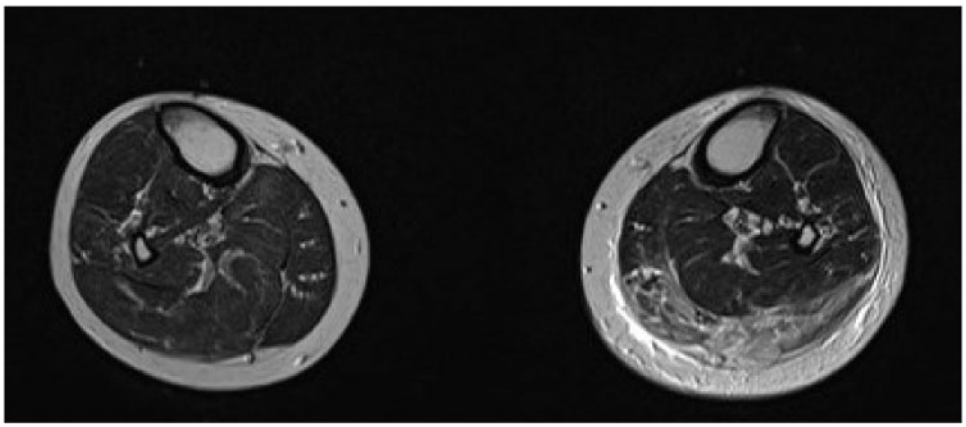
Fig. 1 MRI of the calves



Axial T2 fat-saturated sequence demonstrating diffuse muscle oedema within the soleus and medial and lateral heads of gastrocnemius of the left calf.

multi-muscle involvement. MRI findings include space occupying lesions, myositis and sub-cutaneous oedema and can therefore lead to diagnostic uncertainty. Biopsy is commonly considered the gold standard for identification of muscle pathology but is in fact an undesirable procedure in this condition, due to poor wound healing in the affected population. Treatment is largely conservative, and includes analgesia, physiotherapy to prevent muscle contractures and optimization of glycaemic control [2]. Immunosuppression, for inflammatory muscle disease, is not warranted, and indeed steroids would be ill-advised in a patient who already has a complication of poor glycaemic control. Several pathogenic mechanisms have been postulated in DMI including microangiopathic disease, artherosclerotic occlusion and thrombosis leading to muscle infarct. Furthermore initial muscle injury may be perpetuated by a cycle of hypoxia–reperfusion injury and an inflammatory response leading to muscle oedema and compartment syndrome [3].

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Ruth Smith [1], Nikhil Kotnis[2], Adrian Highland[2], Rachel Tattersall[1] and Stuart Carter[1]

[1]*Rheumatology Department and* [2]*Radiology Department, Sheffield Teaching Hospitals, Sheffield, UK*
Accepted 5 July 2019
Correspondence to: Ruth Smith, Rheumatology Speciality Registrar, Royal Hallamshire Hospital, Glossop Road, Sheffield S10 2JF, UK. E-mail: ruthsmith4@nhs.net

References

1 Trujillo-Santos AJ. Diabetic muscle infarction: an underdiagnosed complication of long standing diabetes. Diabetes Care 2003;26:211–5.

2 Kapur S, McKendry RJ. Treatment and outcomes in diabetic muscle infarction. J Clin Rheumatol 2005;11:8–12.

3 Silberstein L, Britton KE, Marsh FP, Raftery MJ, D'Cruz D. An unexpected cause of muscle pain in diabetes. Ann Rheum Dis 2001;60:310–2.

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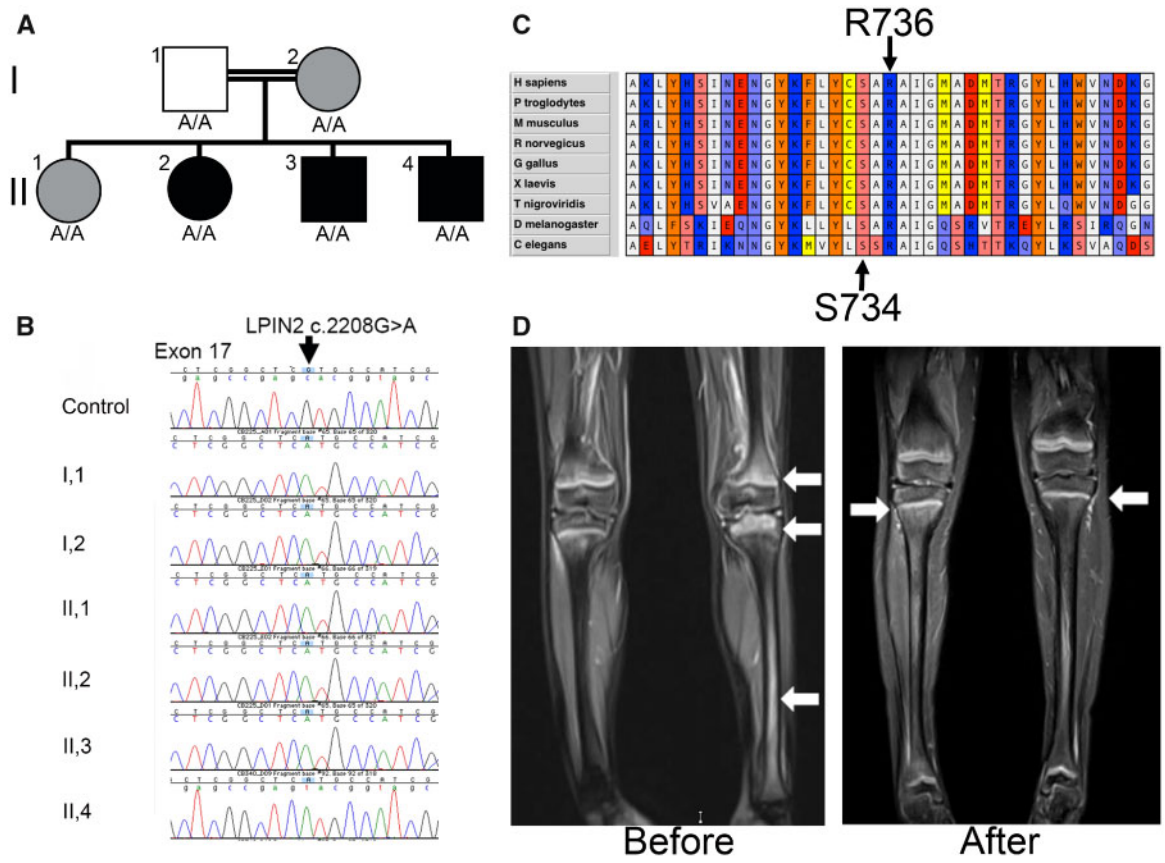
Majeed syndrome: description of a novel mutation and therapeutic response to bisphosphonates and IL-1 blockade with anakinra

Rheumatology key message

- Clinical variability in Majeed syndrome, favourable response to IL-1 blockade and recommendations for genetic screening.

Sir, Majeed syndrome, resulting from biallelic mutations in *LPIN2*, is a rare autosomal recessive autoinflammatory syndrome, originally described as a triad of chronic recurrent multifocal osteomyelitis (CRMO) or chronic non-bacterial osteomyelitis (CNO), congenital dyserythropoietic anaemia (CDA) and inflammatory neutrophilic dermatosis [1–3]. The CNO can affect various bones including the mandible, clavicle, spine and tibia [4]. Unlike sporadic CNO, which usually affects children between 4 and 15 years [4], CNO in Majeed syndrome is earlier in onset and is often refractory to conventionally prescribed NSAIDs and steroids [2]. The CDA reflects bone marrow ineffective erythropoiesis, with typical morphological abnormalities (e.g. binucleate erythroblasts, inter-nuclear bridging). The anaemia is microcytic and highly variable, ranging from sub-clinical to transfusion-dependent [2], and is distinct from anaemia of chronic disease. The inflammatory neutrophilic dermatosis or Sweet syndrome

Fig. 1 Family affected by Majeed syndrome



(**A)** Pedigree, the genotype of *LPIN2* c.2208 is shown under each individual. Black symbols indicate severely affected individuals, grey symbols represent mildly affected individuals and the white symbol indicates the father, who manifested no clinical symptoms. (**B**) Chromatograms from a control sample (top) and family members as indicated (left), all showing homozygosity for the c.2208 G > A missense change in exon 17 of *LPIN2*. (**C)** Alignment of lipin-2 amino acid sequence from a variety of species showing the R736 residue altered in the family reported here is conserved to the nematode *C. elegans*, indicating ~600 million years of evolutionary conservation. This region of the protein is highly conserved, and residue S734 is also indicated for comparison as this is an established cause of Majeed syndrome. (**D)** MRI images showing inflammation in the affected limb and knee joint of the patient before (arrows show active osteitis) and after (arrows show resolving residual osteitis) treatment with anakinra.

can present as pustulosis, plaques, nodules or ulceration [1–3] and has been recognized as being variably present in Majeed syndrome [2] while penetrance of the CNO and CDA has been described as complete.

We describe a consanguineous Pakistani family where the index child presented in infancy with a conglomeration of features indicative of possible Majeed syndrome: failure to thrive, recurrent fevers, irritability, limb pains, osteitis on whole body MRI, severe microcytic anaemia (CDA on bone marrow examination) and high inflammatory markers (CRP 110 mg/L, ESR 90 mm/h). An extensive immunology/infectious diseases workup was inconclusive or normal. The proband's DNA was screened using the Oxford Red Cell Panel [5], which includes ~50 genes implicated in inherited anaemias, including *LPIN2*, which revealed a homozygous G > A transition in *LPIN2* (c.G2207A) leading to replacement of a highly conserved arginine at position 736 with histidine (p.R736H) (Fig. 1B). Further questioning revealed the mother and elder sister had both suffered milder forms of anaemia with limb pains requiring only NSAIDs. The proband's two brothers, mother and father were found to be homozygous for this variant (Fig. 1C). R736H is predicted to be pathogenic by Polyphen2 (with a probability of 1) and is present in only 6 out of 245 402 alleles in the Gnomad database (http://gnomad.broadinstitute.org/). Arginine 736 lies in a highly conserved region of lipin-2 and is two amino acids away from the previously reported pathogenic S734L change (Fig. 1C), and both missense changes affect buried residues, likely affecting stability of this region.

Initial management for mild intermittent osteitis involved NSAIDs and infrequent oral corticosteroids to which there

was partial transient response. At the age of 6, due to ongoing symptomatic osteitis (Fig. 1D), a therapeutic trial of bisphosphonates (3 monthly intravenous pamidronate) as for sporadic CNO was initiated. Transient improvement in bone pain (partial improvement of bone lesions on MRI scan) was observed with a slight improvement in inflammatory markers.

Due to ongoing nocturnal bone pain, new lesions on MRI with synovitis adjacent to bone lesions, intermittent high inflammatory markers (ESR highest 190, CRP highest 134, Hb lowest 69) and poor growth (0.4th centile for weight and height), IL-1 blockade with daily subcutaneous anakinra (1 mg/kg) was commenced. This resulted in resolution of bone pain, significant improvement of bone lesions on MRI scan, normalization of inflammatory markers (ESR 2, CRP 0.2, Hb 107), improved appetite with weight gain, improved sleep and school attendance, and significant improvement in CHAQ and pain visual analog score scores, and negated the need for regular NSAIDs.

Since then, the proband's two younger brothers have developed severe bone pains (with confirmed osteitis by MRI), moderately high inflammatory markers and chronic microcytic anaemia, responding favourably to anakinra, clinically behaving like the proband rather than the mother or elder sister. The father has been asymptomatic apart from non-specific knee pains. We characterized the *LPIN2* locus in this family and found it to be identical over the extent of the gene, suggesting the loci are identical by descent and the phenotypic variability is unlikely to originate from segregation of an alternative *LPIN2* allele.

There is no clear genotype/phenotype correlation between the severity of the genetic change and degree of anaemia, and identical mutations can lead to widely different phenotypes [1, 2, 6], suggesting the influence of modifying factors. Clues to this may be obtained by comparing the transcriptional response in cells from differentially affected patients.

The protein encoded by *LPIN2*, lipin-2, is a magnesium-dependent phosphotidate phosphatase (peroxidase–antiperoxidase) catalysing the conversion of phosphatidic acid to diacylglycerol, a key step in lipid metabolism. The previously reported S734L variant affects only the peroxidase–antiperoxidase activity of lipin-2 [7] and the close proximity of the R736H mutation reported here means it may have a similar effect. Given the involvement of IL-1 in Majeed syndrome, it strongly suggests impaired lipid metabolism increases IL-1 production. Mechanistically, impaired lipin-2 peroxidase-antiperoxidase function could increase inflammasome activity and therefore increase IL-1 production through a failure to preserve the proper lipid environment. Such an environment is required by the purinergic receptor $P2X_7R$ to maintain cellular potassium levels that thereby prevent inflammasome assembly [8]. Further work is required to explain the link with microcytic anaemia.

In conclusion we report a novel *LPIN2* mutation causative of Majeed syndrome with widely variable expressivity and penetrance in one consanguineous family and no evidence of skin involvement. Although there was partial response to bisphosphonates in our patients, we propose use of IL-1 blockade as evidenced by the sustained improvement with anakinra. IL-1 blockade whether by anakinra or canakinumab in Majeed syndrome is supported by recent evidence of the role of lipin-2 in the inflammasome and highlights the key role of IL-1 signalling in Majeed syndrome. Finally, due to the variable penetrance and expressivity, we propose that *LPIN2* be included individually in gene panels for both microcytic anaemia and bone autoinflammatory disease where genetic cause is indicated by a young age of onset, evidence of high levels of systemic inflammation, additional features such as fevers, skin lesions consanguinity or a positive family history consistent with CRMO or a lack of response to therapy with bisphosphonates.

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Noémi B. A. Roy[1,2,*], Ahmad I. Zaal[3,4,*], Georgina Hall[5], Nick Wilkinson[6], Melanie Proven[7], Simon McGowan[8], Ria Hipkiss[7], Veronica Buckle[9], Akhila Kavirayani[3,*] and Christian Babbs[9,*]

[1]*Department of Haematology, Oxford University Hospitals NHS Foundation Trust,* [2]*Oxford BRC Haematology Theme, University of Oxford,* [3]*Paediatric Rheumatology, Nuffield Orthopaedic Centre, Oxford University Hospitals NHS Foundation Trust, Oxford,* [4]*Children's Hospital, Damascus University, Damascus, Syria,* [5]*Paediatric Haematology/Oncology Unit, Oxford University Hospitals, Oxford,* [6]*Paediatric Rheumatology, Evelina Children's Hospital, Guy's and St Thomas' NHS Foundation Trust, London,* [7]*Molecular Haematology Laboratory, Oxford University Hospitals NHS Foundation Trust,* [8]*Computational Biology Research Group, MRC Weatherall Institute of Molecular Medicine, University of Oxford and* [9]*MRC Molecular Haematology Unit, MRC Weatherall Institute of Molecular Medicine, University of Oxford, Oxford, UK*

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Correspondence to: Christian Babbs, MRC Weatherall Institute of Molecular Medicine, University of Oxford, John Radcliffe Hospital, Headington, Oxford, OX3 0QP, UK.
E-mail: christian.babbs@imm.ox.ac.uk

*Noémi B. A. Roy, Ahmad I. Zaal, Akhila Kavirayani and Christian Babbs contributed equally to this paper.

References

1 Ferguson P, Chen S, Tayeh M *et al*. Homozygous mutations in LPIN2 are responsible for the syndrome of chronic recurrent multifocal osteomyelitis and congenital dyserythropoietic anaemia (Majeed syndrome). J Med Genet 2005;42:551–7.

2 Herlin T, Fiirgaard B, Bjerre M *et al*. Efficacy of anti-IL-1 treatment in Majeed syndrome. Ann Rheum Dis 2013;72:410–3.

3 Al-Mosawi Z, Al-Saad K, Ijadi-Maghsoodi R, El-Shanti H, Ferguson P. A splice site mutation confirms the role of LPIN2 in Majeed syndrome. Arthritis Rheum 2007;56:960–4.

4 Girschick H, Raab P, Surbaum S *et al*. Chronic non-bacterial osteomyelitis in children. Ann Rheum Dis 2005;64:279–85.

5 Roy N, Wilson E, Henderson S *et al*. A novel 33-gene targeted resequencing panel provides accurate, clinical-grade diagnosis and improves patient management for rare inherited anaemias. Br J Haematol 2016;175:318–30.

6 Rao A, Gopalakrishna D, Bing X, Ferguson P. Phenotypic variability in Majeed syndrome. J Rheumatol 2016;43:1258–9.

7 Donkor J, Zhang P, Wong S *et al*. A conserved serine residue is required for the phosphatidate phosphatase activity but not the transcriptional coactivator functions of lipin-1 and lipin-2. J Biol Chem 2009;284:29968–78.

8 Lordén G, Sanjuán-García I, de Pablo N *et al*. Lipin-2 regulates NLRP3 inflammasome by affecting p2x7 receptor activation. J Exp Med 2017;214:511–28.

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Comment on: Thymectomy in patients with myasthenia gravis increases the risk of autoimmune rheumatic diseases: a nationwide cohort study

SIR, We read with great interest the paper by Chang *et al.* [1] and wish to add our perspective and comment on the topic. It has long been known that autoimmune diseases share a common background of genetic, hormonal, environmental and immune system defects, which was termed by us many years ago as the Mosaic of Autoimmunity [2]. We suggested this term to acknowledge the fact that rearranging the factors known to be involved in the induction of autoimmune diseases will lead to different patterns of diseases or different diseases. Triggers involved in the induction and emergence of autoimmune disease could be a drug, environmental exposures both physical and chemical, with the major cause related being various infections. Later on, some 25 years ago we (Y.S.) further described the phenomenon of shifts in autoimmune diseases, which we had termed the Kaleidoscope of Autoimmunity [3, 4]. One of the longest-known examples is that of Rhupus described by Panush who described the coexistence of features of both RA along with those of SLE. At times these patients make a full transition from one disease to another. For example, primary APS, which was induced in a patient with myasthenia gravis two years following thymectomy [5], or two cases of immune thrombocytopenia, which developed chronic active hepatitis following a successful splenectomy that led to a complete recovery from the immune thrombocytopenia. This phenomenon of switching from one disease to another autoimmune disease in the same patient has since been described by many others, using the same terminology. Occasionally, drugs being used for one indication lead to the development of another autoimmune disease; for example, D-penicillamine, which has been used in the past as a therapy for scleroderma, RA and Wilson's disease, and has been associated with the induction of lupus-like syndromes. Thus, neutralizing an immune-related organ led to the cure of one autoimmune disease but to the emergence of another, apparently unrelated, second autoimmune disease.

Other features of the Kaleidoscope of Autoimmunity include the occurrence of multiple autoimmune diseases in one patient as well as the familial autoimmunity, both also described by us and others. Examples of these include the co-occurrence of SLE and Hashimoto's thyroiditis, SLE and myasthenia gravis, Sjögren's syndrome with multiple autoimmune diseases, progressive systemic sclerosis and polymyositis, or primary biliary cirrhosis, as well as many other similar associations.

The introduction of biologics as treatment for many of the autoimmune diseases in the past 20 years has brought about the similar phenomena of de novo emergence immunogenicity of another disease. TNF-inhibitors in RA have been involved with new cases of SLE or SLE-like disease as well as new onset of psoriasis, uveitis and even sarcoidosis [6].

Recently, another piece of information was introduced into this puzzle: upon the introduction of immune checkpoint inhibitors as a standard of care for the immunotherapy of various malignancies, which has brought about a large and expanding spectrum of autoimmune and systemic inflammatory toxicities and reactions, known as immune-related adverse events. These include colitis, autoimmune hepatitis, pneumonitis, myocarditis, nephritis, autoimmune endocrinopathies with hyperthyroidism and hypothyroidism, hypophysitis, hypogonadism, pancreatitis, primary adrenal insufficiency and type 1 diabetes. Furthermore, various neurologic syndromes including myasthenia gravis-like syndrome, neuropathy and transverse myelitis have been described as well as uveitis and episcleritis, and a growing spectrum of rheumatic immune-related adverse events including RA-like arthritis both seronegative and RF and anti-CCP positive arthritis, psoriasis and psoriatic arthritis, Sjögren's syndrome, myositis and myalgia, lupus-like disease, scleroderma, polymyalgia rheumatic and giant cell arteritis, sarcoidosis and immune cytopenias [7, 8].

We thus suggest that the paper published by Chang and his co-authors presents another feature of the Kaleidoscope of Autoimmunity.

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