Supplementary Methods:

SLE and MAS clinical features included were: fever, malar rash, photosensitivity, oral or nasal ulcers, alopecia, arthritis, serositis (pericarditis, pleuritis, or peritonitis), nephritis, neuropsychiatric symptoms (delirium, psychosis, or seizures), and headaches. Patients with clinical evidence of lupus nephritis underwent kidney biopsy and were classified based on WHO (World Health Organization) and/or ISN (International Society of Nephrology) categories: mesangial (class II), membranous (class V), and/or proliferative (class III or IV) nephritis classes.[7]

The cSLE laboratory features included in Table 1 were: white blood cell (WBC or leukocytes), and thrombocytes, lymphocytes, DAT (Direct Antiglobulin Test) or Coombs status, and complement levels (C3, C4). Autoantibody status was reported for anti-nuclear antibodies (ANA), anti-double stranded DNA (dsDNA), anti-Smith (Sm), and anti-phospholipid antibodies (anti-cardiolipin [ACL], and lupus anticoagulant [LAC]). Additional laboratory features assessed in the MAS patients (Supplementary Table 1) were: hemoglobin, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), Ferritin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactose dehydrogenase (LDH), prothrombin time (PTT), d-Dimer, fibrinogen and triglycerides. Ten of the 19 MAS patients underwent bone marrow aspirate to look for hemophagocytosis.

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Supplementary Table S1. Frequency of clinical and laboratory MAS features in the childhood-onset systemic lupus erythematosus (cSLE) patient with Macrophage activation syndrome (MAS) (n=19)

		Total (%)	Median (IQR)[a]
Clinical features:			
	Fever[b]	18 (95)	
	Generalized lymphadenopathy	7 (37)	
	CNS dysfunction[c]	6 (35)	
	Hepatomegaly[d]	4 (21)	
	Splenomegaly	5 (26)	
	Hemorrhage[e]	3 (18)	
Laboratory features[f]:			
	Hemoglobin	17 (89)	99.00 (83.00-109.50)
	WBC	14 (74)	2.50 (1.70-5.10)
	Neutrophils	11 (58)	1.20 (1.00-3.30)
	Platelet count	11 (58)	105.00 (88.50-177.50)
	ESR	16 (84)	57.00 (40.00-109.50)
	CRP (n=17)	10 (59)	2.80 (0.90-21.40)
	Ferritin	19 (100)	2212 (1035-4566)
	AST	19 (100)	91 (58-196)
	ALT	15 (79)	73.00 (49.00-132.50)
	LDH	19 (100)	1140 (848-1381)
	PTT	7 (37)	32.50 (30.30-39.30)
	d-Dimer	19 (100)	2200 (1848-3008)
	Fibrinogen	3 (16)	3.00 (2.50 - 3.40)
	Triglycerides (n=17)	13 (76)	2.70 (2.00-3.50)
Hemophagocytosis in bone marrow aspirate/biopsy (n=10)		1 (10)	

[a] The median and interquartile range [IQR 25%-75%] values for the most abnormal laboratory value at MAS presentation and prior to MAS treatment.
[b] ≥ 38.0 degrees Celsius.
[c] irritability, disorientation, lethargy, headache, seizures, or coma (excluding infection, drugs, or metabolic causes)
[d] as per imaging and/or physical examination.
[e] pulmonary hemorrhage, cerebral hemorrhage, hematochezia, epistaxis, or gum bleeding with heavy menstruation.
[f] Total (%) are the proportion of MAS patients with abnormal Hospital for Sick Children (HSC) laboratory reference values at time of MAS diagnosis and prior to MAS treatment.
MAS: macrophage activation syndrome; cSLE: childhood-onset systemic lupus erythematosus; CNS: central nervous system, WBC: white blood cells; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; AST: aspartate aminotransferase; ALT: alanine aminotransferase; LDH: lactose dehydrogenase; PTT: prothrombin time.

Supplementary Table S2. HLH low-frequency non-synonymous variants in childhood-onset systemic lupus erythematosus (cSLE) patients without Macrophage activation syndrome (MAS)

Chr	Start Position	Gene	Ref/Alt Allele	SNP[a]	AA change	CADD score[b]	MAS MAF[c]	Non-MAS MAF[c]	Referent population[d]	
									MAF	Ancestry
1	235872503	*LYST*	G/A	NR[e]	A3344V	33.00	0	8.06E-03	NR	ADM
1	235878543	*LYST*	C/T	rs543359025	V3248I	27.90	0	8.06E-03	7.51E-04	SAS
1	235922341	*LYST*	T/C	rs112601869	D2271G	22.80	0	8.06E-03	0.02	AFR
1	235938235	*LYST*	A/G	rs559869925	I1871T	21.00	0	8.06E-03	4.52E-03	SAS
1	235938329	*LYST*	A/C	rs115330112	S1840A	18.55	0	8.06E-03	4.39E-03	ADM
1	235940415	*LYST*	C/G	rs773800745	G1803A	21.80	0	8.06E-03	7.97E-06	ADM
1	235945254	*LYST*	C/T	rs149991106	D1666N	20.40	0	8.06E-03	1.85E-04	AFR
1	235956873	*LYST*	A/T	NR	M1349K	24.20	0	8.06E-03	NR	EUR
1	235969405	*LYST*	T/C	rs145666408	K1011E	13.30	0	8.06E-03	1.99E-05	ADM
1	235969976	*LYST*	A/C	rs35261143	F820L	18.02	0	8.06E-03	1.06E-04	EUR
1	235972734	*LYST*	G/A	rs77848653	P462S	13.59	0	8.06E-03	9.05E-03	AFR
1	235973750	*LYST*	T/C	rs3768067	H123R	12.67	0	8.06E-03	8.77E-04	ADM
2	32449832	*NLRC4*	C/A	rs61754192	A929S, A264S	5.58	0	8.06E-03	0.01	EUR
2	32463365	*NLRC4*	C/A	rs149451729	G786V, G121V	17.64	0	8.06E-03	2.32E003	ADM
3	128200715	*GATA2*	C/G	NR	A350P, A364P	24.70	0	8.06E-03	NR	ADM
5	77311370	*AP3B1*	C/T	rs146503597	V950M, V999M	13.98	0	0.02	4.13E-03, 6.62E-03	ADM, EUR
5	77335015	*AP3B1*	G/T	rs139344924	F838L, F887L	22.50	0	8.06E-03	0.01	EUR
5	77406104	*AP3B1*	A/T	rs62001050	I726K, I775K	8.27	0	8.06E-03	0.03	AFR
5	77461466	*AP3B1*	C/G	rs150000996	A400P, A351P	24.80	0	8.06E-03	8.00E-04	ADM
5	77471634	*AP3B1*	T/C	rs142025324	I308V, I357V	19.00	0	8.06E-03	2.42E-03	EUR
5	77477483	*AP3B1*	C/T	NR	D264N, D215N	20.90	0	8.06E-03	NR	EUR
5	156649936	*ITK*	C/T	rs1156578676	P187S	16.18	0	8.06E-03	1.59E-05	ADM
5	156671321	*ITK*	C/A	rs150270557	Q428K	22.40	0	8.06E-03	1.75E-04	ADM
10	72358722	*PRF1*	T/C	rs28933375	N252S	14.50	0	8.06E-03	6.16E-03	EUR

10	72360387	*PRF1*	G/A	rs35947132	A91V	23.70	0	0.02	0.05, 4.32E-03	EUR, SAS
14	23282336	*SLC7A7*	G/A	rs11568438	A91V, A91E	27.50	0	8.06E-03	0.02	EUR
14	23282544	*SLC7A7*	C/T	rs777499742	D22N	11.15	0	8.06E-03	7.96E-06	ADM
17	73826491[f]	*UNC13D*	G/A	rs35037984	R928C	15.31	0.026	0.02	0.02, 0.02	ADM, SAS
17	73832719	*UNC13D*	C/T	rs200109035	R411Q	22.50	0	8.06E-03	5.86E-04	ADM
19	7706658	*STXBP2*	C/T	rs181216956	T166M, T163M, T177M	4.15	0	0.02	0.02, 0	EAS, SAS
19	7707128	*STXBP2*	C/T	rs753879238	R232W, R246W, R235W	25.90	0	8.06E-03	0	SAS
19	7709596	*STXBP2*	G/A	rs114628602	D399N, D413N, D402N	25.00	0	8.06E-03	1.12E-04	ADM
19	7710134	*STXBP2*	C/T	rs141309384	A444V, A433V, A430V	15.52	0	0.02	8.26E-03, 0.01	ADM, EUR
19	7711222	*STXBP2*	G/A	rs749915574	V493I, V479I, V482I	16.07	0	8.06E-03	1.17E-04	EAS
19	7712364	*STXBP2*	A/G	rs61736586	R552G, R566G, R555G	18.00	0	8.06E-03	0.03	AFR
X	77150892	*MAGT1*	G/A	rs140854076	R6W	14.62	0	8.06E-03	2.33E-03	ADM

[a] dbSNP database <https://www.ncbi.nlm.nih.gov/snp/>.

[b] CADD PHRED-scaled score <https://cadd.gs.washington.edu/>.

[c] Calculations for MAF in: MAS = # of alleles in cohort/(2*19); non-MAS = # of alleles in cohort/(2*62).

[d] Ancestry-specific referent minor allele frequency (MAF) of variant reported, unless SLE cohort variant from admixed population; variants in referent population variant from gnomAD exome dataset or TOPMed accessed on November 19, 2020; when 2 or more patients in the cohort carried the same variant, all referent population MAF were reported in respective order.

[e] NR = Variant not reported in dbSNP or referent population of gnomAD or TOPMed.

[f] Same variant found in MAS (see Table 3) and non-MAS cohorts.

HLH: hemophagocytic lymphohistiocytosis; cSLE: childhood-onset systemic lupus erythematosus; MAS: macrophage activation syndrome; Chr: Chromosome; Ref/Alt: reference/alternative; SNP: single nucleotide polymorphism; AA: amino acid; CADD: CADD: combined annotation dependent depletion; MAF: minor allele frequency; ADM – admixed, AFR – African, EAS – East Asian, EUR- European (non-Finnish), SAS – South Asia.