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IL17A and *IL17RA* gene polymorphisms in Fanconi anemia

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Abstract: Fanconi anemia is a rare autosomal recessive disease. In this disease, cytokine pathways can induce the bone marrow failure that is observed in individuals with Fanconi anemia. Interleukin IL-17 exhibits a protective effect in organisms because it induces neutrophil recruitment and shows a pathological role in several models of autoimmune diseases, periodontal disease, cancer, allograft rejection, and graft versus host disease. Polymorphisms in the *IL17A* and *IL17RA* genes were evaluated from DNA in saliva, comparing individuals with or without Fanconi anemia, using models of genotypic transmission (additive, dominant, and recessive). Polymorphisms in the *IL17A* and *IL17RA* genes (rs2241044 [C allele], rs879577 [C allele], rs9606615 [T allele], and rs2241043 [C allele]) were risk factors for developing Fanconi anemia. We also performed an analysis of gene markers with clinical variables in the Fanconi group. Polymorphisms in the *IL17A* gene (rs3819025 [A allele] and rs2275913 [G allele], respectively) were associated with an age of less than 20 years (p = 0.026; RP 0.65) and the female sex (p = 0.043; RP 0.88). The *IL17RA* gene was also associated with age and the presence of leukoplakia (a potentially malignant oral disorder). An age of less than 20 years was associated with rs917864 (T allele; p = 0.036; RP 0.67). The presence of leukoplakia was associated with rs17606615 (T allele; p = 0.042; RP 0.47). To our knowledge, this is the first study that associates *IL17A* and *IL17RA* gene polymorphisms with Fanconi anemia and examines rs2241044 polymorphisms in scientific literature thus far.

Keywords: Fanconi Anemia; Interleukin-17; Receptors, Interleukin-17.

Introduction

Fanconi anemia (FA) is a rare autosomal recessive disease that is usually characterized by progressive bone marrow failure, congenital abnormalities, and a striking predisposition to the development of hematological malignancies and solid tumors.[1] Androgens can be used to treat the bone marrow failure, but hematopoietic stem cell transplantation (HSCT) is the only curative treatment for the hematological complications related to this disease.[2] Although results after HSCT have improved dramatically over the past decade, HSCT is associated with an increased risk of developing solid tumors in patients with FA.[1,3] The risks of developing head and neck cancer, for

example, are estimated to be 500–700 times likelier in patients with FA undergoing HSCT versus patients in the general population.[2,4] Furthermore, oral squamous cell carcinoma (OSCC) is the most common type of cancer that develops in FA patients.[5] The mechanisms underlying the development of cancer in this population have not been fully investigated nor reported in the literature.[6]

Neutrophil recruitment is one of the main functions associated with interleukin IL-17. To induce neutrophil recruitment, innate cells producing IL-17 are strategically positioned to quickly recruit neutrophils and thus detect lesions in and infections of the mucosa[7,8]. This initial production of IL-17 is necessary for neutrophil recruitment and resistance to infections. Innate IL-17-producing cells not only interact with pathogens during infection, but are also critical in physiological conditions that contain microbial flora and maintain mucosal homeostasis.[7,8]

In the tumor microenvironment, the inflammatory response involves the recruitment and activation of neutrophils to sites through the release of chemokines and cytokines, including that of IL-17.[9] Silva et al.[9] observed increases in gene and protein expression of IL-17 in patients with oral cancer, and this may be because IL-17 is involved in the initial activation of the immune system and improvement of inflammation induced by cancer. A previous study reported that the increased release of IL-17 by immunocytes that infiltrate tumors can promote the progression of the neoplastic processes observed in OSCC.[10]

From what is known, no previous studies associating gene polymorphisms of *IL17A* and *IL17RA* in a large sample of patients with FA exist. The authors hypothesize that single nucleotide polymorphisms (SNPs) in the *IL17A* and *IL17RA* genes are associated with the development of Fanconi anemia.

Methodology

Sample and data collection

The study was approved by the Human Research Ethics Committee of the Complexo Hospital de Clínicas da Universidade Federal do Paraná (Nº 2469.076/2011-04). Subjects were divided into two groups: the case group was composed of 98 individuals with FA who participated in the IV Brazilian FA Meeting (Curitiba, Brazil). The control group was composed of 30 healthy individuals from the southern region of Brazil who visited the Dental Clinic of the Pontifícia Universidade Católica do Paraná (PUCPR) for routine consultation. Subjects completed personal, medical, and dental history questionnaires, and (within a protocol approved by an Institutional Review Board) signed a consent form after being advised of the nature of the study (Human Research Ethics Committee of PUCPR; Nº 25141813.4.0000.0020).

The inclusion criteria for the case group included individuals who were previously diagnosed with FA in their referral services (assessed by salivary samples). No exclusion criteria were listed for this group. Inclusion criteria for the control group included individuals being over 18 years of age. The exclusion criteria included individuals with any systemic or dental comorbidity (such as periodontitis or odontogenic infections), or having some form of kinship with individuals who have or have had FA.

All participants, or guardians, signed an informed consent form, and answered a questionnaire regarding sociodemographic information and medical history. In the case group, clinical variables (such as HSCT, graft versus host disease [GVHD], and leukoplakia statuses) were also collected.

For each subject, unstimulated saliva was collected in a sterile Falcon tube for 5 minutes, and 500 μL aliquots were frozen at -80º C and stored until analysis.

DNA extraction

DNA was collected from salivary samples obtained from patients. The obtained buccal epithelial cells were subjected to centrifugation, at 2600 g for 10 minutes, to be sedimented. This process resulted in a supernatant (which was discarded) and a cell pellet, where the pellet was resuspended in a 1300 μL extraction buffer (10 mM Tris-HCl [pH 7.8], 5 mM EDTA, 0.5% SDS). Ten microliters of proteinase K (20 mg/mL) were added to the solution, remaining overnight at 65º C. DNA purification was performed by adding 10 M ammonium acetate, precipitated with isopropanol, and resuspended with 50 μL of 10 mM Tris (pH 7.6) and 1 mM EDTA.[11] The obtained DNA was stored at -20º C.

Genotyping

The tag SNP markers of the *IL17A* and *IL17RA* genes were selected according to functional relevance criteria reported in qualified articles. In this search, aspects such as the quality and impact of the journals were considered. Grouping articles, in which a similarity in the specific pathology addressed in the article in question was observed, was also performed. After this initial selection, we tried to confirm the relevance of these tag SNPs in the SNPinfo[12] NIH web page. Two tag SNPs (rs3819025 and rs2275913) for the *IL17A* gene and six tag SNPs (rs2241044, rs9606615, rs2241049, rs917864, rs879577, and rs2241043) for the *IL17RA* gene were selected. The polymorphisms were genotyped by the technique of real-time PCR (Applied Biosystems 7500 Real-Time PCR System–Waltham, Massachusetts).

Statistical analysis

Nominal variables were expressed as number and frequency, and were analyzed by Pearson's chi-square or Fisher's exact tests. Continuous variables were expressed as mean ± standard deviation, and were analyzed by Mann-Whitney U tests. Values of $p < 0.05$ were considered significant. Bonferroni correction was done for multiple comparison testing, and p-values < 0.002 were considered significant for genotype associations. For the multivariate analysis, a binary logistic regression model was used, and only variables with a p-value of < 0.20 were included at the beginning of the composition of the first model; thereafter, variables with a p-value > 0.05 were excluded for the composition of the final model. Haploview 4.2 (MIT—Harvard broad institute) software was used to estimate the Hardy–Weinberg equilibrium, estipulate the associated or reference allele for each tag SNP. SPSS (IBM - Armonk, New York) version 20.0 was used for all statistical analyses.

Results

Clinical and sociodemographic variables

Both the case and control groups were composed mainly of females. The mean ages of individuals in the control and case groups were 43.8 ± 13.9 and 20.2 ± 7.8, respectively. Other clinical characteristics of individuals in the case group are shown in Table 1.

Genetic analysis

Polymorphisms for models of genotypic transmission (additive, dominant, and recessive) were evaluated for the control and case groups. Furthermore, the allele frequencies in the control group were found to be in Hardy-Weinberg equilibrium.

Polymorphisms in the *IL17A* (rs3819025) and *IL17RA* (rs2241044, rs9606615, rs2241049, rs917864, rs879577, and rs2241043) genes showed a statistically significant difference when analyzed between the control and case groups for additive, dominant, and recessive models (Tables 2 and 3). After Bonferroni correction was performed, only five SNPs in the *IL17RA* gene (rs9606615, rs2241049, rs917864, rs879577, and rs2241043) maintained significance ($p < 0.002$).

The adjusted final model for logistic regression, which compared individuals with or without FA, showed that FA was associated with four polymorphisms (rs2241044 [p = 0.011], rs9606615 [p < 0.001], rs879577 [p = 0.001], rs2241043 [p < 0.001]).

We also performed a nested analysis of gene markers with clinical variables in the case group. Polymorphisms in the *IL17A* gene showed an association of FA regarding an age of less than

Table 1. Sociodemographic and clinical characteristics of the study population.

Variables	Control group (n = 30)	Case group (n = 98)	p-value
Age*	44.0 (24.0-62.0)	20 (7.0-39.0)	< 0,001[a]
Sex**			
Male	12 (40.0)	44 (45.4)	0.605[b]
Female	18 (60.0)	53 (54.6)	
HSCT***	-	79 (82.3)	-
Leukoplakia***	-	31 (34.4)	-
GVHD***	-	30 (41.1)	-

HSCT: hematopoietic stem cell transplantation; GVHD: graft versus host disease.
**Median (minimum and maximum); ***Absolute number (percentage); [a]Mann-Whitney U; [b]Pearson's chi-square test.

Table 2. Genotypic analysis in the additive model of the tag SNPs in the *IL17* and *IL17RA* genes.

dbSNP*	Groups	Genotypes n (%)			p-value**
IL17A					
		GG	AG	AA	
rs3819025	Control	1 (2.2)	28 (34.6)	1 (50.0)	0.009
	Case	44 (97.8)	53 (65.4)	1 (50.0)	
		GG	AG	AA	
rs2275913	Control	9 (15.5)	19 (32.2)	1 (14.3)	0.166
	Case	49 (84.5)	40 (67.8)	6 (85.7)	
IL17RA					
		AA	AC	CC	
rs2241044	Control	3 (13.0)	26 (35.1)	1 (3.3)	0.238
	Case	20 (87.0)	48 (64.9)	29 (96.7)	
		CC	CT	TT	
rs9606615	Control	18 (69.2)	8 (25.8)	4 (6.6)	< 0.001
	Case	8 (30.8)	23 (74.2)	57 (93.4)	
		AA	AG	GG	
rs2241049	Control	6 (27.3)	21 (51.2)	3 (4.6)	< 0.001
	Case	16 (72.7)	20 (48.8)	62 (95.4)	
		CC	CT	TT	
rs917864	Control	21 (35.0)	9 (28.1)	0 (0.0)	0.001
	Case	39 (65.0)	23 (71.9)	33 (100.0)	
		CC	CT	TT	
rs879577	Control	21 (43.8)	4 (8.7)	3 (10)	< 0.001
	Case	27 (56.3)	42 (91.3)	27 (90)	
		CC	CT	TT	
rs2241043	Control	1 (2.1)	22 (32.4)	6 (54.5)	< 0.001
	Case	47 (97.9)	46 (67.6)	5 (45.5)	

*Identification of NCBI-based polymorphisms; **Fisher's exact test.

20 years, the rs3819025 (A allele) SNP (p = 0.026; RP 0.65), and the female sex (rs2275913 [G allele; p = 0.043; RP 0.88]). The *IL17RA* gene was also associated with age and the presence of leukoplakia. An age of less than 20 years was associated with the rs917864 (T allele) SNP (p = 0.036; RP 0.67). The presence of leukoplakia was associated with the rs17606615 (T allele) SNP (p = 0.042; RP 0.47). Other variables (such as HSCT, GVHD, and subject relation) were not associated with gene markers of *IL17A* and *IL17RA*.

Discussion

The aim of this study was to investigate whether polymorphisms in the IL-17 (*IL17A* and *IL17RA*) genes, where IL-17 protein expression is linked to important physiological functions, could be associated with FA. In our results, we found that some polymorphisms were risk factors for the development of FA.

The loss of function of the FA/BRCA pathway in FA affects DNA repair mechanisms. Abnormally

Table 3. Genotypic analysis for the dominant and recessive models of the *IL17A* and *IL17RA* genes.

dbSNP*	Models/groups	Genotypes		p-value	OR (95%CI)
IL17A					
rs3819025	Dominant A	GG	GA/AA	< 0.001**	0.04 (0.06–0.32)
	Control	1 (2.2)	29 (34.9)		
	Case	44 (97.8)	54 (65.1)		
	Recessive A	AA	GA/GG	0.371**	3.34 (0.20–55.15)
	Control	1 (50.0)	29 (23.0)		
	Case	1 (50.0)	97 (77.0)		
rs2275913	Dominant A	GG	GA/AA	0.052***	0.42 (0.17–1.02)
	Control	9 (15.5)	20 (30.3)		
	Case	49 (84.5)	46 (69.7)		
	Recessive A	AA	GA/GG	0.558**	0.53 (0.06–4.59)
	Control	1 (14.3)	28 (23.9)		
	Case	6 (85.7)	89 (76.1)		
IL17RA					
rs2241044	Dominant C§	AA	AC/CC	0.187**	0.42 (0.11–1.55)
	Control	3 (13.0)	27 (26.0)		
	Case	20 (87.0)	77 (74.0)		
	Recessive C	CC	AC/AA	0.003**	0.08 (0.01–0.62)
	Control	1 (3.3)	29 (29.9)		
	Case	29 (96.7)	68 (70.1)		
rs9606615	Dominant T	CC	CT/TT	< 0.001***	15.00 (5.35–42.03)
	Control	18 (69.2)	12 (13.0)		
	Case	8 (30.8)	80 (87.0)		
	Recessive T	TT	CT/CC	< 0.001**	0.08 (0.02–0.26)
	Control	4 (6.6)	26 (45.6)		
	Case	57 (93.4)	31 (54.4)		
rs2241049	Dominant G	AA	GA/GG	0.641***	1.28 (0.45–3.63)
	Control	6 (27.3)	24 (22.6)		
	Case	16 (72.7)	82 (77.4)		
	Recessive G	GG	GA/AA	< 0.001**	3.35 (1.33–8.08)
	Control	3 (4.6)	27 (42.9)		
	Case	62 (95.4)	36- (57.1)		
rs917864	Dominant T	CC	CT/TT	0.006*	0.93 (0.55–1.58)
	Control	21 (35.0)	9 (13.8)		
	Case	39 (65.0)	56 (86.2)		
	Recessive T	TT	CT/CC	< 0.001**	1.48 (1.28–1.71)
	Control	0 (0.0)	30 (32.6)		
	Case	33 (100.0)	62 (67.4)		
rs879577	Dominant C§	CC	CT/TT	< 0.001***	7.66 (2.92–20.10)
	Control	21 (43.8)	7 (9.2)		
	Case	27 (56.3)	69 (90.8)		
	Recessive C	TT	CT/CC	0.058**	0.30 (0.685–1.10)
	Control	3 (10.0)	25 (26.6)		
	Case	27 (90.0)	69 (73.4)		
rs2241043	Dominant C	TT	CT/CC	< 0.001**	0.03 (0.05–0.29)
	Control	1 (2.1)	28 (35.4)		
	Case	47 (97.9)	51 (64.6)		
	Recessive C	CC	CT/TT	0.00***	4.85 (1.36–17.30)
	Control	6 (54.5)	23 (19.8)		
	Case	5 (45.5)	93 (80.2)		

*Identification of NCBI-based polymorphisms; **Fisher's exact test. ***Pearson's chi-square test;

high levels of several proinflammatory cytokines, such as tumor necrosis factor alpha and interferon gamma, can contribute to disease progression and are associated with increased apoptosis.[13] The effect on cytokine pathways can favor the bone marrow failure that is observed in FA patients. Our results showed that *IL17A* and *IL17RA* gene polymorphisms were associated with FA, in a large sample of FA patients.

The relationship between IL-17 and immune-mediated diseases is already well-reported in the literature.[14-21] Associations with other diseases (such as periodontal disease, cancer, allograft rejection, and GVHD) have also been studied.[10,22-28] IL-17 is present in the tumor bed of most solid tumors and in hematopoietic neoplasms, which is why these studies highlight the IL-17/IL-17R axis as being a potentially new immunotherapeutic target.[27]

The study by Silva et al.[9] demonstrated that IL-17 immunolocation in OSCC samples was positive in the cytoplasm of neoplastic cells, where some samples showed high IL-17 counts in comparison to healthy individuals. Similar to the IL-17 expression observed in the tumor stroma, an extensive percentage of IL-17 immunostaining was observed in the cytoplasm of OSCC neoplastic cells. The results by Silva et al.[9] still showed an expression of IL-17, and IL-17 mRNA expression was significantly higher in patients with OSCC versus healthy controls. Other authors[26] have also demonstrated that the spatial distribution of IL-17+ cells suggests specific interactions between various types of cells that express IL-17 and other cells in the tumor microenvironment, implying that IL-17+ cells likely play a role in oral carcinogenesis. In other studies,[10,28] some researcher demonstrated that IL-17 levels were higher in the blood serum of patients with OSCC versus healthy controls, where this difference was associated with advanced stages of tumor invasion.[28]

OSCC is the most common tumor in patients with FA. Failure in DNA repair mechanisms is the most likely reason for the development of cancer in these patients, where the risk of OSCC development increases after HSCT.[1,29] Our results demonstrate that some polymorphisms in the *IL17A* and *IL17RA* genes have alleles that are risk factors for the development of FA. In nested analyses, we also found that leukoplakia was associated with FA (rs9606615 [T allele]). Leukoplakia is a potentially malignant oral disorder. Leukoplakia was observed in 12% of patients with FA in a cohort of 138 patients, with a higher prevalence at a mean age of 16 years.[30] Future longitudinal studies should evaluate the results of these polymorphisms and their associations with important clinical characteristics (bone marrow failure, HSCT, clinical presentation of potentially malignant lesions [such as leukoplakia], and OSCC). Such studies will help contribute to the understanding of aspects involved in the pathophysiology of FA – particularly, the process of carcinogenesis and the tropism of oral carcinogenesis.

In the nested analysis, we also observed an association between the rs2275913 (G allele) and rs917864 (T allele) SNPs with an age of less than 20 years (this association was also observed in the control group; Table 3). Female sex was also associated with the rs2275913 (G allele) SNP (where this association was not observed in the control group). In their review of 121 cases of OSCC in FA, Furquim et al.[6] observed a prevalence higher than 75% in patients with OSCC who were younger than 25 years of age, but these results were not statistically different to the prevalence of OSCC and sex. Conversely, female patients tended to develop more second primary tumors than did male patients.

After Bonferroni correction, only five SNPs (rs9606615, rs2241049, rs917864, rs879577, and rs2241043) in the *IL17RA* gene maintained significance levels, and the adjusted final model for logistic regression showed association to four polymorphisms (rs9606615 [$p < 0.001$], rs879577 [$p = 0.001$], rs2241043 [$p < 0.001$], and rs2241044 [$p = 0.011$]).

The 1000Genome database was used to search the minimum allele frequency (MAF) for significant tag SNPs. The C allele in the rs9606615 SNP was 34.5% lower than our results (57%) for the same SNP. For the rs9606615 SNP, the T allele (89.5%) displayed a higher frequency. Other studies found that this polymorphism was significantly associated with asthma,[15] psoriatic arthritis,[20] autoimmune thyroid disease,[18] and carotid intima-media thickness.[19]

For the rs879577 SNP, we found a higher frequency of the C allele (67.6%) in the FA group.

In the 1000Gnenome database, this missense variant, presenting 27.1% for T allele MAF. The same gene polymorphism was found in other studies assessing alopecia,[16] psoriasis,[21] Crohn's disease,[17] and papillary thyroid câncer.[25]

The rs2241043 SNP showed a higher frequency in the C allele (85.3%) in the FA group, but in the 1000Genome database, the MAFs for the C and T alleles were 53.7% and 46.3%, respectively. In other studies that focused on psoriatic arthritis[20] and carotid intima-media thickness,[19] significant results for this polymorphism were not found. However, Park et al.[15] demonstrated that rs2241043 gene polymorphisms decrease the risk of aspirin-exacerbated respiratory diseases.

The MAF for the C allele was 42.3% in the rs2241044 SNP. This marker, together with the prior SNP, appeared in multivariate analyses. For the rs2241044 SNP, we found a higher frequency (79.1%) of the C allele in individuals with FA. Medrano et al.[14] included the rs2241044 SNP in their study on celiac disease, although this SNP was not analyzed in their sample. Thus, no other study analyzing this gene polymorphism has been conducted.

In their study on *IL17A* gene polymorphisms in GVHD, Karimi et al.[24] found a higher frequency of the GG genotype (rs2275913) in patients who developed GVHD after unrelated HSCT versus patients who did not present with GVHD. In addition, after multivariate analysis, the researchers found a higher frequency in men with GVHD when compared to men without GVHD. AA genotype (rs2275913) results were associated with a higher chance for the development of severe versus mild grades of GVHD. We did not find rs2275913 as being a risk factor for FA. In the increased frequency of the G allele (rs3819025), after adjustment by multivariate analysis, they found a higher frequency of GVHD in mild degrees. Thus, they suggest *IL17A* as a marker for predicting GVHD after unrelated allografts. In our results, patients with FA presented with a higher frequency of the rs3819025 (G allele) SNP when compared with control patients. In addition, 82.3% of individuals with FA underwent HSCT and 41.1% manifested GVHD (Table 1), but in the nested analysis, we did not observe an association of FA with HSCT or GVHD.

In two studies, Espinoza et al.[22,23] found a higher frequency of the AA genotype (rs2275913) associated with severe grades of GVHD. Our results did not demonstrate rs2275913 as a risk factor for the development of FA. In another association, the researchers claim that the donor's *IL17A* genotype does not influence the results of HSCT. Though individuals in our sample underwent HSCT (82.3%) and manifested GVHD (41.1%), a bias in comparison with these studies exists, since they do not report whether the underlying disease (with indication for HSCT) was a consequence of FA. In the nested analyses, we also did not observe an association with donor relation, HSCT, or GVHD.

Our results present new observations regarding FA that have never been previously described. We found that *IL17A* and *IL17RA* gene polymorphisms contribute significantly as risk factors for the development FA. We also demonstrated an association of FA with a potentially malignant oral disorder, leukoplakia, bringing a new perspective to studies that search for answers to the understanding of OSCC carcinogenesis in FA patients. Clearly, these results should be confirmed with more extensive studies and associated with clinical variables (such as the phenotypic characteristics of individuals, specificities of treatment, variables related to HSCT [mainly GVHD], and potentially malignant oral disorder).

Conclusion

To conclude, *IL17A* and *IL17RA* gene polymorphisms, including the SNPs rs2241044 (C allele), rs879577 (C allele), rs9606615 (T allele), and rs2241043 (C allele), were associated with the development of FA. When comparing individuals with or without FA, an association between age (rs3819025 [A allele]; rs917864 [T allele]), sex (rs2275913 [G allele]) and leukoplakia (rs17606615 [T allele]) were also associated with the development of FA, as observed via nested analyses.

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