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MCP1-2518 A/G Genetic Polymorphism and Susceptibility to Pulmonary Tuberculosis among Tribes of Jhargram district

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Abstract
Association of variability in the clinical outcome of persons infected with pulmonary tuberculosis (PTB) is determined by multiple factors including host genetic variations. MCP-1 has important role in protective immunity against *Mycobacterium tuberculosis*, the causative bacteria for tuberculosis. The motto of the present study is to find out whether chemokine, gene polymorphisms were associated with susceptibility or resistance to TB in the tribal population of Jhargram, West Bengal, India. Monocyte chemoattractant protein-1 (MCP-1) -2518 A/G genetic polymorphisms were studied by polymerase chain reaction based methods in pulmonary tuberculosis infected patients (n=56) with normal healthy individuals (n=60). A significantly increased frequency of GG genotype of MCP1 polymorphism was observed among PTB patients compared to healthy controls ($P<0.05$). This information recommends that GG genotype of MCP1 polymorphism is associated with susceptibility to PTB in infected patients.

Keywords: Tuberculosis, tribes, MCP1, gene polymorphism, genotype, alleles

Introduction
Tuberculosis is a major problem of developing countries like India. India, being a developing country and contain one-fourth of the worldwide tuberculosis (TB) risk (Bregani *et al*. 1013). In 2015, 28 lakh cases challenged in TB and near 4.8 lakh die due of TB in India (Raizada *et al*. 2014)) [2]. As indicated by the report of Govt. of India, tribal population is 8.6% of India's total population (Thomas *et al*. 2015) [3]. Tribal people face various health hazards including maternal and child mortality, malnutrition, tuberculosis, anaemia and other communicable and genetic diseases (Hill *et al*. 2009) [4]. As the tribes have unhygienic life-style, liquor consumption, poor financial condition, poverty make them vulnerable to different diseases (Subramanian *et al*. 2006) [5]. For these, weakness and nutritional status, different infectious and hereditary diseases like tuberculosis is exceptionally predominant to them (Thomas *et al*. 2015) [3].

Tuberculosis is the major killer disease of backward and tribal populated districts of a state. In West Bengal, the condition of Jhargram is like that (Maiti *et al*. 2011) [6].

In spite of the fact that TB is a communicable and irresistible disease, recent studies demonstrate that particular qualities with various polymorphisms show the host weakness to tuberculosis (Azad *et al*. 2012) [7]. The interaction between *Mycobacteriumtuberculosis* with environment and host genetic factors are play a crucial role in tuberculosis development (van der Eijk *et al*. 2007) [8]; Möller and Eileen 2010).

The monocyte chemoattractant protein-1 (MCP-1), additionally referred to as CCL2 (Chemokine) [C-C motif] ligand 2) present in human chromosome 17 (17q11.2). It encodes a protein of 76 amino acids with molecular weight 13 kD (Deshmane *et al*. 2009) [10]. This gene belongs in the C-C chemokine family. C-C chemokineis described by two adjoining cysteine residues near the amino terminus of the molecule. It is a powerful chemotactic factor for monocytes (Ben-Selma *et al*. 2011; Chu *et al*. 2007; Flores-Villanueva *et al*. 2005) [11, 12, 13]. They are involved in the recruitment of lymphocytes and monocytes and control migration of these cells to sites of cell injury and cellular immune reactions (Carr *et al*. 1994) [14]. MCP-1is created by the microbial stimulation; it helps in the proliferation of macrophages and T lymphocytes for controlling the TB (Serbina *et al*. 2008; Xu *et al*. 2009; Yang *et al*. 2009) [15, 17]. The increased amounts of MCP-1 were additionally identified in broncho-alveolar liquid of TB patients (Xu *et al*. 2009; Yang *et al*. 2009) [17]. There are numerous polymorphisms in the region of the MCP-1 and among them one vital polymorphism named -2518A/G (rs1024611) was commonly examined (Ben-Selma *et al*. 2011) [11]. This polymorphism is situated on the promoter region of the MCP-1 gene. There are some experiments have done to identify the relationship between the -2518A/G polymorphism with TB susceptibility (Ben-Selma *et al*. 2011; Flores-Villanueva *et al*. 2005; Xu *et al*. 2009; Yang *et al*. 2009; Alagarasu *et al*. 2009; Feng *et al*. 2011; Buijtels *et al*. 2008; Ganachari *et al*. 2010; Thye *et al*. 2009; Zhang *et al*. 2012) [11, 13, 17, 18, 19, 20, 21, 22, 23].To determine whether these genes have susceptibility to TB, this study has performed to know the role of MCP-1 polymorphism intuberculosisof TB infected population and non-TB population.

Materials and Methods
Patients
Hundred sixteen individuals from Jhargram District were recruited for this study. Among them fifty six individuals are patient of pulmonary tuberculosis (PTB) and sixty individuals are healthy non-tuberculosis people. Diagnosis of PTB patients were based on laboratory and clinical data. TB patients are affirmed by sputum smear positivefor *M. tuberculosis* and chest X-ray detection relying upon World

Health Organization (WHO) and Renewed National Tuberculosis Control Programme (RNTCP) standard (Muniyandi *et al*. 2015) [24]; WHO 2011). Most of the patients were under the therapy with anti-tuberculosis drugs and DOTS treatment (D'souza *et al*. 2009). Informed written consent wastaken from all the participants and this study was approved by the ethical committee of Vidyasagar University, Paschim Medinipur, West Bengal.

Sample collection and DNA isolation

Peripheral blood samples were collected in EDTA coated vials (HiAnticlot PW131, Himedia, India). Genomic DNA was extracted by utilizing the blood genomic isolation kit (MB504-250PR, Himedia, India) and then the purified DNA was kept in -20°C. Quantity and purity were determined by spectrophotometry.

Assay

This is the pioneer work on MCP1 for tuberculosis in Jhargram district of West Bengal. Genotyping was performed by 3-stepsPolymerase Chain Reaction (PCR) in Applied Biosystem thermal-cycler and it is followed by Restriction Fragment Length Polymophism (RFLP) and then 2% Agarose gel electrophoresis.

MCP-1 genomic variants were detected by polymerase chain reaction followed by restriction enzyme fragment analysis. MCP1 is a 930-bp fragment shown in Table 1. Extracted DNA samples were amplified to obtain fragments including the polymorphic region -2518A/G by designing primers. The following primers were used: forward 5′-CCGAGATGTTCCCAGCACAG-3′ and reverse 5′-CTGCTTTGCTTGTGCCTCTT-3′. Polymerase chain reaction (PCR) was carried out under the following conditions: initial denaturation at 94°C for 5 minute, followed by 35 cycles of denaturation at 94°C for 30 sec, annealing at 56 °C for 1minute, extension at 72°C for 1minute and a final extension at 72°C for 7 minute. A PCR restriction fragment length polymorphism (RFLP) assay was applied to identify the genotypes of 2518A/G CCL2 polymorphism. The product was digested with PVUII restriction endonuclease(NEB #R0151, New England Biolabs, Beverly, MA)at 37°C for 24 hours.The resulting product separated on 2%agarose gel and visualized them using ethidium bromide staining and ultraviolet light(Gel Documentation System, Biorad).PvuII digested the 930bp long chain into 708bp and 222bp fragments.Samples with a single 930bp band were identified as A/A, samples with 3 bands of 930bp, 708bp, and 222bp were typed as A/G and those with 2 bands of 708bp and 222bp were typed as G/G genotype (Rovin *et al*. 1999; Tucci *et al*. 2004) [27, 28].

Table 1: Details of the primers, restriction endonucleases used for the MCP1 2518A/G polymorphism study

Gene and polymorphism	Primers	Fragment length	Annealing temperature	Restri-ction enzyme used	Homozygote polymorphic (bp)
MCP1 2518A/G	5′-CCGAGATGTTCCCAGCACAG-3′ 5′-CTGCTTTGCTTGTGCCTCTT-3′	930bp	56°C	PvuII	930, 708, 222

Statistical analysis

All data were analysed by SPSS 20.0 software (IBM Corporation, Somers, NY, USA). Data were expressed as mean ± standard deviation (x±SD) and chi square test was done for the homogeneity distribution of these tuberculosis and non-tuberculosis group. Genotype frequencies comparisons between groups were presented as Odds Ratio (OR) and 95% Confidence Interval (CI). All P values were two-sided and the level of significance was set at $P<0.05$.

Result

The gene MCP1 2518A/G (rs1024611) is situated in human chromosome17 (chr.17q11.2) (Singh *et al*. 2014). Another name of MCP1 is CCL2 or CC- chemokine motif-2 which is the first human chemokine discovered (Van Coillie, Van Damme and Opdenakker 1999). This MCP1 -2518A/G can be digested by the enzyme PvuII. The restriction endonuclease is an isoschizomer and high fidelity enzyme. The sequence of this enzyme is

5'….C A G ↓ C T G….3'

3' ….G T C ↑ G A C….5'

This gene MCP1 2518A/G is digested by PvuII endonuclease and provides three polymorphic bands for different alleles. After the digestion of PvuII, genotyping of MCP1 2518 A/G polymorphism show 708bp and 222bp fragments which indicates heterozygous and homozygous GG genotype respectively. That means when an individual has GG genotype, the MCP1 -2518A/G gene will give two bands, those are 708bp and 222bp regions. But AA genotype does not digested by the enzyme and it has the only 930bp band. The total length of this polymorphism is 930bp, as the homozygous A allele does not digested by the enzyme PvuII, it remain its total length of 930bp. Thus the individual who possesses this AA genotype provide only single band under UV ray in agarose gel electrophoresis. While AG heterozygous shows three fragments, those are 930bp, 708bp and 222bp bands. The AG heterozygous individuals possess both A and G allele. As these two alleles are present, it gives all the bands after digestion, both 930bp region for A allele and 708bp, 222bp regions for G allele (Fig 1).

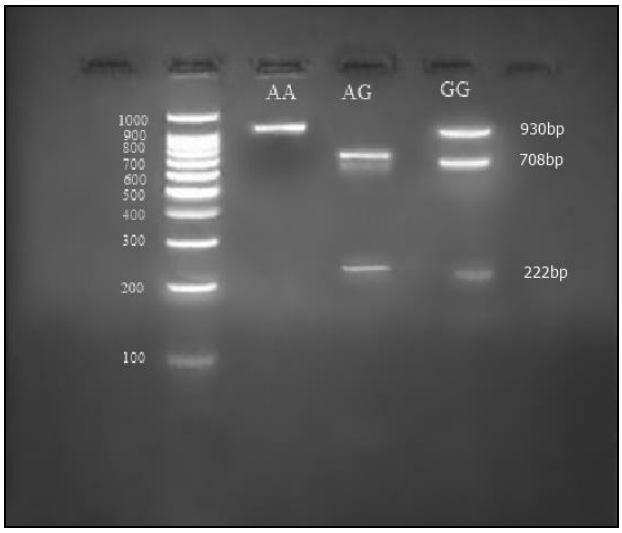

Fig 1: The electrophoresis of gene MCP1 -2518A/G after enzymatic digestion (PvuII) and PCR product

Statistical analysis

χ^2 test was used for comparison of the allelic/genotypic distribution of MCP1 -2518A/G polymorphism in non-

tuberculosis and tuberculosis population as expected and observed frequencies of categorical variables clearly shows statistically significant values ($p<0.05$). The chi-square test is made to determine where the populations are similar or equal or homogenous in characters because random sampling has done for this meta-analysis.

This meta-analysis was done to evaluate the relationship among the MCP1 -2518A/G polymorphisms susceptibility to tuberculosis. A meta-analysis is formal, quantitative study with epidemiological analysis used systematically to evaluate the health survey of the community from various aspects. It includes more precise estimation of the effect of risk factors for disease and quantitative review of the research work (Haidich 2010) [67].

Table 2: Genotype distribution of MCP1 -2518A/G for TB and non-TB individuals

Occurrence of tuberculosis	Polymorphism of MCP1 Gene		
	AA	AG	GG
Tuberculosis	23	19	14
Non-tuberculosis	34	22	4

Suppose, Null hypothesis (H_0) = not homogeneous distribution of tuberculosis and non-tuberculosis individuals (Occurrence of tuberculosis and polymorphism of MCP1 gene are independent)

Alternative hypothesis (H1) = homogenous distribution of tuberculosis and non-tuberculosis individuals (Occurrence of tuberculosis and polymorphism of MCP1 gene are associated)

Here, chi-square test for homogeneity is applied to calculate the degrees of freedom of sample data, p-value association, expected frequency counts etc. with this statistical analysis. The P-value is determined on the basis of chi-square statistic and the degrees of freedom. After the calculation the degrees of freedom (DF) is 2 from Table2 and Chi square value is 7.11. The computed χ^2 is 7.11 which is higher than the critical χ^2 value for0.05 level ($\chi^2_{0.05(2)}$=5.99). Hence, the computed χ^2 is considered significant. We reject the null hypothesis and conclude that the 'occurrence of tuberculosis' and 'polymorphism of MCP1gene' are not independent i.e.; they are associated ($p<0.05$).

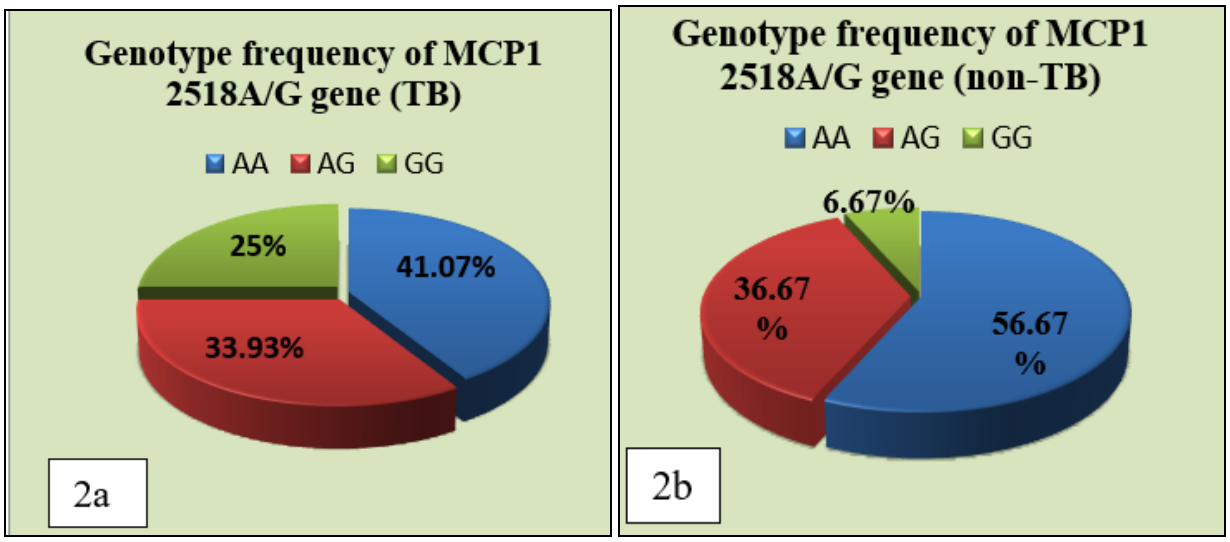

Fig 2 (a, b): Percentage distribution of genotype frequency in MCP1 -2518A/G gene of TB patients and non-TB individuals

The Fig 2(a) shows the percentage distribution of genotype frequency of MCP1 -2518A/G gene of tuberculosis infected individuals. Here 25% are homozygous G allele, 33.93% are heterozygous for both A and G allele and 41.07% is homozygous A allele.

Fig 2(b) shows the percentage distribution of genotype frequency of MCP1 2518A/G gene of non- TB individuals. Where 6.67% are homozygous G allele and 56.67% are homozygous A allele. 36.67% contain both A and G allele in heterozygous condition.

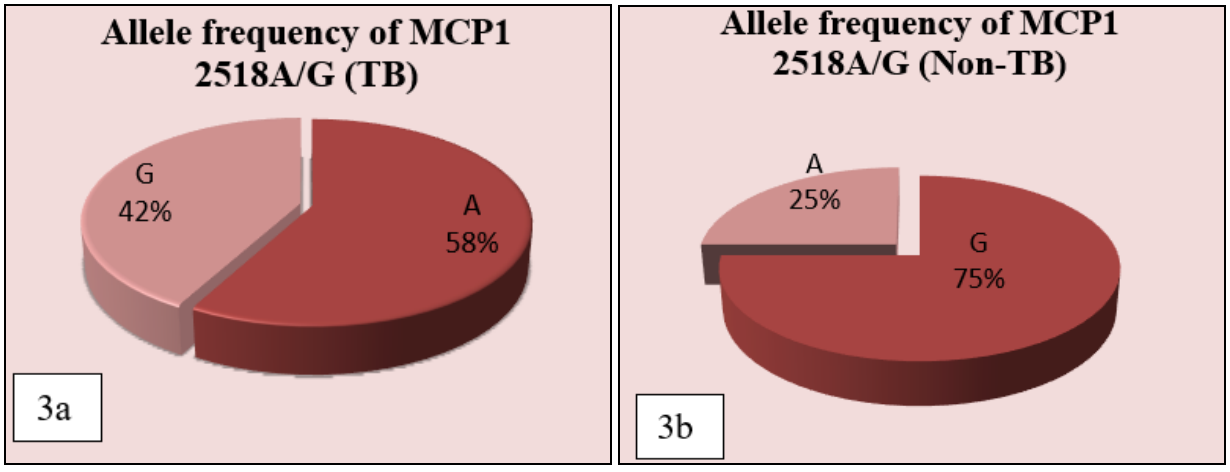

Fig 3 (a,b): Percentage distribution of allele frequency of MCP1 -2518A/G gene of TB patients and non-TB individuals

Fig 3 elucidates the percentage distribution with regard to gene frequency of MCP1 -2518A/G of TB and non-TB individuals. Fig 3(a) shows 58% of A gene and 42% of G gene in tuberculosis individuals. Whereas, Fig 3(b) shows 75% A gene and 25% of G gene is present in non-TB individuals. From this Fig 3, the percentage of G gene (42%) in TB individual is more than the G gene (25%) in non-TB individual.

Table 3: Percentage and frequency distribution of genotypes of TB and non-TB individuals

For pulmonary tuberculosis individuals	**Number of individuals (n)**	**AA (n=23)**	**AG (n=19)**	**GG(n=14)**
	Percentage	(23×100)/56=41.07%	(19×100)/56=33.93%	(14×100)/56=25%
	Frequency	0.41	0.33	0.25
For non-tuberculosis individuals	Number of individuals (n)	AA (n=34)	AG (n=22)	GG(n=4)
	Percentage	(34×100)/60=56.67%	(22×100)/60=36.67%	(4×100)/60=6.67%
	Frequency	0.56	0.36	0.06

Among the total population of pulmonary tuberculosis infected individuals, the G allele is present 33.93% in heterozygous condition and homozygous G allele is present at 25% from Table 3. As the G allele is responsible for pulmonary tuberculosis susceptibility, the chance of G allele in PTB individual is 33.93% + 25% = 58.93%. Homozygous A allele is present in 41.07% and heterozygous A allele in 33.93%. As the G allele is responsible for TB vulnerability, so, it is important to calculate the percentage of G allele only.

In the non-tuberculosis individual, the homozygous A allele is 56.67% and heterozygous A allele is 36.67%. Whereas the deleterious G gene is present 36.67% in heterozygous condition and 6.67% in homozygous condition. So, the chance of G allele in non-TB individual is 36.67% + 6.67% =43.34%.

From this Table3, it is shown that 43.34% of non-TB individual has G allele whereas 58.93% of TB infected individual contain G allele. So, it is clear from this Table 3, that the G allele is more susceptible in TB individuals than non-TB individuals.

Odds ratio and confidence interval

An odds ratio (OR) is a measure of the relationship between an introduction (exposure) and a result (outcome). It is a chance proportion of population study. The OR shows to the odds that an outcome will happen given a specific exposure, contrasted with the odds of the result or outcome happening in the absence of that particular exposure or presentation (Bland and Altman 2000).

In statistics, a confidence interval (CI) is an interval which estimates (of a population parameter) the calculation from the observed data. The confidence level is the frequency (i.e., the proportion) of possible confidence intervals that contain the true value of their corresponding parameters (Nakagawa and Cuthill 2007) [44], Tangwongcharoen and Titiroongruang 2017).

OR>1 means positive relationship in between disease and genotype

OR<1 means negative relationship in between disease and genotype.

An Odds Ratio (OR) is a measurement of association between certain property (genotype) and another property (disease) in a population. The OR is also used to Fig out if a particular exposure (tuberculosis) which is a risk factor present or not.

At first, it is need to calculate the odds that the population has particular genotype and assume the person already has disease (tuberculosis). Next step, it is need to calculate the odds that the population has particular genotype but the persons do not have the disease tuberculosis. After that these two groups are compared.

Table 4: The odds ratio and confidence interval of MCP1 genotype GG is associated with development of pulmonary tuberculosis

MCP1	**Tuberculosis patients (N=56)**	**Healthy tuberculin negative individuals (N=60)**	**p- value**	**OR**	**95% CI**
	n (frequency)	n (frequency)			
AA	23 (0.41)	34 (0.56)	-	1	-
AG	19 (0.34)	22 (0.37)	0.554	1.27	0.56-2.87
GG	14 (0.25)	4 (0.07)	0.009	5.17	1.51-17.71

Odds Ratio (OR) is a population parameter. Here, the odds ratio (OR) is used to determine whether the particular genotype GG is a risk factor for the particular disease tuberculosis. 95% confidence interval (CI) is used to estimate the accuracy of OR. 95% confidence interval reflects a significance level of 0.05 (White *et al.* 2011, Szumilas 2010) [64].

Our result shows that the GG genotype was strongly associated with active tuberculosis patients (41% vs. 25%, *p* =.009) in comparison to the healthy non-tuberculosis group. The Table 4 shows that the bad exposure that is tuberculosis patients as exposed group (GG genotype; n=14) and normal group (AA genotype; n=23) are compared with the good outcome that means non-tuberculosis individuals which belongs the exposed group (GG genotype; n=4) and normal group (AA genotype; n=34). The resulting Odds Ratio is 5.17 at p<0.01 level.

95% Confidence Interval (CI) is under 1.51-17.71. An odds ratio more than 1 means there is a positive relationship between tuberculosis and GG genotype. As the comparative values of OR of GG and AA genotype is statistically significant, it means the exposed GG genotype positively related for TB.

Beside this homozygous GG genotype, the heterozygous G (AG) also has deleterious effect. So, the AG genotype is considered as exposed group. In tuberculosis, exposed group (AG genotype; n=19) and normal group (AA genotype; n=23) is compared with non-TB individuals, exposed group (AG genotype; n=22) and normal group (AA genotype; n=34). The resulting OR is 1.27 without significant level and 95% confidence interval is 0.56-2.87. Although the comparative values of AA and AG genotypes is 1.27 but it is not accepted because the p value is 0.554 which is far more than the normal value of 0.05 level of significance.

Table 5: The odds ratio and confidence interval for allele G of the MCP-1 is associated with development of pulmonary tuberculosis

MCP1	Tuberculosis patients (N=56)	Non-tuberculosis individuals (N=60)	p- value	OR	95% CI
	n (frequency)	n (frequency)			
A	65 (0.58)	89 (0.74)	-	1	-
G	47 (0.42)	31 (0.25)	0.009	2.075	1.19-3.61

When gene frequency is considered, the G allele of MCP1 -2518A/G was strongly associated with active tuberculosis patients (0.42% vs. 0.25%, p =0.009) in comparison to the healthy tuberculosis-negative group. In Table 5, G gene is considered as deleterious gene. It shows that the exposed group (G gene; n=47) and normal group (A gene; n=65) of tuberculosis patients are compared with the exposed group (G gene; n=31) and normal group (A gene; n=89) of non-TB individuals. The resulting Odds Ratio is 2.075 at p<0.01 level. 95% Confidence Interval (CI) is under 1.19-3.61. An odds ratio more than 1 means there is a positive relationship between tuberculosis and G gene. So, the G allele of MCP1 -2518A/G was more common to the tuberculosis patients compared to healthy non-TB individuals. So, it can be concluded that the G allele is responsible for the progression of TB infection.

Our result shows strong evidence that, the allele G and genotype GG of MCP1 2518A/G is associated with increased risk of tuberculosis disease to the tribal group of Jhargram.

Discussion

The distribution of MCP1 -2518A/G genotypes are AA, AG and GG (Figure2b) observed in normal healthy people was 56.67%, 36.67% and 6.67% respectively, compared to 41.07%, 33.93% and 25% in PTB patients (Figure2a). The allele frequency of wild type A allele was found to be 75% in normal against 58% in cases while as variant allele (G) frequency was seen as 25% in normal and 42% in PTB respectively (Figure3a&b). Chi-square test was used for comparison of the allelic/genotypic distribution of MCP1 -2518A/G in normal and PTB population. Expected and observed frequencies of categorical variables clearly showstatistically significant values (p<0.05).G allele and GG genotype of MCP1 were significantly increased in patients which appear to be risk factors, as compared to those of normal individuals. This study is compared with the studies showing increased risk for MCP1 (-2518A/G) GG genotype and G allele of tuberculosisin the population of Zambia, Tunisia (Azad *et al*. 2012) [7]. Association of GG genotype of MCP1 -2518 A/G polymorphism with susceptibility to PTB and it has been shown in Korean and Mexican PTB patientsand also in Asian and South American population (Flores-Villanueva *et al*. 2005; Feng *et al*. 2012) [13, 29]. The MCP1 GG genotype not only associates with PTBsusceptibility, this genotype has capable of other diseases like urinary bladder cancer (Pandith *et al*. 2013) [30], endometrial cancer (Attar *et al*. 2010) [31], nasopharynx-cancer (Tse *et al*. 2007) [32], Alzheimer's disease (Fenoglio *et al*. 2004) [33], HIV associated dementia (Gonzalez *et al*. 2002) [34] in India and many other countries.

The Table 4 and 5 shows the G allele of MCP1 was more common to the tuberculosis patients compared to the healthy non-TB individuals. So, it can be concluded that the G allele is responsible for the progression of TB infection. This result revealsstrong evidence that the allele G and genotype GG of MCP1 -2518A/G are associated with increased risk of tuberculosis disease to the tribal people of Jhargram. This data shows significant level of homogeneity chi-square value at p<0.05 significant levels.

MCP1 -2518 A/G is associated with the increased susceptibility to tuberculosis and it inhibits the cytokine IL12p40 production (Dorman and Holland 2000; van de Vosse *et al*. 2004; Casanova *et al*. 2002; Ottenhoff *et al*. 2002) [35, 36, 37, 38]. This interleukin help in the IFN-γ induced protection from tuberculosis (Edwards *et al*. 2012) [39]. Khader *et al*. (2006) [40] demonstrated the IL-12p40 help in the initiation of T cell response and T cell activation on microbial attack to the lung. The key component of tuberculosis is initiated T cell activation and the induction of chemokine reacting quickly and positively in dendritic cells. The GG genotype of MCP1 is the highest MCP1 plasma levels and lowest IL12p40 plasma concentrations in tuberculosis patients (Ben-Selma *et al*. 2011; Xu *et al*. 2009; Edwards *et al*. 2012; Cooper *et al*. 2007) [11, 39, 41]. Monocyte is the major source of MCP1 and IL12p40 but the plasma levels of these two molecules are negatively correlated (Ben-Selma *et al*. 2011) [11]. Flores-Villanueva *et al*. (2005)) [13] found that there was a significant negative correlation between these two molecules by ELISA test.

After this study, it is observed that the significant association of the MCP1 susceptibility, allele G with disease progression in tribes of Jhargram (OR 2.075, 95% CI 1.19-3.61) (Table5). More production of MCP1 suppresses IL-12p40 production which is responsible for deriving the IFNγ response. IFNγ is a chief macrophage activating cytokine and it acts as a basic molecule in protection against *Mycobacteria* (Hussain *et al*. 2011) [42].

At first a healthy individual is contaminated from an infected individual by the aerosol transmission of droplets containing *M.tuberculosis*. Within lungs, *M.tuberculosis* enters and resides in the alveolar macrophages and dendritic cells (Cooper 2009; Wolf *et al*. 2007) [43, 44]. When *M.tuberculosis*interacts with these alveolar macrophage and dendritic cells, various cytokines including Tumor Necrosis Factor-α(TNF), interleukin (IL) 12release (Seder *et al*. 1993; Oppmann *et al*. 2000; Sasindran and Torrelles 2011)) [45, 46, 47]. IL-12 accelerates the capability to naive $CD4^+$ T cells which develop IFNγ production. This data shows that IL-12 has great effect on the inductive phase of T-cell by enhancing the IFNγ production which influences the immunity (Seder *et al*. 1993) [45]. Dendritic cells infected with *M. tuberculosis* in lung, move to lymph node and help in better T-cell activation (Khader *et al*. 2006; Demangel *et al*. 2002) [40, 48]. The infection of cytokines and activation of the different $CD4^+$T cell subpopulations indicate the protection in tuberculosis which are activated in the initial phase of infection produces cytokines like IL-12p40, IFNγ (Jung *et al*. 2005; Fan *et al*. 2012) [49, 50].

Non-activated macrophages are the usual habitat of *M. tuberculosis*, which block the phagosome fusion with lysosome, thus avoiding itsdestruction (Cooper and Khader. 2008; Cavalcanti *et al*. 2012) [51, 52]. IFNγ activated macrophages invert this blockage, form phagolysosomes and able to eliminate the bacteria from the infection sites (Lawn *et al*. 2009) [53]. The 19KD lipoprotein and *M.*

Tuberculosis components influence to the production of IL-12 by macrophages, then mobilizing the Th1 cytokine pathway (Cavalcanti *et al*. 2012) [52]; Gehring *et al*. 2003; Pai *et al*. 2003) [54, 55].

There are various clinical and experimental cases have been done for the understanding of IFNγ production for the control of tuberculosis (Tavares *et al*. 2006; Nienhaus *et al*. 2008; Costa *et al*. 2010) [56, 57, 58]. One of the main functions of IFNγ is the activation of macrophage and they apply microbicidal activities. It also helps in the enhancement of major histocompitibility complex class I and class II and stimulates the differentiation of $CD4^+$T cell to Th1 subpopulation (Flesch *et al*. 1995; Fenton *et al*. 1997; Oberholzer *et al*. 2000) [59, 60, 61]. IFNγ transcribes many genes of macrophages including oxygen free radical, nitric oxide- these help to eliminate *M.tuberculosis* (Cooper 2009) [43].

IL-12p40, IFNγ help in generation of Th1 cells, action of macrophages and elimination of bacteria. Interferon-γ (IFNγ) is important for defence mechanism against *Mycobacterium tuberculosis (*Adewole *et al*. 2013) [62]. Th1 response is essential for effective immunity against *Mycobacterium.* This response is directed by IFNγ secreting CD_4^+ T cells. This CD_4^+ T are presented with processed *Mycobacterium* antigens by dendritic cells and macrophages, which also secrete IL-12 and induce Th1 response (Adewole *et al*. 2013; Moura *et al*. 2004) [62, 63]. According to Hussain *et al*, (2010) [64] IFNγ level was high in both clinically diagnosed and confirmed TB patients as compared to a control group.

The present investigation explores the role of chemokine gene variants in susceptibility to tuberculosis of tribal people in Jhargram District of West Bengal. Genetic factors sometimes play an important role in determining the progression from latent period to active disease in tuberculosis of endemic countries. Various factors are responsible for tuberculosis in different polymorphisms.

When we study the population dynamics and geographical distribution of genomic sequences in human kind, it is quite feasible to construct phylogenetic trees. It provides us the scope to build a better interrelation between human and *M. tuberculosis* evolutionary paths (Barnes *et al*. 2011;Comas *et al*. 2010) [65, 66].

Accumulation of high frequencies genes which leads to increase in functionally relevant variants could either reduce the resistance to tuberculosis of human or hold a balance of its evolutionary pathways. Polymorphisms enhance the ability to protect against tuberculosis whereas homozygotic selection puts a species at high risk of TB and other diseases. The deeper understanding of these studies might explore newer avenue of PTB diagnosis (Parwati *et al*. 2010; Miller 2009) [67, 68].

As the human are diploid organisms and these two copies are expressed at same level or sometimes not (Serre *et al*. 2008) [69]. So this change may due to allelic expression imbalance (Zhang *et al*. 2005) [70].The cis-acting mutations may alter the regulation for one allele through a change to promoter or enhancer regions or even through 3′ UTR mutations that affect mRNA stability or microRNA binding and their role in association with a wide spectrum of inflammatory diseases (Pham *et al*. 2012) [71].

It is very important that there are gene-gene interactions in between human and *M. tuberculosis* strains. Not only that the environmental factors has great influence on both of host pathogen interaction it also depends on thefactors related with ethnicity, cultural, and geographic distributions of both human and the bacteria (Pham *et al*. 2012; Schmidt 2008**;** Khaliq *et al*. 2015)) [71, 72, 73]. That's why there are many polymorphisms and allele frequencies are found and different results also found in different places throughout the world.

Conclusion

This is very important to know the genetic and epigenetic relationship in the tuberculosis disease to develop the detection, conformation and control of this disease. The identification of functional genetic polymorphisms is very important tool for assessment of TB risk and yield next generation biomarker. In conclusion it is very important to know about the genetic cause and evolution of tuberculosis for both the pathogen and host. To control of TB in a particular region to diagnose the both genetic and environmental cause with the improvement of health care facilities, socioeconomic status as well as common welfare of poor tribal people. These should help to tackle this global problem successfully for mankind.

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