A case of episodic and refractory arthritis due to a novel variant of NLRP12

It was with great interest that I read the paper by Gupta *et al* describing novel NLRP12 variant is linked to familial cold autoimmunity syndrome phenotype.[1] Here, we reported a patient present with phenotypes of episodic and refractory arthritis due to another novel variant in NLRP12.

A 28-year-old man presented at the age of 20 years with episodic pain, swelling and erythematous skin rash in his wrists, metacarpophalangeal, interphalangeal, knee and ankle joints. His symptoms typically occur once per 1–2 months and sometimes with the increased frequency of episodes to three to four times in 1 week. No identifiable factors were found to trigger the onset. Symptoms lasted from several hours to 3–5 days and subsided spontaneously. His erythrocyte sedimentation rate and C-reactive protein level were elevated during periods of symptoms with normalisation during remission. He was negative for rheumatoid factor, antinuclear antibody and anticitrullinated peptide antibody. No synovitis was detected by ultrasound or MRI in the affected joints. Numerous empirical treatments including nonsteroidal antiinflammatory drugs, colchicine, glucocorticoid (prednisone 10 mg/day), methotrexate and hydroxychloroquine failed to reduce recurrent episodes or relief symptoms. Then, after a sudden onset, only a wait to see strategy can be used for him to wait for the spontaneous remission.

Whole exome sequencing revealed a novel heterozygous mutation in the exon 3 of the *NLRP12* gene (c.1771C>A: p.L591M) on chromosome 19. By using Sanger Sequencing, we did not find this mutation in his parents, indicating that it might be a de novo mutation. This missense variant is extremely rare and absent in >200 000 individuals who have been well-sequenced with high depth at the *NLRP12* region in gnomAD and TOPMed. It is predicted to be deleterious and probably damaging the protein function by different in silico computational tools including PANTHER, polyphen2 and SIFT. *NLRP12* is a novel member of the inflammasome complex and acts as a negative regulator of inflammation.[2 3] We found peripheral mononuclear cells (PBMC) from this patient showed markedly increased NF-κB activity and IL-1β production after tumour necrosis factor alpha (TNFα) stimulation, as compared with arthritis patients non-carrying this variant and healthy controls, supporting the functional significance of this heterozygous mutation in *NLRP12*.

Compared with the patient under discussion in this journal present with familial cold autoimmunity syndrome phenotype,[1 4] the distinct clinical manifestations in our case are recurrent transient episodes of arthritis and erythematous skin rash. This patient has ever been diagnosed as palindromic rheumatism and undifferentiated arthritis. A diagnosis of *NLRP12* associated systemic autoinflammatory disorder was therefore made. Due to non-availability of interleukin-1 inhibitor in China, the patient was treated with tofacitinib and had a modest benefit from it. Our case highlights the importance of screening autoinflammatory disorder and *NLRP12* in patients with unexplained episodic and refractory arthritis.

Jiajia Wang, Qian Zhang, Lingxiao Xu, Chengyin Lv, Rui Liu, Miaojia Zhang, Wenfeng Tan

Department of Rheumatology, The First Affiliated Hospital of Nanjing Medical University, China, Nanjing, Jiangsu, China

Correspondence to Dr Wenfeng Tan, Department of Rheumatology, The First Affiliated Hospital of Nanjing Medical University, Nanjing 210029, China; tw2006@njmu.edu.cn

Contributors The conception and design of the correspondence, acquisition of data, and analysis and interpretation of data: WT, MZ and JW; Involved in care of the patient: JW and WT; Drafting the article: JW, LX and WT; Revising it critically for important intellectual content: JW, QZ, LX, RL and CL; Final approval of the version to be submitted: all authors; Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: all authors.

Funding This work was supported from the National Natural Science Foundation of China (NSFC): 81971532 (WT).

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; internally peer reviewed.

JW and QZ contributed equally.

JW and QZ are joint first authors.

LX, CL, RL and MZ are joint senior authors.

To cite Wang J, Zhang Q, Xu L, *et al*. *Ann Rheum Dis* 2022;**81**:e33.

Received 20 January 2020
Accepted 24 January 2020
Published Online First 17 February 2020

Ann Rheum Dis 2022;**81**:e33. doi:10.1136/annrheumdis-2020-217023

ORCID iD
Wenfeng Tan http://orcid.org/0000-0002-5160-2023

REFERENCES

1 Gupta L, Ahmed S, Singh B, *et al*. Novel NLRP12 variant presenting with familial cold autoimmunity syndrome phenotype. *Ann Rheum Dis* 2021;80:e117.
2 Coulon P-G, Dhanushkodi N, Prakash S, *et al*. Nlrp3, NLRP12, and IFI16 inflammasomes induction and caspase-1 activation triggered by virulent HSV-1 strains are associated with severe corneal inflammatory herpetic disease. *Front Immunol* 2019;10:1631.
3 Zaki MH, Vogel P, Malireddi RKS, *et al*. The NOD-like receptor NLRP12 attenuates colon inflammation and tumorigenesis. *Cancer Cell* 2011;20:649–60.
4 Ghosh K. *NLRP12* gene mutation in India: case finding and diagnosis made easy in the days of whole exome sequencing. *Ann Rheum Dis* 2021;80:e152.