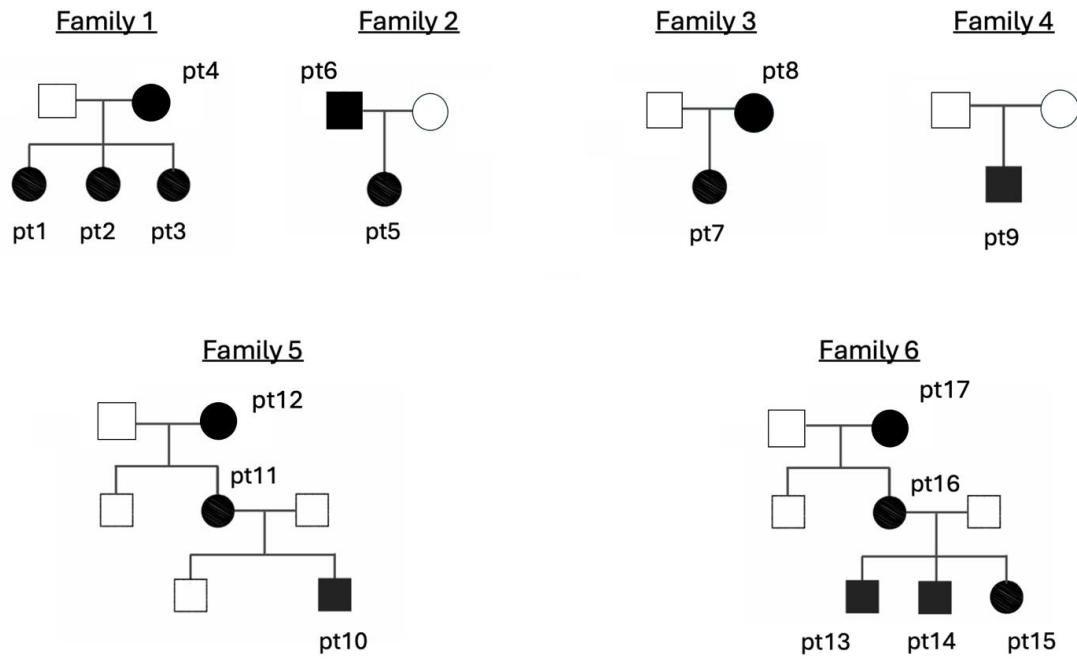


SUPPLEMENTARY MATERIAL

Supplementary File 1. Genetic, clinical and laboratory characteristics of the whole cohort. Laboratory markers are reported at the diagnosis (off therapy).

*parents, **grandparents (see pedigrees in supplementary file 2). ACMG, American College of Medical Genetics and Genomics; NPI, Neuropsychiatric involvement; IS, Interferon score; NA, Not Available; PGA, Physician's Global Assessment scale; CRP, C-Reactive Protein.

Family	Variant	ACMG class	Pt	Age at analysis	Age at onset	Recurrent fever	Oral aphthosis	Genital ulcers	Gastrointestinal disease	Arthritis/tenosynovitis	Skin disease	NPI	Autoimmunity	IS	CXCL9 (pg/ml)	CXCL10 (pg/ml)	PGA	CRP (mg/dl)	
1	p.His577AlafsTer95	5	1	18	6	+	+							NA	28576	6665	0	0	
			2	24	5	+	+		+	+		+	NA	5170	9143	0	0		
			3	21	5		+		+	+		+	4.3	909	431	3	0.59		
			4*	57	5	+	+	+				+	NA	14916	3980	0	0		
2	p.Met476ProfsTer6	4	5	18	3		+	+	+		+		23.9	4574	3183	1	0		
			6*	49	5	+	+	+	+				3.5	23521	8869	0	0		
3	p.Lys759GlnfsTer10	4	7	13	1	+	+	+	+			+		14.3	138	67	3	2.3	
			8*	47	6	+	+	+						1.4	3143	408	0	0	
4	Exon 7-9 del	5	9	11	8				+				+	15	5348	1100	1	0.54	
5	p.Gln379Ter	4	10	22	1	+	+	+	+			+		9.4	50	50	4	3.8	
			11*	52	6		+							22.5	NA	NA	2	0.3	
			12**	71	6		+	+						2.2	NA	NA	0	0.2	
6	p.Arg183Ter	5	13	11	3	+	+	+	+			+	+	8.9	50	50	2	2.1	
			14	12	4		+		+				+	+	6.5	12546	477	2	1.6
			15	4	1		+						+		19.6	NA	NA	1	0.46
			16*	34	4	+	+						+	+	34.3	NA	NA	1	0.9
			17**	65	5							+	+	+	1.3	NA	NA	0	0.1

Supplementary File 2. Genetic pedigrees of the whole cohort of patients.

Supplementary File 3. Autoimmune profile of the cohort and treatments received.

ANA, antinuclear antibodies; ENA, extractable nuclear antigens; anti-dsDNA, anti-double-stranded DNA antibodies; C3, complement component 3; C4, complement component 4; RF, Rheumatoid Factor; ACPA, Anti-Citrullinate Protein Antibodies; IVIg, Intravenous Immunoglobulin.

Family	Variant	Pt	ANA	Other autoimmune laboratory findings (ENA, anti-dsDNA, low C3 or C4, antiphospholipid antibodies, RF, ACPA)	Treatments
1	p.His577AlafsTer95	1	Negative	-	None
		2	Negative	-	NSAIDs, methotrexate, etanercept
		3	Negative	-	Methotrexate, hydroxychloroquine, IVIg, etanercept, leflunomide
		4*	Negative	-	None
2	p.Met476ProfsTer6	5	Negative	-	Mesalazine, methotrexate, adalimumab
		6*	Negative	-	None
3	p.Lys759GlnfsTer10	7	Negative	-	Colchicine, methotrexate
		8*	Negative	-	None
4	Exon 7-9 del	9	Negative	-	Adalimumab
5	p.Gln379Ter	10	ANA + (1:320, speckled)	-	Adalimumab, hydroxychloroquine, apremilast
		11*	ANA + (1:640, speckled)	Mild elevation of IgM anticardiolipin antibodies (17 U/ml)	None
		12**	Negative	-	None
6	p.Arg183Ter	13	Negative	-	Adalimumab, upadacitinib, talidomide
		14	Negative	-	Colchicine, apremilast, upadacitinib
		15	Negative	-	Colchicine
		16*	Negative	-	None
		17**	ANA + (1:160, speckled)	RF+, ACPA+	Methotrexate, etanercept, adalimumab, golimumab, tofacitinib