Supplementary Note: clinical histories

P1

P1 was first seen at the Clinical Center of the National Institutes of Health as a 14-year-old boy with a significant history of recurrent fever, parotitis, joint inflammation and colitis. At age 4, he started having episodes of recurrent fever with severe painful parotid gland swelling, lymphadenopathy and hepatosplenomegaly. At age 8, he developed pain and swelling of his ankle and knee joints, which progressively worsened to polyarthritis affecting the atlantoaxial, sacroiliac, and multiple other joints. He had frequent loose stools and two episodes of hematochezia. He did not present with any skin rash, and his skin biopsy for dermal fibroblast culture did not reveal histological evidence of inflammation. Given his clinical history, he had been diagnosed with polyarticular juvenile idiopathic arthritis or chronic recurrent multifocal osteomyelitis. His treatment included glucocorticoids and methotrexate, without much improvement.

On initial examination at the National Institutes of Health at age 14, he was wheelchair-dependent and had prominent painful swelling of the left ankle joint. Magnetic resonance imaging scan detected high intensities in his ankle and atlantoaxial joints suggestive of active joint inflammation. Synovial fluid aspiration demonstrated marked leukocytosis with neutrophil predominance; cultures were negative. Colon biopsy showed dense infiltration of lymphocytes and neutrophils in crypts and the lamina propria, whereas liver biopsy showed diffuse glycogen deposition in the absence of inflammatory cell infiltrate. This histopathology contrasts with *Sharpin*-deficient mice, which display significant eosinophilic esophagitis and focal periportal liver inflammation. Muscle biopsy was not performed due to the absence of myopathic clinical features. At age 16, the patient presented with moderate conductive hearing loss associated with chronic group A streptococcal otitis media. Despite initial tympanostomy tube drainage and adenoidectomy his ear infection persisted, which necessitated tympanoplasty surgery at age 21. No hypogammaglobulinemia (IgG: 1506 mg/dL; IgA: 303 mg/dL; IgM: 243 mg/dL), or deficit in IgG subclasses (IgG1 717 mg/dL; IgG2: 508 mg/dL; IgG3: 79.3 mg/dL; IgG4: 49.4 mg/dL) was observed, and no autoantibodies were detected. Immunophenotyping of leukocyte surface markers also did not show major abnormalities (Supplementary Data Table 1). Vaccine responses against PCV-13, VZV, HiB, diphtheria and tetanus were all positive (Supplementary Data Table 2). No family history was noted.

P2

P2 was born to non-consanguineous parents of Iranian origin. No family history was noted. She had prolonged jaundice until day 40, and a blood count at that time revealed neutropenia (absolute neutrophil count: 493 cells/µl), which resolved later during the first year of life. No infectious episodes were noted. At five months, the infant had her first unprovoked febrile episode, accompanied by lymphadenopathy and vomiting, without a specific infectious source. The episodes of fever repeated every 12 to 20 days and lasted for 3 to 4 days. The initial diagnosis was PFAPA, and prednisolone during fever episodes was initiated, and subsequently switched to daily cimetidine, colchicine, and dexamethasone. During the febrile episodes, there was a left shift of neutrophils, monocytosis, and elevated ESR and CRP levels. Low IgG level was observed at 8 months (IgG: 401 mg/dL; IgA: 30 mg/dL; IgM: 44 mg/dL), which was normalized at age 2. The response to tetanus and

hepatitis B vaccines was positive. She never had a rash, hepatosplenomegaly, or arthritis. No muscle weakness was noted. The patient had normal development, and ophthalmologic examinations were normal. The cardiac evaluation was normal except for mild mitral valve prolapse. Genetic analysis for mutations in the MEFV gene showed a heterozygous E148Q variant, and colchicine replaced cimetidine. No response was seen during one year of its use.

At age 4, she experienced fever associated with a reduced level of consciousness and was hospitalized. She had leukocytosis with a left shift and an elevation in CRP, ferritin, and D-dimer. Brain CT scan and cardiac evaluation were normal. With a provisional diagnosis of macrophage activation syndrome (MAS) or multisystem inflammatory syndrome in children (MIS-C), she received IVIg and pulsed methylprednisolone. The patient became conscious and afebrile and was discharged on prednisolone after four days. Weekly etanercept was added to her treatment. Three months later, however, she developed a high fever and decreased level of consciousness for the second time. She was kept at home and, after eight hours, transferred to the hospital, where she suffered respiratory and cardiac arrest. Resuscitation was unsuccessful. An infectious cause including SARS-CoV2 was suspected, although infectious disease workup was not performed. No autopsy was conducted.

Supplementary Data Table 1. Peripheral blood lymphocyte surface markers

		SHARPIN Pt (14yo)				HOIP Pt (7yo)				Normal range	
		%		Count		%		Count		%	Count
Total T Cells	CD3	80.4		2307	**High**	77.9		1799		60.0-83.7	714-2266
T cell subsets	CD4/CD3	51.1		1467		53.8		1243		31.9-62.2	359-1565
	CD8/CD3	25.2		723		19		439		11.2-34.8	178-853
	CD4/CD8 ratio	2.03				2.83				1.11-5.17	
	CD3+CD4-/CD8-	3.1		89		4.8		111		1.3-9.2	18-185
	CD4/CD3/CD62+/CD45RA+	15.2		436		28.8		665		7.6-37.7	102-1041
	CD4/CD3/CD62+/CD45RA-	27.4		788	**High**	17		393		10.4-30.7	162-614
	CD4/CD3/CD62-CD45RA-	8.4		241	**High**	5.4		125		2.3-15.6	42-225
	CD4/CD3/CD62-CD45RA+	0.2		6		2.5	**High**	58	**High**	0-1.5	0-29
	CD8/CD3/CD62+/CD45RA+	12.9		370		11.6		268		5.7-19.7	85-568
	CD8/CD3/CD62+/CD45RA-	6.2		178		3.1		72		1.5-10.3	25-180
	CD8/CD3/CD62-/CD45RA-	3.7		106		2.4		55		1.1-9.2	24-175
	CD8/CD3/CD62-/CD45RA+	2.3		66		1.9		44		0.7-7.8	11-172
	CD3/CD4/CD31/CD45RA	8.7		251		25.7	**High**	593	**High**	1.6-20.2	34-426
	CD3/CD4/CD45RA-/CXCR5	4.8		138		4.5		104		1.8-8.9	35-172
	CD3/CD8/CD57	NA		NA		3.2		74		<16.2	<397
	CD3/CD4/CD25/FoxP3	1.9		55		1	**Low**	23	**Low**	1.6-4.3	25-89
B cell subsets	CD20	13.3		382	**High**	17.5		404	**High**	3.0-19.0	59-329
	CD19	13.3		382	**High**	17.5		404	**High**	3.3-19.3	61-321
	CD20/CD27	2.1		60		0.2	**Low**	5	**Low**	0.8-3.6	13-68
	CD20/CD38	13.1		377	**High**	16.9		390	**High**	1.2-17.6	30-282
	CD20/CD10	7.7	**High**	220	**High**	4.3		100		0.6-6.0	13-127
	CD20/IgM-/CD38++	0.1		3		0		0		0-0.1	0-2
	CD20/IgM+/CD10+	2.9	**High**	83	**High**	2.5		58		0.1-2.8	2.0-60
	CD20/CD38+/CD10+	3	**High**	86	**High**	2.4		55		0.1-2.7	0-63
	CD20/CD27+/IgM+	0.6		17		0.1	**Low**	2	**Low**	0.3-2.5	6.0-50
	CD20/CD27+/IgM-	1.3		37		0.1	**Low**	2	**Low**	0.3-2.2	6.0-43
	CD19/CD24hi/CD38hi	2.9	**High**	83	**High**	2.5	**High**	58	**High**	0.3-2.2	6.0-48
	CD19/CD24-/CD38++	0.6	**High**	17	**High**	0.1		2		0-0.3	0-8
	CD19/CD21low/CD38low	0.1		3		0.1		2		0.1-0.8	1.0-16
NK Cells	CD16+orCD56+/CD3-	6	**Low**	172		4.7	**Low**	109	**Low**	6.2-34.6	126-729
	CD16+orCD56+/CD3+	10		287		6.5		150		2.2-12.4	29-299

Supplementary Data Table 2. Vaccine responses

	SHARPIN P1		
PCV-13*	Pre	Post (4-weeks)	2-fold increase
Serotype 1	N/A**	N/A**	N/A**
Serotype 3	0.4	1.3	(+)
Serotype 4	2.4	10.6	(+)
Serotype 5	1.5	2.1	(-)
Serotype 14	8.8	8.7	(-)
Serotype 19F	4.5	15.2	(+)
Serotype 23F	14.8	17.2	(-)
Serotype 6B	0.3	3.5	(+)
Serotype 7F	6.6	3.5	(-)
Serotype 18C	0.3	0.8	(+)
Serotype 19A	0.4	5.6	(+)
Serotype 9V	7.4	28.5	(+)
2-fold increase rate			**63% (positive)*** **

* Note that serotype 6A was not included in the assessment.

** Serotype 1 was not quantitated due to technical reasons.

*** Antibody concentrations increased by 2-fold or greater for at least 50% of serotypes when comparing the pre- and post-vaccination results.

	SHARPIN P1	Cutoff	
VZV IgG (index)	343	165	**Positive**
HiB IgG (mg/L)	>9.00	0.15	**Positive**
Diphtheria IgG (IU/ml)	0.03	0.01	**Positive**
Tetanus IgG (IU/ml)	0.48	0.01	**Positive**

Supplementary Data Table 3: inborn errors of cell death (IECD)

	Autoinflammation	Immunodeficiency	Immunophenotype	Cell Death	Mouse phenotype	Treatment
Sharpenia	Fever Parotitis Arthritis GI inflammation Growth failure	Chronic otitis media by group A streptococcus	Abnormalities in germinal center development	Apoptosis (> Necroptosis)	Dermatitis	Anti-TNF
HOIP deficiency	Fever Arthritis GI inflammation Dermatitis Growth failure	Viral encephalitis Skin abscesses Sepsis	Hypogammaglobulinemia Low T cells Low memory B cells Vaccine failure	Apoptosis (> Necroptosis)	Embryonic lethal	Anti-TNF IVIG
HOIL-1 deficiency	Fever GI inflammation Dermatitis Growth failure	Sepsis Meningitis	Hypogammaglobulinemia Low memory B cells Vaccine failure	Apoptosis (> Necroptosis)	Embryonic lethal	Corticosteroids HSCT
RELA haploinsufficiency	Fever GI inflammation Dermatitis Arthritis	No	(*)	Apoptosis	Exacerbation in inducible models (**)	Anti-TNF
RIPK1 deficiency	Fever Dermatitis GI inflammation Growth failure	Sepsis Pneumonia Skin abscesses UTI	Low T cells Low memory B cells	Apoptosis and necroptosis	Neonatal lethal	Anti-TNF HSCT
CRIA	Fever Lymphadenopathy GI inflammation	No	No major abnormalities	Apoptosis and necroptosis	Embryonic lethal in homozygous knock-in mice	Anti-IL6

Otulipenia/ORAS	Fever Panniculitis GI inflammation Sterile abscess formation Growth failure	(***)	No major abnormalities	Apoptosis	Embryonic lethal	Anti-TNF HSCT
TBK1 deficiency	Fever Arthritis Vasculitis Basal ganglia calcification Growth failure	No	No major abnormalities	Necroptosis (>apoptosis)	Embryonic lethal	Anti-TNF

* One patient is noted to have $CD4^+$ T lymphoproliferation. ** TNF-induced dermatitis and dextran sulfate sodium (DSS)-induced colitis. *** Susceptibility to staphylococcal infections in haploinsufficient carriers of *OTULIN* mutations. Abbreviations; CRIA: cleavage-resistant RIPK1-induced autoinflammation; ORAS: otulin-related autoinflammatory syndrome; HSCT: hematopoietic stem cell transplantation, UTI: urinary tract infection.