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INTERRELATIONSHIP OF INTERLEUKIN-17F (IL-17F) SINGLE NUCLEOTIDE POLYMORPHISM (RS763780) WITH SUSCEPTIBILITY TO HELICOBACTER PYLORI INFECTION

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Abstract

Helicobacter pylori infection is caused by Gram negative bacteria that enters the body and lives in the digestive tract. The bacterium is responsible for causing ulcers in the lining of the stomach and can lead to stomach cancer. Many genetic and environmental factors are involved in the onset and severity of the H. pylori infection. This study was designed to identify the association of Single Nucleotide Polymorphism (SNP) rs763780 in the IL-17F gene with the H. pylori infection. Total 120 samples were taken, including 60 H. pylori infected patient samples and 60 healthy individual samples. DNA was extracted from the blood samples using Organic Phenol Chloroform method. The extracted DNA was genotyped using Tri-primer PCR method. From genotyping analysis, it was found that TT genotype was greater in controls samples as compared to infected individuals and CT genotype was found greater in infected individuals' samples than in control samples. Similarly, in case of allelic frequency, C allele frequency was greater in cases as compared to control samples. From results it was concluded that C allele significantly increased the risk of getting H. pylori infection and polymorphism in IL-17F (T>C) can be possibly involved in the susceptibility to H. pylori infection.

INTRODUCTION

H. pylori is micro-aerophilic, negatively stained bacteria that has a helical shape. It possesses polar flagella for movement and infects the epithelial lining of stomach. The bacterium was discovered by Barry Marshall and Robin Warren and both received a noble prize for their discovery in 2005 [1]. H. pylori colonize the stomach of greater than 85% of the populations in the subcontinent [2]. Rate of prevalence of adolescence infection with H. pylori differs greatly ranging from as low as 1.8% to as high as 65% in developed nations [3,4]. It colonizes the pyloric region of the human stomach and persists for a lifetime, leading to a state of chronic inflammation [5]. The bacterium is usually associated with persistent gastric mucosa inflammation, but still more than 80% infected population remains asymptomatic [6].

H. pylori can remain in the harsh conditions of the stomach for decades because of the failure of host immune system to eradicate the infection due to different immune escaping strategies that are adopted by the bacterium and also due to the complicated intrinsic genetic changes that are acquired by this bacterium [7]. One of the successful immune evasion strategies that are adopted by the H. pylori is escaping the recognition by Pattern Recognition Receptors (PRR). PRR recognizes Pathogen Associated Molecular Patterns (PAMPs) and this recognition leads to the activation of number of extra-cellular and

intra-cellular signaling pathways that eventually leads to inflammatory response which is necessary for the clearance of a pathogen [8]. H. pylori escape the detection of Toll Like Receptors (TLRs) by modifying its surface molecules, including the modification of Lipid-polysaccharide (LPS) and flagellin [9]. Presence of H. pylori in stomach for long term leads to the progression of lethal diseases including Mucosa Associated Lymphoid Tissue Lymphoma (MALT lymphoma) [10]. There are various risk factors that are actively playing role in the development of symptomatic H. pylori infection. Risk factors that are reported to be associated with the development of H. pylori infection include smoking, diet, consumption of restaurant food, meat, and non-filtered water [11]. H. pylori produces large number of virulence factors including CagA, NapA and VacA which are involved in the development of infection. Among several factors, CagA is the most important virulent factor and is encoded by cag-A gene which lies within the cytotoxin associated protein pathogenicity island (CagPAI) of H. pylori genome [12].

H. pylori injects Cag-A protein with the help of a type IV secretion system and starts interfering with the numbers of host signaling pathways including NFkβ which is involved in the modulation of inflammatory reaction and MAPKs which are involved in complex cellular activities like differentiation, development and apoptosis [13]. Such an interference with signaling pathways consequently affects vital functions of the host including apoptosis [14]. Moreover, CagA(C) strains induce release of the pro-inflammatory cytokines including Tumor Necrosis Factor-a, Interleukin-1b and Interleukin-8; these cytokines lead to oxidative stress and damage the DNA [15].

In H. pylori infection the innate and adaptive, both immune systems are activated [16]. However, the specific reaction of immune system in the infections of H. pylori is mediated by TH1 and TH17 cells that are reported to be actively playing role in the production of Interferon-gamma and Interleukin-17 [17]. Recently, Th17 cells are regarded as essential in immunity against the infection of fungi and bacteria that are outside of the cell due to their involvement in the activation, recruitment and migration of neutrophils and by the production of antimicrobial molecules like defensing [18]. Th17 cells are categorized by the release of IL-17, but their importance is not just limited to that as they also involved in the production of several other cytokines as well which play a crucial role in different diseases. Additional pro-inflammatory cytokines released by human Th17 cells along with IL-17 include TNF-α, IL-22, and IL-26 [19]. Multiplication of Th17 cell is required for the preservation of the Th17 cell population and such multiplication is conciliated by IL-23 and IL-21[20]. IL-17 is a pro-inflammatory cytokine that induces the expression of numerous cytokines, chemokines and several cell adhesion molecules [21].

IL-17 family includes six proteins and these are: IL-17A, IL-17B, IL-17C, IL-17D, IL-17E and IL-17F, but IL-17A and IL17F are of great importance because both of them are involved in the inflammation process [22]. IL-17A and IL-17F are related to one another as they have 55% identical amino acids and also share a common receptor [23]. IL-17A and IL-17F are synthesized by large number of cells containing myeloid cells (e.g., kidneys and lungs) and Paneth cells in the intestinal crypts However, epithelial cells are involved in the production of IL-17B, IL-17C and IL-17D [24]. Th17 cell signature cytokine is IL-17F which is regarded as an essential mediator of cell mediated immunity, because of its function in the defensive process against different pathogens [25]. In reaction to Pathogen-Associated Molecular Patterns (PAMPs), Antigen Presenting Cells (APCs) synthesize IL-23 and IL-1β to promote IL-17 release [24].

Gene of IL-17F is located on p-arm of chromosome number six having 3 exons and 2 introns. An increase in the level of IL-17F has been seen as a response against bacterium Helicobacter pylori in gastric mucosa of stomach of the infected patients, especially in chronic stage [26]. The most frequent and usual types of genetic variations in a population are Single Nucleotide Polymorphisms. SNPs can act as a biological marker, helping scientists to find out genes that are linked with disease. SNPs can be involved in the causation of disease, affecting function of the gene, when they occur within the regulatory region of the gene [27].

IL-17 gene genetic polymorphism has remained a center of attraction and several different kind of studies have been conducted to validate its function in the progression of different autoimmune, hematological and non-hematological disorders such as RA [28,29] Multiple sclerosis [30], Psoriasis [31], acute

myeloid leukemia [32], gastric cancer [33] and lung cancer [34]. IL-17F polymorphism has seen to affect the coding region of gene replacing histidine with arginine (His-Arg). The change was observed at amino acid 161 and this Single Nucleotide Polymorphism is responsible for the over-expression of IL-17F which leads to the development of autoimmune diseases including Primary Immune Thrombocytopenia (PIT) [35]. IL-17 polymorphism (G-197A/ rs 22759133) has been linked with gastric cancer, in which mutation in the promoter region of the gene causes the up-regulation of IL-17, which in return up regulates the immune response that involves IL-17 [36]. IL-17F polymorphisms have a major effect on the expression and activity of IL-17F which may result in susceptibility to many diseases including H. pylori infection.

This study was conducted for the first time and no such study was carried out in Mardan region to investigate the frequency distribution of IL-17F (763780) polymorphism in H. pylori patients among the Mardan population. The study will help in understanding the epidemiology of H. pylori infection in Mardan region.

2. Methodology

2.1. Study Subject

The present study was conducted from March 2021 to May 2021 in Health Biotechnology Laboratory, Abdul Wali Khan University Mardan. Samples were collected from different areas of Mardan (Rustam, Shahbaz Garhi, Swabi, Takht Bhai and Mardan City). Total 120 individuals were included in the study including 60 H. pylori infected individuals and 60 normal individuals. Blood samples of the patients infected with H. pylori were collected in EDTA tubes with the prior consent of the patients. Positive cases were serologically diagnosed and individuals that were counted as control had no immunological disease. Demographic and clinical data of samples including cases and control were recorded on a specially designed questionnaire.

2.2. DNA Extraction and Genotyping

DNA was isolated from 500µl of whole blood samples using traditionally old organic Phenol Chloroform Isoamyl Alcohol method and Genotyping of the IL-17F gene variant rs763780 was carried through Tri-primer PCR technique using a set of three primers, including two forward and a common reverse primer details of which are given in table 1. PCR amplification was then performed in 96-well plates on a thermocycler (T100, Bio-Rad).

Table 1: Primers sequences for IL-17F gene.

S. No	Primer	Sequence	Length
1	IL-17F	F1: ATATGCACCTCTTACTGCACAC	22bp
		F2: GATATGCACCTCTTACTGCACAT	23bp
		R: TACCCCTCGGAAGTTGTACAG	21bp

The amplification conditions were set as the initial denaturation at temperature 94°C for 5 minutes, followed by 35 cycles of denaturation at 94°C for 30 seconds, annealing for 30 seconds at 62°C, and extension at 72°C for 60 seconds. The final extension was performed at 72°C for 5 minutes. The PCR products were resolved in 2% agarose gel, and the genotype calls for each subject were recorded using the visual inspection method of the gel.

3. Results

3.1. Demographic and Clinical Manifestation of H. pylori Patients

A total of 120 blood samples were taken from people in which 60 samples were diagnosed positive for H. pylori infection and 60 samples were taken from healthy individuals. Samples that were taken from healthy individuals were used as control. Exclusion criteria was set for samples in which samples that were diagnosed positive for diseases like diabetes and arthritis were excluded. Samples that had no other infection were considered for the study. Clinical data of selected samples is given in table 2.

Table 2: Clinical Data of Selected Samples

Gender		socio-economic status			Smoking		Diet		Marital status	
Male	Female	Upper	Middle	Lower	Smokers	Non Smokers	Veg	Non-veg	Married	Unmarried
73%	27%	8%	58%	34%	27%	73%	47%	53%	56%	44%

Among the selected patients 55% had family history of infection while 45% were the first in the family who contracted the infection. Moreover, Severity of infection was 77% acute and 23% chronic. It was also found that people at the age between 20-30 years were more susceptible to H. pylori infection (Figure 1).

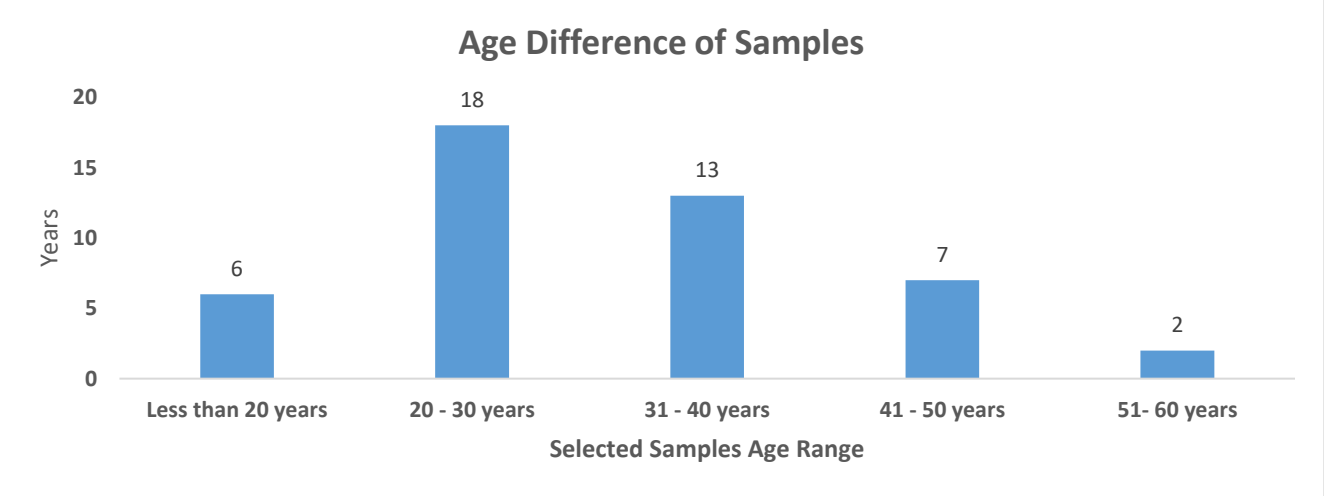

Figure 1: Age difference of selected sample.

3.2. Extracted DNA Examination on 1% Agarose Gel

Extraction of DNA was done from venous blood of selected samples by standard protocol of Organic Phenol Chloroform Isoamyl Alcohol method. The extracted DNA was processed on 1% agarose gel for 25 minutes by keeping voltage at 120 and current at 400 amperes. The gel was then visualized under UV light as can be seen in figure 2 and calls were made for each well.

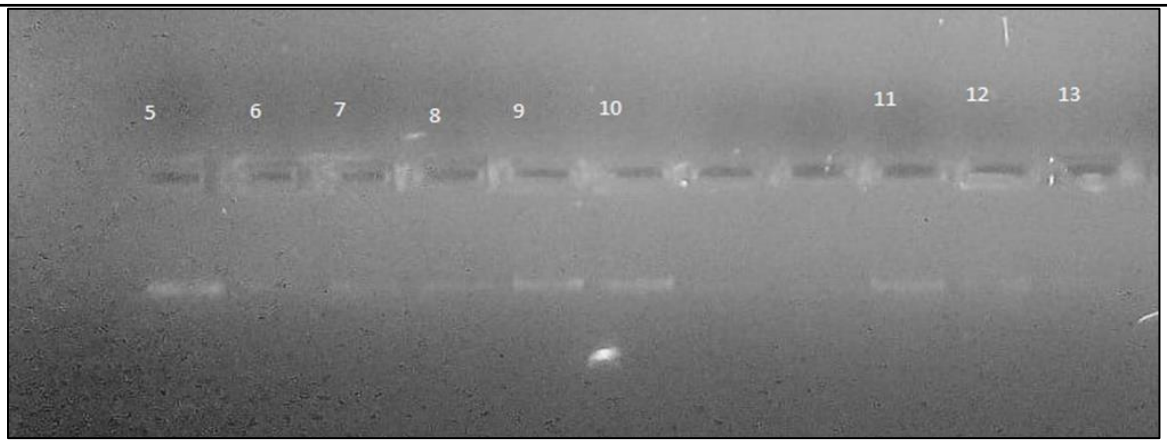

Figure 2: Extracted DNA Examination on 1% Agarose Gel Electrophoresis

3.3. Genotyping through Tri- Primer PCR

Genotyping was performed through Tri primer PCR method. Extracted DNA of each selected sample was processed with separate forward primers and was then loaded in separate wells. Genotypic and allelic analysis was done by observing the wells of agarose gel. In figure 3 genotyping of 6 individuals has been done, processing their extracted DNA with separate forward primers (C and T).

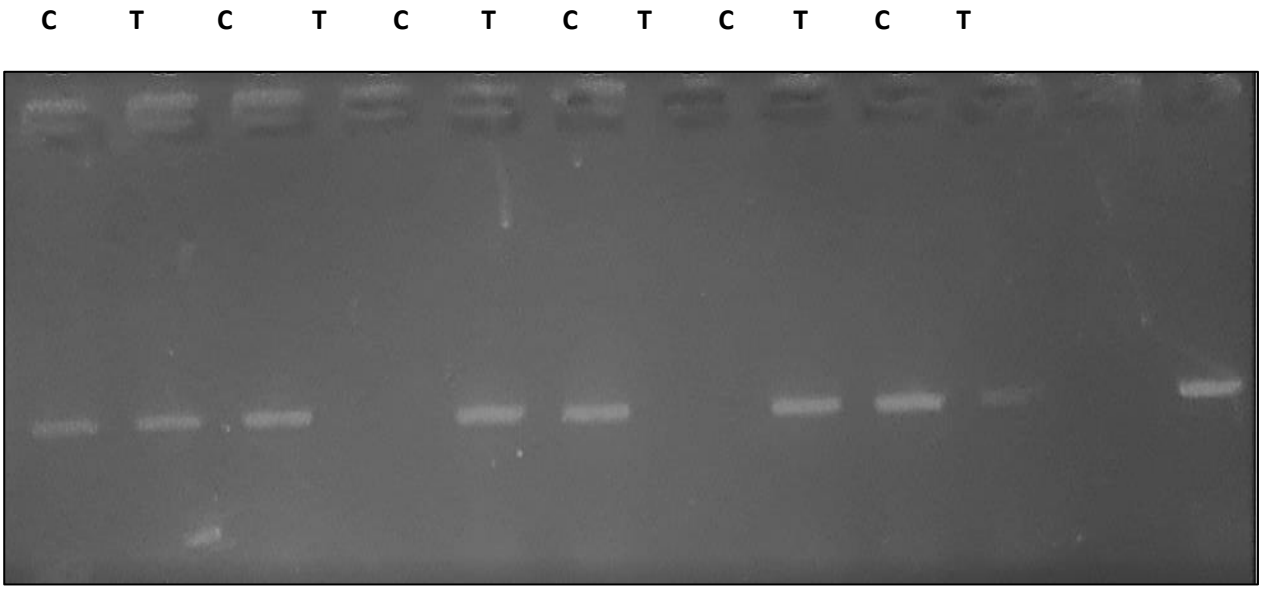

Figure 3: IL-17F Variants (rs763780) Gel Picture Signify Genotype in Cases

3.4. Interrelation of IL-17F rs763780 with H. Pylori Patients

Genotypic data of selected samples was taken by processing the extracted DNA using Tri-primer PCR technique. Genotype frequency was found as 35% for TT genotype, CC 10% for CC genotype and 55% for CT genotype in selected samples that were diagnosed with H. pylori infection. However, in control samples genotype frequency was found as 66% for TT genotype, 5% for CC genotype, and 28% CT genotype. Comparatively, TT genotype was found greater in control samples as compared to the samples that were taken from infected individuals. In contrast, CT genotype was found greater in cases than control samples.

In case of allelic frequency percentage of T allele in selected samples that were diagnosed with H. pylori infection was found as 62.5% and that of the C allele was 37.5% whereas in control the allelic frequency was found as 80.83% for the T allele and 19.1% for C allele. The C allele frequency was greater in cases as compared to control samples which suggests the involvement of C allele as the predisposing factor for H. pylori patients in IL-17F rs763780. Details of genotypic and allelic frequencies and numbers of individuals carrying those frequencies are given in table 3.

Table 3: Genotype and allele frequencies of samples (cases and control).

			Cases	Controls
IL-17F rs 763780	**Genotype**	TT	21 (35%)	40 (66%)
		CC	6 (10%)	3 (5%)
		CT	33 (55%)	17 (28%)
	Allele	T	75 (62.5%)	97 (80.83%)
		C	45 (37.5%)	23 (19.1%)

4. Discussion

Helicobacter pylori is negatively stained acid-resistant bacteria that has a helical shape and is regarded as the most important human pathogen. Helicobacter pylori have 4 to 7 flagella which help in the motility of the bacterium and keep it intact in the stomach mucus layer [37]. In this study H. pylori was prevalent between people having age between 20-30 years. Similarly, in other cross-sectional studies, a positive relation between age and H. pylori infection prevalence was shown [38].

Furthermore, in the current prevalence study of H. pylori infection a total of 120 samples were taken. Among 120 samples, 88 samples were reported to be from males and 32 samples were from females. From analysis of different studies based on sex-differences of prevalence of Helicobacter pylori infection, it was found that male sex was correlated with H. pylori infection [39]. Similar prevalence study of H. pylori infection concluded that rate of infection is 62% in females and over 68% in males [40].

In addition, it was found in the study that among total 120 individuals 70 individuals had a socio-economic status of middle class, 40 individuals had status of lower class and 10 belonged to the upper class. In a similar study, based on socio-economic status, daily routine and H. pylori infection in the people of Lanyu, Taiwan it was identified that H. pylori infection was more frequent in people that belonged to groups that had lower family wages and education levels [41].

Moreover, variations in genes that are related to inflammation are thought to play a role in the outcome of different infections. In this study, we aimed to find out the frequency of IL-17F polymorphism in the population of Mardan. In the study T>C change was observed, and it was found that IL-17F C allele was present in greater proportion in diseased individuals and was relatively less frequent in normal individuals. A similar, investigative study was conducted in Sudan by Nouh S. Mohamed et al., in 2020 in which he concluded that the proneness to gastric cancer and other pro-inflammatory diseases is linked with the polymorphism of IL-17A and IL-17F. It was also indicated in the study that the risk of H. pylori increases with polymorphism of IL-17A and IL-17F [42].

In another investigative study that was conducted by Tomoyuki Shibata in 2009, relationship between gastric cancer and polymorphisms of IL-17A (rs2275913) and IL-17F (rs763780) genes was determined. It was found in the study that the number of IL-17A A/A homozygote was remarkably higher in gastric cancer group than in non-cancer group. It was concluded from the results that polymorphism of IL-17A gene was remarkably associated with the advancement of gastric cancer, especially intestinal-type cancer [43].

In conclusion, in this study it was found that H. pylori infection is more common in people that were non-vegetarian having age between 20-30 years. Moreover, 55% samples that were diagnosed positive for H. pylori had family history of infection. In this study the

relationship between polymorphism of IL-17F and H. pylori infection in Mardan population was also identified. It was found that IL-17F C allele significantly increased the rate of H. pylori infection in Mardan region. For the first time, a study investigated the frequency distribution of IL-17F (763780) polymorphism among Mardan population and no such study was conducted before. Both the allelic and genotypic frequencies were determined in the study. From this study it was concluded that polymorphism in IL-17F gene was associated with H. pylori infection susceptibility. Further detailed investigation is required to find out the specific relationship between mutations in IL-17F and H. pylori infection.

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