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*Original Article*

# CCR2 polymorphism and HIV: mutation in both mother and child is associated with higher transmission

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**Abstract:** C-C motif chemokine receptor 2 (CCR2) is one of the co-receptors of HIV found on the surface of the target cell and studied as genetic factors known to be associated with HIV infection. This study investigates the influence of mothers' and children's CCR2 polymorphism on HIV acquisition in children. A cross-sectional study was performed in five hospitals in the Northern Region of Cameroon. Blood samples were collected from HIV-infected mothers and their exposed babies. DNA was extracted from the Buffy coat using the QIAamp®DNA mini kit (Qiagen). The DNA extract was subjected to Polymerase Chain Reaction (PCR) followed by Restriction Fragment Length Polymorphism. Hardy-Weinberg Equilibrium (HWE) was verified. A total of 113 HIV-positive mothers, and their 113 children (25 infected and 88 non-infected) under 15 years were enrolled. There was a significant relationship between mothers and children's polymorphisms (P = 0.000). There was a concordance of 57.5% between mothers and children genotypes (Kappa = 0.2, P = 0.001). Mothers carrying the *CCR2-64I* allele were 1.2 times more likely to have HIV-infected children compared to those without mutation (OR = 1.2, 95% CI: 0.5-3.0). Likewise children carrying the mutated phenotypes were 1.4 times more likely to be HIV-infected compared to those without mutation (OR = 1.4, 95% CI: 0.6-3.5). This risk increased to 2.0 (95% CI: 0.5-8.3) for children whose mothers also carried mutation, and decreased to 0.96 (95% CI: 0.2-3.8) for those whose mothers carried the wild type phenotype. In cases of a mutant phenotype in both mother and child, more attention should be paid during follow-up of children born from HIV-positive mother.

**Keywords:** Gene polymorphism, CCR2 mother-child concordance, HIV-1 MTCT, northern region, Cameroon

## Introduction

The perinatal Human Immunodeficiency Virus type 1 (HIV-1) infection is influenced by a combination of factors [1]. Both maternal and infant host factors can influence the susceptibility of a fetus or infant to acquire or avoid the infection. These factors may be shared between mother and child [2]. Since the discovery of allelic variants of HIV co-receptors, the genetic background of chemokines has been studied in order to find associations between allelic variants and inflammation-related diseases as well as infectious diseases [3]. Mother-To-Child Transmission (MTCT) of HIV-1 has been correlated with a wide range of factors: viral, maternal and behavioral. A growing body of evidence also suggests that genetic polymorphisms in human leukocyte antigen (HLA) and chemokine receptor genes are important determinants of the risk of MTCT of HIV-1 [4].

A number of studies have suggested that host genetic factors are important determinants of both MTCT and acquisition of HIV by infants. Both chemokine receptor 5 (*CCR5*) and *CCR2*

gene polymorphisms have been shown to play essential roles in the susceptibility to HIV-1 infection [5]. The CCR2 gene is located at band p21 of chromosome 3 and contains three exons distributed over 7 kb of the genomic sequence. It has been shown to be an additional co-receptor during cellular infection of several HIV-1 strains [6]. The CCR2 allele is a prominent receptor for the Monocyte Chemoattractant Protein (MCP) group of C-C chemokines and is among the most important genetic factors known to be associated with host protection against HIV-1 infection. A G-to-A transition polymorphism at position 190 changes CCR2 codon 64 from valine to isoleucine, introducing a conservative change in the first transmembrane domain [7]. This leads to two forms of the CCR2 gene: *CCR2-64V* (wild type allele) and *CCR2-64I* (mutant allele). A possible mechanism of protection against HIV infection involves the *CCR2-64I* mutated allele encoding a protein variant of the CCR2 receptor with increased affinity to dimerize with HIV co-receptor CXCR4 as compared to the *CCR2-64V* wild allele. The dimerization reduces the amount of CXCR4 available for HIV binding, therefore reducing the chances of HIV entering the host cell [8]. So, the mutation reduces the binding efficacy of HIV to its ligand, leading to protection against HIV acquisition. Studies of *CCR2* polymorphism regarding HIV-1 MTCT have been focused either on the mother to determine the role of *CCR2-64I* mutation in MTCT or on infants to find its effect on their acquisition of HIV. Studies carried out in children reported a protective role of *CCR2-64I* mutation in pediatric HIV-1 infection in Argentina [9]. In the cohorts of children from France and Western Kenya, the researchers failed to find any impact of *CCR2* genotype on perinatal transmission [10, 11]. The *CCR2*-A/A genotype was associated with higher risk of transmission as compared to G allele carriers. This suggested a modest effect of *CCR2* genotypes on MTCT in mother-infant pairs in sub-Saharan Africa [12]. Maternal *CCR2-64I* may partially protect against MTCT of HIV-1 [12]. The *CCR2-64I* allele frequency in both mothers and children did not differ by HIV-1 transmission status regardless of maternal viral load, viral subtypes, immune status or placental malaria status [11]. Many studies have been carried out on the association of HLA concordance/discordance HIV-1 MTCT. It was found that the HLA alleles, particularly the class I concordance between maternal and neonatal HLA, may regulate the risk of perinatal HIV-1 transmission [13]. One study provided the first evidence that maternal-child Major Histocompatibility Complex (MHC) discordance is associated with protection from HIV-1 infection [14]. Another study from Zimbabwe demonstrates that mother-child HLA-G concordance/discordance is not associated with either intrauterine or peripartum transmission [4].

The contribution of both mother and child CCR2 64I alleles to child HIV acquisition has hitherto not been investigated. The objective of this study was to investigate the influence of mothers' CCR2 polymorphism and children's CCR2 polymorphism on HIV acquisition.

## Materials and methods

### *Setting and study period*

The study was carried out in five health facilities of the Northern Region of Cameroon: the Garoua Regional Hospital; the District Hospitals of Guider, Figuil and Lagdo and the Djamboutou Catholic Hospital in 2016.

### *Ethical statement*

The study protocol was reviewed and approved by the Cameroon National Ethical Committee for Research on Human Health (CNECRHH) under the No 2013/11/375/L/CNERSH/SP. Permission to collect and analyze samples was obtained and authorization granted by the Ministry of Public Health (MoH) and the Directors of the different health facilities. The national and international regulations guiding the use of human subjects in biomedical research were followed during the study. Written informed consent was obtained from the mothers as well as the parental consent for their children.

### *Enrolment and sample collection*

In 2016, mother-child pairs consulting in the PMTCT unit in the above-mentioned setting received the proposition to participate in this study. Among them, 113 mother-child pairs were recruited. The mothers were all HIV-infected and aged between 16 and 43 years. The children were under 15 years of age, comprising 25 HIV-infected and 88 HIV-exposed uninfected. Five milliliters of blood sample were

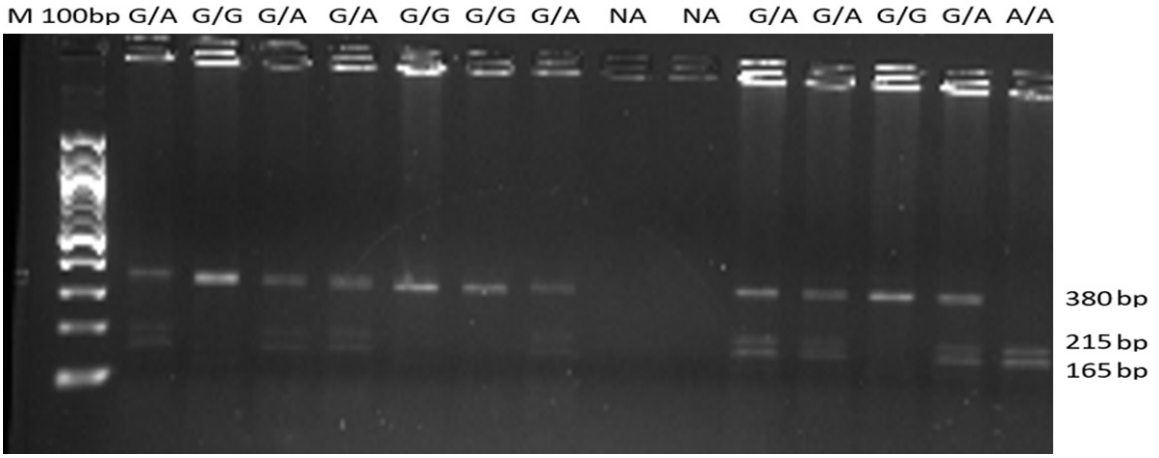


**Figure 1.** Electrophoregram showing the polymorphism of CCR2 gene in selected participants. M 100 bp: 100 base pair molecular weight marker; G/G: Homozygous wild type genotype; G/A: Heterozygous genotype; A/A: Homozygous mutated genotype.

collected from mother and child. Plasma was used to determine the HIV status and buffy coat was conserved at 30°C for DNA extraction and polymorphic analyses.

*Human immunodeficiency virus testing*

The HIV status of mothers and children older than 18 months was established by the Determine HIV 1/2 test (Alere Medical Co., Ltd. 357 Matsuhidai, Matsudo-shi, Chiba). For positive samples, a confirmation test was done with OraQuick kit (OraSure Technologies, Inc. Bethlehem). For children less than 18 months, their HIV status was determined by PCR using Abbott qualitative realtime PCR kits (Abbott TM mSample Preparation System DNA, Promega Corporation. Madison WI 53711 USA) following the manufacturer's instructions.

*Isolation of genomic deoxyribonucleic acid and genotyping*

Using the QIAamp®DNA mini kit (Qiagen, 40-724 Hilden, Germany) according to the manufacturer's protocol, genomic DNA was extracted from 200 µL of buffy coat samples from HIV-positive mothers and their children, and kept frozen at -30°C.

PCR and RFLP were used for the genotyping of *CCR2*. The following pair of primers was used for the PCR: Forward 5'-CTTCATCATCCTCCTG-ACAATCG-3', Reverse 5'-GACCAGCCCCAAGTT-GACTATC-3') [15]. A 380-base pair (bp) fragment was amplified in a 25 µL volume reaction. The reaction mix was subjected to amplification using the following conditions: initial denaturation at 95°C for 3 minutes, 40 cycles of denaturation at 94°C for 30 seconds, annealing at 63°C for 30 seconds, extension at 72°C for 30 seconds and a final extension at 72°C for 10 minutes. A 10 µL volume of the PCR product was digested overnight using 5 units of *Fok I* restriction enzyme (New England Biolabs). The digested product was migrated on 2% agarose gel, stained with ethidium bromide and visualized under UV light. Two fragments of 215 bp and 165 bp were observed for samples with a mutant homozygous genotype. There were three fragments on the gel at 380 bp, 215 bp and 165 bp for heterozygous genotypes. Only one fragment at 380 bp was present for those with the wild type genotype (**Figure 1**).

*Statistical analyses*

The statistical analyses were performed using the IBM-SPSS version 21 and STATA version 14. Odd Ratios (OR) with 95% Confidence Interval (CI) were used as measure of association. Genotype concordance was measured by an overall agreement (%) together with Kappa coefficient. Concordance here is defined as identical genotype between mother and child. The allelic frequencies were calculated as (h+ 2H)/2N, where h is the number of samples with a heterozygous mutation genotype, H is the number of samples with a homozygous mutation genotype, and N the total number of sam-

**Table 1.** Distribution of CCR2-64I allele in mothers and children

| Gene variants | Mothers n (%) | Children n (%) |
|---|---|---|
| G/G | 54 (47.8) | 53 (46.9) |
| G/A | 50 (44.2) | 54 (47.8) |
| A/A | 9 (8.0) | 6 (5.3) |
| Total | 113 (100.0) | 113 (100.0) |
| CCR2-64I frequencies (%) | 30.1 | 29.2 |
| $X^2$-HWE | 0.30 | 2.77 |
| P-HWE | 0.58 | 0.10 |

**Table 2.** Concordance between mother and child genotypes

| Mother's genotype | Child's genotype | | | |
|---|---|---|---|---|
| | G/G n (%) | G/A n (%) | A/A n (%) | Total n (%) |
| G/G | 34 (63.0) | 20 (37.0) | 0 (0.0) | 54 (47.8) |
| G/A | 19 (38.0) | 28 (56.0) | 3 (6.0) | 50 (44.2) |
| A/A | 0 (0.0) | 6 (66.7) | 3 (33.3) | 9 (8.0) |
| Total | 53 (46.9) | 54 (47.8) | 6 (5.3) | 113 |

Concordance = 100*(34+28+3)/113 = 57.5%. G/G: Homozygous wild type genotype; G/A: Heterozygous genotype; A/A: Homozygous mutated genotype.

**Table 3.** Concordance between mother and child phenotypes

| Mother phenotype | Child phenotype | | |
|---|---|---|---|
| | Wild type n (%) | Mutant n (%) | Total n (%) |
| Wild type | 34 (63.0) | 20 (37.0) | 54 (47.8) |
| Mutant | 19 (32.2) | 40 (67.8) | 59 (52.2) |
| Total | 53 (46.9) | 60 (53.1) | 113 (100) |

ples. Chi-squared test was used for the assessment of HWE.

## Results

*Chemokine c-c motif receptor 2 genotyping*

In mothers, a prevalence of 47.8% was observed for the homozygous wild type genotype, 44.2% for the heterozygous genotype and 8.0% for the homozygous mutant genotype. In children, the observed results were 46.9% for the homozygous wild type genotype, 47.8% for the heterozygous genotype and 5.3% for homozygous mutant genotype. Allelic frequencies of 30.1% and 29.2% were respectively reported in mothers and children. The results of the study revealed a genotypic distribution in equilibrium with the HW Law ($X^2$ = 0.30 and P = 0.58 in mothers; $X^2$ = 2.77 and P = 0.10 in children) (**Table 1**).

*Concordance between mother and child genotypes*

There was a concordance between mother and child genotypes (P = 0.00) and an overall concordance of 57.5% between mother and child polymorphism (Kappa = 0.24; P = 0.001) (**Table 2**).

When a mother was homozygous for the mutation (64I/64I), her child had 66.7% probability to be heterozygous (V/64I).

A high level of concordance (67.8%) was observed when both mother and children had the mutated phenotype (**Table 3**).

*Mothers' genotypes/phenotypes and children's human immunodeficiency virus status*

Heterozygous genotype G/A was 4.9% higher in mothers who transmitted HIV to their infants compared to non-transmitters (95% CI: [-0.29, 0.20]) (**Table 4**).

Mothers carrying the mutated phenotype were 1.2 times more likely to have HIV-infected children compared to those without mutation (OR = 1.2, 95% CI: [0.5, 3.0]) (**Table 5**).

*Chemokine c-c motif receptor 2 phenotype concordance and human immunodeficiency virus transmission*

Children carrying the mutation were 1.4 times more likely to be HIV-infected compared to those without (OR = 1.4; 95% CI: [0.6, 3.5]). This risk increased to 2.0 (95% CI: [0.5, 8.3]) for children whose mothers carried the CCR2 64I allele, and decreased to 0.96 (95% CI: [0.2, 3.8]) for those whose mothers did not carry it (**Table 6**). The CCR2 mutation rate was higher in HIV-positive children compared to HIV-negative ones. Overall, 60% of HIV-positive children versus 51.1% of HIV-negative children had the mutated phenotype.

Heterozygote genotype G/A (**Table 7**), was higher by 14.1% in mothers with HIV+children compared to those with HIV-children (95% CI: [-17.0%, 45.1%]). The homozygote genotype A/A

**Table 4.** Mothers' genotypes and children's HIV status

| Mother's genotype | HIV-children n (%) | HIV+children n (%) | Total n (%) | Genotype frequency difference (95% CI) |
|---|---|---|---|---|
| G/G | 43 (48.9) | 11 (44.0) | 54 (47.8) | -4.9 [-0.20, 0.29] |
| G/A | 38 (43.1) | 12 (48.0) | 50 (44.2) | 4.9 [-0.29, 0.20] |
| A/A | 7 (8.0) | 2 (8.0) | 9 (8.0) | 0 [-0.12, 0.12] |
| Total | 88 (100.0) | 25 (100.0) | 113 (100.0) | |

**Table 5.** Mothers' phenotypes and children's HIV status

| Mother's phenotype | HIV-children n (%) | HIV+children n (%) | Total n (%) | OR (95% CI) |
|---|---|---|---|---|
| Wild type | 43 (48.9) | 11 (44.0) | 54 (47.8) | 1 |
| Mutant | 45 (51.1) | 14 (56.0) | 59 (52.2) | 1.2 [0.5, 3.0] |

**Table 6.** Children's HIV status according to their phenotypes and those of their mothers

| Mother's phenotype | Child's phenotype | HIV-children n (%) | HIV+children n (%) | Total n (%) | OR (95% CI) |
|---|---|---|---|---|---|
| Wild type | Wild type | 27 (62.8) | 7 (63.6) | 34 (63) | 1 |
| | Mutant | 16 (37.2) | 4 (36.4) | 20 (37.0) | 0.96 [0.2, 3.8] |
| Mutant | Wild type | 16 (35.6) | 3 (21.4) | 19 (32.2) | 1 |
| | Mutant | 29 (64.4) | 11 (78.6) | 40 (67.8) | 2.0 [0.5, 8.3] |
| Overall | Wild type | 43 (48.9) | 10 (40.0) | 53 (46.9) | 1 |
| | Mutant | 45 (51.1) | 15 (60.0) | 60 (53.1) | 1.4 [0.6, 3.5] |

**Table 7.** Children's HIV status in relation with their genotypes and those of their mothers

| Mother's genotype | Child's genotype | HIV-children n (%) | HIV+children n (%) | Total n (%) | Genotype frequency difference (95% CI) |
|---|---|---|---|---|---|
| G/G | G/G | 27 (62.8) | 7 (63.6) | 34 (63.0) | 0.8 [-31.0, 32.7] |
| | G/A | 16 (37.2) | 4 (36.4) | 20 (37.0) | -0.8 [-32.7, 31.0] |
| G/A | G/G | 16 (42.1) | 3 (25.0) | 19 (38.0) | -17.1 [-46.2, 12.0] |
| | G/A | 20 (52.6) | 8 (66.7) | 28 (56.0) | 14.1 [-17.0, -45.1] |
| | A/A | 2 (5.3) | 1 (8.3) | 3 (6.0) | 3.0 [-14.1, 20.2] |
| A/A | G/A | 5 (71.4) | 1 (50.0) | 6 (66.7) | -21.4 [-98.4, 55.5] |
| | A/A | 2 (28.6) | 1 (50.0) | 3 (33.3) | 21.4 [-55.5, 98.4] |

was higher by 3.0% (95% CI: [-14.1%, 20.2%]) for muted homozygous children.

## Discussion

The objective of this study was to investigate the influence of mother-child *CCR2 64I* alleles concordance on HIV acquisition in children.

A concordance was found between mother and child genotypes (P = 0.00). In fact, each living being receives half of its genetic information from its mother and the other half from its father. In general, many different gene variants are observed in a given population, and are called alleles. A child may inherit two similar alleles or two different alleles from his mother and father. In any case, a child must have a concordant allele with his mother and a concordant allele with his father.

In our study, children carrying the mutated allele (CCR2 64I) were more likely to be HIV-infected than those carrying the wild type allele (CCR2 64V), with increased risk when the mothers also carried the mutation. Implying that the mutation is a risk factor instead of the protective factor.

Our results can find explanations from other studies that showed that the mutated allele-*CCR2 64I*-might diminish the expression of CCR5 and CXCR4 on the cell surface, CCR5 and CXCR4 being major co-receptors for HIV [16]. In addition, few HIV strains use CCR2 as a co-receptor. Therefore, *CCR2-64I* could be regarded as a gene whose expression induces changes on other genes situated on the same chromosomal segment or in a haplotype [17].

A previous study carried out in Cameroon (Centre Region) suggested the non-implication of *CCR2 64I* genotype in the protection against HIV acquisition by the babies from mothers [17] whereas other researchers revealed a protective role of the *CCR2-64I* allele on MTCT. In fact,

the study have shown that the prevalence of the *CCR2-64I* allele was significantly higher (P = 0.03) among HIV-1 exposed uninfected children [9]. In another study done on Kenyan children, the *CCR2* genotype was determined for 445 HIV-seropositive mothers and their infants. The *CCR2-64I* allele frequency of both mothers and children did not differ according to HIV-1 status, regardless of maternal viral load, viral subtype, immune status, or placental malaria status. The results did not indicate an effect of *CCR2-64I* on perinatal HIV transmission [11]. In another study, both homozygous children for the *CCR2-64I* allele and the heterozygous children were found to be equally distributed in the infected (1.6% and 21% respectively) and uninfected (1.9% and 26.3% respectively) groups (P<0.22). The lack of protection or exposure by CCR2-64I mutation was thus observed in this French pediatric HIV infection study group [10].

Our findings are contradictory to other studies that showed a protective role of *CCR2-64I*. The mechanism by which *CCR2-64I* confers protection from disease progression remains unknown. The CCR2 receptor acts as a minor co-receptor for HIV-1 and the polymorphism CCR2-64I did not alter its properties as a chemokine receptor or, as an HIV co-receptor.

CCR2 and HLA are among the genes studied as determinants of the risk of MTCT of HIV-1. Studies carried out on HLA in relation to MTCT showed that maternal HLA-G 14 bp insertion genotype and HLA-G concordance between mother and child were not associated with the risk of perinatal HIV transmission [18]. In Nairobi, concordance of DRB genes between mother and child showed a threefold increase in the risk of perinatal transmission of HIV-1. A significantly higher percentage of HIV-1 perinatally infected children were DRB-concordant with their mothers, while a significantly higher percentage of perinatally uninfected children were DRB discordant. DPA1, DPB1 and DQB1 concordances between mother and child had no significant influence on perinatal HIV transmission [19].

We looked at the *CCR2* alleles concordance between mother and child in our study for the first time. Our findings indicated that concordance in the mutation in mother and child increased the risk of acquisition in mutated children by 2 fold.

A recent study has suggested that haplotypes containing delta 32 *CCR5*, 190G *CCR2 (CCR2 64V)* and 744A *CX3CR1* were associated with resistance to HIV infection. Haplotypes are groups of SNPs that are generally inherited together. They can have stronger correlations with diseases or other phenotypic effects compared with individual SNPs [20]. Future work will look at the effects of combinations of other HIV related genes on MTCT in Cameroon.

These results comfort the idea that transmission is due to a combination of several factors including ethnicity.

## Conclusion

The risk of acquiring HIV was higher for children carrying the mutated allele and increased for children whose mothers also carried the mutated allele. Our study has brought a contribution towards understanding CCR2 genetic variations with respect to the role of mother polymorphism together with child polymorphism in HIV acquisition. In cases of a mutant phenotype in mother and child, more attention should be paid during follow-up of exposed children as this increases the risk of HIV transmission and acquisition in children.

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## Disclosure of conflict of interest

None.

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