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

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- 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

Fellay et al. Science 2007
Rauch et al. Submitted
Additive genetic score

Survival/Progression

Fellay et al,

rs2395029 (HLA-B*5701)
rs9264942 (HLA-C -35)
rs9261174 (ZNRD1)
rs333 (CCR5Δ32)
GWAS Results

• We have reached experimental power conditions to identify most common human (Caucasian) variation influencing susceptibility to HIV
• We can know 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
The viral cycle
$K_A/K_S$ values of 140 candidate and 100 control genes
Genes with undergoing further positive evolutionary pressures in humans

Genes under selective pressure in primates

Genes with signs of selective pressure in humans

<table>
<thead>
<tr>
<th>IFNGR1</th>
<th>DEFB1</th>
<th>IL4R</th>
</tr>
</thead>
<tbody>
<tr>
<td>28</td>
<td>3</td>
<td>21</td>
</tr>
</tbody>
</table>
The MHC region displays a cluster of low p values in GWA (Fellay, Science 2007, Fellay et al, Submitted)

Martin et al, Bioinformatics 2009

...and selective pressure signals (Pritchard PLoS Gen 2006)
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

Legend:
- Neighborhood
- Gene Fusion
- Co-occurrence
- Co-expression
- Experiments
- Databases
- Textmining
- Homology
Expression variants influencing HIV-1 disease?

- 48,000 transcripts
- 260 genes differentially expressed during HIV-1 infection
- 1.3 mio. gene-centric SNPs
- 190 genes under cis-acting SNP modulating expression

OAS1

Susceptibility to West Nile Virus

Susceptibility to HIV?
siRNA/shRNA screens

Zhou et al. Cell Host Microbe 2008

• >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
Lost in translation
We have a problem

Any treatment change

Toxicity related treatment change

B. Ledergerber, SHCS
#1 - Exploiting environmental interactors
Dyslipidemia as common genetic trait

Sabatti et al. + Aulchenko et al.
- NR1H3/MADD-FOLH1
- CTCF-PRMT7
- DNAH11
- TMEM57
- rs2624265
- rs9891572
- CR1L
- AR
- GCKR
- LIPC
- LDLR
- APOB
- ABCA1
- FADS1/2/3
- BAZ1B/BCL7B/TBL2/MLXIPL
- NUP93/HERPUD1/CETP
- SARS/CELSR2/PSRC1/SORT1/MYBPHL
- GCNT4/HMGCR/POK
- CEACAM16/TOMM40/APOE
- LPL/SLC18A1
- ANGPTL3/DOCK7/ATG4C
- BUD13/APOA1/C3A4/A5
- MVK/MMAB
- NCAN/CILP2/CSPG3/PBX4
- TRIB1/FAM84B
- LIPG/ACCA2
- ABCG5/ABCG8

Sabatti et al.
- LCAT
- PCSK9
- GALNT2
- ANGPTL4
- PLTP
- HNF1A
- TIMD4/HAVCR1
- XKR6/AMAC1L2
- HNF4A
- TTC39B
- MAFB

Aulchenko et al.

Kathiresan et al.

Manolio Nat Genet 2009
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
Contribution of multiple variants to non HDL-C

Variability explained by the SNPs: 7.6%
Variability explained by ART: 3.9%
Contribution of multiple variants to HDL-C

Variability explained by the SNPs: 6.2%

Variability explained by ART: 1.5%
Contribution of multiple variants to **Triglycerides**

Variability explained by the SNPs

- **6.8%**

- APOA5 (rs3135506)
- APOA5 (rs662799)
- ABCA1 (rs2066714)
- GCKR (rs780094)
- LPL (rs6586891)

Variability explained by ART

- **6.2%**

- ART GROUP 3
- CD4+ COUNT
- MALE SEX
- ART GROUP 2
- BODY MASS INDEX
- WAIST CIRCUMFERENCE

CAUCASIAN ETHNICITY

IV DRUG USE

FASTING

DECREASING

INCREASING

Triglycerides (log10 mmol/L)
Proportion of individuals with sustained hypercholesterolemia

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

Genotype score

<table>
<thead>
<tr>
<th>Genotype score</th>
<th>ART group</th>
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<tbody>
<tr>
<td>I</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td></td>
</tr>
<tr>
<td>III</td>
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</table>

48.3%: Unfavorable genes + unfavorable ART

10.6%: Favorable genes + favorable ART
Proportion of individuals with sustained hypertriglyceridemia

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

- **60.8%**: Unfavorable genes + unfavorable ART
- **13.3%**: Favorable genes + favorable ART
#2 - Exploiting functional knowledge
Distribution of Efavirenz AUC values


Extensive metabolizer

Rapid metabolizer

Slow metabolizer
EFV metabolic pathways

EFV-N-gluc → 8-OH-EFV

EFV → 7-OH-EFV

CYP2A6>2B6

CYP2B6>3A5>3A4

8-OH-EFV → 8,14-(OH)₂-EFV

...UGT?

8,14-(OH)₂-EFV-Ο-gluc

...UGT?

EFV metabolic pathways
CYP2A6 CYP2A6 & CYP3A4 and Efavirenz Pharmacokinetics

Di Iulio, PGG 2009, Arab CPT 2009
Calmy et al - Therapeutic drug monitoring (TDM) enables efavirenz dose reduction in virologically-controlled patients. IAS Cape Town 2009.

Therapeutic range

Calmy et al - Therapeutic drug monitoring (TDM) enables efavirenz dose reduction in virologically-controlled patients. IAS Cape Town 2009.
Discontinuation of efavirenz according to genetic background

<table>
<thead>
<tr>
<th>Time to discontinuation (days)</th>
<th>EFV discontinuation (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>without GR</td>
</tr>
<tr>
<td></td>
<td>with GR</td>
</tr>
<tr>
<td>0</td>
<td>71.2%</td>
</tr>
<tr>
<td>60</td>
<td>28.1%</td>
</tr>
</tbody>
</table>

aHR = 3.43 (CI95% 1.48 - 7.1)  
P = 0.004
#3 - Exploiting discrepancy
Chromosomal location of locus of susceptibility to HIV-1 and to Hepatitis C

Fellay et al. Science 2007
Rauch et al. Submitted
The power of discordant phenotype and genotype pairs (resequencing + recombinant mapping)
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.