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Length Variation of DC-SIGN and L-SIGN Neck-Region has no Impact on Tuberculosis Susceptibility

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ABSTRACT: The C-type lectins DC-SIGN and L-SIGN are important pathogen-recognition receptors of the human innate immune system. Both lectins have been shown to interact with a vast range of infectious agents, including *Mycobacterium tuberculosis*, the etiologic agent of tuberculosis in humans. In addition, DC-SIGN and L-SIGN possess a neck region, made up of a variable number of 23 amino acid tandem repeats, which plays a crucial role in the tetramerization of these proteins and support of the carbohydrate recognition domain. The length of the neck region, which shows variable levels of polymorphism, can critically influence the pathogen binding properties of these two receptors. We therefore investigated the impact of the DC-SIGN and L-SIGN neck-region length variation on the outcome of tuberculosis by screening this polymorphism in a large cohort of Coloured South African origin. The analyses of 711 individuals, including 351 tuberculosis patients and 360 healthy controls, revealed that none of the DC-SIGN and L-SIGN neck-region variants or genotypes seems to influence the individual susceptibility to develop tuberculosis. *Human Immunology 68, 106–112 (2007).* © American Society for Histocompatibility and Immunogenetics, 2007. Published by Elsevier Inc.

KEYWORDS: Tuberculosis; susceptibility; DC-SIGN; L-SIGN; neck region; genetics

ABBREVIATIONS

DC-SIGN	dendritic cell-specific ICAM-3 grabbing nonintegrin
L-SIGN	dendritic cell-specific ICAM-3 grabbing nonintegrin related
PRRs	pattern recognition receptors
TB	Tuberculosis

INTRODUCTION

The innate immune system is the first line of host defense against pathogens [1]. Early recognition and uptake of microbes by host professional phagocytes, such as macrophages and dendritic cells, are crucial for downstream immune responses and pathogen clearance. Phagocytic cells express a range of cellular receptors, known as pattern recognition receptors (PRRs), involved in the sensing of microorganisms [1]. These proteins bind to conserved microbial ligands, promoting phagocytosis and antigen presentation, and trigger intracellular signaling and cytokine secretion. The quality of this initial pathogen recognition can have important consequences in both the outcome of infection and the pathogenesis of infectious disease. Two particular PRRs of the C-type lectin receptor family—dendritic cell-specific intercellular adhesion molecule (ICAM)-3 grabbing nonintegrin (DC-SIGN) and dendritic cell-specific ICAM-3 grabbing nonintegrin related (L-SIGN, also known as DC-SIGNR)—have recently been the focus of considerable attention [2–6]. These two lectins, which can act as both cell adhesion receptors and pathogen recognition receptors, are encoded by two genes located on chromosome 19p13.2-3 within a ~26 kb segment [7, 8]. DC-SIGN and L-SIGN exhibit high nucleotide (73%) and

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aminoacid (77%) identity, and identical exon-intron organization [8]. An additional characteristic of both lectins is the presence of a neck region, made up of primarily 7 highly conserved 23 amino acid repeats, that separates the carbohydrate recognition domain (CRD) involved in pathogen binding from the transmembrane region. In regard to expression profiles, DC-SIGN is expressed mainly on endocytic cells, such as dendritic cells and macrophages, whereas L-SIGN is expressed on endothelial cells in liver and lymph nodes, and in cells lining placental capillaries [9–11]. DC-SIGN and L-SIGN share the ability to bind high–mannose oligosaccharides through their CRD, and have been shown to recognize a vast range of microbes, such as HIV-1, Ebola, Hepatitis-C virus, severe acute respiratory syndrome-associated coronavirus (SARS)-coV, and *Mycobacterium tuberculosis* [12, 13].

M. tuberculosis, the causal agent of tuberculosis in humans, remains a leading cause of morbidity and mortality worldwide [14]. Interactions between the tubercle bacillus and host phagocytes are crucial for immunity to mycobacteria and for TB pathogenesis [15]. *M. tuberculosis* can interact with PRRs involved in signal transduction leading to the secretion of cytokines and other mediators of the immune response [16]. In this context, DC-SIGN has been shown to be an important *M. tuberculosis* receptor on the surface of human monocyte-derived DCs [17, 18] and, more recently, it has been shown that L-SIGN can also interact with the tubercle bacillus [19]. Both DC-SIGN and L-SIGN bindings to *M. tuberculosis* are mediated by the mycobacterial cell-wall component mannosylated lipoarabinomannan (ManLAM). In addition, the observation that DC-SIGN may mediate intracellular signaling events leading to cytokine secretion has led some authors to propose that this lectin could be used by pathogens, including *M. tuberculosis*, as a part of an immune evasion strategy to their own advantage [17, 20]. From a genetic perspective, there is increasing evidence that host genetic factors determine differences in host susceptibility to mycobacterial infection and might contribute to the pattern of clinical disease [21, 22]. In this context, we have recently shown that the combination of two DC-SIGN promoter variants (−871G and −336A) is associated with a decreased risk of developing tuberculosis in a South African cohort [23].

However, the extent to which the length of the neck region of both DC-SIGN and L-SIGN might have an impact on the host susceptibility to TB is unclear at present. This tandem-repeat region, which shows a varying degree of length polymorphism [9, 24], is involved in assembling both lectins into a tetrameric protein conformation on the cell surface, and the length of this region can critically influence the pathogen-binding properties of the CRD of these proteins [25–27]. At the population level, the length of the DC-SIGN neck region is highly conserved (mainly 7 repeats), whereas the L-SIGN neck region exhibits an extraordinarily high level of heterozygosity [28]. Furthermore, several studies suggest that the number of DC-SIGN and/or L-SIGN repeat units can contribute to the risk of HIV-1 [29, 30] and SARS infections [31], as well as to HCV replication efficacy [32].

In light of the ability of both DC-SIGN and L-SIGN to bind *M. tuberculosis*, the fact that neck-region length variation may determine the ligand-binding capacities of these lectins and the observation that variation in these regions is associated with a number of infectious diseases, we hypothesized that length variation in the DC-SIGN and L-SIGN neck regions might affect individual susceptibility to TB. To test this hypothesis, we explored the relationship between the DC-SIGN and L-SIGN tandem repeat variation in the neck region and susceptibility to TB in a large cohort of South African Coloured origin.

PATIENTS AND METHODS

Study Cohort

The study was conducted in a cohort of 711 individuals, including 351 TB patients and 360 healthy controls, living in the Cape Town area. Our study population comes from two suburbs of Cape Town that have been extensively studied because of their uniform ethnicity (South African Coloured) and socioeconomic status as well as a high incidence of TB and a low prevalence of HIV [33]. The annual risk of infection (ARI) in these suburbs was estimated at 2.5% in 1987 and at 2.8–3.5% in 1999, and it is therefore highly likely that, in such an environment, the vast majority of controls have been exposed to *M. tuberculosis* [34, 35]. TB patients were bacteriologically-confirmed (smear-positive and/or culture-positive) to present pulmonary tuberculosis (PTB). Their mean age (±standard deviation) was 36.7 (±10.9), and 51.8% were male. Controls were unrelated healthy individuals, from the same community, with the same socioeconomic status, access to health facilities, and chance of diagnosis, with neither signs nor previous history of TB (mean age 34.6 [±12.5], 22% male). All subjects were HIV-negative and older than 18 years. Informed consent was obtained from all participants, and the study was approved by the ethics committee of the Faculty of Health Sciences, Stellenbosch University, South Africa.

Molecular Analyses of the DC-SIGN and L-SIGN Neck-Region Length Polymorphisms

The DC-SIGN and L-SIGN repeat regions in exon 4 were polymerase chain reaction (PCR) amplified from genomic DNA using the following primers: 5′-AGG

CTTGGCACACAGTAGGTG-3′ and 5′-CAACGA CCATCTCAGGCCCAAGA-3′ for DC-SIGN, and 5′-AGGGCTTGGCACACAGTAGGTG-3′ and 5′-ACC CTTGATGTGCAGGAACT-3′ for L-SIGN. PCR amplifications were performed in a final volume of 25 μl using 20 ng of genomic DNA, 0.0016 μg/μl of each primer, 200 μM of dNTP, 1.5 mM of MgCl2, and 0.5 U of BioTaq (Bioline, Randolph, MA, USA). Cycling conditions were as follows: 5 minutes at 94°C, followed by 35cycles of 30 seconds at 94°C, 30 seconds at 60°C, and 1 minute at 72°C. Alleles were distinguished by fragment length after agarose gel electrophoresis and ethidium bromide staining. The difference among alleles is the multiple of 69 nucleotides, which represents the length of each repeat. Because of the high sequence identity (73%) of DC-SIGN and L-SIGN, special care was taken to design primers that specifically amplified the neck region of both genes. Some representative alleles (bands) of both genes were confirmed by direct sequencing to ensure specific amplifications of DC-SIGN and L-SIGN neck-region alleles.

Statistical Analyses

Allele and genotype frequencies were obtained by direct counting. Differences between cases and controls for both allele and genotype frequencies were determined using a two-sided χ^2 test, and a Fisher's exact test when appropriate. Odds ratio (OR) was calculated with 95% confidence intervals (CI). All analyses were performed using STATA 8.2

RESULTS AND DISCUSSION

The allelic and genotype frequencies of the DC-SIGN and L-SIGN neck-region tandem repeats in the 351 TB patients and 360 healthy controls are summarized in Tables 1 and 2, respectively. Both patients and controls, which are ethnically matched, belong to the South African Coloured population. It is worth mentioning that population stratification between the two study groups, a situation that can lead to spurious associations, was excluded in a previous study by analyzing the entire cohort for a panel of 25 independent genomewide single nucleotide polymorphism (SNP) markers [23]. When examining the allelic frequencies of repeat units for DC-SIGN and L-SIGN neck regions, no statistical differences were observed between TB cases and healthy controls (Table 1).

In the case of DC-SIGN, the 7-repeat allele was by far the most frequently observed, with a frequency of more than 98%. As to L-SIGN, the 7-repeat and the 6-repeat alleles account for more than 80% of the overall diversity. We next examined whether the frequency distributions of DC-SIGN and L-SIGN neck-region genotypes were significantly distorted between cases and controls. Again, no significant differences were detected between diseased individuals and healthy controls for both DC-SIGN and L-SIGN. In regard to DC-SIGN, low genotypic variation was observed in accordance with the allelic data. The 7/7 genotype accounted for nearly all genetic variation (more than 96%), and genotypes 7/4, 7/5, 7/6, and 7/8 were observed at very low frequencies (Table 2). For L-SIGN, the genotypes 7/7 and 7/6 were present at similar frequencies (30–36%), followed by 7/5 (~12%), 6/6 (~6%), 6/5 (~5%), and 9/7 (~4%).

The results of the present study indicate that the number of repeats of the DC-SIGN and L-SIGN neck regions does not seem to influence the host susceptibility to develop TB. In the case of DC-SIGN, our results are in agreement with a recent case-control study in a cohort of northwestern Colombian origin [36]. In this report, the authors analyzed DC-SIGN neck-region variation in a cohort of 110 tuberculosis patients and 299 matched controls, and observed no statistical differences between the two study groups. Thus, both studies support the notion that length variation of the DC-SIGN neck region does not influence the host susceptibility to develop TB.

TABLE 1 DC-SIGN and L-SIGN neck-region allelic frequencies (in %) among patients with tuberculosis and healthy controls

	DC-SIGN				*L-SIGN*			
Alleles	Patients (n^a = 702)	Controls (n^a = 720)	*P*	OR (95% CI)	Patients (n^a = 702)	Controls (n^a = 720)	*P*	OR (95% CI)
4	0.14	0	0.49	nc	0.43	0.69	0.50	0.61 (0.15–2.58)
5	0.28	0	0.24	nc	9.40	11.81	0.14	0.78 (0.55–1.09)
6	1.28	0.97	0.58	1.32 (0.49–3.57)	28.49	24.17	0.06	1.25 (0.99–1.59)
7	98.15	98.89	0.25	0.60 (0.25–1.45)	58.40	59.72	0.61	0.95 (0.77–1.17)
8	0.14	0.14	1.00	1.02 (0.06–16.43)	0.43	0.97	0.22	0.44 (0.11–1.70)
9	0	0	—	nc	2.85	2.64	0.81	1.08 (0.57–2.05)

Abbreviation: nc, not computable.

[a] Number of chromosomes analyzed.

TABLE 2 DC-SIGN and L-SIGN neck-region genotype frequencies (in %) among patients with tuberculosis and healthy controls

	DC-SIGN				*L-SIGN*			
Genotypes	Patients (n^a = 351)	Controls (n^a = 360)	*P*	OR (95% CI)	Patients (n^a = 351)	Controls (n^a = 360)	*P*	OR (95% CI)
4\4	0	0	—	nc	0	0.28	1.00	nc
5\4	0	0	—	nc	0.28	0	1.00	nc
5\5	0	0	—	nc	0.57	2.50	0.06	0.22 (0.04–1.04)
6\4	0	0	—	nc	0.28	0.56	1.00	0.51 (0.05–5.67)
6\5	0	0	—	nc	5.13	5.28	0.93	0.97 (0.50–1.88)
6\6	0	0	—	nc	7.12	5.83	0.48	1.24 (0.68–2.26)
7\4	0.28	0	1.00	nc	0.28	0.28	1.00	1.03 (0.06–16.46)
7\5	0.57	0	0.24	nc	12.25	13.33	0.67	0.91 (0.58–1.41)
7\6	2.56	1.94	0.58	1.33 (0.49–3.60)	36.18	29.72	0.07	1.34 (0.98–1.83)
7\7	96.30	97.78	0.24	0.59 (0.24–1.44)	31.34	35.28	0.27	0.84 (0.61–1.14)
8\6	0	0	—	nc	0	0.28	1.00	nc
8\7	0.28	0.28	1.00	1.03 (0.06–16.46)	0.85	1.67	0.51	0.51 (0.13–2.05)
9\6	0	0	—	nc	1.14	0.83	0.72	1.37 (0.30–6.17)
9\7	0	0	—	nc	4.56	3.89	0.66	1.18 (0.57–2.46)
9\9	0	0	—	nc	0	0.28	1.00	nc

Abbreviation: nc, not computable.

[a] Number of individuals.

In the context of other infectious diseases, the only positive association published so far between DC-SIGN neck-region variation and susceptibility to infectious disease is restricted to HIV-1 infection [29]. In this study, the authors observed an excess of heterozygous individuals for DC-SIGN tandem-repeats in a group of repeatedly-exposed seronegative individuals as compared to the groups of HIV-1 seronegative and HIV-1 seropositive individuals. These observations were interpreted as heterozygosity in the DC-SIGN neck region being associated with reduced susceptibility to HIV-1 infection [29]. At the level of the general population, it is of interest that the DC-SIGN neck region exhibits very low levels of polymorphism [9, 28]. Indeed, we recently screened the entire Human Genome Diversity Panel (HGDP-CEPH panel), which is composed of more than 1,000 control individuals from 52 different ethnic groups, for repeat variation in the neck regions of both DC-SIGN and L-SIGN [28]. For DC-SIGN, we observed that the 7-repeat allele accounts for nearly all genetic variation (~99%), and that the other alleles, which range from 2–10 repeats, are present at very low frequencies. In addition, the levels of sequence variation in the entire DC-SIGN coding-region, particularly of those that affect amino-acid identity, were found to be extremely low [28]. The low levels of genetic variation observed in the DC-SIGN coding region are also reflected in the context of disease association studies. Indeed, the different associations published so far between DC-SIGN genetic variation and susceptibility to infectious diseases always involve polymorphisms in the DC-SIGN promoter region, and not in its coding region [23, 37, 38]. For example, we have previously shown that the combination of two DC-SIGN promoter variants (−871G and −336A) is associated with a reduced risk of developing TB in the same South African cohort analyzed here [23]. Furthermore, the genetic variation in DC-SIGN that has been associated with protection against parenteral HIV-1 infection [37] and with the severity of dengue pathogenesis [38] also involves polymorphisms (i.e. −336A/G) restricted to the DC-SIGN promoter region. Taken together, all these studies support the view that it is the variation in the amount of DC-SIGN protein being produced that can influence infectious disease susceptibility, and not differences in the DC-SIGN protein itself or variation in its neck region.

Our study presents the first investigation of the role of L-SIGN neck-region variation in susceptibility to TB. A number of studies have already explored possible correlations between L-SIGN neck-region variation and susceptibility to other infectious diseases [30–32, 39]. For example, the L-SIGN tandem-repeat 7/5 genotype has been recently associated with an increased protection against HIV-1 infection in high risk individuals [30]. However, this association remains controversial because a previous study failed to detect such an association [39]. In the context of Hepatitis C virus (HCV) infection, a study comparing the frequency distribution of L-SIGN neck-region polymorphisms in a group of infected patients with noninfected individuals failed to demonstrate any statistical difference between the two study groups [32]. However, the same authors did observe an association between neck-region polymor-

phisms and individual HCV viral loads, and suggested that length variation in the L-SIGN neck region affects HCV replication efficacy. Finally, a recent study focusing on susceptibility to SARS infection has shown that individuals who are homozygous for L-SIGN neck-region repeats are better protected against SARS infection [31]. However, our results clearly indicate that the L-SIGN neck-region allele/genotype frequencies are not statistically different between TB patients and healthy controls in our large South African cohort (Tables 1 and 2). Thus, our data seem to exclude length variation in the L-SIGN neck region as a factor influencing TB susceptibility.

More generally, our study clearly illustrates the advantages of using admixed populations in the context of disease association studies. Indeed, the South African Coloured population represents a present-day homogenous population who originated from the variable admixture of different populations, such as African Khoisan and Bantu-speakers, Malaysians, Indians, and Europeans [40, 41]. Consequently, the South African Coloured population presents a large degree of genetic diversity, resulting in a high number of alleles or genotype combinations that can be used in association studies. For example, the L-SIGN genotypes 6/5, 7/5, and 9/7 are observed at relatively high frequencies among the South Africans (providing evidence for the genetic input received from European and Asian populations), whereas they are rare or even absent in other subSaharan African populations [28]. The presence of these genotypes in the South African population offers a unique opportunity for testing their association with disease in a single population, a hypothesis that would be difficult to test in other African populations because these genotypes are found at a very low frequency, or are even absent.

In summary, our results show that the length of the neck regions of both DC-SIGN and L-SIGN are not associated with an increased or decreased host susceptibility to develop TB, at least in our South African cohort. These data are in contrast with other disease association studies where the tandem-repeat polymorphisms of DC-SIGN and/or L-SIGN seem to contribute to different susceptibilities to HIV-1 and SARS infections, and to the HCV replication efficacy [29–32].

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