#295

Please also see abstract #317

Host Genetic Predictors of Plasma Kynurenine/Tryptophan Among Treated HIV+ Ugandans

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Background

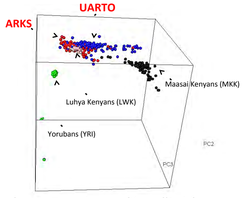
- Plasma kynurenine/tryptophan (KT) ratio is a biomarker of indoleamine 2,3-dioxygenase-1 (IDO) activity, which is associated with microbial translocation and persistent immune activation in HIV disease (Favre Sci Transl Med 2010).
- We have recently demonstrated that KT ratio is a strong independent predictor of mortality in HIV+ Ugandans initiating antiretroviral therapy (ART) (Byakwaga JID 2014).
- We performed a genomewide association study of common polymorphisms associated with plasma KT ratio levels among HIV-infected Ugandans with ART-mediated viral suppression.

Methods

- We performed genome (Illumina OmniExpress) and exome (Affymetrix Axiom) array genotyping among 597 HIV+ ART-suppressed participants from two Ugandan cohorts (UARTO and ARKS).
- After quality control measures, we performed imputation using the 1000 Genomes reference panel.
- Over 16 million SNPs were tested in association with plasma $\log_{10}$KT ratio levels measured at 6 and 12 months of ART suppression.
- Linear mixed models adjusted for cohort, gender, pregnancy, and population ancestry were used to assess the association between SNPs and $\log_{10}$KT ratio.

Results

UARTO and ARKS Participants Demonstrate Similar Ancestry to Other East Africans



** Plot of first three principal components used to adjust for ancestry, shown in comparison to other 1000 Genome African populations: LWK and MWK in Kenya, East Africa and YRI in Nigeria, West Africa.*

Descriptive Characteristics

Characteristics	ARKS (N=177)	UARTO (N=420)
Age	34 (29-40)	35 (29-40)
Female	76 (43%)	292 (70%)
Baseline CD4+ Count (cells/mm^3)	116 (25-250)	137 (80-206)
Baseline HIV RNA ($\log_{10}$ copies/mL)	5.2 (4.9-5.5)	5.1 (4.1-5.5)

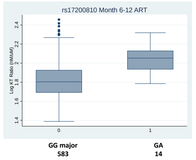
SNPs in Candidate Genes Associated with KT Ratio

SNP	Coef	P	CHR	Location	MAF	Candidate Gene
rs17200810[a]	0.22	1.41 x E-06	6	3'	0.02	TNF
rs34451538	0.18	3.90 x E-06	6	5'	0.03	TNF
rs276565[b]	0.05	5.30 x E-06	6	5'	0.10	IFNGR1
rs114064880	0.23	5.33 x E-06	6	5'	0.12	TNF
rs11575838	0.23	7.13x E-06	6	3'	0.07	TNF
rs2770148[c]	0.06	2.94 x E-05	9	Intron 2	0.05	TLR4

[a] Genotyped, transcription factor binding site (TFBS) for several transcription factors (e.g., IRF4, JUND, RUNX). [b] Genotyped, in active H3K27Ac mark regulatory region. [c] In linkage disequilibrium (LD) with genotyped SNP rs1413088

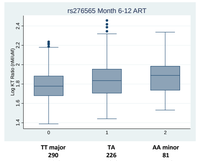
SNPs in Candidate Genes Lie in Putative Functional Regions and Correlate with IL-6, sCD14, sCD163 Levels

rs17200810 *TNF* (3')



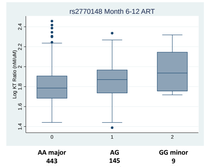
- Genotyped SNP
- Several TFs predicted to bind in region including RELA, IRF4, JUND

rs276565 *IFNGR1* (5')



- Active regulatory region - H3K27Ac histone mark
- ⇧copies of minor allele also associated with ⇧IL-6, ⇧sCD163, ⇧sCD14 levels

rs270148 *TLR4* (intron 2)



- In LD with genotyped SNP
- Active regulatory region - H3K27Ac histone mark
- ⇧copies of minor allele also associated with ⇧sCD163

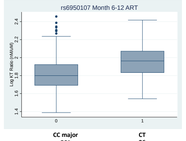
Genomewide SNPs Associated with Plasma KT Ratio

SNP	Coef	P	CHR	Location	MAF	Nearest Gene(s)
rs56185965	0.19	8.73 x E-09	3	intergenic	0.02	CSPG5, ELP6
rs6950107[a]	0.16	7.14 x E-08	7	intron 6	0.03	PTPRN2
rs17085469	0.08	7.75 x E-08	18	5'	0.10	RP11-736G13.1
rs13041834[b]	0.07	3.13 x E-07	20	intergenic	0.12	CYP24A1 BCAS1, MIR4756
rs75257475[c]	0.09	2.95 x E-07	18	intron 1	0.07	PTPRM
rs200564710	0.11	3.20 x E-07	5	intergenic	0.05	HOMER1, PAPD4
rs114598920	0.14	3.73 x E-07	3	intron 1	0.03	CLSTN2
rs115718192	0.21	4.13 x E-07	3	intergenic	0.02	TFRC, SDHAP1

[a] TFBS (SNP predicted to decreases binding to SMAD3 which is downstream of TGF-b signaling). [b] Active H3K27Ac mark region. 5' of microRNA MIR4756, in LD with genotyped SNP. [c] TFBS (SNP predicted to change binding to FOSL2; FOSL2+JUN dimers form AP-1 complex), in LD with 11 other 10 x E-07 SNPs, incl. a genotyped SNP

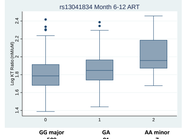
Genomewide SNPs May Alter Transcription Factor Binding Sites and Correlate with D-dimer, IL-6, and sCD163 Levels

rs6950107 *PTPRN2* (intron 6)



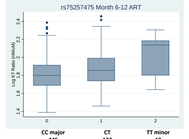
- Encodes a PTP = type I diabetes autoantigen
- Predicted to decrease SMAD3 binding (TGF-β → SMAD3/SMAD4/JUN/FOS → AP-1)
- ⇧copies of minor allele also associated with ⇧D-dimer, ⇧IL-6

rs75257475 *PTPRM* (intron 1)



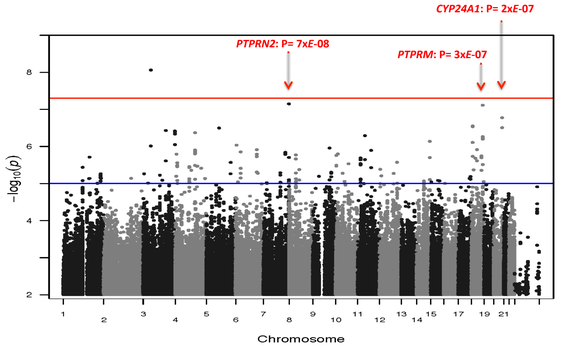
- Also encodes a PTP
- In LD with genotyped SNP
- FOSL2 predicted to bind in region (JUN/FOSL→ AP-1)

rs13041834 CYP24A1 (5')



- in LD with genotyped SNP
- Active regulatory region - H3K27Ac histone mark
- ⇧copies of minor allele also associated with ⇧sCD163

Manhattan Plot of Genomewide SNPs



Conclusions

- SNPs in *TNF*, *IFNGR1*, and *TLR4* candidate genes were associated with plasma KT ratio during ART.
- The GWAS results suggest at least two potential novel pathways involved in IDO regulation.
  - Protein tyrosine phosphatases may influence IDO immunoregulation via AP-1 mediated signaling
  - Vitamin D and IDO may share a common pathway to influence immune dysfunction in chronic HIV disease.
- Several candidate gene and genomewide SNPs were also associated with elevated markers of monocyte activation and inflammation.
- Replication of our findings in the ACTG cohort is currently underway.

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