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Review Article

LRRK2 Polymorphisms in Leprosy – A Systematic Review Linking Genetic Susceptibility to Immune Dysregulation and Disease Outcome

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Leprosy, caused by *Mycobacterium leprae*, remains a major cause of peripheral neuropathy and disability in endemic regions. Although multidrug therapy effectively reduces bacterial burden, immune-mediated complications such as Type 1 Reactions (T1R) continue to contribute to morbidity. Host genetic factors are increasingly recognised as modifiers of inflammatory responses, and Leucine-Rich Repeat Kinase 2 (LRRK2) has emerged as a gene of interest due to its roles in immune regulation and neuroinflammatory pathways. This analysis has been carried out to synthesise current evidence on LRRK2 polymorphisms associated with leprosy and T1R, evaluate population-specific effects, assess methodological quality and risk of bias, and explore biologically plausible mechanistic overlaps with neuroinflammatory conditions such as Parkinson's disease. A structured literature search was conducted across PubMed, Scopus, and Google Scholar to identify human genetic studies published between 2010 and 2024. Eligible studies examined associations between LRRK2 variants and leprosy-related outcomes using genotyping, whole genome sequencing, deep resequencing, or functional assays. Risk of bias was assessed across five domains using a modified Newcastle–Ottawa framework. Nine studies were included, encompassing Han Chinese, Colombian, Vietnamese, Brazilian, and multi-ethnic populations. Common variants including rs1873613, R1628P, and Thr2397 were frequently reported. R1628P was associated with reduced risk of T1R but increased risk of Parkinson's disease in neurological cohorts, indicating pleiotropic effects. Functional analyses suggested interactions between LRRK2 and immune regulatory pathways, including NOD2 signalling. One study had low risk of bias, five had moderate risk, and three had high risk, with confounding and selection bias as the most frequent concerns. This study shows that LRRK2 polymorphisms are associated with variation in leprosy susceptibility and immune-mediated reactions, with effects that appear to be population-specific and context-dependent. While genetic and functional data support a role for LRRK2 in immune regulation during leprosy, further large-scale and multi-ethnic studies are required to validate these findings and clarify their clinical relevance.

Keywords: Leprosy; Type 1 Reaction, LRRK2, Genetic Polymorphism, Host susceptibility, Immunogenetics

Introduction

Leprosy is a chronic infectious disease caused by *Mycobacterium leprae* and remains a significant public health concern in several endemic regions despite the availability of effective multidrug therapy (WHO 2024, Sharma & Singh 2022).

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Although treatment has substantially reduced bacterial load and transmission, the disease continues to be associated with considerable morbidity due to immune-mediated inflammatory complications, particularly Type 1 (reversal) reactions (T1R) (van Brakel et al 2012, Walker & Lockwood 2008). These acute episodes of inflammation can result in irreversible nerve damage, functional impairment, and long-term disability even after microbiological cure, underscoring the need for early identification of individuals at risk (van Brakel et al 2011, Saunderson 2017).

Host genetic factors are increasingly recognised as important determinants of both susceptibility to leprosy and the development of reactional states (Misch et al 2008, Zhang et al 2021). Variations in genes involved in innate immunity, autophagy, and inflammatory signalling have been associated with differential host responses to *M. leprae* (Alter et al 2011). Among these, Leucine-Rich Repeat Kinase 2 (LRRK2) has emerged as a gene of particular interest due to its dual role in immune regulation and neuroinflammatory pathways (Wang et al 2015, Fava et al 2016).

LRRK2 encodes a multidomain protein with kinase activity that participates in intracellular signalling, vesicular trafficking, mitochondrial homeostasis, and regulation of inflammatory responses in immune cells (Cook et al 2017, Wallings & Tansey 2019). While initially identified in the context of familial Parkinson's disease, LRRK2 has subsequently been shown to influence macrophage activation, cytokine production, and interactions with intracellular pathogen recognition pathways (Gardet et al 2010). These functions are biologically relevant to the immunopathogenesis of leprosy, particularly in the context of exaggerated inflammatory responses such as T1R.

Several genetic association studies across diverse populations have reported links between LRRK2 polymorphisms and leprosy-related outcomes (Cardona-Castro et al 2015). Both common and rare variants including rs1873613, R1628P, and Thr2397 have been associated with either increased susceptibility to leprosy or modulation of T1R risk (Fava et al 2019, Zhang et al 2020). Notably, some variants demonstrate population-specific effects, suggesting that ancestry, genetic background, and environmental context influence the phenotypic impact of these polymorphisms. Furthermore, selected LRRK2 variants implicated in leprosy overlap with those associated with Parkinson's disease, indicating potential shared immune-neuroinflammatory mechanisms rather than direct clinical overlap (Fava et al 2020, Dallmann-Sauer et al 2023).

Advances in genomic technologies have enabled the identification of both common susceptibility alleles and rare variants with potentially larger biological effect sizes (Manry et al 2017, Dallmann-Sauer et al 2021). Complementary functional studies such as expression quantitative trait locus analyses, protein-interaction assays, and cytokine profiling, have provided mechanistic support for the role of LRRK2 in modulating host immune responses to infection (Gardet et al 2010, Dallmann-Sauer et al 2023).

Given the expanding and heterogeneous literature on this topic, a systematic synthesis of available evidence is needed. This review therefore aims to (i) summarise the association between LRRK2 polymorphisms and leprosy susceptibility and T1R, (ii) evaluate population-specific effects, (iii) assess the methodological quality and risk of bias of published studies, and (iv) explore biologically plausible mechanistic links between LRRK2, immune regulation, and neuroinflammatory pathways. By integrating

genetic, functional, and epidemiological evidence, this review seeks to clarify the role of LRRK2 in leprosy pathogenesis and to inform future research directions in immunogenetics and precision medicine for leprosy.

Methodology

Study design

This study was conducted as a systematic review of published human genetic association studies examining the role of *Leucine-Rich Repeat Kinase 2* (LRRK2) variants in leprosy and its immune-mediated complication, Type 1 (reversal) reactions (T1R). The review followed established methodological principles for systematic reviews, including the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Page et al 2021) and adapted quality appraisal frameworks for observational genetic studies (Wells et al 2011). The overall study selection process is illustrated in the PRISMA flow diagram (Fig. 1).

Search strategy

A comprehensive literature search was conducted in PubMed, Scopus, and Google

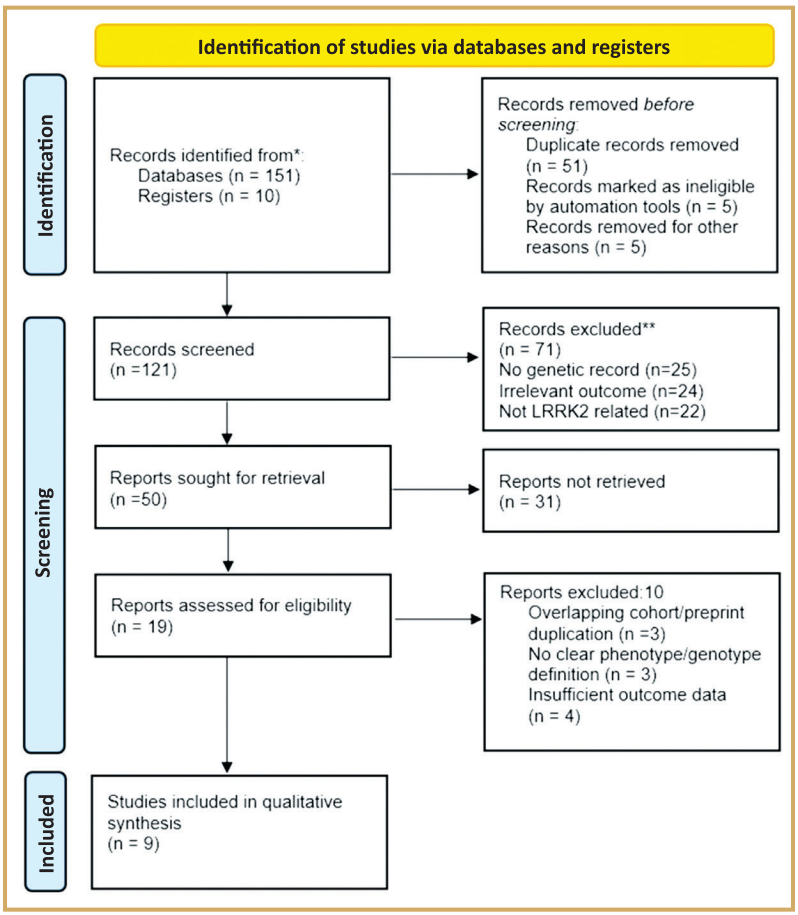

Fig. 1 : PRISMA flow diagram illustrating the study selection process for the systematic review.

Scholar to identify relevant studies published between January 2010 and December 2024. The search strategy combined keywords and Boolean operators as follows: "LRRK2" OR "Leucine-rich repeat kinase 2" AND "leprosy" OR "Hansen's disease" AND "Type 1 Reaction" OR "reversal reaction" OR "T1R" AND "polymorphism" OR "variant" OR "mutation" OR "genetics". The relative frequency of search terms and their combinations is visualised using a word cloud (Fig. 2). The search was restricted to human studies published in English. Reference lists of eligible articles were manually screened to identify additional relevant publications. Grey literature and non–peer-reviewed sources were excluded.

Eligibility criteria

Studies were included if they: (i) involved human participants diagnosed with leprosy or experiencing T1R; (ii) investigated LRRK2 gene variants or haplotypes; (iii) reported associations with leprosy susceptibility, reactional states, or immune response; and (iv) used recognised genetic methodologies such as SNP genotyping, genome-wide association analysis, whole genome sequencing, deep resequencing, or functional assays. Exclusion criteria included in vitro-only studies, animal experiments, case reports without original genetic data, review articles, and studies lacking clear phenotype or genotype definitions. Reasons for exclusion were documented at each screening stage and are presented in the PRISMA flow diagram (Fig. 1).

Study selection

Two reviewers independently screened titles and abstracts for relevance, followed by full-text evaluation of potentially eligible articles. Disagreements were resolved by consensus. A

Fig. 2 : Word cloud for search terminologies.

total of nine studies met the inclusion criteria and were included in the final qualitative synthesis.

Data extraction

Data were extracted using a structured data collection form. Extracted variables included author, year of publication, country and population studied, sample size, study design, genetic methods used, LRRK2 variants analysed, primary outcomes, and key findings. These data are summarised in Table 1, which presents the characteristics of included studies.

Risk of bias assessment

Methodological quality and risk of bias were assessed across five domains: selection bias, measurement bias, confounding, reporting bias, and overall risk of bias. This assessment was adapted from the Newcastle–Ottawa Scale for observational studies (Wells et al 2011) and applied consistently across all included studies. Each domain was rated as low, moderate, or high risk of bias. The results of this assessment are summarised in Fig. 3 and described in the Results section.

Data synthesis

Given the heterogeneity of study designs, populations, outcome definitions, and effect measures, a formal meta-analysis was not performed. Instead, a narrative synthesis approach was adopted, focusing on the direction and consistency of associations across studies, population-specific effects, and biological plausibility based on functional evidence. This approach has been recommended when quantitative pooling is inappropriate (Higgins et al 2020).

Rationale for mechanistic integration

Mechanistic findings related to immune signalling and neuroinflammation were integrated to contextualise genetic associations. The inclusion of Parkinson's disease–related literature was based on shared involvement of LRRK2 in inflammatory and immune regulatory pathways rather than on clinical overlap between the diseases.

Outcome measures

The primary outcome was the association between LRRK2 variants and susceptibility to leprosy or development of T1R. Secondary outcomes included functional evidence of immune modulation, interaction with other immune genes such as NOD2, and potential implications for genetic risk stratification.

Results

A total of nine studies met the eligibility criteria and were included in this systematic review. These studies were published between 2013 and 2023 and investigated the association between *Leucine-Rich Repeat Kinase 2* (LRRK2) variants and leprosy susceptibility or Type 1 Reactions (T1R). The studies were conducted across diverse geographic regions and ethnic populations, including Han Chinese, Colombians, Vietnamese, Brazilians, and multi-ethnic cohorts, thereby allowing for comparative interpretation across different genetic backgrounds. The genetic approaches employed included targeted SNP genotyping, genome-wide association analyses, whole genome sequencing, deep resequencing, and functional validation assays (Table 1).

Genetic associations with leprosy and T1R

Across the nine studies, both common and rare LRRK2 variants were identified. Commonly investigated variants included rs1873613, R1628P, and Thr2397, whereas rare variants were primarily identified through deep resequencing and whole genome sequencing approaches. The clinical outcomes assessed included leprosy susceptibility, early-onset disease, and the development or protection from T1R (Table 1).

Table 1: Detailed summary of study characteristics, including methodology, key findings, limitations, and translational implications.

Study (Author, Year)	Country / Population	Study Design & Methods	LRRK2 Variant(s) Studied	Key Findings	Main Limitations
Fava et al (2016)	Brazil (leprosy patients with and without T1R)	SNP association scan (156 variants), eQTL analysis	Multiple common SNPs	LRRK2 variants associated with T1R susceptibility	Limited functional validation
Wang et al (2015)	China (Han Chinese)	Genotyping of 13 variants, evolutionary selection analysis	Thr2397, others	Thr2397 associated with enhanced immune response and protection	Limited generalisability
Fava et al (2020)	Brazil (T1R-affected vs T1R-free patients)	Rare variant analysis, targeted sequencing	Rare non-synonymous variants	Rare variants overlap between T1R and Parkinson's disease	Not designed to assess common variants
Dallmann-Sauer et al (2023)	Multi-ethnic cohorts	Whole genome sequencing, functional assays	LRRK2 and NOD2 variants	LRRK2–NOD2 interaction linked to early-onset leprosy	Restricted data access, limited replication
Marcinek et al (2013)	Multi-ethnic cohort	SNP genotyping, HWE testing	rs1873613	rs1873613A increases risk, G allele protective	Small sample size, population stratification
Dallmann-Sauer et al (2021)	Multi-ethnic cohorts	Whole genome sequencing, functional validation	R1398H and others	Variants affect immune responsiveness	Gene frequency variability
Fava et al (2019)	Brazil	Deep resequencing, burden testing (SKAT)	R1628P, others	R1628P protective for T1R but risk for PD	Limited sample size
Zhang et al (2020)	China (Han Chinese)	Genotyping in leprosy cohorts	R1628P, PARK2 variants	Shared mutations influence T1R and PD	Lack of replication
Cardona-Castro et al (2015)	Colombia	Genotyping of 36 variants	rs1873613	rs1873613 associated with leprosy susceptibility	Population-specific findings

Genetic associations with leprosy and T1R

Across multiple cohorts, the rs1873613A allele was consistently associated with increased susceptibility to leprosy, particularly in Colombian and multi-ethnic populations. In contrast, the rs1873613G allele appeared to be protective in some cohorts. Variants R1628P and Thr2397 were more frequently associated with reduced risk of T1R and milder inflammatory phenotypes, particularly in Han Chinese, Brazilian, and Vietnamese populations. These findings indicate that LRRK2 polymorphisms modulate host immune responses rather than acting solely as binary susceptibility markers.

Notably, the R1628P variant demonstrated pleiotropic associations. It was protective against T1R in leprosy cohorts but has been reported as a risk variant for Parkinson's disease in neurological studies. This dual association suggests that LRRK2-mediated immune regulation may have context-dependent effects depending on tissue type, immune environment, and disease state.

Methodological quality and risk of bias

The methodological quality of the included studies varied. One study (Fava et al 2019) was assessed as having low risk of bias across all domains. Five studies were assessed as having moderate risk of bias, primarily due to moderate concerns related to selection bias and residual confounding. Three studies (Fava et al 2020, Marcinek et al 2013, Dallmann-Sauer et al 2023) were assessed as having high risk of bias, largely attributable to small sample sizes, population stratification, or deviations from Hardy–Weinberg equilibrium.

Measurement bias was generally low, reflecting the use of validated genotyping platforms and laboratory techniques. However, confounding and selection biases were the most frequently observed limitations. The distribution of risk of bias across domains is illustrated in Table 2.

Stratified and functional insights

Direction of genetic effects

Analysis of the direction of genetic effects demonstrated consistent trends across populations (Fig. 3). The rs1873613A allele was associated with increased susceptibility, whereas R1628P and Thr2397 were associated with reduced inflammatory risk. These trends varied in magnitude across ethnic groups, indicating that ancestry-specific genetic architecture influences phenotypic expression.

Functional validation

Functional studies provided mechanistic support for the observed genetic associations. Studies employing eQTL analysis demonstrated altered expression of immune regulatory

Table 2 : Risk of bias assessment.

Study	Selection Bias	Measurement Bias	Confounding Bias	Reporting Bias	Overall RoB
Fava et al., 2016	Low	Low	Moderate	Low	Moderate
Wang et al., 2015	Low	Low	Moderate	Unclear	Moderate
Fava et al., 2020	Moderate	Moderate	High	Low	High
Dallmann-Sauer et al., 2023	Moderate	Low	Moderate	Moderate	Moderate
Marcinek et al., 2013	High	Low	High	Low	High
Dallmann-Sauer et al., 2021	Moderate	Low	Moderate	Low	Moderate
Fava et al., 2019	Low	Low	Low	Low	Low
Zhang et al., 2020	Moderate	Low	Moderate	Low	Moderate
Cardona-Castro et al., 2015	Moderate	Low	High	Low	Moderate

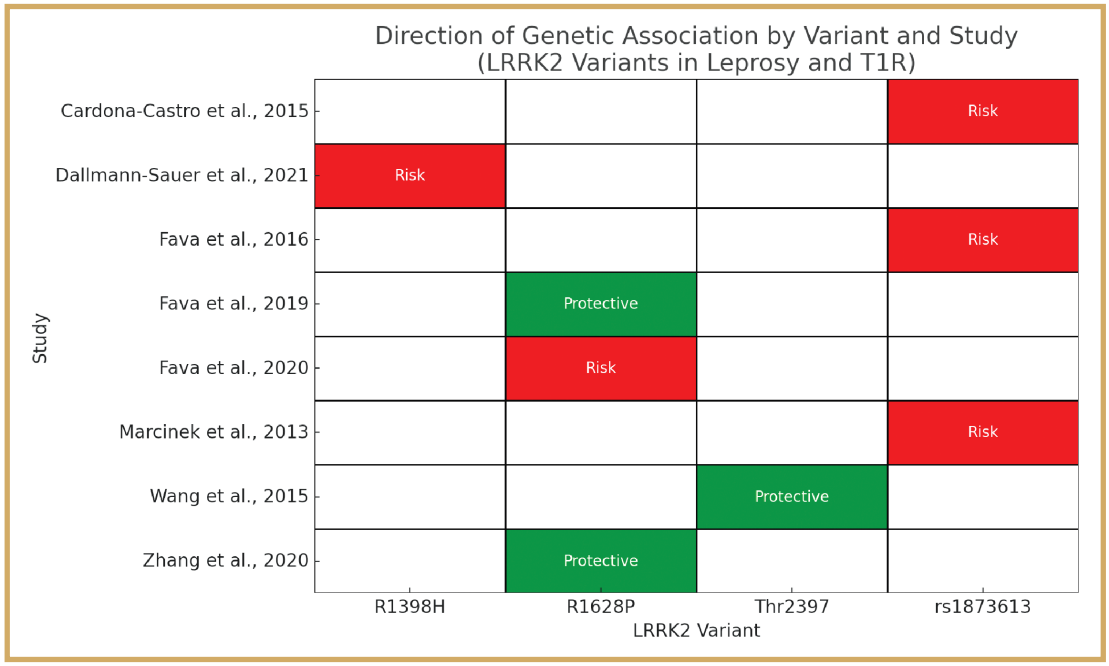

Fig. 3 : Direction of genetic association (risk or protective) of R1398H, R1628P, Thr2397 and rs1873613 with leprosy or type 1 reactions across included studies.

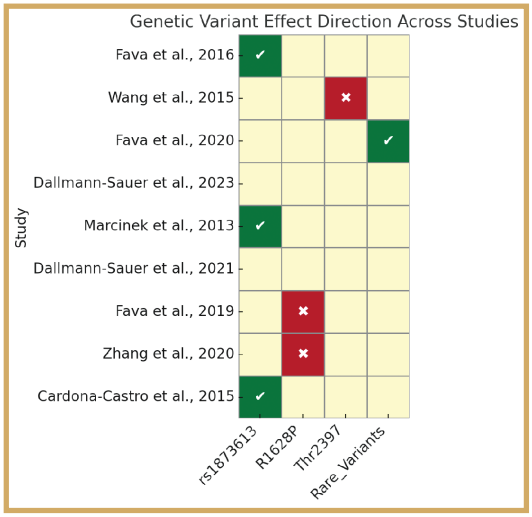

Fig. 4 : Genetic variant effect direction across study groups.

genes in carriers of specific LRRK2 variants. Co-immunoprecipitation and confocal microscopy experiments revealed interactions between LRRK2 and NOD2, suggesting a role in innate immune signalling. Cytokine profiling showed modulation of TNF-α, IL-6, and other inflammatory mediators, supporting a functional role of LRRK2 in regulating inflammatory responses to leprosy (Fig. 4).

Variants such as R1398H and R1628P were shown to influence kinase activity, autophagy, and vesicular trafficking, all of which are biologically relevant to the intracellular survival of *M. leprae* and the host inflammatory response.

Common versus rare variants

LRRK2 variants were classified into common and rare categories based on their frequency and

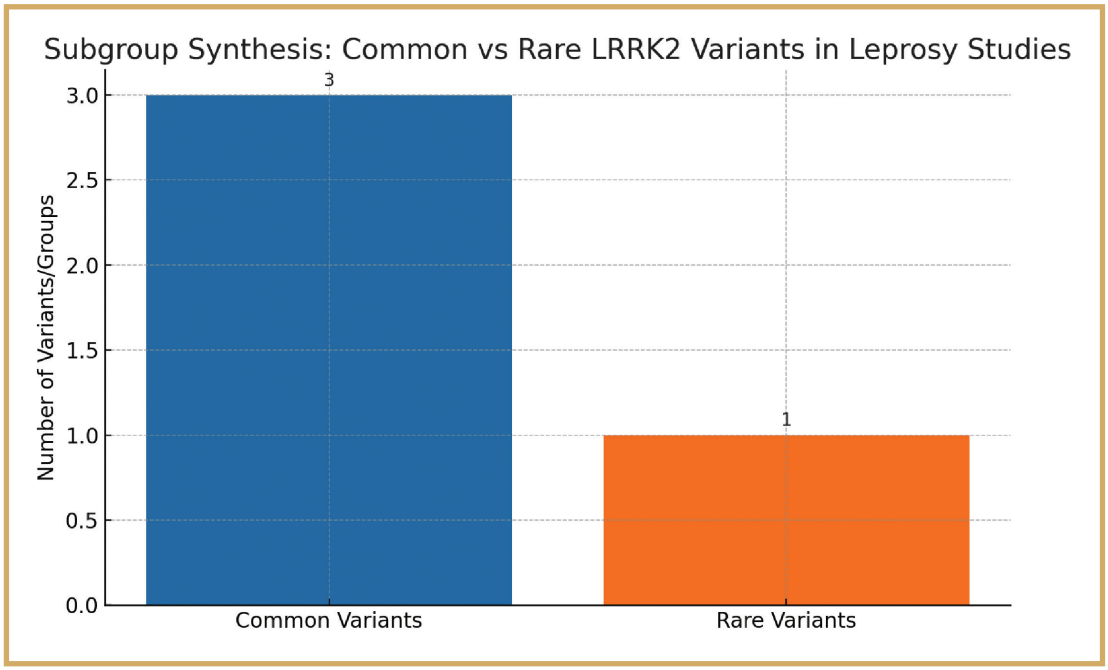

Fig. 5 : Bar graph showing common and rare variant differentiation.

Table 3 : Reported role of the LRRK2.

Classification	Examples	Reported Role
Common	rs1873613, R1628P, Thr2397	Widely studied; reproducible effects
Rare	Novel variants from WGS (Fava et al 2020)	Linked to T1R and shared with PD

method of detection (Table 3, Fig. 5). Common variants were widely studied and demonstrated reproducible associations across multiple cohorts. Rare variants, identified primarily through deep resequencing and burden testing, exhibited larger effect sizes within specific populations and overlapped with variants implicated in neuroinflammatory diseases such as Parkinson's disease. However, these rare variant findings require cautious interpretation due to limited replication and smaller sample sizes.

Population-specific patterns

Distinct population-specific patterns were observed. Colombian cohorts showed strong association with rs1873613A, Han Chinese cohorts demonstrated protective effects of Thr2397, and Brazilian and Vietnamese cohorts consistently showed protective associations of R1628P with respect to T1R. These differences underscore the importance of ethnic diversity in genetic research and caution against extrapolating risk markers across populations without population-specific validation.

Summary of key findings

In summary, this review identifies LRRK2 as a significant immunogenetic modulator of leprosy

and T1R, with both susceptibility-enhancing and protective variants exerting population-specific effects. Functional studies support the biological plausibility of these associations by demonstrating the involvement of LRRK2 in immune signalling and inflammatory regulation. While the evidence base is still limited by heterogeneity and sample size constraints, the converging genetic and functional data suggest that LRRK2 plays a meaningful role in leprosy immunopathogenesis.

Discussion

This systematic review synthesises current evidence on the role of *Leucine-Rich Repeat Kinase 2* (LRRK2) gene variants as modulators of leprosy susceptibility and Type 1 Reactions (T1R). Across nine genetic studies conducted in diverse populations, both common and rare LRRK2 variants were associated with altered host immune responses to *Mycobacterium leprae*. Frequently reported variants included rs1873613, R1628P, and Thr2397, each demonstrating either risk-enhancing or protective effects depending on population context (Fava et al 2016, Wang et al 2015, Cardona-Castro et al 2015). The consistent identification of LRRK2 across independent cohorts supports its biological relevance in leprosy immunopathogenesis rather than a chance association.

A key observation is the pleiotropic nature of the R1628P variant, which was reported as protective against T1R in Brazilian and Vietnamese cohorts (Fava et al 2019, Zhang et al 2020) but associated with increased Parkinson's disease risk in neurological studies. This duality is biologically plausible given LRRK2's involvement in immune regulation, mitochondrial function, and neuroinflammatory signalling pathways (Gardet et al 2010, Wallings & Tansey 2019). Rather than implying a direct clinical overlap between leprosy and Parkinson's disease, these findings suggest that LRRK2 acts as a context-dependent immunomodulator whose effects vary according to tissue environment, immune activation state, and disease context.

The rs1873613 variant was consistently associated with increased leprosy susceptibility, particularly in Colombian and multi-ethnic cohorts (Marcinek et al 2013, Cardona-Castro et al 2015), while the alternative allele appeared protective in some populations. Similarly, the Thr2397 variant in Han Chinese populations was associated with enhanced immune responsiveness and reduced inflammatory burden (Wang et al 2015). These population-specific effects underscore the importance of ancestry-informed genetic analyses and caution against extrapolating genetic risk markers across populations without validation.

From a methodological perspective, the quality assessment revealed important limitations across the evidence base. Although measurement bias was generally low due to robust genotyping platforms, selection bias, residual confounding, and limited sample sizes were frequent concerns (Fava et al 2020, Marcinek et al 2013, Dallmann-Sauer et al 2023). Only one study demonstrated low risk of bias across all domains (Fava et al 2019), highlighting the need for larger, better-powered, and more methodologically consistent investigations that incorporate population structure, environmental exposures, and gene–environment interactions.

Functional studies strengthened the biological plausibility of the genetic associations. Evidence demonstrating interactions between LRRK2 and NOD2 (Dallmann-Sauer et al 2021, 2023), modulation of cytokine signalling, and alterations in autophagy and intracellular trafficking support a mechanistic role for LRRK2 in immune

regulation during leprosy. Rare variant overlap between T1R and neuroinflammatory disorders further supports the concept of LRRK2 as a shared regulatory node in inflammatory pathways (Fava et al 2020). Together, these findings position LRRK2 as a biologically relevant contributor to leprosy pathogenesis operating through immune modulation rather than as a simple susceptibility gene.

Conclusion

This systematic review consolidates current evidence supporting the involvement of *Leucine-Rich Repeat Kinase 2* (LRRK2) gene variants in the pathogenesis of leprosy and its immune-mediated complication, Type 1 Reactions (T1R). Across nine human genetic studies conducted in diverse populations, both common variants (including rs1873613, R1628P, and Thr2397) and rare variants were associated with altered disease susceptibility and inflammatory responses. These findings indicate that LRRK2 functions at the interface of innate immunity and inflammatory regulation, influencing host responses to *Mycobacterium leprae* rather than acting as a simple binary susceptibility gene.

Several LRRK2 variants exhibited pleiotropic and population-specific effects, reinforcing the concept of LRRK2 as a context-dependent immunomodulator. Functional evidence demonstrating interactions between LRRK2 and immune signalling pathways, including NOD2-mediated responses, cytokine regulation, and autophagy, supports the biological plausibility of these genetic associations. Although methodological variability and moderate risk of bias in some studies limit definitive inference, the convergence of genetic and functional data provides consistent support for LRRK2's role in leprosy immunopathogenesis.

Future research should prioritise large-scale, multi-ethnic and multi-centre genetic studies to validate existing associations and identify additional variants of relevance. Integrating genomic data with transcriptomic, epigenetic, and functional immunological analyses, and exploring gene–environment interactions and epistatic relationships with other immune-related genes such as NOD2, PARK2, and RIPK2, will be essential for refining mechanistic understanding and improving risk prediction and management strategies in leprosy-endemic settings.

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