

Different familial association patterns of autoimmune diseases between juvenile-onset systemic lupus erythematosus and juvenile rheumatoid arthritis

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The aim of this study was to determine if the prevalence of autoimmune disorders in the relatives of patients with systemic lupus erythematosus (SLE) is greater than that of relatives of patients with juvenile rheumatoid arthritis (JRA). Interviews were used to obtain histories of the following autoimmune disorders among living or deceased first-, second-, and third-degree relatives of 91 SLE and 110 JRA families: ankylosing spondylitis, SLE, rheumatoid arthritis (RA), JRA, multiple sclerosis, juvenile dermatomyositis, Sjögren's syndrome, myasthenia gravis, psoriasis, and thyroid diseases. There were statistically significant differences between the SLE and JRA probands in mean age and gender ratio (19.1 ± 4.8 vs 14.0 ± 5.5 years; M (male)/F (female): 17/74 vs 62/48, $p < 0.005$). The prevalence rate of autoimmune diseases in relatives of SLE families (20.9%) was greater than in JRA families (11.8%), but not statistically significantly so. The mean age (18.0 ± 5.3 vs 14.0 ± 4.3 years), mean age at diagnosis (13.4 ± 4.3 vs 7.9 ± 3.9 years) and gender ratio (F/M, 16/3 vs 5/8) of the patients with affected relatives between these 2 groups all had statistically significant differences. A higher prevalence of SLE in relatives was found in SLE families than in JRA cases. Furthermore, this study revealed a higher incidence of autoimmune disorders among second- and third-degree relatives of SLE or JRA probands versus first-degree ones, especially sisters (including 1 pair of twins) and the maternal aunt in SLE families. These data demonstrate that the prevalence of autoimmune disorders in the relatives of patients with SLE is greater than those of relatives of patients with JRA. This suggests that clinically different autoimmune phenotypes may share common susceptibility genes, which may act as risk factors for autoimmunity.

Key words: Autoimmune diseases, juvenile rheumatoid arthritis, multifactorial inheritance, systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by a loss of immunological tolerance to self antigens [1]. It is a complex disorder of unknown etiology [2]. Juvenile rheumatoid arthritis (JRA) is defined as arthritis in a child under the age of 16 years affecting one or more joints, lasting for at least 6 weeks and currently also having no other known etiology [3]. Environmental and genetic factors are commonly implicated in the pathophysiologies of both SLE and JRA [1,4-6].

The familial occurrences of SLE, as well as the development of other autoimmune disorders (AIDs) in the relatives of patients with SLE or JRA have been frequently described, often with the inference that these clusters of cases support the concept of a role for genetic factors in etiology [7]. There are also instances where perinatal influences have been suggested as having a

role in pathogenesis [8]. Despite these reports, the relative importance of genetic and environmental factors remains unclear.

Recent investigations have strengthened the likelihood that genetic factors play a major role in the development of SLE or JRA [9,10]. These include: 1) the demonstration of greater concordance for SLE or JRA in monozygotic versus dizygotic twins [7]; 2) the association of SLE or JRA with certain genetically-determined human leukocyte antigens (HLA), but varying among different races [11].

Several studies have shown an increased prevalence of AIDs among relatives of probands with JRA, idiopathic inflammatory myopathies, or SLE [12]. In the present study, we investigate whether other autoimmune diseases are clustered in juvenile-onset SLE or JRA pedigrees, and determine if the prevalence of autoimmune diseases in the relatives of patients with juvenile-onset SLE is greater than that of relatives of patients with JRA.

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Patients and Methods

Patients

Ninety one Taiwanese patients with juvenile-onset SLE (under 20 years old) at National Taiwan University Hospital (NTUH) were enrolled in this study during the period 1996 to 2002. All of the patients fulfilled the 1982 revised diagnostic criteria (American College of Rheumatology criteria) for SLE [13].

Another 110 Taiwanese patients with JRA, as defined by the American College of Rheumatology criteria [3], and who were recruited into this study, attended the special children's rheumatoid clinic at NTUH over the last 7 years. This population excludes patients with definite juvenile ankylosing spondylitis or spondylarthropathy, but not HLA-B27-positive patients who meet the criteria for JRA [14].

Family history

The purpose of our study was explained to the patient during first contact over the telephone. Family history was then assessed by an in-person or phone interview with the patient and/or their parents [15]. Variables collected included age at onset of SLE or JRA, number and types of relatives, genders of relatives, and the history and types of autoimmune disease [16]. A history of the following disorders, as diagnosed by a physician, was obtained during the interview: ankylosing spondylitis (AS), SLE, RA, JRA, multiple sclerosis (MS), juvenile dermatomyositis (JDM), Sjögren's syndrome (SS), myasthenia gravis (MG), psoriasis, and thyroid diseases (TD) [16]. Detailed pedigree information was also acquired, including up to 3 degrees of relatives: parents, siblings, offspring, grandparents,

uncles, and aunts of the probands. Both living and deceased relatives were considered in this study.

Statistical analysis

Data was analyzed and statistical significance measured using the Fisher's exact test and the Student's *t* test.

Results

Baseline information

We collected data for 115 and 131 patients with juvenile-onset SLE and JRA, respectively, for the period 1996 to 2002 at NTUH; this included outpatients and inpatients. Interviews were completed with the families of 91 SLE and 110 JRA patients from November 2002 to January 2003. Twenty four SLE and 21 JRA patients from our database were excluded for various reasons: only "probable" or "possible" diagnosis of SLE or JRA; failure to contact; patients no longer followed-up; non-Taiwanese; lack of valid information about the family; refusal; deceased patients; and adoptees [15].

Characteristics of the 91 SLE and 110 JRA patients who were included are summarized in Table 1. The differences in mean age and gender ratio of the probands were statistically significant between the 2 groups (age, 19.1 ± 4.8 years vs 14.0 ± 5.5 years; M/F, 17/74 vs 62/48, $p=0.000$). However, the mean age of male and female patients within each group was not significantly different in the SLE group (M/F, $19.4 \pm 4.8/18.9 \pm 4.8$ years, $p=0.70$) or the JRA group (M/F, $14.4 \pm 5.3/13.3 \pm 5.7$ years, $p=0.33$). Other demographic variables did not differ between the families of SLE and JRA patients (Table 1).

Table 1. Demographic information for the study patients

Category	Systemic lupus erythematosus n = 91 (%)	Juvenile rheumatoid arthritis n = 110 (%)
Probands		
Gender (male/female) ^a	17/74 (18.7/81.3)	62/48 (56.4/43.6)
Age (mean \pm standard deviation; years) ^a	19.1 \pm 4.8	14.0 \pm 5.5
Prevalence of familial autoimmune disorders	24 (26.4)	21 (19.1)
Relatives with autoimmune disorders		
Total no. of relatives	35	24
Gender (male/female)	10/25 (28.6/71.4)	9/15 (37.5/62.5)
First-degree	6 (17.1)	5 (20.8)
Twins	2 (8.3) ^b	0 ^c
Systemic lupus erythematosus	17 (48.6)	5 (20.8)
Juvenile rheumatoid arthritis	1 (2.86)	3 (12.5)

^a $p < 0.05$.

^bThe 2 relatives were also probands.

^cOne female proband has a twin sister with arthralgia and spinal recent stiffness.

Table 2. Frequency of autoimmune disorders in families^a

No. of relatives with history of an autoimmune disorder	Families of systemic lupus erythematosus n = 91 (%)	Families of juvenile rheumatoid arthritis n = 110 (%)
0	67 (73.6)	89 (80.9)
1	16 (17.6)	19 (17.3)
2	6 (6.6)	1 (0.9)
3	1 (1.1)	1 (0.9)
4	1 (1.1)	-

^aAll $p > 0.05$.

Overall frequency of autoimmune disorders

Of the 91 SLE families, 24 (26.4%) had at least 1 relative with a history of an autoimmune disorder, compared to 21 out of 110 JRA families (19.1%) [$p = 0.237$] (Tables 1 and 2). The mean age (SLE vs JRA, 18.4 ± 5.2 vs 15.1 ± 4.9 years, $p = 0.033$), mean age at diagnosis (SLE vs JRA, 13.7 ± 4.1 vs 8.3 ± 3.9 years, $p = 0.000$) and gender ratio (SLE vs JRA, F/M = 21/3 vs 6/15, $p = 0.000$) of the patients with affected relatives between these 2 groups also had statistically significant differences. However, the gender distribution of patients with or without affected relatives within each group was not significant.

When families were stratified by number of affected relatives, the prevalence rate of autoimmunity among SLE families was 16 (17.6%) with 1 affected relative, 6 (6.6%) with 2 affected relatives, and 1 (1.1%) with 3 affected relatives each (Table 2). The corresponding prevalence rates among JRA families were lower, but not dissimilar [19 (17.3%), 1 (0.9%), and 1 (0.9%), respectively]. The distribution of clinical subtypes of JRA probands with affected relatives was: 13 patients belonging to the pauciarticular type, 6 patients belonging to the polyarticular type, 1 patient belonging to a systemic type, and 1 patient who could not be confirmed as a subtype of JRA.

Prevalence of autoimmune disorders among individuals

There were 35 and 24 affected relatives in the respective SLE and JRA families studied, with gender ratios (female:male) of 25:10 (71.4%:28.6%) and 15:9 (62.5%:37.5%) [$p = 0.574$]. Concerning the degrees of relatives for the SLE and JRA probands, there were 6 first-degree affected relatives, 9 second-degree affected relatives, 9 third-degree affected relatives, and 11 affected relatives beyond the third-degree in the SLE families. The prevalences among JRA families were 5 first-degree, 8 second-degree, 5 third-degree, and 6 beyond the third-degree. When the various types of

relatives were compared, a higher prevalence of was observed among sisters (7 relatives in total, including 2 who were twins) and maternal aunts (9 relatives in total). This was not the case for mothers (6 relatives) nor fathers (5 relatives), especially in SLE relatives [the corresponding prevalences were 5 (including 2 who were twins), 6, 4, and 2, respectively] (Table 3).

Prevalence of individual disorders

When the prevalence of individual disorders was analyzed (Table 4), none were statistically significantly different among the SLE and JRA families. SLE in relatives, however, was higher in SLE families than in JRA families ($p = 0.054$). According to the degree of affected relatives of SLE and JRA probands, the prevalence rate of SLE was statistically significant only in third-degree relatives [7 (77.7%) vs 0, $p = 0.024$] (Fig. 1). However, the gender distribution (female/male) of SLE affected relatives in SLE and JRA families was 15/2 (88.2%/11.8%) and 4/1 (80.0%/20.0%) [$p = 1.00$] (Fig. 2).

Discussion

Evaluations of selected SLE and JRA pedigrees previously suggested that there may be an increased incidence of other AIDs in such families [17]. Most of these studies compared the prevalence of AIDs in the relatives of patient versus non-patient families. Only a few studies compared the differing prevalence of AIDs in families between juvenile-onset SLE and JRA. The purpose of our study was to investigate whether other AIDs are clustered in juvenile-onset SLE or JRA pedigrees.

In this study of Taiwanese juvenile-onset SLE and JRA families, the overall frequency of AIDs in relatives was 26.4% and 19.1%, respectively (Table 5). The prevalence rate in SLE families was higher than that in JRA families, but did not reveal any statistically significant difference. Focussing on the prevalence of

Table 3. Familial cases of systemic lupus erythematosus and juvenile rheumatoid arthritis

Family relationship	Systemic lupus erythematosus (n = 35)	Juvenile rheumatoid arthritis (n = 24)
Female/male	25/10	15/9
Female twins ^c /maternal aunt	2 (SLE)	-
Male twins	-	-
Daughter ^a /mother	2 (SLE _{x1} , TD _{x1})	-
Daughter ^a /father	-	1 (SLE)
Son ^a /mother	1 (SLE)	1 (TD)
Son ^a /father	-	2 (AS _{x1} , psoriasis _{x1})
Sister ^a /sister	2 (SLE _{x1} , JRA _{x1})	1 (SLE)
Sister/brother ^b	-	2 (JRA)
Grandson ^a /grand-ma	-	5 (RA _{x3} , TD _{x2})
Grand-daughter ^a /grand-ma	1 (TD)	-
Niece ^a /maternal aunt	3 (SLE _{x2} , SS _{x1})	1 (SS)
Niece ^a /paternal aunt	1 (SLE)	-
Nephew ^a /maternal aunt	-	2 (TD)
Nephew ^a /uncle	-	1 (RA)
>Third degree cousin	5 (SLE _{x4} , AS _{x1})	3 (SLE _{x2} , TD _{x1})
Aunt/nephew/cousin	1 (SLE ^a /psoriasis)	-
Mother/son/cousin	-	(AS ^a /SLE)
Grand-pa/grand-daughter/cousin	1 (TD ^a /TD)	-
Uncle/nephew/cousin/cousin	-	1 (AS ^a /AS/JRA)
Father/son/grand-pa	1 (AS ^a /AS)	-
Sister/sister/maternal aunt	1 (SLE ^a /SLE)	-
Mother/daughter/maternal aunt/grand-ma	1 (MG ^a /SLE/RA)	-
Father/son/cousin	1 (TD ^a /TD)	-
Paternal aunt/niece/cousin _{x3}	1 (TD ^a /TD _{x2} , MG _{x1})	-

Abbreviations: SLE = systemic lupus erythematosus; JRA = juvenile rheumatoid arthritis; AS = ankylosing spondylitis; RA = rheumatoid arthritis; MS = multiple sclerosis; JDM = juvenile dermatomyositis; SS = Sjögren's syndrome; MG = myasthenia gravis; TD = thyroid diseases

^aThe proband of the family.

^bThe 2 individuals are in 1 family.

^cThe 2 individuals are in 1 family.

Table 4. Prevalence of the different disorders among all relatives of systemic lupus erythematosus and juvenile rheumatoid arthritis patients

Disorder	Systemic lupus erythematosus relatives n = 35 (%)	Juvenile rheumatoid arthritis relatives n = 24 (%)	<i>p</i>
Systemic lupus erythematosus	17 (48.6)	5 (20.8)	0.054
Juvenile rheumatoid arthritis	1 (2.9)	3 (12.5)	0.294
Rheumatoid arthritis	1 (2.9)	4 (16.7)	0.148
Ankylosing spondylitis	3 (8.6)	4 (16.7)	0.427
Multiple sclerosis	-	-	-
Juvenile dermatomyositis	-	-	-
Sjögren's syndrome	1 (2.9)	1 (4.17)	1.00
Myasthenia gravis	2 (5.7)	-	0.51
Psoriasis	1 (2.9)	1 (4.17)	1.00
Thyroid diseases	9 (25.7)	6 (25.0)	1.00

SLE in relatives, 16.5% of the SLE probands have at least 1 relative with SLE. In addition, most of the AIDs cases in the relatives of the SLE probands were SLE (48.6%), but AIDs (especially among JRA) did not

occur in the relatives of JRA probands to a significant degree.

The familial occurrence of SLE in SLE families has been described and reviewed since 1978. By increasing

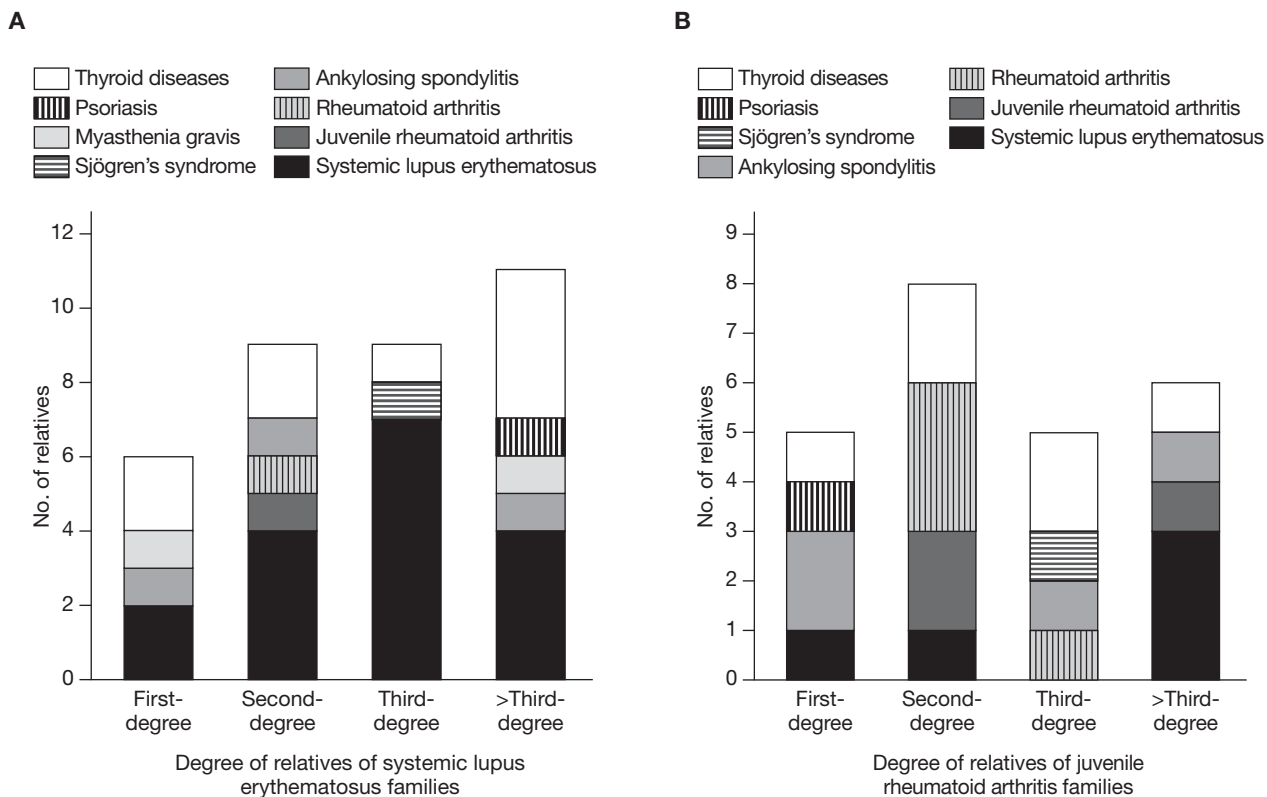


Fig. 1. Prevalence of individual autoimmune disorders in relatives of different degrees of **(A)** systemic lupus erythematosus (SLE) families and **(B)** juvenile rheumatoid arthritis (JRA) families; only the prevalence rate of SLE between the affected relatives of SLE and JRA probands in third-degree relatives was statistically significant [7 (77.7%) vs 0, $p=0.024$].

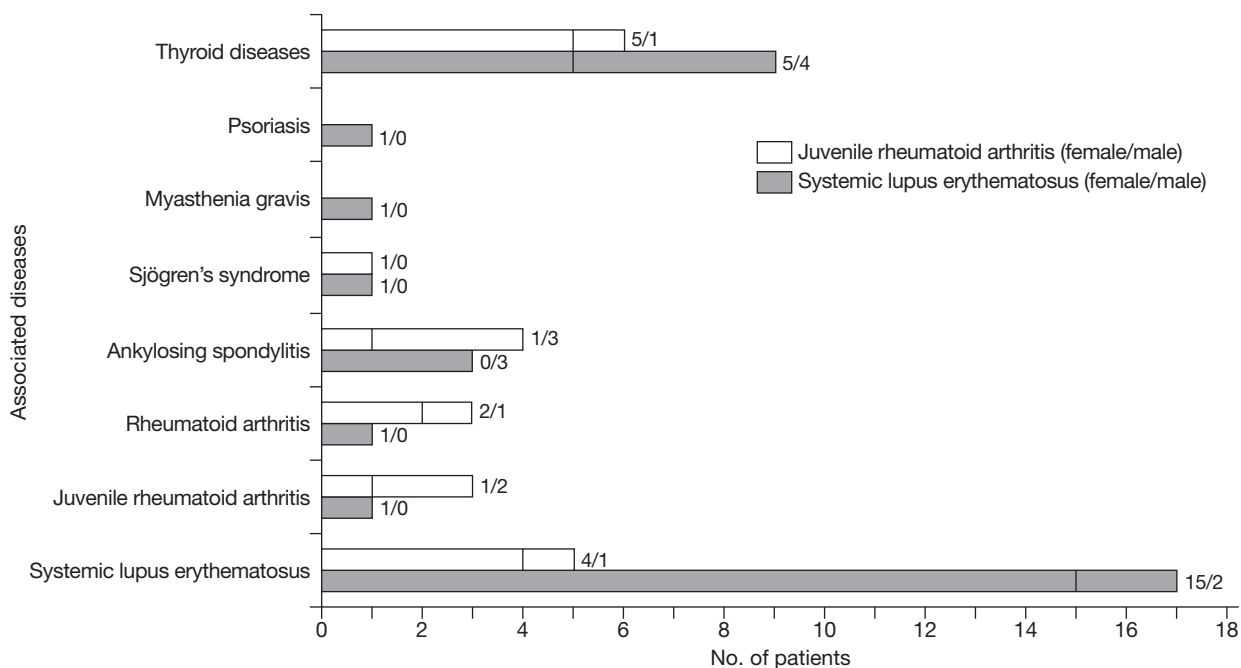


Fig. 2. Autoimmune diseases in the relatives of systemic lupus erythematosus (SLE) and juvenile rheumatoid arthritis (JRA) patients showing the gender distribution (female/male) among affected relatives in SLE and JRA families. The number of SLE-affected relatives in SLE and JRA families was 15/2 (88.2%/11.8%) and 4/1 (80.0%/20.0%), respectively ($p=1.00$).

Table 5. Distribution of systemic lupus erythematosus and juvenile rheumatoid arthritis probands in different AIDs of relatives

Autoimmune disorders in relatives	No. of systemic lupus erythematosus proband	No. of juvenile rheumatoid arthritis proband
Systemic lupus erythematosus	15	5
Juvenile rheumatoid arthritis	1	3
Rheumatoid arthritis	1	4
Ankylosing spondylitis	2	3
Sjögren's syndrome	1	1
Myasthenia gravis	2	-
Psoriasis	1	1
Thyroid diseases	5	6

the period of observation, Dubois [18] and Buckman et al [19] documented a rising prevalence of SLE in the relatives of their patients with lupus – from 2% in 1963 to 12% in 1978. Estes and Christian noted a 7% incidence of familial SLE in their 10-year prospective study [20]. Our prevalence of familial SLE in SLE families is higher than in other studies; different races may have different contributions by genes within the major histocompatibility complex (MHC) and complement components [7].

In the United States, only about 300 affected “sibpairs” (ASPs) with JRA are believed to exist [21]. Six of the 12 ASPs described by Clemens et al, from Europe came from among 2000 patients with JRA who visited their clinics [22]. JRA affected sibpair families had an increased prevalence of autoimmunity (15%). The most frequent autoimmune disorder was Hashimoto thyroiditis (5.3%) [16].

The entire AIDs prevalence in relatives of our JRA probands is lower (11.8%) without any specific AIDs cases present. The most frequent autoimmune disorder is thyroid disease (25%). Thyroid diseases include Hashimoto thyroiditis, Grave's disease, and goiter. Because they are hard to distinguish clearly by families, the true rate of autoimmune-related thyroid disease is unknown.

HLA associations in JRA have been described for some of the subtypes, particularly among the pauciarticular and polyarticular groups [11,16,23,24]. This finding confirms the conclusions of Clemens et al [22], that there is a genetic predisposition among some families to develop pauciarticular JRA rather than other forms. There was greater agreement in course type compared with the findings of Clemens et al, who concluded that the course is undoubtedly influenced by genetic as well as environmental factors [22]. This study describes 13 pauciarticular JRA probands (61.9%) with affected relatives, 7 JRA probands having 2 other

subtypes, and a residual unknown in 1 case. Furthermore, non-HLA genes or chromosome regions have thus far been reported to be associated with JRA [4,25].

The familial clusters of other autoimmune diseases were described early. More than 15% of unselected French MS patients had a family history of AIDs affecting first-degree relatives. Kerzin-Storarr et al found that 13.6% of patients with MG had a first degree-relative affected by AIDs [26]. The high variation in prevalence of AIDs in relatives among different study groups may be due to different AIDs being implicated and different relative groups collected. Differences in race could also be a factor.

Genetic predisposition was originally based on the observation of an increased frequency of SLE in identical twins, and among first-degree relatives. An increased frequency of immune abnormalities in relatives of patients with SLE was also a consideration. Interestingly, our study reveals a higher incidence among second- and third-degree relatives of SLE or JRA probands rather than first-degree relatives. This includes sisters (including a pair of twins) and a maternal aunt in SLE families. In most pedigrees with AIDs and SLE, the index case was female and a mother-and-child pattern was present. Our data are consistent with the female predominance of AIDs, and with the autosomal dominant pattern of transmission suggested in some familial AIDs [17]. However, the parent-and-child pattern in this study is less frequent.

This study has its limitations, and steps were taken to minimize them. Parents of a child with AIDs or arthritis may be more likely to be aware of arthritis or AIDs among their relatives. Most relatives with a history of AIDs were difficult to contact to confirm their diagnoses, except for parents or sisters/brothers. Furthermore, endpoints were used for confirmation when these were available (e.g., L-thyroxine for hypothyroidism, methotrexate for RA, and the like).

This suggests that different autoimmune phenotypes may share common susceptibility genes, which together may confer risk for autoimmunity, even in HLA or non-HLA regions [27]. Otherwise, sex hormones and environmental factors may also have a role in triggering and modifying disease onset and autoimmune production. Further study is recommended to analyze the genomes of patients and their affected relatives and further confirm the relationship between genetic factors and AIDs. Furthermore, estradiol and androgen metabolism, or any role for viruses, ultraviolet light, and drugs should be further clarified.

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