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Family-based genetics identifies association of *CUBN*, *IL1RL1* and *PRKN* variants with leprosy in Bangladesh

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Previous studies have demonstrated the association between the occurrence of leprosy and several host genetic variants that can vary across different ethnic groups and populations. Since leprosy susceptibility genes have not been investigated in detail in the Bangladeshi population that still includes highly endemic areas, we here studied known associations between leprosy and 13 genetic markers located in 11 genes in a leprosy endemic area in Bangladesh for which an association with leprosy was previously found in an isolated former leprosy colony in the Brazilian Amazon. For this study, a family-based analysis using 60 parent-affected child trios was performed, followed by a case-control study of 210 leprosy patients and 189 healthy controls from the same area (endemic controls). Genotypes for 11 markers were determined by TaqMan SNP genotyping. In the family-based study, a significant association was found between leprosy and three single nucleotide polymorphisms, rs1801224, rs13001714, and rs1801582, located in the *CUBN*, *IL1RL1*, and *PRKN* genes, respectively. These findings were not replicated in the case-control sample. Variants in the *CUBN*, *IL1RL1*, and *PRKN* genes were associated with leprosy in Bangladesh, validating the initial Brazilian finding in a population sample of distinct ethnic background.

Keywords Leprosy, Bangladesh, Genetics, Association study, Family-based

Leprosy is a chronic infectious disease caused by *Mycobacterium leprae* and *M. lepromatosis* that affects skin and peripheral nerve cells that can cause permanent disabilities[1]. The leprosy prevalence has globally decreased over the years due to efficient treatment with multidrug therapy (MDT) consisting of a combination of rifampicin, clofazimine, and dapsone. However, the disease still poses a significant challenge to public health, especially in low- and middle-income countries, bearing more than 180,000 reported new cases annually[2]. Leprosy can present in different clinical manifestations depending on the hosts' immune response against the mycobacteria, ranging from tuberculoid (TT) disease, characterized by the presence of few skin lesions with undetectable bacilli and strong cell-mediated immunity, lepromatous (LL) disease, defined by the presence of multiple lesions with high bacillary load and strong humoral immunity. Borderline patients (BT, BB, BL) display variable combinations of TT and LL features between these two poles[3,4].

It is widely accepted that clinical leprosy, as an outcome of infection with *M. leprae*, will likely require a combination of pathogen burden as well as environmental and genetic susceptibility factors, meaning that sole exposure to the pathogen is insufficient to trigger disease manifestations. The interindividual variability of leprosy phenotypes is largely controlled by genetically determined host characteristics[5]. This hypothesis has been investigated through various observational studies, including twin studies[6,7], familial aggregation studies[8], and complex segregation analyses[9–13]. A population-based complex segregation analysis in the Prata Village, an isolated former leprosy colony located in the Brazilian Amazon allowed to identify a major gene effect controlling leprosy susceptibility in the Prata Village, indicating its ideal fit for genetic association studies[12].

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Over the past century, more than 30 *loci* throughout the human genome have been associated with leprosy phenotypes through molecular studies in leprosy endemic populations, suggesting that the host genetic background strongly influences leprosy susceptibility and pathogenesis[3,14]. The first positional cloning candidate *loci* to harbor leprosy susceptibility genes were located at the 10p13, 6q25-27, and 6p21 (the human leukocyte antigen – HLA) chromosomal regions, as described in Indian and Vietnamese populations[15,16]. A subsequent high-resolution linkage disequilibrium (LD) mapping of the 6p21.3 region led to the identification of a functional single nucleotide polymorphism (SNP) in the HLA class III gene *LTA* as a risk factor for early-onset leprosy in the Vietnamese and North Indian populations[17,18]. Moreover, SNPs in *MRC1*, *CUBN*, and *NEBL* genes, located in the 10p13 region, were also associated with MB leprosy in the Vietnamese and Indian populations[15,19,20]. Fine-mapping association studies performed to investigate the 6q25-q27 region further, showed that two SNPs at the regulatory region shared by *PACRG* and *PRKN* (formerly known as *PARK2*) genes were strongly associated with leprosy[16,21]. The first genome-wide association study (GWAS)[22], performed on a Chinese population, identified *NOD2* polymorphisms, among others, associated with leprosy. Variants of *IL23R* were associated with leprosy in Vietnamese and Chinese populations[23,24], whereas an increased number of copies of this receptor were found in Indian leprosy patients[25].

Although combining different molecular strategies and study designs has identified several genes associated with leprosy, validating these findings in different population samples of distinct ethnic backgrounds is not always successful. This may be explained by diverse genetic backgrounds amongst populations or intrinsic differences between studies. To identify risk factors for leprosy, it thus remains of interest to further investigate and validate the association of genetic markers with leprosy in different leprosy endemic areas worldwide. The present work targeted a population sample from a leprosy endemic area in Bangladesh, to validate the association between leprosy and 13 genetic variants located in 11 genes (*ADO*, *BCL10*, *CCDC88B*, *CUBN*, *DELEC1*, *IL1RL1*, *IL12RB2*, *IL23R*, *LTA*, *NOD2*, and *PRKN*). These genes were all previously demonstrated to be associated with an increased risk of leprosy in different independent studies and populations[22,24,26,27], including the Prata Village, an isolated former leprosy colony located in the Brazilian Amazon (Mira et al., unpublished).

The association between host genetics and leprosy has been understudied in Bangladesh, a country presenting areas with high leprosy endemicity. To date, only two studies have addressed host genomics in the context of leprosy in the Bangladeshi population. The first one found an association between leprosy and the variant N248S of the Toll-like receptor 1 (*TLR1)* gene[28]; the second investigated the role of *TIRAP* S180L polymorphism in malaria, sepsis, and leprosy, but identified no significant association for any of the investigated diseases[29]. This study further explores genetic associations with leprosy in Bangladesh, applying a combination of a powerful family-based design and an independent case-control replication sample.

Materials and methods

Study design and ethics statement

The discovery, family-based sample consisted of 60 family trios composed of one affected offspring ($n = 60$) and both progenitors ($n = 118$, including a multi-case family) recruited in Bangladesh. In addition, a replication, case-control sample of 210 leprosy patients and 189 unrelated endemic controls (EC) was enrolled from the same population (Fig. 1; Table 1).

Subjects from both sets were recruited in four districts of Bangladesh (Nilphamari, Rangpur, Panchagar, and Thakurgaon) according to the Helsinki Declaration (2008 revision), and the study was approved by the National Research Ethics Committee (BMRC/NREC/2016–2019/214). Participants were informed about the study objectives and their right to refuse to take part or withdraw without consequences for their treatment. All subjects gave informed consent before enrollment, and all patients received treatment according to national guidelines.

DNA isolation

Whole blood was obtained by venipuncture and transferred to heparin tubes. According to the manufacturer's instructions, DNA isolation was performed using QIAamp DNA Blood Midi Kit (Qiagen, Hilden, Germany) or automated Maxwell RSC Whole Blood DNA Kit (Maxwell, San Diego, CA).

SNP selection and genotyping

The 13 genetic markers selected for the present study were previously identified to be associated with leprosy susceptibility in an exon-sequencing-based study involving a family-based population sample from the Prata Village, a former leprosy colony isolated in the Brazilian Amazon state of Pará (Mira et al., unpublished). Markers were selected if (i) causing an amino-acid change, (ii) predicted to be deleterious in silico, (iii) predicted as an eQTL, or (iv) explained (through linkage disequilibrium - LD) previous leprosy association findings. Fluorescence-based genotyping was performed using TaqMan Genotyping (Thermo Fisher Scientific, Waltham, MA), as implemented in the QuantStudio 6 Flex Real-Time PCR System (Applied Biosystems, Foster City, CA). Mixes contained 20 ng of purified DNA, 0.5 µl of TaqMan SNP Genotyping Assay (Thermo Fisher, including forward and reverse primers and two TaqMan probes labeled differently, with VIC and FAM dyes, Table S1) and 5 µl of TaqMan Genotyping Master Mix in a final volume of 10 µl. Genotypes were determined with Thermo Fisher Cloud Genotyping Application (Thermo Fisher Scientific) by analyzing the allelic discrimination plots.

Statistical analysis

Family-based association analyses were performed using the transmission disequilibrium test (TDT) as implemented in FBAT v2.0.4Q[30] and PLINK v1.90b6.18[31]. Haplotypic analysis of the *IL1RL1* gene was performed using the hbat function on FBAT. Hardy-Weinberg equilibrium (HWE) and linkage disequilibrium (LD) were

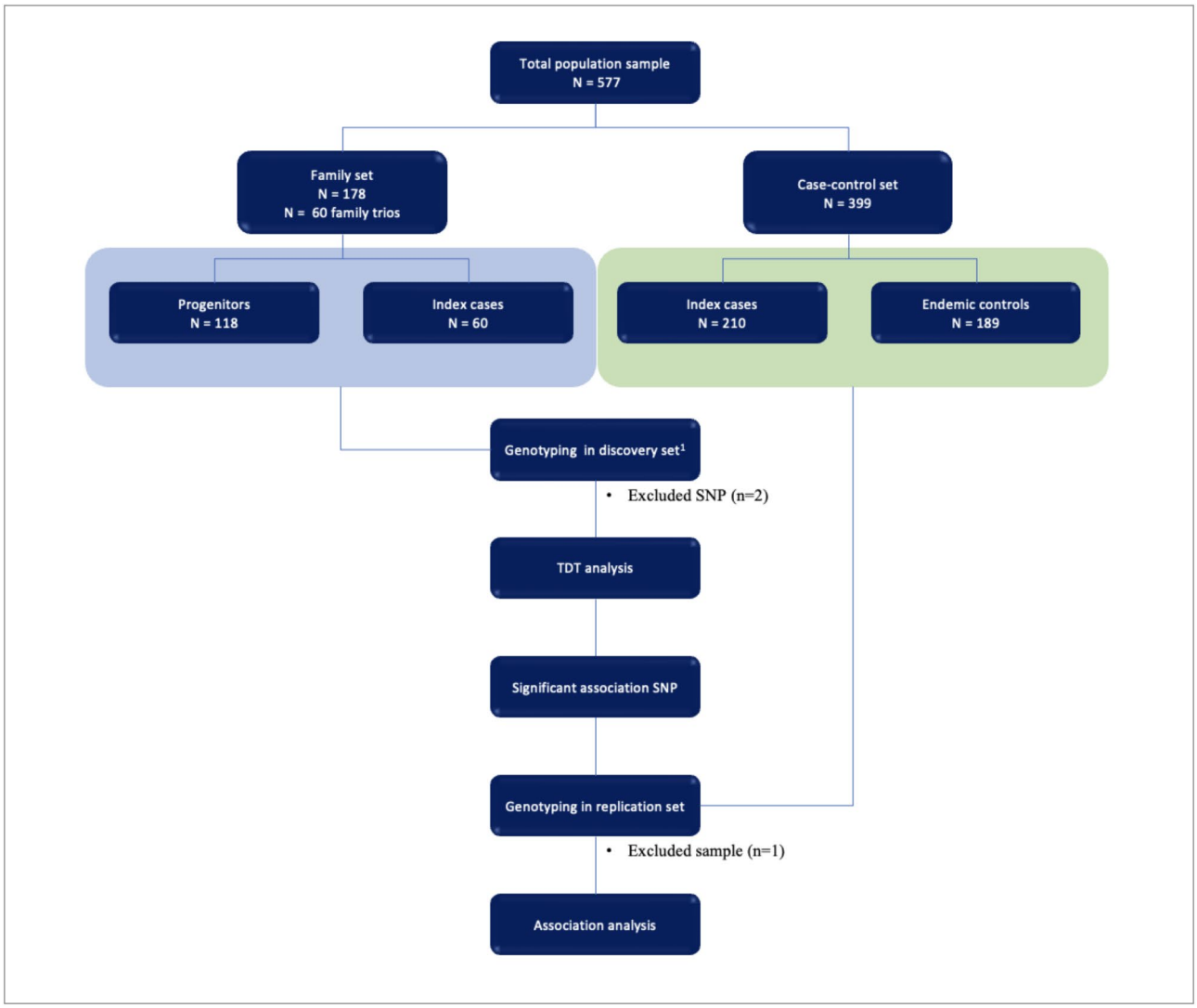

Fig. 1. Schematic representation of the study design. The selection of tested SNPs ($n = 13$) was based on the identification of susceptibility genes in a previous study in a Brazilian population, former leprosy colony in the Brazilian Amazon (Mira et al., unpublished data). Two SNPs were excluded from the analysis due to low allele frequency in Bangladesh (rs1801225) and high amplification failure rate (rs224082). One sample of endemic controls was excluded due to non-amplification. The light blue box indicates discovery samples; the light green indicates replication samples. *TDT* Transmission disequilibrium test, *SNP* Single-Nucleotide Polymorphism.

	Family set ($n = 60$)		**Case-control set ($n = 399$)**		
Group	**BT patients ($n = 50$)**	**BL/LL* patients ($n = 10$)**	**BT patients ($n = 143$)**	**BL/LL** patients ($n = 67$)**	**Endemic controls ($n = 189$)**
Age (median)	21	26	35	35	36
Females	12	1	66	8	115
Male	38	9	77	59	74
BI (n)	BI-0 (43) BI-und (7)	BI-4 (2) BI-5 (2) BI-6 (6)	BI-0 (143)	BI-2 (1) BI-3 (3) BI-4 (21) BI-5 (24) BI-6 (18)	NA

Table 1. Description of the study populations. Characteristics of leprosy affected offspring (family set) and of leprosy patients and controls (case-control set). *3 BL, 7 LL; **37 BL, 30 LL. *RJ* Ridley & Jopling, *BT* borderline tuberculoid, *BL* borderline lepromatous, *LL* lepromatous, *BI* bacteriological index, *BI-und* bacteriological index undetermined, *NA* not applicable.

Gene	dbSNP ID	Chromosomal region	Allele	AF	IF	*p*-value[a]
BCL10	rs1060846	1p22.3	A	0.396	41	0.741
CCDC88B	rs542907	11q13.1	A	0.438	32	0.450
CUBN	rs1801224	10p13	G	0.429	33	**0.045**
DELEC1	rs2285316	9q33.1	G	0.308	39	0.139
IL1RL1	rs1041973	2q12.1	A	0.104	21	0.100
	rs13001714		G	0.329	37	**0.016**
IL12RB2	rs10489627	1p31.3	G	0.292	40	0.167
IL23R	rs10889677	1p31.3	A	0.637	20	0.806
LTA	rs1041981	6p21.33	A	0.254	33	0.176
NOD2	rs3135499	16q12.1	C	0.204	27	0.768
PRKN	rs1801582	6q26	C	0.746	13	**0.047**

Table 2. Analysis of the association between candidate gene markers and leprosy per se in the family set. The TDT results are shown for the dominant model, using the complete sample of 60 family trios. *dbSNP ID* marker identification in the SNP database, *AF* allele frequency, *IF* number of informative families. [a]Raw p-values in bold are < 0.05.

Haplotype	Frequency	Allele rs1041973	Allele rs13001714	IF	Z	*p*-value
#1	0.592	***C***	***A***	43	2.540	**0.011**[a]
#2	0.304	***C***	G	39	-2.258	**0.024**[b]

Table 3. Haplotypic analysis between leprosy and variants of the IL1RL1 gene. *IF* number of informative families, *Z* Z score; p-values < 0.05 are in bold. The risk allele of each marker is in bold and italics. [a]Additive model; [b]Dominant model.

estimated using Haploview Software (version 4.2)[32]. To check for the independence of positive association signals in the family-based sample, we performed a pseudo-sibling analysis generating three matched unaffected pseudo-sibs for each offspring, using parental genotype data[33], followed by a conditional logistic regression analysis (LOGISTIC function) to generate the odds ratio, as implemented in SAS software v.9.1 (SAS Institute, Cary, North Carolina, USA).

Markers associated in the TDT were tested for replication in the case-control set. Comparative analysis between cases and controls was performed using a common logistic regression adjusted by sex. Analysis was carried out using R v4.0.4[34] with the package SNPassoc[35].

Results

First, to allow for proper analysis, a sample lacking integrity or sufficient DNA quantity was excluded from the analysis due to its failure to amplify (Fig. 1). For all tested markers except rs1801225 and rs224082, the genotyping success rate was >95%, Thus, rs1801225 and rs224082 were excluded from the analysis due to MAF < 0.05 for rs1801225 and a 79.2% rate of failed amplifications for rs224082. Allele frequencies for the remaining 11 markers were in HWE in the control population, and weak LD was detected between the *IL1RL1* gene markers ($r^2 = 0.22$).

Family-based association analysis included 50 BT (83%) and 10 BL/LL (17%) leprosy-affected offspring (Table 1). TDT following the dominant model showed a significant association of allele C of *PRKN* marker rs1801582 (p-value = 0.047) with leprosy per se (Table 2). Allele G of *CUBN* marker rs1801224 (p-value = 0.045) and allele G of *IL1RL1* marker rs13001714 (p-value = 0.016) were associated with leprosy protection. Finally, allelic distribution of *IL1RL1* marker rs1041973 showed a trend towards leprosy protection for allele A (p-value = 0.100), although not statistically significant. A haplotype analysis including *IL1RL1 markers* revealed a protective association between leprosy and haplotype #2, which contains the protective allele of the marker rs13001714, under the dominant model (p-value = 0.024). Additionally, haplotype #1, containing the risk alleles of the two independent *IL1RL1* markers, was significantly associated with susceptibility to leprosy per se under the additive model (p-value = 0.011; Table 3). Pseudo-sibs conditional regression analysis confirmed the associations for *CUBN* marker rs1801224 and *IL1RL1* rs13001714 (Table 4).

The three markers showing evidence for association with leprosy (rs1801582, rs1801224, and rs13001714) were tested in a replication case-control sample set (Fig. 1). Significant differences in the sex distribution between cases and controls were observed, with a higher number of males in the case group (p-value = $5.31 \cdot 10^{-7}$, Mann–Whitney U test). No difference was observed in the age between cases and controls; however, a significant difference in the age was found between patients in the case group and index patients in the family set (p-value = $2.97 \cdot 10^{-13}$, Mann-Whitney U test). Association analysis adjusted by sex did not show a significant association of any of the three markers with leprosy in the case-control sample set. However, *IL1RL1* marker rs13001714 showed a tendency for association (p-value = 0.133) under the dominant model (Table 5).

Gene	dbSNP ID	m/M	*p*-value[a]	OR (95% CI)
CUBN	rs1801224	G/T	**0.0293**	**0.444 (0.214–0.921)**
IL1RL1	rs1041973	A/C	0.1075	0.472 (0.189–1.177)
IL1RL1	rs13001714	G/A	**0.0135**	**0.417 (0.209–0.835)**
PRKN	rs1801582	G/C	0.9304	1.031 (0.519–2.048)

Table 4. Results of conditional logistic regression analysis in Bangladesh family-based set after pseudo-sibs generation. *dbSNP ID* marker identification in the SNP database; *m/M* minor/Major alleles; *OR* odds ratio; *CI* confidence interval and p-value (in bold p-values < 0.05). [a]Results relative to dominance for the most frequent allele.

Gene	dbSNP ID	Genotype	Cases	Controls	OR (95% CI)[a]	*p*-value[a]
CUBN	rs1801224	GG + GT	136 (0.67)	124 (0.67)	0.89 (0.57–1.39)	0.611
		TT	67 (0.33)	60 (0.33)		
IL1RL1	rs13001714	GG + AG	130 (0.62)	102 (0.54)	1.37 (0.91–2.07)	0.133
		AA	80 (0.38)	87 (0.46)		
PRKN	rs1801582	GG + GC	103 (0.50)	86 (0.55)	1.11 (0.74–1.67)	0.619
		CC	104 (0.50)	103 (0.45)		

Table 5. Case-control replication analysis of markers associated with leprosy in the family-based analysis in Bangladesh. Logistic regression analysis adjusted by sex. *dbSNP ID* marker identification in the SNP database, *OR* odds ratio, *CI* confidence interval. [a]Results of the association analysis (p-value and OR) are shown for the dominant model.

Association analysis stratified by leprosy type (BT vs. BL/LL) did not reveal any further association signal with these phenotypes (data not shown).

Discussion

It is widely accepted that host genetics play a significant role in susceptibility to leprosy phenotypes, including leprosy per se, clinical forms of disease, and the occurrence of leprosy reactions[3,21,22,36]. Nevertheless, differences in the pattern of association of genetic variants and leprosy are found between distinct populations, emphasizing the importance of replicating and validating genetic associations in populations from diverse ethnic backgrounds. To date, the only reported genetic association with leprosy susceptibility in the Bangladeshi population involves the homozygous genotype (S248 variant) of the *TLR1* gene. The heterozygous SN genotype was found to be protective against leprosy[28].

Family-based analysis in a Bangladeshi population revealed evidence for an association between leprosy and one marker of each of the three previously identified leprosy susceptibility genes *CUBN* (rs1801224), *IL1RL1* (rs13001714), and *PRKN* (rs18015820). For the *IL1RL1* gene, an additional marker (rs1041973) showed borderline significant association (p-value = 0.100). Weak LD ($r^2 = 0{,}22$) between the two *IL1LR1* markers suggests two independent association signals. Replicating the results in the case-control sample was unsuccessful, although suggestive evidence for association was observed for rs13001714 (p-value = 0.133). The lack of validation is possibly due to the observed difference in the age of leprosy onset between the two samples as the leprosy cases in the family-based set were younger adults (median age = 26) than those in the case-control sample (median age = 35). Furthermore, the slightly higher percentage of BL/LL leprosy cases in the case-control sample, or lack of power in the relatively small case-control sample also impeded proper validation for genetic associations. Moreover, family-based genetic association studies resist classic confounders such as population stratification and poor definition of unaffected controls[37], often providing more reliable results than case-control studies.

This report represents the first study validating the association between leprosy and *CUBN* variants, first observed in a Vietnamese population for rs10904831[19], a marker in very low LD ($r^2 = 0.08$) with rs1801224, indicating at least two independent signals. Interestingly, previous genome-wide linkage analysis conducted in India and Vietnam identified a susceptibility locus on chromosome 10p13[15,16], where *CUBN* is located, suggesting that this region may be involved in leprosy polarization. *CUBN* encodes Cubilin, a receptor for intrinsic factor-vitamin B12 complexes[38]. It was shown that Rv1819c, a homolog of the *M. leprae* protein ML2084 in *Mycobacterium tuberculosis*, is involved in vitamin B12 uptake[39]. Thus, host's Cubilin may compete with mycobacterial proteins during infection[19].

An association between leprosy per se and *IL1RL1* was previously found in a Chinese population. The *IL1RL1* gene is located on the 2q12.1 chromosomal region in a cluster containing the *IL18* receptor genes[40]. *IL1RL1* encodes the receptor of IL-33 that regulates the expression of Th2 cytokines[41]. Binding of IL1RL1-IL-33 leads to the activation of nuclear factor-kB (NF-kB), essential for mycobacterial immunity[40]. A study published in 2013[42] demonstrated that missense variations in *IL1RL1* can increase levels of its gene product (namely ST2) and

consequently alter its signaling pathway via (i) an increase in ST2 expression, amplifying IL-33 responsiveness; and (ii) increased activation of IL-33 through enhanced NF-κB and AP-1 signaling pathways.

Variants in the *PRKN* gene have been identified as major leprosy susceptibility *locus*[16,21]. Interestingly, the *PRKN* association observed in the TDT was not replicated in the pseudo-sib analysis or the case-control sample set. This is likely due to the low information content of marker rs1801582, evidenced by the small number of 13 informative families in the TDT (Table 2). *PRKN* codes Parkin, a protein part of the E3 ubiquitin ligase complex, involved in regulating the immune response to mycobacteria and other intracellular pathogens[43,44]. Parkin regulates autophagy of damaged molecules, intracellular pathogens, or organelles such as mitochondria (mitophagy)[5]. The Parkin-mediated xenophagy eliminates mycobacteria and is crucial to inhibiting the replication of *M. tuberculosis* in macrophages[44]. In addition, Parkin is involved in other immunological pathways by regulating the levels of cytokines IL-6 and MCP-1 *(CCL2)*[43]. de Léséleuc and collaborators demonstrated that silencing *PRKN* in three different human cell types (Schwann cells, THP-1 macrophages, and monocyte-derived macrophages) and stimulating these cells with mycobacteria or LPS led to a significant and selective decrease in IL-6 and MCP-1 levels[43]. Furthermore, variants in the *PRKN* promoter region were significantly correlated with *CCL2* and *IL6* transcript levels after stimulation with *M. leprae* sonicate in whole blood assays[43]. To investigate how *PRKN* variants affect the interaction of its protein with pro- and anti-inflammatory molecules, a study conducted in 2014 analyzed the genotypes of 829 leprosy patients and 1,476 unrelated healthy controls from Northern India[45]. Through combined genotype analysis and in-silico protein-protein interaction (PPI) modeling, the authors proposed that the variants rs9365492 and rs9355403, located in the regulatory region of *PRKN*, interact with SNPs in *IL-10*, *IL-6*, *TGFBR2*, *TNF*, and *BTNL2-DR* genes; increasing the risk of leprosy susceptibility (combined OR = 2.54). Conversely, an interaction between parkin and SNPs in *BAT1*, *NFKBIL1*, *LTA*, *TNF-LTB*, *IL12B*, and *IL10RB* was identified (combined OR = 0.26), suggesting a significant protection against leprosy. Finally, there is a large body of evidence involving Parkin in the pathogenesis of Parkinson's disease[46].

Our results must be interpreted with two potential limitations in mind: (i) both sample sizes are relatively small; and (ii) p-values have not been adjusted for multiple testing. However, these limitations are addressed by the study's context, which was designed to validate candidate genes/markers selected based on previous positive association results. In this context, our positive validation evidence obtained through a robust family-based approach compensates for any potential lack of statistical power. Moreover, independent validation of association findings in different population samples is a more effective way to detect false positives compared to overly conservative statistical corrections like Bonferroni.

In summary, our results in the family-based sample provide additional evidence of the association between leprosy and variants of the *CUBN*, *IL1RL1*, and *PRKN*, genes previously identified to be involved in leprosy pathogenesis in ethnically distinct populations[21,22,24,26,27]. For the described genetic markers, the association with leprosy in the Bangladeshi population adds to the goal of identifying a genetic profile for leprosy-risk. Such a profile, potentially combined with other biomarkers, could be applied to target preventive postexposure prophylactic (PEP) strategies in leprosy endemic areas, thereby catalyzing disease prevention, diagnosis and control.

Data availability

The authors state that all data produced in the study are available. Data requests can be addressed to the corresponding author, Annemieke Geluk, via email at a.geluk@lumc.nl.

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Declarations

Competing interests

The authors declare no competing interests.

Additional information

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