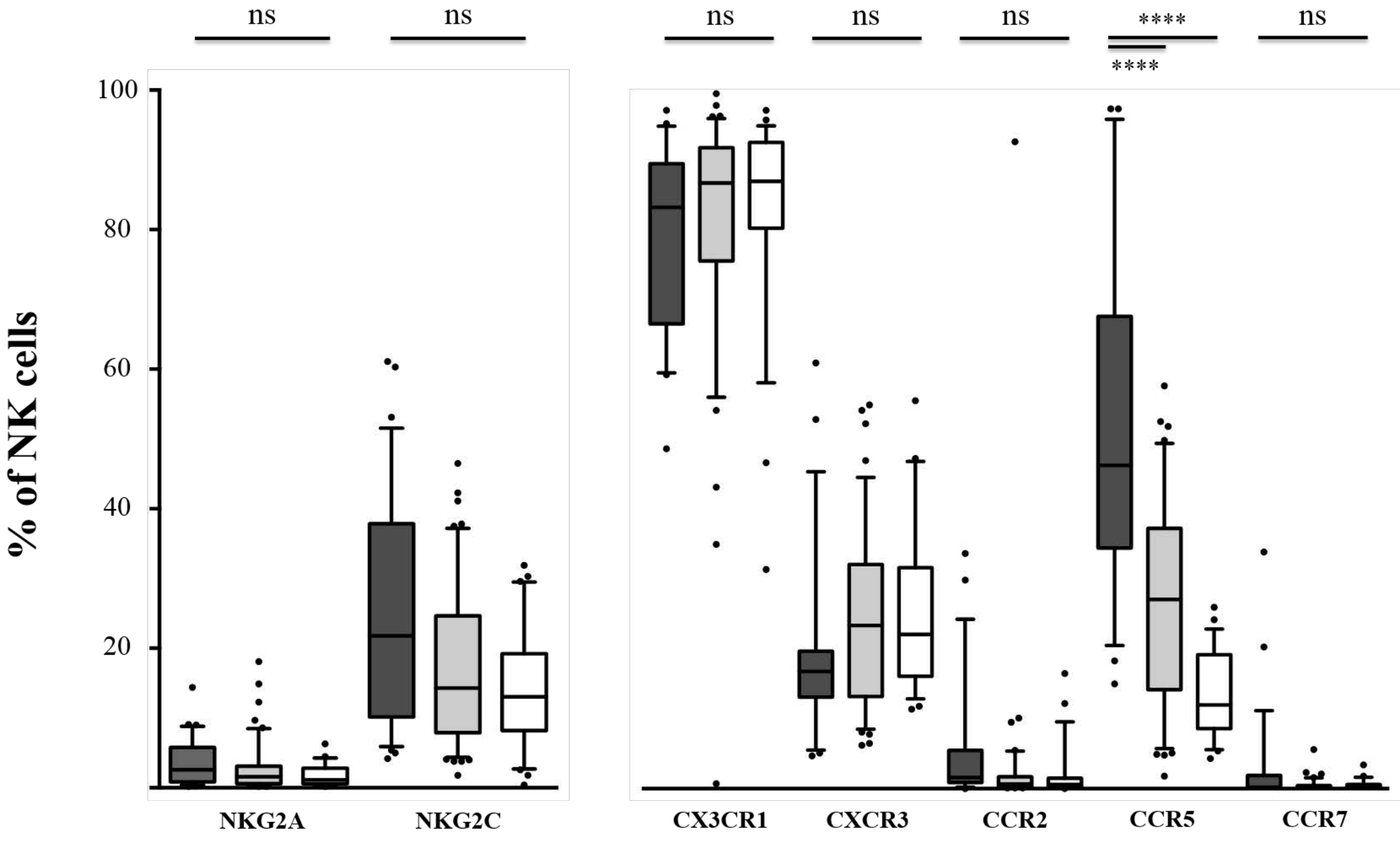

Figure S1. Detailed NK cells phenotyping in the 3 groups.

No statistical differences for all these markers excepted for CCR5.

Each point represents an outlier (error bars, 10th and 90th percentiles).

**** $p < 0.0001$ - *** $p < 0.001$ - ** $p < 0.01$ - * $p < 0.05$ - ns (not significant).

Statistics : Mann-Whitney U test (2 groups) and Kruskal-Wallis test (3 groups)

MFI : median fluorescence intensity.

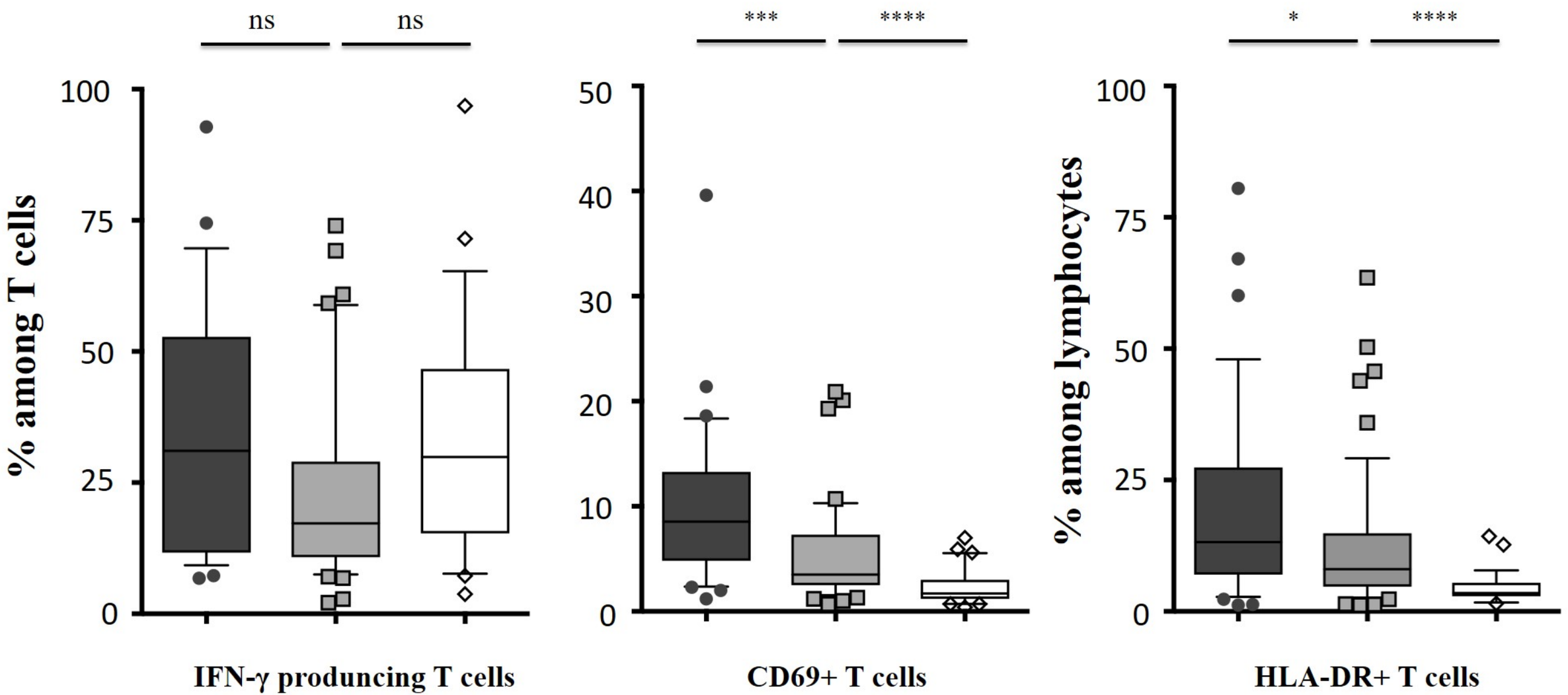

Figure S2. T cells phenotyping in the 3 groups.

No statistical difference in the capacity of T cells to produce IFN-γ (in vitro PMA-ionomycin stimulation).

Higher T cells expression of activation markers (CD69 and HLA-DR) in HLH patients.

Each point represents an outlier (error bars, 10^{th} and 90^{th} percentiles).

**** $p < 0.0001$ - *** $p < 0.001$ - ** $p < 0.01$ - * $p < 0.05$ - ns (not significant).

Statistics : Mann-Whitney U test (2 groups) and Kruskal-Wallis test (3 groups)

MFI : median fluorescence intensity.

Table S1A. Lymphocyte blood counts in the 3 groups.

		HLH	DC	HC	*p*
		n = 68	n = 34	n = 34	
Lymphocytes/mm³					
Total		574 [182 - 1810]	1240 [518 - 4348]	1910 [1324 - 2641]	< 0.001
B cells (*CD19*⁺)		54 [2 - 225]	109 [25 - 533]	226 [111 - 369]	< 0.001
T cells (*CD3*⁺)		474 [135 - 1412]	981 [340 - 2816]	1441 [945 - 1990]	< 0.001
	CD3⁺*CD4*⁺	268 [46 - 612]	563 [178 - 1340]	869 [603 - 1313]	< 0.001
	CD3⁺*CD8*⁺	202 [26 - 571]	353 [106 - 1292]	443 [271 - 722]	< 0.001
NK cells (CD3⁻CD56⁺)		32 [7 - 98]	128 [39 - 632]	210 [109 - 401]	< 0.001

Statistics: Kruskal-Wallis test

Table S1B. Lymphocyte counts during HLH and after recovery.

	During HLH	After recovery	*p*
	n = 15	n = 15	
Lymphocytes/mm³			
Total	430 [202 - 1366]	1103 [410 - 2259]	0.002
B cells (*CD19*⁺)	32 [0 – 123]	34 [0 – 272]	0.94
T cells (*CD3*⁺)	410 [135 - 1256]	883 [288 - 1712]	0.01
NK cells (*CD3*⁻*CD56*⁺)	33 [5 - 75]	111 [50 - 417]	0.0002

Statistics: Mann-Whitney U-test

Table S2A. Characteristics of the heterozygous HLH-gene mutations identified

Gene	Base change	AA change	SIFT	Polyphen-2	RsID	MAF (%)
PRF1	**c.C272T**	**p.A91V**	**Deleterious**	**Probably damaging**	rs35947132	4.6
	C1139G	p.P380R	Tolerated	Benign	rs530097547	0.02
	C65T	pP22L	Tolerated	Benign	rs528937278	0.02
	A755G	p.N252S	Tolerated	Benign	rs28933375	0.76
	cG530A	p.R177H	Tolerated	Benign	rs774503938	-
STX11	c.A829G	T277A	Tolerated	Benign	rs9496891	4.1
UNC13D	c.A2542C	p.I848L	Tolerated	Benign	rs144968313	0.06
	c.G2983C	A995P	Tolerated	Benign	rs138760432	0.06
	c.C904T	p.L302F	Tolerated	Benign	rs55661958	0.02
	c.C2782T	p.R928C	Tolerated	Benign	rs35037984	2.25
	c.C536G	**p.T179R**	**Deleterious**	**Probably damaging**	-	-
	c.G2696A	p.R899Q	Tolerated	Benign	rs1456196107	0.00
	c.G2955_4A		In silico prediction: no splicing effect	-	rs760466426	0.003
	C.G2830+7A		In silico prediction: no splicing effect		rs 201023196	0.04
LYST	**c.A6482C**	**p.E2161A**	**Deleterious**	Benign	rs147756847	0.6
	c.C1384T	p.P462S	Tolerated	Benign	rs77848653	0.01
	c.T574G	p.L192V	Tolerated	Benign	rs7524261	0 .07
	c.G3050A	p.S1017N	Tolerated	Benign	rs10465613	4.7
	c.A3208G	p.I1070V	Tolerated	Benign	rs150321124	0.01
	c.A3989C	p.D1330A	Tolerated	Benign	rs74641549	4.4
	C7352-7354 delTTC	p.LL2451L	In frame deletion			0.05
	c.T7793A	p.F2598Y	Tolerated	Benign	rs34642241	2.6
	c.G8411A	p.G2804D	Tolerated	Benign	rs35333195	4.4
	c.C7870T	**p.R2624W**	Deleterious	**Probably damaging**	rs150306354	0.37
	c.A143G	p.H48R	Tolerated	Benign	rs200132460	0.008
	c.C8216T	**p.T2739I**	Tolerated	**Probably damaging**	rs1443276945	-

AA: amino acid
SIFT: Sorting Intolerant From Tolerant - *Program that predicts whether an amino acid substitution affects protein function*
PolyPhen-2 : Polymorphism Phenotyping v2
SIFT and Polyphen-2 are softwares predicting possible impact of AA substitution
rsID : reference SNP (Single Nucleotide Polymorphism) identity
MAF: mean allele frequency

Table S2B. Detailed mutations in the 15 patients out of 29 with an acquired HLH

Patients	PRF1	UNC13D	STX11	LYST
1		c.A2542C; p.I848L c.G2983C; p.A995P		c.A6482C; p.E2161A
2	**c.C272T; p.A91V***	c.C904T; p.L302F		c.C1384T; p.P462S
3				c.T574G; p.L192V c.G3050A; pS1017N c.A3208G; pI1070V c.A3989C; p.D1330A c.T7793A; p.F2598Y c.G8411A; p.G2804D c.7352-7354del; p.L2451L
4	c.C1139G; p.P380R			
5				**c.C7870T; p.R2624W***
6			c.A829G; pT277A	
7				**c.A6482C; p.E2161A***
8				c.A143G; p.H48R
9	c.C65T; p.P22L			
10		c.G2955-4A		
11	c.A755G; p.N252S			
12	c.G530A; p.R177H	c.C2782T; p.R928C		**c.C8216T; p.T2739I***
13		c.G2830+7A		
14		**c.C536G; p.T179R***		
15	**c.C272T; p.A91V***	c.G2696A; p.R899Q		

*** Mutations predicted in silico to be deleterious**