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The Association of Polymorphisms in HLA Class I and TAP Genes with Resistance to *HIV*-1 Infection

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Introduction

• Human leukocyte antigen (HLA)-restricted immune responses are reportedly involved in resistance to HIV infection;

• To examine relationships of HLA class I and the transporter associated with antigen processing (TAP) genes with resistance to human immunodeficiency virus-1 (HIV-1) infection.

Methods

• Cases: 100 persistently seronegative men repeatedly exposed to HIV-1;

• Controls: 184 seroconverters with lower risk;

• Selection criteria: number of different insertive anal sexual partners during 2.5 years prior to 2nd visit of MACS, and no overlap between the study groups;

• HLA genotyping: sequence-specific oligonucleotide probing method supplemented by direct sequencing;

• TAP variant typing: sequence specific oligonucleotide hybridization and DNA single strand conformation polymorphism technique;

• Statistical methods: univariate frequency analysis and multiple logistic regression

Table 1: Individual alleles with significant statistical associations at P<0.1 level

HLA/TAP Variants	HRSNs (Number)	LRSCs (Number)	Odds Ratio	95% C.I.	P-Value
A*6601*	0	6	0.17	(0.01, 2.45)	0.094
A*6802	4	1	7.63	(0.84,69.17)	0.054
B*1302	9	6	2.92	(1.01,8.45)	0.040
B*3502*	0	6	0.14	(0.01, 2.44)	0.093
TAP1 637 gly	24	33	1.65	(0.91, 3.01)	0.099
TAP2 665 ala	55	75	2.26	(1.35, 3.79)	0.002

Table 2: Statistical associations between supertypes and HIV resistance

Super-Types	HRSNs (Number)	LRSCs (Number)	Odds Ratio	95% C.I.	P-Value
A1	40	119	0.89	(0.54, 1.45)	0.633
A2	49	123	1.43	(0.87, 2.33)	0.154
A3	48	128	1.20	(0.74, 1.96)	0.465
A24	30	84	1.03	(0.61, 1.76)	0.909
B7	57	152	1.24	(0.76, 2.03)	0.387
B27	21	64	0.87	(0.48, 1.57)	0.649
B44	48	134	1.05	(0.65, 1.71)	0.839
B58	11	31	1.01	(0.46, 2.21)	0.973
B62	22	49	1.64	(0.88, 3.06)	0.119

Table 3: Statistical associations between supertype A2 and HIV resistance

Alleles	HRSNs (Number)	LRSCs (Number)	Odds Ratio	95% C.I.	P-value
A*0201	40	73	1.01	(0.62,1.67)	0.957
A*0205	3	1	5.66	(0.58,55.14)	0.127
A*0206	2	1	3.73	(0.33,41.71)	0.284
A*0212*	0	1	0.61	(0.03, 5.08)	1.000
A*6802	4	1	7.62	(0.84,69.17)	0.054
A2/6802	49	75	1.40	(0.86, 2.28)	0.182
A2/6802 (w/o A*0201)	9	4	4.45	(1.33, 4.84)	0.009
A*0201 Subgrp	40	74	0.99	(0.60, 1.63)	0.972
A*0205 Subgrp	9	3	5.97	(1.58, 22.58)	0.005

Table 4: Statistical associations between B*35 Px, PY and HIV resistance

HLA Alleles	HRSNs (Number)	LRSCs (Number)	Odds Ratio	95% C.I.	P-Value
PY					
B*3501	14	18	1.49	(0.71, 3.14)	0.290
B*3508	1	1	1.84	(0.11,29.71)	1.000
Combined	15	19	1.53	(0.74, 3.17)	0.247
Px					
B*3502*	0	6	0.14	(0.01, 2.44)	0.093
B*3503	2	6	0.60	(0.12, 3.04)	0.717
B*5301	1	6	0.30	(0.04, 2.51)	0.428
Combined	3	18	0.29	(0.08, 0.99)	0.037

Table 5: Multiple logistic regression excluding men with CCR5 double deletions

Variables	Odds Ratio	95% C.I.	P-value
A*0205 Subgroup	5.75	(1.38, 23.86)	0.016
Px	0.31	(0.07, 1.38)	0.124
B*1302	2.04	(0.62, 6.78)	0.242
TAP1 637 gly	1.88	(0.09, 3.61)	0.058
TAP2 665 ala	2.10	(1.20, 3.67)	0.009

Results

Univariate Analysis

• A*6802 (Odds Ratio [OR], 7.63; 95% confidence interval [CI], 0.84-69.17; P=0.05) and B*1302 (OR, 2.92; 95% CI, 1.01-8.45; P=0.04) were found marginally associated with HIV-1 resistance (Table 1) ;

• The significant resistance association of the A2/6802 supertype excluding A*0201 (OR, 4.45; 95% CI, 1.33-4.84, P=0.009) was due completely to the effects of the A*0205 subgroup (Table 2);

• Susceptibility to HIV-1 infection was associated with the recently identified Px subfamily (OR, 0.29; 95% CI, 0.08-0.99; P=0.04) of B*35 (Table 3);

• TAP2 665 ala was associated with HIV-1 resistance (OR, 2.26; 95% CI, 1.35-3.79; P=0.002), see Table 4;

Multiple Logistic Regression Analysis:

• No single HLA allele association was statistically significant, but the TAP2.3 variant (OR, 2.10; 95% CI, 1.20-3.67; P=0.009) and the A*0205 subgroup (OR, 5.75; 95% CI, 1.38-23.86; P=0.02) remained significantly associated with HIV-1 resistance (Table 5).

Discussion

• A*0205 subgroup: alleles share similar structure in the binding groove and preferentially bind some peptides with common anchor residues;

• Px alleles: Different binding preference at the C terminus may influence peptide binding capacity;

• TAP2 665 ala: May confer greater efficiency in transporting peptides eliciting a strong protective immune response or may be in linkage disequilibrium with other genes;

Conclusion

• The HLA A*0205 subgroup and the TAP2 665 ala variant appear to be associated with resistance to HIV-1 infection.