SHORT COMMUNICATION

Parent-of-origin Effect in Alopecia Areata: A Large-scale Pedigree Study

Silke REDLER[1,2], F. Buket Ü. BASMANAV[2], Bettina BLAUMEISER[3], Natalie GARCIA BARTELS[4], Gerhard LUTZ[5], Aylar TAFAZZOLI[2], Roland KRUSE[6], Hans WOLFF[7], Markus BÖHM[8], Ulrike BLUME-PEYTAVI[4], Tim BECKER[9,10], Markus M. NÖTHEN[2,11] and Regina C. BETZ[2]

[1]Heinrich-Heine-University, Medical Faculty, Institute of Human Genetics, University of Düsseldorf, Universitätsstr. 1, DE-40225 Düsseldorf, [2]Institute of Human Genetics, University of Bonn, Bonn, Germany, [3]Department of Medical Genetics, University of Antwerp, Antwerp, Belgium, [4]Clinical Research Center for Hair and Skin Science, Department of Dermatology and Allergy, Charité-Universitätsmedizin Berlin, Berlin, [5]Hair & Nail, Dermatological Practice, Wesseling, [6]Dermatological Practice, Paderborn, [7]Department of Dermatology, University of Munich, Munich, [8]Department of Dermatology, University of Münster, Münster, [9]Institute for Medical Biometry, Informatics and Epidemiology, University of Bonn, [10]German Center for Neurodegenerative Diseases (DZNE), and [11]Department of Genomics, Life & Brain Center, University of Bonn, Bonn, Germany. E-mail: silke.redler@med.uni-duesseldorf.de

Accepted Mar 22, 2017; Epub ahead of print Mar 28, 2017

Alopecia areata (AA) is a common hair loss disorder of autoimmune origin. Research suggests that the aetiology of AA involves both genetic and environmental factors. Several genetic risk loci have been identified (1–4). In the general population, the estimated lifetime risk of AA is 1–2%, with similar rates being reported in both sexes (5, 6). Several studies have reported familial clustering in patients with AA (7–9). However, many of these studies involved limited sample sizes. Moreover, only a few studies have reported rates of affected individuals for specific degrees of relatedness (7, 9, 10). In a previous report, our group presented comprehensive data on the pattern of familial aggregation in 206 AA families. In this cohort, we found a frequency of 5.5% for first-degree relatives, and approximately 7% for parents (7). In other AA cohorts, rates of affected individuals as high as 10% have been reported in parents (9, 10). These high rates indicate a parent-to-child transmission of genetic susceptibility variants. However, to our knowledge, no study to date has specifically investigated a parent-of-origin effect in AA. A parent-of-origin effect is present if the disease is inherited more frequently from either the maternal or the paternal side, or if phenotypic expression differs depending on whether the disease is inherited from the mother or the father. A parent-of-origin effect points to specific molecular mechanisms (e.g. genomic imprinting), which may suggest directions for follow-up studies. Epidemiological and molecular genetic studies have reported parent-of-origin effects in several complex autoimmune disorders, including conditions displaying comorbidity or genetic overlap with AA, such as multiple sclerosis, psoriatic arthritis, and inflammatory bowel disease (11–14).

The aim of the present study was to investigate a possible parent-of-origin effect in AA.

METHODS

Systematic analysis was performed in 2,230 3-generation pedigrees, drawn from our previously reported and clinically well-characterized Central European AA sample (**Table I**). Information concerning the rates of affected individuals of parents, other first-degree relatives and second-degree relatives was obtained in interviews with all 2,230 patients with AA. For 206 of these patients, a direct interview with parents was also conducted. Ethical approval was obtained from the respective ethics committees and informed consent from all of the patients.

Table I. Data on the present 2,230 3-generation Central European alopecia areata (AA) pedigrees

	n	Frequency %
Overall sample	2,230	
Females	1,640	73.54
Males	590	26.46
First-degree relative with AA	291	13.05
Sibling/child	145	6.55
Mother	79	3.54
Father	66	2.96
Second-degree relative with AA	212	9.51

RESULTS

A total of 145 of the 2,230 patients with (6.5%) reported having one affected parent: mother ($n=79$; 54.5%) or father ($n=66$; 45.5%). This is not suggestive of preferential transmission from either the paternal or the maternal side ($p=0.319$). None of the patients reported having 2 affected parents. In a subsequent step, we investigated whether sex-specific transmission patterns (maternal vs. paternal inheritance) may lead to dissimilarities in AA phenotypic expression. For this purpose, we subgrouped our data according to disease severity and age of onset. Disease severity was defined according to AA subphenotype in the patient: patients with patchy AA were classified under the category "mild phenotype"; and patients with alopecia totalis or alopecia universalis were classified under the category "severe phenotype". Of the 79 patients with an affected mother, 40 displayed severe AA. This proportion did not differ significantly from that observed in patients with an affected father (28 of 66 patients; $p=0.324$). Similarly, no significant difference was found between the 2 groups in terms of the proportion of patients with an early age of onset (<20 years) (38/79 vs. 30/66; $p=0.751$). These data suggest that a parent-of-origin effect in the phenotypic expression of AA is unlikely.

doi: 10.2340/00015555-2658
Acta Derm Venereol 2017; 97: 862–863

DISCUSSION

The present study had 2 limitations. First, although our sample is one of the largest reported AA cohorts worldwide, the number of pedigrees with an affected parent was relatively small, which limited the statistical power of this study. Assessment of larger cohorts is required to generate conclusive data on parent-of-origin effects in AA. This is particularly the case if genomic imprinting involves only a small minority of those genes that contribute to the aetiology of AA. Secondly, the methodology used to obtain data on the rates of affected individuals status of parents was suboptimal. In 206 families, information on family history was obtained via a direct interview with the respective parents (7). In the remaining patients, information concerning a family history of AA was obtained from the patients only. Therefore, reporting bias secondary to a limited awareness of family history cannot be excluded. Moreover, some parents may have been unaware of their own hair loss disorder due to: (*i*) the presence of a very mild AA phenotype; (*ii*) failure to recall episodes of AA in early childhood; or (*iii*) the fact that their AA phenotype was not yet manifest at the time their affected offspring was interviewed. However, biases of this nature are unlikely to have had a preferential impact on families with paternal or maternal transmission, and we anticipate that any such influence on the present results would be small.

Whereas pedigree analyses are limited to data on the rates of affected individuals status of family members, molecular genetic analyses can provide insights into parent-of-origin effects at the level of individual genetic susceptibility variants. For example, for known susceptibility variants that typically exhibit parent-of-origin effects, true effect sizes can be underestimated when the parent-of-origin effects are not taken into account during association testing (14, 15). Furthermore, research has shown that, in genome-wide association studies, accounting for parent-of-origin effects can lead to the identification of additional susceptibility variants. This, in turn, could elucidate a proportion of the "missing heritability" phenomena in complex disorders (14, 16). Therefore despite the negative finding in the present family study, it seems reasonable to conclude that molecular genetic analyses are now warranted to determine whether parent-of-origin effects occur in AA.

ACKNOWLEDGEMENTS

The authors thank all patients for their participation. R.C.B. is a past recipient of a Heisenberg Professorship from the German Research Foundation (DFG). M.M.N. and R.C.B. are current members, and TB is a past associated member, of the DFG-funded Excellence Cluster ImmunoSensation.

The authors declare no conflicts of interest.

REFERENCES

1. Jagielska D, Redler S, Brockschmidt FF, Herold C, Pasternack SM, Garcia Bartels N, et al. Follow-up study of the first genome-wide association scan in alopecia areata: IL13 and KIAA0350 as susceptibility loci supported with genome-wide significance. J Invest Dermatol 2012; 132: 2192–2197.
2. Petukhova L, Duvic M, Hordinsky M, Norris D, Price V, Shimomura Y, et al. Genome-wide association study in alopecia areata implicates both innate and adaptive immunity. Nature 2010; 466: 113–117.
3. Redler S, Angisch M, Heilmann S, Wolf S, Barth S, Buket Basmanav F, et al. Immunochip-based analysis: high-density genotyping of immune-related loci sheds further light on the autoimmune genetic architecture of alopecia areata. J Invest Dermatol 2015; 135: 919–921.
4. Betz RC, Petukhova L, Ripke S, Huang H, Menelaou A, Redler S, et al. Genome-wide meta-analysis in alopecia areata resolves HLA associations and reveals two new susceptibility loci. Nat Commun 2015; 6: 5966.
5. Safavi KH, Muller SA, Suman VJ, Moshell AN, Melton LJ, 3rd. Incidence of alopecia areata in Olmsted County, Minnesota, 1975 through 1989. Mayo Clin Proc 1995; 70: 628–633.
6. Mirzoyev SA, Schrum AG, Davis MD, Torgerson RR. Lifetime incidence risk of alopecia areata estimated at 2.1% by Rochester Epidemiology Project. J Invest Dermatol 2014; 134: 1141–1142.
7. Blaumeiser B, van der Goot I, Fimmers R, Hanneken S, Ritzmann S, Seymons K, et al. Familial aggregation of alopecia areata. J Am Acad Dermatol 2006; 54: 627–632.
8. Yang S, Yang J, Liu JB, Wang HY, Yang Q, Gao M, et al. The genetic epidemiology of alopecia areata in China. Br J Dermatol 2004; 151: 16–23.
9. Shellow WV, Edwards JE, Koo JY. Profile of alopecia areata: a questionnaire analysis of patient and family. Int J Dermatol 1992; 31: 186–189.
10. van der Steen P, Traupe H, Happle R, Boezeman J, Strater R, Hamm H. The genetic risk for alopecia areata in first degree relatives of severely affected patients. An estimate. Acta Derm Venereol 1992; 72: 373–375.
11. Rahman P, Gladman DD, Schentag CT, Petronis A. Excessive paternal transmission in psoriatic arthritis. Arthritis Rheum 1999; 42: 1228–1231.
12. Akolkar PN, Gulwani-Akolkar B, Heresbach D, Lin XY, Fisher S, Katz S, et al. Differences in risk of Crohn's disease in offspring of mothers and fathers with inflammatory bowel disease. Am J Gastroenterol 1997; 92: 2241–2244.
13. Ebers GC, Sadovnick AD, Dyment DA, Yee IM, Willer CJ, Risch N. Parent-of-origin effect in multiple sclerosis: observations in half-siblings. Lancet 2004; 363: 1773–1774.
14. Kong A, Steinthorsdottir V, Masson G, Thorleifsson G, Sulem P, Besenbacher S, et al. Parental origin of sequence variants associated with complex diseases. Nature 462: 868–874.
15. Hanson RL, Kobes S, Lindsay RS, Knowler WC. Assessment of parent-of-origin effects in linkage analysis of quantitative traits. Am J Hum Genet 2001; 68: 951–962.
16. Stridh P, Ruhrmann S, Bergman P, Thessen Hedreul M, Flytzani S, Beyeen AD, et al. Parent-of-origin effects implicate epigenetic regulation of experimental autoimmune encephalomyelitis and identify imprinted Dlk1 as a novel risk gene. PLoS Genet 2014; 10: e1004265.