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Original article

Study of the role of IL-17F gene polymorphism in the development of immune thrombocytopenia among the Egyptian children

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ABSTRACT

Background: Interleukin 17F (IL-17F) is a pro-inflammatory cytokine that is recently proved to have a crucial role in the emergence of autoimmune diseases; it induces the expression of various cytokines, chemokines, and adhesion molecules. IL-17F polymorphism is subsequently related to enhanced IL-17F expression and activity; which may result in susceptibility to many autoimmune diseases including primary immune thrombocytopenia (PIT).

Aim of the study: This case-control study aimed to investigate the possible association between IL and 17F gene single nucleotide polymorphism (SNP) at rs 7488A/G and PIT susceptibility in Egyptian pediatric patients.

Subjects and methods: A total of 50 children with PIT with a mean age of 7 years, together with 50 age and sexmatched healthy controls were enrolled in the study for evaluation. Polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) was used for detection of IL-17F polymorphism at rs7488A/G.

Results: Regarding the genotypes distribution, the frequencies of the AA, AG and GG genotypes were 96, 2, and 2% in PIT patients and 90, 10 and 0% in the control group respectively. The A and G allele frequencies were 97 and 3% in the patients' group versus 95 and 5% in the control group. There was no significant difference in either genotypes or allelic distribution between PIT patients and the controls.

Conclusion: Our study suggests that IL17F gene polymorphism at rs7488A/G may not contribute to the susceptibility in development of primary immune thrombocytopenia in the Egyptian children.

1. Introduction

Primary immune thrombocytopenia (PIT) is an acquired autoimmune disorder characterized by a low platelet count that occurs in the absence of underlying disease; which is attributed to the vagueness of the disease's pathogenesis. Decreased platelet count usually results from increased platelet destruction together with inadequate platelet production [1].

PIT is considered the most common autoimmune cytopenia in the childhood; 2.2–5.3 per 100,000 children aged 18 years or less are diagnosed with PIT every year [2]. Fortunately, childhood PIT is known to have a favorable prognosis [3].

Though the pathogenesis of PIT is still rendered unclear, yet there are many theories that emphasize the involvement of multiple mechanisms comprising antiplatelet antibodies secreted by auto-reactive B lymphocytes, platelet destruction mediated by T cells, poor functionality of regulatory T cells accompanied with their reduced number [4].

Innovative data had supported the hypothesis of CD4 T cell plasticity which in turn leads to diverse immune responses, based on the type of impact made by the inflammatory environment; this could be exemplified in T helper 17 (Th17) cell that can easily become an Interferon γ (IFN-γ) producer [5].

CD4 T cells are capable to modify their profile for which interleukin they are going to produce; in addition they can attain "mixed" phenotype features in a classically defined lineage [6]. Thus, nowadays their role is now interpreted as network of responses rather than distinctive elements [7], since the balance between these subsets has been involved in the regulation of several immune responses [1]. Ogawara et al. [8] had shown that increased T helper 1/T helper 2 (Th1/Th2) ratio was correlated with PIT development. Moreover, another study made by Ji et al. [9] had shown the role of up-regulated Th 17 cells in the pathogenesis of PIT.

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IL-17F is a signature cytokine secreted from Th17 cells, apart from playing a crucial role in the defensive mechanism against pathogens and autoimmunity; it has shown to function differently from other members of the IL-17 cytokine family, especially IL-17A. Hence IL-17F is considered a principal mediator of cellular immunity by preserving the expression of essential cytokines that induce pro-inflammatory responses [10].

IL-17F gene is located on chromosome No. 6p 12.3, it has 3 exons interposed with 2 introns [11]. IL-17F rs763780 polymorphism affects the coding region of the gene by causing Histidine to Arginine (His-to-Arg) substitution at amino acid 161, this SNP leads to up-regulation of IL-17F and consequently the development of autoimmune diseases comprising PIT [12].

2. Aim of the study

This is a case-control study aiming to analyze IL-17F polymorphism at rs7488A/G among Egyptian children diagnosed with PIT and healthy children to evaluate its contribution to PIT susceptibility.

3. Subjects and methods

3.1. Subjects

This case-control study involved a total of 50 Egyptian pediatric patients diagnosed with ITP (28 acute and 22 chronic) who attended the Pediatric Hematology outpatient clinic – Abu El Rish – Cairo University Hospital, as well as 50 age and sex matched healthy children as controls. Thereafter an informed consent was attained from each participant or from his/her guardians. The study was approved by Ethical Committee of Clinical Pathology, Cairo University. An informed written consent was obtained from all the patients participating in the study. The work has been carried out in accordance with the code of ethics of the World Medical Association (Declaration of Helsinki) for experiments in humans. PIT diagnosis was established via history taking together with physical examination and laboratory investigations. Inclusion criteria were obtained for these patients and incorporated a Complete Blood Count (CBC) results that revealed an isolated thrombocytopenia ($<100 \times 10^9$/l), without anemia or leucopenia and Bone Marrow Aspirate (BMA) that showed a megakaryocytic morphology compatible with the diagnosis of PIT. Furthermore; patient's history showed no concomitant autoimmune disorders, no medications known to cause thrombocytopenia, no associated viral disorders or suspicion of malignancy. Exclusion criteria comprised infants with age <6 months, manifestations of active infection, splenomegaly and secondary causes of PIT, such as systemic lupus erythematosis (SLE). Nonetheless, a further classification was done on our PIT patients based on the duration of the disease. They were divided into acute "newly diagnosed" cases as well as chronic cases of more than 12 months duration. The disease duration in our PIT chronic patients ranged from 13 to 48 months with a median of 30 months. Peripheral blood samples were withdrawn from all the acute cases before starting any medications. On the other hand, PIT chronic cases were receiving Glucocorticoids as the main line of treatment in such cases, but none of them had been treated with it at least 4 months prior to sampling.

3.2. Methods

3.2.1. Genomic DNA extraction

Two ml of anti-coagulated peripheral venous blood were withdrawn from all ITP cases as well as controls for Genomic DNA extraction using Prime-Prep Genomic DNA Isolation Kit (GENET BIO, Korea), manufacturers' instructions were followed and extracted DNA samples were stored at −20°.

3.2.2. Genotyping

IL-17F + A/G genotyping was carried out by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) technique using TECHNE, Thermal Cycler instruments (TECHNE, Version 3.1) and the following pairs of primers were used: forward primer: 5′ GTTCCCATCCAGCAAGAGAC-3′, reverse primer: 5-AGCTGGGAATGCAAACAAAC-3′[13,14].

The PCR cycles conditions were as follows: 94 °C for 3 min; 35 cycles at 94 °C for 30 s, 60 °C for 30 s and 72 °C for 30 s; and a final elongation step at 72 °C for 7 min. The PCR products were visualized after electrophoresis in 2% agarose gel and ethidium bromide staining under UV light (Uvitec). The amplified PCR products were digested with the NlaIII restriction endonuclease (New England BioLabs Inc.) and analyzed in 2% agarose gel. Three patterns were observed following digestion and electrophoresis: a single 412 bp fragment (individuals homozygous for the IL-17F G allele, lacking the NlaIII site), three fragments of 412, 288 and 124 bp in length (heterozygous individuals) or two fragments of 288 and 124 bp (individuals homozygous for the IL-17F A allele).

3.2.3. Statistical methods

Data management and analysis were performed using Statistical Package for Social Sciences (SPSS-17). Numerical data were summarized using means and standard deviations or medians and ranges. Categorical data were summarized as percentages. Comparisons between the two groups with respect to numeric variables were done by the Mann-Whitney test. To compare more than two groups with respect to numeric variables, Kruskal-Wallis test followed by the post hoc Dunn test for non-parametric data was performed. The chi-square test was used to compare the groups with respect to categorical data. To assess the degree of association between the numeric variables, the Spearman correlation for nonparametric data was used. P values ≤ 0.05 were considered significant.

4. Results

The study involved 50 patients suffering from ITP; 22 (44%) of them fulfilled the criteria of chronic PIT [11 (50%) boys and 11 (50%) girls]; their mean age was 7.91 ± 3.37. 28 (56%) children had acute ITP [16 (57.1%) boys and 12 (57.1%) girls]; their mean age was 6.29 ± 3.49 years. In addition, 50 age and Sex-matched healthy children [28 (57.0%) boys and 22 (43.0%) girls] were included as a control group. Their mean age was 7.42 ± 3.21 years. The descriptive data of the studied subjects are illustrated in Table 1 and 2.

Regarding genotypes distribution, the wild genotype (AA) frequency was 96% in the PIT patients compared to 90% in the control group. The heterozygous mutant (AG) genotype frequency was 2% in PIT group compared to 10% in the control group while the homozygous mutant (GG) genotype frequency was 2% and 0% respectively in patients and control groups, The difference in genotypes distribution (AG, AA, GG) was not statistically significant (p = 0.1, 0.3, 0.5 respectively).

Similarly, the frequency of both homozygous GG and heterozygous AG mutant genotypes was comparable between both groups (4% vs 10% in cases and control groups respectively, p = 0.24).

On the other hand, our study showed no statistically significant difference between the allelic distribution of the IL17F (A7488G) SNP in the studied groups; where the mutant allele G frequency was 3% and 5% in patients and control groups respectively, (p = 0.47). Data are presented in Table 3 and 4 and Fig. 1.

Table 1
Clinical and laboratory characteristics of ITP patients.

	ITP (n = 50)	Acute ITP (n = 28) (56%)	Chronic ITP (n = 22) (44%)
Age (years)			
Range	2–14	2–13	2–14
Mean ± SD	7 ± 3.50	6.29 ± 3.49	7.91 ± 3.37
Sex (no, %)			
Male	27 (54%)	16 (57.1%)	11 (50%)
Female	23 (46%)	12 (42.9%)	11 (50%)
Management			
Corticosteroids	50 (100%)	28 (100%)	22 (100%)
IV Ig	7 (14%)	3 (10.7%)	4 (18.2%)
Immunosuppressive	10 (20.0%)	1 (3.6%)	9 (40.9%)
PLT transfusion	4 (8%)	3 (10.7%)	1 (4.5%)
Laboratory data			
Hemoglobin (g/dl)			
Range	7–13	7–13	8–13
Mean ± SD	10.23 ± 1.60	9.95 ± 1.62	10.60 ± 1.53
TLC ($\times 10^9$/l)			
Range	4.1–15.4	5.8–15.4	4.1–15
Mean ± SD	9.19 ± 2.47	9.41 ± 2.49	8.92 ± 3.07
Platelets ($\times 10^9$/l)			
Range	5–216	5–87	55–216
Mean ± SD	72.42 ± 56.15	31.79 ± 22.47	124.14 ± 41.29

Table 2
clinical and laboratory characteristics of the control group.

Item	Control group (n = 50)
Age (years)	
Range	1–13
Mean ± SD	7.42 ± 3.214
Sex (no, %)	
Male	28 (57%)
Female	22 (43%)
Laboratory data	
Hemoglobin (g/dl)	
Range	11–15
Mean ± SD	13.15 ± 1.026
TLC ($\times 10^9$/l)	
Range	4.3–11
Mean ± SD	7.595 ± 1.7837
Platelets ($\times 10^9$/l)	
Range	155–432
Mean ± SD	291.48 ± 69.96

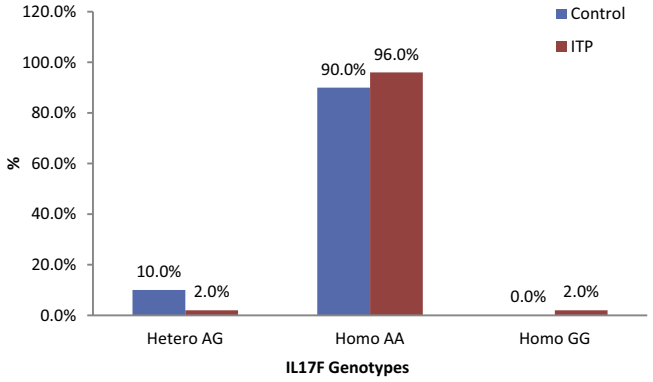

Fig. 1. Distribution of IL17F genotype allelic frequencies between the studied groups: (Hetero AG, Homo. AA and Homo GG).

The association between the IL17F (rs 7488 A/G) SNP with disease severity in terms of onset, the degree of thrombocytopenia, response to glucocorticoid therapy could not be assessed owing to the small number of patients [2 (4%)] having the mutation.

5. Discussion

IL-17 is a potent pro-inflammatory cytokine that is able to recruit neutrophils and monocytes and induce the activation of various cytokines, including IL-1, IL-6, IL-8, and interferon-ɤ (IFN-ɤ) and thus ending up in an immune-mediated inflammatory reaction via the expression of IL-17 receptors [15]. Several studies demonstrated that genetic polymorphisms of *IL-17* were shown to be linked to various autoimmune diseases such as inflammatory bowel disease, asthma, and PIT [16].

In the present study, no association was found between the IL17F (rs7488A/G) SNP and PIT susceptibility in the studied population, both genotypes and allelic distribution were comparable among patients and control groups.

Lately, IL-17F genetic polymorphism has been the centre of attraction since various studies have been executed to validate the potential role of this genetic polymorphism in development of different autoimmune diseases such as rheumatoid arthritis [17,18], psoriasis [19], multiple sclerosis [20], together with hematological diseases such as acute myeloid leukemia [21], and non-hematological malignancies including gastric cancer [22], lung cancer [23] and colo-rectal cancer [24,25].

The results obtained in this study showed that the Wild genotype AA frequency was 96% in the PIT patients compared to 90%

Table 3
IL17F genotype allelic Frequencies between PIT patients and the Control group.

IL17F Genotypes		Group		Total	P. value
		Control N = 50	ITP N = 50		
Hetero AG		5 (10.0%)	1 (2.0%)	6	0.3
Homo AA		45 (90.0%)	48 (96.0%)	93	0.1
Homo GG		0 (0.0%)	1 (2.0%)	1	0.5
Total	A allele	95 (95.0%)	97 (97.0%)	192 (96.0%)	0.47
	G allele	5 (5.0%)	3 (3.0%)	8 (4.0%)	

Table 4
IL17F genotype allelic distribution of the total of homozygous and heterozygous frequencies in the studied groups.

IL17F Genotypes	Control N = 50	ITP N = 50	Total	P. Value
Mutant	5 (10.0%)	2 (4.0%)	7	0.24
Wild	45 (90.0%)	48 (96.0%)	93	

in the control group. The Heterozygous mutant genotype frequency (AG) was 2% in PIT group compared to 10% in the control group while the homozygous mutant genotype (GG) frequency was 2% and 0% respectively in patients and control groups, with no statistical difference in the genotypes distribution (AG, AA, GG) (p = 0.1, 0.3, 0.5 respectively). Furthermore, there was no statistical difference between the allelic distribution (A allele, G allele) in the studied groups; where the mutant allele frequency (G) was 3% and 5% in patients and control groups respectively, (p = 0.47).

Regarding genotype distribution, our results were consistent with Li et al., 2015. However, this study showed that G (mutant) allele in PIT patients was significantly lower than in normal controls (total PIT 3.6% vs controls 7.7%, $P = .026$; chronic PIT 3.5% vs controls 7.7%, $P = .031$). Moreover, in their study, there was no association between IL and 17F polymorphisms and any of the clinical parameters in PIT patients, also the study revealed no association between gene distribution and acute onset of the disease, age, glucocorticoids therapy or disease course.

IL17F 7488A/G SNP association with various autoimmune diseases was a focus for research, Erkol et al. [26] demonstrated in their study the influence of polymorphisms of interleukin-17A and -17F genes on susceptibility and activity of rheumatoid arthritis. They found no significant difference regarding genotypes or allelic frequency distributions of the IL-17A G197A, the IL-17F 7383A/G, and 7488A/G polymorphisms between patients and healthy controls.

Previous studies of the association of IL17F SNP and PIT yielded variable results, for instance, a study by Saitoh et al., [12] showed that the frequency of the IL-17F 7488 mutant Arg161 genotype is significantly lower among the chronic PIT patient group in comparison to the control group (0% vs. 4.8%, $P < 0.05$). This inferred that IL-17F 7488 mutant (GG) genotype has less ability to potentiate an immunologic reaction in the development of chronic PIT.

Moreover, another recent study executed by Liu et al. [27] on Chinese patients revealed that the frequencies of IL-17F "A7488G" wild allele A were significantly higher in PIT patients in comparison to the healthy controls with a result of 31.85% vs. 18.98% and a P value of <0.01. Furthermore, PIT patients had significantly higher frequencies of AA and AG genotypes than the healthy controls, these findings could validate the incrimination of IL17 F polymorphism in PIT development in such patients.

On the other hand, an Egyptian study was done by Mokhtar et al., [4] aimed to investigate the possible association between PIT development in the childhood and the several genetic polymorphisms in tumor necrosis factor (TNF)-alpha, interleukin (IL)-10, IL-6, IL-17 and IL-1Ra, the results obtained revealed a significant higher mutant genotype of IL-17F ($P = 0.0001$) among the patient's group compared to the control group yet the discrepancies between our results and these results could be attributed to the ethnic difference between the studied populations, the frequency of the variant allele being low in both the patient and control groups in the present work.

The study limitations here could be attributed to the relatively small sample size enrolled in the study, thus further studies with larger cohorts are recommended to validate the role of these SNPs as molecular contributors to the addressed pathology. Likewise, IL-17F serum levels should have been examined in order to study the link between the studied genetic polymorphism and its serum levels.

6. Conclusion

IL17F gene polymorphism might not contribute to the susceptibility of primary immune thrombocytopenia development in the Egyptian children, yet it has to be stated that further investigations with larger cohorts are recommended for better characterization of patients prone for disease as well as for identification of other novel molecular markers that could impact the disease course and consequently disease morbidity and mortality.

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Disclosure of interest

All Authors of this manuscript declare no conflict of interest.

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