

# Pre- vs. post-pubertal onset of vitiligo: multivariate analysis indicates atopic diathesis association in pre-pubertal onset vitiligo

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## Summary

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### Accepted for publication

2 April 2012

### Funding sources

No external funding.

### Conflicts of interest

None declared.

DOI 10.1111/j.1365-2133.2012.11002.x

**Background** Limited epidemiological data exist that compare clinical features of pre- and post-pubertal nonsegmental vitiligo.

**Objectives** To compare factors associated with pre- and post-pubertal onset vitiligo. **Patients and methods** A prospective observational study was conducted of patients with vitiligo attending the clinic between 1 January 2006 and 1 July 2011. The Vitiligo European Task Force questionnaire was completed for each patient and thyroid function and antithyroid antibodies were screened. Other forms of vitiligo (segmental, focal, mucosal, not classifiable) were excluded.

**Results** A total of 679 patients were included; 422 had post-pubertal and 257 pre-pubertal onset of vitiligo. Vitiligo universalis was seen only in post-pubertal onset. In univariate analysis, there was no significant statistical difference for sex, Koebner phenomenon or disease activity between both groups; thyroid disease or presence of thyroid antibodies was more frequent in post-pubertal onset [odds ratio (OR) 0.31,  $P < 0.003$ ] whereas atopic dermatitis was more often associated with or preceding pre-pubertal onset (OR 2.42,  $P = 0.006$ ). In multivariate analysis, halo naevi, family history of vitiligo, premature hair greying, atopic dermatitis and previous episode of spontaneous repigmentation were independently associated with pre-pubertal onset. In contrast, stress as onset factor, personal history of thyroid disease and acrofacial type were associated with post-pubertal onset.

**Conclusions** Pre-pubertal onset vitiligo is strongly associated with personal and family history of atopy, suggesting that the predisposing immune background in vitiligo is not limited to autoimmunity, as also noted in alopecia areata. This study also suggests reconsidering the epidemiological data on sex ratio in vitiligo.

Vitiligo is an acquired disease characterized by a progressive loss of melanocytes resulting in patchy depigmentation. In caucasian populations, the prevalence of the disease is around 0.5–1%.<sup>1–3</sup> Vitiligo can be classified into three major forms, namely non-segmental vitiligo or vitiligo according to the recent international consensus conference,<sup>4</sup> segmental vitiligo and mixed vitiligo, which is the association of a characteristic segmental involvement associated usually in a second step with the onset of bilateral vitiligo patches.<sup>5</sup> Vitiligo, the commonest form of the disease, is characterized by symmetrical bilateral patches. Diverse clinical subtypes of vitiligo have been described, including generalized, acrofacial and universalis types. The autoimmune or autoinflammatory involvement in nonsegmental vitiligo has been now largely supported by genome-wide asso-

ciation studies and clinico-epidemiological data.<sup>6–10</sup> Moreover, in a recent genome-wide association study, the VITGEN consortium group reported a quantitative trait locus in the major histocompatibility complex class II region associated with generalized vitiligo age of onset.<sup>7</sup> The exact prevalence of vitiligo in the paediatric age group is unknown. Howitz et al.<sup>2</sup> in Denmark found that approximately 25% of the patients noted the onset of vitiligo before the age of 10 years. The mean age of onset varied among different studies from 4 to 8 years.<sup>2,11–13</sup> Vitiligo can occur in infants as young as 3 months. There are reports of congenital vitiligo, although whether these reports concern piebaldism or true 'congenital vitiligo' is unclear.<sup>14</sup>

To date, very few reports have addressed differences between true paediatric vitiligo or pre-pubertal onset vitiligo

(before the age of 12 years) and later-onset vitiligo (after the age of 12 years, herein referred to as post-pubertal onset vitiligo).<sup>3,15,16</sup> Until now, no study has aimed to identify weighted factors associated with one or the other form using logistic regression procedures.

We herein present the result of a prospective observational study aiming to identify weighted factors associated with pre- and post-pubertal onset vitiligo using univariate and multivariate logistic regression procedures.

## Patients and methods

We conducted an observational study in the setting of a prospective cohort of patients attending the University hospital-based vitiligo clinic of the Department of Dermatology and Paediatric Dermatology of Bordeaux, France between 1 January 2006 and 1 July 2011. All patients with vitiligo or non-segmental vitiligo defined as an acquired progressive bilateral hypomelanosis according to the Vitiligo European Task Force (VETF) definition were enrolled in the study.<sup>17</sup> Mixed vitiligo, the association of a characteristic segmental involvement associated usually in a second step with the onset of bilateral vitiligo patches,<sup>5</sup> and other forms of vitiligo (segmental, focal, mucosal, not classifiable) were excluded. The VETF questionnaires were completed for each patient attending the clinic at the first visit.<sup>17</sup> The VETF form provides a wide range of demographic and clinical information including sex, age, age at onset of the disease, phototype, site of involvement and distribution patterns, Koebner phenomenon (KP, defined in the VETF grid as depigmentation on scars), presence of halo naevi, family history of vitiligo, personal and/or family history of chronic autoimmune or autoinflammatory diseases (thyroid disease, atopy, rheumatoid arthritis, psoriasis, type 1 diabetes mellitus, alopecia areata, inflammatory bowel disease), family history of premature hair greying (more than 50% of white hair before the age of 40 years) with family trees if needed, emotional stress at onset and response to treatment if any. Finally, staging and spreading were assessed as recommended by the VETF group following natural light and Wood lamp examination.

The presence of halo naevi was assessed by dermatologists participating in the study. Indeed, as recommended by the VETF, all trained dermatologist investigators involved in the study performed a double examination of the whole body under natural light and Wood lamp examination.

## Statistical analysis

Descriptive characteristics were first carried out according to the age of onset of vitiligo, pre-pubertal onset, (> 12 years old) vs. post-pubertal onset ( $\leq$  12 years old). Basic summary statistics, such as proportions and mean  $\pm$  SD, were used to characterize population attributes. To identify factors associated with pre-pubertal onset and post-pubertal onset, comparisons between groups were conducted by univariate and multivariate unconditional logistic regression. All potential

predictors of pre-pubertal onset and post-pubertal onset were firstly assessed individually, and odds ratios (OR), the corresponding 95% confidence intervals (CIs) and P-values were computed. The OR significance was determined by the Wald chi-squared test, and predictors with  $P < 0.20$  were subsequently assessed using multivariate analysis with a forward stepwise selection procedure. Possible interactions and multicollinearity were examined; whenever two or more potential risk factors were highly correlated, the predictor that was known as being more clinically important was selected for entry. Finally, the goodness-of-fit of the final model was assessed by using the logistic regression diagnostics procedure. All P-values  $\leq 0.05$  were considered to be statistically significant. The Hosmer–Lemeshow test was performed to test the fit of the model. Statistical analyses were performed using SAS<sup>®</sup> software version 9.1.3 (SAS Institute Inc., Cary, NC, U.S.A.).

## Results

### Patient demographics and clinical characteristics

Patient characteristics are presented in Table 1. A total of 679 patients were included; 257 (92 males and 164 females; one not specified) in the pre-pubertal onset group and 422 (146 males and 276 females) in the post-pubertal onset (sex ratio M:F, 1 : 2 in both groups). Disease duration was  $\leq 3$  years in 53.7% and 34.8%, respectively, in patients with pre-pubertal and post-pubertal onset disease. Mean age at time of consultation was  $41.6 \text{ years} \pm 13.9$  (mean  $\pm$  SD; range 13.5–74) in the post-pubertal onset group and  $16.0 \text{ years} \pm 12.5$  (mean  $\pm$  SD; range 0.25–66) in the pre-pubertal onset group. Phototypes ranged from I to VI and there were no significant differences in their spread between the two groups. Acrofacial type was present in 2.1% of patients with pre-pubertal onset and up to 8.8% in patients with post-pubertal onset. Universal vitiligo was seen only in patients with later-onset disease (2.2%). With regard to halo naevi, these were seen more often in patients with very early pre-pubertal onset (39.5%) compared with patients with post-pubertal onset (14.8%).

Thyroid disease or antithyroid antibodies were found in 30.5% of patients with pre-pubertal onset and 39.3% of patients with post-pubertal onset. With regard to the localization of the lesions, the trunk ( $P = 0.02$ ) and the limbs ( $P < 0.0001$ ) were more often spared post-pubertal onset vitiligo compared with pre-pubertal onset vitiligo, whereas this was the opposite for head and neck involvement ( $P = 0.001$ ) (Table 2).

### Univariate analysis

Results of the univariate logistic regression of very early-onset vs. later-onset disease for patient characteristics are presented in Table 3. There were no significant statistical differences for distribution of sex, disease activity in the last 6 months and the presence of Koebner phenomenon. Stress as onset factor

**Table 1** Description of patient's characteristics according to the age of onset in nonsegmental vitiligo ( $\leq 12$  years vs.  $> 12$  years)

|                                                                                                              | Pre-pubertal<br>onset vitiligo<br>( $\leq 12$ years),<br>n = 257; n (%) | Post-pubertal<br>onset vitiligo<br>( $> 12$ years),<br>n = 422; n (%) |
|--------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------|-----------------------------------------------------------------------|
| <b>Demographic and clinical data</b>                                                                         |                                                                         |                                                                       |
| Sex (n = 678; one not specified)                                                                             |                                                                         |                                                                       |
| Male                                                                                                         | 92 (35.9)                                                               | 146 (34.6)                                                            |
| Female                                                                                                       | 164 (64.1)                                                              | 276 (65.4)                                                            |
| Duration of disease (n = 679)                                                                                |                                                                         |                                                                       |
| $\leq 3$ years                                                                                               | 138 (53.7)                                                              | 147 (34.8)                                                            |
| $> 3$ years                                                                                                  | 119 (46.3)                                                              | 275 (65.2)                                                            |
| Depigmentation on scars (Koebner phenomenon) (n = 641)                                                       |                                                                         |                                                                       |
| No                                                                                                           | 133 (54.1)                                                              | 221 (55.9)                                                            |
| Yes                                                                                                          | 113 (45.9)                                                              | 174 (44.1)                                                            |
| Emotional stress as onset factor (n = 648)                                                                   |                                                                         |                                                                       |
| No                                                                                                           | 150 (61.0)                                                              | 155 (38.6)                                                            |
| Yes                                                                                                          | 96 (39.0)                                                               | 247 (61.4)                                                            |
| Pruritus preceding depigmentation (n = 646)                                                                  |                                                                         |                                                                       |
| No                                                                                                           | 198 (81.1)                                                              | 302 (75.1)                                                            |
| Yes                                                                                                          | 46 (18.9)                                                               | 100 (24.9)                                                            |
| Phototype (n = 669)                                                                                          |                                                                         |                                                                       |
| I                                                                                                            | 24 (9.6)                                                                | 74 (17.7)                                                             |
| II, III                                                                                                      | 172 (68.8)                                                              | 250 (59.7)                                                            |
| IV, V                                                                                                        | 54 (21.6)                                                               | 95 (22.6)                                                             |
| Presence of halo naevus (n = 623)                                                                            |                                                                         |                                                                       |
| No                                                                                                           | 144 (60.5)                                                              | 328 (85.2)                                                            |
| Yes                                                                                                          | 94 (39.5)                                                               | 57 (14.8)                                                             |
| Previous episode of repigmentation (n = 652)                                                                 |                                                                         |                                                                       |
| No                                                                                                           | 99 (39.6)                                                               | 196 (48.8)                                                            |
| Yes, spontaneous                                                                                             | 57 (22.8)                                                               | 56 (13.9)                                                             |
| Yes, following solar exposure                                                                                | 27 (10.8)                                                               | 65 (16.2)                                                             |
| Yes, following treatment                                                                                     | 67 (26.8)                                                               | 85 (21.1)                                                             |
| Type of vitiligo (n = 643)                                                                                   |                                                                         |                                                                       |
| Acrofacial                                                                                                   | 5 (2.1)                                                                 | 35 (8.8)                                                              |
| Generalized                                                                                                  | 237 (97.9)                                                              | 357 (89.0)                                                            |
| Universalis                                                                                                  | 0 (0.0)                                                                 | 9 (2.2)                                                               |
| Total affected area (continuous, 1%) [mean (SD)]                                                             | 1.82 (3.10)                                                             | 3.82 (6.62)                                                           |
| <b>Presence of antithyroid antibodies, personal and familial history of autoimmune or endocrine diseases</b> |                                                                         |                                                                       |
| Presence of thyroid disease/antithyroid antibodies (n = 492)                                                 |                                                                         |                                                                       |
| No                                                                                                           | 130 (69.5)                                                              | 185 (60.7)                                                            |
| Yes                                                                                                          | 57 (30.5)                                                               | 120 (39.3)                                                            |
| Personal history of other (nonthyroid) autoimmune/inflammatory disease (n = 605)                             |                                                                         |                                                                       |
| No                                                                                                           | 204 (85.4)                                                              | 324 (88.5)                                                            |
| Yes, atopic dermatitis                                                                                       | 25 (10.5)                                                               | 18 (4.9)                                                              |
| Yes, type 1 diabetes mellitus                                                                                | 2 (0.8)                                                                 | 5 (1.4)                                                               |
| Yes, psoriasis                                                                                               | 3 (1.2)                                                                 | 14 (3.8)                                                              |
| Yes, alopecia areata                                                                                         | 3 (1.2)                                                                 | 4 (1.1)                                                               |
| Yes, lupus                                                                                                   | 2 (0.8)                                                                 | 1 (0.3)                                                               |
| Family history of premature hair greying (n = 646)                                                           |                                                                         |                                                                       |
| No                                                                                                           | 139 (56.5)                                                              | 292 (73.0)                                                            |
| Yes                                                                                                          | 107 (43.5)                                                              | 108 (27.0)                                                            |

**Table 1** Continued

|                                                          | Pre-pubertal<br>onset vitiligo<br>( $\leq 12$ years),<br>n = 257; n (%) | Post-pubertal<br>onset vitiligo<br>( $> 12$ years),<br>n = 422; n (%) |
|----------------------------------------------------------|-------------------------------------------------------------------------|-----------------------------------------------------------------------|
| <b>Family history of vitiligo (n = 664)</b>              |                                                                         |                                                                       |
| No                                                       | 155 (62.2)                                                              | 294 (70.8)                                                            |
| Yes                                                      | 94 (37.8)                                                               | 121 (29.2)                                                            |
| <b>Family history of autoimmune/inflammatory disease</b> |                                                                         |                                                                       |
| <b>Autoimmune thyroiditis (n = 664)</b>                  |                                                                         |                                                                       |
| No                                                       | 158 (62.7)                                                              | 311 (75.5)                                                            |
| Yes                                                      | 94 (37.3)                                                               | 101 (24.5)                                                            |
| <b>Atopic dermatitis (n = 622)</b>                       |                                                                         |                                                                       |
| No                                                       | 191 (85.3)                                                              | 383 (96.2)                                                            |
| Yes                                                      | 33 (14.7)                                                               | 15 (3.8)                                                              |
| <b>Type 1 diabetes (n = 641)</b>                         |                                                                         |                                                                       |
| No                                                       | 192 (83.8)                                                              | 370 (89.8)                                                            |
| Yes                                                      | 37 (16.2)                                                               | 42 (10.2)                                                             |
| <b>Psoriasis (n = 654)</b>                               |                                                                         |                                                                       |
| No                                                       | 218 (86.5)                                                              | 369 (91.8)                                                            |
| Yes                                                      | 34 (13.5)                                                               | 33 (8.2)                                                              |
| <b>Alopecia areata (n = 601)</b>                         |                                                                         |                                                                       |
| No                                                       | 217 (97.7)                                                              | 376 (99.2)                                                            |
| Yes                                                      | 5 (2.3)                                                                 | 3 (0.8)                                                               |
| <b>Crohn disease (n = 604)</b>                           |                                                                         |                                                                       |
| No                                                       | 215 (98.6)                                                              | 384 (99.5)                                                            |
| Yes                                                      | 3 (1.4)                                                                 | 2 (0.5)                                                               |

**Table 2** Distribution of lesions in pre- and post-pubertal onset vitiligo

|                | Pre-pubertal<br>onset vitiligo<br>(≤ 12 years),<br>n (%) | Post-pubertal<br>onset vitiligo<br>(> 12 years),<br>n (%) | p <sup>a</sup> |
|----------------|----------------------------------------------------------|-----------------------------------------------------------|----------------|
| Head and neck  |                                                          |                                                           |                |
| No             | 56 (23.0)                                                | 52 (13.0)                                                 | 0.001          |
| Yes            | 187 (77.0)                                               | 349 (87.0)                                                |                |
| Limbs          |                                                          |                                                           |                |
| No             | 37 (15.0)                                                | 126 (31.4)                                                | < 0.0001       |
| Yes            | 210 (85.0)                                               | 275 (68.6)                                                |                |
| Hands and feet |                                                          |                                                           |                |
| No             | 55 (22.4)                                                | 102 (25.4)                                                | 0.38           |
| Yes            | 191 (77.6)                                               | 299 (74.6)                                                |                |
| Trunk          |                                                          |                                                           |                |
| No             | 73 (29.4)                                                | 155 (38.7)                                                | 0.02           |
| Yes            | 175 (70.6)                                               | 246 (61.6)                                                |                |
| Genital        |                                                          |                                                           |                |
| No             | 133 (54.1)                                               | 201 (51.1)                                                | 0.47           |
| Yes            | 113 (45.9)                                               | 192 (48.9)                                                |                |

<sup>a</sup>P, chi squared test.

(OR 0.40,  $P < 0.0001$ ), disease duration (OR 0.46,  $P < 0.0001$ ), acrofacial type of vitiligo (OR 0.22,  $P = 0.002$ ) and autoimmune thyroiditis or presence of antithyroid antibodies (OR 0.31,  $P = 0.003$ ) were all positively associated

**Table 3** Univariate logistic regression for pre-pubertal ( $\leq 12$  years) vs. post-pubertal onset vitiligo ( $> 12$  years)

|                                                                    | OR (95% CI)       | N   | P (Wald test) |
|--------------------------------------------------------------------|-------------------|-----|---------------|
| Sex (male/female)                                                  | 0.94 (0.68–1.30)  | 678 | 0.72          |
| Disease activity in the last 6 months (yes/no)                     | 0.85 (0.60–1.20)  | 670 | 0.35          |
| Previous episode of spontaneous repigmentation (yes/no)            | 1.79 (1.19–2.69)  | 653 | 0.005         |
| Presence of Koebner phenomenon (yes/no)                            | 1.08 (0.78–1.49)  | 641 | 0.64          |
| Stress as onset factor (yes/no)                                    | 0.40 (0.68–1.30)  | 648 | $< 0.0001$    |
| Pruritus before depigmentation (yes/no)                            | 0.70 (0.47–1.04)  | 646 | 0.07          |
| Disease duration ( $> 3$ years/ $\leq 3$ years)                    | 0.46 (0.33–0.63)  | 679 | $< 0.0001$    |
| Total body surface involvement ( $> 1\%$ / $\leq 1\%$ )            | 0.48 (0.34–0.68)  | 625 | $< 0.0001$    |
| Type of vitiligo                                                   |                   | 643 |               |
| Acrofacial vitiligo (yes/no)                                       | 0.22 (0.08–0.57)  |     | 0.002         |
| Generalized vitiligo (yes/no)                                      | 1.52 (1.08–2.16)  |     | 0.017         |
| Halo naevus (yes/no)                                               | 3.75 (2.56–5.51)  | 623 | $< 0.0001$    |
| Family history of premature hair greying (yes/no)                  | 2.08 (1.49–2.91)  | 646 | $< 0.0001$    |
| Family history of vitiligo (yes/no)                                | 1.47 (1.06–2.05)  | 664 | 0.02          |
| Personal history of autoimmune/autoinflammatory disease (yes/no)   | 0.86 (0.58–1.27)  | 605 | 0.43          |
| Autoimmune thyroiditis/presence of antithyroid antibodies (yes/no) | 0.31 (0.17–0.66)  |     | 0.003         |
| Atopic dermatitis (yes/no)                                         | 2.42 (1.29–4.53)  |     | 0.001         |
| Diabetes type 1 (yes/no)                                           | 0.65 (0.13–3.39)  |     | 0.61          |
| Alopecia areata (yes/no)                                           | 1.23 (0.27–5.56)  |     | 0.64          |
| Psoriasis (yes/no)                                                 | 0.34 (0.10–1.21)  |     | 0.09          |
| Family history of autoimmune disease (yes/no)                      | 2.08 (1.51–2.86)  | 632 | $< 0.0001$    |
| Autoimmune thyroiditis (yes/no)                                    | 1.83 (1.30–2.57)  |     | 0.001         |
| Atopic dermatitis (yes/no)                                         | 3.99 (2.12–7.50)  |     | $< 0.0001$    |
| Diabetes type 1 (yes/no)                                           | 1.52 (0.94–2.43)  |     | 0.08          |
| Alopecia areata (yes/no)                                           | 2.76 (0.65–11.65) |     | 0.16          |
| Psoriasis (yes/no)                                                 | 1.79 (1.08–2.97)  |     | 0.02          |

OR, odds ratio; CI, confidence interval.

**Table 4** Multivariate logistic regression for pre-pubertal ( $\leq 12$  years) vs. post-pubertal onset vitiligo ( $> 12$  years) ( $N = 516$ ), final model

|                                                                                        | AOR (95% CI)       | N   | P (Wald test) |
|----------------------------------------------------------------------------------------|--------------------|-----|---------------|
| Disease duration ( $> 3$ years/ $\leq 3$ years)                                        | 0.474 (0.30–0.738) | 516 | 0.001         |
| Stress as onset factor (yes/no)                                                        | 0.293 (0.19–0.449) |     | $< 0.0001$    |
| Personal history of autoimmune thyroiditis/presence of antithyroid antibodies (yes/no) | 0.168 (0.05–0.498) |     | 0.001         |
| Family history of premature hair greying (yes/no)                                      | 1.845 (1.19–2.857) |     | 0.006         |
| Previous episode of spontaneous repigmentation (yes/no)                                | 2.033 (1.21–3.414) |     | 0.007         |
| Family history of atopic dermatitis (yes/no)                                           | 2.916 (1.33–6.394) |     | 0.008         |
| Family history of vitiligo (yes/no)                                                    | 1.723 (1.10–2.686) |     | 0.016         |
| Halo naevus (yes/no)                                                                   | 3.359 (2.08–5.415) |     | $< 0.0001$    |
| Acrofacial type (yes/no)                                                               | 0.125 (0.02–0.598) |     | 0.009         |

AOR, adjusted odds ratio; CI, confidence interval.

with post-pubertal onset. On the contrary, previous episode of repigmentation (OR 1.79,  $P = 0.005$ ), generalized vitiligo type (OR 1.52,  $P = 0.017$ ), presence of halo naevi (OR 3.75,  $P < 0.0001$ ), family history of premature hair greying (OR 2.08,  $P < 0.0001$ ), family history of vitiligo (OR 1.47,  $P = 0.02$ ), concomitant atopic dermatitis (OR 2.42,  $P = 0.001$ ) and family history of autoimmune diseases (OR 2.08,  $P < 0.0001$ ) were positively associated with pre-pubertal onset vitiligo.

### Multivariate analysis

When conducting multivariate analysis, disease duration of more than 3 years, stress as onset factor, personal history of autoimmune thyroiditis or antithyroid antibodies and acrofacial type were independently associated with post-pubertal onset vitiligo. In contrast, family history of premature hair greying, previous episode of repigmentation, family history of atopic dermatitis, family history of vitiligo and the presence of halo naevi were independently associated with pre-pubertal onset vitiligo (Table 4).

### Discussion

Until now, very few studies have compared pre- and post-pubertal onset vitiligo.<sup>3,15,16</sup> Furthermore, these studies have restrictively used correlation tools with no formal measurement of the risk using odds ratios. In the present study, we found significant differences in clinical characteristics and evolution of pre- and post-pubertal onset vitiligo.

In our study, there was no difference for sex ratio (M:F, 1 : 2) between pre- and post-pubertal onset vitiligo. Until now, it has been stated that in vitiligo both sexes are equally affected.<sup>18</sup> However, this assertion should be questioned as vitiligo is now commonly admitted to be, at least partly, an autoimmune disease. Indeed, one of the major shared features among autoimmune diseases is the female sex predominance.<sup>19</sup>

In a recent study, we found that 44% of patients acknowledge that their disease has been triggered by emotional stress.<sup>6</sup> Others have also reported a significant difference in the mean number of stressful events between patients with vitiligo and control subjects.<sup>20</sup> In the current study, patients with post-pubertal onset vitiligo recalled a stressful event with statistically significantly higher frequency than those with pre-pubertal onset vitiligo, which was further assisted by parents when they consulted in the paediatric unit. However, patients with pre-pubertal onset vitiligo might be less able to recall such an event when seen first in adulthood and we cannot thus exclude a recall bias for this difference.

We found that pre-pubertal onset of vitiligo is strongly associated with a family history of vitiligo, providing further evidence for a greater genetic component than in post-pubertal onset vitiligo. This finding is in contradiction with a recently published study,<sup>16</sup> although the latter study may lack statistical power as the study population was far smaller than in our study. In addition, we found an independent positive association of pre-pubertal onset vitiligo and a family history of premature hair greying, which questions the nature of hair greying in the context of vitiligo as linked either to stemness or redox status or autoimmunity.<sup>21</sup> This association between childhood-onset vitiligo and increased family history of premature hair greying has long been reported. Indeed, in 1987 Halder *et al.*<sup>15</sup> reported an increased incidence of family history of premature hair greying in childhood-onset vitiligo compared with both control children without vitiligo and patients with adult-onset vitiligo.

In accordance with a recently published study,<sup>22</sup> we found that the presence of halo naevi was independently associated with vitiligo onset before the age of 12 years. The halo naevus is a clinical marker of cellular immune response against abnormal melanocytic cells, naevocytes, which may indirectly pertain to the process targeting normal melanocytes in vitiligo. In a previous study, we found a strong link between halo naevi associated nonsegmental vitiligo and premature hair greying, suggesting that the latter may involve an autoimmune process.<sup>23</sup> This hypothesis may be reinforced by the fact that in our population of patients with vitiligo with pre-pubertal onset, halo naevi usually precede vitiligo. In contrast, the acrofacial type of vitiligo was positively associated with post-pubertal onset vitiligo, and vitiligo universalis was found only in the post-pubertal onset group of patients. Post-pubertal onset of vitiligo was independently associated with the presence of a personal history of autoimmune thyroiditis or presence of antithyroid antibodies.

The hypothesis that the age of onset of vitiligo is related to genetic background is reinforced by another important finding

of this study. Indeed, we found a higher prevalence of personal and family history of atopic dermatitis in patients with pre-pubertal onset vitiligo, compared with patients with post-pubertal onset disease. Very few studies have investigated the relation between personal and family history of atopy and vitiligo and this association has been reported in only one other study.<sup>16</sup> Atopic dermatitis, where pruritus is the major symptom, is characterized locally by a T-helper 2 cytokine imbalance, and in contrast to vitiligo, clinical signs of inflammation such as erythema and oedema are the rule during flares. In vitiligo, clinical inflammation is rare but found in skin biopsies at the edge of progressing lesions.<sup>24</sup> However, in our study, we also found that pruritus was present in almost 19% of patients with pre-pubertal vitiligo onset and in almost 25% of patients with post-pubertal vitiligo onset. Previous studies have reported that white skin in patients with vitiligo exhibits a loss of contact hypersensitivity. In addition, elective anatomical sites for atopic dermatitis and vitiligo are usually not the same. Indeed, atopic dermatitis usually involves flexural areas whereas vitiligo most commonly involves edges, which are more commonly subjected to repeated frictions. Thus, it may be interesting to explore further the relationship between vitiligo and atopic dermatitis. In particular, to what extent atopic dermatitis may improve after vitiligo onset may be of interest as three additional susceptibility loci already associated with allergic disorders and T-cell differentiation, namely TSLP (thymic stromal lymphopoietin), FOXP3 (forkhead box P3) and CTLA-4 loci, were recently found to be associated with vitiligo.<sup>25</sup> Alopecia areata, which shares with vitiligo the usual absence of clinical inflammation, has also been associated with genetic variants of CTLA-4.<sup>26</sup> Alopecia areata has as well been found to be associated with a history of atopy and autoimmune diseases.<sup>27–30</sup> However, we acknowledge that one of the limitations of our study, with regard to the family history of autoimmune diseases, is the possibility of false positive/negative recall bias.

We found that patients that have pre-pubertal onset of vitiligo had a greater chance for spontaneous repigmentation. This may argue for early treatment of children with vitiligo, as it is well known that in vitiligo, treatment is more efficient in recently developed lesions compared with older lesions.<sup>31</sup>

In conclusion, our study clearly shows that pre-pubertal and post-pubertal onset vitiligo have different clinical features and possibly different genetic backgrounds. The clinically based associations of thyroid abnormalities and post-pubertal onset vitiligo and atopic dermatitis and pre-pubertal onset vitiligo should guide further epidemiological studies. Moreover, a next step in genetic studies may be to take into account both the different clinical forms of nonsegmental vitiligo and the accompanying signs of atopic and allergic disorders in addition to autoimmune or autoinflammatory diathesis.

### What's already known about this topic?

- Until now, no study has aimed to identify weighted factors associated with pre- and post-pubertal onset of vitiligo.

## What does this study add?

- Pre-pubertal onset vitiligo is strongly associated with personal and family history of atopy, suggesting that the predisposing immune background in vitiligo, as already noted in alopecia areata, is not limited to autoimmunity.

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