

Study on Polymorphism of IFNG and Its Receptor Gene and Susceptibility to Tuberculosis

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Abstract: Tuberculosis is a chronic infectious disease caused by Mycobacterium tuberculosis infection and is a major global public health event at present, most studies focus on the susceptibility to tuberculosis from the aspects of population host susceptibility gene IFNG and its receptor gene polymorphisms plays an important role in the infectivity of tuberculosis. In this paper, the known IFNG and its receptor gene loci and gene mutation defects are described to provide new ideas for exploring the treatment of tuberculosis in the future.

1. Introduction

Tuberculosis is an infectious disease, a major cause of ill health and one of the leading causes of death worldwide. Around a quarter of the world's population is infected with Mycobacterium tuberculosis. At present, most of the studies focus on the susceptibility of tuberculosis from the aspect of population host susceptibility genes. To identify the occurrence and progress of the disease and to find the prevention and treatment of tuberculosis. Interferon-gamma (IFNG)/Interferon-gamma receptor1 (IFNGR1) were studied in this paper.

The relationship between gene polymorphisms, gene mutations, gene defect, and susceptibility to tuberculosis was reviewed and prospected.

IFN- γ and TNF- α affect B-cell proliferation and differentiation into immunoglobulin secreting cells, encoded by IFNG gene, is a cytokine involved in the pathogenesis of tuberculosis and plays an important role in the pathogenesis of tuberculosis. IFN- γ is mainly produced by activated T lymphocytes (including CD4 + and CD8 + T) and natural killer cells. IFN- γ binds to specific receptors and has the functions of anti-virus, anti-proliferation, activating macrophages and promoting their activity. CD4 + and CD8 + Th1 effector T cells of the adaptive immune system, naive CD4 + and CD8 + T cells produce IFN-g1 immediately after initial activation. Compared with CD4 + and CD8 + T cells, The release of IL-2 from Th1 cells appears to be the primary stimulus for IFN-g sequential synthesis. This way, IFN-g can be rapidly induced and secreted in the early stage of infection. NKT cells develop innate

immunity to tumors and a range of infections, and they rapidly secrete cytokines, such as IFN-g. However, initial CD4 + and CD8 + T cells can acquire the ability to efficiently transcribe the gene encoding IFN-g within a few days. This process depends on their proliferation, differentiation, and up-regulation of IFN-g promoting transcription factors and remodeling of chromosomes within the IFN-g genome. By default, initial CD8 + T cells are programmed to produce IFN-g cytotoxic effectors, while CD4 + T cells can differentiate into many effector lineages, with only Th1 CD4 + T cells producing significant amounts of IFN-g. The effector differentiation process of CD4 + T cells and CD8 + T cells, the nature of the infectious pathogen, and the influence of the cytokine environment in which the innate immune system responds to the pathogen. These differences in initiation conditions, in turn, lead to stable changes in the chromatin structure of genes encoding IFN-g, promoting high levels of expression of Th1 CD4 + and CD8 + effector T cells or silencing the expression of other effector T cells [1]. In the early stage, the human IFN- γ gene was accurately located in band 4 of chromosome 12 (12q14), and then the study of IFN- γ and its receptor in the field of tuberculosis has been greatly expanded^[2]. Studies have shown that the early appearance of IFN- γ -producing lymphocytes plays an important role in the defense against pulmonary tuberculosis infection, and mice and humans lacking components of the IFN- γ signaling pathway are highly susceptible to tuberculosis.

The IFN- γ receptor is composed of two integral membrane proteins, the α and β subunits. The α subunit, encoded by the IFNGR1 gene, regulates the potency of IFN- γ signaling³. The IFNGR1 gene, located at 6p23.3, consists of seven exons and encodes the ligand-binding chain (α) of the IFN-gamma receptor, which plays an important role in receptor trafficking and signaling. IFNGR1 is associated with a variety of diseases and widely exists in a variety of immunocompetent cells. Deficiency of IFNGR1 gene leads to abnormal expression of IFNGR1 protein on the surface of phagocytes, which can not recognize the natural ligand IFN- γ secreted by T cells and NK cells, resulting in the failure of phagocytes to be activated and play their role in phagocytosis of mycobacteria Ying Wenjing, Liu Danru, Sun Jinyi, et al. Two cases of mycobacterial susceptibility caused by IFNGR1 gene mutation. Chinese Journal of Evidence-Based Pediatrics, 2017, 12 (4): 295-299. DOI: 10.3969/j.issn.1673-5501.2017.04.011.]. Mutations in the IFNGR1 gene and defective expression of the ligand-binding chain (α) of the IFN-gamma receptor cause severe disseminated BCG disease. The beta subunit is encoded by the IFNGR2 gene, and mutations in the IFNGR2 gene are rare. Defects in either of the IFNGR1 and IFNGR2 receptor subunits can alter IFN- γ signaling, thereby affecting host susceptibility to tuberculosis [2].

Scholars at home and abroad have done a lot of research work on the relationship between IFNG and its receptor gene polymorphism and tuberculosis.

2. Polymorphism of IFNG Gene

2.1. 243056 1 site of rs

As early as 2003, Dolores et al [3]. investigated the association of single-base variation polymorphisms found in *ifn- γ* (rs2430561) and interleukin-10 with cytokine production and tuberculosis susceptibility in peripheral blood monocytes. Multivariate logistic regression analysis showed that individuals with homozygous *ifn- γ* (rs2430561) A allele had a 3.75-fold increased risk of TB (95% confidence interval, 2.26-6.23, $p = 0.0017$). Peripheral blood mononuclear cells from patients with the AA genotype had reduced stimulation to produce interferon at diagnosis and after completion of polymorphic hybridization compared with non-AA homozygous patients. Multifactorial analysis of treatment showed that AA genotype and absolute lymphocyte count were the only independent predictors of interferon production. In contrast, differences in interleukin-10

production rates associated with interleukin-10 polymorphisms did not affect susceptibility to TB. Therefore, A genetic defect that produces IFNG in homozygotes of the (rs2430561) A allele may lead to an increased risk of developing TB in them [4]. In the same year, Mandarosu et al. Rossouw Manda, Nel Hendrik J, Cooke Graham S et al.]. Relationship between tuberculosis and polymorphic NFkappaB binding sites in interferon gamma genes.. J Biomedical Engineering, 2003,26(2): 391-391 [5]. (in Chinese) In the South African population, the IFNG polymorphism rs2430561 was significantly associated with tuberculosis ($p = 0.0055$). The transcription factor NF κ B binds preferentially to the rs2430561 T allele, and this preferential binding suggests that genetic variability in IFN- γ and expression may be important for the development of tuberculosis.2006 Graham S. Cook et al. Disease associations with genes encoding IFNG were studied.Results: Within the IFNG gene, the rs2430561 genotype did not have a significantly increased incidence in control cases (OR, 1.1695% CI, 0.89-1.51: $p = 0.25$).That is, IFNG production and genetic variation can affect the risk of tuberculosis.2013 Chen Shen et al. The IFNG rs2430561 allele in the female subgroup may be the allele of susceptibility to tuberculosis in the study of IFNG polymorphism and susceptibility to tuberculosis in children of Han nationality in North China.The higher rs2430561 allele expression in the extrapulmonary TB subgroup is associated with low IFN- γ expression, and adequate IFN- γ expression is important not only for the onset of TB but also for limiting its spread to the lung [6]. 2017 Zhang Wei et al. A meta-analysis evaluated the association between IFNG rs2430561 polymorphism and TB susceptibility. The IFNG rs2430561 polymorphism was found to play an important role in protecting individuals from tuberculosis and extrapulmonary tuberculosis. The meta-analysis suggests that IFNG rs2430561 polymorphism may be associated with TB susceptibility and could serve as a predictive biomarker [7-9]. 2019 Asma Gulnaz et al. Genotyping was performed to examine the association between IFNG and TB incidence and drug resistance in the Pakistani population [10]. The IFNG polymorphism rs2430561 was significantly different between cases and controls. The incidence of wild-type genotype (TT) was significantly higher in control group (43.2%) than in case group (25.3%)(odds ratio [OR] = 0.77, $p < 0.0001$). The incidence of AA (38.57%) was significantly higher than that of the control group (22.6%)(OR = 1.46, $p < 0.0001$). Heterozygous genotype frequency (TA) was not significantly different between control groups and cases. The variant allele (A) occurs about twice as often in cases as in controls. Women and the elderly have higher rates of disease. Finally, IFNG rs2430561 polymorphism was not associated with drug sensitivity or resistance [11]. IFNG rs2430561 genotype polymorphism was significantly associated with TB susceptibility, and the T allele had a protective effect on TB [12].

2.2. Rs1861 494 site

In 2013, Yu Yang et al., a study from Zhengzhou, China, found a potential association between IFNG rs1861494 and tuberculosis. A 2014 study by Mohammed Varahram et al also found that IFNG rs1861494 was significantly higher in patients with RS1861494 than in controls ($P < 5\%$, OR = 0.50, 95% CI: 0.3). A 2018 study conducted in Argentina. IFNG rs1861494 polymorphism (G \rightarrow A) was found, and the results showed that IFNG rs1861494 is a biomarker of tuberculosis resistance in the Argentine population [13]. Polymorphism of ifng gene in latent tuberculosis infection.. Markers of Disease, 2019, 2019:8410290. IFNG rs1861494 was significantly associated with latent tuberculosis infection (LTBI), and CC + CT genotypes were associated with a 50% reduced risk of LTBI ($P=0.046$, OR=0.50, 95% CI: 0.25-0.99). In the same year, Wu Shouquan et al. Another study found that IFNG rs1861494 allele C was associated with an increased risk of tuberculosis (OR=1.25, 95%CI:1.06-1.48, $P = 0.009$). CT (OR=1.28, 95%CI: 1.01-1.63, $P=0.040$) and CC (OR=1.51, 95%CI: 1.04-2.19, $P=0.031$) were also risk factors for TB compared with TT genotypes. In

subgroup analyses, age < 25 years (OR=2.40, 95% CI: 1.70-3.38, P<0.001) and males (OR=1.31, 95% CI: 1.03-1.66, P=0.030) were more strongly associated with TB. In addition, IFNG rs1861494 is associated with antituberculosis treatments outcomes (OR=0.70, 95% CI: 0.52-0.91, P=0.017). Zhang Xiaodong, Zhang Xiaodong, et al. Relationship between interferon gamma single nucleotide polymorphism and pulmonary tuberculosis. *Journal of Biomedical Engineering*, 2016, 23(3):1493-1493. The results showed that ifn- γ rs1861494 (C/T) single nucleotide polymorphism was associated with tuberculosis in Himachal Pradesh, India [14].

2.3. Rs206970 5 site

The results showed that under genotypic, dominant and additive models, the small allele "A" of rs2069705 in IFNG significantly increased the risk of tuberculosis (P < 5%) [15].

2.4. Rs2069 718 site

2017 Li Jiong et al [16], The IFNG gene (rs2069718) was genotyped in patients with spinal tuberculosis, patients with pulmonary tuberculosis, and control subjects. The rs2069718 genotype was found to be significantly associated with pulmonary tuberculosis (TT, p=0.007 CT, D =0.008) but not with spinal tuberculosis. In general, there is a difference in rs2069718 genetic distribution between patients with spinal tuberculosis and pulmonary tuberculosis in the Han Chinese population. Results from the India 2022 study¹⁷ showed that the rs2069718 (C/T) SNP in IFN- γ was associated with tuberculosis in the Himachal Pradesh population of India.

2.5. Rs1861493

The results of the India 2022 study showed that the association of IFNG gene rs1861493 genotype "AA" was associated with higher plasma IFN- γ levels in the Himachal Pradesh population, India.

3. Polymorphism of IFNGR1 gene

3.1. Rs 1327475, Rs 7749390, Rs 2234711

2014 Lv Jieqiong et al. [17] Three SNPs (rs2234711, rs1327475, and rs7749390) in the IFNGR1 gene were observed to be significantly associated with the risk of tuberculosis. For SNP rs2234711, individuals carrying the C allele (equivalent to T) showed a reduced risk with an adjusted OR (95% CI) of 0.82 (0.76-0.91). Additive modeling showed an approximately 14% reduction in risk for each additional allele (OR: 0.86, 95% CI: 0.72-0.95). In addition, there was a strong linkage disequilibrium between rs 2234711 and rs3799488. Haplotype rs2234711T-rs3799488C significantly increased the risk of TB compared with the common rs2234711C-rs3799488C haplotype (adjusted OR: 1.24, 95% CI: 1.09-1.41). 2019 Wu Shouquan et al ^[15]. Of studies found a significant association between IFNGR1 rs2234711 and LTBI, Allele A increased the risk of LTBI by 55% (P = 0.047, OR = 1.55, 95% CI: 1.00-2.40). IFNGR1 rs2234711 was also detected to affect the production of IFNG.

3.2. Rs9376268, Rs1327474 sites

2017 He Shumei et al. 18 The results showed that IFNGR1 genotypes rs9376268 and rs1327474 mutants had a protective effect on the risk of pulmonary tuberculosis, dominant and additive models (P < 5%). Blocking rs1327474 significantly reduced the risk of pulmonary

tuberculosis ($P < 1\%$), while blocking haplotypes "C-G-G-A-T" "T-G-G-G-T" and "C-G-G-G-T" significantly increased the risk of PTB ($P < 1\%$). These results suggest that IFNGR1 variants may be closely associated with the risk of pulmonary tuberculosis in the Tibetan population in China.

Some studies have come to the opposite conclusion, such as Minnewport in 2003. [18] The conclusion was that no association between IFNGR1 polymorphism and tuberculosis was found in the African population of the Gambia. Another study from the Gambia in 2004. [19] No association was found between IFNGR1 and tuberculosis in the Gambian population sample.

4. Defects and Mutations of IFNG Gene

Hereditary mycobacterial susceptibility syndrome (MSMD) belongs to BCG disease, which is caused by a small number of children who are infected with BCG vaccine because of their autoimmune status and low immune function. But it can also occur in adulthood^[23]. The most important immune pathway for the body to clear BCG infection is the IFNG pathway, which is a cytokine produced by T cells or NK cells after IL-12, IL-23 stimulation. MSMD patients lack the cells or cytokines in the above pathways, and are prone to serious complications after BCG vaccination. MSMD is characterized by susceptibility to hypovirulent mycobacteria, salmonella, and chronic mucocutaneous candidiasis^[23]. 2022 Kosuke Noma et al. [20] The study of MSMD has clarified that MSMD is divided into two groups: isolated MSMD and syndromic MSMD. 18 genes found, 13 (IFNGR1, IFNGR2, IFNG, STAT1, IRF8, IL12RB1, IL12RB2, IL23R, IL12B, SPPL2A, TYK2, NEMO, CYBB) resulted in isolated MSMD. Characterized by a selective susceptibility to one or more mycobacteria and associated infections; AR (autosomal recessive) in 8 (STAT1, IRF8, ZNFX1, TYK2, ISG15, RORC, TBX21) is caused by complete functional defects. Dysfunction of the AR part of JAK1 (STAT1) leads to syndromic MSMD, which involves a combination of mycobacterial disease infection phenotypes and other clinical phenotypes. Of the 3 genetic causes described, AR-IFNG deficiency is classified as isolated MSMD, while AR-T-bet and ZNFX1 deficiency is classified as syndromic MSMD. Multifocal osteomyelitis is a representative symptom of MSMD and has been reported to have a high incidence in patients with MSMD due to impaired IFNG response, such as AD (autosomal dominant) IFNGR1, AD IFNGR2, or AD STAT1 deficiency. Poor IFNG response leads to impaired osteoclast differentiation and inhibited bone resorption, which has been shown to be associated with multifocal osteomyelitis in MSMD.

4.1. Defects and Mutations of IFNGR1 Gene

1999 Emmanuel Joanguet et al. [21] Hot spots of small deletions of IFNGR1 in humans are reported. These deletions are a major predisposition to infections caused by hypovirulent Mycobacterium species. In recent years, the number of reported cases has gradually increased. China reported in 2017^[4]. Two children developed BCG disease within 3 months after birth, with an axillary lymph node enlargement as the initial manifestation, and gradually spread to the lungs, intestines, central nervous system and bone marrow. The ages of diagnosis were 4 and 6 years old respectively. There was no defect in routine immune function evaluation. The release of IFN- γ and the expression of IFNGR1 protein were significantly lower than normal. A homozygous mutation of c.665 G > a (p.G219R) was found in one patient, whose parents were heterozygous for c.665 G > a (p.G219R); One patient had compound heterozygous mutations of c.665 G > A (p.G219R) and c.310C > A (p.A104N), which were inherited from the mother and the father respectively. The mutation in one patient was de novo and had not been previously reported. Two cases were treated with IFN- γ after the diagnosis, and the infection of BCG was controlled, and no other adverse reactions were found. Conclusion Mutation of IFVGR1 gene may lead to hereditary mycobacterial

susceptibility syndrome. It is necessary to consider the possibility of the disease when there is no defect in the routine immune evaluation of children with BCG disease. The detection of related proteins, IFN- γ release test, and gene analysis are helpful for the diagnosis. IPN- γ therapy was effective to some extent. 2019 Mahsima Shabani et al. [22] A 2-year-old male from Iran, whose parents are close relatives, developed a novel biallelic mutation in exon 6 of IFNGR1 gene, complicated with multiple bacterial virus, fungal infection and PCR positive *M. tuberculosis* in bone marrow aspirates is reported. 2020 Gaspard Koerner et al. [23] We report the diagnosis of hereditary mycobacterium susceptibility syndrome in two children living in Kuwait who are homozygous with a small deletion of the IFNGR1 gene. [24] Three patients with MSMD are described who have novel or novel combinations of nonmorphological variants in which functional assays are essential to determine the extent of the interferon gamma receptor signaling defect.

4.2. IFNGR2 Gene Mutation

Carmen Olega Quintas et al. [29] used whole exon sequencing to study three unrelated MSMD patients from two regions of Turkey (P1, P2) and India (P3). P1 and P2 are homozygous for the start codon mutation of IFNGR2 (C.1a > G), while P3 is homozygous for the second codon mutation (C.4delc). Three patients were diagnosed with MSMD after BCG vaccination. Germline biallelic mutations of IFNGR2 have been shown to cause partial or complete deficiency of IFN- γ receptor 2 (IFN- γ R2). Some patients with IFN-gamma-R2 deficiency express a dysfunctional molecule on the cell surface. Overexpressed mutant alleles produce small amounts of full-length IFN- γ R2, resulting in impaired, but not eliminated, response to IFN- γ . This defines a new partially recessive IFN-gamma-R2 deficiency. Autosomal recessive (AR) total IFN-gamma-R2 deficiency is the most severe IFN-gamma-R2 deficiency and is characterized by a complete loss of protein function, which is characterized by high plasma levels of IFN-gamma. [25] and eliminate IFN- γ in all cell types [26]. Due to the very poor prognosis, hematopoietic stem cell transplantation (HSCT) is the only known curative treatment, and gene therapy may be a potentially attractive option in the future. Partial IFN-gamma-R2 deficiency. These patients showed similar levels of cellular response damage to IFN- γ , but did not completely eliminate these responses. Although onset is early, infection is relatively mild. Plasma IFN- γ levels are high, but clinical outcomes are relatively good.

By sorting out the literature in the past 20 years from 2003 to 2022, we know that IFNG and its receptor gene polymorphisms are associated with tuberculosis susceptibility. Polymorphisms of rs2430561, rs1861494, rs2069705, rs2069718. The T alleles of rs2430561, rs9376268 and rs1327474, Plays an important role in protecting individuals from TB. Rs2430561 is associated with extrapulmonary tuberculosis. Rs1861494 and rs2234711 were significantly associated with LTBI, and rs2234711 was associated with anti-TB treatment; rs1861494, but rs2430561 was not associated with drug susceptibility or resistance. Rs2234711 and genotype AArs1861493 were associated with higher plasma interferon-gamma levels. The defects and mutations of IFNGR1 and IFNGR2 genes make us realize that a small number of infants will be infected by BCG vaccine, and even die of disseminated infection in severe cases, which improves our understanding and diagnosis of MSMD. Some sites are the same, but the results are different. There are also a few countries or regions that have not found the correlation between IFNG and its receptor gene polymorphism and tuberculosis, which may be related to the insufficient number of samples and ethnic differences. Because the gene encoding IFN- γ is polymorphic and complex, and the research sites are different, it is more necessary to study the correlation between its gene polymorphism and tuberculosis in different populations and races in the world. In the future, the correlation between IFNG and its receptor gene polymorphisms and drug sensitivity or multi-drug resistant pulmonary tuberculosis, and the correlation with extrapulmonary tuberculosis are worthy of further study, and provide new ideas and

theoretical basis for the development of new drugs.

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Data Availability

The datasets used during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

The author states that this article has no conflict of interest.

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