Functional and Structural Characterization of Exonic SNPs associated with Leprosy Risk: an *In Silico* Analysis

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INTRODUCTION

Leprosy, caused by *Mycobacterium leprae*, shows variations in individual susceptibility, which may be linked to genetic differences in the exome. Exonic single nucleotide polymorphisms (SNPs) can influence immune response and disease progression. This study aimed to analyze, *in silico*, the functional and structural impact of exonic SNPs associated with leprosy susceptibility.

METHODS

Literature data on leprosy-risk SNPs were retrieved from PubMed and SciELO. Analyses were conducted on synonymous (sSNP) and non-synonymous SNPs (nsSNP). For sSNPs, predictions included effects on mRNA structure (RNAfold, CycleFold, Kinefold), splicing (MaxEnt Scan, Ex Skip), and miRNA binding (TargetScan Score). For nsSNPs, protein damage was assessed using SIFT, PolyPhen 2, PhD-SNP, SNPs & GO, and Predict SNP 2. Pathogenicity filters identified 11 nsSNPs for further analysis of stability (CUPSAT), functionality (MutPred), and evolutionary conservation (ConSurf).

RESULTS

The functional and structural effects of sSNPs associated with the higher risk of leprosy are described in Table 1.

Gene	SNP ID	RNAfold (Energy) in ΔΔG (Kcal/mol)	Kinefold (Pseudoknots) (Kcal/mol)	Cyclefold (Noncanonical base pairings)	MaxEntScan in ΔΔG (Kcal/mol)	EX SKIP	TargetScan and Target Scan S (Score)	Global MAF*
TGFBR2	rs2228048	0.20	1.4	7.1	15.36	Without mut: 50, 111, 0,45 /With mut: 57, 111, 0.51	-0.21	0.103
NFKBIL1	rs2230365	-0.30	-0.8	7.2	-22.14 (equal)	Without mut: 48, 56, 0.86 /With mut: 48, 60, 0.80	-0.02	0.1418
FCN1	rs10858293	0.50	1.7	6.6	-1.73 (equal)	Without mut: 29, 66, 0.44 /With mut: 29, 70, 0.41	-0.03	0.2456
TLR2	rs3804099	0.20	0	6.3	-22,53 (equal)	Without mut: 37, 98, 0.38 /With mut: 34, 96, 0.35	-0.01	0.4147
PINK1	rs4704	0.30	0.4	5.8	-19.32 (equal)	Without mut: 14, 42, 0.33 /With mut: 14, 43, 0.33	-0.02	0.5873
IL10	rs3180946	0.00	17.1	6.9	-25.71 (equal)	Without mut: 57, 71, 0.80 /With mut: 51, 71, 0.72	-0.35	0.1849

*Frequency of existing variant in 1000 Genomes combined population.

The functional effects of nsSNPs associated with higher leprosy risk are described in Table 2.

Gene	SNP ID	Amino Acid Change	SIFT	Poly Phen 2	PhD-SNP	SNPs & GO	Predict SNP 2#	FunSeq	CADD	DANN	GWAVA	FATHMM
TLR2	rs5743708	R753Q	D	D	D	D	D	D	T	D	D	D
TLR1	rs4833095	N248S	T	T	T	T	T	D	T	T	a	D
PTPN22	rs2476601	W620R	T	T	T	T	T	T	T	T	D	T
TAP1	rs1057141	I333V	T	T	T	T	T	D	T	T	D	T
TAP1	rs1135216	D637G	T	T	T	T	T	T	T	T	a	T
TAP2	rs2228396	A565T	T	T	T	T	T	D	T	T	D	T
TAP2	rs241447	T665A	D	T	T	T	T	T	T	T	T	T
CFH	rs1065489	E936D	T	D	T	T	T	T	T	T	a	T
TLR1	rs5743618	S602I	T	T	T	T	T	T	T	T	D	T
TLR2	rs3804100	S450R	T	T	T	T	T	T	T	T	T	T
SLC29A3	rs780668	S158F	a	D	D	T	D	T	D	D	D	D
HIF1A	rs142179458	D349N	T	T	D	D	D	D	D	D	a	D
GAL3ST4	rs3823646	A467V	T	T	T	T	D	D	D	D	a	D
APOE	rs429358	C156R	T	T	T	D	D	D	D	D	a	D
APOE	rs7412	R202C	D	D	T	D	D	D	D	D	D	T
NCKIPSD	rs145562243	R176L	D	D	T	T	D	D	D	D	D	T
CARD9	rs149308743	R494H	D	D	T	T	T	D	D	D	T	T
IL23R	rs76418789	G149R	D	D	D	D	T	D	T	T	T	T
TYK2	rs55882956	R703W	D	D	D	D	T	T	D	D	T	T
IL27	rs181206	L119P	T	D	T	T	T	T	T	D	a	T
MRPS5	rs200730619	Y137C	T	T	D	T	T	T	T	T	a	T
IL-17F	rs763780	H161R	T	T	T	T	T	T	T	T	a	T
SLC22A9	rs1801401	T314N	T	T	T	T	T	T	T	T	D	T
NOD2	rs104895438	A612T	D	D	T	D	D	D	N	D	a	D
LACC1	rs3764147	I254V	T	T	T	T	T	N	N	N	D	N
TLR5	rs2072493	N592I	T	T	T	T	T	N	D	N	N	D
PKLR	rs1052176	R569W	T	D	D	D	T	N	N	N	a	N
ENPP1	rs1044498	K173Q	T	B	N	D	N	N	N	N	A	N
IRAK2	rs708035	D431E	T	B	N	N	N	N	N	N	D	N

a Not found. *Frequency of existing variant in 1000 Genomes combined population. # Predict SNP 2. D= Deleterious. T= Tolerated.

The structural effects of nsSNPs associated with higher leprosy risk are described in Table 3.

Gene	SNP ID	Stability	SS Element	Torsion	Predicted ΔΔG (kcal/mol)
TLR2	rs5743708	Stabilising	Other (turns, coils, etc.)	Favourable	1.01
SLC29A3	rs780668	Destabilising	Helix	Unfavourable	-1.0
HIF1A	rs142179458	Destabilising	Other (turns, coils, etc.)	Favourable	-0.66
APOE	rs429358	Destabilising	Helix	Favourable	-3,63
APOE	rs7412	Stabilising	Helix	Unfavourable	8.67
NCKIPSD	rs145562243	Destabilising	Other (turns, coils, etc.)	Unfavourable	-5.53
CARD9	rs149308743	Destabilising	Helix	Unfavourable	-0.13
IL23R	rs76418789	Destabilising	Other (turns, coils, etc.)	Unfavourable	-0.67
TYK2	rs55882956	Stabilising	Other (turns, coils, etc.)	Unfavourable	0.76
NOD2	rs104895438	Destabilising	Helix	Unfavourable	-2.24
PKLR	rs1052176	Stabilising	Sheet	Favourable	0.3

The structural patterns in relation to the molecular alterations and conservation of the nsSNPs associated with a higher risk of leprosy are described in Table 4.

Gene	SNP ID	MutPred		ConSurf Conservation Profile
		PROSITE and ELM Motifs	Molecular Mechanisms	
TLR2	rs5743708	None	None	Highly conserved, exposed, functional residue.
SLC29A3	rs780668	ELME000053, ELME000063, ELME000173, ELME000333, ELME000336	Altered Transmembrane protein; Loss of Loop; Loss of Strand	Highly conserved, exposed, functional residue.
HIF1A	rs142179458	None	None	Variable, exposed residue.
APOE	rs429358	None	None	Average conserved, exposed residue.
APOE	rs7412	None	None	Highly conserved, exposed, functional residue.
NCKIPSD	rs145562243	None	None	Conserved, exposed residue.
CARD9	rs149308743	None	None	Average conserved, exposed residue.
IL23R	rs76418789	ELME000008, ELME000053, ELME000102, ELME000106, ELME000146, PS00004	Gain of Disulfide linkage at C144; Altered Transmembrane protein; Loss of Sulfation at Y153	Highly conserved, exposed, functional residue.
TYK2	rs55882956	None	None	Variable, exposed residue.
NOD2	rs104895438	ELME000052, ELME000336	None	Highly conserved, buried, structural residue.
PKLR	rs1052176	ELME000106, ELME000173	Loss of Intrinsic disorder; Altered Ordered interface; Altered Transmembrane protein; Gain of Strand; Loss of Relative solvent accessibility; Altered DNA binding; Loss of O-linked glycosylation at S574; Gain of GPI-anchor amidation at N566	Highly conserved, buried residue.

CONCLUSIONS

This study identified 12 exonic SNPs (1 sSNP and 11 nsSNPs) as potential candidates for further *in vivo* studies on leprosy. These SNPs reveal complex interactions between genetic variations and their functional consequences, contributing to the understanding of disease mechanisms.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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