

CCR2 Genetic Polymorphism And Its Potential Effect On HIV Acquisition In A Population Of Children Living In The Northern Region Of Cameroon

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Background and objectives: The association of chemokine receptor-2 (*CCR2*) polymorphism with HIV transmission or disease progression remains highly controversial. The role of *CCR2-64I* allele in HIV infection may differ from one population to another because of their genetic background. The objectives of this study were to characterize the *CCR2* genetic polymorphism and to determine its potential effect in HIV acquisition in children living in the Northern Region of Cameroon.

Materials and methods: A cross-sectional study was carried out in five health facilities in the Northern region of Cameroon. DNA was extracted from the Buffy coat of each participant using the QIAamp[®] DNA mini kit. The DNA extract was then subjected to polymorphic analyses. *CCR2* genotypes were analyzed by polymerase chain reaction (PCR) and restriction fragment length polymorphism (RFLP). The Chi-Squared test was used for the assessment of the Hardy-Weinberg equilibrium.

Results: A total of 134 children under 15 years comprised of 38 HIV-exposed infected (28.36%) and 96 HIV-exposed un-infected (71.64%) participants were recruited. Prevalences of 44.78% wild type homozygous, 48.52% heterozygous and 6.7% mutant homozygous alleles were found in the overall population. An allelic frequency of 29.69% for the mutant allele *CCR2-64I* was found in HIV-exposed un-infected individuals as compared to 34.21% in HIV-infected children ($p=0.47$).

Conclusion: The *CCR2-64I* allele is relatively common in the Northern Region of Cameroon, with a similar distribution among HIV-exposed un-infected and infected children. As this allele alone does not seem to confer protection against HIV-1 infection, further studies using genotype-combination of *CCR2* polymorphism and other single nucleotide polymorphisms would be of great relevance in both HIV prevention and novel therapeutic strategies.

Keywords: HIV acquisition, *CCR2* gene, pediatric population

Introduction

Of the estimated 36.9 million people living with HIV worldwide, approximately 1.8 million are children under 15 years of age^{1,2} of whom 90% live in Africa.³ This alarming situation is partly explained by the fact that sub-Saharan Africa is home to nearly 90% of pregnant women living with HIV. Because the immune system of children is not fully developed, their infection is more severe than in adults. They may experience the same common pediatric infections as HIV-negative children but

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cannot fight them as effectively. Cameroon is among the 22 countries with a high burden of HIV mother-to-child transmission (MTCT).⁴ A recent study carried out in Cameroon showed differential HIV prevalence according to the regions, ranging from 6.3% in the Southern Region to 1.5% in the Far North Region. The Northern Region, dominated by the Fulbe people, has one of the lowest prevalence rates (1.6%) among individuals aged from 15 to 49 years. The prevalence in children from 0 to 14 years was 0.2%.⁵ However, this region has the second highest rate of MTCT (7.8%). The prevalence of HIV among pregnant women in Cameroon is 5.7%, which is above the general level found among people aged from 15–49 (3.4%). Early Infant Diagnosis (EID) data collected from the Reference Laboratories database and Point of Care devices in Cameroon showed a national HIV positivity rate of 5% in 2017 for children exposed to HIV. In the Northern Region of Cameroon, this positivity rate is much higher (7.8%).⁶ More than 90% of HIV infections in children result from MTCT. Several maternal factors, including low CD4+ lymphocyte counts, high viral load, immune response, advanced disease status, smoking and drug abuse have been implicated in an increased risk of this transmission. However, the molecular mechanisms of HIV-1 MTCT and differential infection in neonates/infants remain poorly understood.

Studies have shown that chemokine and chemokine receptors involved in the modulation of innate and adaptive immune processes also act as co-receptors to HIV. They help viral attachment and entry into host cells. Polymorphisms in genes encoding chemokine such as stromal cell derived factor 1 (*SDF1*) and chemokine receptors such as C-C motif chemokine receptor 2 (*CCR2*) have been implicated in differential outcomes of HIV infection and disease progression.⁷ *CCR2-64I* polymorphism is one of the important variations that modulate this infection.⁸ This is by a single nucleotide substitution of a valine residue for an isoleucine at position 64 in the *CCR2* receptor.⁹ It occurs in a transmembrane segment of the receptor and is unlikely to significantly alter the structure or function of the *CCR2* receptor.¹⁰ The effect of chemokine and chemokine receptor genetic polymorphisms like *CCR2-64I* associated with HIV-1 transmission and/or rate of disease progression in infected subjects remains highly controversial.^{11–13} Several studies have investigated whether the *CCR2-Val64Ile* polymorphism affects susceptibility to Human Immune deficiency Virus type-1 (HIV-1), but the results have been inconclusive. The

meta-analysis of Mouafo et al¹¹ clearly showed this controversy as they revealed a protective role of *CCR2-64I* on MTCT using infant and maternal samples from population in Malawi, South Africa and Uganda. On the contrary, *CCR2-64I* was found to have no effect on MTCT in mothers in Western Kenya. A protective role of the allele was found in a study carried out by Mangano et al.¹⁴ Another study by Mabuka et al¹⁵ reported a partial protection while others found that this allele seemed not to confer protection against HIV infection.^{16,17} The infant's genetics can alter the risk for HIV-1 infection. To our knowledge, this is the first study to report the frequencies of *CCR2* chemokine receptor variants in a pediatric population in this area, considering their ethnic background. The study is intended to determine the distribution of the *CCR2* polymorphism and its potential effect on HIV acquisition in children living in the Northern Region of Cameroon. Identifying genetic susceptibility variants could help in predicting disease course.

Materials And Methods

Patient Selection

A total of 134 children under 15 years, comprised of 38 HIV-infected and 96 HIV-exposed un-infected individuals, were recruited from August 2015 to October 2016. Five (5) mL of total blood were collected in EDTA tubes from each participant. The plasma was used for HIV diagnosis and the Buffy coat for genomic DNA extraction prior to genotyping. Only children whose mothers provided parental consent were enrolled, and a questionnaire was administered to them. The parental consent was written. Also, this study was conducted in accordance to the Declaration of Helsinki.

The study protocol was reviewed and approved by the Cameroon National Ethical Committee for Research on Human Health (N°2013/11/375/L/CNERSH/SP). Permission to collect and analyze samples was obtained through authorizations given by the Ministry of Public Health (MoH) and the Directors of the different health facilities.

Setting

The study was carried out in five health facilities of the Northern region of Cameroon: the Garoua Regional Hospital; the District Hospitals of Guider and Figuil, the Hospitals of Laine and Djamboutou.

HIV Testing

For children older than 18 months, the detection of HIV antibodies was performed using the Determine HIV1/2 test

(Alere Medical Co., Ltd. 357 Matsuhidai, Matsudo-shi, Chiba). For positive samples, a confirmation was done with the OraQuick test (OraSure Technologies, Inc. Bethlehem). For children less than 18 months, HIV diagnosis was performed by PCR using Abbott qualitative Real-time PCR kits (Abbott TM mSample Preparation System DNA» Promega Corporation. Madison WI 53711 USA). EID is an important step to link infants infected with HIV to ART and to reduce infant morbidity and mortality. The Abbott qualitative Realtime PCR was used in this study for the detection of HIV-1 nucleic acids. The lower limit of detection of the test is 2500 copies/mL. When the number of copies is ≥ 2500 copies/mL, the test detects the presence of nucleic acids and the result is "Detected." If the number is below 2500 copies/mL,^{18,19} the test does not detect nucleic acids and the result is "Not detected." This is a limit and to overcome this limit, children are followed up until 18 months for a negative serology

DNA Extraction

Genomic DNA was extracted from the buffy coat using the QIAamp® DNA mini kit (Qiagen, 40724 Hilden, Germany) according to the manufacturer's instructions. The extract was then re-suspended in 200 μ l AE buffer (Qiagen, 40724 Hilden, Germany) and stored at -20°C for further analyses.

CCR2 Genotyping

Polymerase Chain Reaction and Restriction Fragment Length Polymorphism (PCR-RFLP) were used for *CCR2* genotyping.

The following pairs of primers were used for the PCR: Forward 5'-CTTCATCATCCTCCTGACAATCG-3', reverse 5'-GACCAGCCCCAAGTTGACTATC-3' as previously described.²⁰ A 380 base pair (bp) fragment was amplified in a 25 μ L volume reaction containing 0.2 μ M of each primer, 1X PCR buffer containing MgCl_2 , 200 μ M of each dNTP (Thermo Scientific), 0.625 Units of *Taq* polymerase (Roche Diagnostic, One Lambda, USA) and 5 μ L (2–5 ng) of genomic DNA. The reaction mix was subjected to amplification using the following conditions: initial denaturation at 95°C for 3min, followed by 40 cycles of denaturation at 94°C for 30S, annealing at 63°C for 30S, extension at 72°C for 30S and a final extension at 72°C for 10 min. A 10 μ L volume of the PCR product was digested overnight using 5 Units of *FokI* restriction enzyme (New England Biolabs). The digested product was separated on 2% agarose gel, stained with ethidium bromide and visualized under UV light, then photographed. The mutated allele (*CCR2-64I*) was susceptible to *FokI* restriction digestion. The PCR product was then cleaved, giving rise to two fragments of 215 bp and 165 bp. The wild type allele (*CCR2-64V*) lacked the sequence recognised by *FokI*, leaving the 380 bp PCR product undigested. Two fragments of 215 and 165 bp were seen in the gel if a person was homozygous for the mutation. For the heterozygous, there were three fragments on the gel at 380 bp, 215 bp and 165 bp (Figure 1). Only one fragment was seen at 380 bp if the *CCR2* gene fragment did not have the mutation and the person was of a wild type.

Statistical Analyses

For the calculation of allelic frequencies, the following formula was used: $F = (h + 2H)/2N$, where F is the frequency, H is

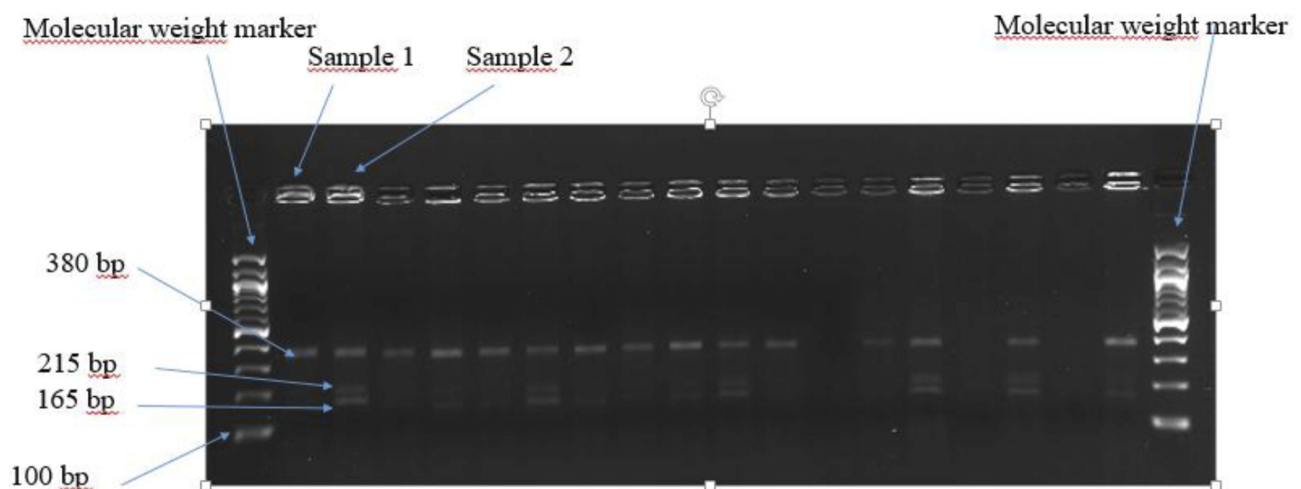


Figure 1 Electrophoregram showing the polymorphism of *CCR2 64I* in selected participants. Sample 1: Wild type homozygous. Sample 2: Heterozygous.

the number of samples with a homozygous mutation genotype, h is the number with a heterozygous mutation genotype and N the total number of samples. Hardy Weinberg Equilibrium (HWE) was tested using Chi-Squared. The allelic frequencies of the *CCR2-64I* and *CCR2-64V* alleles were compared between the HIV positive and negative groups.

Results

Demographic Characteristics

To determine the distribution of *CCR2-64I* genetic variants, 134 participants under 15 years were recruited. Among them were 64 girls (47.76%) and 70 boys (52.24%).

Genotyping

The prevalences of 44.78% for the G/G genotype (homozygous wild type genotype), 48.51% for the G/A genotype (heterozygous genotype) and 6.71% for the A/A genotype (homozygous mutant genotype) were identified in our study population. This is the first time the prevalence of the *CCR2* gene variant has been described in a pediatric group in the Northern Region of Cameroon. Overall, 39.48% HIV-positive (15/38) and 46.88% HIV-negative (45/96) were wild type *CCR2*, 52.63% HIV-positive (20/38) and 46.88% HIV-negative (45/96) were heterozygous *CCR2-64I* carriers and 7.89% HIV-positive (3/38) and 6.25% HIV-negative (6/96) were homozygous mutants for *CCR2-64I* (Table 1). The allelic frequency of *CCR2-64I* was 29.69% in the HIV negative group and 34.21% in the HIV-positive group (Table 2). There were no significant differences between the two groups with respect to the distribution of *CCR2-64I* ($p=0.47$).

The Hardy-Weinberg Equilibrium (HWE) analysis revealed that all genetic variants for *CCR2-64I* in the studied population were in equilibrium ($p=0.09$).

Allelic Frequency Of *CCR2-64I* And HIV Status

Allelic frequencies according to the HIV status are presented in Table 2.

Table 2 Allelic Frequencies And HIV Status In The Study Population

CCR2 Gene Alleles	HIV Infected (%)	HIV Un-Infected (%)	Total (%)	P-value
Mutant type (CCR2-64I)	34.21	29.69	30.97	P=0.47
Wild type (CCR2-64V)	65.79	70.31	69.03	

The allelic frequency of *CCR2-64I* in HIV-infected children (34.21%) was not significantly higher than that observed in HIV-exposed un-infected children (29.69%) with $p=0.47$. This suggests that the *CCR2-64I* allele seems not to confer protection against HIV infection in children of the Northern Region of Cameroon.

Discussion

In this study, the Abbott qualitative Real-time PCR was used for the detection of HIV-1 nucleic acids. Infants infected with HIV usually have very high HIV-1 RNA levels without any treatment. But given the fact that children receive nevirapine at birth that may reduce viremia, a sample with “Not detected” result cannot be presumed negative for HIV-1. It is well known that genetic background has an impact on HIV infection and progression to AIDS, but little is known about the genetic background of Cameroon Northern Region pediatric population in relation to this disease. The Northern Region of Cameroon is dominated by the Fulbe people. In this study, 134 participants were enrolled. Among them were 38 HIV-infected (28.36%) and 96 HIV un-infected (71.64%) children. *CCR2-64I* is relatively common in this population. The *CCR2-64I* variant occurred with a frequency of 30.97% which is comparable to what was reported in the study of Ma et al²¹ with frequencies ranging from 10.8% to 31.3% in Cameroon and that of Nkenfou et al²⁰ with a frequency of 17.6% in the Western Region of Cameroon. Among other African populations, frequencies ranging from 10%–30% have been reported.

Table 1 Frequency And Distribution Of *CCR2* Genotypes And Their Association With HIV Status

CCR2 Genotypes	HIV Infected Children N=38 (%)	HIV Un-Infected Children N=96 (%)	Total N=134 (%)	HWE χ^2, P
G/G (wt/wt)	15 (39.48)	45 (46.88)	60 (44.78)	2.91, 0.09
G/A (wt/mut)	20 (52.63)	45 (46.88)	65 (48.51)	
A/A (mut/mut)	3 (7.89)	6 (6.25)	9 (6.71)	

Abbreviations: wt, wildtype; mut, mutant; HWE, Hardy Weinberg Equilibrium.

The frequencies of the *CCR2-64I* allele in African populations have been higher than what has been observed in Caucasians (7%–10%), while Asian populations show a wider range from 1%–30%.²² A study on subjects selected from different regions of Jordan showed that this allele is common among Jordanians, with a prevalence of 17.5%.⁸ The *CCR2-64I* mutation appears to be common in all ethnic groups,¹⁰ and the observation is in accordance with the theory that it is an ancient one.²³ The *CCR2-V64I* mutation affects the function receptor on the outside of the cell.²⁴ This may further impact disease acquisition and progression. *CCR2* polymorphism is associated with risk of MTCT probably because of its role as an HIV-1 coreceptor or by modulating the early immune response.²⁵ To evaluate the potential effect of *CCR2-64I* on HIV infection in this pediatric population, we compared its allelic frequency between the HIV non-infected group and the HIV infected group and no significance was found. The frequency was not significantly higher in HIV seropositive participants (34.21%) than in the seronegative participants (29.69%). This may imply that *CCR2-64I* do not protect against the infection in the pediatric population of the Cameroon Northern Region. This lack of association may explain in part the high MTCT rate in this part of the country. A study conducted in the Western Region of Cameroon (which has an HIV prevalence of 2.3%) reported a *CCR2-64I* allele frequency of 17.62%. The seronegative group showed a frequency (18.7%) that was not significantly higher than that observed in seropositive ones (12.5%). This result suggested that the *CCR2-64I* allele is not associated with HIV infection. Our result is comparable to that reported by Brouwer et al¹⁶ among Kenyan children. Their results did not indicate an effect of the allele of interest on perinatal HIV transmission. Another study carried out in a Guangxi Province population, a Chinese ethnic group, showed no significant difference in frequencies of *CCR2-64I* ($\chi^2=1.795$, $p=0.180$) between the group of healthy individuals and the group of HIV-positive patients.¹⁷ Due to such controversial results, a meta-analysis carried out by Ding et al,²⁶ aiming to clarify the relationship between the polymorphism of *CCR2-V64I* and the risk of HIV-1 infection also found that it has no effect on susceptibility to it in the total population. On the contrary, some studies reported a protective role of *CCR2-64I* in HIV MTCT.^{14,15} A possible mechanism of protection involves the *CCR2* 190A (64I) allele encoding a protein variant of the *CCR2* receptor with increased affinity to dimerize with HIV co-receptor CXCR4 as compared to the *CCR2* 190G (64V) variant. The dimerization reduces the amount of CXCR4 available for HIV binding, therefore reducing the chances of

HIV entering the host cell.⁷ Scientists believe that the roles of *CCR2-64I* allele may differ in different populations because of variation in genetic backgrounds. Overall, this implies that HIV acquisition or protection may be an association of several factors.

The limit of our study is the lack of viral load data.

Conclusion

Our study found that there was no association between *CCR2* polymorphism and HIV infection in children in Northern Cameroon. *CCR2-64I* does not seem to play a protective role in our population as shown in other studies. Can this thus explain the high transmission rate of HIV in this region? We suggest further investigations on: (a) other single nucleotide polymorphisms to determine their possible role in HIV infection in Northern Cameroon; and (b) whether lack of protection by *CCR2* may be a factor that increases the rate of MTCT in North Cameroon.

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Author contributions

MNN: conception, design, sample collection, and manuscript preparation. CNN: conception, design, sample collection, and interpretation. BAT: conception, design, interpretation and manuscript preparation. LCMM, ENN and BD: Sample collection and interpretation. CK: Data interpretation and critical review of the manuscript. GNT: design and interpretation. WFM and AN: conception and design. All authors contributed towards data analysis, drafting and critically revising the paper, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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