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Nramp1 (SLC11A1) Gene Polymorphisms and Tuberculosis Susceptability: Review

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Abstract

Tuberculosis remains one of the important infectious diseases in the world. Studies suggest that host genetic factors affect human susceptibility to tuberculosis. The natural resistance-associated macrophage protein 1 (NRAMP1) gene appears to play a role in the pathophysiology of a number of intracellular infections, including mycobacteria. To find out the association between NRAMP1 (SLC11A1) gene polymorphism and tuberculosis many studies have been conducted in different populations. The results obtained were not consistent and reported that the susceptibility of polymorphic varients to tuberculosis is population specific. The NRAMP1 gene polymorphism showed an increased risk for tuberculosis in African population while some Asiatic population didn't show any association.

Keywords: Polymorphism . Resistance. Susceptible. Tuberculosis.

Introduction

Tuberculosis (TB) is the most common and often deadly infectious disease caused by various strains of mycobacterium, usually *mycobacterium tuberculosis* in humans [33]. The control of mycobacterium infections has been an important issue in the world. The pulmonary localization of the *M. tuberculosis* is the most common presentation of tuberculosis disease, but extra pulmonary disease can affect other organs of the human body [25]. The specific reason for why the majority of infected individuals never progress to active tuberculosis was not yet revealed by research but it is known that environmental factors, host genes, *M. tuberculosis* virulence and various risk factors such as HIV infection, receipt of immunosuppressive therapy and diabetes mellitus

[46] may all contribute to the final outcome of the infection. The interaction between these different factors as well as the impact of these factors on susceptibility or disease development is unknown. As a complex interaction of genetic and environmental factors has been accepted for the development of tuberculosis and other infectious diseases, specific genes have been studied for association with the infection susceptibility. Here the NRAMP1 gene polymorphism with susceptibility or resistance to mycobacterial infection is reviewed shortly.

NRAMP1 gene

Several genomic and proteomic studies have been conducted in the expectation of revealing the human immune defense mechanism against infection and obtaining vital information on the treatment and prevention of tuberculosis. Various animal studies have publicized that susceptibility and resistance to mycobacteria and other intracellular pathogens are controlled by the *Bcg* gene on chromosome 1 [55, 9]. Bcg^s and Bcg^r are the two phenotypes of this gene associated with susceptibility and resistance respectively [22]. Candidate gene for *Bcg* was isolated using a cloning method, and termed it as *Nramp1* (natural resistance associated macrophage protein 1) by Vidal et al. [66] Human *NRAMP1* gene, an analogue of the mouse *Nramp1* gene, was discovered by Cellier et al. [11] from chromosome 2q35.

NRAMP1 gene, also known as SLC11A1 (solute carrier family 11, member 1), encodes a protein that functions as a divalent ion channel [54]. This protein localizes to late endosome / lysosome [23] is responsible for altering the phagolysosomal environment such as pH, and in this way prevents the replication of the intracellular pathogen [7]. S*LC11A1* is associated with pH dependant transport of divalent cations (Fe^{2+}, Mg^{2+}) through the phagosome membranes, are essential for many cellular functions. Fe^{++} ion can inhibit growth of *Mycobacterium tuberculosis* [10]. Experimental studies suggest that the transport is from the lumen of the phagolysosome to the cytosol, which prevents the acquisition of these cations by intracellular pathogens [19]. *SLC11A1* gene have pleiotropic effects on macrophage function, that include increased chemokine KC, tumour necrosis factor-α, interleukin-1β, inducible nitric oxide synthase and major histocompatability complex class II expression; all are important in resistance to intracellular pathogens [6].

Many genetic polymorphisms have been reported to date, and it has been suggested that they may influence the gene's function [37, 34]. Many single-nucleotide polymorphisms (SNPs) have no effect on cell function, but some SNPs, especially if they affect the function of the gene, could predispose people to disease or influence their response to a drug [52]. In recent times, number of genes have been investigated in various case control studies, of which the natural resistance –associated macrophage protein (NRAMP1) is thought to be important in the intracellular killing of Mycobacteria.

NRAMP1 gene polymorphic studies

NRAMP1 gene has several polymorphisms [37], among which the most widely studied are INT4, D543N and 3'UTR. A G/C single nucleotide change in intron 4(469_14G/C) was termed as INT4, a non-conservative single-base substitution at codon 543 that changes aspartic acid (Asp) to asparagine (Asn) was termed as D543N, and a TGTG deletion in the 3' untranslated region (1729_55del4) was termed 3'UTR [27]. *The first study to describe the association between SLC11A1 (NRAMP1) polymorphisms and TB susceptibility was reported in 1998 on a population from West Africa [7].*

Bellamy et al. (1998) [7] conducted a large case-control study in Gambia (West Africa), to analyze the association of polymorphic variants of the *NRAMP1* gene such as a dinucleotide repeat, $(CA)_{n,}$ in the 5' region, INT4, D543N, TGTG deletion in 3'UTR region with tuberculosis. The study revealed that polymorphisms in INT4 and in the 3'UTR region have a strong association with tuberculosis susceptibility and subjects heterozygous for these two variants were four times higher among patients with tuberculosis than those bearing the most common *NRAMP1* genotype. Richard et al. (1998) [50] reported subjects' heterozygote for INT4, 3'UTR (TGTG) and D543N variants are at increased risk for TB in Gambia. A study from Guinea-Conakry repotted that both INT4 and 3'UTR polymorphisms are significantly associated with tuberculosis [12]. INT4, 3'UTR (TGTG) and D543N variants did not show any association with pulmonary TB in Morocco [17]. A study conducted among a high-incidence community in South Africa reported that homozygotes for the TGTG deletion (1729+55del4) in the 3'UTR of NRAMP1 showed susceptibility to tb while 5' (GT)n allele appears to be associated with protection against tb [26]. Heterozygosity for a CAAA insertion/deletion polymorphism in 3'UTR of the NRAMP1 gene was associated with protection against TB in both HIV-positive and HIV-negative TB cases in Malawi, suggesting that the SLC11A1 protein may have a role in innate TB immune responses that influence susceptibility even in immunocompromised individuals. However, other variants of NRAMPI were not associated with TB in Malawi [18]. A novel trinucleotide (ATA) n repeat polymorphism in intron 8 of SLC11AI was analyzed for susceptibility to tuberculosis (TB) infection in individuals originating from eight globally diverse human populations with adults and cord blood samples from newborns in the Gambian population. There was no significant association between this marker and pulmonary TB [5]. A significant association between pulmonary tuberculosis and a microsatellite marker in the $5'(CA)_n$ locus in the NRAMP1gene was observed in East-African subjects [58]. NRAMP1 3'-UTR and D543N polymorphisms were found to be associated with susceptibility to mycobacterial infection in Tunisian populations in relation to age and sex [8].

A mixed case control study among African-Americans and Caucasians revealed INT4 polymorphism was associated with TB only in African-Americans and D543N, 3'UTR and $5'(GT)_n$ were not associated with TB in both populations. This study also revealed that multilocus analyses between polymorphisms in SLC11A1 and 11 TB candidate genes detected interactions between SLC11A1 and inducible nitric oxide

synthase (NOS2A) in Caucasians and toll-like receptor 2 (TLR2) in African-Americans [65].

NRAMP1 was strongly linked to tuberculosis susceptibility in Canadian Aboriginal community [21]. A study from Texas accounted that the 5'(GT)n polymorphism of NRAMP1 modifies TB susceptibility in Caucasian population, and could possibly be associated to the site of infection among HIV-negative individuals and HIV-co infected TB [40]. Using a family-based control design, a study performed among ethnically diverse families from the Greater Houston area with at least one child affected by tuberculosis disease, found allelic variants of the NRAMP1 gene significantly associated with pediatric tuberculosis and also hypothesized that NRAMP1 influences the speed of progression from infection to tuberculosis disease [41]. In Peruvian population INT4-D543N-3'UTR haplotypes showed an association with pulmonary TB while there was no association of NRAMP1 with miliary TB, and a possible association of D543N to the pleural form was suggested [62]. There is no noticeable association between the D543N and 3′-UTR variants of NRAMP1 and pulmonary tuberculosis in Mexican mestizo population [46].

Carriage of Nramp1 variant alleles at loci INT4 and 5'(CA)n conferred a significantly increased risk of having microscopy-positive TB compared with microscopy-negative TB in Denmark . The study also revealed, the Nramp1 alleles were not associated with increased risk for the development of cavities seen on chest radiographs, or with extra pulmonary tuberculosis. The results designate that variant alleles in the Nramp1 gene are associated with increased mycobacterial replication rather than susceptibility for tuberculosis and may thus confer increased risk of severe disease in the population of Denmark [57]. Study from Poland reported that INT4 polymorphism is not associated with TB infection but both D543N and 3'UTR polymorphisms are associated with susceptibility to infection [16]. A study conducted in the Greek population showed lack of association between polymorphisms such as D543N and 3'UTR with overt pulmonary tuberculosis and also concluded that INT4-NRAMP1 polymorphism may have a role in the development of culture-positive pulmonary tuberculosis after an initial *M. tuberculosis* latent infection [42].

Parisa Farnia et al. (2008) [47] reported that their study in Iran (Tehran) aimed to investigate the Nramp1 gene variants among workers exposed to TB bacilli (1-2 hours per day for 1 to 20 years) who did not develop the diseases with those who developed the disease through recent transmission showed the result that only homozygous patterns of Nramp1 gene were associated with pulmonary TB. So they concluded this might be one of the reasons why the TB-exposed healthcare workers did not develop TB, even after long periods of working with TB bacillus. While another study reported there was no association between allele variants at locus INT4, D543 and 3'UTR of SLC11A1 (NRAMP1) in patients versus controls in Iranian population [45]. There were no associations between NRAMP1 gene polymorphisms and TB in Turkish patients [4].

In India, a study conducted in south India suggests that *NRAMP1* gene polymorphisms may not be associated with the susceptibility to pulmonary and spinal TB in the Indian population [57]. Singh et al. (2011) [60] reported that a significant association between NRAMP1 gene variants, 577G/A and INT4, with PTB susceptibility and subsequent disease progression in East India.

1. However in Chinese, the D543N and INT4 variants were associated with more severe forms of TB [1, 67] while another study reported that 3'UTR polymorphisms were associated with TB susceptibility but the INT4 polymorphism is not associated with pulmonary tuberculosis in Chinese Han population [35]. The 3'UTR polymorphism of NRAMP1 gene is associated with susceptibility to tuberculosis in Hans [15]. Later another study reported that polymorphism of 3'UTR locus in NRAMP1 gene might affect their susceptibility to TB in Han population living in the northern part of China but no significant association was observed between TB and INT4 polymorphism in the same population [2]. The G > C mutation of intron 4 of NRAMP1 gene showed susceptibility to pulmonary TB in workers exposed to silica dusts while NRAMP1 D543N did not show any association with PTB [48]. In Chinese iron miners the INT4 variant of NRAMP1 gene is significantly associated with PTB while D543N polymorphisms was not susceptible and the data also showed a 3.26-fold increased risk of PTB for iron miners carrying both the NRAMP1 D543N G/G and NRAMP1 INT4 G/C or C/C genotypes [49]. Study among Chinese confirmed the association between SLC11A1 and TB susceptibility and demonstrated for the first time that the association was restricted to females and the young age group [31]. Jing Jin et al. (2009) [28] reported TGTG+/delete and TGTG delete/delete genotypes at the 3'UTR locus in the SLC11A1 (NRAMP1) gene were associated with pediatric tuberculosis in China. The study also revealed a significant association between the 3'UTR locus and Tb in female children. A study among Chinese Tibetans showed the result that 5' (GT)9/INT4 G, 3'UTR TGTG/D543N G haplotypes created a lower risk but 3'UTR TGTG del/D543N A haplotypes rendered a higher risk to pulmonary tuberculosis [13]. A study was conducted among Chinese Han population suffering from drug-sensitive TB and drug-resistant TB so as to identify the correlation between gene polymorphisms and the development of drug-resistant TB. The study reported that the in Chinese Han population the genotype and allelic frequencies of INT4 site were different for drug-sensitive TB group from that of drug-resistant TB group. This result indicates that the INT4 sites on SLC11A1 gene probably associated with the development of drug-resistant TB in this population [39].
2. In Korea 3'UTR (TGTG) polymorphism affect host susceptibility to smear-positive TB whereas INT4 polymorphism is not associated with smear-positive TB [51]. Another study from Korea reported that the INT4 and 3'UTR polymorphisms were closely related to tuberculous pleurisy [30].Heterozygotes for INT4, D543N, and 3'UTR were associated with human susceptibility to non-tuberculous mcobacterial (NTM) lung disease [32].

3. In the Thai population, there was no association of the INT4, D543N or 3'UTR variants with susceptibility to TB, or with the severe form of TB [36, 64]. In Cambodians, the D543N and 3'UTR heterozygous variants were associated with TB susceptibility and resistance respectively [14].
4. NRAMP1 gene polymorphisms including INT4, D543N and 3'UTR were not associated with TB susceptibility, TB severity or anemia in Indonesian population [53].The M. tuberculosis Beijing genotype, which comprised 29.8% of all isolates, was strongly associated with two polymorphisms in NRAMP1 such as the D543N G allele and the 3'UTR insertion/insertion genotype in Indonesian population. These findings hold up the hypothesis of co evolution of M. tuberculosis and the human immune system [63]. No significant association was found between D543N, 3'UTR and INT4 variants and tuberculosis in South Sulawesi, Indonesia [24]. None of the polymorphisms in D543N, 3'UTR and INT4 investigated in Nramp1/Slc11a1 were associated with TB in Indonesian population [44]. But another study published that INT4 and D543N polymorphisms did not show any correlation with susceptibility to TB infection, but 3' UTR polymorphism did show significant correlation with susceptibility to TB infection in Indonesia [29].

In Japanese population diverse results were obtained from studies. Two independent populations from Tokyo and Osaka were subjected for the study, a weak association between D543N and tuberculosis in the Tokyo population was found in contrast there was a significant association with the 5' promoter (GT)n in both populations [20]. In Japanese, heterozygosity for D543N variant was associated with the presence of cavity lesions but the INT4 variant did not show any association [20]. The NRAMP1 gene might be involved in susceptibility to pulmonary *Mycobacterium avium* complex infection [61]. Another study revealed, the *SLC11A1* genetic polymorphisms at the INT4 and D543N sites, particularly D543N, were associated with active pulmonary tuberculosis, in a Japanese population [3]. A study from Japan publicized that the variations of D543N and 3'UTR are significantly associated with the incidence of MDR-TB, longer time to sputum culture conversion, and cavity formation [10].

Discussion

Delgado et al. (2002) reported [14] that the frequencies of genetic variants of VDR, NRAMP1, IL-10, and IL-1 genes are population-specific and discrete environmental and natural selective factors have probably resulted in population-specific immunogenetic adaptations to clinical TB. Later Li et al. (2006) [35] reported that studies suggested an ethnicity specific effect of *SLC11A1* polymorphisms on TB risk. The study also reported the four gene polymorphisms that have been studied for NRAMP1 [3′-UTR, D543N, INT4 and 5′-(GT)n] do not show a significant association with tuberculosis in a European population but significant association among most of these variants has been found in African and some Asian population [35]. The reports described here also shows the same result as showed above. This underline the need

for understanding the frequency of a particular polymorphism in specific populations before assigning to it specific infectious-disease associations. Genetic variants of NRAMP1 polymorphisms described here, may serve as markers of unidentified genetic factors that may play a significant role in host immunity to TB in different populations. To elucidate the issue further studies are required on the function of this gene and its genetic varients.

Conclusion

1. To draw a conclusion about the association of NRAMP1 polymorphisms with susceptibility to tuberculosis (TB) in humans is difficult because conflicting results were obtained from different studies performed in different populations. The inconsistency between the studies may be due to various factors including ethnicity-related differences in gene polymorphisms, differences in clinical severity of the patients between studies, unknown cofactors like socio-economical factors, nutritional status, other co-infections or different genetic interactions or whether another functional polymorphism exists within the NRAMPl gene. The study of ethnic-specific genetic associations with TB susceptibility may lead to a novel method of TB therapy and prophylaxis in an ethnic-specific manner.

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