Familial Aggregation of Autoimmune Disease in Juvenile Dermatomyositis

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KEY WORDS

juvenile dermatomyositis, systemic lupus erythematosus, diabetes mellitus type I, psoriasis, celiac disease, interferons

ABBREVIATIONS

JDM—juvenile dermatomyositis

IFN—interferon

SLE—systemic lupus erythematosus

OR—odds ratio

CI—confidence interval

All of the authors included in the manuscript made substantial contributions to the acquisition and analysis of data and the drafting and critical revision of the manuscript, and all of the authors approve of the final submitted manuscript.

www.pediatrics.org/cgi/doi/10.1542/peds.2010-3022

doi:10.1542/peds.2010-3022

Accepted for publication Jan 27, 2011

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

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FINANCIAL DISCLOSURE: The authors have indicated that they have no personal financial relationships relevant to this article to disclose.

Funded by the National Institutes of Health (NIH).

WHAT'S KNOWN ON THIS SUBJECT: Autoimmune diseases frequently run in families, and some families are predisposed to multiple types of autoimmune disease. Genetic factors and specific immune system mediators frequently are shared between autoimmune diseases and may provide insight into the familial tendency toward autoimmunity.

WHAT THIS STUDY ADDS: We report the prevalence of autoimmune conditions in families of children with juvenile dermatomyositis. Lupus and type 1 diabetes were significantly increased in these families, suggesting shared pathogenic factors. A family history of lupus was associated with increased serum interferon- α .

abstract

OBJECTIVE: Familial aggregation of autoimmune diseases likely reflects shared pathogenic factors between different diseases. Familial aggregation of autoimmunity has not been examined in juvenile dermatomyositis. Interferon- α is thought to be a pathogenic factor in both systemic lupus erythematosus and juvenile dermatomyositis, and we have previously demonstrated familial aggregation of serum interferon- α .

METHODS: Family histories were obtained from 304 families of children with juvenile dermatomyositis via 3-generation structured interviews performed by the same person. Rates of autoimmune disease in families of children with juvenile dermatomyositis were compared with published population rates. Serum interferon- α , tumor necrosis factor- α , and neopterin were measured using standard techniques.

RESULTS: A total of 51% of families of children with juvenile dermatomyositis reported at least 1 additional member affected by an autoimmune disease. In particular, both type 1 diabetes and systemic lupus erythematosus were significantly more common than would be expected (odds ratio >5 , $P \leq 1 \times 10^{-7}$ for both). Pedigree analysis showed particularly strong familial clustering of systemic lupus erythematosus with little decrease in incidence across generations, suggesting the possibility of rare causal genes with large effect. Untreated subjects with juvenile dermatomyositis with a family history of systemic lupus erythematosus had higher serum interferon- α than those who did not ($P = .047$).

CONCLUSIONS: We find strong familial aggregation of specific autoimmune diseases in families of children with juvenile dermatomyositis, suggesting that these conditions share pathogenic factors. Higher serum interferon- α in juvenile dermatomyositis patients with a family history of systemic lupus erythematosus suggesting that interferon- α is one such shared factor. *Pediatrics* 2011;127:e1239–e1246

Juvenile dermatomyositis (JDM) is a pediatric inflammatory myopathy characterized by symmetrical muscle weakness and pathognomonic rash in children. JDM onset occurs at a mean age of 6.7 years, and the incidence is 3.2 children per million children each year.¹ The pathogenesis of JDM is multifactorial, and a number of genetic loci have been implicated in disease susceptibility and disease manifestations.^{2–5} Environmental factors likely play a role as well because recent infection of the upper respiratory and/or gastrointestinal systems has been associated temporally with the onset of JDM in 2 studies.^{6,7} In taking patient histories, we have observed a high incidence of autoimmune disease in family members of children with JDM. We hypothesized that there might be a greater prevalence of autoimmune disease in family members of children with JDM than that reported for the general population.

Interferon (IFN)- α is a pleiotropic type 1 interferon that exerts a number of proinflammatory effects on the immune system and is classically involved in viral defense. Dysregulation of the IFN- α system in autoimmune disease has been observed in a number of autoimmune diseases, including systemic lupus erythematosus (SLE),^{8,9} Sjögren's syndrome,^{10,11} and JDM.^{12,13} In JDM, IFN- α levels were highest in patients with the shortest duration of symptoms, suggesting that IFN- α is involved in the early stages of disease pathogenesis.¹² In SLE, we have previously shown that serum IFN- α levels are heritable in SLE families, clustering as a heritable risk factor.¹⁴ A number of genetic polymorphisms have been associated with the high serum IFN- α trait in SLE,^{15–18} including some established genetic risk factors for SLE, such as protein tyrosine phosphatase nonreceptor type 22 (*PTPN22*), secreted phosphoprotein 1 (*SPP1* or

OPN), IFN regulatory factor 5 (*IRF5*), and IFN regulatory factor 7 (*IRF7*).^{19–22} Although the genetic contribution to JDM is not currently well defined, studies have implicated the same *PTPN22* variant associated with high IFN- α in SLE as a susceptibility factor for JDM.²³ In addition to IFN- α , serum levels of tumor necrosis factor- α and neopterin are elevated in subjects with JDM,^{4,24} and in the case of tumor necrosis factor- α , a promoter polymorphism has been associated with increased levels of tumor necrosis factor- α in JDM patients.⁴

We hypothesized that the rates of SLE and some other autoimmune conditions would be higher in JDM family members than rates in the general population. Given that a number of SLE risk factors are associated with higher IFN- α , and at least 1 of these risk factors is shared with JDM, we also hypothesized that JDM patients with a family history of SLE would have higher IFN- α than those patients without a family history of SLE. To test these hypotheses, we examined 3-generation family history data in a large JDM cohort to determine whether SLE and other autoimmune diseases were more common in JDM families. In addition, we examined serum IFN- α , tumor necrosis factor- α , and neopterin levels in JDM patients in the context of family history to determine whether a family history of autoimmune disease was predictive of serum markers in children with JDM.

PATIENTS AND METHODS

Patients, Prevalence Data, and Samples

At the time of this study, the Division of Rheumatology database of Children's Memorial Hospital in Chicago, Illinois, contained data for 308 children with documented definite or probable JDM, according to the criteria of Bohan and Peter.²⁵ Adopted children were ex-

cluded because of the lack of biological family history, leaving 304 children for the study. Family histories were obtained via 3-generation structured interviews on first visit to the clinic and every 36 months thereafter, by the same person (Lauren M. Pachman, MD, IRB no 2008–13590 and no 2002–11762), including data from all JDM patients seen during the period of time from 1971 to 2008. Autoimmune diseases specifically queried include rheumatoid arthritis, type 1 diabetes, psoriasis, SLE, inflammatory bowel disease, multiple sclerosis, celiac disease, scleroderma, vasculitis, myasthenia gravis, polymyositis, dermatomyositis, and JDM. Although data were obtained for self-reports of thyroiditis, these data were not included in our analysis because it frequently can be asymptomatic. The autoimmune diseases included in this study are characterized by specific symptoms that would generally bring the subject to medical attention.

Reports of autoimmune disease in relatives of children with JDM were classified by degree of relation to the JDM proband (first-, second-, or third-degree relative). The total number of relatives assessed at each degree of relation was estimated by counting the exact number of relatives in a random sampling of 10% of the pedigrees included in the study. In this sample, the average number of family members with data per family was 22.7 (SD: 8.15). The rate of autoimmune disease in the JDM relatives was then calculated as the number of cases divided by the estimated total number of relatives for whom data were provided. Serum samples were available from 106 of the children with JDM, and 18 of these subjects had serum samples available at initial diagnosis before beginning medical therapy.

TABLE 1 Concomitant Autoimmune Diseases in JDM Patients

Concomitant Autoimmune Disease	Number of JDM Patients Affected	Percentage of JDM Patients Affected	Reported Population Prevalence, %
Celiac disease	4	1.32	0.75 ⁽³⁹⁾
Psoriasis	2	0.66	2.2 ⁽⁴⁰⁾
Inflammatory bowel disease	1	0.33	0.39 ⁽⁴¹⁾

Concomitant autoimmune diseases could have been diagnosed prior to or after the diagnosis of JDM.

Measurement of Serum IFN- α Activity

We used a sensitive and reproducible bioassay to detect serum IFN- α activity,^{14,26} which has previously been informative in studies of JDM as well as other autoimmune conditions.^{12,27} In this bioassay, reporter cells (WISH cells, American Type Culture Collection no CCL125) are used to measure the ability of sera to cause IFN-induced gene transcription. The reporter cells are cultured with patient sera for 6 hours and then lysed, and 3 canonical IFN- α -induced transcripts are measured using reverse transcriptase polymerase chain reaction. Relative expression data from the 3 transcripts are then normalized using the means and SDs of healthy donor sera ($n = 141$) run in the same assay,¹⁴ and data are presented as an IFN- α activity score.

Measurement of Serum Tumor Necrosis Factor- α and Neopterin Levels

Serum tumor necrosis factor- α levels were assayed using a commercial enzyme-linked immunosorbent assay (Meso Scale Discovery, Gaithersburg, MD), following the manufacturer guidelines. Neopterin levels in serum were determined by the Henning neopterin immunoassay (Henning, Berlin, Germany).

Statistical Analysis

χ^2 distribution and Fisher's exact test were used to detect differences in the proportion of JDM family members with a given condition compared with the proportion of individuals affected in the general population. In these models, the counts in relatives were compared with expected counts in the general population on the basis of published estimates using a sample of the same size as the number of JDM family

members being assessed in each calculation. The published reference used as the estimate for population prevalence is provided for each condition in Tables 1, 2, and 3. In the familial aggregation analyses, we used a Bonferroni correction to establish a threshold P value for significance correcting for the number of autoimmune diseases considered ($n = 12$, P values $< 4.2 \times 10^{-3}$ were considered significant). Quantitative IFN- α data were nonnormally distributed, so the Mann-Whitney U test was used to compare differences between medians.

RESULTS

Concomitant Autoimmune Diseases in JDM Patients

Among 304 children with definite or probable JDM, 7 children (2.30%) had at least 1 additional autoimmune disease, including celiac disease, psoriasis, and inflammatory bowel disease (Table 1). Given the small number of JDM subjects with an additional autoimmune disease, there were no statistically significant differences in the rates of these second autoimmune conditions in JDM patients compared with the general population. At the time of diagnosis, the mean age of the children was 6.7 years. We do not have

TABLE 2 Prevalence of Autoimmune Disorders in JDM Families

Autoimmune Disease in Family History	Percentage of JDM Families, $n = 304$	Estimated Percentage of JDM Relatives Affected, %	Reported Population Prevalence, %	Estimated Risk in JDM Relatives Compared With the General Population	P
Rheumatoid arthritis	15.79	0.94	1.0 ⁽⁴²⁾	0.93 (0.67–1.33)	.72
Type 1 diabetes	15.69	0.85	0.15 ⁽⁴³⁾	5.74 (2.92–11.3)	8.6×10^{-9}
Psoriasis	13.73	0.77	2.2 ⁽⁴⁰⁾	0.35 (0.25–0.48)	8.0×10^{-12}
Lupus (SLE)	11.51	0.61	0.10 ⁽⁴⁴⁾	5.89 (2.64–13.1)	1.0×10^{-7}
Inflammatory bowel disease	5.88	0.30	0.39 ⁽⁴¹⁾	0.77 (0.43–1.38)	.38
Multiple sclerosis	3.62	0.18	0.08 ⁽⁴⁵⁾	2.40 (0.85–6.82)	.14
Celiac disease	1.97	0.10	0.75 ⁽³⁹⁾	0.14 (0.06–0.31)	1.1×10^{-8}
Dermatomyositis	0.99	0.04	0.02 ⁽⁴⁶⁾	3.00 (0.31–28.9)	.62
Scleroderma	0.66	0.03	0.03 ⁽⁴⁷⁾	1.00 (0.14–7.10)	1.0
Myasthenia gravis	0.66	0.03	0.01 ⁽⁴⁸⁾	2.00 (0.18–22.1)	1.0
Vasculitis	0.33	0.01	0.002 ⁽⁴⁹⁾	N/A	N/A
Polymyositis	0	0	0.004 ⁽⁵⁰⁾	N/A	N/A

"Estimated" indicates that the number of relatives assessed was determined using a sampling method as described in the PATIENTS AND METHODS section. Risk in relatives compared with the population is expressed as an OR with the 95% confidence interval (CI) in parentheses. NA indicates that one of the groups had a zero count for that condition.

TABLE 3 Rates of SLE, Type 1 Diabetes, Psoriasis, and Celiac Disease in JDM Family Members by Degree of Relation to the JDM Proband

Degree of Relation to JDM Proband	Number of SLE Cases in Relatives	Risk of SLE in Relatives, OR (95% Confidence Interval)	<i>P</i>	Number of Type 1 Diabetes Cases in Relatives	Type 1 Diabetes Risk in Relatives, OR (95% Confidence Interval)	<i>P</i>	Number of Psoriasis Cases in Relatives	Risk of Psoriasis in Relatives, OR (95% Confidence Interval)	<i>P</i>	Number of Celiac Cases in Relatives	Risk of Celiac in Relatives, OR (95% Confidence Interval)	<i>P</i>
First degree, <i>n</i> = 1224	4	4.01 (0.45–35.9)	.37	6	3.00 (0.61–14.94)	.29	18	0.66 (0.36–1.21)	.22	2	0.22 (0.05–1.02)	.06
Second degree, <i>n</i> = 3672	20	5.02 (1.71–14.7)	1.5×10^{-3}	43	7.24 (3.08–17.0)	1.2×10^{-5}	28	0.34 (0.22–0.52)	3.1×10^{-7}	2	0.07 (0.02–0.30)	1.0×10^{-6}
Third degree, <i>n</i> = 1836	15	7.55 (1.72–33.1)	2.2×10^{-3}	8	2.67 (0.71–10.1)	.15	6	0.15 (0.06–0.35)	4.6×10^{-7}	3	0.21 (0.06–0.74)	.01

Number of relatives is indicated as "n" in each category, and this was estimated using a sampling method as described in the PATIENTS AND METHODS section. Risk in relatives compared with the population is expressed as an OR with the 95% CI in parentheses.

systematic long-term follow-up data regarding concomitant autoimmune diseases for these children, and it is possible that other autoimmune conditions could arise later in life in some of these subjects. This is an important caveat because many of the autoimmune conditions queried typically are adult-onset conditions. After data collection for this study stopped in 2008, we have noted 2 additional children with JDM who later developed concomitant psoriasis and 1 child who had psoriasis first and then developed JDM.²⁸ Inclusion of these subjects in the frequency calculation resulted in a prevalence of psoriasis in JDM, which is only slightly lower than the general population (1.6%).

Familial Aggregation of Autoimmune Disease in JDM Families

A total of 51% of the JDM families reported having at least 1 member with 1 of the autoimmune conditions queried in this study within their extended 3-generation family. The most commonly reported autoimmune diseases in the JDM families were rheumatoid arthritis, type 1 diabetes, psoriasis, SLE, inflammatory bowel disease, and multiple sclerosis (Table 2). Among these autoimmune diseases, SLE and type 1 diabetes were strongly enriched in the JDM family members (odds ratio [OR]: >5 and *P* value $\leq 1 \times 10^{-7}$ for each condition). Both psoriasis and celiac disease were reported less commonly in JDM relatives than would be expected in the general population (OR: 0.35 and 0.14 and *P* values 8.0×10^{-12} and 1.1×10^{-8} , respectively). Rheumatoid arthritis, inflammatory bowel disease, multiple sclerosis, scleroderma, dermatomyositis, myasthenia gravis, vasculitis, and polymyositis were present at rates that were not significantly different than the general population (Table 2).

Rates of Autoimmune Diseases by Degree of Relation in JDM Families

Next, we examined the rates of the 4 autoimmune diseases, which were either increased or decreased in JDM families, in greater detail by taking into account the degree of relation to the JDM proband. Interestingly, the ORs for SLE did not decrease significantly by degree of relation, and a significant increase in SLE prevalence, compared with population controls, was maintained in both second- and third-degree relatives, which would survive correction for multiple comparisons (Table 3). In examining individual pedigrees, a very strong clustering of SLE in particular families was observed, in which multiple family members were affected with SLE across the generations. A trend toward increased incidence of type 1 diabetes in third-degree relatives was observed, but this did not surpass our statistical threshold of $P < 4.2 \times 10^{-3}$ (Table 3), and the familial clustering of type 1 diabetes in individual pedigrees was not as strong. Most pedigrees had 1 relative affected by type 1 diabetes. In the case of both psoriasis and celiac disease, the decreased incidence of these conditions was relatively consistent across the relatives with different degrees of relation (Table 3).

Serum IFN- α Is Higher in JDM Patients With a Family History of SLE

High serum IFN- α has been implicated as a primary causal factor in human SLE,¹⁴ and we have previously demonstrated that serum IFN- α levels are high in some children with JDM.¹² We compared serum IFN- α activity levels in JDM patients stratified by treatment status and presence or absence of a family history of SLE. In the newly diagnosed untreated JDM patients, those with a positive family history of SLE had higher serum IFN- α than patients with

FIGURE 1

Serum IFN- α activity in JDM patients stratified by family history of SLE and medical treatment status. Dots indicate individual JDM patients, and each dot is a unique patient. Lines show the median, error bars show the interquartile range, and *P* values are calculated using the Mann-Whitney *U* test.

no family history of SLE ($P = .047$) (Fig 1). When children were taking active immunosuppressive therapy, serum IFN- α levels generally were lower and were not significantly associated with a family history of SLE. There was no significant difference in serum IFN- α comparing untreated JDM patients with a family history of type 1 diabetes to those without a family history of type 1 diabetes ($n = 6$ vs $n = 12$, respectively, $P = .54$; data not shown). We also examined concentrations of tumor necrosis factor- α and neopterin in the same sera and did not find any significant difference in serum tumor necrosis factor- α or neopterin levels in JDM patients stratified by family history of SLE or type 1 diabetes ($P > .05$ for all; data not shown).

DISCUSSION

Familial aggregation of autoimmunity has been observed in a number of conditions, including type 1 diabetes, rheumatoid arthritis, and SLE.^{29–33} These studies strongly support the concept of shared pathogenic factors underlying different autoimmune diseases. Al-

though environmental factors may play a role in these familial associations, it is likely that shared autoimmune disease risk genes account for a significant portion of this familial tendency toward autoimmunity. The similarities and differences in familial associations between conditions begin to establish a map of probable pathogenic connections between human autoimmune conditions. Recognition of the familial aggregation of particular autoimmune conditions with JDM is important in improving the resolution of this map and also can provide some directions for future study. In Fig 2, we integrate the newly described familial associations with JDM with published data regarding familial autoimmunity.

Limitations of our study are typical of family-history studies. The data describing the prevalence of autoimmunity in JDM families are dependent on reports from relatives and could not be validated by medical examination or records. Three-generation structured interviews were conducted by the same interviewer in this study, and

FIGURE 2

Diagram showing familial associations with JDM in the context of previously reported familial autoimmune disease associations. Conditions that are increased in family members are indicated by connecting lines with arrowheads, whereas conditions that are decreased in relatives are indicated by connecting lines. T1DM indicates type 1 diabetes; CEL, celiac disease; IBD, inflammatory bowel disease; RA, rheumatoid arthritis; PSOR, psoriasis. The 4 lines originating from the JDM box represent the 4 significant associations described in this study, and other connectors represent previously reported associations in published literature.^{29–31}

the autoimmune diseases were all specifically queried of the JDM family members, with updates conducted at regular intervals. This method should help to standardize potential reporting differences between families to the degree possible in this study design. Another limitation is that the number of family members assessed at each degree of relation was estimated using a sampling method. The fact that the incidence of rheumatoid arthritis, inflammatory bowel disease, multiple sclerosis, dermatomyositis, scleroderma, myasthenia gravis, vasculitis, and polymyositis were all very close to the reported population rates would suggest that these estimates are accurate. Potential differences in the incidence of JDM or other autoimmune diseases over time are not controlled in this study, and the references used for population prevalence data do not span the exact same time frame as the collection of data from the JDM patients and families. The IFN- α analysis is limited to some degree by the low number of untreated serum samples available, but the inflammatory myopathy clinic is referral based, and many

of the children had been initially treated elsewhere before inclusion in this study.

As susceptibility genes and pathogenic molecular pathways are identified in autoimmune disorders, we will begin to understand the forces shaping the diagram illustrated in Fig 2. In the case of JDM, genetic associations have been reported between the HLA locus (including the tumor necrosis factor- α gene), and the *PTPN22* gene, which is outside the HLA locus.^{2,4,23} The association between *PTPN22* and JDM susceptibility is shared with many autoimmune diseases including SLE, rheumatoid arthritis, and type 1 diabetes.³⁴ Interestingly, the allele associated with all of these autoimmune diseases is associated with protection against Crohn's disease.³⁵ Although we do not see a statistically significant protection from inflammatory bowel disease in the relatives of our JDM patients, this allele illustrates the paradigm that the same genetic variation can predispose to 1 autoimmune disease and protect from another.³⁶ This phenomenon could help to explain why having a family member with JDM actually confers a decreased risk for some autoimmune diseases in our study.

JDM is a rare condition that affects ~3.2 children per million children per year.¹ The genetic risk factors reported to date are relatively common alleles in the general population, characterized by ORs for disease of 2 or less. It is quite possible that rare alleles that confer a much greater risk of JDM and other autoimmune conditions also exist but have not yet been discovered. Our family data support this possibility because aggregation of a rare condition, SLE, in JDM families is particularly strong. This high proportion of SLE affected subjects in a given family in which there also is a child with JDM would suggest single rare genetic

variants of large effect (OR: >2.0). Rare variants of large effect have been discovered previously in SLE using family-based methods,³⁷ and our data would suggest that a genetic variant with a large effect on both JDM and SLE could be discovered using similar methods.

Increased activation of the IFN- α pathway plays a role in multiple autoimmune diseases, including SLE and JDM,^{8,10,12} and a familial predisposition to high serum IFN- α has been demonstrated in SLE families.^{14,38} We present an important corollary to these data, demonstrating that a family history of SLE is associated with higher serum IFN- α in newly diagnosed JDM patients. These data support the idea that increased IFN- α signaling is important in the initiation of multiple autoimmune diseases, including JDM, and some shared genetic risk factors in this pathway would be expected. By exploring genetic associations with the high IFN- α trait in JDM patients,⁵ we have detected a gender-specific gene-gene interaction between cytokine gene variants involving the osteopontin gene, which has been shown to modulate IFN- α levels in SLE patients.²¹ These data taken together support the idea that genetic influences that result in increased IFN- α pathway activation underlie some of the shared predisposition to SLE and JDM demonstrated in this study. It is likely this model could apply more generally and that genetic influences on other cytokines could influence the increased incidence of other specific autoimmune conditions we have observed in JDM families.

CONCLUSIONS

We find strong familial aggregation of SLE and type 1 diabetes in JDM families, and it is likely that these conditions share pathogenic factors with JDM. Serum IFN- α is higher in children with JDM who have a family history of

SLE, suggesting that IFN- α could be 1 such factor common to these 2 diseases. In addition, JDM families with a history of SLE frequently had many SLE-affected members, suggesting the possibility that a rare genetic variant of large effect may be contributing to susceptibility to both JDM and SLE in these families. Interestingly, both celiac disease and psoriasis were found at significantly lower rates in JDM families than would be expected in the general population. It is possible that these conditions were underreported in relatives because we did not observe a statistically significant decrease in the rate of these conditions in children with JDM, but the low number of children with JDM who had concomitant autoimmune conditions limits our ability to make statistical inference on the basis of these data. It also is possible that some of the factors predisposing to JDM are protective against these 2 conditions, resulting in a lower incidence of these 2 conditions in family members. We can now integrate JDM family data with published studies describing familial aggregation of other autoimmune diseases, enriching our understanding of the familial nature of human autoimmune disease.

ACKNOWLEDGMENTS

Timothy B. Niewold received support from the National Institutes of Health (NIH) (NIH K08 AI083790 and NIH P30 DK42086), the National Institute of Allergy and Infectious Diseases Clinical Research Loan Repayment (AI071651), the NIH Clinical and Translational Science Award (CTSA) Core Subsidy Grant and CTSA Pilot Grants (UL1 RR024999), the Lupus Research Institute Novel Research Grant, the Alliance for Lupus Research Target Identification in Lupus Grant, and the Arthritis National Research Foundation Eng Tan Scholar Award. Stephanie C. Wu was supported by the Arthritis Foundation and the

Greater Chicago Chapter's Georgeson Medical Scholar Student Research Fellowship. Molly Smith was supported by the Wellesley College American Cities

Scholar's Program. Lauren M. Pachman was supported by the NIH National Institute of Arthritis and Musculoskeletal and Skin (R01 AR48289) and Cure

JM Program of Excellence in Juvenile Myositis Research.

We thank Lisa Amoroso, MS, for her contributions to this project.

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