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Pediatric Granulomatous Arthritis

An International Registry

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Objective. **Blau syndrome and its sporadic counterpart, early-onset sarcoidosis, share an identical phenotype featuring the classic triad of arthritis, dermatitis, and uveitis and are associated with mutations of *CARD15* in 50–90% of cases. We chose the term "pediatric granulomatous arthritis" to refer to both. An international registry was established in the spring of 2005 to define the phenotype spectrum and establish the mutation frequency and variants.**

Methods. **Histologically confirmed granuloma and arthritis were required for inclusion. Probands and relatives were genotyped for *CARD15*. Deidentified clinical information was collected.**

Results. **One year after the inception of the registry, 61 individuals from 22 pedigrees had been entered. Seven pedigrees with 19 individuals (8 affected, 11 unaffected) had clinical disease that was atypical, and none of the individuals in those pedigrees showed mutations. There were 9 classic simplex pediatric granulomatous arthritis pedigrees including 19 individuals (9 affected, 10 unaffected) and 6 classic multiplex pedigrees with 22 individuals (17 affected, 5 unaffected). Cutaneous presentation was the most common. Arthritis was polyarticular in 96% of patients. Isolated eye disease was never the presenting symptom, but significant/severe visual impairment was observed in 41% of patients. Eye disease was bilateral in 21 of 22 patients and was complicated by glaucoma in 6 of 22 patients and by cataracts in 50% of patients. Skin biopsy was the best diagnostic approach (because of accuracy and low invasiveness).**

Conclusion. **In this series, the first combining familial and sporadic pedigrees and, to our knowledge, the largest, we further defined the phenotype and showed that all affected classic (and no nonclassic) pedigrees carry a mutation and that there is no asymptomatic carriage. If these data are confirmed, mutation analysis rather than tissue sampling may prove to be the most efficient diagnostic procedure.**

Several genetic syndromes have been recently classified as systemic autoinflammatory diseases caused by mutations affecting innate immunity. Examples include tumor necrosis factor receptor–associated periodic syndrome, familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS), and neonatal-onset multisystem inflammatory disease (NOMID). These illnesses have in common an activation of the inflammatory response without consistently detectable autoantibodies. In each of these syndromes, genetic mutations which lead to the disease are known. In FCAS, MWS, and NOMID, mutations are found in or near the NACHT domain of cryopyrin, a protein encoded by *CIAS1*. Blau syndrome, or familial juvenile systemic granulomatosis, is also an autosomal-dominant, autoinflammatory disease that includes noncaseating granulomatous inflammation affecting the joint, skin, and uveal tract (the triad of arthritis, dermatitis, and

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uveitis, respectively) (1,2). The gene responsible for Blau syndrome, *CARD15*, also encodes a protein containing a NACHT domain (3). Mutations within or near this domain correlate extremely well with disease development (4,5). Both genes encode proteins that can participate in inflammatory signaling cascades.

The granulomatous inflammation seen in Blau syndrome also characteristically appears in patients without a family history of the syndrome who have been diagnosed as having early-onset sarcoidosis. The controversy surrounding the relationship between Blau syndrome and early-onset sarcoidosis has been settled. Clinical observations over the past 20 years and recent molecular work by 2 independent research teams, building upon elegant preceding linkage studies (6), have demonstrated that Blau syndrome and early-onset sarcoidosis are the *same* disease (7,8). To date, 9 different genetic mutations leading to substitutions in or near the NACHT domain of *CARD15* have been documented in affected patients with either the familial or the sporadic presentation (4,9,10). Of those, R334W and R334Q are the most prevalent. The largest reported collection of families with the familial form to date (5) showed that only 50% of the pedigrees with at least 1 affected member carried a mutation in *CARD15*, while in a more recent series of 10 sporadic cases from Japan, 90% exhibited mutations (9). With the purpose of defining the clinical spectrum, natural history, most common patterns of presentation, and prevalence of the mutations, and to investigate the most effective diagnostic protocols, a DNA repository and international registry were established in the spring of 2005. A list of contributors to the registry is shown in Appendix A.

The present report describes clinical and genetic findings 1 year after the inception of the registry, concerning the largest collection of families assembled to date with both familial and sporadic pedigrees. Our observations suggest that Blau syndrome and early-onset sarcoidosis should now be referred to as pediatric granulomatous arthritis, and this proposed nomenclature will be used in this report while we recognize that consensus has not yet been achieved.

PATIENTS AND METHODS

Center recruitment. *Directory.* Internet address directories of pediatric rheumatologists were provided by the Rheumatology Section of the American Academy of Pediatrics and the Pediatric Rheumatology Collaborative Study Group for North America. Addresses for Latin American rheumatologists were provided by the Permanent Pediatric Committee of the Pan American League of Associations for Rheumatology, and European addresses were obtained from the Pediatric Rheumatology International Trials Organization Web site.

Invitation. Centers were contacted electronically with a brief project summary and invitation. If the investigator reported interest and availability of cases by return e-mail, a second communication was sent electronically.

Recruitment. The followup electronic mailing included the study protocol, an electronic data collection form, and suggested templates for parental permission and assents. Each collaborator was invited to negotiate with his/her Institutional Review Board/Ethics Committee to avoid direct contact/disclosure between coordinating center and research volunteers and to protect their identities.

Enrollment. The completed clinical data form was returned by fax or return e-mail. Upon review and approval by the coordinating center (duPont Children's Hospital), a registry code number was assigned. If the case was accepted, electronic communication was triggered directly between the genotyping/DNA repository center (Casey Eye Institute, Oregon Health and Science University) and the submitting collaborator.

Inclusion criteria. The phenotype is still not completely defined. Therefore, we followed the strategy used for the previous pediatric sarcoidosis registry created by Lindsley and Petty (11) and utilized an inclusive set of criteria, as follows: 1) core symptoms (polyarthritis plus uveitis plus tan-colored rash) *or* 2) any core symptom plus granulomatous inflammation observed by biopsy *or* 3) disseminated granulomatosis.

DNA repository. Genomic DNA samples associated with a registry code number and without clinical data or participant identity are stored at the Casey Eye Institute.

Ethical and regulatory considerations. The study was approved by the Institutional Review Boards of the duPont Children's Hospital (Nemours-DE-IRB) and Oregon Health and Science University. Participating centers were treated as individually covered institutions under US regulations by the Privacy Rule. The Casey Eye Institute is also treated as an independent covered institution and receives coded samples with no identifiers. The duPont Children's Hospital and the 2 regional coordinating centers (University of Leuven and Hospital de Niños JM Gutierrez) receive only deidentified clinical information. Results of genetic studies are sent from the Casey Eye Institute to duPont Children's Hospital and the regional centers, from which they are communicated to the submitting collaborators. No genetic information beyond the *CARD15* genotype is provided to the submitting collaborator, who then chooses whether to offer mutation information to the research volunteer. Justification of return of genetic information is based on the following principles: 1) association of mutations in the *CARD15* gene and disease phenotype are supported by sound scientific data, 2) the presence of the mutation is of useful disease confirmatory value, 3) information on mutation results could be relevant to family planning, and 4) the genetic test for rare *CARD15* mutations is not routinely available in clinical testing laboratories.

The utilized code is constructed without identifying elements and includes the name of the city in which the collaborator practices, the pedigree number of the center, and the type of family member in the given pedigree. For example, the proband for the first pedigree from the city of Florence is

Table 1. Numbers of affected and unaffected individuals, phenotype of granulomatous disease, and *CARD15* genotype of affected individuals in each family included in the registry*

Family (type)*	No. of affected individuals enrolled	No. of unaffected individuals enrolled†	Disease phenotype‡	Genotype§
1 (M)	4	1	Classic PGA¶	R334W
2 (M)	2	3	Classic PGA	R334Q
3 (M)	4	1	Classic PGA	R334Q
4 (M)	2	0	Classic PGA	R334W
5 (S)	1	2	Classic PGA	R334W
6 (S)	1	2	Classic PGA	R334W
7 (S)	1	3	Adult-type sarcoidosis	Wild type
8 (M)	2	1	Panniculitis	Wild type
9 (S)	1	0	Disseminated granulomatosis	Wild type
10 (S)	1	1	Classic PGA	R334Q
11 (M)	3	0	Classic PGA	R334W
12 (S)	1	2	Classic PGA	R334W
13 (S)	1	0	Panniculitis	Wild type
14 (S)	1	3	Classic PGA	R334Q
15 (S)	1	1	Classic PGA	R334W
16 (M)	2	0	Classic PGA	Pending
17 (S)	1	0	Neurosarcoidosis	Wild type
18 (S)	1	5	Isolated polyarthritis	Wild type
19 (S)	1	0	Classic PGA	R334W
20 (S)	1	2	Isolated bone lesion	Wild type
21 (S)	1	0	Classic PGA	E383K
22 (S)	1	0	Classic PGA	W490L

* Families are listed by consecutive numbers and type of pedigree (M = multiplex; S = simplex).
† Number genotyped, if different from number enrolled.
‡ As described in Results and Discussion.
§ *CARD15* genotype relevant to Blau syndrome/early-onset sarcoidosis. Numbers refer to amino acid position of the protein. Letters are official 1-letter amino acid abbreviations. *CARD15* mutations associated with Crohn's disease and common *CARD15* polymorphisms are not listed.
¶ PGA = pediatric granulomatous arthritis.

FLORENCE.001.Proband. All the participating centers are in urban localities with >20,000 inhabitants, and there were no primary participants age >90 years.

Genotype analysis. Genomic DNA was obtained directly from collaborating sites or was extracted from blood samples (or, in 1 case, from a buccal swab sample). For genotyping, genomic DNA was subjected to polymerase chain reaction (PCR) amplification using either FastStart Taq DNA polymerase with GC-Rich solution (Roche Diagnostics, Mannheim, Germany) or Optimase Polymerase (Transgenomic, Omaha, NE), and a touchdown PCR strategy. Primers were designed to amplify regions of the *CARD15* gene containing the known Blau syndrome mutations encoding substitutions at position 334, known common non–disease-associated polymorphisms, and the 3 Crohn's disease (CD)–associated mutations. The resultant PCR products were subjected to denaturing high-performance liquid chromatography (dHPLC) analysis to screen for the presence of mutations/polymorphisms (WAVE; Transgenomic). Amplicons that screened positive by dHPLC were subsequently subjected to direct DNA sequencing (in both directions) to confirm the mutation/polymorphism. If no Blau syndrome mutation was detected, the entire coding region of exon 4 was sequenced in both directions to identify any unknown mutations present in the sample.

Clinical information and disease classification. A data collection form was administered and information extracted by the contributors from existing medical records. The data collected included the description of disease onset and the pattern of joint, skin, and ocular involvement as well as the presence of other organ involvement. Biopsy reports and relevant laboratory data were also requested. Finally, results of an ophthalmologic evaluation were recorded, including information on biomicroscopy, ocular pressure, visual acuity, and surgical history. Severity of visual impairment was assessed according to the World Health Organization definition (12). Briefly, moderate visual impairment was defined as visual acuity between 6/18 and 3/60, and severe visual impairment was defined as 3/60 or less in the better eye with best correction.

For the purpose of clinical stratification, we defined the phenotype as "classic" pediatric granulomatous arthritis if the core symptoms of arthritis, dermatitis, and uveitis were present, consistent with Blau syndrome. Furthermore, it was recognized that particular non–core disease manifestations may be included in the classic presentation. These included liver granuloma, erythema nodosum, large-vessel vasculitis, and cranial neuropathy. Alternatively, if the core symptoms deviated substantially from the above description, we referred to the disease presentation as "atypical."

Table 2. Description of ocular findings in 22 patients with classic pediatric granulomatous arthritis and ocular involvement*

Family (ID)†	Uveitis‡			Complications§								Visual acuity¶		
	Ant	Vitr	Chr	Vsc	KP	Cat	Gla	BK	ME	RD	OE	OD	OS	Duration#
1 (C)	Y	Y	Y	Y	N	Y	Y	Y	Y	N	N	20/40	20/50	22
1 (D)	Y	Y	Y	N	N	Y	N	N	N	N	N	20/25	20/25	44
1 (E)	Y	Y	Y	N	N	Y	Y	Y	N	N	N	20/200	20/200	Unk.
2 (5)	Y	N	N	N	N	Y	N	Y	N	N	N	20/50	20/50	5 (2)
2 (1)	Y	Y	Y	N	N	Y	N	Y	N	N	Y	20/100	20/40	26 (21)
3 (1)	Y	Y	N	N	N	N	N	N	N	N	N	20/20	20/40	16 (15)
3 (2)	Y	N	N	N	N	N	N	N	N	N	N	20/20	20/20	11 (5)
3 (3)	Y	N	N	N	N	N	N	N	N	N	N	20/20	20/20	5 (4)
3 (4)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	20/20	20/20	24 (20)
4 (5)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	20/50	Enucl.	16 (14)
4 (6)	Y	Y	Y	N	Y	Y	Y	Y	Y	N	Y	20/100	20/200	42 (42)
5 (1)	Y	Y	N	N	N	Y	N	N	N	N	N	25/30	25/30	21 (20)
6 (1)	Y	Y	Y	Y	G	N	N	Y	N	N	N	9/10	10/10	7 (7)
10 (1)	Y	Y	Y	N	N	N	N	N	N	N	N	10/10	10/10	3 (<1)
11 (1)	Y	Y	Y	N	G	Y	N	Y	N	N	N	1/20	1/20	15
11 (3)	Y	Y	Y	Y	N	N	N	N	N	N	N	20/20	20/20	Unk.
12 (1)	Y	Y	Y	N	N	Y	N	N	Y	N	Y	8/10	10/10	5
14 (1)	Y	Y	Y	Y	N	N	N	N	Y	N	Y	10/10	10/10	13 (12)
16 (1)	Y	Y	Y	N	Y	N	N	Y	N	N	Y	Sev.	Sev.	10 (8)
16 (2)	Y	Y	Y	N	Y	N	N	Y	N	N	N	Unk.	Unk.	1.5 (1)
19 (1)	Y	N	N	Y	N	N	Y	N	N	N	N	20/20	20/20	5
22 (1)	Y	N	N	N	N	N	N	N	N	N	N	6/10	9/10	3 (<1)

* For bilateral disease, complications listed are for the more severely affected side. Y = present; N = absent; Unk. = unknown.
† Family number as used in Table 1 (ID = unique identifier for individuals within a given family).
‡ Ant = anterior uveitis; Vitr = vitreous involvement; Chr = choroidal/retinal involvement.
§ Vsc = retinal vascular disease; KP = keratic precipitates; Cat = cataract; Gla = glaucoma; BK = band keratopathy; ME = macular edema; RD = retinal detachment; OE = optic nerve edema; G = granulomatous.
¶ Most recent visual assessment, using World Health Organization metric scale. OD = right eye; OS = left eye; Enucl. = enucleated eye; Sev. = severe loss of visual acuity.
# Disease duration in years (ocular disease duration in years when available).

RESULTS

A total of 23 probands (with or without additional family members) were entered into the registry. One case of sporadic disease was excluded based on predefined inclusion criteria (the absence of granuloma in the synovial biopsy specimen). The mean age at enrollment was 18.8 years (range 4–49 years) for all participants, and the mean age at disease onset was 26.5 months (range 2–168 months) for the affected participants.

Clinical findings. Of the 22 probands/families studied, 15 presented with the classic phenotype of pediatric granulomatous arthritis (9 sporadic cases and 6 multiplex families in which all affected members exhibited the classic phenotype of pediatric granulomatous arthritis), and 7 had clinical disease that was atypical (Table 1). Within the 15 families with classic pediatric granulomatous arthritis, there were 26 affected individuals (23 Caucasians and 3 biracial [Caucasian/African American] individuals; 16 males and 10 females). Of the 6 multiplex pedigrees with classic pediatric granulomatous arthritis, 4 were bigenerational, 1 was trigenerational, and 1 was monogenerational (2 affected siblings). These multiplex pedigrees correspond to classically denominated Blau syndrome, while the 9 simplex pedigrees correspond to early-onset sarcoidosis.

Of the 26 affected individuals, onset was cutaneous in 15, articular in 7, simultaneous skin and joint in 1, and unknown in 3. No cases of isolated ocular onset were seen. There was no difference in pattern when the multiplex and simplex pedigrees were compared. The type of onset was concordant within 4 multiplex pedigrees and discordant within 2 multiplex pedigrees.

Core system involvement in patients with pediatric granulomatous arthritis. Arthritis was polyarticular in 96% of the affected participants and pauciarticular in 4%. The typical pattern of boggy synovitis was observed in 76% of the patients, while in the rest the synovitis was either "dry" or nonexuberant. Only 40% developed the typical hypertrophic tenosynovitis as described (13,14). Eye involvement was seen in 22 individuals. Table 2 depicts the extent and duration of eye disease. A chronic

persistent course was almost always observed; only 1 patient presented with a single episode. Ocular disease followed disease onset in 21 of 22 patients and was simultaneous with onset in 1. There was no isolated ocular onset or course. Only 7 of 22 patients had involvement limited to the anterior chamber or combined with vitritis (intermediate uveitis). Various degrees of panuveitis were observed in the rest. The disease was bilateral in 21 of 22 patients, but the degree of involvement was generally asymmetric. Fifty percent of the patients developed cataracts, and approximately one-third (6 of 22) had secondary glaucoma at the time of data collection. Nine of the 22 patients had significant or severe visual impairment.

The typical tan-colored, scaly, ichthyosiform rash was seen in 88% of the affected individuals. In 1 patient, the lesions were coalescent into plaque-like lesions. Data were incomplete for 1 patient, and there was no skin involvement in 3 patients. It is possible that in some individuals the rash could have been transient or undetected.

Additional manifestations in patients with pediatric granulomatous arthritis. Two patients also had 1 episode of erythema nodosum–like lesions during the course of the disease. No cases of large-vessel vasculitis were observed in this group. An episode of palpable purpura was observed in 1 patient, and liver granulomata were found on biopsy in another.

Disease extension. One patient from a multiplex pedigree and with 15 years of disease developed new onset of lymphadenopathy and a few areas of ground-glass opacities of the lungs. The lymph node biopsy revealed typical giant cell granuloma.

Atypical forms. Three individuals from 2 families in this series presented with granulomatous panniculitis (2 had uveitis). None of the patients with panniculitis had Blau syndrome/early-onset sarcoidosis mutations in the *CARD15* gene. Another participant presented at age 24 months with disseminated granulomatosis and early involvement of bone marrow and the reticuloendothelial system. Two patients had adult-type sarcoidosis, one with white matter central nervous system involvement and the other with typical hilar adenopathy and aortitis. One patient had granulomatous polyarthritis and no rash or uveitis. Finally, 1 patient had an isolated granulomatous lytic lesion of the proximal tibia with associated knee synovitis. As in the patients with panniculitis, no Blau syndrome/early-onset sarcoidosis *CARD15* mutations were found in these 5 additional "atypical" cases (Table 1).

Genetic findings. Genotyping of the *CARD15* gene was accomplished in 51 individuals. In 2 additional affected individuals, the presence of a *CARD15* mutation was disclosed via personal communication with the physician submitting the contribution to the registry. Genotype data from 36 samples representing pedigrees with the classic phenotype of pediatric granulomatous arthritis and 14 samples from pedigrees with an atypical phenotype are depicted in Table 1. Substitutions R334Q and R334W were predominant. One case (family 21) exhibited a *CARD15* mutation that encodes a glutamic acid–to-lysine substitution at position 383. This mutation has been described in 1 other Blau syndrome family from Italy (10). Interestingly, a novel mutation resulting in a tryptophan-to-leucine substitution at position 490 has been found in the participant from family 22 (Dr. M. Gattorno: personal communication to CDR). No Blau syndrome/early-onset sarcoidosis mutation was found in any asymptomatic family member. All patients with the classic pediatric granulomatous arthritis phenotype who were genotyped had a *CARD15* mutation.

In addition to the known Blau syndrome/early-onset sarcoidosis mutations and careful sequencing analysis of exon 4 for potential new Blau syndrome mutations, we analyzed the 3 mutations associated with CD: R702W, G908R, and 1007frameshift. In families 5 and 15, the frameshift mutation was observed in the proband and 1 parent. Both of these probands have classic pediatric granulomatous arthritis disease and no evidence of CD to our knowledge. Clinical data were not available on the parent in either family with the CD 1007frameshift mutation. In addition, an unaffected parent in family 10 was found to have the R702W mutation, and it is not known whether this individual has CD. Finally, the G908R mutation was present in the proband and 1 parent in family 20. Again, any evidence of CD in the family was not noted. For common, non–disease-associated polymorphisms of *CARD15*, we observed allele frequencies in this cohort to be in the range of those observed in Caucasians in other reported studies (data not shown).

DISCUSSION

The present report summarizes the clinical and genetic findings concerning the largest collection of patients with pediatric granulomatous arthritis assembled to date. We provide data on natural history of eye disease, performance of diagnostic tests, and the spectrum of disease phenotype. Our data confirm that early-onset sarcoidosis and Blau syndrome are clinically and genetically identical. The registry revealed other forms of granulomatous disease that are poorly defined

but distinct from pediatric granulomatous arthritis both clinically and genetically. We refer to them as pediatric systemic granulomatosis and granulomatous panniculitis.

The clinical spectrum of pediatric granulomatous arthritis has evolved over the years. Early reports of the sporadic form were limited to a triad of polyarticular arthritis with onset before age 5 years, uveitis, and rash (13,14), referred to as the "core symptoms" in this report. With time, the spectrum of the disease was expanded by reports of granulomata of the liver (15) and, more significantly, involvement of large vessels (16–18). Noteworthy, however, is the early recognition that some patients experienced dissemination of granulomatous inflammation in the advanced stage of the disease with multiple organ failure, widespread granuloma formation, and significant mortality (19). In our series, the non-core symptoms were limited to erythema nodosum and liver granuloma, and we found no patients with large-vessel vasculitis.

The spectrum of the familial form of pediatric granulomatous arthritis described by Blau (1) has broadened (20). Early reports stressed the restrictive character of disease phenotype (1,14) to the point of excluding reports that suggested otherwise, as in the febrile disease with vasculitis described by Rotenstein et al (21) and the family reported by Jabs et al which featured cranial neuropathy and lacked ichthyosiform rash (2). The contention that the familial form includes "non-core" manifestations was initially suggested by reports by that and other groups (2,22) and was definitely demonstrated in the present study, which confirmed the presence of such involvement in mutation-positive pedigrees. Still, the very severe forms of familial granulomatosis characterized by vasculitis and malignant hypertension may not be the same disease.

In our study, we found no pedigrees carrying the *CARD15* mutation that exhibited either disseminated features or malignant hypertension as in Rotenstein et al's reported family (21). Further, our patients with either disseminated disease or granulomatous panniculitis showed the wild-type form of *CARD15* on genetic testing. Unfortunately, the only other report describing mutation analysis and pedigrees with vasculitis does not provide a detailed clinical description of these pedigrees' involvement (5). Taken together, the findings indicate that a "spectrum model" as suggested by Manouvrier-Hanu et al (23), describing a classic (core) form, an atypical (extra-core symptoms) form, and a systemic form, may, in light of our genotyping results, be modified to encompass only the first 2 forms, since the systemic forms do not show *CARD15* mutation. Based on our clinical and genetic findings, pediatric granulomatous arthritis includes granulomatous boggy synovitis/tenosynovitis (polyarticular and oligoarticular), uveitis of variable severity, and a conspicuous ichthyosiform rash as the most relevant manifestations. Secondarily, erythema nodosum and, perhaps, vasculitis (the latter not found in this series) may be seen as well. In addition, granulomas can be found in the liver and, perhaps, in other organs, but the resulting morbidity in these locations may be minimal.

The rather relaxed inclusion criteria in this registry followed the strategy of similar preceding efforts (11) and led to the recognition of other subsets of pediatric granulomatosis characterized by involvement of bone, bone marrow, spleen, and subcutaneous tissue with prominent clinical manifestations in the affected organ systems (to be reported elsewhere). Pedigrees with those other subsets did not exhibit mutated forms of *CARD15*. Similarly, a patient in this series with neurosarcoidosis and another with hilar adenopathy and aortitis failed to show mutations in the *CARD15* gene, an expected finding given the absence of such mutations in reported studies of adult sarcoidosis (24,25) or sarcoidosis-associated uveitis (26).

Our data support the use of the less invasive skin biopsy as a diagnostic test, since it proved to be diagnostic in all cases in which the typical ichthyosiform rash was present and is less invasive than the synovial biopsy, which was not positive in all affected patients, perhaps due to sampling problems. Although in our series the mutation analysis yielded positive findings in all patients who presented with classic pediatric granulomatous arthritis, this was not consistent with findings reported by Wang et al (mutation was detected in only 50% of their pedigrees) (5). Therefore, we cannot yet recommend the use of genetic testing as a substitute for biopsy.

The most relevant morbidity associated with pediatric granulomatous arthritis is ocular involvement. In our study, one-third of affected individuals had a poor or extremely poor visual outcome. Such evolution seems to be independent of the type of substitution and is not associated with disease duration, but it seems to be observed mainly in the multiplex pedigrees. Although one of us (JTR) and others have previously characterized the ophthalmic findings in Blau syndrome (27), the present report expands observations on uveitis and ocular complications in a larger number of patients. All of the 14 genotyped classic pediatric granulomatous arthritis pedigrees demonstrated the presence of the *CARD15* mutation in their affected members, while the

mutation was absent from the unaffected members of the multiplex pedigrees and from all of the non-index cases of the simplex pedigrees. The absence of mutation-negative affected individuals in our study contrasts with the 50% negativity in the series described by Wang et al (5). In that series, the 10 pedigrees were described as displaying the "classic Blau syndrome phenotype." Even though the presence of at least 2 of 3 core symptoms was reported in all affected family members, detailed clinical information was not provided. This information would have been particularly vital regarding the 5 families in whom the mutation was not detected.

Reports to date examining *CARD15* mutations in either Blau syndrome or early-onset sarcoidosis cohorts have demonstrated *CARD15* mutations in 21 of 27 pedigrees or cases studied (4,5,7–10). A total of 9 unique amino acid substitutions that are considered to cause disease have been identified. Of these, 2 mutations at arginine 334 are most common, responsible for 14 of 27 pedigrees or cases reported. There was also a predominance of R334 substitution in our registry cohort (12 of 14 pedigrees genotyped). It should be noted that one of the simplex pedigrees (family 5) in the present report was the subject of an earlier case report (8). Of the 7 mutations affecting amino acids other than arginine at position 334, each has been found in only 1 case or pedigree. Two were discovered in families with Blau syndrome (L469F and E383K), and 5 were reported in cases of early-onset sarcoidosis (H496L, T605P, N670K, M513T, and D382E). In the present study, a second example of the E383K replacement has been found, and a previously unreported W490L substitution has been identified (Dr. M. Gattorno: personal communication to CDR).

All of these mutations are located in exon 4 of *CARD15*. The protein contains different functional motifs, including a centrally located NACHT domain. All but 2 of the Blau syndrome/early-onset sarcoidosis mutations are found within the NACHT or NACHT-associated domain of *CARD15*. Detailed structure-function analyses will be needed to fully elucidate the consequences of these mutations for the protein and its role in the development of inflammatory disease.

In this series, we combined families and individuals from both multiplex and simplex pedigrees since the clinical equivalence of the familial form (Blau syndrome) and the sporadic form (early-onset sarcoidosis) has been demonstrated. This contention had been proposed by Miller (28) and Blau (29) many years before the genetics of the disease became known. We suggested the adoption of a single name for this condition—pediatric granulomatous arthritis—to reflect the fact that both represent the same pathologic process.

Efforts to expand the size of this sample are under way. Elucidating the best sight-sparing early therapeutic strategies, investigating associated genetic predictors of severity, and advancing the in vitro work to understand the downstream effects of *CARD15* mutations are some of the more pressing needs to which future research efforts should be directed. Several lines of investigation implicate activation of NF-κB, a potent inflammatory signaling molecule. This suggests that biologic agents targeted at blocking interleukin-1 and tumor necrosis factor (TNF) may have therapeutic potential. Eighteen of the 35 living affected patients in this study (with both typical and atypical disease) are receiving anti-TNF therapy. Anecdotal reports suggest a beneficial effect of infliximab in controlling the articular symptoms (30). Understanding the arthritogenic mechanisms of this mutation not only could help in the selection of more specific treatment strategies, but it might also shed light on other pediatric diseases affecting the synovial membrane and the uveal tract, such as juvenile idiopathic arthritis.

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APPENDIX A: REGISTRY CONTRIBUTORS

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