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RANTES and CCR5 Gene Polymorphisms and Risk of HIV-1 Infection and Progression

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Abstract: The advanced stage of human immunodeficiency virus type 1 (HIV-1) infection is acquired immunodeficiency syndrome (AIDS), which takes 2-15 years to develop depending on individuals. This variation is due to Regulated upon Activation, Normal T-cell Expressed and Secreted (RANTES) and chemokine receptor 5 (CCR5) polymorphism. The 32 base pairs deletion of CCR5 and RANTES-403 confer resistance to HIV-1. However, the prevalence and association of these protective markers and HIV-1 was not studied in Northwest Ethiopia. Hence, a review was conducted to investigate the prevalence and association of RANTES-403 and CCR5Δ32 with HIV-1. RANTES-403, evaluated by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) and CCR5Δ32, evaluated by polymerase chain reaction (PCR). The prevalence of CCR5Δ32 homozygous in seronegative group was much higher than the prevalence in seropositive. Hence, CCR5Δ32 was very strongly associated with HIV-1 infection. Even if the review was in light of allocation bias, the significant association of CCR5Δ32, in contrast to RANTES-403, with HIV-1 infection suggests that people with CCR5Δ32 are resistant to HIV-1 infection. Hence, it is better to conduct detail review, systematic review, research with intensive search to provide more conclusive result with clear association.
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Keywords: CCR5Δ32, HIV-1/AIDS, polymorphism, RANTES-403

Introduction

Human immunodeficiency virus type 1 (HIV-1) infection is the serious medical and public health issue of present generation (WHO, 2016). This pandemic situation of AIDS stimulated a plethora of longitudinal cohort studies which are designed to mitigate the factors that regulate the HIV-1 infection, disease progression and the immune defenses (Phair *et al*., 1992). In recent years genetic studies have led to the discovery of various major histocompatibility (MHC) and non MHC encoded genes, which directly or indirectly influence the susceptibility and resistance to HIV-1 infection and acquired immunodeficiency syndrome (AIDS) (Shin *et al*., 2000). CCR5 and RANTES genes are non MHC encoded genes (Carrington *et al*., 2001). The site specific mutations in these genes determine the susceptibility or resistance to HIV-1 infection and AIDS (An *et al*., 2002).

An armed resistance and slow progression for HIV-1 and AIDS is evolutionally related with polymorphisms in genes, chemokine co-receptor (CCR5) and CC chemokine ligands (RANTES) (Korostishevsky, 2006). Chemokine receptor 32 nucleotide base deletion (CCR5Δ32) and a -403 single nucleotide polymorphisms RANTES (RANTES-403) are crucial for resistance and slow progression of HIV-1 (Easterbrook *et al*., 1999).

The best genetic feature characteristics of CCR5Δ32 deletion is that; influence cell surface expression of CCR5, results synthesis of a short and nonfunctional CCR5 protein, reduction in the number of CCR5-positive target cells and consequently, it could influence individual susceptibility to HIV-1 and progression (Enrique *et al*., 2001).

Moreover, CCR5Δ32 is presented by immune cells like; activated memory Th1 lymphocytes, macrophages, peripheral blood-derived dendritic cells. Several of the chemokine receptors CC or CXC co receptors are used by HIV-1 as entry cofactor (Admas and Berhane, 2016). From these, CCR5 is the major co receptor for entry of HIV-1, but 32 bp-deleted CCR5 contributes for HIV-1 resistance and slow progression to AIDS (McNicholl *et al*., 1997, Balci *et al*., 2017).

However, the geographical distribution and prevalence of CCR5Δ32 and RANTES-403 is far from clear (Galvani and Novembre, 2005).

CCRΔ32 has estimated origin of evolutionary history about 700 years ago, with a 95%

confidence interval (CI) of 275–1875 years (Martinson *et al.,* 1997). But other indicated, CCR5Δ32 arose in Scandinavia 1000 -1200 years ago and spread northward to Iceland, Eastward to Russia and Southward to Central and Southern Europe by viking dissemination (Balci *et al*., 2017).

Moreover, this naturally protective polymorphism (CCR5Δ32) is not so frequent and its prevalence shows a declining trend on transition from the North Europe (16%), Southeast towards Mediterranean region (4%), over 20.93% Ashkenazi, 14.71% Iceland, 9.78% Russia, 4.69% Gujarat, 4% Sardinia, 10% over Caucasian population of Europe (Galvani and Novembre, 2005, Ferreira-Fernandes *et al.*, 2015), while it is almost absent in some African (0.45% in Nigeria with CI (00-0.90)) (Martinson *et al.*, 1997). One evidence reported by Admas and Berhane (2016) in University of Gondar Teaching Hospital, Ethiopia the prevalence of CCR5Δ32 was 0% homozygosity and 2% heterozygosity. Based on the ashtray study the present study was conducted with large sample size, varied study area and diversified study population.

In today's world, there are a number of conflicting reported evidences which are involved in the CCR5Δ32 and RANTES-403 polymorphism worldwide distribution, frequency and actual pathogenesis and resistance against HIV-1 (Martinson *et al*., 1997).

Firstly, a cohort study of Ugandan population shows no association between CCR5 polymorphisms and the rate of disease progression (Ramaley, 2002).

Secondly, similar expression level of CCR5 was found in HIV-1 exposed uninfected female prostitutes and in unexposed control individuals from Kenya (Fowke, 1998). Thirdly, in vitro infection study revealed that peripheral blood monocyte cells isolated from HIV-1-highly exposed uninfected and unexposed women carrying different CCR5 haplogroups, had no differences in susceptibility to HIV-1 infection (Kulkarni, 2003).

Studies are totally clandestine; they have no biases in the semblance of reports; and they are not uniformed direction of conclusions.

Nevertheless, resistance contribution of CCR5Δ32 and RANTES-403 has been interpreted by immunologist, molecular pathologist, virologist and pathologists (Sharma *et al*., 2011). Homozygous for CCR5Δ32 have nearly complete resistance to HIV-1 infection despite repeated exposure, and HIV-1 infected heterozygouss for CCR5Δ32 delay the onset of AIDS (Nkenfou *et al*., 2013).

If heterozygous do become infected, they have reduced HIV-1 viral loads with slowed progression to AIDS by an additional 2-3 years (Liu, 1996, Zimmerman, 1997). According to Galvani and Novembre (2005) CCR5Δ32 heterozygotes, express less than half the wild type levels of CCR5 receptor, which slows down HIV-1 replication, spread and pathogenesis.

Active systemic inflammation has recently been shown to share in the atherogenic process by altering the histological nature of blood vessels. These changes have been monitored by assaying the acute phase reactants together with the circulating inflammatory monokines such as IL-1 and TNF-α. Damaged blood vessels, altered blood glucose metabolism and creation of a hypercoagulable state due to platelet activation may dramatize the pathologic process leading to arterial occlusion rather than narrowing with a possible fatal outcome (Abbas, 2013).

However, CCR5Δ32 deletion evolved in response to selection by other than HIV-1 pathogen (Ting *et al.*, 2015). The general leading concept under pathophysiology is that, both CCR5 and RANTES polymorphism expression levels vary among individuals and this may affect the risk of HIV-1 transmission and progression (Nkenfou *et al.*, 1997, O'Brien and Moore, 2000).

The basis for this variation was genetic polymorphism. Yet, the wording of CCR5 and RANTES polymorphism distribution, prevalence, protective role and association against HIV-1 susceptibility and progression does not being limited under studies understanding. Thus, there exists a loophole in the resistance and progression under these polymorphisms, because which does not limit and regulate all of the pathogenesis of HIV-1 infection (Shih *et al*., 2014).

Salem *et al.* (2009), indicated that studying the interaction between HIV-1 and chemokine systems advanced our understanding of the pathogenesis and resistance. Consequently, the investigation of resistance-conferring variants in different populations may be useful for prophylactic measures and chemotherapeutic approaches to prevent or cure HIV-1 infection effectively (Korostishevsky *et al.*, 2006).

There have been reports in the literature, that CCR5Δ32 and RANTES-403 polymorphism reduce the risk of HIV-1 infection and associated with slower progression, even they have protective role despite repeated exposure the frequency and their protective role has not been well studied. Therefore, this review attempts to search out and compile the frequency and prevalence of those genes and progressors, and whether those protective markers have protective role. Therefore the general objective of this review was to search and compile the frequency and association of the CCR5Δ32 and

RANTES-403 polymorphism with HIV-1 resistance and the progression among seropositive and seronegative groups.

RANTES and CCR5 Polymorphisms and Risk of HIV-1

2.1. Pathogenesis and Epidemiology of HIV-1/AIDS

HIV-1 infection has become prevalent worldwide and is clearly the defining medical and public health issue of our generation ranks among the greatest infectious disease. Since its discovery in 1981, the disease has progressively spread to various regions of the world (Gonzalez *et al.*, 2001). AIDS was first recognized as a new disease in 1981 and a retrovirus, now termed HIV, Type I (HIV-1) was subsequently identified as the causative agent HIV-1 was first identified in 1983 and HIV-2 in 1985. HIV-1 was first recognized by the U.S. Centers for Disease Control and Prevention (CDC) (Balci *et al.*, 2017).

At the start of the 21st century, the prevalence of HIV-1 infection stabilized at about 0.8% with vulnerable age group most affected young persons from 15 to 24 years of age, accounted for 45% of new HIV-1 infections. (WHO, 2016). By 2012 the AIDS related death decreased to 1.6 million (Balci *et al*., 2017).

Currently only 70% of people with HIV-1 know their status but approximately 36.7 million people living with HIV-1, 1 million died from HIV-1 and 1.8 million becoming newly infected in 2016 globally. African region is the most affected region with 25.6 million people living with HIV-1 which accounts for almost 2 third of the global total of new HIV-1 infection (WHO, 2017).

New HIV-1 infection fell by 39%, and HIV-1 related deaths fell by one thirds with 13.1 million lives saved due to ART in the time period of 2000-2016 (WHO, 2017). The first evidence of HIV-1 epidemic in Ethiopia was detected in 1984. Since then, AIDS has claimed the lives of millions and has left behind hundreds of thousands of orphans (FMoH, 2014).

According to the 2011 EDHS data HIV-1 prevalence varies from region to region (0.9% in Southern Nations, Nationalities and Peoples (SNNPR), 4.9% in Addis Ababa, 6.5% in Gambela), the urban prevalence is 4.2% which is seven times higher than that of the rural (0.6%) and gender (1.9% female versus 1.0 male) during 2011 (CSA and ICF, 2016). But 2014 single point related estimates of Ethiopia national HIV-1 prevalence was 1.14% (FMoH, 2016).

HIV Timeline and Sub Types

Molecular epidemiologic data suggest that, Lentiviruses similar to HIV have been found in a variety of primate species, and some of these are associated with a disease process called simian AIDS (Klatt, 2016).

Unlike other retroviruses, the primate lentiviruses are not transmitted through the germ line, and no endogenous copies of the virus exist in the genome of susceptible species (Emerman and Malim, 1998). HIV that infects human, has been derived from the simian immunodeficiency virus, called SIVcpz, of the *Pan troglodytes troglodytes* subspecies of chimpanzee. The lentivirus strain SIVcpz is highly homologous with HIV-1 and another form of simian immunodeficiency virus found in sooty mangabeys (SIVsm) has similarities as well and likely gave rise to HIV-2 (Heeney *et al*., 2006).

HIV-1 is the predominant HIV type throughout the world while HIV-2 is mostly found in West Africa. HIV-1 was subsequently identified as the causative agent HIV infection. Of HIV-1, two subtypes can be distinguished based on nucleotide sequence relationships, i.e. group M (‘majority’) and group O (‘outlier’) (Wasnik, 2011). In group M, at least ten genetically different subtypes have been identified (from A to J). Group O contains virus strains that are very divergent compared to those of group M (Kaur and Mehra, 2009).

HIV-1 viruses that preferentially infect T-cells are known as T-tropic or X4 strains, while those strains that can infect both macrophages and T-cells are called M-tropic or R5 strains (Admas and Berhane, 2016).

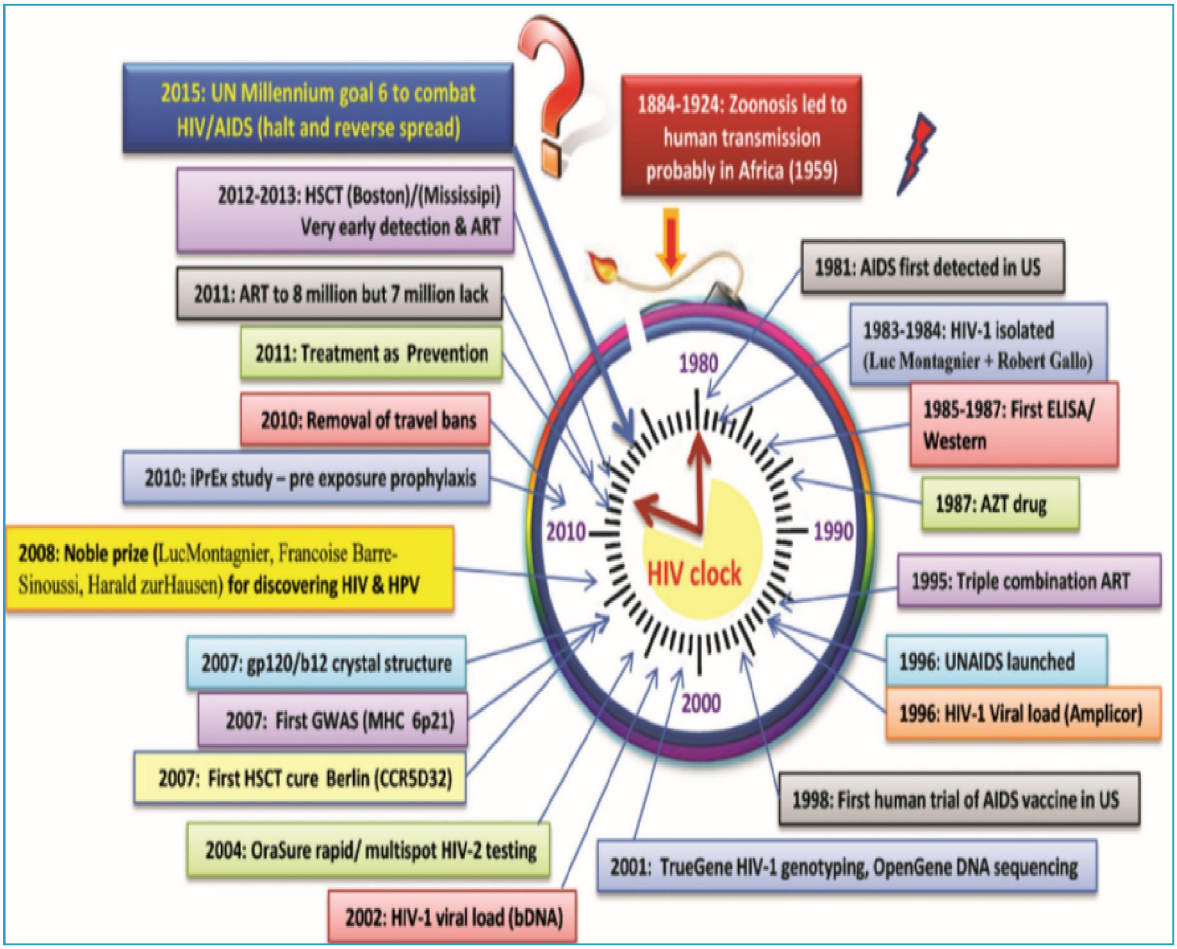

Figure 1 HIV clock' showing major landmarks in research and therapy relating HIV/AIDS pandemic since its inception apparently in early 1980s'. ART, antiretroviral therapy; HSCT, hematopoietic stem cell transplantation; GWAS, genome-wide association studies; HPV, human papilloma virus (Kaur *et al.*, 2010)

Scientific Events with HIV-1/AIDS

Since the recognition of AIDS there were different discoveries related to it. In 1981 AIDS first detected by US, 1983-1984 HIV-1 isolated as the causative agent of AIDS, 1987 drug developed, 1995 triple combination ART, 1996 UNAIDS launched, 1996 HIV-1 Viral load, 1998 first human trial of HIV-1/AIDS vaccine in US, 2001 trugene HIV-1 genotyping, open gene DNA sequencing, 2002 HIV-1 Viral load, 2004 Multispot HIV-2 testing, 2007 first cure Berlin (CCR5Δ32), 2007 first (MHC 6p21), 2007 gp120/b12 crystal structure, 2008 novel prize for discovering HIV-1 and human papilloma virus (HPV) genome wide association, 2010 pre-exposure prophylaxis, 2010 removal of travel bans, 2011 treatment as prevention, 2011 ART to 8 million but 7 million lack, 2012-2013 early detection and ART, 2015 UN millennium goals 6 to compact HIV-1/AIDS (halt and revers spread). Future in need of vaccine and therapy (Kaur *et al.*, 2013).

Microscopic Structure of HIV-1

The mature HIV-1 virion is an icosahedral sphere with a diameter of approximately 100 nm (Wasnik, 2011).

The outer shell, viral envelope is a lipid bilayer, from host membrane origin, that embeds host cell proteins and spikes. These spikes consist of two viral envelope proteins (env): an outer protruding cap glycoprotein (gp) 120 and a stem gp41, which are non-covalently attached to each other. These glycoproteins are formed by cleavage of a larger precursor gp160, by a cellular protease. Located within the viral envelope is the matrix, made of an HIV-1 protein called p17 and here in the viral conical core or capsid, which is made of the viral protein p24 (core antigen) (Kaur *et al.*, 2010).

The viral core contains two single strands of HIV-1 RNA, multiple reverse transcriptase, nucleocapsid proteins p6 and p7, protease p11 and integrase p32 (Kaur *et al.*, 2010).

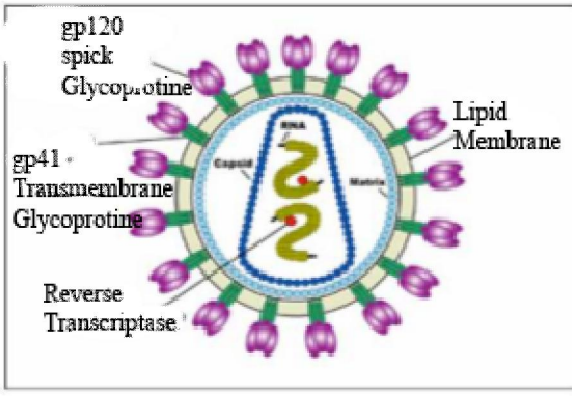

Figure 2 Structure of HIV-1 (Kaur *et al.*, 2010)

The HIV-1 genome exists of nine different genes where of three (gag, pol and env) are common in all retroviruses. Gag is the gene coding for the viral core proteins, pol codes for the viral enzymes reverse transcriptase, integrase and protease and env codes for the envelope glycoproteins. The other genes are responsible for the organization of the virus life cycle (Kaur *et al.*, 2010)

To ensure the effective production of new virion by its host cells the viral genome is flanked at each site by long terminal repeat sequences that can bind cellular proteins to activate transcription under control of viral signals (Klatt, 2016, Kaur *et al.*, 2013).

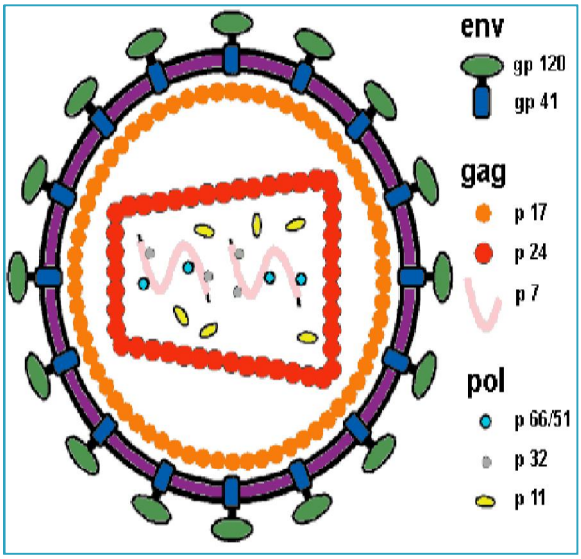

Figure 3: The genome of HIV, similar to retroviruses in general, contains three major genes--gag, pol, and env (Clare, 2003)

Pathogenesis of HIV-1

HIV-1 infectivity

T helper cells are the main target for HIV-1 infection and other cells such as macrophages, monocytes, dendritic cells, langerhans cells and microglial brain cells can also be infected with HIV-1, because they have some surface CD4.

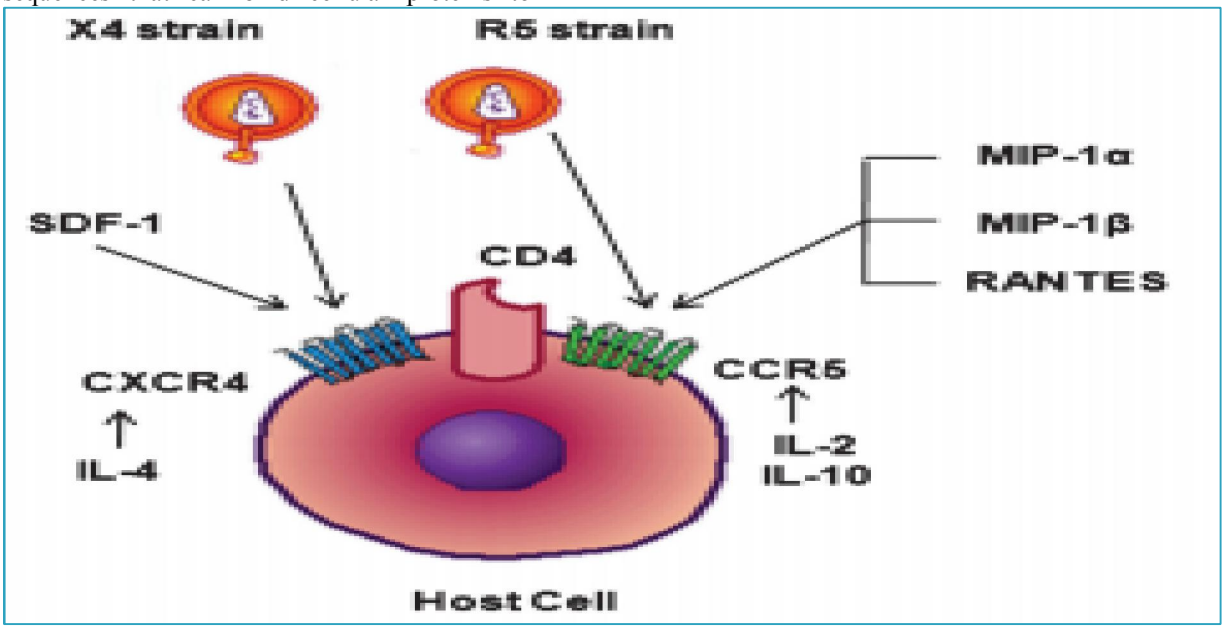

Figure 4: Chemokines and their receptors network guiding the HIV entry.

CCR5 and CXCR4 co-receptor utilization by the HIV R5 and X4 virions in the macrophages and T cells respectively. MIP-1, macrophage inflammatory protein-1; RANTES, regulated upon activation normal T cell expressed and secreted; SDF-1, stromal derived factor-1; CCR5, receptor 5 for β family (cysteine-cysteine, sor CC) of chemokines; CXCR4, receptor for α family (cysteine-Xcysteine, or CXC) of chemokines (Kaur *et al.*, 2013).

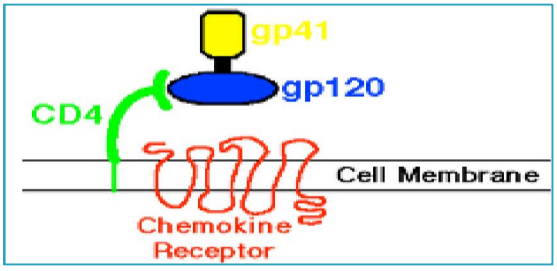

Figure 5 HIV entry into a host cell begins with gp120 binding to CD4 receptor (Kaur *et al.*, 2013)

T helper cells are the main target for HIV-1 infection, because they express high numbers of CD4 molecules on their cell surface and bind the virus with high affinity (Tresoldi *et al.*, 2002). HIV-1 viruses that preferentially infect T-cells are known as T-tropic or X4 strains, while those strains that additional can infect both macrophages and T-cells are called M-tropic or R5 strains (Clare, 2003).

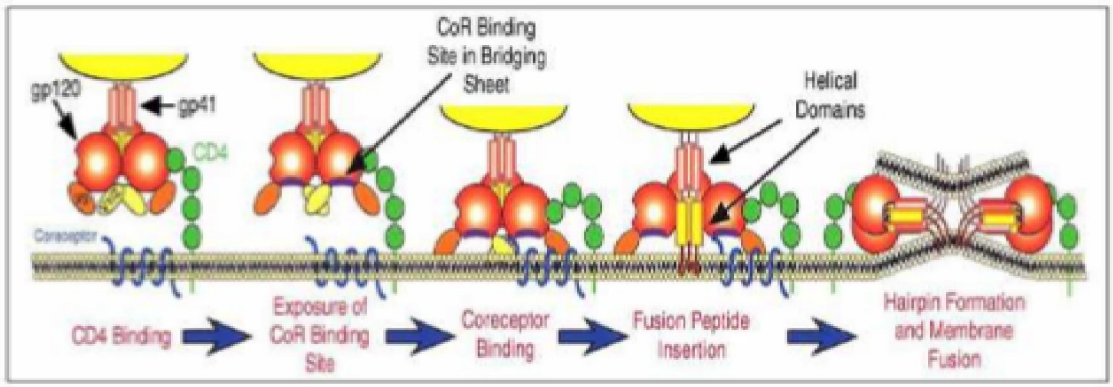

Figure 6: Schematic Presentation on HIV-1 entry Processes (Kaur *et al.*, 2013)

HIV-1 can infect dendritic cells by this CD4-CCR5 route, but another route using mannose-specific C-type lectin receptors such as can also be used. Dendritic cells are one of the first cells encountered by the virus during sexual transmission. They are currently thought to play an important role by transmitting HIV-1 to T-cells when the virus is captured in the mucosa by dendritic cells (Kaur *et al.*, 2010).

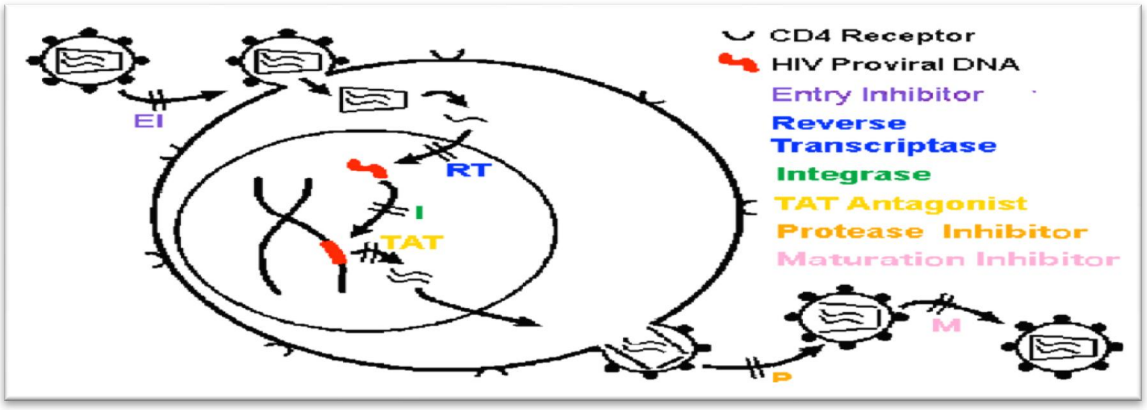

Figure 7: potential target points in the HIV life cycle for drugs (Stephens, 2012)

The presence of FEZ-1, which occurs naturally in neurons, is believed to prevent the infection of cells by HIV-1 (Stephens, 2012).

HIV-1 Replication

HIV-1 replicates by invading immune cells (Clare, 2003). Since macrophage and T-cell possess CD4 proteins that are why the virus easily invades them (Stephens *et al.,* 1998). HIV-1 is an extraordinarily variable virus that lacks proofreading mechanisms accompanied by high error rate (0.2-2 mutations per genome per cycle), high replication rate, an apparent high tolerance and selection for change (Sharma *et al.,* 2011).

For attachment and subsequent entry of the virus to the target cells requires both the CD4 proteins and one of the main co receptors (CCR5 and CXCR4) or minor co- receptor like CCR2 and CCR3 (Suresh *et al.,* 2006). HIV-1 enters by the adsorption of glycoproteins on its surface to receptors on the target cell followed by fusion of the viral envelope with the cell membrane and the release of the HIV-1 capsid into the cell. (Kaur *et al*., 2013). This allows for a more stable two-pronged attachment, which allows the N-terminal fusion peptide gp41 to penetrate the cell membrane (Stephens, 2012).

After fusion occurs, the viral particle is taken into the cell and uncoating of the particle exposes the viral genome (Klatt, 2016). Repeat sequences in gp41 then interact, causing the collapse of the extracellular portion of gp41 into a hairpin. This loop structure brings the virus and cell membranes close together, allowing fusion of the membranes and subsequent entry of the viral capsid (Klatt, 2016). After HIV-1 has bound to the target cell, the HIV-1 RNA and various enzymes, including reverse transcriptase, integrase, ribonucleases, and protease, are injected into the cell (Gao *et al.,* 2010). During the microtubule based transport to the nucleus, the viral single strand RNA genome is transcribed into double strand DNA (Klatt, 2016). This DNA becomes integrated into the host cell's genome and is called a provirus. The provirus can remain in a latent state for a long period of time, during which viral replication does not occur (Khamadi *et al.*, 2005).

Viral DNA within the cell nucleus, transcribed into genomic RNA and mRNA, which are transported to the cytoplasm (Khamadi *et al.*, 2005). Translation of mRNA occurs, with production of viral proteins and assembly of viral particles (Clare, 2003). The intact virion bud out from the host cell membrane and acquire their envelope during the process. These viruses can then proceed to infect additional host cells (Martin *et al.*, 1998).

1.2. Chemokines for HIV-1 Susceptibility and Resistances

1.2.1. C Chemokine Receptors and Ligands Immunology

Chemokines are low molecular weight (Ferreira-Fernandes *et al.,* 2015) cell surface proteins that bind small peptides called chemokine ligand (McNicholl *et al.,* 1997) proteins that, mediate the migration of immune cells during inflammatory responses (Griffih *et al.,* 2014). The chemokine receptors are widely distributed on hematopoietic and other cells including; activated memory Th1 lymphocytes, macrophages, peripheral blood-derived dendritic cells, endothelial cells, epithelium, vascular smooth muscle, and fibroblasts (Ferreira-

Fernandes *et al*., 2015). The expression of CCR5 was also reported in $CD4^+$ hematopoietic progenitor cells, langerhans' cells, neurons, astrocytes and thymocytes (McDermott *et al.*, 2000).

Chemokines can be classified into three groups based on the number and location of conserved cysteine; C, CC, and CXC. Chemokine receptors are grouped into families on the basis of the chemokine ligands they bind: CC, CXC, or both (Dean *et al.,* 1996). Extracellular portions are involved in chemokine binding, while intracellular portions are involved in cell signaling. The effect of receptor-ligand interactions is usually mediated through G-protein coupled interactions; results in alterations in cell function such as activation, motion or migration usually along a chemokine concentration gradient and varies depending on the chemokine bound and the cell type (Murphy, 1996). Some chemokine receptors have a role in infectious disease susceptibility or pathogenesis. Several of the CC or CXC receptors are used by HIV-1 or HIV-2 as entry cofactors (McNicholl *et al.*, 1997).

Along with the CD4 receptor, CCR5 is utilized as a major HIV-1 co-receptor for entry of macrophage-tropic HIV-1 variants (called R5) into the cells. RANTES is the major ligand of CCR5 (Mack *et al.,* 1998).

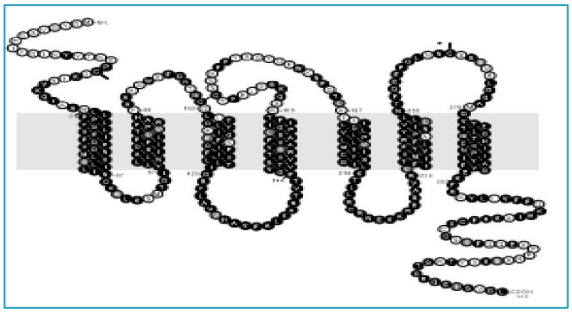

Figure 8: Predicted structure and amino acid sequence of CCR5 (Paxton *et al.*, 2001).

Highly exposed, HIV-1 negative men had high circulating levels of several chemokines, such as RANTES (Kumar *et al.*, 2016). These data led to the hypothesis that chemokines might prevent HIV-1 infection by binding to the elusive HIV-1 entry cofactor. Since the discovery of CD4 in the 1980s as an HIV-1 receptor, it had become apparent that other factors were required for HIV-1 to enter cells (Paxton *et al.*, 2001). Mouse cells expressing CD4 could not be infected with HIV-1 (Kulkarni, 2003). Both CCR5 and RANTES expression levels vary among individuals, and this may affect the risk of HIV-1 transmission and progression. The basis for this variation includes genetic polymorphism (Ferreira-Fernandes *et al*., 2015).

1.2.1.1. Polymorphism and Detection

Every person carries two copies of each chromosome except the sex chromosomes. However, evolutionally there is DNA sequence differences (Weber and May, 1989). When studied in the context of a population, these differences in DNA sequences are called polymorphisms; they may occur in coding regions (exons) or noncoding regions of genes. (Housman, 1995). At these sites, a person is most likely to carry two alternative DNA sequences, accurately marking the two alternative chromosomes (Weber and May, 1989)

The chemokine CCR5 gene and its polymorphisms (CCR5Δ32) is localized on chromosome 3p21.3-p2499. In the CCR5 gene, open reading frame (ORF) CCR5Δ32 creates a truncated protein that fails to reach the cell surface (Mack *et al.,* 1998). This most studied polymorphism is present in various regions of the world with different prevalence (Bleul *et al.*, 1997).

Methods that exploit genetic polymorphism will also be essential for finding genes that predispose people to more common conditions in which inheritance patterns are complex (Housman, 1995).

Two techniques, Southern blotting and the polymerase chain reaction (PCR), can measure the length of the DNA sequence at the polymorphic site. Very short sequences only, two, three or four base pairs long, can also vary highly. For these, the PCR is preferred. (Housman, 1995). In the case of PCR, the positions in the flanking DNA of sequences homologous to the oligonucleotide PCR primers define the fixed points (Nakamura *et al.,* 1987).

PCR techniques are conceptually simple, highly specific, sensitive, and amenable to full automation (Linz *et al*., 1990).

1.2.1.2. Epidemiology, and Distribution of CCR5Δ32

The epidemiology and geographical distribution of CCR5Δ32 is far from clear (Martinson *et al.,* 1997). However, it provides insight into evolutionary history of it. Estimation for the origin of CCR5Δ32 of about 700 years ago, with a 95% confidence intervals CI of 275-1875 years. Contrarily in other studies CCR5Δ32 arose in Scandinavia 1000-1200 years ago and

then spread Northward to Iceland, Eastward to Russia and Southward to Central and Southern Europe by Viking dissemination (Khamadi *et al.*, 2005).

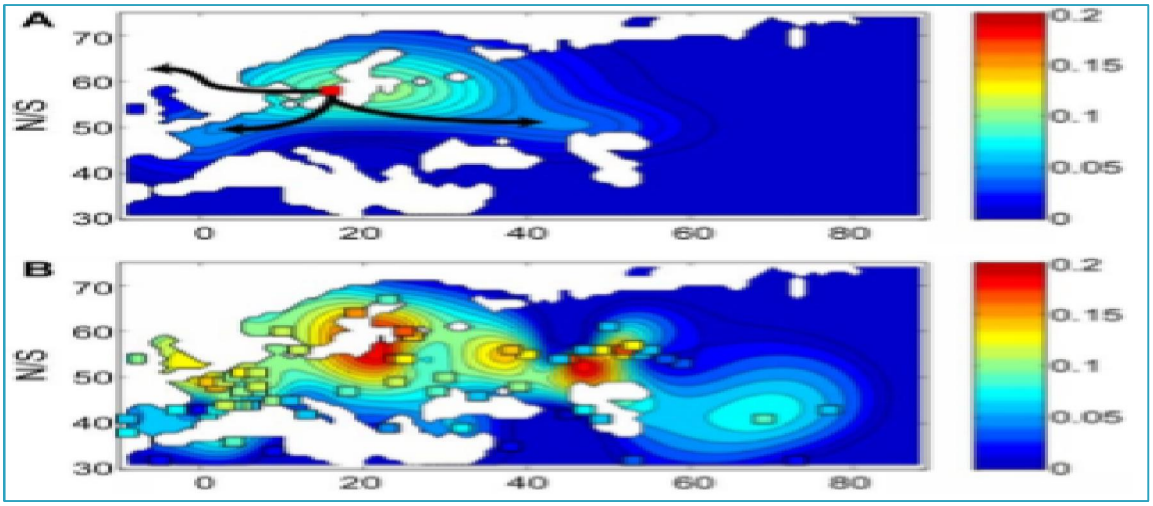

Figure 9 Fig. 1.A.A schematic representation of Viking hypothesis of Lucotte. The red square represents a Scandinavian origin of the allele. The black arrows represent dissemination of CCR5-D32 by Vikings southwards towards France and the Mediterranean, eastwards towards Russia, and northwest towards Iceland. Contour lines and color represent the frequency in Europe at an intermediate stage of the allele's migration out of Scandinavia. B. The modern- as observed allele frequencies. Squares mark locations of sampled allele frequencies, and color within the squares denotes the observed frequencies. Contour lines represent interpolated allele frequencies. Data are from (Kaur *et al.*, 2013)

However, this naturally protective polymorphism is not so frequent and its prevalence shows a declining trend on transition from the north Europe (16%), southeast towards Mediterranean region (4%) and gradually disappears among African and East Asian populations (Kaur *et al.*, 2013). The frequencies of CCR5Δ32 is over 20.93% in Ashikenazi (Martinson *et al.*, 1997), 14.71% in Iceland (Khamadi *et al*., 2005), 9.78% in Russia, 4.69% in Gujarat: Baltic countries to 4% in Sardinia (Easterbrook *et al*., 1999, Khamadi *et al*., 2005), with an average of 10% over Caucasian population of Europe, while it is almost absent in some African (0.45% in Nigeria with CI 00 - 0.90), Japanese and Chinese ethnic groups (Martinson *et al.*, 1997).

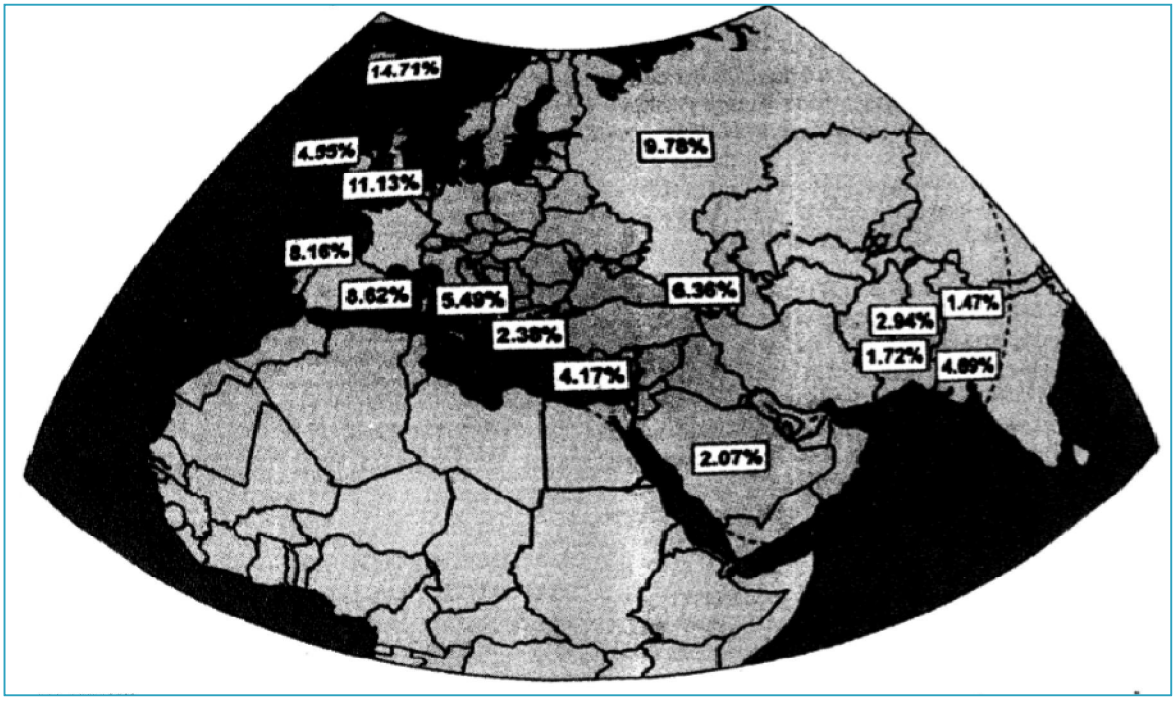

Figure 10 The Frequency of CCR5 D32 in Europe (Jang *et al.*, 2007)

2.

2.2. Immunology and Epidemiology of RANTES

Regulated upon activation, normal T cell expressed and secreted (RANTES) is a CC chemokine that is chemo-attracts of leukocytes (McDermott *et al*., 2000). Human RANTES gene/RANTES spans 8.8 kb on the short arm of chromosome 17q11.2-q12 and has the characteristic three exon-two intron organization of the CC chemokine family (Jang *et al.*, 2007). This is found to be highly expressed in the activated T lymphocytes, macrophages, fibroblasts, platelets, mesangial cells, epithelial cells, megakaryocytes and some tumors (McDermott *et al*., 2000). In 1995, RANTES was shown to be the most potent member of CC chemokine released by $CD8^+$ T-cells that were able to suppress the replication of non-syncitium inducing HIV-1 strains in vitro (Jang *et al*., 2007).

The precise mechanism of HIV-1 suppression by RANTES is not yet fully understood but does not require full signal transduction via RANTES-specific receptors. It might be mediated by simply preventing access of the viral envelope protein (gp120) to CCR5, but it might also involve CCR5 dimerization and internalization following RANTES binding (Mack *et al*., 1998). Several studies have shown that HIV-1 infected patients who have higher levels of RANTES in serum are partially protected against HIV-1 infection and disease progression (Zanussi *et al*., 1996, Polo *et al*., 1999, Paxton *et al*., 2001). AIDS patients produce much less RANTES than those from long term non progressors (Paxton *et al*., 2001). However, a recent study measured RANTES in serum samples and found that higher levels of RANTES were associated with faster progression (McDermott *et al.*, 2000).

As described above, RANTES is an inhibitor of R5 strains of HIV-1. As expected, RANTES-403 is associated with delayed progression to AIDS **(**Liu *et al*., 1999**).**

The prevalence of this allele is approximately 15% in eastern Asia, 5% to 8% in southeastern Asia, and 2% in Europeans and European Americans; it is absent in Africans and African Americans **(**Shioda *et al*., 2006**).**

2.2.1.1. Susceptibility, Progression and Resistance with HIV-1

There is extensive variation among individuals in susceptibility to HIV-1 (Nolan, 2004). While a range of socioeconomic factors contributes to this heterogeneity, a proportion of the heterogeneity can also be attributed to host genetics, particularly at loci associated with HIV-1 cell entry, the expression of competing ligands, immune recognitions and antigen presentation (McNicholl *et al*., 1997). The intensity of the protective effect combined with the prevalence of the allele determine

the number of AIDS cases prevented by a given restriction allele (Galvani and Novembre, 2005).

Genetic studies led to the discovery of various major histocompatibility complex (MHC) and non-major histocompatibility encoded genes, which directly or indirectly influence the susceptibility and resistance to HIV-1 infection (Nkenfou *et al.*, 1997). These genes and their mutated forms and their products which play a major role in determining the susceptibility or resistance to HIV-1 infection (Shioda *et al*., 2006). The major histocompatibility encoded genes which determine HIV-1 resistance or susceptibility are human leukocyte antigen (HLA-B57, HLA-B58, HLA-B27, HLA-Bw4 and HLA-A11) in Southeast Asian (Sharma *et al.,* 2011). On the other hand, non-major histocompatibility encoded genes are CCR5, CCR2, RANTES, CXCL12, CXCR6, CCL3L1, Interleukin-10 (IL-10), and interferon gamma. The site specific mutations in these genes determine the susceptibility or resistance to HIV-1 infection (Kumar *et al*., 2016).

Among these protective candidate genes CCR5 is the major co-receptor for the entry of HIV-1 (Verma *et al*., 2007). RANTES is the major ligands of CCR5 co receptor which inhibit infection (OF *et al.*, 2013). Individual who have one of CCR5Δ32 and RANTES-403 allele or both of them with homogeneity are resistant to HIV-1infection and with heterogeneity is slow progressor and somewhat resistant, among the participants who did not have these polymorphisms are highly susceptible to HIV-1 infection and rapid progression (Galvani and Novembre, 2005). In future the study of host genes in relation to HIV-1 infection may provide the researchers to develop newer chemotherapeutic approaches to prevent or cure HIV-1 infection effectively (Kumar *et al.*, 2016).

2.2.1.2. Progression and Vulnerability to HIV-1

HIV-1 infection causes for a progressive decline in peripheral $CD4^+$ T-cell numbers, T-cell dysfunction, thymic dysfunction and defects in both number and functions of antigen presenting cells such as dendritic cells and monocytes (Stephens, 1998). The progress of the disease commonly precedes in 3 stages; (i) acute primary infection, (ii) asymptomatic chronic phase, and (iii) symptomatic phase and progression to AIDS (Stephens *et al.*, 1998). This is due to many of HIV-1-infected patients show different rates of disease progression because of the host immunogenetic background and the degree of viral virulence (virus genetic) (Dorak *et al.*, 2005).

The most advanced stages of HIV-1 infection is AIDS, which can take from 2-15 years to develop depending on the individual (WHO, 2016). Although, a number of variations are seen in different patients, without therapeutic intervention, majority (70-80%) of HIV-1 infected individuals develop AIDS after 3-5 years of clinical latency (Salem *et al.*, 2009). On the contrary, about 10% individuals, known as rapid progressors (RP), develop AIDS within 3 years or less (Martin *et al*., 1998). Whereas long-term non-progressors (LTNPs) (about 5%), remain asymptomatic for 7 and more years following viral infection (Nolan, 2004). Further, the presence of some highly exposed persistently seronegative groups suggests (Korostishevsky *et al.*, 2006) the importance of natural and acquired immunity to HIV-1 (Dean *et al*., 1996).

2.2.1.3. Chemokine CCR5Δ32 and HIV-1 Immunology

Genetic variability in the CCR5 co-receptor has been of considerable interest and it is so far the only genetic locus illustrated with translational value against HIV-1 (Libert, 1998). A natural knockout of CCR5 to CCR5Δ32 renders this receptor nonfunctional and blocks the virus from gaining entry (Kaur *et al.*, 2013). Mutations in the CCR5 promoter region determine the level of CCR5 gene transcription and production of the corresponding mRNA (Jang *et al.,* 2007).

The best genetic feature of CCR5Δ32, that results in synthesis of a short, nonfunctional CCR5 protein and the absence of cell surface CCR5 expression (Salem *et al.,* 2009). Thus, the mechanism of protection most likely involves a reduction in the number of CCR5-positive target cells (Korostishevsky *et al*., 2006). Homozygotes for CCR5Δ32 have nearly complete resistance to HIV-1 infection despite repeated exposure and HIV-1 infected heterozygotes for CCR5Δ32 delay the onset of AIDS (Nkenfou *et al*., 2013). If heterozygotes do become infected, they have reduced HIV-1 viral loads with slowed progression to AIDS by an additional 2-3 years (Verma *et al.*, 2007). CCR5Δ32 heterozygotes, express less than half the wild type levels of CCR5 receptor, which slows down HIV-1 replication, spread and pathogenesis (Galvani and Novembre, 2005, McDermAott *et al.*, 1998).

2.2.1.4. RANTES-403 and HIV-1 Immunology

The promoter genotype RANTES-403 has been shown to be associated not only with HIV-1 susceptibility (Vega *et al*., 2017) but also with a slower rate of $CD4^+$ T-cell depletion in HIV-1-infected and delayed onset of AIDS in European Americans (Ping *et al.*, 2002). Similarly, RANTES haplotype comprising RANTES-403 was found to be associated with lower susceptibility to infection and slower disease progression (Vega *et al*., 2017). Further, RANTES-403 decrease susceptibility to HIV-1 infection compared to the ancestral haplotype pair (Shem *et al*., 2016).

However, this association was not found in African Americans. RANTES-403 genotype was associated with lower susceptibility to HIV-1 infection (Paxton *et al.*, 2001). In a RANTES-403 A/G has protective effect, but this does not apply to African-American populations or other populations of North Americans with HIV-1 infection. However, Japanese study failed to find any effect of RANTES-403 on acquiring HIV-1 infection. For the RANTES-403 polymorphism, the results suggest that there may be a significant association between the RANTES-403 polymorphism and reduced susceptibility to HIV-1 infection, this imply RANTES-403 allele be a protective factor for HIV-1 progression (Paxton *et al*., 2001). Here the haplotype pair RANTES-403 correlated with slower progression to AIDS lacking CCR5Δ32 (Jang *et al*., 2007).

Conclusion

This review was presented on the protective marker genes prevalence and association for HIV-1 infection resistance and the disease progressors. The polymorphisms of these infection and progression modifying genes were searched out in both seronegative and seropositive. Hence, the chemokine CCR5Δ32 was found with very strong significant association with HIV-1 resistances. Hence, the CCR5Δ32 homozygous individuals were likely to be protected from HIV-1 infection. However, RANTES-403 had no significance association with HIV-1 resistances and susceptibility as the review indicated.

Recommendation

From the genetic epidemiological review conducted on the two protective markers in HIV-1 infection and in light of the data searching of the population due to data-base searching biases. If academician and researchers are interested to do with it, it is better to review and design research with more data base searching to provide more conclusive result with clear association.

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