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IL23R(*Arg381Gln*) Functional Polymorphism Is Associated with Active Pulmonary Tuberculosis Severity

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The purpose of our study was to investigate the association between a functional single nucleotide polymorphism (SNP) in the interleukin-23 receptor gene (*IL23R*; rs11209026, 1142 $G^{wild\ type} \rightarrow A^{reduced\ function}$, Arg381Gln) and disease severity outcome in pulmonary tuberculosis (TB) in the Tunisian population. SNP was investigated in a population of 168 patients with active pulmonary TB (cases were stratified into patients with minimal/moderate lung involvement, i.e., patients with minimal/moderate disease [Pmd], and patients with extensive lung involvement, i.e., patients with active disease [Pad]) and 150 healthy subjects. Genotype analyses were carried out using the PCR-restriction fragment length polymorphism method. We have found that the *IL23R* reduced-function allele 1142A and genotypes AA and AG were overrepresented, especially in the Pad subgroup compared with the control group (51% versus 18% [$P = 10^{-8}$], 33% versus 5% [$P = 10^{-8}$], and 36% versus 26% [$P = 5 \times 10^{-3}$], respectively). Additionally, comparison of the Pad and the Pmd groups showed that the A allele and AA genotype seemed to be associated with 2.79-fold ($P = 4 \times 10^{-5}$) and 7.74-fold ($P = 10^{-5}$) increased risks of TB with minimal/moderate lung involvement, respectively. Our results demonstrate that the reduced-function polymorphism 1142G → A encoded by *IL23R* influences the outcome of disease severity of active pulmonary TB in Tunisian patients.

Tuberculosis (TB) is a chronic infectious disease caused by *Mycobacterium tuberculosis*. It has been estimated that there are 8.8 million (range, 8.5 million to 9.2 million) incident cases of TB and 1.1 million (range, 0.9 million to 1.2 million) deaths from TB among HIV-negative people (45). Among those infected by *M. tuberculosis*, only 5 to 10% develop clinical disease (45). Among those individuals, some have identifiable risk factors, such as acquired immunodeficiency disorders, old age, alcohol usage, corticosteroid consumption, diabetes mellitus, malnutrition, and cigarette smoking (3, 4). Additionally, studies of the concordance rate of TB among monozygotic and dizygotic twins highlighted the importance of host genetic factors in determining the development of disease (10, 20).

Cellular immunity plays an important role in controlling the growth of *M. tuberculosis*. Thus, an effective host defense against *M. tuberculosis* infection requires the coordinated actions of both the innate and adaptive immune systems (19). Interleukin-23 (IL-23) has been found to contribute to the development of Th1-like $CD4^+$ T-cell responses. The heterodimeric cytokine IL-23 is secreted by activated macrophages and dendritic cells (DCs) and induces clonal expansion of memory $CD4^+$ T cells (30, 35). IL-23 is composed of a p40 subunit, shared with IL-12, and a unique p19 subunit, signaling through interleukin-12 receptor β (IL-12Rβ) and a unique IL-23 receptor (IL-23R) chain (34). In addition to its direct action on T cells, IL-23 induces the secretion of IL-12 and gamma interferon (IFN-γ) by DCs *in vitro* (6). This suggests that IL-23 has indirect involvement in the activation of antigen-presenting cells (APCs). Studies with gene-deficient mice reveal that a number of roles that were previously accredited to IL-12 may be dependent on IL-23 (15). In *M. tuberculosis* infection, the absence of the p40 subunit common to IL-12 and IL-23 results in more marked susceptibility to *M. tuberculosis* infection than IL-12 p35 deficiency, suggesting an important role for IL-23 in mycobacterial infections (13). Additionally, Van de Wetering et al. suggested that the synergy of IL-23 with IL-18 is likely important in initiating Th1 differentiation early in infection, whereas the synergy between IL-18 and IL-12 may be important in a further Th1 response in subsequent stages of infection (41).

IL-23 is secreted by activated macrophages and DCs, induces memory T-cell proliferation, and is the critical factor required for T-cell IL-17 expression in response to bacterial challenge (2). IL-23 exerts its activity through its receptor (IL-23R), expressed in the Th17 subset of T lymphocytes (44). These newly characterized $CD4^+$ T cells were originally identified through their ability to secrete high levels of the proinflammatory cytokine IL-17 upon stimulation (23, 35). Furthermore, IL-17 promotes neutrophilic inflammation by upregulating CXC chemokines and hematopoietic growth factors (22). Several recent studies have reported the important role of IL-23 and IL-17 in the induction of a neutrophil-mediated protective immune response against extracellular bacterial or fungal pathogens, such as *Escherichia coli* (8, 39), *Klebsiella pneumoniae* (21), *Porphyromonas gingivalis* (47), *Pseudomonas aeruginosa* (18), *Citrobacter rodentium* (33), and *Bacteroides fragilis* (11).

In regard to *M. tuberculosis* infections, recent studies have demonstrated a greater sensitivity in IL-12/IL-23 $p40^{-/-}$ mice than in IL-12 $p35^{-/-}$ animals (13, 24). Moreover, macrophages rapidly express IL-23 when exposed to mycobacterial antigens, suggesting an immune-stimulatory role for this cytokine during infection (5, 43). This finding was supported by Happel and collaborators (22). They reported that pulmonary administration of adenovirus vectors expressing IL-23 can improve host resistance to *M. tuberculosis* in wild-type mice (22). However, studies using

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TABLE 1 Demographic and clinical data for tuberculosis patients and controls[a]

Study group	No. of cases	Gender (no. M:no. F)	Mean (range) age (yr)
pTB	168	127:41	44 (14–78)
Pmd	123	100:23	39 (14–65)
Pad	45	27:18	45 (37–78)
Healthy	150	135:15	35 (24–55)

[a] pTB, pulmonary tuberculosis; Pmd, pulmonary patients with minimum/moderate lung involvement; Pad, pulmonary patients with extensive lung involvement; M, male; F, female.

IL-23-deficient mice have shown that the absence of IL-23 has little or no effect on host resistance to *Toxoplasma gondii*, *Cryptococcus neoformans*, and *M. tuberculosis* infection, unless IL-12 is also absent (27, 29, 31). These studies suggest that, compared to the dominant role of IL-12, the role of IL-23 in chronic infections is more subtle. Recently, Khader and collaborators have reported that IL-23 plays an essential role in chronic infection. They showed that this cytokine is required for long-term control of *M. tuberculosis* and B-cell-follicle formation in the infected lung (26).

IL-23 mediates its activity through IL-23R. IL-23 is a heterodimeric cytokine composed of a p19 subunit and a p40 subunit, with the latter being shared with IL-12 (12, 25), a Th1-promoting cytokine (29, 40) which has also been considered a candidate susceptibility gene in many autoimmune diseases. The IL-23 receptor also shares a subunit, IL-12 receptor β1 (IL-12Rβ1), with the IL-12 receptor, but it is the specific subunit of the IL-23 receptor, named IL-23R. IL-23 stimulates the proliferation of Th17 cells, a T-cell population which produces inflammatory cytokines such as IL-17, tumor necrosis factor, and IL-6 (28).

Several polymorphisms within the IL-23R gene (*IL23R*; such as the 1142G → A polymorphism encoded by *IL23R* [*IL23R* 1142G → A]; rs11209026, 1142 $G^{\text{wild type}} \rightarrow A^{\text{reduced function}}$, Arg381Gln) have been associated with immune-related diseases, including inflammatory bowel disease, psoriasis, and ankylosing spondylitis (9, 17, 36, 42). However, to date, there have been no studies evaluating the association between this polymorphism and the risk of development of active TB in the world or in Tunisian patients.

In our study, we have investigated the association between *IL23R* (1142G → A) and the risk of development of active pulmonary TB and its severity in TB patients in Sousse, Tunisia, a region characterized by a moderate TB prevalence (31 new cases per 100,000 population) and incidence (25 cases/100,000 population/year) and a predominating *M. tuberculosis* strain (46).

MATERIALS AND METHODS

Study populations. One hundred sixty-eight patients with active pulmonary TB from Sousse, Tunisia, which is in the central region of the country, were enrolled in this study (Table 1). One hundred fifty healthy blood donors (135 males and 15 females) were studied as controls.

Patients and healthy blood donors were selected over the period from January 2009 to June 2010. Individuals with a history of severe pathologies, including HIV infection, cardiovascular disease, asthma, or atopy autoimmune diseases, and cancer were excluded from the study. An informed written consent was obtained from all individuals prior to blood sampling. Moreover, our study was approved by the ethics committee of the Farhat Hached University Hospital.

Patients were recruited from the Pneumology Unit, CHU Farhat Hached, and the health care service, Sousse, Tunisia. Inclusion criteria for the patients in this group were determined according to the criteria defined by the American Thoracic Society (1).

Diagnosis of active pulmonary TB was based on clinical symptoms, the presence of acid-fast bacilli in sputum smears, and culture on Lowenstein-Jensen and Coletsos medium in all cases.

Pulmonary TB patients whose radiological lung tissue involvement ($n = 168$) was available were further stratified into pulmonary patients with minimal ($n = 80$)/moderate ($n = 43$) disease or lung involvement (Pmd) and pulmonary patients with advanced disease and extensive lung involvement (Pad; $n = 45$), according to non-HIV-related TB guidelines for disease classification (14, 32).

All controls had the same ethnic and geographic origins and lived in the same city as the TB patients. The inclusion criteria for the control group were the absence of acute or chronic pulmonary disease, a negative history for TB, and proof of being healthy.

DNA extraction and genotyping. Genomic DNA was isolated from fresh whole blood-EDTA and buffy-coat lymphocytes of TB patients and controls using a Wizard Genomic DNA purification kit (Promega Corporation, Madison, WI), according to the manufacturer's instructions.

To genotype Arg381Gln (1142G → A), a PCR-restriction fragment length polymorphism (RFLP) method was used as previously reported (42). Briefly, 100 ng of genomic DNA was added to 25 μl of a reaction mixture containing 1 mM each primer. The forward and reverse primers were 5′-CTTTTCTGGCAGGGTCATTTTG-3′ and 5′-AAGTTGTTTCC TGGGGTAGTTGTG-3′, respectively. The remainder of the mixture consisted of 1× PCR GoTaq buffer (Promega), 1.5 mM $MgCl_2$, 0.2 mM deoxynucleoside triphosphates, and 1 U GoTaq Hot Start polymerase (Promega). The mixture was then initially subjected to 95°C for 10 min, followed by 40 cycles of denaturation for 30 s at 95°C, annealing for 1 min at 53°C, and extension for 1 min and 30 s at 72°C; final extension was for 7 min at 72°C. Amplifications were performed in a MyCycler thermal cycler (Bio-Rad). RFLP of the PCR product was used for the detection of

TABLE 2 *IL23R* 1142 G → A allele and genotype frequencies in pulmonary tuberculosis cases and controls[a]

Allele or genotype	No. (%) of patients				pTB cases vs controls		Pmd vs controls		Pad vs controls	
	pTB ($n = 168$)	Pmd ($n = 123$)	Pad ($n = 45$)	Controls ($n = 150$)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)
Allele										
A	113 (34)	67 (27)	46 (51)	55 (18)	10^{-5}	2.26 (1.53–3.32)	12×10^{-3}	1.67 (1.09–2.55)	10^{-8}	4.66 (2.72–7.98)
G	223 (66)	179 (73)	44 (49)	245 (82)						
Genotype										
AA	24 (14)	9 (7)	15 (33)	8 (5)	9×10^{-4}	3.91 (1.57–10.05)	0.25	1.78 (0.59–5.39)	10^{-8}	13.79 (4.47–44.04)
AG	65 (39)	49 (40)	16 (36)	39 (26)	10^{-3}	2.17 (1.29–3.67)	9×10^{-3}	1.99 (1.14–3.48)	5×10^{-3}	3.02 (1.25–7.3)
GG	79 (47)	65 (53)	14 (31)	103 (69)						

[a] pTB, pulmonary tuberculosis; Pmd, pulmonary patients with minimal/moderate lung involvement; Pad, pulmonary patients with extensive lung involvement.

TABLE 3 *IL23R* 1142 G → A allele and genotype frequencies in pulmonary patients with extensive lung involvement and pulmonary patients with minimal/moderate lung involvement[a]

Allele or genotype	No. (%) of patients		*P*	OR (95% CI)
	Pad ($n = 45$)	Pmd ($n = 123$)		
Allele				
A	46 (51)	67 (27)	4×10^{-5}	2.79 (1.64–4.75)
G	44 (49)	179 (73)		
Genotype				
AA	15 (33)	9 (7)	10^{-5}	7.74 (2.54–24.2)
AG	16 (36)	49 (40)	0.31	1.52 (0.63–3.67)
GG	14 (31)	65 (53)		

[a] Pad, pulmonary patients with extensive lung involvement; Pmd, pulmonary patients with minimal/moderate lung involvement.

IL23R 1142G → A alleles. RFLP analysis was performed by incubating 5 μl of PCR product with 5 U of Hpy188I restriction endonuclease (New England BioLabs, MA) at 37°C for 3 h in a final restriction digestion volume of 20 μl. The restriction fragments (wild-type DNA yields fragments of 288, 103, 82, and 35 bp, whereas DNA containing the G1142A polymorphism yields fragments of 323, 103, and 82 bp) were separated by electrophoresis on 2% agarose gels (Sigma) containing ethidium bromide (0.5 mg/ml; Sigma) and observed under UV illumination using a Gel Doc XR system (Bio-Rad).

Statistical analysis. All genotypes were tested for Hardy-Weinberg equilibrium using a χ^2 test between the observed and expected numbers separately in patients and controls (37).

Statistical analysis was performed by Epi Info (version 6.0) software (Centers for Disease Control and Prevention, Atlanta, GA). The associations between the allelic/genotype frequencies and the clinical forms of TB, as well as the odds ratio for susceptibility to infection, were obtained by the χ^2 test. A *P* value of <0.05 was considered statistically significant.

RESULTS

Hardy-Weinberg equilibrium. In this study, evaluation of Hardy-Weinberg equilibrium showed that the genotype frequencies of the *IL23R* 1142G → A polymorphism were in Hardy-Weinberg equilibrium in the pulmonary TB, Pmd TB, and Pad TB groups and healthy blood donors ($P \leq 0.05$).

Association of the *IL23R* 1142G → A reduced-function polymorphism with pulmonary tuberculosis. We have used PCR-RFLP to examine the status of the *IL23R* gene polymorphism linked to $G^{\text{wild-type}} \rightarrow A^{\text{reduced-function}}$ phenotypes.

The frequency distributions of different *IL23R* 1142G → A genotypes are summarized in Table 2. We observed that the *IL23R* 1142A (reduced-function) allele was significantly overrepresented in the pulmonary TB group in comparison to the control group (34% versus 18%; odds ratio [OR] = 2.26, 95% confidence interval [CI] = 1.53 to 3.32) (Table 2). Moreover, when this group was stratified into pulmonary patients with minimal/moderate lung involvement (Pmd) and pulmonary patients with extensive lung involvement (Pad), we found that the 1142A allele was significantly more frequent in these two groups (27% versus 18% [$P = 12 \times 10^{-3}$] and 51% versus 18% [$P = 10^{-8}$], respectively) (Table 2). Additionally, the 1142A allele seemed to be associated with the increased risk of development of TB with minimal/moderate lung involvement (OR = 1.67, 95% CI = 1.09 to 2.55) and TB with extensive lung involvement (OR = 4.66, 95% CI = 2.72 to 7.98).

Three genotypes, AA, AG, and GG, were observed in the different TB and control groups (Table 2). The AA and AG genotypes were significantly more frequent in pulmonary TB patients and pulmonary patients with extensive lung involvement (Pad) than in the control group (14% versus 5% [$P = 9 \times 10^{-4}$] and 33% versus 5% [$P = 10^{-8}$], respectively, for the AA genotype and 39% versus 26% [$P = 10^{-3}$] and 36% versus 26% [$P = 5 \times 10^{-3}$], respectively, for the AG genotype). Additionally, these genotypes seemed to be associated with an increased risk for development of active pulmonary TB with extensive lung involvement (Table 3).

When the frequency distribution of different allele and genotypes of the *IL23R* 1142G → A single nucleotide polymorphism (SNP) was adjusted by gender in the Pmd, Pad, and control groups, we found that (i) the A allele seemed to be associated with an increased risk of development of TB with minimal/moderate lung involvement (OR = 1.67, 95% CI = 1.02 to 2.74, $P = 0.031$) and extensive lung involvement (OR = 3.37, 95% CI = 1.89 to 7.38, $P = 2 \times 10^{-5}$) only in men (Tables 4 and 5) and (ii) men harboring the AA genotype seemed to be at greater risk of development of active TB with extensive lung involvement than women (OR = 12.06, 95% CI = 2.97 to 51.4, $P = 10^{-4}$) (Table 5).

DISCUSSION

An increased number of association studies have implicated polymorphisms located in promoter regions or coding regions

TABLE 4 *IL23R* 1142G → A allele and genotype frequencies in Pmd and control groups, by gender[a]

Allele or genotype	No. (%) of patients						Male and female Pmd vs male and female control cases		Male Pmd vs male control cases		Female Pmd vs female control cases	
	Pmd ($n = 123$)			Controls ($n = 150$)								
	M + F	M	F	M + F	M	F	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)
Allele												
A	67 (27)	46 (23)	21 (46)	55 (18)	41 (15)	14 (47)	12×10^{-3}	1.67 (1.09–2.55)	0.031	1.67 (1.02–2.74)	0.93	0.96 (0.34–2.67)
G	179 (73)	154 (77)	25 (54)	245 (82)	229 (85)	16 (53)						
Genotype												
AA	9 (7)	7 (7)	2 (9)	8 (5)	5 (4)	3 (20)	0.25	1.78 (0.59–5.39)	0.22[b]	2.27 (0.61–8.7)	0.58[b]	0.67 (0.04–10.72)
AG	49 (40)	32 (32)	17 (74)	39 (26)	31 (23)	8 (53)	9×10^{-3}	1.99 (1.14–3.48)	0.08	1.68 (0.89–3.15)	0.3[b]	2.13 (0.32–14.36)
GG	65 (53)	61 (61)	4 (17)	103 (69)	99 (73)	4 (27)						

[a] Pmd, pulmonary patients with minimal/moderate lung involvement; M, male; F, female.
[b] Fisher's exact test.

TABLE 5 *IL23R* 1142G → A allele and genotype frequencies in Pad and control groups, by gender[a]

Allele or genotype	No. (%) of patients						Male and female Pad vs male and female control cases		Male Pad vs male control cases		Female Pad vs female control cases	
	Pad ($n = 45$) (%)			Controls ($n = 150$)								
	M + F	M	F	M+F	M	F	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)
Allele												
A	46 (51)	22 (41)	24 (67)	55 (18)	42 (16)	13 (43)	10^{-8}	4.66 (2.72–7.98)	2×010^{-5}	3.37 (1.89–7.38)	0.057	2.62 (0.86–8.09)
G	44 (49)	32 (59)	12 (33)	245 (82)	228 (84)	17 (57)						
Genotype												
AA	15 (33)	8 (30)	7 (39)	8 (5)	5 (4)	3 (20)	10^{-8}	13.79 (4.47–44.04)	10^{-4b}	12.06 (2.97–51.4)	0.059[b]	11.67 (0.66–426.07)
AG	16 (36)	6 (22)	10 (56)	39 (26)	32 (24)	7 (47)	5×10^{-3}	3.02 (1.25–7.3)	0.34[b]	1.41 (0.44–4.44)	0.09[b]	7.14 (0.55–202.27)
GG	14 (31)	13 (48)	1 (5)	103 (69)	98 (72)	5 (33)						

[a] Pad, pulmonary patients with extensive lung involvement; M, male; F, female.
[b] Fisher's exact test.

of cytokine receptor genes, such as the gamma interferon receptor (10, 20) and interleukin-10 receptor, as we have recently reported (7), to be host factors influencing the development of active TB. This is the first study demonstrating that the *IL23R* 1142G → A functional polymorphism is associated with increased susceptibility to active pulmonary TB and its severity in Tunisian patients. In fact, our result showed that patients carrying the *IL23R* 1142A allele or AA genotype had 2.79- and 7.74-fold increased risks of developing active TB with extensive lung involvement, respectively.

Recently, Khader and collaborators have reported that IL-23 plays a crucial role in the long-term immune response against *M. tuberculosis* (26). They showed that IL-23 is required for long-term containment of *M. tuberculosis*, as well as the expression of CXCL13 within and the maintenance of B-cell follicles within the lung lesions. Additionally, they demonstrated that IL-17RA and IL-22 were involved in B-cell-follicle development at distinct times during infection and that IL-23 is necessary for the expression of both of these cytokines in the lung.

Many studies have revealed that several single nucleotide polymorphisms in the *IL23R* gene are associated with immune-related diseases, including inflammatory bowel disease, psoriasis, and ankylosing spondylitis (9, 17, 36, 42). The most studied SNP was *IL23R* R381Q. Sarin et al. indeed showed that the 381Q variant has a reduced percentage of cells that secrete IL-17 and IL-22 in response to IL-23 stimulation and reduced levels of STAT3 phosphorylation and IL-17 and IL-22 production in T-cell subsets (38). The group of Pidasheva et al. also showed reduced STAT3 phosphorylation in response to IL-23 in T cells with the 381Q variant, although they did not find reduced numbers of IL-17- or IL-22-producing cells (36). Sarin et al. showed that IL-23-induced IFN-γ production is not affected in the 381Q variant (38), and Pidasheva et al. showed that IFN-γ-producing cells are not reduced (36). Another group has also shown that the 381Q variant of IL-23R is comparable to the wild-type variant in an overexpression system, when analyzing the ability to induce IFN-γ and IL-10 production (16). The heterogeneity of these results could be related to the cytokines investigated or the use of different cell types, such as retrovirally transduced T-cell blasts (16) rather than isolated primary $CD8^+$ T cells expressing the endogenous wild type or R381Q IL23R variant (38).

To our knowledge, no study in the world has investigated the association between the *IL23R* R381Q reduced-function polymorphism and the risk of development of active pulmonary TB. This is the first study demonstrating an association between the *IL23R* R381Q reduced-function polymorphism and pulmonary active TB and its severity in the Tunisian population. Our result has shown that patients carrying the A allele of the *IL23R* R381Q reduced-function polymorphism had 2.26-, 1.67-, and 4.66-fold increased risks of developing pulmonary TB, pulmonary TB with minimal/moderate lung involvement, and pulmonary TB with extensive lung involvement, respectively. Additionally, comparison of the Pad (advanced TB) and Pmd (mild to moderate TB) groups showed that the A allele and AA genotype of the 1142G → A polymorphism seemed to be associated with 2.79- and 7.74-fold increased risks of advanced disease and disease of minimal/moderate severity, respectively. The A allele of the *IL23R* R381Q polymorphism corresponds to decreased IL-23-dependent IL-17 and IL-22 production, which may impair the immune response against *M. tuberculosis* infection, resulting in pulmonary TB development.

Interestingly, in our study, the *IL23R* 1142A allele appeared to be associated with 1.67- and 3.37-fold increased risks of development of active TB with minimal/moderate lung involvement and extensive lung involvement, respectively, in males. Additionally, men with the AA genotype appeared to be at a 12.06-fold increased risk of development of the active form of pulmonary TB with extensive lung involvement.

In conclusion, our study shows for the first time that the *IL23R* 1142G → A reduced-function polymorphism seems to be associated with an increased risk of development of a severe form of active pulmonary TB. Further studies with both adult and pediatric populations in ethnically diverse settings are needed to confirm our findings.

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W.B.-S. performed the experiments and wrote the manuscript. J.B. conceived the project, supervised experiments, and revised the manuscript. Both W.B.-S. and J.B. read and approved relevant portions of the manuscript.

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