

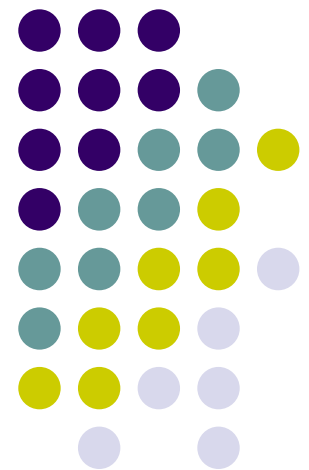
Protective HLA Class I Alleles Select for Early Escape Mutations in Conserved Regions of HIV

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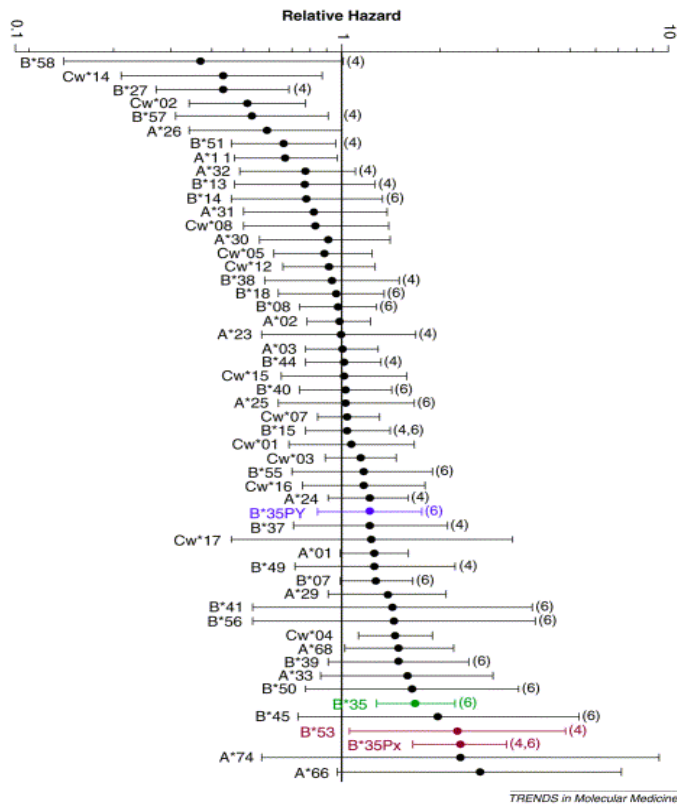


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Some HLA alleles are more protective than others



HLA Allele Relative Hazard



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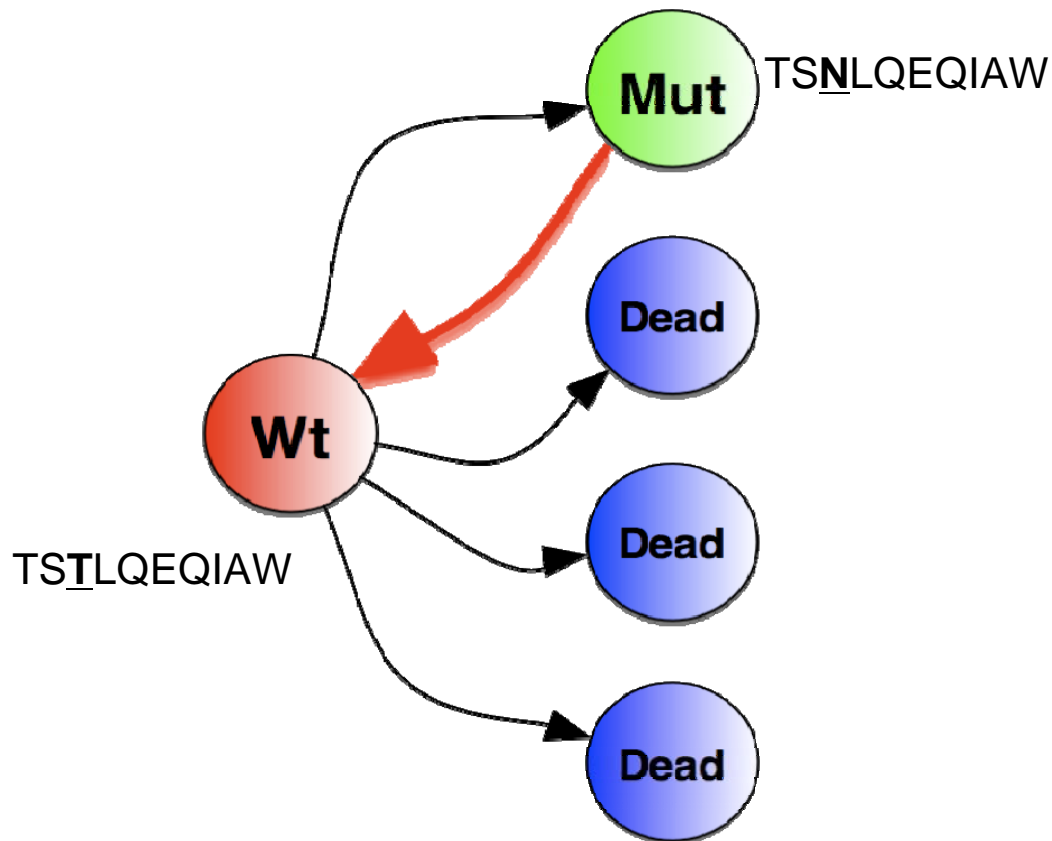
B35, B53
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B27, B57

Why are some CD8+ T cell responses more effective than others?



1) Fitness Cost



2) Immunodominance

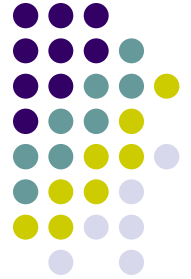
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Hypothesis



The control of HIV associated with particular HLA alleles is linked to their ability to restrict ***acute phase*** CD8 responses selecting for escape mutations at ***conserved positions***

Strategy



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Full HIV genome sequences

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98 chronic patients

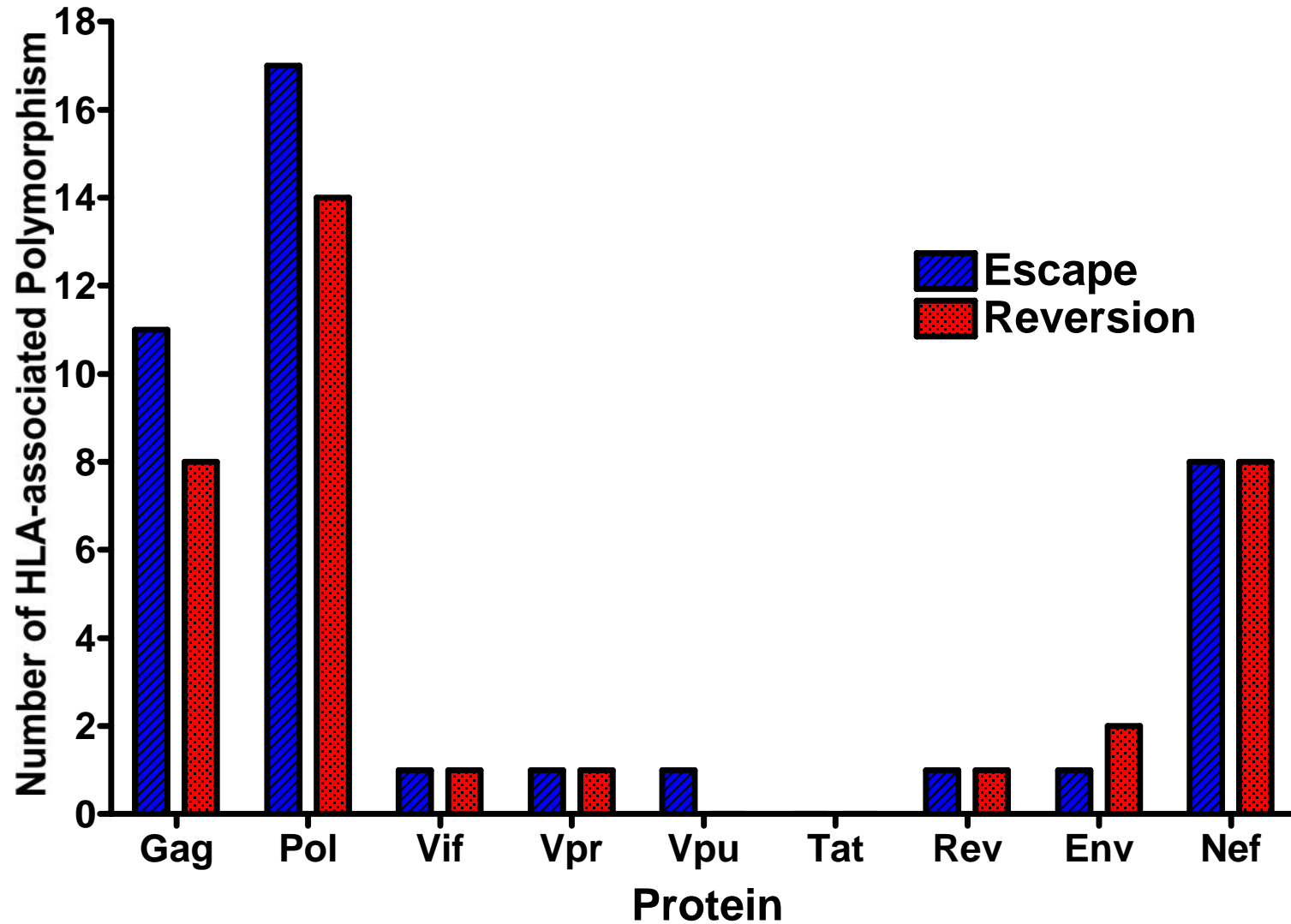
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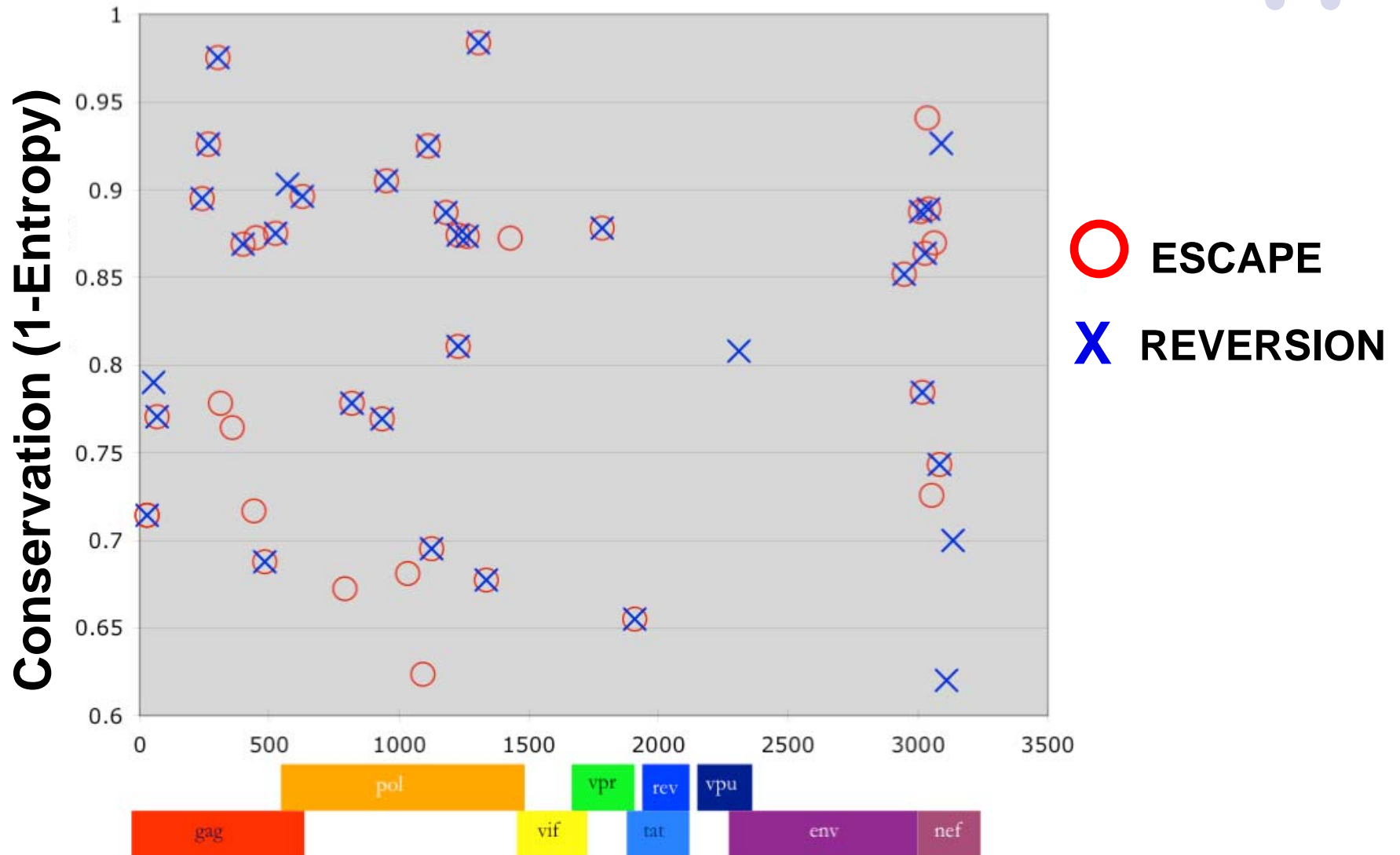
Phylogenetic Analysis

HLA-associated Polymorphisms (CTL escapes)

Do HLA associations cluster at specific regions within the genome?



Majority of HLA-Driven Escaping Residues Revert Back to Consensus Amino Acids

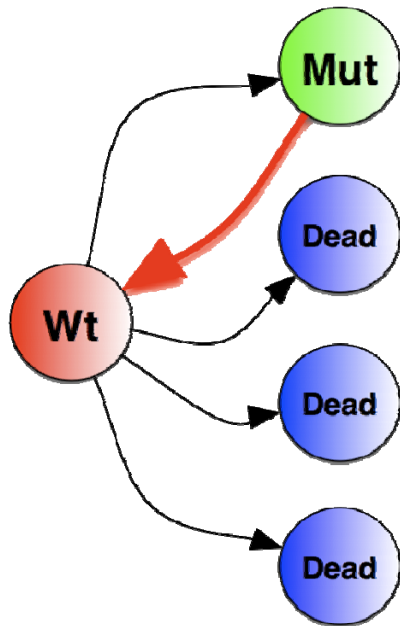




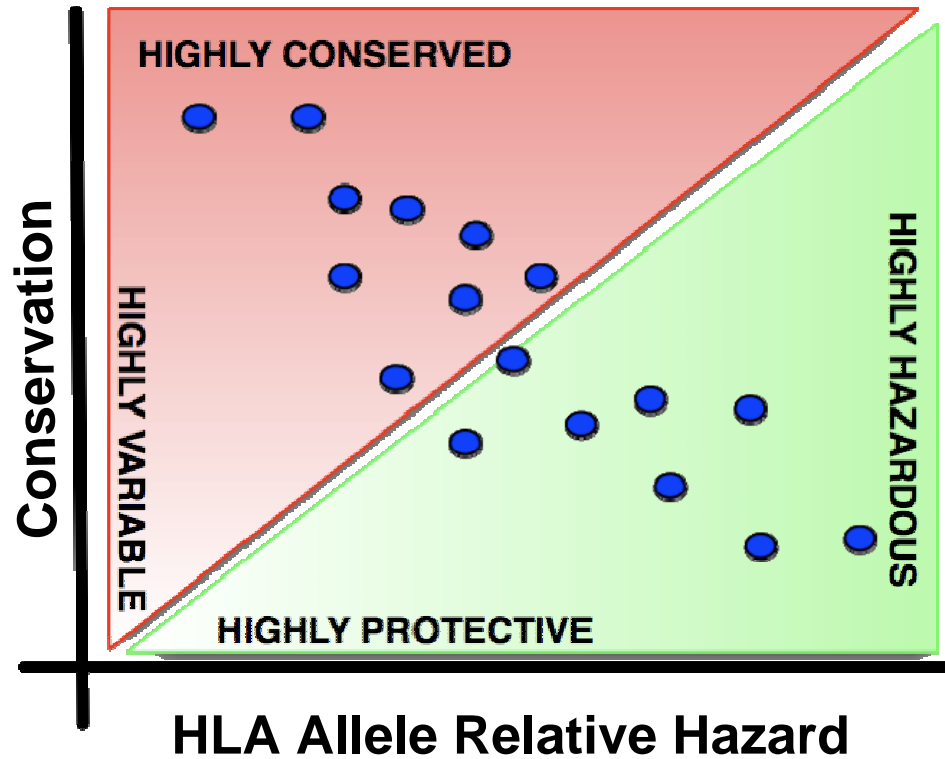
Analysis

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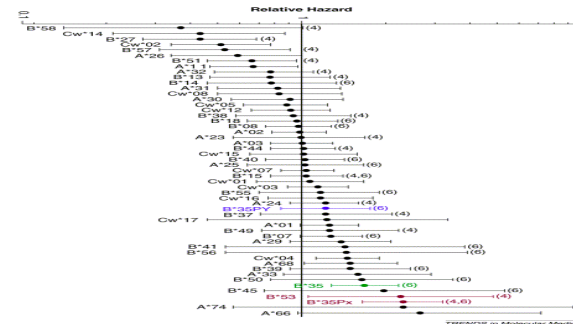
HLA-associated polymorphisms



Conservation



HLA Allele Relative Hazard

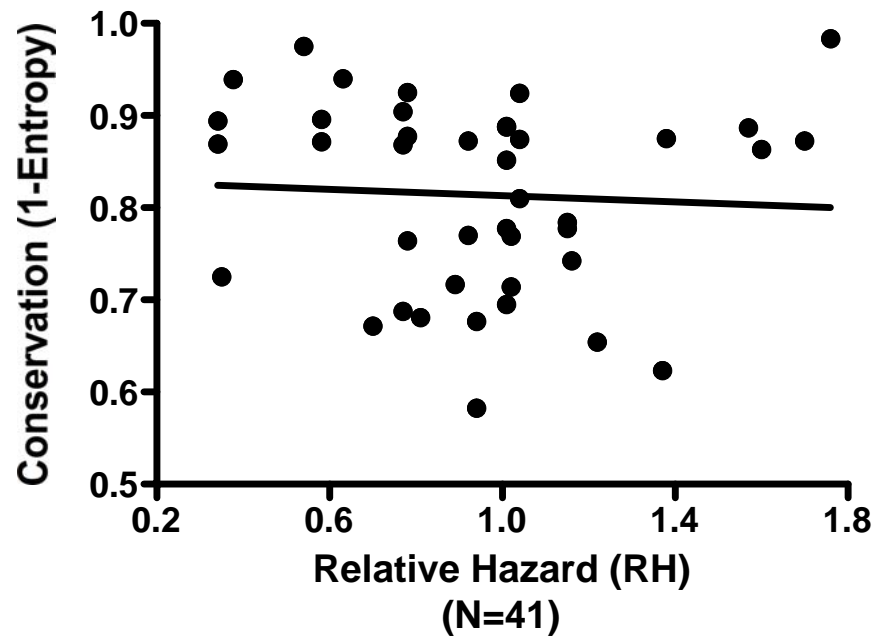


Why are some CD8+ T cell responses more effective than others?



1) All HLA Associated Mutations

$R=-0.1482$; $P=0.3553$

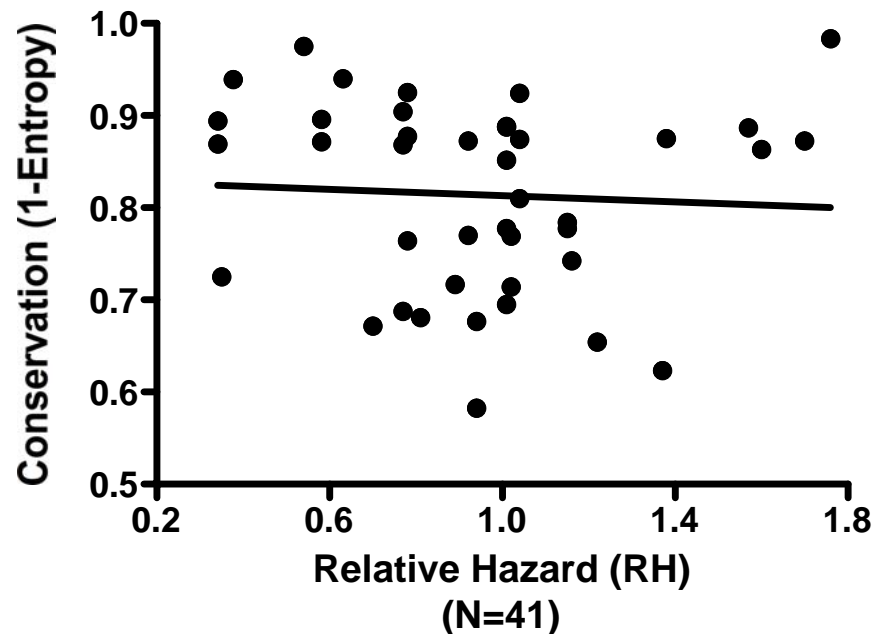


Why are some CD8+ T cell responses more effective than others?



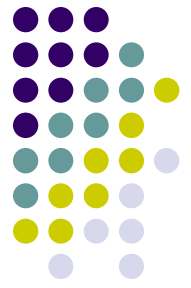
1) All HLA Associated Mutations

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2) Acute phase responses (immunodominant)

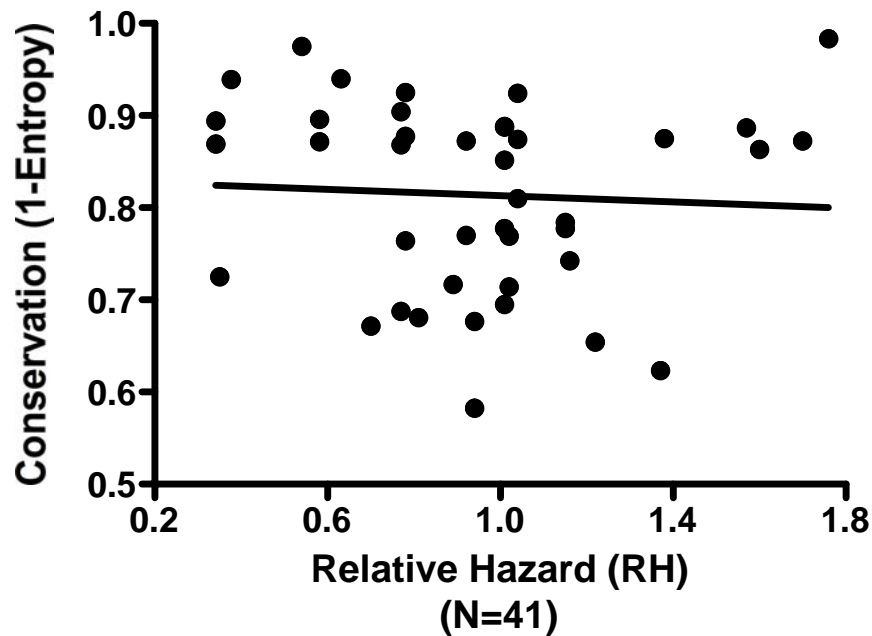
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Why are some CD8^T responses at conserved positions in early infection more effective than others?

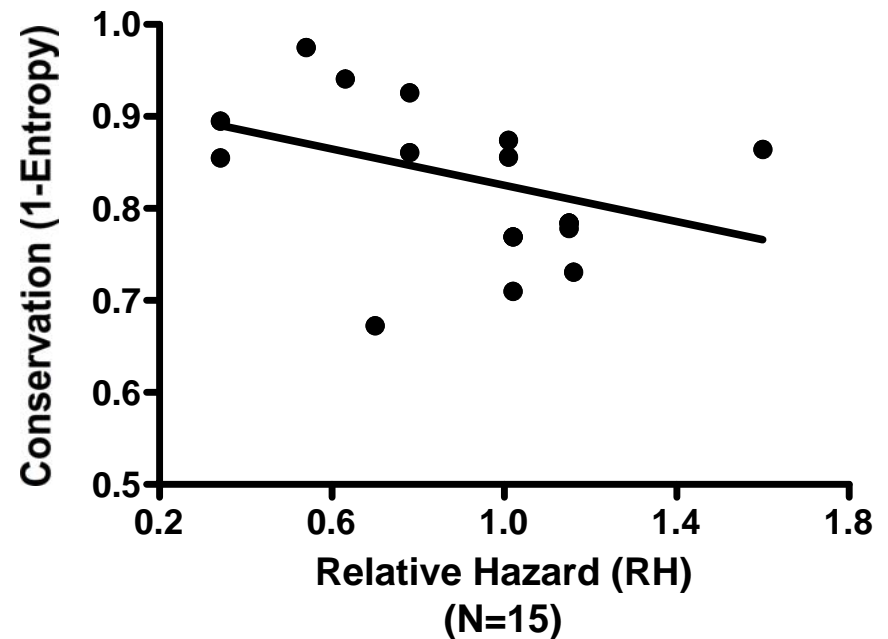
1) All HLA Associated Mutations

R=-0.1482; P=0.3553

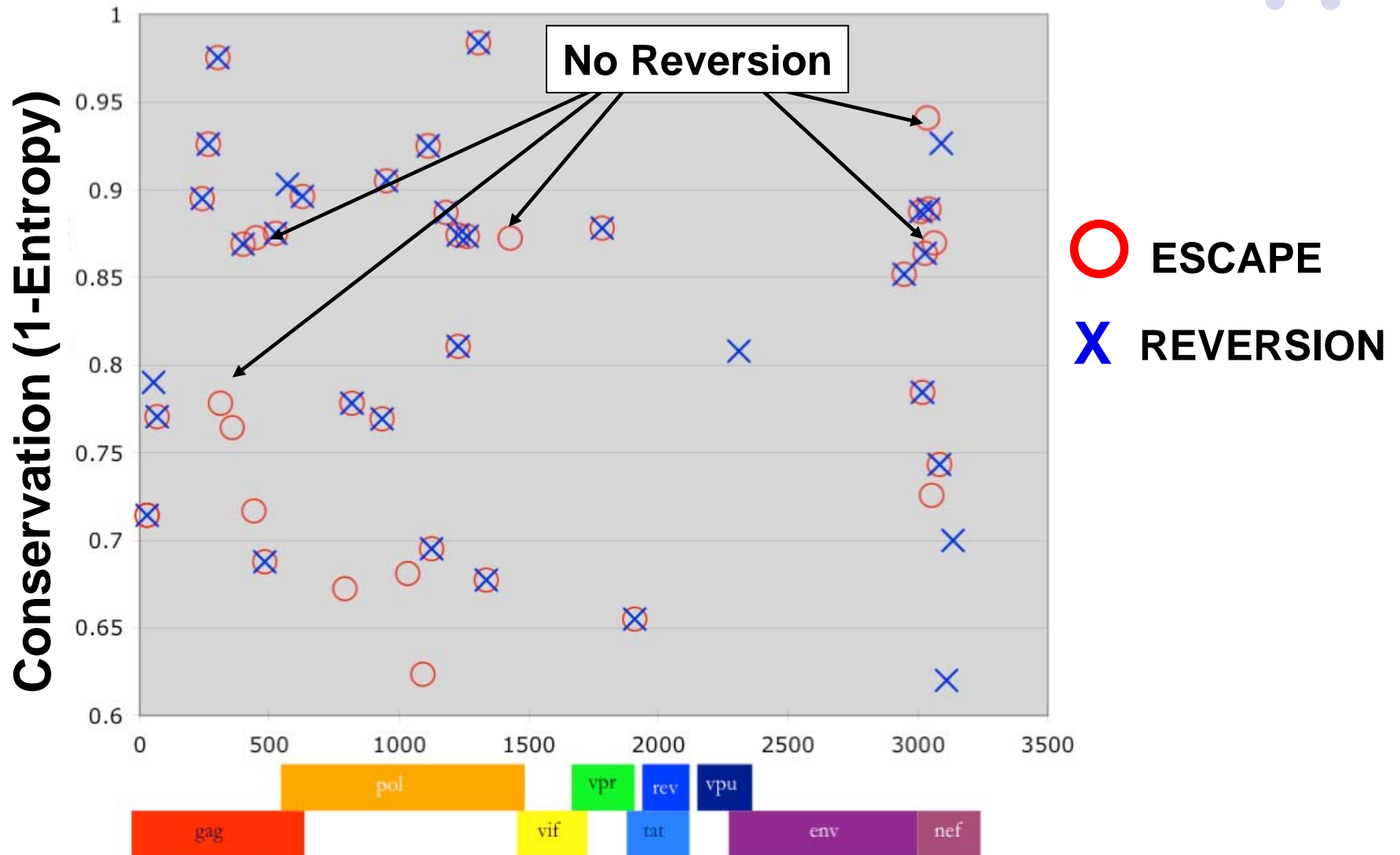


2) Acute phase responses (immunodominant)

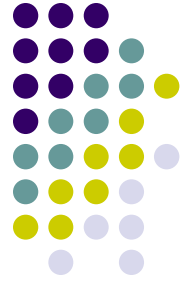
R=-0.5650; P=0.0282



Majority of HLA-Driven Escaping Residues Revert Back to Consensus Amino Acids



Why some escape mutations do not have detectable reversion?



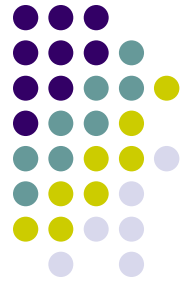
Low Viral Fitness Cost

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Compensatory Mutation

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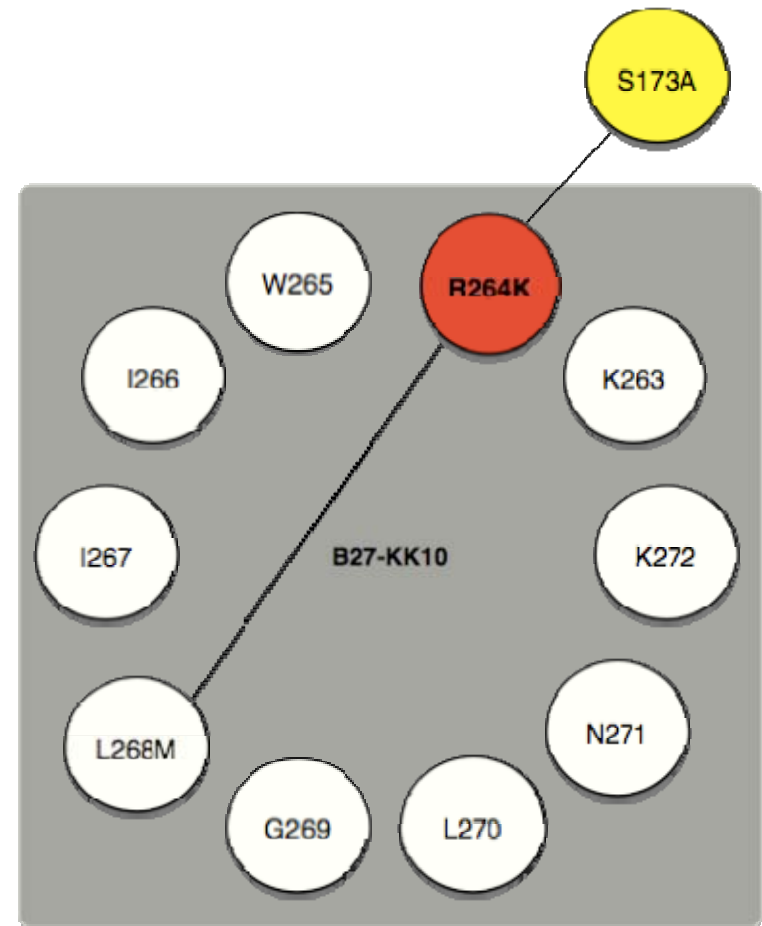
Covariation Network for B27- KK10 R264K Escape Mutation



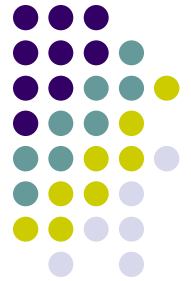
KK10 Mutation Patterns in B27+ patients

	M	F	173	A	L	...	E	I	Y	264	268	K	R	W	I	L	G	L	N	K	I	V	
L8146
F758
M124
AC160	M
AC88	M
11504	M
F7148	K	.	.	M
17630	.	.	A	K	.	.	M
18030	.	.	A	K	.	.	M
M101	.	.	A	K	.	.	M
SW	.	.	A	K	.	.	M
O25	.	.	A	K	.	.	M
CRO339X	.	.	A	K	.	.	M
PRLS24	.	.	A	K	.	.	M
L8129	.	.	A	K	.	.	M
007 96	.	.	A	K	.	.	M
777 96	.	.	A	K	.	.	M
CRO312W	.	.	T	K	.	.	M
CRO206U	.	.	V	K	.	.	I
L8118	.	.	T	T
L8159	T

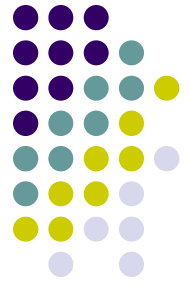
Computational Prediction



Why some escape mutations do not have detectable reversions?

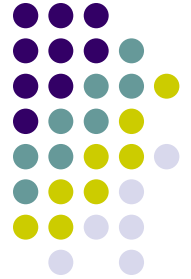


Conclusions



- Protective HLA alleles select for viral sequence polymorphisms in conserved regions of HIV-1
- Suggest potential importance of early immunodominant CD8+ T cell responses to the outcome of HIV-1 infection
- Compensatory mutations may play an important role in determining the impact of CTL escape mutations on viral replication capacity
- Vaccine designed to elicit CD8+ T cell responses may need to focus responses against regions of the virus that would exact a substantial impact on viral fitness

Acknowledgements



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Bruce Walker

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Jonathan Carlson

NCI

Mary Carrington

And all the patients

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