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PADI4 (rs2240340), PDCD1 (rs10204525), and CTLA4 (231775) gene polymorphisms and polyarticular juvenile idiopathic arthritis

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ABSTRACT

Background: Certain single nucleotide polymorphisms (SNPs) in genes such as *PADI4* (coding for peptidyl arginine deiminase 4), *PDCD1* (coding for programmed cell death 1), and *CTLA4* (coding for cytotoxic T-lymphocyte-associated protein 4) are linked to rheumatoid arthritis (RA). However, links between SNPs rs2240340, rs10204525 and rs231775 in *PADI4, PDCD1* and *CTLA4* respectively, and juvenile idiopathic arthritis (JIA), the commonest type of childhood arthritis, are unclear. We aimed to determine whether any of these SNPs are associated with JIA, and to clinical indices disease activity score (JADAS 71) and functional disability score (CHAQ).
Methods: We genotyped the three SNPs in 150 children with polyarticular JIA and 160 healthy children, recording standard health questionnaires, clinical features and laboratory markers.
Results: The TT genotype of *PADI4* rs2240340 (aOR/95%CI 2.64: 1.31–5.30, P = 0.006) and CT genotype of *PDCD1* rs10204525 (aOR/95%CI 4.99: 2.98–8.36, P < 0.0001) were associated with JIA. The AG+GG genotype of *CTLA4* rs231175 was modestly linked to disease activity (aOR/95% CI 2.44 (1.19–5.04), p = 0.015). *PADI4* rs2240340 was linked to CHAQ score (genotypes p = 0.013, alleles p = 0.006), whilst *PDCD1* rs10204525 was linked to anti-CCP antibodies (genotypes p = 0.004), RF (genotypes p = 0.01), and the CHAQ score (genotypes p = 0.005, alleles p = 0.013).
Conclusions: There are various roles for these SNPs in *PADI4, CTLA4* and *PDCD1* in the diagnosis and, potentially, in the management of JIA.

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Introduction

Juvenile idiopathic arthritis (JIA) is the most common cause of chronic arthritis in children [1]. Global incidence and prevalence rate of JIA are unavailable. In Egyptian children, the prevalence of JIA is 3.4/100,000 children [2], consistent with the prevalence in Taiwan at 3.8/100,000 [3], but lower than in the USA (incidence 10.3/100,000, prevalence 57.6/100,000) [4], Nordic countries (incidence 15.0/100,000) [5], and in the Republic of Bashkortostan (Russia) (prevalence 83.9, incidence 17.2/100,000 children) [6]. These differences may be due to environmental and (more likely) genetic factors [7,8].

PADI4 encodes type IV peptidylarginine deiminase (PADI), one of five known isoforms, which catalyzes the post-translationally change of arginine within peptides to citrulline. Anti-cyclic citrullinated peptide antibodies (anti-CCP) are formed against citrullinated polypeptides [9]. Previous studies reported that anti-CCP is specific to rheumatoid arthritis (RA) and are obvious in the early stages of the disease proposing that citrullination by *PADI4* should be closely related to RA onset or might trigger the disease by itself [9]. Single nucleotide polymorphism (SNP) rs2240340 in *PADI4* is associated with RA [10,11]. *PDCD1*, coding for programmed cell death molecule (PD-1), has links with many autoimmune diseases, including RA and JIA [12–14]. PD-1, which is expressed on T-cells, B-cells, and activated monocytes, plays an essential role in cell-mediated immunity [12]. Triggering of receptors on T cells, B cells, endothelial, and epithelial cells results in release of the two ligands PD-L1 and PD-L2. These ligands cause inhibition of the immune response by binding to the PD-1 and consequently preventing the differentiation of self-antigen specific inflammatory T-cells [12]. The rs10204525 SNP of *PDCD1* is functional, and may alter the expression of PD-1 [15,16] that could contribute to autoimmune diseases. *CTLA4*, codes for Cytotoxic T-Lymphocyte Antigen 4, an inhibitory receptor expressed on the activated and regulatory T lymphocytes. It acts to regulate T-cell activation [17]. The A49G (rs231775) SNP is also functional [18], and has been linked with several autoimmune diseases, including JIA [19,20].

We hypothesised a link between the SNPs in *PADI4* (rs2240340), *PDCD1* (rs10204525) and *CTLA4* (rs231775), and the presence of JIA, its activity, and laboratory and clinical features.

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Patients and methods

We tested our hypothesis in a case-control study of 150 children with polyarticular JIA (arthritis affecting ≥5 joints during the first 6 months of disease) patients, all diagnosed according to International League of Associations for Rheumatology (ILAR) classification criteria [1]. All patients were recruited from the outpatient clinics of Physical Medicine and Rheumatology Departments as well as the Paediatrics Department of El Fayoum University Hospital over a period from January 2019 to June 2019. A medical history, general clinical examination and musculoskeletal examination (each individual joint examined bilaterally) were undertaken in each child. Exclusion criteria were age >16 years, infectious disease in the past three months, or use of steroids or other immunosuppressive treatment within the past six months, comorbidity or disability disease-related arthritis including concurrent autoimmune disease, malignancy, rheumatic fever, other types of JIA or spondyloarthropathy. Controls were 160 apparently healthy children not complaining of any concurrent diseases. The present study was approved by The Faculty of Medicine Fayoum University Ethics Committee (No. R98-892019-64). All procedures involving human biological material were per the ethical standards of Helsinki. Written informed consent was obtained from parents of children before entering the study.

Assessment of disease activity was by Juvenile Arthritis Disease Activity Score (JADAS 71), which takes a combination of different activity markers to give an accurate assessment, and this approach allows a better uniformity among physicians in evaluating the disease activity [21,22]. Components of JADAS 71 include (a) an active joint count (AJC) (the number of joints with swelling or with limitation of movement with either pain upon movement or tenderness, it is contained complete joint count and ranging from 0 to 71 [21]); (b) patient/parent global assessment of overall well-being (PT-VAS), and physician global assessment of overall disease activity (MD-VAS)(MD-VAS and PT-VAS were measured on a 10 cm visual analogue scale where 0 = best and 10 = worst); and (c) ESR (ESR value was normalized to a 0–10 scale according to specific formula) [22]. By the combination of AJC, PT-VAS, MD-VAS, and ESR score, the total score of JADAS 71 was calculated. It ranges from 1 to 101, and patients were classified into inactive disease (JADAS 71 ≤ 1) and active disease (JADAS 71 > 1) [21]. Parents rated their child's or children rated their own disease functional status disabilities using the Childhood Health Assessment Questionnaire (CHAQ). With a summed score ranging from 0 to 24, CHAQ divides patients into four categories (without any difficulty, with some difficulty, with much difficulty and unable to do) [23]. Venous blood samples were collected for (a) ESR, (b) after centrifugation at 4°C, for serum for ELISA for Rheumatoid factor (RF) and anti-Cyclic-Citrullinated Peptide (anti-CCP), and (c) in tubes containing EDTA for DNA extraction.

DNA was extracted by DNA extraction kit (QIAamp® Whole Blood Genomic DNA Purification Mini Kit (50) Venlo, Netherlands, German) according to the manufacturer's procedure. Quantitation of DNA was done utilizing the NanoDrop1-1000 spectrophotometer (NanoDrop innovations, Inc., Wilmington, USA). Genotyping of the three single-nucleotide polymorphisms (SNPs) using predesigned primer/probe sets for *PADI4* rs2240340 (C/T) [C__16176717_10], *PDCD1* rs10204525 (C/T) [C____172862_20] and *CTLA4* rs231775 (A/G) [C___2415786_20] (supplied by Thermo Fisher Scientific, Inc. Waltham, Massachusetts, USA) was performed by the real-time polymerase chain reaction with TaqMan allelic discrimination assay (Applied Biosystems, USA). DNA amplification was performed in a 25 µl volume containing 12.5 µl TaqMan genotyping master mix, 1.25 µl primer/probe, 1to 20 µl of purified genomic DNA, and 11.25 µl H2O. Thermal cycling conditions of PCR included denaturation at 95 C for 10 min, PCR reaction was carried out for 45 cycles at 92°C for 15 sec then annealing and extension at 60°C for 90 sec. Real-time PCR was performed using Applied Biosystems™ Real-Time PCR system.

The sample size was calculated using G power version 3, which required a minimal sample size of 133 in each group needed to get power level 0.90, alpha level 0.05 and 15% as an expected difference in the proportion of subjects with TT in *PADI4* SNP rs2240340 (C/T) between cases and controls (25% vs.10%). For increased assurance, the sample size was increased by 10% to reach 150 in the two groups.

Deviation from Hardy-Weinberg equilibrium (HWE) was tested for each polymorphism using a Chi-square test. The collected data were organized, tabulated and statistically analysed using SPSS software statistical computer package version 22 (SPSS Inc, USA). For quantitative data, age was presented as mean and standard deviation (SD), Independent t test was used as a test of significance. Other numeric data were presented as median and inter-quartile range (IQR); Mann-Whitney U test and Kruskal-Wallis test were used in comparing between any two or three groups, respectively. Qualitative data were presented as number and percentages, chi square (χ^2) was used as a test of significance. Adjusted Odds ratios (ORs) for age and sex with 95% confidence intervals (CI) for the association of the study groups with genotype and allele frequencies of the different polymorphisms were calculated using multivariate logistic regression analysis. Adjusted Odds ratios (ORs) for age and sex with 95% confidence intervals (CI) of genotypes and alleles of different polymorphisms associated with disease activity in cases group were estimated. Significance was adopted at $P \leq 0.05$.

Results

The 150 JIA patients (95 girls and 55 boys) had a mean age [SD] of 10.5 [3.5]. The 160 healthy children were aged (10.1 [3] years; P = 0.223) and included (96 girls and 64 boys, P = 0.546). The median [IQR] value of ESR was significantly increased in JIA 27.5 [13–60] mm/hour versus controls 8 [7–9.5], the median [IQR] of anti-CCP 17 [11–68] and RF 32 [16–55] were significantly increased in JIA compared to controls 12 [8.5–17] for anti-CCP and 11 [7–17.5] for RF (P < 0.0001 for each). Patient data according to laboratory investigations, disease activity markers and disability score are shown in (Table 1).

The prevalence of three examined SNPs genotypes (*PADI4* rs2240340, *PDCD1* rs10204525, *CTLA4* rs231775) and alleles in JIA patients, and healthy controls are summarized in (Table 2). The frequencies of *PADI4* rs2240340, *PDCD1* rs10204525 and *CTLA4* rs231775 genotypes were in agreement with Hardy–Weinberg equilibrium (HWE) in controls (P > 0.05).

In *PADI4* rs2240340, the TT genotype and T allele were significantly linked with JIA. In *PDCD1* rs10204525, the heterozygous CT genotype, (CT+TT) in a dominant model and T allele were more frequent in the JIA than the controls. However, there were no differences in the frequency distribution of the *CTLA4* rs231775 polymorphism in JIA patients compared to controls. Only *CTLA4* SNP rs231775 was significantly linked with active versus inactive JIA (Table 3).

Links between the SNPs and CHAQ and laboratory features are shown in Table 4. *PADI4* SNP rs2240340 was linked with CHAQ score, but not with anti-CCP or RF levels. Genotypes (but not alleles) of *PDCD1* SNP rs10204525 were linked to anti-CCP and RF levels, but both genotypes and alleles were linked to CHAQ score. *CTLA4* SNP rs231775 was linked very slightly with anti-CCP levels.

Table 1. Laboratory and clinical data in JIA patients.

Parameter	JIA (n = 150)
Anti-cyclic citrullinated peptide (anti-CCP) (IU/ml)	
Positive (≥ 20 IU/ml) n (%)	60 (40.0%)
Negative (< 20 IU/ml) n (%)	90 (60.0%)
Rheumatoid factor (RF) (IU/ml)	
Positive (≥ 20 IU/ml) n (%)	80 (53.3%)
Negative (< 20 IU/ml) n (%)	70 (46.7%)
Active Joint Count (AJC)	
Inactive (no joints with active arthritis) n (%)	40 (26.7%)
Low (≤ 4 active joints) n (%)	35 (23.3%)
Moderate (5–7 active joints) n (%)	20 (13.3%)
Severe (≥ 8 active joints) n (%)	55 (36.7%)
Patient/parent global assessment of overall well-being (PT-VAS)	
Low < 2 of 10, n (%)	20 (13.3%)
Moderate 2–4 of 10, n (%)	55 (36.7%)
Severe ≥ 5 of 10, n (%)	75 (50.0%)
Physician global assessment of overall disease activity (MD-VAS)	
Low < 4 of 10, n (%)	75 (50.0%)
Moderate 4–6 of 10, n (%)	50 (33.3%)
Severe ≥ 7 of 10, n (%)	25 (16.7%)
Juvenile Arthritis Disease Activity Score (JADAS 71) (0–101 score)	
Inactive ≤1, n (%)	75 (50.0%)
Active >1, n (%)	75 (50.0%)
Childhood Health Assessment Questionnaire (CHAQ)	
Without any difficulty, n (%)	25 (16.7%)
With some difficulty, n (%)	65 (43.3%)
With much difficulty, n (%)	55 (36.7%)
Unable to do, n (%)	5 (3.3%)

Table 2. Association between target SNPs and JIA.

Genotypes and Alleles	JIA cases n (%)	Controls n (%)	Adjusted OR (95% CI), P-value
PADI4 rs2240340 C/T			
CC	65 (43.3%)	88 (55.0%)	1
CT	50 (33.3%)	56 (35.0%)	0.10 (0.58–1.72), 0.985
TT	35 (23.3%)	16 (10.0%)	2.64 (1.31–5.30), 0.006
Dominant			
CC	65 (43.3%)	88 (55.0%)	1
CT+TT	85 (56.7%)	72 (45.0%)	1.38 (0.85–2.25), 0.198
Recessive			
CC+CT	115 (76.7%)	144 (90.0%)	1
TT	35 (23.3%)	16 (10.0%)	2.64 (1.37–5.09), 0.002
Allele			
C	180 (60.0%)	232 (72.5%)	1
T	120 (40.0%)	16 (27.5%)	1.60 (1.12–2.27), 0.009
PDCD1 rs10204525 C/T			
CC	55 (36.7%)	112 (70.0%)	1
CT	90 (60.0%)	40 (25.0%)	4.99 (2.98–8.36), <0.0001
TT	5 (3.3%)	8 (5.0%)	1.63 (0.50–5.30), 0.415
Dominant			
CC	55 (36.7%)	112 (70.0%)	1
CT+TT	95 (63.3%)	48 (30.0%)	4.45 (2.71–7.31), <0.0001
Recessive			
CC+CT	145 (96.7%)	152 (95.0%)	1
TT	5 (3.3%)	8 (5.0%)	0.79 (0.25–2.50), 0.693
Allele			
C	200 (66.7%)	264 (82.5%)	1
T	100 (33.3%)	56 (17.5%)	2.55 (1.73–3.76), <0.0001
CTLA4.I rs231775 A/G			
AA	56 (37.3%)	77 (48.1%)	1
AG	88 (58.7%)	75 (46.9%)	1.39 (0.86–2.25), 0.175
GG	6 (4.0%)	8 (5.0%)	0.68 (0.22–2.14), 0.512
Dominant			
AA	56 (37.3%)	77 (48.1%)	1
AG+GG	94 (62.7%)	83 (51.9%)	1.33 (0.83–2.12), 0.242
Recessive			
AA+AG	144 (96.0%)	152 (95.0%)	1
GG	6 (4.0%)	8 (5.0%)	0.55 (0.18–1.68), 0.296
Allele			
A	200 (66.7%)	229 (71.6%)	1
G	100 (33.3%)	91 (28.4%)	1.10 (0.77–1.57), 0.591

Discussion

We present data on SNPs in three genes, and their relationship with JIA. Firstly, *PADI4* rs2240340 was markedly different in JIA compared to age and sex matched healthy controls, and was linked to CHAQ score but not to disease activity or laboratory markers. Hisa et al from Japan reported rs2240340 of *PADI4* in different variants of JIA, but no significant links were detected compared to adults with RA [24]. However, its association with RA has been reported in several populations [10,11,25–28]. Two studies reported that rs2240340 was tightly linked to other functional SNPs in exons of *PADI4*, such as synonymous (rs1748033) SNP [11] and non-synonymous (rs874881) SNP [26]. In addition, RA susceptible haplotype of four exonic *PADI4* SNPs, flanked by 13 non-exonic disease-associated SNPs including rs2240340 result in significantly

Table 3. Association between target SNPs and activity of JIA.

Genotypes and Alleles	Active JIA n (%)	Inactive JIA n (%)	Adjusted OR (95% CI), P-value
PADI4 rs2240340 C/T			
CC	30 (40.0%)	35 (46.7%)	1
CT	25 (33.3%)	25 (33.3%)	1.86 (0.80–4.35), 0.150
TT	20 (26.7%)	15 (20.0%)	1.70 (0.70–4.15), 0.243
Dominant			
CC	30 (40.0%)	35 (46.7%)	1
CT+TT	45 (60.0%)	40 (53.3%)	1.79 (0.86–3.71), 0.119
Recessive			
CC+CT	55 (73.3%)	60 (80.0%)	1
TT	20 (26.7%)	15 (20.0%)	1.30 (0.58–2.90), 0.520
Allele			
C	85 (56.7%)	95 (63.3%)	1
T	65 (43.3%)	55 (36.7%)	1.44 (0.88–2.35), 0.143
PDCD1 rs10204525 C/T			
CC	25 (33.3%)	30 (40.0%)	1
CT	50 (66.7%)	40 (53.3%)	1.60 (0.79–3.28), 0.195
TT	0 (0.0%)	5 (6.7%)	– – -
Dominant			
CC	25 (33.3%)	30 (40.0%)	1
CT+TT	50 (66.7%)	45 (60.0%)	1.32 (0.67–2.65), 0.422
Recessive			
CC+CT	75 (100.0%)	70 (93.3%)	1
TT	0 (0.0%)	5 (6.7%)	– –
Allele			
C	100 (66.7%)	100 (66.7%)	1
T	50 (33.3%)	50 (33.3%)	0.94 (0.57–1.56), 0.820
CTLA4 rs231775 A/G			
AA	21 (28.0%)	35 (46.7%)	1
AG	49 (65.3%)	39 (52.0%)	2.29 (1.11–4.75), 0.026
GG	5 (6.7%)	1 (1.3%)	9.65 (0.97–95.67), 0.053
Dominant			
AA	21 (28.0%)	35 (46.7%)	1
AG+GG	54 (72.0%)	40 (53.3%)	2.44 (1.19–5.04), 0.015
Recessive			
AA+AG	70 (93.3%)	74 (98.7%)	1
GG	5 (6.7%)	1 (1.3%)	5.51 (0.59–51.57), 0.135
Allele			
A	91 (60.7%)	109 (72.7%)	1
G	59 (39.3%)	41(27.3%)	1.79 (1.07–2.99), 0.025

more stable *PADI4* mRNA than that of non-susceptible haplotype, suggesting that variants in intronic or non-coding regions may affect transcriptional regulation, thus leading to the pathogenic implications [27]. Whether this is also the case in JIA is unknown.

Secondly, we found that *PDCD1* SNP rs10204525 is also strongly linked to JIA in genotypic, dominant and allelic models. Although there was no link with disease activity, there were strong links between genotypes and anti-CCP antibodies, RF and CHAQ score. This fails to support the report of Tejeda et al on North Europeans who found no link between this SNP and JIA [29]. PDCD1 rs10204525 is not a risk variant for type 1 diabetes mellitus development in two different studies [30,31]. Pathophysiology suggests a link between *PDCD1* rs10204525 mutant homogenous TT genotype with higher PD-1^{+}T cells than heterogeneous CT or wild homogenous CC genotypes [15,16]. *PDCD1* gene encodes PD-1 protein, PD-1 is an immunosuppressive molecule expressed on T cell [12]. Along with its inhibitory function, the expression of PD-1 on T cells should be decreased in patients with JIA. This suggests that risk TT and, in turn, its associated increased expression of PD-1^{+}T cells appears controversial to its function. However, there is also evidence suggesting that PD-1 expressed on follicular helper T cells (a subset of CD4^{+}T cells) contributes to B-cell activation, and promoting antibody production [32]. Therefore, we speculate that in addition to its function as an inhibitory costimulatory molecule, PD-1 might have other effects in JIA.

Thirdly, regarding rs231775 within *CTLA4*, after adjusting for age and sex, we found no links with JIA, although it was linked weakly to disease activity. There were no links with laboratory markers or CHAQ score. These data are in part agreement with three studies done on Europeans [20,33,34], and *CTLA4* rs231775 variant was reported to be associated with adult RA [19]. *CTLA4* is a protein receptor constitutively expressed on T cells but only upregulated on active T cells resulting in inhibitions of T cell activation and maintenance of immune tolerance [17]. Thus, it appears that defective *CTLA4* expression and/or function are associated with autoimmune diseases. the *CTLA4* rs231775 A/G polymorphism changes threonine to alanine at position 17 in the leader sequence of *CTLA4*, resulting in reduced T cell *CTLA4* expression, thus interfering with its normal function of T cell down regulation [18]. The effect of rs231775 on *CTLA4* expression level and the documented function of *CTLA4* may explain the association between rs231775 and the activity of the disease.

In this study, *PDCD1* rs10202545 was significantly linked with anti-CCP and RF at genotype level but not on the level of alleles. Our finding fails to support a study reporting no significant association between rs10204525 and RF positive JIA [29]. Regarding *CTLA4* rs231775, there was a significant association between rs231775 and anti-CCP negative JIA at both levels (genotypes and alleles). These data supports and extends that of a previous result reporting that rs231775 G allele in linked to for anti-CCP and RF positive RA only when in combination with CT60/G allele [35].

No definite associations between genotypes or alleles and severe disability were found. This result may be due to CHAQ having a good correlation with disease activity during active disease but a poor correlation during inactive disease. Therefore, CHAQ is only useful for assessing functional ability during active disease [36]. Limitations of this study included relatively small sample size, so future research with a larger sample size may be required to confirm the results of this study. Finally, we speculate that the SNPs in *PADI4* and *PDCD1* may be risk factors for JIA, but acknowledge that this can only be determined by long-term follow up of children with these gene variants.

Table 4. Association between target SNPs and CHAQ and laboratory indices.

	Genotypes				Alleles		
Parameter	1/1	1/2	2/2	P-value #	1	2	P-value#
			PADI4 rs2240340 C/T				
Anti-CCP status IU/ml	17 (10–60)	16 (11–74)	19 (14–62)	0.809	17 (10–68)	17.5 (14–65)	0.683
RF status IU/ml	20 (16–52)	37.5 (14–55)	34 (17–60)	0.768	27.5 (16–53.5)	34.5 (17.0–55.5)	0.518
CHAQ score							
Without any difficulty n (%)	5 (7.7)	10 (20)	10 (28.6)	0.013	20 (11.1)	30 (25)	0.006
With some difficulty n (%)	35 (53.8)	15 (30)	15 (42.9)		85 (47.2)	45 (37.5)	
With much difficulty & Unable to do n (%)	25 (38.5)	25 (50)	10 (28.6)		75 (41.7)	45 (37.5)	
			PDCD1 rs10204525 C/T				
Anti-CCP status IU/ml	19 (10–48)	15.5 (11–68)	52 (51–53)	0.004	17 (10.5–68)	16.5 (12.5–65)	0.860
RF status IU/ml	30 (16–52)	27 (16–55)	66 (60–67)	0.01	30 (16–52)	34 (16.5–58)	0.416
CHAQ score							
Without any difficulty n (%)	10 (18.2)	15 (16.7)	0	0.005	35 (17.5)	15 (15)	0.013
With some difficulty n (%)	15 (27.3)	45 (50)	5 (100)		75 (37.5)	55 (55)	
With much difficulty & Unable to do n (%)	30 (54.5)	30 (33.4)	0		90 (45)	30 (30)	
			CTLA4 rs231775 A/G				
Anti-CCP status IU/ml	52 (11–70)	16 (12–60)	12.5 (9–17)	0.045	18 (11–68)	16 (10.0–60)	0.042
RF status IU/ml	34 (14–56)	30 (17–55)	24.5 (16–45)	0.823	34 (16–55.5)	30 (17–53.5)	0.810
CHAQ score							
Without any difficulty n (%)	5 (8.9)	19 (21.6)	1 (16.7)	0.059	29 (14.5)	21 (21.0)	0.064
With some difficulty n (%)	21(37.5)	40 (45.5)	4 (66.7)		82 (41)	48 (48)	
With much difficulty & Unable to do n (%)	30 (53.6)	29 (33)	1 (16.7)		89 (44.5)	31 (31)	

Chi square test. 1/1, wild homozygous genotype. 1/2, heterozygous genotype. 2/2, mutant homozygous genotype. 1, wild allele. 2, mutant allele. Lab data median (IQR).

This study represents an advance in biomedical science because it points to the potential for SNPs rs2240340 in *PADI4*, rs231775 in *CTLA4* and rs10204525 in *PDCD1* in the diagnosis and management of JIA.

Summary

What is known about this topic.

- JIA is a complex disease in which specific genetic loci together account for about 60% of its inheritability.
- *PADI4* rs2240340 is linked to rheumatoid arthritis
- *PDCD1* rs10204525 and *CTLA4* rs123775 have functional consequences.

What this study adds.

- *PADI4* rs2240340 and *PDCD1* rs10204525 are strongly linked to JIA, but not to disease activity
- *CTLA4* rs231775 AG genotype is weakly linked to JIA disease activity.
- *PADI4* rs2240340 is linked to CHAQ score, whilst *PDCD1* rs10204525 is linked to anti-CCP antibodies, RF, and the CHAQ score.

Disclosure Statement

No potential conflict of interest was reported by the authors.

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