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 ERAP1 (p = 0.002), IL23R (p = 0.01), LCE3C, LCE3B-del (p = 0.00049) and HLA-C*06 (p = 3.15 × 10⁻5). Psoriasis severity was associated with a large number of polymorphisms tagging IFIHI1 and ERAP1 (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.

Accepted Jan 14, 2014; Epub ahead of print Apr 29, 2014


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
typing 5% of the samples were analysed in duplicate; all ge-
homozygotes and heterozygotes. As quality control on the SNP
C*06 (2), which does not allow distinction between
primers for previous described PCR (2).

Acta Derm Venereol 94 was found (59%) in the cases, which was also present
characteristics are reported in Table I. A female preponderance
ranged between 18% and 100%. Patient cohort charac-
teristics consisted of 151 cases and 450 controls, which
were divided in 2 groups based on psoriasis severity scores; psoriasis severity scores for each individual were used. Patients
were compared to our previous study (27). To test
Koebner-positive patients and the others as Koebner-negative
psoriasis was assessed by a clinician using 3 different severity
scores: 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 pso-
rias 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 × 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 asso-
ciations 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 charac-
teristics are reported in Table I. A female preponderance
was found (59%) in the cases, which was also present
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 1.24–4.74), ERAP1 (OR 1.55,
95% CI 1.18–2.03), LCE3C_LCE3B-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 ± SD at onset of
psoriasis in our cohort was 8.2 ± 4.1 years. The group of
children with an early onset (< 10 years; n = 86) had a
mean age at onset of 5.5 ± 2.2 years, and the other group
(≥10 years; n = 53) had a mean age at onset of 12.7 ± 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>
<thead>
<tr>
<th>Table I. Patient cohort characteristics</th>
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<tbody>
<tr>
<td><strong>Cohort characteristics</strong></td>
</tr>
<tr>
<td>Number of cases</td>
</tr>
<tr>
<td>Male, n (%)</td>
</tr>
<tr>
<td>Age, years, mean ± SD (range)</td>
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<tr>
<td><strong>Psoriasis characteristics</strong></td>
</tr>
<tr>
<td>Age at onset of psoriasis, years, mean ± SD (range)</td>
</tr>
<tr>
<td>Duration of psoriasis, months, mean ± SD (range)</td>
</tr>
<tr>
<td>Time of follow-up, months, mean ± SD (range)</td>
</tr>
<tr>
<td><strong>Family history of psoriasis, n (%)</strong></td>
</tr>
<tr>
<td>First-degree relatives</td>
</tr>
<tr>
<td>Up to the third degree relatives</td>
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<tr>
<td>Severe psoriasis, n (%)</td>
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<tr>
<td>Nail involvement, n (%)</td>
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<tr>
<td>Koebner-positive patients, n (%)</td>
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</tbody>
</table>

*Data were available for 139 subjects. SD: standard deviation.
Table II. Genetic associations with paediatric-onset psoriasis (stratified by age of onset adjusted for sex)

<table>
<thead>
<tr>
<th>Single nucleotide polymorphism</th>
<th>Gene</th>
<th>Allele</th>
<th>Frequency of risk alleles</th>
<th>Odds ratio (95% confidence interval)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs11209026</td>
<td>IL23R</td>
<td>G/A</td>
<td>0.97</td>
<td>2.42 (1.23 to 4.74)</td>
<td>0.010</td>
</tr>
<tr>
<td>rs3213094</td>
<td>IL12B</td>
<td>T/C</td>
<td>0.13</td>
<td>0.72 (0.50 to 1.05)</td>
<td>0.088</td>
</tr>
<tr>
<td>rs27524</td>
<td>ERAP1</td>
<td>A/G</td>
<td>0.43</td>
<td>1.55 (1.18 to 2.03)</td>
<td>0.002</td>
</tr>
<tr>
<td>rs17716942</td>
<td>IFIH1</td>
<td>T/C</td>
<td>0.88</td>
<td>1.16 (0.79 to 1.72)</td>
<td>0.047</td>
</tr>
<tr>
<td>rs240993</td>
<td>TRAF3IP2</td>
<td>T/C</td>
<td>0.29</td>
<td>1.09 (0.82 to 1.45)</td>
<td>0.132</td>
</tr>
<tr>
<td>direct PCR</td>
<td>LCE3C_LCE3B</td>
<td>DEL/WT</td>
<td>0.72</td>
<td>1.67 (1.25 to 2.22)</td>
<td>0.00049</td>
</tr>
<tr>
<td>direct PCR</td>
<td>HLA-C*06</td>
<td>POS/NEG</td>
<td>0.78</td>
<td>17.1 (10.5 to 27.9)</td>
<td>3.15E-30</td>
</tr>
</tbody>
</table>

*The first allele is the allele associated with psoriasis. DEL: deletion; WT: wild type; POS: positive; NEG: negative.
Significant p-values are shown in bold.

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).
suggest an association 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 establish genetic risk factors are likely to be more helpful in 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 paediatric cohort we did not find these associations. We did, however, identify an association between psoriasis severity and IFIHI1 and ERAP1. IFIHI1 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 aminopeptidase, 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.

ACKNOWLEDGEMENTS

We thank all patients and volunteers for participating in this study.

The authors declare no conflict of interest.

REFERENCES


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

<table>
<thead>
<tr>
<th></th>
<th>HLA-C*06&lt;sup&gt;+&lt;/sup&gt;</th>
<th>HLA-C*06&lt;sup&gt;+&lt;/sup&gt;</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Positive n (%)</td>
<td>Negative n (%)</td>
<td></td>
</tr>
<tr>
<td>Only first degree relatives with psoriasis</td>
<td>Yes 51 (39.2)</td>
<td>39 (76.5)</td>
<td>12 (23.5)</td>
</tr>
<tr>
<td></td>
<td>No 79 (68.8)</td>
<td>51 (77.2)</td>
<td>18 (22.8)</td>
</tr>
<tr>
<td>Up to third degree relatives with psoriasis</td>
<td>Yes 88 (67.7)</td>
<td>67 (76.1)</td>
<td>21 (23.9)</td>
</tr>
<tr>
<td></td>
<td>No 42 (32.3)</td>
<td>33 (78.6)</td>
<td>9 (21.4)</td>
</tr>
</tbody>
</table>

<sup>*</sup>Data were available for 130 subjects.


17. Purcell S, Cherny SS, Sham PC. Genetic Power Calculator: design of linkage and association genetic mapping studies of complex traits. Bioinformatics 2003; 19: 149–150.


