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Genomic variants-driven drug repurposing for tuberculosis by utilizing the established bioinformatic-based approach

Lalu Muhammad Irham [a], Wirawan Adikusuma [b], Dyah Aryani Perwitasari [a,*]

[a] Faculty of Pharmacy, Universitas Ahmad Dahlan, Yogyakarta, Indonesia
[b] Department of Pharmacy, University of Muhammadiyah Mataram, Mataram, Indonesia

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ABSTRACT

A major challenge in translating genomic variants of Tuberculosis (TB) into clinical implementation is to integrate the disease-associated variants and facilitate drug discovery through the concept of genomic-driven drug repurposing. Here, we utilized two established genomic databases, namely a Genome-Wide Association Study (GWAS) and a Phenome-Wide Association Study (PheWAS) to identify the genomic variants associated with TB disease and further utilize them for drug-targeted genes. We evaluated 3.425 genomic variants associated with TB disease which overlapped with 200 TB-associated genes. To prioritize the biological TB risk genes, we devised an in-silico pipeline and leveraged an established bioinformatics method based on six functional annotations (missense mutation, *cis*-eQTL, biological process, cellular component, molecular function, and KEGG molecular pathway analysis). Interestingly, based on the six functional annotations that we applied, we discovered that 14 biological TB risk genes are strongly linked to the deregulation of the biological TB risk genes. Hence, we demonstrated that 12 drug target genes overlapped with 40 drugs for other indications and further suggested that the drugs may be repurposed for the treatment of TB. We highlighted that *CD44*, *CCR5*, *CXCR4*, and *C3* are highly promising proposed TB targets since they are connected to *SELP* and *HLA-B*, which are biological TB risk genes with high systemic scores on functional annotations. In sum, the current study shed light on the genomic variants involved in TB pathogenesis as the biological TB risk genes and provided empirical evidence that the genomics of TB may contribute to drug discovery.

1. Introduction

Currently, tuberculosis (TB) is still a major health problem in the world. TB infection is the second leading infectious killer after corona virus disease 2019 (COVID-19) and the 13th leading cause of death [1]. Based on the Global TB Report on 2021, the estimation of TB cases was 824.000, with 393.323 notified as TB cases, 3.110 death due to TB, and 33.366 cases in pediatric. However, the treatment success rate reached 83% and the treatment coverage reached 48% [2]. The standard regimen for TB treatment still comprises isoniazid, pyrazinamide, rifampicin, and ethambutol given for two months, followed by rifampicin and isoniazid administered for four months [3]. Unfortunately, the patients still experience some side effects, such as drug resistance [4]. As such, more effective antituberculosis drugs are needed as the regimen has been less effective.

A previous review mentioned that TB patients can be categorized into three risk groups: the lowest risk group that can be treated successfully in 4 months, the moderate risk group that is treatable within 6 months, and the highest risk group that can be cured in more than 6 months due to therapy failure and relapse [5]. Moreover, the risk for adverse drug reactions, such as hepatotoxicity experienced by 2.4% of TB patients due to the combination of oral antituberculosis [3]. The hepatotoxicity due to oral antituberculosis can decrease the patients' adherence to taking TB medications, leading to treatment failure or drug resistance. Some adverse drug reactions are minor and treatable without treatment discontinuation; however, hepatotoxicity may cause treatment discontinuation [6].

In addition, there is evidence that the development of novel therapeutic agents must be focused on the treatments of Multidrug-resistant tuberculosis (MDR-TB) and Extensively drug-resistant tuberculosis (XDR-TB) [7]. Drug repurposing is an alternative way to identify new drugs for the treatment of TB by utilizing old drugs for other indications [8]. The mechanism of novel therapeutic agents may be related to the mechanisms of autophagy and apoptosis [7]. Some drugs, such as

* Corresponding author.
E-mail address: dyah.perwitasari@pharm.uad.ac.id (D.A. Perwitasari).

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sulphonamides, sulfanilamide, sulfadiazine, carbapenem, metformin, verapamil, statin, and fluoroquinolone, are listed as targeted medications for TB, with the emphasis on the mechanisms as immunomodulators [9]. Other medications, such as bedaquline, delamanid, and pretonamid received regulatory approval as an immunomodulator tentatively. Thus, the effort to find out novel therapeutic agents for TB must be applied after there is an accurate diagnosis to avoid drug resistance. A possible combination of the drugs must be considered carefully to determine the synergistic effects [10].

In today's era of genomic medicine, healthcare can be improved tremendously [11]. Genomic-based approach nowadays has the potential to be used for the development of new drugs using various approaches, including the bioinformatic-based approach [12]. The explosion of genomic information allows us to effectively hypothesize which drugs from one disease indication can be used for another indication; further, this information provides the opportunities for scientists to develop drugs more specifically and precisely [13]. An example of successful precision therapy used in most clinics is imatinib, which is a tyrosine kinase inhibitor originally developed for the treatment of chronic myelogenous leukaemia (CML). It was later repurposed for the treatment of gastrointestinal stromal tumors (GISTs) that possess a mutated tyrosine kinase that imatinib is also able to target. As an alternative, high-throughput screening has been used to identify novel targets on a large scale [14]. In the current study, we utilized the germline variants and prioritized the most important biological TB risk genes based on the scoring system from strict functional annotations and established a bioinformatic method. In the final step, we employed the biological TB risk genes to find drug-targeted genes for TB pharmacotherapy.

2. Methods

2.1. Prioritization of genomic variants associated with susceptibility to TB

Our current study utilized the Genome-Wide Association Study (GWAS) and Phenome-Wide Association Study (PheWAS) databases to identify variants associated with the susceptibility to TB disease. These two databases were accessed on March 14, 2022. GWAS and PheWAS are freely accessible databases that can help everyone find the connections between genetic variants and traits in samples from various populations. The GWAS and PheWAS studies are primarily focused on understanding the biology of diseases and provide a large number of variants associated with phenotype susceptibility [15]. Next, we prioritized the genes with strict functional annotations to identify biological TB risk genes. Further, these genes would be prioritized for drug-targeted genes based on the drug databases (Fig. 1).

2.2. Prioritization of TB-associated genes

We evaluated the variants that met the inclusion criteria for this study. We used the criteria of statistical significance with a p-value $< 5 \times 10^{-8}$ (https://www.ebi.ac.uk/gwas) for the GWAS-based approach and a p-value < 0.05 (https://phewascatalog.org/) for the PheWAS-based approach, respectively. We ascertained that the duplicate single nucleotide polymorphisms (SNPs) were removed, and we finally focused on the unique SNPs. After identifying the variants associated with TB, we further focused on the identification of expanded variants from HaploReg version 4.1 with the criteria of r^2 value (>0.8) [16]. The aim of this step was to identify the proxy SNPs in Linkage Disequilibrium (LD) [16]. An LD value between genetic variants is commonly expressed as r^2 because this coefficient allows the detection of an association between an observed genotype and an unobserved causal variant with a linear sample size requirement. After this step, we identified 3.425 variants encoding 200 genes that would later be prioritized as TB-associated genes.

2.3. Prioritization of biological TB risk genes

We demonstrated six functional annotations as the strict criteria to prioritize the biological TB risk genes. Biological TB risk genes are crucial information that guides us to understand that genomic information plays an important role in the pathogenesis of TB based on the functional annotation criteria. The selection criteria were adopted from those of Okada Y et al., which were later prioritized for the drug repurposing for rheumatoid arthritis [16]. These annotations have also been applied for the repurposing of drugs for several other diseases, including chronic hepatitis B [17], atopic dermatitis [18], asthma [19], and colorectal cancer [20].

The following are six criteria that we used in prioritizing TB-associated genes. The first annotation that we applied was missense variants encoding genes leading to the amino acid changes in protein level [21]. Second, we assessed the *cis* expression quantitative trait loci

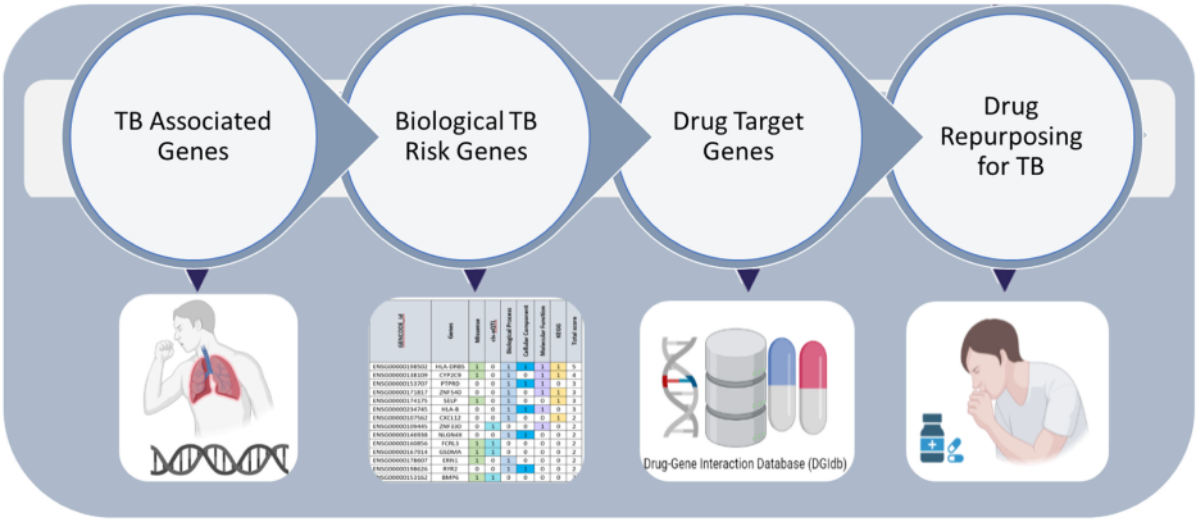

Fig. 1. This model illustrates how the genomic variants-based approach can be translated into clinical implantation for drug repurposing for TB.

(*cis*-eQTL) effects in the whole blood and lung tissues; gene expression signature can indicate a phenotype of the disease. Furthermore, we leveraged the fact that the *cis*-eQTL are regions with nucleotides correlated with alterations in gene expression. Therefore, the variants may cause changes in gene expression in the direction of the tissues involved (i.e., our analyses focused on the whole blood and lungs). The identified variants cause an upregulation of gene X, leading to an increased risk of TB disease. In that case, an inhibitor of its protein product may be considered a repositioning candidate. Gene ontologies include biological process as the third criterion, cellular component as the fourth criterion, and molecular function as the fifth criterion. To construct gene ontologies, the Database for Annotation, Visualization, and Integrated Discovery (DAVID) online tool version 6.8 was used (https://david-d.ncifcrf.gov/tools.jsp) [22]. The aim of constructing these gene ontologies was to understand the relationship between diseases and biological protein networks. If the genes involved in the biological protein networks were related to TB pathogenesis, it would be important to inhibit the protein.

The criterion of the Kyoto Encyclopedia of Genes and Genomes (KEGG) was the final functional annotation that we utilized in this step. The KEGG pathway enrichment analysis was performed by using the DAVID online tool. The genes implicated in KEGG determine the types of molecular pathways enriched on the TB-associated genes. Pathway-specific signature is important to be noted as it can indicate the phenotypes of some diseases. Through the signature, we were able to understand which genes were deregulated in the phenotype of TB.

Genes overlapping with TB play a causal role in TB pathogenesis. It is important to consider the TB causal relationship and the drug-targeted genes for TB disease. In addition, the functional annotations that we used have been validated by Okada Y et *al*. to prioritize the most likely causal gene relationship with Rheumatoid Arthritis and to find the drug candidates for its treatment [16]. The genes that overlapped with the functional annotations were prioritized as the genes with a score of 1. We then prioritized the genes with a minimum score of 2 to identify biological TB risk genes. In our analyses, we set the threshold of a biological score ≥2 to find a much higher number of genes as biological TB risk genes and candidates for TB drug targets.

2.4. Prioritization of TB drug targets

To prioritize the TB drug targets, we leveraged the STRING database. This step aimed to expand biological TB risk genes to obtain more drug-targeted genes. Next, we mapped the drug-targeted genes onto Drug-Gene Interaction Database (DGIdb version 4.0, www.dgidb.org) [23] to find potential drugs for TB. DGIdb version 4.0 is a freely accessible database that comprehensively integrates various databases to overlap druggable genes with drugs. This database is comprehensively integrated into the drug databases, including DrugBank [24], Guide to Pharmacology [25], Gene Ontology [26], OncoKB [27], PharmGKB [28], and the Therapeutic Target Database [29].

3. Results

3.1. Identification of genomic variants of TB

Through the GWAS and PheWAS studies, we discovered 252 variants associated with TB susceptibility (Supplementary Table 1). In the next step, we utilized the HaploReg version 4 to expand the SNPs based on the proxy SNPs with the highest r^2 value (>0.8). Based on this analysis, we identified 3.425 SNPs of TB. Further, we overlapped the genomic variants of TB SNPs, and finally, we identified 200 TB-associated genes. The subsequent step was to prioritize the TB-associated genes based on the criteria of functional annotations that we demonstrated.

3.2. Identification of TB-associated genes

Based on the six functional annotations that we demonstrated, we mapped the variants onto the corresponding genes with missense/nonsense mutations as one of the non-synonymous changes in a single base substitution of different types of amino acid in the resulting protein. In this step, we identified 16 genes with missense mutations. Next, we demonstrated whether the TB-associated genes that we identified had *cis*-eQTL in the whole blood and lung tissues. Then, we utilized this annotation with the knowledge that functional rules of variants affect protein expression. Thirty-one genes with *cis*-eQTL and 19 genes with biological process, 10 genes of cellular component, 7 genes of molecular function, and 6 genes the KEGG were discovered in the current research. It is important to note that *cis*-eQTL has the highest number compared to other functional annotations. This means that the TB-associated genes that we discovered were more expressed in the blood and the lung tissues since the mycobacterium tuberculosis affected these tissues.

3.3. Identification of biological TB risk genes

Our study showed that the higher the threshold of biological score applied, the smaller the number of biological genes identified, limiting the number of drug targets we could observe (i.e., we found 1 biological TB risk gene for a threshold score ≥ 5, 1 biological TB risk gene for a threshold score ≥ 4, 4 biological TB risk genes for a threshold score ≥ 3, and 8 biological TB risk genes for a threshold score ≥ 2). Finally, 14 biological TB risk genes were successfully identified with a threshold score ≥ 2 (Table 1 and Supplementary Table 2). The distribution score of each criterion is shown in Fig. 2A and Fig. 2B. Furthermore, we expanded 14 biological TB risk genes with 50 interactions by using the STRING database to achieve more drug-targeted genes. As a result, we found 64 drug-targeted genes of 14 expanded biological TB risk genes.

3.4. Drug candidates to be repurposed for TB

In this step, we discovered 426 gene pairs with 64 drug-targeted genes from the curated PPI networking adapted from the STRING database (Fig. 3). To overlap the drug-targeted genes with the drug candidates, we used the DGidb drug database. Unfortunately, not all drug-targeted genes that we identified had pharmacological activities. Therefore, these might potentially miss the drug-targeted genes (undruggable). Our analysis showed that only four biological TB risk genes were linked to 12 drug-targeted genes among 64 drug-targeted genes. These 12 drug-targeted genes overlapped with 40 potential drugs for TB that were druggable (genetically-driven druggable) (Fig. 4). We highlighted that *CD44, CCR5, CXCR4,* and *C3* are highly promising proposed TB targets since they are connected to *SELP* and *HLA-B*, which are biological TB risk genes with high systemic scores on functional annotations. The current study emphasized that the biological TB risk genes can be translated into clinical implementation through genomic variant-driven drug repurposing for TB disease.

4. Discussion

In the present study, we prioritized TB-associated genes for drug repurposing for TB. We hypothesized that prioritizing TB genetic variants using six functional annotations would enable us to translate and deepen our understanding of risk genes of TB pathogenesis. So far, the medications for TB patients are still limited with some side effects, such as drug resistance and low compliance of patients due to adverse events of the medications. Therefore, the rationale of the current study in response to the lack of new clinical drugs for TB was to propose drug repurposing to provide more useable therapeutic drugs for TB patients. It is most notable that the concept of drug repurposing has several advantages. The drug candidates have clear mechanisms for pharmacological action, pharmacokinetic profiles, metabolic pathways, and toxic

Table 1
Biological TB risk genes according to the six functional annotations.

GENCODE_id	Genes	Missense	*cis*-eQTL	Biological Process	Cellular Component	Molecular Function	KEGG	Total score
ENSG00000198502	*HLA-DRB5*	1	0	1	1	1	1	5
ENSG00000138109	*CYP2C9*	1	0	1	0	1	1	4
ENSG00000153707	*PTPRD*	0	0	1	1	1	0	3
ENSG00000171817	*ZNF540*	0	0	1	0	1	1	3
ENSG00000174175	*SELP*	1	0	1	0	0	1	3
ENSG00000234745	*HLA-B*	0	0	1	1	1	0	3
ENSG00000107562	*CXCL12*	0	0	1	0	0	1	2
ENSG00000109445	*ZNF330*	0	1	0	0	1	0	2
ENSG00000146938	*NLGN4X*	0	0	1	1	0	0	2
ENSG00000160856	*FCRL3*	1	1	0	0	0	0	2
ENSG00000167914	*GSDMA*	1	1	0	0	0	0	2
ENSG00000178607	*ERN1*	1	0	1	0	0	0	2
ENSG00000198626	*RYR2*	0	0	1	1	0	0	2
ENSG00000153162	*BMP6*	1	1	0	0	0	0	2

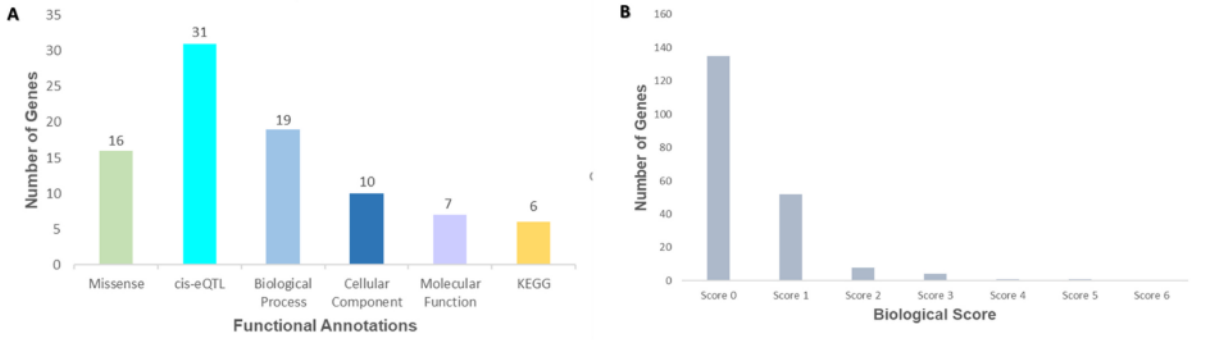

Fig. 2. Tuberculosis (TB) genomic-drug repurposing process. (A) Six criteria of functional annotation-derived TB biological risk genes. (B) Bar chart showing the number of genes and scores for each criterion.

reactions [30]. Herein, we focused on the repurposed drugs for TB in this study based on the established bioinformatic approach.

It is important to note some findings that the following twelve promising targets overlapped with 40 drugs that could be repurposed for TB treatment: *C3, VWF, CALM1, CD44, SELP, NOS1, CCR4, CCR5, CXCR4, FKBP1A, CACNA1C*, and *RYR2*. Among the twelve promising targets, *CD44, CCR5, CXCR4,* and *C3* are highly promising TB targets since they are linked to *SELP* and *HLA-B* as biological TB risk genes with high systemic scores on functional annotations. A study conducted in Indonesia with pulmonary tuberculosis patients showed a significant association between *HLA-B*4006* and new pulmonary TB patients and between *HLA-B*1802, HLA-B*4001* and *HLA-DRB1*1101* with recurrent pulmonary TB [31]. This study was conducted on 257 pulmonary TB patients and 236 healthy subjects. Another study conducted in Mali also presented a significant association between *HLA-B* alleles (B*07:02, B*08:01, B*14:02, B*15:03, B*15:10, B*18:01, B*42:01, B*42:02, B*51:01 and B*81:01) and *M. tuberculosis* (75%) [32]. This study indicated important information regarding the genomic variants associated with TB disease.

Besides, the cytoskeleton plays a critical role in the regulation of cell migration and phagocytosis to control Mycobacterium TB infection. *CD44* is an adhesion molecule connected to the actin cytoskeleton and is implicated in inflammatory processes. *In vivo* studies showed that *CD44* plays a role in the protective immunological response to pulmonary TB, marked by decreased survival rate and increased mycobacterial outgrowth in the *CD44* mice's lungs and livers. The *CD44* protein mediates phagocytosis and recruitment of Macrophages for the eradication of pulmonary tuberculosis by mycobacterium TB [33]. As a result, *CD44* can be a promising target for the treatment of TB by using hyaluronic acid [34–36]. In this study, we identified hyaluronic acid that targeted *CD44*.

C–C Motif Chemokine Receptor 5, also known as *CCR5*, has an active role in the migration of Th1 cells and macrophages; both are crucial for the protection of immune response to Mycobacterium TB. The *CCR5* mice induced a Th1 response and controlled Mycobacterium TB infection effectively [37]. The pathogen modified *CCR5* to increase *IL-10* production during Mycobacterium TB infection, suggesting that *CCR5* might be involved in the control of the host immune response. Infection with Mycobacterium enhanced *CCR5* expression in macrophages, allowing downstream signaling to become active. *CCR5* plays a significant part in the pathogen's immune subversion process [38]. This study found maraviroc that targeted *CCR5* so that it can be a novel drug candidate for TB therapy.

Further, our bioinformatics analysis confirmed *CXCR4* and *C3* as highly potential drug repositioning targets for TB. *CXCR4* is associated with plerixafor drug. *CXCR4* can be found mostly in alveolar macrophages. Infection of macrophages with Mycobacterium TB raised *CXCR4* surface expression *in vitro*, but illness amelioration decreased *CXCR4* expression *in vivo* [39]. In the case of TB infection, *CXCR4* can be a potential novel therapy. Next, *C3* plays an essential role in the pathogenesis and the treatment of TB [40]. Albumin and lipoprotein (a) levels increased dramatically in treated TB patients although *C3* levels decreased significantly. This result might be attributed to better inflammation, lipid metabolism, reduced immune system and complemented system activation. As a result, albumin, lipoprotein (a), and *C3* levels can be used as biomarkers to cure TB [41]. Our current research showed that genomic variants can help identify biomarker diagnostics and become drug candidates for TB at the same time.

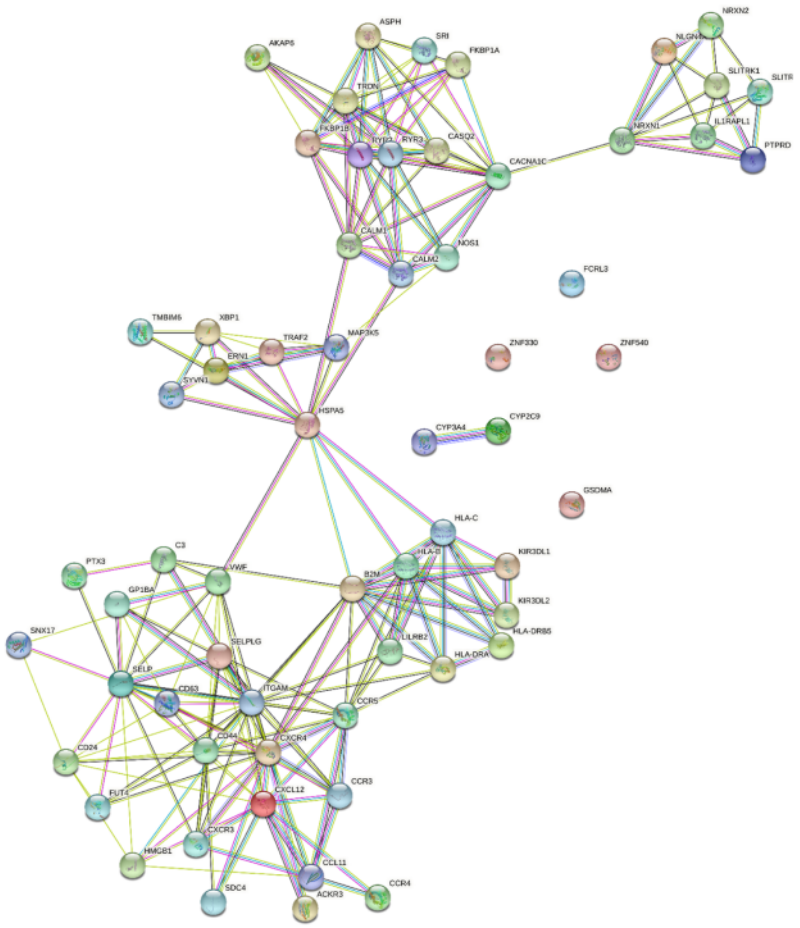

Fig. 3. Protein-protein interaction among biological TB risk genes with 426 gene pairs.

4.1. Limitation and strengths

Our findings have not been reported so far by the previous studies that utilized genomic data and bioinformatics. However, we acknowledged that the current study still has some limitations that may not be avoidable; one of which is not all drug-targeted genes that we identified were druggable. Therefore, some of the biological TB risk genes might not overlap with the approved drugs (undruggable). Our analysis showed that only four biological TB risk genes were linked to 12 drug-targeted genes (18.75%) of 64 drug-targeted genes. These 12 drug-targeted genes overlapped with 40 potential drugs for TB that were druggable (genetically driven druggable). According to the previous study, not all drug-targeted genes are druggable, as shown in the study of Finan et al. in which only 4479 (22%) among 20,300 protein-coding genes are druggable [42]. Finally, we proposed that the functional studies (*in vitro* and *in vivo*) of the biological risk genes and the genes targeted by these drugs still require further investigation to ascertain the role of drug-targeted genes, especially in alleviating the problem of drug resistance in TB treatment.

5. Conclusion

In conclusion, 12 drug-targeted genes overlapped with 40 drugs for other indications that might be repurposed for TB. Among the twelve promising targets in the study, we highlighted that *CD44, CCR5, CXCR4,* and *C3* are highly promising proposed TB targets. Genomic studies are useful to identify TB-associated genes and may serve as targets for drug repurposing. This study shed light on the genomic variants that might be involved in TB pathogenesis and provided evidence that the use of genomic information can help in drug discovery.

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Author contributions

L.M.I. and D.A.P conceived and designed the study. L.M.I and W.A performed the computational analysis. L.M.I wrote the manuscript. L.M.I., W.A and D.A.P revised the manuscript. L.M.I and D.A.P supervised and coordinated this study. All authors read and approved the manuscript and made significant contributions to this study.

Declaration of competing interest

The authors declared no conflict of interest.

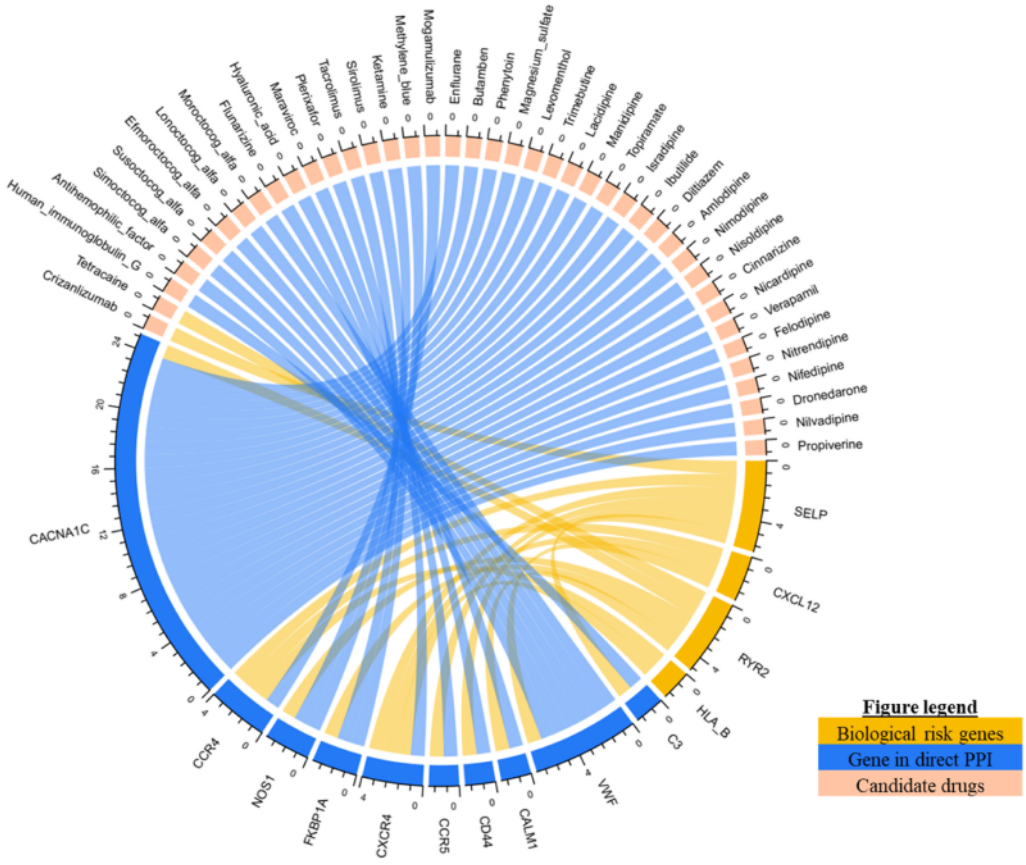

Fig. 4. Identification of potential 40 drugs to be repurposed for TB which overlapped with 12 drug-targeted genes.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

Abbreviations

Cis-eQTL	*Cis*-expression Quantitative Trait Locus
CML	Chronic myelogenous leukaemia
COVID-19	Corona Virus Disease 2019
DAVID	Database for Annotation, Visualization and Integrated Discovery
DGIdb	Drug-Gene Interaction Database
GISTs	Gastrointestinal stromal tumours
GWAS	Genome-Wide Association Study
KEGG	Kyoto Encyclopedia of Genes and Genomes
LD	Linkage Disequilibrium
MDR-TB	Multi Drug-resistance
ORA	Over-Representation Analysis
PheWAS	Phenome-Wide Association Study
PID	Primary Immuno-deficiency
PPIs	Protein-Protein Interactions
SNP	Single Nucleotide Polymorphism
TB	Tuberculosis
XDR-TB	Extensively Drug-resistance

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbrep.2022.101334.

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