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Gene polymorphisms in patients with pulmonary tuberculosis from Mozambique

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Abstract Several host and environmental factors contribute to tuberculosis outcome, interestingly single nucleotide polymorphisms (SNPs) in candidate genes have been evaluated in populations with different ethnicities and TB infection. In the present study we focused on SNPs in cytokine and inflammatory mediator genes: tumor necrosis factor (*TNF*) −308G>A (rs1800629), interleukin-10 (*IL10*) −819C>T (rs1800871), interferon-gamma (*IFNG*) +874T>A (rs2430561), and leukotriene A4 hydrolase (*LTA4H*) rs1978331, rs17525495 and rs2660898 in a case–control study involving 102 pulmonary tuberculosis patients and 456 controls from Mozambique. *LTA4H, IL10* and *IFNG* SNPs showed no associations with pulmonary tuberculosis. However, distribution of the *TNF* −308A allele, genotype and carrier frequencies showed a significant risk association with tuberculosis that was maintained after adjustment for non-genetic variables and Bonferroni correction (AA genotype, OR = 1.9, $p_{Bonf} < 0.001$; A allele OR = 2.9, $p_{Bonf} = 0.005$ and GA/AA carrier OR = 2.6, $p_{Bonf} = 0.035$). Interestingly, this association has not been reported in a sub-Saharan African population before. Our results suggest a role of −308 *TNF* polymorphism and tuberculosis susceptibility.

Keywords Tuberculosis · *TNF* · *LTA4H* · *IFNG* · *IL10* · Mozambican

Introduction

Tuberculosis (TB) caused by the intracellular pathogen *Mycobacterium tuberculosis*, still remains a public health concern. Data from the Global Tuberculosis report [1] estimated a global incidence of 8.7 million cases, most of them occurring in Asia and Africa. Furthermore, worldwide reports indicate an increase on multidrug resistant strains [2]. Approximately 1.1 million of all TB cases are also co-infected with HIV; from which 39 % of individuals reside in Africa. More specifically in 2011, Mozambiqués TB new case notifications reached a total of 43.200 cases [3].

The fate of TB infection depends on a variety of factors such as pathogen strain, environmental conditions, and the host genetic background [4, 5]. TB infects mainly macrophages in lungs, and Th1-mediated immunity is considered the protective response against *M. tuberculosis*. In this regard, cytokines such as interferon-gamma (IFN-γ) and tumor necrosis factor (TNF) are a crucial part of the immune response that restrains the spread of bacilli through the formation of granuloma for mycobacterial containment [6]. IFN-γ knockout mice models are unable to control pathogen replication, while TNF as a pro-inflammatory cytokine, plays a key role in immune response against TB activating microbicidal responses in macrophages and also during granuloma organization [7], it has been shown that anti-TNF treatment for autoimmune diseases can disorganize granuloma and induce TB

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progression [8]. On the other hand, Interleukin-10 (IL-10) is an anti-inflammatory cytokine that shows increased levels in TB patients [9], apparently limiting the immune response against bacteria and favoring chronic TB infection [5]. Recently leukotriene A4 hydrolase gene, *LTA4H*, that express the enzyme responsible for leukotriene B4 synthesis, is a key regulator of TNF levels, and can be considered a pro-inflammatory eicosanoid that has also been associated with mycobacterial infections [10].

Several articles support the participation of host genetics as a key component in TB outcome [11] for which case–control association studies have been frequently used to search for candidate genes in TB susceptibility [12]. Meta-analysis aided to combine published data from different populations with distinct ethnic backgrounds enabling consensus estimates for genetic polymorphisms in association with TB for several candidate genes such as: *IFNG, TNF, IL10, CCL2, DC-SIGN, NRAMP1, P2X7, VDR,* and *MBL* [13–20]. Nevertheless, the genetic associations in African populations that are not reported in meta-analysis are unknown or misrepresented since few TB association studies have been performed in Sub-Saharan Africans other than South Africans [11, 21, 22]. Here we present the first case–control study in a Mozambican population and pulmonary tuberculosis as outcome. We tested SNPs in −308G>A *TNF* (rs1800629), +874T>A *IFNG* (rs2430561) and −819C>T *IL10* (rs1800871) that had been previously evaluated across many populations and through meta-analysis [18, 23, 24] [25]. Also we evaluated rs1978331G>A, rs17525495G>A and rs2660898G>T SNPs in the recent candidate *LTA4H* gene. We observed that for this specific population *TNF* −308G>A was associated with tuberculosis among Mozambicans.

Study participants and tuberculosis diagnosis

SNPs were evaluated in pulmonary tuberculosis cases (PTB) and compared with healthy controls (HC). TB case enrollment took place in Mavalane, Polana Caniço and Machava hospitals from Mozambique. A total of 102 PTB cases were selected according suggestive criteria for TB disease such as clinical respiratory symptoms, continuous coughing for at least 2 weeks, weight loss, chest pain, fever, weakness and fatigue. Laboratory confirmation was based upon two positive results for sputum baciloscopy and Ziehl-Neelsen staining. Finally, positive TB cases presented radiological evidence compatible with TB. We excluded individuals with extrapulmonary forms of tuberculosis.

Control group was recruited from Maputo Central hospital and consisted of 456 healthy blood donors without previous clinical history or laboratory criteria suggestive of TB infection. Both PTB cases and HC were HIV negative. All participants agreed to participate in the study and signed an informed consent form. The study was approved by local ethics committee in Mozambique under protocol N°399/CNBS/11.

Genotyping

Genomic DNA was extracted from whole blood samples using QIAamp blood DNA extraction kit (QIAGEN, Germany). Polymorphisms were genotyped by real-time PCR using the following TaqMan probes: *TNF* −308G>A (rs1800629) assay ID C___7514879_10, *IL10* −819C>T (rs1800871) assay ID C___1747362_10, *LTA4H* polymorphisms rs1978331G>A assay ID C__11700137_1_, rs17525495G>A assay ID C__25593629_10 and for T>G rs2660898 assay ID C__16265302_10 (Life Technologies, CA, USA). Specifically for *IFNG* +874T>A (rs2430561) a custom probe was utilized. Reactions were performed with 10–40 ng of template in a final volume of 5 μL including 2.5 μL of TaqMan Genotyping Master Mix (Life Technologies, CA, USA) and 0.125 μL of each TaqMan probe. Allelic discrimination was performed in StepOne Plus instrument (Life Technologies, CA, USA).

Statistical analysis

Assessment of statistical power reached 0.80 for Odds Ratio (OR) values larger than 1.8, considering our sample size and a minor allele frequency (MAF) of 0.15. Frequencies for genotype, allele and carrier of the minor allele for each polymorphism were compared between PTB and HC. ORs were calculated using unconditional logistic regression models adjusting for non-genetic covariates gender and geographic region (North, Center and South of Mozambique). Finally, adjustment for multiple comparisons was performed using Bonferroni method considering *p* values resulting from inclusion of non-genetic covariates in regression model. Analyses were performed using R software for Windows version 2.11.1 with the "genetics" and "stats" packages as previously described [26, 27].

Results

The characteristics of the study population are detailed in Table 1. PTB cases were composed by 45 females and 57 males; mean age 33.8 ± 13, HC included 82 females and 364 males; mean age 32.3 ± 11. Participants of the study were divided according their origin (different geographic regions in Mozambique: North, Center and South) for statistical adjustments, but the majority of both PTB cases

Table 1 Characteristics of the individuals included in the study

	PTB N = 102 n (frequency)	HC N = 456 n (frequency)	ANOVA *p* value
Age (mean ± SD)	33.8 ± 13	32.3 ± 11	
Gender*			0.38
Female	45 (0.44)	82 (0.18)	
Male	57 (0.56)	364 (0.80)	
Region**			0.04
North	0 (0.0)	29 (0.06)	
Centre	10 (0.10)	32 (0.07)	
South	92 (0.90)	295 (0.65)	

PTB pulmonary tuberculosis, *HC* healthy controls, *n* number of individuals, *SD* standard deviation

* Information was missing for 10 HC (0.2)

** Information was missing for 100 HC (0.22)

(90 %) and HC (65 %) were originated from the Southern region.

Total counts, frequencies for genotypes, alleles, carriers, and also *p* values for HWE corresponding to each SNP are detailed in Table 2 together with the logistic regression analysis. Cases and controls followed HWE for the SNPs evaluated except for deviation in HC for *LTA4H* rs2660898 (p value < 0.001); therefore we excluded this SNP from further analysis. We found no evidence of association for the *IL10*, *IFNG* and *LTA4H* polymorphisms in none of the comparisons at genotype, allele or carrier level.

For *TNF*−308G>A (rs1800629) we observed an increased frequency for heterozygote and homozygote genotypes when comparing PTB cases and HC as well as allele and carriers of the minor A allele. Odds ratio values indicated a significant association towards susceptibility before and after correction for co-variates. The adjusted OR values were as follows: GA genotype = 1.9, p value = 0.04; OR for AA genotype = 1.9, p value < 0.001; A allele OR 2.9, p value = 0.001 and finally OR 2.6, p value < 0.001 for A carriers. After Bonferroni correction, significance was maintained for AA genotype ($p_{Bonf} < 0.001$), allele ($p_{Bonf} = 0.005$) and carrier comparisons ($p_{Bonf} = 0.035$)

Discussion

There are few studies reporting TNF −308G>A SNP frequencies among sub-Saharan Africans and TB. As presented here in the Mozambican population, a significant risk association for the TNF −308A contrasts to the results from the study performed in the geographically adjacent population from Malawi [28], in which it was evaluated the influence of the three cytokine gene SNPs also tested here (*TNF* −308, *IL10* −819 and *IFNG* +874) within a similar sample size (161 cases and 416 controls), but none of these polymorphisms showed significant differences amongst TB cases and controls. The other study to evaluate an African population enrolled a different ethnically population from the North, in 76 cases and 95 controls from Tunisia with no associations reported in *TNF* and *IL10* SNPs [29]. A recent meta-analysis in which 18 studies were pooled showed an association of the −308 A allele towards susceptibility when the populations were stratified according to Asian ethnicity (OR 1.22) [23]. Unfortunately, only the two studies mentioned above [28, 29] evaluated such polymorphisms in African populations, therefore further studies focusing in Africans are needed in order to reach a consensus for the *TNF* association shown in the present work. The genetic diversity in African populations is well known for its heterogeneity [30], a fact that could explain the divergent results observed for *TNF* −308 and TB in such populations. However, *TNF* −308A has been associated with high TNF levels when other mycobacterial stimuli *M. leprae*, is used in vivo or in vitro [27, 31]. Recently, using zebrafish as a mycobacterial disease model, authors conclude that misbalanced TNF/LTA4H levels are both detrimental, on one hand excessive levels could lead to a state of increased inflammation and cell necrosis as opposed to low levels in which the microbicidal activity is insufficient to contain disease [32], the latter agrees with evidence involving treatment with TNF antagonists as a risk factor in developing TB [33]. Thus, it is likely that higher TNF production during *M. tuberculosis* infection progressing from latent to active disease could be responsible to exacerbated inflammation leading to the disease state in a way that −308A carriers would in fact exhibit higher risk to develop TB.

Regarding the *IL10* −819 SNP our results seem to fit in accordance with other reports in literature where African populations from Gambia [34], Ghana [35] and South Africa [36] also found no association with pulmonary TB. Interestingly, meta-analysis also proved no association for this SNP and TB, instead suggested a significant association towards protection for the *IL10* -1082 SNP (OR 0.55, p value = 0.01) in the Caucasian sub-group [24].

The *IFNG* +874 T allele showed discrepant results among sub-Saharan Africans with one study suggesting protection towards TB [37] while another study failed to replicate such association [38]. Also, in West Africans there was no evidence of association with this SNP and PTB as outcome [39]. In the Mozambican population we found no significant association for this polymorphism and PTB. Although other two publications suggested association in Egyptians [40] and Tunisians [41], for both studies control groups did not fulfill Hardy–Weinberg criteria,

Table 2 Alelle, genotype and carrier frequencies of polymorphisms in cases and controls; logistic regression results for association with pulmonary tuberculosis

SNPs	Genotype/Allele	PTB N = 102	HC N = 456**	OR (*p* value)	95 % CI	OR (*p* value) *	95 % CI*
	GG	51 (0.52)	271 (0.74)	- Reference -			
TNF-308	GA	33 (0.34)	91 (0.25)	1.93 (1ex−3)	[1.17–3.17]	**1.90 (0.04)**	[1.04–3.46]
G>A	AA	14 (0.14)	5 (0.01)	14.9 (2ex−16)	[5.13–43.1]	**1.9 (2.3ex−5)**	[4.94–78]
(rs1800629)	Allele G	135 (0.69)	633 (0.86)	- Reference -			
	Allele A	61 (0.31)	101 (0.14)	2.82 (1ex−4)	[1.68–4.77]	**2.88 (1ex−3)**	[1.52–5.49]
	A carriers	47 (0.48)	96 (0.26)	2.60 (6ex−5)	[1.64–4.12]	**2.61 (7ex−3)**	[1.50–4.56]
	GG	57 (0.74)	248 (0.7)	- Reference -			
LTA4H	GA	18 (0.23)	95 (0.27)	0.82 (0.51)	[0.46–1.47]	0.82 (0.55)	[0.42–1.59]
G>A	AA	2 (0.03)	11 (0.03)	0.79 (0.76)	[0.17–3.67]	0.63 (0.59)	[0.12–3.41]
(rs1978331)	Allele G	132 (0.86)	591 (0.83)	- Reference -			
	Allele A	22 (0.14)	117 (0.17)	0.84 (0.63)	[0.42–1.69]	0.8 (0.56)	[0.36–1.76]
	A carriers	20 (0.26)	106 (0.3)	0.82 (0.49)	[0.47–1.43]	0.79 (0.47)	[0.42–1.5]
	GG	44 (0.75)	352 (0.79)	- Reference -			
LTA4H	GA	14 (0.24)	88 (0.2)	1.27 (0.46)	[0.67–2.43]	1.05 (0.9)	[0.49–2.22]
G>A	AA	1 (0.02)	5 (0.01)	1.6 (0.67)	[0.18–14.0]	1.89 (0.59)	[0.19–19.2]
(rs17525495)	Allele G	102 (0.86)	792 (0.89)	- Reference -			
	Allele A	16 (0.14)	98 (0.11)	1.27 (0.56)	[0.57–2.83]	0.8 (0.58)	[0.36–1.76]
	A carriers	15 (0.26)	93 (0.21)	1.29 (0.43)	[0.69–2.42]	1.0 (1.0)	[0.56–1.79]
	CC	40 (0.40)	131 (0.36)	- Reference -			
IL10-819	CT	48 (0.48)	180 (0.49)	0.87 (0.58)	[0.54–1.41]	0.85 (0.57)	[0.48–1.50]
C>T	TT	12 (0.12)	56 (0.15)	0.70 (0.33)	[0.34–1.44]	0.75 (0.49)	[0.33–1.70]
(rs1800871)	Allele C	128 (0.64)	442 (0.6)	- Reference -			
	Allele T	72 (0.36)	292 (0.4)	0.85 (0.49)	[0.54–1.35]	0.86 (0.58)	[0.50–1.48]
	T carriers	60 (0.60)	236 (0.64)	0.83 (0.43)	[0.53–1.31]	0.82 (0.47)	[0.48–1.41]
	AA	66 (0.65)	203 (0.56)	- Reference -			
IFN+874	AT	32 (0.32)	136 (0.38)	0.72 (0.18)	[0.45–1.16]	0.96 (0.20)	[0.40–1.20]
T>A	TT	3 (0.03)	21 (0.06)	0.44 (0.19)	[0.13–1.52]	0.37 (0.15)	[0.1–1.42]
(rs2430561)	Allele C	164 (0.81)	542 (0.75)	- Reference -			
	Allele T	38 (0.19)	178 (0.25)	0.70 (0.22)	[0.41–1.23]	0.66 (0.20)	[0.35–1.24]
	A carriers	35 (0.35)	157 (0.44)	0.69 (0.11)	[0.43–1.10]	0.65 (0.11)	[0.38–1.10]

PTB pulmonary tuberculosis, *HC* healthy controls, *OR*, Odds ratio, *CI* confidence interval, *ex* exponent

* Values after adjustment for non-genetic covariates

** *p* values for HWE in HC: *TNF* −308G>A = 0.52, *LTA4H* rs1978331G>A = 0.75, *LTA4H* rs17525495G>A = 0.96, *IL10* −819C>T = 0.73, *IFNG* +874T>A (rs2430561) = 0.89

therefore such results have to be evaluated with caution. A meta-analysis from our group suggested a protective significant association for *IFNG* +874T [18], results that were reinforced with a recent meta-analysis [25]. Equally as the previous SNPs, ethnic stratification suggested that the protection association was restricted to the Asian subgroup (OR 0.71, *p* value = 0.03).

As for *LTA4H* polymorphisms, recent studies suggested a highly relevant association with promoter SNP rs17525495 and protection from TB meningitis [10]. In our study neither rs17525495 nor rs1978331 SNPs displayed significant association with PTB, and since rs2660898 did not follow HWE it had to be excluded from association comparisons. Previously, results from a large Russian population also showed no association for *LTA4H* SNPs [42]. Nevertheless, it would be premature to discard relevance of polymorphisms in this region, for which further studies are required.

In summary, our results suggest a risk association for *TNF* −308 and pulmonary TB in the first case–control study in Mozambican population. We also consider that a dense SNP mapping at *TNF* locus may be necessary, in order to better elucidate association in the 6p21 region and TB.

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