Polymorphisms of Fatty Acid Elongase 2 Gene Affects Risk of Pulmonary Tuberculosis in China Han Population

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Abstract
Background: As an infectious disease closely related to Mycobacterium tuberculosis, autoimmunity, inflammation, environment and heredity, the relationship between the single nucleotide polymorphism of elongase 2 gene and the susceptibility to tuberculosis is still unknown.
Methods: Between January 2016 and November 2018, a hospital-based case-control study was conducted. This epidemiological survey was conducted in both hospitals every three months. rs3798719, rs1570069, and rs2236212 in ELOVL2 gene were detected by Sanger sequencing.
Results: Stratified by gender, the genotypes and allele frequencies of rs3798719, rs1570069 and rs2236212 showed significant differences between the two groups ($\chi^2 = 6.987, P = 0.030$). Genetic modeling showed that rs3798719 was statistically different in the overdominance model ($\chi^2 = 4.784, OR = 1.414, 95\% CI: 1.036-1.929, P < 0.05$). The polymorphism of rs2236212 between male TB patients and healthy controls was statistically different in the dominance model. ($\chi^2 = 4.192, OR = 0.507; 95\% CI: 0.262-0.981, P < 0.05$).
Conclusion: The rs3798719 of ELOVL2 gene may be associated with susceptibility to TB in female population and the rs2236212 of ELOVL2 gene may be associated with TB incidence in male patients.

Keywords: Tuberculosis; ELOVL2; Genes; Single nucleotide polymorphism; China

Introduction

Tuberculosis (TB) is a predominantly airborne infectious disease caused by Mycobacterium tuberculosis and is one of the top ten causes of death worldwide. The 2018 WHO report showed that 10 million people had tuberculosis and 1.6 million died from the disease (including 300,000 people living with HIV) in 2017 (1). Interestingly, only 5% to 15% of population who have tuberculosis develop the disease (2), suggesting that the development of M. tuberculosis infection to TB is determined by multifactors, for example, the host’s genes and immuno response (3). The n-3 and n-6 polyunsaturated fatty acids (PUFAs) have important biological significance...
and are closely related to human health (4-6). Adding n-3 and n-6 PUFAs to the diet may reduce the risk of active TB in the Chinese population (7). The biosynthesis of n-6/n-3 PUFAs originates from a series of precursor fatty acids derived from continuous carbon chain extension and dehydrogenation of fatty acids (8). Fatty acid elongase 2 (ELOVL2) is located on chromosome 6 (6p24.2) and encodes the long-chain fatty acid lengthening enzyme; as such, ELOVL2 gates an important rate-limiting step in the PUFA metabolic pathway and its activity directly affects the synthesis of PUFAs (9-10).

A single nucleotide polymorphism (SNP) of the ELOVL gene is correlated with fatty acid composition in a number of tissues of the human body. Fatty acid composition varies among people with different ELOVL genotypes (11-13). The incidence of infectious disease involves autoimmunity, inflammation, environment and genetic fingerprint. The relationship between TB and SNPs of ELOVL2 gene is still unclear.

In this study, we explored 3 SNPs of the ELOVL2 gene (rs3798719, rs1570069, rs2236212) in a Han Chinese patient population, aimed to provide further insight into the association between the gene polymorphism of PUFA and TB.

**Materials and Methods**

Between January 2016 and November 2018, a hospital-based case-control study was conducted in Huainan Oriental Tumor Hospital, China and physical examination center of Huainan First People's Hospital. During the study period, an epidemiological survey was conducted in both hospitals every three months. Of these cases, the TB patients were diagnosed by sputum smear, culture and chest radiography. According to the “Diagnostic criteria for pulmonary tuberculosis” issued by the Ministry of Health of China, TB was diagnosed based on *M. tuberculosis* positive sputum smear, positive sputum culture and pulmonary lesions (15). The control group was excluding the history of tuberculosis, chronic obstructive pulmonary disease, pneumoconiosis, asthma, lung cancer, hypertension, tumor, diabetes, and other infectious diseases.

Informed consent was obtained from all participants and the study was approved by the Ethics Committee of School of Medicine, Anhui University of Science and Technology, Anhui, China (NO.2016012).

In total, 656 qualified subjects (326 cases and 330 control subjects) were enrolled. There were 232 males (71.2%) and 94 females (28.8%) in the case group, with an average age of 55.3±14.7 years. Totally, there were 225 males (68.2%) and 105 females (31.8%) in the control group, with an average age of 57.6±13.9 years.

Dietary patterns were assessed by a modified Food Frequency Questionnaire (FFQ). The FFQ optimized a previous questionnaire by adding dietary features of the target population, including 24 food groups that Chinese people commonly eat (14). Each item represents a food group, and participants were asked how often (daily, weekly, monthly, annually, or never) they consumed each item. We assessed the reliability and validity of the FFQ (Coefficients between 0.71 and 0.89 for major food groups).

About 5 mL of peripheral venous blood was harvested from all participants with vacuum anticoagulant tubes and stored at -80 °C until use. Genomic DNA was extracted and purified from whole blood using a commercially available genomic DNA extraction kit (Cat. #DP304-03, TianGen, Beijing, China) according to manufacturer's manual. The forward and reverse primers that were used in PCR. Genotyping was performed by Sanger sequencing (Sangon Biotech, Shanghai, China), based on the Applied Biosystems (ABI) Prism BigDye Terminator v3.1 Cycle Sequencing Kit and was run on an ABI 3730XL Genetic Analyzer.

The Chinese version of the International Physical Activity Questionnaire was used to survey the physical activity of the study population. The questionnaires were used to collect information about the following features: Physical activity, which was categorized into 3 levels: strenuous exercise, medium-intensity exercise, and low-intensity exercise, medium-intensity exercise, low-intensity exercise.
intensity exercise (16), Passive smoking (defined as non-smokers exposed to smoke for more than 15 minutes per day), Residence, either rural (living in the rural area more than 10 years and still living in rural area) or urban (living in the urban area more than 10 years and still living in urban area), economic status, sorted into high (family per month income more than 3000 CNY), average (1500-3000 CNY), or low (lower than 1500 CNY); and alcohol intake (defined as men drinking more than 20 g and women more than 10 g per day).

Data were manual loaded into EpiData 3.0 using double data entry approach. SPSS (version 21.0, IBM) was used to identify dietary patterns by factor analysis. We used chi-square tests for categorical variables to identify significant differences in proportion between groups. Logistic regression was used to identify the contributors of TB. In the analysis of additive interaction, the variables are required to be considered as dichotomies, so in the analysis of dietary patterns. Each pattern compares the highest quartile group with the lowest quartile group. We set Diabetes = No, Age < 40, Residence = Urban, Passive smoking = No, Medium-intensity exercise > 3 times/week, BMI > 18.5, Western food = Q4, High VD and Calcium = Q4, Traditional Chinese = Q1, High animal protein = Q4 as control, and protective factors as exposure. P < 0.05 was considered statistically significant.

**Results**

There were 326 TB cases and 330 control subjects enrolled in the study. In logistic regression analyses, after adjusting for confounders, lower economic status, smoking and alcohol drinking, <3 times/week of low-intensity, lower BMI, low protein/fat and animal protein dietary pattern, high vegetarian dietary pattern were associated with risk of tuberculosis (Table 1).

| Variable                  | Tuberculosis | OR(95%CI) a | OR(95%CI) b |
|---------------------------|--------------|-------------|-------------|
| Gender                    |              |             |             |
| male                      | 232 (71.2)   | 1.152(0.825-1.607) | 0.940 (0.697-1.266) |
| female                    | 94 (28.8)    | 1.000       | 1.000       |
| Occupation                |              |             |             |
| Worker/farmer             | 99 (30.4)    | 1.422(0.823-2.458) | 1.015(0.831-1.240) |
| individual                | 120 (36.8)   | 1.429(0.838-2.436) |             |
| civil servants            | 75 (23.0)    | 0.957(0.550-1.664) |             |
| students                  | 32 (9.8)     | 1.000       | 1.000       |
| Marital status            |              |             |             |
| unmarried                 | 90 (27.6)    | 1.197(0.531-2.696) | 0.894(0.582-1.372) |
| Married                   | 205 (62.9)   | 1.356(0.619-2.971) | 0.924(0.499-1.711) |
| Death of a spouse         | 12 (3.7)     | 1.000       | 1.000       |
| Economic status           |              |             |             |
| Wealthy                   | 29(8.9)      | 0.402(0.248-0.649) * | 0.635(0.404-0.998) * |
| General                   | 40(12.3)     | 0.536(0.346-0.831) * | 0.787(0.503-1.231) |
| poor                      | 257(78.8)    | 1.000       | 1.000       |
| Passive smoking           |              |             |             |
| Yes                       | 259 (64.6)   | 5.379(3.795-7.625) * | 4.651 (2.199-9.859) * |
| No                        | 65 (35.4)    | 1.000       | 1.000       |
| Alcohol drinking          |              |             |             |
| Yes                       | 223 (68.6)   | 2.338(1.699-3.215) * | 1.925 (1.299-2.852) * |
| No                        | 102 (31.4)   | 1.000       | 1.000       |

Table 1: Difference of anthropometric characteristics of in cases and controls
Stratified by gender, the genotypes and allele frequencies of rs3798719, rs1570069 and rs2236212 showed significant differences between the two groups ($\chi^2 = 6.987, P = 0.030$), and the rest variables were not statistically different as shown in Table 2.

Genetic modeling showed that rs3798719 between the case and control group was statistically different in the overdominance model ($\chi^2 = 4.784$, OR = 1.414, 95% CI: 1.036-1.929, $P < 0.05$) (Table 3). The polymorphism of rs2236212 between male TB patients and healthy controls was statistically different in the dominance model. ($\chi^2 = 4.192$, OR = 0.507; 95% CI: 0.262-0.981, $P < 0.05$) (Table 4).

### Table 2: Associations between the SNP genotypes of ELOVL 2 and the risk of PTB

| Variable | Genotype | PTB | HC | OR(95% CI) | $\chi^2$ | P  |
|----------|----------|-----|----|------------|---------|----|
| All subjects |          |     |    |            |         |    |
| rs3798719 | C/C      | 161 | 183| 0.682(0.323,1.439) | 5.797   | 0.055 |
|           | C/T      | 153 | 127|               |         |    |
|           | T/T      | 12  | 20 |               |         |    |

*a* Unadjusted; *b* Adjusting for gender, age, residence, education, economic status, passive smoking, drinking, married status, physical activity * $P < 0.05
| SNP-ID   | Genotype       | PTB  | HC  | OR(95%CI)       | $\chi^2$ | P     |
|----------|----------------|------|-----|----------------|----------|-------|
| rs3798719 | dominance      | CC+CT/TT | 314 12 | 310 20 | 0.592(0.285-1.232) | 2.001 | 0.157 |
|          | recessive      | TT+CT/CC  | 165 161 | 147 183 | 0.784(0.577-1.065) | 2.421 | 0.120 |
|          | additive       | CC/TT     | 161 12 | 183 20 | 0.682(0.323-1.439) | 1.020 | 0.313 |
|          | overdominance  | TT+CC/CT  | 173 153 | 203 127 | 1.414(1.036-1.929) | *4.784 | 0.029 |
| rs1570069 | dominance      | AA+AG/GG  | 62 264 | 59 271 | 0.927(0.625-1.376) | 0.142 | 0.707 |
|          | recessive      | AG+GG-AA  | 325 1 | 325 5 | 0.200(0.023-1.721) | 2.642 | 0.104 |
|          | additive       | AA/GG     | 1 264 | 5 271 | 4.871(0.565-41.971) | 2.536 | 0.111 |
|          | overdominance  | AA+GG/AG  | 265 61 | 276 54 | 1.177(0.786-1.761) | 0.625 | 0.429 |
| rs2236212 | dominance      | CC+CG/GG  | 298 28 | 297 33 | 0.846(0.498-1.435) | 0.387 | 0.534 |
|          | recessive      | GG+CG/CC  | 184 142 | 180 150 | 0.926(0.681-1.260) | 0.239 | 0.625 |
|          | additive       | CC/ GG    | 142 28 | 150 33 | 0.896(0.515-1.559) | 0.150 | 0.698 |
|          | overdominance  | CC+GG/C   | 170 156 | 183 147 | 1.142(0.840-1.553) | 0.722 | 0.396 |

PTB: tuberculosis patients; HC: healthy controls *$P<0.05$

Table 3: Analysis results of different genetic models

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In this study, we found that ELOVL2 genotype polymorphisms were significantly related to the development of tuberculosis. Specifically, we observed significant different frequencies of the rs3798719 SNP in the overdominance model between the case and control groups. According to gender stratification analysis, we found that in the overdominance model, the rs2236212 of ELOVL2 SNP is distributed statistically differently between male TB patients and healthy controls. In the homozygous and recessive models, female TB patient and healthy control genotypes differ in the frequency of the of rs3798719 of ELOVL2 SNP.

Associations of polymorphisms in ELOVL2 and susceptibility to TB have not been reported, but n-6/n-3 PUFAs had benefits for preventing the development of TB (7, 22-24). Furthermore, ELOVL2 encodes elongase 2, critical to n-6/n-3 PUFAs biosynthesis (17). An in vivo study demonstrated that the ELOVL2 gene played a key role at two penultimate steps of PUFA synthesis in Atlantic salmon (17). In addition, the levels of 22:6 n-3 and 22:5 n-6 PUFAs and cumulative level of 20:4 n-6, 20:5 n-3, 22:5 n-3 and 22:4 n-6 PUFAs were lower in an ELOVL2 partial knockout mouse model (18).

Epidemiological studies support the linkage between ELOVL2 gene polymorphisms and PUFA variation. For instance, ELOVL2 polymorphisms were significantly related to Autism spectrum disorder risk by lowering the level of long-chain polyunsaturated acids (19). Lemaitre et al. analyzed five European cohorts with a genome-wide association study (GWAS) of 8,868 individual and showed that ELOVL2 gene polymorphism was correlated with n-3 PUFAs and that rs2236212 carriers had significantly decreased levels of DHA (13). To elucidate the relationship between blood plasma concentration of PUFAs and genetic factors, 1,075 participants were included for GWAS of plasma levels of six types of n-3 and n-6 PUFAs. Besides FADS gene cluster, the strongest association region in this GWAS was chromosome 6 (ELOVL2), mapped to the region encoding long-chain fatty acid (21-23). A GWAS conducted by the Shanghai Institute of Nutrition reported that the variation of rs2281591 by ELOVL2 gene was positively cor-

### Discussion

| SNP-ID     | Genotype   | PTB   | HC   | OR(95%CI)          | χ²   | P   |
|------------|------------|-------|------|--------------------|------|-----|
| rs3798719  | dominance  | CC+CT/TT | 115 117 | 125 100 | 1.272(0.880-1.837) | 1.642 | 0.200 |
|            | recessive  | TT+CT/CC | 221 11 | 213 12 | 0.883(0.382-2.045) | 0.084 | 0.772 |
|            | additive   | CC/TT  | 115 11 | 125 12 | 0.761(0.320-1.808) | 2.024 | 0.364 |
|            | overdominance | TT+CC/CT | 126 106 | 137 88 | 1.310(0.903-1.900) | 2.023 | 0.155 |
| rs1570069  | dominance  | AA+AG/GG | 45 187 | 46 179 | 1.068(0.675-1.690) | 0.079 | 0.779 |
|            | recessive  | AG+GG/AA | 1 231 | 4 221 | 4.181(0.464-37.698) | 1.914 | 0.166 |
|            | additive   | AA/GG  | 1 187 | 4 179 | 0.997(0.623-1.595) | 1.915 | 0.384 |
|            | overdominance | AA+GG/AG | 44 188 | 42 183 | 0.981(0.613-1.568) | 0.007 | 0.935 |
| rs2236212  | dominance  | CC+CG/GG | 217 15 | 198 27 | 0.507(0.262-0.981) | 4.192 | 0.041 |
|            | recessive  | GG+CG/CC | 99 133 | 96 129 | 1.000(0.690-1.449) | 0.000 | 0.999 |
|            | additive   | CC/CG  | 99 15 | 96 27 | 0.480(0.242-0.952) | 4.532 | 0.104 |
|            | overdominance | CC+GG/CG | 114 118 | 123 102 | 1.248(0.864-1.803) | 1.399 | 0.237 |

PTB: tuberculosis patients; HC: healthy controls *P < 0.05

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related with erythrocyte membrane DPA levels, while the variation of rs3734398 was negatively correlated with DHA level (26). Despite this breadth of investigation into the link between EVOLV2 polymorphisms and PUFAs, the gene’s connection with TB has been understudied.

The relationship between the n-6/n-3 series of PUFAs and risk for TB is still elusive (7, 24-29). The ability of EPA/DHA to control the growth of M. tuberculosis has been demonstrated in animal studies, including mouse and guinea pig models (24, 25). While omega-3 fatty acids tended to increase pathogen death in an in vivo study, and omega-6 increases survival of M. tuberculosis in mice (25). Other studies have likewise reported a limited and inconclusive relationship between n-6/n-3 PUFAs and TB (21-24). Additionally, EPA has been shown to increase mycobacterial growth by reducing TNFa secretion in macrophages (26). DHA reduces the ability of J774A.1 cells to control tuberculosis in response to activation by IFNc, by modulation of IFNc receptor signaling and function (27). In contrast to these data, a recent 15-year longitudinal cohort study of 63,257 Chinese people aged 45 to 74 in Singapore showed that n-6/n-3 PUFAs reduced the risk of pulmonary tuberculosis in a dose-dependent manner (7). Thus, n-6/n-3 PUFAs targeting to M. tuberculosis could be a new assist treatment strategy to alleviate the pulmonary impairment caused by M. tuberculosis infection. However, it should be confirmed by further epidemiological studies.

To understand better the mechanism by which n-6/n-3 PUFAs influence TB, further examination of PUFAs role in inflammatory responses should be conducted. n-6/n-3 PUFAs are beneficial to host by enhancing ability to fight tuberculosis and regulate inflammation and immune factors (24, 28-31). The n-3 PUFAs have effects on immune cells function. For example, there are three main properties (production and secretion of cytokines and chemokines, the capacity of phagocytosis and the polarization into classically activated or alternatively activated macrophages) of macrophage biology that have been identified to be altered by omega-3 fatty acids (32-33). Meanwhile, Omega-3 fatty acids and their metabolites can modulate neutrophil function by neutrophil migration, phagocytic capacity, as well as the production of reactive oxygen species and cytokines (34-36). Moreover, DHA regulates placental inflammation by inhibiting the NLRP3 inflammasome and NF-κB signaling pathways (37). An in vitro study indicated that DHA and EPA reduced LPS-induced inflammation in HK-2 cells and PUFA promoted anti-inflammatory effect at the transcription level in vivo (38, 39). In a rat model of colitis, the synergistic effect of a diet rich in omega-3 PUFA and olive oil played a protective role in inflammatory bowel disease (40). Epidemiologic evidence also revealed that DHA supplements reduce serum c-reactive protein and other markers of inflammation in men with hypertriglyceridemia (41). In summary, elucidation of the mechanism between n-6/n-3 PUFAs and the risk of pulmonary tuberculosis is critical to shed lights on the supplement of n-6/n-3 series PUFAs as an intervention means to prevent tuberculosis.

Three SNPs of the ELOVL2 gene were selected for this study, which are in line with the gene frequencies of Asian population in Hapmap database. However, we only found a difference in women, not in the whole population. The low sample size (303 cases) could be one cause. A large sample size and cross validation by other groups should be used to study the relationship between ELOVL2 gene polymorphisms and the risk of TB.

Conclusion

We investigated the association of three SNP (rs3798719, rs1570069, and rs2236212) of the ELOVL2 gene with TB susceptibility. The rs3798719 SNP may be associated with susceptibility to M. tuberculosis infection in women and the rs2236212 SNP may be associated with TB occurring in male subjects.

Our study provide direct evidence for screening population with genetic susceptibility to tuberculosis, which alerts early prevention of TB. Our
work provides new avenue for the diagnosis and treatment of TB.

Ethical considerations
Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Conflict of interest
All authors declare that they have no conflict of interest.

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