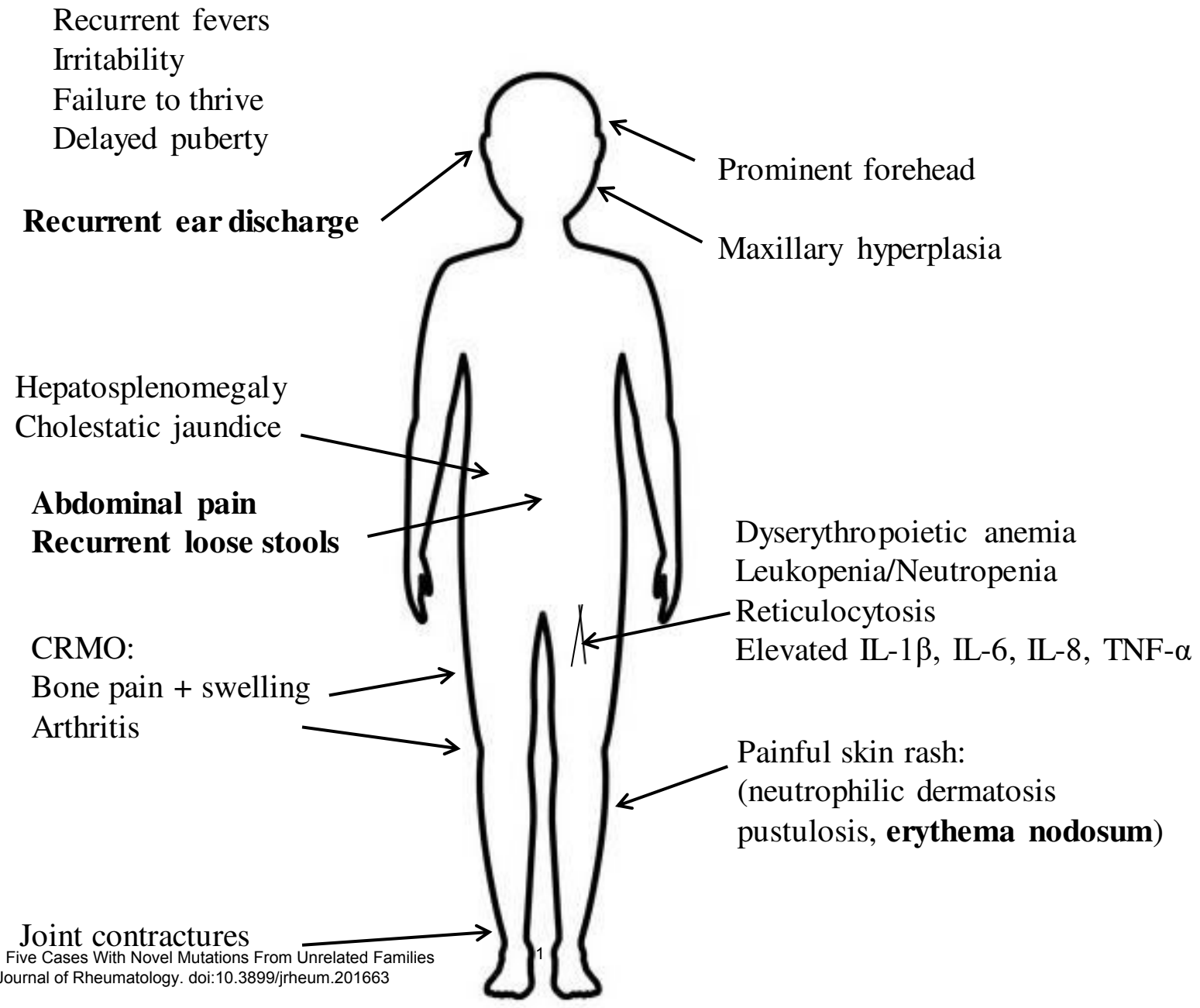
Supplementary Figure 1: Summary of clinical manifestations of patients with Majeed syndrome as described in literature. New features seen in the Indian cohort of patients are shown in bold font.



Online supplement to: Majeed Syndrome: Five Cases With Novel Mutations From Unrelated Families in India With a Review of Literature. The Journal of Rheumatology. doi:10.3899/jrheum.201663

Supplementary Table 1: Radiological features and treatment of our patient cohort with Majeed syndrome:

Patient number	**1**	**2**	**3**	**4**	**5**
Radiological findings:					
Skeletal survey	Subtle, smooth periosteal reaction along the left proximal tibial metadiaphysis	Generalized reduced bone density, ankylosis b/l elbows, osteophytes left elbow, flexion deformity right elbow. Subchondral sclerosis along the proximal articular surface of ulna	Not done	Not done	Not done
Bone scan	Mild diffuse early and late-stage uptake in the entire left lower extremity with more focal uptake along the proximal tibia corresponding to the radiographic abnormality and mild areas of increased uptake in the tenth and eleventh vertebral	Normal	Increased uptake on early and late phase images around the right wrist, knee and ankle	Increased uptake in proximal and distal epiphysis left tibia with possible extension in the shaft on both phases	Increased blood flow around right ankle and delayed increased uptake along the distal right femur and left tibia A follow up bone scan with SPECT after seven years - increased early and late phase uptake around the right wrist and ankle
MRI	*Marrow and periosteal edema along the left distal	Not done	Right proximal humeral, radial head, distal radial	MRI left lower extremity: small left hip joint effusion,	Moderate left talonavicular effusion with mild

	femoral metadiaphysis and bone marrow edema in the left talus and navicular. Subtle asymmetrical marrow edema at proximal metaphysis left tibia. Spine and other bones were normal. The long bones showed multiple transverse metaphyseal lines ("zebra lines"), likely due to pamidronate treatment		metaphyseal, carpal, left distal radial metaphyseal, third metacarpal, right more than left distal femoral, left more than right proximal tibial bone marrow edema with subtle periosteal edema and fluid along the lower extremity and left third metacarpal regions. The lesions were transphyseal with extension of bone marrow edema in the epiphyseal regions in addition to metadiaphysis in bilateral proximal tibia and mild to moderate bilateral elbow joint effusions	mild left femoral neck edema and left proximal medial tibial metaphyseal bone marrow edema. <u>Repeat b/l lower extremity screening MRI</u>: Distal femoral metaphyseal bone marrow edema with periostitis and bilateral left more than right proximal tibial bone edema. [#] Resolution of the previous lesions in both lower limbs. Mild bone marrow edema in the left distal metadiaphyseal region of the radius and adjacent pronator quadratus muscle in the distal	to moderate edema in the left talus, navicular, cuboid, cuneiform bones, 2nd and 3rd metatarsal bases and the right 5th metatarsal shaft

				forearm with mild edema in the medial end of both clavicles	
Treatment:					
Treatment	Pamidronate, methotrexate, p.r.n naproxen	Pamidronate, p.r.n diclofenac	Oral prednisolone, methotrexate, azathioprine, sulfasalazine, Pamidronate	Pamidronate, p. r. n naproxen	Oral prednisolone, methotrexate, azathioprine, sulfasalazine, etanercept, adalimumab, pamidronate

[*] = Two years into treatment; [#]= One year into treatment
Abbreviations: b/l = Bilateral; y = years; m = months

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Supplementary Table 2: Novel *LPIN2* mutations identified in this cohort of patients and support for their pathogenicity based on *in silico* predictions and ACMG classification

Patient	Genomic coordinates	Codon change/ Amino acid substitution	gnomAD MAF	Consequence	SIFT	Mutation Taster	PolyPhen	CADD	SpliceAI	ACMG classification
1	Chr18: 2922166G>A	c.2206C>T; p.R736C	0.000003984	Missense	D	D	PD	32	-	VUS (PM1, PM2, PP3)
2	Chr18: 2924439-2924441	c.2041delT; p.W681fs	0	Frameshift	-	-	-	-	-	Pathogenic (PVS1, PM2, PP3)
3	Chr18: 2923768_ 2923769del	c.2174+4_ 2174+5del	0	5' splice site intronic variant affecting 4 nucleotides downstream donor splice site of exon 16	-	-	-	-	0.97	VUS (PM2, PP3)
4	Chr18: 2924522C>T	c.1961G>A; p.G654D	0	Missense	D	D	PD	29.9	-	VUS (PM1, PM2, PP3)
5	Chr18: 2928584C>G	c.1620+5G>C	0	5'splice site intronic variant affecting 5 nucleotides downstream of donor splice site of exon 11	-	D	-	22.5	0.7	VUS (PM2, BP4)

NM014646.2, All five variants are conserved across all species.
ACMG classification criterion: Pathogenic moderate 1 (PM1) = Located in a mutational hot spot and/or critical and well-established functional domain (e.g., active site of an enzyme) without benign variation; **Pathogenic moderate 2 (PM2)** = Absent from controls (or at extremely low frequency if recessive) in Exome Sequencing Project, 1000 Genomes or ExAC; **Pathogenic supporting 3 (PP3)** = Multiple lines of computational evidence support a deleterious effect on the gene or gene product (conservation, evolutionary, splicing impact, etc); **Pathogenic Very strong (PVS1)** = Null variant (nonsense, frameshift, canonical +/−1 or 2 splice sites, initiation codon, single or multi-exon deletion) in a gene where loss of function (LOF) is a known mechanism of disease; **Benign supporting 4 (BP4)** = Multiple lines of computational evidence suggest no impact on gene or gene product (conservation, evolutionary, splicing impact, etc)

Abbreviations: D=Deleterious; PD = Probable Damaging; VUS = Variant of uncertain significance; MAF = Minor allele frequency; ACMG = American College of Medical Genetics and Genomics

Supplementary Table 3: Salient features of twenty-five molecularly confirmed patients with Majeed syndrome reported in literature:

Authors/ number (n)	**Ancestry**	**Consanguinity**	**Gender/ Age – onset /diagnosis**	**Features**	**Pathogenic variant**
Ferguson et al. (3, 15-17) n = 6	Arabic Sibship 1	+	F/9m/NA	Failure to thrive Recurrent fever CRMO Microcytic anemia [a] Skin lesions Hepatosplenomegaly	Homozygous for c.2201C>T; p.Ser734Leu
			M/NA/NA		
	Arabic Sibship 2	+	M/6m/NA		
			M/10m/NA		
		+	[*] F/3w/NA	Failure to thrive	Homozygous for

	Arabic Sibship 3			[b] Recurrent fever [c] CRMO [d] Microcytic anemia [*] Splenomegaly [#] Irritability [#] Delayed Puberty [#] Pustulosis [#] Contractures: UL/LL [#] Maxillary bone hyperplasia [#] Prominent forehead [#] Splenectomy	c.540_541del; p.Cys181*
			[#] M/2m/NA		
Al – Mosawi et al. (18) **n = 1**	Arabic	+	F/Neonatal/ UC	Recurrent fever CRMO Microcytic anemia Reticulocytosis Mild neutropenia Cholestatic jaundice	Homozygous for c.2327+1G>C; p.Arg776Serfs*66

				Hepatosplenomegaly	
Herlin et al. (14) **n = 2**	Turkish Sibship 4	+	M/6m/29m	CRMO Microcytic anemia Elevated IL-1β, IL-6, IL-8 TNF-α	Homozygous for c.1312_1313del; p.Ser439Trpfs*15
			[$] M/3m/13m	[$] Recurrent fever	
Rao et al. (19) **n = 2**	Indian Cousins		M/2y/15y	Failure to thrive Delayed puberty CRMO Microcytic anemia Mild leucopenia Hepatosplenomegaly	Homozygous for c.2241_2243delinsGG; p.Tyr747*
			M/8y/13y	Failure to thrive CRMO Mild Microcytic anemia	
Fernandes et al. (20) **n =1**	NA	NA	M/6y/12y	CRMO Alpha – thalassemia minor	Homozygous for c.2327 + 1G>C; p.Arg776Serfs*66

Moussa et al. (21) **n =2**	Arabic Sibship 5	+	[@] M/6m/5y	CRMO Microcytic anemia ([@]mild)	Homozygous for c.2201C>T; p.Ser734Leu
			F/4y/14y		
Al – Mosawi et al. (22) **n = 2**	Arabic Sibship 6	+	[⊥] M/11m/UC	CRMO Microcytic anemia [⊥] Recurrent fever [⊥] Neutropenia	Homozygous for c.2327+1G>C; p.Arg776Serfs*66
			F/15m/UC		
Karacan et al. (23) **n =1**	Turkish	NA	M/NA/9y	NA	Homozygous for c.1456del; p.Glu486Lysfs*20
Roy et al. (11) **n = 6**	Pakistani Family	+	F/Infancy/NA	Irritability Failure to thrive Recurrent fever [e] CRMO Microcytic anemia	Homozygous for c.2207 G>A; p.Arg736His
			M/NA/NA (2 siblings)	CRMO Microcytic anemia	
			Mother/ NA/NA		

			F (sib)/NA/NA	Mild anemia Limb pain	
			Father/NA/NA	Non-specific knee pain	
Liu et al. (13) **n =1**	Chinese	No	M/6m/UC	Recurrent fever Microcytic anemia Severe neutropenia	Compound heterozygous for c.2327 + 1G > C; p.Arg776Serfs*66 and c.1691_1694del; p.Arg564Lysfs*3
Bhuyan et al. (9) **n = 1**	American		F/12m/4y	Dyserythropoietic anemia Bone pains	Compound heterozygous c.1550G>A; p.Arg517His and 17.8kb deletion of exons 7 to 18

In addition to these, twenty-five patients with pathogenic or likely pathogenic variants in *LPIN2*, six other patients (12) were reported to have a homozygous mutation in *LPIN2*, but these variants were not described. [a] =Skin lesion resembling Sweet syndrome; [b]= high grade; c = extensive involvement; [d] = transfusion dependent; [e] = nocturnal pain

Abbreviations: M=Male; F =Female; 3^0= 3rd degree; NA= Not Available; w=weeks; m=months; y=years; CRMO =Chronic Recurrent Multifocal Osteomyelitis; UC = Unclear; UL = Upper Limb; LL = Lower Limb.