



Relationship Between TNF-238G>A Polymorphism and Predisposition to Pulmonary Tuberculosis Infection in The Indonesian Population (A Pilot Study)

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ABSTRACT *Previous studies suggested that genetic factors exerted huge influence in susceptibility to Tuberculosis. Tumor Necrosis Factor Alpha (TNF- α), which is encoded by the TNF gene, play a role on pulmonary macrophage function in isolating and controlling Mycobacterium tuberculosis infection. Polymorphisms on the promoter region of the TNF gene have been predicted to affect its transcriptional activity. Therefore, these polymorphisms are an excellent candidate to further study the role of TNF- α in susceptibility to Tuberculosis. 100 pulmonary tuberculosis patients (case) and 100 healthy individuals (controls) were recruited for this pilot study. DNA samples from cases and controls were genotyped for the TNF -238G>A SNP (rs361525) using LightSNip genotyping assay. Our results showed no significant difference in the distribution of TNF -238 genotypes in case and control subjects ($P = 0.4335$). Further investigation on TNF -238 allele frequencies between case and control studies also yields no significant difference ($P=1.000$; $OR=1.000$; %95CI [0.246597 – 4.055200]) which may suggest that there are no association with predisposition to Tuberculosis infection. In conclusion, this pilot study showed that the TNF -238G>A SNP is not associated with susceptibility to Tuberculosis.*

BACKGROUND

Tuberculosis (TB) is a fatal but curable disease, resulting from pulmonary alveolar infection by *Mycobacterium tuberculosis* (MTB). Despite the implementation of the DOTS (Directly Observed Treatment Short-course) strategy since 1994, Indonesia currently still has the fifth largest TB incidence in the world (WHO 2014). TB is known to be contagious, and is still responsible for high mortality worldwide (WHO 2014). However, it is reported that only 10% of people infected with MTB progress to active TB disease (Bellamy 1998; Kleinnijenhuis *et al.* 2011; Murray, Styblo & Rouillon 1990).

Observations on this disease in several human populations with different race and ethnicities, showed higher TB infection in certain populations (Motulsky 1989; Stead *et al.* 1990). This suggests that genetic factors played a role in susceptibility to TB infection. Twin studies have also been conducted, which further demonstrates the genetic nature of susceptibility to TB (Comstock 1978; Kallmann & Reisner 1943). However, the exact genetic factors or molecular mechanisms involved, to date, remains elusive.

Single nucleotide polymorphisms (SNPs) are known to be the most prevalent genetic variations found among humans. Several candidate genes which have known biological function related to TB infection in humans such as HLA (Human Leucocyte Antigen), TLR (Toll-like receptor), CD209 (C-type lectin DC-SIGN) and IRF1 (Interferon Regulatory Factor 1), have been investigated and SNPs found in these genes showed

association with susceptibility or protection to TB (Ding *et al.* 2012; Kim *et al.* 2005; Kobayashi *et al.* 2012; Vannberg *et al.* 2008). Many of the genes found to significantly affect susceptibility to TB played a role in immune regulation pathways. Thus host genetic factors, which participated in the host immune response, are excellent candidates to study and further understand genetic susceptibility to TB.

The pro-inflammatory cytokine Tumor Necrosis Factor Alpha (TNF- α), encoded by the *TNF* gene, is produced mainly by macrophages and other white blood cells derived from monocytes. Mechanistic studies have shown that TNF- α play a huge role in MTB infection particularly in macrophage activation, recruitment to site of infection and granuloma formation which contains and controls the disease (Flesch & Kaufmann 1990; Flynn *et al.* 1995; Lin *et al.* 2007; Mohan *et al.* 2001). Moreover, a study in rheumatoid arthritis patients treated with the Anti-TNF drug Infliximab showed that patients with latent TB progress to active TB following treatment with Infliximab (Keane *et al.* 2001).

Thus, it is postulated that the regulation of TNF- α might affect susceptibility to TB. Single nucleotide polymorphisms (SNP) found on the promoter region of the *TNF* gene, such as rs361525 (TNF -238) and rs1800629 (TNF -308), have been vastly studied (Abraham & Kroeger 1999).

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Polymorphisms on promoter region of the TNF gene were predicted to influence its transcriptional activity (Goldfeld, Doyle & Maniatis 1990). In relation to TB susceptibility, TNF -238 polymorphism have been showed to increase the risk of active TB (Amirzargar *et al.* 2006; Correa *et al.* 2005; Oliveira *et al.* 2004).

Others have also reported that polymorphisms in the promoter region of TNF have been associated with susceptibility or increased severity to other infectious agents such as Hepatitis B virus, A/H1N1 virus, Malaria parasite and *Helicobacter pylori* (Flori *et al.* 2005; Höhler *et al.* 1998; Morales-Garcia *et al.* 2012; Yea *et al.* 2001). Therefore, we proposed that certain TNF promoter genetic variants, might affect susceptibility to TB, specifically in the Indonesian population. The study of disease susceptibility genes will allow us to understand better the infection mechanism of TB which in turn will allow us to devise a better strategy for TB disease prevention and eradication.

METHODS

Study Participants

100 TB patients and 100 healthy individual were recruited for the study. All patients and controls are of Indonesian background with Javanese and Sundanese ethnicity, sex and age. Active TB patients were confirmed by Acid-Fast Bacilli smear test. All study participants had signed an informed consent form and this study was approved by the Universitas YARSI Research Ethics Committee.

SNP genotyping

DNA were extracted using the QIAamp DNA blood mini kit (Qiagen,

Hilden, Germany) according to the manufacturer's instructions. Extracted DNA were quantified using a Qubit 2.0 Fluorometer (Invitrogen, California, USA) prior to SNP genotyping. Genotyping of the TNF -238 SNP were accomplished using LightSNiP rs361525 TNF G-238A genotyping assay based on the SimpleProbe probe genotyping system (TIB MOLBIOL, Berlin, Germany) on a LightCycler 480 II real-time PCR instrument (Roche Applied Science, Mannheim, Germany). Realtime PCR was performed in a 5 µL reaction mixture containing approximately 10 ng of genomic DNA, 1X of 10X Lightcycler FastStart DNA Master Hybprobe, 1X of 20X LightSNiP reagent mix (primers and probes mix) and 3 mM MgCl₂, using 384-well plates. The PCR conditions are as follow: initial denaturation at 96°C for 4 minutes; 40 cycles of denaturation at 96°C for 30 seconds, annealing at 55 °C for 30 seconds, and elongation at 72°C for 30 seconds; and a final elongation step at 72°C for 5 minutes.

Data Interpretation and Statistical Analysis

Due to the unavailability of control samples with known genotypes, the LightSNiP assay results, particularly from control samples, were calibrated with the genetic frequency of rs361525 from public genetic population data on dbSNP (http://www.ncbi.nlm.nih.gov/projects/SNP/snp_ref.cgi?rs=361525). This is our method to define unknown arbitrary genotypes used in the assay. X² test and Fisher exact test were used to assess correlation between genotypes or alleles and phenotypes of both cases and controls, where appropriate. P value of <0.05 was considered

statistically significant. Odd ratios estimate relative risk with 95% confidence with. GraphPad Prism Software version 5.06 (GraphPad, San Diego, USA) was used for all statistical calculations.

RESULTS

The LightSNip assay was assessed by melting analysis which is shown in figure 1. Each distinct melting curve represents 1 sample and each melting peaks represent different alleles/genotypes. As the required known genotype controls were not available, arbitrary genotypes AA, AB and BB, were used to define the homozygous and heterozygous melting peaks. The genotype frequencies of for the healthy controls are 96%, 4% and 0% for AA, AB and BB respectively. According to the public SNP database on TNF-238, G (Guanine) is the frequent allele and A (Adenine) is the rare allele, particularly in Asian populations. Thus, we can assume that the arbitrary genotypes AA, AB and BB can be translated to GG, GA and AA genotypes respectively.

As shown in Table 1, frequency of the homozygous GG genotype was relatively similar between TB patients (cases) and healthy individuals

(controls) which were 97% and 96% respectively. The heterozygous GA genotype was present at 2% and 4% for cases and controls respectively. However, the homozygous AA genotype was found only in TB patients. Assessment of Hardy-Weinberg Equilibrium showed that population of the control group does not deviate from Hardy-Weinberg proportions ($p=0.838298$).

Statistical analysis between genotype frequencies of cases and controls showed no significant differences between groups ($P = 0.4335$). TNF-238 allele frequencies between cases and controls were shown in Table 2. No significant differences in allele frequencies were found between case and control group ($P=1.000$; $OR=1.000$; %95CI [0.246597 - 4.055200]). The curve peaks at the left hand side stand for the arbitrary A allele and at the right hand side (red) stands for the B allele. Single peaks represent homozygotes (AA - Blue or BB - green) while double peaks represent heterozygotes (AB - red). Due to unavailability of known genotype controls, arbitrary genotypes were used and correlation with public SNP population database was utilized to determine true genotypes.

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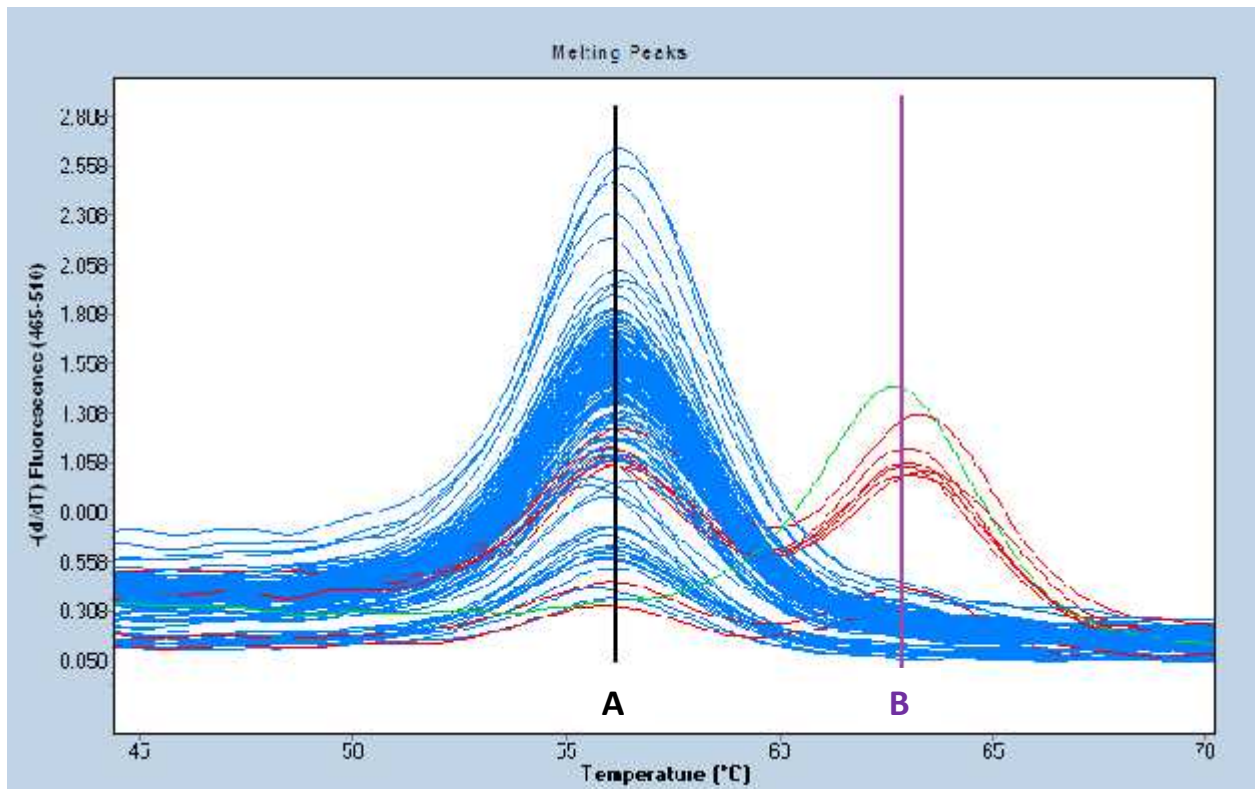


Figure 1. Melting analysis to determine TNF -238 genotypes in cases and controls.

Table 1. Genotype frequencies of the TNF -238 SNP between cases (TB patients) and controls (Healthy individuals)

Genotype	TB patients [n (%)]	Controls [n (%)]
GG	97 (97)	96 (96)
GA	2 (2)	4 (4)
AA	1 (1)	0 (0)

P = 0.4335

Table 2. Allele frequencies of the TNF -238 SNP between cases (TB patients) and Controls (Healthy Individuals)

Allele	TB patients [n (%)]	Controls [n (%)]
G	196(98)	196(98)
A	4(2)	4(2)

P=1.000; OR=1.000;
%95CI [0.246597 - 4.055200]

DISCUSSION

Our current data showed no association between TNF -238 genotype (P = 0.4335) and allele (P = 1.000) variants with susceptibility to TB. Thus, our study contradicts the reports by Oliveira *et al.* in the Brazilian population, Correa *et al.* in the Northwestern Colombian (Spanish) population and Amirzargar *et al.* in the Iranian population at the same SNP position (Amirzargar *et al.* 2006; Correa *et al.* 2005; Oliveira *et al.* 2004). In spite of these inconsistencies with the previously mentioned studies, there appears to be abundant reports which suggests that TNF-238 alone does not correlate well with increased risk of susceptibility to TB (Anoosheh, Farnia & Kargar 2011; Ates *et al.* 2008; Selvaraj *et al.* 2001; Vejbaesya *et al.* 2007). TNF promoter polymorphism was known to be ethnic-specific (Baena *et al.* 2002). In terms of ethnicity, the previous studies by Anoosheh *et al.*, Selvaraj *et al.*, Ates *et al.* and Vejbaesya *et al.*, were conducted in the Iranian, Indian, Turkish and Thai populations respectively. Therefore, the positive studies by Amirzargar *et al.*, Oliveira *et al.* and Correa *et al.* may not correspond well with our study, due to differences in population genetic backgrounds. The study by Vejbaesya *et al.*, which was done in the Thai

population, was presumed to be the closest to us in terms of ethnicity and genetic background (Hatin *et al.* 2014).

A study in The Cambodian population showed that the TNF -238A allele was quite rare in that specific population, with frequency below 2% in healthy individuals (Delgado *et al.* 2002). Our study showed that the A allele was at most 2% in the population, as shown in the controls, which was consistent with the study in the Cambodian population. Furthermore, TNF -238A frequency in the Thai population from the study by Vejbaesya *et al.* was quite close (3.4%) with the study in the Cambodian population. On the other hand, the study in the Colombian population showed that the frequency of the TNF-238A allele in healthy individuals was much higher (11%) than both Cambodia and Thailand (Henao *et al.* 2006). Therefore, these studies highlight the differences in TNF promoter polymorphisms frequencies between populations, which further support the result of this study.

The influence of TNF promoter polymorphisms on transcriptional activity of TNF polymorphism is currently a controversial topic in the field. There are 10 SNPs that have been discovered in the promoter region of the TNF-gene: -1031T>C, -863C>A, -

857C>A, -851C>T, -419G>C, -376G>A, -308G>A, -238G>A, -162G>A and -49G>A. Several TNF promoter polymorphisms have been studied regarding their effect on TNF transcriptional activity and gene expression. Among those TNF promoter polymorphisms, TNF -308G>A is the most well studied (Bayley, Ottenhoff & Verweij 2004). A study by Wilson *et al.* in human B cell line showed that the A allele of TNF -308 had higher transcriptional activity compared to the G allele (Wilson *et al.* 1994). Studies by Kroeger *et al.* and Abraham *et al.* confirmed the previous study, which showed that TNF -308 influenced TNF gene expression (Abraham & Kroeger 1999; Kroeger, Carville & Abraham 1997). However, others have not been able to duplicate the previous results (Brinkman *et al.* 1995; Knight *et al.* 2003; Mekinian *et al.* 2011).

On the other hand, several studies investigating the functional significance of TNF -238G>A have not found concrete evidence related to increased or decreased TNF promoter transcriptional activity or gene expression (Huizinga *et al.* 1997; Kaijzel *et al.* 1998; Pociot *et al.* 1995; Uglialoro *et al.* 1998). Nonetheless, several studies in various infectious diseases have shown the importance of TNF -238 G>A in disease susceptibility, albeit with currently unknown molecular mechanism. In another study, Skoog *et al.* showed evidence that TNF -863C>A reduced TNF plasma levels and transcriptional activity of TNF by 31% (Skoog *et al.* 1999). Moreover, Higuchi *et al.* also showed increased TNF transcriptional activity in individuals of Japanese descent with TNF -1031C and -863A alleles (Higuchi *et al.* 1998).

However, no known study have shown significant associations between these SNPs with susceptibility to Tuberculosis. Elahi *et al.* have hypothesized that due to the abundance of SNPs in the promoter region of TNF, other SNPs in the coding region of TNF might have higher functional significance in relation to TNF gene function (Elahi *et al.* 2009). Therefore, a comprehensive screen of all available SNPs on the TNF gene needs to be investigated thoroughly for future gene-disease association studies particularly in the study of Tuberculosis.

CONCLUSION

In conclusion, our pilot study showed that the TNF -238 (rs361525) is not associated with susceptibility to Tuberculosis particularly in the Indonesian population. Although bigger sample size may help in obtaining more reliable results, screening of all SNPs in the TNF gene or other TB susceptibility candidate genes may be a better avenue for future studies.

Limitations of this study

We currently do not supply a known genotype control for the SNP melting analysis, which may affect the accuracy of the genotype calls. Therefore, further assessment of the genotype by sequencing is required to confirm the different genotypes found. Lastly, it is also essential to confirm whether the differences in genotype, affect the gene expression levels of TNF, by monitoring the mRNA levels of this gene initially *in-vitro*. Others have also showed the limitations of single SNP association study (reviewed in (Bayley, Ottenhoff & Verweij 2004)),

therefore we propose the inclusion of all SNPs in the promoter and coding region of TNF gene for further analysis, and assess the association with phenotype by haplotype configurations.

Competing interests

The authors declare that they have no competing interests.

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