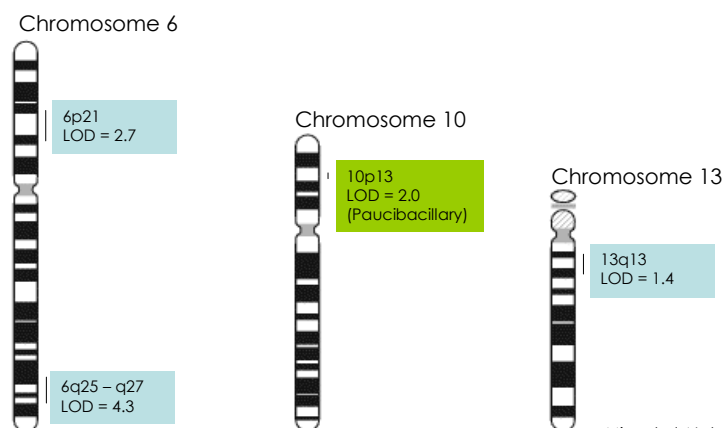


# POSITIONAL CLONING OF LEPROSY SUSCEPTIBILITY LOCI

Erwin Schurr  
McGill Centre for the Study of Host Resistance  
McGill University  
Montreal, QC, Canada

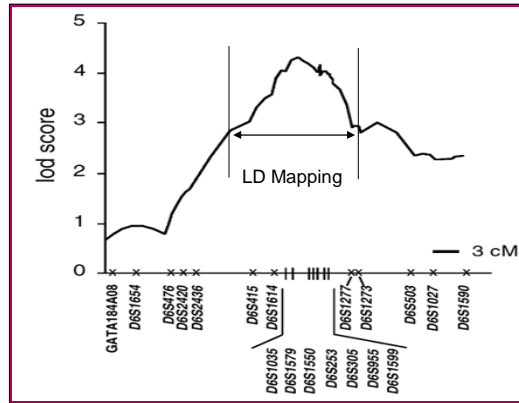
## Genome scan, 2003

- 86 Vietnamese multiplex families
- 388 markers tested for linkage with leprosy *per se*



Mira et al., Nature Genet 2003

## Chromosome Region 6q25-q27



Mira et al. Nature Genet 2003

## High Resolution Association Mapping

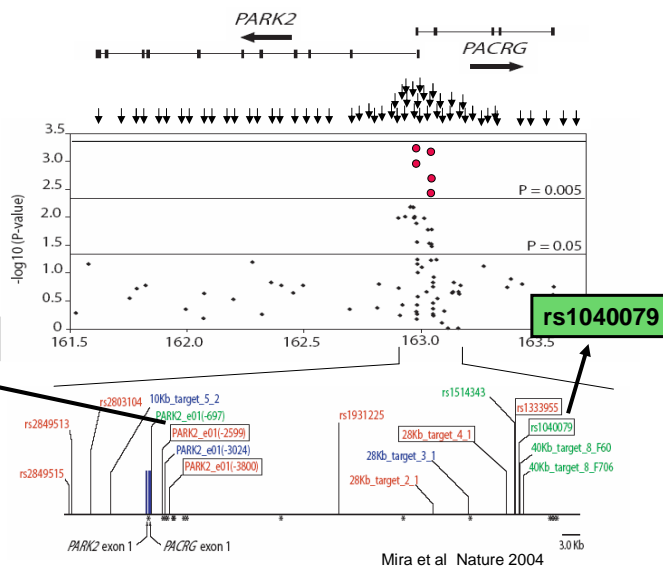
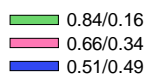
Gene Map: 2 Genes

SNP Map: 81 SNPs

Association Plot

PARK2\_e01(-2599)

Association Map



Mira et al Nature 2004

# Chromosome region 6p21

- Objective: Identify susceptibility variants located in the linked chromosomal region on 6p21 by systematic association scanning of SNP markers located in the linkage peak confidence interval

## Study design I



- 197 simplex families
- Approximately 50% PB and 50% MB



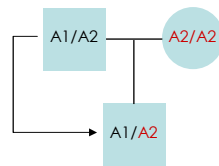
- 385 cases and 399 controls
- 51% PB and 49% MB



- 364 cases and 371 controls
- 30% PB and 70% MB

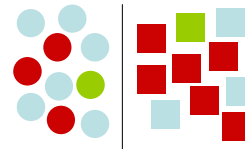
# Study design II

- Family based transmission disequilibrium test



$a = \# \text{ of } A1/\text{not}A2 \text{ transmissions}$   
 $b = \# \text{ of } A2/\text{not}A1 \text{ transmissions}$   
 Test statistic =  $(a - b)^2 / (a + b)$   
 $X^2$  distribution  
 Conditional logistic regression

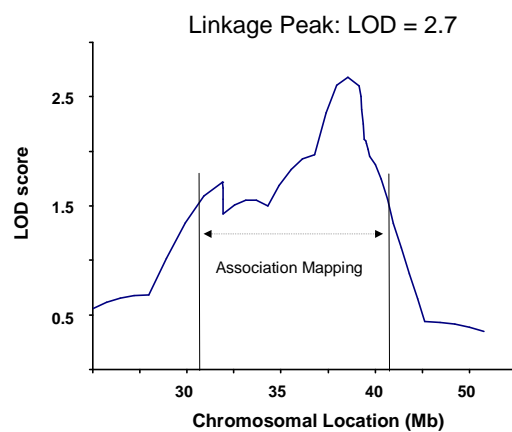
- Case – control



	CC	CT	TT
Cases	6	1	3
Control	3	1	6

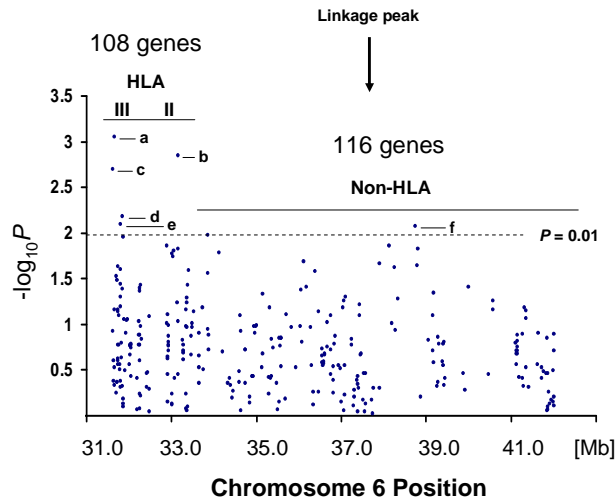
$s$   
 Test statistic =  $\sum_{\text{all cells}} (\text{observed} - \text{expected})^2 / \text{expected}$   
 $X^2$  distribution  
 Logistic regression

## Chromosome region 6p21 linkage peak



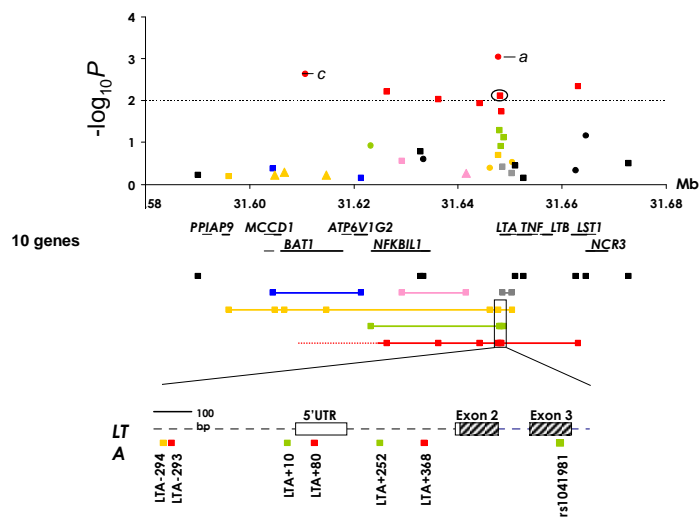
Mira et al Nature Genet 2003

## Low resolution association scan



Alcais et al Nature Genet 2007

## Linkage disequilibrium fine mapping of 90kb interval overlapping LTA



Alcais et al Nature Genet 2007

## Replication in the Indian sample

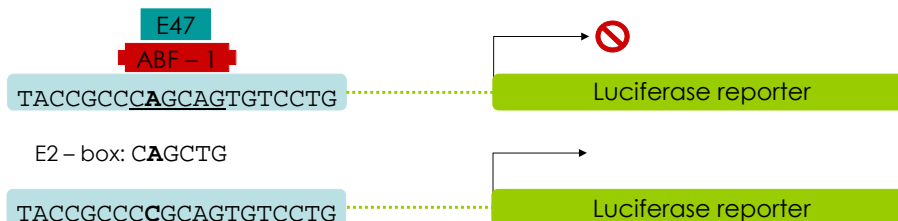
	LTA-294 rs2844482	LTA-293 rs2071590	LTA+10 rs1800683	LTA+80 rs2239704	LTA+252 rs909253	LTA+368 rs746868
<b>Vietnamese</b>						
Bin structure						
MAF§	0.16	0.26	0.50	0.30	0.49	0.30
Univariate OR (95% CI) P	ns	1.97 (1.30-2.99) 0.0009	ns	1.74 (1.16-2.60) 0.007	ns	1.63 (1.09-2.43) 0.02
Multivariate OR (95% CI) P	ns	1.97 (1.30-2.99) 0.0009	ns	ns*	ns	ns*
<b>Indian</b>						
Bin structure						
MAF§	0.22	0.26	0.28	0.42	0.28	0.41
Univariate OR (95% CI) P	1.78 (1.29-2.45) 0.0004	ns	ns	ns	ns	ns
Multivariate OR (95% CI) P	1.82 (1.38-2.41) 0.00003	ns	ns	1.60 (1.10-2.33) 0.01	ns	ns*

\* Any SNP in the bin is sufficient to explain the observed association with leprosy

§ MAF (Minor Allele Frequency) corresponds to the frequency of the risk allele for each of the associated SNPs

## Functional role for LTA +80

- Knight et al. 2002
- ABF – 1
  - Transcriptional repressor
  - Lymphoid tissue specific
  - Binds only if 'A' allele at LTA+80
- Consistent with 'A' allele as risk factor for leprosy

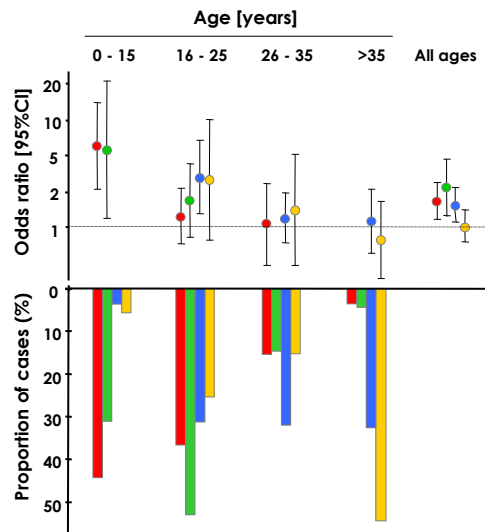


## Replication in Brazilian sample

	Additive	Dominant	Recessive
	$P$ [OR(95% CI)]	$P$ [OR(95% CI)]	$P$ [OR(95% CI)]
<b>LTA+80</b> MAF:0.414	0.79 [0.96 (0.762-1.209)]	0.95[1.01(0.72-1.43)]	0.48[0.86(0.57-1.30)]

No replication in the Brazilian sample: WHY?

## The effect of LTA+80 is strongly age-dependent



Alcais et al Nature Genet 207



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