CD209 Genetic Polymorphism and Tuberculosis Disease

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Background. Tuberculosis causes significant morbidity and mortality worldwide, especially in sub-Saharan Africa. DC-SIGN, encoded by CD209, is a receptor capable of binding and internalizing Mycobacterium tuberculosis. Previous studies have reported that the CD209 promoter single nucleotide polymorphism (SNP)-336A/G exerts an effect on CD209 expression and is associated with human susceptibility to dengue, HIV-1 and tuberculosis in humans. The present study investigates the role of the CD209 -336A/G variant in susceptibility to tuberculosis in a large sample of individuals from sub-Saharan Africa. Methods and Findings. A total of 2,176 individuals enrolled in tuberculosis case-control studies from four sub-Saharan African countries were genotyped for the CD209 -336A/G SNP (rs4804803). Significant overall protection against pulmonary tuberculosis was observed with the -336G allele when the study groups were combined (n = 914 controls vs. 1,262 cases, Mantel-Haenszel 2x2 \( \chi^2 = 7.47, P = 0.006, \) odds ratio \( R = 0.86, 95\% CI 0.77–0.96 \)). In addition, the patients with -336GG were associated with a decreased risk of cavitary tuberculosis, a severe form of tuberculosis disease (n = 557, Pearson’s 2 \( \chi^2 = 17.34, P = 0.00003, \) odds ratio \( R = 0.42, 95\% CI 0.27–0.65 \)). This direction of association is opposite to a previously observed result in a smaller study of susceptibility to tuberculosis in a South African Coloured population, but entirely in keeping with the previously observed protective effect of the -336G allele. Conclusion. This study finds that the CD209 -336G variant allele is associated with significant protection against tuberculosis in individuals from sub-Saharan Africa and, furthermore, cases with -336GG were significantly less likely to develop tuberculosis-induced lung caviation. Previous in vitro work demonstrated that the promoter variant -336G allele causes down-regulation of CD209 mRNA expression. Our present work suggests that decreased levels of the DC-SIGN receptor may therefore be protective against both clinical tuberculosis in general and cavitary tuberculosis disease in particular. This is consistent with evidence that Mycobacteria can utilize DC-SIGN binding to suppress the protective pro-inflammatory immune response.

Citation: Vannberg FO, Chapman SJ, Khor CC, Tosh K, Floyd S, et al (2008) CD209 Genetic Polymorphism and Tuberculosis Disease. PLoS ONE 3(1): e1388. doi:10.1371/journal.pone.0001388

INTRODUCTION

Mycobacterium tuberculosis infection causes significant morbidity and mortality throughout the world, particularly in resource-poor countries. M. tuberculosis infects one third of the human population and approximately two million persons die of tuberculosis every year [1]. Over the next 20 years the WHO estimates that another billion people will become newly infected with M. tuberculosis and more than 25 million will die from the disease, despite the availability of antibiotics [2,3]. In sub-Saharan Africa, the rates of tuberculosis range from 50 to greater than 300 per 100,000 individuals [2]. It is now well-established that there is a host genetic component to susceptibility to tuberculosis [4]. Evidence to support this includes the observation of familial clustering of disease with higher concordance of tuberculosis disease in monozygotic versus dizygotic twins [5], the ethnic clustering of tuberculosis disease with a higher prevalence of tuberculosis in individuals of recent African descent [6], as well as the demonstration of both common polymorphisms and rare mutations which confer susceptibility to mycobacterial species in humans [7].

Dendritic Cell-Specific ICAM3-Grabbing Non-integrin (DC-SIGN), encoded by CD209 on chromosome 19p13.3, is a C-type lectin that is expressed on subsets of dendritic cells (DCs) and alveolar macrophages [8–10]. DC-SIGN has been demonstrated to bind a variety of ligands [11]; endogenous ligands include endothelial cells through ICAM-2, T-lymphocytes through ICAM-3, neutrophils through MAC-1 and various endogenous glycosylated structures [11–15]; exogenous ligands include glyco-sylated moieties on M. tuberculosis, M. leprae, Bacillus Calmette-Guérin (BCG), Helicobacter pylori, Streptococcus pneumoniae, Klebsiella pneumoniae, HIV-1, HIV-2, SIV-1, Dengue virus, Ebola Virus, Cytomegalovirus, Hepatitis C virus, Schistosoma mansoni, Leishmania pifanoi and Candida albicans [10,16–28] (and reviewed in [29]).

DC-SIGN is a major receptor for M. tuberculosis on immune cell subsets and has been shown to bind mannosylated liposalubronanman (ManLAM) present on virulent, but not avirulent, strains of Mycobacterium spp. [13]. This binding can lead to internalization of...
M. tuberculosis and infection of DCs and alveolar macrophages [22]. DC-SIGN may also have additional roles in suppressing Toll-like receptor (TLR) signaling, thereby influencing Th1/Th2 balance (proinflammatory/anti-inflammatory) and causing M. tuberculosis-induced immune suppression [22,29]. This effect is mediated by ManLAM and increased secretion of ManLAM from Mycobacteria may be crucial to tuberculosis disease progression [29].

There has been considerable recent interest in the role of CD209 variation in human susceptibility to infectious diseases including M. tuberculosis and M. leprae, HIV-1, and Dengue [18,30–32]. All but the M. leprae case-control study found an association of the CD209 -336A/G promoter SNP with infectious disease susceptibility or protection. Martin and colleagues demonstrated that the -336G allele was associated with susceptibility to parental and non-parental HIV-1 infection, although this was not replicated in individuals of recent African descent [31]. Sakuntabhai and colleagues found that the -336G allele was protective against Dengue fever versus Dengue hemorrhagic fever, but not against controls [32]. Barreiro and colleagues found an association between the -871G and -336A alleles and protection against tuberculosis in South African Cape Coloureds, but not against leprosy in Pakistan [18,30]. Although the CD209 -871 SNP was found to be the polymorphism most significantly associated with tuberculosis susceptibility in the South African Cape Coloureds, Barreiro and colleagues found that this SNP is not polymorphic in other African countries. The relatively high prevalence of the -871 SNP in the South African Cape Coloureds cases and controls is due to their inherent admixture with European and Asian populations.

Sakuntabhai and colleagues also presented evidence that the CD209 -336G allele disrupts a potential SP-1-like transcription factor binding site and that this allele is associated with lower expression of M. tuberculosis binding and signaling events, and in an attempt to replicate the findings of Barreiro and colleagues in a larger population, we genotyped the CD209 -336A/G SNP in five tuberculosis case-control studies from four different sub-Saharan African countries.

**METHODS**

**Sample Information**
The tuberculosis case control studies from The Gambia (A), Republic of Guinea and Guinea Bissau [33], The Gambia (B) [34], and Malawi [35] have been previously described in detail. Briefly, tuberculosis case definitions for all studies depended upon confirmation of M. tuberculosis positivity by culture, smear, or histology. HIV-1 testing was routinely performed and the percentage of HIV-1 positive individuals among the tuberculosis index cases and controls for the various studies are as follows: The Gambia (A), cases 7.5%, controls 5.2%; Republic of Guinea, cases 9.0%, controls 5.1%; Guinea Bissau, cases 23.8%, controls 16.2%; Malawi, cases 62.2%, controls 33.5%. The Gambia (B) cohort has 330 confirmed HIV-1 negative tuberculosis cases, with an additional 17 cases which were not tested for HIV-1.

**Statistical Analysis**
Statistical analysis of genotype associations and logistic regression was performed using the program SPSS v14.0. The genotypic and allelic tests of association utilized Pearson’s chi-square test with the respective degrees of freedom. All statistics are two-tailed. If the unadjusted $P$ value was significant then further analysis was carried out using a stepwise forward binary logistic regression correction to adjust for the potential confounding factors of HIV status, age, ethnicity, and sex. Mantel-Haenszel for the combined analysis was performed using SPSS by weighting cases by frequency and stratifying by population. The Gambian (B) study utilizes the Gambian (A) study controls for this Mantel-Haenszel analysis. The Breslow-Day and Tarone’s tests for homogeneity of odds ratios were found to be non-significant indicating that the odds ratio for each study did not significantly deviate from the overall, combined odds ratio. All control genotype distributions were in Hardy-Weinberg equilibrium ($P>0.20$).

**RESULTS**
The CD209 -871A/G and -336A/G SNPs were initially genotyped in 329 tuberculosis cases and 327 control individuals from The Gambia (study group A) [33]. The CD209 -871 SNP was found to be associated with a decreased risk of tuberculosis in The Gambia (A) [33]. The overall odds ratio for the combined analysis was 0.70 (95% CI 0.51–0.96, $P=0.029$).

The -336A allele was found to be the polymorphism most significantly associated with tuberculosis susceptibility in the South African Cape Coloureds, Barreiro and colleagues found that this SNP is not polymorphic in other African countries. The relatively high prevalence of the -871 SNP in the South African Cape Coloureds cases and controls is due to their inherent admixture with European and Asian populations.
be polymorphic with controls and cases both having a 2.3% allele frequency (allelic \( P = 0.98 \)) consistent with the Barreiro result [30] and the HapMap project which found variation at this SNP to be very rare to absent in individuals of African descent. The allelic equivalence between cases and controls and the rarity of this SNP precluded genotyping in further populations. For the CD209 -336A/G SNP, however, an overall genotypic association with clinical tuberculosis was observed for this cohort (3x2 \( \chi^2 \), 2 degrees of freedom) for CD209 -336A/G (rs4804803) from 2176 individuals enrolled in tuberculosis case control studies from The Gambia (A), Republic of Guinea and Guinea-Bissau (ref. 33), The Gambia (B) (ref. 34) and Malawi (ref. 35). Significance levels of \( P < 0.05 \) is indicated in bold.

Table 1. CD209 -336A/G SNP in Patients Enrolled in Tuberculosis Case Control Studies in Four Countries

| Variant | The Gambia | Republic of Guinea | Guinea-Bissau | Malawi |
|---------|------------|--------------------|--------------|--------|
|         | Cases (A)  | n = 329            | n = 151      | n = 162 | n = 244 |
|         | Controls   | n = 327            | n = 180      | n = 141 | n = 295 |
| AA      | 26.7       | 28.0               | 22.0         | 32.7    | 43.5    |
| AG      | 52.6       | 48.1               | 48.0         | 39.5    | 42.6    |
| GG      | 7.7        | 6.9                | 30.0         | 27.8    | 13.9    |
| \( \chi^2 \) | 7.79 | –                  | 0.24         | 2.71    | –       |
| \( P \) value | 0.020 | 0.097              | …            | 0.258   | –       |

Genotypic frequency and genotypic association (3x2 \( \chi^2 \), 2 degrees of freedom) for CD209 -336A/G (rs4804803) from 2176 individuals enrolled in tuberculosis case control studies. The Gambia (A), Republic of Guinea and Guinea-Bissau (ref. 33), The Gambia (B) (ref. 34) and Malawi (ref. 35). Significance levels of \( P < 0.05 \) is indicated in bold.

CD209 and clinical correlates of tuberculosis

The CD209 -336A/G SNP was further examined in the cases for association with clinical correlates of tuberculosis, with no significant difference between sex, HIV status, age, haemoptysis, number of zones affected on chest radiograph, duration of cough or degree of sputum positivity. However, a significant association was obtained between CD209 -336GG genotype status and lung cavitation in tuberculosis patients. Patients homozygous for the CD209 -336GG allele were associated with 2.4-fold protection against cavitary tuberculosis disease (\( n = 557 \), Pearson’s \( \chi^2 = 17.34, P = 0.00003 \), odds ratio = 0.42, 95%CI 0.27–0.65, \( \chi^2 \) Bonferroni corrected = 1.19*10^{-4}) (Figure 1 and Table 3).

DISCUSSION

There is increasing evidence to support an important role for DC-SIGN in the pathophysiology of a number of infectious diseases, including M. tuberculosis infection.

Functional evidence suggests that the -336G variant has lower basal expression of CD209 when compared to the -336A ancestral allele [32]. Extrapolation of these in vitro experiments to in vivo CD209 expression suggests that -336G individuals would have lower levels of DC-SIGN on DCs and alveolar macrophages when compared to -336A individuals. Barreiro and colleagues found an association with the -336A allele and protection against tuberculosis and suggest that higher levels of DC-SIGN may be beneficial in protection against tuberculosis disease.

Table 2. CD209 -336A/G SNP Allelic Association in Tuberculosis Case Control Studies

| Variant | The Gambia (A) | The Gambia (B)* | Republic of Guinea | Guinea-Bissau | Malawi | Overall (M-H) |
|---------|---------------|----------------|--------------------|--------------|--------|---------------|
| G allele | 353 (54.0%)   | 353 (54.0%)    | 142 (47.0%)        | 142 (50.4%)  | 215 (36.4%) |
| G allele Cases | 309 (47.0%) | 333 (48.0%)    | 176 (48.9%)        | 154 (47.5%)  | 172 (35.2%) |
| Odds Ratio | 0.75 | 0.79            | 1.08               | 0.89         | 0.95   | 0.86          |
| 95% CI | 0.64–0.94 | 0.64–0.97       | 0.79–1.46          | 0.65–1.23    | 0.74–1.22 | 0.77–0.96     |
| \( P \) value | 0.010 | 0.028           | 0.632              | 0.488        | 0.684   | 0.006         |

The allelic \( P \) value for 2176 individuals enrolled in tuberculosis case control studies. The Gambia (A), Republic of Guinea and Guinea-Bissau (ref. 33), The Gambia (B) (ref. 34) and Malawi (ref. 35). *The Gambia (B) study utilizes The Gambia (A) controls. Significance levels of \( P < 0.05 \) are indicated in bold.
Here we report studies of the CD209-336A/G SNP in multiple tuberculosis case control groups based in The Gambia, Republic of Guinea, Guinea-Bissau, and Malawi. These studies, taken together, reveal a genetic association with the -336G allele and protection against tuberculosis. This protection was independent of HIV-1 status as assessed by logistic regression as well as removing all known HIV-1 cases from the analysis (Table S1). These results differ from the Barrerio study [30]. This discrepancy could reflect a chance finding in the original single study group, since the confidence interval for this population overlaps with those of our three smaller studies (Figure 2). Barreiro and colleagues studied a South African Coloured population known to have the -871 variant, which was absent in all of the sub-Saharan African populations previously genotyped and very rare (<2.5%) in this study. Indeed, it was the -871 variant which showed the most compelling evidence of association, with the -336 variant failing to reach even the nominal significance level of \( P=0.05 \) after correcting for multiple testing. Due to the relative absence of the -871 variant in the African populations genotyped in this present study we could not ascertain the effect of this variant in susceptibility to tuberculosis and it is entirely possible that the -871/-336 haplotype drives differential CD209 expression patterns but further work will be needed to confirm this.

Subgroup analysis suggested a significant association between CD209 -336GG genotype status and protection against lung cavitation. The potential role of DC-SIGN in cavitory tuberculosis disease is novel and warrants further investigation. In this study we are not able to distinguish between cavitory tuberculosis caused by progression from primary infection, re-infection, or indeed by canonical post-primary reactivation disease. Cavitory tuberculosis in this setting defines a particularly severe manifestation of tuberculosis. Pulmonary cavitation in tuberculosis is known to be associated with the production of Th2 cytokines such as IL-4, which have in turn been demonstrated to result in higher surface expression levels of DC-SIGN in DCs [38–40]. This raises the interesting question of whether individuals homozygous for the -336G allele may, in part, be protected from expressing high levels of DC-SIGN and therefore less prone to the Th2 shift induced by ManLam binding to DC-SIGN [22,29,41,42].

Figure 1. CD209-336GG and M. tuberculosis-induced lung cavitation. This figure describes the percent of individuals with the CD209-336GG genotype who presented with cavitory tuberculosis disease. doi:10.1371/journal.pone.0001388.g001

Table 3. CD209 -336A/G and Clinical Correlates of Tuberculosis

| Clinical Correlates | Status   | CD209-336A/G variant* | Total | \( P \) value | Odds Ratio | 95% CI       |
|---------------------|----------|-----------------------|-------|--------------|------------|-------------|
| Sex                 | Male     | AA:AG                 | 573 (73.4%) | 208 (26.6%) | 781        | 0.293       | 0.871 0.673–1.127 |
|                     | Female   | GG                    | 389 (76.0%) | 123 (24.0%) | 512        |             |               |
| HIV                 | Negative | AA:AG                 | 831 (73.8%) | 295 (26.2%) | 1126       | 0.255       | 1.306 0.823–2.073 |
|                     | Positive | GG                    | 92 (78.6%)  | 25 (21.4%)  | 117        |             |               |
| Age Groups          | 0–19     | AA:AG                 | 100 (75.8%) | 32 (24.2%)  | 132        | 0.996       |               |
|                     | 20–29    | GG                    | 363 (74.1%) | 127 (25.9%) | 490        |             |               |
|                     | 30–39    | GG                    | 264 (74.6%) | 90 (25.4%)  | 354        |             |               |
|                     | 40–49    | GG                    | 145 (74.4%) | 50 (25.6%)  | 195        |             |               |
|                     | 50–99    | GG                    | 90 (73.8%)  | 32 (26.2%)  | 122        |             |               |
| Haemoptysis         | No       | AA:AG                 | 281 (77.2%) | 83 (22.8%)  | 364        | 0.858       | 0.959 0.604–1.523 |
|                     | Yes      | GG                    | 113 (77.9%) | 32 (22.2%)  | 145        |             |               |
| Cavitiation         | No       | AA:AG                 | 194 (69.8%) | 84 (30.2%)  | 278        | 0.0000313  0.421 | 0.278–0.636 |
|                     | Yes      | GG                    | 236 (84.6%) | 43 (15.4%)  | 279        |             |               |
| No. Zones affected  | 1–3      | AA:AG                 | 182 (77.1%) | 54 (22.9%)  | 236        | 0.931       | 0.982 0.658–1.468 |
|                     | 4–6      | GG                    | 247 (77.4%) | 72 (22.6%)  | 319        |             |               |
| Duration of cough   | 0–8 weeks| AA:AG                 | 271 (79.0%) | 72 (21.0%)  | 343        | 0.259       | 1.285 0.831–1.989 |
|                     | >8 weeks | GG                    | 123 (74.5%) | 42 (25.5%)  | 165        |             |               |
| Degree of sputum positivity | + | AA:AG | 12 (66.7%) | 6 (33.3%) | 18 | 0.604 | | |
|                      | ++       | GG                    | 162 (75.7%) | 52 (24.3%) | 214 | | | |
|                      | +++      | GG                    | 337 (76.8%) | 102 (23.2%) | 439 | | | |

* Combined West African tuberculosis case control data. Significance level of \( P<0.05 \) is indicated in bold.

doi:10.1371/journal.pone.0001388.t003
Maturation of DCs, defined by DC upregulation of co-stimulatory molecules such as CD80/CD86, can occur on exposure to TLR ligands. This process can however be inhibited by a variety of unknown mechanisms. One possible mechanism of inhibition of DC maturation is the binding of pattern recognition receptors to molecular patterns present on host cells [43]. This process, in theory, would cause DC anergy and a reduction in the pro-inflammatory response, even in the presence of pathogen-associated molecular patterns. Virulent Mycobacterium spp. have evolved mechanisms to more heavily decorate the cell wall lipoglycoconjugates with (1→2) mannosylated termini which closely resemble the high mannose N-linked oligosaccharides of newly produced glycoproteins in eukaryotic cells [44]. Perhaps this molecular mimicry could be part of the mechanism by which virulent strains of M. tuberculosis modulate the immune response. If so, DC-SIGN is a prime target for this virulence strategy.

Overall, our results suggest that lower levels of DC-SIGN on immune subsets may be protective against tuberculosis in the sub-Saharan Africa setting. The findings implicate the involvement of DC-SIGN in the pathogenesis of clinical tuberculosis in general, and severe, cavitary tuberculosis in particular. This has wider implications since it provides further evidence that M. tuberculosis may use the DC-SIGN receptor to subvert the immune response.

**SUPPORTING INFORMATION**

**Table S1**  
CD209 -336A/G SNP Allelic Association in Tuberculosis Case Control Studies Excluding All HIV-1 Positive Cases and Controls. The allelic P value for HIV-1 negative individuals enrolled in tuberculosis case control studies. The Gambia (A), Republic of Guinea and Guinea-Bissau (ref. 33), The Gambia (B) (ref. 34) and Malawi (ref. 35). *The Gambia (B) study utilizes The Gambia (A) controls. Significance levels of P<0.05 are indicated in bold.  
Found at: doi:10.1371/journal.pone.0001388.s001 (0.06 MB DOC)

**ACKNOWLEDGMENTS**

**Author Contributions**
Conceived and designed the experiments: PF SC CK FV AH CL KT.  
Performed the experiments: FV.  
Analyzed the data: FV SF.  
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Wrote the paper: FV.

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PLoS ONE | www.plosone.org 6 January 2008 | Issue 1 | e1388