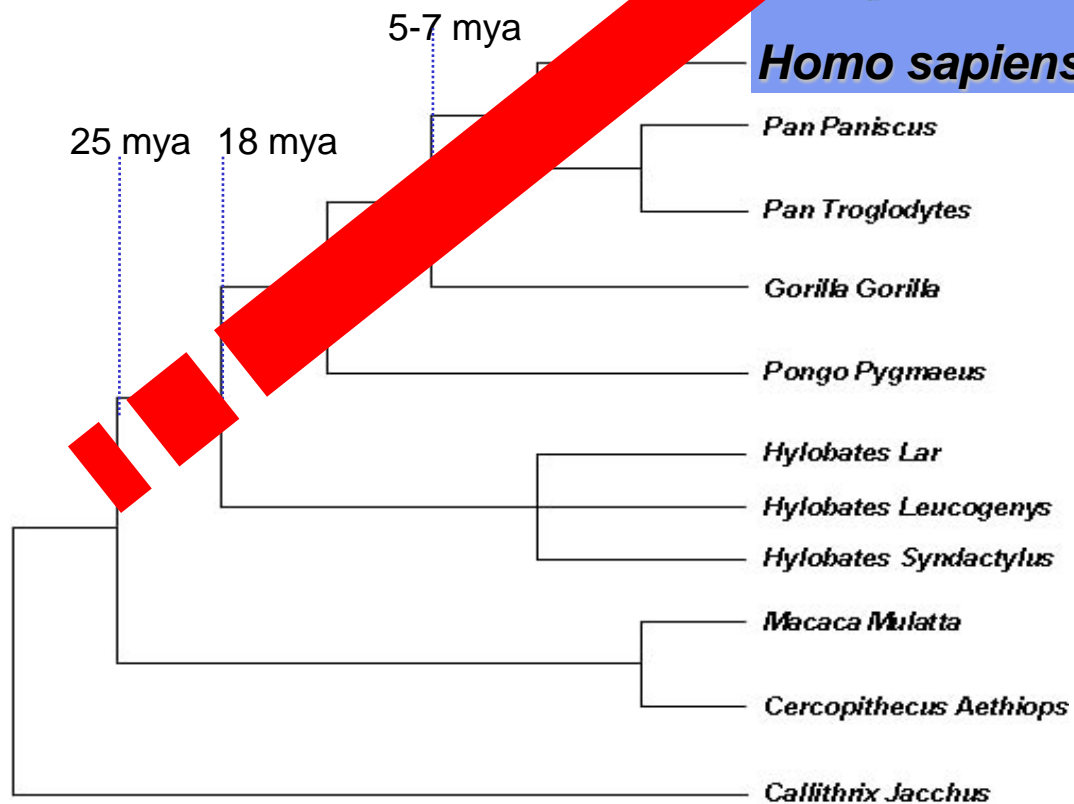


40 million years

50,000 years



Homo sapiens



25 mya

18 mya

5-7 mya

Pan Paniscus

Pan Troglodytes

Gorilla Gorilla

Pongo Pygmaeus

Hylobates Lar

Hylobates Leucogenys

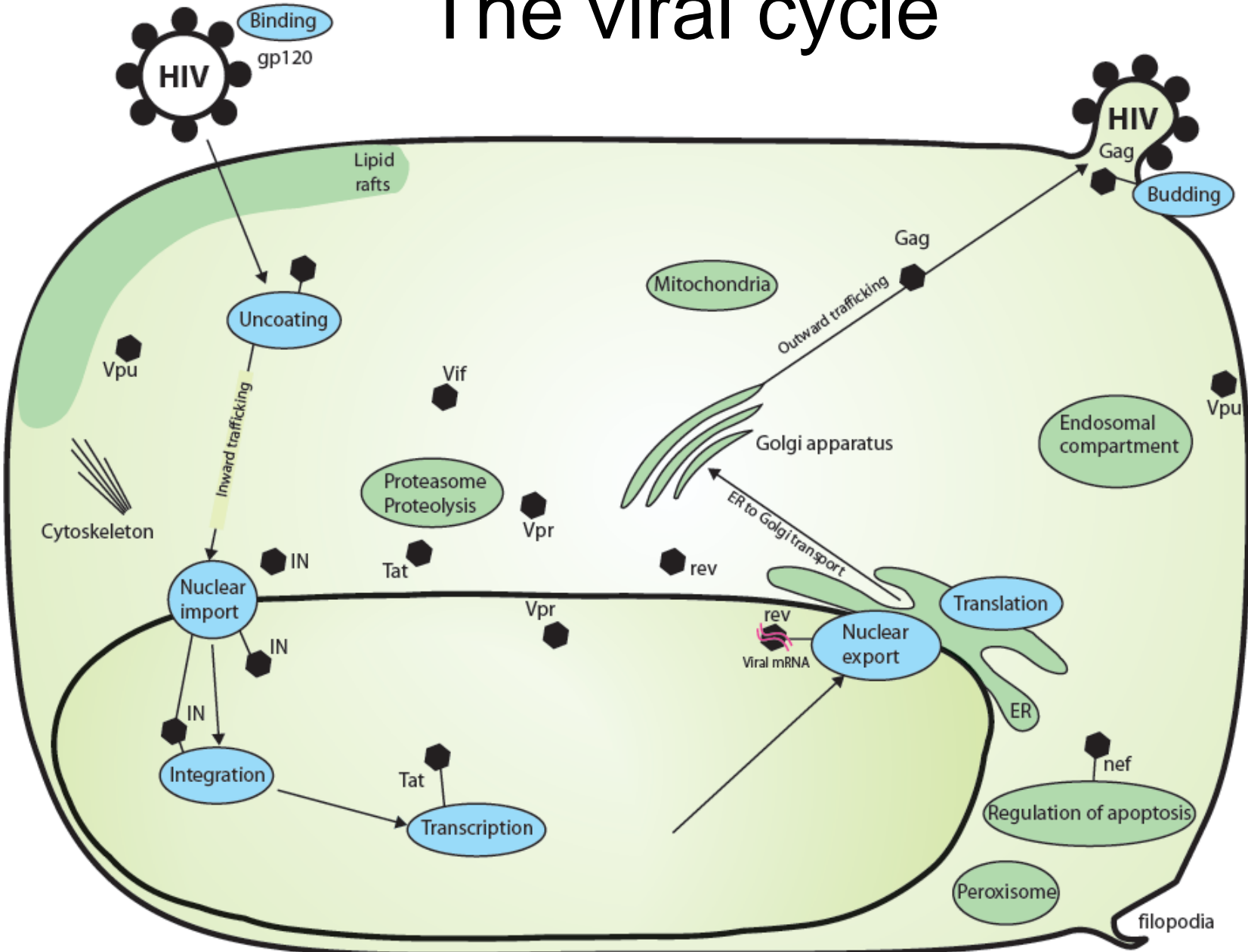
Hylobates Syndactylus

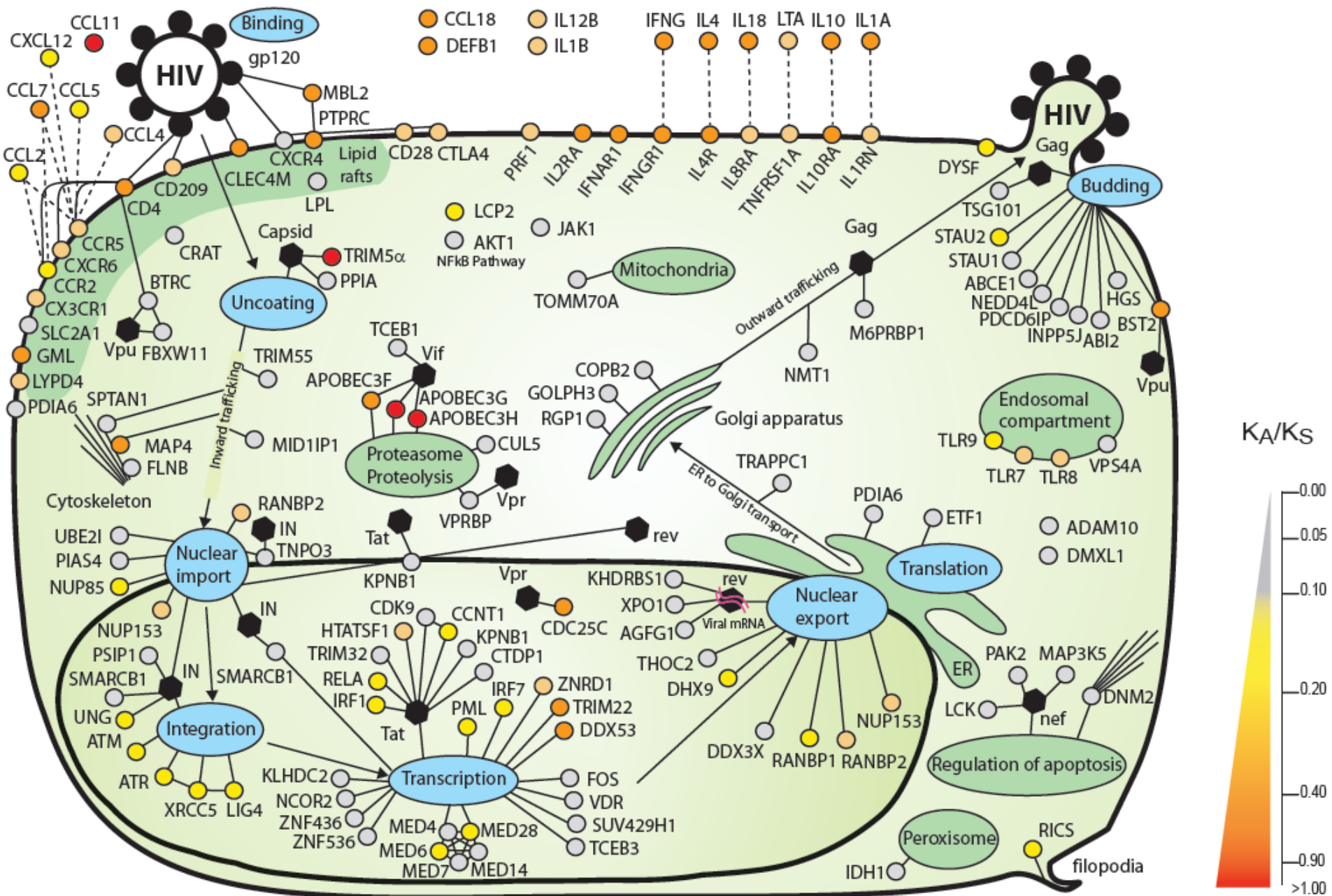
Macaca Mulatta

Cercopithecus Aethiops

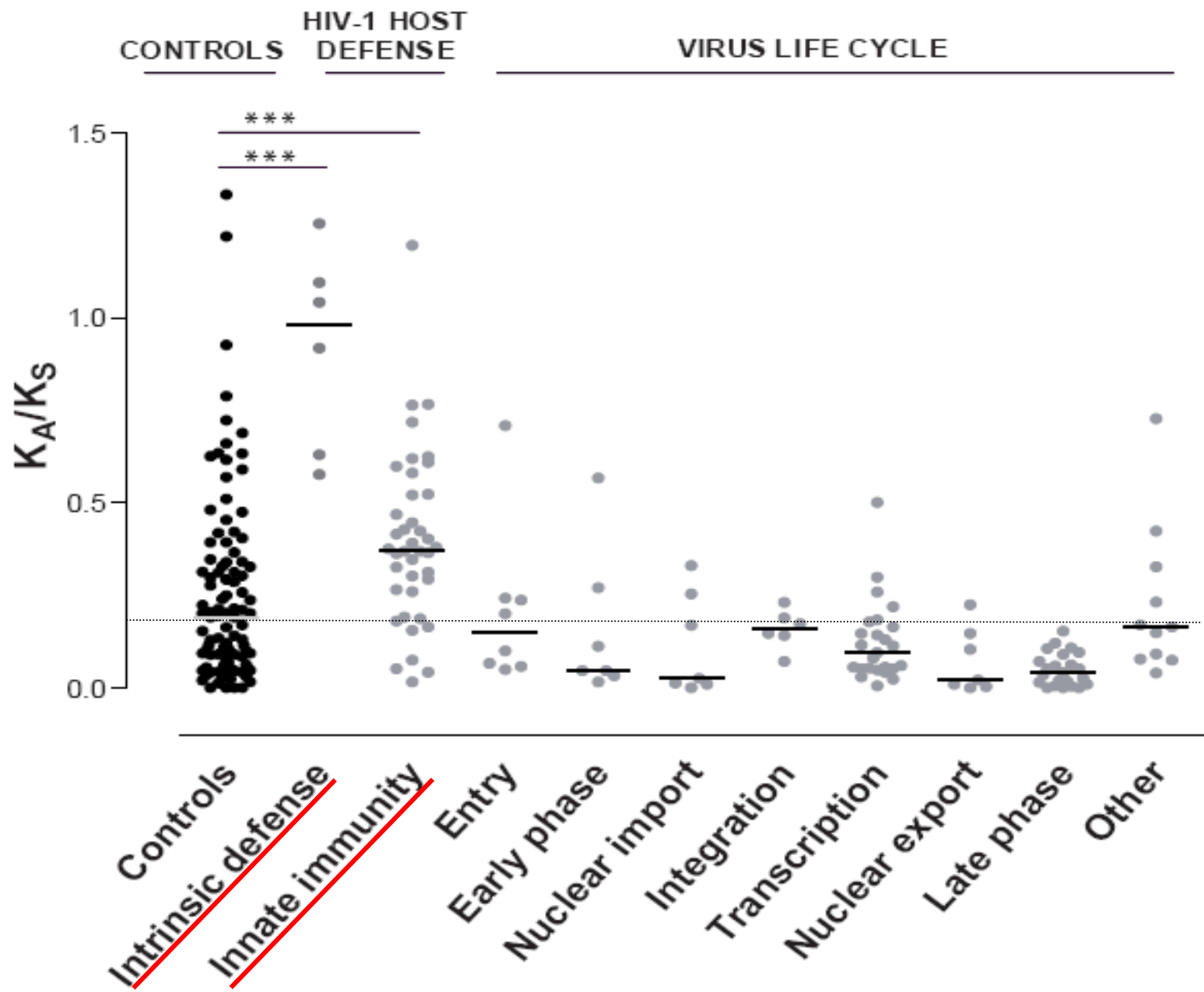
Callithrix Jacchus

The viral cycle

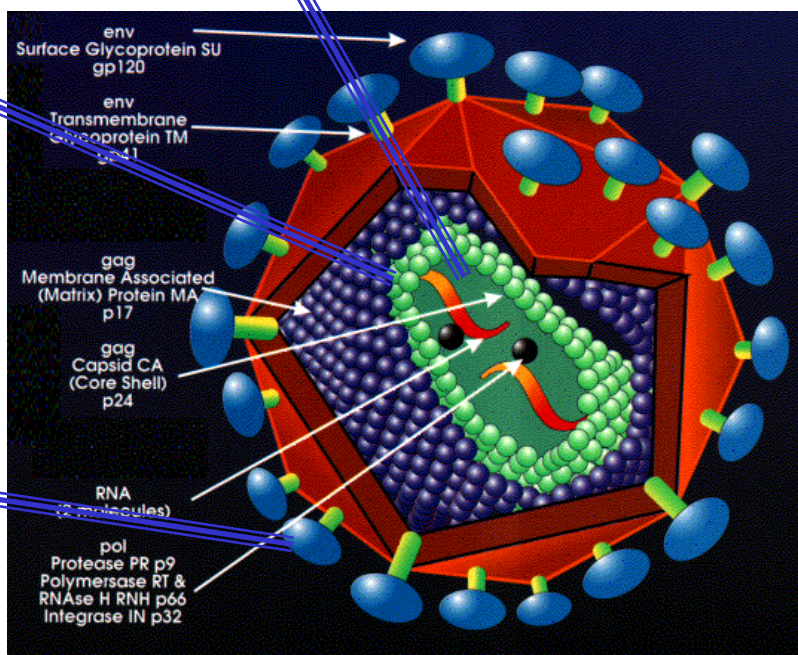
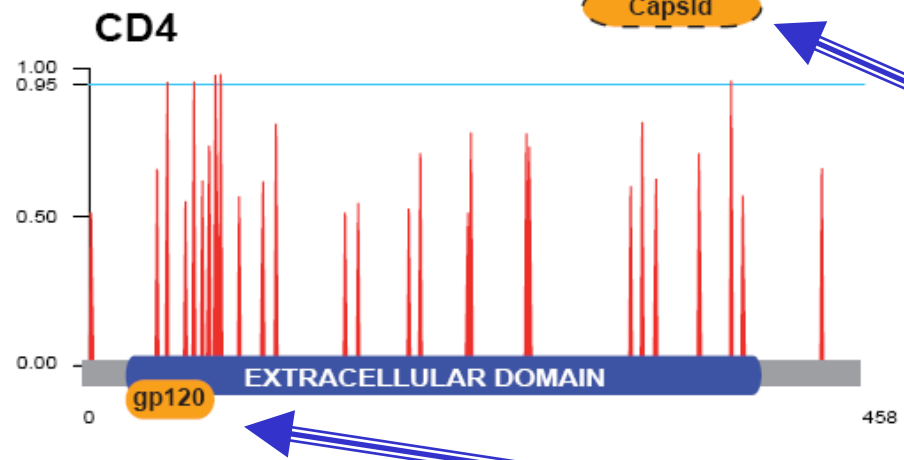
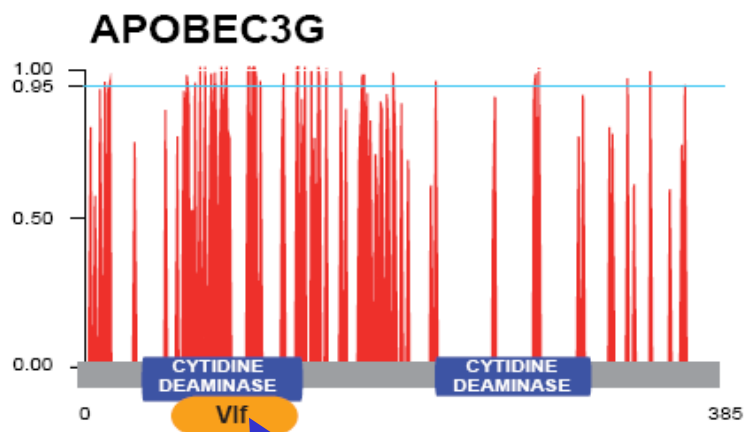
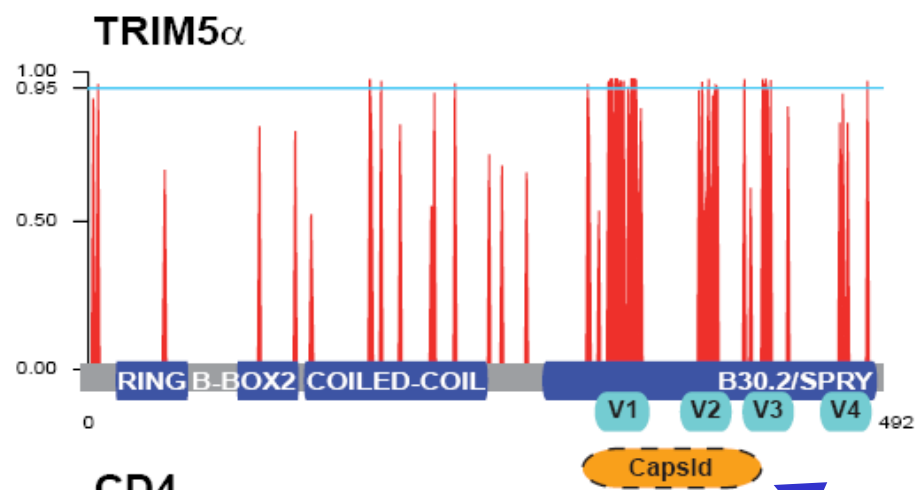




K_A/K_S values of 140 candidate and 100 control genes

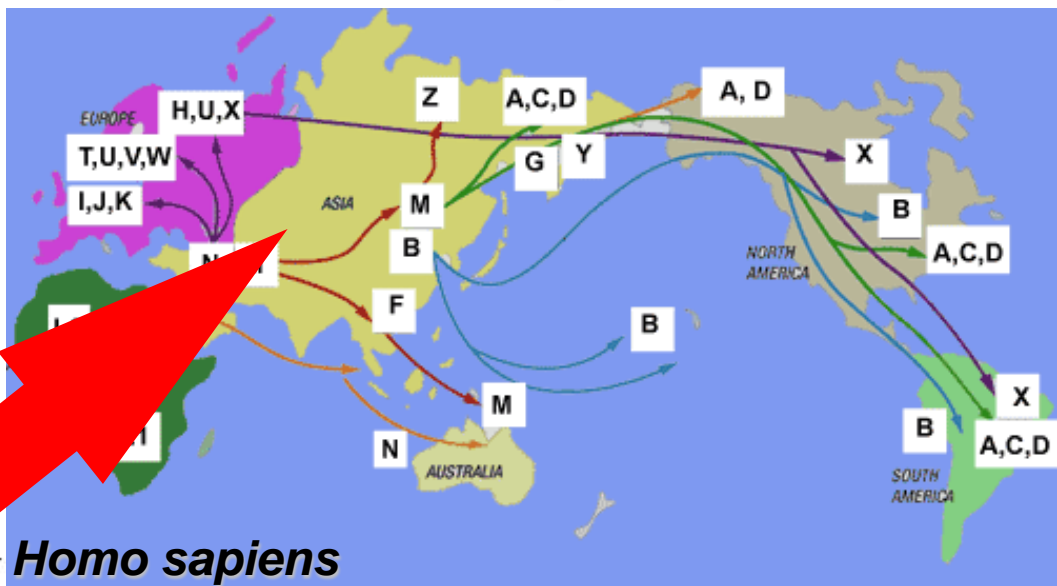


Codon-specific analysis – Top evolved genes in primates

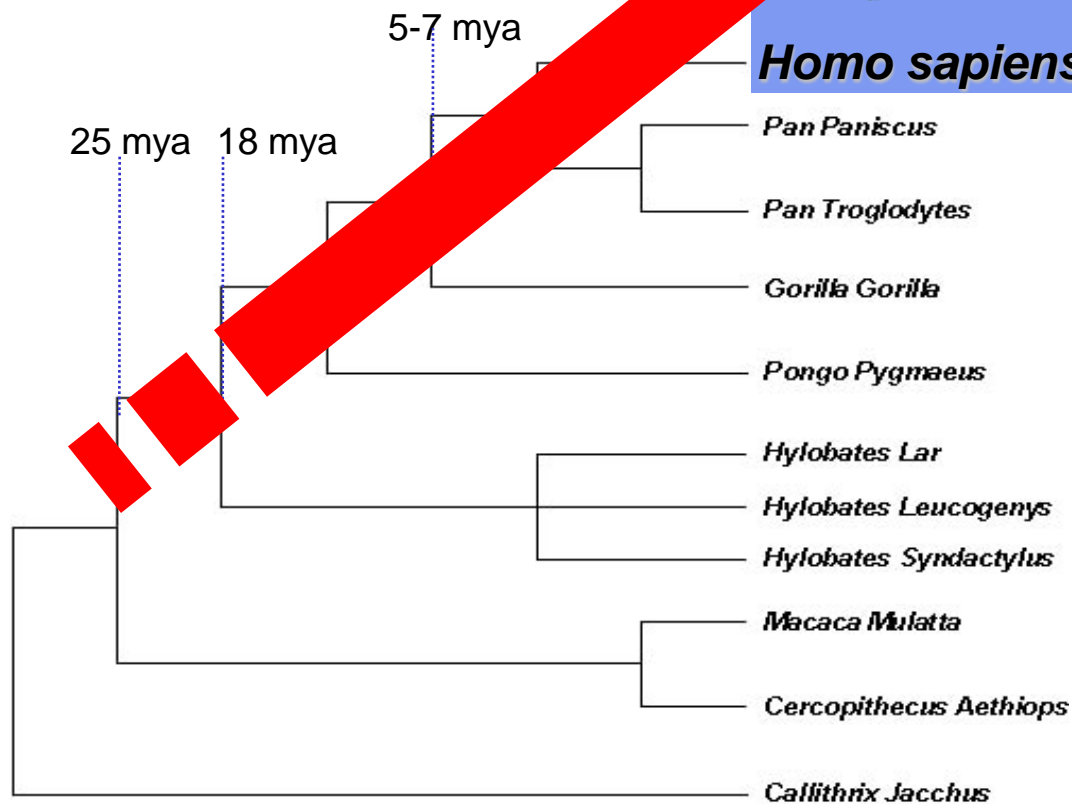


40 million years

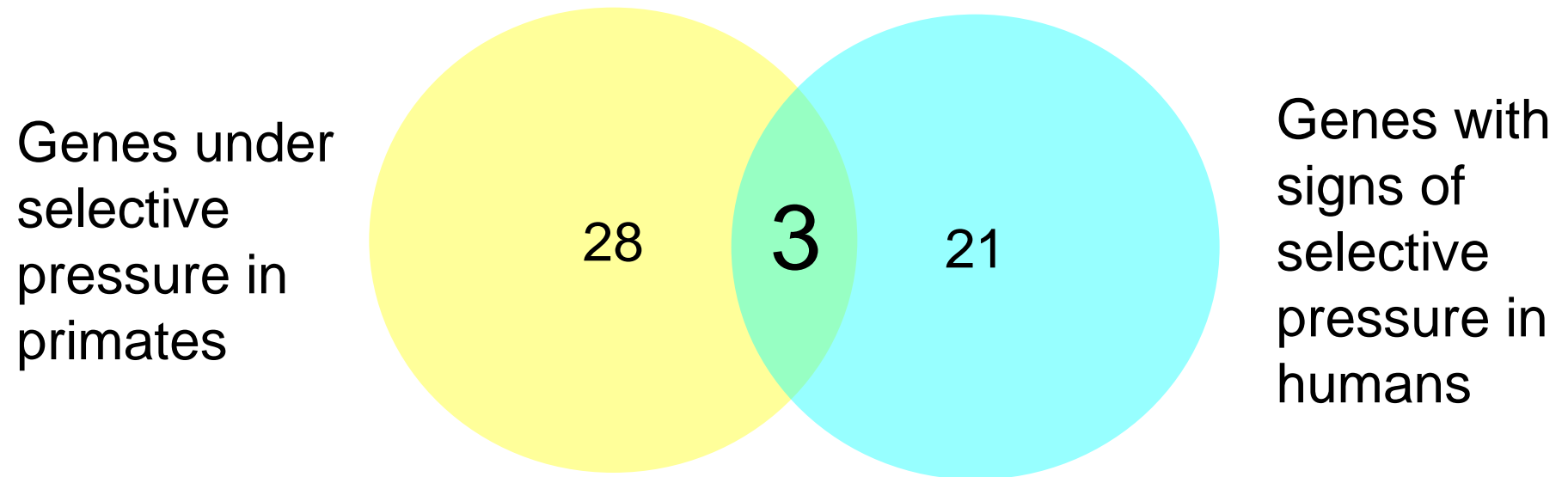
50,000 years



Homo sapiens



Genes with undergoing further positive evolutionary pressures in humans



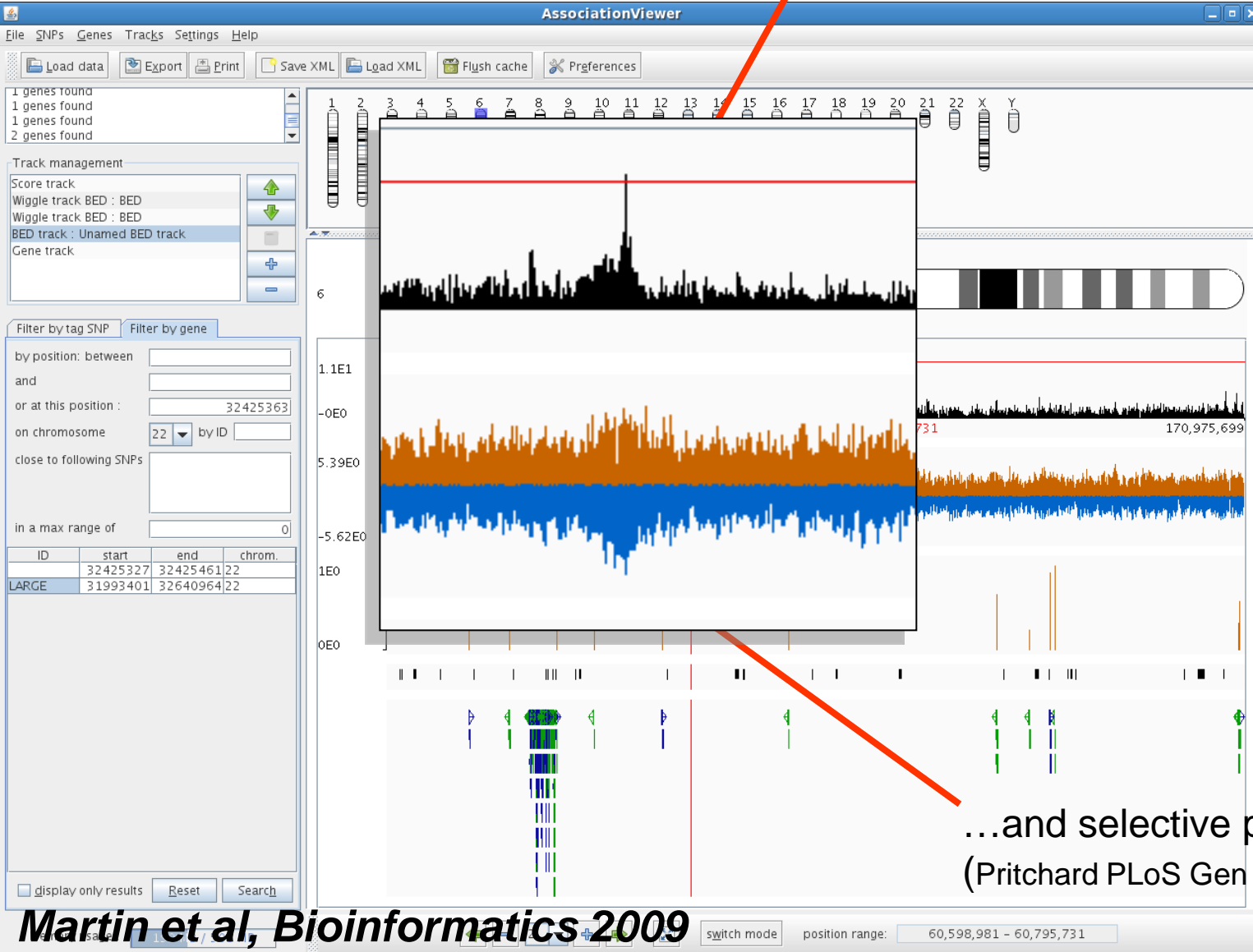
IFNGR1

DEFB1

IL4R

Analysis of positive selection in the human genome using the HapMap data

The MHC region displays a cluster of low p values in GWA (Fellay, Science 2007, Fellay et al, Submitted)

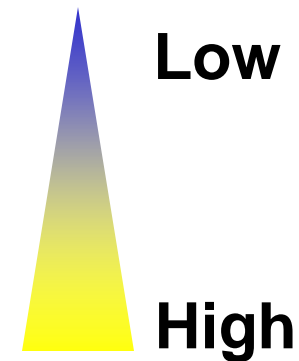
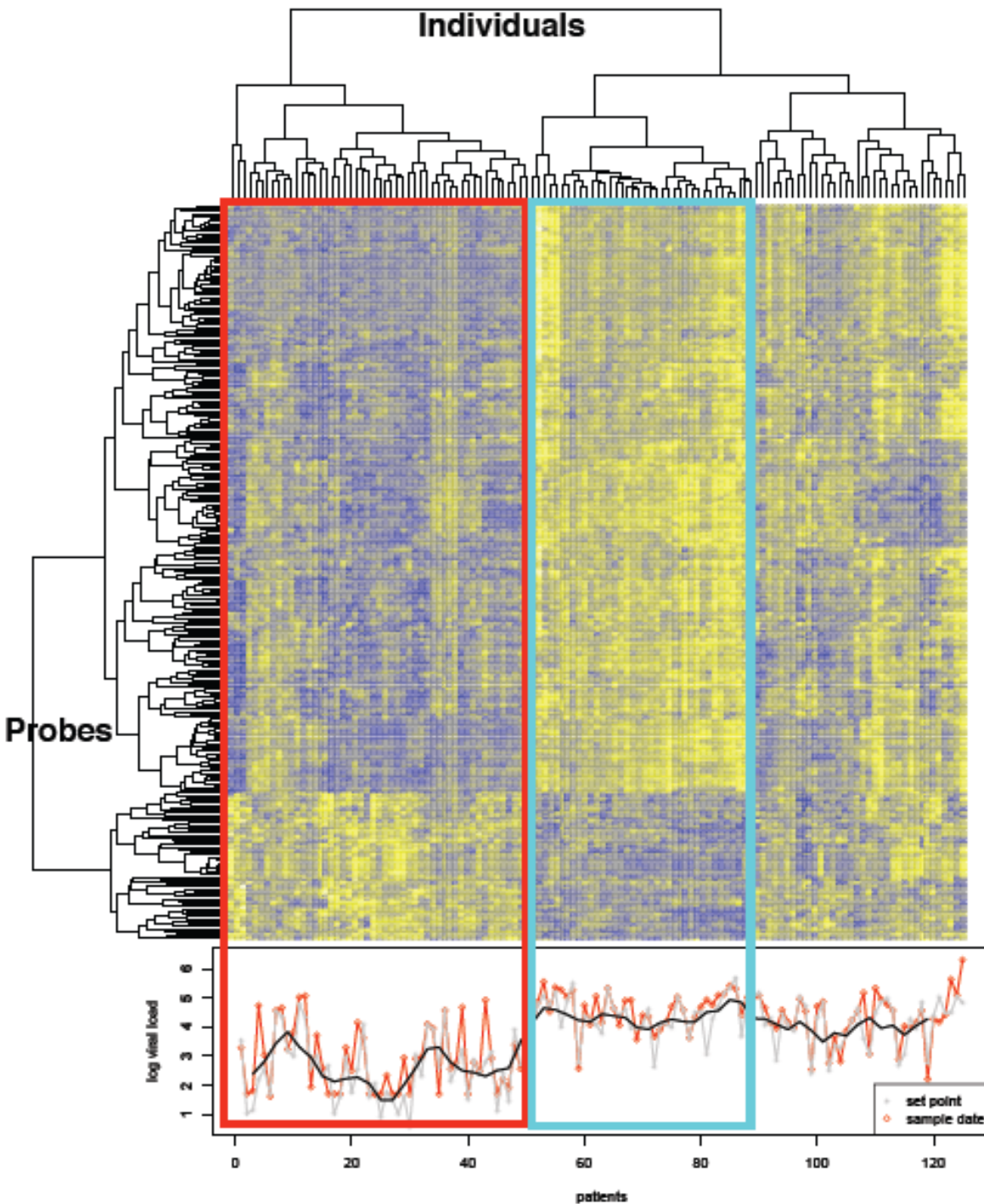


Evolutionary Results

- Evolutionary genomic analysis in primates identifies three groups of genes with different evolutionary history.
- Top-rank positive selected genes carry residues that discriminate among incoming retroviruses, incl. HIV-1
- Recent (human) signals of positive selection appear less likely to modulate susceptibility to HIV-1.

#3 - Exploiting data integration

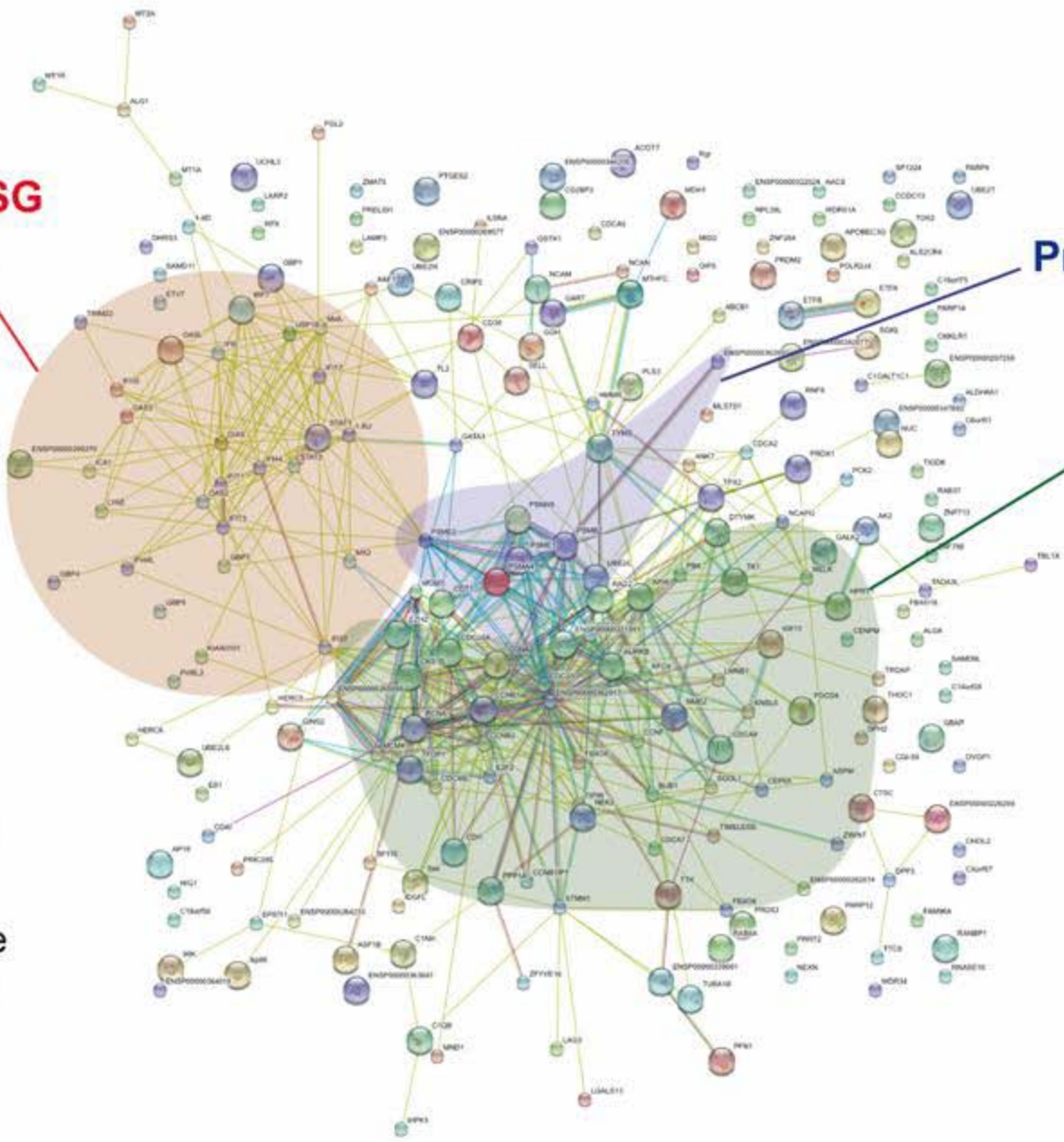
Transcriptome analysis in CD4 T cells from 127 HIV-infected individuals



IFN signalling and ISG

Proteasome

Cell cycle

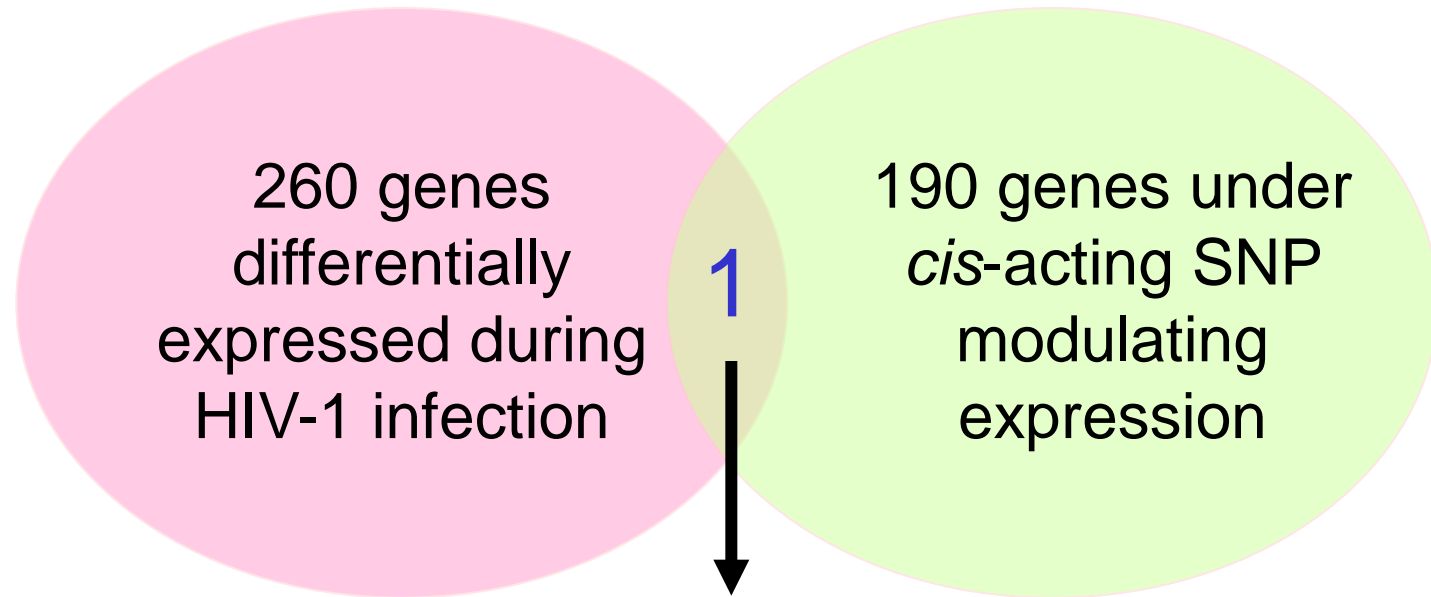


- Green line: Neighborhood
- Red line: Gene Fusion
- Blue line: Co-occurrence
- Black line: Co-expression
- Purple line: Experiments
- Cyan line: Databases
- Yellow-green line: Textmining
- Grey line: Homology

Expression variants influencing HIV-1 disease?

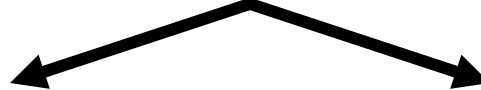
48000 transcripts

1.3 mio. gene-centric SNPs



1

OAS1



Susceptibility to West Nile Virus

Susceptibility to HIV?

siRNA/shRNA screens

Brass et al. *Science* 2008.

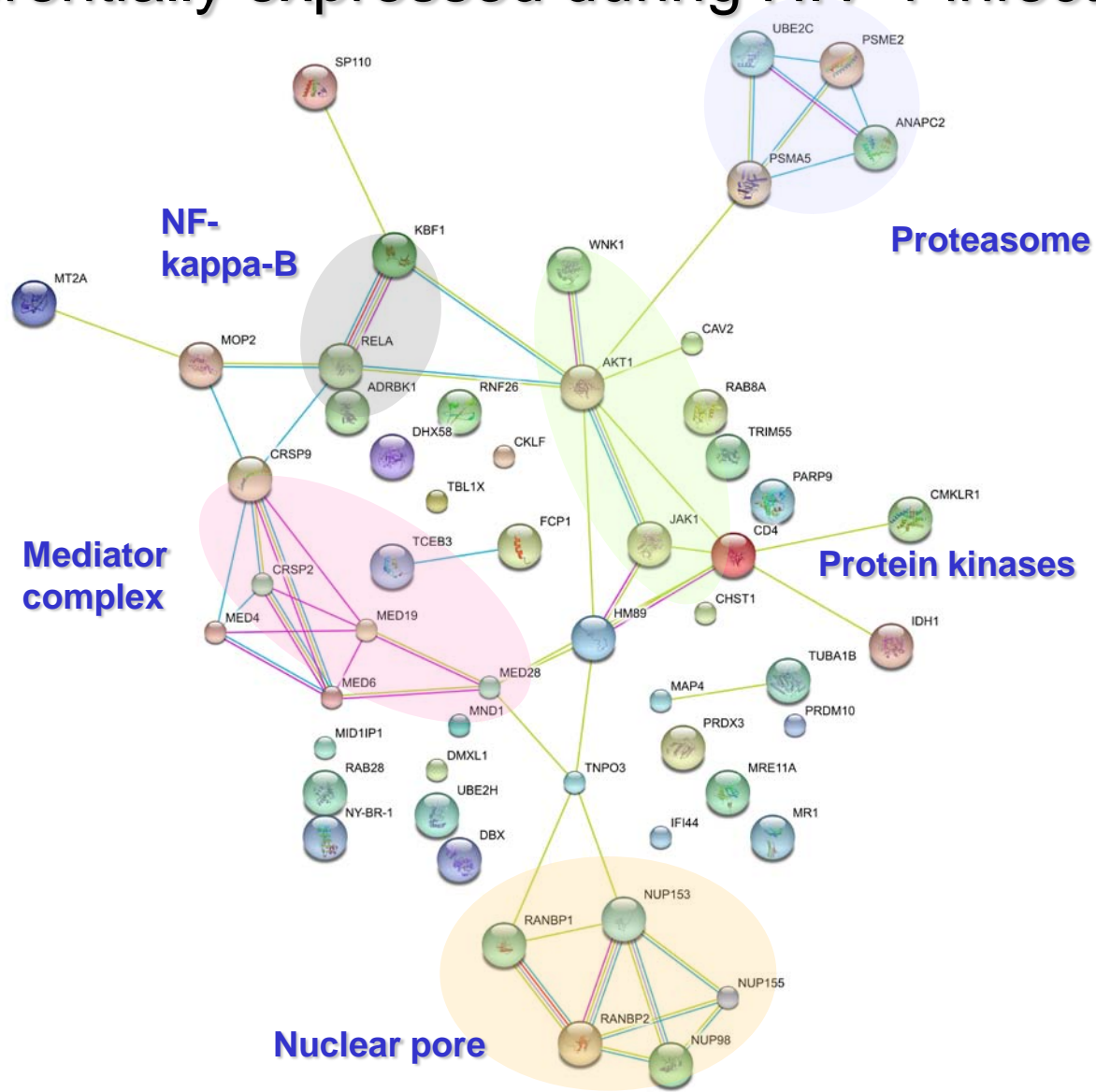
Konig et al. *Cell* 2008.

Zhou et al. *Cell Host Microbe* 2008

Jeung et al. *J Biol Chem* 2009.

- >1000 gene candidates
- Only 3 genes common to at least three studies.
- 38 genes common to 2 or more studies.
- No restriction factors identified

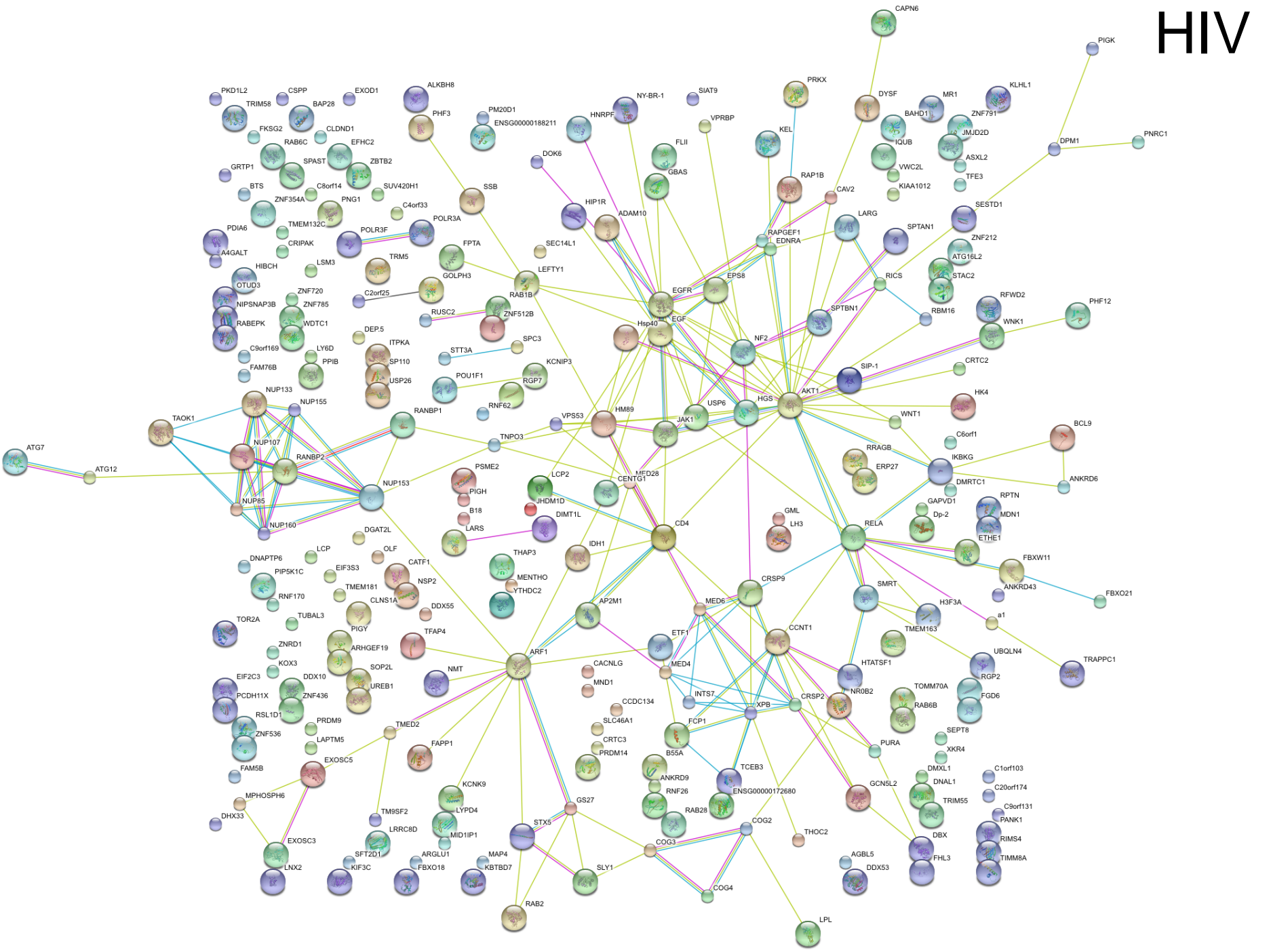
Predicted interaction networks of genes identified as HIV dependency factors in silencing screens and differentially expressed during HIV-1 infection.

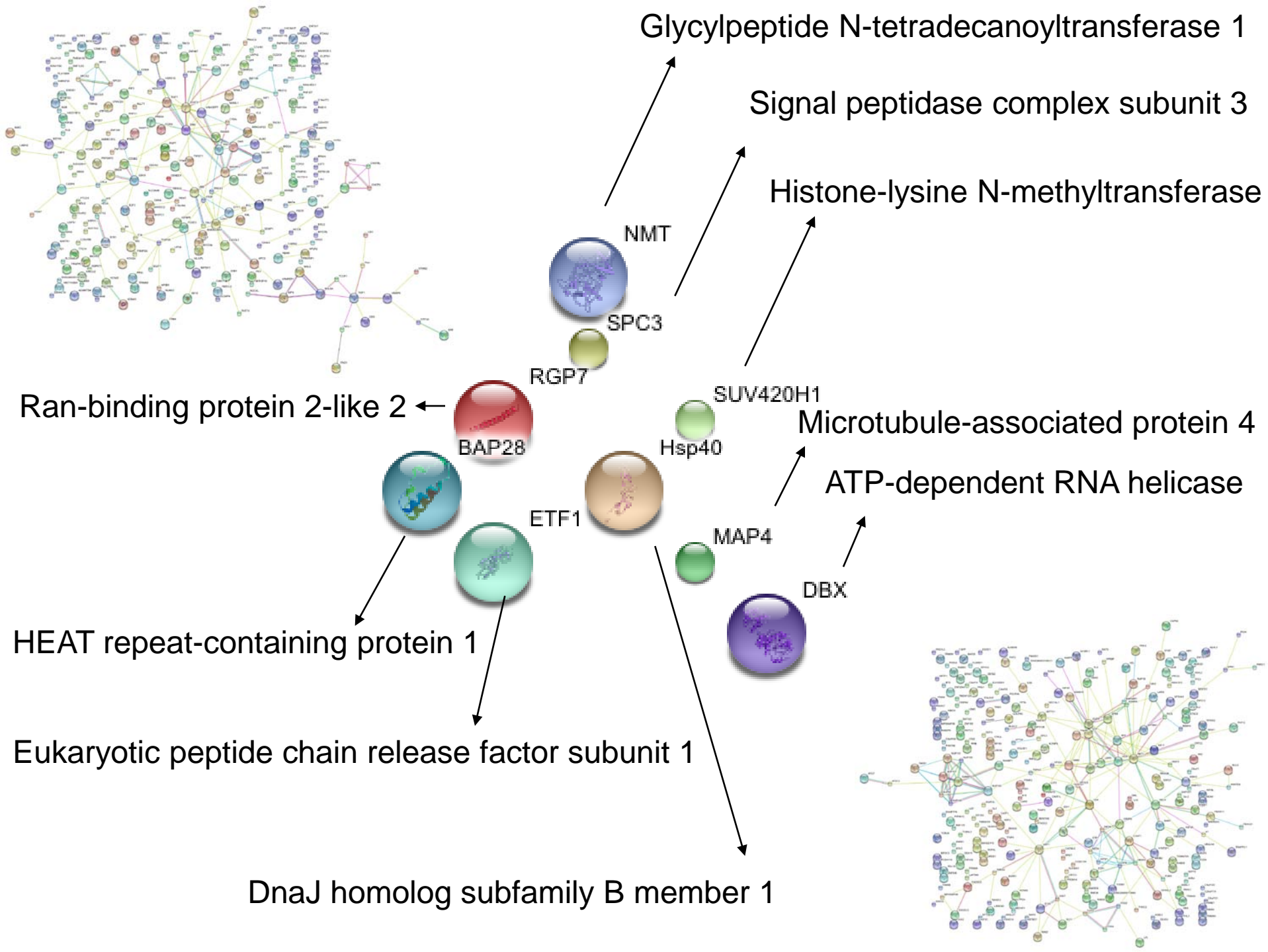


Comparative analysis HIV-HCV

- **Brass et al. *Science* 2008 – HIV**
HIV-IIIB virus and TZM-bl cells
- **Li & Brass et al. *PNAS* 2009 – HCV**
JFH-1 genotype 2a virus and the Huh 7.5.1 human hepatocellular cell line

HIV

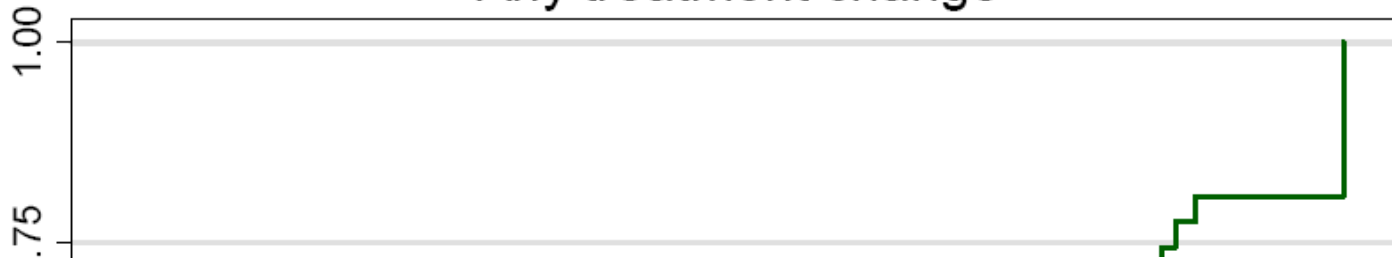




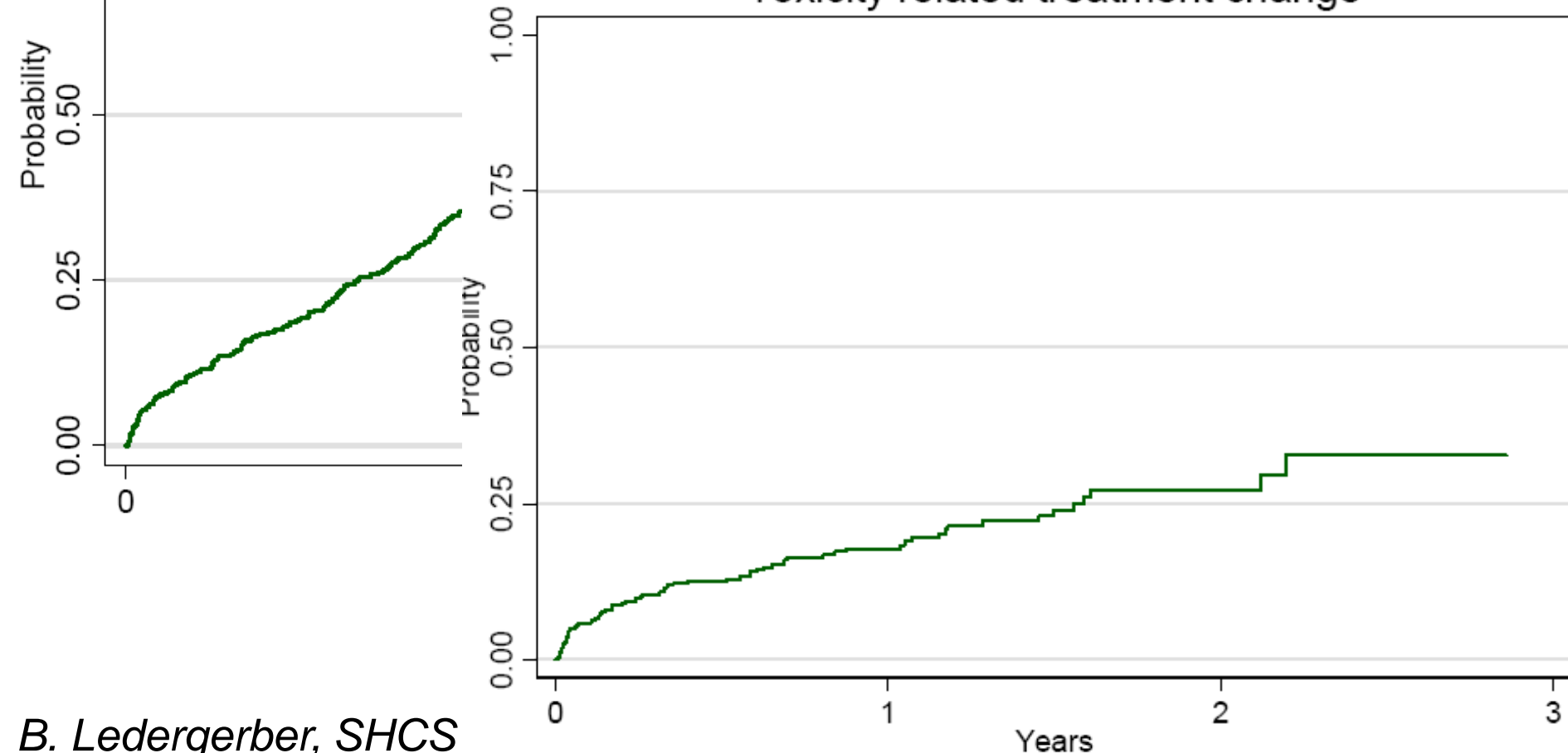
Lost in translation

We have a problem

Any treatment change

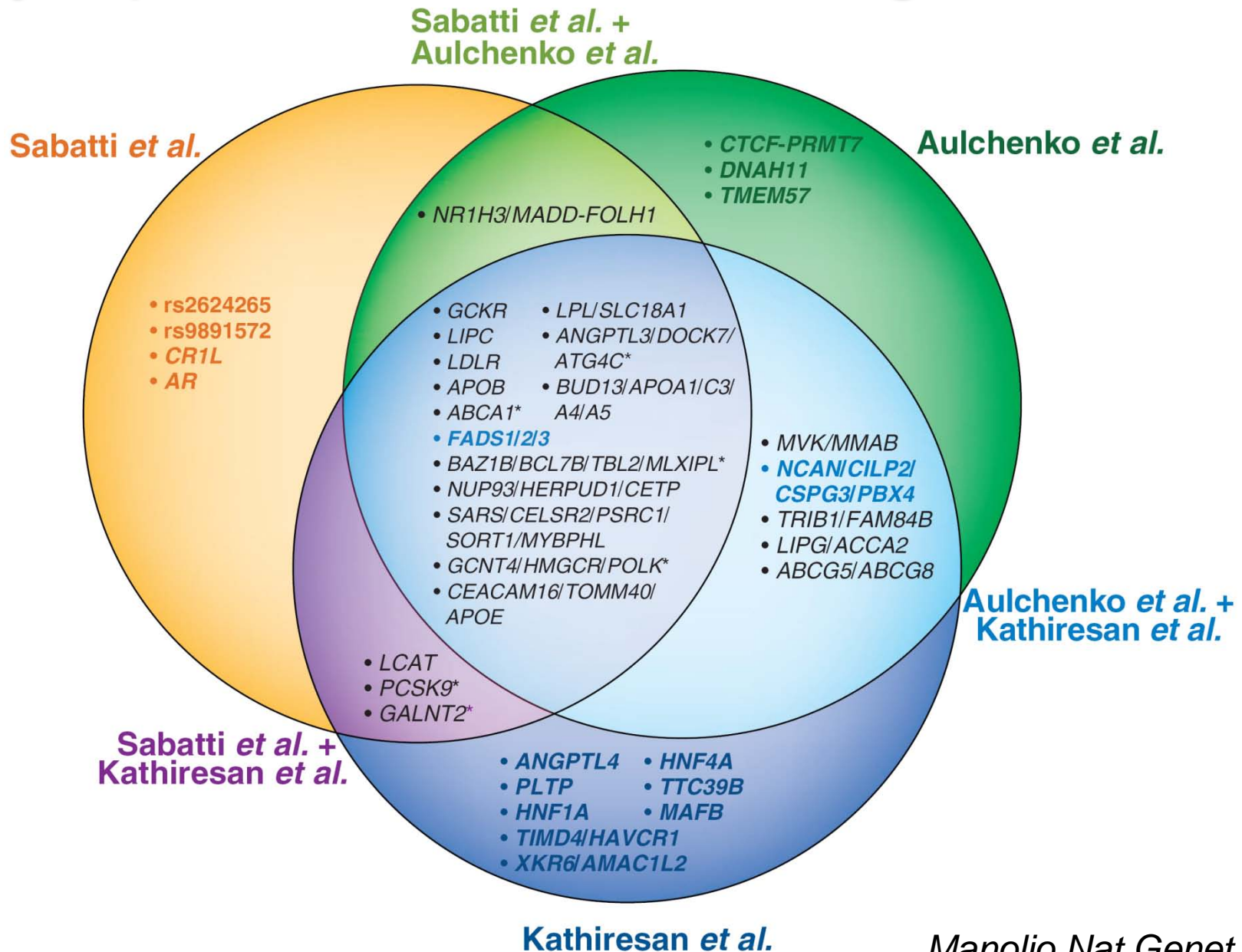


Toxicity related treatment change

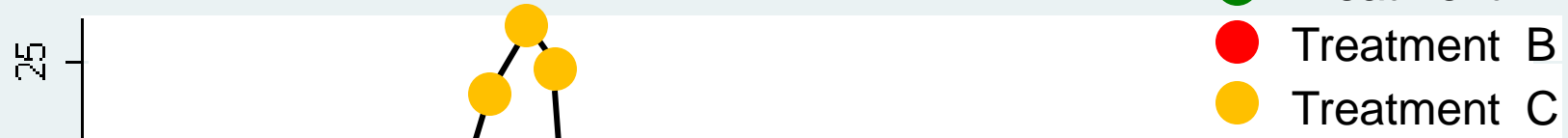


#1 - Exploiting environmental interactors

Dyslipidemia as common genetic trait



Longitudinal lipid determinations: Examples of 3 individuals



□ Individuals **750**

□ N lipid determinations during study period: **34,000**

□ Median duration of follow up: **7.6 years**

0

1

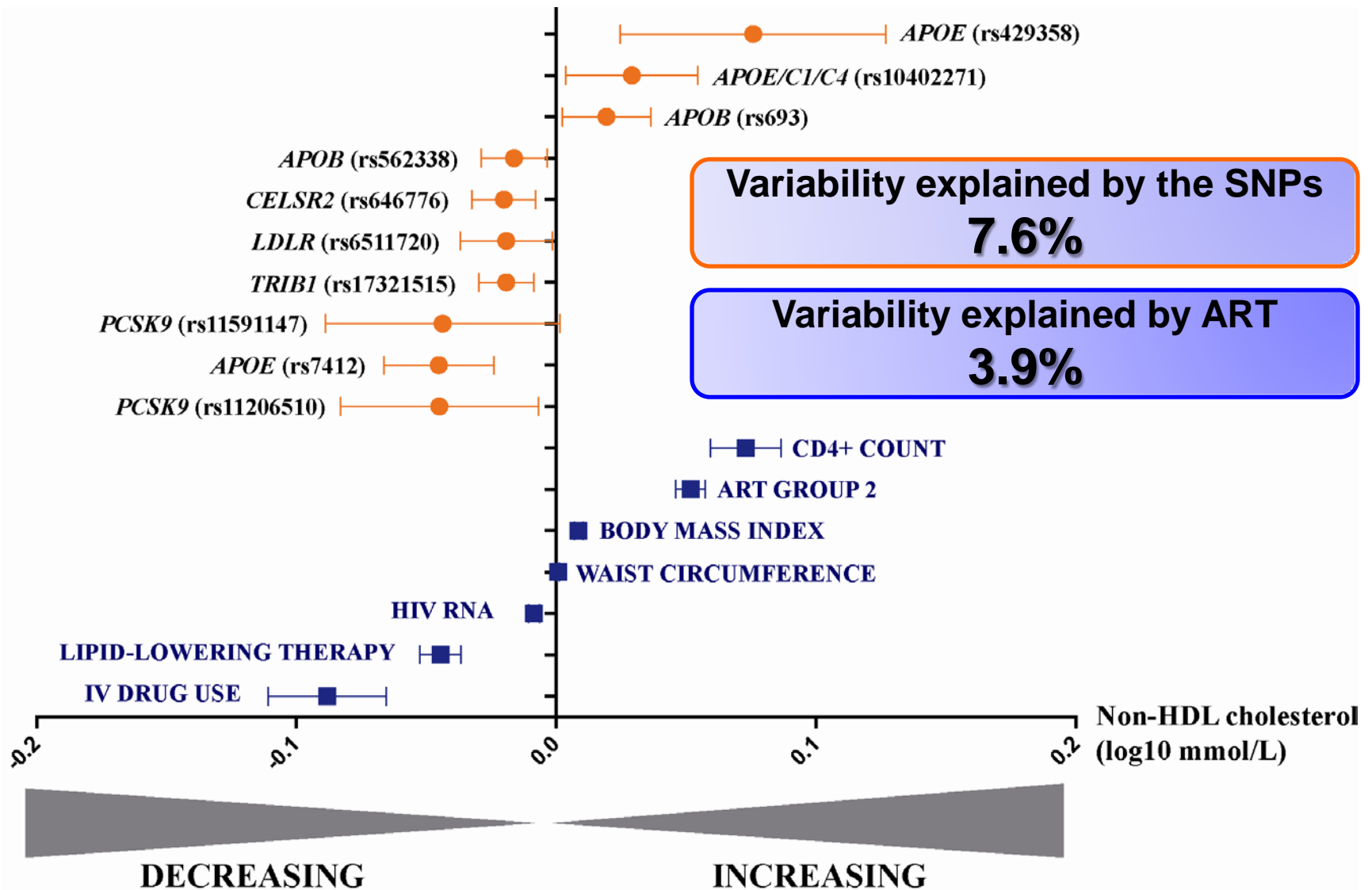
2

3

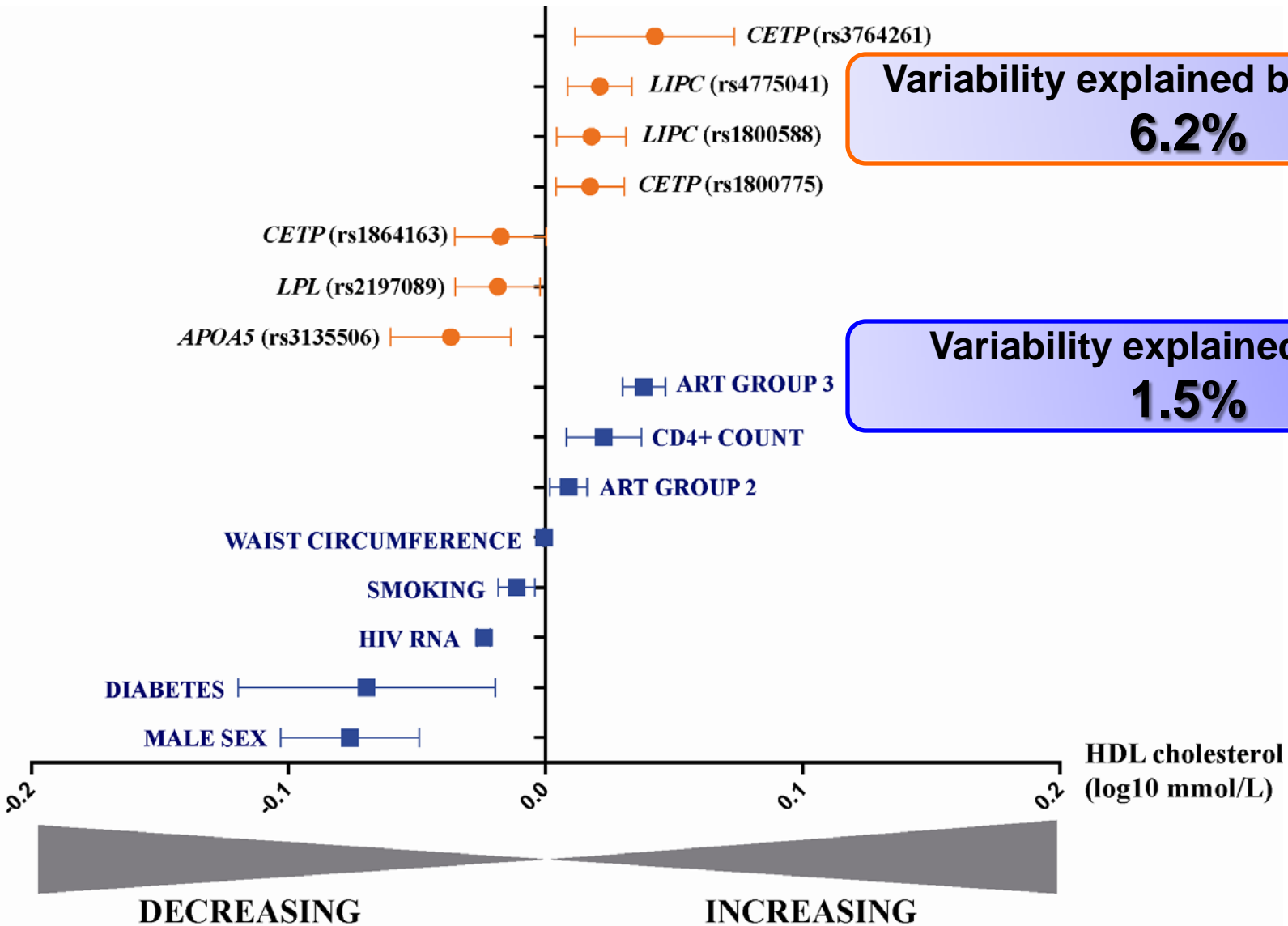
4

t_trig_y

Contribution of multiple variants to non HDL-C



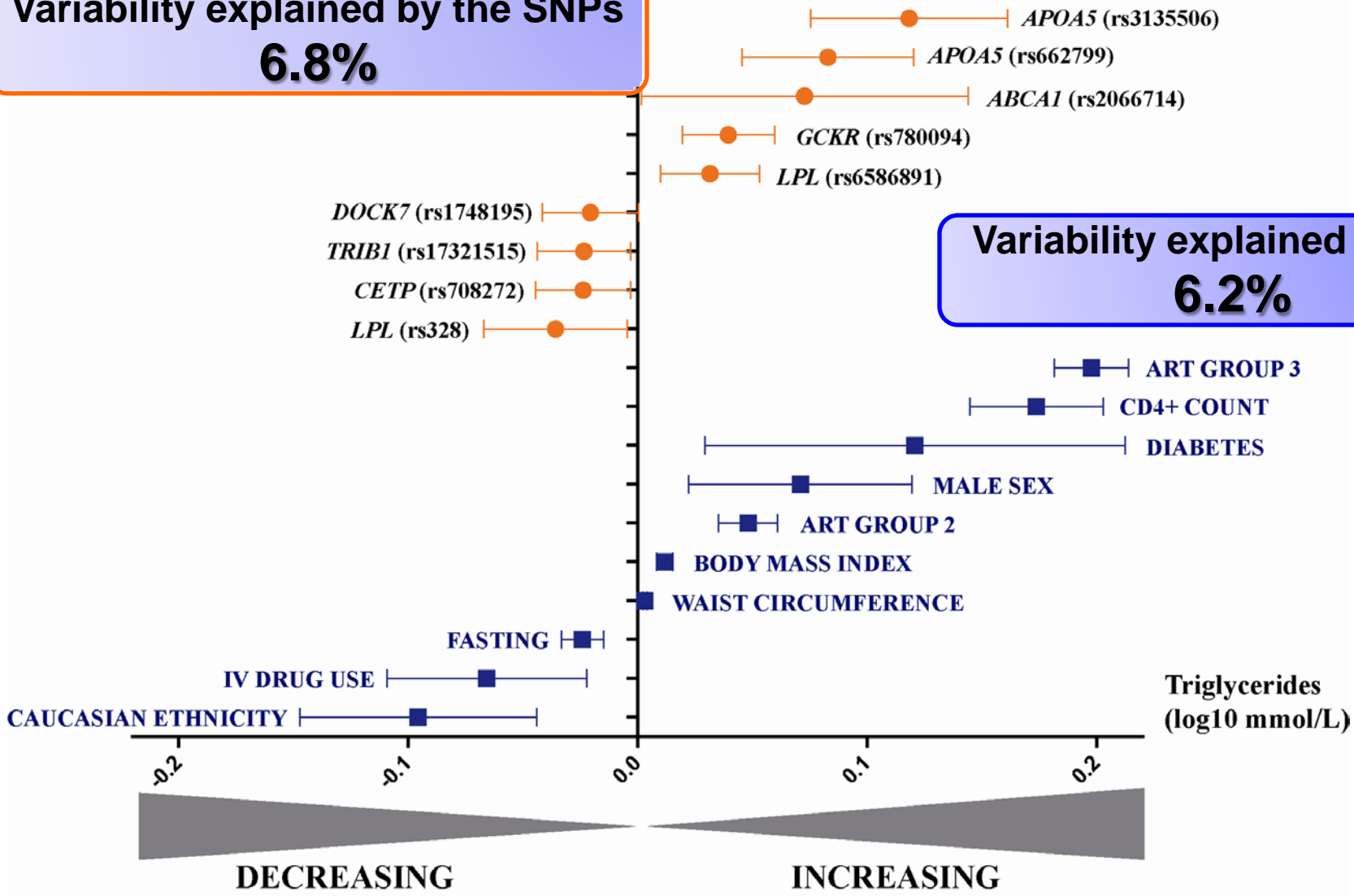
Contribution of multiple variants to HDL-C



Contribution of multiple variants to Triglycerides

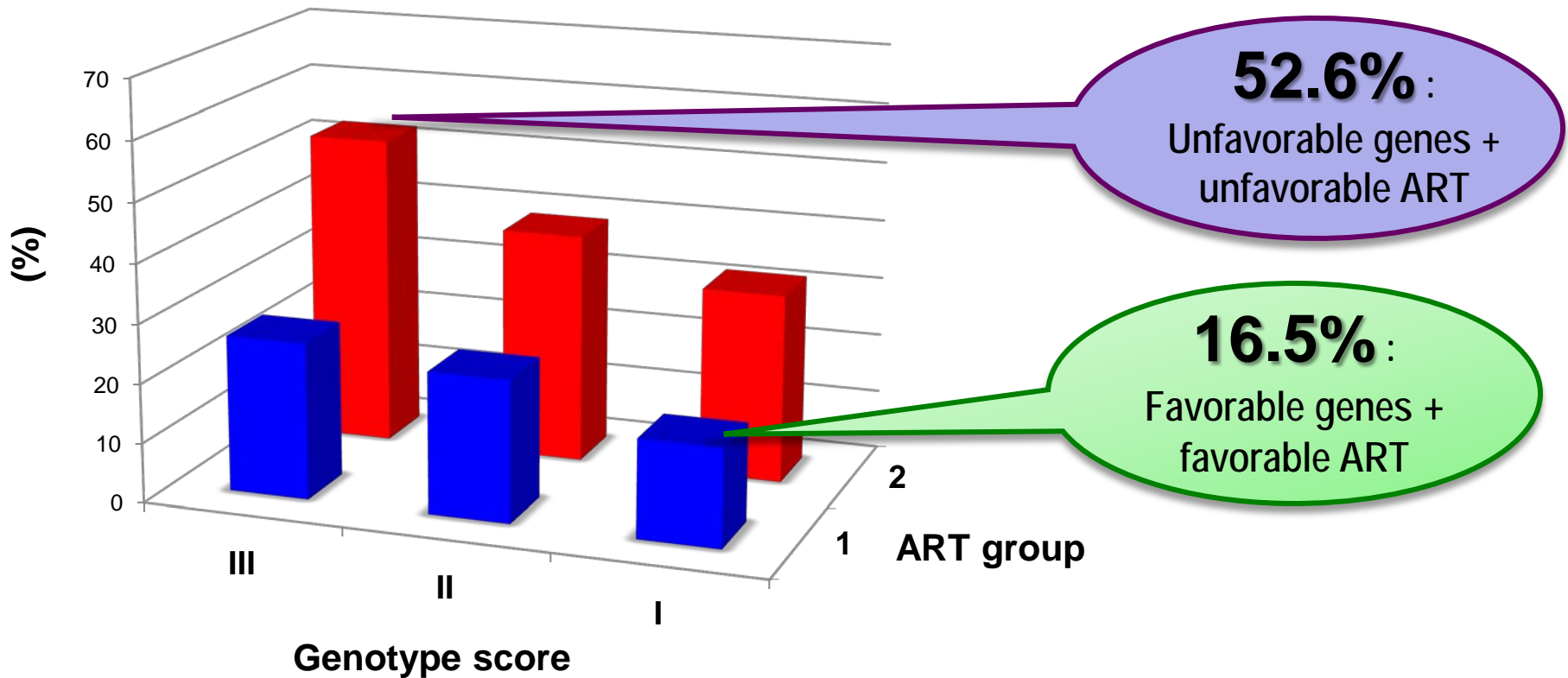
Variability explained by the SNPs
6.8%

Variability explained by ART
6.2%



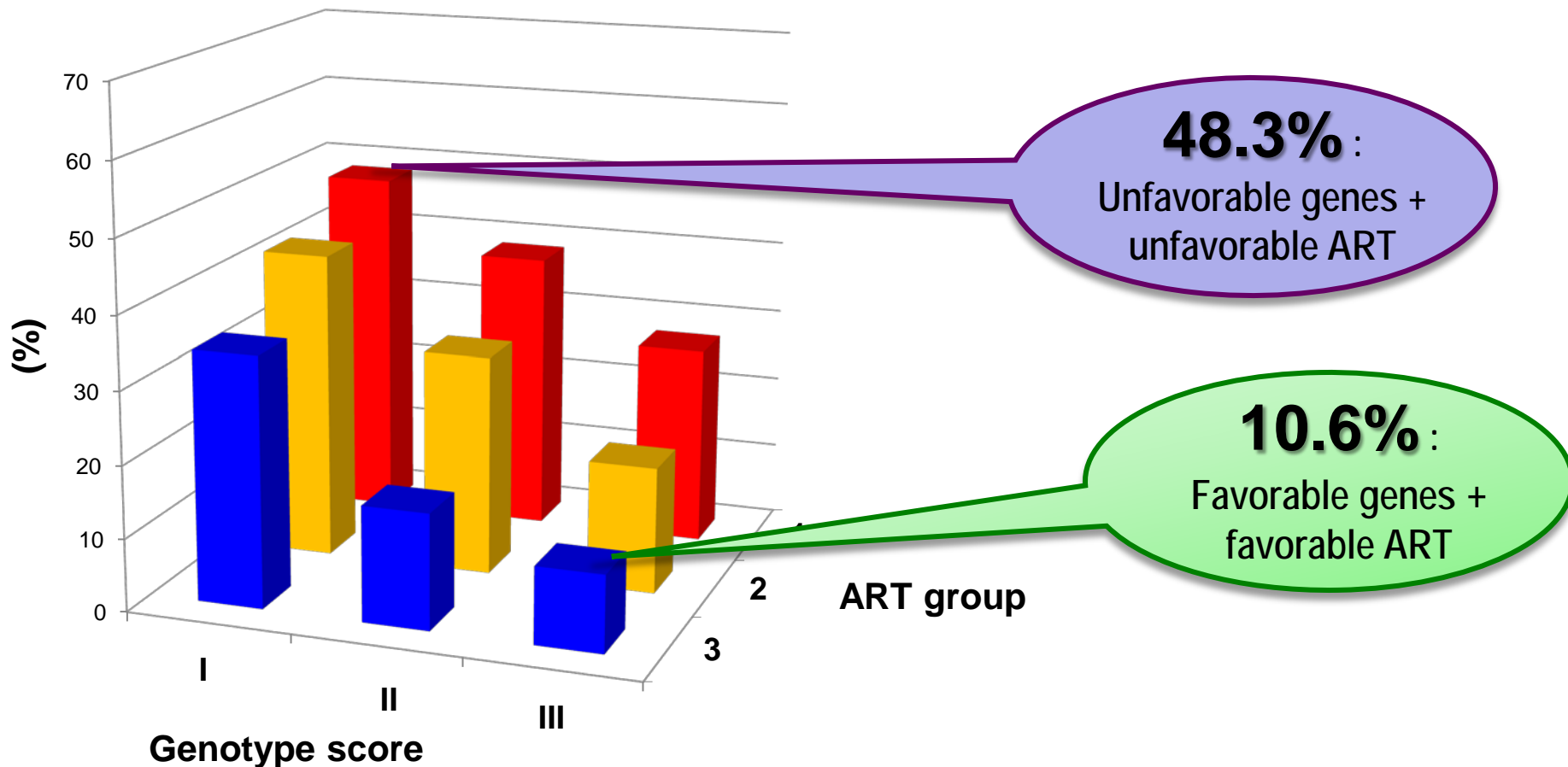
Proportion of individuals with sustained hypercholesterolemia

Def: $\geq 2/3$ of Non-HDL-C values during study period are $>$ NCEP-ATP-III cutoff (4.1 mmol/L [160mg/dl])



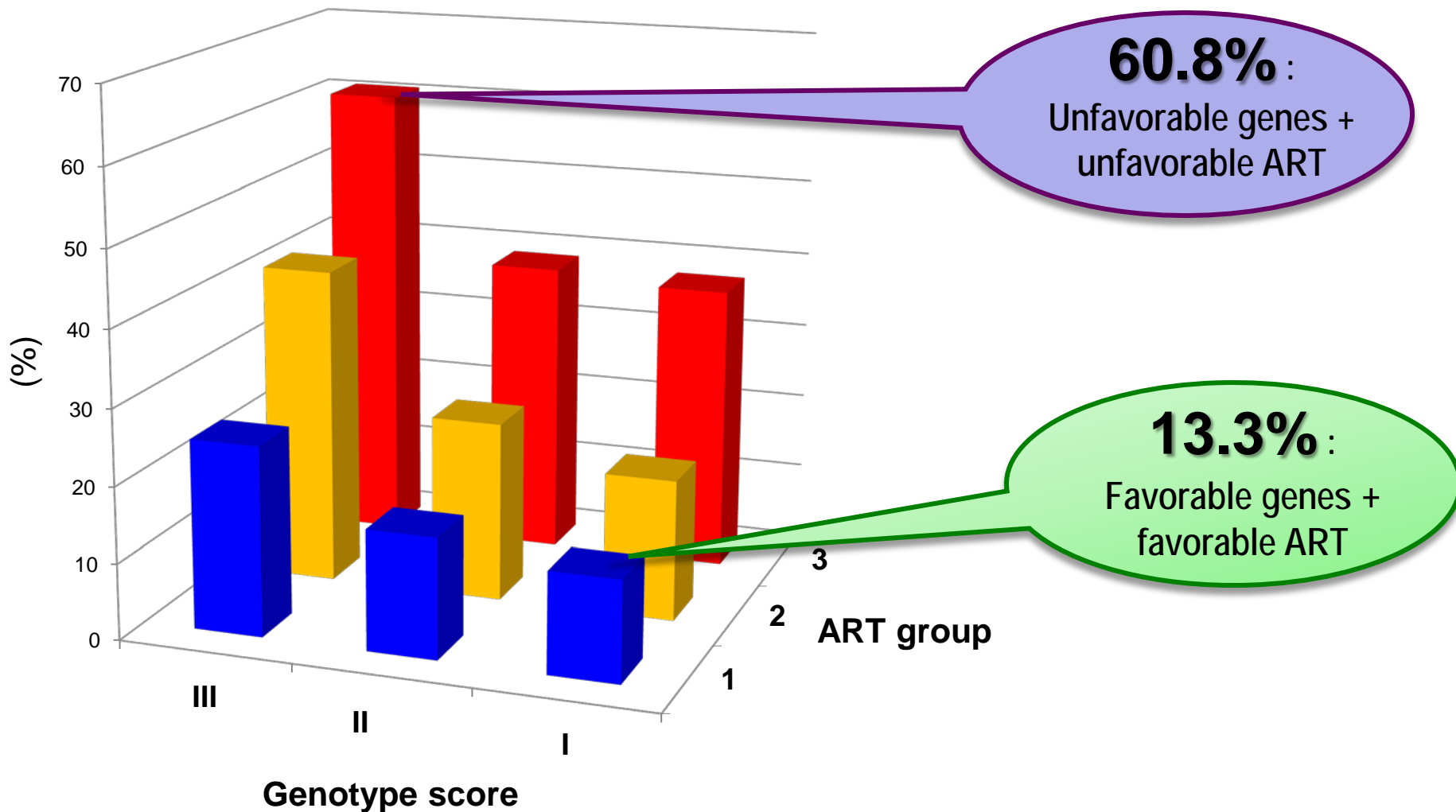
Proportion of individuals with sustained low HDL-cholesterol

Def: $\geq 2/3$ of HDL-C values during study period are $<$ NCEP-ATP-III cutoff (1.04 mmol/L [40mg/dl])



Proportion of individuals with sustained hypertriglyceridemia

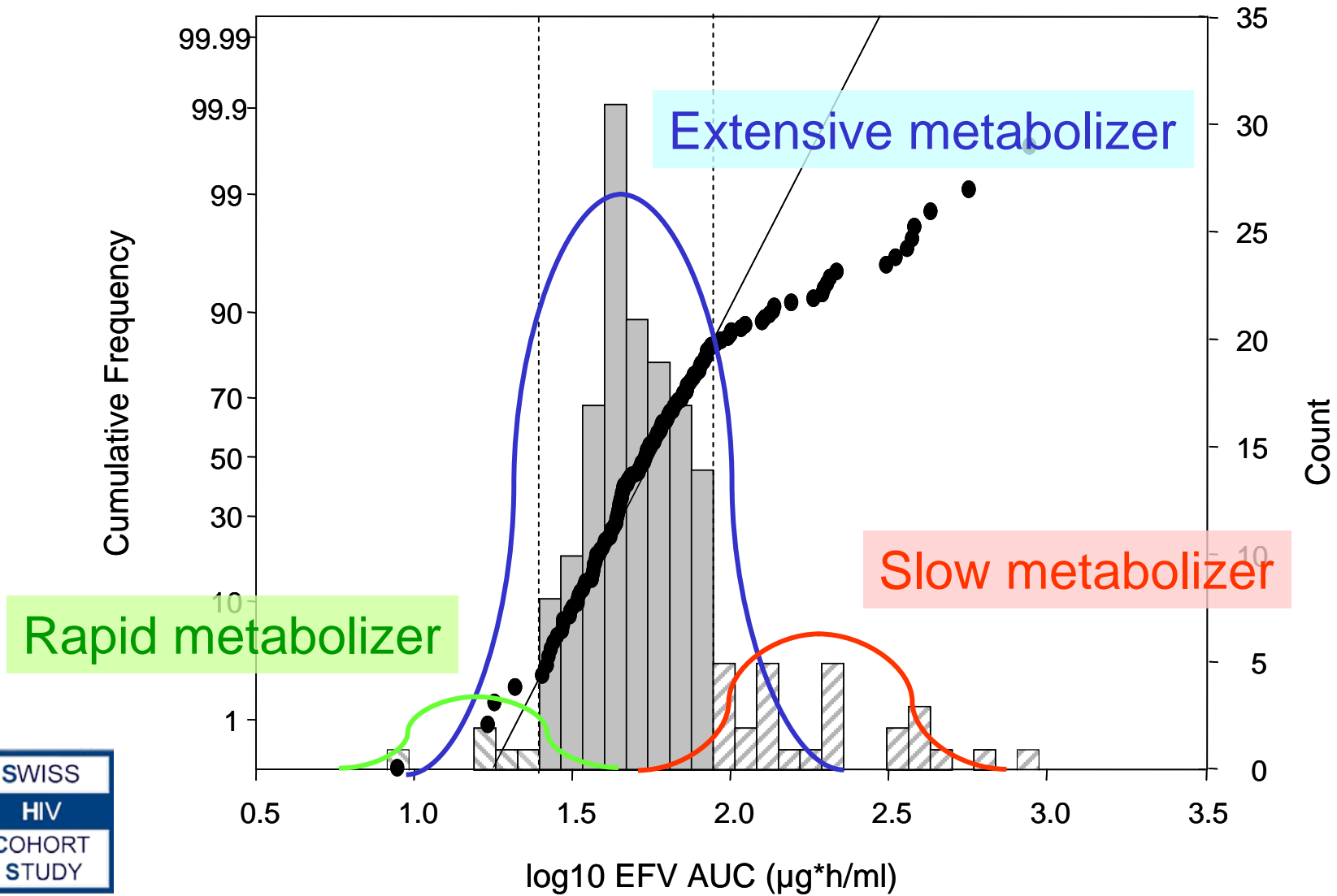
Def: $\geq 2/3$ of TG values during study period are $>$ NCEP-ATP-III cutoff (2.26 mmol/L [200 mg/dl])



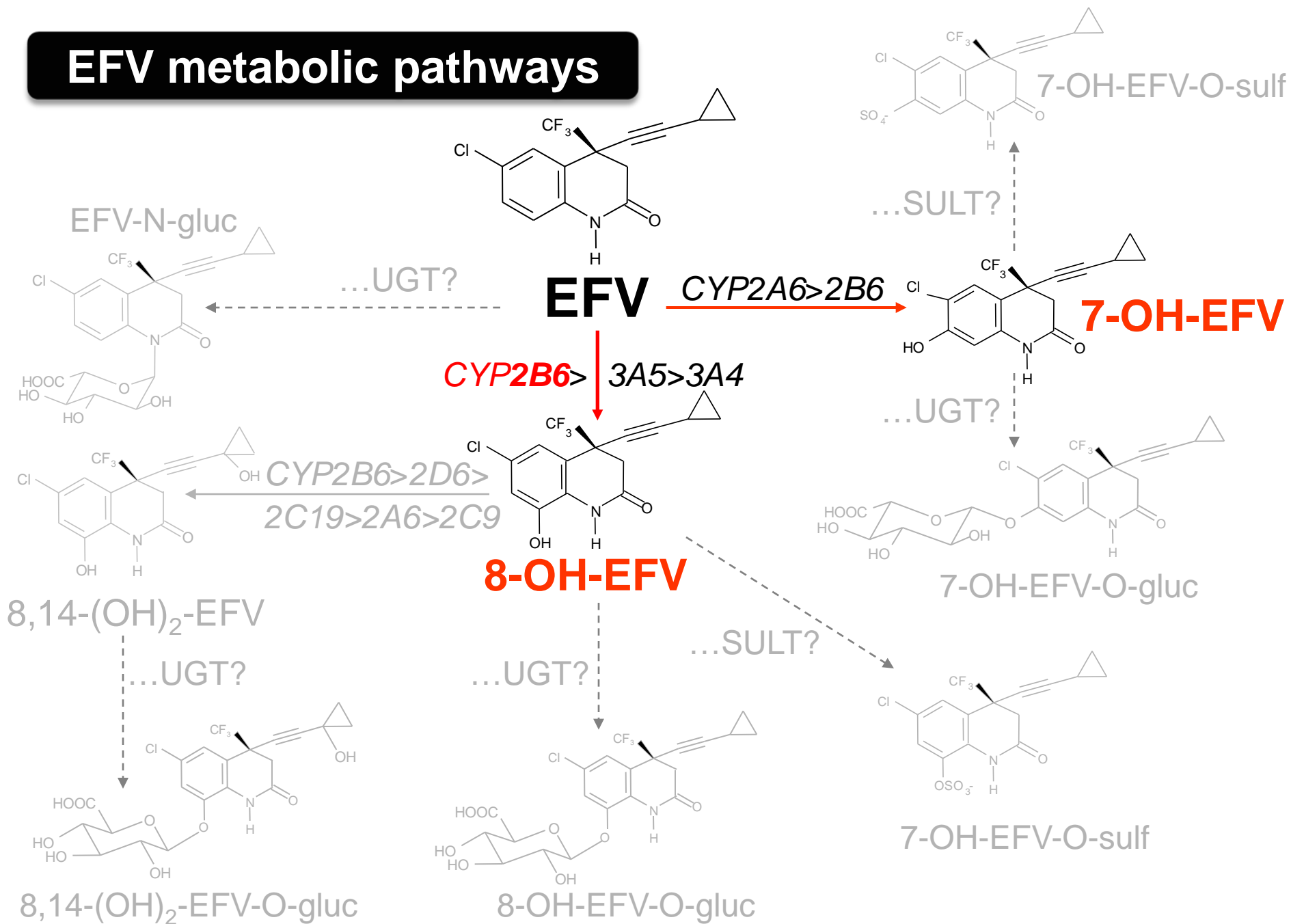
#2 - Exploiting functional knowledge

Distribution of Efavirenz AUC values

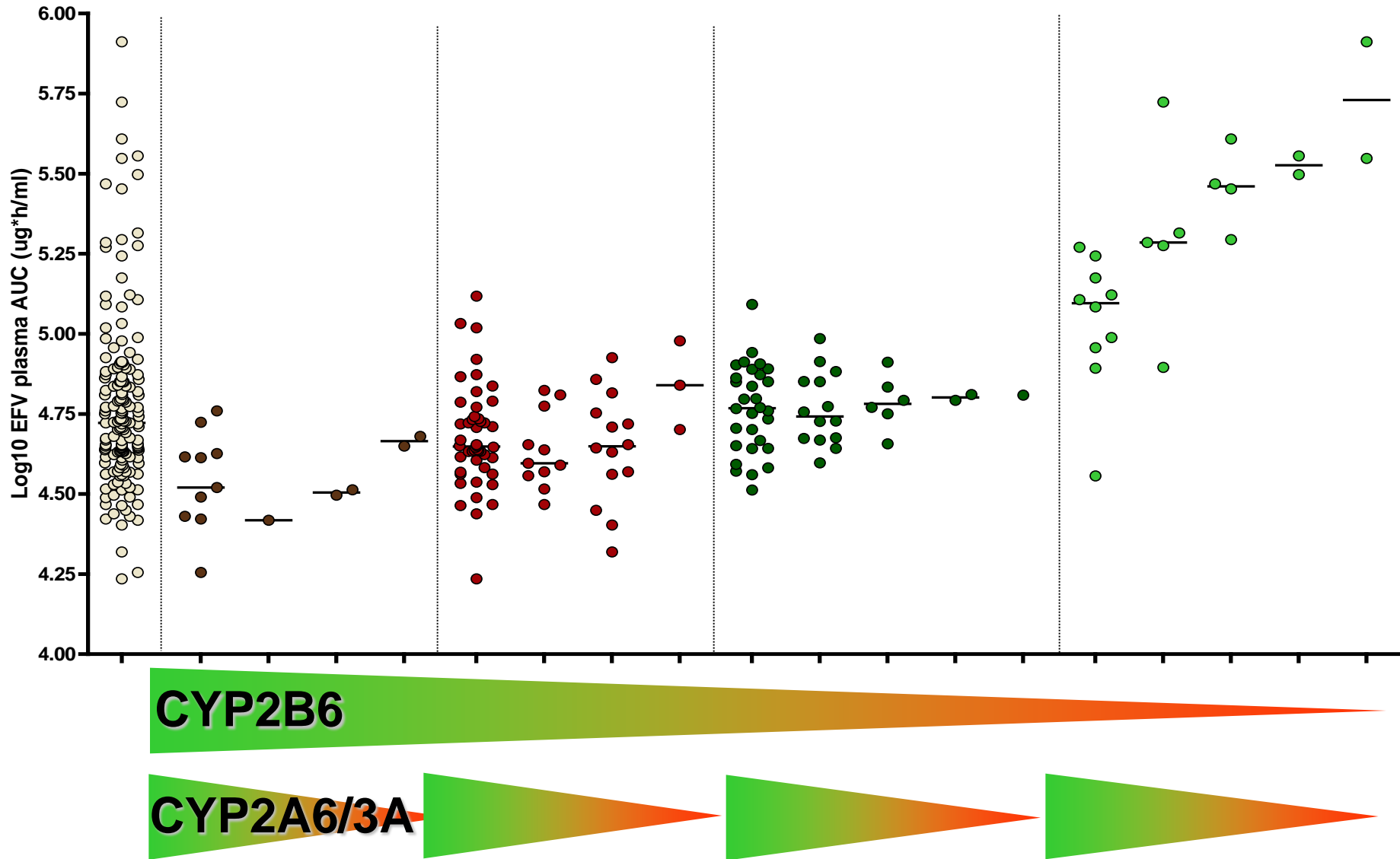
Rotger et al. Clin Pharm Ther 2007



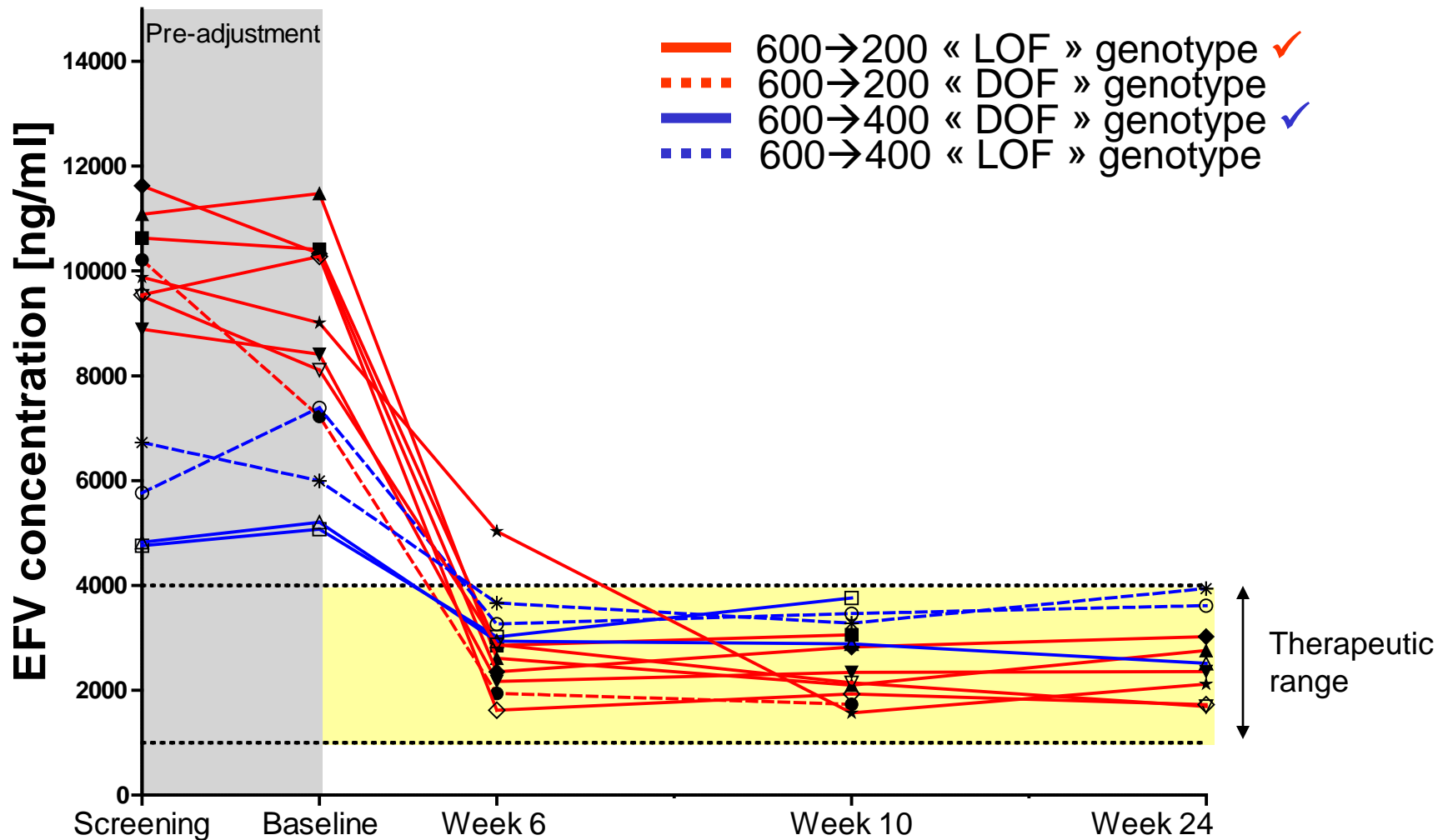
EFV metabolic pathways



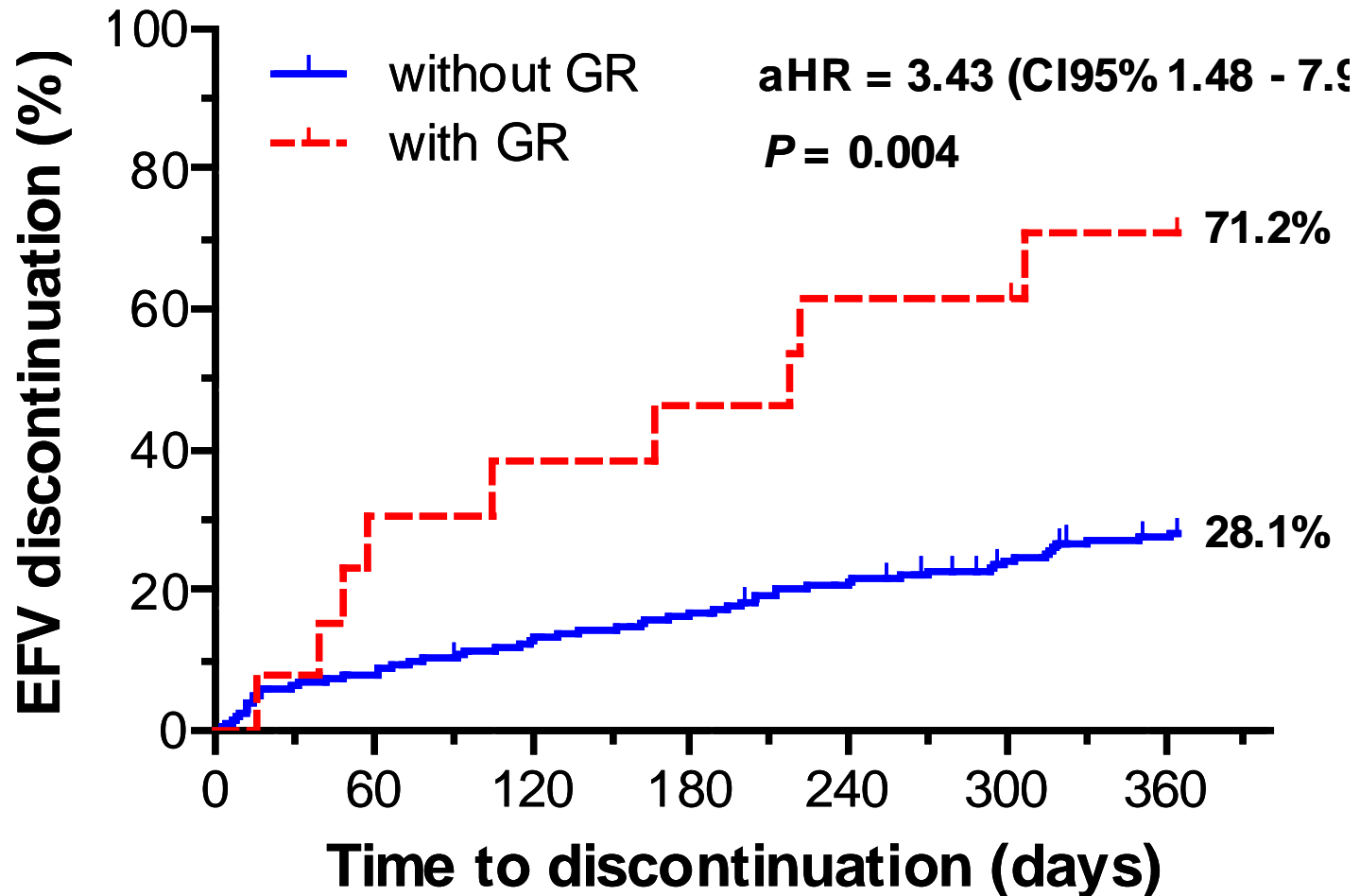
CYP2A6 CYP2A6 & CYP3A4 and Efavirenz Pharmacokinetics



TDM vs Genotype-driven efavirenz dose adjustment

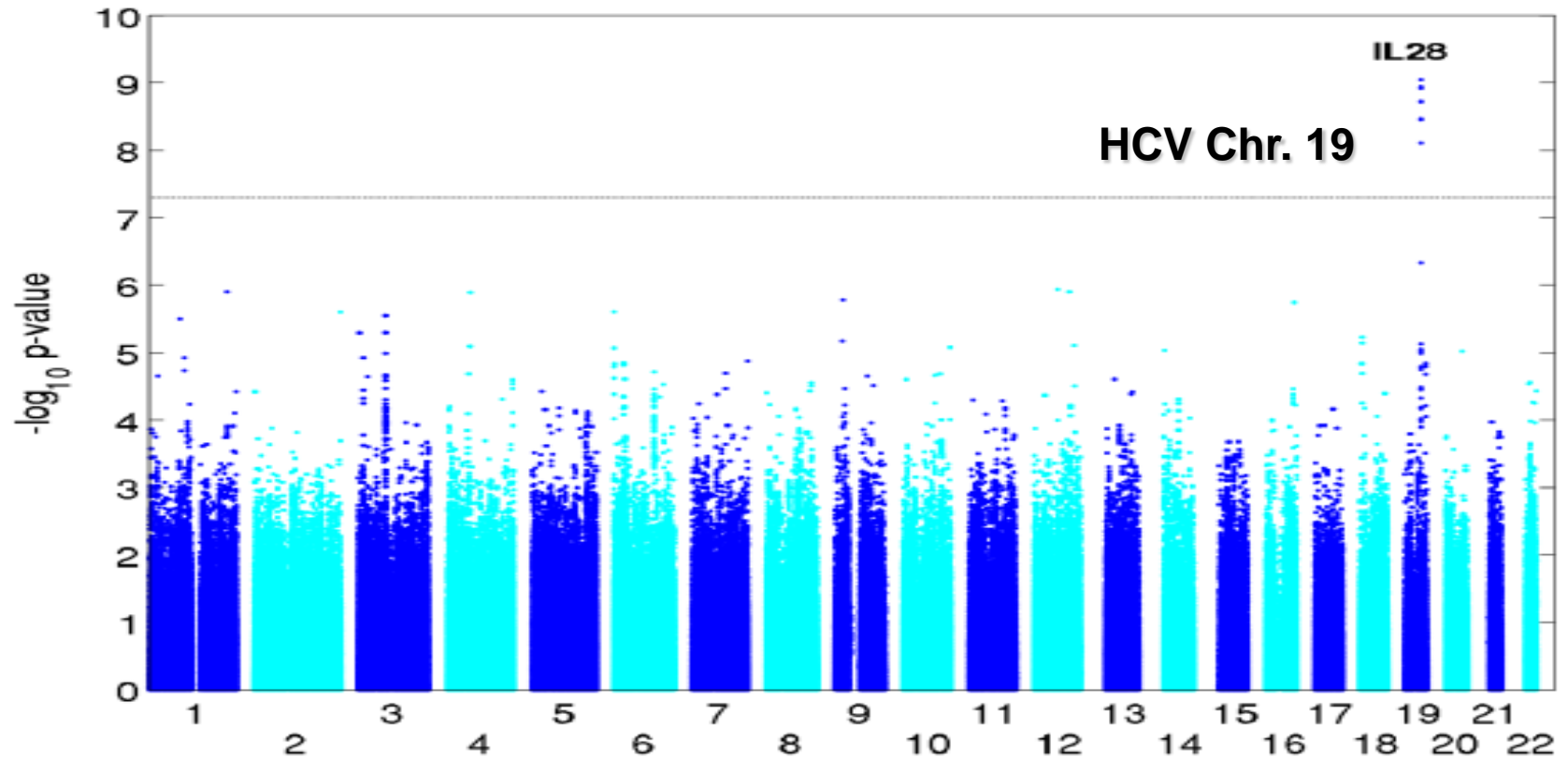


Discontinuation of efavirenz according to genetic background



#3 - Exploiting discrepancy

Chromosomal location of locus of susceptibility to HIV-1 and to Hepatitis C



Final Conclusions

- The genetic basis of disease susceptibility to infection are likely to be expressed differently.
- Evolutionary pressures are expected to have a major role.
- Integration of data in vitro/in vivo can be an important tool in discovery
- Pharmacogenetics proper can exploit the wealth of drug-gene interaction.

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