GMR
The Original by FUNPEC-RP

Genetic polymorphism at Interleukin-7 receptor gene at +510 position and its impact on pain and other symptoms among HIV and AIDS patients

T.C. Nangammbi[1], G.T. Moloro[1, 2] and A. Samie[2]

[1]Tshwane University of Technology, Department of Nature Conservation, South Africa
[2] University of Venda, Department of Microbiology, South Africa

Corresponding author: T.C. Nangammbi
E-mail: nangammbitc@tut.ac.za

Genet. Mol. Res. 18 (4): gmr18292
Received February 28, 2019
Accepted October 07, 2019
Published November 30, 2019
DOI http://dx.doi.org/10.4238/gmr18292

ABSTRACT. Genetic polymorphism of cytokine genes has been shown to be associated with susceptibility to diseases. We investigated the frequency of the IL-7 receptor-α +510 CT SNP in relation to pain and other symptoms among HIV and AIDS patients attended at various South African hospitals for treatment. Demographic as well as clinical data was obtained through structured interviews and patient files were consulted. A total of 107 mouth wash samples were obtained from volunteers, and DNA was extracted from these samples using the Qiagen protocol. Genotyping of the IL-7 receptor +510 CT SNP was conducted using sequence specific PCR. The CC and TC genotypes were the most common, while the TT genotype was rare (47.7, 45.8 and 6.5% respectively). The CC genotype was more common among patients who had body pain at the time they went for testing (χ^2 = 4.75; P = 0.029) while the TC genotype was more common among those that did not have pain (χ^2 = 6.86; P = 0.009). The TC genotype was also more common among patients who did not have genital sores (χ^2 = 4.663; P = 0.031). The TT genotype was more common among patients whose infection state had improved as well as among those who had tuberculosis, although the differences were not significant. We concluded that the CC genotype is associated with pain while the TC

genotype is protective of pain and genital sores. Further studies will be needed to confirm these hypotheses in larger populations.

Key words: Opportunistic infections; HIV; Interleukin-7 receptor; Genetic Polymorphism; Single Nucleotide Polymorphism; Limpopo province

INTRODUCTION

Interleukin-7 (IL-7) is a 25 kilo Dalton glycoprotein encoded by the IL-7 gene, which is involved in the regulation of lymphopoiesis. It is the most recently cloned bone marrow derived cytokine regulating T-cell homeostasis through a CD4 driven feedback loop (Gougeon and Chiodi, 2010). Thymic generation of T-lymphocytes with a wide variety of antigen receptor specificities is dependent upon IL-7 levels. While IL-7 functions to maintain proliferation and maturation of T-lymphocytes, IL-2 restores immune function during HIV-1 infection. Biological effects of IL-7 are mediated via the hematopoietic IL-7 receptor (IL-7R) complex (Noguchi et al., 1994).

The interleukin-7 receptor is a heterodimer protein expressed on the surface of cells, such as naïve and memory T-cells (Muegge et al., 1993). It consists of two different smaller protein chains, namely IL-7-specific-α chain (CD127), which binds IL-7 and thymic stromal lymphopoietin; and a common *y*-chain (CD132), commonly shared by many cytokines and is found to be a cofactor for V(D)J rearrangement of the T cell receptor beta (TCRß) during early T cell development (Muegge et al., 1993). Deficiency of a functional IL-7 receptor gene leads to a variety of health complications, including infections from opportunistic pathogens (Samie et al., 2014). Interleukin-7 receptor plays a critical role in the development of immune cells.

Several health complications are associated with Interleukin-7 receptor deficiency, they include T-cell acute lymphoblastic leukemia, T-cell lymphopenia, multiple sclerosis, rheumatoid arthritis, juvenile idiopathic arthritis, and severe combined immunodeficiency (O'Doherty et al., 2009). Reduced levels of lymphocytes (CD4+ cells and CD8+ cells) in HIV individuals can be associated with IL-7 receptor genetic polymorphism since the receptors are expressed by stromal cells (Vranjkovic et al., 2007). This could have an impact on the susceptibility of certain individuals to opportunistic infections. Therefore, polymorphism of the receptor can be associated with infection by different opportunistic infections (Migueles and Connors, 2010). Most HIV individuals are prone to multiple infections mostly due to impaired immune response (Smith et al., 2005). Manifestation of opportunistic infections in some HIV individuals of related genotypes can lead to early death, due to their higher susceptibility to common opportunistic infections (Migueles and Connors, 2010).

HIV is a lentivirus (a member of the Retrovirus family) that causes AIDS, a condition in humans in which gradual failure of the immune system allows life-threatening opportunistic infections and cancers to thrive (Weiss, 1993). With gene identification progressing rapidly, determination of the functional effects of haplotypes influencing disease susceptibility is the next major step in studies of diseases with complex genetics. Sequencing IL-7Rα has revealed the existence of four SNPs, namely; +510 CT, +1237 AG, +2087 TC, and +3110 AG, which all give rise to amino acid substitutions (Shamim et al., 2006). Demographic factors such as age, sex, ethnicity, and viral characteristics can also

play an important role in susceptibility to opportunistic infections (Kiryluk et al., 2007). The clinical implications of these factors are only beginning to be understood, though significant advances have led to an understanding of the interactions between genetics and host factors (Tang and Kaslow, 2003).

Occurrence of specific infections and their distribution in African populations is not clearly understood. It has been suggested that the genotype of individuals could play an important role in their susceptibility to different diseases, including infectious and non-infectious diseases (King and Aberg, 2008). Though much investigation has been done, very little data exist on the genetic polymorphism of the host genotypes and the occurrence of pain, particularly among HIV and AIDS patients in the African continent. Furthermore, the scientific literature on this topic is almost nonexistent in developing countries and very limited studies have been conducted in South Africa (Samie et al., 2014). Considering the importance of IL-7 in the human immune system, it has become interestingly important to observe genetic distribution in the local population in order to improve our understanding of the occurrence and potential prognosis of opportunistic infections among these patients. Here, we studied polymorphism of the IL-7R alpha gene at the +510 locus and its relation to pain and opportunistic infections among HIV and AIDS patients in the Limpopo Province, South Africa.

MATERIAL AND METHODS

Ethical considerations

Ethical approval was obtained from the University of Venda Research, health and ethical committee. Authorization to collect samples from the hospitals was obtained from the Department of Health, Limpopo, in Polokwane. Ethical clearance was also obtained from the ethical committees of the different hospitals where the study was conducted, which included Tshilidzini, Elim and Donald Frazer. Patients were informed about the study and those who agreed to take part were given a consent form to read and sign. All interviews were confidential and the aims of the study thoroughly explained to the patients.

Sample collection and processing

Mouth wash samples were collected from consenting participants (Cheng et al., 2005) and DNA was purified using the QIAamp blood mini kit from QIAGEN® following the instructions from the manufacturer. The eluates containing the DNA were stored in the freezer until further analysis. Data on the demographics of the patients as well as current and previous exposure to opportunistic infections was collected from the participants through the use of a structured questionnaire.

Sequence specific polymerase chain reaction (ssp-pcr)

Genotyping of the IL-7 receptor gene was conducted using SSP-PCR for the +510 CT SNP. A 25 µl reaction was prepared as previously described by Shamim et al. (2006). The specific primer was mixed with respective common primer for the detection of each genotype. The following primers were used in PCR: IL7REx2F 5’-GGTTGGTTG GTTTTGAAGCAT-3’,

which was the common primer, and IL7REx2R1g 5'-ATTTCAAATTCCAGATTGGTGG-3'; IL7REx2R2a 5'-TATTTCAAATTCCAGATTGGTGA-3' as specific primers. The PCR products were analyzed using 2.5% agarose in TAE buffer stained with ethidium bromide and viewed under a UV-transilluminator.

Data analysis

Statistical Package for Social Science (SPSS, Inc., 2009, Chicago, IL, www.spss.com) version 24.01 was used to analyze the results, and differences were considered significant if the P-value was less than 0.05. The chi square test was used to determine potential differences in the distribution of the genotypes. Graphical representations and tables were prepared from the data.

RESULTS

Demographic information for the sample population

A total of 107 participants were recruited in the study (Table 1). Most of the patients were recruited from Donald Fraser Hospital. Most of the participants were females. The age of the participants varied from 18 to 80 years and most of the patients were aged between 26 and 45 years. Most of the study participants were single, while 10.4% were divorced. Most of the participants indicated that they got infected around Vhembe district. Other participants got infected from other areas such as Gauteng and Zimbabwe. These results are summarized in Table 1.

Table 1. Demographic characteristics of the study participants.

	Characteristics	Percent	Total
Gender	Female	71.7%	106
	Male	28.3%	
Hospital	Donald Fraser	50.5%	107
	Elim	19.6%	
	Tshilidzini	28%	
	Univen	1.9%	
Age groups	18 to 25 Years	7.8%	102
	26 to 45 years	57.8%	
	46 to 80 years	34.3%	
Marital status	Single	44.3%	106
	Married	31.1%	
	Divorced	10.4%	
	Widowed	14.2%	
Place of Infection	Gauteng	6.5%	107
	Mopani	2.8%	
	Vhembe	85%	
	Zimbabwe	2.8%	
	Unknown	2.8%	

PCR amplification for the detection and identification of the +510 genotypes

With the aid of a comparison ladder, bands were identified on the agarose gel photos and were used to identify the different genotypes as shown in Figure 1.

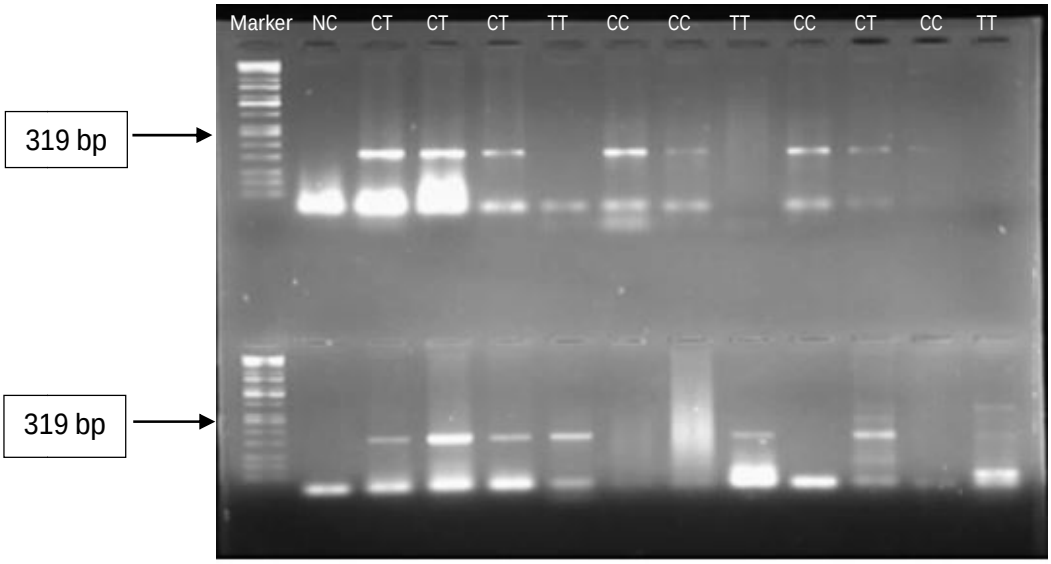

Figure 1. A representative sample of the UV-transilluminator photos taken after Gel-electrophoresis of the PCR product of the +510 CT genotypes: NC = negative control.

General distribution of +510 CT genotypes

Analysis of the data showed significant differences in the frequency of the +510 CT polymorphism in association with the patients' infections (Figure 2). Analysis showed that the TC and CC genotypes were the most common of the +510 CT SNPs, while the TT genotype was rare.

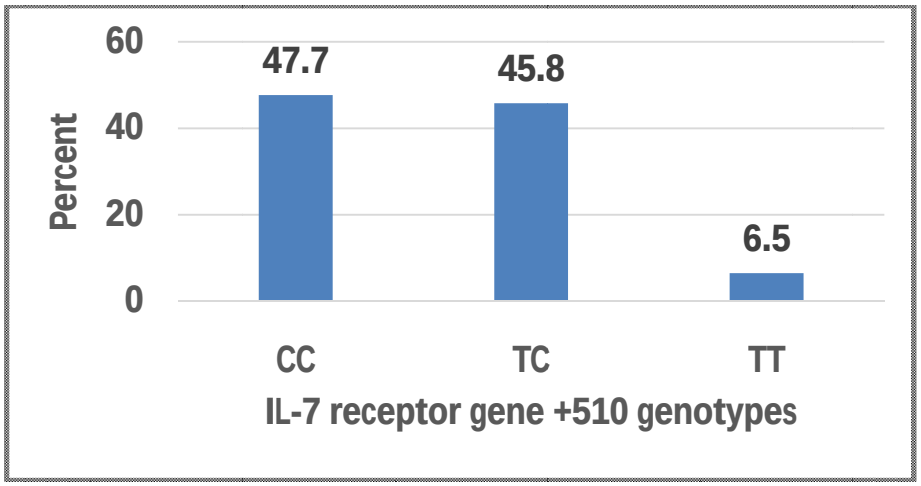

Figure 2. Overall distribution of the different genotypes of the IL-7 +510 CT polymorphism in the South African HIV positive population.

IL-7R gene polymorphism in relation to immunological characteristics of the participants

The immunological and virological characteristics of the study participants were obtained from their files. In a total of 98 participants with records, 20 had a CD4 count lower than 50 cells/µL while 78 individuals had a CD4 count of above 50. Overall, more individuals with TT genotype had CD4 count lower than 50 cells/µL although the difference was not significant. Also, more participants with TT genotype had a CD4 count of between 50 and 200, which is an indication that the TT genotype could be more susceptible to infection because of lower CD4 counts. Among the 70 participants with CD4 count less than 300 cells/µL, 10% expressed the TT genotype of the +510 SNP; while 0% of the participants with CD4 count more than 300 cells/µL carried the TT genotype. However, there were differences in the distribution of these genotypes (Table 2). There was no significant difference in the distribution of the genotype according to the viral load of the participants, though those with TC genotypes tended to have higher viral loads.

Table 2. Genetic polymorphism of the IL-7 receptor at +510 position in relation to immunological and virological characteristics of the study participants.

Genotypes 510	CD4 count above 50 cells/µL	CD4 count less than 50 cells/µl	Total	Statistics (Chi square and p value)	Odds Ratio; 95% Confidence Interval
CC	38 (48.7%)	7 (35%)	45 (45.9%)	χ^2=1.206 ;P=0.272	0.567; 0.204 – 1.573
TC	36 (46.2%)	10 (50%)	46 (46.9%)	χ^2=0.095 ; P =0.758	1.167; 0.437 – 3.118
TT	4 (5.1%)	3 (15%)	7 (7.1%)	χ^2=2.339 ; P =0.126	3.265; 0.668 – 15.96
	78	20	98		
	CD4 count less than 50 or higher than 200 cells/µL	CD4 count between 50 and 200 cells/µL			
CC	25 (41%)	20 (54.1%)	45 (45.9%)	χ^2=1.584 ; P =0.208	1.694; 0.743 – 3.861
TC	30 (49.2%)	16 (43.2%)	46 (46.9%)	χ^2=0.326 ; P =0.568	0.787; 0.346 – 1.790
TT	6 (9.8%)	1 (2.7%)	7 (7.1%)	χ^2=1.767 ; P =0.184	0.255; 0.029 – 2.204
	61	37	98		
	CD4 Less than 300 cells/µL	CD4 More than 300 cells/µL			
CC	32 (45.7%)	13 (46.4%)	45 (45.9%)	χ^2=0.004 ; P =0.949	1.029; 0.427 – 2.479
TC	31 (44.3%)	15 (53.6%)	46 (46.9%)	χ^2=0.692 ; P =0.405	1.452; 0.602 – 3.499
TT	7 (10%)	0	7 (7.1%)	χ^2=3.015 ; P =0.082	0.692; 0.604 – 0.794
	70	28	98		
	Viral load undetectable	Viral load detectable (Above 25 viral copies/µL)			
CC	7 (50%)	4 (40%)	11 (45.8%)	χ^2=0.235 ;p=0.628	0.667; 0.129 – 3.446
TC	6 (42.9%)	6 (60%)	12 (50%)	χ^2=0.686 ;p=0.408	2.000; 0.384 – 10.41
TT	1 (7.1%)	0	1 (4.2%)	χ^2=0.745 ;p=0.388	0.565; 0.395 – 0.809
	14	10	24		

IL-7R gene and occurrence of opportunistic infections

Of all the participants in this study, 77 individuals had been HIV positive for two years or less while 27 individuals had been HIV for more than two years. Genetic polymorphism at +510 position of the IL-7 receptor gene did not appear to affect longevity among the HIV participants although more participants with the TC genotypes tended to have been HIV positive for more than two years. Of all the participants, 84 did not have pain at the time of testing while 17 participants had had bodily pain. Based on the medical conditions, individuals of the CC genotypes of the +510 SNP tended to have pain at testing while those who carried the TC genotype tended to have no pain. Therefore, it appears that the CC genotype is associated with pain while the TC genotype was protective of pain. The

differences were significant ($P < 0.05$). Though the TT genotype appeared to be protective of localized pain, the difference was not significant. Other infections showed no significant differences among the genotypes (Table 3).

Table 3. Distribution of different genotypes of the +510 locus on the IL-7 receptor gene in relation to the general health conditions among HIV and AIDS patients.

Genotypes	Has been HIV for 2 years or less	Has been HIV for more than 2 years	Total	Statistics (Chi square and P value)	Odds Ratio; 95% Confidence Interval
CC	38	11	49	χ^2=0.027; P=0.870	1.152; 0.210 – 6.317
TC	34	14	48	χ^2=0.476; P =0.490	1.362; 0.566 – 3.280
TT	5	2	7	χ^2=0.595; P =0.441	0.706; 0.290 – 1.715
Total	77	27	104		
	No pain at testing	Pain at testing			
CC	35	12	47	χ^2=4.75; P =0.029	3.360; 1.086 – 10.400
TC	44	3	47	χ^2=6.86; P =0.009	0.195; 0.052 – 0.728
TT	5	2	7	χ^2=0.74; P =0.390	2.107; 0.373 – 11.886
Total	84	17	101		
	No localized pain	Localized pain			
CC	4	13	17	χ^2=0.01; P =0.917	1.083; 0.239 – 4.904
TC	3	15	18	χ^2=1.12; P =0.291	2.308; 0.479 - 11.119
TT	2	0	2	χ^2=6.58; P =0.011	0.200; 0.103 – 0.358
Total	9	28	37		
	No Fatigue	Fatigue			
CC	25	16	41	χ^2=0.14; P =0.713	1.173; 0.501 – 2.747
TC	29 (50%)	16	45	χ^2=0.07; P =0.785	0.889; 0.381 – 2.075
TT	4	2	6	χ^2=0.04; P =0.849	0.844; 0.146 – 4.869
Total	58	34	92		
	No vision problem	Vision problem			
CC	32	18	50	χ^2=0.13; P =0.724	1.156; 0.516 – 2.590
TC	31	17	48	χ^2=0.05; P =0.823	1.097; 0.489 – 2.461
TT	6	1	7	χ^2=1.332; P =0.249	0.300; 0.035 – 2.593
Total	69	36	105		
	No skin problems	Skin Problems			
CC	32	18	50	χ^2=0.092; P =0.761	0.884; 0.309 – 1.958
TC	30	17	47	χ^2=0.065; P =0.799	0.902; 0.405 – 2.004
TT	3	4	7	χ^2=1.236; P =0.266	2.362; 0.500 – 11.164
Total	65	39	104		

Effects of the different genotypes of the +510 locus on the IL-7 Receptor gene in relation to opportunistic infections among HIV and AIDS patients.

Of all the participants, 71 individuals had infection at the time they tested for HIV while 31 individuals had no infection. Less participants carrying the TT genotype of the +510 SNP had no infection than those who had infection. In an overall evaluation of the progression of the disease in terms of infection level, individuals with the TT genotype tended to have an improvement while those carrying the CC and TC genotypes tended to have less improvement. This is an indication that the TT genotype could be protective of infection although the results are not statistically significant. Again, individual's carrying the TT genotype at +510 SNP showed a much higher improved infection state even with tuberculosis although these individuals tended to have more sore on the mouth and in the genitals. This is supported by the much lower CI value of between 0.590-0.810. Less participants carrying the TC genotype of the +510 SNP had sores in their genitals at the time they were tested compared to participants carrying TT and CC genotypes. This indicates that the TC genotype could be protective of sores in the genitals and in this case, the p-value was statistically significant ($\chi^2 = 4.663$; $P = 0.031$) (Table 4).

Table 4. Distribution of the different genotypes of the +510 locus on the IL-7 receptor gene in relation to opportunistic infections among HIV and AIDS patients.

Genotypes	No infection	Infection at testing	Total	Statistics	OR, 95% CI
CC	14	34	48	χ^2=0.06; P=0.80	1.116; 0.478 – 2.602
TC	16	31	47	χ^2=0.55; P =0.46	0.727; 0.312 – 1.694
TT	1	6	7	χ^2=0.92; P =0.340	2.769; 0.319 – 24.03
	31	71	102		
	Improved infection state	Unchanged infection state			
CC	25	11	36	χ^2=0.067; P =0.795	1.144; 0.414 – 3.104
TC	22	10	32	χ^2=0.121; P =0.728	1.198; 0.492 – 3.323
TT	4	0	4	χ^2=1.744; P =0.187	0.691; 0.590 – 0.810
	51	21	72		
	No TB	Had TB			
CC	35	15	50	χ^2=0.837; P =0.360	0.378; 0.044 – 3.276
TC	33	15	48	χ^2=0.127; P =0.722	1.165; 0.503 – 2.699
TT	6	1	7	χ^2=0.010; P =0.919	1.045; 0.451 – 2.418
	74	31	105		
Genotypes	No genital warts	Genital warts	Total	Statistics	OR, 95% CI
CC	42	8	50	χ^2=1.152; P =0.283	1.905; 0.579 – 6.263
TC	44	4	48	χ^2=1.335; P =0.248	0.485; 0.139 – 1.687
TT	6	1	7	χ^2=0.025; P =0.874	1.194; 0.132 – 10.796
Total	92	13	105		
	No sores on genitals	Sores on genitals			
CC	40 (44.4%)	10 (66.7%)	50	χ^2=2.545; P =0.111	2.500; 0.791 – 7.905
TC	45	3	48	χ^2=4.663; P =0.031	0.250; 0.066 – 0.946
TT	5	2	7	χ^2=1.250; P =0.264	2.615; 0.459 – 14.910
	90	15	105		
	No sores on lips	Had sores on lips			
CC	45	5	50	χ^2=1.432; P =0.232	0.500; 0.158– 1.580
TC	40	8	48	χ^2=0.409; P =0.522	1.429; 0.477 – 4.276
TT	5	2	7	χ^2=1.250; P =0.264	2.615; 0.459 – 14.910
	90	15	105		

DISCUSSION

HIV-1 infection is characterized by a progressive immunodeficiency, which is reflected by a steady decline of CD4+ T cells. Disease progression varies considerably from patient to patient. Although more than 99% of human DNA sequences are the same, variations in DNA sequence can have a major impact on how humans respond to disease as well as environmental factors such as bacteria, viruses, toxins, chemicals; drugs and other therapies. This makes SNPs valuable for biomedical research and for developing pharmaceutical products or medical diagnostics (Vranjkovic et al., 2007). Due to weak or impaired signaling for immune response, HIV individuals may die, mostly due to manifestation of opportunistic infections. The distribution of the +510 SNP in our study population was similar to that found in European populations although there was a lower representation of the TT genotype which was around 6.5% in our population compared to 11% in the study by Shamim et al. (2006).

The level of CD4 count is important for HIV patients in terms of prognosis. Generally, patients with a CD4 count less than 200 and more so those with CD4 count less than 50 are very susceptible to opportunistic infections. In our study, the TT genotype was more common among patients with lower CD4 count less than 50cell/µl and less than 300cells/µl while individuals with CC genotypes tended to have average CD4 counts. Although the differences were not statistically significant, this shows that there is a possibility that the +510 CT SNP has an impact on the progression of the diseases by having an impact on the lymphocytes differentiation and maturation. A study conducted among HIV patients in Ghana, showed that changes particularly deletions on the glutathione S-

transferases genes was associated with normal CD4 counts (Kuleape et al., 2018). Our results suggest that the IL-7 receptor gene at +510 polymorphism affects the level of CD4 count among HIV positive patients however there is no data on the association with the serum level of IL-7 receptor itself. Shamim and colleagues have studied the impact of IL-7 receptor gene polymorphism among transplantation and allergy patients (Shamim et al., 2011). However there is no data available on the impact of the polymorphism on this gene as well as the level of the protein in the serum on the level of CD4 count. Studies on the transmembrane protein gene known as FAS and FAS ligand showed that polymorphism on this gene is associated with apoptosis of CD4 cells (Hermes et al., 2015). Indicating that a number of genes could be associated with the variation of CD4 counts among HIV and AIDS patients who have started ARV treatment.

Bodily pain is a general feeling that can results from different causes. These causes could include changes in the physiology as a consequence of infection or other diseases such as cancer. The sensation of general bodily pain are quite frequent among HIV and AIDS patients as well as the general population with huge cost to the governments in excess of 100 billion Dollars in the USA (Knezevic et al., 2018). The authors also suggested that pharmacogenomics could also be used in the improvement of pain management among patients and doing so will probably reduce cost and sufferings among such individuals. Several genes have been identified as contributing to pain modulations (Knezevic et al., 2018). IL-7 receptor gene polymorphism however have not been studied in relation to pain except for some pains that could be due to the hematopoietic cancer. In our study we found a statistically significant association between the IL-7 receptor alpha at +510 polymorphism and general bodily pain among HIV and AIDS patients. Other studies showed that opioid receptor genes were associated with Rheumatism pain (Olesen et al., 2018). Young et al. (2012) have indicated that although the determination of the genetics of pain is still in its infancy, it is clear that a number of genes play a critical role in determining pain sensitivity or susceptibility. For example, Salhi and colleagues have also associated cytokine genes as obvious candidates for the control of human susceptibility to infection and pain in general (Salhi et al., 2008). Therefore, the present study is a further contribution showing that IL-7 receptor gene is one of those associated to pain modulation. A study conducted in Iran stated that opportunistic infections of the skin and mucosa, malignancies, and certain systemic infections are of major significance in HIV infected patients (Foroughi et al., 2012). In our study a number of patients experienced dermatological infections. Most participants with TT genotype had skin infections. Although the difference was not statistically significant. It could be argued that the patients carrying this genotype might be susceptible to skin infections.

The IL-7 receptor gene carries a number of polymorphisms which have not been thoroughly investigated for their potential association with opportunistic infections. In a previous study, our group showed that polymorphism at +1237 locus of the IL-7 receptor gene was associated with diarrhea while individuals carrying the heterozygote genotypes seemed to be more susceptible to chest pain indicating that polymorphisms at different genes may affect the quality of life of people living with HIV (Samie et al., 2014). Contrary to previous findings, individuals carrying the heterozygote genotype seemed to be protected against pain and this was statistically significant while those with the CC genotype were at more risk of pain. This therefore indicates that different locus of the IL-7 receptor gene might control different physiological process in the individuals that carry them. It is

important to indicate that very few studies have investigated the potential association between IL-7 receptor gene polymorphism and disease evolution among HIV infected individuals. Other authors have however indicated that, the overall health status of HIV infected patients varies and has been shown to be affected by a certain number of cytokines such as IL-10 and IL-7 (Naicker et al., 2009; Vandergeeten et al., 2013). HIV infections are associated with several changes in cellular behavior that has been in some cases associated with the expression of receptors. In a study by Badzar et al. (2009), the expression of CD127 was linked to a reduction of T cells among HIV -infected individuals although this was not linked to the signaling of IL-7 receptor. Several studies have found association between different genetic polymorphism with diseases such as tuberculosis. In the present study, we did not find a significant association between the IL-7 receptor gene at +510 polymorphism and tuberculosis. However there was a significant association between the TC genotype and the absence of genital sores. Cobat et al. (2009) studied genetic variants controlling susceptibility to infection in 400 children and young adults in 128 families in the Western Cape, where TB is highly endemic. By using a genome-wide linkage search, they found that most of the subjects tested were likely to have been exposed to TB, but about 20% did not show delayed type hypersensitivity (DTH) in a skin antigen test, appearing to be naturally resistant to infection by *M. tuberculosis* (Cobat et al., 2009). Elsewhere, a study by Inabo indicated that nicotine inhibits the antibody forming cell response and lymphocyte proliferation, which can prevent the development of a protective immune response to opportunistic microbial pathogens (Inabo, 2005).

Sexually transmitted diseases (STDs) are very common in the general population and more so among HIV positive patients (Castro and Alcaide, 2016). The type of STDs included in this study are genital warts, sores on genitals and sores on the lips. These STDs were tested on patients who had no infection and those who had infection at testing. The results of the present study showed that TC genotype of the +510 SNP is protective of sores in the genitals. Similarly, Aydogan et al. (2014) had found that IL-6 gene at -174 SNP has an impact on genital warts. Most oral lesions among HIV positive patients are caused by opportunistic pathogens such as *Candida* spp or HSV, which manifest because of weakened immunity. Oral lesions give the participants difficulty to eat, swallow, taste food, and also affect the participants' appetite. In this study, individual's carrying the TT and TC genotypes at IL-7 receptor gene +510 SNP tended to have more sore on the mouth. Although the difference was not statistically significance. Dill et al. (2015) also found that polymorphism on IL-1B gene is associated with oral lesions.

We determined the distribution of the locus +510 of IL-7 receptor alpha gene polymorphism in the South African community in relation to pain and other opportunistic infections and found a significant association between the +510 CT homozygote genotype (CC) and pain compared to the heterozygote genotype (TC). The study therefore provides data that can support individualized therapy that could modify the course of diseases among HIV patients as well as the general population. Further studies are needed to confirm these hypotheses in larger populations.

ACKNOWLEDGMENTS

We thank all the patients who participated in the study and the hospitals involved. The study was funded by the National Research Foundation of South Africa (NRF) and the Research and Publication committee of the University of Venda.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

REFERENCES

Aydogan K, Ozakin C, Saricaoglu H, Sigirli D, et al. (2014). Relationship between the interleukin-6-174 gene and mannose-binding lectin codon 54 gene polymorphisms and condyloma acuminatum. *J. Eur. Acad. Dermatol. Venereol.* 28(10): 1306-1312.

Bazdar DA, Kalinowska M and Sieg SF (2009). Interleukin-7 Receptor Signaling Is Deficient in CD4⁺ T Cells from HIV-Infected Persons and Is Inversely Associated with Aging. *J. Infect. Dis.* 199 (7): 1019-1028.

Castro JG and Alcaide ML (2016). High Rates of Sexually Transmitted Infections in HIV-Infected Patients Attending an STI Clinic. *South Med. J.* 109(1): 1-4.

Cheng JR, Guan SF, Wang XL, Han LH, et al. (2005). (Feasibility of genetic polymorphisms analysis using genomic DNA obtained from human buccal cells) – article in Chinese. *Ai Zheng* 24(7): 893-897.

Cobat A, Gallant CJ, Simkin L, Black GF, et al. (2009). Two loci control tuberculin skin test reactivity in an area hyperendemic for tuberculosis. *Blood.* 121(21): 4321-4329.

Dill A, Letra A, Chaves de Souza L, Yadlapati M, et al. (2015). Analysis of multiple cytokine polymorphisms in individuals with untreated deep carious lesions reveals IL1B (rs1143643) as a susceptibility factor for periapical lesion development. *J. Endod.* 41(2): 197-200.

Foroughi M, Koochak HE, Roosta N, Paydary K, et al. (2012). Prevalence of dermatologic manifestations among people living with HIV/AIDS in Imam Khomeini Hospital in Tehran, Iran. *J. AIDS/HIV Res.* 4(2): 56-59.

Gougeon ML and Chiodi F (2010). Impact of gamma-chain cytokines on T cell homeostasis in HIV-1 infection: therapeutic implications. *J. Inter. Med.* 267(5): 502-514.

Hermes RB, Santana BB, Lima SS, Neris MFR, et al. (2015). FAS -670 A/G polymorphism may be associated with the depletion of CD4(+) T lymphocytes in HIV-1 infection. *Hum. Immunol.* 76(10): 742-746.

Inabo HI (2005). The relationship between drug abuse and microbial infections. *Afr. J. Biotechnol.* 4(13): 1588-1590.

King J and Aberg JA (2008). Clinical impact of patient population differences and genomic variation in efavirenz therapy. *AIDS.* 22(14): 1709-1717.

Kiryluk K, Martino J and Gharavi A (2007). Genetic Susceptibility, HIV Infection, and the Kidney. *Clin. J. Am. Soc. Nephrol.* 2: S25-S35.

Knezevic NN, Tverdohleb T, Knezevic I and Candido KD (2018). The Role of Genetic Polymorphisms in Chronic Pain Patients. *Int. J. Mol. Sci.* 19(6): E1707.

Kuleape JA, Tagoe EA, Puplampu P, Bonney EY, et al. (2018). Homozygous deletion of both GSTM1 and GSTT1 genes is associated with higher CD4+ T cell counts in Ghanaian HIV patients. *PLoS One.* 13(5): e0195954.

Migueles S and Connors M (2010). Long-term Non-progressive Disease among Untreated HIV-Infected Individuals: Clinical Implications of Understanding Immune Control of HIV. *JAMA.* 304(2): 194-201.

Muegge K, Vila MP and Durum SK (1993). Interleukin-7: a cofactor for V(D)J rearrangement of the T cell receptor beta gene. *Science.* 261(5117): 93-95.

Naicker DD, Werner L, Kormuth E, Passmore J, et al., and the CAPRISA Acute Infection Study Team (2009). Interleukin-10 Promoter Polymorphisms Influence HIV-1 Susceptibility and Primary HIV-1 Pathogenesis. *J. Infect. Dis.* 200(3): 448-452.

Noguchi M, Nakamura Y and Russell SM (1994). Interleukin-2 receptor gamma chain: a functional component of the interleukin-7 receptor. *Science.* 262(5141): 1877-1880.

O'Doherty C, Alloza I, Rooney M and Vandenbroeck K (2009). IL-7Rα polymorphisms and chronic inflammatory arthropathies. *Tissue Antigen.s* 74(5): 429-431.

Olesen AE, Nielsen LM, Feddersen S, Erlenwein J, et al. (2018). Association between Genetic Polymorphisms and Pain Sensitivity in Patients with Hip Osteoarthritis. *Pain Pract.* 18(5): 587-596.

Salhi A, Rodrigues V Jr, Santoro F, Dessein H, et al. (2008). Immunological and genetic evidence for a crucial role of IL-10 in cutaneous lesions in humans infected with Leishmania Braziliensis. *J. Immunol.* 180: 6139-6148.

Samie A, Moloro GT and Nangammbi TC (2014). Interleukin-7 Receptor Gene Polymorphism At +1237 Locus And Its Effect on Susceptibility to Opportunistic Infections among HIV and AIDS Patients in Limpopo Province, South Africa. *Genet. Mol. Res*. 13(4): 8757-8766.

Shamim Z, Ryder LP, Christensen IJ, Toubert A, et al. (2011). Prognostic significance of interleukin-7 receptor-α gene polymorphisms in allogeneic stem-cell transplantation: a confirmatory study. *Transplantation.* 91(7): 731-736.

Shamim Z, Ryder LP, Heilmann C, Madsen H, et al. (2006). Genetic polymorphisms in the genes encoding human interleukin-7 receptor-α: prognostic significance in allogeneic stem cell transplantation. *Bone Marrow Transplant.* 37: 485-491.

Smith D, Richman D and Little S (2005). HIV Superinfection. *J. Infect. Dis.* 192(3): 438-444.

Tang J and Kaslow RA (2003). The impact of host genetics on HIV infection and disease progression in the era of highly active antiretroviral therapy. *AIDS.* 17: 51-60.

Vandergeeten C, Fromentin R, DaFonseca S, Lawani MB, et al. (2013). Interleukin-7 promotes HIV persistence during antiretroviral therapy. *Blood.* 121(21): 4321-9.

Vranjkovic A, Crawley AM, Gee K, Kumar A, et al. (2007). IL-7 decreases IL-7 receptor α (CD127) expression and induces the shedding of CD127 by human CD8+ T cells. *Int. Immunol*. 19(12): 1329-1339.

Weiss RA (1993). How does HIV cause AIDS? *Science.* 260(5112): 1273-1279.

Young EE, Lariviere WR and Belfer I (2012). Genetic basis of pain variability: recent advances. *J. Med. Gen.* 49(1): 1-9.

