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INVESTIGATIVE REPORT

Genotype–Phenotype Correlations in a Prospective Cohort Study of Paediatric Plaque Psoriasis: Lack of Correlation Between HLA-C*06 and Family History of Psoriasis

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This study aims to investigate associations between observed clinical parameters and known genetic risk factors of psoriasis in a well-defined prospective cohort of paediatric patients with plaque psoriasis ($n=151$). Significant associations were found for paediatric-onset psoriasis with *ERAPI* ($p=0.002$), *IL23R* ($p=0.01$), *LCE3C*, *LCE3B*-del ($p=0.00049$) and *HLA-C*06* ($p=3.15 \times 10^{-30}$). Psoriasis severity was associated with the single nucleotide polymorphisms tagging *IFIH1* and *ERAPI* ($p<0.05$). An onset before 10 years of age was associated with *IL12B* ($p=0.02$). Nail psoriasis was more often seen in *HLA-C*06*-negative patients ($p=0.008$). Remarkably, family history is clearly not associated with *HLA-C*06* in this specific group. The large proportion of patients with a positive family history in *HLA-C*06* negative patients (and the lack of correlation between the two) indicates that other genes, either alone or interaction between two or more genes, may have significant effects on heritability. **Key words: genotype-phenotype correlations; paediatric psoriasis; genetic risk factors; clinical parameters.**

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Psoriasis is a clinically heterogeneous skin disease with a complex genetic background (1–3). It affects around 2% of the population and in approximately 30% of these patients the disease first appears during childhood (1, 4). By means of genome-wide association studies, the number of genome regions identified to be associated with psoriasis increased recently to 36 (5). Different pathways evidently play a role in the pathophysiology of psoriasis, as the innate and adaptive immune system, the Th17 pathway and the skin barrier function are genetically linked with psoriasis (2, 3, 6–13). Some studies have investigated correlations between genetic risk factors of psoriasis and clinical parameters, and these were mainly focused on major histocompatibi-

lity (MHC) gene *HLA-C*06* (14–23). In a cohort of adult psoriasis patients a strong association was demonstrated between psoriasis severity and single nucleotide polymorphisms (SNPs) tagging *HLA-C*06* and a deletion of *LCE3B* and *LCE3C* (22, 34). Several studies have shown that early age at onset may be associated with distinct genetic factors, such as *ERAPI* and *HLA-C*06* (14, 17, 23, 24). Previous studies detected an association between *HLA-C*06* and early onset psoriasis (onset <30 or 40 years), and a positive family history of psoriasis and early onset of psoriasis (14, 16, 17, 20), suggesting an association between *HLA-C*06* and family history of psoriasis in patients with early onset psoriasis. This association has however, never been investigated. Data about associations between clinical parameters and genetic risk factors in paediatric psoriasis are lacking. The current study aims to investigate associations between observed clinical parameters and known genetic risk factors of psoriasis in a well-defined cohort of paediatric patients with plaque psoriasis.

MATERIALS AND METHODS

Sample collection

DNA samples were obtained from children with psoriasis referred to the outpatient clinic of the Department of Dermatology of the Radboud University Medical Center. Only patients of European descent with a primary diagnosis of plaque-type psoriasis, before the age of 18 years, were included in this study. Patients with guttate psoriasis were excluded. The phenotype classification is based on phenotype at examination and not at onset of disease. We obtained clinical data from our prospective observational paediatric psoriasis registry in daily clinical practice, called Child-CAPTURE (Continuous Assessment of Psoriasis Treatment Use Registry). In this registry, patient characteristics including age at onset, family history of psoriasis (up to the third-degree relative) and Koebner phenomenon are recorded at the first visit. Psoriasis severity and presence of observed nail psoriasis by the physician are recorded every visit.

The characteristics of the control group of European descent were previously described (24). Only self-reported data were available for all controls, and individuals reported to have psoriasis were excluded from this study. All participants/parents gave written informed consent.

Genotyping

Genotyping was executed as previously described (24). In short, SNP genotyping was performed using Taqman[®] SNP

genotyping assays (assay IDs C_920306_20, C_1272298_10, C_3056837_10, C_34244955_10, and C_29927086, for SNPs rs240993, rs11209026, rs27524, rs17716942, and rs3213094, respectively) according to the manufacturer's recommendations (Applied Biosystems, Nieuwerkerk aan den IJssel, The Netherlands). *LCE3C_LCE3B*-del genotyping was performed using a previous described PCR (2). *HLA-C*06:02* itself (rather than a tagging SNP) was determined by PCR with sequence specific primers for *C*06* (2), which does not allow distinction between homozygotes and heterozygotes. As quality control on the SNP typing 5% of the samples were analysed in duplicate; all genotypes were concordant. The SNPs, *LCE3C_LCE3B*-del and *HLA-C*06:02* were successfully genotyped in the psoriasis and control samples with genotyping success rates between 97.9% and 99.7%, 99.1% and 95.8%, respectively. For SNP genotyping, genotype cluster plots were evaluated prior to analysis to ensure satisfactory assay performance.

Statistical analysis

No deviations from Hardy-Weinberg equilibrium were found in the control groups. Logistic regression analyses were performed in SPSS software 20.0 (SPSS Inc., Chicago, IL, U.S.A.) using co-dominant models. The odds ratio (OR) and 95% confidence interval (CI) were calculated using homozygosity for the non-risk variant (from previous studies) as a reference for the case-control study. Age at onset was analysed comparing 2 groups; before 10 years and at or after 10 years. Clinical severity of psoriasis was assessed by a clinician using 3 different severity scales: Psoriasis Area and Severity Index (PASI; range 0–72), Physician Global Assessment (PGA; range 0–5) and Body Surface Area (BSA; range 0–100) (25). The highest reported psoriasis severity scores for each individual were used. Patients were divided in 2 groups based on psoriasis severity scores; mild-to-moderate and severe psoriasis. Mild-to-moderate psoriasis was defined as those patients that have never reached PASI ≥ 10 , PGA ≥ 3 or BSA ≥ 10 . Severe psoriasis was defined as those patients that have ever reached PASI ≥ 10 , PGA ≥ 3 or BSA ≥ 10 . Nail psoriasis was scored by using the Nail Psoriasis Severity Index (NAPSI; range 0–80) (26). Koebner phenomenon was assessed based on a 4-point scale, how often a psoriasis plaque appeared after skin damage of their non-involved skin: never, rarely, often, or very common. The individuals who responded with “often” or “very common” were considered as Koebner-positive patients and the others as Koebner-negative patients, which is in line with our previous study (27). To test for the association with psoriasis clinical variables, chi-square tests were executed from the allele frequency table (2 \times 2 tables). Logistic regression analyses were performed to calculate ORs and 95% CIs. The level of significance was considered to be 0.05. Power calculations were performed using the Genetic Power calculator (28).

RESULTS

Cohort characteristics

The investigated cohort for the replication of the associations between paediatric-onset psoriasis and healthy controls consisted of 151 cases and 450 controls, which is a doubling of the number of cases compared to our previous study (24). The power to detect an association ranged between 18% and 100%. Patient cohort characteristics are reported in Table I. A female preponderance was found (59%) in the cases, which was also present

Table I. Patient cohort characteristics

Cohort characteristics	
Number of cases	151
Male, <i>n</i> (%)	57 (41.0)
Age, years, mean \pm SD (range) ^a	13.0 \pm 4.1 (4–18)
Psoriasis characteristics ^a	
Age at onset of psoriasis, years, mean \pm SD (range)	8.2 \pm 4.1 (0–17)
Duration of psoriasis, months, mean \pm SD (range)	32.9 \pm 35.9 (1–154)
Time of follow-up, months, mean \pm SD (range)	17.8 \pm 15.4 (0–54)
Family history of psoriasis, <i>n</i> (%)	
First-degree relatives	53 (38.1)
Up to the third degree relatives	94 (67.6)
Severe psoriasis, <i>n</i> (%)	77 (55.4)
Nail involvement, <i>n</i> (%)	40 (28.8)
Koebner-positive patients, <i>n</i> (%)	43 (30.9)

^aData were available for 139 subjects.

SD: standard deviation.

in the control group (60.9%) (24). For a total of 139 psoriasis patients clinical data were available from our Child-CAPTURE registry (see below). We found no significant phenotype differences between patients with an age at onset < 10 years and ≥ 10 years.

Replication of genetic associations with paediatric-onset psoriasis

Logistic regression analysis of our extended cohort demonstrated the same associations with 4 of the 7 tested loci as in our previous study (24), albeit this time with increased significance. The 4 genes were *IL23R* (OR 2.42, 95% CI 1.23–4.74), *ERAP1* (OR 1.55, 95% CI 1.18–2.03), *LCE3B_LCE3C*-del (OR 1.67, 95% CI 1.25–2.22), and *HLA-C*06* (OR 17.1, 95% CI 10.5–27.9) (Table II).

Associations with clinical psoriasis characteristics

Age at onset of psoriasis. The mean age \pm SD at onset of psoriasis in our cohort was 8.2 \pm 4.1 years. The group of children with an early onset (< 10 years; *n* = 86) had a mean age at onset of 5.5 \pm 2.2 years, and the other group (≥ 10 years; *n* = 53) had a mean age at onset of 12.7 \pm 2.0 years. For *IL12B*, analysed using SNP rs3213094, we demonstrated a significant association between age at onset < 10 years and the risk (T) allele, with an OR of 2.59 (95% CI 1.14–5.88, *p* = 0.02); 17% of patients with an age at onset < 10 years carried this risk allele, compared to 7.5% of the patients with an age at onset ≥ 10 years (Table III). None of the other analysed loci showed significant associations.

Family history of psoriasis. In 38.1% (*n* = 53) of the patients a first-degree relative stated to have psoriasis. Two thirds of the patients (67.6%, *n* = 94) reported a positive family history of psoriasis up to third degree relatives. However, we found no significant associations between family history of psoriasis (first and up to third degree relatives) and the allele frequency of the psoriasis

Table II. Genetic associations with paediatric-onset psoriasis (stratified by age of onset adjusted for sex)

Single nucleotide polymorphism	Gene	Allele ^a	Frequency of risk alleles			P _{Trend}	Odds ratio (95% confidence interval)
			Patients	Controls			
rs11209026	<i>IL23R</i>	G/A	0.97	0.92	0.010	2.42 (1.23 to 4.74)	
rs3213094	<i>IL12B</i>	T/C	0.13	0.18	0.088	0.72 (0.50 to 1.05)	
rs27524	<i>ERAP1</i>	A/G	0.43	0.33	0.002	1.55 (1.18 to 2.03)	
rs17716942	<i>IFIH1</i>	T/C	0.88	0.86	0.445	1.16 (0.79 to 1.72)	
rs240993	<i>TRAF3IP2</i>	T/C	0.29	0.27	0.132	1.09 (0.82 to 1.45)	
direct PCR	<i>LCE3C_LCE3B</i>	DEL/WT	0.72	0.60	0.00049	1.67 (1.25 to 2.22)	
direct PCR	<i>HLA-C*06</i>	POS/NEG	0.78	0.17	3.15E-30	17.1 (10.5 to 27.9)	

^aThe first allele is the allele associated with psoriasis.

DEL: deletion; WT: wild type; POS: positive; NEG: negative.

Significant *p*-values are shown in bold.

risk factors. Remarkably, even *HLA-C*06* showed no significant association with family history of psoriasis (first degree relatives $p=0.92$ and up to third degree relatives $p=0.76$). In patients with a positive family history up to third degree relatives 76.1% were *HLA-C*06* positive and in patients with only first-degree relatives with psoriasis, 76.5% were *HLA-C*06* positive. In patients with a negative family history up to third degree relatives, 78.6% were *HLA-C*06*-positive compared to 77.2% in patients with no first-degree relatives with psoriasis (Table IV).

Psoriasis severity. In our cohort 55.4% ($n=77$) of the patients were classified as having severe psoriasis. Significant associations were demonstrated between severe psoriasis and the risk (T) allele of SNP rs17716942 (*IFIH1*) with an OR of 2.41 (95% CI 1.14–5.12, $p=0.019$) and the risk (A) allele of SNP rs27524 (*ERAP1*, OR 1.64, 95% CI 1.01–2.67, $p=0.047$) (Table III).

Nail involvement. In *HLA-C*06* negative patients we found a significant increase of nail involvement (OR 0.32, 95% CI 0.14–0.76, $p=0.008$, Table III). None of the other psoriasis risk alleles showed a positive or negative association with this clinical parameter.

Koebner-phenomenon. Forty-three patients (30.9%) were Koebner-positive. None of the investigated risk factors showed a significant association with Koebnerization in our cohort.

DISCUSSION

This is the first study to report associations between clinical parameters and genetic risk factors in a prospective paediatric psoriasis cohort. We could confirm and strengthen, in a larger patient group, our previous findings that paediatric-onset psoriasis is associated with *HLA-C*06*, *LCE3C_LCE3B* deletion and SNPs in the *ERAP1* and *IL23R* loci (24). We performed additional analyses based on clinical data from these children and demonstrated that age at onset, psoriasis severity and nail psoriasis are associated with different genetic risk factors of psoriasis. Remarkably, family history of psoriasis is clearly not associated with *HLA-C*06* in this specific group.

For analysis of a possible effect of age at onset, we divided the patients into 2 groups with a cut-off point at 10 years of age, which is in line with data previously published by Lysell et al. (23). They demonstrated, in a Swedish cohort, that *ERAP1* showed an association, albeit weak, with a psoriasis onset between 10 and 20 years. Also the strongest association with *HLA-C*06* was found for this age group. We did not, however, find associations between age at onset and *ERAP1* and *HLA-C*06* in the Dutch paediatric psoriasis patients, which may be due to ethnic variation. In our cohort, an age at onset before 10 years was demonstrated to be associated with *IL12B*, which encodes the p40 subunit of interleukin (IL)-23 and IL-12 and is involved in both the IL12/Th1 pathway and IL23/Th17 pathway of psoriasis (29, 30).

Table III. Significant associations between clinical characteristics and psoriasis risk factors

Gene/locus	Clinical characteristics	Frequency of risk allele	Odds ratio (95% confidence interval)	<i>p</i> -value
<i>IL12B</i> /rs3213094	Age at onset			
	<10 years	0.17	2.59 (1.14–5.88)	0.020
≥10 years	0.08			
<i>ERAP1</i> /rs27524	Psoriasis severity			
	Mild-to-moderate psoriasis	0.36	1.64 (1.01–2.67)	0.047
	Severe psoriasis	0.48		
<i>IFIH1</i> /rs17716942	Psoriasis severity			
	Mild-to-moderate psoriasis	0.83	2.41 (1.14–5.12)	0.019
	Severe psoriasis	0.92		
<i>HLA-C*06</i> /direct PCR	Nail involvement			
	Yes	0.61	0.32 (0.14–0.76)	0.008
	No	0.83		

Table IV. Distribution of family history of psoriasis and HLA-C*06 in our cohort of paediatric psoriasis

	n (%)	HLA-C*06 ^a		p-value
		Positive n (%)	Negative n (%)	
Only first degree relatives with psoriasis				
Yes	51 (39.2)	39 (76.5)	12 (23.5)	0.92
No	79 (60.8)	61 (77.2)	18 (22.8)	
Up to third degree relatives with psoriasis				
Yes	88 (67.7)	67 (76.1)	21 (23.9)	0.76
No	42 (32.3)	33 (78.6)	9 (21.4)	

^aData were available for 130 subjects.

Previous studies detected associations between *HLA-C*06* and early onset psoriasis, and between a positive family history and early onset of psoriasis in groups of mainly adult patients (14, 16, 17, 19). These findings suggest an association between *HLA-C*06* and a positive family history. In our paediatric cohort, however, with 67.6% of the patients having a positive family history up to third degree relatives, including 38.1% with first degree relatives with psoriasis, and a total of 77.8% *HLA-C*06* positive patients, an association between family history and *HLA-C*06* was not found. This is due to the fact that similar proportions of *HLA-C*06* positivity in both the group with a positive family history (first degree relatives 76.5% vs up to the third degree relatives 76.1%) and a negative family history (first degree relatives 77.2% vs up to the third degree relatives 78.6%) were found (Table IV). Although our cohort is relatively small, it is highly unlikely that increasing the number of cases would reveal such an association. Previous studies reported an association of *HLA-C*06* with type 1 psoriasis (early onset, positive family history) but not with type 2 (late onset, no positive family history) (14, 16). There are, however, several discrepancies with regard to the age criteria. Type 1 psoriasis is variably and loosely defined, depending on the study, as having an onset before 30 or 40 years and by a positive family history. Clearly this cannot be a comprehensive classification as there are many patients with early onset and negative family history and also patients with adult onset that have a positive family history. We analysed truly paediatric patients (onset < 18 years), which is by definition not type 2 psoriasis, but neither necessarily type 1 because of the requirement of positive family history.

Although the lack of correlation between *HLA-C*06* and positive family history comes somewhat as a surprise, it is clearly not unprecedented. Gudjonsson et al. (19), demonstrated in a large mixed cohort of paediatric and adult-onset psoriasis that also many of the *HLA-C*06* positive patients have a negative family history. Based on our own data and those of Gudjonsson et al. (19) we would argue that the historic classification of type 1 and 2 psoriasis is no longer meaningful. Classifications based on the presence of established genetic risk factors are likely to be more helpful in

future studies for personalised approaches with respect to prognosis and treatment. Even when age of onset is used as a classifier, the distinction between paediatric (< 18 years) and adult psoriasis (≥ 18 years) is probably more informative than the cut-off point of age 30 or 40 years, which is used in early and late onset psoriasis.

The most striking clinical association in our paediatric cohort with any of the genetic risk factors was the observation that nail psoriasis was found more often in *HLA-C*06* negative patients ($p < 0.008$). This association has been previously reported for a larger cohort (unstratified for age) by Gudjonsson et al. (19).

Psoriasis severity in adults was previously demonstrated to be associated with *HLA-C*06* and *LCE3C* *LCE3B* deletion (17, 19, 20, 22). In our pediatric cohort we did not find these associations. We did, however, identify an association between psoriasis severity and *IFIH1* and *ERAP1*. *IFIH1* encodes the interferon-induced with helicase C domain 1 (innate immune system), which triggers type I interferon in response to microbial infection (31), and variants are associated with type 1 diabetes (32). *ERAP1* encodes an amino peptidase, which regulates the quality of peptides bound to MHC class I molecules, such as *HLA-C*06* (33).

A limitation of this study is the modest sample size for genetic studies. Considering that only children were included, it is, however, the largest cohort described with clinical features. In our cohort more than 50% of the patients was defined as severe psoriasis which could introduce a selection bias.

In conclusion, our findings suggest that genetic polymorphisms in both innate and adaptive immunity play a role in paediatric plaque psoriasis severity and age at onset of psoriasis. We confirm earlier associations found in adult psoriasis between *HLA-C*06* with respect to nail involvement. The large proportion of patients with a positive family history in *HLA-C*06* negative patients (and the lack of correlation between the two) indicates that other genes, either alone or interaction between two or more genes (34), may have significant effects on heritability.

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The authors declare no conflict of interest.

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