

Repeat-Region Polymorphisms in the Gene for the Dendritic Cell–Specific Intercellular Adhesion Molecule–3–Grabbing Nonintegrin–Related Molecule: Effects on HIV-1 Susceptibility

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In 1716 individuals—801 human immunodeficiency virus (HIV)–1–seropositive individuals, 217 high-risk HIV-1–seronegative individuals, and 698 general HIV-1–seronegative individuals—from a Seattle cohort and a Multicenter AIDS Cohort Study cohort, the association between HIV-1 susceptibility and repeat-region polymorphisms in the gene for the dendritic cell–specific intercellular adhesion molecule–3–grabbing nonintegrin–related molecule (*DC-SIGNR*) was investigated; 16 genotypes were found in the *DC-SIGNR* repeat region. The *DC-SIGNR* homozygous 7/7 repeat was found to be associated with an increased risk of HIV-1 infection (17.5% in high-risk HIV-1–seronegative individuals vs. 28.5% in HIV-1–seropositive individuals; $P = .0015$), whereas the *DC-SIGNR* heterozygous 7/5 repeat tended to be correlated with resistance to HIV-1 infection (35.5% in high-risk HIV-1–seronegative individuals vs. 27.6% in HIV-1–seropositive individuals; $P = .0291$). These findings suggest that *DC-SIGNR* polymorphisms may influence susceptibility to HIV-1.

Polymorphisms in host genes play critical roles in resistance to HIV-1 infection and in the rate of disease progression [1].

Dendritic cell (DC)–specific intercellular adhesion molecule–3–grabbing nonintegrin (DC-SIGN) is able to bind the HIV-1 gp120 surface protein with high affinity and to enhance *trans*-infection of T cells by HIV-1 [2]. The DC-SIGN–related molecule (DC-SIGNR) shows functions similar to those of DC-SIGN [3]. Some studies have shown that mRNA encoding the DC-SIGNR is present in DCs, although the level of expression of the DC-SIGNR is lower than that of DC-SIGN [3–5]. One of our previous studies has detected DC-SIGNR mRNA in DCs and found that most DC-SIGNR transcripts at mucosal HIV-1 transmission sites are alternatively spliced isoforms [6]. Because DCs are among the first cells encountered by HIV-1 during sexual transmission, it has been proposed that HIV-1 uses DCs as carriers to gain entry into lymph nodes, with subsequent infection of CD4⁺ T cells [2].

Both *DC-SIGN* and the *DC-SIGNR* are organized into 3 domains: an N-terminal cytoplasmic region, a neck region containing 7 repeats of the 23-amino-acid sequence, and a C-terminal domain with homology to C-type lectins [4]. One of our recent studies has indicated that polymorphisms in the *DC-SIGN* repeat region reduce the risk of HIV-1 infection [7]. The *DC-SIGNR* repeat region is polymorphic [3, 8]. The present study assessed, in both a Seattle cohort and a Multicenter AIDS Cohort Study (MACS) cohort, whether polymorphisms in the *DC-SIGNR* repeat region could affect HIV-1 susceptibility and subsequent disease progression in (1) multiply exposed HIV-1–seronegative or high-risk HIV-1–seronegative individuals, (2) general HIV-1–seronegative individuals, and (3) HIV-1–positive individuals.

Subjects and methods. Informed consent was obtained from all subjects, and human-experimentation guidelines of the US Department of Health and Human Services and of

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the authors' institutions were followed during the collection of clinical samples. After 17 individuals (10 from the Seattle cohort and 7 from the MACS cohort) who were homozygous for *CCR5-Δ32* had been excluded, a total of 1716 individuals—1109 from the Seattle cohort and 607 from the MACS cohort—were evaluated.

The Seattle cohort, which was enrolled at the Fred Hutchinson Cancer Research Center Vaccine Trials Unit and the University of Washington Primary HIV Infection Clinic between 1993 and 2004, was evaluated after 10 HIV-1-seronegative individuals (3 of whom were from the multiply exposed group) who were homozygous for *CCR5-Δ32* [7] had been excluded; the remaining 1109 individuals included 94 HIV-1-seronegative individuals who had been multiply exposed to HIV-1 through unprotected sexual activity with partners known to be HIV-1 positive, 698 general HIV-1-seronegative individuals, and 317 HIV-1-seropositive individuals. Of the 317 HIV-1-seropositive individuals, 230 were seroconverters who were estimated to have been infected between their last seronegative HIV-1 test and their first seropositive HIV-1 test. The 94 multiply exposed HIV-1-seronegative individuals were selected because they were healthy HIV-1-seronegative adult volunteers who had engaged in unprotected penile/vaginal or anal sex with a known HIV-1-seropositive individual either (1) more than 5 times during the 6 months prior to entry into the study or (2) more than 2 times per week for a period of 4 months during the 2 years prior to entry into the study. Details of eligibility for entry into the study, as well as additional epidemiologic features of the multiply exposed HIV-1-seronegative individuals, have been provided elsewhere [7, 9].

The MACS cohort was evaluated after 7 individuals who were homozygous for *CCR5-Δ32* were excluded; the remaining 607 individuals included 123 high-risk HIV-1-seronegative individuals and 484 HIV-1-seropositive individuals. Of the 484 HIV-1-seropositive individuals, 452 were seroconverters who were estimated to have been infected between their last seronegative HIV-1 test and their first seropositive HIV-1 test. The inclusion of the high-risk HIV-1-seronegative individuals and the HIV-1-seropositive individuals was based on criteria described elsewhere [10–13].

The *DC-SIGNR* repeat region was genotyped by use of the following pair of primers: L28 (5'-TGTCCAAGTCCCCAGC-TCCC-3') and L32 (5'-GAACTACCAAATGCAGTCTTCAA-ATC-3') [3]. Polymerase chain reaction (PCR) amplification was performed in a volume of 50 μ L containing 0.25 mmol/L of each dNTP, 1.0 μ mol/L of each primer, 2.5 mmol/L MgCl₂, and 1.0 U of Expand High Fidelity PCR System Enzyme in 1 \times reaction buffer (Boehringer Mannheim). The cycle conditions were as follows: 94°C for 5 min, followed by 35 cycles of 94°C for 5 s and 70°C for 1 min and by 1 cycle of 70°C for 10 min.

Alleles were differentiated on the basis of 3%-agarose gel electrophoresis and ethidium-bromide staining.

A χ^2 test was used to determine whether the distribution of *DC-SIGNR* repeat-region genotypes was independent of whether the group studied was high-risk HIV-1 seronegative or HIV-1 seropositive. In the combined Seattle-MACS cohort, there were 5 genotypes—5/5, 6/5, 7/5, 7/6, and 7/7—that were present at frequencies of >5.0%. All of the other, rarer genotypes (i.e., those that were present at frequencies of <5.0%) were considered as a single group. A 3 \times 6 contingency table was used to analyze the association between the genotype and the risk of HIV-1 infection. Because *CCR5-Δ32* homozygosity confers high resistance to HIV-1 infection, the 17 individuals who were homozygous for *CCR5-Δ32* were excluded from these and further analyses. $P < .05$ was considered to be statistically significant.

The correlation between the presence of a particular genotype and the risk of HIV-1 was evaluated by use of a χ^2 test; odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. All P values are 2-sided. Because there were 6 genotype comparisons, the significance level, α , was adjusted to 0.0083 (0.05/6). All statistical analyses were performed by use of PRISM (version 4.0) and InStat (version 3.0) (GraphPad Software).

Results. Among the 1716 individuals in the combined Seattle-MACS cohort, there were 16 different genotypes in the *DC-SIGNR* repeat region (table 1); the allele frequencies in this combined cohort were 0.06% for allele 3, 2.53% for allele 4, 29.36% for allele 5, 15.24% for allele 6, 53.12% for allele 7, 0.15% for allele 8, and 1.54% for allele 9 (table 2), which are comparable to the frequencies that have been reported elsewhere [3].

Of the 16 genotypes identified, 11 were present at frequencies of <5%, thereby limiting the intergroup comparability of these genotypes; therefore, all of these less frequent genotypes were considered as a group, and a 3 \times 6 contingency table including this genotype group and the 5 individual genotypes—5/5, 6/5, 7/5, 7/6, and 7/7—present at frequencies of >5.0% was used. The distribution of *DC-SIGNR* genotypes among the high-risk HIV-1-seronegative individuals ($n = 217$) was significantly different than that among the HIV-1-seropositive individuals ($n = 801$) ($P = .0263$). The frequency of the *DC-SIGNR* homozygous 7/7 genotype was significantly lower among the high-risk HIV-1-seronegative individuals (17.5%) than among the HIV-1-seropositive individuals (28.5%) (OR, 1.874 [95% CI, 1.279–2.747]; $P = .0015$, $\alpha = 0.0083$). Although the frequency of the *DC-SIGNR* heterozygous 7/5 genotype was significantly higher among the high-risk HIV-1-seronegative individuals (35.5%) than among the HIV-1 seropositive individuals (27.6%) (OR, 0.6928 [95% CI, 0.5039–0.9525]; $P = .0291$) when a single comparison was used, it was not statistically higher when the significance level was adjusted for multiple

Table 1. Distribution of DC-SIGN-related repeat-region genotypes among multiply exposed HIV-1-seronegative/high-risk HIV-1-seronegative (ES/HRSN), general HIV-1-seronegative (HIV-1⁻), and HIV-1-positive (HIV-1⁺) individuals, in a Seattle cohort and a Multicenter AIDS Cohort Study (MACS) cohort.

Genotype	ES/HRSN			HIV-1 ⁺			HIV-1 ⁻ , Seattle	ES/HRSN, HIV-1 ⁺ and HIV-1 ⁻		
	Seattle	MACS	Seattle and MACS	Seattle	MACS	Seattle and MACS		Seattle	MACS	Seattle and MACS
4/4	0 (0.00)	1 (0.81)	1 (0.46)	1 (0.32)	1 (0.21)	2 (0.25)	2 (0.29)	3 (0.27)	2 (0.33)	5 (0.29)
5/3	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.32)	1 (0.21)	2 (0.25)	0 (0.00)	1 (0.09)	1 (0.16)	2 (0.12)
5/4	1 (1.06)	0 (0.00)	1 (0.46)	4 (1.26)	7 (1.45)	11 (1.37)	6 (0.86)	11 (0.99)	7 (1.15)	18 (1.05)
5/5	11 (11.70)	9 (7.32)	20 (9.22)	25 (7.89)	44 (9.09)	69 (8.61)	49 (7.02)	85 (7.66)	53 (8.73)	138 (8.04)
6/4	0 (0.00)	1 (0.81)	1 (0.46)	1 (0.32)	2 (0.41)	3 (0.37)	3 (0.43)	4 (0.36)	3 (0.49)	7 (0.41)
6/5	11 (11.70)	9 (7.32)	20 (9.22)	29 (9.15)	46 (9.50)	75 (9.36)	51 (7.31)	91 (8.21)	55 (9.06)	146 (8.51)
6/6	4 (4.26)	4 (3.25)	8 (3.69)	9 (2.84)	13 (2.69)	22 (2.75)	18 (2.58)	31 (2.80)	17 (2.80)	48 (2.80)
7/4	3 (3.19)	6 (4.88)	9 (4.15)	15 (4.73)	13 (2.69)	28 (3.50)	15 (2.15)	33 (2.98)	19 (3.13)	52 (3.03)
7/5	35 (37.23) ^a	42 (34.15) ^b	77 (35.48) ^c	79 (24.92)	142 (29.34)	221 (27.59)	189 (27.08)	303 (27.32)	184 (30.31)	487 (28.38)
7/6	15 (15.96)	18 (14.63)	33 (15.21)	53 (16.72)	70 (14.46)	123 (15.36)	116 (16.62)	184 (16.59)	88 (14.50)	272 (15.85)
7/7	12 (12.77) ^d	26 (21.14) ^e	38 (17.51) ^f	95 (29.97)	133 (27.48)	228 (28.46)	217 (31.09)	324 (29.22)	159 (26.19)	483 (28.15)
8/5	0 (0.00)	1 (0.81)	1 (0.46)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.16)	1 (0.06)
8/6	0 (0.00)	1 (0.81)	1 (0.46)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.14)	1 (0.09)	1 (0.16)	2 (0.12)
8/7	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.21)	1 (0.12)	1 (0.14)	1 (0.09)	1 (0.16)	2 (0.12)
9/5	0 (0.00)	2 (1.63)	2 (0.92)	0 (0.00)	3 (0.62)	3 (0.37)	4 (0.57)	4 (0.36)	5 (0.82)	9 (0.52)
9/7	2 (2.13)	3 (2.44)	5 (2.30)	5 (1.58)	8 (1.65)	13 (1.62)	26 (3.72)	33 (2.98)	11 (1.81)	44 (2.56)
Total	94	123	217	317	484	801	698	1109	607	1716

NOTE. Data are no. (%) of individuals.

^a Seattle ES vs. HIV-1⁺: odds ratio, 0.5595 (95% confidence interval, 0.3429–0.9130); $P = .0271$.

^b MACS HRSN vs. HIV-1⁺: $P = .3544$.

^c Seattle/MACS ES/HRSN vs. HIV-1⁺: odds ratio, 0.6928 (95% confidence interval, 0.5039–0.9525); $P = .0291$.

^d Seattle ES vs. HIV-1⁺: odds ratio, 2.924 (95% confidence interval, 1.524–5.612); $P = .0014$.

^e MACS HRSN vs. HIV-1⁺: $P = .1890$.

^f Seattle/MACS ES/HRSN vs. HIV-1⁺: odds ratio, 1.874 (95% confidence interval, 1.279–2.747); $P = .0015$.

genotype comparisons ($P = .0291$, $\alpha = 0.0083$). These results suggest that, in the combined Seattle-MACS cohort, the DC-SIGNR homozygous 7/7 genotype is associated with an increased risk of HIV-1 infection, whereas the DC-SIGNR heterozygous 7/5 genotype may be associated with a reduced risk of such infection.

Among the 1109 individuals in the Seattle cohort, there were 15 different genotypes in the DC-SIGNR repeat region (table 1); the allele frequencies in this cohort were 0.05% for allele 3, 2.43% for allele 4, 26.15% for allele 5, 15.42% for allele 6, 54.19% for allele 7, 0.09% for allele 8, and 1.67% for allele 9 (table 2). The distribution of DC-SIGNR genotypes among the multiply exposed HIV-1-seronegative individuals ($n = 94$) was significantly different than that among the HIV-1-seropositive individuals ($n = 317$) ($P = .0159$). The frequency of the homozygous DC-SIGNR 7/7 genotype was significantly lower among the multiply exposed HIV-1-seronegative individuals (12.8%) than among the HIV-1-seropositive individuals (30.0%) (OR, 2.924 [95% CI, 1.524–5.612]; $P = .0014$, $\alpha = 0.0083$). Although the frequency of the DC-SIGNR heterozygous 7/5 genotype was significantly higher among the multiply exposed HIV-1-seronegative individuals (37.2%) than among the HIV-1-seropositive individuals (24.9%) (OR, 0.5595 [95% CI, 0.3429–0.9130]; $P = .0271$) when a single comparison was

used, it was not statistically higher when the significance level was adjusted for multiple genotype comparisons ($P = .0271$, $\alpha = 0.0083$).

Among the 607 individuals in the MACS cohort, there were 16 different genotypes in the DC-SIGNR repeat region (table 1); overall, the allele frequencies in this cohort were similar to those in the Seattle cohort (table 2). Within the MACS cohort, the frequency of the DC-SIGNR heterozygous 7/5 genotype among the high-risk HIV-1-seronegative individuals (34.15%) was not significantly different from that among the HIV-1-seropositive individuals (29.34%) ($P = .3544$), and this was also true of the distribution of DC-SIGNR genotypes in general ($P = .3463$), although the frequency of the DC-SIGNR homozygous 7/7 genotype tended to be lower among the high-risk HIV-1-seronegative individuals (21.14%) than among the HIV-1-seropositive individuals (27.48%) ($P = .1890$).

Because genotypes often can vary on the basis of ethnic origin, and because most of the subjects in the present study were white, the aforementioned analyses also were performed on white subjects only. In these additional analyses, both the significance and the trend were similar to those seen in the Seattle cohort and the MACS cohort individually and in the combined Seattle-MACS cohort (data not shown).

Discussion. The results of the present study suggest that

Table 2. Distribution of *DC-SIGN*-related repeat-region alleles among multiply exposed HIV-1-seronegative/high-risk HIV-1-seronegative (ES/HRSN), general HIV-1-seronegative (HIV-1⁻), and HIV-1-positive (HIV-1⁺) individuals, in a Seattle cohort and a Multicenter AIDS Cohort Study (MACS) cohort.

Allele	ES/HRSN			HIV-1 ⁺			HIV-1 ⁻ , Seattle	ES/HRSN, HIV-1 ⁺ and HIV-1 ⁻		
	Seattle	MACS	Seattle and MACS	Seattle	MACS	Seattle and MACS		Seattle	MACS	Seattle and MACS
3	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.16)	1 (0.10)	2 (0.12)	0 (0.00)	1 (0.05)	1 (0.08)	2 (0.06)
4	4 (2.13)	9 (3.66)	13 (3.00)	22 (3.47)	24 (2.48)	46 (2.87)	28 (2.01)	54 (2.43)	33 (2.72)	87 (2.53)
5	69 (36.70)	72 (29.27)	141 (32.49)	163 (25.71)	287 (29.65)	450 (28.09)	348 (24.93)	580 (26.15)	359 (29.57)	939 (29.36)
6	34 (18.09)	37 (15.04)	71 (16.36)	101 (15.93)	144 (14.88)	245 (15.29)	207 (14.83)	342 (15.42)	181 (14.91)	523 (15.24)
7	79 (42.02)	121 (49.19)	200 (46.08)	342 (53.94)	500 (51.65)	842 (52.56)	781 (55.95)	1202 (54.19)	621 (51.15)	1823 (53.12)
8	0 (0.00)	2 (0.81)	2 (0.46)	0 (0.00)	1 (0.10)	1 (0.06)	2 (0.14)	2 (0.09)	3 (0.25)	5 (0.15)
9	2 (1.06)	5 (2.03)	7 (1.61)	5 (0.79)	11 (1.14)	16 (1.00)	30 (2.15)	37 (1.67)	16 (1.32)	53 (1.54)
Total	188	246	434	634	968	1602	1396	2218	1214	3432

NOTE. Data are no. (%) of alleles.

individuals with the *DC-SIGNR* homozygous 7/7 genotype in the *DC-SIGNR* repeat region have an increased risk of HIV-1 infection ($P = .0015$), although this association was much stronger in the Seattle cohort ($P = .0014$) than in the MACS cohort ($P = .1890$). Individuals with the *DC-SIGNR* heterozygous 7/5 genotype in the *DC-SIGNR* repeat region were more frequent in the multiply exposed HIV-1-seronegative or high-risk HIV-1-seronegative group, both in the Seattle cohort ($P = .0271$) and in the combined Seattle-MACS cohort ($P = .0291$), although, because of the adjustment for multiple comparisons, the difference was not statistically significant. Furthermore, in the MACS cohort, individuals with the 7/5 genotype were not significantly more frequent in the high-risk HIV-1-seronegative group (34.2%) than in the HIV-1-seropositive group (29.3%). In a preliminary study, we had found that *DC-SIGNR* repeat-region polymorphisms had no effect on HIV-1 disease progression measured in terms of time to development of AIDS, time to AIDS-related death, time to <200 CD4⁺ cells/mm³ of blood, and viral load (data not shown).

Because other genetic polymorphisms may also affect the risk of HIV-1 infection and disease progression, we also screened the Seattle cohort for polymorphisms including *CCR5-Δ32*, *CCR5* promoter polymorphisms, *CCR2-64I*, *SDF1-3'A*, *RANTES-28G* and *-403A*, the coding sequences of *CCR5* and *RANTES*, and the *DC-SIGN* repeat region [7]. We found that, except for *CCR5-Δ32* homozygosity and *DC-SIGN* repeat-region variants, no polymorphisms were associated with resistance to HIV-1 infection in the individuals studied [7]. To avoid the potential influence that *CCR5-Δ32* homozygosity and *DC-SIGN* repeat-region variants might have on the results for the *DC-SIGNR*, we performed similar analyses after excluding the individuals who were either homozygous for *CCR5-Δ32* or heterozygous for *DC-SIGN* repeat-region variants; we found that our results for the *DC-SIGNR* remained the same. These observations strengthen our findings that the *DC-SIGNR* homozygous 7/7 genotype is associated with an increased risk

of HIV-1 infection, whereas the *DC-SIGNR* heterozygous 7/5 genotype may be associated with a decreased risk of HIV-1 infection.

In contrast to the results of the present study, Lichterfeld et al., in their comparison of 134 healthy volunteers and 391 HIV-1-seropositive individuals, did not detect any association between *DC-SIGNR* repeat-region polymorphisms and HIV-1 transmission [14]. We suggest that Lichterfeld et al.'s different results can be explained by their study's different cohort structure. To investigate this possibility, we further analyzed the distribution of *DC-SIGNR* repeat-region genotypes and alleles—comparing it in *all* of our HIV-1-seronegative subjects versus our HIV-1-seropositive subjects. No significant differences between these 2 groups were revealed, either in the Seattle cohort or in the combined Seattle-MACS cohort; therefore, the probable explanation for Lichterfeld et al.'s failure to detect any association between *DC-SIGNR* repeat-region polymorphisms and HIV-1 transmission is that their study did not include highly exposed HIV-1-seronegative individuals. The discrepancy between our results and those reported by Lichterfeld et al. highlights the need for a large collaborative meta-analysis, which also has been proposed elsewhere [15]. Our results, from a comparison, in 2 cohorts, of multiply exposed HIV-1-seronegative individuals versus HIV-1-seropositive individuals, suggest that *DC-SIGNR* polymorphisms may influence susceptibility to HIV-1 infection. However, this association should be interpreted with caution, because we failed to detect any significant difference, in the distribution of *DC-SIGN* repeat-region genotypes, between the general HIV-1-seronegative individuals and the HIV-1-seropositive individuals, which suggests that these associations, although statistically significant, may be biologically minor. Nonetheless, the mechanism whereby *DC-SIGNR* repeat-region polymorphisms affect HIV-1 transmission remains an area for future study and has the potential to affect the prevention of HIV-1 transmission.

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