Germline *HAVCR2* mutations and their relation to the clinical spectrum of subcutaneous panniculitis-like T-cell lymphoma and hemophagocytic lymphohistiocytosis: results from a multicenter study and meta-analysis

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Supplementary Appendix

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This supplemental material has been provided by the authors to give readers additional information about their work.

Table of Contents

Table of Contents (continued)

Supplementary Methods

1. Design of a multicenter study

A multicenter retrospective cohort enrolled patients with subcutaneous panniculitis-like T-cell lymphoma (SPTCL) with or without hemophagocytic lymphohistiocytosis (HLH) and patients with idiopathic HLH, which are those with HLH alone without secondary causes of HLH such as infections, autoimmune diseases, and malignancies, during January 2009-June 2022 from 9 study sites in Thailand. The local institutional review boards from 4 adult hematology (Department of Medicine, King Chulalongkorn Memorial Hospital, Chulalongkorn University and Thai Red Cross Society, Bangkok; Department of Medicine, Maharaj Nakhorn Chiang Mai Hospital, Chiang Mai University, Chiang Mai; Department of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok; Department of Medicine, Udon Thani Medical Education Center, Udon Thani Hospital, Udon Thani) and 5 pediatric hematology-oncology centers (Department of Pediatrics, King Chulalongkorn Memorial Hospital, Chulalongkorn University and Thai Red Cross Society, Bangkok; Department of Pediatrics, Srinagarind Hospital, Khon Kean University, Khon Kean; Department of Pediatrics, Phramongkutklao Hospital, Phramongkutklao College of Medicine, Bangkok; Department of Pediatrics, Maharaj Nakhorn Chiang Mai Hospital, Chiang Mai University, Chiang Mai; Department of Pediatrics, Siriraj Hospital, Mahidol University, Bangkok) ethically approved the study protocol.

Diagnosis of SPTCL and/or HLH based on pathological specimens (e.g., bone marrow biopsies, skin and subcutaneous tissue biopsies) was reviewed and revalidated by the hematopathologists at the study sites. As previously described,[1] SPTCL was diagnosis by tumor cells expressing CD3, CD8, T-cell intracytoplasmic antigen 1 (TIA-1), T-cell receptor beta F1 (BF1), and granzyme B, but not CD4, CD56 and Epstein-Barr virus-encoded small RNA (EBER). Clonality of SPTCL was assessed by polymerase chain reaction (PCR) analysis of T-cell receptor gene rearrangement. HLH was defined according to the HLH-2004 criteria.[2] The term of 'HLH-like systemic illnesses' was applied to those who did not complete the HLH-2004 criteria but were clinically consistent with HLH.[3] To be counted as HLH-like systemic illnesses, the patients had to fulfill all the following systemic symptoms/features, i.e., fever, cytopenias, elevated serum ferritin level ≥500 µg/L, and the presence of hemophagocytosis in bone marrow. Data on treatments of SPTCL and/or HLH/HLH-like systemic illnesses (e.g., corticosteroids, immunosuppressive therapy, chemotherapy, and intravenous immunoglobulin) based on the discretion of the treating physicians, and the disease outcomes during the follow-ups were collected.

2. Detection of germline HAVCR2^{Y82C} mutation

DNA was extracted from bone marrow or peripheral blood using Gentra Puregene Blood Kits (Qiagen N.V., Hilden, Germany). The sequences of primers to detect *HAVCR2* exon 2 mutations were forward primer: 5'-GGAAGCTGAGGGTGTATTTCT-3' and reverse primer: 5'-TCAGAGCCAGCTAAA GATTCC-3'. The primer covered 3 reported pathogenic variants (p.Y82C, p.I97M and p.T101I). PCR was performed from 100 ng of DNA. After 5 minutes at 94°C, 30 cycles of amplification using 60 seconds at 94°C, 60 seconds at 56°C and 60 seconds at 72°C were performed, with a subsequent 5-minute

extension at 72°C. The amplified products were 249 base pairs (bp) in length covering p.Y82C, p.I97M and p.T101I loci. PCR products were purified and sent for Sanger sequencing.

3. Whole exome sequencing and sequencing analysis

The samples were processed following the standard whole exome sequencing (WES) pipeline at Novogene CAP lab (Novogene Co. Ltd., Beijing, China). DNA libraries were prepared using NOVO DNA Library Prep Kit followed by IDT system to capture DNA coding sequences. Five hundred ng of genomic DNA were processed through fragmentation, end-repair and A-tailing, adapter ligation, PCR1 amplification, IDT probe hybridization, capture, and PCR2 amplification. The quality of WES libraries was analyzed followed by a quality check using Fragment Analyzer (Advanced Analytical Technologies Inc., Ankeny, IA). Libraries with an average size of 450 bp (range 300-600 bp) were quantified by quantitative PCR (qPCR) in QuantStudio 12K (Thermo Fisher Scientific, Waltham, MA) using KAPA qPCR quantification kit (KAPA Biosystems Inc., Wilmington, MA). The libraries were normalized and pooled as per manufacturer protocol (Illumina Inc., San Diego, CA). Sequencing was performed using NovaSeq 6000 platform (Illumina Inc., San Diego, CA). For the analytical pipeline, common single nucleotide polymorphism (SNP) variants (heterozygous allele frequency >1% in genome aggregation database [gnomAD] heterozygous allele frequency all populations, and homozygous allele frequency >0.00001% in gnomAD homozygous allele frequency all populations) were excluded (https://gnomad.broadinstitute.org/). The remaining exceedingly rare variants were then filtered on the basis of the variant type and position in the gene. Only genes related to lymphoma and immune regulation were selected. Based on the guideline from the American College of Medical Genetics and Genomics (ACMG),[4] only pathogenic variants, likely pathogenic variants and variants with unknown significance (VUS) were selected for our analysis.

4. Statistical analysis for a multicenter study

Continuous variables were described as medians and interquartile ranges (IQR). The Wilcoxon rank-sum test was used to compare continuous data between 2 groups. The Kruskal-Wallis H test was used to compare continuous data between more than 2 groups. Categorical parameters, in frequencies and percentages, were compared between groups using the Chi-square or Fisher's exact test as appropriate. P-values lower than 0.05 were considered statistically significant.

5. Data sources and study search for a systematic review and meta-analysis

Two authors (C.M. and C.P.) independently performed a systematic search in MEDLINE, Embase, and Cochrane Library databases from their inceptions to July 15, 2022. Our search terms consisted of "subcutaneous panniculitis-like T-cell lymphoma", "hemophagocytic lymphohistiocytosis", "*HAVCR2* gene", and "*TIM3* gene"; full strings of which are available in the next section. After combining search results from the different databases, duplicates were excluded. This study was conducted without language limitation according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines and the International Prospective Register of Systematic Reviews (PROSPERO) registration (CRD42022341310).[5]

6. Full search terms

6.1 Ovid MEDLINE

#1 hemophagocytic lymphohistiocytosis.mp. OR lymphohistiocytosis, hemophagocytic/

#2 hemophagocytic syndrome.mp. OR lymphohistiocytosis, hemophagocytic/

#3 #1 OR #2

#4 subcutaneous T-cell lymphoma.mp.

#5 subcutaneous panniculitis-like T-cell lymphoma.mp.

#6 #4 OR #5

#7 *HAVCR2* gene.mp.

#8 *TIM3* gene.mp.

#9 #7 OR #8

#10 #3 AND #6

#11 #9 OR #10

6.2 Embase

#1 'hemophagocytic syndrome'/exp OR 'hemophagocytic lymphohistiocytosis'

#2 'subcutaneous T-cell lymphoma'

#3 '*HAVCR2* gene'

#4 '*TIM3* gene'

#5 #1 AND #2

#6 #3 AND #4

#7 #5 OR #6

6.3 Cochrane Library

#1 ("hemophagocytic syndrome") OR ("hemophagocytic lymphohistiocytosis") (Word variations have been searched)

#2 ("subcutaneous T-cell lymphoma") OR ("subcutaneous panniculitis-like T-cell lymphoma") (Word variations have been searched)

#3 ("*HAVCR2* gene") OR ("*TIM3* gene") (Word variations have been searched)

#4 #1 AND #2

#5 #3 OR #4

7. Study selection for a systematic review and meta-analysis

The retrievable studies were independently reviewed by two authors (C.M. and C.P.). Clinical trials, observational studies, case series and case reports describing *HAVCR2* mutational statuses among patients with SPTCL and/or HLH were eligible to be included in the systematic review. Preprints and conference abstracts were allowed, while studies of the same populations with other more mature

studies, reviews, and editorials were excluded. Only studies with at least 10 participants were qualified for the quantitative synthesis. Conflicts were resolved by mutual consensus among reviewers.

8. Data extraction and quality assessment for the included studies

Study design, study center(s), study period, numbers of patients with *HAVCR2* mutations and/or HLH/HLH-like systemic illnesses, participant age, study limitations, and other relevant factors were extracted from the eligible studies. The primary outcome was the risk factors associated with HLH/HLH-like systemic illnesses, including *HAVCR2* mutational statuses, age at diagnosis, and sex.

The secondary outcomes were the prevalence of *HAVCR2* mutations, either homozygosity, compound heterozygosity, or heterozygosity, and the mean age at diagnosis. Google Translate was employed for screening non-English studies. The risk of bias for cohort studies was evaluated by the Newcastle-Ottawa scale, consisting of 3 domains: participant selection (0-4 scores), comparability between groups (0-2 scores), and outcome ascertainment (0-3 scores).[6] Each study was assigned into a group of poor, moderate, or high quality.

9. Statistical analysis for a conventional meta-analysis

The meta-analysis using the DerSimonian and Laird random-effects model was performed to estimate the pooled odds ratios (pORs) with 95% confidence intervals (CIs) for risk factors associated with HLH/HLH-like systemic illnesses which were binary variables. For those reported as continuous variables, the pooled differences in means (pMDs) with 95% CIs were synthesized. The pooled prevalence of *HAVCR2* mutations and HLH/HLH-like systemic illnesses was also reported. Any continuous variables reported in medians were converted into means before the quantitative data synthesis.[7] The influence of factors on outcomes of interest or estimated effect sizes was determined by meta-regression analysis based upon restricted maximum likelihood estimation, if appropriate.[8] Studies or study subgroups with sample sizes ≥2 were allowed to be analyzed in the meta-regression models.

The publication bias would be examined by funnel plots and Egger's regression if ≥10 studies were aggregated in the potential model. If p-value of Egger's regression was <0.1, the publication bias was considered significant. The inter-study heterogeneity in each meta-analysis model was assessed by the I^2 statistic (ranging from 0-100%) which could be classified into low (I^2<25%), moderate (I^2=25-60%), or substantial heterogeneity (I^2>60%).[9]

Supplementary Table S1 Characteristics of 34 patients in the present cohort.

No.	Age at first diagnosis (year)	Sex	Hb (g/dL)	WBC ($x10^9$/L)	ANC ($x10^9$/L)	Platelets ($x10^9$/L)	Serum ferritin (ng/mL)	HLH in BM	Fever	HLH-2004 score	SC nodule	*HAVCR2* mutational status	Time to relapse (month)	Survival (month)*	Mortality*	Treatment
1	16	Female	8.9	1.47	1.11	84	6997	Y	Y	6	Y	Homozygous	14	60	Alive	CsA/dexamethasone/IVIg
2	16	Female	7.2	1.32	0.73	51	86100	Y	Y	6	N	Homozygous	NR	15	Alive	Chemotherapy (EPOCH)
3	12	Female	10.4	2.06	1.40	113	71955	Y	Y	4	N	Homozygous	NR	1	Alive	Chemotherapy
4	22	Female	9.5	2.20	1.25	202	113	N	Y	1	Y	Homozygous	69	175	Alive	CsA
5	27	Female	11.2	7.20	5.83	320	N/A	N	Y	1	Y	Homozygous	17	49	Alive	CsA
6	26	Female	11.9	8.66	7.84	191	N/A	N	Y	1	Y	Homozygous	41	41	Alive	CsA/prednisolone
7	32	Female	11.2	3.57	2.86	202	N/A	N	N	0	Y	Homozygous	NR	37	Alive	CsA/prednisolone
8	23	Female	5.7	3.10	1.90	161	20187	Y	Y	4	Y	Homozygous	NR	20	Alive	CsA/prednisolone
9	60	Female	11.0	5.89	4.20	399	538	N	Y	1	Y	Homozygous	NR	23	Alive	CsA/prednisolone
10	28	Male	8.3	1.23	0.84	61	66100	Y	Y	5	Y	Homozygous	NR	113	Alive	CsA/prednisolone
11	8	Female	11.6	8.10	4.80	447	251.7	N	Y	0	Y	Homozygous	NR	1	Alive	Chemotherapy
12	9	Male	11.0	1.50	0.76	157	5752	Y	Y	3	N	Homozygous	NR	14	Alive	Chemotherapy
13	14	Male	11.8	3.60	2.00	142	5750	Y	Y	4	Y	Homozygous	2	4	Alive	Chemotherapy
14	10	Male	7.3	27.60	12.10	10	9035	Y	Y	7	Y	Homozygous	NR	3	Dead	Chemotherapy
15	8	Female	9.7	3.10	1.60	193	>15000	Y	Y	6	Y	Homozygous	NR	14	Alive	Chemotherapy
16	9	Male	11.5	2.10	0.70	205	563	Y	Y	6	Y	Homozygous	NR	18	Alive	Chemotherapy
17	11	Male	11.5	3.70	1.70	185	3709	N	Y	2	Y	Homozygous	36	71	Alive	Chemotherapy
18	13	Male	9.8	5.20	4.40	218	583	Y	Y	5	N	Homozygous	24	42	Alive	Chemotherapy
19	6	Male	10.0	2.60	1.10	250	179	N	Y	1	Y	Homozygous	NR	2	Alive	CsA/prednisolone
20	49	Male	8.8	1.73	0.22	44	10581	Y	Y	4	N	Homozygous	NR	4	Alive	Chemotherapy
21	18	Male	10.9	1.97	1.53	90	5967	Y	Y	5	Y	Heterozygous	NR	4	Alive	Dexamethasone/IVIg
22	31	Male	7.5	1.30	0.80	90	12273	Y	Y	5	Y	Heterozygous	NR	35	Alive	CsA/prednisolone
23	19	Female	11.2	3.03	1.59	236	168	N	Y	2	Y	Heterozygous	NR	40	Alive	CsA/prednisolone
24	12	Female	N/A	N/A	N/A	N/A	N/A	N	Y	1	Y	Heterozygous	NR	17	Alive	Prednisolone
25	16	Female	9.2	2.10	1.60	275	1595	Y	Y	5	Y	Heterozygous	NR	31	Alive	Chemotherapy
26	34	Female	11.7	5.96	4.44	273	N/A	N	N	0	Y	Heterozygous	NR	48	Alive	CsA/prednisolone
27	30	Female	N/A	N/A	N/A	N/A	8349	Y	Y	6	N	Heterozygous	NR	1	Dead	Chemotherapy
28	15	Female	11.3	5.70	2.18	289	N/A	N	N	0	Y	Wild-type	NR	26	Alive	Chemotherapy
29	62	Male	14.2	4.20	2.20	235	N/A	N	N	0	Y	Wild-type	NR	32	Alive	CsA/prednisolone
30	23	Female	16.4	4.51	2.76	267	N/A	N	N	0	Y	Wild-type	22	74	Alive	CsA
31	39	Female	12.9	4.30	3.20	118	N/A	N	Y	1	Y	Wild-type	NR	32	Alive	CsA/prednisolone
32	36	Female	12.2	3.40	1.90	300	N/A	N	N	0	Y	Wild-type	NR	21	Alive	CsA/prednisolone
33	59	Female	13.4	3.17	1.09	170	N/A	N	N	0	Y	Wild-type	41	157	Alive	CsA
34	33	Female	12.7	6.11	3.81	290	N/A	N	N	0	Y	Wild-type	45	95	Alive	CsA/prednisolone

Abbreviations: ANC, absolute neutrophil count; BM, bone marrow; CsA, cyclosporine A; EPOCH, etoposide, prednisolone, vincristine, cyclophosphamide, and doxorubicin; Hb, hemoglobin; HLH, hemophagocytic lymphohistiocytosis; IVIg, intravenous immunoglobulin; N, no or absent; N/A, not available; NR, not reached; SC, subcutaneous; Y, yes or present. *Until death or the last follow-up.

Supplementary Table S2 Comparison of potential factors by *HAVCR2* mutational statuses.

Potential factors	Homozygous/compound heterozygous *HAVCR2* mutated	Heterozygous *HAVCR2* mutated	*HAVCR2* wild-type	P-value
Analysis of the present cohort (N=34)				
No. of participants (n)	20	7	7	
Age (year), median (IQR)	15 (9.5-26.5)	19 (16-31)	36 (23-59)	0.02
HLH-2004 score, median (IQR)	4 (1-6)	5 (1-5)	0 (0-0)	0.003
Relapse, n (%)	7 (35.0)	0 (0)	3 (42.9)	0.17
Analysis of individual patient data from 4 cohorts (N=127)*				
No. of participants (n)	66	12	43	
Age (year), median (IQR)	23 (12-32)	24.5 (17-31)	39 (25-55)	<0.001
HLH-2004 score, median (IQR)	4 (1-5)	5 (1-5)	0 (0-0.5)	0.002
Relapse, n (%)	22 (33.3)	1 (8.3)	9 (20.9)	0.07

Abbreviations: HLH, hemophagocytic lymphohistiocytosis; IQR, interquartile range.
* There were 4 cases with unknown HLH status and 4 cases with unknown mutational status. In which, there were 2 cases with unknown both HLH and mutational statuses.

Supplementary Table S3 Whole exome sequencing of 6 patients (5 homozygous and 1 heterozygous *HAVCR2* mutations) with selected variants involving hemophagocytic lymphohistiocytosis and subcutaneous panniculitis-like T-cell lymphoma.

No.	Cat*	Pathway	Gene	Type	Chr	Genome position	Depth	VAF (%)	Exon	c.DNA	Protein	RefSeq ID	End	dbSNP	g1000	esp5400	SIFT	Polyphen2
2	B	Immune response	*HAVCR2*	SNP	5	156533787	243	100	2	c.245A>G	p.(Tyr82Cys)	NM_032782	156533787	rs184868814	0.0062	0.0001	1	1
2	C	Immune response	*JAK3*	SNP	19	17951110	151	39.1	9	c.1183C>T	p.(Arg395Cys)	NM_000215	17951110	rs777790283			0.99	0.594
2	B	PIDD	*CASP10*	SNP	2	202050594	178	41	2	c.94G>A	p.(Gly32Arg)	NM_032977	202050594	rs375838979			0.99	0.982
2	B	PIDD	*NCF1*	SNP	7	74193642	283	20.1	4	c.269G>A	p.(Arg90His)	NM_000265	74193642	rs201802880			0.97	0.172
2	C	PIDD	*CARMIL2*	SNP	16	67687080	129	58.1	29	c.3043C>A	p.(Pro1015Thr)	NM_001013838	67687080	rs2052762868			0.94	0.61
2	B	Epigenetic modifier	*KMT2C*	SNP	7	151945007	696	59.9	14	c.2512G>A	p.(Gly838Ser)	NM_170606	151945007	rs2479172			1	0.999
2	C	Epigenetic modifier	*ARID1A*	SNP	1	27023042	431	54.8	1	c.148A>G	p.(Met50Val)	NM_006015	27023042	rs1216784088			0.71	0
2	B	Cell adhesion	*FAT1*	SNP	4	187542527	239	55.2	10	c.5213A>G	p.(Gln1738Arg)	NM_005245	187542527	rs756726302			0.39	0.996
2	C	ATP binding	*ACACB*	SNP	12	109675114	301	41.2	33	c.4591G>A	p.(Glu1531Lys)	NM_001093	109675114	rs775667215			0.32	0.403
2	C	DIAP	*NLRP13*	SNP	19	56443601	311	43.7	1	c.77A>G	p.(Gln26Arg)	NM_176810	56443601	rs76565431	0.0068	0.0002	0.4	0.065
2	C	Microtubule activity	*PCM1*	INDEL	8	17796382	171	45.6	5	c.476_477delinsGT	p.(Asn159Ser)	NM_006197	17796382	rs754721723				
3	B	Immune response	*HAVCR2*	SNP	5	156533787	142	100	2	c.245A>G	p.(Tyr82Cys)	NM_032782	156533787	rs184868814	0.0062	0.0001	1	1
3	B	Immune response	*CBL*	SNP	11	119169205	97	48.4	15	c.2389A>G	p.(Ser797Gly)	NM_005188	119169205	rs138151048			1	0.039
3	B	PIDD	*NCF1*	SNP	7	74193642	226	58.4	4	c.269G>A	p.(Arg90His)	NM_000265	74193642	rs201802880			0.97	0.172
3	B	DIAP	*NLRP4*	SNP	19	56390170	97	51.5	9	c.2707T>C	p.(Cys903Arg)	NM_134444	56390170				1	1
3	B	Cytokine	*IL16*	SNP	15	81593713	98	37.8	15	c.3178G>C	p.(Gly1060Arg)	NM_001172128	81593713	rs200434957	0.0004		0.99	0.668
3	B	Epigenetic modifier	*KMT2C*	SNP	7	151945007	254	37.4	14	c.2512G>A	p.(Gly838Ser)	NM_170606	151945007	rs2479172			1	0.999
3	C	Epigenetic modifier	*BAZ2A*	SNP	12	56997420	258	41.9	17	c.3109T>C	p.(Cys1037Arg)	NM_013449	56997420	rs374255148			0.63	0
3	B	Phosphoinositol signaling	*PDCD11*	SNP	10	105203050	117	53.8	33	c.5084T>G	p.(Leu1695Arg)	NM_014976	105203050				0.98	0.03
3	B	Cell adhesion	*FAT1*	SNP	4	187518177	189	54.5	25	c.12517A>G	p.(Thr4173Ala)	NM_005245	187518177				0.95	0.338
3	C	Microtubule activity	*PCM1*	INDEL	8	17796382	102	33.3	5	c.476_477delinsGT	p.(Asn159Ser)	NM_006197	17796382	rs754721723				
12	B	Immune response	*HAVCR2*	SNP	5	156533787	158	100	2	c.245A>G	p.(Tyr82Cys)	NM_032782	156533787	rs184868814	0.0062	0.0001	1	1
12	B	PIDD	*NCF1*	SNP	7	74193642	217	40.6	4	c.269G>A	p.(Arg90His)	NM_000265	74193642	rs201802880			0.97	0.172
12	C	PIDD	*WAS*	SNP	X	48547051	64	100	10	c.934C>T	p.(Pro312Ser)	NM_000377	48547051				0.76	0.01
12	B	Epigenetic modifier	*KMT2C*	SNP	7	151945007	295	45.1	14	c.2512G>A	p.(Gly838Ser)	NM_170606	151945007	rs2479172			1	0.999
12	B	Epigenetic modifier	*KMT2D*	SNP	12	49424177	89	20.2	42	c.13885A>C	p.(Thr4629Pro)	NM_003482	49424177	rs1942838087			0.99	0.997
12	B	Epigenetic modifier	*BAZ2A*	SNP	12	57000067	118	48.3	12	c.2229G>C	p.(Lys743Asn)	NM_013449	57000067	rs186484382	0.0002		0.96	0.996
12	C	Microtubule activity	*PCM1*	INDEL	8	17796382	132	99.2	5	c.476_477delinsGT	p.(Asn159Ser)	NM_006197	17796382	rs754721723				
12	C	Cytokine	*IL16*	SNP	15	81592411	204	52.4	14	c.2744G>C	p.(Arg915Thr)	NM_001172128	81592411	rs199597387	0.0002	0.0001	0.72	0.012
18	B	Immune response	*HAVCR2*	SNP	5	156533787	146	100	2	c.245A>G	p.(Tyr82Cys)	NM_032782	156533787	rs184868814	0.0062	0.0001	1	1
18	B	Immune response	*CBL*	SNP	11	119156193	142	54.9	11	c.1858C>T	p.(Leu620Phe)	NM_005188	119156193	rs2227988	0.0112	0.0008	0.96	0.997
18	C	Immune response	*MAST2*	SNP	1	46476606	115	46.1	10	c.1183C>G	p.(Gln395Glu)	NM_015112	46476606				0.9	0.542
18	B	PIDD	*NCF1*	SNP	7	74193642	208	54.3	4	c.269G>A	p.(Arg90His)	NM_000265	74193642	rs201802880			0.97	0.172
18	B	Epigenetic modifier	*KMT2C*	SNP	7	151935853	146	25.3	15	c.2591A>G	p.(Glu864Gly)	NM_170606	151935853	rs4024420			0.93	0.655
18	B	Epigenetic modifier	*KMT2D*	SNP	12	49424177	87	35.6	42	c.13885A>C	p.(Thr4629Pro)	NM_003482	49424177	rs1942838087			0.99	0.997
18	C	Epigenetic modifier	*NUP98*	SNP	11	3726529	128	48.4	22	c.2983C>T	p.(Arg995Cys)	NM_016320	3726529	rs144100440	0.0002	0.0001	0.98	0.609
18	C	Microtubule activity	*PCM1*	INDEL	8	17796382	123	44.7	5	c.476_477delinsGT	p.(Asn159Ser)	NM_006197	17796382	rs754721723				
18	C	ATP binding	*MLKL*	SNP	16	74709610	126	54.8	8	c.1091C>A	p.(Thr364Lys)	NM_152649	74709610	rs34389205	0.0004		0	0.001
18	C	DIAP	*NLRC3*	SNP	16	3613733	189	63	5	c.1205G>A	p.(Arg402His)	NM_178844	3613733	rs774251355			0.99	
18	C	Others	*PIEZO1*	SNP	16	88793562	223	46.6	24	c.3340C>G	p.(Gln1114Glu)	NM_001142864	88793562	rs373706590	0.0008		0.9	0.044

Abbreviations: Cat, category; Chr, chromosome; INDEL, insertion and deletion variant; PIDD, primary immune deficiency disease; Polyphen2, polymorphism phenotyping v2; SIFT, sorting intolerant from tolerant; SNP, single nucleotide polymorphism; VAF, variant allele frequency.

* Category B means likely pathogenic. Category C means variant of uncertain significance (VUS).

** All sequencing applied human genome assembly GRCh37/hg19.

Supplementary Table S3 Whole exome sequencing of 6 patients (5 homozygous and 1 heterozygous *HAVCR2* mutations) with selected variants involving hemophagocytic lymphohistiocytosis and subcutaneous panniculitis-like T-cell lymphoma. (continued)

No.	Cat*	Pathway	Gene	Type	Chr	Genome position	Depth	VAF (%)	Exon	c.DNA	Protein	RefSeq ID	End	dbSNP	g1000	esp5400	SIFT	Polyphen2
20	B	Immune response	*HAVCR2*	SNP	5	156533787	163	100	2	c.245A>G	p.(Tyr82Cys)	NM_032782	156533787	rs184868814	0.0062	0.0001	1	1
20	B	PIDD	*LRBA*	SNP	4	151727507	76	47.4	33	c.5434C>T	p.(Arg1812Cys)	NM_001199282	151727507	rs368625168		0.0001	1	0.996
20	B	PIDD	*NCF1*	SNP	7	74193642	277	29.6	4	c.269G>A	p.(Arg90His)	NM_000265	74193642	rs201802880			0.97	0.172
20	B	PIDD	*RAG1*	SNP	11	36595340	214	50.5	2	c.486T>A	p.(Asp162Glu)	NM_000448	36595340	rs753042511			1	0.978
20	C	Epigenetic modifier	*KMT2C*	SNP	7	151945204	239	46.4	14	c.2315C>T	p.(Ser772Leu)	NM_170606	151945204	rs4024453			1	0.261
20	C	Microtubule activity	*PCM1*	INDEL	8	17796382	109	36.7	5	c.476_477delinsGT	p.(Asn159Ser)	NM_006197	17796382	rs754721723				
20	C	Others	*PIEZO1*	SNP	16	88800411	140	47.1	17	c.2232T>G	p.(His744Gln)	NM_001142864	88800411	rs369862544	0.0008		0.64	0
23	B	Immune response	*HAVCR2*	SNP	5	156533787	172	63.9	2	c.245A>G	p.(Tyr82Cys)	NM_032782	156533787	rs184868814	0.0062	0.0001	1	1
23	C	Immune response	*CACNA1C*	INDEL	12	2791130	32	65.6	43	c.5459_5461delinsTGG	p.(Pro1820_Met1821delinsLeuVal)	NM_001129830	2791130	rs71441836				
23	C	Immune response	*PIK3CD*	SNP	1	9776549	62	33.9	6	c.652G>T	p.(Ala218Ser)	NM_005026	9776549					
23	B	PIDD	*NCF1*	SNP	7	74193642	544	45.2	4	c.269G>A	p.(Arg90His)	NM_000265	74193642	rs201802880			0.97	0.172
23	B	Epigenetic modifier	*KMT2C*	SNP	7	151935853	57	24.6	15	c.2591A>G	p.(Glu864Gly)	NM_170606	151935853	rs4024420		0.006	0.93	0.655
23	C	Epigenetic modifier	*KDM6B*	INDEL	17	7750177	229	79.9	9	c.789_791del	p.(Pro264del)	NM_001080424	7750177	rs61462443				
23	B	Transcription binding factor	*PDCD11*	SNP	10	105160184	50	70	3	c.133A>G	p.(Lys45Glu)	NM_014976	105160184	rs150893869	0.0206	0.0044	0.99	0.761
23	C	RNA processing	*DDX11*	SNP	12	31244809	1124	22.9	10	c.1242+4T>C		NM_001257144	31244809	rs2111769				
23	C	Microtubule activity	*CLIP1*	INDEL	12	122825589	106	43.4	11	c.2159_2161del	p.(Ala720del)	NM_001247997	122825589	rs774720519				
23	C	Cell adhesion	*FAT1*	SNP	4	187524464	173	46.2	19	c.11216C>T	p.(Ala3739Val)	NM_005245	187524464	rs74511500	0.0367	0.0008	1.12	0.42

Abbreviations: Cat, category; Chr, chromosome; INDEL, insertion and deletion variant; PIDD, primary immune deficiency disease; Polyphen2, polymorphism phenotyping v2; SIFT, sorting intolerant from tolerant; SNP, single nucleotide polymorphism; VAF, variant allele frequency.

* Category B means likely pathogenic. Category C means variant of uncertain significance (VUS).

** All sequencing applied human genome assembly GRCh37/hg19.

Supplementary Table S4 Quality assessment for 6 included observational studies according to the Newcastle-Ottawa Scale (NOS)[6] for non-randomized studies.

Study (Year)	Cohort design	Scored NOS†			Overall NOS	Quality grading‡
		Selection	Comparability	Outcome		
Gayden et al (2018)[10]	Retrospective	●●●●	●●	●●●	●●●●●●●●	High
Polprasert et al (2019)[1]	Retrospective	●●●●	●●	●●●	●●●●●●●●	High
Cheng et al (2020)[11]	Retrospective	●●●●	●	●	●●●●●●	Low
Sonigo et al (2020)[12]	Retrospective	●●●●	●	●●●	●●●●●●●●●	High
Koh et al (2021)[3]	Retrospective	●●●●	●●	●●●	●●●●●●●●●	High
Present cohort (2023)	Retrospective	●●●●	●●	●●●	●●●●●●●●●	High

† A study can be given a maximum of 4, 2, and 3 stars (●) within the Selection, Comparability, and Outcome domains, respectively. A maximum of total 9 stars can be given for a study with the highest quality.

‡ Quality of each study is graded according to the following thresholds of NOS:
High quality: 3-4 stars in the Selection AND 1-2 stars in the Comparability AND 2-3 stars in the Outcome domains
Moderate quality: 2 stars in the Selection AND 1-2 stars in the Comparability AND 2-3 stars in the Outcome domains
Low quality: Less than 5 stars in overall NOS OR 0-1 star in the Selection OR 0 star in the Comparability OR 0-1 star in the Outcome domains

Supplementary Table S5 The pooled data on patient characteristics based on statuses of hemophagocytic lymphohistiocytosis (HLH)/HLH-like systemic illnesses.

Characteristics	Pooled prevalence or weighted mean (95% confidence interval; I^2)		
	Overall population	Presence of HLH/HLH-like systemic illnesses	Absence of HLH/HLH-like systemic illnesses
No. of participants (n)	207	64	143
Any *HAVCR2* mutations (%)	51.6% (30.3-72.4%; I^2=87%) [6 studies; n=207]	76.6% (53.9-90.2%; I^2=49%) [6 studies; n=64]	33.5% (17.4-54.5%; I^2=75%) [6 studies; n=143]
Homozygous/compound heterozygous *HAVCR2* mutation (%)	50.3% (33.1-67.5%; I^2=78%) [5 studies; n=174]	71.2% (53.4-84.2%; I^2=34%) [5 studies; n=61]	31.3% (16.5-51.3%; I^2=65%) [5 studies; n=113]
Heterozygous *HAVCR2* mutation (%)	7.5% (2.8-18.6%; I^2=54%) [5 studies; n=174]	12.4% (5.4-26.2%; I^2=7%) [5 studies; n=61]	10.3% (5.2-19.5%; I^2=3%) [5 studies; n=113]
HAVCR2^{Y82C} mutation (%)	54.5% (29.1-77.8%; I^2=89%) [5 studies; n=174]	75.5% (46.0-91.8%; I^2=65%) [5 studies; n=61]	35.3% (12.8-67.0%; I^2=82%) [5 studies; n=113]
Other *HAVCR2* mutations (%)	8.6% (4.0-17.4%; I^2=29%) [5 studies; n=174]	8.3% (3.3-19.2%; I^2=0%) [5 studies; n=61]	10.5% (5.4-19.4%; I^2=3%) [5 studies; n=113]
Male sex (%)	34.8% (26.8-43.7%; I^2=0%) [4 studies; n=121]	50.8% (37.2-64.2%; I^2=0%) [4 studies; n=52]	25.2% (16.2-36.9%; I^2=0%) [4 studies; n=69]
Age at diagnosis (year)	30.4 years (25.3-35.5; I^2=8%) [4 studies; n=121]	26.5 years (19.1-33.8; I^2=69%) [4 studies; n=52]	32.7 years (27.9-37.5; I^2=25%) [4 studies; n=69]
Asian ethnicity (%)	92.5% (23.8-99.8%; I^2=91%) [4 studies; n=121]	86.9% (31.7-99.0%; I^2=82%) [4 studies; n=52]	87.1% (20.3-99.4%; I^2=81%) [4 studies; n=69]
Family history of SPTCL (%)	6.8% (2.0-20.9%; I^2=0%) [2 studies; n=38]	11.5% (3.4-32.7%; I^2=0%) [2 studies; n=21]	5.3% (0.7-29.4%; I^2=0%) [2 studies; n=17]
HLH-2004 score (mark)	3.3 marks (1.6-5.0; I^2=92%) [3 studies; n=58]	4.9 marks (4.6-5.3; I^2=0%) [3 studies; n=33]	0.8 marks (0.3-1.4; I^2=66%) [2 studies; n=25]
Relapsed rate (%)	34.8% (24.4-46.9%; I^2=22%) [3 studies; n=94]	29.6% (16.6-47.0%; I^2=0%) [3 studies; n=35]	38.7% (24.7-54.8%; I^2=26%) [3 studies; n=59]

Abbreviations: HLH, hemophagocytic lymphohistiocytosis; SPTCL, subcutaneous panniculitis-like T-cell lymphoma.

Supplementary Table S6 The pooled data on patient characteristics based on *HAVCR2* mutational statuses.

Characteristics	Pooled prevalence or weighted mean (95% confidence interval; I^2)			
	HAVCR2 mutated	Homozygous/compound heterozygous *HAVCR2* mutated	Heterozygous *HAVCR2* mutated	*HAVCR2* wild-type
No. of participants (n)	98	84	14	111
HAVCR2^{Y82C} mutation (%)	89.5% (71.6-96.7%; I^2=55%) [6 studies; n=98]	89.4% (71.6-96.5%; I^2=49%) [6 studies; n=84]	90.0% (62.2-98.0%; I^2=0%) [3 studies; n=13]	N/A
Other *HAVCR2* mutations (%)	12.9% (4.1-33.6%; I^2=62%) [6 studies; n=98]	13.6% (4.6-33.8%; I^2=56%) [6 studies; n=84]	10.0% (2.0-37.8%; I^2=0%) [3 studies; n=13]	N/A
Male sex (%)	37.3% (28.0-47.7%; I^2=0%) [5 studies; n=92]	39.2% (29.0-50.4%; I^2=0%) [5 studies; n=80]	22.7% (6.6-55.2%; I^2=0%) [2 studies; n=11]	24.5% (16.4-34.9%; I^2=0%) [5 studies; n=84]
Age at diagnosis (year)	28.3 years (22.3-34.3; I^2=13%) [5 studies; n=92]	28.3 years (22.0-34.5; I^2=12%) [5 studies; n=80]	25.5 years (17.1-34.0; I^2=33%) [2 studies; n=11]	40.2 years (36.6-43.9; I^2=0%) [5 studies; n=84]
Asian ethnicity (%)	87.3% (46.2-98.2%; I^2=81%) [5 studies; n=85]	90.8% (37.7-99.4%; I^2=84%) [4 studies; n=67]	92.1% (60.2-98.9%; I^2=0%) [2 studies; n=11]	55.1% (4.9-96.7%; I^2=84%) [5 studies; n=71]
Family history of SPTCL (%)	11.1% (3.2-31.8%; I^2=0%) [2 studies; n=25]	11.7% (3.4-33.4%; I^2=0%) [2 studies; n=24]	N/A	8.1% (1.1-41.2%; I^2=0%) [2 studies; n=13]
HLH/HLH-like systemic illnesses (%)	51.9% (41.1-62.4%; I^2=59%) [6 studies; n=97]	55.1% (34.1-74.4%; I^2=66%) [5 studies; n=79]	34.9% (4.9-84.8%; I^2=55%) [2 studies; n=11]	13.4% (5.1-30.8%; I^2=52%) [6 studies; n=110]
HLH-2004 score (mark)	3.5 marks (2.0-5.1; I^2=89%) [3 studies; n=50]	3.5 marks (2.0-5.1; I^2=89%) [3 studies; n=43]	N/A	N/A
Relapsed rate (%)	35.7% (22.3-51.7%; I^2=40%) [4 studies; n=75]	39.4% (26.6-53.7%; I^2=18%) [4 studies; n=64]	15.2% (3.0-51.4%; I^2=0%) [2 studies; n=11]	27.7% (18.5-39.3%; I^2=0%) [4 studies; n=70]
Necrosis in BM (%)	50.0% (35.3-64.7%; I^2=0%) [2 studies, n=42]	54.6% (29.3-77.8%; I^2=54%) [2 studies, n=34]	39.8% (2.6-94.3%; I^2=67%) [2 studies, n=8]	33.3% (17.6-53.9%; I^2=0%) [2 studies, n=24]
Granulomatous inflammation in BM (%)	9.6% (0.8-59.5%; I^2=69%) [2 studies, n=42]	10.3% (1.0-56.5%; I^2=62%) [2 studies, n=34]	18.1% (3.6-56.9%; I^2=0%) [2 studies, n=8]	49.0% (3.5-96.2%; I^2=77%) [2 studies, n=24]
Lipogranuloma in BM (%)	11.9% (5.0-25.6%; I^2=0%) [2 studies, n=42]	10.2% (3.3-27.8%; I^2=2%) [2 studies, n=34]	30.6% (5.2-77.9%; I^2=33%) [2 studies, n=8]	22.4% (10.0-42.7%; I^2=0%) [2 studies, n=24]

Abbreviations: BM, bone marrow; HLH, hemophagocytic lymphohistiocytosis; N/A, not applicable; SPTCL, subcutaneous panniculitis-like T-cell lymphoma.

Supplementary Table S7 The pooled odds ratios (pORs) and pooled differences in means (pMDs) for potential factors associated with the presence of hemophagocytic lymphohistiocytosis (HLH)/HLH-like systemic illnesses.

Potential factors	Pooled estimates for associations				
	Types of estimates	No. of included studies	No. of participants (n)	Values of estimates (95% CI; I^2)	P-value
Presence *vs.* absence of HLH/HLH-like systemic illnesses					
Male sex	pOR	4	121	2.97 (1.28-6.85; I^2=3%)	0.01
Age at diagnosis	pMD	4	121	-6.02 years (-15.40 to 3.35 years; I^2=54%)	0.21
Any *HAVCR2* mutations *vs.* *HAVCR2* wild-type	pOR	6	207	6.75 (1.65-27.64; I^2=56%)	0.008
Homozygous/compound heterozygous *HAVCR2* mutation *vs.* others	pOR	5	174	4.67 (1.07-20.35; I^2=65%)	0.04
Heterozygous *HAVCR2* mutation *vs. HAVCR2* wild-type	pOR	3	53	6.41 (0.94-43.58; I^2=0%)	0.06
HAVCR2^{Y82C} mutation	pOR	5	174	7.06 (1.05-47.51; I^2=65%)	0.04
Other *HAVCR2* mutations	pOR	3	93	0.66 (0.16-2.70; I^2=0%)	0.56
Relapsed disease	pOR	3	94	0.68 (0.27-1.73; I^2=0%)	0.42
HLH-2004 score	pMD	2	44	4.2 marks (3.4-5.0 marks; I^2=36%)	<0.001

Abbreviations: CI, confidence interval; HLH, hemophagocytic lymphohistiocytosis; pMD, pooled difference in means; pOR, pooled odds ratio.

Supplementary Table S8 The pooled odds ratios (pORs) and pooled differences in means (pMDs) for potential factors associated with *HAVCR2* mutational statuses.

Potential factors	Pooled estimates for associations				
	Types of estimates	No. of included studies	No. of participants (n)	Values of estimates (95% CI; I^2)	P-value
Any *HAVCR2* mutations *vs. HAVCR2* wild-type					
Male sex	pOR	5	176	1.62 (0.77-3.40; I^2=0%)	0.21
Age at diagnosis	pMD	5	176	-10.47 years (-17.68 to -3.26 years; I^2=38%)	0.004
Asian ethnicity	pOR	2	60	30.88 (3.46-276.05; I^2=0%)	0.002
Presence of HLH/HLH-like systemic illnesses	pOR	6	207	6.75 (1.65-27.64; I^2=56%)	0.008
Relapsed disease	pOR	4	145	1.17 (0.52-2.62; I^2=0%)	0.70
Presence of necrosis in BM	pOR	2	66	1.91 (0.64-5.68; I^2=0%)	0.24
Presence of granulomatous inflammation in BM	pOR	2	66	0.06 (0.01-0.53; I^2=0%)	0.01
Presence of lipogranuloma in BM	pOR	2	66	0.52 (0.13-2.15; I^2=0%)	0.37
Homozygous/compound heterozygous *HAVCR2* mutation *vs. HAVCR2* wild-type					
Male sex	pOR	5	164	1.86 (0.87-3.96; I^2=0%)	0.11
Age at diagnosis	pMD	5	164	-10.51 years (-18.26 to -2.76 years; I^2=41%)	0.008
Presence of HLH/HLH-like systemic illnesses	pOR	5	162	6.27 (1.09-36.20; I^2=67%)	0.04
Relapsed disease	pOR	3	85	1.58 (0.59-4.22; I^2=0%)	0.37
Presence of necrosis in BM	pOR	2	58	1.83 (0.59-5.69; I^2=0%)	0.30
Presence of granulomatous inflammation in BM	pOR	2	58	0.07 (0.01-0.60; I^2=0%)	0.02
Presence of lipogranuloma in BM	pOR	2	58	0.36 (0.04-2.96; I^2=19%)	0.34
Heterozygous *HAVCR2* mutation *vs. HAVCR2* wild-type					
Male sex	pOR	3	54	1.51 (0.27-8.56; I^2=0%)	0.64
Age at diagnosis	pMD	2	42	-12.92 years (-23.97 to -1.87 years; I^2=0%)	0.02
Presence of HLH/HLH-like systemic illnesses	pOR	3	53	6.41 (0.94-43.58; I^2=0%)	0.06
Relapsed disease	pOR	2	42	0.37 (0.03-3.90; I^2=30%)	0.40
Presence of necrosis in BM	pOR	2	32	1.35 (0.05-39.49; I^2=60%)	0.86
Presence of granulomatous inflammation in BM	pOR	2	32	0.18 (0.02-1.89; I^2=0%)	0.16

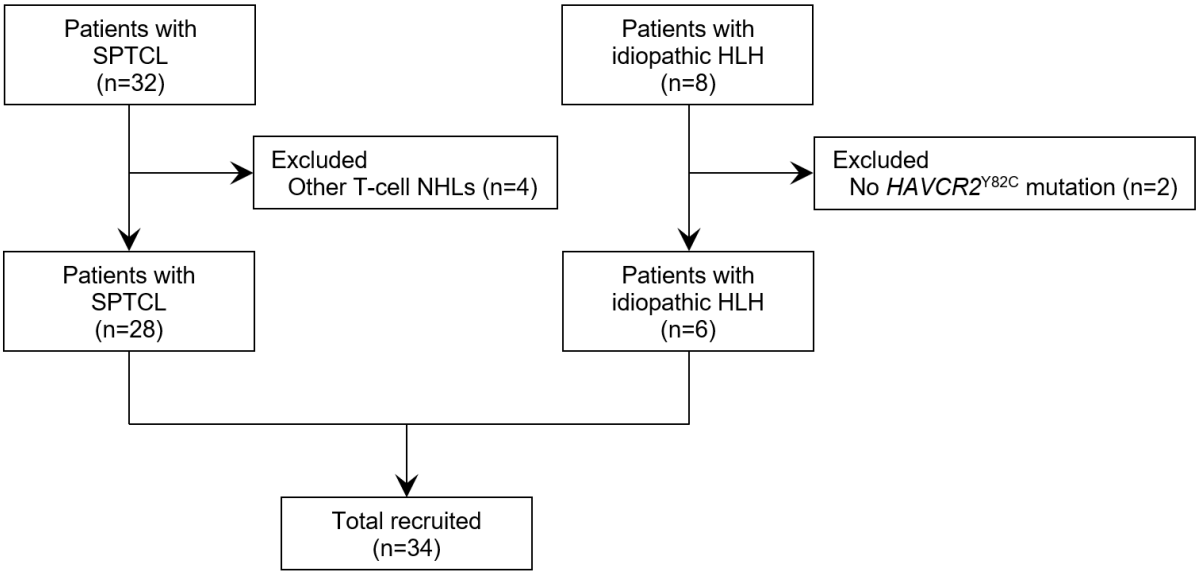
Abbreviations: BM, bone marrow; CI, confidence interval; HLH, hemophagocytic lymphohistiocytosis; pMD, pooled difference in means; pOR, pooled odds ratio.

Supplementary Table S8 The pooled odds ratios (pORs) and pooled differences in means (pMDs) for potential factors associated with *HAVCR2* mutational statuses. (continued)

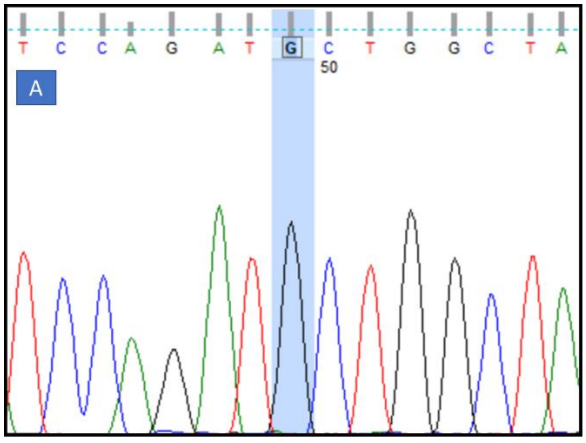
Potential factors	Pooled estimates for associations				
	Types of estimates	No. of included studies	No. of participants (n)	Values of estimates (95% CI; I^2)	P-value
Homozygous/compound heterozygous *HAVCR2* mutation *vs.* heterozygous *HAVCR2* mutation					
Male sex	pOR	3	68	1.76 (0.37-8.29; I^2=0%)	0.47
Age at diagnosis	pMD	2	52	-4.30 years (-13.22 to 4.63 years; I^2=0%)	0.35
Presence of HLH/HLH-like systemic illnesses	pOR	3	67	2.23 (0.49-10.13; I^2=10%)	0.30
Relapsed disease	pOR	2	52	3.35 (0.51-22.14; I^2=0%)	0.21
Presence of necrosis in BM	pOR	2	42	1.94 (0.03-134.13; I^2=78%)	0.76
Presence of lipogranuloma in BM	pOR	2	42	0.29 (0.01-10.35; I^2=65%)	0.49

Abbreviations: BM, bone marrow; CI, confidence interval; HLH, hemophagocytic lymphohistiocytosis; pMD, pooled difference in means; pOR, pooled odds ratio.

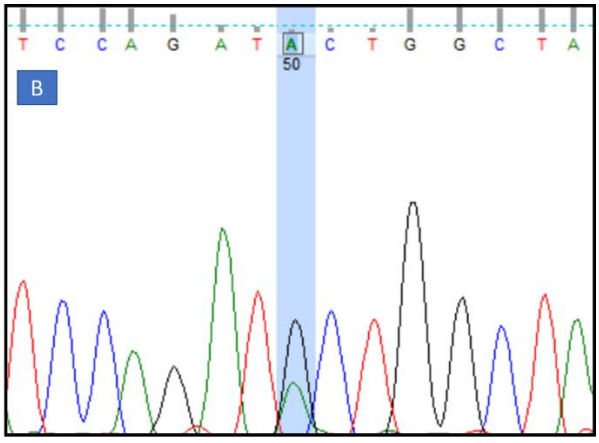
Supplementary Figure S1 Study flow diagram for a multicenter study. Abbreviations: HLH, hemophagocytic lymphohistiocytosis; NHL, non-Hodgkin lymphoma; SPTCL, subcutaneous panniculitis-like T-cell lymphoma.



Supplementary Figure S2 Direct sequencing of *HAVCR2*^{Y82C} mutations: Panel (A) for homozygous mutation and Panel (B) for heterozygous mutation.

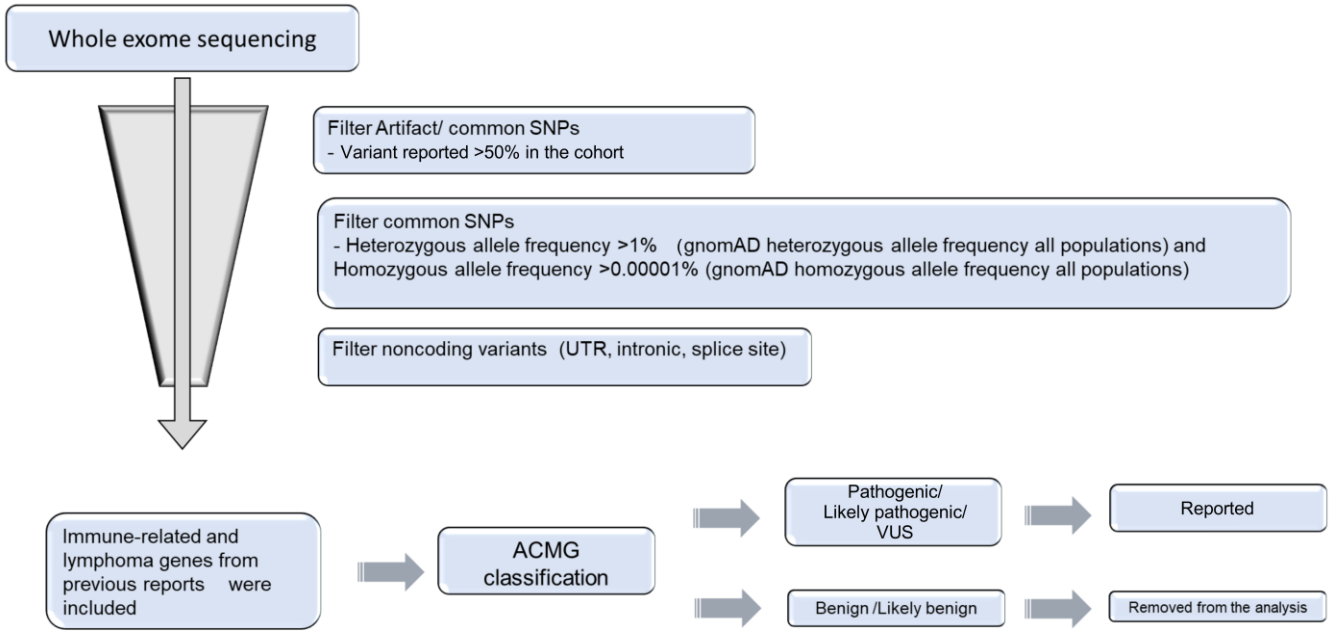


Homozygous *HAVCR2*^{Y82C} mutation

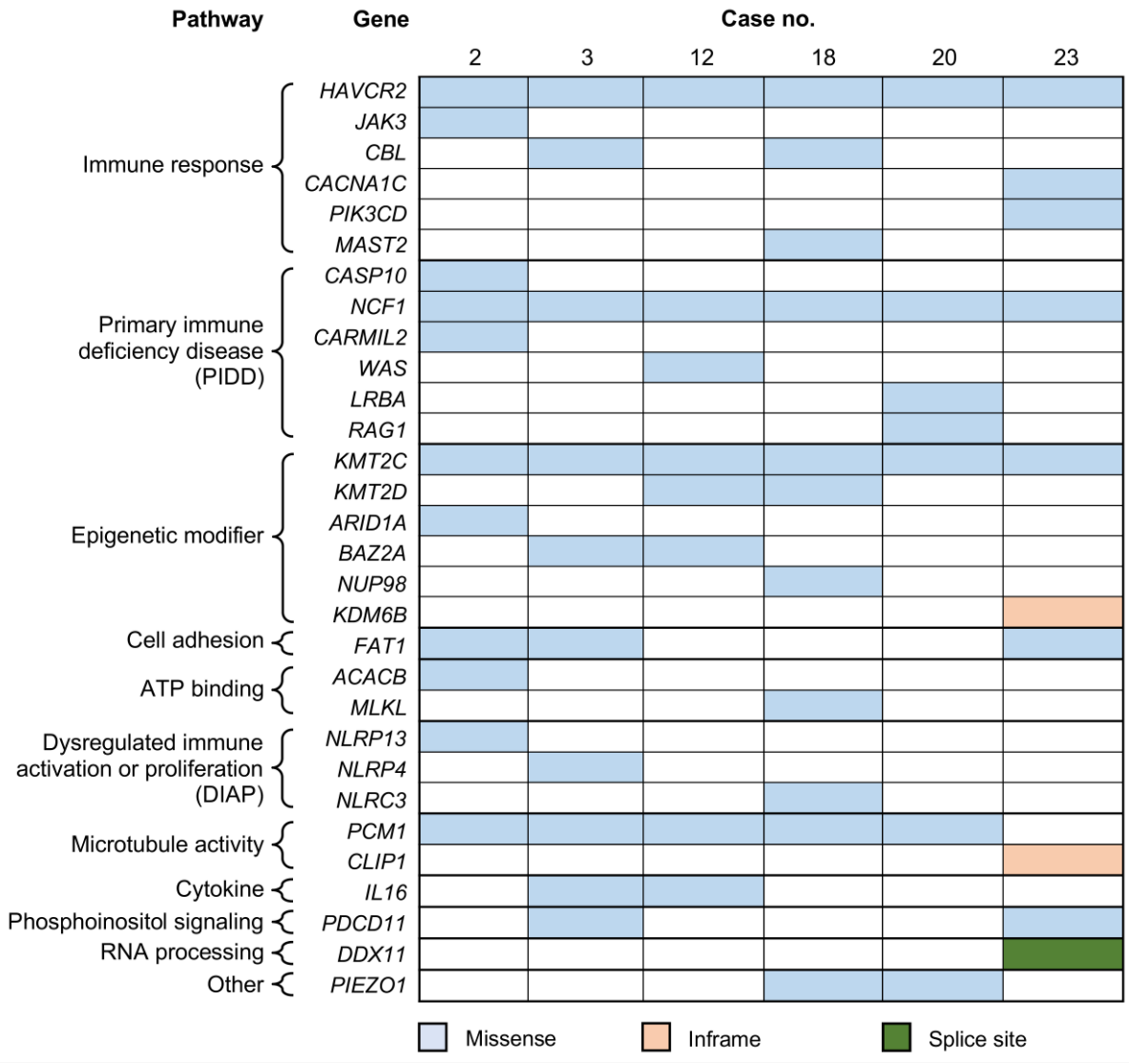


Heterozygous *HAVCR2*^{Y82C} mutation

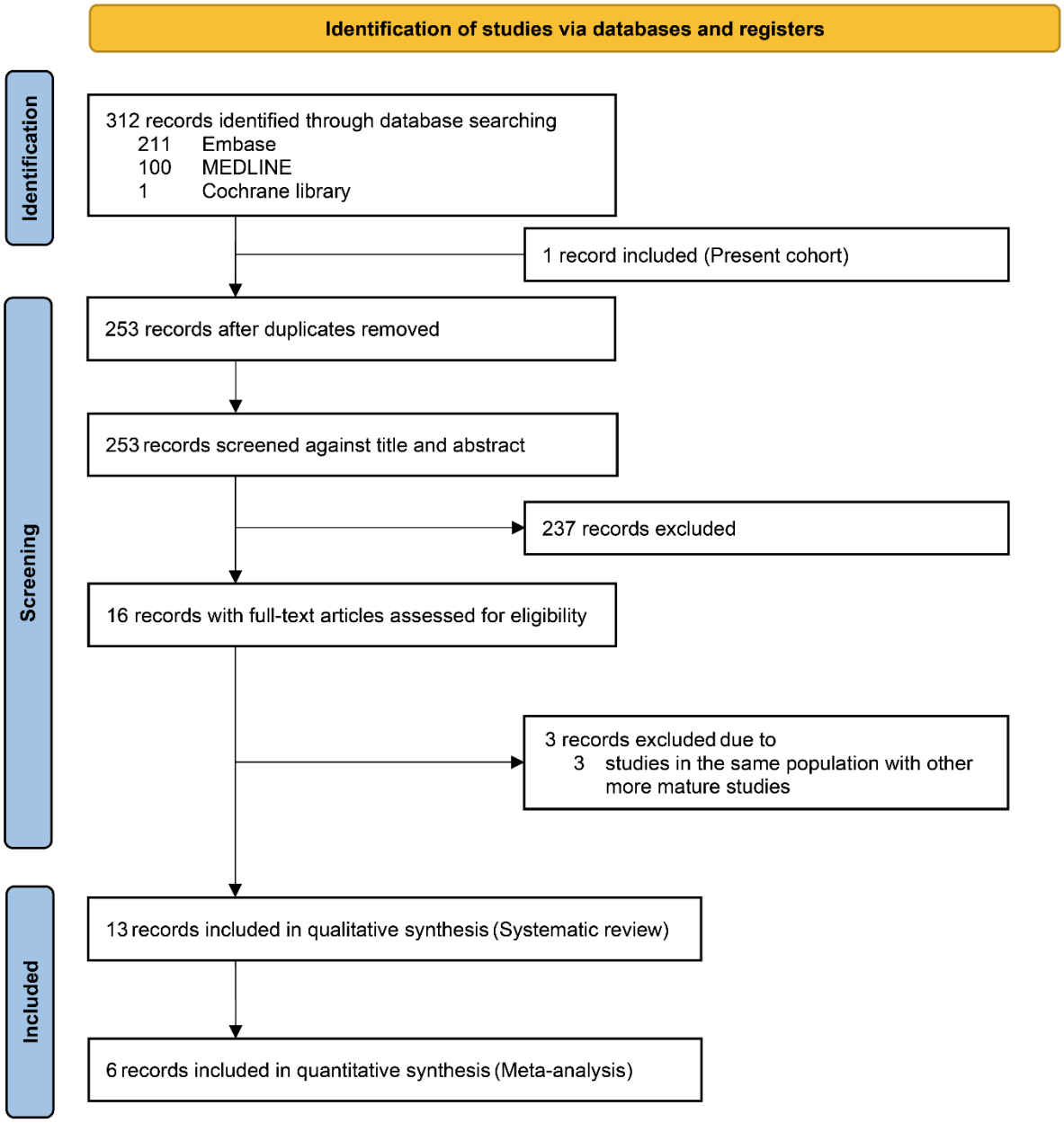
Supplementary Figure S3 Analytical pipeline for whole exome sequencing analysis. Abbreviations: ACMG, American College of Medical Genetics and Genomics; SNP, single nucleotide polymorphism; UTR, untranslated region; VUS, variant of unknown significance.



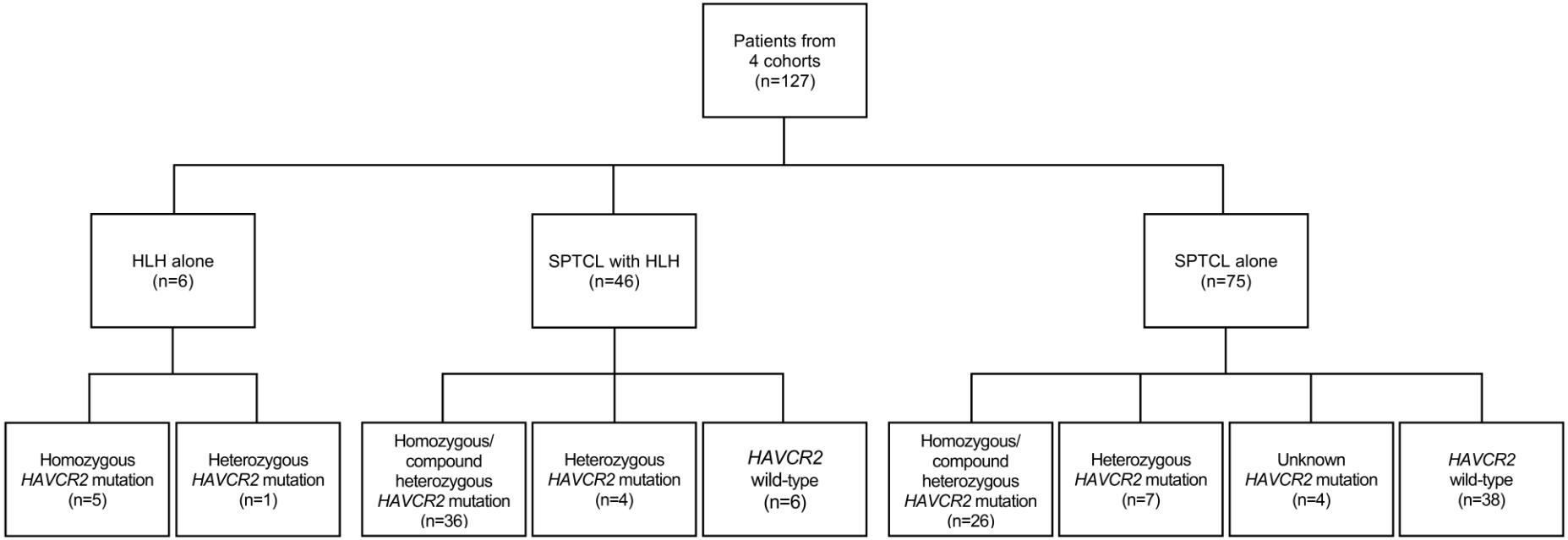
Supplementary Figure S4 Mutational landscape of whole exome sequencing in 6 patients with *HAVCR2* mutation.



Supplementary Figure S5 Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flow diagram for study search and selection.



Supplementary Figure S6 Diagram of case distribution from individual patient data from 4 cohorts (N=127) based on clinical phenotypes and *HAVCR2* mutational statuses.



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