Prof Pran Nath Chhuttani RAE 2025

Padma Bhushan Prof P.N. CHHUTTANI
(1915 – 1996)

- One of the Founders of PGIMER, Chandigarh
- Longest serving Director (1969-78)
- Recipient of several awards: Dr BC Roy award

Dr PN Chhuttani oration started
by NAMS in 1999
to promote Tropical Medicine
and Communicable Diseases

Recognition of academic excellence
In the field of
Tropical Medicine and
Communicable Diseases

The Big Three

Tuberculosis/Lep
Malaria
HIV/AIDS

How Does The Host Immunity Variation Influence Communicable Disease Expression ?

Prof Narinder K Mehra

Former Dean and National Chair, AIIMS New Delhi

Vice President (Intl. affairs)
Indian National Science Academy

Hon Emeritus Scientist, ICMR

President, Indian Soc Histocompatibility & Immunogenetics
narin.mehra@gmail.com

NAMS Apr 2026

Three Infectious Diseases

Leprosy : *M. leprae* infection

- Elimination of Leprosy as a public health problem globally was achieved in 2005 **(<1 per 10,000).** Latest goal released by NLEP, Govt of India is to eliminate leprosy at all levels by 2027
- Disease still common in India, Brazil and Indonesia. The 2025 Prevalence rate in India is **0.57 per 10,000 population**. In Mar 2021, 79,898 pts were under MDT therapy across India.
- Despite COVID-19 disruption of health services, 65,147 new cases were identified. Rate of visible deformities was 1.1 per million population.

Tuberculosis : *M.Tb* infection

- An estimated global total of 10.7 million cases of TB in 2024, equivalent to **134** per 100,000 population, an increase of 4.5% from 2020 (10.1 million) : *SE Asia (largest burden of 25% globally, of which India alone contributes 45%), Africa (23%), Western Pacific (18%), Americas (2.9%), Europe (2.2%).*
- India's TB incidence for 2022 is **199** per 100,000 population, down 18% from **237**, baseline year 2015. The TB mortality also showed a similar decline: **28** per 100,000 in 2015 to **23** in 2022.

AIDS: HIV-1 infection

- An estimated 39 million (33.1-45.7 million) people are living globally with HIV at the end of 2022
- 1.3 million acquired HIV in 2022 and this number has reduced by 38% since 2010, Deaths have reduced by 51% in the same period. 69% fewer deaths in 2022 from the peak in 2004.
- Most pts are able to maintain suppressed viral loads because of the very effective anti-viral therapy

The Multifactorial etiology of Infectious Diseases

Variability of the pathogen
Phenotype of the host
Genetic variability of the host

Important Genetic Factors that Influence Host Immunity to mycobacterial and viral infections

Host Genetic Factors Control Immune Response to infectious diseases

Human MHC
Human Leukocyte Antigens
HLA Alleles
A*11:01, B*15:03, B*46:01, DRB!:!5:01

Toll Like Receptors
e.g. TLR7 variants

Cytokine Gene Polymorphism and Chemokines
e.g. IL-1, IL-6, CXCR-6 variants

Interferons
e.g. IFNAR1 and IFNAR2 variants

The immune system remains redundant if the foreign peptide is not presented to it formally by the HLA molecule

- Ag presentation
- MHC is the *'Master Regulator'*

My story *Started with studies to understand Immunology of Leprosy*

10-12M cases of Leprosy worldwide, of which 5-7M in India alone

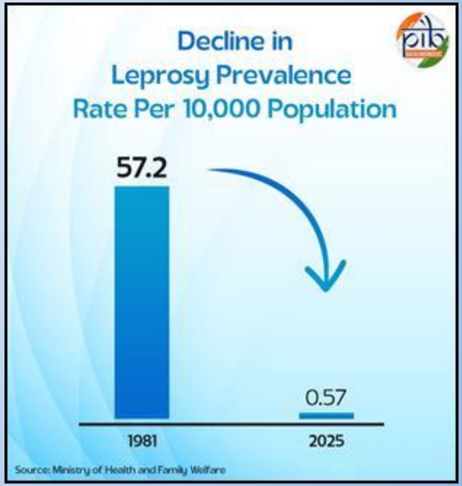
Early 70s at AIIMS

"Immunology of Leprosy in the Experimental Mouse Model"

- *Thymectomy*
- *Total body irradiation*
- *Bone marrow reconstitution*
- *M. leprae inoculation*

Baruj Benacerraf
Nobel Prize

Derrick Brewerton
1924-2021



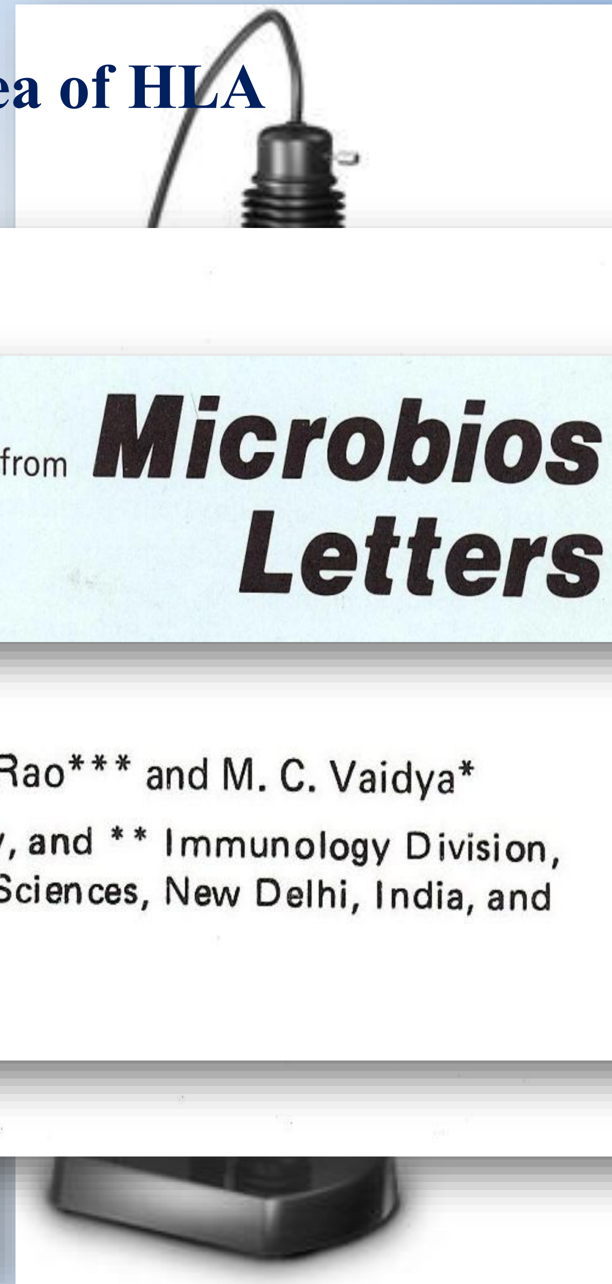
A few landmark discoveries of the time

1972: Baruj Benacerraf discovers Ir genes
1973: Derrick Brewerton showed strong association of HLA-B27 gene with AS

1974: Could there be a similar association with Leprosy?
GMLF in Wardha : disease highly prevalent, every village, every home had a case

My first publications in the area of HLA

1974 – Our good old Monocular



Tissue Antigens (1975), 5, 85–87
Published by Munksgaard, Copenhagen, Denmark

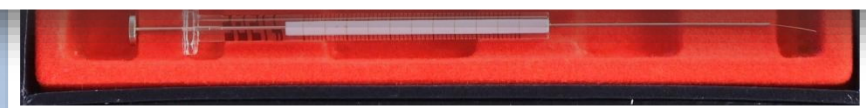
Reprinted from **Microbios Letters**

HLA antigens and leprosy

N. K. Mehra*, A. Dasgupta**, S. K. Ghei*, M. S. Nilakanta Rao*** and M. C. Vaidya*

*Cellular Immunology Laboratory, Department of Anatomy, and ** Immunology Division, Department of Microbiology, All India Institute of Medical Sciences, New Delhi, India, and ***Gandhi Memorial Leprosy Foundation, Wardha, India

New Delhi, India



HLA in Infections – became our focus

Human Leukocyte Antigen (HLA)-Linked Control of Susceptibility to Pulmonary Tuberculosis and Association with HLA-DR Types

S. P. N. Singh, N. K. Mehra, H. B. Dingley, J. N. Pande, and M. C. Vaidya

From the Departments of Anatomy (Cellular Immunology Laboratory) and Medicine, All-India Institute of Medical Sciences, New Delhi; and Lala Ram Sarup Tuberculosis Hospital, Mehrauli, India

The Journal of Infectious Diseases 1983;148(4):676

W. VAN EDE
VAN ROOD

Department c
*Department

Chapter 6

Susceptibility Factors in Pulmonary Tuberculosis: Special Emphasis on HLA

NK Mehra, R Rajalingam

The Journal of Infectious Diseases 1996;173:669-76

Polymerase Chain Reaction–Based Sequence-Specific Oligonucleotide Hybridization Analysis of HLA Class II Antigens in Pulmonary Tuberculosis: Relevance to Chemotherapy and Disease Severity

R. Rajalingam, N. K. Mehra, R. C. Jain, V. P. Myneedu, and J. N. Pande

Departments of Histocompatibility and Immunogenetics and of Medicine, All India Institute of Medical Sciences, and Lala Ram Sarup Institute of Tuberculosis and Allied Diseases, New Delhi, India

HLA in Infections – became our focus

LETTERS

nature genetics
Vol. 39 | No. 4 | April 2007

for the Development of Hepatotoxicity during

Stepwise replication identifies a low-producing lymphotoxin-α allele as a major risk factor for early-onset leprosy

Alexandre Alcaïs[1,
Meenakshi Singh[5],
Ngyuen Thu Huo

04;189:805-11

Distribution of CCR2 polymorphism in HIV-1-infected and healthy subjects in North India

G. Kaur,* P. Singh,
& N. K. Mehra*

Departments of [1]Trans

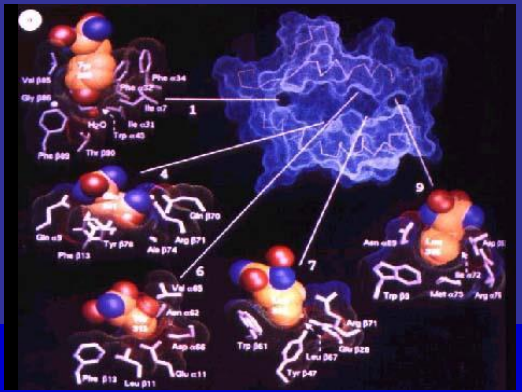
Immunogenetic basis of HIV-1 infection, transmission and disease progression

Paras Singh, Gurvinder Kaur, Gaurav Sharma, Narinder K. Mehra*

Department of Transplant Immunology and Immunogenetics, All India Institute of Medical Sciences, Ansari Nagar, New Delhi 110029, India

Vaccine 2008;26:2966-80

How HLA diversity determines disease susceptibility ?



Hypothesis

"Susceptibility to a disease is determined by the <u>overall binding capability</u> of an HLA molecule with peptides"

↓

Number of epitopes bound and avidity of binding

↓

'<u>efficient</u>' versus '<u>inefficient</u>' presenters

Autoimmune disease

Greater overall self antigen derived peptide binding & presenting capability of HLA molecule

↓

greater susceptibility

Infectious disease

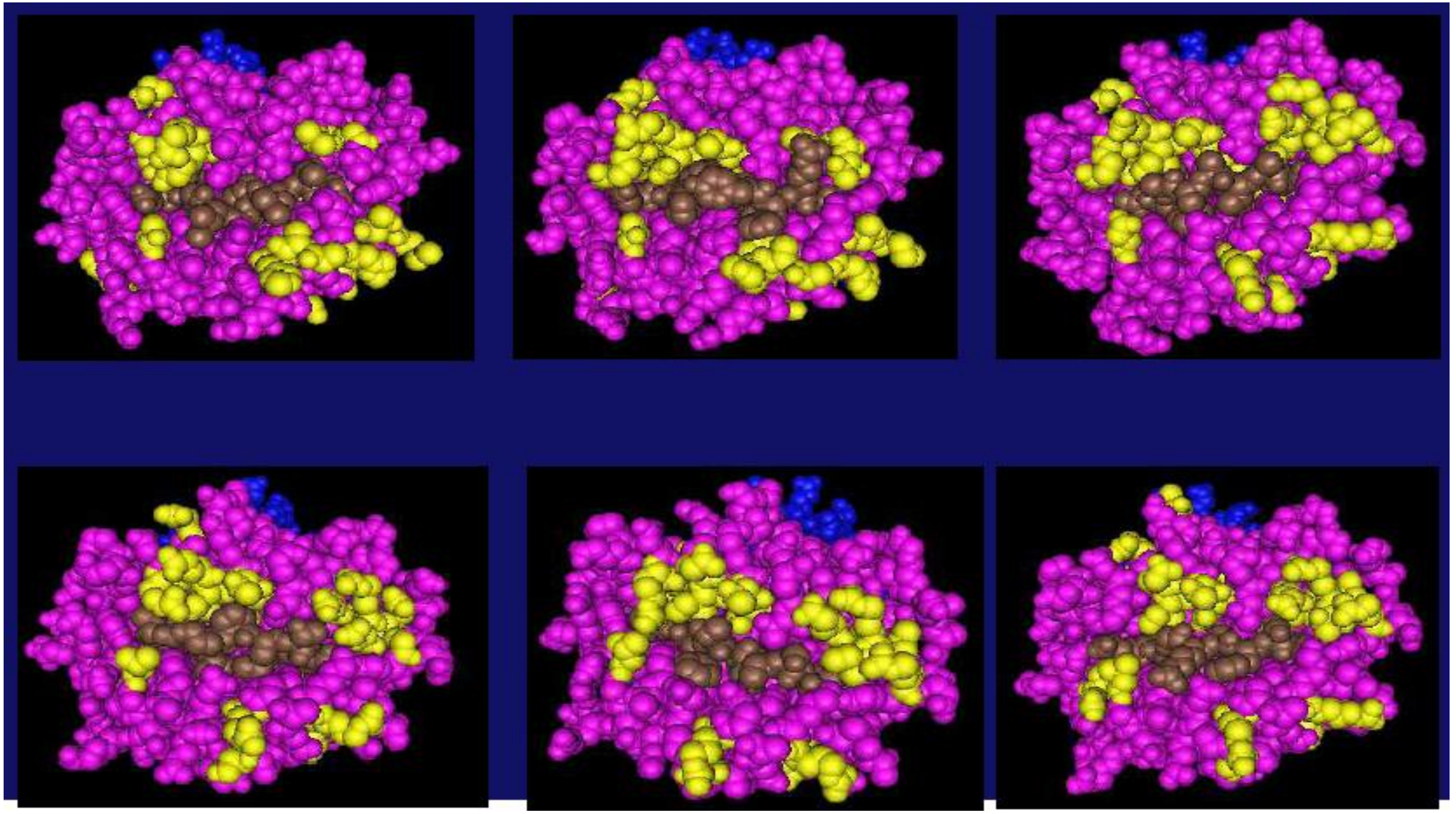
Lower overall foreign peptide binding & presenting capability of the HLA molecule

↓

greater susceptibility

Every HLA allele presents a different peptide

HLA Class II Molecule : Pockets **1, 4,** 6, 7, 9



HLA polymorphism has been shown to affect transcription or protein function

1999: A Landmark Study in Leprosy

Arginine at Positions 13 or 70-71 in Pocket 4 of HLA-DRB1 Alleles Is Associated with Susceptibility to Tuberculoid Leprosy

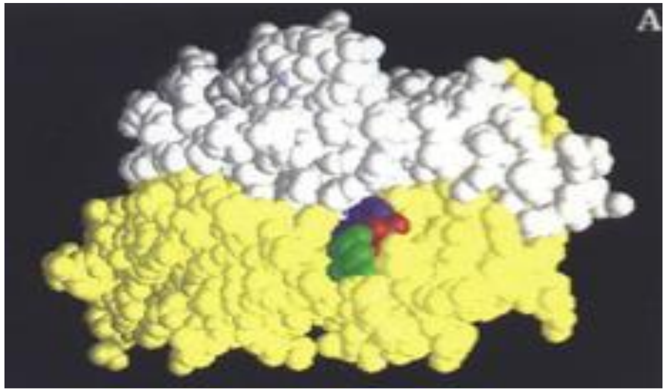
By Loukia Zerva,* Bojana Cizman,* Navinder K. Mehra,‡ Souresh K. Alahari,§ Ramachandran Murali,* Chester M. Zmijewski,* Malek Kamoun,* and Dimitri S. Monos*

*From the *Department of Pathology and Laboratory Medicine, University of Pennsylvania Medical Center, Philadelphia, Pennsylvania 19104; ‡All India Institute of Medical Sciences, Histocompatibility and Immunogenetics Department, New Delhi-110029, India; and the §Department of Pharmacology, The University of North Carolina at Chapel Hill, Chapel Hill, North Carolina 27599*

J. Exp. Med. © The Rockefeller University Press • 0022-1007/96/03/829/08 $2.00
Volume 183 March 1996 829–836

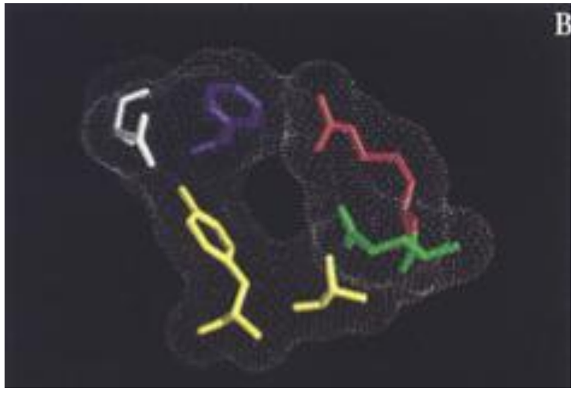
Table 2. *Association of DRB1 Alleles with TL*

Alleles	Patients		Controls		rr	Corrected p
	n = 54	%	n = 44	%		
DRB1*15	37	69	14	32	4.7	0.0063[*]
DR6 positives	n = 16	%	n = 12	%		
DRB1*1301	4	25	8	67	0.17	0.033[‡]
DRB1*1404	12	75	4	33	6	0.033
DR2 negatives	n = 15	%	n = 27	%		
DRB1*1404	6	40	1	4	7.1	0.034[§]



	9	10	11	12	13	16	32	37	47	57	60	67	70	71	74	
DRB1*1301	E	Y	S	T	S	H	H	N	Y	D	Y	I	D	E	A	Negative Association among DR6 positive individuals.
DRB1*1404	-	-	-	-	G	Y	-	F	H	A	H	L	R	R	E	Positive Association among DR6 positive individuals.
DRB1*1501 or 1502	W	Q	P	K	R	-	Y	S	-	-	-	-	Q	A	-	Positive Association

Figure 1. Residues that differ among DR alleles that are positively and negatively associated with TL. Amino acid residues are indicated that are different between DRB1*1301 and DRB1*1404 or between DRB1*1301 and DRB1*15 allele. Residues at positions 13, 37, 70, and 71 were different in both comparisons. DRB1*1301 ($S^{13}N^{37}D^{70}E^{71}$) → DRB1*1404 ($G^{13}F^{37}R^{70}R^{71}$) or → DRB1*15 ($R^{13}S^{37}Q^{70}A^{71}$).

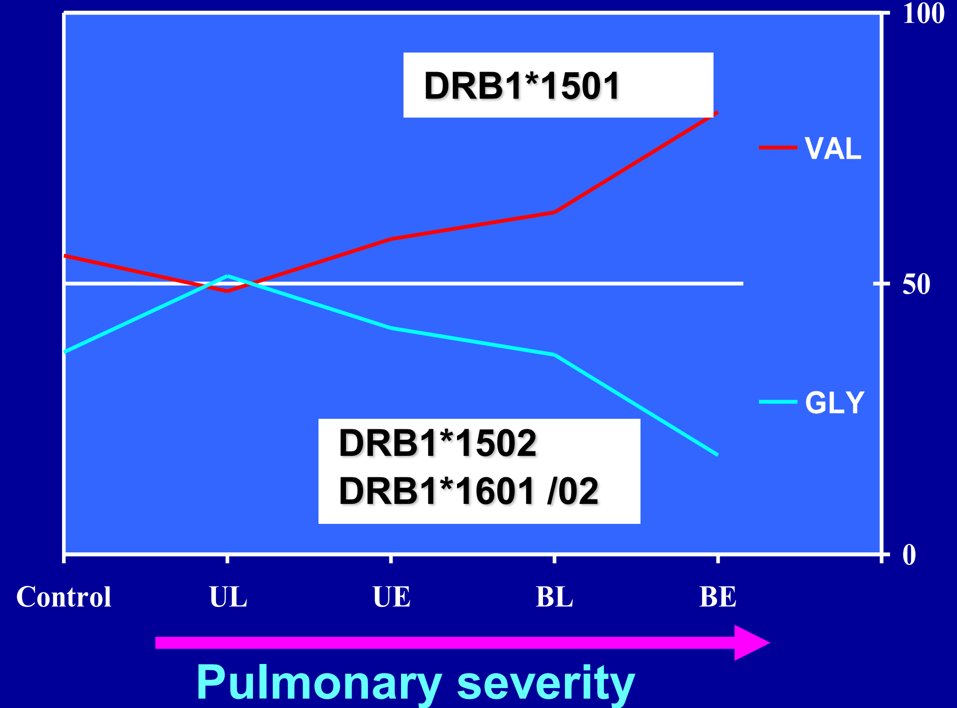


Polymorphic amino acid residues in the peptide binding pockets of HLA-DRB1 alleles

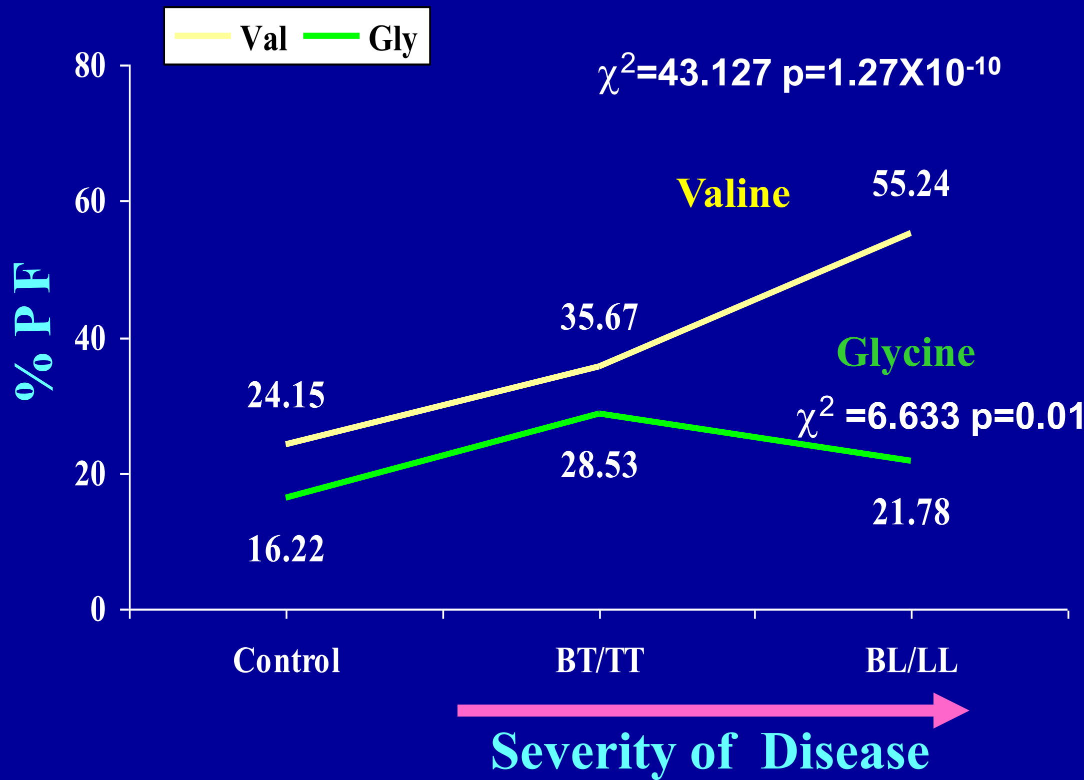
	Amino acid residues in the DRb chains																		
	Pocket 1				Pocket 4						Pocket 7					Pocket 9		Pocket 6	
DRB1	85	86	89	90	13	26	70	71	74	78	28	47	61	67	71	9	57	11	13
*0101	V	G	F	T	F	L	Q	R	A	Y	E	Y	W	L	R	W	D	L	F
*15011	V	V	F	T	R	F	Q	A	A	Y	D	F	W	I	A	W	D	P	R
*15021	V	G	F	T	R	F	Q	A	A	Y	D	F	W	I	A	W	D	P	R
*1602	V	G	F	T	R	F	D	R	A	Y	D	Y	W	L	R	W	D	P	R
*0301	V	V	F	T	S	Y	Q	K	R	Y	D	F	W	L	K	E	D	S	S
*0302	V	G	F	T	S	F	Q	K	R	Y	E	Y	W	L	K	E	D	S	S
*0401	V	G	F	T	H	F	Q	K	A	Y	D	Y	W	L	K	E	D	V	H
*0402	V	V	F	T	H	F	D	E	A	Y	D	Y	W	I	E	E	D	V	H
*0403	V	V	F	T	H	F	Q	R	E	Y	D	Y	W	L	R	E	D	V	H
*0404	V	V	F	T	H	F	Q	R	A	Y	D	Y	W	L	R	E	D	V	H
*0405	V	G	F	T	H	F	Q	R	A	Y	D	Y	W	L	R	E	S	V	H
*0406	V	V	F	T	H	F	Q	R	E	Y	D	Y	W	L	R	E	D	V	H
*0407	V	G	F	T	H	F	Q	R	E	Y	D	Y	W	L	R	E	D	V	H
*1101	V	G	F	T	S	F	D	R	A	Y	D	F	W	F	R	E	D	S	S
*1102	V	V	F	T	S	F	D	E	A	Y	D	F	W	I	E	E	D	S	S
*1104	V	V	F	T	S	F	D	R	A	Y	D	F	W	F	R	E	D	S	S
*1201	A	V	F	T	G	L	D	R	A	Y	E	F	W	I	R	E	V	S	G
*1202	A	V			G	L	D	R	A	Y	E	F	W	F	R	E	V	S	G
*1301	V	V	F	T	S	F	D	E	A	Y	D	F	W	I	E	E	D	S	S
*1302	V	G	F	T	S	F	D	E	A	Y	D	F	W	I	E	E	D	S	S
*1404	V	V	F	T	G	F	R	R	E	Y	D	Y	W	L	R	E	A	S	G
*1410	V	V	F	T	H	F	R	R	E	Y	D	Y	W	L	R	E	A	V	H
*0701	V	G	F	T	Y	F	D	R	Q	V	E	Y	W	I	R	W	V	G	Y
*0801	V	G	F	T	G	F	D	R	L	Y	D	Y	W	F	R	E	S	S	G
*0803	V	G	F	T	G	F	D	R	L	Y	D	Y	W	I	R	E	S	S	G
*0804	V	V	F	T	G	F	D	R	L	Y	D	Y	W	F	R	E	D	S	G
*0901	V	G	F	T	F	Y	R	R	E	V	H	Y	W	F	R	K	V	D	F
*1001	V	G	F	T	F	L	R	R	A	Y	E	Y	W	L	R	E	D	V	F

V/G dimorphism at $^{86}\beta$ of DRB1*15/16 alleles

Tuberculosis



Leprosy



NKM/ AIIMS

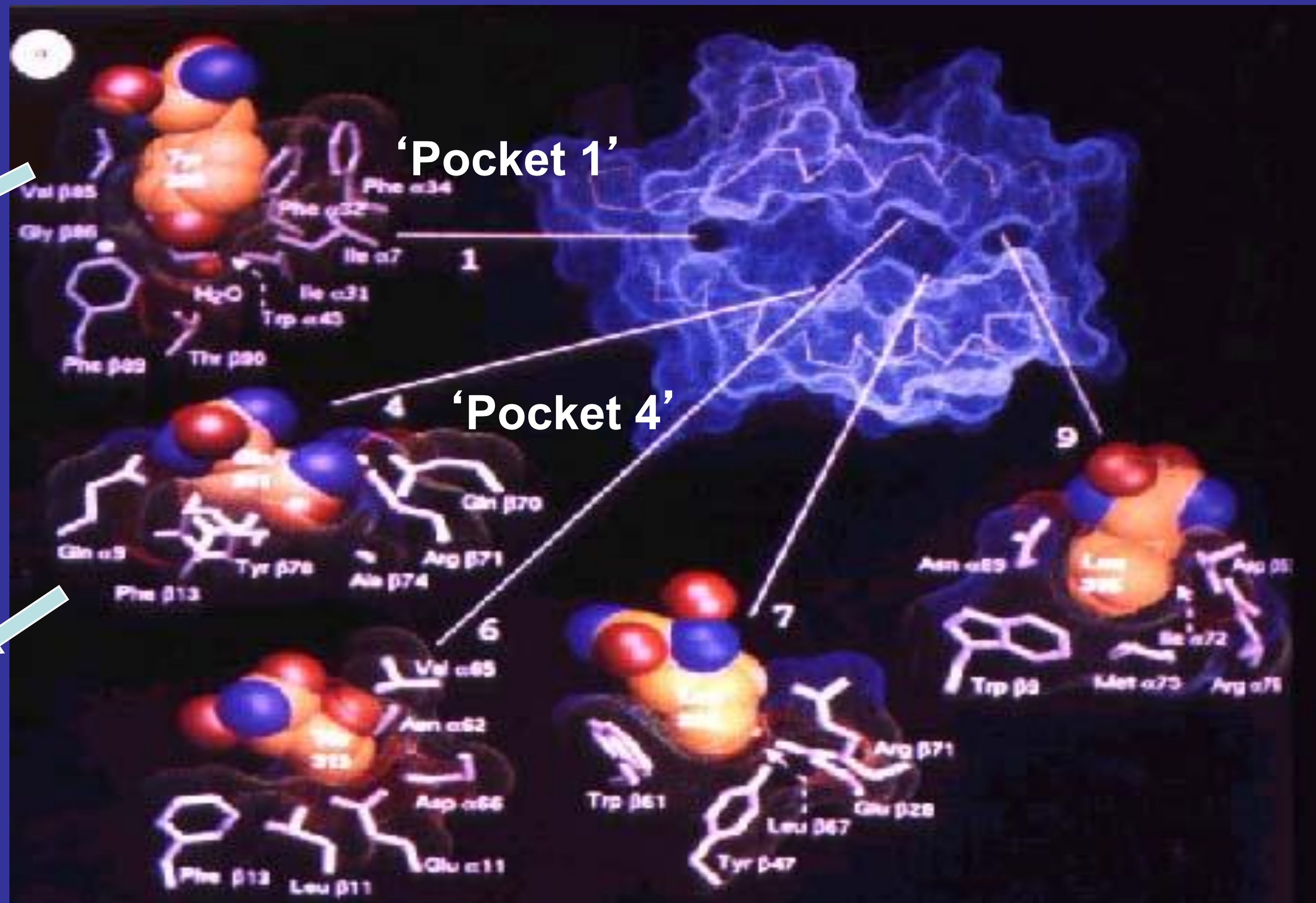
MHC peptide binding Motif

Mycobacterial Infections : *net charge residues*

Severity of disease

Valine Severe form

Glycine Mild form



Disease Susceptibility

Pos/Neu Leprosy

Neg/Neu PTB

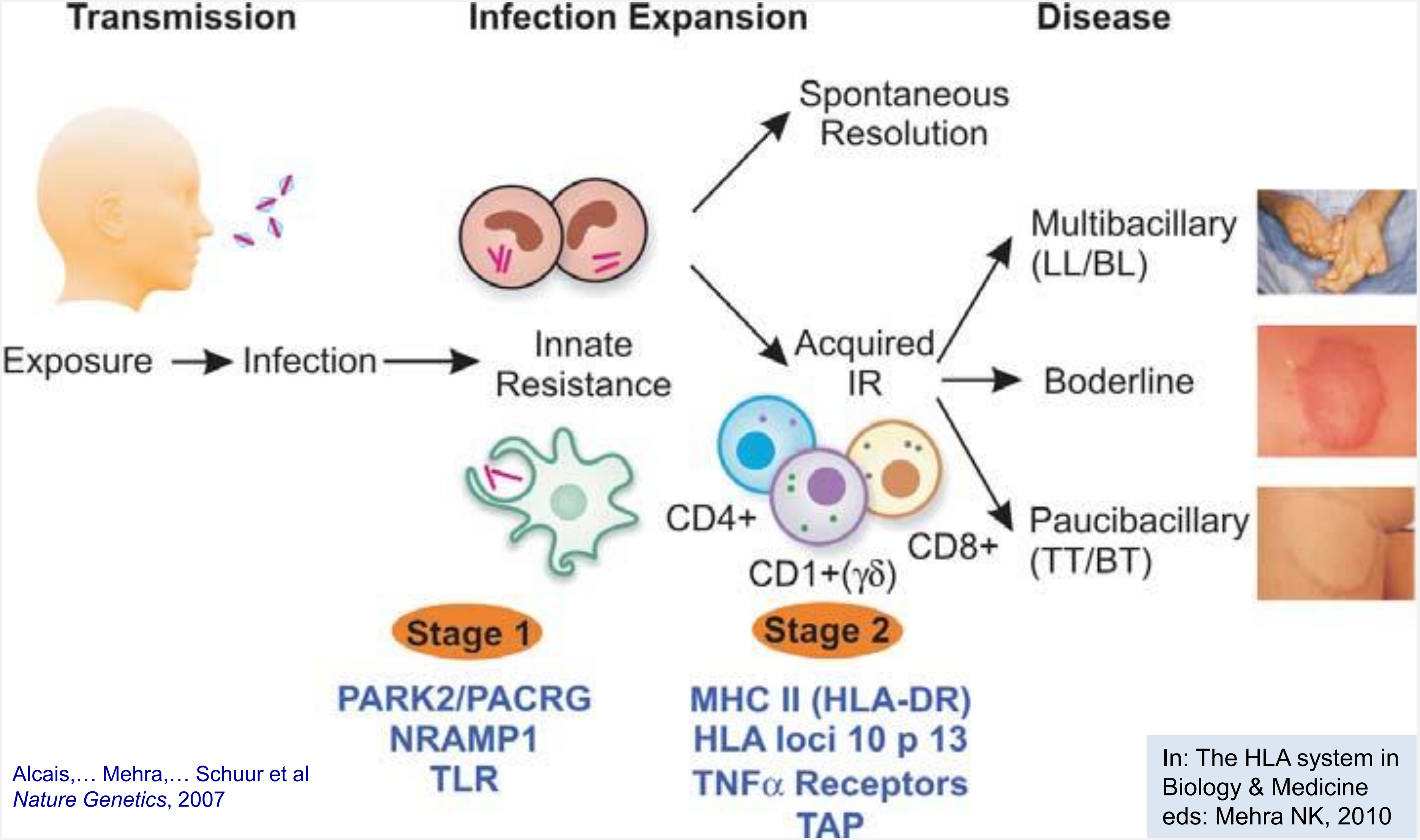
In: The HLA system in Biology & Medicine eds: Mehra NK, 2010

Zerva,Cizman,Mehra,… Monos et al *J Exp Med* 1996
Alcais,… Mehra,… Schuur et al *Nature Genetics*, 2007
J infec dis, 1979,1980,1983, 1996, 2004, 2006

Two stage model of genetic influence on human immunity in leprosy:

Stage 1: *genes influence development of leprosy per se*

Stage 2: *genes influence host immune response*

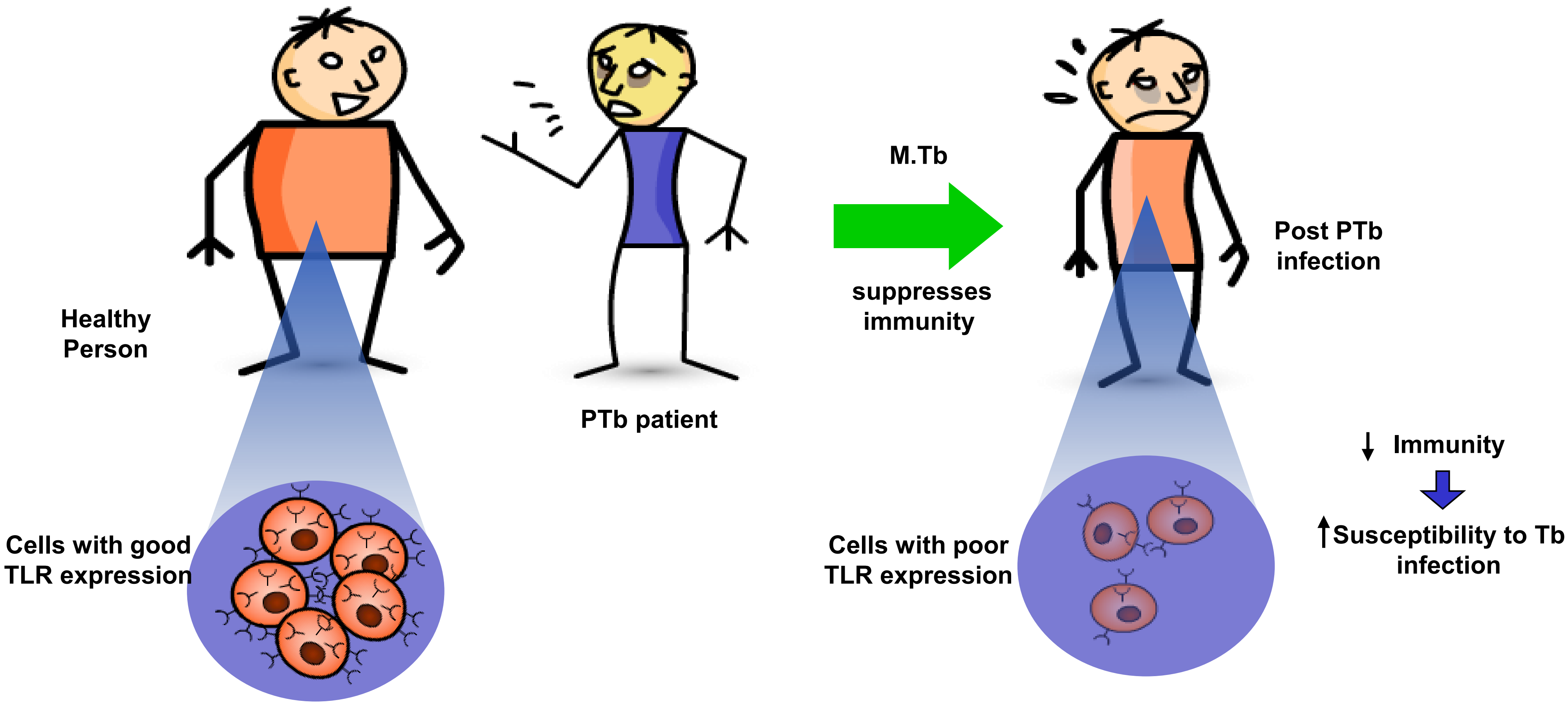


Alcais,… Mehra,… Schuur et al
Nature Genetics, 2007

In: The HLA system in Biology & Medicine
eds: Mehra NK, 2010

TLR Expression Studies

- Family of pattern recognition receptors that form a critical first line of defense in innate immunity system
- They detect conserved molecular patterns associated with pathogens (PAMPs) or cellular damage



This data indicates that there is a significant reduction of innate immunity after the M. tb infection

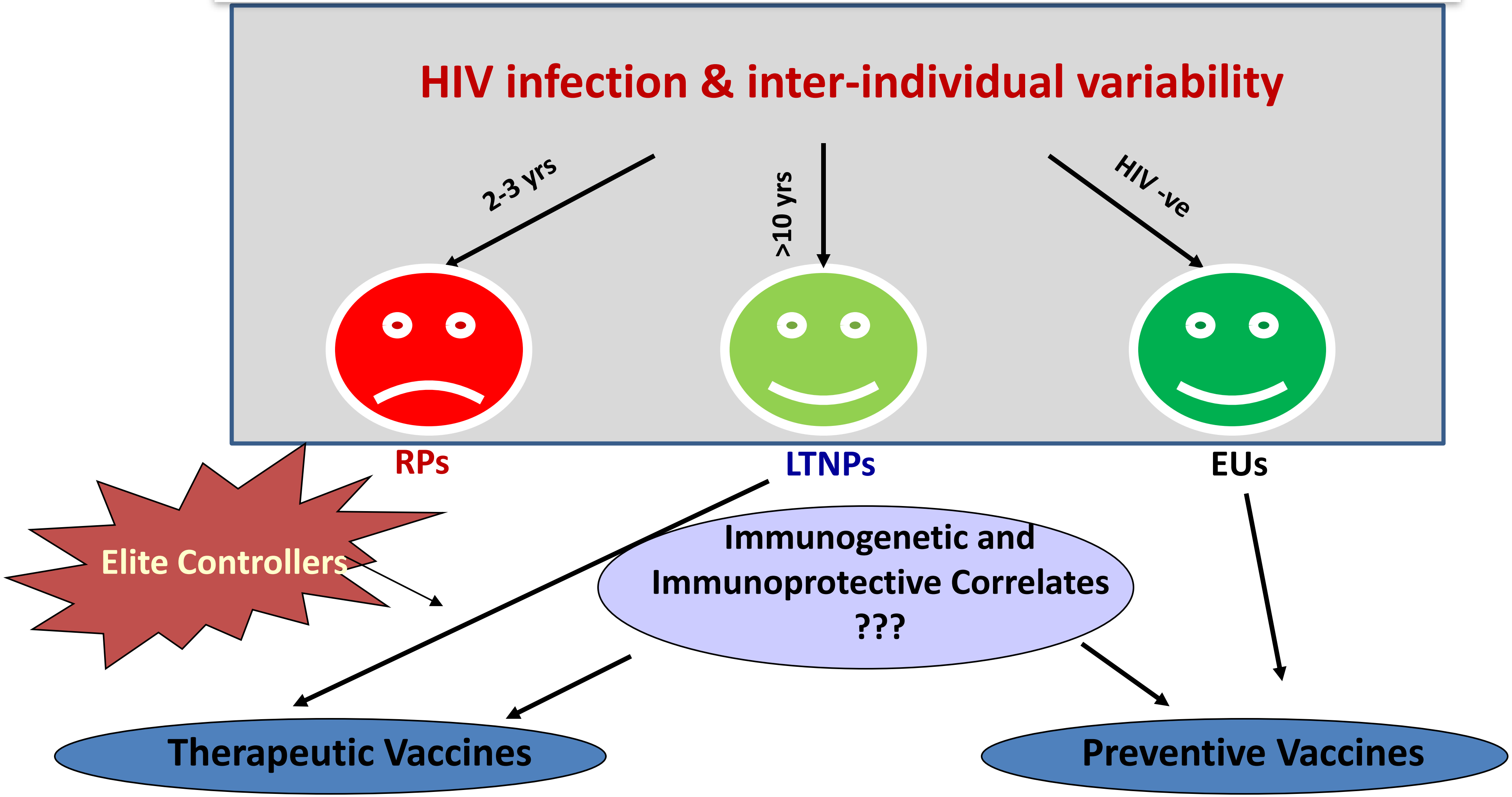
Which further Hampers the anti-tuberculosis adaptive immunity

Table 23.1: Leprosy and tuberculosis are multigenic diseases: Gene loci implicated in mycobacterial susceptibility have been grouped into (i) Those that control immune responsiveness (ii) Candidate genes that control susceptibility per se and (iii) Genome wide scan suggesting involvement of other genes

Genes/locus	*Chromosome location*	*Main function of protein encoded/ immune function of gene product(s)*	*Disease*	*References*
Gene controlling immune response				
MHC class II (DR2)	6p21.3	Immune response genes	TB, leprosy	7-15
Cytokine genes	On different chromosomes	Immune response genes	TB, leprosy	16
SLC11A1	2q35	Acquired antibacterial immunity (Divalent cation transporter)	TB and leprosy	17, 18
C4B	6p21.3	Opsonization and immune complex clearance	Leprosy	19
CTL4A	2q31-33	Negative regulator of T cell activation	Leprosy	20
Col3A	2q31-33	Extracellular matrix structural constituent	Leprosy	20
Candidate genes/marker Controlling Susceptibility				
HSPA1A	6p21.3	Heat shock protein	Leprosy	21
MICA	6p21.3	Augment T cell activation	Leprosy	22
CCL2	17q11.2-q12	Monocyte chemoattractant protein-1 chemokine	TB	23
P2X7	12q24	ATP receptor	TB	24
DC-SIGN	19p13.3	C-type lectin receptor on dendritic cells	TB	25
TAP2	6p21.3	Peptide translocation	TB, Leprosy	26
TNFα	6p21.3	Pleiotropic both innate and acquired immunity	Leprosy	18, 27
VDR	12q12-14	Suppression of inflammation	TB, Leprosy	15, 28
TLR2	4q32	Role in pathogen recognition and activation of innate immunity	TB, Leprosy	15, 29, 30
PARK2, PACRG	6q25	E3 polyubiquitin ligase	Leprosy	31, 32
Genome wide scan				
	10p13	-	Susceptibility to Leprosy	33
	20p12	-	Susceptibility to leprosy	34
	6q25, 10p13	-	Susceptibility and severity of leprosy	35
	17q11	-	Paucibacillary leprosy	36, 37

In: The HLA system in Biology & Medicine eds: Mehra NK, 2010

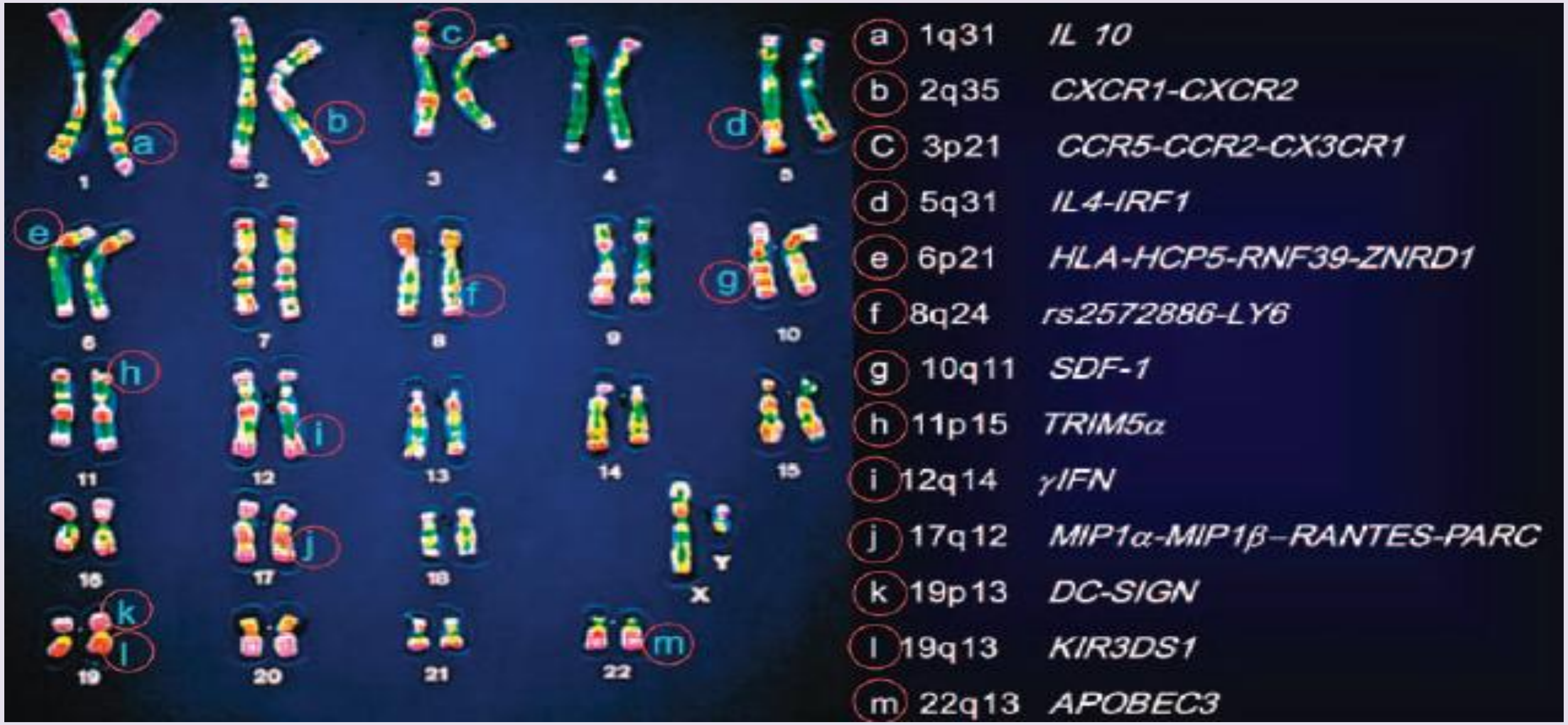
HIV: *Why Study Immunogenetic Basis ?*



Genetic variability influences susceptibility to HIV-1 infection, rate of disease progression, response to ART & may be IR to vaccination ?

Sharma G, Kaur G, Mehra N **2011 IJMR**

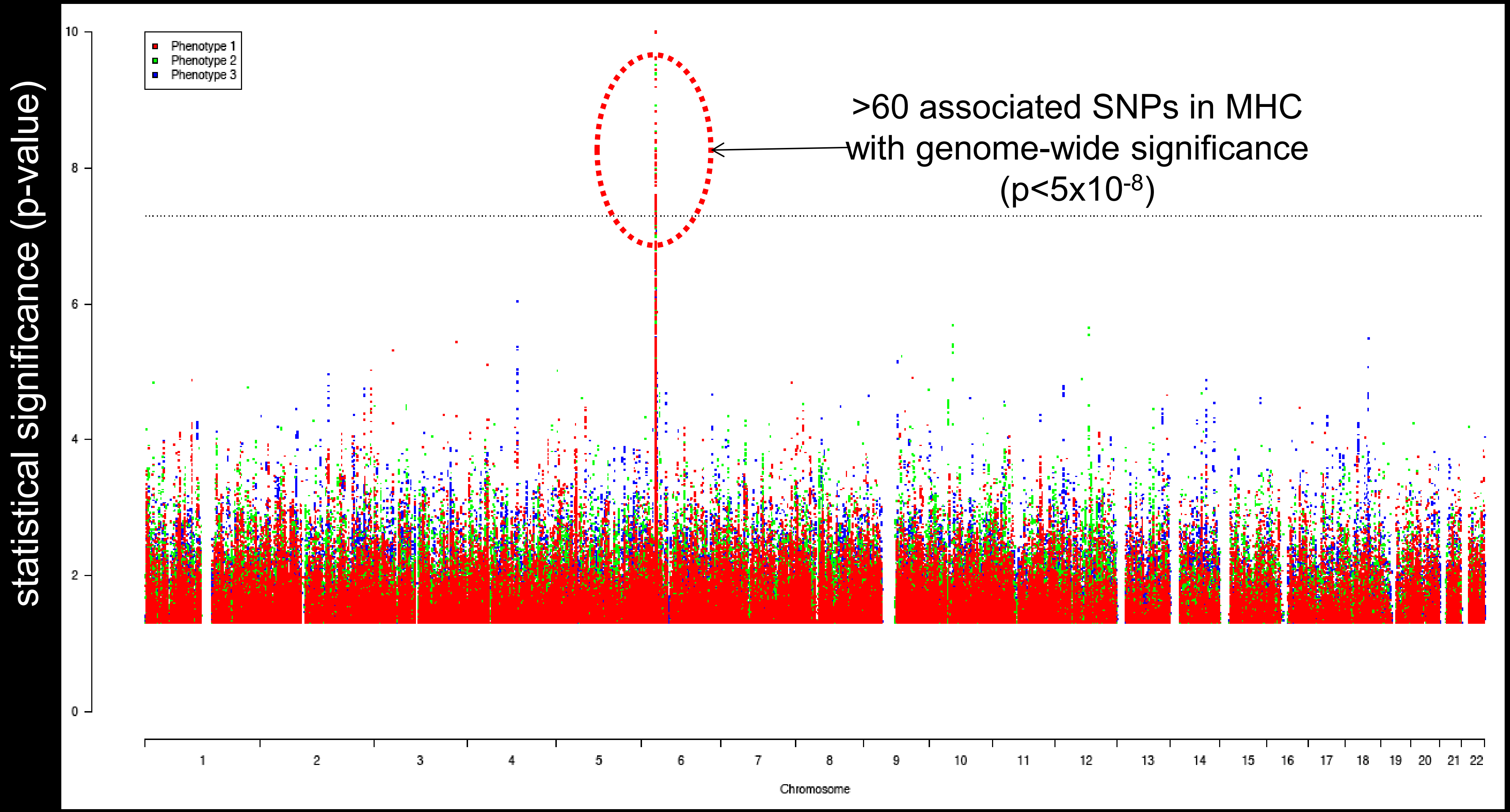
Host Genetic Variation and HIV Disease



Chemokines	Cytokines+ Receptors	HIV-1 Co-receptors	Immune Response	Others
SDF-1 MIP-1α MIP-1β RANTES	IL-10 IL-4-IRF1 γIFN CXCR1-CXCR2	CCR5–CCR2 DC–SIGN	HLA KIR	HCP5-RNF39-ZNRD1 rs2572886-LY6 TRIM5α APOBEC3G PARC

Kaur G, Mehra NK Tissue Antigens 2009

The MHC has the greatest genome-wide effect on control of viral load

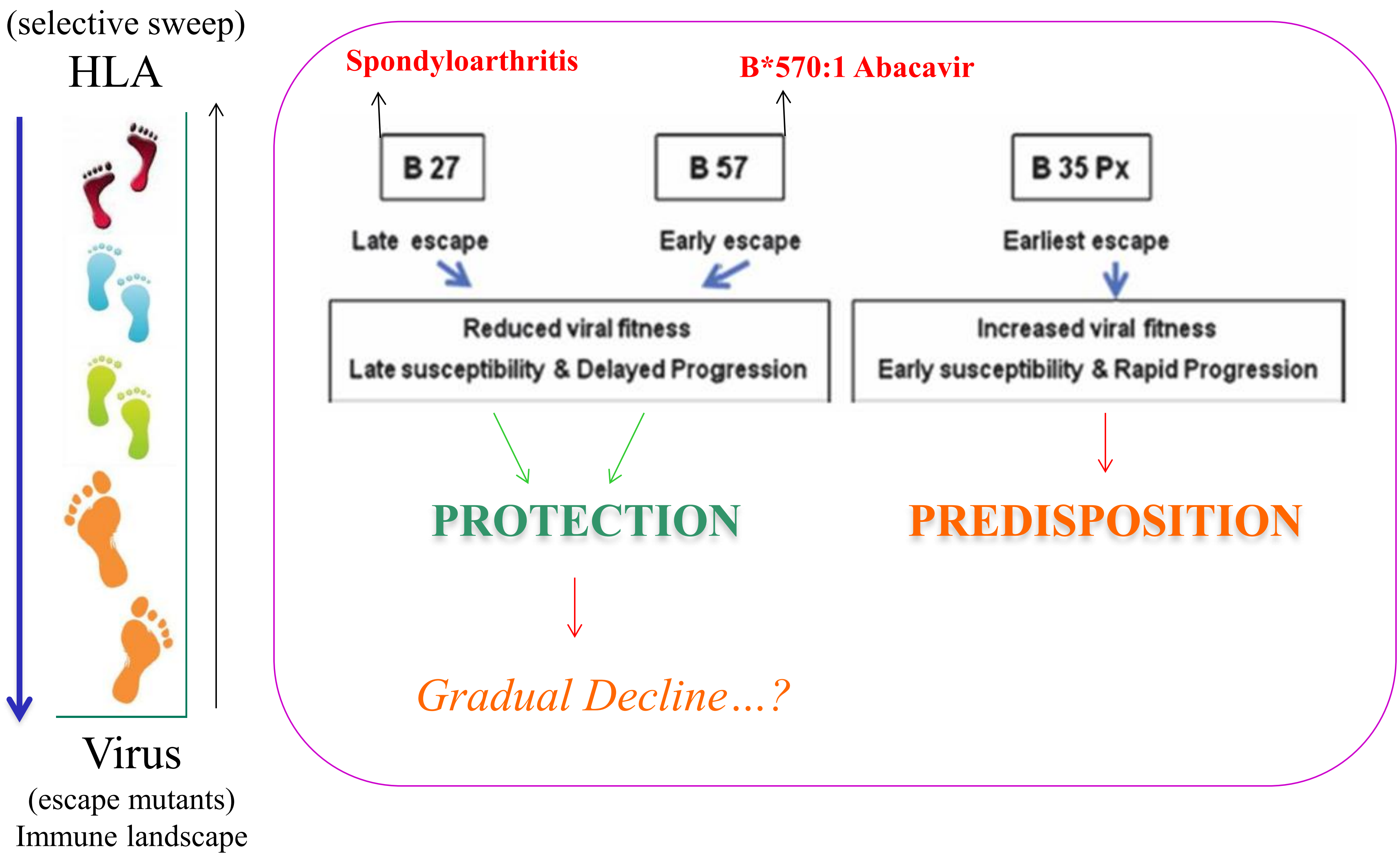


HIV/AIDS: Cumulative Polygenic Effect

Gene	Gene variant	Chrm	Association	Refs
HIV Entry - Coreceptors				
CCR5	Δ32	3p21	Resistance to infection, delay AIDS	Liu *et al.* 1996
CCR5	C20S	3p21	Prevent HIV infection in the presence of D32	Arenzana *et al.* 2006
CCR5	A29S	3p21	Controversial	"
CCR5	R60S	3p21	Controversial	"
CCR5	C101X	3p21	Prevent HIV infection in the presence of D32	"
CCR5	G106R, C178R, C269F	3p21	HIV resistance /Delay AIDS	"
CCR5	P1 [Promoter haplotypes]	3p21	Accelerate AIDS	"
CCR5	59029AA	3p21	Accelerate AIDS	"
CCR5	HHC Promoter haplogroup	3p21	Accelerate AIDS in Japanese	Kageyama *et al.* 2001
CCR5	HHE Promoter haplogroup	3p21	Accelerate AIDS in Caucasians	Ming *et al.* 2005
CCR2	64I	3p21	Delay AIDS in some cohorts	Smith *et al.* 1997
CX3CR1	I249/M280	3p21	Accelerate AIDS	Arenzana *et al.* 2006
DC-SIGN	Promoter variant	19p13	Parenteral infection	Lama *et al.* 2007
Coreceptor ligands				
MIP-1 α (CCL3L1)	Gene copy number	17q12	Increase susceptibility to infection	Gonzalez *et al.* 2005
MIP-1β (CCL4L1)	L2	17q12	Increase susceptibility to infection	Colobran *et al.* 2005
RANTES (CCL5)	-403A , -28G (promoter)	17q12	Delay AIDS	McDermott *et al.* 2000
RANTES (CCL5)	In 1.1C (intronic)	17q12	Accelerate AIDS	Heeney *et al.* 2006
SDF-1(CXCL12)	3' A	10q11	Delay AIDS?	Winkler *et al.* 1998
MCP1/MCP3/Eotaxin	H7 haplotype	17q11	Decrease susceptibility to infection	Lama *et al.* 2007
Post HIV Entry				
TRIM 5α	Haplotype 9	11p15	Increase HIV transmission	Lama *et al.* 2007
TRIM 5α	136Q,43Y	11p15	Protection against HIV infection	"
APOBEC3G	186R, C40693T	22q13	Accelerate AIDS, Increase HIV transmission	"
TSG101	-183C	11p15	Accelerated CD4 T cell decline	"
Acquired / Innate immunity				
HLA	B*27	6p21	Delay AIDS	Stephens 2005
	B*18	6p21	Rapid progression	"
	B*57	6p21	Delay AIDS	"
	B*35Px	6p21	Accelerate AIDS	"
KIR3DS1	3DS1 + HLA-Bw4-80Ile	19q13; 6p21	Delay AIDS	Goudieri *et al.* 2005
	3DL1 + HLA-B*57	19q13; 6p21	Delay AIDS	Lopez *et al.* 2005
Cytokine genes				
Th1([γ-IFN)	+874T allele	12q14	Delay the onset	Kang *et al.* 2006
Th2 (IL10)	IL10-5′-592A	1q31	Accelerate disease progression	Konekov *et al.* 2002
Th2 (IL4)	-590T	5q31	Accelerate disease progression	Tang *et al.* 2002

Sharma G, Kaur G, Mehra N **2011 IJMR**

Trinity of HLA-B alleles in HIV-1 infection



Sharma G, Kaur G, Mehra N 2011 IJMR

Human Immunology **68**, 454–461 (2007)

Published by Elsevier Inc.

Polymorphism in the *CCR5* Gene Promoter and HIV-1 Infection in North Indians

Gurvinder Kaur, P. Singh, C.C. Rapthap, N. Kumar, M. Vajpayee, S.K. Sharma, A. Wanchu, and N.K. Mehra

ABSTRACT: The clinical course and outcome of human immunodeficiency virus-1 (HIV-1) infection are highly variable among individuals. CCR5 is the primary coreceptor that mediates entry of HIV-1 (R5) into permissive host cells. In this study, five SNPs (59029G/A, 59353T/C, 59356C/T, 59402A/G, and 59653C/T) in the promoter region and a deletion of 32 bp (Δ32) in the *CCR5* gene were evaluated in 180 chronically HIV-1–infected North Indians. The study showed the following: (1) the protective *CCR5* Δ32 allele was absent; (2) the frequency of *CCR5**59402A allele in the HIV-infected people (66.4%) was higher than in healthy subjects (57.1%, $p = 0.027$) and in the CDC stage C patients (76%) versus stages A and B patients together (60%; $p = 0.002$); (3) homozygous *CCR5**59402 AA genotype was significantly increased in the seropositive subjects (46.1%) compared with healthy control subjects (30.2%; $p = 0.008$) and in the CDC stage C patients (59.2%) compared with stage A and B subjects (37.6%, $p = 0.007$); and (4) an increased frequency of homozygous ACCAC haplotype was present in the seropositive stage C patients (32.4%) versus 15.6% in patients in stages A plus B ($p = 0.013$). These observations suggest an association of *CCR5**59402A with increased likelihood of acquisition of HIV-1 and development of AIDS in the Asian Indian population. Further studies are required to confirm these findings and understand the effect of *CCR5* polymorphisms on the outcome of HIV-1 infection. *Human Immunology 68, 454–461 (2007).* © American Society for Histocompatibility and Immunogenetics, 2007. Published by Elsevier Inc.

KEYWORDS: Chemokine receptors; polymorphism; HIV-1; CCR5; AIDS

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Genomic architecture of HIV-1 infection: Current status & challenges

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Immunogenetic basis of HIV-1 infection, transmission and disease progression

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APOBEC3H polymorphisms and susceptibility to HIV-1 infection in an Indian population

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Human APOBEC3H (A3H) is a member of APOBEC cytidine deaminase family intensively constraining the HIV-1 replication. A3H is known to be polymorphic with different protein stability and anti-HIV-1 activity *in vitro*. We recently reported that A3H haplotypes composed of two functional polymorphisms, rs139292 (N15del) and rs139297 (G105R), were associated with the susceptibility to HIV-1 infection in Japanese. To confirm the association of A3H and HIV-1 infection in another ethnic group, a total of 241 HIV-1-infected Indian individuals and ethnic-matched 286 healthy controls were analyzed for the A3H polymorphisms. The frequency of 15del allele was high in the HIV-1-infected subjects as compared with the controls (0.477 vs 0.402, odds ratio (OR) = 1.36, $P = 0.014$). Haplotype analysis showed that the frequencies of 15del–105R was high (0.475 vs 0.400, OR = 1.36, permutation $P = 0.037$) in the HIV-1-infected subjects, confirming the association of A3H polymorphisms with the susceptibility to HIV-1 infection.

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Impact of novel TRIM5α variants, Gly110Arg and G176del, on the anti-HIV-1 activity and the susceptibility to HIV-1 infection

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Objective: TRIM5α is one of the factors contributing to intracellular defense mechanisms against HIV-1 infection. We investigated the association of TRIM5α sequence variations with the susceptibility to HIV-1 infection in Japanese and Indian.

Design: Sequence variations in TRIM5α were investigated in HIV-1-infected patients and ethnic-matched controls. Functional alterations caused by rare variants were analyzed.

Methods: We sequenced TRIM5α-exon 2 in both Japanese (94 HIV-1-infected patients and 487 controls) and Indian (101 HIV-1-infected patients and 99 controls). Frequency of variants and haplotypes were compared between the HIV-1-infected patients and controls. Functional analyses were performed for two rare variants, Gly110Arg and G176del.

Results: The frequency of 43Tyr-allele in the Indian HIV-1-infected patients was significantly lower than that in the ethnic-matched controls (odds ratio = 0.52, 95% confidence interval = 0.31–0.89, $P = 0.015$). A similar tendency was observed in Japanese sample, although it was not statistically significant (odds ratio = 0.67, 95% confidence interval = 0.43–1.05, $P = 0.095$). On the other hand, haplotype analyses revealed that the haplotype carrying the 43Tyr-allele was significantly associated with the reduced susceptibility to HIV-1 infection in both ethnic groups. Functional analysis revealed that Gly110Arg variant weakened the anti-HIV-1 and anti-HIV-2 activities of human TRIM5α, whereas the truncated G176del-TRIM5 enhanced the antiviral activity of coexpressed TRIM5α. Epidemiological data were consistent in that Gly110Arg and G176del were associated with the susceptibility to and protection from HIV-1 infection, respectively.

Conclusion: Both common and rare variants of TRIM5α are associated with the susceptibility to HIV-1 infection.

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Keywords: association, HIV-1, polymorphism, susceptibility, TRIM5

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Status of TIM-1 exon 4 haplotypes and CD4+T cell counts in HIV-1 seroprevalent North Indians

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ABSTRACT

The *TIM* (T cell/transmembrane, immunoglobulin and mucin) proteins are crucial regulators of Th1/Th2 immune responses and have been implicated in several diseases including HIV-1/AIDS. The *TIM1* exon 4 that codes for mucin domain is highly diverse, with sequence variants associated with varying phenotypes. In this study, *TIM1* exon 4 was sequenced among 227 HIV-1 seroprevalent and 288 healthy non infected individuals from North Indian population and haplotypes established. A novel but rare haplotype D1* was identified among the healthy and differed from D1 by a synonymous substitution G>T at Thr208Thr. The *TIM1* haplotype diversity showed no association with susceptibility to HIV-1 infection. The seroprevalent individuals carrying D3A had relatively higher median CD4+T cell counts (368/μl) than those without (313/μl; $p = 0.02$). A comparison of CD4+T counts between D3-A individuals on ART or ART naïve did not show any significant difference plausibly due to confounding nature of ART and other factors.

CONCLUSIONS

- Communicable diseases continue to pose a challenge for the health care system

- **How does host immunity variation influence communicable disease expression?**

  The answer lies at the intersection of immunogenetics, infectious disease and population biology with HLA being the master regulator and most powerful immunogenetic determinant

- The same pathogen can cause wildly different outcomes across individuals – from asymptomatic carriage to severe disease or death – largely because host immunity variation shapes the battlefield

- Immune variables include:

  Favorable HLA, TLR hypofunction, strong Th1 bias, excessive inflammatory response, Regulatory T-cell (Treg) abundance

- Understanding the MHC peptide binding motif could help in developing screening tools to monitor susceptibility /progression, predicting population specific genetic propensity and finally vaccine responsiveness in clinical trials

- The information could enable clinicians adapt treatment modalities

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