REVIEW

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A systematic review of natural resistance-associated macrophage protein 1 (NRAMP1) gene and susceptibility to tuberculosis: What is the link for ocular tuberculosis?

Ahmad Ashraf Amalius[1*], Budu[2], Muh. Nasrum Massi[3], Batari Todja Umar[2], Rahmawati Minhajat[4], Mirna Muis[5], Irda Handayani[6], Najdah Hidayah[7]

[1]Doctoral Study Program, Universitas Hasanuddin, Makassar, Sulawesi, Indonesia;
[2]Department of Ophthalmology, Faculty of Medicine, Universitas Hasanuddin, Makassar, Sulawesi, Indonesia;
[3]Department of Clinical Microbiology, Faculty of Medicine, Universitas Hasanuddin, Makassar, Sulawesi, Indonesia;
[4]Medical Hematology and Oncology, Department of Internal Medicine, Faculty of Medicine, Universitas Hasanuddin, Makassar, Sulawesi, Indonesia;
[5]Department of Radiology, Faculty of Medicine, Universitas Hasanuddin, Makassar, Sulawesi, Indonesia;
[6]Department of Clinical Patology, Faculty of Medicine, Universitas Hasanuddin, Makassar, Sulawesi, Indonesia;
[7]National Research and Innovation Agency, Jakarta, Indonesia.

*Corresponding author:
Ahmad Ashraf Amalius;
Doctoral Study Program, Universitas Hasanuddin, Makassar, Sulawesi, Indonesia;
ahmad_amalius@yahoo.co.id

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ABSTRACT

Introduction: The host genetic factors play a crucial role in determining susceptibility to tuberculosis (TB), and one such candidate gene is Natural Resistance-Associated Macrophage Protein 1 (NRAMP1). NRAMP1 is involved in the regulation of intracellular iron homeostasis, an essential nutrient for MTb survival within macrophages. Several polymorphisms of the NRAMP1 gene have been extensively studied for their association with TB susceptibility. However, the specific role of these NRAMP1 gene polymorphisms in the development of ocular tuberculosis, a rare but potentially severe form of TB, remains poorly understood.

Methods: This study was a systematic review conducted according to the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA). A comprehensive search was performed in the PubMed, Cochrane, and Science Direct databases for original, full-text studies of NRAMP1 gene related to tuberculosis infection. Ethnic, polymorphisms of NRAMP1 evaluated, and its association to TB susceptibility were recorded and summarized qualitatively.

Results: There were 41 studies included in our systematic review. No study of NRAMP1 gene polymorphism in regards to ocular tuberculosis was found. Polymorphisms of the NRAMP1 gene, such as 3'UTR TGTG ins/del, D543N, INT4, and (GT)n, have been investigated for their potential role in determining the susceptibility or immunity to Mycobacterium tuberculosis infection. However, the findings regarding the relationship between NRAMP1 gene polymorphism and tuberculosis are still inconsistent, with controversies and discrepancies among different studies.

Conclusion: NRAMP1 gene polymorphisms showed important involvement to tuberculosis infection susceptibility, therefore its relation to ocular tuberculosis is suggested.

Keywords: *NRAMP1, polymorphisms, tuberculosis, ocular tuberculosis.*
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INTRODUCTION

Tuberculosis (TB) is an infectious disease that remains difficult to control. The World Health Organization (WHO) stated that in 1990, there were approximately 1.7 billion cases of TB, with about one-third of the world's population infected with Mycobacterium tuberculosis (MTb). Furthermore, the WHO estimated that in 2016, there would be 10.4 million new TB cases (10% among patients infected with HIV) with 1.7 million deaths (including 374,000 among HIV-infected individuals).[1,2] TB primarily affects the lungs in 80% of patients, while the remaining 20% can have the disease affecting other organs, including the eyes.[3]

Ocular tuberculosis, or TB in the eyes, presents a complex clinical problem due to its wide spectrum of clinical presentations, making diagnosis challenging. Ocular TB can be primary if the eyes are the primary entry point for Mycobacterium tuberculosis (MTb) into the body, or secondary due to hematogenous spread from distant sites such as the lungs. Primary disease is rare and includes lesions of the eyelids, conjunctiva, cornea, and sclera, while the uveal tract, retina, and optic nerve are involved in secondary disease. Inflammation of the uveal tract is the most common ocular manifestation of this disease due to its high blood supply.[4]

Natural Resistance-Associated Macrophage Protein 1 (NRAMP1) is considered a strong candidate gene for human tuberculosis susceptibility, and several studies have been conducted to evaluate the relationship between NRAMP1 and tuberculosis.[5,6] Natural Resistance-Associated Macrophage Protein (NRAMP) functions as a transporter of proton/divalent cations and plays a role in the availability of iron within the phagosome. Mycobacterium tuberculosis, the causative agent of tuberculosis, is an intracellular microorganism that replicates within the phagosome of host macrophages. MTb competes with the host for acquiring iron to survive and grow.[7]

The NRAMP1 gene is expressed not only in macrophages but also in blood cells

Table 1. Search Strategy

Database and Registers	Keywords	Hits
PubMed	("natural resistance associated macrophage protein 1"[Title] OR "NRAMP1"[Title] OR "SLC11A1"[Title]) AND "Tuberculosis"[Title]	72
Cochrane	((NRAMP1) OR (SLC11A1)) AND (tuberculosis)	3
Science Direct	((NRAMP1) OR (SLC11A1)) AND (tuberculosis)	742

known as peripheral blood mononuclear cells (PBMCs). This gene encodes a protein that functions as a channel for divalent ions, including Fe++. Deficiency of Fe++ ions can inhibit the growth and ultimately kill MTb. If a mutation occurs in the NRAMP1 gene, resulting in the absence of NRAMP1 protein production, there will be a decrease in NRAMP1 protein expression, leading to the loss or reduction of MTb growth inhibition, allowing the bacteria to proliferate freely.[8]

Eleven variants of NRAMP1 gene polymorphisms have been identified at the gene locus as single nucleotide polymorphisms (SNPs) in specific regions, and four of them have been found to have significant genetic associations with active tuberculosis infection, including 3'UTR, D543N, promoter 5' (GT)n, and INT4.[9]

Currently, there have been numerous studies on the association between NRAMP1 and tuberculosis. However, studies specifically focusing on the NRAMP1 gene and susceptibility to ocular tuberculosis are still limited.

METHODS

Literature search

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines were followed for conducting and reporting meta-analysis data. The eligibility criteria were extracted into keywords utilizing the Boolean operator, searched in electronic databases and registers of PubMed, Cochrane, and Science Direct to find eligible journals. We also evaluate the references of the relevant articles. The last search was run on June 6th, 2023. The search words include: "natural resistance associated macrophage protein 1" OR "NRAMP1" OR "SLC11A1" AND "tuberculosis" (Table 1).

Type of Studies

The current systematic review included all studies prior to June 6th 2023 with full-text available, evaluating gene polymorphism of NRAMP1 to susceptibility of tuberculosis. Articles with the type of case report, qualitative and economic studies, review, animal study, cadaveric and anatomic were excluded from the current study.

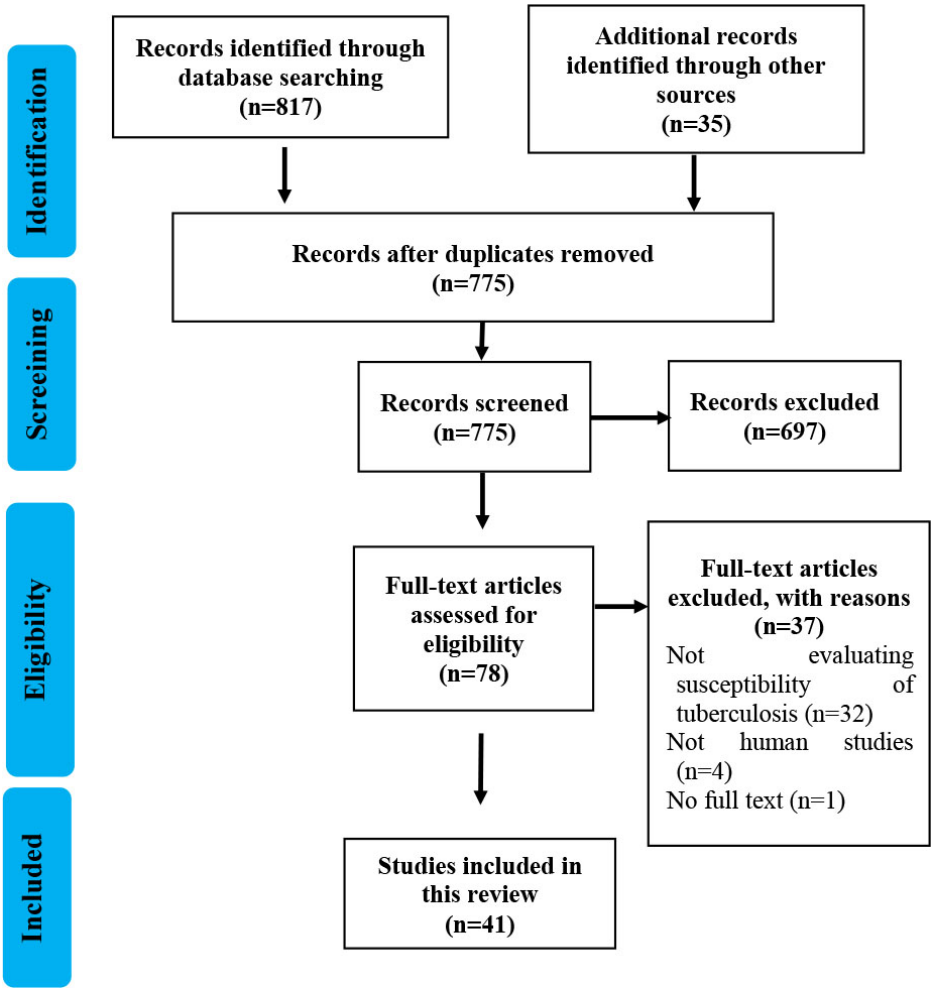

Figure 1. PRISMA Flow Diagram.

Type of Participants

This review included studies with tuberculosis patients and evaluating the polymorphisms of NRAMP1 gene.

Study Selection

The study selection process was conducted by three authors in order to minimize the likelihood of expunge the potentially relevant studies. When disagreement took place, the decision of the first, second and third author was considered. Study selection started with disposing of duplicate records. Title and abstract screening were performed to exclude the irrelevant studies. Subsequently, studies that passed the first evaluation were further evaluated, in order to evaluate its compliance for the inclusion and exclusion criteria for this review.

Data Collection Process

All authors used electronic data collection form to collect the required data from each of the articles.

Data Items

The data items were the author's name, year of publication, ethnic, number of patients, study base, age, and main result of the study. We also noted the polymorphism evaluated for each study.

RESULTS

Searching Result

Initial search identified 852 studies. After removing duplicate articles, we obtained 775 articles. Out of these, 697 articles were excluded based on screening of titles and abstracts. A total of 78 studies were assessed for eligibility, and ultimately, 41 studies were included in this review. The flowchart of the study selection process according to PRISMA guidelines can be seen in Figure 1.

Polymorphism of NRAMP1 In Relation to Tuberculosis

The NRAMP1 gene polymorphisms that have been extensively studied include 3'UTR TGTG ins/del (deletion of TGTG in the 3' untranslated region), D543N (single nucleotide substitution of G to A at codon 543, resulting in the replacement of aspartic acid with asparagine), INT4 (single nucleotide substitution of G to C in intron 4), and (GT)n in the 5' promoter region.[10]

Among the various NRAMP1 gene polymorphisms, such as (GT)n, 136del9, 274C/T, 469 +14 G/C (INT4), 577-18G/A, 823C/T, A318V, 1465-85G/A, D543N, 1729 +55 del4 (3'UTR), and (CAAA) n/(CA)n, only a few are associated with susceptibility (or immunity) to M. tuberculosis. Polymorphisms such as 5'(GT)n, 274C/T, INT4, D543N, and 3'UTR have also shown inconsistent findings, with controversies regarding their role in susceptibility, immunity, or lack of association. The complete summary of all studies related to NRAMP1 gene polymorphism and tuberculosis provided in Table 2.

The Relationship Between NRAMP Gene Polymorphism and Ocular Tuberculosis

The NRAMP1 (Natural Resistance-Associated Macrophage Protein 1) gene is involved in regulating the intracellular transport and distribution of divalent cations, particularly iron and manganese. Several single nucleotide polymorphisms (SNPs) have been identified within the NRAMP1 gene, and some of these polymorphisms have been associated with altered susceptibility to various infectious diseases, including tuberculosis. These polymorphisms can affect the functionality of NRAMP1, leading to altered intracellular trafficking of essential metals and potentially influencing the immune response against Mycobacterium tuberculosis in ocular tissues.[50,51]

The precise mechanism by which NRAMP1 gene polymorphism influences susceptibility to ocular tuberculosis is not fully understood. However, it is believed that alterations in the transport of divalent cations, particularly iron, within macrophages and other immune cells can impact the immune response against Mycobacterium tuberculosis. Iron is an essential nutrient for the survival and replication of mycobacteria, and its availability within host cells can affect the growth and pathogenesis of the bacteria. NRAMP1 polymorphisms may affect iron levels within ocular tissues, thereby modulating the intracellular environment for mycobacterial replication and altering the host immune response in ocular tuberculosis.[33,51]

Additionally, NRAMP1 gene polymorphism may also impact the production and activity of various cytokines involved in the immune response against tuberculosis. Studies have reported associations between specific NRAMP1 polymorphisms and altered cytokine profiles in individuals with ocular tuberculosis. Cytokines play a crucial role in regulating the inflammatory response and promoting the recruitment and activation of immune cells at the site of infection. Changes in cytokine production and activity influenced by NRAMP1 gene polymorphisms may modulate the immune response in ocular tissues, affecting disease susceptibility, severity, and clinical outcomes.[52,53]

Ocular tuberculosis, a rare manifestation of tuberculosis, can occur through several mechanisms. The primary route of infection is believed to be hematogenous dissemination, where Mycobacterium tuberculosis bacilli reach the eye via the bloodstream from a distant primary site of infection, usually the lungs. The bacilli can enter the eye through the rich vascular supply of the uveal tract, choroid, or retina. Another possible route is direct extension from adjacent structures, such as the paranasal sinuses or lymph nodes, through the ethmoidal or nasolacrimal ducts. Additionally, reactivation of latent tuberculosis in the eye can also occur in individuals with compromised immune systems, leading to ocular involvement. Once inside the eye, the mycobacteria can elicit an inflammatory response, resulting in various clinical manifestations, including choroiditis, granulomatous uveitis, retinal vasculitis, and optic nerve involvement.[54,55,56]

DISCUSSION

NRAMP1 (Natural Resistance-Associated Macrophage Protein 1) is a gene that encodes a transmembrane protein involved in the transport of divalent cations, particularly iron and manganese, across the phagosomal membrane of macrophages. These cations are essential for the growth and survival of Mycobacterium tuberculosis, the causative agent of tuberculosis. Several single nucleotide polymorphisms (SNPs) have been identified in the NRAMP1 gene, some of which have been associated with altered susceptibility to tuberculosis. One such SNP is a coding region polymorphism, resulting in an amino acid change at position 172 (D543N), which has been linked to increased susceptibility to tuberculosis.[49,57]

The NRAMP1 gene polymorphisms affect the function and expression of the NRAMP1 protein, thereby modulating the intracellular availability of iron and manganese in macrophages. It has been observed that certain NRAMP1 polymorphisms, such as the D543N variant, result in decreased transport activity of the NRAMP1 protein, leading to impaired intracellular killing of Mycobacterium tuberculosis. This compromised ability to restrict mycobacterial growth within macrophages may contribute to increased susceptibility to tuberculosis.[58,59]

Furthermore, NRAMP1 gene polymorphisms have been associated with altered production and secretion of various pro-inflammatory cytokines

involved in the immune response against Mycobacterium tuberculosis. For instance, the D543N polymorphism in NRAMP1 has been correlated with reduced tumor necrosis factor-alpha (TNF-α) production in response to mycobacterial antigens. TNF-α plays a critical role in orchestrating the immune response against tuberculosis, including the recruitment and activation of immune cells. Altered cytokine production influenced by NRAMP1 polymorphisms may disrupt the immune response against tuberculosis, contributing to increased susceptibility to the disease.[60,61]

The NRAMP1 gene is expressed in various immune cells, including macrophages, dendritic cells, and neutrophils, which play crucial roles in the innate immune response against Mycobacterium tuberculosis. NRAMP1 polymorphisms may impact the phagosome maturation process, affecting the fusion of phagosomes with lysosomes and subsequent intracellular killing of mycobacteria. Studies have demonstrated that NRAMP1 gene polymorphisms can lead to defective phagosome maturation and impaired acidification of phagosomes, promoting mycobacterial survival and replication within host cells. This compromised intracellular killing of mycobacteria may contribute to increased susceptibility to tuberculosis.[38,62]

It is important to note that the association between NRAMP1 gene polymorphisms and tuberculosis susceptibility may vary among different populations due to genetic diversity and environmental factors. Further research is needed to elucidate the precise mechanisms by which NRAMP1 polymorphisms influence susceptibility to tuberculosis and to explore potential gene-gene and gene-environment interactions that may modulate disease outcomes.[63,64]

Polymorphism in SLC11A1 at the D543N and INT4 loci is believed to contribute more to the progression of TB infection rather than increasing susceptibility to infection.[53] A study conducted by Nugraha and Anggraini in 2011[19] showed that the expression of NRAMP1 protein, examined through immunohistochemistry, decreased in individuals with the D543N polymorphism. This suggests that the NRAMP1 protein encoded by the NRAMP1 gene with the D543N polymorphism may be unstable and prone to rapid degradation.[10] The expression of NRAMP1 protein is also four times higher in individuals with the 5'(GT)n allele polymorphism in the promoter region.[65]

A meta-analysis including 82 case-control studies found that the four genotype variants, namely 3'-UTR, D543N, INT4, and 5'(GT)n, were significantly associated with an increased risk of TB. Overall, the D543N polymorphism, specifically the carrier of allele A (AA+AG), increased the risk of TB by 31% compared to the GG homozygous carrier. Meanwhile, the 3'-UTR TGTG polymorphism with the TGTG deletion carrier (TGTG+/−+TGTG−/−) increased the risk of TB by 45% compared to the insertion homozygous carrier (TGTG+/+). The INT4 polymorphism, specifically the carrier of allele C (CC+CG), had a 27% increased risk of TB compared to the GG homozygous carrier. Lastly, the (GT)n polymorphism in carriers of alleles other than allele 3 increased the risk of TB by 35% compared to the allele 3 carrier.[66]

CONCLUSION

In conclusion, several studies investigating the NRAMP1 gene polymorphisms and susceptibility to tuberculosis found various results. Various polymorphisms of the NRAMP1 gene, such as 3'UTR TGTG ins/del, D543N, INT4, and (GT)n, have been investigated for their potential role in determining the susceptibility or immunity to Mycobacterium tuberculosis infection. However, the findings regarding the relationship between NRAMP1 gene polymorphism and tuberculosis are still inconsistent, with controversies and discrepancies among different studies. In regards to ocular tuberculosis, no studies exist to evaluate its association. Further research is needed to elucidate the precise molecular mechanisms underlying the association between NRAMP1 gene polymorphism and the susceptibility to tuberculosis, particularly ocular tuberculosis, which may help in the development of targeted therapies and prevention strategies for this infectious disease.

CONFLICT OF INTEREST

The authors declare no competing interest.

ETHICAL CONSIDERATION

Not required.

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None.

AUTHOR CONTRIBUTIONS

All authors had contributed to manuscript writing and agreed for the final version of manuscript for publication.

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Table 2. **Summary of studies regarding NRAMP1 gene polymorphism related to susceptibility of tuberculosis**

Author, year	Ethnic	Number of patients vs control	Study Base	Mean age ± SD, Patient vs control	Result
Li, 2022[11]	Chinese	227[a] vs 516	Hospital	44.82 ± 0.973 vs 44.43 ± 0.586	Detecting D543N. Associated with spinal TB.
Medapati, 2017[12]	India	91 vs 88	Population	NA	Detecting (GT)n repeat and 3'UTR. Interaction between the NRAMP1 (GT)n repeat and the NRAMP1 3/UTR deletion on the risk of developing TB.
Jafari, 2016[13]	Iran	96 vs 122	Hospital	51 ± 31 **vs 48 ± 27**	Detecting INT4, D543N, and 3'UTR. No significant differences in genotype and allele frequencies of investigated NRAMP1 polymorphisms between patient and control groups.
Wu L, 2015[14]	Chinese	151 vs 453	Population	NA	Detecting INT4, D543NA and 3'UTR. The distribution of NRAMP1- 3'UTR (TGTG/del)was significantly different between pulmonary TB patients and healthy control.
Fernandez-Mestre, 2015[15]	Venezuela	89 vs 50	Hospital	NA	Detecting INT4, D543, and 3′UTR. Association of the NRAMP1 3′UTR polymorphism with M. tuberculosis infection and disease progression.
Wu F, 2013[16]	Chinese	213 vs 211	Population	NA	Detecting 3'UTR. Polymorphisms in the NRAMP1 gene associated with susceptibility to TB.
Tiksnadi, 2013[17]	Indonesia	123[1] vs 123	Hospital	35.9 ± 11.3 overall	Detecting D543N and 3' UTR. no association between NRAMP1 polymorphism with the propensity for development of pulmonary tuberculosis or tuberculous spondylitis. In fact, NRAMP1 may provide protection against the development of tuberculous spondylitis.
Ben-Selma, 2012[18]	Tunisian	168[b] vs 127	Hospital	NA	Detecting 3'-UTR and D543N. association of NRAMP1 3'-UTR and D543N polymorphisms with susceptibility to mycobacterial infection.
Nugraha, 2011[19]	Indonesia	69 vs 43	Hospital	NA	Detecting D543N, 3' UTR, and INT4. Homozygous TGTG deletion in 3'UTR of NRAMP1 was found more frequent in lung tuberculosis patients.

Author, year	Ethnic	Number of patients vs control	Study Base	Mean age ± SD, Patient vs control	Result
Solgun, 2011[20]	Turkey	49 vs 50	Hospital	NA	Detecting (D543N, 3'-UTR and INT4). the INT4, G543A and 3-UTR loci microsatellite polymorphisms in the NRAMP1 gene were not associated with tuberculosis.
Hatta, 2010[21]	Indonesian	58 vs 198	Hospital	34.0 ± 13.1 vs 32.0 ± 12.9	Detecting D543N, 3'UTR, INT4. Nramp1/slc11a1 polymorphism is associated with host susceptibility to PB leprosy but not to tuberculosis
Ates, 2009[22]	Pakistani	112 vs 80	Hospital	46.3 ± 11.4 vs 53.1 ± 7.3	Detecting5' promoter (GT)(n), D543N, 3'UTR, INT4. No associations between NRAMP1 gene polymorphisms and TB
Jin, 2009[23]	Chinese	136 vs 435	Hospital	5.7 ± 4.6 vs 5.8 ± 4.1	Detecting 3'UTR and INT4. 3'UTR locus in the SLC11A1 gene were associated with pediatric tuberculosis.
Meng, 2009[24]	Chinese	224 vs 225	Population	44 vs 49	Detecting 3'UTR. pPlymorphisms of NRAMP1 gene are associated with suscepti-bility to tuberculosis.
Merza, 2009[25]	Iranian	117 vs 60	Hospital	NA	Detecting INT4, D543, and 3'UTR. No association
Asai, 2008[26]	Japanese	57 vs 51	Hospital	48 vs 51	Detecting G/C at intron 4 (496+14G/C), D543N, and TGTG deletion in 3′ untranslated region (1729+55del4). D543N was found closely associated with both pulmonary tuberculosis (p = 0.009) and M. avium-intracellulare infection (p = 0.01). The polymorphism of intron 4 was closely associated only with pulmonary tuberculosis (p = 0.05).
Farnia, 2008[27]	Iranian	71 vs 39	Hospital	46.7 vs 34.1	Detecting INT4, D543, and 3'UTR. Individuals with homozygous type mutation have an increased risk of developing tuberculosis.
Su, 2008[28]	Chinese	54[a] vs 60	Hospital	46 vs 40	Detecting D543N. Polymorphisms of D543N locus in NRAMP1 gene might affect their susceptibility to spinal tuberculosis
Leung, 2007[29]	Chinese	278[c] vs 282	Hospital	65.0 ± 18.4 vs 65.0 ± 18.2	Association between SLC11A1 and TB susceptibility and demonstrated for the first time that the association was restricted to females and the young age group.

Author, year	Ethnic	Number of patients vs control	Study Base	Mean age ± SD, Patient vs control	Result
Moreno, 2007[30]	Mexican	94[c] vs 100	Population	NA	Detecting D543N and 3′-UTR. D543N and 3′-UTR variants of NRAMP1/ SLC11 A1 gene are not significantly associated with pulmonary tuberculosis
Qu, 2007[31]	Chinese	61[c] vs 122	Hospital	NA	Detecting INT4 and D543N. variant NRAMP1 INT4 may play a role in the development of pulmonary TB
Sahiratmadja, 2007[32]	Indonesian	378[c] vs 436	Hospital	29 vs 33	Detecting INT4, D543N and 3'UTR. NRAMP1 gene polymorphisms were not associated with TB susceptibility, TB severity or anaemia
Soborg, 2007[33]	Tanzanian	399[c] vs 408	Population	NA	Detecting 5′(CA)n microsatellite. A significant association between pulmonary tuberculosis and a microsatellite marker in the 5′(CA)n locus in the SLC11A1 gene compared with controls (38% versus 30% odds ratio 1.45, 95% CI: 1.06–1.9, P = 0.014)
Vejbaesya, 2007[34]	Thais	149 vs 147	Hospital	NA	Detecting INT4, D543N, and the 3' untranslated region. No significant differences in the distribution of the genotype frequencies
Druszczynska, 2006[35]	Polish	126 vs 124	Hospital	51.0 ± 16.0 vs 50.0 ± 14.0	Detecting INT4. No association between the polymorphisms of the NRAMP-INT4 and TB.
Hsu, 2006[36]	Chinese	105 vs 95	Hospital	50.1 ± 22.9 vs 45.9 ± 13.7	Detecting INT4, D543N, 77-385C/T, 3-UTR (CAAA) deletion, and 5-(CA) n microsatellite. INT4 and 5-(CA) n, were significantly associated with susceptibility to tuberculosis (p = 0.0070 and p = 0.0031, respectively)
Taype, 2006[37]	Peruvian	507 vs 513	Hospital	29.0 ± 11.4 vs 32.6 ± 9.4	Detecting INT4, D543N, and 3'UTR. Support association between SLC11A1 and TB, particularly to the common pulmonary form.
Zhang, 2005[38]	Chinese	127[c] vs 91	Hospital	52.3 ± 13.3 vs NA	Detecting INT4 and D543N. The NRAMP1 variants were not associated with pulmonary M. tuberculosis infection. However, genetic variants of NRAMP1 may have an effect on bacilli growth and on outcomes of pulmonary tuberculosis.

Author, year	Ethnic	Number of patients vs control	Study Base	Mean age ± SD, Patient vs control	Result
Fitness, 2004[39]	Malawi	514 vs 913	Population	NA	Detecting 3'UTR. Associated with protection against TB in both HIV-positive (OR = 0.70, 95% CI = 0.49-0.99, P = 0.046) and HIV-negative (OR = 0.65, 95% CI = 0.46-0.92, P = 0.014) TB cases
Liu, 2004[40]	Chinese	120[c] vs 240	Hospital	27.7 ± 12.7 vs 27.3 ± 9.2	Detecting INT4, D543N, and 3'UTR. Association found in D543N and 3'UTR.
Abe, 2003[5]	Japanese	95 vs 90	Hospital	58 vs 61.4	Detecting INT4, D543N, and 3'UTR. No association was seen between susceptibility to tuberculosis and NRAMP1 polymorphisms. However, D543N A allele were significantly more likely than others to develop a cavitary lesion.
Duan, 2003[41]	Chinese	147 vs 145	Hospital	43.5 vs 48.9	Detecting 3'UTR. 3'UTR polymorphisms of NRAMP1 gene are associated with susceptibility to tuberculosis.
Awomoyi, 2002[42]	Gambian	329[c] vs 324	Hospital	36 vs 32	Detecting SLC11A1 5′ promoter region (GT)n polymorphism. SLC11A1 influences tuberculosis susceptibility by regulation of interleukin-10.
Delgado, 2002[43]	Cambodian	358 vs 106	Hospital	42.2 ± 14.1 vs 37.5 ± 12.9	Detecting INT4, D543N and 3' untranslated region, and –236C/T. Heterozygosity for 2 linked polymorphic NRAMP1 variants, D543N and 3' untranslated region, were associated with TB susceptibility and resistance.
Liaw, 2002[44]	Chinese	48 vs 49	Hospital	56 vs 49	Detecting 274C/T, 577-18G/A, A318V, D543N and 3' untranslated region (UTR). No allelic associations were identified between the NRAMP1 alleles and tuberculosis susceptibility.
Ma, 2002[45]	American	135 vs 108	Hospital	52.2 ± 11.2 vs 61.4 ± 14.8	Detecting D543N, 3UTR, and 5(GT)n. 5'(GT)n polymorphism of NRAMP1 modifies TB susceptibility
Puzyrev, 2002[46]	Russian	58 vs 127	Hospital	19.3 ± 15.2 vs 39.1 ± 3.3	Detecting 469 + 14 G/C (INT4), 1465 - 85 G/A, and C274T polymorphisms. None of the polymorphisms was associated with TB.

Author, year	Ethnic	Number of patients vs control	Study Base	Mean age ± SD, Patient vs control	Result
Selvaraj, 2002[47]	Indian	57[b] vs 100[c] vs 112	Hospital	Pulmonary TB males: 40.5 ± 1.3 Pulmonary TB females: 38.9 ± 2.5 Spinal TB males: 39.5 ± 3.3 Spinal TB females: 45.8 ± 2.5 Control males: 40.5 ± 1.4 Control females: 36.8 ± 1.1	Detecting 823 C/T (exon 8), deletion of TGTG in the 3'-UTR (3' untranslated region) and D543N. The study suggests that NRAMP1 gene may not be associated with the susceptibility to pulmonary and spinal TB.
Gao,2000[9]	Japanese	202[c] vs 267	Hospital	57.8 ± 15.8 vs 45.4 ± 16.8	Detecting 5'promoter (GT)n, INT4, Asn543Asp, and 3'UTR variants. Variants of NRAMP1 are associated with active tuberculosis.
Ryu, 2000[48]	Korean	192 vs 192	Hospital	NA	Detecting 3'UTR. association was found between the Korean tuberculosis patients and polymorphisms in the 3'UTR of the NRAMP1 gene (OR 1.845; 95% CI 1.097-3.104; chi2 = 5.424; P = 0.020)
Bellamy, 1998[49]	Gambian	410[c] vs 417	Hospital	34.7 ± 13.2 vs 30.3 ± 7.5	Detecting 5'(CA)n, INT4, D543N, and 3'UTR. Four NRAMP1 polymorphisms were each significantly associated with tuberculosis.

[a] Cases with osseous tuberculosis
[b] Cases with extra-pulmonary tuberculosis
[c] Cases with pulmonary TB