Identification of a novel missense mutation in the NOD2 gene in a Chinese child with early-onset sarcoidosis

Sir,

Early-onset sarcoidosis is known to appear in children younger than 4 years of age, and is characterized by a distinct triad of skin, joint and eye disorders without pulmonary involvement. Blau syndrome has been identified as the familial phenotype of this type of granulomatous autoinflammatory disease. Both are monogenic syndromes caused by mutations in the *NOD2* gene.[1] We found a novel p. Y563D mutation in *NOD2* gene in a Chinese boy with early-onset sarcoidosis.

A 6-year-old Chinese boy presented to the Institute of Dermatology, Chinese Academy of Medical Sciences and Peking Union Medical College with subcutaneous nodules over the joints and multiple asymptomatic papules over the trunk and limbs. He had developed subcutaneous nodules over the ankle and wrist joints, which was accompanied by symmetric polyarthritis affecting the wrist, ankle and proximal interphalangeal joints, two years back. He also developed multiple non-pruritic papules over the trunk and limbs, six months ago. His medical history was normal except for cleft lip and palate, which were repaired at 10 months of age. No familial history of similar disease was present. On dermatological examination, numerous 1–2 mm sized, red flat-topped papules covered the trunk and extremities [Figure 1a and b]. Coexisting subcutaneous nodules were found over the affected joints and the dorsum of hand and foot [Figure 1c and d]. Camptodactyly of the fingers was observed. No abnormalities were detected in ophthalmological examinations. Routine blood tests, serum calcium level, hepatic function panel and urine analysis tests showed normal results. The serum angiotensin-converting enzyme was 135 U/L (reference range, 20–100 U/L). A tuberculin test was negative. Chest radiographs were unremarkable. Radiographs of the involved joints revealed swollen soft tissue, with no bone abnormalities. Skin biopsy demonstrated noncaseating granulomas admixed with scant lymphocytes infiltration [Figure 1e]. Polarized microscopy

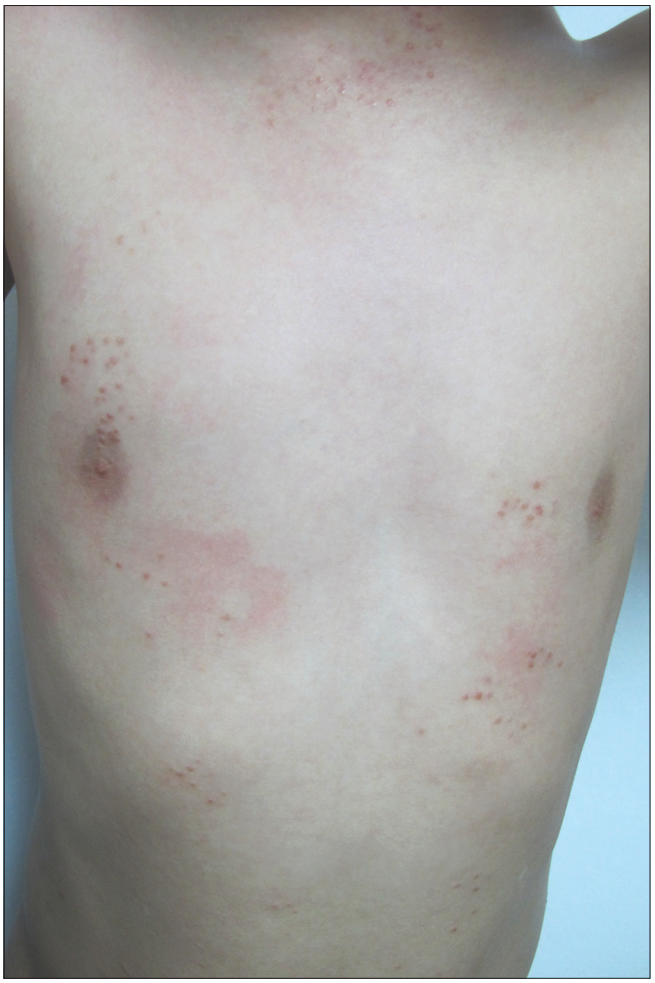

Figure 1a: Numerous 1–2 mm, red-brown to pinkish tan flat-topped papules on the trunk

Access this article online	
Quick Response Code:	Website: www.ijdvl.com
	DOI: 10.4103/ijdvl.IJDVL_645_16

How to cite this article: Wang X, Zhang X, Zhang W, Sun J. Identification of a novel missense mutation in the NOD2 gene in a Chinese child with early-onset sarcoidosis. Indian J Dermatol Venereol Leprol 2018;84:645.

Received: July, 2016. **Accepted:** April, 2017.

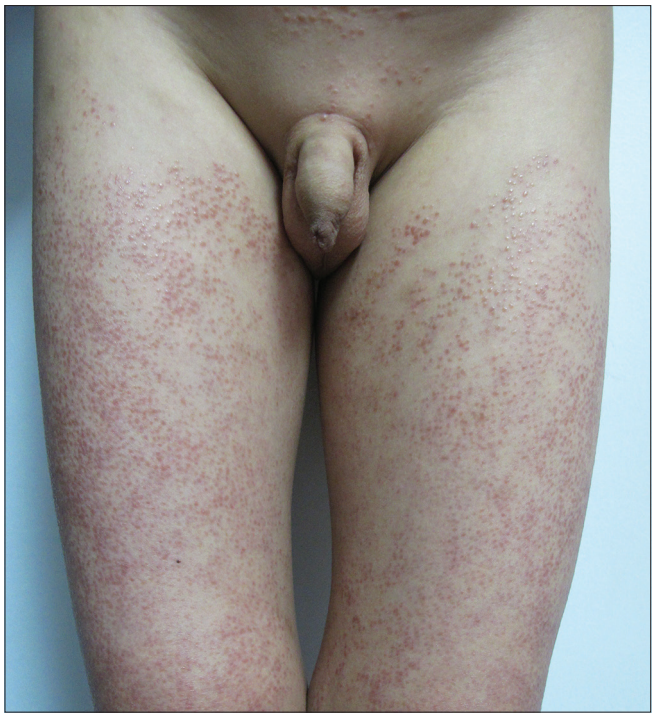

Figure 1b: Numerous 1–2 mm, red-brown to pinkish tan flat-topped papules on extremities

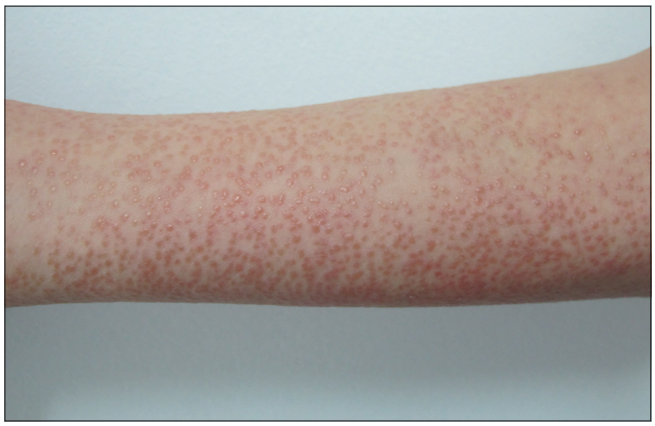

Figure 1d: Subcutaneous nodules over the affected joints and the dorsum of the hand, and finger joints are fixed at the flexor positions, showing camptodactyly

failed to reveal foreign material. Periodic acid-Schiff and Fite's staining were negative for organisms.

Genetic analysis via direct sequencing of the *NOD2* gene revealed a heterozygous missense mutation in c. 1687 T>G (p. Y563D) [Figure 2], which was not detected in his unaffected parents, and a heterozygous synonymous mutation c. 1761 T>G (p. R587R), which was inherited from his father [Figure 3]. The experimental program Polymorphism phenotyping v2 (http://genetics.bwh.harvard.edu/pph2/) predicted that this missense mutation is "probably damaging" with a score of 0.999.

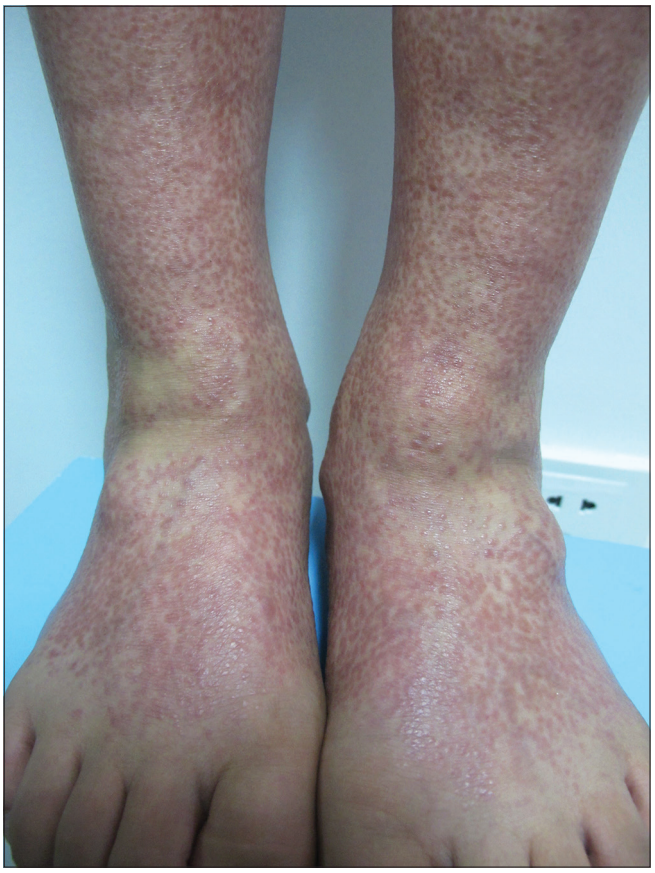

Figure 1c: Red circle indicates subcutaneous nodules over the affected joints and the dorsum of the foot

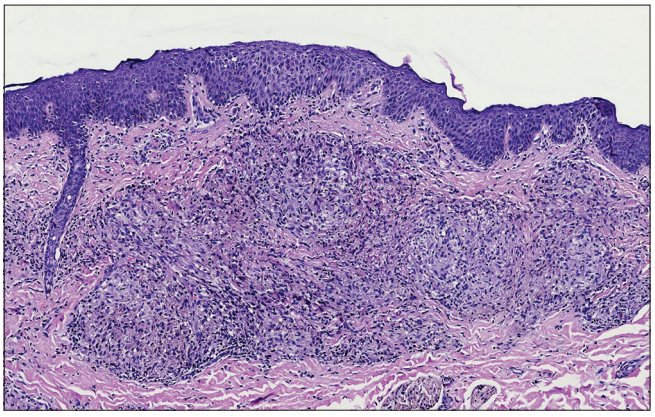

Figure 1e: Histopathology reveals non-caseating granulomas (H and E, ×100)

The presence of clinical characteristics, typical histological hallmarks, along with a negative familial history supported a diagnosis of early-onset sarcoidosis, which was confirmed by the mutational analysis of the *NOD2* gene. Treatment with oral prednisone (1 mg/kg/d) and MTX 5 mg/w for 2 months was associated with marked improvement.

Blau syndrome/early-onset sarcoidosis is mainly characterized by early onset and one or more recurrent manifestations of the triad of symptoms. Histological examination can confirm

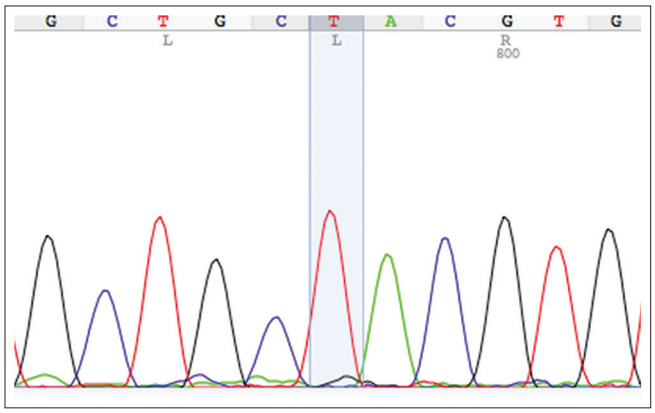

Figure 2a: Mutational analysis shows a heterozygous novel mutation in exon 4 of the NOD2 gene (c. 1687 T>G, p. Y563D), which was absent in his unaffected parents. The DNA sequence of patient's father

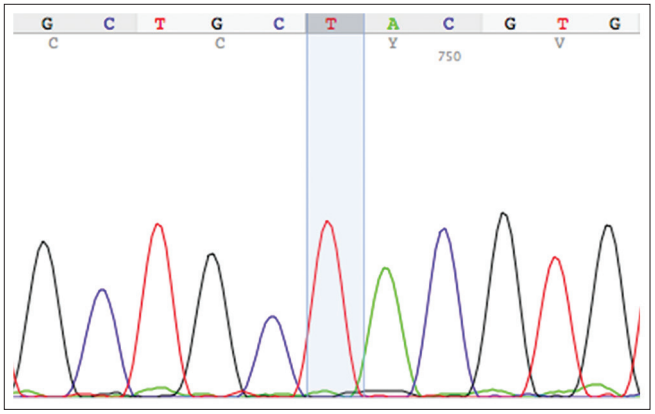

Figure 2b: Mutational analysis shows a heterozygous novel mutation in exon 4 of the NOD2 gene (c. 1687 T>G, p. Y563D), which was absent in his unaffected parents. The DNA sequence of patient's mother

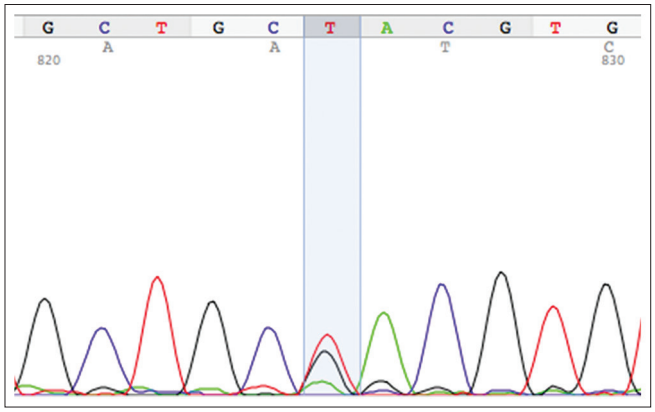

Figure 2c: Mutational analysis shows a heterozygous novel mutation in exon 4 of the NOD2 gene (c. 1687 T>G, p. Y563D)

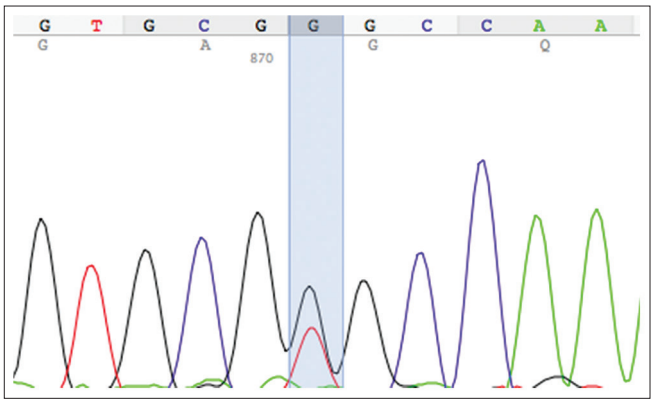

Figure 3a: Mutational analysis shows a heterozygous synonymous mutation in exon 4 of the NOD2 gene (c. 1761 T>G, p. R587R) inherited from his father. The DNA sequence of patient's father

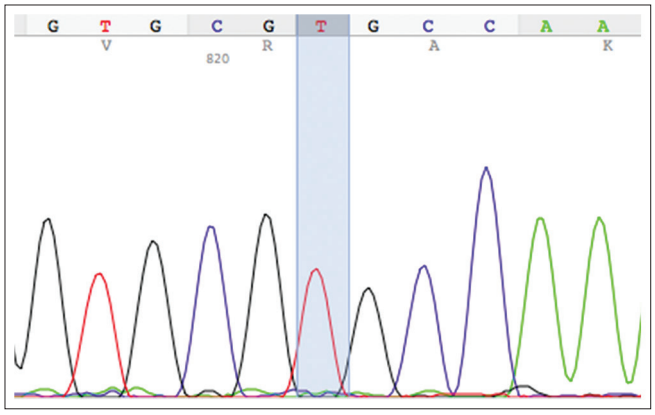

Figure 3b: The DNA sequence of his mother was not found the mutation in exon 4 of the NOD2 gene

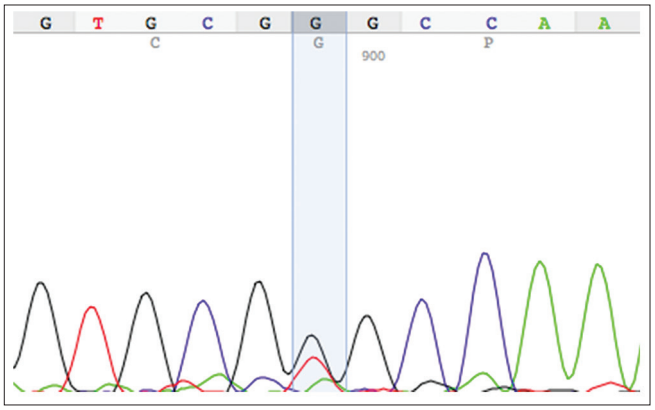

Figure 3c: Mutational analysis shows a heterozygous synonymous mutation in exon 4 of the NOD2 gene (c. 1761 T>G, p. R587R) inherited from his father. The DNA sequence of the patient

the presence of naked sarcoidal granulomas. The clinical picture needs to be corroborated by identification of the possible *NOD2* gene mutation. The most frequently observed mutations of Blau syndrome/early-onset sarcoidosis are mis-sense substitutions involving exon 4, and the ones mainly affecting the arginine residue at position 334 (R334W/Q). The Y563H mutation in *NOD2* has been described in five cases of 2 Brazilian families of Blau syndrome.[2] Our patient was born with congenital cleft lip and palate, which was not a feature reported in previous reports. Furthermore, we found

a novel missense Y563D mutation in *NOD2*, which was not recognized in the genomes of his parents, confirming the sporadic origin of the mutation.

There is no established treatment modality for Blau syndrome/early-onset sarcoidosis. Nonsteroidal anti-inflammatory drugs, corticosteroids, and immunosuppressive drugs may be helpful. When patients are unresponsive to the combination of corticosteroids and immunosuppressant agents, the tumor necrosis factor-a inhibitor infliximab should be considered.[3] Our patient was given oral prednisone and methotrexate, resulting in dramatic improvement.

In conclusion, we report a sporadic clinical case of a Chinese patient suffering from early-onset sarcoidosis with congenital cleft lip and palate that reveal a novel missense mutation Y563D in the *NOD2* gene.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

Xiaopo Wang, Xiaofeng Zhang[1], Wei Zhang, Jianfang Sun

Department of Pathology, Institute of Dermatology, Chinese Academy of Medical Sciences and Peking Union Medical College, Nanjing, Jiangsu, [1]Department of Dermatology, Institute of Plastic Surgery, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

Correspondence: Dr. Jianfang Sun, Department of Pathology, Institute of Dermatology, Chinese Academy of Medical Sciences and Peking Union Medical College, 12 Jiangwangmiao Road, Nanjing, Jiangsu 210042, China.
E-mail: pysblk@aliyun.com

References

1. Caso F, Galozzi P, Costa L, Sfriso P, Cantarini L, Punzi L. Autoinflammatory granulomatous diseases: From Blau syndrome and early-onset sarcoidosis to NOD2-mediated disease and Crohn's disease. RMD Open 2015;1:e000097.
2. Jesus AA, Fujihira E, Watase M, Terreri MT, Hilario MO, Carneiro-Sampaio M, *et al.* Hereditary autoinflammatory syndromes: A Brazilian multicenter study. J Clin Immunol 2012;32:922-32.
3. Caso F, Costa L, Rigante D, Vitale A, Cimaz R, Lucherini OM, *et al.* Caveats and truths in genetic, clinical, autoimmune and autoinflammatory issues in Blau syndrome and early onset sarcoidosis. Autoimmun Rev 2014;13:1220-9.