Ali et al. Genome Biology 2010, 11(Suppl 1):P5
http://genomebiology.com/2010/11/S1/P5

Genome Biology

POSTER PRESENTATION Open Access

A replicative association study of Chromosome 6p21.3 with susceptibility to leprosy in an Indian population - 'a string hypothesis'

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From Beyond the Genome: The true gene count, human evolution and disease genomics
Boston, MA, USA. 11-13 October 2010

Introduction

Leprosy is a chronic infectious disease, caused by *Mycobacterium leprae,* which affects mainly the skin and nerves of the host and results in characteristic deformity and disability. The role of host genetic factors in conferring susceptibility to this disease has long been a focus of research, with the discovery of many loci by segregation, twin and case-control studies [1,2]. Here we propose how a perturbation involving a 'string' of DNA, co-evolved with a cluster of genes, provides a basis to the susceptibility to a this complex disease.

Materials and methods

We conducted a systematic three-stage, high resolution scan of the 6p21.3 chromosomal region of 177kb, within HLA class I and III region, with 111 SNPs genotyped using Sequenom Mass Array. We included a total of 2301 individuals, including patients and controls from the North Indian population and replicated our results in an East Indian population, from the geographically distinct state of Orissa.

Results

We identified SNP variants along the length of the 'string' of 6p21.3 with multiple genes from HLA class III and HLA class II that were significantly associated with leprosy and its polar subgroups. Table 1

Table 1 Significant *P*-values for SNPs in 6p21.3 region

SNP (rs-ID)	Function	Significant *P*-value
rs2523504	BAT1 promoter	5.1 E-05
rs2230365	NFKBIL1 exon3	8.6E-06
rs13192469	LTA 13kb upstream	1.5E-04
rs36221459	LTA promoter	4.9E-04
rs1800629	TNF-308 promoter	5.5E-04
rs769178	TNF-LTB downstream	8.8E-04
rs3135365	HLA class II BTNL2-DRA	1.73E-22
rs7773756	HLA class II BTNL2-DRA	2.8E-17

Conclusion

In addition to discovering the function of the genes *BAT1* and *BTNL2,* we also established the functional status of the SNPs through *in-vitro* reporter assays. Furthermore, our assessment of an interaction of multiple genes in unison within the 'string' provided us with a graded risk to leprosy, which is dependant on the combination of genotypes of the significantly associated functional SNPs. Our results provide the first demonstration of the genome combinations of the polar forms of leprosy and the role of independent SNPs/genes in reaction states of the leprosy.

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Published: 11 October 2010

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doi:10.1186/gb-2010-11-S1-P5
Cite this article as: Ali *et al.*: A replicative association study of Chromosome 6p21.3 with susceptibility to leprosy in an Indian population - 'a string hypothesis'. *Genome Biology* 2010 **11**(Suppl 1):P5.