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# UNIVERSITÀ DEGLI STUDI DI TORINO

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## **CLINICAL AND GENETIC ASPECTS OF BLAU SYNDROME: A 25-YEAR FOLLOW-UP OF ONE FAMILY AND A LITERATURE REVIEW**

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### Keywords

Blau syndrome; Autoinflammatory syndromes; Granulomatous arthritis/rash/uveitis; CARD15; NOD2

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### Abstract

Blau syndrome (BS) is a rare familial disease transmitted as an autosomal dominant trait, characterized by arthritis, uveitis, skin rash and granulomatous inflammation. Until now BS has been observed in 136 persons belonging to 28 families as well as in 4 sporadic cases. The gene responsible for BS has recently been identified in the nucleotide-binding domain (NBD) of caspase recruitment domain (CARD15/NOD2), also involved in the pathogenesis of Crohn's disease. In addition to three missense mutations (R334Q, R334W and L469F) previously identified, a new CARD 15 mutation (E383K) has recently been described in a family followed by us for the past 25 years. The characteristics of this family which, to our knowledge, is the only one affected with BS in Italy, are the object of this manuscript. Both the proband and her daughter were originally affected with a papulonodular skin eruption and then with mild arthritis of the hands and feet. The proband, but not the daughter, complained of severe chronic bilateral uveitis, followed by glaucoma and, a few years later, by cataracts. Histological examination of skin biopsies from both subjects and a joint biopsy (daughter only), showed non-caseating granulomas with multinucleated giant cells which, at electron microscopy, revealed "comma-shaped bodies" in epithelioid cells, thought to be a marker for BS. The disease is presently well controlled with low doses of prednisone for the mother and non-steroidal anti-inflammatory drugs (NSAIDs) plus low doses of prednisone, when necessary, for the daughter. As in Crohn's disease, CARD15/NOD2 mutation is believed to be responsible for the granulomatous autoinflammatory reactions probably triggered by microorganisms in BS.

## Introduction

Blau syndrome (BS) is a rare familial disease characterized by arthritis, uveitis, skin rash and granulomatous inflammation [1]. In 1985 Blau described 4 generations of a family with eleven members affected with granulomatous disease of the skin, eyes, and joints. Ten had arthritis; two had skin, eye, and joint involvement; one had skin and joint disease, and one had iritis only [1]. Observing that the disease was transmitted as an autosomal dominant trait and only partially resembling sarcoidosis, he considered it a new syndrome. Eleven years later the BS locus was mapped by Tromp et al. by genotyping 72 of the 74-member pedigree with dinucleotide-repeat markers to the chromosomal region 16q12.1–13 which also contains one of several inflammatory bowel disease susceptibility loci [2]. Significant progress was further made when Miceli-Richard et al. observed that the gene responsible for BS was in the caspase recruitment domain (CARD15), also called NOD2 [3]. Three missense mutations (R334Q, R334W and L469F) were identified by these investigators in the nucleotide-binding domain (NBD) of CARD15/NOD2 in four French and German families with Blau syndrome. Thus, in addition to Crohn's disease, CARD15/NOD2 appears to be involved in susceptibility to a second granulomatous disorder [4]. A new CARD 15 mutation (E383K) has recently been identified in a family followed by us over the past 25 years [5]. As this, to our knowledge, is the only diagnosed family in Italy, we hope that a description of its characteristics and the disease course over such a long time period may contribute to better understanding of BS.

## A family with Blau syndrome

The proband, a 31-year-old Caucasian woman, with arthritis of hands and feet and a papulonodular skin eruption was referred to our Unit in 1984. The patient reported that she had developed chronic, bilateral uveitis and glaucoma when she was 20 and cataracts a few years later. She underwent an iridectomy when she was 24 and a cataract operation 7 years later. Symmetrical arthritis involving fingers, wrists and feet, and skin manifestations, consisting in widespread papules and firm subcutaneous nodules on the extremities, made their appearance during adolescence and intermittently thereafter although well controlled by non-steroidal anti-inflammatory drugs (NSAIDs).

The patient presented with asymptomatic, diffuse, miliary brownish papule and firm subcutaneous nodules, varying in size from 5 to 30 mm in diameter, on the dorsa of hands and feet and on the extensor leg surfaces. Arthritis was evident on the bilateral metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints. Neither red nor hot, the joints were only slightly tender and swollen. The bilateral 1st and the 2nd metatarsophalangeals (MTP) of the feet were similarly involved. Camptodactylia (flexion contractures of the fingers and toes) was not present. Radiographs of hands and feet revealed only a slight periosteal enlargement of the bone and a chest X-ray was negative. Results of all laboratory tests including inflammatory indices were normal. Human leukocyte antigen (HLA) typing revealed A2, A3; B8, B21; DR3, DR7. Skin biopsy specimens of the forearms were processed for light and electron microscopy examination. The specimens were fixed in formalin for histologic assessment, embedded in paraffin and thin sections were obtained with hematoxylin–eosin, PAS, PAS-diastase and Weigert–van Gieson. Small fragments were fixed in glutaraldehyde for ultrastructural examination, post-fixed in osmium tetroxide, dehydrated in ethanol solution and embedded in epon. Semithin sections were stained with toluidine blue and observed with a light microscope and ultrathin sections were stained with uranyl acetate and observed with a transmission electron microscope.

Histology revealed non-caseating granulomas, containing several histiocytes and multinucleated giant cells with strong PAS positivity and rare lymphocytes and eosinophils (Fig. 1a). Transmission electron microscopy showed polypoid histiocytes with abundant cytoplasm containing a well-developed Golgi complex and endoplasmic reticulum, profuse mitochondria, lysosomes and glycogen granules, probably determining PAS positivity (Fig. 1b). Pleomorphic cytoplasmic inclusions were found in a few cells. Some collagen fibers were in close apposition to cellular membranes, often surrounded by a cytoplasmic process of histiocytes, but without clear evidence of phagocytosis. Capillary vessels with swollen endothelial cells due cellular infiltrates were found. Due to the limited efficacy of NSAIDs, low doses of steroids (methylprednisolone 4 mg/day) were introduced and are continued even now with satisfactory control of all disease manifestations.

One month after her first examination in our Division, the proband consulted us about her five-year-old daughter who had recently developed skin manifestations similar, although less severe, to her own. No therapy was prescribed at that time as the entity of the disturbances was negligible. Four years later, however, she developed arthritis with slight swelling of all fingers of both hands and moderate pain. As there was a simultaneous worsening of dermatitis, she was admitted to the Dermatological Department of the University of Padova. All routine laboratory investigations, including serum lipids, rheumatoid factor and antinuclear antibodies, were within normal limits. A skin biopsy, of the right forearm, revealed some granulomas, prevalently composed of PAS positive histiocytes and multinucleated giant cells without intracellular lipids, similar to those observed in the proband. BS was diagnosed, but no specific treatment was prescribed except for NSAIDs which were to be taken when necessary for a few days time for pain control.

The daughter was admitted to our Rheumatological Unit when she was 12 because of painful arthritis. At the physical examination she presented asymptomatic erythematous papules on the extremities, in particular on the extensor leg surfaces, symmetric arthritis involving PIP and MCP of the hands (|Fig. 2) and 1st MTP of the feet, which were swollen, tender and slightly warm. Radiographs revealed periarticular swelling and slight space narrowing of the PIP and of the first right MTP of the hands. Laboratory investigation showed a slightly elevated erythrocyte sedimentation rate (ESR) 26 mm 1st h (NV < 20 mm) and policlonal hypergammaglobulinemia 22.5 % (total proteins 7.7 mg/dl). Rheumatoid factor and antinuclear antibodies (ANA) were absent. HLA typing revealed A23, A24, B18, B51, Bw4, DR11, DRw52, and DQw7. An electrocardiogram was normal and chest X-ray as well as abdominal ultrasound were negative. An ophthalmologic examination was, curiously, negative. Synovial biopsy specimens, of the third left PIP, were similar to the skin biopsies previously taken, in particular with regards to the non-caseous granulomas. The diagnosis of BS was confirmed but steroids were not prescribed because of the patient's age and NSAIDs were begun. One year later, when the patient was 13, she presented bilateral anterior uveitis, successfully treated with topical drugs. However, some weeks later, since arthritis and skin lesions were worsening, low doses of oral steroids were introduced for one–two week cycles, obtaining a good response. Continuing with the same therapeutic regimen (mean weeks/year on steroids are 4 even now), the disease is under control without relevant impairment of the quality of life.

All the members of the proband's family underwent genetic investigation two years ago. No one in her family, composed of two sisters and brother, her husband, and her other daughter, showed symptoms of BS. A new CARD15 E383K mutation was found only in the patients described here.

## Discussion

### Clinical aspects

To our knowledge, BS has been observed until now in 154 persons belonging to 41 families (Table 1) [1], [2], [3], [4], [5], [6], [7], [8], [9], [10], [11], [12], [13], [14], [15], [16], [17], [18], [19], [20], [32], [33] and [34] and in 4 sporadic cases [21], [22] and [23]. Joint discomfort is the most frequently reported symptom, followed by skin and eye disturbances. Camptodactyly, considered a common finding in BS by Blau [1], and subsequently described in some cases, was not a symptom in our patients. The most frequent joint involvement in BS is inflammatory arthritis, with moderate redness, warmth and tenderness, associated with synovial cysts particularly affecting wrists and dorsa of the hands, and tenosynovitis, which contributes to the frequently observed periarticular swelling. Arthritis symmetrically involving wrists, MCP, 1st MTP, PIP of hands and feet, ankles and rarely elbows, has a chronic evolution in these patients and may lead to deformity of fingers and to wrist ankylosis. Joint involvement almost always has a juvenile onset, presenting as painless cysts on the back of feet and wrists which may evolve into mild “boutonniere finger deformities” [12] and [24]. Traditional X-rays show the typical deformities of periarticular swelling and, at times, joint space narrowing [12] and [24]. Although deformities are frequently seen, especially when there is camptodactyly, bone erosion has never been reported.

Various skin manifestations have been described and can be classified as two main types: a papulonodular tender brownish rash and multiple, firm, subcutaneous plaques only apparent on palpation. In the proband and her daughter, the principal skin manifestation was a papulonodular, painless often diffuse rash. It has been seen that its onset is almost always during childhood. As it is often mild and regresses spontaneously it can even go unnoticed. In some cases the eruptions are described as erythematous, in other intermittent and/or generalized [17]. A skin biopsy shows non-caseating granulomas with multinucleated giant cells [1], [2], [6], [8] and [14]. The electron microscopy may reveal “comma-shaped bodies” in epithelioid cells [14] which seem to be a marker for BS [12] and [14].

Eye involvement, often the most severe aspect of BS [1], [15], [18] and [20], may present as granulomatous anterior frequently bilateral uveitis, which can evolve into a cataract and band keratopathy, frequently requiring surgery [18]. Other findings include vitritis, granulomatous disks, and bilateral disseminated chorioretinal lesions that are surrounded by retinal hemorrhages and progressive subretinal fibrosis [1], [2] and [18]. Fundus modifications at times resemble those in sarcoid uveitis [18].

Involvement of other organs has rarely been described in BS. In particular, in contrast to sarcoidosis [24], the lungs are seldom affected. The only visceral involvement that has been reported until now are hepatic

[10], or renal granulomatoses [13], ichthyosis [19] and, on the basis of a vast study by Wang X et al., large vessel arteritis and cranial neuropathy [14].

Some authors have recently proposed that early-onset sarcoidosis may represent the sporadic counterpart of BS, sharing an identical phenotype and associated with mutations of CARD15 in 50–90% of cases [25]. Both pathologies have been included in the “pediatric granulomatous arthritis family” and an international registry was established in the spring of 2005.

Due to its rarity and the variations in the severity and evolution of its expressions, treatment of BS is based on empiric experience. The major concern regards eye involvement, which may, at times, be severe [1], [5] and [18]. At the quiescent stage, low-dose glucocorticoids are generally satisfactory, as was the case in the proband we treated [15]. High doses of glucocorticoids are, however, necessary in some acute stages. Since disease onset is often during childhood its long term use especially at high doses, may be problematic. Additional treatment with immunosuppressive agents, such as methotrexate and azathioprine, has been attempted in the past. So-called “biologic” anti-cytokine agents such as infliximab, a tumour necrosis factor (TNF)- $\alpha$  inhibitor and anakinra, an anti-IL1, have recently been demonstrated to be effective in refractory cases [21] and [31].

#### Genetic aspects

Once the disease and its familial transmission were described by Blau [1] and the locus was mapped by Tromp et al. on the chromosomal region 16q12.1–13 [2], the most significant progress in the study of BS was made by Miceli-Richard et al. who reported that the responsible gene is in the caspase recruitment domain (CARD15) [3]. These authors identified three missense mutations (R334Q, R334W and L469F) in the nucleotide-binding domain (NBD) of CARD15/NOD2 in four French and German families with Blau syndrome. The two most frequent mutations in the other families were those located in codon 334. An additional CARD15 mutation (E383K) has recently been identified in the proband's family described here [5] and sporadic de novo mutations have subsequently been reported [21], [22] and [23].

CARD 15/NOD2 encodes a 1.040 amino-acid protein that structurally consists in two N-terminal CARDS linked to a NBD, and multiple leucine-rich repeat (LRR) at its carboxyl terminal region [3], [5] and [26]. CARD15 is mapped to chromosome 16q12, is expressed predominantly in a monocytic lineage, and may interact with lipopolysaccharide (LPS) structures by its LRR domains to activate nuclear factor kappa-B (NF- $\kappa$ B). It is interesting that mutations involving LRR appear to predispose to Crohn's disease, while those in the NBD are unique to BLAU syndrome [2] and [3]. CARD15/NOD2, a member of the CED4/APAF1 family of apoptosis regulators, binds directly to a muramyl dipeptide (MDP) that is common to all bacteria [27], leading to NF- $\kappa$ B activation. The majority of the CD associated variants of CARD15/NOD2, localized in the LRRs, result in defective NF- $\kappa$ B activation and bacterial clearance [28] and [29]. All CARD15/NOD2 mutations described until now in BS are located in the region encoding the NBD [3], [5] and [14]. Although bacteria's role in its pathogenesis has not been demonstrated, BS has recently been found to be associated with a distinctive mutation in CARD15/NOD2, which encodes for an intracellular toll-like receptor [30].

Studying the host cell interaction with bacterial challenge (*Salmonella typhimurium*) in U937 cells expressing wild type human NOD2 (NOD2wt), mutant NOD2 (NOD2Blau) or vector control (VC), Kim et al. found that the invasion of target cells was diminished in the presence of NOD2Blau and that the expression of TNF- $\alpha$  mRNA was enhanced in all cell lines following bacterial invasion. NOD2Blau was, however, associated with a more rapid decline in TNF- $\alpha$  expression. The kinetics of intracellular bacteria clearance indicated a relative defect in NOD2Blau compared to controls.

Although mutations conferring susceptibility to BS occur in a domain (NBD) independent of LRR interactions which are thought to induce defective clearance of bacteria [28] and [29], it has been observed that CARD15/NOD2 mutation of codon 334 seems to cause a four-fold higher activation of NF- $\kappa$ B, compared to wild type alleles [5] and [35].

#### Take-home messages

- Blau syndrome is a prototype of autoinflammatory syndrome without fever and detectable acute phase reaction, which may be useful to better understand mechanisms and role of non-caseating granuloma in inflammation.
- The expanding clinical heterogeneity of the pediatric granulomatous diseases syndromes and the high prevalence of sporadic cases should alert clinicians to the possible genetic basis of the condition and support the inclusion of DNA analysis as a diagnostic test.

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Fig. 1.

Skin biopsy showing (a) the presence of non-caseating granulomas, containing several histiocytes and multinucleated giant cells with strongly PAS positivity and rare lymphocytes and eosinophils; electron microscopy showing (b) polypoid histiocytes with abundant cytoplasm containing lysosomes and glycogen granules.

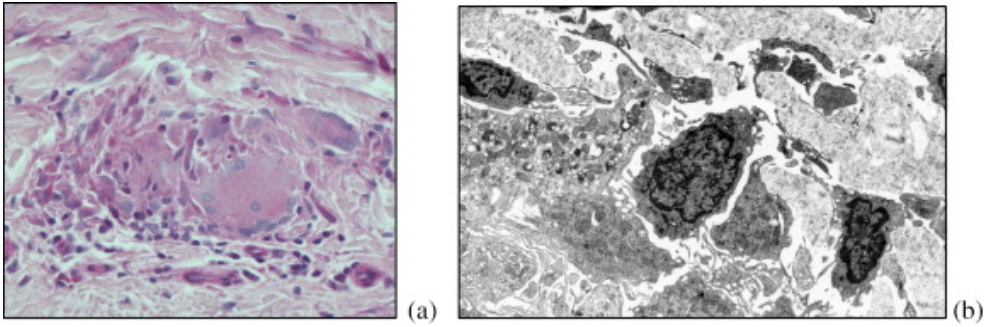


Fig. 2.

Daughter. Hands with symmetrical enlargement of interphalangeal joints.



Table 1.  
Reported families with Blau syndrome (2008)

Authors	Families	Members affected	Generations	Joint involvement	Skin involvement	Eye involvement	Visceral involvement
Blau (1985)	1	11	4	10	3	3	None
Jabs (1985)	1	4	3	4	No	3	None
Pastores (1990)	1	3	2	3	2	3	None
De Chadarévian (1993)	1	2	2	2	2	2	None
Hafner (1993)	1	2	2	2	1	1	None
Moraillon (1996)	1	2	2	2	1	No	None
Saini (1996)	1	3	2	3	1	1	Hepatic granulom.
Tromp (1996)	1	16	4	13	8	6	Not evaluated
Scerri (1996)	1	2	2	2	2	2	None/Neurological inv.
Manouvier-Hanu (1998)	1	4	2	4	2	2	None
Ting (1998)	1	3	2	2	3	No	Renal granulom.
Miceli-Richard (2001)	4	11	2	9	7	5	None
Wang X (2002)	10	50	2-4	50	40	33	Large vessel arteritis and cranial neuropathy
Latkany (2002)	8	16	3	15	9	16	None
Ewida (2002)	1	4	2	4	4	2	None
Alonso (2003)	1	4	2	4	4	2	None
Kurokawa (2003)	1	3	2	3	2	3	None
Masel (2005)	1	1	1	1	1	1	Ichthyosis
Van Duist (2005)	1	2	2	1	1	1	None
Snyers and Dahan (2006)	1	3	2	3	2	2	None
Shaffer (2007)	1	4	3	0	2	3	None
Becker (2007)	1	4	2	4	0	3	Pneumonitis