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長船健二	iPS細胞作製の最先端と作製されたiPS細胞株間の特性差異についての最新の知見	実験医学増刊（再生医療の最前線2010）	28	55-61	2010

長船健二	iPS細胞技術を用いた腎臓再生医療の開発	腎と透析	69	368-373	2010
中畑龍俊	対談「血液および血液疾患を語る(22)　造血幹細胞の体外増幅―ｉＰＳ細胞の応用も含めて―」	最新医学	66(1)	123-132	2011
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中畑龍俊	iPS細胞は長寿へ導く夢のタイムマシーンである（特集02　カラダを再生する画期的な細胞の誕生）	Back Up	30	8-12	2011
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森嶋達也、平家俊男	ヒトiPS細胞からの好中球分化誘導	血液内科	63	332-338	2011
斎藤潤	インフラマソームとその関連疾患の最近の知見	日本臨床免疫学会雑誌	34	20-28	2011
中畑龍俊	再生医療の進歩（Ⅱ再生医療の進歩）	小児科診療	75(1)	57-63	2012
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Role of the *NOD2* Genotype in the Clinical Phenotype of Blau Syndrome and Early-Onset Sarcoidosis

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Objective. **Blau syndrome and its sporadic counterpart, early-onset sarcoidosis (EOS), share a phenotype featuring the symptom triad of skin rash, arthritis, and uveitis. This systemic inflammatory granulomatosis is associated with mutations in the *NOD2* gene. The aim of this study was to describe the clinical manifestations of Blau syndrome/EOS in Japanese patients and to determine whether the *NOD2* genotype and its associated basal NF-κB activity predict the Blau syndrome/EOS clinical phenotype.**

Methods. **Twenty Japanese patients with Blau syndrome/EOS and *NOD2* mutations were recruited. Mutated *NOD2* was categorized based on its basal NF-κB activity, which was defined as the ratio of NF-κB activity without a *NOD2* ligand, muramyldipeptide, to NF-κB activity with muramyldipeptide.**

Results. **All 9 mutations, including E383G, a novel mutation that was identified in 20 patients with Blau syndrome/EOS, were detected in the centrally located NOD region and were associated with ligand-independent NF-κB activation. The median age of the patients at disease onset was 14 months, although in 2 patients in Blau syndrome families (with mutations R334W and E383G, respectively) the age at onset was 5 years or older. Most patients with Blau syndrome/EOS had the triad of skin, joint, and ocular symptoms, the onset of which was in this order. Clinical manifestations varied even among familial cases and patients with the same mutations. There was no clear relationship between the clinical phenotype and basal NF-κB activity due to mutated *NOD2*. However, when attention was focused on the 2 most frequent mutations, R334W and R334Q, R334W tended to cause more obvious visual impairment.**

Conclusion. ***NOD2*** **genotyping may help predict disease progression in patients with Blau syndrome/EOS.**

Sarcoidosis is a systemic inflammatory disease with unknown etiology, but it can be clinically characterized by swelling of the bilateral hilar lymph nodes and histologically defined by the presence of noncaseating epithelioid cell granulomas. A special subtype called early-onset sarcoidosis (EOS; MIM no. 609464) occurs in children younger than 4 years of age and is characterized by a distinct triad of skin, joint, and eye disorders without apparent pulmonary involvement (1). An autosomal-dominant disease with clinical manifestations similar to those of EOS has been recognized as Blau syndrome (MIM no. 186580) (2,3). The gene responsible for Blau syndrome has been mapped close to the inflammatory bowel disease 1 (*IBD1*) locus by linkage analysis (4), and later the nucleotide-binding oligomerization domain 2 gene (*NOD2*) was identified by Miceli-Richard et al to be responsible for Blau syndrome (5). In the study by Miceli-Richard et al, 2 European patients with EOS had no mutation in *NOD2*; therefore, it remained

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controversial whether Blau syndrome and EOS have the same etiology.

In 2004, we encountered a 27-year-old Japanese man with multiple lichenoid papules. He was almost blind, exhibited camptodactyly, and had a continuous low-grade fever. This case of sporadic systemic granulomatosis with clinical features of EOS showed the same *NOD2* mutation, the arginine-to-tryptophan substitution at amino acid 334 (R334W), as that detected in Blau syndrome (6). Therefore, we expanded this report (6) and retrospectively examined cases of EOS in Japan and observed that 9 of 10 patients with EOS had *NOD2* mutations (7). Until recently, other investigators have also confirmed that Blau syndrome and EOS are clinically and genetically identical across various ethnic groups (8–10).

NOD2 activates NF-κB after recognizing a signal from a bacterial cell wall component, muramyldipeptide, in the cytoplasm of monocytes, and thus can work as an intracellular sensor of bacteria (11,12). *NOD2* has a tripartite domain structure consisting of 2 amino-terminal domains (termed caspase activation and recruitment domains) that are composed of protein–protein interaction cassettes, 1 centrally located NOD, and carboxy-terminal leucine-rich repeats (LRRs) (13). Using assays of NF-κB activity, an impaired ligand-dependent response was demonstrated for 3 Crohn's disease–associated mutations located in *NOD2* LRRs (14,15), whereas enhanced ligand-independent NF-κB activity was demonstrated for *NOD2* alleles associated with Blau syndrome and EOS (5,7,16). However, it remains unknown how increased basal NF-κB activity derived from gain-of-function mutations in *NOD2* affects the pathogenesis of Blau syndrome/EOS and whether a genotype–phenotype correlation exists between the clinical manifestations or onset of Blau syndrome/EOS and *NOD2* mutations.

Because Blau syndrome/EOS is so rare, very few reports are in the literature. Therefore, it was worthwhile to conduct a nationwide survey limited to patients with a specific ethnic background, such as Japanese patients. In this study, we precisely documented the clinical manifestations in a cohort of Japanese patients with Blau syndrome/EOS and *NOD2* mutations, including 9 previously reported cases (7), and explored the genotype–phenotype correlation to the basal NF-κB activity associated with each mutation, especially focusing on the correlation of visual impairment with the most frequent mutations, R334W and R334Q.

PATIENTS AND METHODS

Patients and clinical information. Among patients with clinically diagnosed Blau syndrome/EOS, the 20 patients with *NOD2* mutations were included in this study (7,17–20). None of these mutations were identical to the reported single-nucleotide polymorphisms (SNPs) of *NOD2*, nor were they detected in 100 Japanese healthy volunteers. Clinical information and patient histories were collected from medical records and by direct interviews of the patients and their attending physicians. The presence of each symptom was established as follows: a) persistent or repeated transient skin lesions without definite cause were determined, b) persistent or repeated transient arthritis without definite cause was determined, c) uveitis was diagnosed by an ophthalmologist, and d) remittent or intermittent fever without definite cause was determined under close examination at the time of hospital admission. The age at disease onset was defined as the age of the patient when any of the above-mentioned symptoms appeared.

Clinical evaluation was performed primarily when individual symptoms first appeared that were hardly affected by treatment or disease duration. The severity of visual impairment was assessed in accordance with the World Health Organization definition (21). Briefly, moderate visual impairment was defined as visual acuity between 6/18 and 3/60, and severe visual impairment was defined as acuity of 3/60 or less in the better eye with best correction, as previously described (9). Written informed consent was obtained from the patients and their families, and the study protocol was in accordance with the guidelines of the Institutional Review Board of Kyoto University Hospital.

Genetics analysis. Genomic DNA was extracted from the peripheral blood of the patients, and sequencing of all exons and exon–intron junctions of *NOD2* was performed as previously described (7).

Generation of *NOD2* mutants and NF-κB luciferase assay. Expression plasmids of *NOD2* and its mutants were subcloned into the p3xFLAG-CMV vector, as previously described (7). Blau syndrome/EOS–associated mutants were generated using the QuikChange site-directed mutagenesis kit (Stratagene, La Jolla, CA), as described previously (7). The ability of each construct to induce NF-κB activity was assessed by dual luciferase reporter assay in HEK 293 human embryonic kidney cells, as previously described (7).

Other analyses. We determined the age at the time of this survey, the age at onset of each symptom, and the *NOD2* genotype for all patients as well as the distribution of age at disease onset. Next, we analyzed the relationship between age at disease/symptom onset and basal NF-κB activity due to mutated *NOD2*. Basal NF-κB activity was defined as the ratio of NF-κB reporter activity without muramyldipeptide to NF-κB reporter activity with muramyldipeptide, as determined using the in vitro NF-κB luciferase assay described above. The activity was arbitrarily categorized as low (<0.3), moderate (0.3–0.5), and high (>0.5). Finally, we analyzed the relationship between visual impairment (normal, moderate, severe) and basal NF-κB activity (low, moderate, high) due to individual mutated *NOD2* genes, particularly the 2 most frequent mutations, R334W and R334Q. We did not perform statistical analysis because of the limited number of patients.

Table 1. Demographic and clinical characteristics of the patients with Blau syndrome/early-onset sarcoidosis*

Patient/ age/sex	Genotype	Fever		Skin rash		Arthritis		Uveitis		Visual acuity		Ref.
		Age at onset	Type	Age at onset	Type	Age at onset	Type	Age at onset	Type	OD	OS	
1/15/F†	E383G	2 yr 3 mo	Int	8 mo	LP/SE/EN	3 yr	Poly	11 yr	A/P	20/50	20/67	
2/48/F†	E383G	5 yr	Per	5 yr	LP/SE/EN	11 yr	Poly	11 yr	A/P	HM	Null	
3/36/F	H496L	–	–	1 yr	LP/SE	3 yr	Poly	5 yr	A/P	20/20	20/20	7
4/16/M	R334Q	1 yr 8 mo	Int	6 mo	LP/SE	1 yr 8 mo	Poly	1 yr 10 mo	A/P	20/22	20/22	
5/19/M	R334Q	2 yr 7 mo	Per	1 yr 4 mo	LP/SE/EN	10 mo	Poly	5 yr	A/P	20/50	20/20	17
6/8/F	R334Q	–	–	–	–	3 yr	Poly	–	–	20/20	20/20	
7/8/M	T605P	–	–	7 mo	LP/SE	1 yr 6 mo	Poly	3 yr 3 mo	A/P	20/25	20/50	7
8/18/F	D382E	–	–	3 yr 4 mo	LP/SE	4 yr	Poly	5 yr 4 mo	A/P	20/20	20/25	7, 18
9/13/M	R334W	8 mo	Per	1 yr 3 mo	LP/SE/EN	8 mo	Poly	1 yr 8 mo	A/P	20/29	20/33	
10/32/M	R334W	2 yr	Int	2 yr	LP/SE	1 yr 3 mo	Poly	6 yr	A/P	Blind, 20 yr	Blind, 20 yr	6, 7
11/21/F	R334W	2 yr 1 mo	Per	2 yr 1 mo	LP/SE	6 yr	Poly	4 yr	A/P	20/670	20/330	7, 19
12/33/M	R334W	–	–	2 yr	LP/SE	–	–	13 yr	A/P	20/29	20/20	7
13/31/F	R334W	–	–	2 yr 6 mo	LP/SE	8 yr	Poly	3 yr 6 mo	A/P	20/100	20/200	7
14/10/F†	R334W	1 yr	Per	1 yr	LP/SE	1 yr	Poly	2 yr	A/P	20/40	Null	
15/46/F†	R334W	–	–	44 yr	LP/SE	8 yr	Poly	3 yr	A/P	Blind, 28 yr	Blind, 28 yr	
16/16/M†	R334W	–	–	6 yr	SE	1 yr	Oligo	6 yr	A/P	20/13	20/13	20
17/18/F†	R334W	–	–	12 yr	SE	8 yr	Oligo	12 yr	A/P	20/40	20/25	20
18/8/M	M513T	2 yr 10 mo	Int	2 yr 8 mo	SE	2 yr 9 mo	Poly	2 yr 11 mo	A	20/17	20/17	7
19/15/F	N670K	1 yr 8 mo	Int	5 mo	LP/SE/EN	1 yr 8 mo	Poly	3 yr	A/P	20/200	20/200	7
20/7/M	C495Y	1 yr	Int	1 yr	LP/SE	1 yr	Poly	–		20/20	20/20	

* Patient 5 also had left ventricular dysfunction and pulmonary hemorrhage due to bronchial granuloma. Patient 10 also had interstitial pneumonia. Patient 11 also had hepatosplenomegaly and parotid swelling. Patient 18 also had renal calcification. OD = right eye; OS = left eye; yr = years; mo = months; Int = intermittent; LP = multiple lichenoid papules; SE = scaly erythematous plaques; EN = erythema nodosum–like lesion; Poly = polyarticular; A = anterior; P = posterior; Per = persistent; HM = hand motion; Oligo = oligoarticular.
† Familial case.

RESULTS

Genotype and basal NF-κB activity. The study population comprised 9 male patients and 11 female patients, with a median age of 17 years (range 7–48 years) and a median disease duration of 15 years (range 5–43 years). Fourteen of these 20 cases were sporadic (EOS), and 6 were familial (Blau syndrome). The familial cases were in 3 unrelated families; 2 families (patients 14 and 15 and patients 16 and 17, respectively) had Blau syndrome/EOS symptoms in 2 generations, and 1 family (patients 1 and 2) had Blau syndrome/EOS symptoms in 3 generations. The most frequent heterozygous mutation of *NOD2* was R334W (1000C>T), which was recognized in 2 familial and 5 sporadic cases (total of 9 cases), followed by R334Q (1001G>A) in 3 sporadic cases, and E383G (1148A>G, a novel amino acid substitution) in 2 familial cases (in 1 family). H496L (1487A>T), T605P (1813A>C), D382E (1146C>G), M513T (1538T>C), N670K (2010C>A), and C495Y (1484G>A) were detected in 1 sporadic case each (Table 1).

Nine mutations were identified in the centrally located NOD region (Figure 1a) and were associated with increased basal NF-κB activity in the absence of muramyldipeptide (Figure 1b), which is consistent with the finding of a previous study on Blau syndrome/EOS–associated *NOD2* mutations (16). We also confirmed that 100 healthy control subjects and their genotyped asymptomatic relatives did not have these amino acid substitutions. Therefore, we concluded that these *NOD2* mutations (amino acid substitutions) detected in patients with Blau syndrome/EOS were not SNPs but rather were disease-causing mutations.

Disease onset. The defining characteristic of EOS is its onset in children younger than age 4 years (1). In the present study, despite the median age at disease onset of 14 months, the first clinical symptoms developed at age 5 years or older in 2 patients (patients 2 and 17, who were members of different Blau syndrome families) with the E383G mutation and the R334W mutation, respectively (Table 2). In patient 2, skin rash developed at age 5 years; in patient 17, arthritis developed at age 8 years (Table 1).

The earliest presenting symptom was skin rash in 13 patients (65%), arthritis in 8 patients (40%), and ocular symptoms in 1 patient (patient 15, who had familial Blau syndrome with the R334W mutation) (Table 1). Approximately 95%, 95%, and 90% of pa-

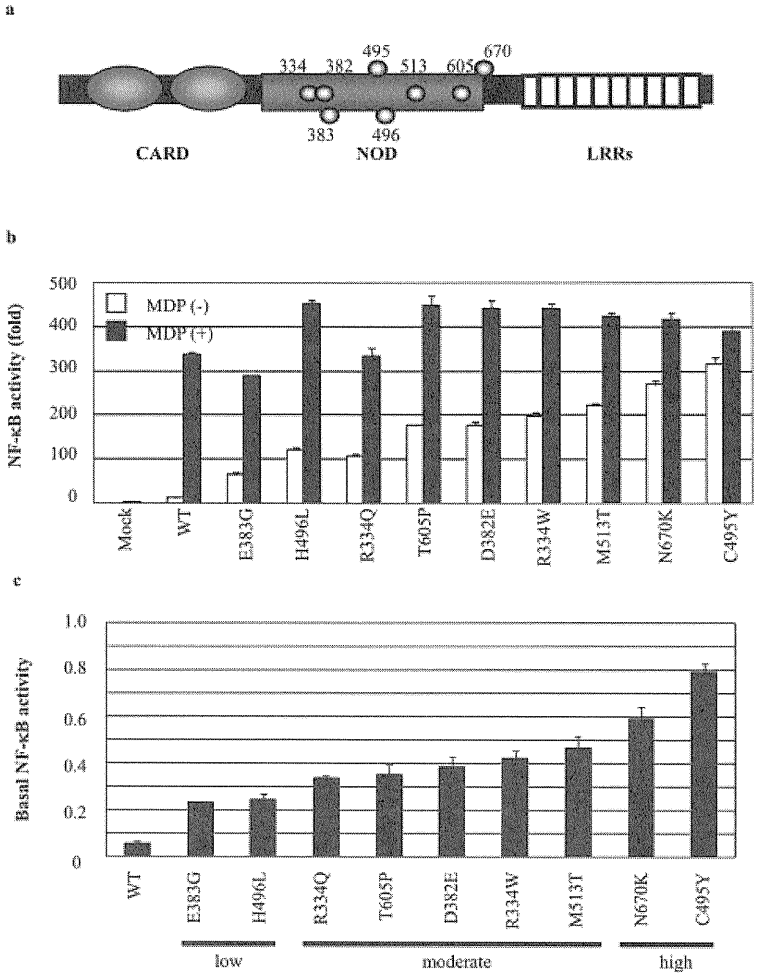

Figure 1. Biologic effects of *NOD2* mutants discovered in patients with Blau syndrome/early-onset sarcoidosis (EOS). **a,** Schematic presentation of NOD-2 protein. Numbers indicate the positions of mutated amino acid residues identified in our cohort. **b,** Increased basal NF-κB activity due to different mutated *NOD2* genes in patients with Blau syndrome/EOS. HEK 293T cells were cotransfected with a *NOD2* mutant together with the NF-κB reporter plasmid and internal control plasmid, and NF-κB reporter activity was measured after 12 hours of incubation with or without muramyldipeptide (MDP; 5 μg/ml). Mock vector and wild-type (WT) *NOD2* were used as controls. Bars show the mean and SD of normalized data (mock without muramyldipeptide = 1) from triplicate cultures. Results are representative of 3 independent experiments. **c,** Basal NF-κB activity due to mutated *NOD2* in patients with Blau syndrome/EOS. Bars show the mean and SD results from 3 independent experiments. CARD = caspase activation and recruitment domain; LRRs = leucine-rich repeats.

tients, respectively, had skin, joint, and ocular symptoms. Consistent with the previous report (1), a triad of skin, joint, and ocular symptoms developed (in this order) in many patients with Blau syndrome/EOS. The median age at onset of rash, arthritis, and uveitis was 24 months, 33 months, and 4.5 years, respectively (Table 2).

The triad of symptoms. All except 1 patient (patient 6 [with the R334Q mutation]) had skin manifestations. Consistent with a previous report (22), the most frequent skin symptom was scaly erythematous plaques with multiple lichenoid papules. Several patients (patients 1 and 2 with the E383G mutation, patient 5

Table 2. Age of the patients at the onset of disease and symptoms*

Age, years	Disease onset (n = 20)	Symptom onset			
		Fever (n = 11)	Rash (n = 19)	Arthritis (n = 19)	Uveitis (n = 18)
0	6 (30)	1 (9)	4 (21)	2 (11)	0 (0)
1	5 (25)	4 (36)	5 (26)	7 (37)	2 (11)
2	4 (20)	5 (45)	5 (26)	1 (5)	2 (11)
3	3 (15)	0 (0)	1 (5)	3 (16)	4 (22)
4	0 (0)	0 (0)	0 (0)	1 (5)	1 (6)
≥5	2 (10)	1 (9)	4 (21)	5 (26)	8 (44)

* Values are the number (%). The median age at disease onset was 1 year 2 months; the median age at onset of fever and rash was 2 years; the median age at onset of arthritis was 2 years 9 months; the median age at onset of uveitis was 4 years 6 months.

with the R334Q mutation, patient 9 with the R334W mutation, and patient 19 with the N670K mutation) had erythema nodosum–like lesions on their lower limbs in addition to solid lichenoid eruptions. Notably, 3 patients (patients 16 and 17 with the R334W mutation and patient 18 with the M513T mutation) showed only scaly erythematous plaques without lichenoid papules (Table 1).

All except 1 patient (patient 12 with the R334W mutation) had joint lesions (polyarticular arthritis in 17 patients and oligoarticular arthritis in 2 [patients 16 and 17]) (Table 1). Both patients with oligoarticular arthritis, who had familial Blau syndrome with the R334W mutation, had camptodactyly without obvious synovial cysts. Camptodactyly with synovial cysts is frequently described as a typical joint sign in patients with Blau syndrome/EOS (10). A consequence of arthritis was the use of a wheelchair for daily mobility in 2 patients (patient 5 with the R334Q mutation and patient 10 with the R334W mutation).

All except 2 patients (patient 6 with the R334Q mutation who also lacked skin eruptions and patient 20 with the C495Y mutation) had ocular lesions. The lesions were bilateral, although visual acuity was asymmetric, as in previous studies (22,23). Moreover, 17 (89%) of all 18 patients with ocular lesions had panuveitis, while only 1 patient (patient 18 with mutation M513T) had anterior uveitis, which demonstrated the predominance of panuveitis over anterior uveitis. Ocular symptoms were the last of the triad to develop in 15 of the 18 patients and the first to develop in only 1 patient (patient 15 with mutation R334W).

Clinical features other than the triad of symptoms. It is noteworthy that 11 patients (55%) experienced fever at a median age of 24 months, almost simultaneously with skin and/or joint symptoms (Table 1). Five patients had persistent fever reaching 38–40°C, and 6 patients had intermittent fever. In particular, in 1 patient (patient 9 with mutation R334W) the disease developed with intermittent fever (which then became persistent fever over the next 6 months) and finger joint swelling. In only 1 previous report (10), fever is mentioned as a clinical symptom of Blau syndrome/EOS, although there are some case reports in which fever was present at disease onset (24).

Four patients had involvement of organs other than the skin, joints, and eyes (Table 1). Two patients had pulmonary lesions (interstitial pneumonitis in patient 10 with the R334W mutation and bronchial granuloma in patient 5 with the R334Q mutation). Bilateral hilar lymph nodes, which are identified by chest radiography and/or computed tomographic scanning, were not observed in any patient. Patient 11 with the R334W mutation exhibited hepatosplenomegaly and parotid swelling (19), and patient 18 with the M513T mutation exhibited renal calcification. No cases of large-vessel vasculitis were observed in this cohort, even though vasculitis has been reported in patients with EOS (25–27).

Triggering factors. BCG vaccination was associated with the onset of disease (i.e., development of multiple papules on the extremities) in 2 patients, although no apparent infection or vaccination was clearly documented in other patients of our cohort. In 1 patient (patient 7 with mutation T605P) who had papules on the extremities, the spread of papules was from the site of BCG vaccination. In the other patient (patient 1 with mutation E383G), Gianotti disease was initially diagnosed, but a close review of her medical history later indicated that her multiple papules were a symptom of Blau syndrome/EOS.

Relationship between the onset of disease/symptoms and basal NF-κB activity due to mutated *NOD2*. Because disease duration and treatment varied among patients, we focused on the onset of disease and of each clinical symptom (i.e., fever, rash, arthritis, and uveitis). We evaluated the relationship between age at the onset of disease/symptoms and basal NF-κB activity due to mutated *NOD2* (defined as the ratio of NF-κB activity without a *NOD2* ligand, muramyldipeptide, to NF-κB activity with muramyldipeptide for each mutated *NOD2*). The calculated basal NF-κB activity ranged from 0.23 to 0.79 (mean 0.42) for mutated *NOD2* and was 0.05 for wild-type *NOD2* (Figure 1c).

Because the number of patients with each *NOD2* mutation was limited, we arbitrarily categorized basal NF-κB activity as low (<0.3), moderate (0.3–0.5), and high (>0.5). According to these criteria, mutations E383G and H496L were associated with low activity; mutations R334Q, T605P, D382E, R334W, and M513T were associated with moderate activity; and mutations

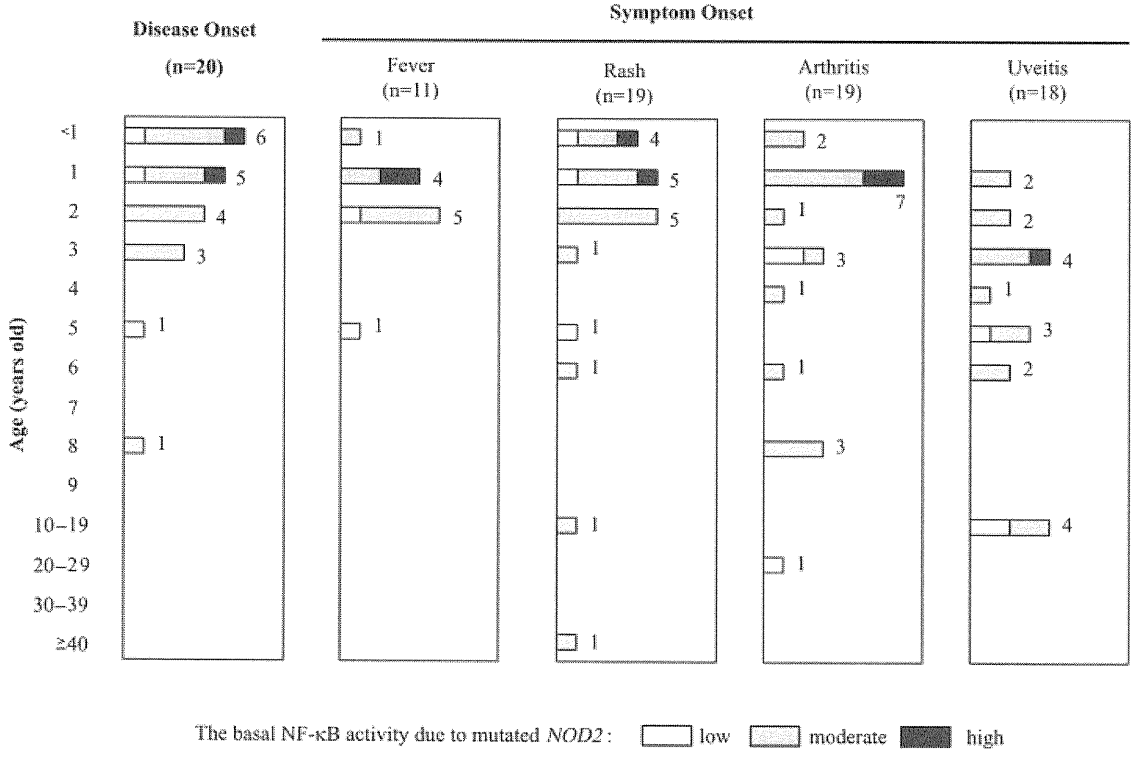

Figure 2. Relationship between age at disease or symptom onset and basal NF-κB activity due to mutated *NOD2*. Among the 9 patients without fever, 8 had moderate and 1 had low basal NF-κB activity. One patient without rash had moderate basal NF-κB activity, and 1 patient without arthritis had moderate basal NF-κB activity. Of 2 patients without uveitis, 1 had high and the other had moderate basal NF-κB activity.

N670K and C495Y were associated with high basal NF-κB activity. Our limited number of patients was insufficient to detect a correlation between the defined basal NF-κB activity and the onset of disease, fever, rash, arthritis, and uveitis (Figure 2). Notably, the age at onset of symptoms varied markedly between patients with the same R334W mutation, even in familial cases (Table 1).

Relationship between visual impairment and basal NF-κB activity due to mutated *NOD2*. The most relevant morbidity associated with Blau syndrome/EOS is ocular involvement, which is usually refractory to conventional treatment. Thus, we next explored the relationship between visual impairment and basal NF-κB activity. There was no clear correlation when the analysis included all recruited patients (Table 3). When we focused on the most frequent genotypes R334Q and R334W, between-genotype differences in visual impairment were observed (Table 4). Basal NF-κB activity was higher in patients with the R334W mutation than in those with the R334Q mutation (Figure 1c). None of the 3 patients with the R334Q mutation had visual impairments, while 4 of 9 patients with the R334W mutation

Table 3. Correlation between visual impairment and basal NF-κB activity*

	Visual impairment			Disease duration, median (range) years
	Normal	Moderate	Severe	
Basal NF-κB activity				
Low	2	0	1	35 (15–43)
Moderate	11	2	2	15 (5–43)
High	1	1	0	10.5 (6–15)

* Except where indicated otherwise, values are the number of patients.

Table 4. Correlation between visual impairment and the 2 most frequent genotypes*

	Visual impairment			Disease duration, median (range) years
	Normal	Moderate	Severe	
Present study				
R334Q	3	0	0	15 (5–19)
R334W	5	2	2	19 (9–43)
Previous study (9)				
R334Q	8	0	0	12 (3–26)
R334W	8	2	1	16 (5–44)

* Except where indicated otherwise, values are the number of patients.

had visual impairments. This result suggests that patients with the R334W mutation were more likely to have visual impairments than were those with the R334Q mutation (Table 4).

DISCUSSION

Blau syndrome/EOS is a rare systemic granulomatosis that has been associated with *NOD2*. In this study, patients with Blau syndrome/EOS and *NOD2* mutations were retrospectively recruited nationwide in Japan, to determine whether the *NOD2* genotype and its functional abnormality predict the Blau syndrome/EOS clinical phenotype. This study is the first to investigate the correlation between the *NOD2* genotype and its functional abnormality and the Blau syndrome/EOS clinical phenotype. Our findings suggest that *NOD2* genotyping may help predict disease progression in patients with Blau syndrome/EOS, although the clinical severity of Blau syndrome/EOS was not clearly associated with basal NF-κB activity due to mutated *NOD2* among the limited number of patients we studied.

The classic Blau syndrome/EOS symptom triad is skin rash, arthritis, and uveitis. Corresponding clinical manifestations include widespread erythematous papules, polyarthritis with boggy synovial swellings, and panuveitis (1,9,10,23), which were also identified in the present study. Rose et al described 2 patients who also had 1 episode of erythema nodosum–like lesions during the course of the disease (9). In our cohort, 5 patients had erythema nodosum–like lesions, suggesting that this should be recognized as one of the skin manifestations associated with Blau syndrome/EOS.

In the current study, 55% of the patients had fever, which always accompanied at least 1 symptom of the classic triad. Arostegui et al also reported that 50% of their cohort had recurrent or persistent fever (10). These findings suggest that fever is one of the important symptoms of Blau syndrome/EOS and is the reason why Blau syndrome/EOS is misdiagnosed as systemic-onset juvenile idiopathic arthritis (JIA). In fact, patient 11 in our study (who had the R334W mutation) experienced persistent fever reaching 40°C and received aggressive immunosuppressive therapy, because systemic-onset JIA was initially diagnosed. This case alerts us to the possibility that patients with Blau syndrome/EOS can sometimes have fever, and that Blau syndrome/EOS can resemble systemic-onset JIA.

Bilateral hilar lymph nodes, which are often seen in adult sarcoidosis, are not observed in Blau syndrome/EOS, but this does not mean that pulmonary lesions do not occur in patients with Blau syndrome/EOS. In fact, 2 patients (patient 5 [with the R334Q mutation] and patient 10 [with the R334W mutation]) had pulmonary lesions; in particular, patient 10 had the first reported case of sporadic EOS in association with the *NOD2* mutation (6). Another case of Blau syndrome/EOS with pulmonary lesions and interstitial pneumonitis, but not bilateral hilar lymph nodes, has also been reported (28). These findings suggest the importance of following up patients with Blau syndrome/EOS to check for not only the classic triad of symptoms but also other abnormalities, including pulmonary lesions.

Blau syndrome/EOS, which usually occurs in children younger than age 4 years, developed at 5 years and 8 years, respectively, in 2 patients in the present study (patient 2 [with the E383G mutation] and patient 17 [with the R334W mutation]). Because both of these patients had a family history of skin rash/arthritis/uveitis, they had been closely monitored by their parents as well as by their physicians. Therefore, it is unlikely that any symptoms that occurred when the patients were younger than 4 years of age were overlooked in these 2 cases. In the literature, there is 1 case of Blau syndrome in which skin rash, persistent fever, and camptodactyly started to develop at age 18 years (10). These findings indicate that the onset of Blau syndrome/EOS can be at age 5 years or older, and that disease onset in a patient younger than 4 years should not be considered requisite for a diagnosis of Blau syndrome/EOS.

In our cohort, the age at disease/symptom onset, organ involvement, and severity of Blau syndrome/EOS varied substantially even within affected families and between individuals with the same *NOD2* mutation (e.g., R334W). In other genetic disorders, identical mutations have been associated with phenotypic variation in unrelated individuals, within a family, and even in monozygotic twins (29). Phenotypic variation in Blau syndrome/EOS has been reported in monozygotic twins; therefore, nongenetic factors such as environmental conditions and/or infectious agents might be involved in phenotypic variation (24). Interestingly, in 2 of our cases, BCG vaccination was an obvious triggering factor. In addition, a previous report noted that cutaneous lesions first arose after BCG vaccination in a patient with Blau syndrome/EOS (30). The BCG vaccine contains muramyldipeptide, a ligand for NOD-2 protein (11,12), which is interesting from a pathophysiologic point of view. However, BCG vaccination did not always cause the onset of disease in patients with Blau syndrome/EOS, because most patients in our cohort were vaccinated with BCG according to the immunization protocol used in areas of