

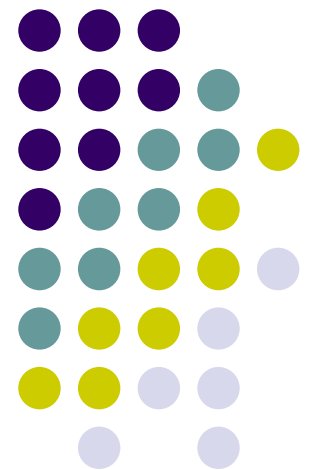
Protective HLA Class I Alleles Select for Early Escape Mutations in Conserved Regions of HIV

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Massachusetts General Hospital

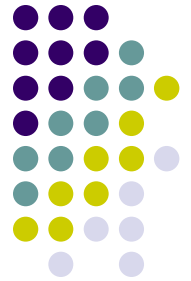
Boston, MA, USA

October 15, 2008

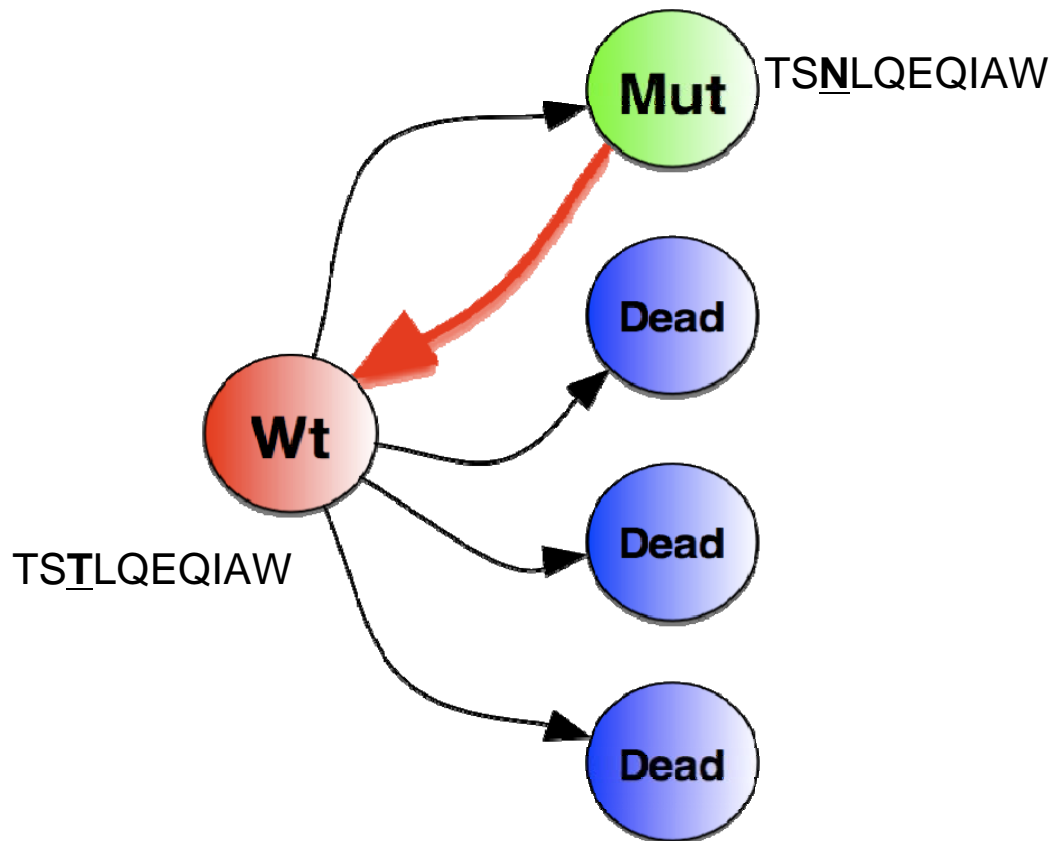


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Why are some CD8+ T cell responses more effective than others?



1) Fitness Cost



2) Immunodominance

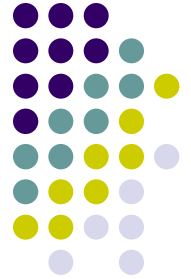
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Hypothesis



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

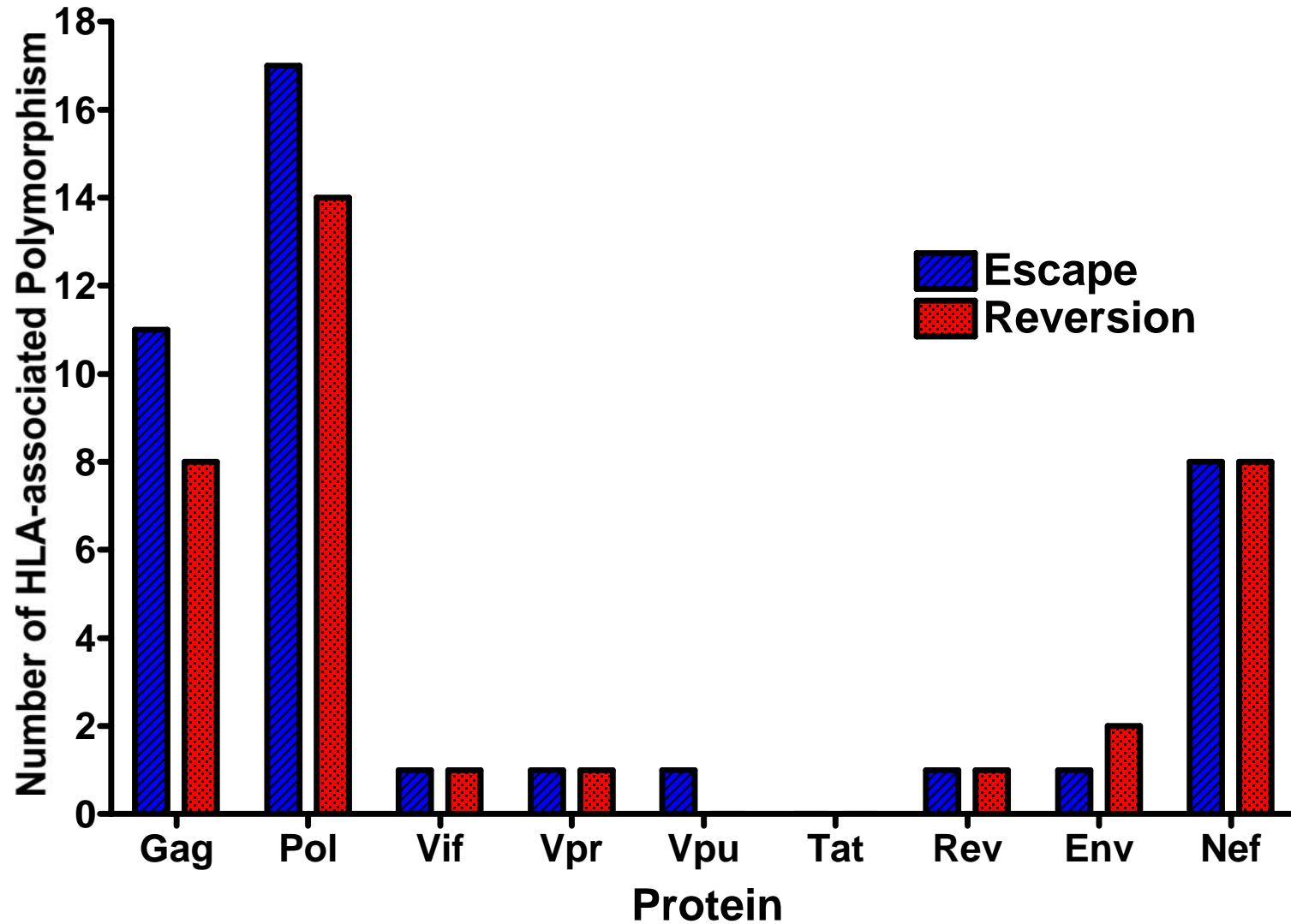
HLA-associated Polymorphisms (CTL escapes)

HLA Associated Mutations Across HIV

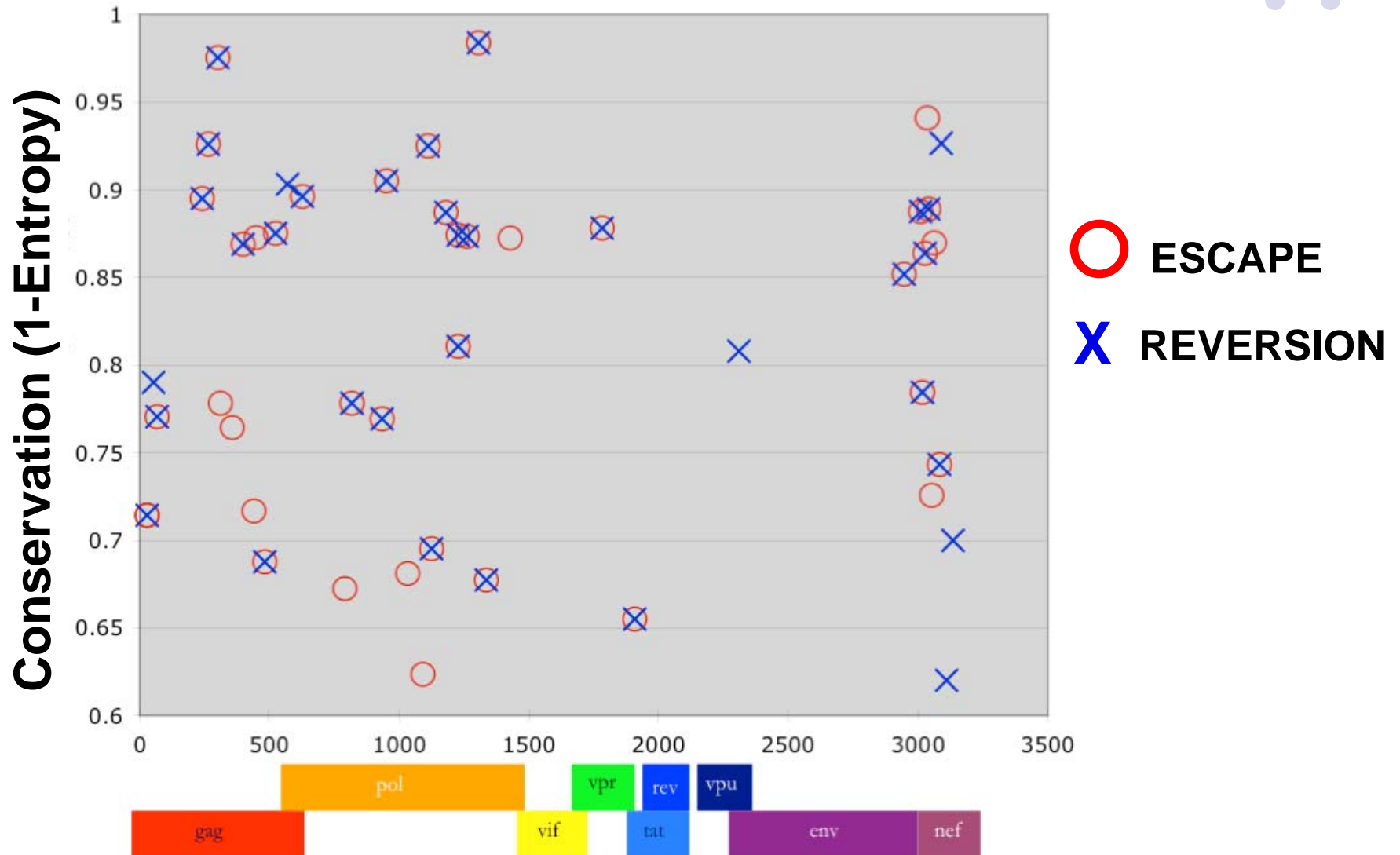


M G A R A S V L S G G E L D R W E K I R L R P G G K **K** K Y K L K H I V W A S R E 40
 A3- K I R L R P G G K **K**
 L E R F A V N P G L L E T **S** E G C R Q I L G Q L Q P S L Q T G S E E L R S L Y N 80
 C04- G C R Q I L G Q L
 T V A T L Y C V H Q R I E I K D T K E A L D K I E E E Q N K S K K K A Q Q A A A 120
 D T G H S N Q V S Q N Y P I V A G T T S **T** L Q E Q I G W M T N
 B57- T S **I** L Q E Q I G W
 E K A F S P E V I P M F S A L **N**
 L K E T I N E E A A E W D R V H P V H A G P I A P G Q M R E P R G S D I A G T T 240
 B57- T
 S **T** L Q E Q I G W M T N N P P I P V G E I Y K **R** W I I L G L N K I V R M Y S P T 280
 S **I** L Q E Q I G W B27- K **R** W I I L G L N K
 S I L D I R Q G P K E P F R D Y V D R F Y K T L R A E Q A S Q E V K N W M T E T 320
 B14- D R F Y K T L R A E
 B45- A E Q A S Q E V K N W
 L L V Q N A N P D C K T I L K G E I Y K **R** W I I L G L N K I V
 B27- K **R** W I I L G L N K
 R V L A E A M S Q V T N S A T **K**
 T A R N C R A P R K K G C W K
 T A R N C
 Y K G R P G N F L Q S R P E P T A P P E E S F R S G V E T T T P P Q K Q E P I D 480
 H K B15- S
 H K G R P G N F B40- Q E P I D
 K E L Y P L T S L R S L F G N D P S S Q \$ 500
 K E L Y

Do HLA associations cluster at specific regions within the genome?



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

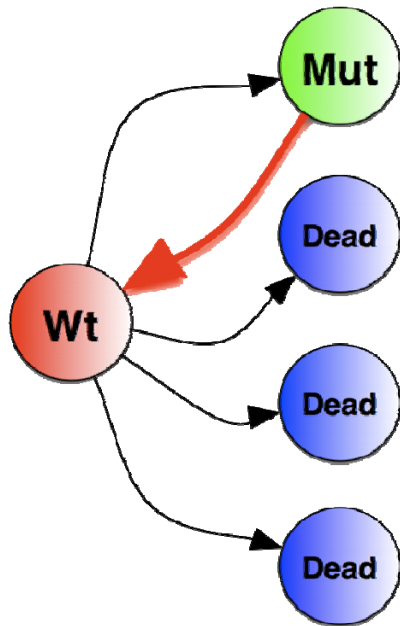




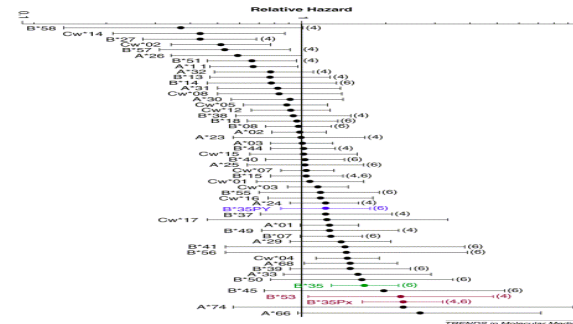
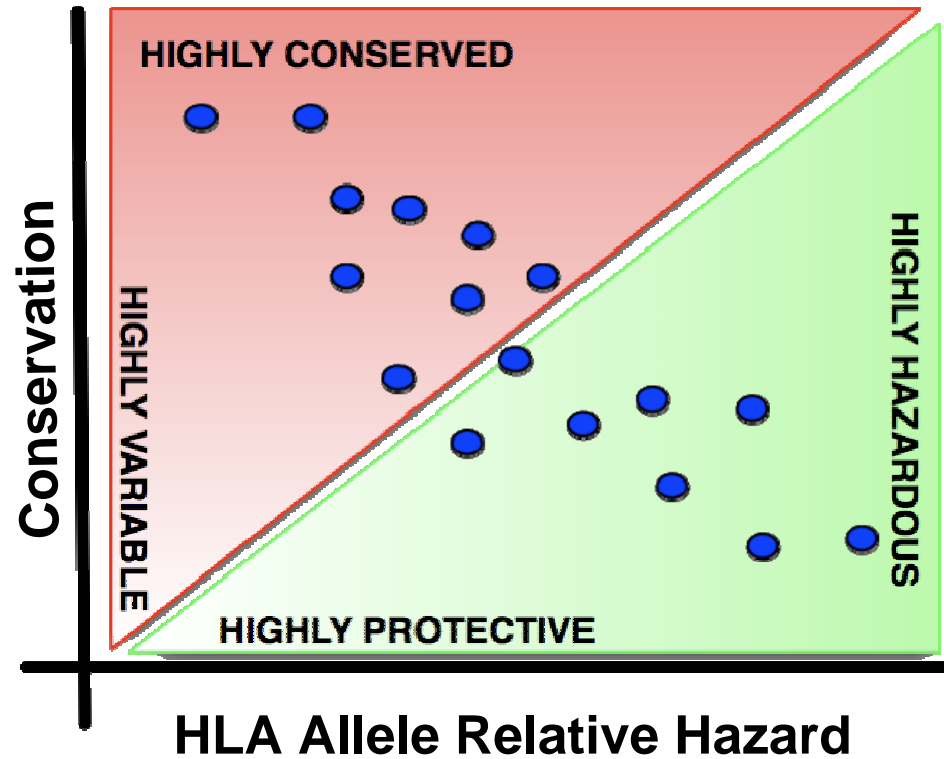
Analysis

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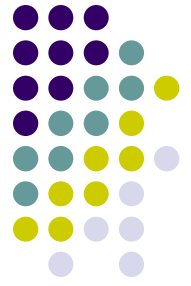
HLA-associated polymorphisms



Conservation

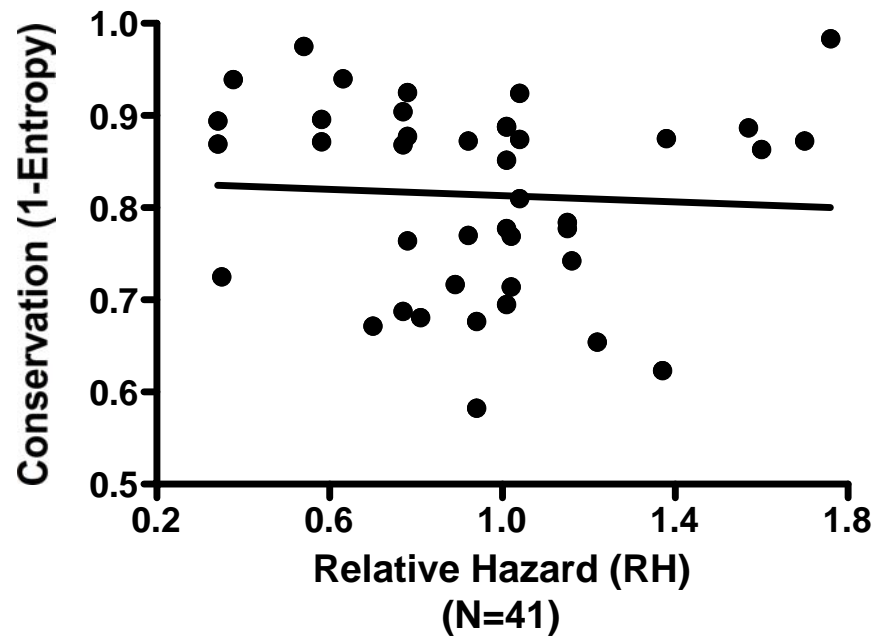


Why are some CD8+ T cell responses more effective than others?



1) All HLA Associated Mutations

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

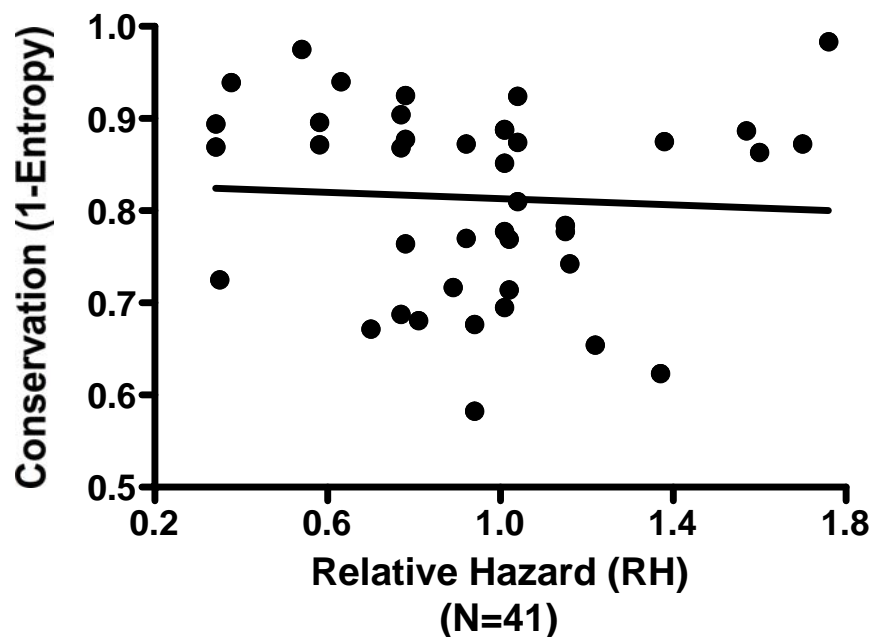


Why are some CD8+ T cell responses more effective than others?



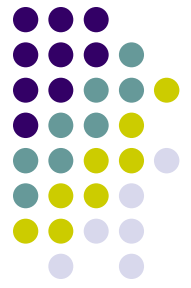
1) All HLA Associated Mutations

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



2) Acute phase responses (immunodominant)

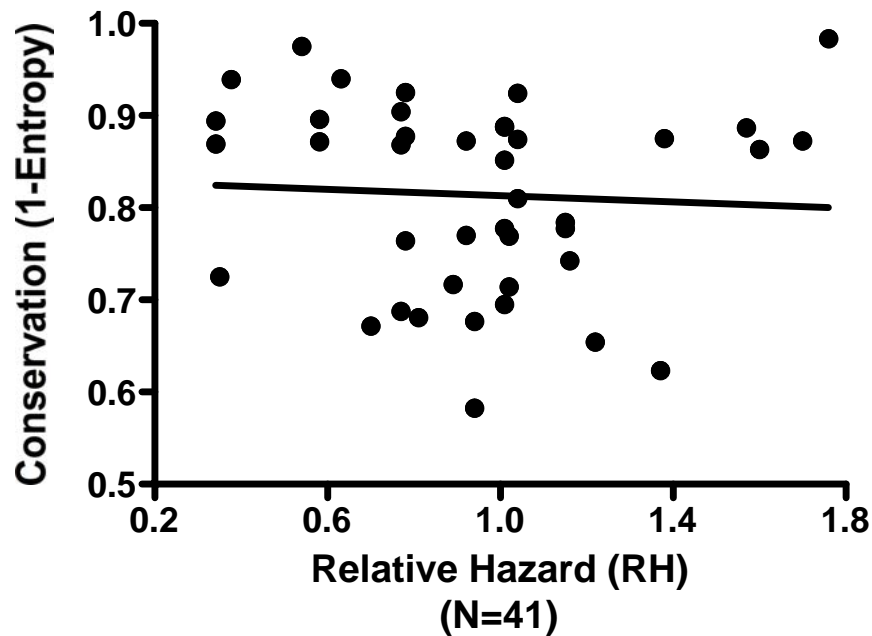
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Why are some CD8⁺T cell responses at conserved positions in early infection more effective than others?

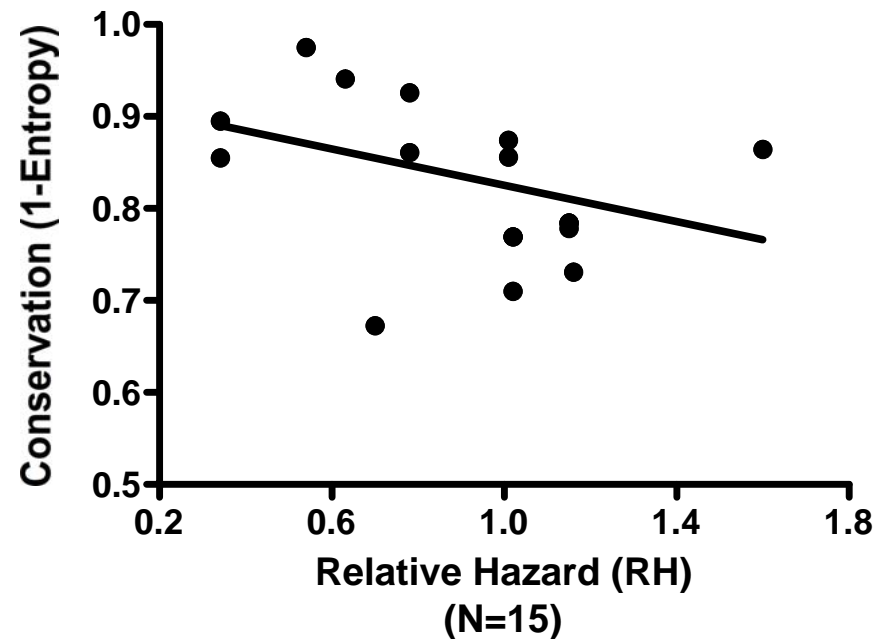
1) All HLA Associated Mutations

R=-0.1482; P=0.3553

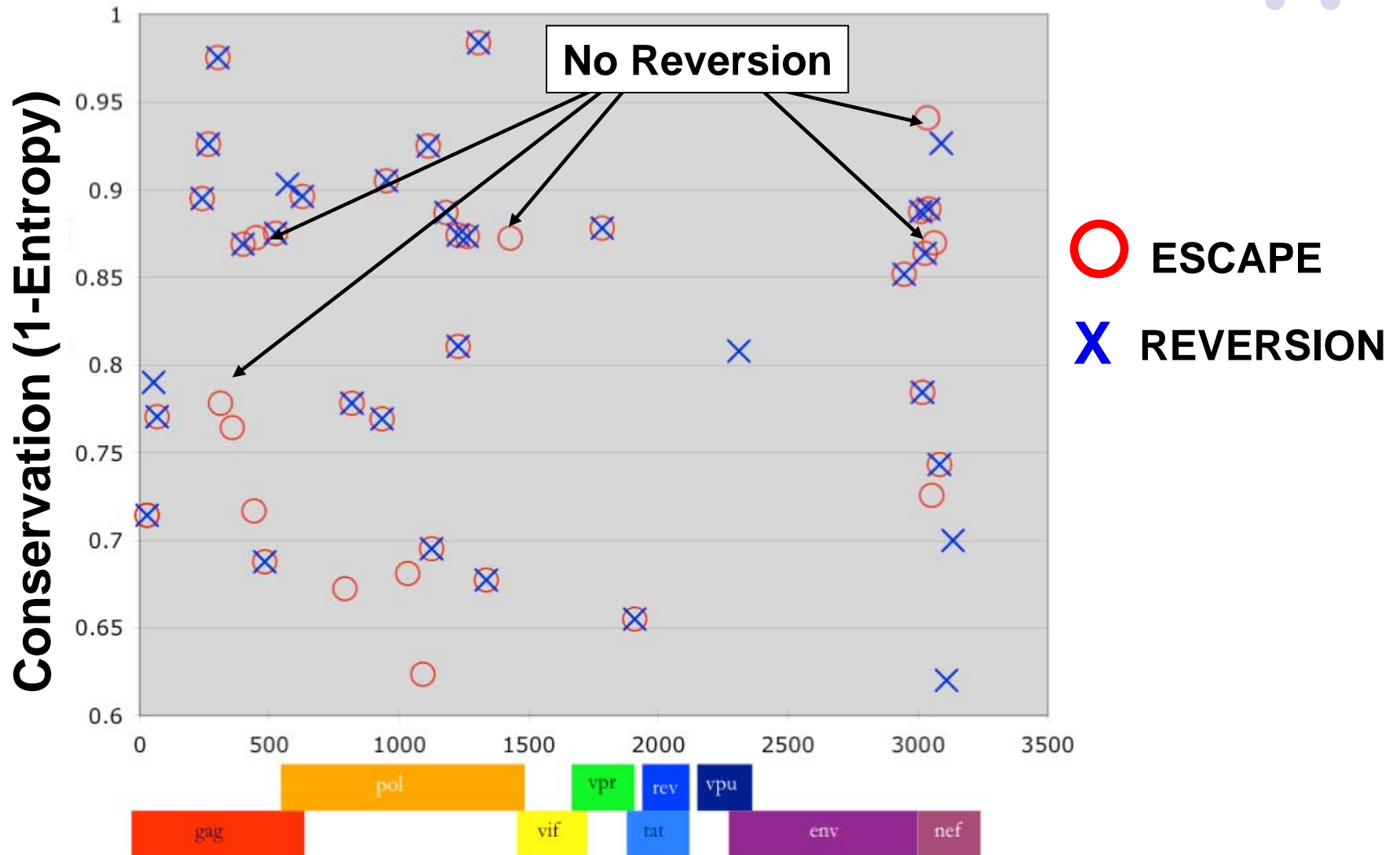


2) Acute phase responses (immunodominant)

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?



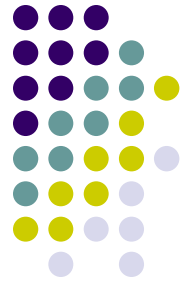
Low Viral Fitness Cost

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Compensatory Mutation

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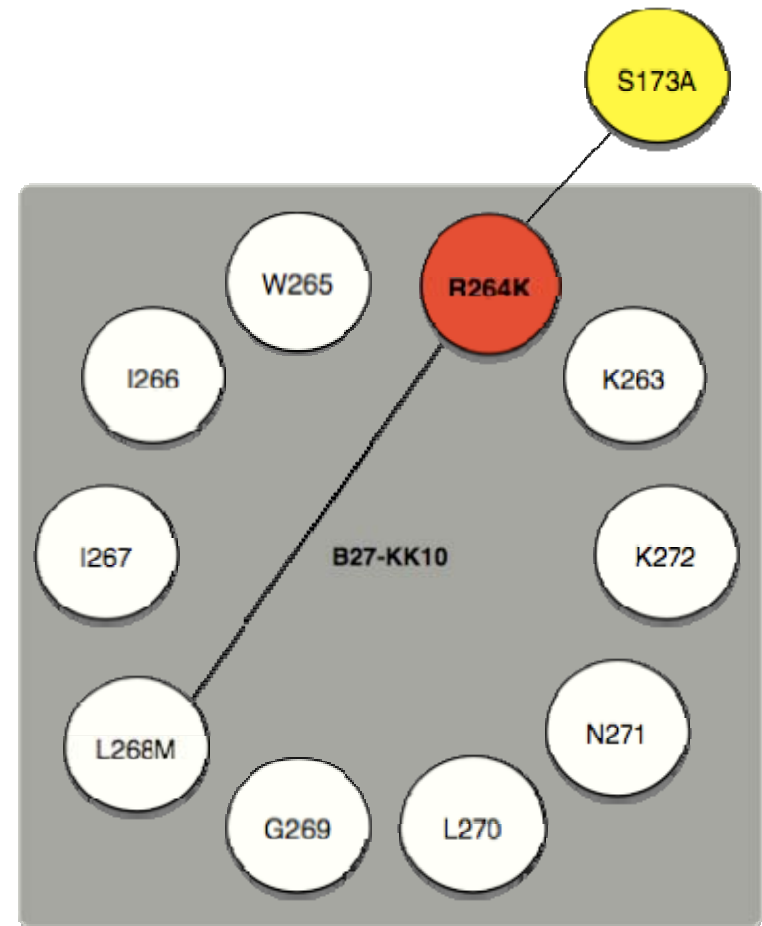
Covariation Network for B27- KK10 R264K Escape Mutation



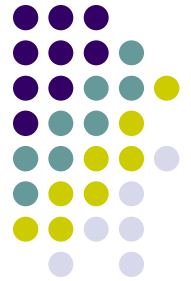
KK10 Mutation Patterns in B27+ patients

	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

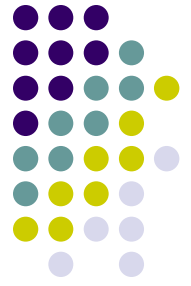
Computational Prediction



Why some escape mutations do not have detectable reversions?

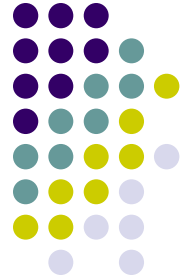


Conclusions



- 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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Zabrina Brumme

Chanson Brumme

Galit Alter

Christian Brander

Marcus Altfeld

Bruce Walker

Microsoft

David Heckerman

Jonathan Carlson

NCI

Mary Carrington

And all the patients

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