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CCR5 promoter polymorphisms and HIV-1 perinatal transmission in Brazilian children

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Abstract

The frequencies of four CCR5 promoter polymorphisms, and of the Δ32 deletion, have been evaluated in Brazilian HIV-1 positive (HIV+) and HIV-1 negative (HIV−) children, both born from HIV-1 positive mothers and healthy controls (HC), with the aim of investigating whether CCR5 polymorphisms could be associated to vertical transmission of HIV-1. One hundred and six HIV-1 positive children and 70 HIV-1 negative children were enrolled from impoverished areas of Recife (Brazil). We recruited also as healthy controls 104 uninfected children from the same ethnic background, matched for age and known to be not at risk for HIV-1 infection. CCR5 polymorphisms were detected by PCR amplification and direct sequencing. Although no significative divergence was found for CCR5 Δ32, CCR5-59356-C/T and CCR5-59653 C/T polymorphisms, the frequency of CCR5-59353-T/C and CCR5-59402-A/G genotypes differed among HIV+, HIV− and HC children. The presence of the CCR5-59353-TT genotype indicated a trend for increased risk of vertical transmission of HIV-1 infection in Brazilian children, while the presence of the CCR5-59402-AA genotype is suggestive for a protective effect against HIV-1 vertical transmission.

Keywords: CCR5; Promoter; Polymorphisms; HIV-1; Vertical transmission

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1. Introduction

The role of chemokines in the inhibition of HIV-1 replication was demonstrated in 1995 (Cocchi et al., 1995) and then CCR5 and CXCR4 were recognized as the most important co-receptors for HIV-1 cell entry (Alkhatib et al., 1996; Deng et al., 1996; Feng et al., 1996). Since then, polymorphisms in genes encoding the chemokines have been analyzed in AIDS patients in order to elucidate their role in HIV-1 infection resistance and pathogenesis (Alkhatib et al., 1996). A deletion of 32bp in CCR5 (*Δ32*) originates a stop codon resulting in a truncated protein, not expressed on cell surface, that is associated with resistance to infection in homozygous individuals and delayed disease progression in heterozygous individuals. The allele and genotype distribution of *CCR5 Δ32* varies among the different geographic areas and has been reported to be rare in Africa where the HIV-1 epidemic exhibits rapid growth (Martinson et al., 1997).

In the last few years, several polymorphisms in the promoter region of CCR5 have been identified, classified into different haplotypes, and associated with AIDS progression in different ethnic groups such as Caucasian (Martin et al., 1998), Afro-American (An et al., 2000) and Chinese (Li et al., 2005). Homozygosity for the CCR5P1 haplotype was associated with a rapid progression to AIDS in both Caucasian and African–American populations (Winkler et al., 2004). CCR5 genetic polymorphisms are not only associated to AIDS progression but also to mother-to-child transmission, as reported by John et al. (2001) who evaluated the effect of four CCR5 promoter polymorphisms on systemic and mucosal HIV-1 replication, disease progression and perinatal transmission in a cohort of 276 HIV-1-seropositive women in Nairobi, Kenya. Likewise, a polymorphism (*CCR5-59356-T/C*) in the regulatory region of the CCR5 gene, has been associated to HIV-1 perinatal transmission in African–American children (Kostrikis et al., 1999).

The effects of CCR5 promoter polymorphisms on levels of expression of CCR5 have been described by several authors. Shieh et al. (2000) analyzed CCR2 and CCR5 promoter polymorphisms in a cohort of Chinese volunteers in Taiwan, showing that an increased number of CD4+ cells expressing CCR5 correlated with CCR5-59029A homozygosity without the interference of both the CCR2-64 and the CCR5 Δ32 mutations. It has also been reported that CCR5-2459 (A/G) promoter polymorphism determines CCR5 expression and predicts the magnitude of HIV-1 propagation, through in vitro infection of peripheral blood mononuclear cells obtained from healthy Caucasian blood donors with macrophage-tropic HIV-1 isolates (Salkowitz et al., 2003).

Recently, Li et al. (2005) demonstrated in a Chinese cohort that in the absence of the CCR2-64I mutation, individuals carrying CCR5P1 haplotype tended to express more surface CCR5 on monocytes and CD4+ cells (Li et al., 2005).

In our study, we have evaluated the frequencies of *CCR5 Δ32* and four CCR5 promoter region polymorphisms (*59353 T/C*, *59356 C/T*, *59402 A/G* and *59653 C/T*) in Brazilian HIV-1 positive and negative children exposed to infection risk, and healthy controls (HC), with the aim of investigating whether CCR5 polymorphisms are associated to vertical transmission.