

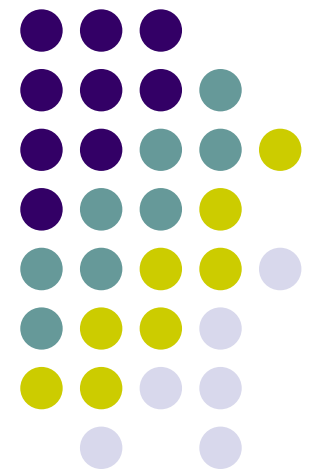
# Protective HLA Class I Alleles Select for Early Escape Mutations in Conserved Regions of HIV

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October 15, 2008

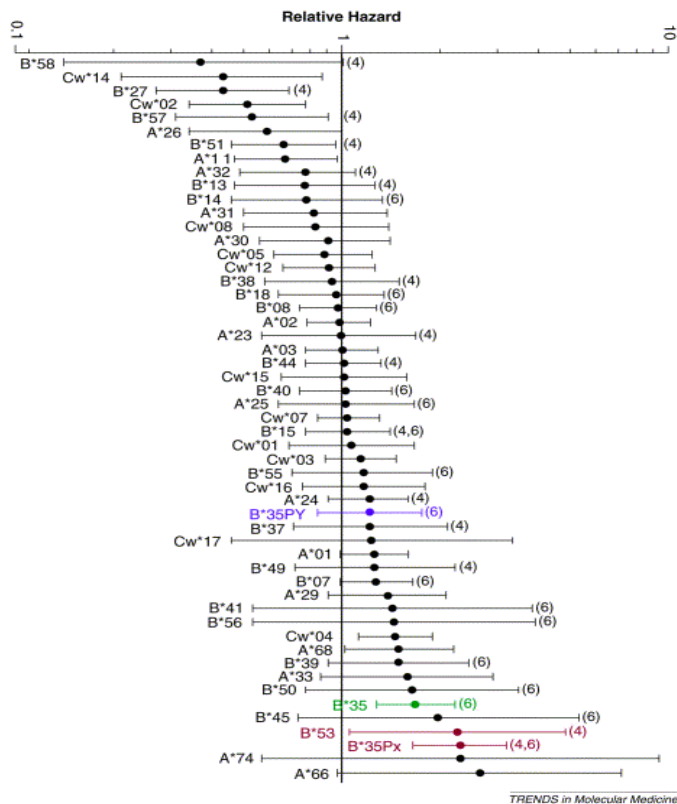


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are needed to see this picture.

# Some HLA alleles are more protective than others



## HLA Allele Relative Hazard

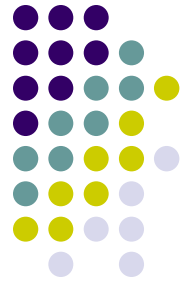


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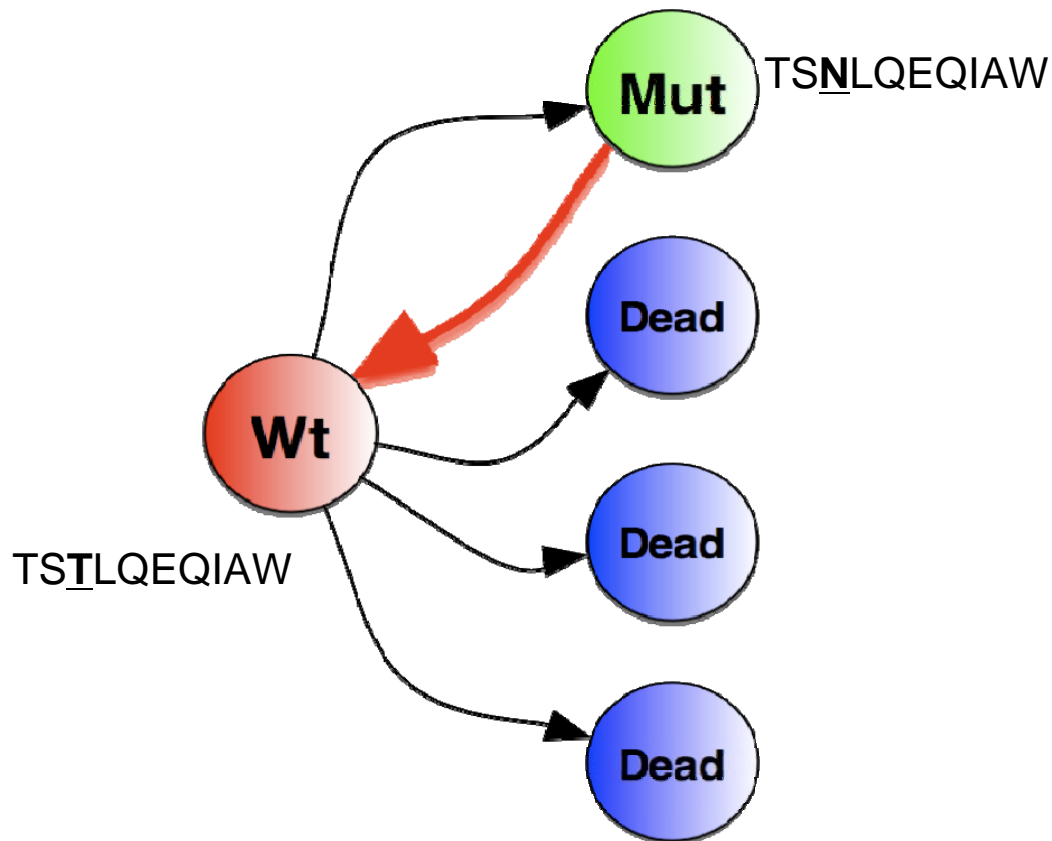
B35, B53  
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B27, B57

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



## 1) Fitness Cost



## 2) Immunodominance

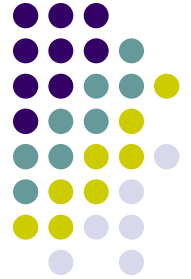
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# Hypothesis



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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are needed to see this picture.

## Full HIV genome sequences

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TIFF (LZW) decompressor  
are needed to see this picture.

## 98 chronic patients

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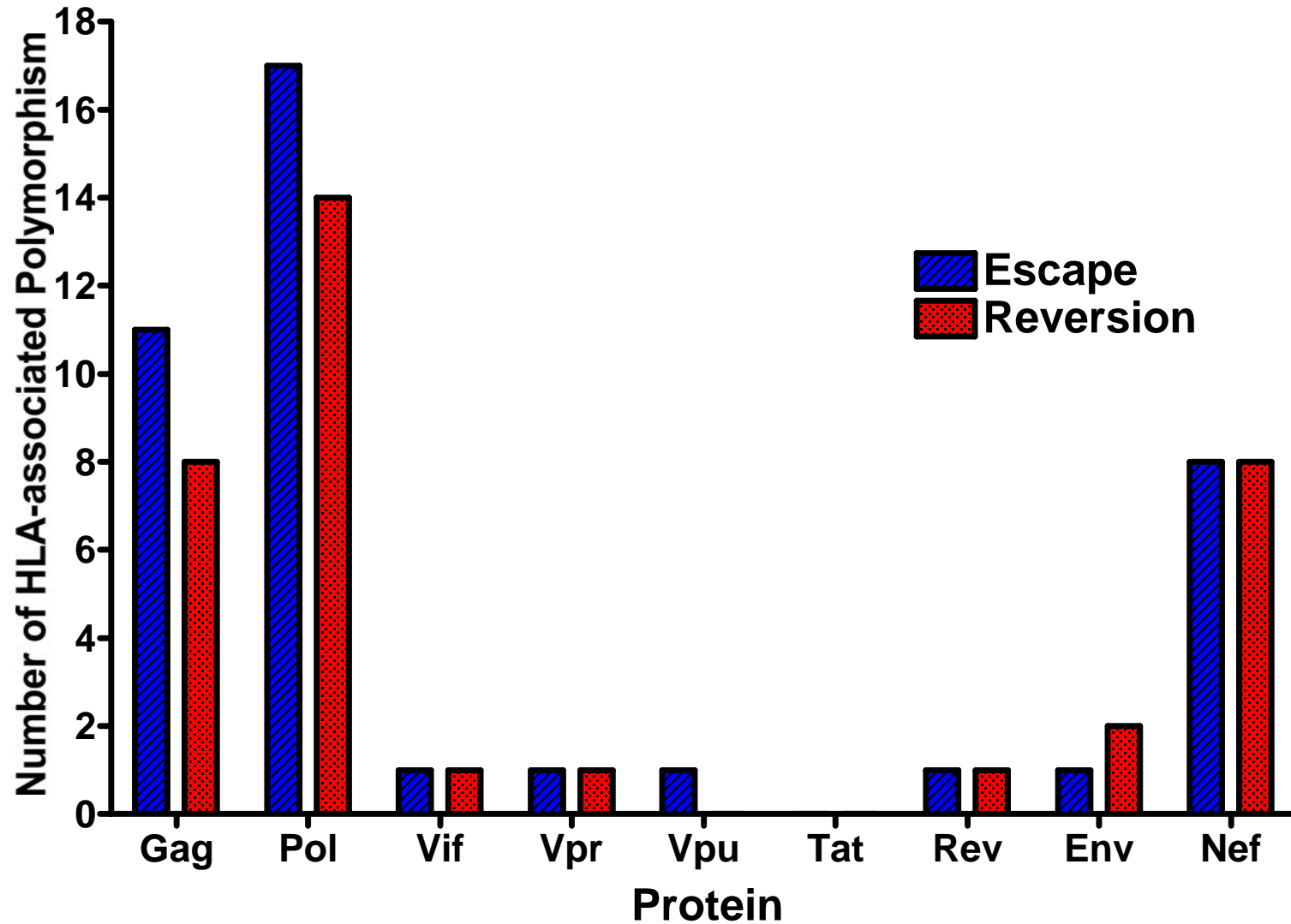
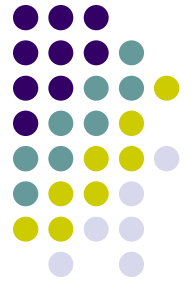
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are needed to see this picture.

## Phylogenetic Analysis

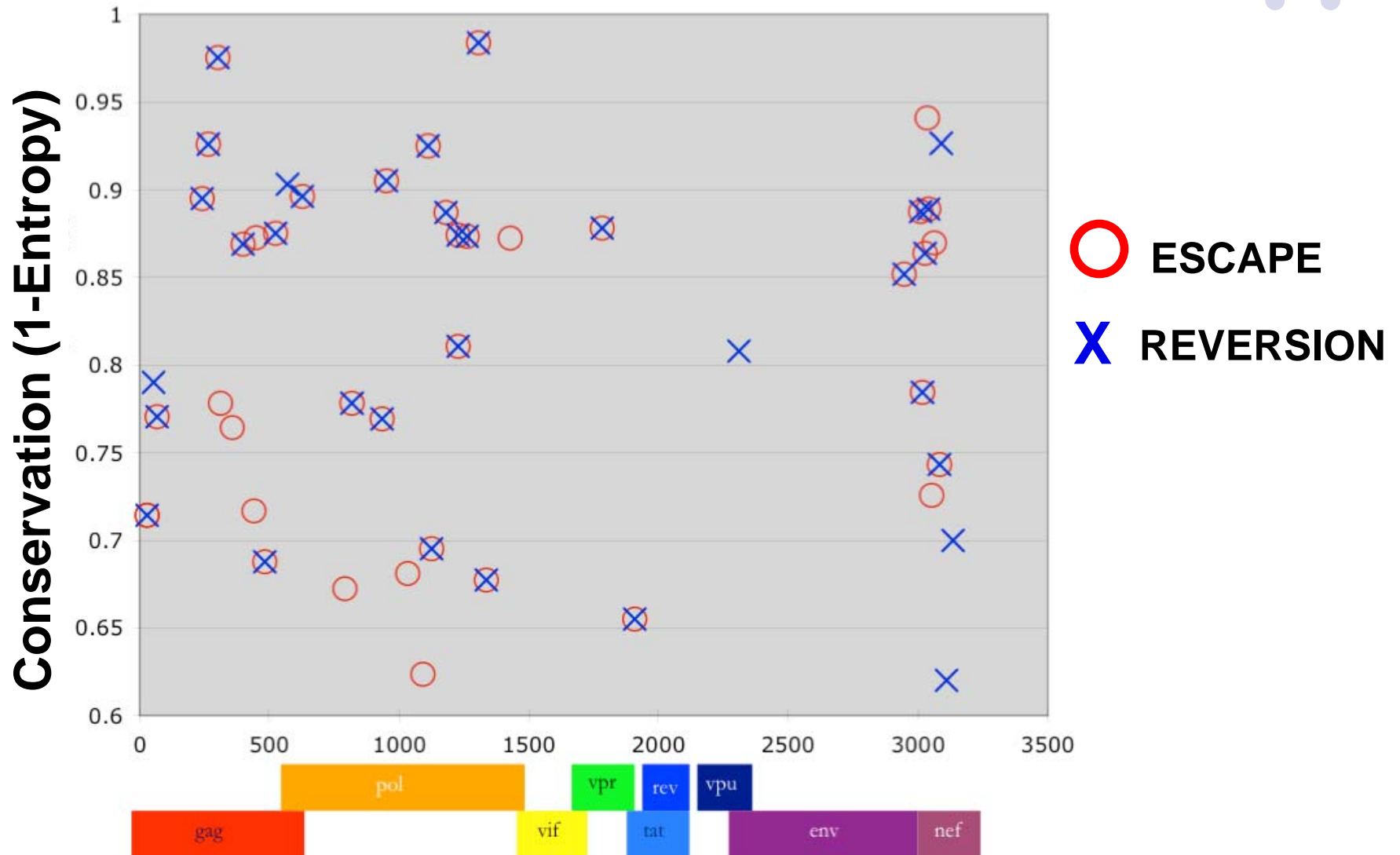
## HLA-associated Polymorphisms (CTL escapes)



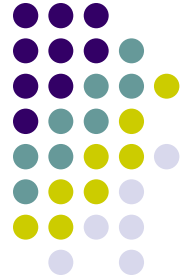
# Do HLA associations cluster at specific regions within the genome?



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



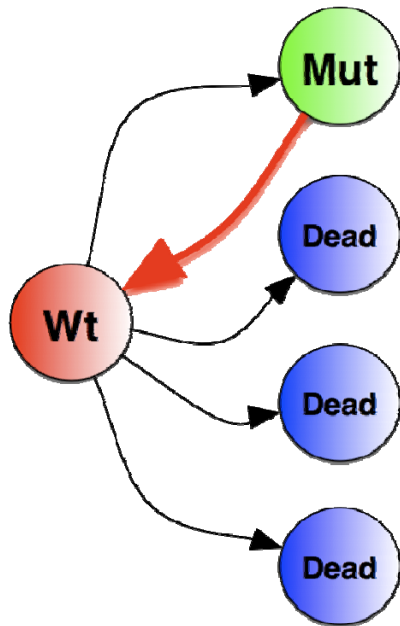




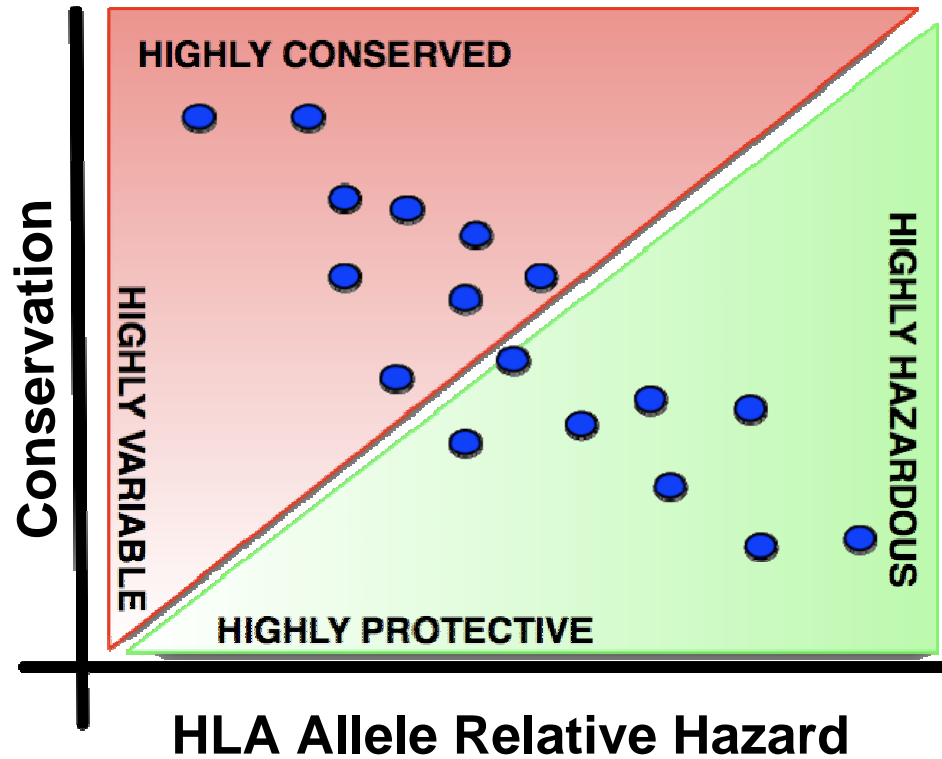
# Analysis

QuickTime™ and a TIFF (LZW) decompressor are needed to see this picture.

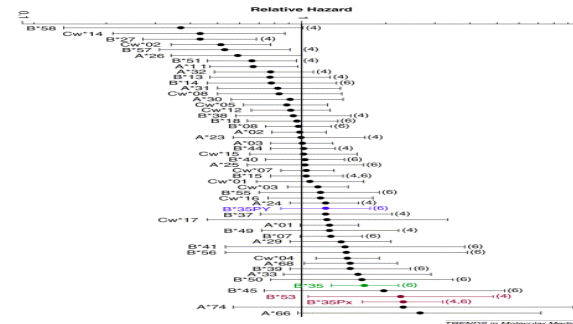
## HLA-associated polymorphisms



## Conservation



## HLA Allele Relative Hazard

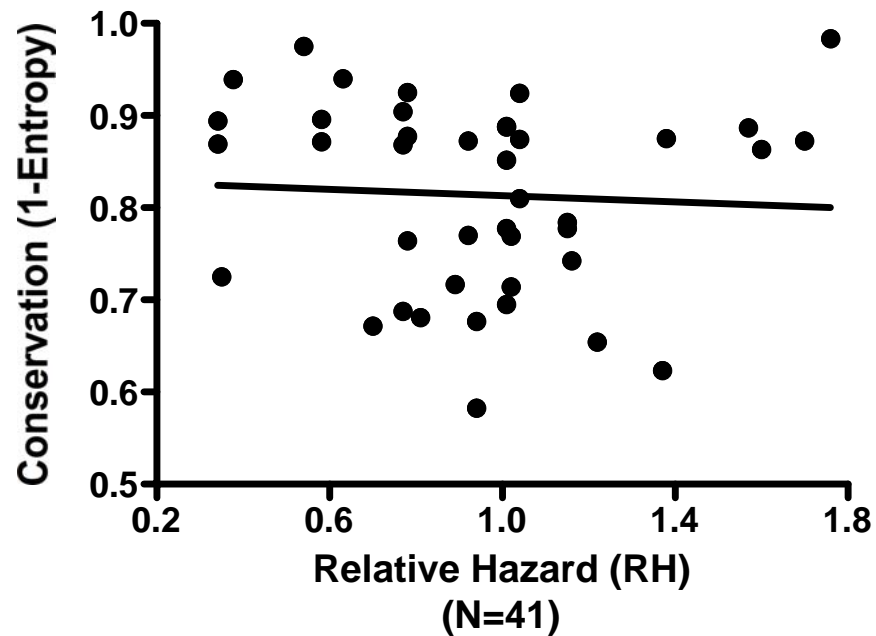


# Why are some CD8+ T cell responses more effective than others?

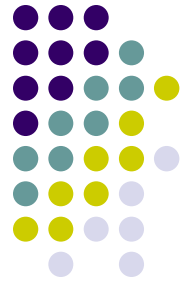


## 1) All HLA Associated Mutations

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

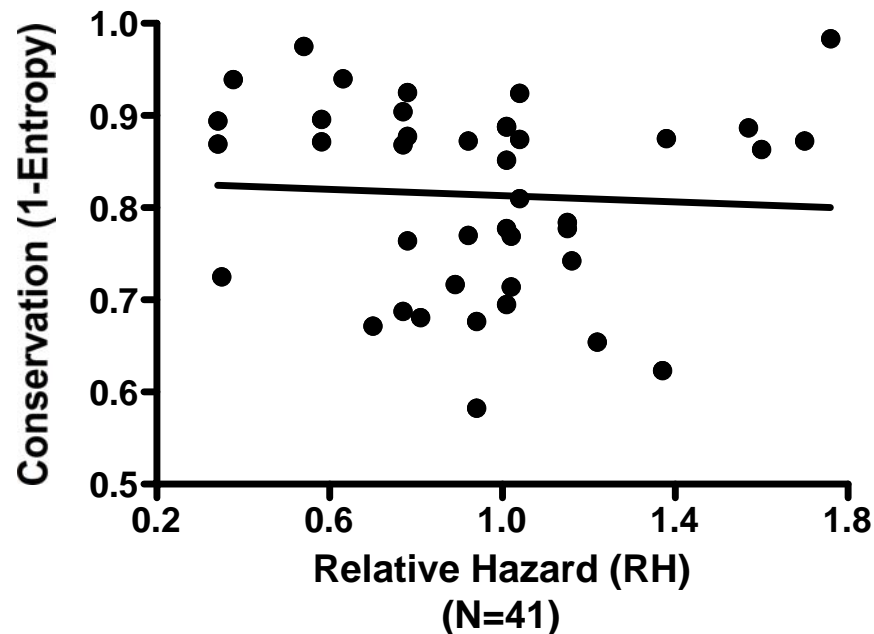


# Why are some CD8+ T cell responses more effective than others?



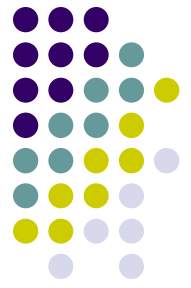
## 1) All HLA Associated Mutations

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



## 2) Acute phase responses (immunodominant)

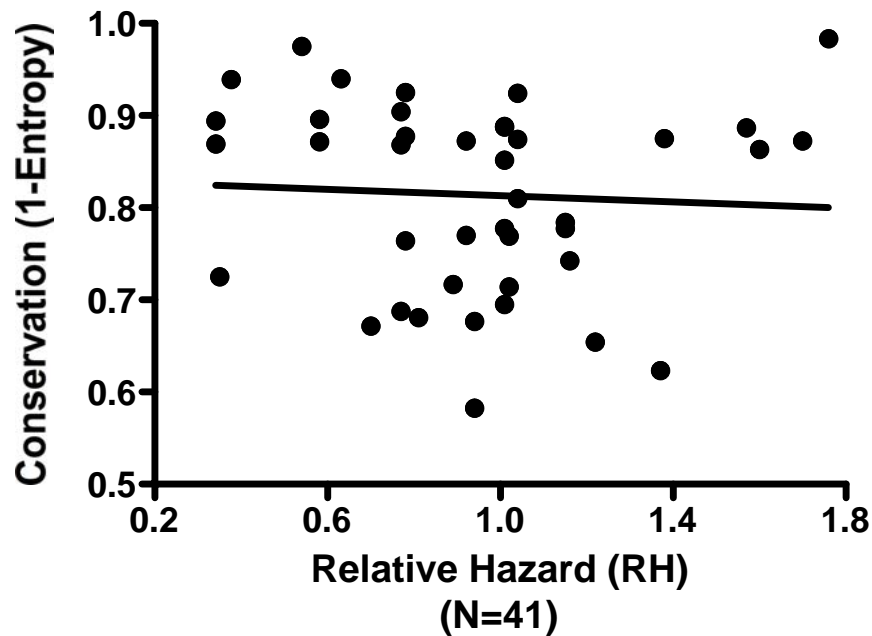
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are needed to see this picture.



# Why are some CD8<sup>T</sup> responses at conserved positions in early infection more effective than others?

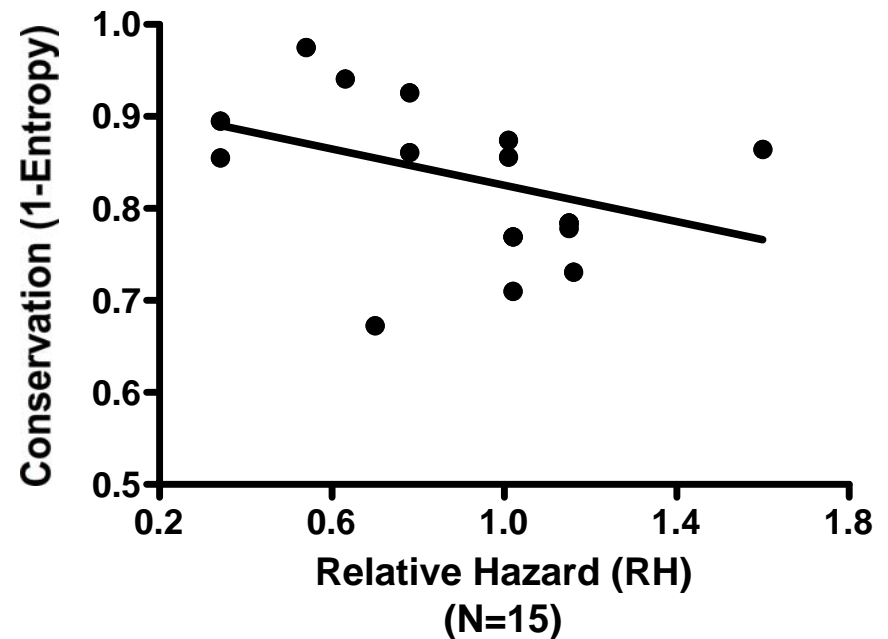
## 1) All HLA Associated Mutations

R=-0.1482; P=0.3553



## 2) Acute phase responses (immunodominant)

R=-0.5650; P=0.0282





# Why some escape mutations do not have detectable reversion?



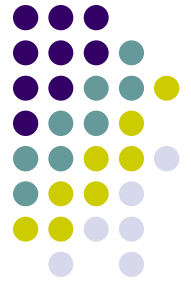
## Low Viral Fitness Cost

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## Compensatory Mutation

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TIFF (LZW) decompressor  
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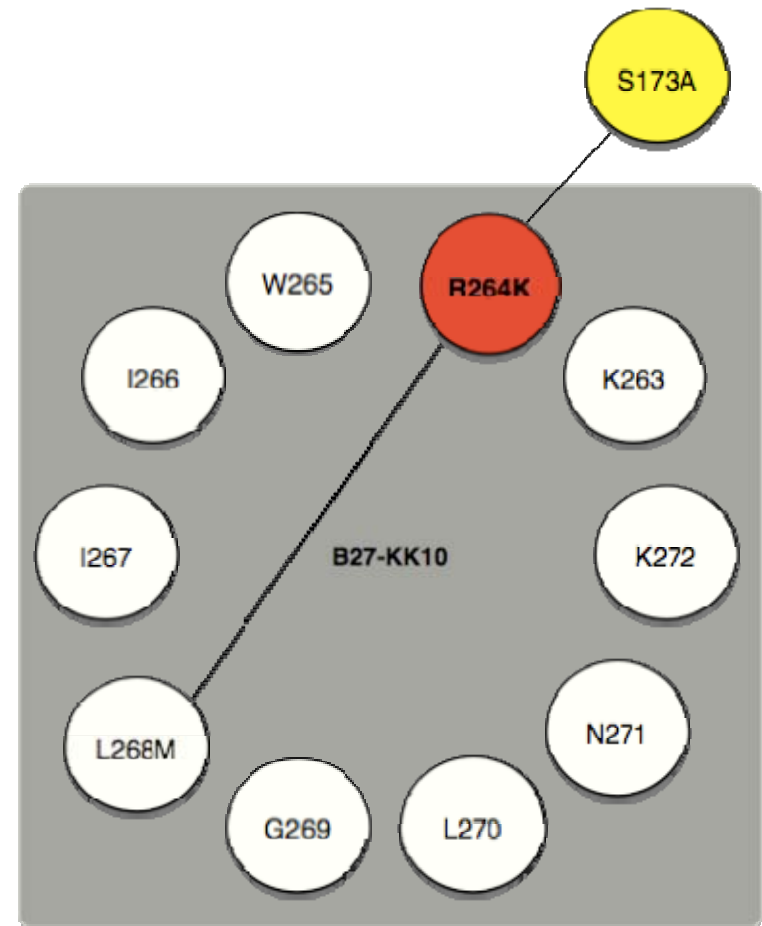
# Covariation Network for B27- KK10 R264K Escape Mutation



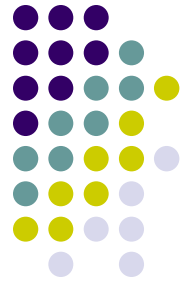
## KK10 Mutation Patterns in B27+ patients

	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?**



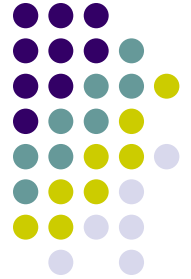


# Conclusions



- 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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Zabrina Brumme

Chanson Brumme

Galit Alter

Christian Brander

Marcus Altfeld

Bruce Walker

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David Heckerman

Jonathan Carlson

## NCI

Mary Carrington

**And all the patients**

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The Bill & Melinda Gates  
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