CASE REPORT

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Novel heterozygous mutations of *TNFRSF13B* in EBV-associated T/NK lymphoproliferative diseases (EBV-T/NK-LPDs)

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1. INTRODUCTION

Epstein-Barr virus (EBV) is able to infect T and/or natural killer (NK) cells and trigger persistent EBV replication and intractable EBV-associated T/NK lymphoproliferative diseases (EBV-T/NK-LPDs) in rare cases,[1,2] especially when the functionalities of tonsillar NK cells[3] and $CD8^+$ T cells[4,5] are impaired. Tumor necrosis factor–like receptors (TNFRs) are part of a superfamily heavily involved in the physiology of immune cells. Mutations in *TNFRSF13B* (encoding the transmembrane activator and cyclophilin interactor [TACI] protein) were previously reported to be associated with common variable immunodeficiency (CVID),[6] indicating the complex imbalance of the immune system caused by TACI deficiency. Increasing evidence also suggests the potential role of TACI in responses of T cells.[7,8] Here we report a series of novel heterozygous *TNFRSF13B* mutations in 6 patients diagnosed with EBV-T/NK-LPDs. In this work, we try to expand the routine panel of genes screened in the patients presenting with EBV-associated proliferative diseases and provide a new possible way to correlate the genetic predisposition, persistent EBV infection, and EBV-T/NK-LPDs etiopathology.

2. CASE REPORTS

2.1. Case presentation

From May 2016 to December 2022, 6 patients in our hospital coincidentally met 2 criteria: be diagnosed with EBV-associated hemophagocytic lymphohistiocytosis (EBV-HLH) or chronic active EBV disease of T/NK-cell type (chronic active EBV disease of T/NK-cell type [CAEBV-T/NK]); potentially deleterious alterations in *TNFRSF13B* with or without other previously confirmed HLH-associated genetic mutations were reported in whole exon sequencing (WES) (**Table 1**). Routine laboratory examinations, diagnostic imaging, dynamic monitoring of biomarkers for prognosis, and corresponding treatments performed in our hospital are displayed in **Table 2**, Figure 1A and Supplementary Figure 1, http://links.lww.com/BS/A80. Examinations listed here were performed within 7 days after the first admission or attack, and the test time was as close as enough to the first admission or attack. In total, 4 of 6 patients had met the current diagnostic criteria for HLH and were given HLH-1994 or HLH-2004 regimen. Hemophagocytosis phenomenon in bone marrow was found in 3 of 6 patients (**Fig. 1B**). Special experiments on EBV infections and the functionalities of CTLs/NK cells are summarized in Figure 1. In all 6 patients, T cells and NK cells were the main targets of EBV infection (**Fig. 1C**), accompanied by the low NK-cell cytotoxicity and relatively normal expression levels of granzyme B/perforin on CTLs/NK cells (**Fig. 1D, E**). Chemotherapies were performed in 4 of the 6 patients (**Table 2**), including Tislelizumab (patient 1), HLH-1994[9] and DEP regimen (patient 2), HLH-1994 regimen (patient 3), HLH-2004[10] and L-GMOX regimen (patient 4), and the HLH-1994 plus rituximab (patient 6). Three of 6 patients (patients 2, 3, and 5) had received the hematopoietic stem cell transplantation (HSCT) (Supplementary Table 1, http://links.lww.com/BS/A81) but 2 of them eventually died of uncontrolled HLH. HSCT was also recommended for patient 4 and patient 6 but not finally performed due to personal reasons. Their present status is not available since they were lost to follow-up.

2.2. Genetic findings

To detect the possible molecular basis of the EBV-T/NK-LPDs, WES was conducted in these patients. Nucleotide substitutions, insertions, and deletions in the whole-exome regions of the human genome were detected. Very rare (minor allele frequency <

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X.D. and T.G. are the first authors.

T.G. contributed equally to this work.

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All data generated or analyzed during this study are included in this published article [and its supplementary information files]. The data presented in this study are openly available in SRA database at reference number [PRJNA938987] and GSA database in BIG Data Center (Beijing Institute of Genomics) at reference number [HRA000877]. Further inquiries can be directed to the corresponding author.

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Table 1

Genetic characteristics of patients with *TNFRSF13B* alterations by whole-exome sequencing.

Patient	Gender	Age	Gene	Type	Exon	Frequency	cDNA	Protein	SIFT	Polyphen2	Mutation taster	MAF (gnomAD)	dbSNP
1	F	36	*TNFRSF13B*	Frameshift deletion	3	43.60%	c.366delG	p.Ser123Valfs*31	-	-	D	-	-
2	M	46	*TNFRSF13B*	Frameshift Deletion	2	40.00%	c.105delC	p.Glu36Lysfs*48	-	-	D	<0.0001	-
			LYST	Missense mutation	34	50.00%	c.8624G>A	p.Arg2875His	D	D	D	0.000121	rs200353560
3	F	32	*TNFRSF13B*	Missense mutation	2	54.40%	c.139T>A	p.Cys47Ser	D	D	D	<0.0001	rs769182186
			NOD2	Missense mutation	4	54.80%	c.922C>T	p.Leu308Phe	D	D	D	-	-
4	F	46	*TNFRSF13B*	Missense mutation	2	54.12%	c.226G>T	p.Gly76Cys	D	D	D	<0.0001	rs146436713
5	M	8	*TNFRSF13B*	Missense mutation	2	49.43%	c.115T>C	p.Tyr39His	D	D	D	-	-
			AP3B1	Missense mutation	13	49.80%	c.1234T>C	p.Tyr412His	D	D	D	0.000014	rs781034104
6	M	16	*TNFRSF13B*	Missense mutation	2	50.40%	c.124C>A	p.Pro42Thr	B	B	B	<0.0001	rs531640813

B = benign, cDNA = complementary DNA, D = deleterious, MAF = minor allele frequency, SIFT = sorting intolerant from tolerant.

0.001), possibly damaging (according to prediction), and disease-related variants were identified as pathogenic genetic aberrations. Genes in the TNF-TNFR superfamily which involves in integrative immune responses were paid particular attention. Sequencing results revealed a series of heterozygous nonsynonymous variants in the *TNFRSF13B* in 6 patients (**Table 1**). Four of 6 mutations were located at the cysteine-rich domain (CRD)1 region of transmembrane activator and CAML interactor (TACI, encoded by *TNFRSF13B*), 1 mutation was located at the CRD2 region which interacts with ligands of TACI, 1 mutation was located at the part between CRD2 and the transmembrane region (**Fig. 2A, B**). The deletion frameshift mutation in *TNFRSF13B* carried by patient 1 (c.366delG, p.S123V**fs***31) had not been reported in the OMIM (http://www.omim.org) and ClinVar database (http://www.ncbi.nlm.nih.gov/clinvar), and probably impaired the expression of TACI due to the extremely truncated protein. The position at which the frameshift deletion in patient 2 (c.105delC, p.Glu36Lys**fs***48, HGMD CD153877) occurred was reported to be disease-causing at HGMD (https://www.hgmd.cf.ac.uk/ac/index.php). The Sanger sequencing (**Fig. 2C**) indicated the same *TNFRSF13B* frameshift deletion of his son. Missense mutations carried by patients 3 (c.139T>A, p.Cys47Ser), 4 (c.226G>T, p.Gly76Cys), 5 (c.115T>C, p.Tyr39His), and 6 (c.124C>A, p.Pro42Thr) were also predicted to be possibly deleterious by the sorting intolerant from tolerant (http://sift.jcvi.org), Polyphen2 (http://genetics.bwh.harvard.edu/pph2), or MutationTaster (https://www.genecascade.org/MutationTaster2021/). The mutation in patient 6 was previously reported in a study on CVID.[11] Taken together, all the 6 *TNFRSF13B* mutations were classified as likely pathogenic.[12] Patient 3 carried a heterozygous *NOD2* mutation which possibly contributed to her diarrhea similar to Crohn disease. Patient 2 also carried a mutated *LYST (*c.c.8624G>A, p.Arg2875His) causing nonselective vulnerability to EBV-HLH,[13] while patient 5 also carried a heterozygous *AP3B1* mutation (c.1234T>C, p.Tyr412His, 49.80%) which contributed to the defects in T/NK-cell degranulation in typical HLH. Apart from patient 2 and patient 5, the other 4 patients lacked a known genetic etiology clearly related to EBV-LPDs.

3. DISCUSSION

In most benign cases of EBV infection, the target cells of EBV were B cells and epithelial cells while in some populations susceptible to EBV infections, fatal diseases can occur, indicating the underlying inborn defects of immunity. Impaired innate and/or adaptive response to EBV may lead to uncontrolled EBV replication and the EBV-T/NK-LPDs in the worst case, including the EBV-HLH and CAEBV-T/NK.

The EBV infection was controlled by both innate and specific immune cells including NK cells and conventional T cells. Signaling via several members of the TNF-TNFR superfamily supports the $CD8^+$ and $CD4^+$ T-cell functions was reported to involve in EBV-specific responses, including the signals delivered by CD27, CD70, 4-1BB, and DcR3. Mutations in CD27 (*TNFRSF7*)[14]-CD70[15] pathway and 4-1BB (*TNFRSF9*)[16] were reported to be associated with severe, atypical EBV infections or EBV-related lymphoma by impairing the expansion and activation of $CD8^+$ EBV-specific T cells. In this work, we report a series of novel heterozygous *TNFRSF13B* mutations in 6 patients diagnosed with EBV-T/NK-LPDs. Functional examinations of NK cells and CTLs revealed significantly low NK cytotoxicity in all 6 patients, indicating weak innate immunity when fighting against EBV. Therefore, it seemed reasonable that the altered immunity to EBV of these 6 patients were the complications of *TNFRSF13B* deficiency. TACI primarily provides signals for class switch recombination in B cells during T cell–independent antibody response.[17,18] It also involves in the physiological processes of follicular helper T (Tfh) cells[7] and Th17.[8] *TNFRSF13B*

Table 2

Clinical and laboratory characteristics* of patients with *TNFRSF13B* alterations.

Patient	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Normal range
Gender	F	M	F	F	M	M	-
Age at onset, y	36	46	32	46	8	16	-
Diagnosis	EBV-LPD	EBV-HLH	EBV-HLH; Crohn disease	CAEBV-T; HLH	CAEBV-NK	EBV-HLH; EBV-T/NK-LPD	-
HLH-2004 criteria	No	Yes	Yes	Yes	No	Yes	-
Fever, °C	39	40	39	39	39	39	-
Lymphadenopathy	Yes	Yes	Yes	Yes	No	Yes	-
Splenomegaly (thickness, cm)	Yes, 5.3 cm	Yes, 13.5 cm	No	Yes, 5.3 cm	Yes, NA	Yes, 4.3 cm	-
Hemophagocytosis	BM	BM	-	-	-	BM	-
EBV-DNA, copy/mL	2.24×10^5	2.11×10^3	4.74×10^4	4.44×10^6	1.71×10^6	1.69×10^6	-
Serum EBV, copy/mL	4.94×10^3	<500	4.38×10^5	1.4×10^4	2.06×10^4	2.95×10^7	-
Serology							
EA-IgG	+	-	+	NA	NA	NA	-
EBVC-IgG	+	+	+	NA	+	NA	-
EBVC-IgM	-	-	-	NA	-	±	-
EBNA-IgG	+	+	+	NA	+	NA	-
White blood cells, 10^9/L	1.52↓	3.4↓	0.91↓	1.43↓	4.25	4.69	3.5–9.5
Neutrophils, 10^9/L	0.84↓	2.02	0.94↓	0.80↓	2.07	4.33	1.8–6.3
Lymphocytes, 10^9/L	0.47↓	0.7↓	0.16↓	0.50↓	0.28↓	-	1.1–3.2
Hemoglobin, g/L	128↓	77↓	61↓	88↓	104↓	119↓	130–175
Platelets, 10^9/L	116↓	27↓	3↓	192	520	23↓	125–350
ESR, mm/H	-	27↑	5	-	4	-	0–15
CRP, mg/L	4.7	118.4	152.1	38.6	5.0	128.34	-
ALT, U/L	68↑	11	65↑	56↑	83↑	120.1↑	<41
AST	58↑	39	141↑	58↑	98↑	310↑	<40
LDH, U/L	222	1519↑	1627↑	290↑	672↑	2465.3↑	135–225
PT, s	13.3	16↑	22.7↑	15.1↑	13.8	13.5	11.5–14.5
APTT, s	42.6↑	48.2↑	90.9↑	57.4↑	49.7↑	32.4	29–42
Triglycerides, mM/L	-	3.91↑	-	1.61	2.83↑	-	<1.7
Fibrinogen, g/L	1.69↓	3.52	0.6↓	2.15	1.95↓	2.46	2.0–4.0
Ferritin, μg/L	232.1	3095.8↑	14323↑	3242.5↑	205.1	41776↑	30–400
sCD25, U/mL	427	>7500↑	>7500↑	-	6049↑	>7500↑	223–710
IL-1β, pg/mL	5.2↑	<5	6.6↑	-	9.4↑	<5	<5
IL-6, pg/mL	<1.50	45.61↑	209.2↑	74.07↑	30.25↑	3.95	<7.0
IL-8, pg/mL	16	21.5	86↑	-	41.2	128↑	<62
IL-10, pg/mL	<5.0	830↑	635↑	-	82.6↑	5.5	<9.1
TNF-α, pg/mL	8.9↑	33.1↑	18.5↑	-	91.6↑	10.8↑	<8.1
IgA, g/L	2.26	1.11	-	-	2.05	-	0.82–4.53
IgG, g/L	12.8	9.8	-	-	22.3↑	-	5.4–15.3
IgM, g/L	0.87	0.51	-	-	0.63	-	0.46–3.04
Complement C3, g/L	0.91	0.8	-	-	0.93	-	0.65–1.39
Complement C4, g/L	0.46↑	0.13↓	-	-	0.85↑	-	0.16–0.38
Chemotherapy and response	Anti-PD-1 antibody (CR)	HLH-1994 regimen (NR); DEP (liposomal doxorubicin, etoposide, and methylprednisolone) regimen (NR)	HLH-1994 regimen (NR)	HLH-2004 regimen (PR); L-GMOX (gemcitabine, oxaliplatin and pegaspargase) regimen plus rituximab (CR)	-	HLH-1994 regimen plus rituximab (CR)	-
Allo-HSCT	No	Yes	Yes	NA	Yes	NA	-
Donor	-	HLA-identical donor from China's bone marrow bank	HLA-identical donor (her brother)	-	HLA-haploidentical donor (his mother)	-	-
CD34+ cells, $\times10^6$/kg	-	5.16	6.42	-	NA	-	-
Outcome	Alive	Death (day 93 after transplantation)	Death (day 10 after transplantation)	NA	Alive	NA	-

Allo-HSCT = allogeneic hematopoietic stem cell transplantation, BM = bone marrow, CR = complete response, EA = anti-EBV early antigen, EBNA = EBV nuclear antigen antibody, EBVC = anti-EBV viral capsid antibody, HLA = human leukocyte antigen, NA = not available, NR = no response, PR = partial response.

*Examinations listed here were performed within 7 d after the first admission or attack, and the test time was as close as enough to the first admission or attack.

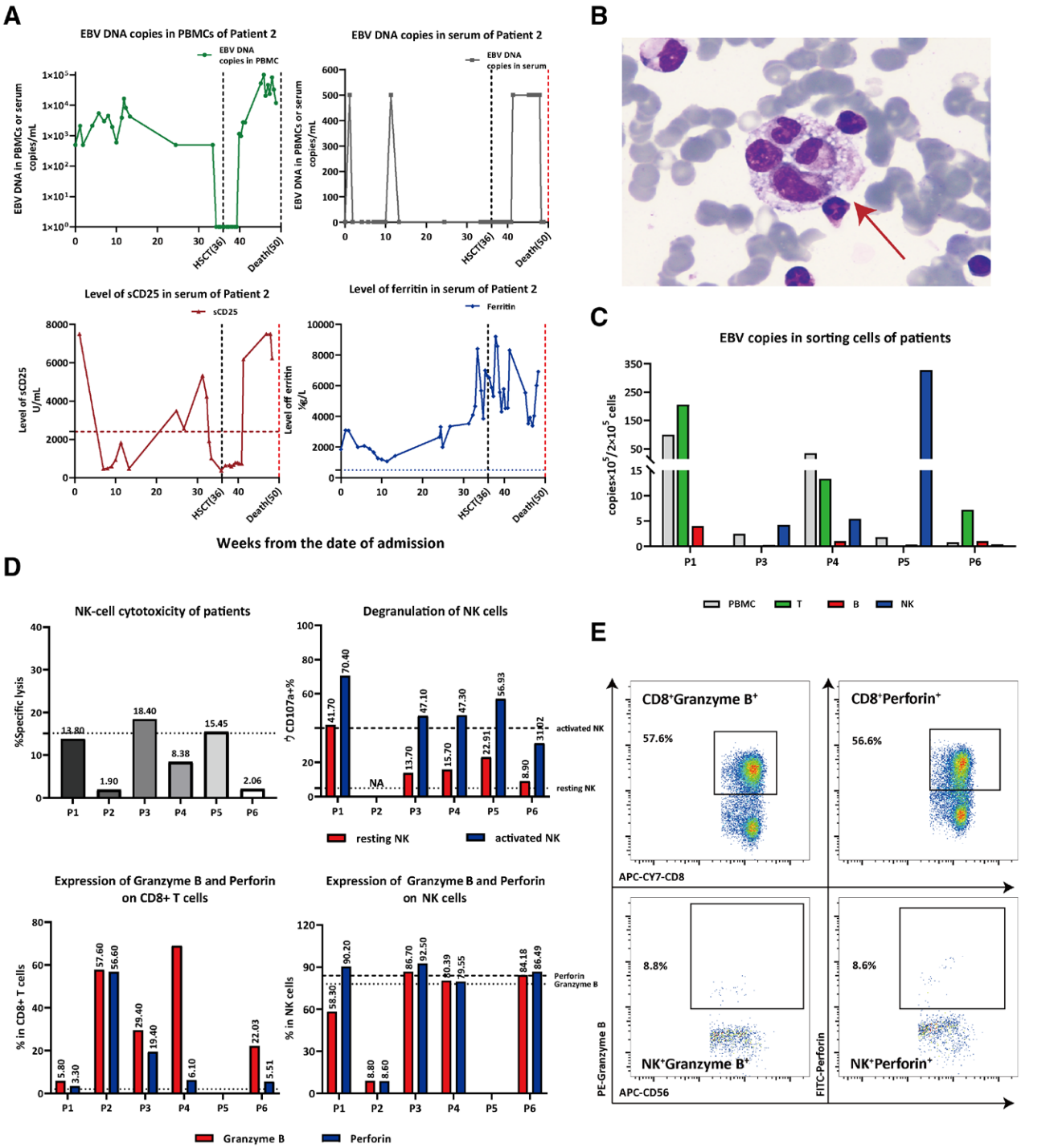

Figure 1. Clinical examinations and immunological and functional phenotypes of patients with *TNFRSF13B* mutations. (A) Level of EBV-DNA copies in PBMC and in serum, sCD25 (normal range: 223–710 U/mL) and ferritin (normal range: 30–400 μg/L) of patient 2 after diagnosis. (B) Bone marrow biopsy showing a hemophagocytic cell (red arrow) from patient 2. (C) EBV-DNA copies quantification of patients' different cell types (PBMCs [gray], T [green], B [red], and NK [blue] cells) by real-time PCR. (D) Function of NK cells and CTLs of patients with *TNFRSF13B* mutations. The dashed line shows the lower limit of normal range (normal range of NK cell cytotoxicity: ≥15.11%, degranulation of resting NK cells: ≥5%, degranulation of stimulated NK cells: ≥40%, perforin expression of CTLs: ≥2%, perforin expression of NK cells: ≥84%, granzyme B expression of CTLs: ≥2%, granzyme B expression of NK cells: ≥78%). (E) Flow cytometry analysis of granzyme B-positive and perforin-positive cells in CD8+T cells and NK cells taken from patient 2. CD8+perforin+, CD3-CD56+perforin+, CD8+granzyme B+, and CD3-CD56+ granzyme B+ cells were gated and analyzed using CD3-PerCP Cy5.5, CD8-APC-Cy7, CD56-APC, PE-granzyme B, and FITC-perforin. CTL = cytotoxic T lymphocyte, EBV = Epstein-Barr virus, NK = natural killer, PBMCs = peripheral blood mononuclear cells, PCR = polymerase chain reaction, sCD25 = soluble CD25.

mutations were mainly reported in CVID and systemic lupus erythematosus (Supplementary Table 2, http://links.lww.com/BS/A82), indicating a complex imbalance of immunity brought by TACI deficiency.[19] The paradox was that the TACI variants were not reported previously to influence NK cells or CTLs,[17,20] while the impaired function of these cells was found in the patients.

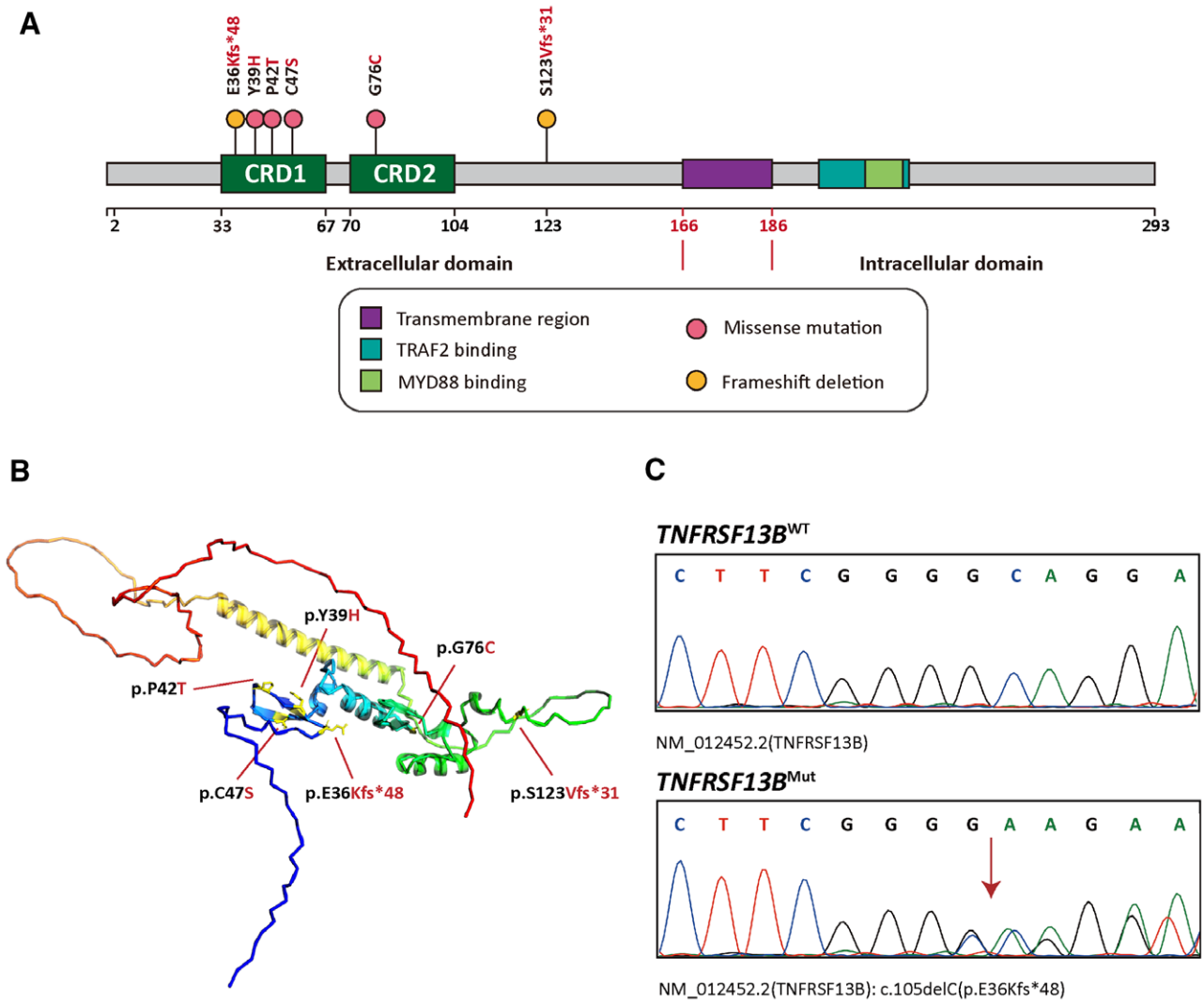

Figure 2. Genetic phenotypes of the patients with *TNFRSF13B* mutations. (A) Location of *TNFRSF13B* alterations in our patients. The numbers below represent amino acid positions. (B) Shown is a 3D model diagram indicating the locations of mutants in the TACI proteins. The figures were prepared via PyMOL (www.pymol.org). Most variants in *TNFRSF13B* were frameshift and missense variants. The numbers represent amino acid position. (C) Sanger sequencing of area surrounding the frameshift *TNFRSF13B* mutation (c.105delC, p. Glu36Lysfs*48) in a reference control subject and son of patient 2. TCAI = transmembrane activator and cyclophilin interactor.

The exact mechanism by which the T or NK cells are infected by EBV has also not been thoroughly investigated. Here we offered 3 speculations on how *TNFRSF13B* mutations predispose T and/or NK cells to EBV infection according to previous studies: the TACI protein involves in the EBV binding process (similar to the molecule CD21)[21]; impaired TACI expression or TACI variants influence the susceptibility of myeloid lineage progenitors to EBV infection[22]; *TNFRSF13B* mutations impair the activity of T and/or NK cells in controlling EBV replication at the secondary lymphoid organs, resulting in the high load of virus and subsequent infection.[23] However, considering of the little expression of TACI on CD16^{dim} NK cells and CTLs (Supplementary Figure 2, http://links.lww.com/BS/A83), their vital role in preventing the EBV infection and eliminating the EBV-infected B cells, and the significantly higher expression of TACI on EBV-transformed B cells compared with the normal B cells (data not shown), this work puts forward the hypothesis that TACI may implicate in the T/NK cell–mediated responses against EBV via the ligand–receptor interactions in EBV-infected B cells. Interestingly, activated NK cells produce soluble B cell activating factor from the TNF family (BAFF), the TACI ligand, when encountering CLL cells. High level of local BAFF protects CLL cells from the NK cell–mediated lysis via unknown mechanisms,[24] also suggesting the possible interactions among the TACI-BAFF network, EBV-infected B cells, and T/NK-cell killing capacity. Further experiments on TACI in our laboratory are underway, and are expected to facilitate the discovery of novel targets against atypical EBV infections. Further experiments with TACI in our laboratory are underway and are expected to facilitate the discovery of novel targets against atypical EBV infections.

Another concern has been the heterozygous *LYST* mutation found in patient 2, and the heterozygous *AP3B1* mutation found in patient 5. Defects in both of the 2 genes were associated with the initiation of primary HLH.[25] Deleterious mutation in *LYST* and *AP3B1* disturbs the vesicle trafficking process in the release of cytolytic particles, interfering the T/NK cell–mediated antiviral responses. However, primary HLH is usually characterized by the homozygous or compound heterozygous mutations, relatively early onset, worse prognosis, and no significant relevance to EBV infection, which was obviously not met in patients 2 and 5. The reasonable theory may be that with the trigger of EBV

infection, heterozygous *LYST/AP3B1/TNFRSF13B* mutation acts as a predisposing allele for EBV-HLH development.

The prognostic value of *TNFRSF13B* mutation is difficult to evaluate due to the very small cohort and the loss to follow-up beyond our control. Judging from the outcome of patients, however, patient 1 who carried only the *TNFRSF13B* missense mutation suffered the disease with much milder symptoms and better prognosis, compared with patients 2 and 3 who carried both HLH-associated genetic mutations and *TNFRSF13B* mutation. This interesting trend could also be interpreted by the theory about "predisposing allele."

Taken together, our findings expand the range of genes routinely screened for in patients with EBV-T/NK-LPDs by reporting a novel set of TNFRSF13B mutations in 6 patients with EBV-HLH and/or CAEBV-T/NK, outlining the need to investigate the role of TNF-TNFR superfamily members in the pathogenesis of intractable EBV infections.

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AUTHOR CONTRIBUTIONS

X.D. and K.S. conceived the project. X.D. and T.G. drafted the manuscript, collected the statistics, and drew the figures. K.S. and W.M. discussed the manuscript. J.W. revised the manuscript. H.L. and J.G. performed part of the experiments. M.X. provided guidance and approved the version to be submitted. All authors contributed to the article and approved the submitted version.

ETHICAL APPROVAL

The studies involving human participants were reviewed and approved by the Medical Ethics Committee of Tongji Hospital, Tongji Medical College of HUST. The number of ethical approval was TJ-IRB20200706. The ethics committee waived the requirement of written informed consent for participation.

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