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Research article

Identification of Genetic Variations Associated with Leprosy Risk as Potential Therapeutic Targets

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Abstract

Host immune reactions are critical in determining the susceptibility and clinical course of leprosy induced by *Mycobacterium leprae*. Genetic susceptibility in immune-related genes, as well as the complexity of its pathogenesis and resistance to available drugs, persists as obstacles to successful leprosy control. The present investigation was conducted to identify host susceptibility genes for leprosy and to assess probable drug repurposing candidates by a genomics-led approach. A bioinformatics approach was applied that utilized leprosy-related Single Nucleotide Polymorphism (SNP) data emerging from Genome-Wide Association Studies (GWAS). Functional annotation was performed with HaploReg, WebGestalt, and g:Profiler according to five biological criteria. The genes with a total score of ≥ 2 were determined to be potential biological leprosy risk genes. Drug repurposing candidates were identified from DrugBank, and confirmation was performed through ClinicalTrials and PubMed. Ninety-six out of 106 GWAS SNPs were included, which were located in 57 genes. Nine genes were determined to be biological leprosy risk genes. The drug-target analysis identified 13 drugs targeting the four genes, among which was methotrexate, which is currently undergoing a clinical trial for leprosy. This work pinpointed critical host susceptibility genes and repositionable drugs, advocating for the incorporation of host-directed therapeutic options in leprosy.

Keywords: Drug repositioning, gene prioritization, leprosy, molecular targets, SNP

Introduction

A leprosy is a chronic infection caused by *Mycobacterium leprae* (M. leprae) or *Mycobacterium lepromatosis* (M. lepromatosis) that primarily affects the skin and peripheral nerves, and it can even lead to disability [1]. More than 200,000 new cases of leprosy are reported annually worldwide [2]. In 2017, 14 countries reported at least 1,000 new cases of leprosy, namely, Brazil, India, Indonesia, Bangladesh, Congo, Madagascar, Myanmar, the Philippines, Mozambique, Ethiopia, Nepal, Nigeria, Sri Lanka, and Tanzania [3]. Stringent control programs in leprosy-endemic countries, including Brazil, India, and Indonesia, have failed to eradicate this disease, which remains a major public health problem. However, the functional genetic mechanisms contributing to the host's susceptibility to leprosy (and their implications for translational medicine) continue to be poorly defined [4].

The clinical manifestations of leprosy patients represent an immune-related spectrum; leprosy is considered an ideal model to study the interaction between the host immune response and infection [5]. Differences in immune responses among individuals determine the susceptibility and type of leprosy disease experienced. One of the immune responses that plays an important role in the pathogenesis of leprosy is Interleukin-10 [6]. Interleukin-10 has anti-inflammatory effects by acting on activated macrophages to terminate the response to microbes and return the system to a resting state after the microbes are destroyed. IL-10 upregulation can decrease macrophage activity in killing bacteria [6]. Although genetic and immunological factors are known to be important in the pathogenesis of leprosy, both have rarely been investigated together. In particular, the effects of leprosy-associated variants on gene expression, immune-related pathways or in a clinically relevant inflammatory response have not been systematically studied, especially among populations generating GWAS signals [7].

A large-scale gene study, namely genome-wide association studies (GWAS), has provided knowledge and understanding of the basic genetics of leprosy. GWAS has reported much single-nucleotide polymorphism (SNP) information related to leprosy [8]. Leprosy-related SNP data can be used to identify and determine the genes that are most responsible as risk factors for leprosy and genes targeted by leprosy drugs. GWAS has identified several SNPs associated with leprosy risk; for example, SNPs in the *LACC1*, HIF1A, SLC29A3, and CDH18 genes have been associated with leprosy susceptibility and clinical phenotypes in the Chinese population [9]. Although several leprosy-associated genetic loci have been identified in previous GWAS, such as SNPs in LACC1, HIF1A, SLC29A3, and CDH18, the functional interpretation and translational relevance of these associations have been poorly achieved. The method presented in this paper goes beyond statistical association and uses GWAS signals combined with multi-layer functional annotation to prioritize true leprosy risk genes. By establishing genetic correlations between host susceptibility genes and immune pathways, as well as pharmacologically druggable targets, it also offers a mechanistic and rational framework for the identification of therapeutic targets and drug repurposing in leprosy [10].

The genetic basis of leprosy is very complex, involving HLA and non-HLA genes. Variants in genes such as PARK2/PACRG, NRAMP1, and MRC1 have been associated with leprosy susceptibility, highlighting the multifaceted nature of genetic influences on the disease[11]. Present multi-drug therapy has been instrumental in achieving the leprosy control and patient outcome; however, emerging hurdles such as antimicrobial resistance, cumulative drug-related toxicities, and protracted treatment duration remain barriers to its monumental success. Such limitations highlight the need for alternative and/or adjunctive therapies to increase effectiveness, tolerability, and possibly duration of treatment[12]. Drug repurposing can be an alternative method of discovering new drugs for leprosy that can save time and costs [13]. The role of bioinformatics in discovering new drugs is vital and is getting bigger as technology develops. Bioinformatics helps speed up, simplify, and make the drug discovery process more efficient [14]. Bioinformatics can analyze genomic and proteomic data to find genes or proteins that play an important role in disease [15]. This study aims to identify genes contributing to leprosy susceptibility and identify drug candidates that can be reused in leprosy treatment.

Materials and Methods

Materials

Leprosy-associated single nucleotide polymorphisms (SNPs) were obtained from published genome-wide association studies (GWAS) through the GWAS Catalog and peer-reviewed literature. Functional annotation and gene prioritization were performed using HaploReg v4.2, WebGestalt, and g:Profiler. Drug–gene interaction data were retrieved from DrugBank, and candidate drugs were further validated using ClinicalTrials and PubMed.

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Methods

The overall study design can be seen in Figure 1. SNP data correlated with leprosy were extracted from the GWAS catalog on 1 February 2025. GWAS is a database used to identify genetic variants associated with specific traits or diseases [16] and can identify associations between diseases and SNPs across the genome [17]. HaploReg is a database designed for functional annotation of SNPs using data from the ENCODE project [18] and to aid functional dissection of GWAS results [19]. Determination of leprosy priority genes using five functional annotation criteria. The Drugbank database was used to identify potential leprosy drugs from approved drugs that target leprosy genes [20]. The ClinicalTrial and PubMed databases were used to ascertain the current status of drugs generated for leprosy therapy. SNPs were selected if they reached genome-wide significance ($P \leq 5 \times 10^{-5}$), were in strong linkage disequilibrium (LD) ($r^2 > 0.8$) with the variants in close vicinity to them, and were mappable to genes with known functional annotations for future analyses.

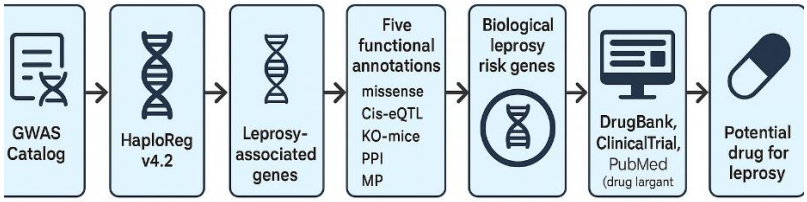

Figure 1. Gene identification scheme and potential drugs for leprosy using genomic database

Biological leprosy risk gene

The priority leprosy susceptibility genes were determined by five functional annotation criteria: missense, cis-eQTL, KO-mice, protein-protein interaction, and molecular pathway. Each gene with a score ≥ 2 is categorized as a biological leprosy risk gene. The scoring system method is based on previous research by Okada et al. (2014) [21].

Each leprosy susceptibility gene was scored based on five criteria. (1). Missense is a gene containing a leprosy susceptibility SNP with linkage disequilibrium (r2 > 0.80) identified as a missense mutation in HaploReg v4.2. (2) Cis-eQTL: genes containing leprosy susceptibility SNPs with significant cis-eQTL effects in the network; (3) Knockout mouse phenotype (KO mice): genes with False Discovery Rate (FDR) significance q < 0.05 in over-representation analysis (ORA) using the Mammalian Phenotype Ontology (MP) from WebGestalt (2019) [22]; (4) Protein-protein interactions (PPIs): genes prioritized by biological processes of the Gene Ontology (GO) category in WebGestalt (2019) [22] . With FDR, q<0.05 was considered significant, and (5) Molecular pathways: Analyses using Kyoto Encyclopedia of Genes and Genomes (KEGG), an online database of biochemical pathways from WebGestalt. Genes generated in KEGG pathways (FDR < 0.05) were awarded one point [23].

Drug mining and prioritization

Identification of drugs that target leprosy susceptibility genes using the Drugbank database. DrugBank is an online database that can be used for in silico drug target discovery, drug design, drug docking or screening, drug metabolism prediction, and drug interaction prediction [24]. The following process was confirmation of drug status using the ClinicalTrial.gov (https://clinicaltrials.gov/) and PubMed databases.

Data analysis

Functional annotation was performed at HaploReg V4.1 to annotate missense variants and cis-expression quantitative trait loci (cis-eQTLs). Over-representation analysis (ORA) was conducted with WebGestalt R and set against knockout mouse phenotypes, protein–protein interaction (PPI) network and molecular pathways. A binary score (1:presence of functional evidence, 0:otherwise) was given to each gene for each category and the sum of scores for all five criteria was calculated. Genes obtained from our multispecies approach (knockout mouse phenotype analysis) were mapped to human orthologs in g:Profiler for their relatedness to human leprosy biology prior to inclusion in the functional annotation scoring.

Results and Discussion

Identification of SLE-associated SNPs

Based on the extraction results from GWAS, 106 leprosy-associated SNPs were obtained. After adjusting the inclusion criteria, 96 SNPs remained. The development results using the Haploreg v4.2 database obtained 57 leprosy-related genes.

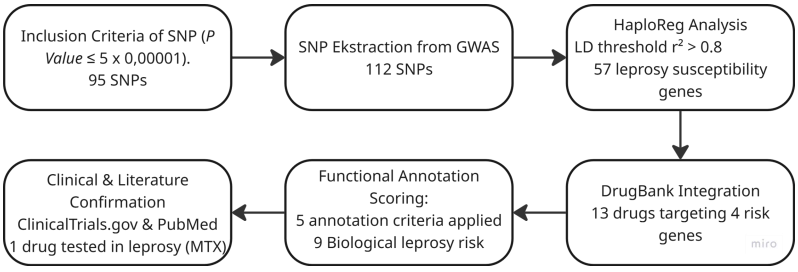

Figure 2. Schematic workflow

Gene-Based Prioritization from Functional Annotation

The prioritization of 57 leprosy susceptibility genes using five criteria resulted in 9 genes with the predicate 'Biological leprosy risk gene ', all of which have a score of 2, as shown in Table 1. Table 1 shows the classification of leprosy susceptibility genes according to the biological linkage based on a framework structured with functional annotation. Fifty-seven candidate genes were analyzed one by one based on five defined functional annotation criteria: if a specific functional annotation occur in the gene, this criterion was assigned to 1. Genes with an aggregate score of ≥ 2 were considered as biological leprosy risk genes, indicating consensus from multiple independent functional evidence.

Another potential bioactive compound as COX-2 inhibitor i.e. ligand 3 was generated two strong hydrogen bond interactions through carbonyl group in the active site by with Ser530 and Tyr385 at distance of 2.54 and 2.23 Å, respectively. This compound was also created two pi-sigma interactions with Ala527 and Val349. Four pi-alkyl interactions were produced by some amino acid residues: Leu351, Phe381, Trp387, and Tyr355. Two alkyl interactions were developed by residues of Leu359 and Val116. Interactions of these ligands were similar with the native ligand (TLF), which included interacted with residues of Ala527, Leu352, Leu531, Tyr385, Val116 and Val349 through pi-

sigma, alkyl, pi-alkyl bond interactions. One strong hydrogen bond interaction was created in the docked-native ligand complex. Meanwhile, phenidone as the standard drug only interacted with four amino acid residues, such as Ala527, Leu352, Gly526 and Met522, through pi-alkyl, amide-pi stacked and pi-sulfur interactions. No hydrogen bond interaction was produced in this standard. Some ligands were also generated strong hydrogen bond interaction such as ligands 4, 6, 8, 10, 11, at distance ranged from 2.09 to 2.97. It was said that an interaction is considered strong if the distance < 4 Å [23].

Table 1. Gene functional annotation score

No	Gene name	Functional annotation					Score
		Missense	Cis-eQTL	KO-mice	PPI	KEGG	
1	*MDM1*	1	1	0	0	0	2
2	*LACC1*	0	1	0	1	0	2
3	*RPS6KA4*	1	1	0	0	0	2
4	*NOD2*	0	1	0	1	0	2
5	*CYLD*	0	1	0	1	0	2
6	*MTHFR*	1	1	0	0	0	2
7	*BATF3*	1	1	0	0	0	2
8	*RIPK2*	0	1	0	1	0	2
9	*HLA-DQA1*	1	1	0	0	0	2

Integrative Analysis for Drug Repurposing

Identification of drugs that target leprosy susceptibility genes using Drugbank, ClinicalTrial, and PubMed databases. This process resulted in 13 drugs targeting four genes (*RPS6KA4*, *NOD2*, *MTHFR*, and *RIPK2*), including one currently in clinical trials for leprosy, methotrexate. The bioactive compounds (ligands 1-13) in E. spinosum interact with the COX-2 protein through a variety of interactions, including alkyl, amide-pi stacking, carbon hydrogen bond, hydrogen bonds, pi-alkyl, pi-donor hydrogen bond, pi-sigma, and pi-sulfur interactions, is presented in Table 2.

Table 2. Drugs and target genes

Drugs	Target Genes	Indications	Clinicaltrial.gov for leprosy	PubMed for leprosy
Flavin mononucleotide	*RPS6KA4*	Iron deficiency anaemia		
Inarigivir soproxil	*NOD2*	adult chronic hepatitis B		
Mifamurtide	*NOD2*	osteosarcoma		
Benazepril	*MTHFR*	antihypertensives		
Cyanocobalamin	*MTHFR*	vit B12 deficiency		
Fluorouracil	*MTHFR*	actinic keratosis, breast cancer		
Folic acid	*MTHFR*	megaloblastic anaemia, folate deficiency		
Menadione	*MTHFR*	blood clotting, factor 2 deficiency		
Methionine	*MTHFR*	protein synthesis		
Methotrexate	*MTHFR*	Lymphoblastic leukaemia	NCT03775460	PMID: 32302727
Riboflavin	*MTHFR*	vit B2 deficiency		
Tetrahydrofolic acid	*MTHFR*	nutritional supplementation		
Fostamatinib	*RIPK2*	chronic immune thrombocytopenia (ITP)		

In order to gain a more profound comprehension of the biological relevance of the prioritized genes, we conducted an investigation into their possible functional roles concerning the etiology of leprosy. Genes identified as biological leprosy risk genes were supported by at least two independent pieces of functional annotation evidence and therefore reflect the convergence of regulatory, structural, or network-level evidence. This multi-annotation support implies that the involved genes are not simple loci; rather, they are likely to be actively implicated in host susceptibility to M. leprae, rather than just genetic associations. A number of the prioritized genes are related to immune recognition, intracellular signaling, and inflammatory regulation, which have been repeatedly demonstrated to affect host-pathogen interactions as well as the disease spectrum in leprosy. As such, genes that met the score

threshold (≥ 2) were also biologically more reliable contributors to leprosy susceptibility and were selected for further drug repurposing analysis.

Table 2 presents the results of our analysis on the repurposing of integrative drugs to link prioritized biological leprosy risk genes with medications listed in DrugBank. The application of this approach led to the identification of 13 approved drugs targeting four genes (RPS6KA4, NOD2, MTHFR, and RIPK2). For subsequent analyses, only drugs with regulatory approval were considered. Further screening utilizing ClinicalTrials.gov and PubMed was conducted to ascertain whether there were any prior records or ongoing trials exploring the application of these drugs in relation to leprosy. Among these drugs, methotrexate has been clinically studied for leprosy, while the other medications represent novel candidates for repurposing. Of the 13 drugs identified, only one has been investigated for leprosy, while the remaining twelve have indications unrelated to the disease. Nevertheless, the selected drugs encompass various therapeutic types, including immunomodulators, metabolic regulators, cardiovascular agents, oncology drugs, and dietary supplements. Although all 13 drugs serve distinct primary uses, they collectively operate within the same host pathways responsible for immune regulation, inflammation, and cellular metabolism associated with the development of leprosy.

From the bioinformatics analysis, 57 genes associated with leprosy were generated. After prioritizing leprosy susceptibility genes using five functional annotation criteria, nine genes remained (Table 1), and only four genes were approved drug targets that could potentially be reused for leprosy. The absence of leprosy-specific drugs among the 13 identified candidates is a biologically expected and meaningful outcome of our genome-guided repurposing strategy. As the analysis was driven by host susceptibility genes identified through GWAS, the resulting drug candidates predominantly target host immune, inflammatory, and metabolic pathways rather than Mycobacterium leprae–specific components.

This discovery is in line with the new trend of host-directed therapy (HDT) in the treatment of infectious diseases, where targeting of host pathways has been gradually accepted as an additional approach to the traditional antimicrobial treatment. The numerous selected compounds such as inarigivir soproxil, mifamurtide, methotrexate, and fostamatinib are all recognized to affect both the innate and adaptive immune responses. This is significant for leprosy as it relates to the disease's immune-related mechanisms [25]. Among the recognized candidates which include inarigivir soproxil, mifamurtide, methotrexate, and fostamatinib, all of them seem to have the ability to change the original and acquired immune responses which, in turn, is a major factor in the immunopathogenesis of lepra [26]. Considering that leprosy is described by a range of immune misregulation rather than just the destruction of tissues caused by the pathogen, addressing the host immune pathways is a reasonable option for therapy [27].

The therapeutic significance of the identified drugs is not in any way reduced by the fact that none of them are currently indicated for leprosy. Rather, it turns them into new candidates for leprosy treatment, as they are the only ones having explored the pharmacological options with safety profiles already established and thus mayprovide a new source of leprosy treatment [28]. The recognition of commonly prescribed drugs including benazepril, folic acid, riboflavin, cyanocobalamin, and methotrexate not only supports the translational ability of the results but also makes it easier for the drugs to be repositioned for leprosy treatment, as having their pharmacokinetics and toxicity profiles well-characterized can be an advantage [29].

In a combined effort, the recognition of 13 drugs that are not related to leprosy highlights the robustness of genome-guided drug repurposing in revealing non-typical therapeutic candidates. The results indicate that the use of host genetic information can not only increase the leprosy treatment options beyond the usual antimicrobial drugs but also provide insights into the mechanisms for conducting future experimental validation [30]. When considered as a whole, the lack of leprosy drugs among the recognized candidates highlights their distinctiveness and enables their classification as potentially beneficial drugs for leprosy treatment, hence requiring more preclinical and clinical trials [31].

The weight placed on leprosy susceptibility genes in the present study was determined by its intersection with five independent functional annotation criteria, including missense variants, cis-eQTL (expression Quantitative Trait Loci), knockout mouse phenotypes, protein-protein interactions, and participation in molecular pathways. Genes that are supported by multiple criteria are more likely to reflect biologically relevant targets and not mere genetic associations [10]. Missense variants result in specific changes to the protein at the amino acid level, supporting a strong likelihood of a functional effect on protein function or structure [32]. Cis-eQTL links strengthen the functional relevance of these associations by connecting genetic variation to tissue-specific changes in gene expression, implying that these genes actively regulate host immune responses involved in leprosy. Functional validation in vivo is provided by evidence from knockout mouse phenotypes; the knockout of the genes results in identifiable biological or immunological phenotypes, lending credibility to the causal argument [10].

Furthermore, prioritized genes are located in known immune and inflammatory networks using protein–protein interaction data, underscoring these genes as core components of host defense[33]. The test of overrepresentation for disease-relevant molecular pathways enrichment in the context of disease-relevant molecular pathways further

indicates that these genes are functioning together within a biologically coherent framework underlying leprosy pathogenesis [34]. The integration of these orthogonal annotations builds higher confidence about target credibility and pharmacological actionability, and it provides a sound biological rationale to prioritize them in genome-guided drug repurposing approaches [35]. Bioinformatics analysis yielded four potential drug targets for leprosy genes, namely the RPS6KA4, NOD2, MTHFR, and RIPK2 genes. The RPS6KA4 (Ribosomal Protein S6 Kinase A4) gene is a member of the ribosomal S6 kinase (RSK) family, which plays an important role in various cellular processes, including cell growth, survival, and proliferation [36]. The RPS6KA4 gene encodes a protein part of the mitogen-activated protein kinase (MAPK) signaling pathway, critical for regulating cell growth and differentiation [37].

NOD2 gene variations, particularly SNPs, have been associated with leprosy susceptibility and resistance. These genetic variations influence the host immune response, potentially affecting the progression and clinical manifestations of the disease [38]. NOD2 recognizes MDP from M. leprae, triggering an immune response that includes the production of cytokines such as interleukin-32 (IL-32), which promotes the differentiation of monocytes into dendritic cells. This pathway is critical for mounting an effective immune response to the pathogen. A meta-analysis confirmed the association of NOD2 polymorphisms, specifically rs8057341, with leprosy risk in Asian and Caucasian populations [39]. The MTHFR gene is known for its role in the homocysteine-methionine pathway, which is involved in various multifactorial disorders, including cardiovascular and neurodegenerative diseases [40]. MTHFR is one of the regulatory enzymes in the folate (FA) cycle that plays an important role in the balance of methionine and homocysteine. MTHFR gene polymorphisms affect the biochemical activity of the enzyme, thereby disrupting the remethylation of homocysteine to methionine. Perhaps this is what can be linked between MTHFR and leprosy related to folic acid [41].

The RIPK2 (Receptor-protein kinase 2) gene, also known as receptor-interacting protein kinase 2, regulates inflammatory responses [42]. RIPK2 is a serine/threonine kinase that plays an important role in propagating inflammatory signaling through its association with pattern recognition receptors (PRRs) [43]. The involvement of RIPK2 in various signaling pathways makes it a promising target for therapeutic intervention in inflammatory diseases and cancer. Existing inhibitors and therapeutic strategies targeting RIPK2 are under investigation, although challenges remain in developing effective treatments [44]. The interaction between RIPK2 and other genes, such as LRRK2 and NOD2, is significant in leprosy. Variants in these genes can influence the immune response, with LRRK2 variants affecting apoptosis and cytokine secretion, which are critical in the body's defense against M. leprae [45].

This study's bioinformatics analysis identified 13 approved drugs in Drugbank that target the 4 leprosy-related genes (Table 2). Of these 13 drugs, one, methotrexate, is currently in clinical trials for leprosy. It is important to note that the drug repurposing component of this study should be viewed as a downstream confirmation of biologically relevant host targets rather than a primary result[46]. The drugs that target the prioritized LS genes can be used to prioritize and validate each of these genes as potential candidates for future drug repurposing because they are biologically relevant[47]. While producing pharmacological actions, many are active in immune or inflammatory pathways central to leprosy pathology. This is an integrative model that connects GWAS-identified genetic risk to cellular processes and, from there, to therapeutic relevance [48].

Some of the hits shown in this study are FDA-approved compounds with known safety profiles, e.g., methotrexate, benazepril, folic acid, riboflavin, and cyanocobalamin, thereby making their translation to the clinic feasible[49]. In contrast, investigative agents, such as inarigivir soproxil and mifamurtide, provide a systemic perspective on immune modulation, but they need to be confirmed by other studies. Methotrexate is, however, an interesting reference for this analysis since evidence from clinical trials confirms its strong clinical potential in leprosy, thus providing further confidence in the approach based on genome-guided prioritization[50]. Altogether, these data are consistent with the idea that host genetic susceptibility could help prioritize biologically meaningful therapeutic targets and select a rational strategy for drug repurposing [51].

One drug targets the RPS6KA4 gene, flavin mononucleotide (FMN), a coenzyme derived from riboflavin, which is essential for various oxidation-reduction reactions in the body, affecting energy metabolism and cell function. It is involved in metabolic pathways that may affect the immune response, potentially influencing susceptibility to infections such as leprosy [52]. Genetic studies show that immune-related genes significantly influence susceptibility to leprosy, suggesting that metabolic factors, including those involving FMN, may modulate the immune response to Mycobacterium leprae [53]. Based on bioinformatics analysis, the drug Inarigivir soproxil targets the NOD2 gene and is currently in a clinical trial (NCT03434353) to Evaluate the Antiviral Activity of Inarigivir (GS-9992) plus tenofovir alafenamide (TAF) for 12 weeks in adults with chronic hepatitis B (CHB) [54]. The interaction between Inarigivir soproxil and leprosy involves complex molecular mechanisms that target Mycobacterium leprae, the causative agent of the disease [29].

Mifamurtide is a drug currently serving as an immunomodulator in treating osteosarcoma. Mifamurtide activates macrophages through its liposomal formulation, which includes phosphatidyl serine-containing lipids that signal macrophages to respond to apoptotic tumor cells [55]. Based on bioinformatics analysis, this drug targets the

NOD2 gene associated with leprosy. It is suggested that mifamurtide may support the treatment of leprosy through its immunomodulatory properties, especially in managing immune responses during reaction episodes [56]. The lack of evidence requires further investigation into mifamurtide's function in treating leprosy.

Cyanocobalamin (vitamin B12) targets the MTHFR gene associated with leprosy. The relationship between cyanocobalamin (vitamin B12) and leprosy mainly revolves around the neurological complications associated with leprosy and the potential therapeutic effects of vitamin B12. Leprosy, caused by Mycobacterium leprae, can cause significant peripheral nerve damage, resulting in symptoms such as neuropathy and deformity [57]. Early treatment of leprosy is essential to prevent permanent disability, highlighting the importance of timely diagnosis and intervention [57]. While cyanocobalamin may provide symptomatic relief, it is not a treatment for leprosy itself, which requires specific multidrug therapy to address the underlying infection; vitamin B12 use should be viewed as a supportive measure rather than a primary treatment for leprosy [57].

Based on bioinformatics analysis, Methotrexate targets the leprosy-associated MTHFR gene and is currently in clinical trials for leprosy (NCT03775460, PMID: 32302727) [58], [59]. A study involving 13 leprosy patients showed that 61.5% responded well to MTX, allowing glucocorticoid discontinuation in more than half of the cases [60]. Early introduction of MTX during a leprosy reaction may improve therapeutic outcomes, although a significant relapse rate of 42% was reported after discontinuation [60]. Fluorouracil also targets the MTHFR gene. So far, no one has reported a direct relationship between fluorouracil and leprosy. As a chemotherapeutic agent, fluorouracil's interaction with other drugs and the immune response may affect the outcome of leprosy treatment [61].

Folic acid also antagonizes the MTHFR gene. There is a complex relationship between folic acid and leprosy. Folic acid deficiency can worsen the severity of leprosy, as evidenced by lower serum folate levels observed in patients with higher bacterial loads [62]. Genetic predisposition to leprosy may interact with nutritional factors, including folic acid, influencing disease outcome [63]. Several limitations to the present study should be mentioned. The leprosy susceptibility genes and drug candidates were prioritized in silico, based solely on GWAS results and through the use of functional analysis tools. While this method should provide a systematic and hypothesis-driven candidate identification, it does not predict cause-and-consequence relationships or functional consequences at the level of molecules and cells. The second point is that there is no evidence (in in vitro/in vivo models) supporting the biological and therapeutic relevance of these targets. Therefore, the results in this research are considered to be a basis for further experimental study rather than an ultimate therapeutic recommendation.

Conclusion

Through genome-guided bioinformatics analysis, we discovered nine host genes associated with leprosy susceptibility, four of which can be applied as drug targets. A total of 13 approved or investigational drugs that act on immune- and metabolism-related host processes were identified for repurposing. Excluding leprosy-specific drugs is a meaningful HDTS and reinforces that the approach should modify the underlying inflammation that contributes to leprosy pathogenesis. The drugs with known safety and pharmacokinetic properties could offer an attractive approach for clinical translation. Taken together, these results highlight the potential of host genetics for developing novel leprosy treatment agents and strongly encourage more preclinical and clinical testing.

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Declarations

Author contribution	:	Adnan Adnan contributed to conceptualization, data curation, bioinformatics analysis, and drafting of the manuscript. Haafidzah Dania and Marwa Mohammed contributed to data interpretation, critical revision of the manuscript, and supervision. All authors read and approved the final manuscript.
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Conflict of interest	:	All authors declare that there is no conflict of interest.
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