

**Supplementary Table S1: Differentially expressed immune-related genes in EBV+ vs. EBV(-) Hodgkin lymphomas, assessed with qRT-PCR**

Gene ID <sup>a</sup>	Alternative gene ID	Protein description <sup>a</sup>	Protein function <sup>a</sup>	PTPRC normalization		GUSB normalization	
				Fold change EBV pos vs. EBV neg	P-value <sup>b</sup>	Fold change EBV pos vs. EBV neg	p-value <sup>b</sup>
IFNG	IFG; IFI	Interferon gamma	This gene encodes a soluble cytokine that is a member of the type II interferon class. The encoded protein is secreted by cells of both the innate and adaptive immune systems. The active protein is a homodimer that binds to the interferon gamma receptor which triggers a cellular response to viral and microbial infections.	3.45	0.073	3.02	0.103
IDO1	IDO; IDO-1; INDO	Indoleamine 2,3-dioxygenase 1	Catalyzes the first and rate limiting step of the catabolism of the essential amino acid tryptophan along the kynurenine pathway. Through its expression in dendritic cells, monocytes, and macrophages this enzyme down-modulates T-cell behavior by its peri-cellular catabolization of the essential amino acid tryptophan.	2.84	0.012	2.49	0.010
CD8A	CD8; Leu2; MAL; p32	T-cell surface glycoprotein CD8 alpha chain	The CD8 antigen is a cell surface glycoprotein found on most cytotoxic T lymphocytes that mediates efficient cell-cell interactions within the immune system. The CD8 antigen acts as a coreceptor with the T-cell receptor on the T lymphocyte to recognize antigens displayed by an antigen presenting cell in the context of class I MHC molecules.	2.33	0.013	2.04	0.026

TBX21	TBET; T-bet; TBLYM; T-PET	T-box transcription factor TBX21	This gene is a member of a phylogenetically conserved family of genes that share a common DNA-binding domain, the T-box. T-box genes encode transcription factors involved in the regulation of developmental processes. This gene is the human ortholog of mouse Tbx21/Tbet gene. Studies in mouse show that Tbx21 protein is a Th1 cell-specific transcription factor that controls the expression of the hallmark Th1 cytokine, interferon-gamma (IFNG).	2.05	0.002	1.80	0.043
ICOSLG	B7H2; B7-H2; B7RP1; B7RP-1; CD275; GL50; ICOSL; ICOS-L; LICOS	ICOS ligand	Ligand for the T-cell-specific cell surface receptor ICOS.	1.94	0.017	1.70	0.066
LAG3	CD223	Lymphocyte activation gene 3 protein	Lymphocyte-activation protein 3 belongs to Ig superfamily and contains 4 extracellular Ig-like domains. It is an inhibitory receptor expressed on T lymphocytes. The sequence data, exon/intron organization, and chromosomal localization all indicate a close relationship of LAG3 to CD4.	1.75	0.045	1.53	0.279
IL1A	IL-1A; IL1-ALPHA; IL1F1	Interleukin-1 alpha	Produced by activated macrophages, IL-1 stimulates thymocyte proliferation by inducing IL-2 release, B-cell maturation and proliferation, and fibroblast growth factor activity. IL-1 proteins are involved in the inflammatory response, being identified as endogenous pyrogens, and are reported to stimulate the release of prostaglandin and collagenase from synovial cells.	-9.19	0.041	-10.49	0.039

IL13	IL-13; P600	Interleukin-13	The protein encoded by this gene encodes an immunoregulatory cytokine produced primarily by activated Th2 cells. This cytokine is involved in several stages of B-cell maturation and differentiation. It up-regulates CD23 and MHC class II expression, and promotes IgE isotype switching of B cells. This cytokine down-regulates macrophage activity, thereby inhibits the production of pro-inflammatory cytokines and chemokines.	-19.31	0.048	-22.06	0.028
IL17A	IL17; CTLA8; IL-17; CTLA-8; IL-17A	Interleukin-17A	The protein encoded by this gene is a proinflammatory cytokine produced by activated T cells. This cytokine regulates the activities of NF-kappaB and mitogen-activated protein kinases. This cytokine can stimulate the expression of IL6 and cyclooxygenase-2 (PTGS2/COX-2), as well as enhance the production of nitric oxide (NO).	-20.67	0.050	-23.60	0.052
IL23R	N/A	interleukin 23 receptor	The protein encoded by this gene is a subunit of the receptor for IL23A/IL23. This protein pairs with the receptor molecule IL12RB1/IL12Rbeta1, and both are required for IL23A signaling. This protein associates constitutively with Janus kinase 2 (JAK2), and also binds to transcription activator STAT3 in a ligand-dependent manner.	-26.54	0.035	-30.31	0.027

**Table legend:** Listed genes were found to be differentially expressed in EBV+ versus EBV(-) CHL (n= 8 and n=13, respectively), according to expression fold change magnitude (FC)  $\geq 1.7$  and p-value  $\leq 0.10$  when normalized to either *PTPRC* (CD45) or *GUSB* expression. Genes are listed according to descending FC when results are normalized using *PTPRC*. Positive FC values indicate overexpression in EBV+ tumors. Negative FC values indicate overexpression in EBV(-) tumors. See also **Figure 4A**.

<sup>a</sup> Official gene name, protein name and function ( <http://www.genenames.org>).

<sup>b</sup> p-value, 2-sided Welch t-test.

N/A, not applicable.

**Supplementary Table S2: Expression of Th17-related genes in EBV+ versus EBV(-) CHL, assessed by qRT-PCR**

Gene ID <sup>a</sup>	Alternative Gene ID <sup>a</sup>	Gene description <sup>a</sup>	Protein Function <sup>a</sup>	PTPRC normalization		GUSB normalization	
				Fold change, EBV (+) vs. EBV (-)	p-value <sup>b</sup>	Fold change, EBV (+) vs. EBV (-)	p-value <sup>b</sup>
CD5L	Spalpha	CD5 molecule like	Acts as a key regulator of metabolic switch in T-helper Th17 cells. Regulates the expression of pro-inflammatory genes in Th17 cells by altering the lipid content and limiting synthesis of cholesterol ligand of RORC, the master transcription factor of Th17-cell differentiation. CD5L is mainly present in non-pathogenic Th17 cells, where it decreases the content of polyunsaturated fatty acyls (PUFA), affecting two metabolic proteins MSMO1 and CYP51A1, which synthesize ligands of RORC, limiting RORC activity and expression of pro-inflammatory genes.	<b>30.45</b>	<b>0.074</b>	<b>31.00</b>	<b>0.071</b>
CSF2	GM-CSF	colony stimulating factor 2	The protein encoded by this gene is a cytokine that controls the production, differentiation, and function of granulocytes and macrophages. The active form of the protein is found extracellularly as a homodimer.	-1.56	0.368	-1.53	0.376
EBI3	IL27B; IL-27B; IL35B;	Epstein-Barr virus induced 3	This gene was identified by its induced expression in B lymphocytes in response Epstein-Barr virus infection. It encodes a secreted glycoprotein belonging to the hematopoietin receptor family, and heterodimerizes with a 28 kDa protein to form interleukin-27 (IL-27). IL-27 regulates T cell and inflammatory responses, in part by activating the JAK/STAT pathway of CD4+ T cells.	-1.07	0.430	-1.05	0.447
IL27p28	IL-27; IL27A; IL30; p28	interleukin 27	The protein encoded by this gene is one of the subunits of a heterodimeric cytokine complex. This protein is related to interleukin 12A (IL12A). It interacts with Epstein-Barr virus induced gene 3 (EBI3), a protein similar to interleukin 12B (IL12B), and forms a complex that has been shown to drive rapid expansion of naive but not memory CD4(+) T cells. The complex is also found to synergize strongly with interleukin 12 to trigger interferon gamma (IFNG) production of naive CD4(+) T cells. The biological effects of this cytokine are mediated by the class I cytokine receptor (WSX1/TCRR).	<b>2.94</b>	<b>0.038</b>	<b>2.99</b>	<b>0.033</b>
PRDM1	BLIMP1; PRDI-BF1	PR/SET domain 1	This gene encodes a protein that acts as a repressor of beta-interferon gene expression. The protein binds specifically to the PRDI (positive regulatory domain I element) of the beta-IFN gene promoter. Transcription of this gene increases upon virus induction. Two alternatively spliced transcript variants that encode different isoforms have been reported.	-1.17	0.340	-1.15	0.395

RORC	NR1F3, RORG, RZRG, TOR	RAR related orphan receptor C	The protein encoded by this gene is a DNA-binding transcription factor and is a member of the NR1 subfamily of nuclear hormone receptors. The specific functions of this protein are not known; however, studies of a similar gene in mice have shown that this gene may be essential for lymphoid organogenesis and may play an important regulatory role in thymopoiesis. In addition, studies in mice suggest that the protein encoded by this gene may inhibit the expression of Fas ligand and IL2. Two transcript variants encoding two different isoforms have been found for this gene. The isoform 2 plays a key role, downstream of IL6 and TGFB and synergistically with RORA, for lineage specification of uncommitted CD4+ T-helper (T(H)) cells into T(H)17 cells, antagonizing the T(H)1 program.	-1.62	0.162	-1.59	0.189
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**Table legend:** Listed are 6 immune genes reported to be involved in Th17/IL-23 pathway, whose expression was assessed by qRT-PCR in EBV+ and EBV(-) CHLs (n=8 and n=13, respectively). In bold type are significantly differentially expressed genes, according to fold change magnitude (FC)  $\geq 2.0$  and p-value  $\leq 0.10$ , when normalized to either *PTPRC* (CD45) or *GUSB* expression. Genes names are listed in alphabetical order. See also **Figure 4B**.

<sup>a</sup> Official gene name, protein name and function ( <http://www.genenames.org>).

<sup>b</sup> p-value, one-sided Welch's t-test.