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Familial Autoimmunity: Maternal Parent-of-Origin Effect in Juvenile Idiopathic Arthritis

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Abstract

Juvenile idiopathic arthritis (JIA) is an autoimmune (AI) disease characterized by chronic arthritis in children. Children with JIA have increased prevalence of other AI diseases. Furthermore, relatives of children with JIA have been shown to have an increased prevalence of AI diseases. Our objective was to determine if there were differences in the prevalence of AI diseases among maternal and paternal relatives of children with JIA. Information about AI diseases among all living first and second degree relatives was collected by structured interviews with families of 121 simplex JIA families, 23 multiplex JIA families and 45 control families. Overall the prevalence of AI diseases was significantly increased among maternal second degree relatives of cases compared to that of controls (14% vs. 4.3%; $p < 0.001$). The prevalence of AI diseases among mothers of JIA cases was three times that of fathers (32.3% vs. 11.4%; $p < 0.0001$). The prevalence of AI diseases among all maternal second-degree relatives of children with JIA was significantly higher than that of all paternal second-degree relatives [14% vs. 7.9%; $p < 0.004$]. Together these results demonstrate that maternal relatives of children with JIA have an increased prevalence of autoimmunity compared to paternal relatives, suggesting that there might be maternal parent of origin effect in JIA.

Keywords

autoimmunity; parent-of-origin effect; genomic imprinting; family history; epigenetic factors

Introduction

Genetic factors are believed to underlie susceptibility to juvenile idiopathic arthritis (JIA) [1]. An increased prevalence of autoimmune (AI) diseases among relatives of probands with JIA patients has been demonstrated [2]. The prevalence of AI diseases is also increased among relatives of probands with inflammatory myopathies or rheumatoid arthritis (RA) [3,4]. These observations suggest that clinically distinct AI phenotypes share common susceptibility factors. Identification of common susceptibility factors that influence AI diseases is complicated by several factors. For instance, close relatives share both genetic and environmental factors. Other factors that could complicate genetic studies include parent-of-origin effects, wherein the gender of the disease transmitting parent could influence the expression of disease in offspring. The objective of the present study was to determine if there

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is a parent-of-origin effect in JIA, utilizing data obtained in our previous case-control study [2].

Materials and methods

A complete description of methods for the case-control study has been published [2]. In summary, structured interviews were conducted to obtain histories of AI diseases among living first and second-degree relatives among 110 simplex and 23 multiplex JIA families, as well as 45 control families. The subjects in this study had originally been classified according to the American College of Rheumatology criteria for JRA [5]. However since the major subtypes of JRA are comparable to the major JIA subtypes, we have chosen to use the term JIA in this paper.[6] It should be noted that children with spondyloarthropathy or psoriatic arthritis were not included. Controls were healthy volunteers matched for age and ethnicity. All subjects were ascertained without prior knowledge of AI diseases within their families. Detailed information about AI diseases among parents, offspring, siblings, grandparents, uncles, and aunts of the probands was collected. The AI diseases included alopecia areata, ankylosing spondylitis, dermatomyositis, Grave's disease, Hashimoto's thyroiditis, type 1 diabetes, inflammatory bowel disease, iritis, JIA, multiple sclerosis, psoriasis, RA and systemic lupus erythematosus. Of the 208 relatives with a history of AI, 87% were either contacted directly or secondary confirmation of AI was obtained either from another relative or history of use of medications like methotrexate or l-thyroxine. The prevalence of AI diseases among parents, maternal and paternal second-degree relatives of cases was compared with the prevalence of AI among the parents, maternal and paternal second-degree relatives of controls respectively. The prevalence of AI diseases among maternal second-degree relatives of cases was compared against that of the paternal second-degree relatives to determine if there were differences. Odds ratios (OR) were calculated using Chi-square tests or Fisher's exact tests where appropriate.

Results

The prevalence of AI was increased among both the mothers and fathers of the probands with JIA compared to that of the controls, although the differences did not reach statistical significance. The prevalence of AI diseases was significantly increased among maternal aunts of cases compared to maternal aunts of controls [OR 13.6; $p < 0.002$]. An increased prevalence of AI diseases was also observed among paternal aunts of cases compared to that of controls [OR 6.1; $p < 0.05$]. The prevalence of AI diseases among all second-degree maternal relatives of cases (14%) was significantly higher than the prevalence of AI diseases among all second-degree maternal relatives of controls (4.3%), [OR 3.6; $p < 0.001$]. Similarly the prevalence of AI diseases among all second-degree paternal relatives of cases (7.9%) was higher than the prevalence of AI diseases among all second-degree paternal relatives of controls (2.9%), but this did not reach statistical significance [OR 2.8; $p < 0.07$].

We then compared the prevalence of AI disorders among relatives of mothers versus the relatives of fathers of the probands with JIA (Table 1). The prevalence of AI among mothers of JIA cases was about three times that of the fathers, 32.3% vs. 11.4%, [OR 3.7; $p < 0.0001$]. The prevalence of AI diseases among maternal aunts and grandmothers combined was significantly higher than that of paternal aunts and grandmothers [22.1% vs. 11.6%; OR = 2.2 (1.3 -3.7), $p < 0.002$]. However, the prevalence of AI diseases among maternal uncles and grandfathers was not significantly elevated compared to that of paternal uncles and grandfathers [4.9% vs. 4.1%; OR = 1.2 (0.5-3.2), $p < 0.7$]. In all, the prevalence of AI diseases among all maternal second-degree relatives was significantly higher than that of all paternal second-degree relatives [14% vs. 7.9%; OR = 1.9 (1.2 -3.0), $p < 0.004$]. When we did similar analyses with relatives of controls, the only significant difference was an increased prevalence

of AI among mothers of controls compared to the fathers of controls, although the 95% confidence intervals were very wide.

Discussion

We have demonstrated an increased prevalence of AI diseases among maternal relatives of probands with JIA compared to that of paternal relatives. This observation raises the possibility that genomic imprinting, defined as the differential behavior of genes depending on the parent-of-origin, could play a role in JIA. Ideally parent-child affected pairs can help to address the role of imprinting. However, there were very few parent-child pairs with JIA. We did observe a significantly increased prevalence of AI disorders among mothers of the JIA probands compared to the fathers ($p < 0.0001$). To our knowledge the role of genomic imprinting in JIA has not been investigated previously. Genomic imprinting has been demonstrated in other complex AI phenotypes. In psoriatic arthritis, another AI disease, imprinting has been identified by epidemiologic and genetic studies [7,8]. In a study of 92 parent-child pairs with psoriatic arthritis, the proportion of paternal transmission was significantly higher than expected [8]. Furthermore, more probands had affected paternal relatives than maternal relatives, although the increase was not statistically significant (62% vs. 38%, $p < 0.2$). A genome wide study of psoriatic arthritis found evidence for linkage at a marker on chromosome 16 when conditioned on paternal transmission but not on maternal transmission, providing evidence for genomic imprinting at a molecular level [7]. Similarly a marker on chromosome 6p demonstrated linkage to psoriasis by affected sibling pair analysis, and the distortion of allele sharing was maximal when the allele was of paternal origin [9].

In contrast to the paternal transmission seen in psoriatic arthritis, evidence of maternal transmission is seen in another AI disease, Crohn's disease. Of 33 parent-child pairs with Crohn's disease in one study, disease susceptibility was transmitted from the mother 28 times ($p < 0.00007$) supporting the role of maternal imprinting [10]. In a genetic study of type-1 diabetes several loci, including the insulin gene, demonstrated parent of origin effects [11]. These studies demonstrate that parent-of-origin effects influence several AI diseases, suggesting that such factors may also be playing a role in susceptibility to JIA.

Other factors that could possibly influence JIA susceptibility include non-inherited maternal MHC antigens. An association between non-inherited maternal HLA alleles and RA has been observed [12]. In a meta-analysis of 248 individuals with RA that were negative for DRB1*04, 23% of mothers had a non-inherited maternal antigen compared to 12% non-inherited paternal antigen ($p < 0.003$). Similarly, in type 1 diabetes, high-risk HLA alleles were significantly more frequent among non-inherited maternal alleles than among non-inherited paternal alleles [13]. These observations suggest that non-inherited maternal antigens could also conceivably play a role in JIA susceptibility.

The significantly increased prevalence of AI disorders among the mothers of probands compared to the prevalence among fathers could reflect differences in prevalence of AI disorders among females and males. But the difference in prevalence of AI disorders among parents of cases was much more statistically significant compared to the differences among parents of controls. The differences in prevalence of AI diseases in maternal versus paternal relatives might also reflect differences in awareness about family history. However, the family history was obtained by structured interviews, and was often taken from both parents. Furthermore in many cases the relatives of the probands were contacted for verification of positive history of AI diseases, suggesting that such a bias is unlikely to play a major role in our study. We did not stratify our analysis by JIA subtypes, since our patient population was originally classified according to the ACR criteria for JRA. However the probands in this study represented the major JIA subtypes (systemic, polyarticular and oligoarticular JIA).

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Table 1
Prevalence of AI diseases among parents, maternal and paternal relatives among cases and controls.

Category of relative	Maternal relatives			Paternal Relatives			OR	95%CI	P
	n with AI disease	Total	Prevalence rate %	n with AI disease	Total	Prevalence rate %			
JIA Families									
Parent ¹	43	133	32.3	14	123	11.4	3.7	1.8-7.7	<0.0001
Aunts	30	169	17.8	17	159	10.7	1.8	0.9-3.6	0.07
Grandmothers	26	84	30.9	9	66	13.6	2.8	1.1-7.2	0.01
All female SDR	56	253	22.1	26	225	11.6	2.2	1.3-3.7	0.002
Uncles	6	173	3.5	7	168	4.2	0.8	0.2-2.8	0.74
Grandfathers	5	53	9.4	2	51	3.9	2.6	0.4-20.1	0.26
All male SDR	11	226	4.9	9	219	4.1	1.2	0.5-3.2	0.70
All SDR	67	479	14.0	35	444	7.9	1.9	1.2-3.0	0.004
Control Families									
Parent ¹	7	40	17.5	1	41	2.4	8.5	0.99-392	0.03
Aunts	1	64	1.6	1	52	1.9	0.8	0.0-30.5	0.89
Grandmothers	5	25	20	2	22	9.1	2.5	0.4-21.4	0.42
All female SDR	6	89	6.7	3	74	4.1	1.7	0.4-9.0	0.52
Uncles	0	57	0	0	50	0	~	-	-
Grandfathers	1	17	5.9	1	12	8.3	0.7	0-28.8	1.00
All male SDR	1	74	1.4	1	62	1.6	0.8	0.0-31.3	1.00
All SDR	7	163	4.3	4	136	2.9	1.5	0.4-6.2	0.76

AI: autoimmune; SDR: second-degree relatives.

¹ Parent refers to mother in the maternal relatives' columns and father in the paternal relatives' columns.