Host genetic diversity

Genome-wide approaches

Affected sib analysis

- Take full sibs, preferably of the same sex
- should share many environmental variables
- Usual design; both sibs affected
- marker should segregate with disease
- can use for candidate loci or for mapping anonymous markers across the genome

Leprosy (*Mycobacterium leprae*) in India

Table 1 · Number of families and sibpairs in the two-stage leprosy genome screen

Number of families	First stage	Second stage
2 affected siblings	84	120
3 affected siblings	8	11
4 affected siblings	1	0
Total families	93	131
Total number of independent sibpairs	103	142

The number of fully independent sibpairs in each family is equal to the number of affected siblings minus one.

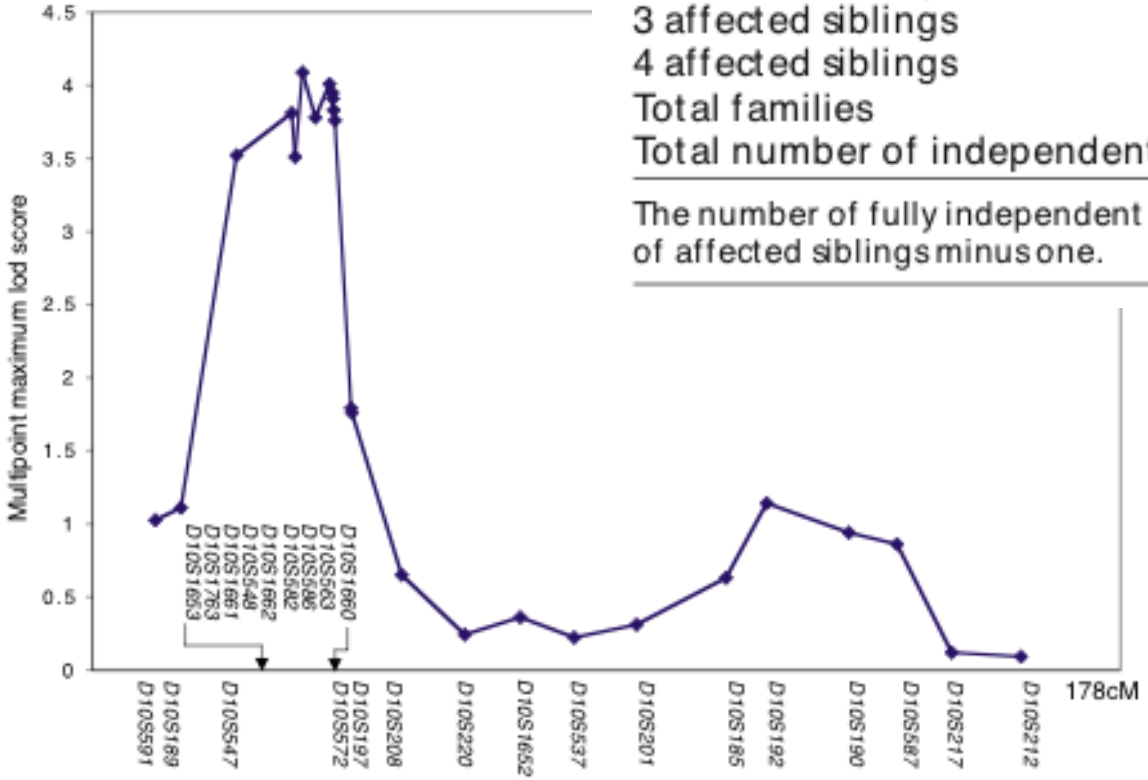


Fig. 1 Maximum likelihood multipoint map for 25 microsatellite markers on chromosome 10, including 8 markers flanking *D10S548*. The maximum multipoint MLS for the region is 4.09 (*P* value=0.000007) and corresponded to *D10S166*.

Siddiqui *et al* (2001)
Nat. Gen. 27: 439-441

Genome wide association studies (GWAS)

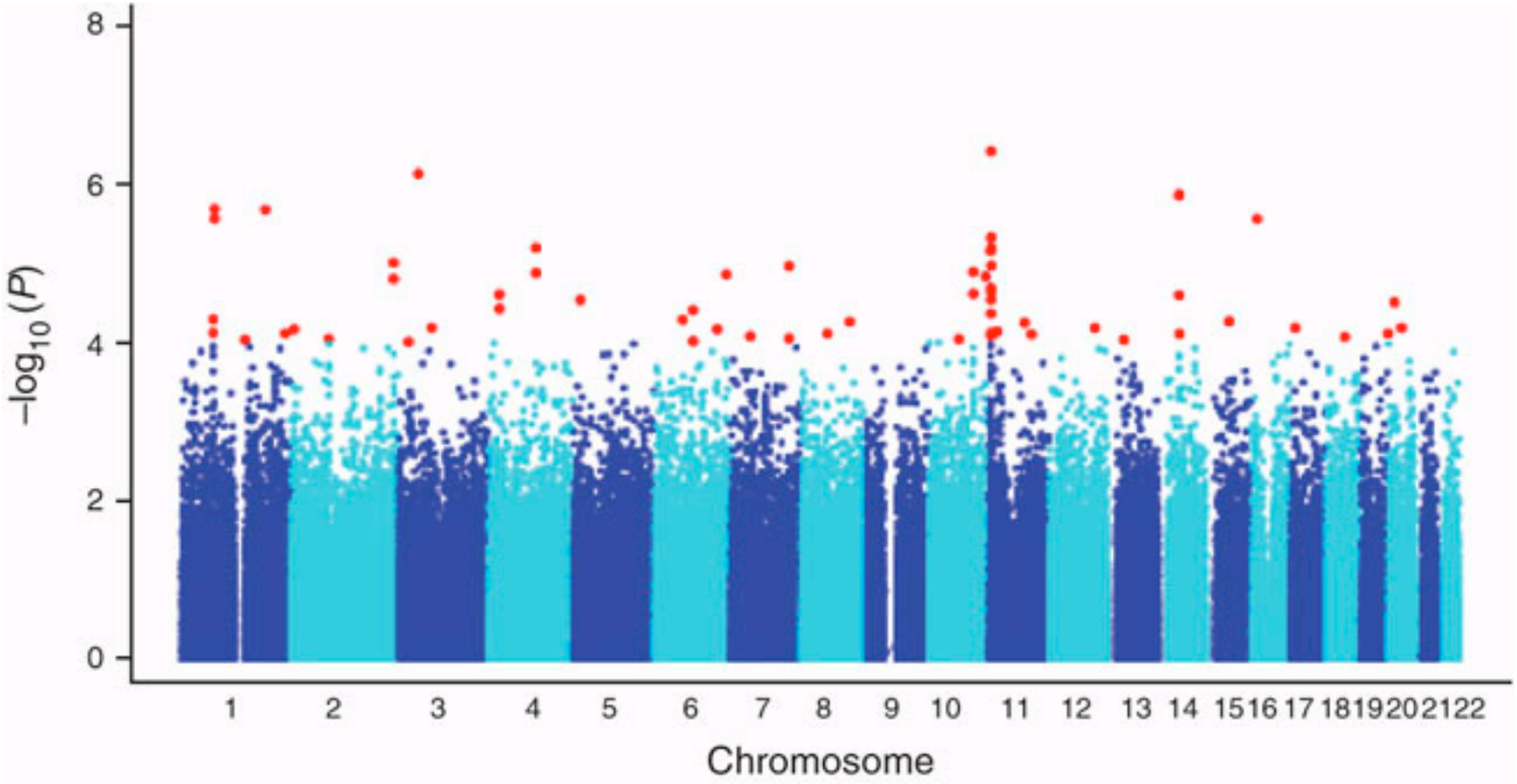
- Genotype pool of unrelated cases versus controls for very high number of loci (500,000 SNPs)
- Rely on linkage disequilibrium between marker and trait (i.e. disease resistance)

GWAS of malaria resistance

- ~1000 cases and ~ 1400 controls from the Gambia
- Type ~ ½ million SNPs using Affy chip
- Described as proof of principle

Jallow et al (2009) Genome-wide signals of association with severe malaria Nature Genetics 41, 657 - 665

GWAS study of malaria



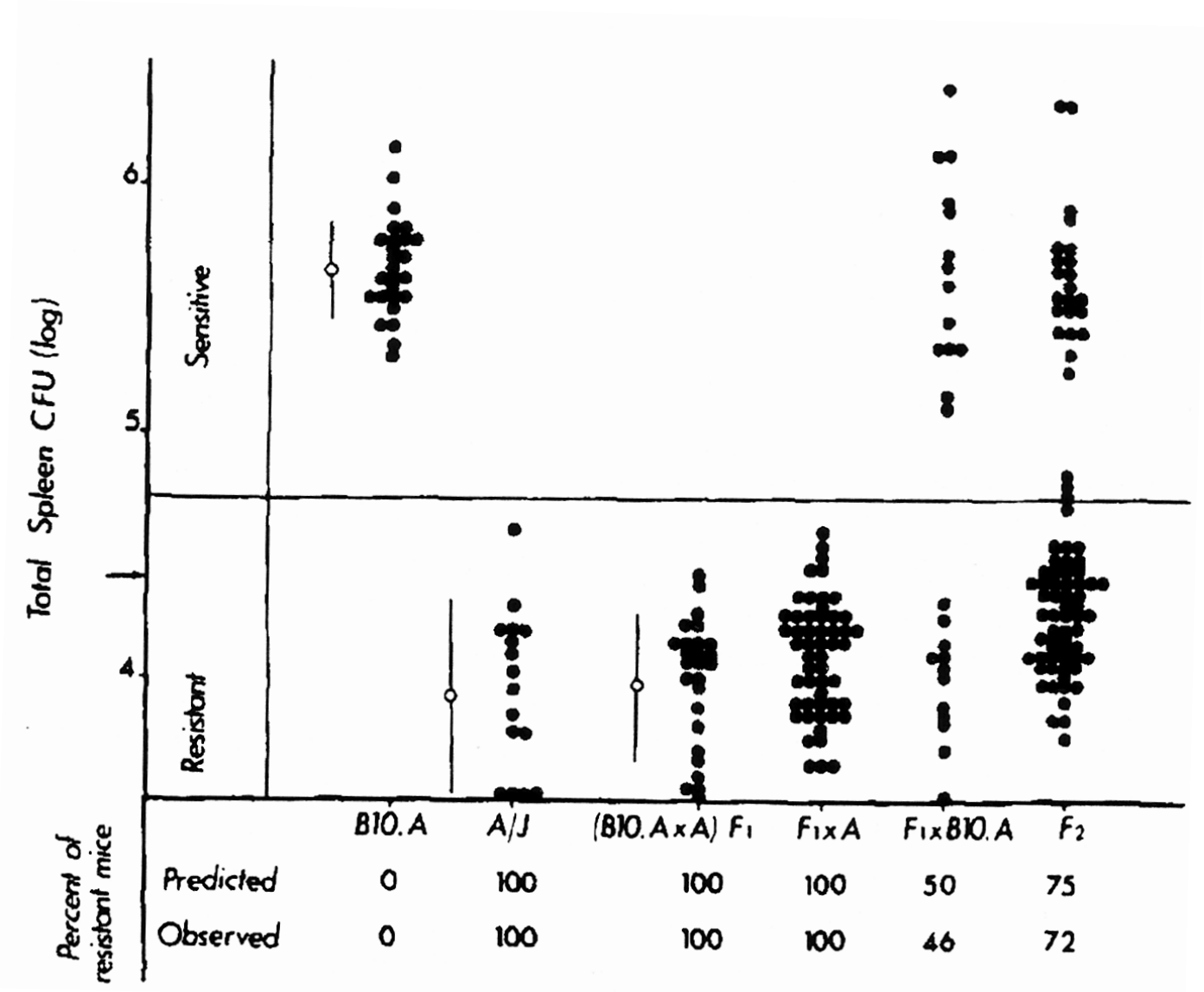
GWAS of malaria resistance

- Difficulties include
  - Population structure
  - Genotype chips designed for caucasian populations
  - Low linkage disequibrium between markers
- Struggles to detect even HbS, the sickle cell anaemia polymorphism and misses many other known resistance loci entirely

MHC

- Clear case of variation at a locus that underlies differences in susceptibility to disease
- Malaria, nematodes, leprosy, HIV progression, Hepatitis B & C persistence, etc.

Nramp1, resistance to mycobacteria, salmonella and Leishmania



Buer & Balling, 2003; Nature Review Genetics 4: 195-205

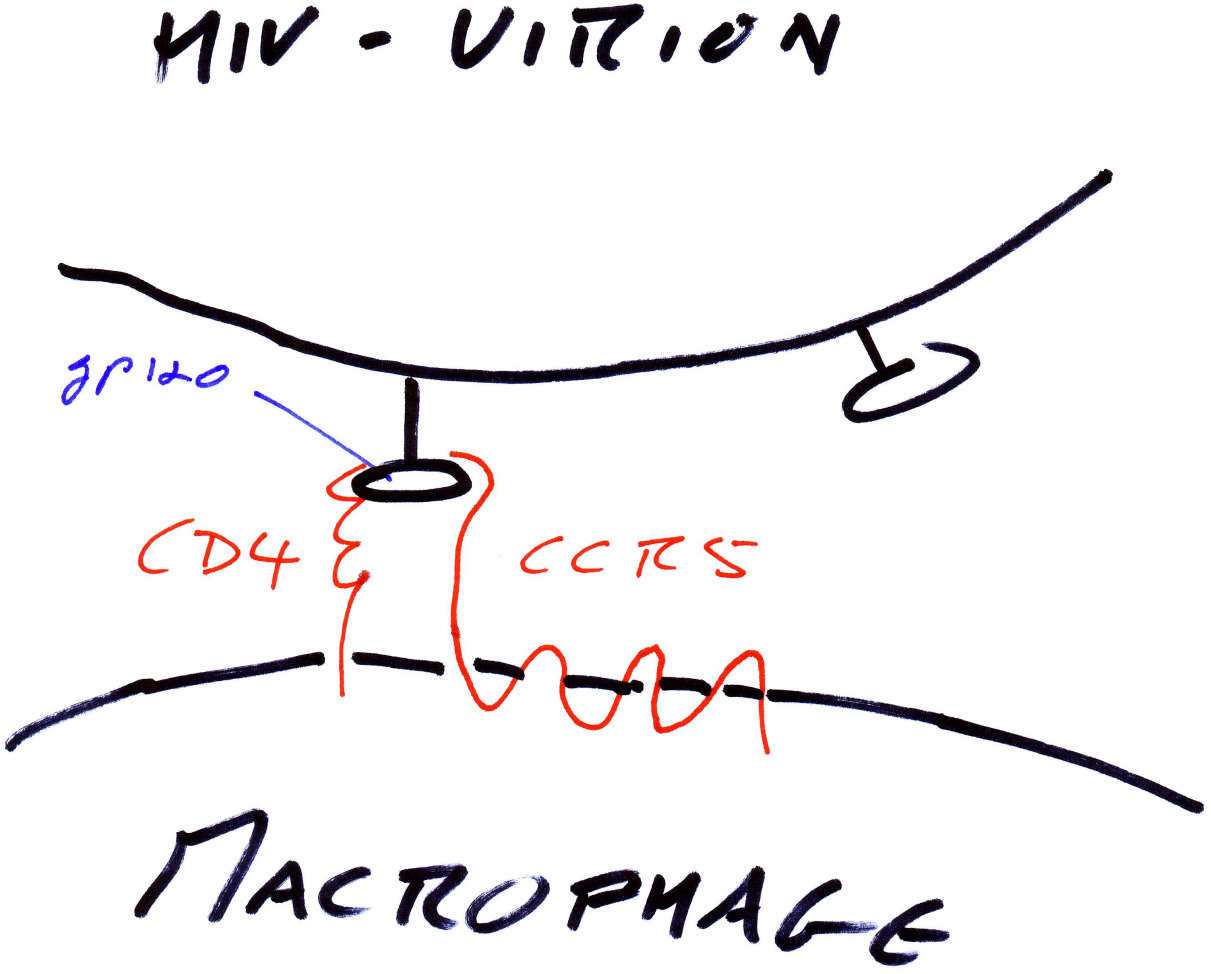
Finding candidate genes

- Knock out mice, esp. for cytokines
- Tells you what happens when protein function lost
- Is this representative of natural variation?

Selection and infectious disease

- CCR5 encodes a chemokine receptor
- Can be used by HIV to gain entry into macrophages
- Polymorphic, Caucasians
- 32bp deletion associated with protection against HIV
- Dean *et al* (1996) Science 273:1856-1862

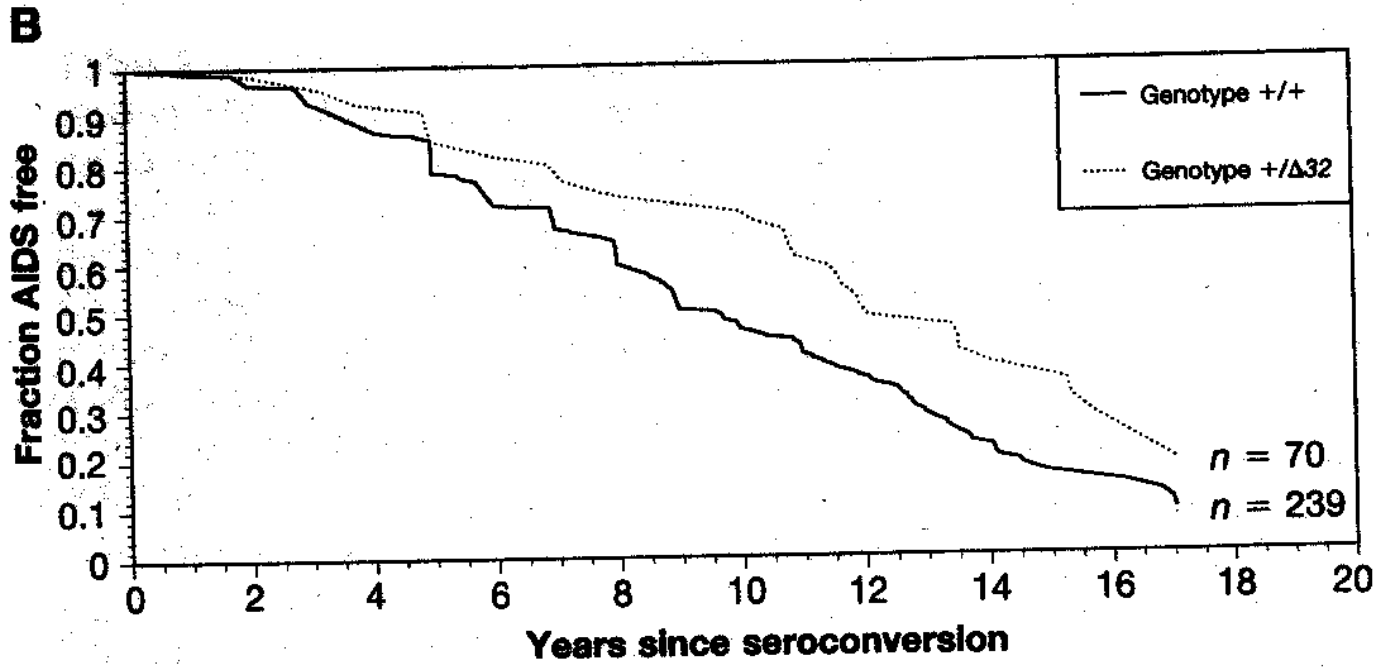
CCR5 and HIV entry



CCR5-Δ32 homozygotes protected against HIV infection

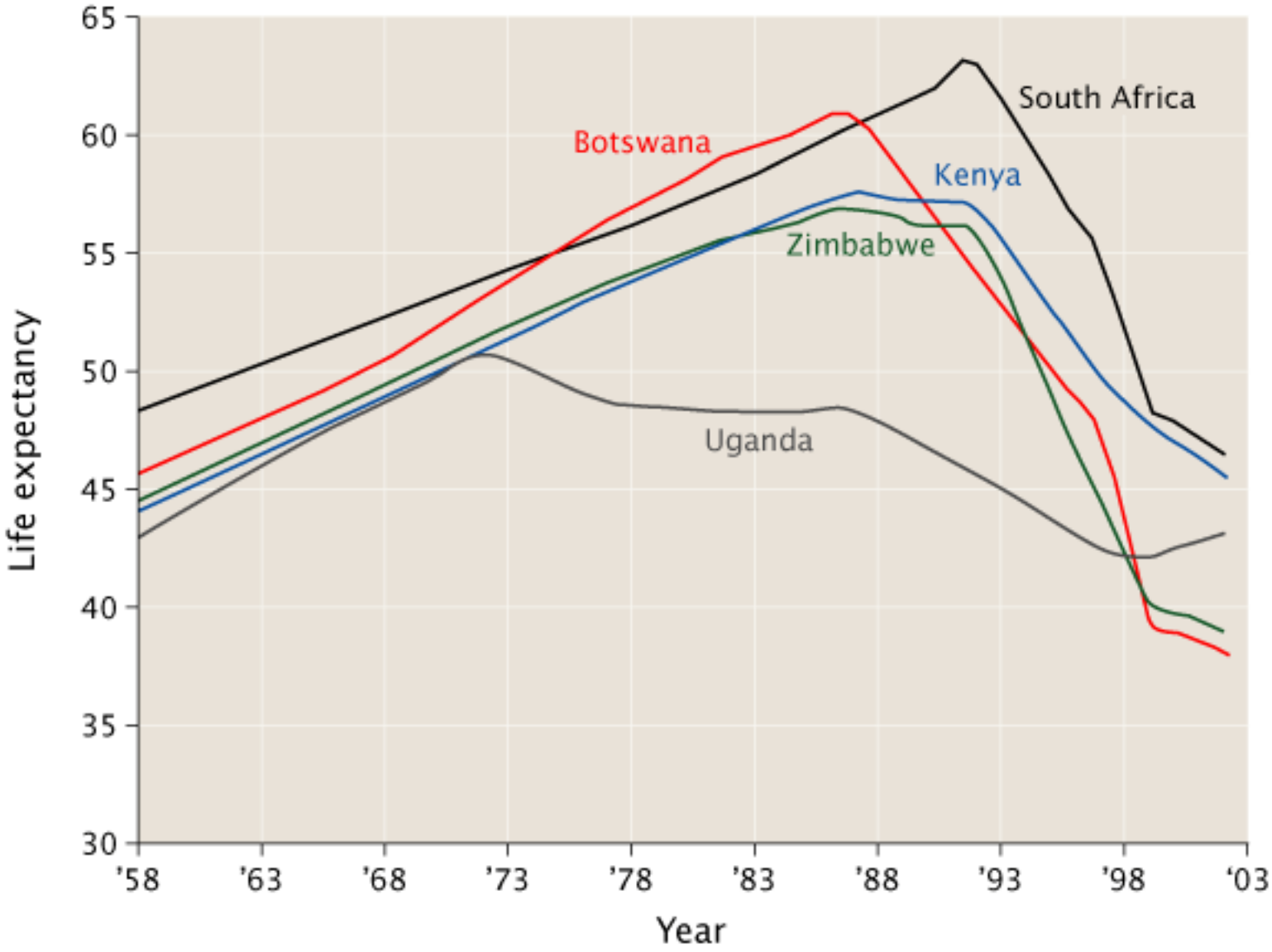
	+/+	+/Δ32	Δ32 /Δ32	Total
HIV +	1148	195	**0**	*1343*
HIV -	508	87	**17**	*612*
Total	*1656*	*282*	*17*	*1955*

CCR5 heterozygotes slow progression to AIDS



Selection on CCR5

- Selection is determined by the environment
- Not constant through time or space
- CCR5 protective during HIV epidemic
- Strongest selection in sub-Saharan Africa
  - Up to 10-30% of population infected in places



(World Bank; World Development Indicators, 2004)

Frequency of Δ32-CCR5 allele

	q	+/+	+/Δ32	Δ32/Δ32
Caucasian	0.11	0.79	0.20	0.01
African	0.017	0.97	0.03	0.0003

Age of CCR5- Δ32 polymorphism

Mutations will probably arise once, therefore associated with one haplotype. Over time, markers within this haplotype will be broken up by recombination and mutation (r).

Probability that haplotype does not change from its ancestor is

$P = (1 - r)^G$

$G \approx -\ln(P)/r$

Stephens (1998) Am J Hum Genet 62: 1507-1515

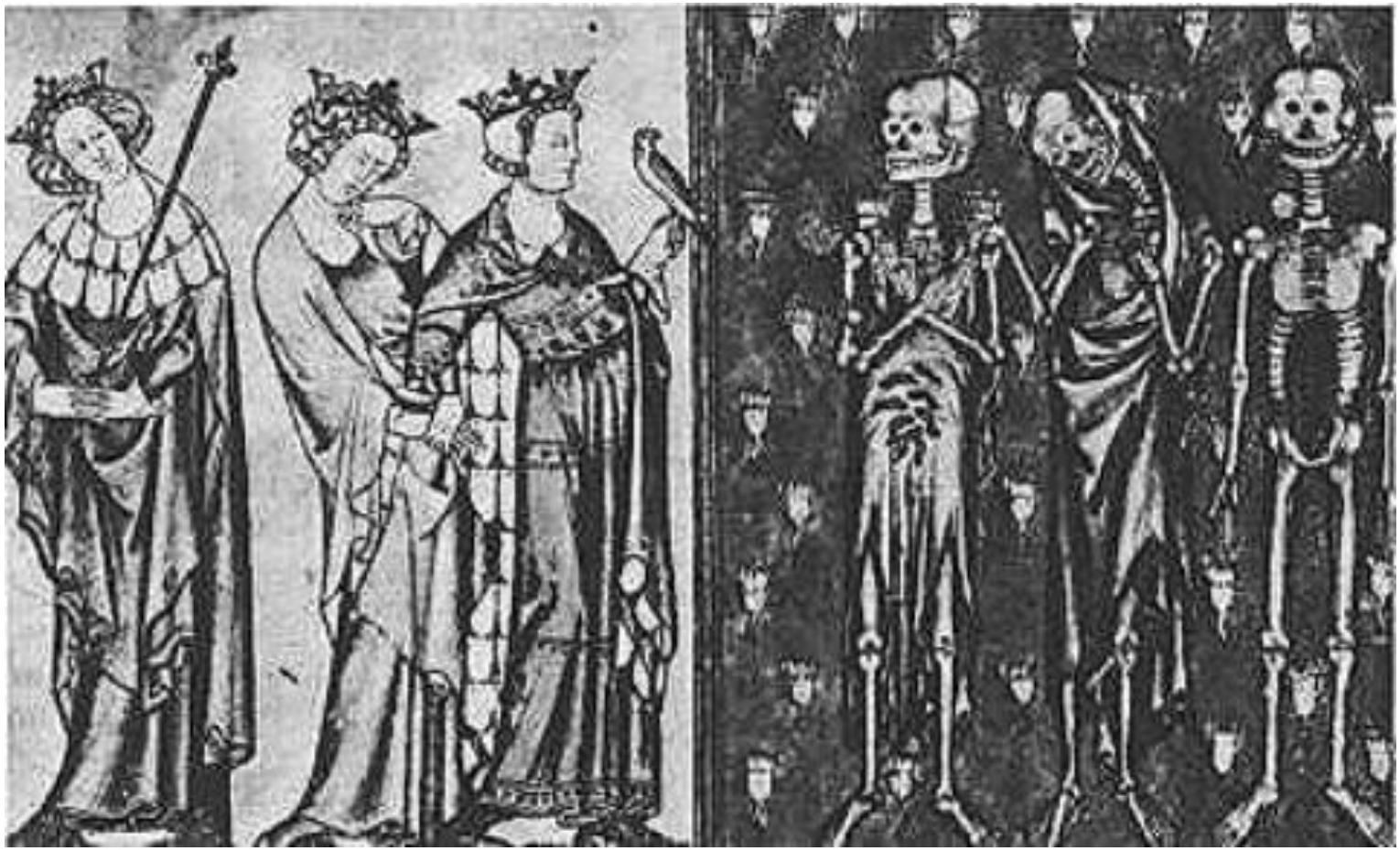
Haplotype frequencies

Haplotype	%
CCR5-GAAT-AFMB	
Δ32-197-215	84.8
Δ32-197-217	6.5
Δ32-193-215	4.3
Δ32-197-219	2.2
Δ32-197-213	2.2

Estimate r as 0.006,
plug into $G = -\ln(P)/r$
$G = -\ln(0.85)/0.006$
= 27.5 generations
@25 years/generation
= 688 years

(although CI = 300 - 1,800 yrs)

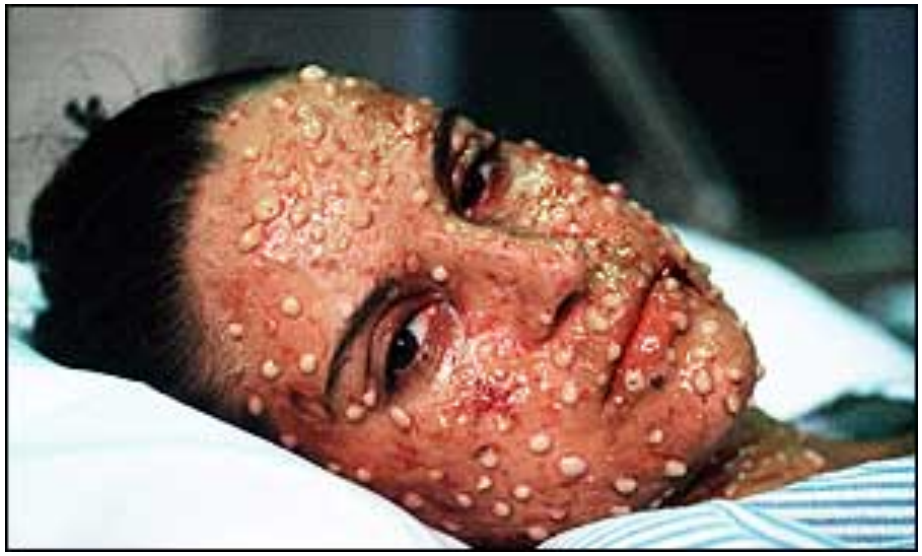
Black death (*Yersinia pestis) 1346 - 1352*



25 - 40% of Europe killed

Problems with bubonic plague hypothesis

- Episodic selection - isolated bouts of very fierce selection - difficult to increase allele frequency at very beginning & no selection after 1750
- KO CCR5 mice show no protection against *Yersinia pestis*
- Smallpox provides a more constant selection pressure, poxviruses also gain entry by chemokine receptors



Galvani & Slatkin (2003) PNAS 100: 15276-79