Review Article

# SARS-CoV-2/COVID-19 and its relationship with NOD2 and ubiquitination

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## ARTICLE INFO

## ABSTRACT

COVID-19 infection activates the immune system to cause autoimmune and autoinflammatory diseases. We provide a comprehensive review of the relationship between SARS-CoV-2, NOD2 and ubiquitination. COVID-19 infection partly results from host inborn errors and genetic factors and can lead to autoinflammatory disease. The interaction between defective NOD2 and viral infection may trigger NOD2-associated disease. SARS-CoV-2 can alter UBA1 and abnormal ubiquitination leading to VEXAS syndrome. Both NOD2 and ubiquitination play important roles in controlling inflammatory process. Receptor interacting protein kinase 2 is a key component of the NOD2 activation pathway and becomes ubiquitinated to recruit downstream effector proteins. NOD2 mutations result in loss of ubiquitin binding and increase ligand-stimulated NOD2 signaling. During viral infection, mutations of either NOD2 or UBA1 genes or in combination can facilitate autoinflammatory disease. COVID-19 infection can cause autoinflammatory disease. There are reciprocal interactions between SARS-CoV-2, NOD2 and ubiquitination.

## 1. Introduction

COVID-19 infection is caused by severe acute respiratory syndrome coronavirus-2(SARS-COV-2). The virus enters the host cell by binding to angiotensin converting enzyme-2(ACE2) [1]. SARS-CoV-2 infection upregulates interferon (IFN) regulatory genes (IRF3 and IRF7) and subsequent increase of type I IFN [2]. Blunted IFN responses are observed in some patients with SARS-CoV-2 infection, and several mechanisms behind the finding include inborn errors in IFN pathways, the presence of autoantibodies against type I IFNs, and viral interferon antagonist proteins [3]. Several studies have shown that host genetic factors increase susceptibility to COVID-19 infection and severity, including genetic association with HLA, ACE and ABO A positive group. By genome wide association study(GWAS), certain chromosomes [3,9,12,19] have been linked to COVID-19 infection [4].

COVID-19 infection stimulates the innate immune response in the early phase, including cytokine storm, and adaptive immune response is activated in the late phase. Earlier studies showed the presence of peripheral blood lymphopenia of both T and B cells in COVID-19 patients [5]. More recent study has shown the presence of persistent IFNγ-producing CD4+ T-helper effector memory cells for up to 6 month after COVID-19 infection. In contrast, SARS-CoV-2-specific IFNγ-secreting cytotoxic effector memory T cells transiently rise but rapidly decrease over time. These data suggest persistence of cellular immune responses after natural infection [6].

COVID-19 infection can lead to autoimmune and autoinflammatory diseases. For example, Kawasaki-like syndrome or multi-inflammatory syndrome in children (MIS-c) has been reported among some COVID-19 patients [7]. Cases of macrophage activation syndrome have also been reported [8]. These two disorders belong to the category of systemic autoinflammatory disease that is characterized by abnormal innate immune response as well as autoinflammatory features. Systemic

autoimmune phenomena such as production of various autoantibodies and antiphospholipid syndrome (APS) are reported [9]. Some patients with COVID19 infection can develop so called long COVID-19 or post-COVID-19 syndrome, and this type of infection can last longer than 3 months. These patients have highly activated innate immune cells, lack naive T and B cells and show elevated expression of type I IFN (IFN-β) and type III IFN (IFN-λ1) that remained persistently high at 8 months after infection [10]. With a wide use of COVID-19 vaccines, several cases of COVID-19 vaccination-induced autoinflammatory disease have been reported [11–13]. These patients were clinically classified as having adult onset Still disease without undergoing genetic testing for periodic fever syndromes. It is unknown whether these patients could harbor genetic variations associated with periodic fever syndromes. It is known that COVID-19 mRNA vaccines induce antibodies against spike proteins in all people immunized (3 weeks after the 2nd vaccine dose) [14] and CD8 cytotoxic T cell response in fewer than 50% patients [15,16]. An increasing number of cases of Guillain-Barre syndrome have been reported following COVID-19 vaccinations [17].

The etiology for the occurrence of autoimmune and autoinflammatory diseases following COVID-19 infection and vaccination is not fully understood. It may be multifactorial, including abnormal activation of immune system and host genetic factors [18]. In this article, we provide a comprehensive review of SARS-CoV-2/COVID-19 infection and its interrelationship with nucleotide-binding oligomerization domain containing 2 (NOD2) and ubiquitination. COVID-19 can trigger autoimmune and autoinflammatory diseases. There is a connection between SARS-CoV2, NOD2, and ubiquitination process.

## 2. Methods

A Pubmed search of relevant literature was performed between 2008 and 2022 using the following key indexing terms. They were SARS-CoV-2, COVID-19, autoimmune disease, autoinflammatory disease, NOD2, ubiquitination, and VEXAS syndrome. Full reports of relevant articles were reviewed. Previous publications known to the authors were also included. Relevant information in English language was incorporated in the review. A case is exemplified.

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## 3. Results

### 3.1. NOD2 structure, function, and genetic association with diseases

NOD2 is a member of the NOD-like receptor (NLR) family and represents a cytosolic innate immune sensor [19]. NOD2 detects a component of a bacterial cell wall, muramyl dipeptide (MDP) and interacts with its adaptor protein, receptor-interacting protein kinase 2 (RIPK2) to stimulate signal transduction cascades. These in turn activate NF-κB and mitogen-activated kinases (MAPKs) and result in the secretion of pro-inflammatory cytokines. Normally, NOD2 protein serves as defense against microbial infections, regulation of the inflammatory process, and apoptosis [20], as well as enhances autophagy to dispose damaged organelles and protect cells. In addition to the role of NOD2 in bacterial and viral infections, genetic variations in the NOD2 gene are known to predispose individuals to developing Crohn's disease, Blau syndrome and Yao syndrome [20]. The NOD2 gene, protein, and associated diseases were schematically depicted previously [20].

### 3.2. Yao syndrome (YAOS, OMIM 617321)

YAOS was initially reported by us in 2011 [21] and has been well characterized since [22–26]. The disease onset can start in both children and adults, and it affects predominantly Caucasian adults with a female to male ratio of 2:1. It does not seem uncommon. A majority of cases are sporadic, and 10% to 15% patients may have a familial aggregation. This disease is characterized by recurrent fever, dermatitis, arthralgia, distal

leg swelling, gastrointestinal and sicca-like symptoms with eyelid swelling [27]. The disease is associated with specific NOD2 gene mutations. Dermatitis primarily manifests as erythematous patches or patchy erythema on the face, trunk or limbs. A skin biopsy is primarily consistent with spongiotic dermatitis, and granulomatous dermatitis is extremely rare. Arthralgia/arthritis is not erosive or deforming. Irritable bowel syndrome-like symptoms are common without endoscopic and pathologic evidence of inflammatory bowel disease. Sicca-like symptoms are common without evidence of primary Sjðgren syndrome. Patients can have chest pain and pericarditis/pleuritis. Elevated acute phase reactants are found in approximately 50% of cases. All patients carry NOD2 variants by NOD2 whole gene sequencing, and nearly all patients carry *NOD2* IVS8$^{+158}$ variant and up to 30% of patients have concurrent NOD2 R702W. Other patients carry NOD2 IVS8$^{+158}$ with L1007fs, G908R or other NOD2 variants. Rarer NOD2 variants can be seen.

YAOS is distinct from other inflammatory diseases, and its diagnosis is dependent on the characteristic phenotype, NOD2 genotype, and exclusion of other diseases. Major differential diagnoses are inflammatory bowel disease, Blau syndrome, sarcoidosis, primary Sjðgren syndrome and hereditary periodic fever syndromes [24]. Therapy includes but is not limited to glucocorticoids, sulfasalazine and biologics. IL-1 inhibitor, canakinumab, has been shown to be effective [28].

### 3.3. Ubiquitination and diseases associated with UBA1 mutations

Ubiquitin is a small protein and is universally distributed in eukaryotic cells and tissues. Ubiquitin modification involves an ATP-dependent enzymatic cascade of ubiquitin molecules. Ubiquitination refers to the addition of ubiquitin to a substrate protein and involves three main steps: activation, conjugation, and ligation. These are mediated by three types of enzymes: ubiquitin activating enzymes, ubiquitin binding enzymes, and ubiquitin ligases [29]. Ubiquitination is classified as mono-ubiquitin and polyubiquitin [30]. The ubiquitin pathway has been implicated in the pathogenesis of various diseases [31]. One example is a recently reported autoinflammatory disease, VEXAS syndrome [32].

### 3.4. VEXAS syndrome

VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic syndrome) is a systemic autoinflammatory disease that was first described in 2020. An overwhelming majority of patients are men in late adulthood and elderly (age 50–70) [32]. In this syndrome, patients present with variable and protean manifestations, one of which is cutaneous finding. Patients can have purpuric macules, dermal, urticarial or eczematous papules or plaques, subcutaneous nodules, morbilliform exanthem, and erythema multiforme-like eruption [33]. These recurrent skin lesions are neutrophilic dermatosis mostly and small to medium-vessel vasculitis occasionally [34]. Another clinical feature is chondritis involving the nose and ears. Hematological manifestation is prominent, including macrocytic anemia, and thrombocytopenia, lymphopenia, venous and arterial thrombosis can occur. Bone marrow vacuolization, one of the more specific pathological findings, is restricted to myeloid and erythroid precursor cells. There may be monoclonal gammopathy of unknown significance, plasma cell dyscrasias, or myelodysplasia but without apparent hematologic malignancies [35]. Other presentations have alveolitis, pulmonary infiltrate, pleural/pericardial effusions, symmetric polyarthritis, and recurrent fevers [35]. Prior to the development of DNA sequencing for this syndrome, patients were commonly diagnosed with giant cell arteritis, polyarteritis nodosa, and Sweet syndrome with relapsing polychondritis mostly [36]. Gastrointestinal symptoms such as abdominal pain and diarrhea are extremely rare. Patients tend to have high levels of acute phase reactants. Glucocorticoids are the main stay of treatment to date. Response to disease-modifying anti-rheumatic drugs is poor. Therapeutic results
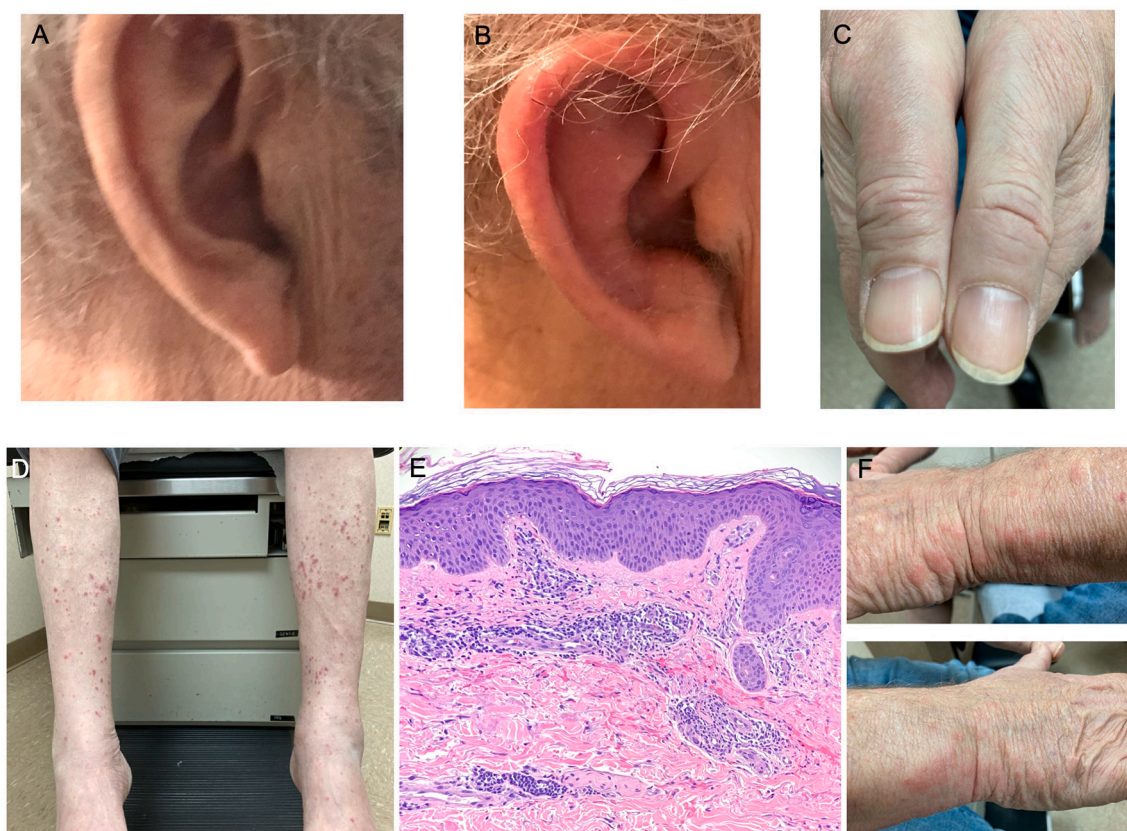
**Fig. 1.** Clinical phenotype and dermatopathological findings. (A) Normal ear (B) Auricular inflammation (C) Right thumb swelling (D) Lower extremity purpuric papules (E) Perivascular infiltrate with lymphocytes and extravasated erythrocytes (direct immunofluorescence staining Declaration of Competing Interest

of IL-1 inhibitors such as anakinra are mixed [32]. Allogenic hematopoietic stem cell transplantation may be a best modality in some cases, although further clinical studies are needed to support its application [37].

Genotyping of VEXAS patients has identified somatic mutations in the X-linked gene UBA1 that affects the codon, methionine-41 (p.Met41) including UBA1 p.Met41Leu, p.Met41Val, and p.Met41Thr [38]. The cytoplasmic UBA1 gene encodes the E1 enzyme that is used for practically all ubiquitin signaling. In part, this supports the production of inactivated UBA1c over UBA1b which impacts the ubiquitination by decreasing its activity and causing hyperinflammation [32].

### 3.5. Case

In this review article, we also report a unique case of autoinflammatory disease associated with combined mutations of both NOD2 and UBA1 genes. In conjunction with the literature, potential mechanisms of the interaction between SARS-CoV2, NOD2, and ubiquitination are illustrated.

A 75-year-old Caucasian male was hospitalized for right external ear chondritis (Fig. 1), sensorineural hearing loss, dizziness, blurry vision, hand pain, and moderate pericardial effusion with negative workup for infection and malignancy. Eight months prior, the patient contracted COVID-19 infection without pneumonia, which resolved within 10 days with supportive care. Afterwards, he required blood transfusion once due to worsening macrocytic anemia. A bone marrow biopsy with flow cytometry showed a small population of monoclonal B cell lymphocytosis with trisomy 12. Treatment with high doses of prednisone improved the above symptoms with normalization of the external ear. With steroid taper, he developed high fever, chills, sore throat, nonproductive cough, and abdominal cramping with transient nonbloody diarrhea. Subsequently, he had another episode of high fevers

and right periorbital cellulitis unresponsive to antibiotics. The symptoms resolved with high doses of prednisone. After a booster injection of COVID-19 mRNA vaccine, he had 3 days of severe left arm pain, low grade fever, mild diarrhea, cough and dyspnea. He then developed arthritis and limb maculopapular lesions with perivascular lymphocyte infiltrate. These symptoms resolved with several doses of prednisone. With elevated acute phase reactants, serology for systemic autoimmune disease was unrevealing. Initial sequencing analysis of DNAs from peripheral leucocytes for periodic fever syndromes revealed two heterozygous NOD2 mutations, IVS8 + 158 and R702W. With negative colonoscopy or pathology for inflammatory bowel disease, Yao syndrome was suspected [24,27]. Given chondritis, macrocytic anemia, and elderly male, further sequencing analysis detected the UBA1 somatic mutation, M41T, leading to the diagnosis of VEXAS syndrome. A series of cytokine levels of plasma were within normal limits except for low IL-2 receptor and elevated IL-10 levels. In a recent follow up, the patient responded to anakinra allowing prednisone taper.

### 3.6. Relationship between SARS-COV-2, NOD2 and ubiquitination

#### 3.6.1. SARS-CoV-2 and NOD2

SSRNA virus enters host cells, where NOD2 plays a role in defense against viral infection. Upon recognition of a viral ssRNA genome, NOD2 uses the adaptor protein, mitochondrial antiviral signaling, to activate IRF3 and innate immune antiviral response [39]. Similar functions of NOD2 are also observed in response to influenza A and parainfluenza viruses [40]. In addition, infection of human fetal brain cells with Zika virus induces the NOD2 expression [41]. What is the role of NOD2 in SARS-CoV2 infection? To date, there is limited data available on study of the association between COVID-19 and NOD2. In a study of multiple myeloma prognostic biomarkers and potential association with COVID-19, differentially expressed genes were identified, including NOD2 gene
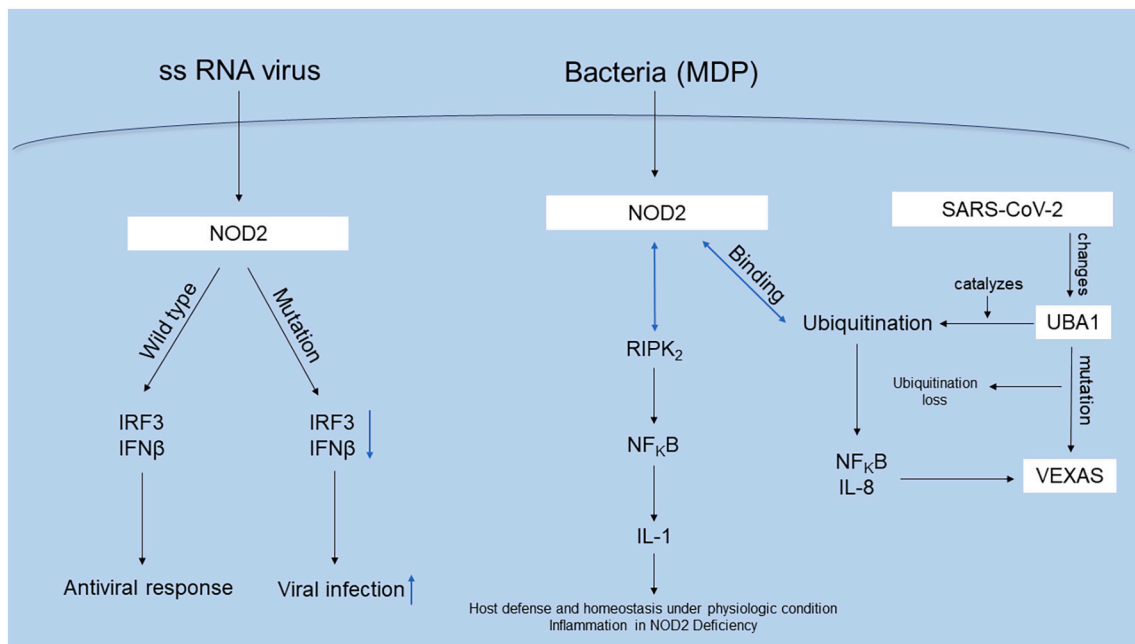
**Fig. 2.** Schematic representation of the interaction between SARS-CoV2, NOD2 and ubiquitination. NOD2, Nucleotide-binding oligomerization domain-containing protein 2; IRF3, Interferon regulatory factor 3; IFN-β, Interferon beta; RIPK2, Receptor interacting protein kinase 2; NFkB1, Nuclear factor kappa B; IL-1, Interleukin 1; UBA1, Ubiquitin-like modifier activating enzyme 1; IL-8, Interleukin 8; VEXAS, Vacuoles, E1 enzyme, X-linked, Autoinflammatory, Somatic..

as an independent factor related to disease prognosis. NOD2 gene was downregulated in patients with mild COVID-19 infection compared with controls but was upregulated in patients with severe COVID-19 compared with patients with mild illness [42]. In a murine study, MDP treatment of Influenza A virus infected animals significantly reduced mortality, viral load, and pulmonary inflammation in a NOD2-dependent manner. Moreover, type I IFN was markedly increased in the lungs following MDP treatment and correlated with a NOD2-dependent enhancement in circulating monocytes [43].

In addition, NOD2 is related to trained immunity(TI) that is defined as a reprograming of the innate immune system evoked by certain exogenous or endogenous insults, leading to immunological memory and more efficient responses to subsequent specific or non-specific challenges [44]. In a study of Bacillus Calmette–Guérin (BCG)-induced TI in mice with NOD2 deficiency, NOD2 signaling pathway is important in the establishment of TI [45]. Similarly, patients with homozygous NOD2 mutations have lesser induction of TI through stimulation of macrophages [46]. Hypothetically, BCG-induced TI may help fight against SARS-COV-2 infection. A number of clinical trials have been underway in this regard [47]. TI could occur in SARS-CoV-2 infection [48].

*3.7. SARS-CoV-2 and ubiquitination*

Coronaviruses like SARS-CoV-2 encode an important multifunctional enzyme named papain-like protease (PLP) that has an intrinsic deubiquitinating activity and plays a crucial role during viral infection of the host cell [49]. PLP is essential for processing viral polyproteins for replication and functions in host immune evasion by cleaving ubiquitin and ubiquitin-like protein conjugates. Therefore, PLP may be a target for antiviral drug development [50]. Ubiquitination provides a universal signal for protein degradation. UBA1 catalyzes the first step in ubiquitin conjugation to mark proteins for degradation through the ubiquitin-proteasome system. SARS-CoV-2 can alter ubiquitination. A recent study has shown that three ubiquitination/deubiquitination enzymes (UBA1, UCHL1, and USP7) are altered and related to COVID-19 infection, with UBA1 and UCHL1 being known autoantigens [51].

*3.8. NOD2 and ubiquitination*

X-chromosome-linked inhibitor of apoptosis protein (XIAP) mediates NOD2 proinflammatory signaling by promoting RIPK2 ubiquitination within the NOD2 signaling complex leading to NF-κB and MAPK activation and production of inflammatory cytokines/chemokines [52]. RIPK2 becomes ubiquitinated by XIAP and other ubiquitin ligases to recruit downstream effector proteins. A lack of ubiquitination might lead to RIPK2 aggregation. NOD2 mutations result in loss of ubiquitin binding and increase ligand-stimulated NOD2 signaling, suggesting that ubiquitin binding provides a negative feedback loop upon NOD2-dependent activation of RIPK2 [53]. Ubiquitin binds to NOD2/CARDs and may specifically influence the downstream balance of cell survival processes with that of other metabolic or inflammatory pathways [54]. Ubiquitin seemed to compete with RIPK2 for the NOD1/2 CARDs and disrupt the architecture of the NODosome [55]. Upon stimulation of NOD2 in human macrophages, endoplasmic reticulum stress sensor activating transcription factor 6 is ubiquitinated, and unfolded protein response is promoted [56].

**4. Discussion**

A full expression of autoinflammatory disease occurred following the COVID-19 infection in our patient with a genetic background of both NOD2 and UBA1 mutations, suggesting concerted contribution of both germline and somatic mutations to autoinflammation with viral infection. The patient did not have a constellation of autoinflammatory symptoms before the COVID-19 infection, suggesting a potential connection between the infection and VEXAS syndrome. Also in support of the link between COVID-19 and VEXAS syndrome is the literature data in this review showing a link between COVID-19 and autoinflammatory diseases or UBA1, a key mutation for VEXAS syndrome.

This case may provide a human milieu to explore the relationship among SARS-CoV-2, NOD2, and ubiquitination. As illustrated above, NOD2 is known to have the capacity to bind ssRNA from influenza A virus, and mice with NOD2 deficiency are hyper susceptible to viral infection [39,57]. Since SARS-CoV-2 is an ssRNA virus, we assume that the same mechanism could apply to our case. UBA1, a ubiquitination

enzyme for protein degradation, catalyzes the first step in the ubiquitin process through conjugation and marking proteins for degradation via the ubiquitin proteasome system. SARS-CoV-2 infection can alter UBA1 and subsequent ubiquitination [51]. Ubiquitin binds to NOD2 and influences the downstream inflammatory pathways. Ubiquitin binding loss potentiates ligand-dependent NF-kB activation and IL-8 secretion [55] (Fig. 2). These molecular interactions may culminate in an auto-inflammatory process.

In summary, both innate and adaptive immune responses are activated during COVID-19 infection. As a result of the immune activation and host genetic factors, autoinflammatory and autoimmune diseases can ensue following the SARS-CoV-2 infection. Both NOD2 and ubiquitination play important roles in defensing against infection, maintaining homeostasis and controlling inflammatory process. There are reciprocal interactions between SARS-CoV-2, NOD2 and ubiquitination. Mutations of either NOD2 or UBA1 genes or in combination can lead to autoinflammatory diseases.

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## Declaration of Competing Interest

The authors declare that there are no conflicts of interest.

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