CC chemokine receptor (CCR)2 polymorphism in Czech patients with myocardial infarction

Jana Petrko a,b, Zuzana Cermako a,c, Jiri Drabek a, Jan Lukl b, Martin Petrek a,*

a Department of Immunology, Palacky University, I.P. Pavlova str. 6, Olomouc, Czech Republic
b Department of Internal Medicine I, Palacky University, Olomouc, Czech Republic
c Blood Centre, Faculty Hospital, Ostrava, Czech Republic

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Abstract

Examining an association between myocardial infarction (MI) and the Val/Ile polymorphism in the gene for CC chemokine receptor (CCR)2 at the position 64 (CCR2-V64I), 122 MI Czech patients and 277 unrelated control (C) subjects were genotyped by PCR-SSP. The frequency of the VI genotype of CCR2-V64I was increased in MI patients in comparison with the control population (P = 0.03). Further analysis revealed that relationship between the VI genotype and MI is specific only for females and, strikingly, this genotype was associated to an early MI onset (before or at the age of 50 years). Females with the VI genotype were seven times more prone to suffer from MI before 50 years than those with the VV genotype (P < 0.01). If the VI genotype of the CCR2-V64I is indeed a risk factor for an earlier MI onset in females must be checked by independent studies in other centres and/or populations.

Keywords: CCR2-V64I; Coronary artery disease; Atherosclerosis

Atherosclerotic inflammation of coronary arteries is a critical process in the pathogenesis of myocardial infarction (MI). Initial phase of atherosclerosis is characterised by migration of monocytes into the vessel wall mediated by chemotactic cytokines such as MCP-1 (CCL2) [1] and fractalkine (CX3CL1) [2]. Effects of these chemokine ligands are mediated via receptor molecules: CC chemokine receptor (CCR)2, binding MCP-1, and CX3C chemokine receptor (CX3CR1), the fractalkine receptor. Both aforementioned receptors are encoded by polymorphic genes. A role for CX3CR1 and its polymorphism in atherosclerosis has been implicated from animal [2] and human [3] data. By contrast, a plausible relevance of the MCP-1 receptor for atherogenesis, based on the observation of alleviation of atherosclerotic process in CCR2−/− mice [4], has not yet been confirmed in humans. We have, therefore, focused on CCR2 gene and investigated whether a single nucleotide polymorphism (SNP) CCR2-V64I is associated with coronary artery disease manifested as MI.

Into a case control, association study we enrolled 122 patients (96 males, 26 females) presenting with MI and 277 age-matched control, healthy subjects (174 males, 103 females). All patients and control subjects were of Czech (Caucasian) origin; cardiovascular symptomatology in control subjects was excluded by questionnaire. Informed consent was obtained both from our patients and control subjects. The criteria for diagnosis of MI were compatible with those recommended by an international consensus [5]. Genotyping for CCR2-V64I polymorphism was performed by PCR with sequence specific primers as previously described [6]. Significance of differences between genotype and gene (allelic) frequencies of the polymorphism in patient and control groups was assessed by standard 2 × 2 χ² analysis by SIGTEST, a computer-based program that uses a Woolf–Haldane correction in cases of small numbers.

The distribution of genotype and gene frequencies of CCR2-V64I polymorphism in Czech patients with MI and control subjects is shown in Table 1. The control
population was in Hardy–Weinberg equilibrium with regard to the distribution of CCR2 genotypes. The frequency of the VI genotype of CCR2-V64I was increased in MI patients in comparison with the control population; patients with the VI genotype were in increased risk of MI (odds ratio, OR 7.2, 95% CI 1.7–30.0, P = 0.01). To further characterise this genotype as a plausible risk factor for MI, we have explored if the association between MI and the VI genotype of CCR2-V64I is present also in patient subsets: first, the probands were subdivided according to their sex and, second according to the age when their first MI symptoms appeared (Table 2). Strikingly, the VI genotype was related to the disease only in female populations; patients with the VI genotype were in Hardy–Weinberg equilibrium with regard to the distribution of CCR2 genotypes. The comparison of the VI genotype frequencies between the two groups of female patients, i.e. between those suffering from MI before and after the age of 50 years, confirmed that the VI genotype may modulate the age of MI onset: the OR exceeded the value of 5.0, the difference however fell just short of significance due to low patients number (P = 0.06).

This is a first report of association of CCR2-V64I polymorphism with coronary artery disease, and specifically with an early manifestation of MI in females. However, our study is not the first investigation of CCR2 polymorphism in this disease condition. Recently, genetic variation at the chemokine receptors CCR5 and CCR2 was explored in Spanish patients with
MI [7]. This study assigned a protective role against early MI to CCR5A32 mutation but association of CCR2-V64I polymorphism with MI was not observed [7]. Another study, directed at six different polymorphisms of the chemokine system in Hungarian population, also did not implicate CCR2-V64I polymorphism in coronary artery disease. By contrast, the authors basing also did not implicate CCR2-V64I polymorphism in cardiovascular system of the chemokine system in Hungarian population, [7]. Another study, directed at six different polymorphisms of the chemokine system in Hungarian population, did not observe association between CCR2-V64I polymorphism with MI was not observed [7].

Although this study was conducted in accordance with the guidelines for proper performance of association studies, including careful characterisation of clinical phenotype [9,10], it has some limitations. The significance of our observations could be strengthened if we recruited more female patients, however we were limited by less frequent occurrence of MI in females. We are also aware that there are many more candidate SNPs in the CCR2 gene or that the functional importance of the polymorphism selected for this study has not been yet clarified. However, for this initial investigation of chemokine polymorphism in coronary artery disease we decided to limit ourselves to CCR2-V64I because of the existence of inter-relationship between this and other SNPs in the region, standardised methodology [6] and mainly because of the fact that the data published so far were controversial and limited only to male population [7,8].

From geneticist point of view, coronary artery disease is a complex disease, in which the interactions between many genes are complemented by environmental and intrinsic factors [9]. Therefore, the mechanisms by which CCR2-V64I SNP may contribute to an earlier manifestation of coronary atherosclerosis in females remain at the level of speculations. Our main reason for reporting the observed association between the VI genotype of CCR2-V64I polymorphism and early MI in Czech females already at this stage of investigations is to invoke replication of our results in another centres and/ or populations. This would be in accordance not only with proper practice for genetic association studies but also with current opinion on their interpretation [10,11].

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References