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Maureen P. Martin  
*National Cancer Institute at Frederick*

Michael M. Lederman  
*Case Western Reserve University*

Holli B. Hutcheson  
*National Cancer Institute at Frederick*

James J. Goedert  
*National Cancer Institute at Bethesda*

George W. Nelson  
*National Cancer Institute at Frederick*

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Association of DC-SIGN Promoter Polymorphism with Increased Risk for Parenteral, but Not Mucosal, Acquisition of Human Immunodeficiency Virus Type 1 Infection

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Basic Research Program, SAIC Frederick, and Laboratory of Genomic Diversity, National Cancer Institute, Frederick, and Viral Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, Maryland; Center for AIDS Research, University Hospitals, Case Western Reserve University, Cleveland, Ohio; Department of Molecular Cell Biology, Vrije Universiteit Medical Center, Amsterdam, The Netherlands; Department of Epidemiology, School of Public Health, University of California, Los Angeles, Los Angeles, and San Francisco Department of Public Health, San Francisco, California; Gulf States Hemophilia Center, University of Texas Health Science Center, Houston, Texas; and Center for Urban Epidemiologic Studies, New York Academy of Medicine, New York, New York

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Dendritic cells (DCs) play a critical role in initiating the immune response by virtue of their ability to capture antigens and present them to T cells (1). Although the precise mechanisms of human immunodeficiency virus (HIV) acquisition are not completely understood, migration of DCs from peripheral tissues and blood to regions of draining lymphoid organs may enable their capture of HIV type 1 (HIV-1) and presentation of virus to CD4+ T cells (16). HIV-1 entry into target cells is mediated by interactions of the viral envelope glycoprotein with CD4 and the chemokine receptors CCR5 and CXCR4 on the target cell membrane, although entry may be influenced by other factors as well. DC-SIGN (DC-specific intercellular adhesion molecule 3 [ICAM-3] grabbing nonintegrin), encoded by the member of the CD209 gene family on chromosome 19p13.2–3, has recently been identified as a DC-specific adhesion receptor that mediates the interaction between DCs and resting T cells through high-affinity binding to ICAM-3 (6). DC-SIGN also binds HIV-1 gp120, facilitating capture of HIV and enhancing in vitro infection of T cells in trans. DC-SIGN-associated HIV-1 remains infectious over a prolonged period, perhaps contributing to the infectious potential of the virus during its transport by DCs from the periphery to lymphoid organs (5). This receptor may represent a common thread in many infectious diseases, as it has also been shown to facilitate direct infection of DCs by a range of infectious agents, such as Dengue virus, Ebola virus, human cytomegalovirus, Leishmania pifanoi amastigotes, and Mycobacterium tuberculosis (reviewed in reference 17). Thus it is plausible that polymorphisms in the gene might have a broad range of influence in the pathogenesis of human infectious disease in general, including HIV-1.

Given the functional activity of DC-SIGN, we proposed that polymorphisms in the coding region and/or promoter region of the associated gene might influence outcomes after HIV-1 exposure. Initial screening for nucleotide variation indicated conservation of DC-SIGN coding sequences. However, several polymorphisms in the gene might have a broad range of influence in the pathogenesis of human infectious disease in general, including HIV-1.

<table>
<thead>
<tr>
<th>Haplotype*</th>
<th>f*</th>
<th>Nucleotide at position:</th>
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<td>139</td>
<td>336</td>
</tr>
<tr>
<td>1</td>
<td>0.28</td>
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</tr>
<tr>
<td>2</td>
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</tr>
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<td>C</td>
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<td>T</td>
</tr>
<tr>
<td>6</td>
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</tr>
<tr>
<td>7</td>
<td>0.04</td>
<td>T</td>
</tr>
<tr>
<td>8</td>
<td>0.03</td>
<td>C</td>
</tr>
</tbody>
</table>

* Only haplotypes with a frequency of >1% are shown. Haplotypes were estimated in compound heterozygotes with the expectation maximization algorithm.

* Corresponding author. Present address: SAIC-Frederick, National Cancer Institute, P.O. Box B, Frederick, MD 21702. Phone: (301) 846-1390. Fax: (301) 846-6771. E-mail: carringt@ncifcrf.gov.
**FIG. 1.** DC-SIGN promoter polymorphisms and susceptibility to parenterally and mucosally acquired infection. (A) Frequency of DC-SIGN promoter polymorphisms in HIV-1-infected individuals (HIV-1 +) and HIV-seronegative individuals (HIV-1 −). *P* values and ORs are listed below each SNP. (B) Frequency of −336C in HIV-1-infected individuals and HIV-negative individuals (HREU, high risk exposed uninfected; all SN, all HIV-seronegative individuals) from all cohorts combined (all) and in individual cohorts (MHCS [Multicenter Hemophilia Cohort Study] and ALIVE [AIDS Linked to Intravenous Experience]).
single-nucleotide polymorphisms (SNPs) were identified in the region 2 kb upstream of the ATG start codon, which includes the promoter region (11). The region was amplified in four overlapping segments of 200 to 300 bp, and analysis of the products was performed using single-strand conformation polymorphism (SSCP), as previously described (3). All variants identified by SSCP were confirmed by sequencing analysis. We genotyped samples from 1,611 European-American (EA) participants in five well-characterized HIV-1 cohorts at risk for parenteral (Multicenter Hemophilia Cohort Study [7], AIDS Linked to Intravenous Experience [18], and Hemophilia Growth and Development Study [9]) or mucosal acquisition (Multicenter AIDS Cohort Study [13] and San Francisco City Clinic Cohort [2]) of HIV-1 infection for the DC-SIGN promoter polymorphisms. Six common and 10 rare variants that defined eight haplotypes with frequencies >1% were identified (Table 1). The frequency distributions of the most common DC-SIGN promoter SNPs (−139T, −336C, −939T, −1180T, and −1466T) were quite rare (frequency ≤ 0.001), so it was not possible to test the influence of this haplotype on the risk of HIV-1 infection. There was no significant association seen with HIV-1 disease progression for any of the individual SNPs or haplotypes.

DCs are believed to play a central role in HIV-1 infection as they may be among the first cells encountered by virus (5). DC-SIGN, a C-type lectin receptor that is exclusively expressed by DCs, can enhance virus infection by efficiently binding to the envelope glycoprotein of both R5 and X4 viruses (5). Levels of DC-SIGN expression on subsets of DCs are variable, however, and Langerhans cells, a subset of DCs that are present in the genital epithelium, do not express DC-SIGN at all (6). Furthermore, infection of these cells is blocked by inhibitors of CCR5 expression and not by C type lectin inhibitors (10). Thus, it is plausible that CCR5-dependent infection of Langerhans cells, and not DC-SIGN-mediated capture of HIV-1, is the major pathway involved in sexual transmission of HIV-1 (14), accounting for the failure to demonstrate a significant association of DC-SIGN polymorphism and mucosal infection. On the other hand, DC-SIGN expressed in lymph nodes and circulating DCs may play a role in HIV-1 acquisition via the parenteral route. In this regard, heterogeneity in expression of DC-SIGN among healthy subjects (4) may determine the ability of these cells to potentiate infection. Polymorphism in the promoter region of CCR5 has been shown to have an effect on HIV-1 disease progression (12), CCR5 surface density (15), and susceptibility of cells to HIV-1 infection (10, 15). Here we show that a polymorphism in the putative promoter region of DC-SIGN is associated with risk of infection via the parenteral route but not the mucosal route. A potential mechanism for this may involve differential constitutive or inducible expression of DC-SIGN on blood DCs as a result of this polymorphism, but this remains to be demonstrated. −336C is located 214 bp upstream of the major transcription start site (11) and is therefore likely to be in a region containing potential binding sites for transcriptional factors. Indeed, a database search (TRANSFAC database) (8) identified a potential Sp1 binding site in the presence of −336C, which is lost when −336T is present. Functional analyses should determine whether or not this is biologically significant.

Although the −336C SNP was quite common in African-Americans, there was no significant association with risk of infection seen for this group. This raises the possibility that the effect seen in Caucasians is not due directly to −336C, but rather to another as yet unidentified SNP on chromosome 19p13.2-3 that is in linkage disequilibrium with −336C in Caucasians but not in African Americans. Alternatively, −336C may exert its protective effect only in the presence of another variant that is common in Caucasians but missing in African-Americans.

Further studies are necessary to demonstrate the role of DC-SIGN promoter polymorphisms identified in this study in the function of DC-SIGN, and consequently their effect on

<table>
<thead>
<tr>
<th>Variant</th>
<th>Phenotypic frequency</th>
<th>Parenteral infection</th>
<th>Mucosal infection</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HIV-1+</td>
<td>HIV-1-</td>
<td>OR</td>
</tr>
<tr>
<td>−139T</td>
<td>0.53</td>
<td>0.63</td>
<td>0.60</td>
</tr>
<tr>
<td>−336C</td>
<td>0.44</td>
<td>0.29</td>
<td>1.87</td>
</tr>
<tr>
<td>−939T</td>
<td>0.52</td>
<td>0.61</td>
<td>0.60</td>
</tr>
<tr>
<td>−1180T</td>
<td>0.75</td>
<td>0.81</td>
<td>0.73</td>
</tr>
<tr>
<td>−1466T</td>
<td>0.69</td>
<td>0.77</td>
<td>0.69</td>
</tr>
</tbody>
</table>
HIV-1 infection. It will also be of interest to determine whether the −336C SNP is associated with protection from or susceptibility to other pathogens known to bind DC-SIGN.

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REFERENCES