Infection, Genetics and Evolution 19 (2013) 312–322

Contents lists available at SciVerse ScienceDirect

Infection, Genetics and Evolution

journal homepage: www.elsevier.com/locate/meegid

HIV mother-to-child transmission: A complex genetic puzzle tackled by Brazil and Argentina research teams

R. Celerino da Silva [a,b], E. Bedin [c], A. Mangano [d], P. Aulicino [d], A. Pontillo [e], L. Brandão [b,f], R. Guimarães [a,b], L.C. Arraes [g], L. Sen [d], S. Crovella [c,h,*]

[a] Department of Genetics, Federal University of Pernambuco, Av. Prof. Moraes Rego, s/n°, CEP 50.670-420, Cidade Universitária, Recife, Pernambuco, Brazil
[b] Laboratory of Immunopathology Keizo Asami, Federal University of Pernambuco, Av. Prof. Moraes Rego, s/n°, CEP 50.670-420, Cidade Universitária, Recife, Pernambuco, Brazil
[c] Institute for Maternal and Child Health – IRCCS "BurloGarofolo" – via dell'Istria, 65/1 34137 – Trieste, Italy
[d] Laboratory of Cellular Biology and Retroviruses, NationalPediatric Hospital "J.P. Garrahan" – CONICET.Combate de los Pozos 1881, (1245), Buenos Aires, Argentina
[e] Laboratory of Medical Investigation in Dermatology and Immunodeficiency LIM-56, Faculty of Medicine, University of São Paulo. Av. Dr Eneas de Carvalho Aguiar, 500 – Predio II – 3 andar CEP 05403-903, Sao Paulo, Brazil
[f] Department of Pathology, Federal University of Pernambuco, Av. Prof. Moraes Rego, s/n°, CEP 50.670-420, Cidade Universitária, Recife, Pernambuco, Brazil
[g] Instituteof Integral Medicine Professor Fernando Figueira – IMIP, Rua dos Coelhos, 300, CEP 50.070-550, Boa Vista, Recife, Pernambuco, Brazil
[h] University of Trieste, Italy

ARTICLE INFO

Article history:
Available online 21 March 2013

Keywords:
Mother-to-child transmission
HIV
Host genome
Immunogenetics markers
Susceptibility
Protection

ABSTRACT

Human immunodeficiency virus (HIV) mother-to-child transmission is a complex event, depending upon environmental factors and is affected by host genetic factors from mother and child, as well as viral genetic elements. The integration of multiple parameters (CD4 cell count, virus load, HIV subtype, and host genetic markers) could account for the susceptibility to HIV infection, a multifactorial trait. The goal of this manuscript is to analyze the immunogenetic factors associated to HIV mother-to-child transmission, trying to unravel the genetic puzzle of HIV mother-to-child transmission and considering the experience in this topic of two research groups from Brazil and Argentina.

© 2013 Elsevier B.V. All rights reserved.

1. Introduction

The mother-to-child transmission (MTCT) or vertical transmission of human immunodeficiency virus type 1 (HIV-1) occurs at an estimated rate of more than 30% and is the major cause of AIDS in children. The transmission can occur at three different times (Newell et al., 1996):

- Prepartum (*in uterus*), due to feto-maternal blood shunts within the placenta;
- Intrapartum (delivery), when infant's oral mucosa is contaminated with infected vaginal secretions;
- Through breast feeding.

Numerous maternal parameters, including mother's advanced clinical stages, low CD4+lymphocyte counts, high viral load, immune response, and disease progression have been implicated in the increased risk of vertical transmission. While the use of antiretroviral therapy (ART) during pregnancy has been shown to reduce the risk of vertical transmission, selective transmission of ART-resistant mutants has also been documented. Elucidation of the molecular mechanisms of vertical transmission might provide relevant information for the development of effective strategies for prevention and treatment (Ahmad, 2011).

The time of delivery and breastfeeding are the principal routes of viral transmission and account for about 70% of pediatric infections in resource-poor countries. The effect of innate immunity (i.e.: anti-microbial peptides, pattern recognition receptors/PRRs) may be of particular relevance because infants are exposed to HIV-1 and acquire infection when the adaptive immune system is still under development.

On the other hand, the risk of in utero transmission is less than 7%; so that even in the absence of virologic suppression with maternal antiretroviral therapy, over 90% of HIV-1-exposed newborns are "naturally" protected from infection in utero. These observations suggest the placenta has evolved mechanisms that restrict establishment of viral infection at the feto-maternal interface. Elucidating these mechanisms may help to determine biologic correlates of protection against HIV-1 transmission in humans (Ahmad, 2011; Johnson and Chakraborty, 2012).

* Corresponding author at: Institute for Maternal and Child Health – IRCCS "BurloGarofolo" – via dell'Istria, 65/134137 – Trieste, Italy. Tel./fax: +39.040.3785540.
E-mail addresses: crovelser@gmail.com, crovella@burlo.trieste.it (S. Crovella).

1567-1348/$ - see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.meegid.2013.03.005

The feto-maternal interface is characterized by intimate contact between uterine decidual cells and invading chorionic villi. For HIV-1 transmission occurring in utero, the virus must cross the selective placental barrier. An individual villus is lined by trophoblasts, which enclose connective tissue stroma containing fetal blood vessels and numerous fetalmacrophages or Hofbauer cells (HCs). The chorionic villi are directly bathed in maternal blood. Moreover maternal cells have been identified in fetal lymph nodes and are involved in fetal T cells development. So the fetus of an HIV-1-infected mother may be exposed to free and cell-associated virus during gestation (Johnson and Chakraborty, 2012).

HIV-1 has been shown to productively infect trophoblasts, however, they exhibit a lower susceptibility to productive HIV-1 infection than CD4+ T cells do. The trophoblasts express no or few receptors/coreceptors required for virus internalization and its entry in these cells is associated with unusual endocytosis (Vidricaire et al., 2007). Moreover HIV-1 may infect trophoblast by T cell adherence (Arias et al., 2003). Fetal trophoblasts are known to express HLA-G, a non-classical class I HLA, involved in immune tolerance during pregnancy. HLA-G is a ligand for NK cell inhibitory receptor KIR2DL4. Both HLA-G and KIR2DL4 have been described to be involved in HIV infection (Huang et al., 2010; Chaichompoo et al., 2010), emphasizing the possible role of trophoblast in HIV transplacental infection.

An HIV-1 virion can potentially encounter HCs after breaching the trophoblast cell layer. HCs express the HIV-1 (co)-receptors CD4, CCR5 and CXCR4, and also DC-SIGN on their cell surface. HCs express very high levels of DC-SIGN. During pregnancy, there is increased expression of DC-SIGN on HCs; this expression has been correlated with increased rates of HIV-1 vertical transmission. Intuitively, the presence of DC-SIGN and HIV-1 (co)-receptors on HCs, should promote viral entry by free or cell-mediated transmission of HIV-1 facilitating infection in the unborn fetus (Johnson and Chakraborty, 2012).

Another aspect to be considered is that cytokines may influence HIV-1 replication in placenta. Placentas from non-transmitting mothers appear to sustain an immunoregulatory (i.e., IL-10, TGF-β) predominance while placentas from transmitting mothers exhibit a pro-inflammatory pattern (i.e., IL-1β, TNF) of cytokine release (Johnson and Chakraborty, 2012).

2. Aim of the review

MTCT is a complex event, which depends on environmental factors and is affected by host genetic factors from mother and child, as well as viral genetic elements. The aim of this work is to review the current knowledge about genetics factors associated to HIV MTCT, using as starting point the previous experience of two research groups from Brazil and Argentina, widely working on the host immunogenetic restriction factors responsible for susceptibility/protection to HIV-1 infection in children.

We categorize the host immunogenetic restriction factors in: soluble innate immune HIV restriction, HIV (co)-receptors, chemokines and cytokines, human leukocyte antigen, natural killer cells receptors and products. Several studies address the role of host immunogenetic variations in MTCT. Table 1 reports selected association studies conducted on MTCT and the polymorphisms analyzed.

3. Soluble innate immune HIV restriction factors

3.1. Human beta defensin (DEFB1)

Defensins are small cationic amphipathic peptides (30–48 amino acids), produced by leukocytes and epithelial cells, especially in mucosa, with direct and indirect antiviral activity. They inactivate viruses interacting with envelope proteins, or acting as chemoattractive on immune cells.

Within the different human defensins, the beta defensin 1 (hBD1), encoded by *DEFB1* gene, has been reported to be involved in the protection against HIV-1 infection (Ricci et al., 2009). Moreover hBD1has been found in oral and vaginal mucosa as well as in breast milk (Armogida et al., 2004; Jia et al., 2001) and for this reason has been deeply investigated as natural factor involved in susceptibility to MTCT.

When considering the impact of genetic variations in *DEFB1* gene expression, we can observe that single nucleotide polymorphisms (SNPs) localized at regulatory region affect DEFB1 expression that varies within individuals depending upon these SNPs.

In this context, Braida et al. (2004) and Milanese et al. (2006) studied the frequencies of three single nucleotide polymorphisms (SNPs) at the 5′-untranslated region of *DEFB1* gene: −52 (G/A); −44 (C/G); and −20 (G/A) (rs1799946, rs1800972, and rs11362, respectively) in MTCT cohorts from Brazil and Italy.

In Braida et al. (2004) study, allele frequencies of the −44 C/G SNP were significantly different in HIV positive Italian children compared to the healthy controls, because of the difference in the frequency of −44 C/C homozygous individuals. The odds ratio for the −44 C/C genotype in HIV-infected children was 3.6 (95% CI = 1.89–6.90). Genotype and allele frequencies of the −20 G/A SNP in HIV positive children were similar to the controls.

In a similar study, Milanese et al. (2006) analyzed a group of Brazilian children and obtained different results reporting a significant increase of the −52 A/A and −20 G/G genotypes in HIV infected children, when compared with healthy controls. These data suggest a role for −52 A/A and −20 G/G genotypes in increasing the susceptibility to infection. They also found a sensible, even if not significant, reduction of the frequency of the −44 G allele. The frequency of this polymorphism was very low in the Brazilian population when compared with other populations, and this fact could account for the lack of statistical significance.

Conversely the association mentioned above was not confirmed in another replica study by Segat et al. (2009a): the authors showed non-significant results comparing the frequencies of *DEFB1* polymorphisms between HIV positive and healthy control groups. Moreover, when the Brazilian HIV positive populations from Milanese's and Segat's studies were compared, a significant difference between the −20 G/A SNP genotype distribution ($p < 10^{-5}$) was found, evidencing that *DEFB1* 5′UTR polymorphisms frequencies could vary among different populations, and even within groups from the same population.

Other research groups performed analogous studies on DEFB1 5′UTR SNPs associating with risk of MTCT in different populations.

Ricci et al. (2009) studied the distribution of −44 C/G (rs1800972) and −52 G/A (rs1799946) polymorphisms in 118 HIV infected and 182 HIV uninfected children, born of HIV infected mothers. The −52 G/G genotype and the −44G/−52G haplotype were associated with protection against HIV infection ($p = 0.03$, OR = 0.52, 95% CI = 0.31–0.86 and $p = 0.014$, OR = 0.50, 95% CI = 0.31–0.83; respectively). They also studied 84 HIV-infected mothers and showed that the −52G/G genotype and the −44G/−52G haplotype were associated with low levels of HIV plasma viremia (<1000 copies/mL) and a consequent lower risk of HIV MTCT ($p = 0.009$, OR = 0.14, 95% CI = 0.03–0.67 and $p = 0.012$, OR = 0.23, 95% CI = 0.08–0.66, respectively).

Segat et al. (2006a) evaluated the frequency of the same three SNPs at the 5′UTR region of *DEFB-1* gene, in a cohort of 130 HIV infected Italian mothers and their children: the frequency of −44 C allele was significantly different in both HIV positive mothers and their children, in comparison with healthy controls. The odds ratio for −44 C allele in children born to HIV infected mothers

Table 1
Association studies conducted in different populations involving HIV mother to children transmission.

Study	Population	N	Variation	MAFs in studied population				MAFs – HapMap			
				HIV+	HIV−	HC	GERAL	Allele referency	CEU	YRB	CHB
HLA											
Kilpatrick et al. (1991)	UK	53	HLA-DR3	0.43	0.15	NA	0.19				
			HLA–A3	0.13	0.42	NA	0.14				
Greggio et al. (1993)	Italy	172	HLA - DRB1-14a	0.00	0.10	0.05	0.06				
			HLA - DRB1 - 13a.4	0.00	0.06	0.04	0.03				
Winchester et al. (1995)	USA	109	HLA - DR2	0.38	0.44	NA	0.42				
			HLA - DRB1∗1501	0.15	0.67	NA	0.20				
			HLA - DRB1∗11011	0.03	0.12	NA	0.07				
			HLA - DRB1∗1102	0.15	0.12	NA	0.13				
			HLA - DRB1∗03011	0.18	0.19	NA	0.18				
Segat et al. (2009)	Brazil	397	HLA-G - rs1707	0.39	0.40	0.41	0.40	C	0.115(C)	0.123(C)	0.047(C)
Fabris et al. (2009)	Brazil	421	HLA-G - rs1704	0.42	0.21	0.40	0.40	–	0.320 (–)	0.430 (–)	0.309 (–)
CCR5-CXCR4											
Mandl et al (1998)	Austria	79	rs333 (CCR5Δ32)	0.11	0.03	NA	0.08	+	0.048 (–)	0.000 (–)	NA
Philpott et al. (1999)	USA	1104	rs333 (CCR5Δ32)	0.02	0.03	NA	0.03				
Mangano et al. (2000)	Argentina	983	rs333 (CCR5Δ32)	0.04	0.04	0.05	0.04				
DEFB1											
Braida et al. (2004)	Italy	217	rs11362 -A	0.38	NA	0.38	0.38	C	0.363 (T)	0.403 (C)	0.435 (T)
			rs1800972 - G	0.10	NA	0.22	0.16	C	0.258 (G)	0.042 (G)	0.125 (G)
			rs1799946 – A	0.52	NA	0.42	0.47	C	0.394 (T)	0.292 (T)	0.405 (T)
Milanese et al. (2006)	Brazil	303	rs11362 -A	0.52	0.42	0.37	0.44				
			rs1800972 – G	0.07	0.13	0.14	0.11				
			rs1799946 – A	0.33	0.46	0.46	0.40				
Segat et al. (2006)	Italy	250	rs11362 –A	NA	0.37	0.38	0.38				
			rs1800972 – G	NA	0.04	0.22	0.10				
			rs1799946 – A	NA	0.55	0.42	0.50				
Ricci et al. (2009)	Italy	384	rs1800972 – G	0.12	0.16	NA	0.15				
			rs1799946 – A	0.20	0.38	NA	0.40				
MBL2											
Boniotto et al. (2000)	Italy	101	Position –550 - H	NA	0.48	0.36	0.39				
			Position – 328 - del	NA	0.14	0.19	0.18				
Boniotto et al. (2003)	Brazil	306	Allele O	0.29	0.19	0.20	0.23				
Mangano et al. (2008)	Argentina	492	Allele X	0.16	0.11	0.15	0.14				
			Allele O	0.25	0.26	0.21	0.24				
			rs1800450 (B)	0.20	0.20	0.18	0.19	C	0.150 (T)	0.009 (T)	0.155 (T)
			rs5030737 (D)	0.05	0.05	0.03	0.04	G	0.071 (T)	0.021 (T)	0.012 (T)
			rs1800451 (C)	0.00	0.00	0.00	0.00	C	0.018 (A)	0.167 (A)	0.012 (A)
PRF1											
Padovan et al. (2011)	Brazil	395	rs885822 – C	0.32	0.49	NA	0.35	G	0.425 (G)	0.133 (G)	0.321 (G)
SDF1											
Mangano et al. (2000)	Argentina	983	SDF1 3'A (rs1801157)	0.18	0.21	0.24	0.20	C	0.208 (T)	0.022 (T)	0.298 (T)
Sei et al. (2001)	USA	127		0.05	NA	NA	NA				
Tresoldi et al. (2002)	Italy	544		0.24	0.26	0.27	0.25				
DC/L-SIGN											
Da Silva et al. (2012)	Brazil	346	rs735240 – A	0.42	0.36	0.40	0.41	G	0.451 (A)	0.333 (A)	0.270 (A)
			rs735239 – G	0.37	0.28	0.29	0.33	A	0.380 (G)	0.003 (G)	0.180 (G)
			rs4804803 - G	0.32	0.41	0.31	0.33	G	0.258 (G)	0.432 (G)	0.042 (G)
			rs11465366 – T	0.02	0.12	0.03	0.03	C	NA	0.085 (T)	NA
			rs2287886 - A	0.27	0.16	0.28	0.26	A	0.305 (A)	0.184(A)	0.303 (G)
INFAMMASOME											
Pontillo et al. (2010)	Brazil	1038	rs1143634 - G	0.40			0.40	G	0.208(A)	0.099(A)	0.015 (A)
Segat et al. (2006)	Brazil		*rs*1946518	0.35	0.44	0.46	0.41	T	0.392 (T)	0.345 (T)	0.390 (G)
			*rs*187238	0.22	0.25	0.26	0.24	G	0.233 (C)	0.142 (C)	0.153 (C)
TRL9											
Ricci et al. (2010)	Italian	300	rs352139 – A	0.49	0.42	NA	0.48	T	0.482 (C)	0.425 (T)	0.405 (C)
			rs352140 - G	0.45	0.42	NA	0.44	C	0.478 (T)	0.305 (T)	0.399 (T)

EIC = Exposed Infected Children.
EUC = Exposed uninfected children.
UUC = Unexposed uninfected children.
IC = Infected children.
UC = Uninfected children.
MC*p* = Mother–child pairs.
IC-IM*p* = infected child-infected mother pairs.
UC-IM*p* = Uninfected child-infected mother pairs.
UC-IM*p* = Uninfected child-infected mother pairs.
IM–Infected mothers.

was 7.09 (95% CI = 3.38–15.3), whereas for HIV infected mothers was 6.42 (confidence interval 3.14–13.4). This results evidenced an elevated frequency of the −44 C allele in HIV infected mothers. Thus, we must consider that antiretroviral drug treatment and

cesarian section of HIV positive mothers successfully prevented the potential risk of vertical transmission.

Several studies tried to unravel the function meaning of DEFB1 5′UTR SNPs associated with MTCT.

Braida et al. (2004) hypothesized that hBD-1 could be very important in protecting the skin and mucosa of newborns by interacting with the viral particles or with cells of the immune response.

Baroncelli et al. (2008) analyzed *DEFB1*–44C/G and −52 G/A polymorphisms in 78 Mozambican HIV infected mothers. They observed significantly lower levels of HIV RNA in breast milk but not in plasma, in women with the −52 G/G genotype versus women with the −52 G/A and −52 A/A genotypes, supporting the hypothesis that different expression of beta-defensins could have an impact on viral replication in breast milk.

Aguilar-Jiménez et al. (2011) performed a study in a group of 74 mothers and their infants, 36 HIV positive pregnant women and 38 pregnant women HIV negative from Colombia. They observed that hBD-1 transcript levels were significantly higher in placenta from seropositive mothers compared with controls. Additionally, the simultaneous presence of A692G A/G and A1836 G/G genotypes, was associated with high expression of hBD-1 in all groups. Contrasting results in levels of hBDs were probably due to viral stimuli, suggesting that HIV could induce an hBD differential expression in placenta, and this peptide could be involved in protection against HIV, at least early in pregnancy.

Considering that polymorphisms in *DEFB1* affect its expression and that MTCT could involve infant oral mucosa, these findings emphasize that human defensin 1 plays a prominent role in mucosal innate immune defense against HIV-1.

Finally, when considering other human beta defensins, it has been reported that beta defensin 2 and 3 (hBD-2 and hBD-3) could contrast the infection from HIV by protecting GHOST X4/R5 cells from virus infection, by directly binding to the viral envelope (Quinones-Mateu et al., 2003). Moreover, Sun et al. (2005) hypothesized an involvement of beta-defensins in HIV oral transmission, emphasizing their protective role in the oral mucosa.

3.2. Mannose binding lectin (MBL2)

Mannose-binding lectin (MBL), a protein secreted by the liver, is an important component of the innate immunity. It is an acute-phase protein that binds specific carbohydrate residues present on some virus, bacteria and yeast, and may mediate phagocytosis or activate the classical pathway of the complement (Garred et al., 2003).

Three different polymorphisms have been described at exon 1 of the *MBL2* gene, which result in single amino acid changes, affecting MBL oligomerization and funcionality. They are localized at codons 52, 54, and 57 at nucleotide positions 223-C/T (Arg52Cys), 230-G/A (Gly54Asp), and 239-G/A (Gly57Glu), respectively. These mutations generate the allelic variants named "B" (codon 54), "C" (codon 57), and "D" (codon 52), collectively designated as "O"; the wild type allele was called "A" (Garred et al., 2003).

MBL is able to bind the HIV glycoprotein complex gp120–gp41 *in vitro* (Garred et al., 2003). *MBL2* polymorphisms have been associated with susceptibility to HIV infection in Brazilian perinatally infected children (Boniotto et al., 2003) and with accelerated disease progression in HIV-infected Italian children born to seropositive mothers (Amoroso et al., 1999).

The distribution of *MBL2* alleles varies among different populations. The *B* allele is present in White, Asian and American indigenous populations. The *C* allele is found almost exclusively in African populations, while the *D* allele is found in White, East Africans and almost absent in Asians (Garred et al., 2003). Three polymorphisms also have been found in the promoter region of *MBL2*, at positions −550 *(H/L)* and −221 (*X*/*Y*) and in the 5′-untranslated region of exon 1 at position −4 (P/Q) (Mangano et al., 2008).

In Mangano et al. (2008) study, the combined genotype *XA*/*XA* associated with a 8-fold risk of HIV MTCT (OR = 8.11; 95% CI = 0.96–67.86). The polymorphism at codon 54 of exon 1, results in the replacement of a glycine with an aspartic acid, reducing the level of MBL in the serum of five to ten times in heterozygous individuals. In HIV infected children, the presence of the Gly54Asp mutation conferred a relative risk of 3.68 (95% CI = 1.1–13.1) for a rapid progression to AIDS.

Boniotto et al. (2000, 2003)) described an association between the mutated *MBL2* O allele and susceptibility to HIV infection in infants. The presence of the allele O confers a relative risk of 1.37 (95% CI = 1.02–1.84) for HIV infection through MTCT. This allele has a dominant negative effect on MBL serum levels, because it determines an incorrect assembly of MBL subunits in the collagen-like domain, producing a more vulnerable protein to degradation by metalloproteinases. In heterozygous individuals, the serum level of the protein was reduced five to ten times, whereas in O/O homozygote, the level of the protein was undetectable (Boniotto et al., 2000, 2003).

In Singh and Spector (2009) study, *MBL2* O/O genotype was associated with more rapid HIV-related disease progression, predominantly in children younger than 2 years, suggestingthat*MBL2* variants are associated with altered HIV disease progression, particularly in young children.

Crovella et al. (2005) investigated *MBL2* polymorphisms in a cohort of 90 Italian HIV pregnant seropositive women and their children, confirming the association of *MBL2* O/O genotype with an increased risk of infection by HIV MTCT. The frequency of the *MBL2* O/O homozygote was higher in HIV infected mothers than in healthy controls. Similarly, the *MBL2* O/O genotype was more frequent in infected children born from HIV positive mothers than in healthy controls. These polymorphisms were also evidenced in children born from HIV positive mothers, but the risk of infection was strongly reduced by cesarean delivery and by antiretroviral treatment.

Assuming that *MBL2* activates the complement system, promoting viral killing, and that variations at exon 1 (polymorphism A/O) lead to deficient levels of circulating protein, studies show that individuals with polymorphism A/O (codons 52, 54 and 57) are more susceptible to HIV MTCT.

4. HIV (Co-)receptors

4.1. C–C chemokine receptor type 5 (CCR5)-C–X–C chemokine receptor type 4 (CXCR4)

CCR5 and CXCR4 are recognized as the most important co-receptors used for HIV to enter the cell.

CCR5 genetic polymorphisms have been associated to MTCT (John et al., 2001). The *CCR5Δ32* mutation occurs in 10% of Caucasian and consists in a deletion of 32bpresulting in a non-functional receptor (Taborda-Vanegas et al., 2011). This mutation was associated with AIDS progression, but evidences suggest that it has no effect on the risk of HIV perinatal transmission (Contopoulos-Ioannidis et al., 2003). This could be explained by the fact that *CCR5* expression is influenced by other factors than *CCR5Δ32*; in fact, *CCR5* expression levels differ considerably among individuals with the same genotype. MTCT could occur via R5X4 or X4 strains able to initiate infection via CXCR4, the alternative co-receptor for HIV (De Souza et al., 2006).

A meta-analysis study including 10 cohorts with 1317 HIV-infected children the *CCR5Δ32* and *CCR64I* alleles were associated

with a decreased risk of death among perinatally infected children, but only for the first years of life (Ioannidis et al., 2003).

Philpott et al. (1999) studied a cohort of 552 children (13% White, 30% Latino and 56% African American) born of Americans infected mothers in relation to the *CCR5Δ32* mutation and they observed variation in allele frequency among the groups, ranging from 0.08 in Whites to 0.02 in both Latinos and African Americans. Approximately, 27% of the children in each ethnic group were infected. Four children were identified as *CCR5Δ32* homozygotes, two uninfected Whites (3.77%) and two uninfected Latinos (1.68%). None of the infected children displayed the *CCR5Δ32* homozygous genotype, suggesting that this mutant genotype may confer protection from HIV mother-to-child transmission.

Similarly, in an Argentinean cohort of 886 children born to HIV seropositive mothers (449 HIV+, 433 HIV−) of Hispanic-Caucasian descendants, only one *CCR5Δ32* homozygous was found among exposed uninfected children (Mangano et al., 2000).

Mandl et al. (1998) studied a group of 79 children born to HIV positive mothers from Austria (45 uninfected and 34 infected by MTCT) and showed that the presence of the defective HIV co-receptor gene *CCR5Δ32* was also associated with MTCT. The mutant allele frequency was 11.1% in uninfected children (17.8% heterozygous, 2.2% homozygous). In the group of infected children, there were only two heterozygous and no *CCR5Δ32* homozygous, corresponding to a significantly reduced mutant allele frequency of 2.9% ($p = 0.05$ compared to HIV negative children). These results suggest that *CCR5/CCR5Δ32* heterozygous children were less susceptible to vertical transmission of HIV.

Some genetic polymorphisms have been described in *CCR5* regulatory region, which, together with the *CCR5Δ32* mutation, define 9 human haplogroups (HHA to HHG2) (Gonzalez et al., 1999 Kostrikis at al. (1999)).

Gonzalez et al. (1999) showed that *CCR5* haplotypes pairs have been associated with different risk of transmission and AIDS progression in a large well-characterized racially mixed cohort of HIV seropositive children. The HHE/HHE haplotype was associated with increased of HIV MTCT susceptibility, disease accelerating and faster progression in Argentinean children. On the other hand, the HHC/HHG2 haplotype was associated with reduced risk of HIV MTCT and disease retarding effects. Additionally, the spectrum of *CCR5* haplotypes associated with disease acceleration or retardation differs between African Americans and Caucasians. Other studies conducted by Mangano et al. (2000, 2001) showed that other haplotypes, such as HHD/HHD (in African American children) and HHC/HHF2 (in Argentinean children) were associated with increased HIV MTCT susceptibility and disease retarding effect.

As expected, considering its role as HIV-1 co-receptor, the CCR5 Δ32 variation is associated with a protection against MTCT. However polymorphisms at*CCR5* gene regulatory region confer increased susceptibility to HIV MTCT.

4.2. C-type lectins (DC-SIGN and L-SIGN)

Some pattern recognition receptors (PRRs) located on the surface of dendritic cells (and other cells) play an important role in HIV transmission. Of particular interest are the DC-SIGN (Dendritic cell-specific ICAM-3-grabbing non-integrin) and L-SIGN (liver/lymph node–specific ICAM-3–grabbing non-integrin) receptors, two C-type lectins, long type 2 integral membrane proteins, involved in both innate and adaptive immunity. They work as pathogen-recognition receptors and are able to detect a wide range of microorganisms, including HIV (Baribaud et al., 2001; da Silva et al., 2011; Sobieszczyk et al., 2011).

The *CD209* gene family encodes both receptors. DC/L-SIGN receptors captures the HIV virus by binding to the gp120, promoting the enhancement of T cell infection *in trans*. Additionally, they can internalize the virus and promote virus degradation in a proteasoma dependent manner (da Silva et al., 2011; Sobieszczyk et al., 2011).

Only a few studies have investigated the possible involvement of DC/L-SIGN receptors in the genetic mechanisms correlated with HIV MTCT (Boily-Larouche et al., 2009; Da Silva et al., 2012).

Da Silva et al. (2012) studied polymorphisms in *DC-SIGN* and *L-SIGN* genes in children (192 HIV+ and 58 HIV−) born to HIV+ mothers, as well as in 96 healthy uninfected children not exposed to HIV, all from Northeast Brazil, and found associations of three SNPs in *DC-SIGN* promoter, being two associated with protection (rs11465366: allele T and G/T genotype; rs4804803: G/G genotype) and one with susceptibility (rs2287886: G/A genotype) to HIV MTCT. It was also observed that variations number tandem repeat (VNTR) in *L-SIGN* exon 4 were associated with susceptibility (5/5 and 6/6 homozygous genotypes) to HIV MTCT.

Another association study (Boily-Larouche et al., 2009) performed in a group of 197 HIV infected mothers and their children from Zimbabwe found that children with two copies of H1 and/or H3 haplotype of L-SIGN were about 3.6 times more at risk for intrauterine HIV MTCT and 5.7 times at risk for intrapartum transmission. The H1 and H3 haplotypes were characterized by two SNP at the promoter region (p-198A) and the intron 2 (int2–180A) that associated with a reduction of the transcriptional activity.

The role of DC-SIGN genetics in MTCT is still confusing: some polymorphisms in DC-SIGN promoter region (rs11465366, rs4804803) are found to be protective, whereas other (rs2287886) appeared to augment the risk of MTCT. L-SIGN variations were invariably associated with susceptibility to HIV MTCT.

4.3. Toll like receptor 9 (TLR9)

Another gene related with MTCT is the Toll-like receptor 9 (*TLR9*). Ricci et al. (2010) studied SNPs (rs352139: c.4–44G > A and rs352140: c.1635A > G) in *TLR9* gene associated to the risk of HIV MTCT in 300 children (118 HIV-infected and 182 HIV-uninfected) born to HIV-infected mothers. TLR9 recognizes pathogen-associated molecular patterns and play a crucial role in the host's innate immune response. The AA and GG haplotypes were associated with a higher risk of HIV infection compared to the prevalent GA haplotype ($p = 0.016$, OR = 3.16, 95% CI = 1.24–8.03 and $p = 0.004$, OR = 5.54, 95% CI = 1.76–17.50, respectively) (Ricci et al., 2010) suggesting a role for TLR9 in the modulation of susceptibility to HIV MTCT.

5. Chemokines and cytokines

5.1. Human beta chemokine ligand 3-like1 (CCL3L1)

Human beta-chemokine (CCL3L1), the most potent ligand for CCR5, may be a dominant HIV-suppressive chemokine (Nibbs et al., 1999; Menten et al., 2002; Townson et al., 2002). *CCL3L1*, a duplicated isoform of the gene encoding *CCL3*, is 30-fold more potent in inhibiting R5 HIV infection when compared with CCL3 (Menten et al., 2002). As a consequence of these duplications, the copy number of *CCL3L1* (gene dose) varies among individuals and can affect chemokine concentrations (Townson et al., 2002; Gonzalez et al., 2005; Meddows-Taylor et al., 2006).

Townson et al. (2002) found that lipopolysaccharide stimulation of peripheral blood mononuclear cells from 35 individuals increased expression of *CCL3L1* mRNA. Samples with higher *CCL3L1* copy number had a significant increase in the ratio *CCL3L1/CCL3* mRNA. A high *CCL3L1* copy number also correlated with increased functional chemokine production. Genetic variation in CCL3L1 gene copy number may affect the susceptibility to progression or

severity of diseases in which this chemokine plays a role, as for HIV infection.

Some studies have shown that genetic variation in *CCL3L1* can affect susceptibility to HIV transmission. Kuhn et al. (2007) study, conducted in 849 HIV infected mothers and their infants of Johannesburg (South Africa), observed a strong association between higher infant CCL3L1 gene copies and reduced susceptibility to HIV in the absence of maternal treatment with nevirapine.

Meddows-Taylor et al. (2006) showed that *CCL3L1* gene copy number was associated with *CCL3* production and with HIV vertical transmission. However, at equivalent *CCL3L1* gene copy numbers, infants who acquired HIV infection relative to their exposed but uninfected counterparts had lower production of *CCL3*, suggesting that they may harbor some non-functional copies of this gene.

Paximadis et al. (2011) study analyzed the influence of intragenic *CCL3* haplotypes and *CCL3L* copy number (CN) in a cohort HIV MTCT from sub-Saharan Africa. The authors observed that *CCL3* Hap-A1 haplotype was associated with high *CCL3L* CN in total ($p = 0.001$) and exposed uninfected infants ($p = 0.006$), the effect was not additive, however, having either Hap-A1 or high *CCL3L* CN was more significantly ($p = 0.0008$) associated with protection from in utero infection than Hap-A1 ($p = 0.028$) or high *CCL3L* CN ($p = 0.002$) alone.

Gonzalez et al. (2005) showed that there are significant inter-individual and inter-population differences in the copy number of a segmental duplication encompassing the gene encoding *CCL3L1*. Mean *CCL3L1* copy number varied in different population groups, being generally highest in Africans, followed by East Asians, Amerindians, Central/South Asians, Middle Easterners and Europeans. Additionally, possession of a *CCL3L1* copy number lower than the population average is associated with markedly enhanced susceptibility to HIV MTCT.

As expected studies showed that individuals with high copy number of *CCL3L1* are protected from HIV MTCT.

5.2. Human alpha chemokine ligand 12 (CXCL12)/Stromal derived factor 1 (SDF1)

SDF1 gene encodes a stromal cell-derived alpha chemokine, member of the intercrine family. The gene product and its receptor CXCR4 can activate lymphocytes (Winkler et al., 1998). Mutations in this gene were associated with resistance to HIV infection (Winkler et al., 1998) and rapid disease progression in children (Tresoldi et al., 2002).

Tresoldi et al. (2002) study suggested that the presence of the *SDF-1 3′A* polymorphism was associated to a rapid disease progression in Italian HIV infected children born to seropositive mothers, but did not protect against MTCT, proposing *SDF-1 3′A* mutation as a marker of disease progression. In contrast, Mangano et al. (2000) did not find any association between the rates of HIV transmission or disease progression with *SDF-1 3′A* genotype in a group of 430 HIV infected children.

Tresoldi's findings are in agreement with other studies (Winkler et al., 1998; Sei et al., 2001) associating the homozygous *SDF-1 3′A* mutation with accelerated onset of AIDS in HIV infected adults (Winkler et al., 1998). These studies showed evidences that a large number of children were infected with MT-2–negative viruses, which are capable of using only the CCR5 receptor. Therefore, it is not surprising that SDF-1, the ligand of CXCR4, may not affect vertical transmission of R5 viruses. However it is possible that SDF-1 has an inhibitory effect on the transmission of X4 viruses harboured by the mother (Winkler et al., 1998).

Furthermore, Sei et al. (2001) did not show any significant difference in the frequency of AIDS development in children during the first 3 years of life in relation to *SDF-1 3′A* genotype. This group of children included 127 subjects (58 Caucasians, 60 African-Americans and 9 Hispanics). The overall frequency of the *SDF-1 3′A*mutation was different in the Italian children of Tresoldi's study with respect to the Caucasian children (41.4% vs. 34.5%, respectively) enrolled in the United States by Sei et al. (2001).

In pediatric AIDS, the protective effect of *CCR5wt*/*Δ32* appears to be abrogated by the *SDF1–3′A* genotype. Singh and Spector (2009) studied SDF1–3′-G/A polymorphism in a cohort of 1049 children with symptomatic HIV infection and observed that the *SDF1–3′*A/A variant was associated with more-rapid disease progression, occurring in <2% of the children.

John et al. (2000) showed that the maternal heterozygous *SDF1* genotype (*SDF1 3′A*/wt) was associated with perinatal transmission of HIV (risk ratio [RR], 1.8; 95% CI = 1.0–3.3) and particularly postnatal breast-milk transmission (RR = 3.1; 95% CI = 1.1–8.6). In contrast, the infant *SDF1* genotype had no effect on mother-to-infant transmission. These data suggest that *SDF1* may affect the ability of the mother to transmit the virus to her infant.

So we can conclude that SDF-1 3′A polymorphism is associated with increased susceptibility to HIV MTCT.

5.3. Interleukin-18 (IL-18)

Segat et al. (2006b) reported that the −607 C variation is associated with an increased susceptibility to MTCT in North East of Brazil, suggesting a role of IL-18 in MTCT, as proposed by Ahmad et al. (2002).

6. Human leukocyte antigen (HLA)

6.1. Human leukocyte antigen (HLA) class 1

Human leukocyte antigen (HLA) class 1 genes, located at *the HLA-A, -B*, and *-C loci*, encode molecules that differentially present endogenous viral peptides to $CD8^+$ T lymphocytes. This class of genes has been so far investigated for its role in the infection of HIV and MTCT. Several polymorphisms in *HLA* genes have been widely studied as candidates for susceptibility to MTCT (Kilpatrick et al., 1991; Greggio et al., 1993; Winchester et al., 1995; Aikhionbare et al., 2001; Fabris et al., 2009; Segat et al., 2009b; Pérez-Núñez et al., 2011).

A serologic HLA typing study found that *HLA-A3-B7-DR2* haplotype was associated with protection against HIV MTCT infection, whereas the *HLA-A1-B8-DR3* haplotype was associated with the predisposition to infection in children (Kilpatrick et al., 1991). Another study showed that *DRB1–13* allele subtypes were associated with protection against MTCT (Greggio et al., 1993).

On other hand, the *HLA-DR3* (DRB1*03011) allele was associated with the occurrence of HIV infection among American Caucasian children and the *HLA-DR13* alleles associated with protection against HIV transmission in African-American but not in Caucasian infants (Winchester et al., 1995). These studies suggest that the variability of viral peptides presentation by HLA molecules, may significantly influence the susceptibility to MTCT.

Another study showed that the concordance or discordance of *HLA* alleles between mother and child could to be a key factor for MTCT, and that *HLA* genotype could influence disease susceptibility in utero by affecting immune responses (Pérez-Núñez et al., 2011).

6.2. HLA-G

Within HLA molecules, HLA-G plays an important role at the maternal-fetal interface. HLA-G is a non-classical HLA molecule from class I involved in immune tolerance by acting as ligand for inhibitory receptors present on natural killer (NK) cells and macrophages. This molecule has a limited distribution in tissues and is

selectively expressed in placental trophoblast cells, at the maternal-fetal interface (Hunt et al., 2000; Moodley and Bobat, 2011).

HLA-G molecules appear to protect the fetus from maternal cytotoxic T lymphocytes (CTLs) and natural killer (NK) cells, playing an important role in pregnancy maintenance (Kovats et al., 1990). Therefore, HLA-G influences HIV MTCT, increasing or decreasing protection of infants against virus transmission.

Aikhionbare et al. (2001) study suggests that mother–child pairs both carrying the identical mutation in *HLA-G* exon 2 may be at higher risk for HIV MTCT: the discordance of *HLA-G* exon 2 was significantly more common among non-transmitting (93%) than transmitting mother–child pairs (40%).

Another studies in a Brazilian population, conducted by Fabris et al. (2009) and Segat et al. (2009b) showed that polymorphisms in *HLA-G* are involved in MTCT.

Fabris et al. (2009) studied 175 perinatally infected and 71 exposed uninfected children born to HIV infected mothers and 175 uninfected children, founding significant differences in allele and genotype frequencies of *HLA-G* 3′ UTR 14-bp polymorphism (rs16375). The 14-bp-deleted allele was significantly more frequent in exposed uninfected children than in HIVpositivechildren, being associated with a reduced risk of HIV MTCT ($p < 0.0001$, OR = 0.37, 95% CI = 0.23–0.58).

Segat et al. (2009a) evaluated the possible association of *HLA-G* 3777G > C and 14-bp deletion/insertion (D/I) polymorphisms with perinatal transmission, and observed that the 3777G > C polymorphism alone has no effect on HIV MTCT, but when linked with the D allele, exerts a positive role in the protection to infection.

HLA-G 14-bp insertion has been associated with a lower mRNA production for most membrane-bound and soluble isoforms in trophoblast samples. Different subjects carrying this polymorphism have been shown to undergo alternative splicing events (Kovats et al., 1990).

Moodley and Bobat (2011) showed that placental *HLA-G1* expression could contribute for MTCT. The authors observed that, in children, the risk for HIV infection increases by 1.3 with every 1 unit increase in *HLA-G1* expression. Females were 3.7 times more likely to become infected than males. A positive correlation was observed between mother's log viral load and HIV vertical transmission ($p = 0.047$; 95% CI = 1.029–11.499). Furthermore, the authors described that *HLA-G1* expression was 3.95 times higher in placentas of HIV-1 infected mothers who transmitted the virus to their children, when compared to mothers with uninfected babies.

These studies indicated that *HLA-G* polymorphism rs16375 alone or combined with 3777G/C as well as a mutation in exon 2 confer protection to HIV MTCT.

7. Natural killer cells receptors and products

7.1. Killer immunoglobulin-like receptors (KIR)

Natural killer (NK) cells perform a vital role in response to pathogen infection, with the ability to directly kill infected cells, produce cytokines and crosstalk with the adaptive immune system. These functions are dependent on activation of NK cells, which is determined by surface receptor interactions with ligands on target cells, as the killer immunoglobulin-like (KIRs) receptors that interact with MCH class 1 (Jamil and Khakoo, 2011).

When considering the susceptibility to HIV infection, is evident the role of HLA and KIR receptors. HIV can down regulate HLA class I expression to block the presentation of viral epitopes and prevent cytotoxic T lymphpcytes (CTL) killing of the infected cells. NK cells eliminate cells that fail to display correct levels of HLA receptors, and one function of KIR in NK cells is to define whether the potential target cells carry the proper set of HLA receptors (Jamil and Khakoo, 2011; Paximadis et al., 2011).

The interaction of KIR and their HLA ligands is complex (Paximadis et al., 2011): some studies showed that polymorphism in these genes may influence HIV MTCT (Winchester et al., 1995; Mackelprang et al., 2008; Paximadis et al., 2011).

During pregnancy, the child shares *MHC* genes with the mother, while the mother is induced to tolerate the paternally derived fetal

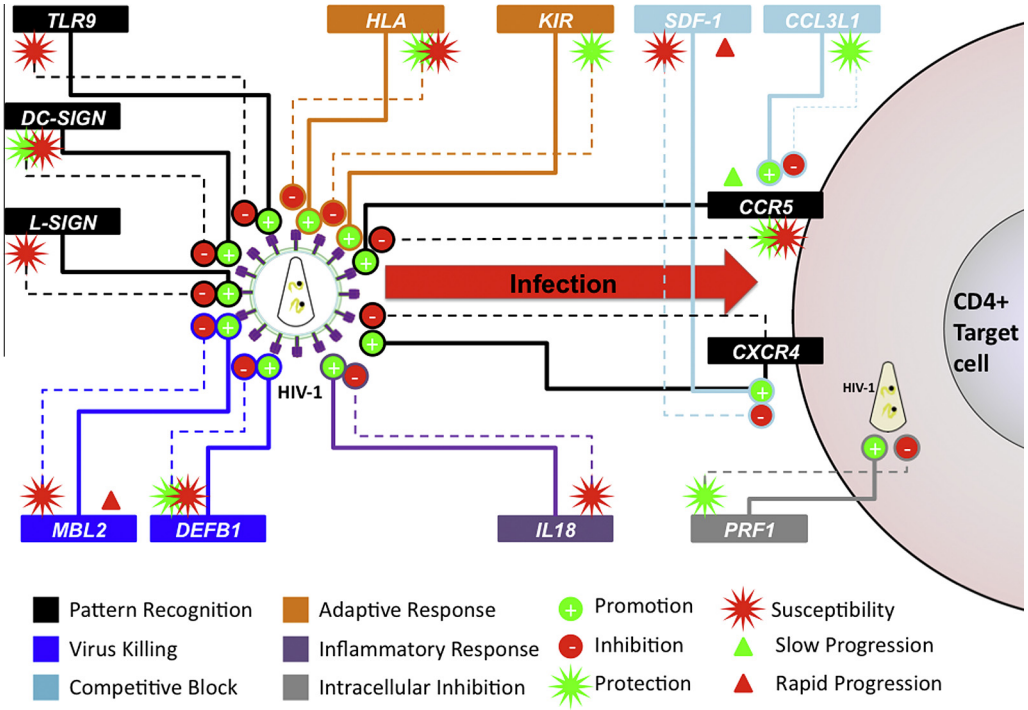

Fig. 1. How genetics can affect innate and adaptive immunity components involved in HIV mother-to-children transmission and progression to AIDS.

Table 2
Minor allele frequencies of SNPs involved in MTCT in different populations.

Study	Population	*N*	Variation	MAFs in studied population				MAFs – HapMap			
				HIV+	HIV−	HC	GERAL	Allele referency	CEU	YRB	CHB
HLA Kilpatrick et al. (1991)	UK	53									
			HLA–DR3	0.43	0.15	NA	0.19				
			HLA–A3	0.13	0.42	NA	0.14				
Greggio et al. (1993)	Italy	172	HLA–DRB1–14a	0.00	0.10	0.05	0.06				
			HLA–DRB1–13a.4	0.00	0.06	0.04	0.03				
Winchester et al. (1995)	USA	109	HLA–DR2	0.38	0.44	NA	0.42				
			HLA–DRB1∗1501	0.15	0.67	NA	0.20				
			HLA–DRB1∗11011	0.03	0.12	NA	0.07				
			HLA–DRB1∗1102	0.15	0.12	NA	0.13				
			HLA–DRB1∗03011	0.18	0.19	NA	0.18				
Segat et al. (2009a)	Brazil	397	HLA-G–rs1707	0.39	0.40	0.41	0.40	C	0.115(C)	0.123(C)	0.047(C)
Fabris et al. (2009)	Brazil	421	HLA-G–rs1704	0.42	0.21	0.40	0.40	−	0.320(−)	0.430(−)	0.309(−)
CCR5-CXCR4											
Mandl et al. (1998)	Austria	79	rs333 (CCR5Δ32)	0.11	0.03	NA	0.08	+	0.048 (−)	0.000 (−)	NA
Philpott et al. (1999)	USA	1104	rs333 (CCR5Δ32)	0.02	0.03	NA	0.03				
Mangano et al. (2000)	Argentina	983	rs333 (CCR5Δ32)	0.04	0.04	0.05	0.04				
DEFB1											
Braida et al. (2004)	Italy	217	rs11362–A	0.38	NA	0.38	0.38	C	0.363 (T)	0.403 (C)	0.435 (T)
			rs1800972–G	0.10	NA	0.22	0.16	C	0.258 (G)	0.042 (G)	0.125 (G)
			rs1799946–A	0.52	NA	0.42	0.47	C	0.394 (T)	0.292 (T)	0.405 (T)
Milanese et al. (2006)	Brazil	303	rs11362–A	0.52	0.42	0.37	0.44				
			rs1800972–G	0.07	0.13	0.14	0.11				
			rs1799946–A	0.33	0.46	0.46	0.40				
Segat et al. (2006)	Italy	250	rs11362–A	NA	0.37	0.38	0.38				
			rs1800972–G	NA	0.04	0.22	0.10				
			rs1799946–A	NA	0.55	0.42	0.50				
Ricci et al. (2009)	Italy	384	rs1800972–G	0.12	0.16	NA	0.15				
			rs1799946–A	0.20	0.38	NA	0.40				
MBL2											
Boniotto et al. (2000)	Italy	101	Position-550–H	NA	0.48	0.36	0.39				
			Position-328–del	NA	0.14	0.19	0.18				
Boniotto et al. (2003)	Brazil	306	Allele O	0.29	0.19	0.20	0.23				
Mangano et al. (2008)	Argentina	492	Allele X	0.16	0.11	0.15	0.14				
			Allele O	0.25	0.26	0.21	0.24				
			rs1800450 (B)	0.20	0.20	0.18	0.19	C	0.150 (T)	0.009 (T)	0.155 (T)
			rs5030737 (D)	0.05	0.05	0.03	0.04	G	0.071 (T)	0.021 (T)	0.012 (T)
			rs1800451 (C)	0.00	0.00	0.00	0.00	C	0.018 (A)	0.167 (A)	0.012 (A)
PRF1											
Padovan et al. (2011)	Brazil	395	rs885822–C	0.32	0.49	NA	0.35	G	0.425 (G)	0.133 (G)	0.321 (G)
SDF1											
Mangano et al. (2000)	Argentina	983	SDF1 3′A (rs1801157)	0.18	0.21	0.24	0.20	C	0.208 (T)	0.022 (T)	0.298 (T)
Sei et al. (2001)	USA	127		0.05	NA	NA	NA				
Tresoldi et al. (2002)	Italy	544		0.24	0.26	0.27	0.25				
DC/L–SIGN											
Da Silva et al. (2012)	Brazil	346	rs735240–A	0.42	0.36	0.40	0.41	G	0.451 (A)	0.333 (A)	0.270 (A)
			rs735239–G	0.37	0.28	0.29	0.33	A	0.380 (G)	0.003 (G)	0.180 (G)
			rs4804803–G	0.32	0.41	0.31	0.33	G	0.258 (G)	0.432 (G)	0.042 (G)
			rs11465366–T	0.02	0.12	0.03	0.03	C	NA	0.085 (T)	NA
			rs2287886–A	0.27	0.16	0.28	0.26	A	0.305 (A)	0.184 (A)	0.303 (G)
INFAMMASOME											
Pontillo et al. (2010)	Brazil	1038	rs1143634–G	0.40			0.40	G	0.208 (A)	0.099 (A)	0.015 (A)
Segat et al. (2006)	Brazil		*rs*1946518	0.35	0.44	0.46	0.41	T	0.392 (T)	0.345 (T)	0.390 (G)
			*rs*187238	0.22	0.25	0.26	0.24	G	0.233 (C)	0.142 (C)	0.153 (C)
TRL9											
Ricci et al. (2010)	Italian	300	rs352139–A	0.49	0.42	NA	0.48	T	0.482 (C)	0.425 (T)	0.405 (C)
			rs352140–G	0.45	0.42	NA	0.44	C	0.478 (T)	0.305 (T)	0.399 (T)

NA = not analyzed.

MHC molecules, in part through natural killer (NK) recognition of MHC polymorphisms (Winchester et al., 1995).

In the context of MTCT Winchester et al. (1995) determined the *HLA-B* alleles of mother and infants. The results revealed that almost half (48%) of mothers who transmitted with low viral loads had *HLA-B*1302, B*3501, B*3503, B*4402 or B*5001* alleles, compared with 8% of non-transmitting mothers ($p = 0.001$). Conversely, 25% of mothers who did not transmit despite high viral loads had B*4901 and B*5301, vs. 5% of transmitting mothers ($p = 0.003$), showing a distinct pattern of allelic involvement able to influence susceptibility to HIV infection. In children *HLA-B* alleles were not associated with virus transmission risk. The *HLA-B*4901* and B*5301 alleles, protective in the mother, both differed respectively from the otherwise identical susceptibility alleles, B*5001 and B*3501, by 5 amino acids encoding the ligand for the KIR3DL1 NK receptor. Results suggest that the probable molecular basis of the observed association involves definition of maternal NK recognition repertoire by engagement of NK receptors with polymorphic ligands encoded by maternal *HLA-B* alleles.

Paximadis et al. (2011) studied the *KIR*, *HLA-B* and *HLA-C* genes of 224 HIV infected mothers and 222 infants (72 infected and 150 uninfected) from South Africa. *KIR2DL2/KIR2DL3* was underrepresented in intrapartum (IP) transmitting mothers ($p = 0.036$). The frequency of homozygous for *KIR2DL3* alone, and in combination

with *HLA-C* haplotype heterozygous (C1C2), was significantly elevated in IP transmitting mothers ($p = 0.034$ and $p = 0.01$ respectively). In infants, *KIR2DL3* in combination with its *HLA-C1* ligand as well as homozygous *KIR2DL3* with *C1C2*, were underrepresented in infected infants compared to exposed uninfected subjects ($p = 0.007$ and $p = 0.03$).

Mackelprang et al. (2008) study analyzed mother–child *HLA* concordance and maternal *HLA* homozygosity in a Kenyan perinatal cohort receiving antenatal zidovudine and found that the risks of overall, in utero and breast milk HIV transmission increased with *HLA* concordance and homozygosity. The increased risk may be due to reduced alloimmunityy or less diverse protective immune responses.

These findings suggest that KIR variants in combination with others components such as HLA-C confer protection to HIV MTCT.

7.2. Perforin(PRF1)

Perforin is an important component of the secretory granule-mediated cell death pathway. It is a protein present in the granules of cytotoxic T lymphocytes (CTLs) and natural killer (NK) cells and plays an important role in the elimination of virus-infected cells (Heintel et al., 2002).

Once released, perforin polymerizes to form transmembrane pores in the phospholipid bilayer of target cells' membranes. Through these pores other components of the lytic granules, such as granzyme A, granzyme B, and granulysin (Heintel et al., 2002) can entry into the cells, leading to the activation of various apoptotic death pathways (Lichtenheld et al., 1988).

Padovan et al. (2011) analyzed *PRF1* gene polymorphisms, localized at coding and untranslated regions (UTRs), in three groups of children from Recife (Brazil): 173 perinatally infected children, 51 HIV exposed-uninfected and 170 children with no exposure to the virus. The rs885822 C allele and C/C genotype were significantly more frequent in HIV exposed-uninfected than in HIV exposed-infected children. The authors suggested that C allele and C/C genotype were associated with a protective effect toward HIV MTCT.

8. Comments

The HIV MTCT is a complex puzzle event of multiple factors that remain incomplete until now. In this article we try to share with the reader the experience of two research groups working on genetic variations of innate and acquired immunity involved in the in the susceptibility to HIV MTCT, by systematically and critically revising our findings in comparison with the literature. The innate immunity is essential in the initial detection of HIV, mounting an efficient response against the virus in newborns, since its adaptive immunity is not well developed yet. Even thus, the children adaptive immune response plays a key role on the MTCT mechanism too. In fact, the interaction of innate and adaptive immune genetic components seems to be essential in the HIVMTCT outcome (see Fig. 1).

Another interesting component in HIV MTCT, is the mother–child genetic interdependency. For example, HLA concordance between the mother and its child was associated with increased risk of HIV MTCT in utero and through breast milk. This increased susceptibility has several possible biological mechanisms. Children with the same HLA of their mothers could be less able to identify HIV that has evaded maternal immune responses via HLA-mediated selection. HLA concordance might also reduce the likelihood of babies' immune response against maternally derived lymphocytes (Mackelprang et al., 2008).

The major limitation of the genetic associations studies described in this review is the small numbers of individuals enrolled in each study. In part, this limitation is due to, fortunately, the highly effective prevention strategies for MTCT that have been successfully introduced in the clinical management of pregnant women. A definitive solution for this problem is the creation of a MTCT consortium, at least at Continental level, with the possibility of analyzing larger groups of children from different ethnic groups worldwide. Ethnicity is the other source of discordant findings, since the uneven distribution of several genetic polymorphisms in distinct ethnic group's accounts for the biases presented in the paragraphs above.

Table 2 describes the minor allele frequencies (MAFs) of all associated genetic variations with HIVMTCT in HIV patients and in different ethnic healthy individuals: data were collected in International HapMap project (http://hapmap.ncbi.nlm.nih.gov/) and NCBI Variation Database (dbSNP) (http://www.ncbi.nlm.nih.gov/snp), International HapMap Project (2013), NCBI Variation Database (2013). The distribution of some genetic variations is clearly associated with the ethnic component and could influence the rate of the HIV infection in such ethnic group.

As a multifactorial event, the MTCT does not depend on the genetic contribution of each individual factor, conferring higher/lower MTCT susceptibility in statistical odd rates. Since the role of various factors have been elucidated in the same population, it would be possible infer the overall risk factors. Until now, it does not exist a genetic association study of MTCT that includes the whole human genome and the available data, unfortunately, do not allow predicting the genetic interaction with statistical power.

As stated before, it would be very useful to create a consortium to increase the number of patients and join forces to better understand the role of each genetic factor in the susceptibility of MTCT, including children with different ethnic backgrounds.

In this article we looked at HIV-MTCT with a "geneticist eye" but the role of environment in MTCT, as described, is also very important. Moreover, studies focusing in the viral variants and subtypes could increase the knowledge and should be considered as an important variable in the future of genetic association studies.

9. Conclusions

The year of 2013 will mark the 32th anniversary of the beginning of AIDS epidemic, and the better understanding of the innate and adaptive immunity factors involved in MTCT susceptibility will be essential for unravelling the mechanisms involved in HIV infection, possibly contributing to the identification of new targets for immunological drugs. Safeguarding the health of mothers and infants provides a strong basis for the growth of new AIDS free generations. For this reason we are aware that in spite of being of scientific interest genetics just provides a little contribution in the fight against MTCT; prevention and the successful introduction in the gynaecological practice of the rapid HIV test as well as the strategies to limit MTCT including cesarian delivery, maternal milk bank to replace breastfeeding do represent the better approach that succeeded to strongly reduce MTCT in most of the world, including Latin America where we do operate.

References

Aguilar-Jiménez, W., Zapata, W., Rugeles, M.T., 2011. Differential expression of human beta defensins in placenta and detection of allelic variants in the DEFB1 gene from HIV-1 positive mothers. Biomedica 31 (1), 44–54.

Ahmad, N., 2011. Molecular mechanisms of HIV-1 mother-to-child transmission and infection in neonatal target cells. Life Sci. 88 (21–22), 980–986.

Ahmad, R., Sindhu, S.T., Toma, E., Morisset, R., Ahmad, A., 2002. Elevated levels of circulating interleukin-18 in human immunodeficiency virus-infected individuals: role of peripheral blood mononuclear cells and implications for AIDS pathogenesis. J. Virol. 76 (24), 12448–12456.

Aikhionbare, F.O., Hodge, T., Kuhn, L., Bulterys, M., Abrams, E.J., Bond, V.C., 2001. Mother-to-child discordance in HLA-G exon 2 is associated with a reduced risk of perinatal HIV-1 transmission. AIDS 15 (16), 2196–2198.

Amoroso, A., Berrino, M., Boniotto, M., Crovella, S., Palomba, E., Scarlatti, G., Serra, C., Tovo, P.A., Vatta, S., 1999. Polymorphism at codon 54 of mannose-binding protein gene influences AIDS progression but not HIV infection in exposed children. AIDS 13, 863–867.

Arias, R.A., Muñoz, L.D., Muñoz-Fernández, M.A., 2003. Transmission of HIV-1 infection between trophoblast placental cells and T-cells take place via an LFA-1-mediated cell to cell contact. Virology 307 (2), 266–277.

Armogida, S.A., Yannaras, N.M., Melton, A.L., Srivastava, M.D., 2004. Identification and quantification of innate immune system mediators in human breast milk. Allergy Asthma Proc. 25 (5), 297–304.

Baribaud, F., Pöhlmann, S., Doms, R.W., 2001. The role of DC-SIGN and DC-SIGNR in HIV and SIV attachment, infection, and transmission. Virology 286, 1–6.

Baroncelli, S., Ricci, E., Andreotti, M., Guidotti, G., Germano, P., Marazzi, M.C., Vella, S., Palombi, L., De Rossi, A., Giuliano, M., 2008. Single-nucleotide polymorphisms in human beta-defensin-1 gene in Mozambican HIV-1-infected women and correlation with virologicparameters. AIDS 22 (12), 1515–1517.

Boily-Larouche, G., Iscache, A.L., Zijenah, L.S., Humphrey, J.H., Mouland, A.J., Ward, B.J., Roger, M., 2009. Functional genetic variants in DC-SIGNR are associated with mother-to-child transmission of HIV. PLoS ONE 4, e7211.

Boniotto, M., Crovella, S., Pirulli, D., Scarlatti, G., Spanò, A., Vatta, L., Zezlina, S., Tovo, P.A., Palomba, E., Amoroso, A., 2000. Polymorphisms in the MBL2 promoter correlated with risk of HIV-1 vertical transmission and AIDS progression. Genes Immun. 1 (5), 346–348.

Boniotto, M., Braida, L., Pirulli, D., Arraes, L., Amoroso, A., Crovella, S., 2003. MBL2 polymorphisms are involved in HIV-1 infection in Brazilian perinatally infected children. AIDS 17, 779–780.

Braida, L., Boniotto, M., Pontillo, A., Tovo, P.A., Amoroso, A., Crovella, S., 2004. A single-nucleotide polymorphism in the human beta-defensin 1 gene is associated with HIV-1 infection in Italian children. AIDS 18, 1595–1606.

Chaichompoo, P., Bostik, P., Stephenson, S., Udompunturuk, S., Kobkitjaroen, J., Pattanapanvasat, K., Ansari, A.A., 2010. Multiple KIR gene polymorphisms are associated with plasma viral loads in SIV-infected rhesus macaques. Cell Immunol. 263 (2), 176–187.

Contopoulos-Ioannidis, D.G., O'Brien, T.R., Goedert, J.J., Rosenberg, P.S., Ioannidis, J.P., 2003. Effect of CCR5-delta32 heterozygosity on the risk of perinatal HIV-1 infection: a meta-analysis. J. Acquir. ImmuneDefic. Syndr. 32 (1), 70–76.

Crovella, S., Bernardon, M., Braida, L., Boniotto, M., Guaschino, S., Ferrazzi, E., Martinelli, P., Alberico, S., 2005. Italian multicentric pilot study on MBL2 genetic polymorphisms in HIV positive pregnant women and their children. J. Matern. Fetal Neonatal Med. 17 (4), 253–256.

Da Silva, R.C., Segat, L., Crovella, S., 2011. Role of DC-SIGN and L-SIGN receptors in HIV-1 vertical transmission. Hum. Immunol. 72 (4), 305–311.

Da Silva, R.C., Segat, L., Zanin, V., Arraes, L.C., Crovella, S., 2012. Polymorphisms in DC-SIGN and L-SIGN genes are associated with HIV-1 vertical transmission in a Northeastern Brazilian population. Hum. Immunol. 73 (11), 1159–1165.

De Souza, P.R., Arraes, L.C., de Lima Filho, J.L., Bruneska, D., Milanese, M., Crovella, S., 2006. CCR5 promoter polymorphisms and HIV-1 perinatal transmission in Brazilian children. J. Reprod. Immunol. 69 (1), 77–84.

Fabris, A., Catamo, E., Segat, L., Morgutti, M., Arraes, L.C., de Lima-Filho, J.L., Crovella, S., 2009. Association between HLA-G 3'UTR 14-bp polymorphism and HIV vertical transmission in Brazilian children. AIDS 14, 1777.

Garred, P., Larsen, F., Madsen, H.O., Koch, C., 2003. Mannose-binding lectin deficiency-revisited. Mol. Immunol. 40, 73–84.

Gonzalez, E., Bamshad, M., Sato, N., Mummidi, S., Dhanda, R., Catano, G., Cabrera, S., McBride, M., Cao, X.H., Merrill, G., O'Connell, P., Bowden, D.W., Freedman, B.I., Anderson, S.A., Walter, E.A., Evans, J.S., Stephan, K.T., Clark, R.A., Tyagi, S., Ahuja, S.S., Dolan, M.J., Ahuja, S.K., 1999. Race-specific HIV-1 disease-modifying effects associated with CCR5 haplotypes. Proc. Natl. Acad. Sci. USA 96 (21), 12004–12009.

Gonzalez, E., Kulkarni, H., Bolivar, H., Mangano, A., Sanchez, R., Catano, G., Nibbs, R.J., Freedman, B.I., Quinones, M.P., Bamshad, M.J., Murthy, K.K., Rovin, B.H., Bradley, W., Clark, R.A., Anderson, S.A., O'connell, R.J., Agan, B.K., Ahuja, S.S., Bologna, R., Sen, L., Dolan, M.J., Ahuja, S.K., 2005. The influence of CCL3L1 gene-containing segmental duplications on HIV-1/AIDS susceptibility. Science 307 (5714), 1434–1440.

Greggio, N.A., Cameran, M., Giaquinto, C., Zacchello, F., Koroliuk, D., Colizzi, V., 1993. DNA HLA-DRB1 analysis in children of positive mothers and estimated risk of vertical HIV transmission. Dis. Markers 11 (1), 29–35.

Heintel, T., Sester, M., Rodríguez, M.M., Krieg, C., Sester, U., Wagner, R., Pees, H.W., Gärtner, B., Maier, R., Meyerhans, A., 2002. The fraction of perforin-expressing HIV-specific CD8 T cells is a marker for disease progression in HIV infection. AIDS 16, 1497–1501.

Huang, J., Burke, P., Yang, Y., Seiss, K., Beamon, J., Cung, T., Toth, I., Pereyra, F., Lichterfeld, M., Yu, X.G., 2010. Soluble HLA-G inhibits myeloid dendritic cell function in HIV-1 infection by interacting with leukocyte immunoglobulin-like receptor B2. J. Virol. 84 (20), 10784–10791.

Hunt, J.S., Petroff, M.G., Morales, P., Sedlmayr, P., Geraghty, D.E., Ober, C., 2000. HLA-G in reproduction: studies on the maternal-fetal interface. Hum. Immunol. 61 (11), 1113–1117.

International HapMap Project. Available in: <http://hapmap.ncbi.nlm.nih.gov/>. [Accessed on 8.01.2013].

Ioannidis, J.P., Contopoulos-Ioannidis, D.G., Rosenberg, P.S., Goedert, J.J., De Rossi, A., Espanol, T., Frenkel, L., Mayaux, M.J., Newell, M.L., Pahwa, S.G., Rousseau, C., Scarlatti, G., Sei, S., Sen, L., O'Brien, T.R., 2003. HIV Host Genetics International Meta-Analysis Group Effects of CCR5-delta32 and CCR2-64I alleles on disease progression of perinatally HIV-1-infected children an international meta-analysis. AIDS 17 (11), 1631–1638.

Jamil, K.M.J., Khakoo, S.I., 2011. 2011.KIR/HLA interactions and pathogen immunity. J. Biomed. Biotechnol. 2011, 298348.

Jia, H.P., Starner, T., Ackermann, M., Kirby, P., Tack, B.F., McCray Jr., P.B., 2001. Abundant human beta-defensin-1 expression in milk and mammary gland epithelium. J. Pediatr. 138 (1), 109–112.

John, G.C., Rousseau, C., Dong, T., Rowland-Jones, S., Nduati, R., Mbori-Ngacha, D., Rostron, T., Kreiss, J.K., Richardson, B.A., Overbaugh, J., 2000. Maternal SDF13'A polymorphism is associated with increased perinatal human immunodeficiency virus type 1 transmission. J. Virol. 74 (12), 5736–5739.

John, G.C., Bird, T., Overbaugh, J., Nduati, R., Mbori-Ngacha, D., Rostron, T., Dong, T., Kostrikis, L., Richardson, B., Rowland-Jones, S.L., 2001. CCR5 promoter polymorphisms in a Kenyan perinatal human immunodeficiency virus type 1 cohort: association with increased 2-year maternal mortality. J. Infect. Dis. 184 (1), 89–92.

Johnson, E.L., Chakraborty, R., 2012. Placental Hofbauer cells limit HIV-1 replication and potentially offset mother to child transmission (MTCT) by induction of immunoregulatory cytokines. Retrovirology 9, 101.

Kilpatrick, D.C., Hague, R.A., Yap, P.L., Mok, J.Y., 1991. HLA antigen frequencies in children born to HIV-infected mothers. Dis. Markers 9 (1), 21–26.

Kostrikis, L.G., Neumann, A.U., Thomson, B., Korber, B.T., McHardy, P., Karanicolas, R., Deutsch, L., Huang, Y., Lew, J.F., McIntosh, K., Pollack, H., Borkowsky, W., Spiegel, H.M., Palumbo, P., Oleske, J., Bardeguez, A., Luzuriaga, K., Sullivan, J., Wolinsky, S.M., Koup, R.A., Ho, D.D., Moore, J.P., 1999. A polymorphism in the regulatory region of the CC-chemokine receptor 5 gene influences perinatal transmission of human immunodeficiency virus type 1 to African-American infants. J. Virol. 73 (12), 10264–10271.

Kovats, S., Main, E.K., Librach, C., Stubblebine, M., Fisher, S.J., DeMars, R., 1990. A class I antigen, HLA-G, expressed in human trophoblasts. Science 248 (4952), 220–223.

Kuhn, L., Schramm, D.B., Donninger, S., Meddows-Taylor, S., Coovadia, A.H., Sherman, G.G., Gray, G.E., Tiemessen, C.T., 2007. African infants' CCL3 gene copies influence perinatal HIV transmission in the absence of maternal nevirapine. AIDS 21 (13), 1753–1761.

Lichtenheld, M.G., Olsen, K.J., Lu, P., Lowrey, D.M., Hameed, A., Hengartner, H., Podack, E.R., 1988. Structure and function of human perforin. Nature 335, 448–451.

Mackelprang, R.D., John-Stewart, G., Carrington, M., Richardson, B., Rowland-Jones, S., Gao, X., Mbori-Ngacha, D., Mabuka, J., Lohman-Payne, B., Farquhar, C., 2008. Maternal HLA homozygosity and mother-child HLA concordance increase the risk of vertical transmission of HIV-1. J. Infect. Dis. 197 (8), 1156–1161.

Mandl, C.W., Aberle, S.W., Henkel, J.H., Puchhammer-Stöckl, E., Heinz, F.X., 1998. Possible influence of the mutant CCR5 Allele on vertical transmission of HIV-1. J. Med. Virol. 55 (1), 51–55.

Mangano, A., Kopka, J., Batalla, M., Bologna, R., Sen, L., 2000. Protective effect of CCR2-64I and not of CCR5-32 and SDF-1 3'A in pediatric HIV-1 infection. J. AIDS 23, 52–57.

Mangano, A., Gonzalez, E., Dhanda, R., Catano, G., Bamshad, M., Bock, A., Duggirala, R., Williams, K., Mummidi, S., Clark, R.A., Ahuja, S.S., Dolan, M.J., Bologna, R., Sen, L., Ahuja, S.K., 2001. Concordance between the CC chemokine receptor 5 genetic determinants that alter risks of transmission and disease progression in children exposed perinatally to human immunodeficiency virus. J. Infect. Dis. 183 (11), 1574–1585.

Mangano, A., Rocco, C., Marino, S.M., Mecikovsky, D., Genre, F., Aulicino, P., Bologna, R., Sen, L., 2008. Detrimental effects of mannose-binding lectin (MBL2) promoter genotype XA/XA on HIV-1 vertical transmission and AIDS progression. J. Infect. Dis. 198 (5), 694–700.

Meddows-Taylor, S., Donninger, S.L., Paximadis, M., Schramm, D.B., Anthony, F.S., Gray, G.E., Kuhn, L., Tiemessen, C.T., 2006. Reduced ability of newborns to produce CCL3 is associated with increased susceptibility to perinatal human immunodeficiency virus 1 transmission. J. Gen. Virol. 87 (Pt 7), 2055–2065.

Menten, P., Wuyts, A., Van Damme, J., 2002. Macrophage inflammatory protein-1. Cytokine Growth Factor Rev. 13, 455–481.

Milanese, M., Segat, L., Pontillo, A., Arraes, L.C., de Lima Filho, J.L., Crovella, S., 2006. DEFB1 gene polymorphisms and increased risk of HIV-1 infection in Brazilian children. AIDS 20, 1673–1675.

Moodley, S., Bobat, R., 2011. Expression of HLA-G1 at the placental interface of HIV-1 infected pregnant women and vertical transmission of HIV. Placenta 32 (10), 778–782.

NCBI Variation Database (dbSNP). Available in: <http://www.ncbi.nlm.nih.gov/SNP/>. [Accessed on 8.01.2013].

Newell, M.L., Dunn, D.T., Peckham, C.S., Semprini, A.E., Pardi, G., 1996. Vertical transmission of HIV-1: maternal immune status and obstetric factors. The European collaborative study. AIDS 10 (14), 1675–1681.

Nibbs, R.J., Yang, J., Landau, N.R., Mao, J.H., Graham, G.J., 1999. LD78beta, a non-allelic variant of human MIP-1alpha (LD78alpha), has enhanced receptor interactions and potent HIV suppressive activity. J. Biol. Chem. 274 (25), 17478–17483.

Padovan, L., Segat, L., Crovella, S., 2011. A polymorphism in PRF1 gene is associated with HIV-1 vertical transmission in Brazilian children. AIDS 25 (4), 535–537.

Paximadis, M., Minevich, G., Winchester, R., Schramm, D.B., Gray, G.E., Sherman, G.G., Coovadia, A.H., Kuhn, L., Tiemessen, C.T., 2011. KIR-HLA and Maternal-Infant HIV-1 Transmission in Sub-Saharan Africa. PLoS ONE 6 (2), p1.

Pérez-Núñez, D., Martínez-Quiles, N., 2011.Genetic factors that Influence HIV Infection: the role of the major histocompatibility complex system, in: Chang, T. L. (Ed.), HIV-Host Interactions, ISBN: 978-953-307-442-9, InTech, Available from: <http://www.intechopen.com/books/hiv-hostinteractions/genetic-factors-that-influence-hiv-infection-the-role-of-the-major-histocompatibility-complexsystem>.

Philpott, S., Burger, H., Charbonneau, T., Grimson, R., Vermund, S.H., Visosky, A., Nachman, S., Kovacs, A., Tropper, P., Frey, H., Weiser, B., 1999. CCR5 genotype and resistance to vertical transmission of HIV-1. J. Acquir. Immune. Defic. Syndr. 21 (3), 189–193.

Pontillo, A., Brandão, L.A., Guimarães, R.L., Segat, L., Athanasakis, E., Crovella, S., 2010. A 3'UTR SNP in NLRP3 gene is associated with susceptibility to HIV-1 infection. J. Acquir. Immune. Defic. Syndr. 54 (3), 236–240.

Quinones-Mateu, M.E., Lederman, M.M., Feng, Z., Chakraborty, B., Weber, J., Rangel, H.R., Marotta, M.L., Mirza, M., Jiang, B., Kiser, P., Medvik, K., Sieg, S.F., Weinberg, A., 2003. Human epithelial beta-defensins 2 and 3 inhibit HIV-1 replication. AIDS 17, 39–48.

Ricci, E., Malacrida, S., Zanchetta, M., Montagna, M., Giaquinto, C., De Rossi, A., 2009. Role of beta-defensin-1polymorphisms in mother-to-childtransmission of HIV-1. J. Acquir. Immune. Defic. Syndr. 51 (1), 13–19.

Ricci, E., Malacrida, S., Zanchetta, M., Mosconi, I., Montagna, M., Giaquinto, C., De Rossi, A., 2010. Toll-like receptor 9 polymorphisms influence mother-to-child transmission of human immunodeficiency virus type 1. J. Transl. Med. 8, 49.

Segat, L., Milanese, M., Boniotto, M., Crovella, S., Bernardon, M., Costantini, M., Alberico, S., 2006a. Italian Group SIGO HIV in Obstetrics Gynecology. DEFB-1 genetic polymorphism screening in HIV-1 positive pregnant women and their children. J. Matern. Fetal. Neonatal. Med. 19 (1), 13–16.

Segat, L., Bevilacqua, D., Boniotto, M., Arraes, L.C., de Souza, P.R., de Lima Filho, J.L., Crovella, S., 2006b. IL-18 gene promoter polymorphism is involved in HIV-1 infection in a Brazilian pediatric population. Immunogenetics 58 (5–6), 471–473.

Segat, L., Catamo, E., Fabris, A., Padovan, L., Morgutti, M., Crovella, S., 2009a. HLA-G 3' UTR haplotypes and HIV vertical transmission. AIDS 23 (14), 1916–1918.

Segat, L., Brandão, L.A.C., Guimarães, R.L., Crovella, S., 2009b. Are defensin beta1 gene polymorphisms associated with HIV infection and virus replication? AIDS 23 (5), 647–649.

Sei, S., Boler, A.M., Nguyen, G.T., Stewart, S.K., Yang, Q.E., Edgerly, M., Wood, L.V., Brouwers, P., Venzon, D.J., 2001. Protective effect of CCR5 D32 heterozygosity is restricted by SDF-1 genotype in children with HIV-1 infection. AIDS 15, 1343–1352.

Singh, K.K., Spector, S.A., 2009. Host Genetic Determinants of HIV Infection and Disease Progression in Children. Pediatr. Res. 65 (5 Pt 2), 55R–63R.

Sobieszczyk, M.E., Lingappa, J.R., McElrath, M.J., 2011. Host genetic polymorphisms associated with innate immune factors and HIV-1. Curr. Opin. HIV. AIDS 6 (5), 427–434.

Sun, L., Finnegan, C.M., Kish-Catalone, T., Blumenthal, R., Garzino-Demo, P., La Terra Maggiore, G.M., Berrone, S., Kleinman, C., Wu, Z., Abdelwahab, S., Lu, W., Garzino-Demo, A., 2005. Human beta-defensinssuppress human immunodeficiency virus infection: potentialrole in mucosalprotection. J. Virol. 79 (22), 14318–14329.

Taborda-Vanegas, N., Zapata, W., Rugeles, M.T., 2011. Genetic and Immunological Factors Involved in Natural Resistance to HIV-Infection. Open. Virol. J. 5, 35–43.

Townson, J.R., Barcellos, L.F., Nibbs, R.J., 2002. Gene copy number regulates the production of the human chemokine CCL3-L1. Eur. J. Immunol. 32 (10), 3016–3026.

Tresoldi, E., Romiti, M.L., Boniotto, M., Crovella, S., Salvatori, F., Palomba, E., Pastore, A., Cancrini, C., de Martino, M., Plebani, A., Castelli, G., Rossi, P., Tovo, P.A., Amoroso, A., Scarlatti, G., 2002. European Shared Cost Project Group, Italian Register for HIV Infection in Children Prognostic value of the stromal cell-derived factor 1 3'A mutation in pediatric human immunodeficiency virus type 1 infection. J. Infect.Dis. 185 (5), 696–700.

Vidricaire, G., Gauthier, S., Tremblay, M.J., 2007. HIV-1 infection of trophoblasts independent of gp120/CD4 interactions butrelies on heparin sulphateproteoglycans. J. Infect. Dis. 195 (10), 1461–1471.

Winchester, R., Chen, Y., Rose, S., Selby, J., Borkowsky, W., 1995. Major histocompatibility complex class II DR alleles DRB1∗1501 and those encoding HLA-DR13 are preferentially associated with a diminution in maternally transmitted human immunodeficiency virus 1 infection in different ethnic groups: determination by an automated sequence-based typing method. Proc. Natl. Acad. Sci. USA 92 (26), 12374–12378.

Winkler, C., Modi, W., Smith, M.W., Nelson, G.W., Wu, X., Carrington, M., Dean, M., Honjo, T., Tashiro, K., Yabe, D., Buchbinder, S., Vittinghoff, E., Goedert, J.J., O'Brien, T.R., Jacobson, L.P., Detels, R., Donfield, S., Willoughby, A., Gomperts, E., Vlahov, D., Phair, J., O'Brien, S.J., 1998. Genetic restriction of AIDS pathogenesis by an SDF-1 chemokine gene variant.ALIVE Study, Hemophilia Growth and Development Study (HGDS), Multicenter AIDS Cohort Study (MACS), Multicenter Hemophilia Cohort Study (MHCS), San Francisco City Cohort (SFCC). Science 279 (5349), 389–393.