Autoinflammatory syndromes

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ABSTRACT

The autoinflammatory disorders are a new and expanding classification of inflammatory diseases characterized by recurrent episodes of systemic inflammation in the absence of pathogens, autoantibodies or antigen specific T cells. These disorders are caused by primary dysfunction of the innate immune system, without evidence of adaptive immune dysregulation.

Innate immune abnormalities include aberrant responses to pathogen associated molecular patterns (PAMPs) like lipopolysaccharide and peptidoglycan, prominent neutrophilia in blood and tissues, and dysregulation of inflammatory cytokines (IL-1β, TNF-α) or their receptors.

The autoinflammatory diseases comprise both hereditary (Familial Mediterranean Fever, FMF; Mevalonate Kinase Deficiency, MKD; TNF Receptor Associated Periodic Syndrome, TRAPS; Cryopyrin Associated Periodic Syndrome, CAPS; Blau syndrome; Pyogenic sterile Arthritis, Pyoderma gangrenosum and Acne syndrome, PAPA; Chronic Recurrent Multifocal Osteomyelitis, CRMO) and multifactorial (Crohn's and Behçet's diseases) disorders. Mutations responsible for FMF, TRAPS, CAPS, PAPA are in proteins involved in modulation of inflammation and apoptosis.

The autoinflammatory concept

The term "autoinflammatory" was coined by Kastner and O'Shea at the end of the last century (1, 2) to describe a group of diseases that did not fit into the classic categorization of immunologic illnesses which consists of autoimmune, allergic, or immunodeficient ones. The autoinflammatory disorders are characterized by recurrent episodes of systemic inflammation, often manifested by fever, as well as inflammation of specific tissues, such as joints, skin, gut, and eyes. While the clinical features of these diseases are often similar to infectious or common rheumatologic diseases, there is no evidence of pathogens, and there is no apparent high titer autoantibodies or antigen specific T cells that are usually seen in autoimmune diseases (2). The prefix "auto" is used because of the apparent absence of outside triggers, and the fact that episodes associated with these disorders are often unprecipitated. However, attacks are sometimes elicited by non-traditional stimuli, such as temperature, exercise, and stress, a feature also observed in some allergic and autoimmune diseases.

In the strictest definition, the autoinflammatory disorders include only the known hereditary periodic fever (HPF) syndromes, such as familial Mediterranean fever (FMF), hyper IgD syndrome with periodic fever (HIDS), tumor necrosis factor (TNF) receptor associated periodic syndrome (TRAPS), and cryopyrin associated periodic syndromes (CAPS) (3). Recently, an entire issue of this journal was devoted to these diseases (in press). As the term has gained wider usage, it has begun to be applied to disorders that share some clinical features, but are not clearly familial, such as periodic fever with aphthous stomatis, pharyngitis, adenitis (PFAPA), and others that do not have fever as a prominent symptom, such as Behçet's disease. As the molecular basis of the HPF disorders have become elucidated, additional genetic diseases with unique clinical features (i.e. granulomas) have been added to the autoinflammatory category based on structural similarities to or interactions with HPF genes, such as Blau syndrome (due to mutations in NOD2) and pyogenic sterile arthritis, pyoderma gangrenosum, and acne (PAPA) syndrome (due to mutations in PSTPIP1). The widest definition includes a number of rare genetic diseases, such as hereditary angioedema or Gaucher's di-

sease, or common diseases such as gout and Crohn's disease (2).

Many of these disorders appear to be due to dysregulation of the innate immune system, the evolutionarily ancient part of our immune defenses that is non-specific and does not require prior sensitization to an antigen. Innate immunity, as opposed to acquired immunity, responds to infection quickly with neutrophils and monocytes, and does not depend on lymphocytes for direction or antibody production. Innate immune abnormalities associated with the autoinflammatory disorders include aberrant responses to pathogen associated molecular patterns (PAMPs), prominent neutrophilia in blood and tissues, and dysregulation of inflammatory cytokines or their receptors.

In several of the autoinflammatory diseases there are abnormal responses to PAMPs like lipopolysaccharide and peptidoglycan, which activate toll-like receptors (TLRs) and NACHT-Leucine Rich (NLR) proteins, such as cryopyrin and NOD2. Mononuclear cells cultured from CAPS patients have heightened responses to lipopolysaccharide, apparently from increased activation of the inflammasome, an intracellular protein complex that regulates caspase 1 cleavage of pro-interleukin (IL)-1β (4). Similar increased responses to PAMPs are seen in cultured whole blood from HIDS patients, but the mechanism is less clear (5). However, cultured monocytes from FMF patients during attacks have decreased responses to LPS (6), which might suggest an inhibitory role of this protein or a loss of function with mutations.

Neutrophils are important effector cells in autoinflammatory disease, as peripheral blood and tissue neutrophilia are common pathologic findings in many of the autoinflammatory disorders. All of the HPF disorders have increased neutrophils in peripheral blood during attacks that return to normal between attacks. CAPS patients have elevated peripheral blood neutrophil counts that increase significantly within hours of a cold challenge and decrease to baseline by the following morning (7). In addition, skin pathology from affected areas of rashes associated with many of the HPFs shows prominent neutrophilic infiltration (7), and massive neutrophilic influx is observed in the peritoneal membrane of FMF patients during abdominal attacks (8).

Inflammatory cytokines such as interleukin (IL)-1β and TNF-α or their respective receptors play a central role in these diseases. Pyrin and cryopyrin (the proteins altered in FMF and CAPS, respectively) are both involved in caspase 1 regulation, affecting the release of IL-1β (9). Evidence is now emerging that the shortage of specific isoprenylated proteins due to mevalonate kinase deficiency in HIDS can induce IL-1β-mediated inflammation (10). Alterations observed in the TNF receptor in TRAPS patients have been shown to cause an impaired receptor shedding, leading to increased or prolonged signaling through the TNF receptor and a decrease in soluble TNF-receptor (s-TNFRSF1A) (1). The remarkable clinical response of CAPS patients to IL-1 receptor blockade with IL-1 receptor antagonist (7, 11), and the excellent response of most TRAPS patients to a TNF receptor fusion protein (12) is further evidence for the major role of these cytokines and their receptors in these diseases.

The expanding family of autoinflammatory diseases is a unique class of inflammatory diseases that is associated with abnormal innate immune function without evidence of adaptive immune dysfunction. While many of the autoinflammatory disorders are rare, these inherited diseases provide a unique opportunity to study the innate immune system starting from a genetic approach. Therefore, elucidating the pathophysiology of the autoinflammatory diseases may allow for a better understanding of much more common immunologic diseases.

Genetics of autoinflammatory disorders (refs. 13-24)

Autoinflammatory diseases include both hereditary [FMF; mevalonate kinase deficiency (MKD); TRAPS; CAPS; Blau syndrome; PAPA; chronic recurrent multifocal osteomyelitis (CRMO)] and multifactorial (Crohn's and Behçet's diseases) disorders. The recent characterization of the causing genes (Table I) has led to the reevaluation of the prevalence of some of these disorders, and to the appearance of genetically based diagnosis for hereditary autoinflammatory diseases. Genetic testing of FMF is now widely available, but only a few specialised laboratories offer analyses of MKD, TRAPS, CAPS, BLAU/EOS, PAPA and CRMO genes. Molecular approaches have poor diagnostic value for multifactorial conditions such as Crohn's disease, but may assist in disease classification or prognosis estimation.

The number of disease associated mutations is growing slowly (Table I). Most are single nucleotide substitutions. Unfortunately, functional tests are lacking for most of these syndromes. In this respect, interpretation of sequence variants spread widely in the general population, or conversely of private variants (found in a single patient), especially conserved missense mutations, should be undertaken with caution.

Most often, the correct diagnosis can be assembled from the concurrence of clinical, biochemical and genetic parameters. However, cases in which criteria of several disease and/or mutated genes cluster have been reported, confusing the clinician while regrettably delaying accurate and relevant patient care. Monogenic mutations have been detected in multifactorial diseases: MEFV in Crohn's disease, Behçet's disease, multiple sclerosis, rheumatoid arthritis, TNFRSF1A in early arthritis and Behçet's disease. An appealing hypothesis is that some "severe mutations" would segregate with specific monogenic disorders, while other "mild mutations" would tend to non-specific inflammation by acting as susceptibility factors in multifactorial diseases. Fortuitous coexistence of highly prevalent mutations in a single individual is also likely.

Hereditary inflammatory disorders have been poorly recognized until recently, because with only a handful of reported cases, they were considered to be orphan diseases and lacked specific tests. Mutations responsible for FMF, TRAPS, CAPS, PAPA are in proteins which are part of (or interact with) the

Table I. Genetic characteristics of hereditary autoinflammatory disorders.

	FMF	MKD	TRAPS	CAPS	BLAU and EOS	PAPA	CRMO
Transmission	Recessive	Recessive	Dominant	Dominant	Dominant	Dominant	Dominant
Year gene discovery	1997	1999	1999	2001	2001	2002	2005
Reference	(2, 3)	(4)	(1)	(5, 6)	(7, 8)	(9)	(10)
Chromosome	16p13.3	12q24	12p13.3	1q44	16p12-q21	15q	18p
Gene	MEFV	MVK	TNFRSF1A	CIAS1	CARD15	PSTPIP1	LPIN2
Protein	Pyrin/ Marenostrin	Mevalonate kinase	TNFRSFIA	Cryopyrin	CARD15	PSTPIP1	Lipin 2
N mutations*	73	54	60	51	9	2	2
Most frequent mutation*	M694V	V377I	R92Q	R260W	Rare families	Rare families	Rare families
De novo mutations	Not reported	Not reported	Rare	>50%	Not reported	Not reported	Not reported
Frequent in the general population	E148Q	V377I	R92Q, P46L	V198M	Not reported	Not reported	Not reported

* Mutation refers to a sequence variant definitely or possibly associated with the corresponding phenotype as recorded in the infevers database at http://fmf.igh.cnrs.fr/infevers/

DDF (Death Domain Fold) protein superfamily, involved in modulation of inflammation and apoptosis. The general scheme that is emerging from a compilation of published data is that the "inflammatory" state of the cell depends on a complex and fragile molecular equilibrium between partners of an expanding set of triggers, mediators, adapters and effectors. Should a proinflammatory event happen, the cell will be precipitated into a cascade of reactions aimed at rapidly recovering homeostasis or proceeding to apoptosis, and if any of the cascade steps are altered a normal cellular state would take longer to regain, or apoptosis would take longer or become impossible. This model fits well with the "periodic" and acute character of autoinflammatory attacks. Now that the culprit genes are being progressively identified, it may be anticipated that additional successes will be obtained in the near future by systematic screening of the remaining orphan molecules (with no mutation-associated disease) in orphan patients (with no mutated gene identified). Sensitive molecular diagnoses could then be achieved by the use of large scale strategies, for example DNA chips focused on all known mutations.

Familial Mediterranean fever

Periodic fever, defined as the occurrence of fever of variable duration separated by symptoms free intervals, was introduced by Shepard Siegal in 1945. Nowadays under the name of HRF are comprised a group of rare disorders characterised by intermittent self-limited inflammatory episodes with fever, synovial/serosal involvement, skin lesions and variable degrees of ocular and neurological disorder. Today, at least 7 clinically different periodic fever types are recognised; FMF is one of these diseases.

FMF is an autosomal recessive hereditary disease characterised by short, recurrent attacks of fever, peritonitis, pleuritis, arthritis and less frequently, erysipelas-like skin lesions.

FMF is known to be very common in some populations living around or near the Mediterranean basin. It affects mostly Jews originating in North African countries, Armenians, Turks and Arabs.

In 1997 the gene associated with FMF, the MEFV (Mediterranean Fever gene) was isolated and localised on chromosome 16p13.3; the encoded protein variously called pyrin or marenostrin is expressed mainly in the neutrophils and monocytes and it is involved on the control of inflammation. Several data demonstrate that pyrin/marenostrin is intimately connected to three important cellular pathways: apoptosis, cytoskeletal signaling and cytokine secretion. These connections occur, at least in part, through the direct interaction of the pyrin/marenostrin protein with two cytosolic protein adaptors: ASC (also called PyCARD or Tms1) and PSTPIP (also called CD2BP1); so pyrin/marenostrin protein could determine an increasing of IL-1β and the NF-KB activation with an impairment of leukocyte apoptosis and a consequent bad control of inflammation (25).

Clinical features of FMF are variable from a patient to another. The main clinical characteristics include painful febrile attacks of few hours to 3-4 days, duration accompanied by pleuritic/ pericarditic chest pain, abdominal pain mimicking an acute abdomen, joints' involvement (arthralgias/arthritis) and erysipela-like skin lesions; inflammation can involve any serosa (orchitis, etc.). During the attacks, the patients display leukocytosis, raised erythrocyte sedimentation rate (ESR) and increasing of other acute phase reactants which result in the range of normality during free intervals.

Diagnosis is clinical and it is based on Tel-Hashomer criteria or more recently on Montpellier criteria. Genetic analysis can confirm diagnosis.

More than 50 mutations have been identified on MEFV and these mutations correlate with the severity of disease; in fact M694V, very common between Jews and Armenians, gives a major risk of amyloidosis, the most severe potential complication of FMF. It is not exactly known why some patients develop a progressive amyloidosis, whereas others do not although latent deposits

may be present; a permanent acute phase response, ideally evaluated with serial measurement of serum protein SAA, the precursor of the AA protein deposited in tissues, seems to be a prerequisite to the development of inflammatory (AA) amyloidosis.
Colchicine is the drug of choice in FMF affected patients; generally the dose of colchicine is 1 or 2 mg/day until to 3 mg/day; the prophylactic treatment by colchicine is effective in preventing both the acute attacks of FMF and the development of amyloidosis.

Clinical features of familial Mediterranean fever in Italians
In the last 8 years, 146 patients (81 males; 65 females) affected with FMF, aged from 3 to 81 years were seen in the adult section of the Periodic Fever Centre, Department of Internal Medicine, Catholic University, Rome.
Clinical diagnosis was established by Tel-Hashomer criteria (123 patients with a definitive diagnosis and 23 patients with a probable diagnosis); genetic testing was performed in 144 patients: in 98 patients at least one mutation was present. All patients can contact us by mail or telephone and understand better the disease through a website (www.conosciamocimeglio.it). A database file of genetic and clinical recordings of patients is available in *Excel*, *Word* and papery format.
Most pts came from the South and the Centre of Italy, probably because of the geographical position of Italy and the migratory changes of the population during last 20 centuries. Some patients came from near countries (Malta, Syria, Tunisia) (26). Consanguinity was found in 11 patients. Thirty-eight patients had a first-degree relative affected by FMF.
In 95 patients the age of onset was under 20 years.
Frequency of attacks ranged from less than 1 attack/month (23.3%) to more than 2 attacks/month (26.7%). According to the Severity score a mild disease was documented in 28.8%, a moderate disease in 55.5% and a severe one in 15.8% of patients. The most typical attack was characterised by fever and abdominal pain (80.8%) followed by fever and articular pain (65.1%) and by fever and thoracic pain (41.8%); only 3 patients had abdominal and thoracic pain or abdominal and articular pain or abdominal, thoracic and articular pain.
Thoracic pain, pleural, pericardial or pleural-pericardial affected 66 patients.
Ninety-seven patients had joint involvement: acute arthritis in 23 patients, arthralgias in 13 patients, and chronic arthritis in 3 patients. Eleven patients complained of myalgias.
Abdominal pain affected 121 patients and was associated to nausea (33.6%), vomiting (33.6%) and in few cases to diarrhoea or constipation.
Cutaneous manifestations were present in 53 patients: erysipela-like lesions in 25 patients, erythema in 21, itching in 4 and psoriasis in 3 patients.
Twenty patients had a compromised renal function, and damage ranged from microalbuminuria to dyalisis; 2 patients carried a phenotype 2.
Reactive hepatomegaly was present in 2 and splenomegaly in 18 patients.
One hundred and twenty-seven patients received colchicine treatment (86.6% good effectiveness; 9.4% mild effectiveness; 3.9% no response), the others refused treatment because fear of azoospermia or intolerance. Menses and physical/psychological stress triggered the attacks in 23 and 9 patients, respectively.
The collected data suggest that the characteristics of this Italian series are: a less severe disease, low prevalence of amyloidosis, higher incidence of late onset, high rate of colchicine responders.

Tumor necrosis factor receptor-associated periodic syndrome
TRAPS is an autoinflammatory disease of genetic origin, autosomal dominantly inherited. It is linked to missense mutations within the TNF receptor gene TNFRSF1A (1). Recurrent episodes of fever, myalgia, rash, abdominal pain, and conjunctivitis that often last longer than 5 days are the most characteristic clinical features of TRAPS.
In 1998, two independent groups of investigators mapped the susceptibility loci for patients with familial Hibernian fever and autosomal dominant familial periodic fever to the same distal region of chromosome 12p (27, 28). These data strongly suggested that the same locus was responsible for the phenotype expressed in both of these syndromes. Review of existing genomic databases revealed several positional candidate genes including CD4, LAG-3, CD27, C1R, C1S, and tumor necrosis factor (TNF) receptor super family 1A (TNFRSF1A). Of these, TNFRSF-1A was particularly attractive in light of the central role that its protein product, the 55-kDa TNF receptor (TNFRSF1A, p55, CD120a) plays in inflammation (29). Moreover, preliminary data indicated reduced levels of soluble p55 in the serum of affected subjects. Following this observation, DNA sequence analysis involving all 10 exons of p55 demonstrated 6 different missense mutations, 5 of which involved highly conserved cysteine residues that were present in all 40 symptomatic patients and in only 2 asymptomatic family members. None of the mutations was found in the normal control chromosome tested (1, 26). Furthermore, it was shown defective receptor shedding for the C52F mutation and the predicted effect on the tertiary structure of the protein supported the hypothesis that these missense mutations were responsible for the observed phenotype. Thus, the discovery of mutations in TNFRSF1A led to a consolidation of these apparently isolated cases into a single nosologic entity subsequently named TRAPS – a name chosen to reflect the involvement of TNFRSF1A in the pathogenesis of the disease.
TRAPS is autosomal dominantly inherited, and although it was originally found that most TNFRS1A mutations occurred in patients of Irish or Scottish ancestry, subsequently mutations from diverse ethnicities were reported, including African-America, Puerto Rican, French, Belgian, Dutch, Portuguese, Italian, Arabic, Jewish, German and Finnish. To date, at least 20 disease-associated TNFRSF1A mutations have been reported. Of these, 19 are single nucleotide missense mutations occurring within exons 2, 3, and 4; the remaining mutation is a splicing mutation that occurs within intron 3. Some

of these mutations occur in substantially more individuals than those who present with clinical symptoms of TRAPS, thus suggesting that there should be as yet unidentified modifying factors that allow for the phenotypic expression of these mutations. In addition, these mutations may cause clinical phenotypes other than TRAPS. It has been suggested that asymptomatic individuals carrying one such mutation may be more prone to a broader group of inflammatory diseases, such as rheumatoid arthritis.

There does not appear to be a distinct correlation between patients' genotypes and their phenotypic presentations, with 2 notable exceptions: first, patients with the R92Q mutation appear to have a more heterogeneous clinical presentation than do other TRAPS patients, and second, patients with TNFRS1A mutations involving cysteine residues appear to be at a greater risk to develop life-threatening AA amyloidosis than those patients with noncysteine mutations. Amyloidosis is the most serious long-term complication of TRAPS. It occurs as a result of the chronic deposition of the cleavage product of serum amyloid A in numerous organs, most commonly the kidneys, but also the liver, adrenals, thyroid, skin, intestine, gall bladder, spleen, testes, and lung. The majority of patients with kidney involvement develop nephrotic syndrome and ultimately renal failure. Interestingly, it has been reported that the anti-TNF drug etanercept was able to reverse renal amyloidosis in a TRAPS patient with the C33Y mutation. In addition, etanercept was effective in preventing the recurrence of amyloidosis in a patient with the C33G mutation who had received a liver transplant for treatment of AA amyloid-induced hepatic failure. However, etanercept was ineffective to prevent renal amyloidosis in a 10-year-old patient with the C52F mutation despite receiving 30 months of this drug 0.4 mg/kg twice weekly, a dose able to reduce her symptoms by more than 90%.

The median age of onset of TRAPS is 3 years with initial presentation ranging from 2 weeks to 53 years of age. Attacks last on average 21 days and occur every 5-6 weeks; however, this is extremely variable. Typical attacks begin with the subtle onset of inflammatory symptoms, most commonly deep muscle cramping, followed by fever, and eventually cutaneous manifestations, arthritis, abdominal, ocular, respiratory, and genitourinary involvement, lymphadenopathy. The most common cutaneous manifestation is a centrifugal migratory, erythematous patch most typically overlying a local area of myalgia. These lesions are tender to palpation, warm, and blanchable. They occur most commonly on the limbs but are also seen frequently on the torso. Other less distinct rashes may be observed and include urticaria-like plaques as well as generalized erythematous serpiginous patches and plaques. Myalgia is nearly always present in TRAPS. It affects only a single area of the body, with centrifugal migration over the course of several days; areas over the involved muscles are warm, tender to palpation, and often associated with an erythematous patch. There is no elevation of serum creatine kinase and aldolase concentrations. Arthralgia is more common than frank synovitis. When arthritis occurs, it is nonerosive, asymmetric, monoarticular, and affects primarily large joints. Abdominal pain is another clinical hallmark of TRAPS, and reflects inflammation within the peritoneal cavity or the musculature of the abdominal wall. Symptoms and signs of an acute abdomen often result in laparotomy and appendecectomy. Ocular symptoms include conjunctivitis, periorbital edema, uveitis and iritis. Laboratory investigations show elevations of the erythrocyte sedimentation rate, C-reactive protein, haptoglobin, fibrinogen and ferritin. A large percentage of patients also demonstrate an elevated acute phase response during clinically asymptomatic periods. There may be neutrophilia, thrombocytosis, and/or low hemoglobin secondary to chronic inflammation. Most patients demonstrate a polyclonal gammopathy. Autoantibodies are not a prominent feature of TRAPS and when present are at low titer.

Preliminary data suggest that etanercept may be effective in decreasing the severity, duration, and frequency of symptoms in TRAPS patients, also providing a therapeutic alternative to glucocorticoid therapy, which has numerous serious, long-term adverse effects. Nonsteroidal antiinflammatory drugs (NSAIDs) can be beneficial in relieving symptoms of fever but are generally unable to resolve musculoskeletal and abdominal symptoms. Colchicine, azathioprine and other immunosuppressive drugs have been tried without success.

Blau syndrome

Blau syndrome (BS) is a rare familial disease characterized by arthritis, uveitis, skin rash and granulomatous inflammation first described by Blau in 1985 (30). Although BS is an autosomal dominant disorder, as largely demonstrated in the 15 families until now studied, two cases with a sporadic granulomatous arthritis lacking a disease history in the parents and sharing the typical R334 mutation, have been recently reported (19, 31). Main aspects of BS are consistent with its inclusion in both groups of autoinflammatory diseases (32) and familial granulomatosis syndromes. In this context, although there is no evidence for bowel inflammation, BS share some features with another granulomatous disease, such as Crohn's disease. Other than for the phenotype, these two diseases express a similar gene susceptibility recently identified as caspase recruitment domain gene CARD15, also known as NOD2, encoding a cellular receptor involved in an NF-κB-mediated pathway of innate immunity (18, 33). However, while CARD15 variants associated with Crohn's diseases are located within or near the C-terminal leucine-rich repeat domain and cause decreased NF-κB activation, BS mutations affect the central nucleotide-binding NACHT domain (NBD) (34). Mutations up to now identified in BS patients are missense changes affecting residues arginine R334 and leucine 469 of the NBD and have been show to result in an increased basal NF-κB activity, consistent with the dominant inheritance of the syndrome. The

encoded multidomain protein is implicated in an NF-κB-mediated pathway of inflammation and apoptosis and is mainly expressed in monocytes, granulocytes and dendritic cells, which are major components of BS granulomas.

An Italian family with BS, having two affected members, the mother and one daughter was studied at the Division of Rheumatology, Padua University (31). The mother, now 52 years, first seen at the age of 10 years, was diagnosed as affected by BS on the basis of classical manifestations, including skin rash at the extensory aspect of upper and lower limbs, non erosive arthritis of the small hand joints and severe bilateral uveitis. The daughter showed similar skin rash and arthritis of the hands since the age of 5 years, without ocular or other organ involvement. In these two subjects we detected a novel CARD15 mutation E383K, which changes a different residue of the NACHT domain, glutamate E383 to lysine (35). The pathogenicity of this mutation is strongly supported by co-segregation with the disease in the family and absence in controls, and by the evolutionary conservation and structural role of the affected glutamate close to the Walker B motif of the nucleotide-binding site in the NACHT domain. Interestingly, all three residues affected by BS mutations correspond to the position of pathogenic mutations in the protein PYPAF1 causing three other autoinflammatory diseases, chronic infantile neurological cutaneous and articular syndrome (CINCA), familial cold autoinflammatory syndrome (FCAS) and Muckle-Wells syndrome (MWS). Furthermore, it has been recently demonstrated that early-onset sarcoidosis (EOS) and BS, other than characteristic clinical features of juvenile-onset systemic granulomatosis syndrome affecting skin, joints, and eyes, share also CARD15 mutations. Among 10 EOS cases retrospectively collected in Japan, heterozygous missense mutations were found in 9 cases, of which 4 showing the R334W reported in BS, and 5 showing novel mutations. All 6 of these variants of CARD15 showed increased basal NF-κB activity. These findings indicate that the majority of EOS and BS cases share the common genetic etiology of CARD15 mutations that cause constitutive NF-κB activation (36).

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