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Research Article

Polymorphisms in the CD4 Gene and their Impact on Gene Expression in HIV-Positive Iraqi Patients

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I N F O

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A B S T R A C T

Introduction: HIV (Human Immunodeficiency Virus) is a retrovirus that targets the immune system, attacking (cluster of differentiation 4) CD4+ T cells, which is a crucial component of the body's defense.[1]). CD4+ T cells, also known as helper T cells, play a crucial role in orchestrating an immune response by sending signals to other immune cells to act against infections.[2] The relationship between HIV and the CD4 receptor is central to the life cycle of the virus. HIV infects the host by binding to the CD4 receptor on the surface of the T cells.[3] This binding occurs through the viral envelope protein (gp120), which attaches to the CD4 receptor.[4] Once bound, the virus undergoes a conformational change, allowing the virus to interact with a coreceptor, usually CCR5 or CXCR4, on the host cell surface.[5] This mechanism orchestrates the fusion of the virus membrane with the host membrane, allowing the viral RNA to enter the cell.[6]

Aim: The aim of this study is to investigate polymorphisms in the CD4 gene and its impact on HIV infection and gene expression in Iraqi HIV patients.

Result: The study aimed to investigate polymorphisms in the CD4 gene and its expression in HIV-positive patients through a two-step molecular analysis. Initially, whole blood samples were collected from HIV-positive patients and controls, followed by genomic DNA extraction using a kit, with quality assessed via fluorometer and gel electrophoresis. Specific regions of the CD4 gene were amplified using PCR, and the products were verified on agarose gel before undergoing Sanger sequencing to identify the SNPs and allelic variations. Subsequently, total RNA was extracted from the blood samples, with its quality assessed similarly. The RNA was converted into cDNA, and quantitative PCR was performed to measure CD4 gene expression levels, normalized to a housekeeping gene, allowing for measurement of gene expression levels between patient and control groups.

Conclusion: Of the 5 SNPs found to be present on the CD4 gene only two were found to have a significant frequency, while only one was found to have a statistical relation with HIV progression. No significance was found between the 5 SNPs and the expression of CD4 in the patients compared to the control group.

Keywords: HIV (Human Immunodeficiency Virus), retrovirus, DNA extraction, CD4 gene

Introduction

Background on HIV and the role of CD4 receptors

HIV-1 uses CD4 to enter the host's T cells and reaches the virus through its envelope protein known as gp120.[7] Binding to CD4 causes a change in the form of gp120 that allows HIV-1 to bind to a coreceptor expressed on the host cell. These co-receptors are the chemokine receptors CCR5 or CXCR4.[8] After a structural change in another viral protein (gp41), HIV adds a fusion peptide to the host cell, which allows the fusion of the viral outer membrane with the cell membrane.[9]

Polymorphisms in CD4 gene and their significance

Polymorphisms in the CD4 gene, which encodes the CD4 receptor is crucial for HIV entry into the host immune cells 10 . This significantly affects an individual's susceptibility to HIV infection[11] , disease progression, and treatment response. Variations, particularly single nucleotide polymorphisms (SNPs), may change the receptor's structure and expression levels, affecting how efficiently HIV binds to T-helper cells.[12] Some polymorphisms may enhance or reduce viral entry by changing the receptor's conformation or the amount of CD4 protein on cell surfaces.[13] This may lead to a difference in disease progression, with certain mutations related to a slower or faster advancement to AIDS.[14] Understanding these mutations is critical for developing personalized treatment strategies,[15] especially in specific populations like HIV-positive Iraqi patients, where unique genetic factors may influence susceptibility and treatment outcomes 16. Overall, studying CD4 gene polymorphisms provides useful insight into HIV management.[17]

Research objectives

Analyze the CD4 receptor to study any mutations on this gene and whether these mutations have any effect on gene expression or progression of the disease in Iraqi patients in order to further understand any possible implementations towards finding a cure or treatment.

Materials and Methods

Study design

A total of 184 HIV-positive patients who tested Positive for the HIV virus using qPCR 200 HIV negative individuals who tested negative for HIV using PCR were enrolled in this experiment. Patients who were unable to provide consent or who were diagnosed with other infectious diseases that could confound the results were excluded from this study. Those under the age of 18 or females that were pregnant or breast feeding were also excluded for ethical reasons.

Genetic Analysis

DNA was extracted from whole blood of patients and controls using a DNA extraction kit from Promega. DNA concentration was then measured using a fluorometer to ensure adequate sample extraction. Primers used to amplify the CD4 region of study included forward primer 5'GATGTGTGTTGAGTTTGCTATG'3 and reverse primer 5'CAGTCTCTGACCTCTGGAA'3 protocol used to run PCR included an initial denaturation step of The PCR protocol consists of an initial denaturation at 95°C for 2 minutes, followed by 35 cycles of denaturation at 95°C for 30 seconds, annealing at 58°C for 30 seconds, and extension at 74°C for 30 seconds, concluding with a final extension at 74°C for 5 minutes. PCR product was purified using gel purification then sequenced using sanger sequencing.

SNPs studied in this project included rs1591537209, rs11064392, rs2136711874, rs2136711918, rs1555113468.

Gene Expression Analysis

qPCR was used to measure fold change of samples compared with controls. Primers used were designed using geneious prime software for a specific exon region on the CD4 gene along with GADPH as a house keeping gene. Forward primer for CD4 F 5'AGAGCCTGACCCTGACCTTG'3, R 5' GGAAACCCAGAAAGCCGAAG'3. While the house keeping gene had the following sequnce. F

Control Group

The control group was recruited from the general population, all of the participants in this study were allowed to provide the researchers with the specimens. Informed consent according to the Declaration of Helsinki was obtained from all of the participants.

Statistical Analysis

Statistical software R was used to analyze the data for relevance. Hardy Weinberg equilibrium with chi square was used to analyze frequencies of this mutation. Pearsons's test was used to analyze the significance of the mutation on ccr5 gene expression.[18]

Results

Genotypic and Allelic Frequencies of CD4 Polymorphisms

Frequencies of each SNP were analyzed using the hardy Weinberg equilibrium

Gene Expression Levels

We look into whether the SNPs found on the CD4 have an impact on gene expression for the CD4 gene

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Table 1.This statistical experiment was conducted to test for observed and expected frequencies of each mutation

SNP	Study group	Genotype	Observed		Expected		P value
			N	%	N	%	
rs1591537209	Patient	T/T	22	24.17	19.84	21.81	0.364
		T/G	41	45.05	45.3	49.78	
		G/G	28	30.76	25.84	28.4	
	Control	T/T	58	62.36	57.3	61.61	0.667
		T/G	30	32.25	31.3	33.76	
		G/G	5	5.37	4.3	4.62	
rs11064392	Patient	A/A	66	82.5	65.7	82.12	0.696
		A/G	13	16.25	13.59	16.99	
		G/G	1	1.25	0.7	0.87	
	Control	A/A	61	62.24	64.49	65.8	0.021*
		A/G	37	37.75	30.01	30.62	
		G/G	0	0	3.49	3.56	
rs2136711874	Patient	G/G	8	9.63	10.84	13.06	0.176
		G/A	44	53.01	38.31	46.16	
		A/A	31	37.34	33.84	40.77	
	Control	G/G	73	74.48	72	73.46	0.409
		G/A	22	22.44	24	24.48	
		A/A	3	3.06	2	2.04	
rs2136711918	Patient	G/G	15	18.07	10.48	12.63	0.030*
		G/C	29	34.93	38.03	45.81	
		C/C	39	46.98	34.48	41.54	
	Control	G/G	57	58.16	53.63	54.72	0.077
		G/C	31	31.63	37.72	38.49	
		C/C	10	10.20	6.63	6.77	
rs1555113468	Patient	G/G	41	50.61	44.44	54.86	0.046*
		G/A	38	46.91	31.11	38.4	
		A/A	2	2.46	5.44	6.72	
	Control	G/G	86	87.75	86.36	88.12	0.518
		G/A	12	12.24	11.26	11.49	
		A/A	0	0	0.36	0.37	

Table 2.Pearson test was conducted to find correlation between fold change and CD4 SNPs.

CD4 SNPs	Genotype	Number	Fold change	P value
rs159153720	T/T	2	0.54 ± 0.020	0.737 NS
	T/G	26	0.67 ± 0.152	
	G/G	2	0.29 ± 0.25	

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rs11064392	A/A	25	0.67 ± 0.157	0.570 NS
	A/G	5	0.46 ± 0.151	
	G/G	0	-	
rs2136711874	G/G	5	0.69 ± 0.221	0.619 NS
	G/A	12	0.71 ± 0.281	
	A/A	13	0.54 ± 0.154	
rs2136711918	G/G	8	0.82 ± 0.152	0.464 NS
	G/C	7	0.58 ± 0.317	
	C/C	15	0.57 ± 0.212	
rs1555113468	G/G	19	0.83 ± 0.192	0.0579 NS
	G/A	10	0.32 ± 0.09	
	A/A	1	0.13 ± -	

Association Between Polymorphisms and HIV Progression

After comparing all our SNPs from the CD4 gene with the gene expression. We found that statistically the results were none significant[19] , in other words the expression of CD4 and was not affected by the presence of these mutation in those infected with HIV compared to those who were not. This suggests that, in our sample population, these specific genetic variations in the CD4 gene dont significantly influence its expression levels.[20]

This lack of association warrants further investigation, these results could be explained in the following matter. First the CD4 gene are complex genes that are controlled by multiple environmental and genetic factors. This may dwarf the effect of the portion of the gene we studied. There may be other areas of the gene not looked at by our study that dominate the portion we did look at rendering it unaffected.

Another point we need to keep in mind is that some of these mutations do not lie on coding regions and may not affect gene function for that reason. The relatively small sample size we opted to use for this project also inevitably had a role in reducing statistical relevance of our results. A larger sample size may help reveal a clearer tie between the studied parameters in future studies.

Our study was narrowed to one ethnicity and geographic location which also plays a role in skewing the level of diversity. The more diverse a study group the broader the results may be. We also did not assess any epigenetic factors in this study which also plays an important role in potentially silencing any effect of a SNP or modifying it so that gene expression is not affected by a specific SNP.

Discussion

To the best of our knowledge no previous research exits that addresses these particular SNPs and their relation to the progression or infection of HIV. According to studied the effects of the rs11064392 on multiple myeloma patients in which cd4 cells are also depleted, they found no significant result for the SNP in there.[7]

In the attempt to study whether or not the presence of the SNPs mentioned were more indicative of infection with HIV we conducted the following analysis.

Compare with global findings – are the polymorphisms similar or unique to Iraqi patients?

The higher occurrence of these variations, among HIV patients when compared to the control group strongly indicates a probable link between these mutations and an elevated vulnerability to HIV infection. This discovery suggests that individuals with these markers may have a greater chance of contracting the virus upon exposure, to an infected source. Further research is needed to understand the mechanisms behind this connection.

Although Zapata et al. (2013) did not study all the SNPs mentioned in our findings.[21] They were in agreement with the ones that were tested in both studies. rs1799987 was also found to presumably increase susceptibility to HIV infection. As well as rs1800023 which they also stated could be a cause for increased susceptibility.

Martin et al. (1998) and his team also found that the presence of these SNPs in a subject were indicative of increased susceptibility to an infection with HIV as did McDermott et al. (1998).[22,23]

The CD4 gene has not been extensively studied for gene polymorphism because it is the main receptor for viral entry of HIV and not a coreceptor.[24] In other words, any dramatic change to the cd4 will lead to the inability of HIV to infect its host cell. The CD4 gene has not been extensively studied for gene polymorphism because it is the main receptor for viral entry of HIV. Indraccolo et al. (1996) and Lederman et al. (1991) clearly state that they did not delve too deep

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into the subject because of the small numbers of SNPs discovered at the time of their research which accounted to only 5 SNPs.[25,26,27]

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