Host Genes and Infectious Diseases

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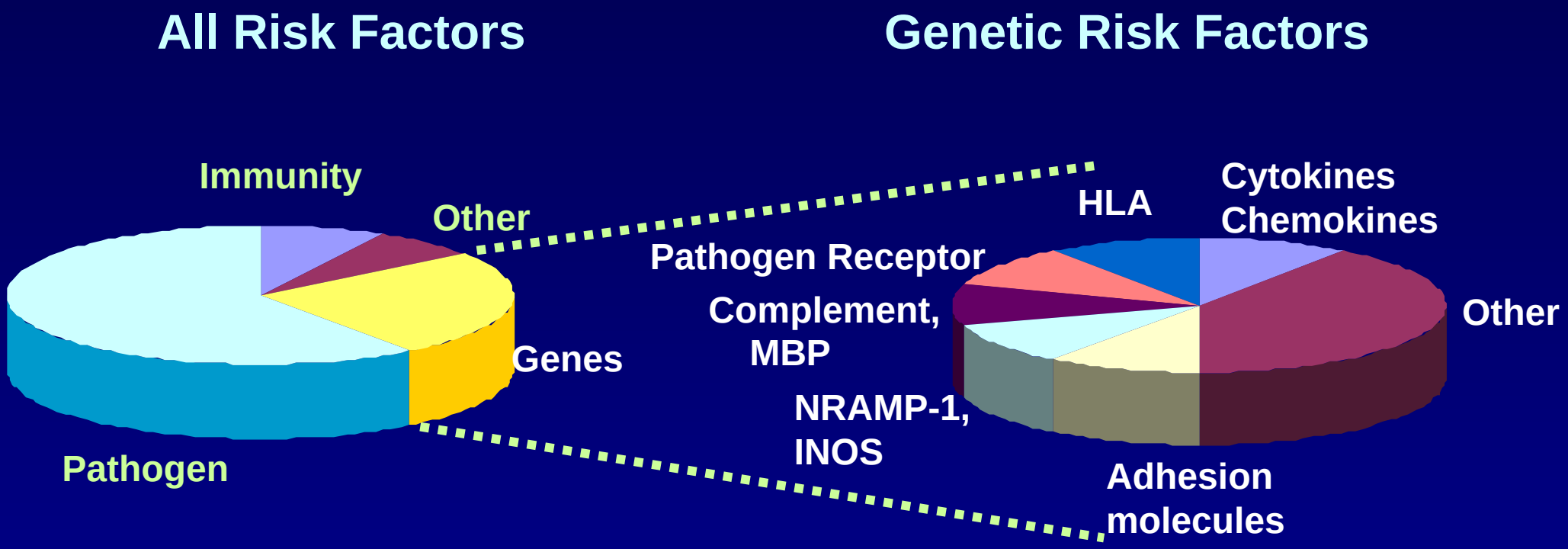
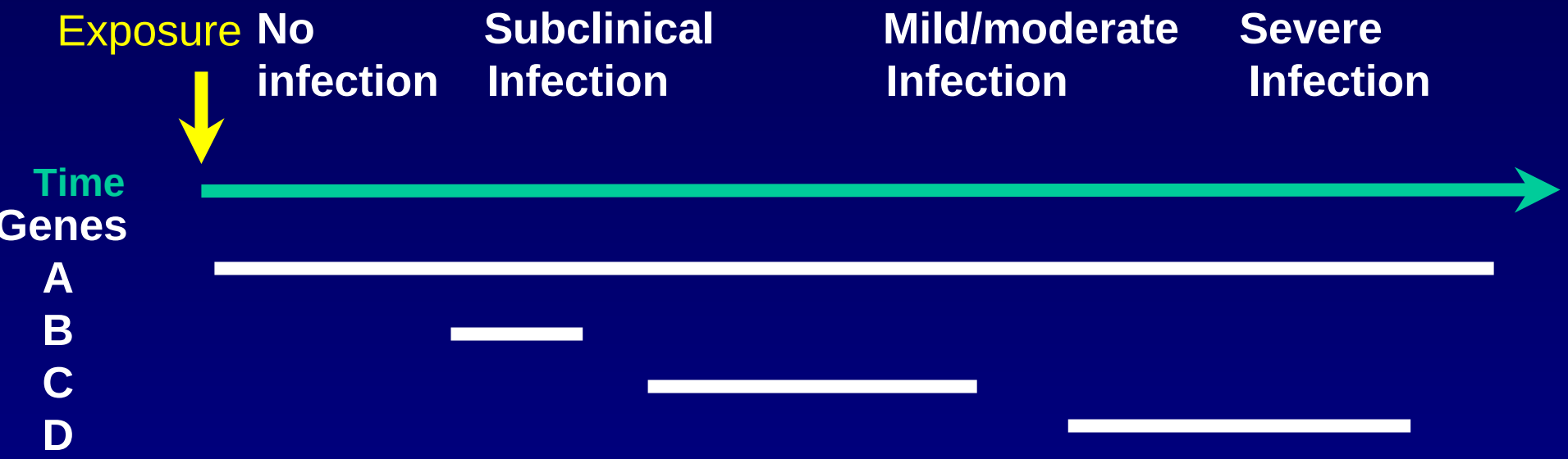
CDC

A Model of Infectious Diseases



Host Genes and Course of Infectious Diseases

Potential Timing of Impact of Host Genes



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Identifying Host Genes Associated with Infectious Diseases

- Genetic approach
  - Candidate gene: twins, families, populations
  - Linkage: twins, families, populations
- Issues to consider
  - Race/ethnicity
  - Sample size
  - Laboratory tools
  - Analytic tools
  - Attributable risks
  - Ethical issues

Host Genes and Infectious Diseases

- Pathogenesis
- Resistance
- Severity
- Vaccine design/evaluation
- Drug design/response

- Malaria
- HIV
- TB

Host Genes and Malaria

- Reduced severity of disease
  - Hemoglobin/RBC proteins (HbS, HbC, α-thall, β-thall, Duffy, G6PD, Erythrocyte Band 3)
  - HLA alleles (B53, DR2)
  - INOS–954 promoter (C allele)
- Increased severity of disease
  - TNFα –308 promoter (A) homozygosity
  - ICAM-1 coding region (T) allele

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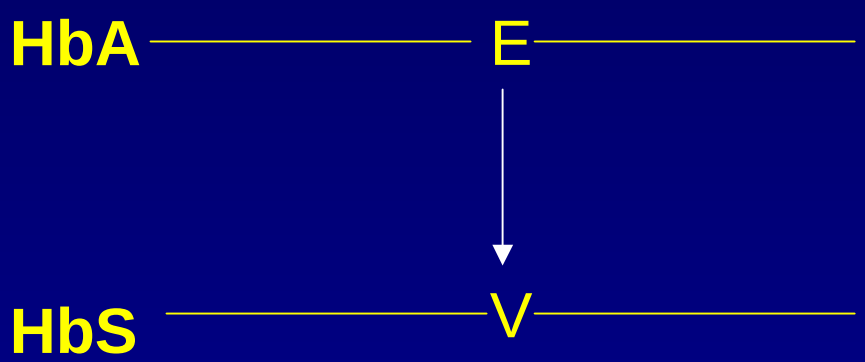
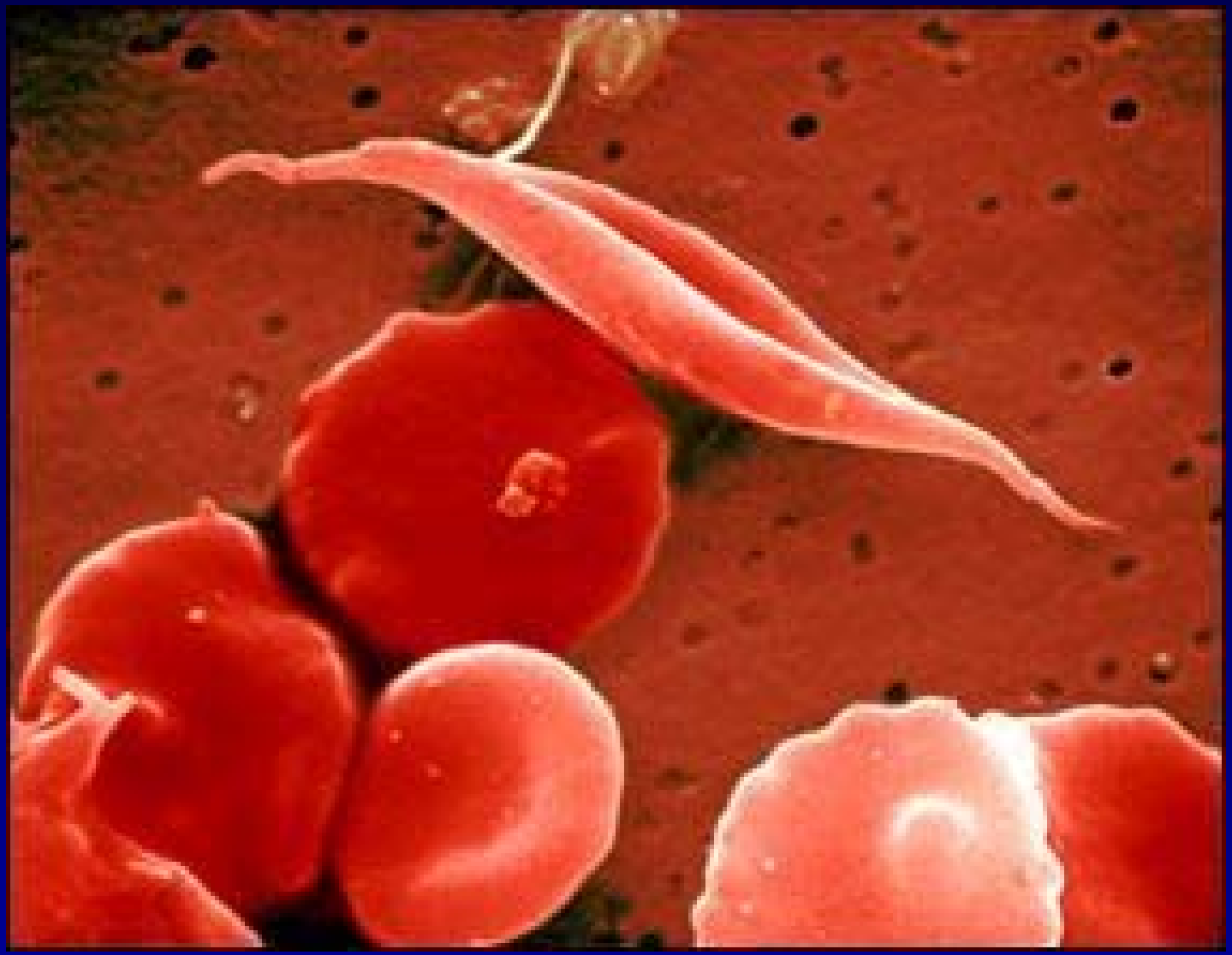
Hemoglobin S and Malaria

Single nucleotide polymorphism in the β-hemoglobin gene **(Chr11)**



Under low O_2 tension HbS polymerizes and RBCs assume sickle shape and adhere easily to blood capillaries

Sickled Red Blood Cell



Slide from Wellcome Trust (www.wellcome.ac.uk)

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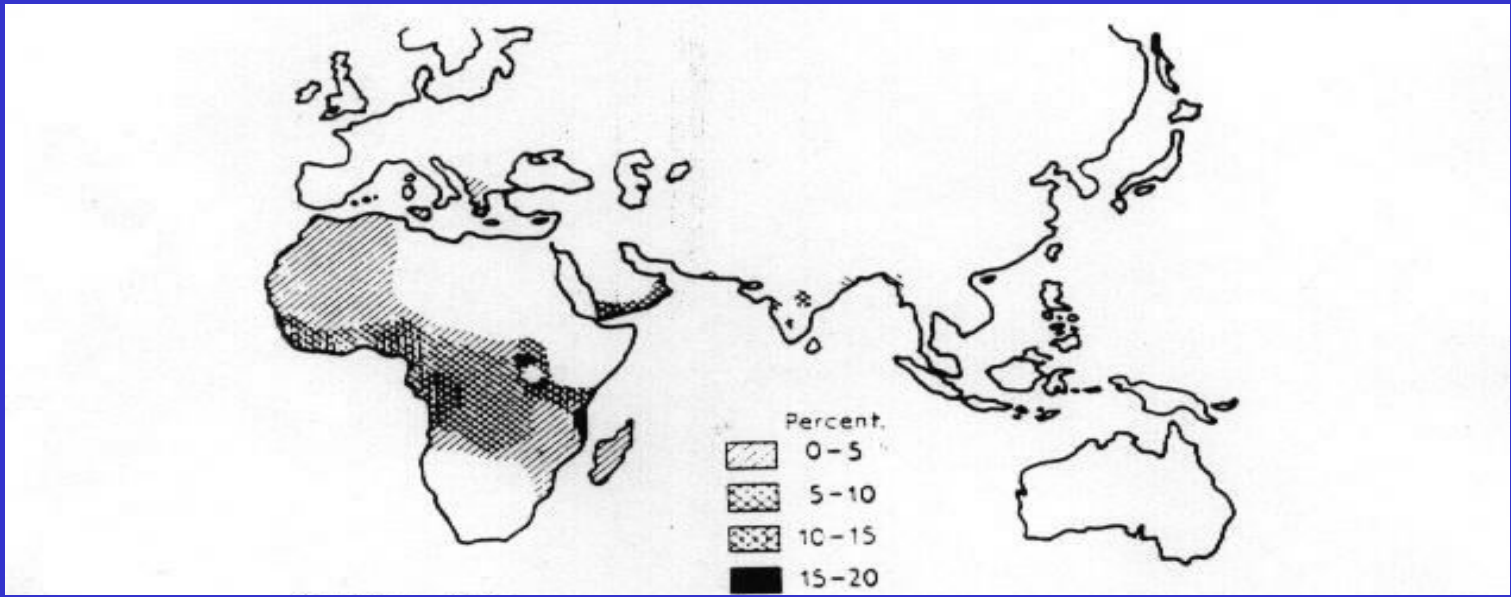
Geographic Distribution of the Sickle Cell (HbS) Gene



Adapted from Harrison et al.

HbS gene distribution: 15-40% in Sub Saharan Africa

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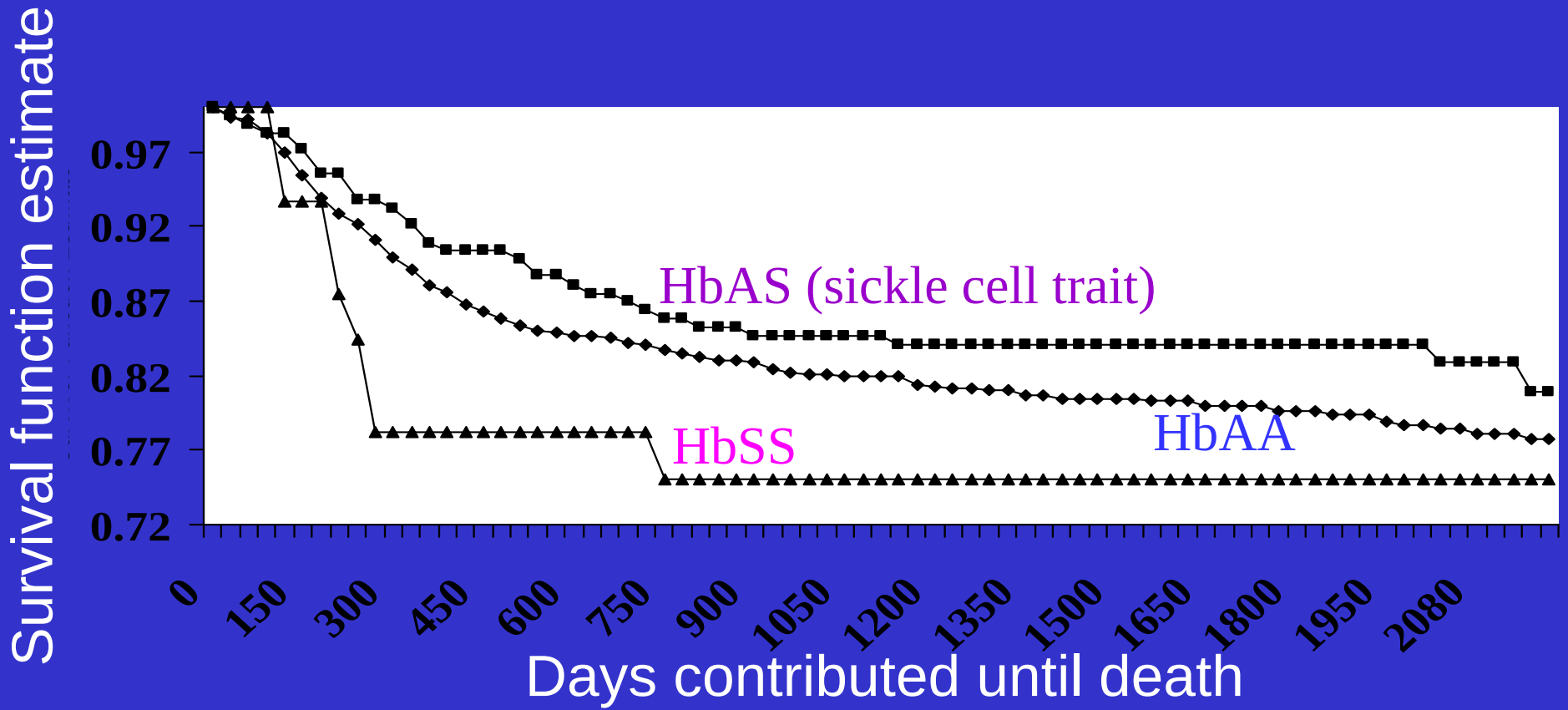
Hemoglobin S and Malaria

- Protective effect of heterozygosity against malaria anemia and severe malaria known for decades
- Mechanism of protection not clear
- Timing of protection unknown

CDC Study, Kisumu, Kenya
Survival of Children by HbS genotype



Aidoo et al, Lancet, in Press

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Survival Advantage of HbS is Before the Onset of Immunity to Malaria

Comparison group	Relat. risk	95% CI	p-value
HbAS vs HbAA during 2 - 16 months of age	0.45	0.2-0.8	.0001
HB AS vs HbAA in first 2 months or > 16 months of age	1.2	0.7-2.1	0.5

Summary - Malaria

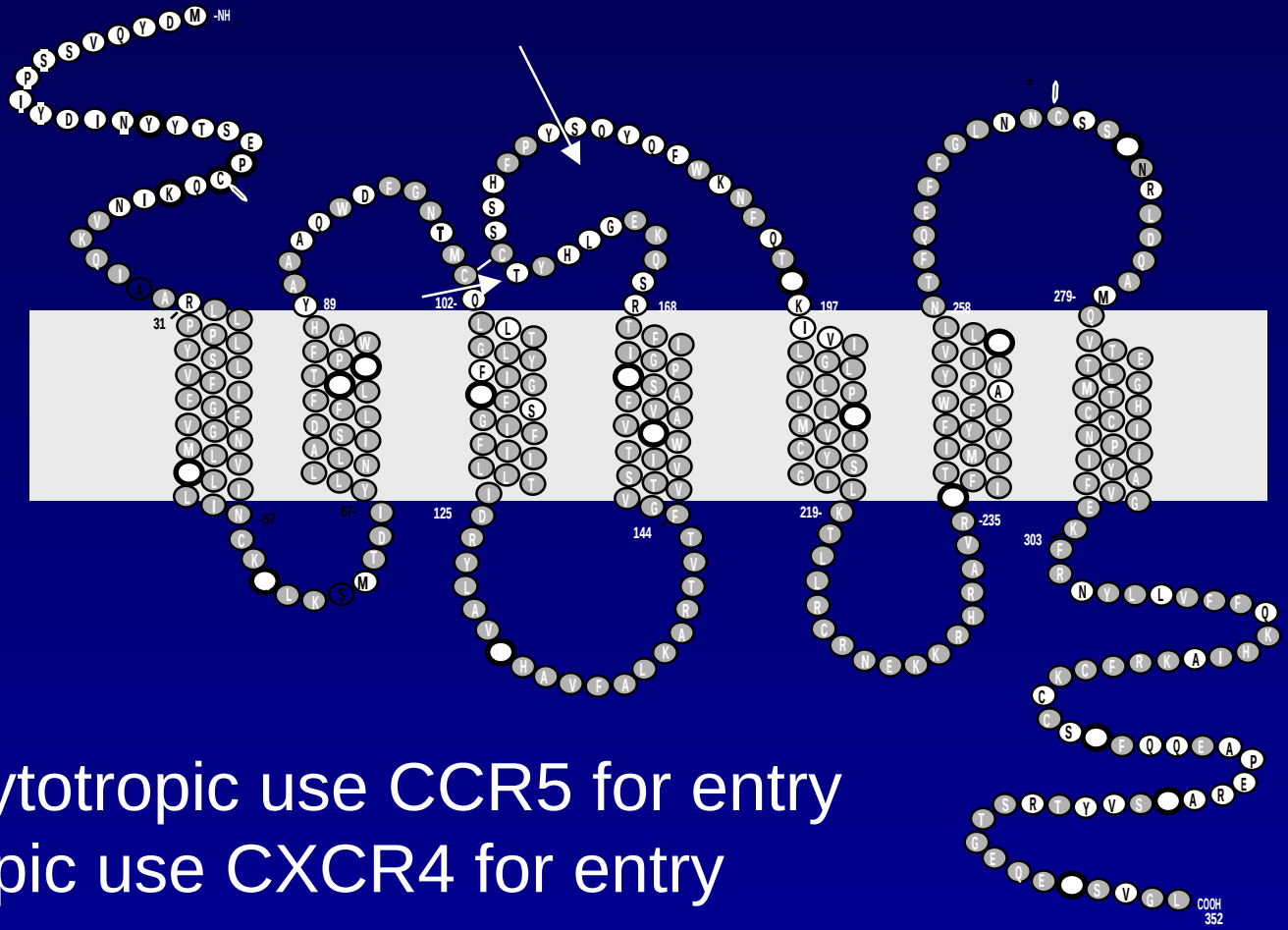
- **CDC Study:**
  - **Sickle cell trait confers highly significant protection against overall mortality**
  - **The time window of protection is between 2 to 16 months of age**

- **Malaria and Host Genetics**
  - **Complex, multifactorial, multigenic**
  - **Implications for pathogenesis, vaccine design**

HIV

- Host Genes Impact Multiple Aspects of Disease
  - Resistance: HLA, CCR5
  - Disease progression: HLA, CCR, SDF, MBP, Vit DR, IL-10, TNF
  - Vaccine responses: HLA
  - Drug responses: HLA, MDR1

Chemokine Receptor (CCR5) used by HIV



Cell Membrane

NSI/monocytotropic use CCR5 for entry
SI/T cell tropic use CXCR4 for entry

Rucker et al,
Cell, 1996, 87:437

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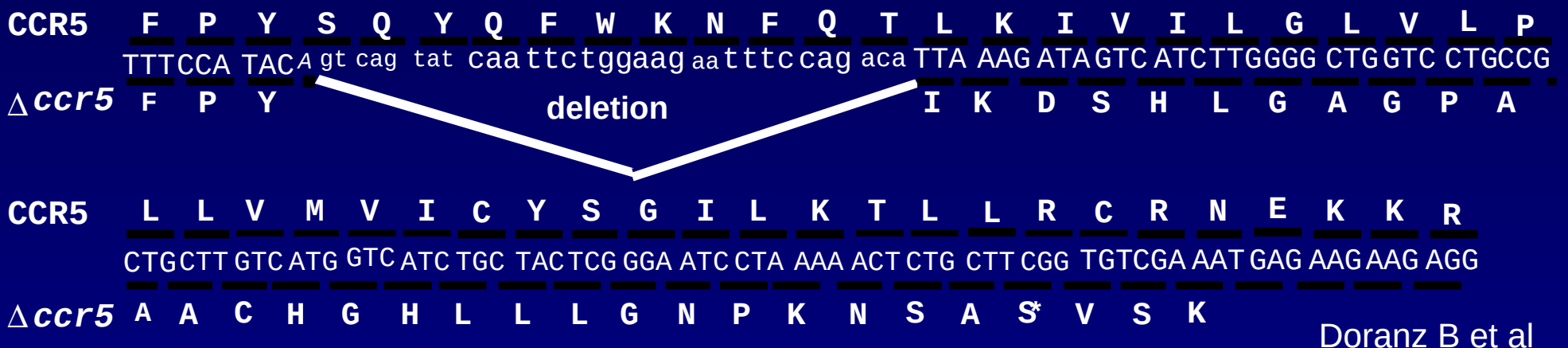
CCR5 and the 32 bp Deletion

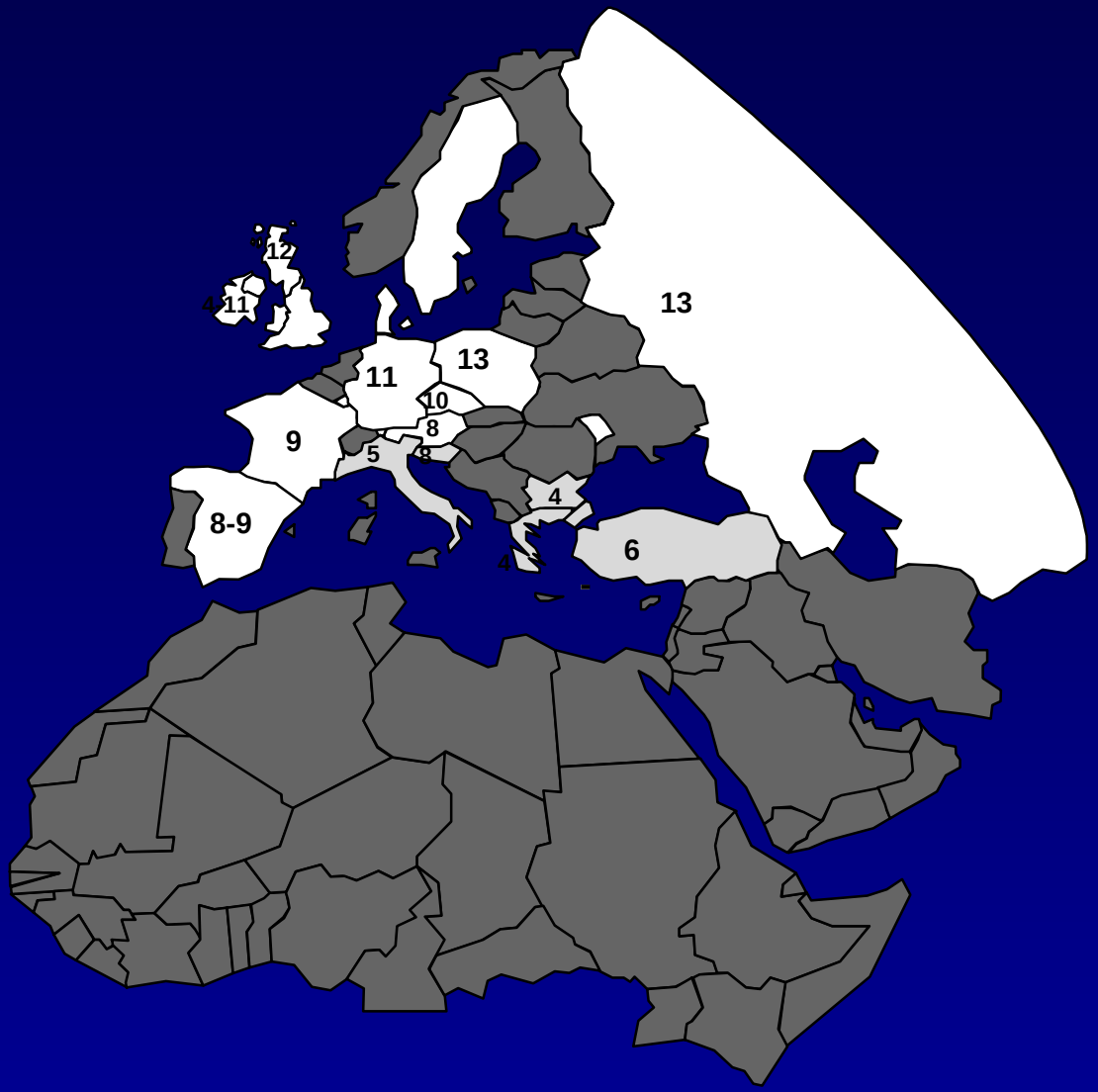


Doranz B et al
Cell, 1996,85,1149

CCR5 Δ 32 Genotype

10% Caucasians are heterozygous, 1% homozygous
Complete resistance to HIV infection (with NSI variants)
Presence delays progression to AIDS
Attractive therapeutic target

Geographic Variation in Δ 32 CCR5 Distribution



FREQUENCY OF MUTANT ALLELE

- 8 % OR HIGHER
- 1 TO 8 %
- 0 % (AND UNKNOWN)

Adapted from Martinson et al, Nat Gen 1997,16; 100

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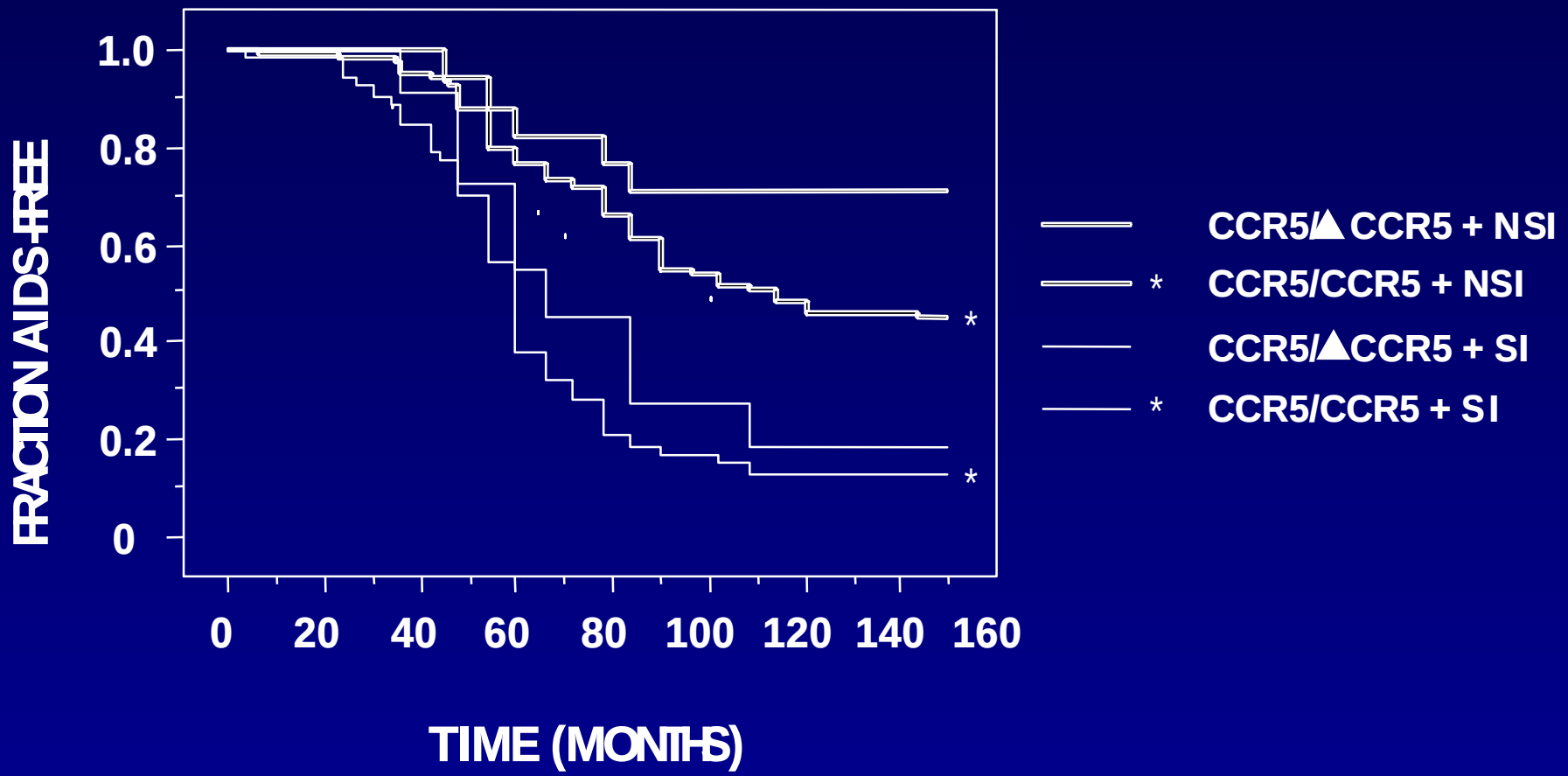
Effect of Δ 32 CCR5 Genotype on HIV Disease Progression



Michael N. et al, Nature Med, 1997

HLA Genotype influences Multiple Aspects of HIV Infection and Disease

- Resistance to infection (HLA-A2 supertype, HLA-A11, HLA discordance)
- Rate of progression to AIDS
  - Delayed: HLA-B27, B57
  - Accelerated: HLA-A1,B8,DR3
- Vaccine responses
  - Enhanced (canarypox HIV vaccine: HLA-B27)
- Drug reactivity (abacavir: HLA-B57)

HLA type and Responses to a Candidate HIV Vaccine

Vaccine Protein	HLA-B27 +	HLA-B27-	OR
Gag	64	15	10.3
Env	36	11	4.6
Any	40	11	5.4

% CTL responses observed at 6 weeks post vaccination with ALVAC-HIV Canarypox vaccines. Kaslow, R et al, JV, 2001, 75; 8681

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HLA Genotype Determines Hypersensitivity to Anti Retroviral Therapy

HLA type	Abacavir Hypersensitive	Abacavir Tolerant	OR
HLA-B57+	78	2	117
B57 Haplotype	72	0	822

% subjects in each group. Mallal S et al, Lancet, 2002, 359;9308
Abacavir = Ziagen (Trizivir when combined with AZT/3TC)
Haplotype = HLA B57-DR7-DQ3

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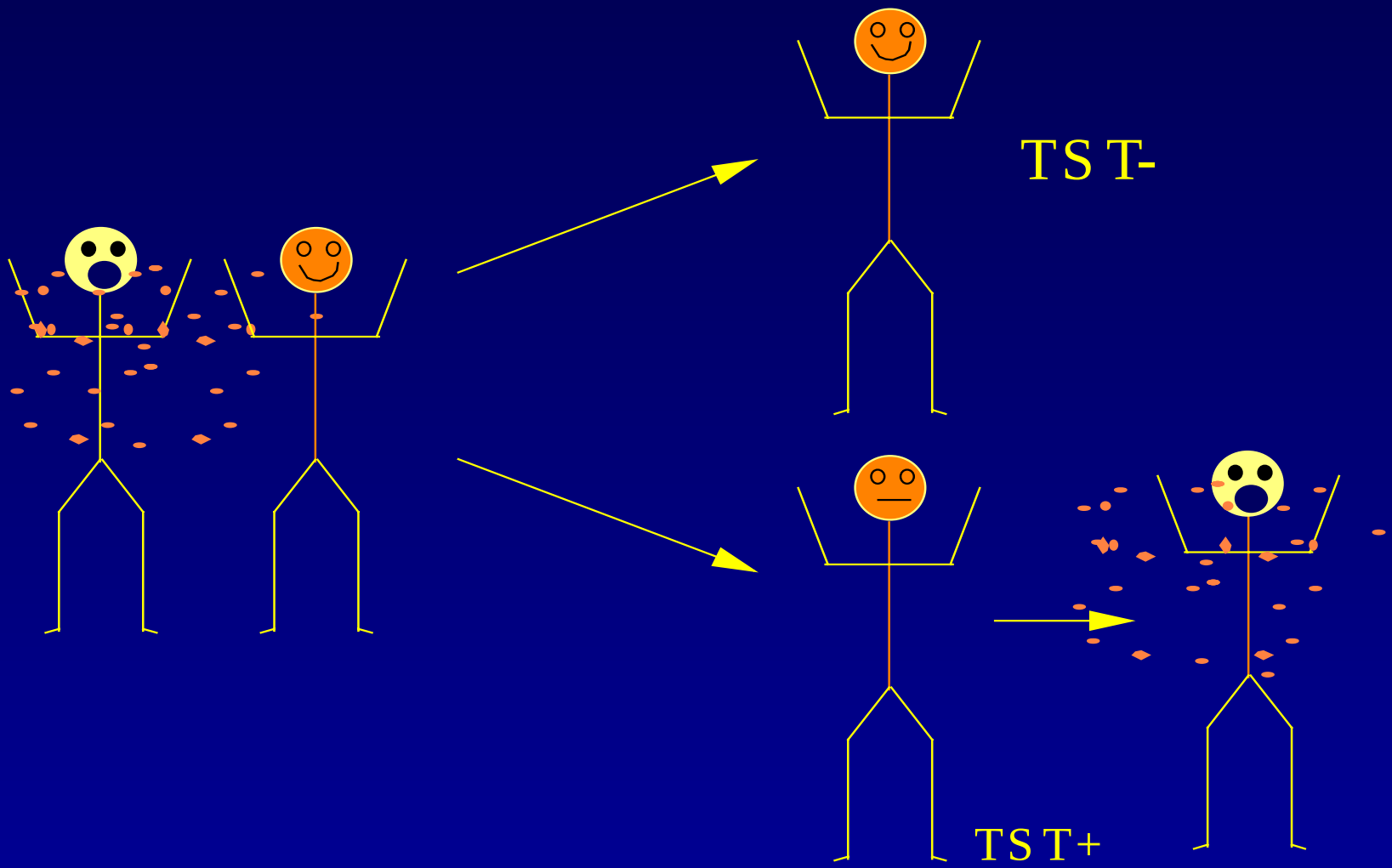
Host Genes and HIV

- Multigenic, complex, multiple aspects
- Implications for therapy and vaccine design

Host Genes and Mycobacterial Infections

TB Pathogenesis



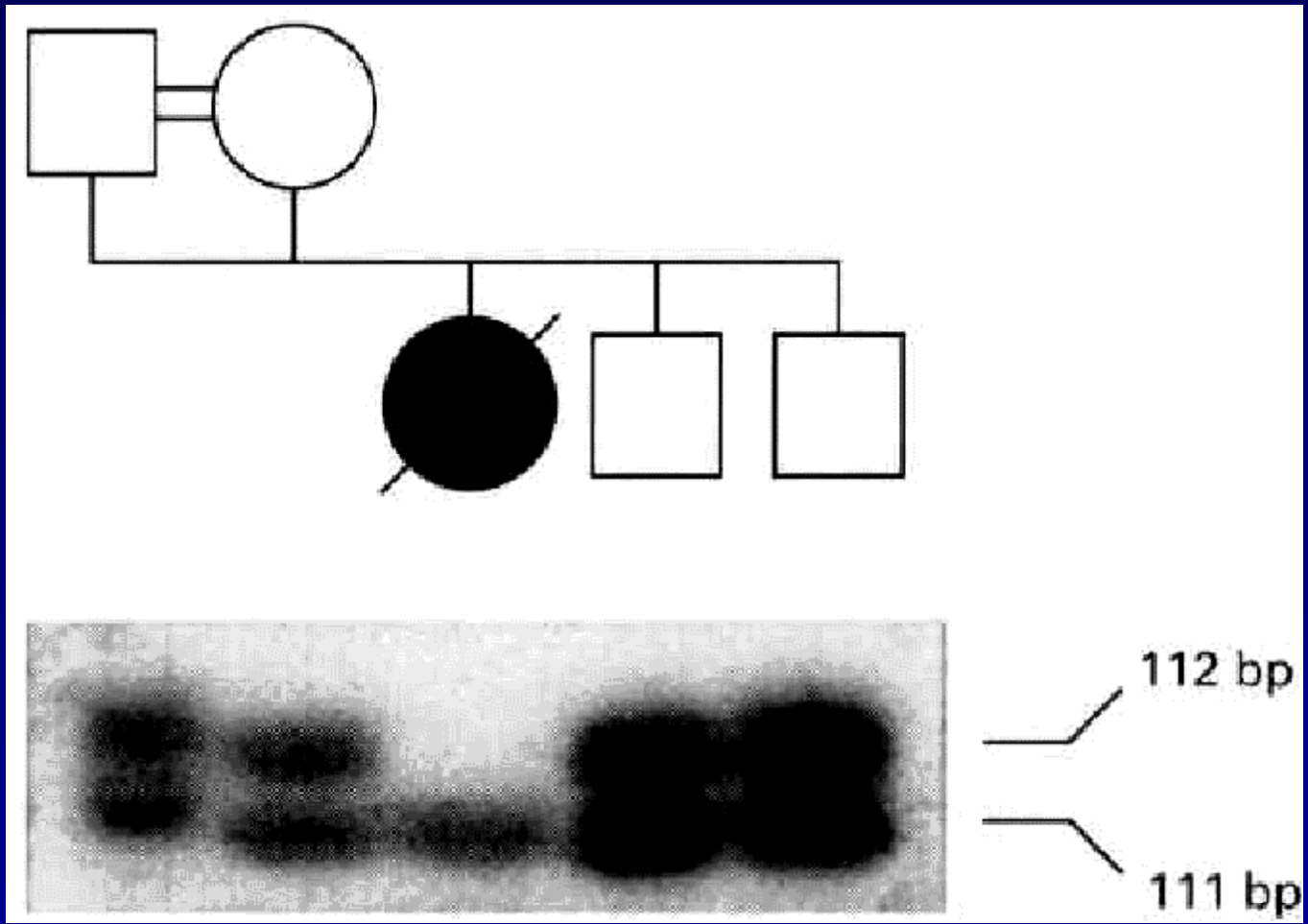
Genes associated with TB

- Immune Genes
  - HLA class DR and DQ (6p21)
  - IL-1RA (2q14)
  - IL-1α (2q14)
  - MBL (10q11)
- Other Genes/loci
  - Vit DR (12q12)
  - NRAMP-1 (2q35)
  - X chromosome
  - Chromosome 15 locus

Importance of Family Studies

- IFN-γ R-1 (6q23)
  - Recurrent *M. avium* and other non-TB mycobacteria
    Newport et al, NEJM, 1996
  - Disseminated BCG infection
    Jouanguy et al, NEJM, 1996
- IL-12 Rβ (5q31)
  - Recurrent atypical mycobacterial infections
    De Jong et al, Science 1998

IFN-γ Receptor Deficiency in an Infant with Fatal BCG Infection



Jouanguy et al. NEJM, 1996

Future Directions Host Genes and Infectious Diseases in Public Health

- Needs:
  - define attributable risks
  - define interaction of risk genotypes with other risk factors
  - identify other genes
- Long term
  - identify populations at high risk for diseases
  - Understand pathogenesis
  - Develop new prevention or therapeutic strategies

The Future….

- New treatments based on genes associated with resistance/susceptibility
- Host genetic typing in the clinic?
- Host genetic typing in epidemics?
- Host genetic typing of populations for prevention or treatment?

CDC's genetics web site: www.cdc.gov/genetics