Association of LMP/TAP Gene Polymorphisms with Tuberculosis Susceptibility in Li Population in China

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Abstract

Background: Tuberculosis (TB) is a contagious disease affected by multiple genetic and environmental factors. Several association studies have suggested that cellular immune response is vital for controlling and preventing of tuberculosis infection. Low molecular weight polypeptides (LMPs) and transporters with antigen processing (TAPs) are the main molecules in the processing and presentation pathway for intracellular antigens. This study was performed to elucidate whether these antigen-processing genes (LMP/TAP) polymorphisms could be associated with the risk of tuberculosis infection in China.

Methodology/Principal Findings: We recruited 205 active pulmonary tuberculosis patients and 217 normal controls from Li population for this study. Four polymorphisms of LMP/TAP genes were determined by PCR-RFLP assay and haplotypes were constructed by software PHASE 1.0. Of the total four polymorphisms, genotype frequencies of LMP7 AA homozygote and CA heterozygote were significantly greater among cases compared to controls, with odds ratio of 3.77 (95% CI: 1.60–8.89; \( P = 0.002 \)) and 2.97 (95% CI: 1.80–4.90; \( P < 0.0001 \)), respectively. The genotypes of TAP1-2 GG homozygote and AG heterozygote were more frequent in subjects with TB than in controls, with odds ratio of 3.94 (95% CI: 1.82–8.53; \( P = 0.001 \)) and 2.87 (95% CI: 1.75–4.71; \( P < 0.0001 \)), respectively. Similarly, we found that haplotype B which carried LMP7 and TAP1-2 variations significantly increased the susceptibility to TB (OR = 3.674, 95% CI: 2.254–5.988; \( P < 0.0001 \)). Moreover, it is noteworthy that the homozygote of wild haplotype A (A/A) may be a strong protection for TB infection.

Conclusions: Our findings suggested that LMP/TAP gene polymorphisms might be risk factors for TB infection among Li population in China.

Introduction

Tuberculosis (TB), the leading cause of morbidity and mortality by a single infectious agent, is still a major health problem in the world. According to the annual report on global control of TB from WHO, about 9.4 million incident cases and 14 million prevalent cases occurred in 2009. Approximately 1.7 million people died of TB, including 0.38 million deaths among the HIV-positive people, and most cases were in the South-East Asia, African and Western Pacific regions (35%, 30% and 20%, respectively) [1].

It is well known that host genetic susceptibility, together with bacterial strains and environmental factors, plays an important role in determining TB predisposition and drug response. Only about 10% of the infected individuals develop the clinical disease while most infected people carry the bacteria without overt symptom [2,3]. To date, many studies have shown evidence of association between host genetic polymorphisms and TB susceptibility, including CCL2/MCP-1, NRAMP1/SLC11A1, IRGM1, IL8, TLR, and NOD2 genes [4–9]. Most of these genes participate in immune response and their polymorphisms may lead to increase genetic susceptibility to TB.

The genes for low molecular weight polypeptides (LMPs) and transporters with antigen processing (TAPs) are located within the MHC class II region of chromosome 6 between the HLA DP and HLA DQ loci, and have been shown to play a critical role in the processing and presentation pathway for intracellular antigens [10]. The LMP genes encode two subunits which form a proteasome complex and mainly involve in the proteolysis of cytoplasm into the endoplasmic reticulum for binding the major histocompatibility complex (MHC) class I molecules. The TAP genes compose a heterodimeric complex which translocates antigenic peptides from cytoplasm into the endoplasmic reticulum for binding the major histocompatibility complex (MHC) class I molecules for presentation to CD8+ cytotoxic T cells [11]. It has been reported that Mycobacterium tuberculosis (Mtb) protein presentation requires the cytosolic proteasomal degradation and subsequent TAP transpor-
tation [13,14]. Although the mechanisms underlying the Class I presentation of Mtb antigens remain enigmatic, studies have demonstrated that it may use multiple processing pathways [15,16]. In addition, a previous report also revealed that TAP-deficient mice exhibited an increased susceptibility to TB that was manifested by a decreased survival after infection, a greater bacterial burden, and more severe tissue pathology [17]. These data establish that MHC Class I antigen-processing pathway which requires cleavage of antigen peptides by LMP2/LMP7 and transportation of peptide fragments into the endoplasmic reticulum by TAP1/TAP2, is vital for controlling the Mtb infection and preventing the development of active TB.

Several polymorphisms within the coding region of LMP and TAP have been detected and are considered to be associated with a number of immune diseases, viral infection diseases, and even malignant tumors [18]–[22]. A few of these polymorphisms (TAP1 and TAP2) have been studied to determine predisposition towards TB in different ethnic groups, which have revealed the susceptibility to TB [23,24]. The aim of this study was to investigate the associations between polymorphisms of LMP and TAP genes and susceptibility to active TB disease in Li population in Hainan province, an island of southern China in the South China Sea. The incidence of TB was 1.5 fold in Li population than in Han population [25]. Concurrently, we also attempted to determine whether the haplotypes covering these SNPs were linked to the development of TB and explored potential risk factors for TB.

Methods

Ethics Statement

This study was approved by the Institution Review Boards of Hainan Center for Disease Control and Prevention and the written informed consents were obtained.

Subjects

Two hundred and five unrelated patients diagnosed with active pulmonary TB were enrolled in this study. These patients were followed up at Hainan Center for Disease Control and Prevention between 2005 and 2008. The diagnosis of pulmonary TB was based on the following criteria: 1) clinical symptom suggestive of TB; 2) chest radiographic evidence of active pulmonary TB in the upper lobes; 3) sputum smear positive with or without chest radiographic evidence of active pulmonary TB; 4) excluding the subjects with diseases such as lung carcinoma, pneumonia, diabetes and other immunosuppressive condition. Patients with the presence of all criteria were recruited. The control group included 217 healthy unrelated adults without history of TB, autoimmune diseases, or other infectious diseases from Li population in Hainan province. The healthy volunteers were from the general population with the same socioeconomic status and ethnic background as that of the patients, and were selected through the population survey of tuberculosis with PPD skin test results <5 mm and remaining uninfected during 2 years.

All subjects of TB cases and normal controls were HIV seronegative and BCG vaccinated. The demographic characteristics were described in Table 1.

Genotyping analysis and haplotype construction

Genomic DNA was extracted from peripheral blood leukocytes of study subjects by standard procedures. Polymorphisms in LMP genes and TAP genes were genotyped using primer pairs as shown in Table 2. The four polymorphisms were detected by polymerase chain reaction (PCR) restriction fragment length polymorphism (RFLP) analysis, which abide by previously described methods [20].

| Table 1. Demographic characteristics for tuberculosis cases and controls. |
|-----------------|-----------------|-----------------|
|                | Case n = 205    | Control n = 217 |
| gender          |                 |                 |
| male            | 138             | 105             |
| female          | 67              | 112             |
| age             |                 |                 |
| male            | 42.20±17.35     | 26.86±12.64     |
| female          | 41.27±15.63     | 27.63±15.17     |
| smoke           |                 |                 |
| male            | 43              | 30              |
| female          | 2               | 2               |
| drink           |                 |                 |
| male            | 45              | 32              |
| female          | 3               | 1               |
| BCG Vaccinated  | Yes             | Yes             |

The amplified products were purified and then digested using specific restriction endonuclease under the different conditions as per the manufacturer’s instructions. After digestion, the fragments were electrophoresed in a 2% agarose gel and were visualized by ethidium bromide staining. The accuracy of genotyping was confirmed by direct sequencing of the random DNA samples (N = 10) from cases and controls for all polymorphic sites. Finally, the PHASE 1.0 software was used to construct the haplotypes for all the four gene polymorphisms [26].

Statistical analysis

The chi-square test was used to compare genotype distribution and allele frequency in the TB patients and control subjects with SPSS 12.0 software packages. Hardy–Weinberg equilibrium was tested by Haplovew 4.2 software. The haplotype frequencies were calculated with PHASE1.0 software. The associations between case and control groups were evaluated by utilizing the unconditional logistic regression model adjusted for gender, age, cigarettes smoking and alcohol drinking. Odds ratio (OR) and 95% confidence interval (95% CI) were estimated and a P value of <0.05 was considered to be significant.

Results

Characteristics of the Participants

The 205 patients with active pulmonary TB and 217 healthy controls with PPD skin test results <5 mm were studied. The demographic characteristics including age, gender, cigarettes smoking, and alcohol drinking were summarized in Table 1.
Considering that all study subjects were BCG vaccinated, we only selected the non-infected individuals as control subjects in this preliminary study.

**Correlation of Genetic Polymorphisms and Tuberculosis**

According to the previous studies of LMP/TAP gene polymorphisms of other diseases [20,22], we selected four non-synonymous coding SNP. Genotypes (homozygote and heterozygote) were confirmed by using restriction fragment length polymorphism (RFLP) method according to different numbers of enzyme fragments. Table 2 listed the SNPs that were selected including their rs numbers and PCR amplification primers.

The genotype distributions for these four polymorphisms did not deviate significantly from Hardy-Weinberg equilibrium in both case and control groups. Table 3 listed the allele and genotype frequencies for all the polymorphisms. Allele frequencies for three polymorphism loci (TAP1-1/TAP1-2/LMP7) were revealed to have significant differences between the TB patients and controls (P<0.01). The genotype frequencies of LMP7 AA homozygote and CA heterozygote were significantly greater among cases compared to the healthy control group, with odds ratio of 3.77 (95% CI: 1.60–8.89; P=0.002) and 2.97 (95% CI: 1.80–4.90; P<0.0001), respectively. Similarly, the genotype of TAP1-2 GG homozygote and AG heterozygote were more frequent in subjects with TB than in controls, with odds ratio of 3.94 (95% CI: 1.82–8.33; P=0.001) and 2.87 (95% CI: 1.75–4.71; P<0.0001), respectively.

Of the other two polymorphisms, the prevalence of the TAP1-1 AG heterozygote was more significantly found in cases than in controls (OR = 1.92, 95% CI: 1.19–3.12, P=0.008), while the frequency of GG homozygote had no considerable difference between the two groups (P=0.583). In the LMP2 polymorphic site, no significant difference was observed in the distribution among cases and controls (P>0.05).

Considering the difference in gender distribution between case and control groups, we further analyzed our data by separating males and females. Similar results were obtained when samples were stratified by gender. Significant associations were observed in LMP7 and TAP1-2 polymorphism sites with either allelic or genotypic analysis (P<0.01). There was a little difference detected for TAP1-1 site in which male showed a trend of association but not in female group (Table 4). Therefore, the possible exerted confounding factor due to difference in gender distribution may be excluded.

**Association of Haplotype with Tuberculosis**

To study the combined effects of the four polymorphic sites in LMP/TAP genes, we next carried out the haplotypic association analysis. The statistical software PHASE 1.0 was used to estimate differences in the haplotype frequencies, which calculated haplotype frequencies with an expectation maximization algorithm. A total of thirteen haplotypes (A-M) were constructed, and all of the haplotypes were found in both case and control groups. The distribution of different haplotypes in each group was summarized in Table 5.

Among the thirteen haplotypes observed in the 205 TB patients and 217 controls recruited for the study, only three haplotypes represented at frequencies >5% (Table 5). These three haplotypes together accounted for >69.9% of the total haplotypes in both case and control groups. Thus, these haplotypes were selected to assess the susceptibility to TB (Table 6).

We noticed these three haplotypes had relatively low frequencies with homozygote haplotypes, which may increase the inaccuracy of haplotype frequency estimation and lead to false-positive inference. Hence, we incorporated the homozygote and heterozygote of each haplotype and evaluated the association of global haplotype distributions with TB. The results showed that only haplotype B significantly associated with tuberculosis in our study population (OR = 3.674, 95% CI = 2.254–5.988, P<0.0001), as depicted in Table 7. No significant differences were observed in the other two haplotypes between the two groups.

**Discussion**

As the second country with the largest number of incidence cases in the world, China is still facing great challenges to TB control. Though the incidence rate has slowly reduced from 99 (per 100 000 population) in 2005 to 96 (per 100 000 population) in 2009, the absolute number of cases continues to increase slightly from year to year [1]. Li population is the only minority nationality lived in Hainan province, with a total population of 1.28 million in 2010. The rate of smear-positive TB was 13.1% in Li population, compared to 9.9% in Han population [25]. Besides the socio-economic factors such as living condition, poverty, treatment delay and poor-quality care, host genetic susceptibility may be another significant risk factor for influencing TB incidence in different population.

In the present study, we focused on the association of polymorphic sites in LMP/TAP genes with TB susceptibility in Li population. We tested four polymorphisms in the coding regions of LMP2, LMP7 and TAP1 genes and observed all the polymorphisms in the subjects enrolled in our study. The polymorphism of LMP2 gene (rs17587) was reported as the
substitution of arginine to histidine [27]. But we did not find histidine at this locus in any of the cases or controls. Instead, a cysteine replacement was observed in this population which was consistent with previous studies [20,22]. These findings suggested that LMP and TAP polymorphisms may differ among populations as reported by other studies.

Table 3. Genotype, allele frequencies of the polymorphisms in the LMP and TAP genes.

| Gene     | Allele | Cases n (%) | P Value | Controls n (%) | Genotype | Cases n (%) | P Value* | OR* (95% CI) |
|----------|--------|-------------|---------|----------------|----------|-------------|---------|--------------|
| LMP2     | C      | 321 (78.29) |         | 347 (79.95)    | CC       | 124 (60.49) |         | 135 (62.21)  |
|          | T      | 89 (21.71)  | 0.553   | 87 (20.05)     | CT       | 73 (35.61)  |         | 77 (35.48)   | 0.691  | 1.33 (0.33–5.33) |
|          |        |             |         |                | TT       | 8 (3.90)    |         | 5 (2.30)     | 0.770  | 0.93 (0.58–1.49) |
| TAP1-1   | A      | 299 (72.93) |         | 352 (81.11)    | AA       | 104 (50.73) |         | 147 (67.74)  |
|          | G      | 111 (27.07) |         | 82 (18.89)     | AG       | 91 (44.39)  |         | 58 (26.73)   | 0.008  | 1.92 (1.19–3.12) |
|          |        |             |         |                | GG       | 10 (4.88)   |         | 12 (5.33)    | 0.583  | 0.74 (0.25–2.18) |
| TAP1-2   | A      | 240 (58.54) |         | 322 (74.19)    | AA       | 66 (32.20)  |         | 121 (55.76)  |
|          | G      | 170 (41.46) | <0.0001 | 112 (25.81)    | AG       | 108 (52.68) |         | 80 (36.87)   | <0.0001 | 2.87 (1.75–4.71) |
|          |        |             |         |                | GG       | 31 (15.12)  |         | 16 (7.37)    | 0.001  | 3.94 (1.82–8.53) |
| LMP7     | C      | 240 (58.54) |         | 314 (72.35)    | CC       | 59 (28.78)  |         | 110 (50.69)  |
|          | A      | 170 (41.46) | <0.0001 | 120 (27.65)    | CA       | 122 (59.51) |         | 94 (43.32)   | <0.0001 | 2.97 (1.80–4.90) |
|          |        |             |         |                | AA       | 24 (11.71)  |         | 13 (5.99)    | 0.002  | 3.77 (1.60–8.89) |

Significant p values are in bold.

*Logistic regression model, adjusted by gender, age, smoke and drink.

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Table 4. Genotype, allele frequencies and sex specific association analysis.

| Gene and sex | n | Allele frequency (%) | P Value | Genotype frequency (%) | P Value* |
|--------------|---|----------------------|---------|------------------------|---------|
| LMP2         |   |                      |         |                        |         |
| M Case       | 138| 213 (77.17)          | 0.159   | 81 (58.69)             | 6 (4.35) |
| F Case       | 67 | 108 (80.60)          | 0.513   | 65 (58.03)             | 3 (2.68) |
| M Control    | 105| 173 (82.38)          |         | 78 (47.92)             | 0.014   |
| F Control    | 67 | 102 (76.12)          | 0.734   | 69 (41.79)             | 7 (6.25) |
| TAP1-1       |   |                      |         |                        |         |
| M Case       | 138| 197 (71.38)          | <0.0001 | 78 (47.92)             | <0.0001 |
| F Case       | 67 | 102 (76.12)          |         | 69 (41.79)             | 7 (6.25) |
| M Control    | 105| 173 (82.38)          |         | 78 (47.92)             | 0.014   |
| F Control    | 67 | 102 (76.12)          |         | 69 (41.79)             | 7 (6.25) |
| TAP1-2       |   |                      |         |                        |         |
| M Case       | 138| 160 (57.97)          | <0.0001 | 62 (59.50)             | <0.0001 |
| F Case       | 67 | 80 (59.70)           |         | 62 (59.50)             | 0.001   |
| M Control    | 105| 158 (75.24)          |         | 34 (32.38)             | 9 (8.57) |
| F Control    | 67 | 80 (59.70)           |         | 34 (32.38)             | 10 (14.92) |
| LMP7         |   |                      |         |                        |         |
| M Case       | 138| 158 (57.25)          | <0.0001 | 55 (52.38)             | 0.001   |
| F Case       | 67 | 82 (61.19)           |         | 55 (52.38)             | 6 (7.27) |
| M Control    | 105| 158 (57.25)          |         | 55 (52.38)             | 6 (7.27) |
| F Control    | 67 | 82 (61.19)           |         | 55 (52.38)             | 6 (7.27) |

Significant p values are in bold.

*Logistic regression model, adjusted by gender, age, smoke and drink.

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Table 5. Haplotypes frequencies of the LMP/TAP genes in cases and controls.

| Haplotypes | Loci [LMP7][TAP1-1][TAP1-2] | Cases n (%) | Controls n (%) |
|------------|-----------------------------|-------------|---------------|
| Number of chromosome | 410 (100) | 434 (100) |
| A | CAAC | 138 (33.66) | 229 (52.76) |
| B | CAGA | 97 (23.66) | 52 (11.98) |
| C | TGAC | 40 (9.76) | 34 (7.83) |
| D | TAGA | 9 (2.20) | 26 (5.99) |
| E | CGGA | 19 (4.63) | 14 (3.23) |
| F | CAAA | 15 (3.66) | 18 (4.15) |
| G | CGAC | 11 (2.68) | 19 (4.38) |
| H | CGAA | 23 (5.61) | 7 (1.61) |
| I | CAGC | 18 (4.39) | 8 (1.84) |
| J | TGGC | 18 (4.39) | 8 (1.84) |
| K | TAAC | 6 (1.46) | 12 (2.76) |
| L | TAGC | 9 (2.20) | 4 (0.92) |
| M | TAAA | 7 (1.71) | 3 (0.69) |

Table 6. Haplotypes distributions of the LMP/TAP genes in cases and controls.

| Haplotypes | Case n | Control n |
|------------|--------|-----------|
| CAAC = A | 67 | 68 |
| /A | 138 | 69 |
| A/A | 0 | 80 |
| CAGA = B | 108 | 166 |
| /B | 97 | 50 |
| B/B | 0 | 1 |
| TGAC = C | 165 | 184 |
| /C | 40 | 32 |
| C/C | 0 | 1 |

Table 7. Distribution of haplotype frequencies in LMP/TAP genes among cases and controls.

| Haplotypes Case n (%) | Control n (%) | P Valuea | OR (95% CI) |
|-----------------------|---------------|----------|-------------|
| CAAC = A | -/- | 67 (32.7) | 68 (31.3) | ---- | |
| /A+A/A | 138 (67.3) | 149 (68.7) | 0.867 | 0.960 (0.594–1.551) |
| CAGA = B | /- | 108 (52.7) | 166 (76.5) | ---- | |
| /B+B/B | 97 (47.3) | 51 (23.5) | <0.0001 | 3.674 (2.254–5.988) |
| TGAC = C | /- | 165 (80.5) | 184 (84.8) | ---- | |
| /C+C/C | 40 (19.5) | 33 (15.2) | 0.317 | 1.358 (0.745–2.474) |

aLogistic regression model, adjusted by gender, age, smoke and drink.

In our study, significant association between LMP/TAP genes and TB was observed when we compared our active TB patients and controls. The subjects containing LMP7 AA homozygote and CA heterozygote were found to be strongly associated with TB infection (OR = 3.77, 2.97, respectively). Similarly, the TAP1-2 polymorphism also exhibited a significant relation to TB infection. For the other two polymorphisms, no statistical significant associations were found at polymorphic sites of LMP2 and TAP1-1 genes to the risk of TB (Table 5). Similar to the individual associations were found at polymorphic sites of LMP2 and TAP1-2 variations significantly increased the susceptibility to TB. Moreover, it is noteworthy that the homozygote of wild haplotype A (A/A) may be a strong protection on TB infection (Table 6). All these results indicated that the LMP7 and TAP1 gene polymorphisms might be risk factors for TB infection among Li population.

The critical roles of the LMP/TAP genes are consistent with the observed association for TB in our study. LMP is a cytosolic proteinase complex which hydrolyzes antigens into 8- or 9-residue peptides, and TAP is a member of the ATP-binding cassette transporter family which translocates antigenic fragments to MHC class I molecules in the endoplasmic reticulum. Previous studies have reported that LMPs proteasomes favor to promote cleavage of peptides after hydrophobic and basic residues but suppress cleavage after acidic residues. This effect results in the generation of peptides that preferentially ended with hydrophobic or basic carboxyl termini [28]. Furthermore, the polymorphisms located at TAP1/TAP2 gene coding region may affect the specificity of peptide presentation [29,30]. Therefore, the interaction of LMP and TAP genes polymorphisms may subsequently interfere with the LMP/TAP-dependent translocation of disease associated peptides.

It is worth mentioning that the LMP and TAP genes are located close and centromeric to the HLA-DBQ1 gene in chromosome 6 MHC class II region [31]. The MHC is the most gene-dense region of the human genome sequenced. It also encodes most polymorphic human proteins, some of which have over 200 allelic variants. Considering that strong linkage disequilibrium exists between HLA-DR and HLA-DQ genes, the strong associations for LMP7 and TAP1 genes might also be in linkage disequilibrium with HLA-DBQ1 gene in our population. This hypothesis should be verified in the further study.

In 1997, Rajalingam R and colleagues first reported a statistical association between alleles in TAP2 region with pulmonary tuberculosis and tuberculoid leprosy susceptibility in the North India populations [23]. In contrast to our study, no significant differences in the prevalence of TAP1 alleles were observed. In addition, another recent study carried out in a Northwestern Colombian population also failed to detect any association of TAP1 gene with TB disease [24]. There may be several reasons for the discrepancy between our findings and those reported results. Recently, Stein took a systematic review from a genetic epidemiological perspective. She illustrated the key influencing factors for the inconsistency in TB literature, such as the phenotype definition both in cases and controls, population differences-more than just geography, complex genetic effects,
In summary, our findings provide the first evidence of the association between LMP gene polymorphism and human susceptibility to TB disease. We also support the hypothesis that MHC class I-mediated antigen presentation may play an important role in the host defense to TB. Since the complexity and versatility of host immune response to *M. tuberculosis*, further studies with multiple genes interaction and multidisciplinary approaches including genomic, proteomic, and immunologic data, collectively, may better confirm the current findings.

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Author Contributions

Conceived and designed the experiments: DW YZ YM. Performed the experiments: DW YZ YM LJ TH FL RL TL. Analyzed the data: DW YZ YM. Contributed reagents/materials/analysis tools: FL RL TL. Wrote the paper: DW YZ YM.

References

1. Global TB. Gomp Report (2010) WHO website. Available: http://www.who.int/chp Accessed 2011 Aug 30.

2. Comstock GW (1978) Tuberculosis in twins: a re-analysis of the Prophit survey. Am Rev Respir Dis 117: 621–624.

3. Schurr E (2007) Is susceptibility to tuberculosis acquired or inherited? J Intern Med 261: 166–173.

4. Feng W, Mokrousova I, Wang BB, Nelson H, Jiao WW, et al. (2011) Tag SNP polymorphism of CCL2 and its role in clinical tuberculosis in Han Chinese pediatric population. PLoS One 6: e14652.

5. Li X, Yang Y, Zhang F, Zhang Y, Lu H, et al. (2011) SLC11A1 (NRAMP1) polymorphisms and tuberculosis susceptibility: updated systematic review and meta-analysis. PLoS One 6: e15381.

6. King KY, Lew JD, Ha NP, Lin JS, Ma X, et al. (2011) Polymorphic allele of human RMRG121 is associated with susceptibility to tuberculosis in African Americans. PLoS One 6: e16371.

7. Mal X, Reich RA, Wright JA, Tooker HR, Tector LD, et al. (2003) Association between interleukin-18 gene alleles and human susceptibility to tuberculosis disease. J Infect Dis 188: 349–355.

8. Ma X, Liu Y, Gwenn BR, Graves EA, Clark AG, et al. (2007) Full-exon resequencing reveals toll-like receptor variants contribute to human susceptibility to tuberculosis disease. PLoS One 2: e1318.

9. Austin CM, Ma X, Graves EA (2008) Common non synonymous polymorphisms in the NOD2 gene are associated with resistance or susceptibility to tuberculosis disease in African Americans. J Infect Dis 197: 1713–1716.

10. York IA, Rock KL (1996) Antigen processing and presentation by the class I major histocompatibility complex. Annu Rev Immunol 14: 369–396.

11. Driscoll J, Brown MG, Finlay D, Monaco J (1993) MHC-linked LMP gene products specifically alter peptidase activities of the proteasome. Nature 365: 262–264.

12. Monaco JJ (1995) Pathways for the processing and presentation of antigens to T cells. J Leukoc Biol 57: 543–547.

13. Lewinsha DM, Grotsch JE, Heinzel AS, Zuo L, Ovendale PJ, et al. (2006) Secreted proteins from Mycobacterium tuberculosis gain access to the cytosolic MHC class-I antigen-processing pathway. J Immunol 177: 437–442.

14. Grotsch JE, Harriff MJ, Slor AG, Neil D, Delpeigne J, et al. (2009) The Mycobacterium tuberculosis phagosome is a HLA-I processing competent organelle. PLoS Pathog 5: e1000374.

15. Neyrolles O, Gould K, Gares MP, Brett S, Janssen R, et al. (2001) Lipoprotein access to MHC class I presentation during infection of murine macrophages with live mycobacteria. J Immunol 166: 447–457.

16. Schable UE, Winau F, Sierling PA, Fischer K, Collins HL, et al. (2003) Aportosis facilitates antigen presentation to T lymphocytes through MHC-I and CD1 in tuberculosis. Nat Med 9: 1039–1046.

17. Behar SM, Dasher CC, Grusby MJ, Wang CR, Brenner MB (1999) Susceptibility of mice deficient in CD1D or TAP1 to infection with Mycobacterium tuberculosis. J Exp Med 189: 1973–1980.

18. Prabahal S, Kingsbury DJ, Griffin TA, Cooper BL, Glass DN, et al. (2001) Polymorphism in the MHC-encoded LMP7 gene: association with JRA without functional significance for immunoproteasome assembly. J Rheumatol 28: 2320–2325.

19. McManus CL, Stewart LC, Miyochi GC, Barnett AH (2000) Assessment of the non-HLA-DR-DQ contribution to IDDM1 in British Caucasian families: analysis of LMP7 polymorphisms. Diabet Med 17: 661–666.

20. Xu C, Qi S, Gao L, Cui H, Liu M, et al. (2007) Genetic polymorphisms of LMP/TAP gene and hepatitis B virus infection risk in the Chinese population. J Clin Immunol 27: 534–541.

21. Lautscham G, Rickinson A, Blake N (2003) TAP-independent antigen presentation on MHC class I molecules: lessons from Epstein-Barr Virus. Microbes Infect 5: 291–299.

22. Cao R, Tian X, Li Y, Jiang P, Ning T, et al. (2005) LMP/TAP2 gene polymorphisms and HPV infection in esophageal carcinoma patients from a high incidence area in China. Carcinogenesis 26: 1280–1284.

23. Rajalingum R, Sisgal DP, Mehra NK (1997) Transporter associated with antigen-processing (TAP) genes and susceptibility to tuberculin response and pulmonary tuberculosis. Tissue Antigens 49: 168–172.

24. Gomez LM, Camargo JF, Castiblanco J, Ruiz-Narvaez EA, Cadena J, et al. (2006) Analysis of IL1B, TAP1, TAP2 and IL28B polymorphisms on susceptibility to tuberculosis. Tissue Antigens 67: 290–296.

25. Lin F, Luo XX (2003) The cohort analysis of new smear positive pulmonary tuberculosis in Li Nationality collective residential regions of Hainan province. Chinese Journal of Antimicrobial 2(5): 302–304.

26. Stephens M, Smith NJ, Donnelly P (2001) A new statistical method for haplotype reconstruction from population data. Am J Hum Genet 68: 949–999.

27. UCSC In-Silico PCR website. Available: http://www.genome.ucsc.edu/cgi-bin/ hgPcr. Accessed 2011 Dec 23.

28. Gazzyokina M, Rock KL, Spies T, Goldberg AL (1994) Peptidase activities of proteasomes are differentially regulated by the major histocompatibility complex-encoded genes for LMP2 and LMP7. Proc Natl Acad Sci U S A 91: 9213–9217.

29. Lapinski PE, Neubig RR, Raghavan M (2001) Walker A lysine mutations of TAP1 and TAP2 interfere with peptide translocation but not peptide binding. J Biol Chem 276: 7526–7533.

30. Alberts P, Daumke O, Deverson EV, Howard JC, Knittler MR (2001) Distinct transport cycle. Curr Biol 11: 242–251.

31. Lin F, Luo XX (2003) The cohort analysis of new smear positive pulmonary tuberculosis in Li Nationality collective residential regions of Hainan province. Chinese Journal of Antimicrobial 2(5): 302–304.

32. Lin F, Luo XX (2003) The cohort analysis of new smear positive pulmonary tuberculosis in Li Nationality collective residential regions of Hainan province. Chinese Journal of Antimicrobial 2(5): 302–304.

33. Stephens M, Smith NJ, Donnelly P (2001) A new statistical method for haplotype reconstruction from population data. Am J Hum Genet 68: 949–999.

34. Rajalingum R, Sisgal DP, Mehra NK (1997) Transporter associated with antigen-processing (TAP) genes and susceptibility to tuberculin response and pulmonary tuberculosis. Tissue Antigens 49: 168–172.

35. Rajalingum R, Sisgal DP, Mehra NK (1997) Transporter associated with antigen-processing (TAP) genes and susceptibility to tuberculin response and pulmonary tuberculosis. Tissue Antigens 49: 168–172.

36. Thye T, Browne EN, Chinbuah MA, Gyapong J, Osei I, et al. (2009) IL10 haplotype associated with tuberculin skin test response but not with pulmonary TB. PLoS One 4: e34920.