Adverse Associations Between CX3CR1 Polymorphisms and Risk of Cardiovascular or Cerebrovascular Disease

Elise Lavergne, Julien Labreuche, Mehdi Daoudi, Patrice Debré, François Cambien, Philippe Deterre, Pierre Amarenco, Christophe Combadière; on Behalf of the GENIC Investigators

**Objective**—We investigated the role of monocyte-recruiting chemokines in cerebrovascular diseases among the subjects of the GENIC case-control study of brain infarction (BI).

**Methods and Results**—Of the genotypes tested, only homozygosity for the rare CX3CR1 alleles was more frequent in cases than in controls: the I249 and M280 alleles were associated with an increased risk of BI (OR, 1.66 and OR, 2.62 with \( P < 0.05 \), respectively). This effect was independent of other established risk factors and uncorrelated with disease severity. The study confirmed previous reports of a dominant protective association between CX3CR1-I249 allele and the risk of cardiovascular history. The risk of BI associated with homozygosity for the rare CX3CR1 alleles was enhanced in patients with no previous cardiovascular events. Ex vivo studies showed that the number of monocytes adhering to immobilized CX3CL1, the CX3CR1 ligand, increased proportionally to the number of CX3CR1 mutated alleles carried by the individual.

**Conclusions**—The rare CX3CR1 alleles were associated with an increased risk of BI and with reduced frequency of cardiovascular history. We propose that the extra adhesion of monocytes observed in individuals carrying rare alleles of CX3CR1 may favor mechanisms leading to stroke. *(Arterioscler Thromb Vasc Biol. 2005;25:847-853.)*

**Key Words:** cerebral infarction ■ genetics ■ leukocytes ■ chemokines ■ inflammation ■ risk factors
Although many studies have focused on CAD, very few reports examine the potential role of chemokines and their receptors in cerebrovascular pathologies. We decided to extend our investigation of the role of chemokines in these syndromes and therefore evaluated a number of chemokines and their receptors in the GENIC case-control study of BI.

Methods

Study Population

The GENIC (“profil GENétique de l’Infarctus Cérébral”) case-control study recruited 510 consecutive patients from all patients admitted to 12 French neurological departments. Controls (n=510) with no history of stroke were recruited from individuals hospitalized at the same institutions for any reason other than neurological disease. Stratification by age (±5 years) and sex was used to match case and control patients. Controls with a cardiovascular history other than stroke were eligible if they had 2 white parents. Two neurologists classified patients into etiologic BI subtypes, as previously described.24

Data Collection and Risk Factor Definition

A structured questionnaire was used to collect information about all subjects. We defined hypertension as a history of treated hypertension and a positive cardiovascular history as a history of MI, angioplasty, coronary artery bypass surgery, or lower-limb arterial disease. We classified subjects as having diabetes if they reported being treated for insulin-dependent or noninsulin-dependent diabetes. Use of lipid-lowering drugs was assessed.

CX3CR1, CCR2, CCR5, and CCL2 polymorphisms were identified with Minor Groove Binder polymerase chain reaction-based amplification technology from Perkin Elmer (Applied Biosystems Division, Cheshire, UK). The primer expression program (Perkin Elmer) was used to design the probes and primers (Table I, available online at http://atvb.ahajournals.org). Each polymerase chain reaction contained 10 to 200 ng of genomic DNA, 900 nM primers, 200 nM probes, and 6 mL of TaqMan Universal polymerase chain reaction master mix (Perkin Elmer). Amplification took place under the following conditions: 50°C for 2 minutes and 95°C for 10 minutes, followed by 40 cycles of 95°C for 15 seconds and 62°C for 1 minute. Real-time detection and analysis were performed on an ABI 7700 thermocycler (Perkin Elmer).

Cells

Peripheral blood mononuclear cells were isolated from heparinized venous blood from healthy volunteers by 1-step centrifugation on a Ficoll separating solution (Biochrom KG, Berlin, Germany). Monocytes isolated by a negative procedure (Dynal Biotech ASA, Oslo, Norway) according to the manufacturer’s instructions were 80% to 95% pure (confirmed by flow cytometric analysis). CX3CL1-expressing human embryonic kidney (HEK) cells were obtained as previously described.

Chemotaxis was performed in a 96-well chemotaxis chamber with a filter porosity of 10 μm (NeuroProbe, Cabin John, Md) as previously described.25 Adhesion experiments used the conventional parallel-plate flow technique. Briefly, CFMDF-labeled monocytes were allowed to interact with HEK cells in the flow chamber at controlled shear stress and the adherent cells were counted.

Statistical Analysis

Allelic frequencies were calculated by gene counting. Hardy–Weinberg equilibrium was tested with the χ² statistic. To compare the overall distribution of the genotypes of each polymorphism among cases and controls, we used the −2 log-likelihood statistic of a logistic regression model adjusted for matching variables (ie, age, sex, and center). To ensure all genotyped controls and cases were entered in the analysis, we did not use a conditional logistic regression analysis for matched sets. For each CX3CR1 polymorphism, genotypic odds ratios (ORs) for BI were calculated by a conditional logistic regression adjusted for matching variables, assuming dominant and recessive models. Polymorphisms and haplotype analysis were adjusted for cerebrovascular history. The log-likelihood of this model was not significantly different from that of a codominant genetic model. Our analysis concerned the entire study group and were subsequently stratified according to the main BI subtypes (ie, atherothrombotic strokes, lacunar strokes, cardioembolic strokes, and strokes of unknown cause); in each stratum, cases were compared with their matched controls. Analyses concerning strokes of undetermined cause are not reported, because this is, by definition, a highly heterogeneous group. The homogeneity across the main subtypes of the association between each CX3CR1 polymorphism and the disease was assessed with the Breslow–Day heterogeneity test. Haplotype analysis was performed to better-characterize the contribution of CX3CR1 polymorphisms to the risk of BI. Pair-wise haplotype disequilibrium was estimated with a log-linear model analysis.26 As previously reported,19,21 the CX3CR1-249I and T280M polymorphisms were in complete linkage disequilibrium; they generated 6 combined genotypes and 3 haplotypes (VT, IT, and IM). ORs for BI associated with VT were calculated by logistic regression adjusted for matching variables, assuming dominant and recessive models. Polymorphisms and haplotype analysis were adjusted for cerebrovascular risk factors (ie, history of hypertension and diabetes, current smoking, total and low-density lipoprotein cholesterol, and cardiovascular history). The homogeneity of the ORs across cerebrovascular risk factors was tested by introducing the corresponding interaction term into models. Statistical testing was 2-tailed, with α set at 0.05. Data were analyzed with the SAS package (SAS Institute, Cary, NC).

Results

Association Between BI and Established Risk Factors

To evaluate the impact of chemokines and their receptors in stroke, we selected a panel of compelling candidate molecules (those previously reported to have genetic variations involved in atherosclerosis, such as CCR5Δ32, CCR2-164 and its ligand CCL2-G2578, CX3CR1-I249, and CX3CR1-M280) and studied their allelic distribution in the GENIC cohort. Table 1 summarizes the general characteristics of the
study subjects. Case subjects had a higher frequency of cerebrovascular risk factors (smoking, hypertension, hypercholesterolemia, and diabetes) and reported a cardiovascular history more frequently than controls.

Distribution of Chemokine and Chemokine Receptor Polymorphisms in the GENIC Study Population

Table 2 shows the distribution of the various genotypes among the case and control subjects. The allelic frequency of each rare allele fell within the range reported in previous studies. The frequencies of the polymorphisms of chemokine receptors and chemokines did not deviate from Hardy–Weinberg equilibrium among cases or controls (data not shown). The similarity of the genotype distribution of the CCR5Δ32 and CCL2-G2578 alleles among cases and controls (P = 0.98 and P = 0.45, respectively) indicated that these polymorphisms had no significant effect on the BI risk. The proportion of individuals carrying the less common CCR2 allele was slightly higher for cases than controls, but not significantly (P = 0.13). The difference in the proportions of those carrying the rare CCR2-I64 allele (heterozygous or homozygous) between the case and control groups was just on the borderline of significance (P = 0.05). Cases were homozygous for the CX3CR1-I249 or the CX3CR1-M280 alleles more often than controls were (Table 2; P = 0.07 and P = 0.04, respectively). When we consider the reference group of subjects homozygous for the frequent allele (VV or TT, respectively), we see that heterozygosity for CX3CR1 polymorphisms did not increase BI risk (Table 3). We therefore computed ORs associated with homozygosity for the I249 allele (OR = 1.68; 95% confidence interval [CI], 1.04 to 2.74) and for the M280 allele (OR = 2.89; 95% CI, 1.23 to 6.47). After adjustments for other cerebrovascular risk factors such as history of hypertension and diabetes, total and low-density lipoprotein cholesterol, current smoking, and cardiovascular history, the associations between BI and the CX3CR1 polymorphisms were slightly attenuated but remained significant (Table 3). No heterogeneity in the association between CX3CR1 polymorphisms and BI was observed according to BI subtype (Table 4), but we note that the power of the analysis was limited by the relatively small number of patients in each category. In addition, the CX3CR1 polymorphisms were not statistically associated with disease severity, as assessed by intima-media thickness, handicap scores, or mortality (data not shown).

Enhanced Risk of BI Associated With Rare CX3CR1 Alleles in Patients With No Cardiovascular History

The association of CX3CR1-I249 and CX3CR1-M280 alleles with an increased risk of BI was intriguing because previous work, including ours, demonstrates that CX3CR1 alleles are associated with a reduced risk of cardiovascular events.19–21

<table>
<thead>
<tr>
<th>Genotype</th>
<th>OR (95% CI)</th>
<th>OR (95% CI)*</th>
<th>OR (95% CI)*†</th>
</tr>
</thead>
<tbody>
<tr>
<td>V249I</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VV</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>VI</td>
<td>0.89 (0.67–1.16), P = 0.38</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>1.59 (0.97–2.63), P = 0.07</td>
<td>1.68 (1.04–2.74), P = 0.04</td>
<td>1.66 (1.00–2.76), P = 0.05</td>
</tr>
<tr>
<td>T280M</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TT</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>TM</td>
<td>1.10 (0.82–1.47), P = 0.55</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MM</td>
<td>2.89 (1.26–6.66), P = 0.01</td>
<td>2.89 (1.23–6.47), P = 0.01</td>
<td>2.62 (1.11–6.18), P = 0.03</td>
</tr>
</tbody>
</table>

ORs are computed by using logistic regression analysis after adjustments for matching variables.
*Computed by comparing the frequency of subjects homozygous for the rare allele with the frequency of carriers of the frequent allele in cases and controls.
†Additional adjustments for history of hypertension and diabetes, total and LDL cholesterol, current smokers, and cardiovascular history.
Consistently with these previous findings, among cases, cardiovascular history was less frequent in those with at least 1 CX3CR1-I249 allele (26.7% VV, 18.7% VI, 10.9% II; \(P < 0.01\)). A similar association was observed with the CX3CR1-M280 allele (24.8% TT, 18.6% TM, 4.8% MM; \(P < 0.04\)).

Haplotype analysis sought to identify alleles associated with risk of BI (Table 5). Only the IM haplotype was positively associated with BI under the recessive model (OR, 2.68; 95% CI, 1.16 to 6.19). Similar results were found after adjustment for cerebrovascular risk factors. Because we had found an interaction between CX3CR1 polymorphisms and cardiovascular history (\(P = 0.05\)), we performed a subgroup analysis according to cardiovascular history. IM homozygosity was associated with an increased risk of BI only among subjects with no cardiovascular history, with an adjusted OR of 4.18 (95% CI, 1.49 to 11.74). In subjects with cardiovascular history, the IM haplotype was associated with a tendency toward reduced risk of BI (OR, 0.09; 95% CI, 0.01 to 1.96). These results were limited, however, by the relatively small number of homozygotes for the rare allele with cardiovascular history.

**CX3CR1 Genotypes and Monocyte Cell Functions**

To investigate how CX3CR1 polymorphisms might affect predisposition to BI or CAD, we evaluated the functional impact of these CX3CR1 allelic variants on monocytes, the cells considered to be key players in atherogenesis. An in vitro chemotactic assay tested cells’ response to soluble CX3CL1 and a cell adherence assay tested their response to membrane-anchored CX3CL1. First, we compared the trans-

### TABLE 4. Association Between CX3CR1 Polymorphisms and Main BI Subtypes

<table>
<thead>
<tr>
<th></th>
<th>V249I Cases</th>
<th>Controls</th>
<th>T280M Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atherothrombotic strokes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>49.5 (53)</td>
<td>45.4 (49)</td>
<td>67.3 (72)</td>
<td>63.9 (69)</td>
</tr>
<tr>
<td>12</td>
<td>37.4 (40)</td>
<td>47.2 (51)</td>
<td>27.1 (29)</td>
<td>33.3 (36)</td>
</tr>
<tr>
<td>22</td>
<td>13.1 (14)</td>
<td>7.4 (8)</td>
<td>5.6 (6)</td>
<td>2.8 (3)</td>
</tr>
<tr>
<td>OR (95% CI), (P)</td>
<td>2.19 (0.75–6.32), 0.15</td>
<td>1.81 (0.38–8.50), 0.45</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lacunar strokes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>53.7 (51)</td>
<td>50.0 (51)</td>
<td>66.3 (63)</td>
<td>71.8 (74)</td>
</tr>
<tr>
<td>12</td>
<td>35.8 (34)</td>
<td>43.1 (44)</td>
<td>29.5 (28)</td>
<td>27.2 (28)</td>
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<tr>
<td>22</td>
<td>10.5 (10)</td>
<td>6.9 (7)</td>
<td>4.2 (4)</td>
<td>1.0 (1)</td>
</tr>
<tr>
<td>OR (95% CI), (P)</td>
<td>1.46 (0.48–4.45), 0.50</td>
<td>4.51 (0.39–51.99), 0.23</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardioembolic strokes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>47.1 (33)</td>
<td>41.7 (30)</td>
<td>73.2 (52)</td>
<td>68.1 (49)</td>
</tr>
<tr>
<td>12</td>
<td>45.7 (32)</td>
<td>51.4 (37)</td>
<td>21.1 (15)</td>
<td>30.5 (22)</td>
</tr>
<tr>
<td>22</td>
<td>7.2 (5)</td>
<td>6.9 (5)</td>
<td>5.6 (4)</td>
<td>1.4 (1)</td>
</tr>
<tr>
<td>OR (95% CI), (P)</td>
<td>1.29 (0.30–5.51), 0.73</td>
<td>4.89 (0.42–57.31), 0.22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strokes of unknown cause</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>54.1 (59)</td>
<td>61.3 (65)</td>
<td>70.6 (77)</td>
<td>77.4 (82)</td>
</tr>
<tr>
<td>12</td>
<td>36.7 (40)</td>
<td>34.0 (36)</td>
<td>23.9 (26)</td>
<td>21.7 (23)</td>
</tr>
<tr>
<td>22</td>
<td>9.2 (10)</td>
<td>4.7 (5)</td>
<td>5.5 (6)</td>
<td>0.9 (1)</td>
</tr>
<tr>
<td>OR (95% CI), (P)</td>
<td>2.28 (0.67–7.75), 0.19</td>
<td>6.80 (0.73–62.86), 0.09</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 4: Association Between CX3CR1 Polymorphisms and Main BI Subtypes

<table>
<thead>
<tr>
<th>Model</th>
<th>Haplotype</th>
<th>OR (95% CI)*</th>
<th>(P)*</th>
<th>OR (95% CI)†</th>
<th>(P)†</th>
<th>OR (95% CI)‡</th>
<th>(P)‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IT</td>
<td>0.84 (0.61–1.16)</td>
<td>0.29</td>
<td>0.90 (0.64–1.27)</td>
<td>0.50</td>
<td>0.94 (0.64–1.35)</td>
<td>0.50</td>
</tr>
<tr>
<td></td>
<td>IM</td>
<td>1.16 (0.87–1.55)</td>
<td>0.32</td>
<td>1.13 (0.83–1.54)</td>
<td>0.90</td>
<td>1.27 (0.91–1.78)</td>
<td>0.90</td>
</tr>
<tr>
<td></td>
<td>Recessive IT</td>
<td>1.16 (0.46–2.90)</td>
<td>0.76</td>
<td>1.26 (0.46–3.40)</td>
<td>0.40</td>
<td>1.77 (0.60–5.17)</td>
<td>0.40</td>
</tr>
<tr>
<td></td>
<td>IM</td>
<td>2.68 (1.16–6.19)</td>
<td>0.02</td>
<td>2.54 (1.07–6.01)</td>
<td>0.002</td>
<td>4.18 (1.49–11.74)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Table 5: Odd Ratios for BI Associated With IT and IM Haplotypes

* Logistic regression adjusted on matching variables.
† Additional adjustments for history of hypertension and diabetes, total and LDL cholesterol, current smokers, and cardiovascular history.
‡ Additional adjustments for history of hypertension and diabetes, total and LDL cholesterol, and current smokers.
Migration and adhesive capacities of monocytes from individuals with various CX3CR1 genotypes. A, Monocytes from individuals homozygous for the CX3CR1-V249 allele (VV; black square, n=5) and heterozygous or homozygous for the CX3CR1-I249 allele (VI; white square, n=3; and II; white circle, n=3) were assayed in a transmigration assay. Data are summarized as the mean±SEM of triplicates from 4 independent experiments and presented as chemotactic index. B, Monocytes from the same individuals were also tested for adhesion in a parallel-plate laminar flow chamber, with coverslips coated with adherent CX3CL1-expressing HEK cells. Adherent monocytes were counted after each flow change. Monocytes from each individual were tested in duplicate in 2 independent experiments. Numbers of individuals per group are indicated above each bar. *P<0.05 between 2 genotype groups.

Discussion

This study shows that only the rarer CX3CR1 alleles, of all the chemokine and receptor alleles tested, were associated with an increased BI risk and they had no effect on disease severity. We also characterized the impact of mutated CX3CR1 alleles on monocyte functional response and found that the number of monocytes adhering to CX3CL1 increases with the number of I249 alleles that an individual carries. These results support the hypothesis that CX3CR1 plays a pathogenic role in cerebrovascular disease.

A few studies report that some chemokine receptor gene variants are associated with susceptibility to CAD. Our study is the first to our knowledge to indicate that the CX3CR1-I249 allele and its genetically linked partner, the CX3CR1-M280 allele, are associated with an increased risk of BI. Because of the linkage disequilibrium between M280 and I249, it is difficult to distinguish the independent contribution of each of these polymorphisms to BI risk. These polymorphisms are not, however, associated with disease severity, as measured by intima-media thickness, handicap scoring, or mortality (data not shown). These results are especially intriguing because previous work, including ours, demonstrated that the rare CX3CR1 allele is associated with a reduced risk of cardiovascular diseases. The effect in each of these studies was dominant, whereas the association with increased BI risk we describe here appeared to be recessive. This difference suggests that different cellular pathways may underlie the mechanisms of these 2 conditions. Of the other alleles tested, the 32-bp deletion in the CCR5 open reading frame, which causes the loss of CCR5 receptors on the lymphoid cell surface, was not significantly associated with either BI risk or cardiovascular history. This finding is concordant with previous epidemiological data as well as with a model of atherogenesis in mice deficient for CCR5 and apolipoprotein E genes. Other reports indicate that the CCR5Δ32 allele reduces risk for early MI and severe CAD by attenuating inflammatory responses. The role of the CCR2/CCL2 axis in atherogenesis is well-established in murine models: both types of deficient mice have fewer and less severe atherosclerotic lesions. CCL2 antagonist has proven potent in controlling plaque formation in mice. In humans, a substitution in the distal regulatory region of the CCL2 gene (CCL2-G2578) has been shown to modulate CCL2 production and to be associated with a reduced risk of severe CAD. Here, we found no association between the less common CCL2 allele and the risk of BI or cardiovascular history. The situation is even more complex for the CCR2-I64 allele, which has a dominant borderline association with increased BI risk. These results are ambiguous, probably because of this allele’s low frequency, and they do not clarify the initial observation that CCR2-I64 is associated with a reduced risk of MI or the subsequent reports that it predisposes its carriers to MI. Further work is needed to clarify the pathogenic impact of these alleles.

In view of its prognostic power for AIDS and cardiovascular and cerebrovascular diseases, understanding the molecular defect caused by CX3CR1 mutations is an important challenge. A recent study reports a global impairment of the CX3CR1-M280 cell response to CX3CL1, ie, ligand-dependent challenge.
binding, calcium response, and adhesive and chemotactic functions. We could not confirm these results and obtained opposite results. Monocytes from individuals carrying the CX3CR1-I249-M280 allele were captured in larger numbers than monocytes from those carrying CX3CR1-V249-T280 allele. This set of results was similar to those we obtained with human peripheral blood mononuclear cells of various genotypes and HEK cells transfected with CX3CR1 variants, and with 2 different techniques of testing adherence. We do not yet have a reasonable explanation for the discrepancies with the previous report from McDermott, but it may be interesting to consider sets of data as reflecting different CX3CR1 functional states. The apparent discrepancies may be artifactual and stem from subtle differences in the techniques or cell environment used. Further work to identify the various transduction steps underlying the CX3CR1-I249-M280 effect might help to clarify these conflicting data.

Monocytes recruited in the intima layer to form atherosclerotic plaque first adhere to and cross the endothelial barrier. Umehara et al suggested, based on an in vitro chemotaxis assay, that membrane-bound CX3CL1 expressed on endothelial cells strengthens monocyte adhesion and thus decreases transmigration of monocytes across endothelial cell monolayers. This phenomenon may reduce atherosclerosis. The decreased lesion infiltration may mimic the pathological phenotype observed in mice deficient for apolipoprotein E and CX3CR1 genes; the first step of monocyte recruitment is unfavorable in these mice because there are fewer monocyte anchors to the endothelial wall. Platelets that express CX3CR1 play a key role in the pathogenesis of atherothrombotic conditions, eg, acute coronary syndromes and cerebrovascular events. In these disease conditions, overexpression of CX3CL1 by vascular endothelial cells may promote platelet adhesion and activation. It is thus likely that CX3CR1 rare allele may favor proatherogenic conditions. Interestingly, platelet activity as measured by mean platelet volume was positively associated with increased risk of BI but not with major coronary events. We propose that the level of chemokines produced by different vascular beds may determine the proatherogenic effect of platelets. In addition, Yoneda et al report a positive correlation between NK cell adhesion to endothelial cells and susceptibility to NK cell-mediated cytolysis. They also found that soluble CX3CL1 markedly suppressed both of these enhanced functions. Thus, CX3CL1, in addition to its monocyte and platelet tethering roles, may favor NK cell–mediated endothelial damage, which can ultimately promote atherothrombotic conditions, as McDermott et al have proposed. More globally, it is conceivable that the risk of cardiovascular or cerebrovascular disease depends on the relation between the systemic release of CX3CL1 that promotes CX3CR1-expressing cell activation and the competing locally expressed membrane-bound CX3CL1, which promotes CX3CR1-expressing cell adherence. To clarify these issues, the CX3CR1-mediated cellular mechanisms predisposing to BI must be characterized.

Consideration of potential mechanisms whereby the CX3CR1-I249M280 haplotype might predispose carriers to BI is also important. We observed the relation between the CX3CR1 polymorphism and BI only with the homozygous genotype, even though the in vitro data from the adhesion assay were significant with the heterozygous genotype. One way to reconcile these 2 sets of data is to hypothesize that the extra monocyte adhesion is not biologically relevant until it exceeds a threshold reached only by individuals homozygous for these rare alleles. The in vitro assay that revealed the specific functional characteristic of the rare allele may not reflect physiological flow conditions; therefore, the discrimination between heterozygous and homozygous cells may be artifactual.

This work showed that naturally occurring mutations in CX3CR1 have a severe impact on susceptibility to BI and CAD. Because of the complexity of pathologies underlying ischemic stroke, which develop over many years and are likely affected by many different factors, further studies are needed to confirm these findings. This work further revealed that CX3CR1 might be considered a powerful prognostic tool and an excellent therapeutic target for cardiovascular and cerebrovascular diseases.

Acknowledgments

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References


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