The Association between Mannan-Binding Lectin Gene Polymorphism and Clinical Leprosy: New Insight into an Old Paradigm

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Background. Mannan-binding lectin (MBL), a soluble protein of innate immunity, is known to play a role in pathogen recognition and clearance. For more than a decade, it has been proposed that MBL deficiency may be protective against intracellular pathogens, such as Mycobacterium leprae.

Methods. The polymorphisms at the promoter and exon 1 regions of the MBL2 gene were assessed by polymerase chain reaction and sequencing performed on 264 patients with leprosy and 214 matched healthy control subjects from southern Brazil.

Results. The distribution of MBL2-gene polymorphisms in patients was significantly different from that in controls, with a decreased frequency of haplotypes/genotypes associated with low expression of circulating MBL in lepromatous patients when compared with tuberculoid patients (odds ratio [OR] for haplotypes, 0.56 [95% confidence interval [CI], 0.33–0.93] [P = .020]; OR for genotypes, 0.31 [95% CI, 0.13–0.71] [P = .004]). The LYPa haplotype was associated with susceptibility to leprosy per se (OR, 2.25 [95% CI, 1.31–3.88] [P = .003]) and to progression to the lepromatous (OR, 2.2 [95% CI, 1.21–4.05] [P = .008]) and borderline (OR, 2.98 [95% CI, 1.29–6.87] [P = .008]) forms of the disease.

Conclusions. These results suggest that MBL2-gene polymorphisms play a role in susceptibility to leprosy per se and in the clinical progression of the disease.

Leprosy, a slow and progressive chronic disease caused by infection with Mycobacterium leprae, has been a threat to humanity since time immemorial. The great majority of individuals are intrinsically resistant to leprosy, and, on exposure to M. leprae, only a small group of infected individuals develop the disease [1, 2]. Most remarkable is the interindividual variability in the development of leprosy, comprising a wide range of manifestations ranging from lepromatous leprosy to tuberculoid leprosy [3]. In lepromatous leprosy, the absence of the Th1-specific response to M. leprae leads to unrestrained proliferation of the bacilli, with progressive and extensive clinical lesions and strong humoral immunity. In contrast, tuberculoid leprosy is associated with a vigorous M. leprae Th1-type immunity, limited lesions, and few, if any, demonstrable bacilli within the granulomas in the dermis or peripheral nerves. In addition, between these 2 polar forms, the clinically and histopathologically less characteristic form, borderline leprosy, can also be found.

Currently, it is well accepted that the progression in the clinical spectrum of leprosy is under genetic influence and is closely related to the host immune response to M. leprae [1, 2].

Mannan-binding lectin (MBL), a soluble protein of innate immunity, is known to play a key role in pathogen recognition and clearance [4–6]. MBL targets invading microorganisms for phagocytosis and complement-mediated killing, by binding to surface carbo-
hydrates such as N-acetyl-d-glucosamine, mannose, N-acetylmannosamine, fucose, and glucose [7]. It has been recognized that MBL binds to a wide range of pathogens, including *M. leprae* [8–12]. On recognition of target microorganisms, MBL triggers the lectin pathway of complement, leading to the generation of multiple opsonic C3b fragments, which ultimately results in organism uptake by phagocytes, mainly by CR1 (CD35) receptors. It is also believed that MBL promotes direct opsonophagocytosis of organisms and clearance of apoptotic cells by various putative receptors, such as C1qRp [13], C1qRp [14], and CR1 [15]. The interaction between MBL and phagocytes promotes the notion that cytokine synthesis thereby plays a significant role in acute as well as chronic inflammation. The MBL2 gene is located on chromosome 10 (q11.2-q21) and includes 4 exons. Polymorphisms in exon 1 and in the promoter of the MBL2 gene have been shown to have a significant effect on the circulating levels of the protein and have been identified as the cause of the most common immunodeficiency known in humans [4].

MBL deficiency is mainly related to 3 structural single-nucleotide polymorphisms (SNPs), in codons 52 (allele D, Arg52Cys), 54 (allele B, Gly54Asp), and 57 (allele C, Gly57Glu) in exon 1 of the MBL2 gene. The wild-type allele is named “A,” whereas alleles B–C are collectively named “O.” These mutations have a profound effect on the assembly and stability of the protein, which leads to low levels of MBL and to functional MBL deficiency in homozygous (e.g., B/B) or compound homozygous (e.g., B/C) carriers, which together are referred to as “O/O” carriers. In addition, 3 major SNPs (termed “H/L,” “Y/X,” and “P/Q”) in the promoter region account for additional effects on the concentration of circulating MBL [16]. To date, 4 main promoter haplotypes (LXP, LYP, LYP, and HYPA) have been described in different populations [16, 17]. Because of the strong linkage disequilibrium between promoter haplotypes and exon 1 variant alleles, only 7 common MBL2 haplotypes—HYPA, LYQA, LYPA, LXP, HYPD, LYPB, and LYQC—have been found among distinct populations; HYPA, LYQA, and LYPA are associated with increased expression of circulating MBL, and LXP, HYPD, LYPB, and LYQC are associated with deficiency of this protein. There is increasing evidence suggesting that MBL2 haplotypes/genotypes associated with low levels of secretion of MBL predispose children and adults to infections as well as to autoimmune diseases [7, 18]; on the other hand, MBL2 haplotypes/genotypes associated with high levels of secretion of MBL may modulate disease severity in chronic disease [19–24] and may confer risk of infection by intracellular pathogens that exploit complement receptors to invade the cells, as is the case with tuberculosis [25] and visceral leishmaniasis [26]. Recently, it has been shown that MBL deficiency confers protection against lepromatous leprosy but not against tuberculosis [27, 28].

Despite the possible role that MBL plays in leprosy, as has been suggested by in vitro and clinical studies [10, 27], data on MBL2-gene polymorphism in leprosy are scarce and not comprehensive. In the present study, we aimed to investigate the association between MBL2-gene polymorphisms and susceptibility to and progression of leprosy.

**SUBJECTS AND METHODS**

*Patients.* A total of 264 patients with leprosy (mean age, 50 ± 16 years [range, 15–94 years]; 113 males and 151 females) from Curitiba in southern Brazil were studied; 214 (81%) were white, 48 (18%) were black, and 2 (1%) were Native American. Diagnosis was based on clinical examination and standard histopathological analysis of affected lesions, and the classification of the leprosy spectrum was based on the clinical and histological criteria of Ridley and Jopling [3]; 150 patients (57%) were diagnosed as presenting with lepromatous leprosy, 36 (14%) with tuberculoid leprosy, 17 (6%) with the indeterminate form, and 37 (14%) with borderline leprosy. In 24 patients (9%), the clinical form was not determined; these patients were included only in the group of all leprosy cases, for the comparisons with the control group. Erythema nodosum leprosum (ENL) was present in 67 (45%) of the 150 patients with lepromatous leprosy and in 6 (16%) of the 37 with borderline leprosy.

The control group consisted of 214 unrelated healthy individuals (mean age, 42 ± 4 years [range, 19–87 years]) who were matched with the patients according to ethnic background. Informed written consent was obtained from all individuals included in the study, and the study was approved by the local medical ethics committee.

**MBL2 genotyping.** A 1059-bp fragment encompassing the promoter and exon 1 of the MBL2 gene was amplified by polymerase chain reaction and was subjected to direct sequencing, as described elsewhere [29]. MBL2 genotypes/haplotypes were defined by the presence of distinct SNPs and the deletion 495_500del6, by use of SeqScape software (version 2.5; Applied Biosystems).

**MBL measurement.** To evaluate the relationship between MBL2 genotypes and MBL concentration in leprosy, we correlated the results regarding MBL2 polymorphisms with the previously reported MBL levels in 199 patients from the same cohort [27].

**Statistical analysis.** The frequencies of MBL2 genotypes, haplotypes, and alleles were obtained by direct counting. For some comparisons, MBL2 haplotypes were divided into those associated with low expression of MBL (LXP, HYPD, LYPB, and LYQC) and those associated with high expression of MBL (HYPA, LYQA, and LYPA). Accordingly, MBL2 genotypes were divided into those associated with low (LXP/LYPA + LXP/LYPB + LXP/LYQC + HYPD/LYPB + HYPD/HYPD + LYPB/HYPB)}
LYQ + LYPB/LYPB + LYQC/LYQC), high (HYP/YPA + HYP/LYPA + HYP/LYQA + LYPA/LYQA + LYPA/LYPB + LYQA/LYQA + LXPA/HYP + LXPA/LYQA + LXPA/LYPB + LXPA/HYPG), and intermediate (HYP/HYPD + HYP/LYPB + HYP/LYQC + HYPD/LYPA + HYPD/LYQA + HYPD/LYPB + HYPD/LYQC + HYPD/LYPB + HYPD/LYQA + LYQA/LYQC) expression of circulating MBL.

Hardy-Weinberg equilibrium was evaluated by use of ARLEQUIN software (version 2000; http://anthro.unige.ch/arlequin/). MBL haplotype/genotype frequencies were compared by contingency-table analysis using the \( \chi^2 \) test. Fisher’s exact test was used when numbers in one of the cells were <5. \( P \) values <.05 were considered to be significant and were corrected (\( P_{\text{corrected}} \)) according to the number of haplotypes or alleles tested. The Kruskal-Wallis test was used to correlate MBL plasma concentrations with MBL2 genotypes. The power of the study to confirm an odds ratio (OR) of 2 for haplotype associations was 97% (EPIinfo 6, April 2001 [http://www.cdc.gov/epiinfo/Epi6/ei6.htm]; Centers for Diseases Control and Prevention, Atlanta, GA).

RESULTS

Table 1 shows the distribution of MBL2 haplotypes in the patients with leprosy and in the healthy control subjects; in both groups, the frequencies of the MBL2 genotypes were in accordance with Hardy-Weinberg equilibrium. The correlation between MBL concentration and MBL2 genotype is shown in figure 1 (\( P < .001 \) [with Bonferroni correction, \( P < .003 \)]). A new haplotype, named “HYPG,” found in 1 patient was related to a previously identified nucleotide change (+1023C→T) at codon 44 in exon 1 [30].

MBL2-haplotype associations. The overall frequency of LYPA in the patients with leprosy was significantly greater (\( P < .002 \)) than that in the control subjects (tables 1 and 2), in both the presence and the absence of the linked variants (50/528 [9%] vs. 19/428 [4%]; OR, 2.25 [95% confidence interval (CI), 1.31–3.88] [\( P = .003 \); \( P_{\text{corrected}} = .020 \)]; and 63/528 [12%] vs. 28/428 [7%]; OR, 1.94 [95% CI, 1.22–3.08] [\( P < .005 \); \( P_{\text{corrected}} = .040 \]) (table 2); it was also greater in both the subgroup of patients with lepromatous leprosy (28/300 [9%] vs. 19/428 [4%]; OR, 2.22 [95% CI, 1.21–4.05] [\( P = .008 \); \( P_{\text{corrected}} = .060 \]) and the subgroup of patients with borderline leprosy (9/74 [12%] vs. 19/428 [4%]; OR, 2.98 [95% CI, 1.29–6.87] [\( P = .008 \); \( P_{\text{corrected}} = .060 \]) than in the control subjects (table 2).

Haplotypes associated with low expression of circulating MBL were significantly less frequent in patients with lepromatous leprosy than in patients with tuberculoid leprosy (119/300 [40%] vs. 39/72 [54%]; OR, 0.56 [95% CI, 0.33–0.93] [\( P = .020 \);
Figure 1. Concentration of circulating mannan-binding lectin (MBL), and corresponding MBL2 genotypes, in patients with leprosy

\(P_{\text{corrected}} = .040\)). The frequency of the defective haplotype HYPD also was lower in patients with lepromatous leprosy than in patients with tuberculoid leprosy (11/300 [4%] vs. 7/72 [10%]; OR, 0.35 [95% CI, 0.13–0.95] \(P = .030; P_{\text{corrected}}\) not significant).

**MBL2 genotype associations.** When only the exon 1 variants (i.e., A/A, A/0, and 0/0) were considered, the distribution of MBL2 genotypes in the patients with leprosy was not significantly different from that observed in the control subjects; however, when the promoter polymorphisms were included, the analysis revealed different associations. The overall distribution of genotypes associated with low expression of circulating MBL was significantly different between the patients with leprosy and the control subjects \((P = .012, P_{\text{corrected}} = .036)\) and between the subgroups of patients with leprosy \((P = .008; P_{\text{corrected}} = .024)\), with the frequency of such genotypes being lower in both the patients with lepromatous leprosy and the patients with borderline leprosy than in the patients with tuberculoid leprosy \((20/150 [13\%] \text{ in patients with lepromatous leprosy vs. } 12/36 [33\%] \text{ in patients with tuberculoid leprosy; OR, 0.31 [95\% CI, 0.13–0.71] } P = .004; P_{\text{corrected}} = .012\) and \(3/37 [8\%] \text{ in patients with borderline leprosy vs. } 12/36 [33\%] \text{ in patients with tuberculoid leprosy; } P = .007; P_{\text{corrected}} = .021\); OR, 0.18 [95\% CI, 0.04–0.69]) (table 3). Moreover, the defective LYPB/LYQC genotype was overrepresented in patients with tuberculoid leprosy, compared with its frequency in patients with lepromatous leprosy \((3/36 \text{ [8\%] vs. } 1/150 \text{ [1\%]; OR, 13.55 [95\% CI, 1.37–134.3] } P = .020; P_{\text{corrected}}\) not significant\) and in control subjects \((3/36 \text{ [8\%] vs. } 2/214 \text{ [1\%]; OR, 9.64 [95\% CI, 1.55–59.8] } P<.020; P_{\text{corrected}}\) not significant\), whereas LXPA/LXPA was decreased in patients with lepromatous leprosy, compared with its frequency in control subjects \((2/150 \text{ [1\%] vs. } 12/214 \text{ [6\%]; OR, 0.23 [95\% CI, 0.05–1.03] } P<.05; P_{\text{corrected}}\) not significant\) (table 3). There was no significant difference in the overall distribution of genotypes coding intermediate or high levels of MBL \((P\) not significant).

However, the frequency of genotypes coding high protein levels was overrepresented in lepromatous patients, compared with its frequency in tuberculoid patients \((81/150 \text{ [54\%] vs. } 13/36 \text{ [36\%]; OR, 2.08 [95\% CI, 0.98–4.4] } P = .050; P_{\text{corrected}}\) not significant\). Analysis of the frequencies of the promoter and exon 1 alleles individually revealed no significant difference between them, and analysis of the haplotypes/genotypes revealed no significant difference with regard to the presence of ENL reaction.

**DISCUSSION**

Leprosy is considered one of the most ancient of human diseases; long before the plague or AIDS threatened mankind, leprosy was causing immeasurable suffering to humanity. Recently, the origin of leprosy has been traced to eastern Africa/the Near East, whence it was disseminated to other regions of the globe via human migration [31].

Sequencing the *M. leprae* genome revealed an absence of more than half of its functional genes and of metabolic pathways [32], which may explain its absolute dependency, for survival, on human macrophage lineage cells. Moreover, *M. leprae* strains from different countries have been shown to exhibit very low genetic variability [31] and may present the lowest level of genetic diversity of any known bacterium [32]. It seems that these genetic variations do not influence bacterial virulence. Consequently, *M. leprae* may be very sensitive to the genetic variation of host proteins or genes that are involved in the course of the disease, variation that could result in either resistance or susceptibility to leprosy.

MBL plays a pivotal role in the recognition of microorganisms during initial and subsequent steps of the immune response, and therefore MBL might have an important function in the *M. leprae*-host interaction. It has been reported that MBL binds to *M. leprae* and enhances the attachment and ingestion of mycobacteria by phagocytes in vitro [10,33], which...
suggests that MBL plays a role in the uptake, pathogen spread, and establishment of leprosy.

For more than a decade it has been proposed that the high frequency of MBL2 mutant alleles observed in various populations may be of some biological advantage [10, 34, 35]. One of the hypotheses is that MBL deficiency may be protective against intracellular pathogens, such as mycobacteria and Leishmania, which use C3b opsonization to invade host cells. In the present study, we have shown, for the first time, an association between haplotypes/compound genotypes associated with low levels of secretion of MBL and protection against the development of lepromatous and borderline leprosy. It is noteworthy that this association was observed only when all haplotypes and/or compound genotypes that code for low or deficient levels of circulating MBL were considered; when promoter or exon 1 variants were analyzed individually, there were no significant results in any comparison between patients with leprosy and control subjects. This is not surprising, because MBL deficiency is determined by different haplotypes/genotypes and by both promoter and exon 1 variants, and it explains, in part, why previous studies have failed to find any association between MBL2 alleles and leprosy. Fitness et al., for example, investigated the exon 1 variants in paucibacillary leprosy cases from northern Malawi [36] and found no association between variant alleles B–D and susceptibility to leprosy. Their finding, however, should be interpreted carefully, because paucibacillary leprosy does not account for all clinical forms of the disease. In the present study, we investigated the entire spectrum of leprosy and found that the latter’s association with haplotypes/genotypes was related to multibacillary leprosy. In a previous study based on protein levels, MBL deficiency was found to be associated not with the predisposition to leprosy “per se” but with protection against lepromatous leprosy [27], a finding that corroborates those of the present study. Taken together, the data on MBL levels and MBL2 polymorphism in leprosy support the use of 100 ng/mL of serum as the cutoff level for the definition of MBL deficiency. In addition, the findings that the defective genotype LYPB/LYQC significantly increased the risk of tuberculoid leprosy (OR, 9.6) and protected against lepromatous leprosy (OR, 0.07) and that defective haplotype HYPD also conferred protection against lepromatous leprosy (OR, 0.35) support the concept that MBL deficiency is associated with leprosy per se but with the development of multibacillary disease, which is the most severe clinical form. Thus, defective MBL2 haplotypes/genotypes might play an advantageous role in the progression of clinical leprosy by disfavoring M. leprae dissemination into host tissues, thereby corroborating the hypothesis that MBL deficiency is protective against intracellular pathogens that use C3 opsonization to enter phagocytes, as is the case for M. leprae. Furthermore, the results of the present study indicate that haplotypes/compound genotypes are more appropriate tools for MBL2-gene association studies, because the study of individual alleles could, to some extent, suggest an erroneous conclusion—for example, because the A allele is included within the defective haplotype LXPA. Although the development of ENL has been found to be associated with complement deficiency [37], the lack of association between MBL2 haplotypes/genotypes and the presence of ENL in multibacillary leprosy suggests that MBL polymorphism or deficiency plays no major role in the development of this reaction in patients with leprosy.

Another interesting finding of the present study is the significant association between the LYPA haplotype and both leprosy per se and its lepromatous and borderline forms, an association that increased by 2-fold both susceptibility to leprosy per se and progression to these 2 clinical forms. LYPA is associated with high expression of protein levels and is believed to be the most ancient haplotype—that which, because of selective forces and gene bottleneck effects, gave rise to the presently known haplotypes [17, 18, 35, 38]. The high prevalence

### Table 2. Significant associations between MBL2 haplotypes and leprosy.

<table>
<thead>
<tr>
<th>MBL2 haplotypes</th>
<th>Patients with leprosy, no. (%)</th>
<th>Control subjects, no. (%)</th>
<th>P</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All (n = 528/264)</td>
<td>Lepromatous (n = 300/150)</td>
<td>Borderline (n = 74/37)</td>
<td>Tuberculoid (n = 72/36)</td>
</tr>
<tr>
<td>MBL2*LYPA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>63 (11.9)</td>
<td>36 (12.0)</td>
<td>11 (14.9)</td>
<td>8 (11.1)</td>
<td>28 (6.5)</td>
</tr>
<tr>
<td>Low expression of MBL</td>
<td>218 (41.3)</td>
<td>119 (39.7)</td>
<td>28 (37.8)</td>
<td>39 (54.2)</td>
</tr>
<tr>
<td>MBL2*HYPD</td>
<td>20 (3.8)</td>
<td>11 (3.7)</td>
<td>4 (6.4)</td>
<td>7 (9.7)</td>
</tr>
</tbody>
</table>

**NOTE.** CI, confidence interval; MBL, mannan-binding lectin; NS, not significant; OR, odds ratio.

- All patients with leprosy.
- All patients with leprosy vs. control subjects.
- All patients with leprosy and all control subjects.
- Patients with borderline leprosy vs. control subjects.
- Patients with tuberculoid leprosy vs. patients with lepromatous leprosy.
Table 3. Significant associations between MBL2 genotypes and leprosy.

<table>
<thead>
<tr>
<th>MBL2 genotypes</th>
<th>Patients with leprosy, no. (%)</th>
<th>Control subjects, no. (%)</th>
<th>( P )</th>
<th>For frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All (n = 528/264)</td>
<td>Lepromatous (n = 300/150)</td>
<td>Borderline (n = 74/37)</td>
<td>Tuberculoid (n = 72/36)</td>
</tr>
<tr>
<td>Low expression of MBL</td>
<td>44 (16.7)</td>
<td>20 (13.3)</td>
<td>3 (8.1)</td>
<td>12 (33.3)</td>
</tr>
<tr>
<td>LYPB/LYQC</td>
<td>4 (1.5)</td>
<td>1 (0.7)</td>
<td>-</td>
<td>3 (8.3)</td>
</tr>
<tr>
<td>LXPA/LXPA</td>
<td>6 (2.3)</td>
<td>2 (1.3)</td>
<td>1 (2.7)</td>
<td>2 (5.6)</td>
</tr>
<tr>
<td>LYPB/YPB</td>
<td>13 (4.9)</td>
<td>10 (6.7)</td>
<td>3 (8.1)</td>
<td>2 (5.6)</td>
</tr>
<tr>
<td>HYPA/HYPD</td>
<td>8 (3.0)</td>
<td>2 (1.3)</td>
<td>2 (5.4)</td>
<td>4 (11.1)</td>
</tr>
<tr>
<td>High expression of MBL</td>
<td>137 (51.9)</td>
<td>81 (54.0)</td>
<td>17 (45.9)</td>
<td>13 (36.1)</td>
</tr>
</tbody>
</table>

NOTE. CI, confidence interval; MBL, mannan-binding lectin; NS, not significant; OR, odds ratio.

a All patients.

b Patients with tuberculoid leprosy vs. patients with lepromatous leprosy.

c All patients with leprosy and all control subjects.

d Patients with tuberculoid leprosy vs. patients with borderline leprosy.

e Patients with tuberculoid leprosy vs. control subjects.

f Patients with lepromatous leprosy vs. all control subjects.

g Patients with borderline leprosy vs. control subjects.
h All patients with leprosy vs. control subjects.

of MBL2 haplotypes/genotypes that are associated with low levels of MBL—in different populations, such as LYQC in Africans and LYPB in South American Amerindians [29, 39]—suggests that strong forces have exerted positive selective pressure on these haplotypes/genotypes, around the globe. Interestingly and uniquely, Australian Aborigines, who have been isolated from other populations and have not yet been exposed to leprosy, have been found to present very low frequencies of both structural and promoter mutations [40]. In fact, 4 of 293 individuals had exon 1 mutations, and each of the 4 individuals showed evidence of admixture with whites, which indicates that these mutations were absent in these Aborigines before European settlement of Australia during the 19th and 20th centuries. Most interesting is that the levels of circulating MBL in Australian Aborigines are the highest thus far reported for any of the world’s populations; and this might also explain, in part, why Australian Aborigines are currently both presenting with the highest regional prevalence of leprosy and at great risk of acquiring the disease [41]. In addition, it is known that tuberculosis remains highly prevalent among these communities, corroborating with the fact that the lack of MBL deficiency in these populations increases their risk for intracellular infections, such as the case of leprosy and tuberculosis [41]. Taken together, these data suggest that over the millennia as leprosy has afflicted humanity and as it migrated across the globe, it has exerted positive selective pressure on MBL haplotypes that would be protective to the disease. The results of the present study support this hypothesis.

It seems reasonable that MBL2 polymorphism plays a dual role as a modifying gene in the pathogenesis of leprosy, with, on the one hand, LYPB increasing susceptibility to the disease per se and, on the other hand, defective haplotypes/genotypes conferring protection against lepromatous and borderline leprosy. These data both corroborate the finding that the progression of M. leprae infection involves the combined effects of several host genes and highlight the important function that MBL might have in early as well as chronic phases of leprosy.

Finally, the results of the present study suggest that, in addition to other mycobacterial diseases, such as tuberculosis, M. leprae infection has exerted positive selective pressure on the origination and increased frequency of defective genotypes in different populations. Although leprosy is not associated with higher mortality in adults, children born to lepromatous mothers have higher mortality [42]. Also, during historic times, the diagnosis of leprosy was associated not only with a “civility” death (resulting in forced divorce, in separation from society and also from the other infected sex, and even in castration) but also with the forcible physical death of the patient and his family [42]. Hence, this mycobacterial infection may effectively influence gene frequencies and reproductive fitness in humans.
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References