

## Supplementary Information

### NFkB target gene sets

The NFkB target gene sets are listed below (Table1). In addition to the previously performed mapping of Affymetrix probesets and corresponding Lymphochip probes based on unique (Unigene) accession numbers <sup>1</sup>, a text search for gene names and Genebank accession numbers was performed to identify additional NFkB target genes represented on the Lymphochip platform.

**Table 1: NFkB Target Gene Sets**

1. Genes included in the subset of 15k genes selected according to a MAD-based variation filter

Gene Name	Common Gene Name(s)	Affymetrix Probe Set(s)	Lymphochip Probe(s)
BCL2	B-cell CLL/lymphoma 2 <sup>(2)</sup>	203685_at	28859; 16789
BCL2A1	BFL1/A1 / BCL2-related protein A1 <sup>(1,2)</sup>	205681_at	28638; 16089; 26039; 24637; 28639
BCL2L1	BCL2-like 1 / BCLxL <sup>(1,2)</sup>	212312_at; 215037_s_at	16454; 24267
BIRC2	baculoviral IAP repeat-containing 2 (c-IAP1) <sup>(2)</sup>	202076_at	28475; 33714; 15917
BIRC3	baculoviral IAP repeat-containing 3 (c-IAP2) <sup>(1,2)</sup>	210538_s_at	30589; 15916; 28474; 19233
C4orf9	gene near HD on 4p16.3 with homology to hypothetical S. pombe gene <sup>(1)</sup>	214661_s_at	n.a.
CCL2	chemokine (C-C motif) ligand 2 (MCP1) <sup>(3)</sup>	216598_s_at	15851; 34426
CCL22	MDC <sup>(1)</sup>	207861_at	36447; 37437
CCL3	MIP-1alpha <sup>(1,2)</sup>	205114_s_at	16426; 26474; 26475; 16822
CCL4	MIP-1beta <sup>(2)</sup>	204103_at	26408; 26409; 28410; 15850
CCND2	Cyclin D2 <sup>(2)</sup>	200951_s_at; 200952_s_at; 200953_s_at; 231259_s_at;	16858; 24787
CCR7	chemokine (C-C motif) receptor 7 <sup>(1,2)</sup>	206337_at	19339; 32655
CD23A	Fc fragment of IgE, low affinity II receptor for (CD23A) / FCER2 <sup>(2)</sup>	206759_at	17521; 35220
CD44	CD44 antigen (homing function and Indian blood group system) <sup>(1,2)</sup>	204489_s_at; 204490_s_at; 209835_x_at; 212014_x_at; 212063_at; 229221_at; 217523_at;	30428; 31594; 28684; 24821; 19271; 16140
CD69	CD69 antigen / p60, early T-cell activation antigen <sup>(2)</sup>	209795_at	16136; 24561
CD83	CD83 antigen / activated B lymphocytes, immunoglobulin superfamily <sup>(1)</sup>	204440_at	16610; 30431; 19239; 28216; 27545; 17066
CFLAR	CASP8 and FADD-like apoptosis regulator / c-FLIP <sup>(2)</sup>	209508_x_at; 208485_x_at; 209939_x_at; 210563_x_at; 210564_x_at; 211316_x_at;	19219; 27384

DUSP1	dual specificity phosphatase 1 <sup>(3)</sup>	211317_s_at; 211862_x_at; 214486_x_at; 237367_x_at; 239629_x_at 201041_s_at; 226578_s_at	26487; 27490; 27478; 17871; 26488; 26517; 26987
DUSP2	dual specificity phosphatase 2 <sup>(2)</sup>	204794_at	27686; 17185
EGR1	early growth response 1 <sup>(3)</sup>	201693_s_at; 201694_s_at; 227404_s_at	24762; 26362; 16960
EMR1	egf-like module containing, mucin-like, hormone receptor-like sequence 1 <sup>(1)</sup>	207111_at	n.a.
HLA-F	major histocompatibility complex, class I, F <sup>(1)</sup>	204806_x_at; 221978_at 204806_x_at	n.a.
ICAM1	intercellular adhesion molecule 1 / CD54 <sup>(1,2)</sup>	202637_s_at; 202638_s_at	16403; 27211; 24268; 28750
IER2	immediate early response 2 / ETR-101 <sup>(3)</sup>	202081_at	n.a.
IER3	immediate early response 3 / IEX-1 <sup>(1)</sup>	201631_s_at	26533; 26460
IL15RA	interleukin 15 receptor, alpha <sup>(1)</sup>	207375_s_at	31845; 16161; 16046
IL2RA	interleukin 2 receptor, alpha <sup>(2)</sup>	211269_s_at	25220; 30448; 32634
IL4RA	interleukin 4 receptor <sup>(2)</sup>	203233_at	28597; 16044; 19298; 19256
IL6	interleukin 6 / interferon, beta 2 <sup>(1,3)</sup>	205207_at	25209; 28748; 16736; 24750
IL8	interleukin 8 <sup>(2)</sup>	202859_x_at	17643; 30444; 32630; 25184
IRF1	interferon regulatory factor 1 <sup>(1,2)</sup>	202531_at	28599; 24405
IRF4	interferon regulatory factor 4 <sup>(2)</sup>	204562_at	16614; 24729; 22122
JUNB	jun B proto-oncogene <sup>(2,3)</sup>	201473_at	28950; 17346
KAI1	kangai 1 / suppression of tumorigenicity 6, prostate; CD82 antigen <sup>(2)</sup>	203904_x_at	16425
KLF10	TGFB inducible early growth response, TIEG1 <sup>(1)</sup>	202393_s_at	28201; 26572; 17704; 16592; 27454
LITAF	LPS-induced TNF-alpha factor <sup>(1)</sup>	200704_at	28695; 34226
LSP1	lymphocyte-specific protein 1 <sup>(1)</sup>	203523_at	27000; 29384; 16400
MYB	v-myb myeloblastosis viral oncogene homolog (avian) <sup>(2)</sup>	204798_at	24988; 19291; 28014; 17496
NCF2	neutrophil cytosolic factor 2 (65kDa, chronic granulomatous disease, autosomal 2) <sup>(1)</sup>	209949_at	29574; 29573
NFkB2	nuclear factor of kappa light polypeptide gene enhancer in B-cells 2 (p49/p100) <sup>(1,2)</sup>	207535_s_at	27660; 17160
NFKBIA	IkBalpha / nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha <sup>(2,3)</sup>	201502_s_at	34886; 24829; 24499; 28424
NK4	natural killer cell transcript 4 <sup>(3)</sup>	203828_s_at	19376; 28586; 16034
PASK	PAS domain containing serine/threonine kinase <sup>(1)</sup>	213534_s_at; 216945_x_at	24442; 31194
PCAM1	Platelet/endothelial cell adhesion molecule / CD31 antigen <sup>(2)</sup>	208981_at; 208982_at; 208983_s_at	24718; 16837
PRKCD	protein kinase C, delta <sup>(1)</sup>	202545_at	28967; 17679
RAFTLIN	KIAA0084 protein / raft-linking protein <sup>(1)</sup>	212646_at	32679; 30246

REL	c-REL / v-rel reticuloendotheliosis viral oncogene homolog (avian) <sup>(2)</sup>	206035_at; 206036_s_at	27705; 17204
RELB	v-rel reticuloendotheliosis viral oncogene homolog B, <sup>(2)</sup>	205205_at	16279; 26921; 28926
RRAS2	related RAS viral (r-ras) oncogene homolog 2 / TC21 <sup>(1)</sup>	208456_s_at; 212589_at; 212590_at	n.a.
SDC4	syndecan 4 (amphiglycan, ryudocan) <sup>(3)</sup>	202071_at	17842; 27296; 28564
SLC2A5	GLUT5 / solute carrier family 2 <sup>(1)</sup> , member 5	204429_s_at; 204430_s_at	17118; 24424; 26431
SMAD7	MAD, mothers against decapentaplegic homolog 7 <sup>(1)</sup>	204790_at	16418; 28817
SOD2	superoxide dismutase 2, mitochondrial <sup>(3)</sup>	216841_s_at; 215223_s_at; 221477_s_at	28770
STAT5A	signal transducer and activator of transcription 5A <sup>(1)</sup>	203010_at	29329; 30027
STX4A	syntaxin 4A (placental) <sup>(1)</sup>	203530_s_at	n.a.
TNFAIP3	A20 / tumor necrosis factor alpha-induced protein 3 <sup>(2,3)</sup>	202643_s_at; 202644_s_at	34761; 28987; 16398; 19267; 28986
TNFRSF5	CD40 / tumor necrosis factor receptor superfamily, member 5 <sup>(2)</sup>	205153_s_at; 222292_at; 35150_at	27399; 16913
TNFRSF6	FAS / tumor necrosis factor receptor superfamily, member 6 <sup>(1)</sup>	204780_s_at; 204781_s_at; 215719_x_at; 216252_x_at	16699; 17626; 29375; 29356
TNFSF2	tumor necrosis factor /TNF superfamily, member 2 <sup>(2)</sup>	207113_s_at	28018; 17500; 24423
TNIP	A20-binding inhibitor of NF-kappaB activation-2 (ABIN-2) <sup>(1)</sup>	218335_x_at; 48531_at; 232160_s_at	n.a.
TPMT	thiopurine S-methyltransferase <sup>(1)</sup>	203672_x_at	n.a.
TRAF1	TNF receptor-associated factor 1 <sup>(1,2)</sup>	205599_at; 235116_at	15921; 26356; 26357; 34621
VIM	Vimentin <sup>(1)</sup>	201426_s_at	23950; 17082; 24417
WTAP	Wilms' tumor 1-associating protein <sup>(1)</sup>	203137_at; 210285_x_at; 214759_at; 227621_at; 229630_s_at;	n.a.

## 2. Genes present on the publicly available Lymphochip dataset but not part of the 15k subset

Gene Name	Common Gene Name(s)	Affymetrix Probe Set(s)	Lymphochip Probe(s)
CX3CL1	small inducible cytokine subfamily D (CX3CL1) <sup>(1)</sup>	203687_at; 823_at	28708; 16395; 17806; 27065; 27053
CXCL1	GRO-1/ chemokine (C-X-C motif) ligand 1 (melanoma growth stimulating activity, alpha) <sup>(3)</sup>	204470_at	28834; 16751
PTGS2	prostaglandin-endoperoxide synthase 2 / COX2 <sup>(3)</sup>	204748_at	28882
TNFSF1	lymphotoxin alpha / TNF superfamily, member 1 / LTA / TNFbeta <sup>(1)</sup>	206975_at	25205; 35085

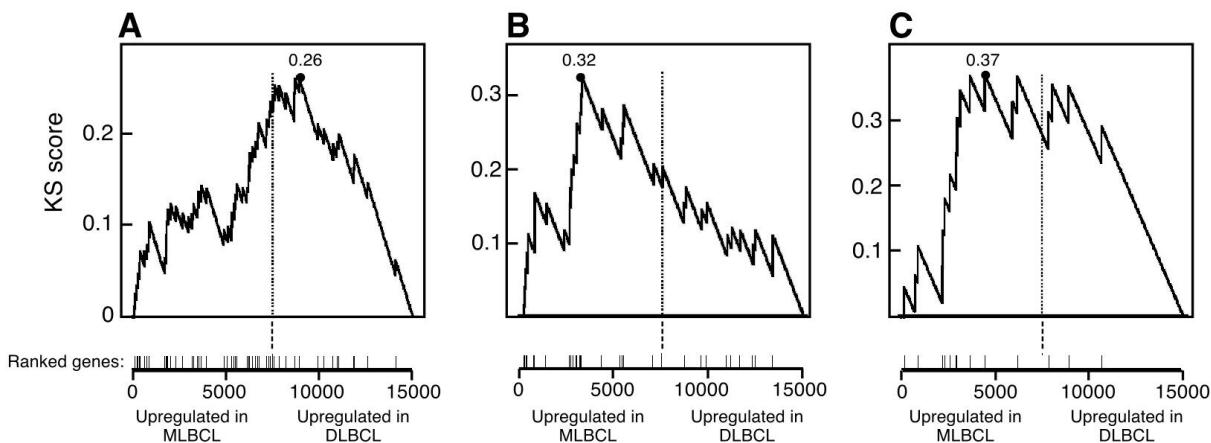
- (1) Geneset 1: NFkB target genes that were downregulated in two HL cell lines expressing an I kB $\alpha$  super-repressor<sup>2</sup>;
- (2) Geneset 2: Previously described NFkB target genes that were differentially expressed at specific stages of normal B-cell development and/or in DLBCLs with “ABC” features<sup>3,4</sup>;
- (3) Geneset 3: NFkB target genes that were downregulated after siRNA silencing of REL-A (p65) in TNF $\alpha$ -stimulated HeLa cells<sup>5</sup>

## Enrichment test

We carried out an enrichment test<sup>6</sup> in order to assess whether the NFkB targets were over-represented in the MLBCL signature. Enrichment was assessed based on the following procedure:

1. 15,000 genes were selected from the U133A/B chips according to a MAD-based variation filter, and ranked according to their SNR with respect to the “MLBCL vs. DLBCL” class membership (i.e. ranked from the most over-expressed to the most under-expressed genes in MLBCL).
2. The set of NFkB target genes were located within the ranked list of 15K genes, and their proximity to the over-expressed end of the list was measured by a Kolmogorov-Smirnoff (KS) score (with a higher score corresponding to a higher proximity).

Permutation of the “MLBCL vs. DLBCL” sample labels, associated re-ranking of the 15K genes, and computation of the corresponding KS score were performed multiple times ( $n=100$ ), so as to compare the observed KS score with the KS score that could be expected by chance under a random class labeling. An empirical p-value was thus computed to quantify the significance of the enrichment of the MLBCL signature for NFkB targets.



**Figure 1 :** Overrepresentation of literature-curated NFkB target gene sets in the MLBCL signature assessed by Gene Set Enrichment Analysis (GSEA): **(A)** Geneset 1 (NFkB target genes that were downregulated in two HL cell lines expressing an I $\kappa$ B $\alpha$  super-repressor<sup>2</sup>),  $p = .05$  ; **(B)** Geneset 2 (Previously described NFkB target genes that were differentially expressed at specific stages of normal B-cell development and/or in DLBCLs with “ABC” features<sup>3,4</sup>),  $p = .02$  ; **(C)** Geneset3 (NFkB target genes that were downregulated after siRNA silencing of REL-A (p65) in TNF $\alpha$ -stimulated HeLa cells<sup>5</sup>)  $p = .08$ .

## Gene expression differential analysis and permutation test

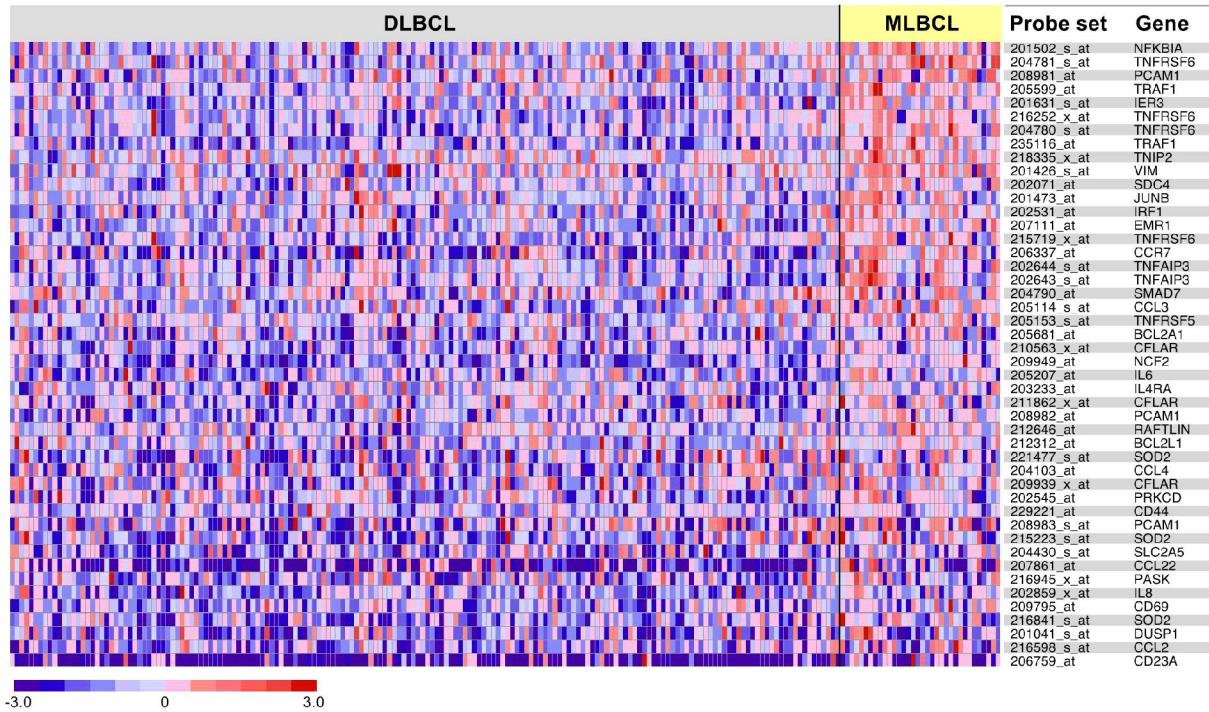
From within the set of  $n = 112$  probesets representing 64 NFkB target genes, genes correlated with the class distinction of interest (e.g., 1=“mediastinal” vs. 0=“non-mediastinal”; or 1=“GCB” vs. 0=“non-GCB”, etc.) were identified by ranking them according to their signal-to-noise ratio (SNR)<sup>7,8</sup>,

$$\text{SNR} = \frac{\mu_1 - \mu_0}{\sigma_1 + \sigma_0},$$

where  $\mu_i$  and  $\sigma_i$  denote, respectively, the sample median and sample standard deviation within class  $i=1,0$ . Similar rankings were obtained by using the t-statistic in place of the SNR. A Monte Carlo simulation of the permutation distribution of the SNR’s was performed by permuting the sample labels indicating class membership 1000 times; thereafter, the observed values in the data were compared to the 99<sup>th</sup> percentile of the permutation. Note that the permuted SNRs are associated with a gene’s rank, not its identity. That is, the p-value for the  $k^{\text{th}}$  ranked gene is computed with respect to the empirical null distribution obtained by repeating the following steps multiple times: i) shuffle the class labels; ii) compute the associated SNR’s for all genes; and iii) select the  $k^{\text{th}}$  SNR (irrespective of the identity of the gene achieving this score). By shuffling the class labels, the expression correlation among the genes is preserved, thus making the permutation test more stringent (i.e., making it harder to achieve statistical significance).

## Results of the permutation analyses

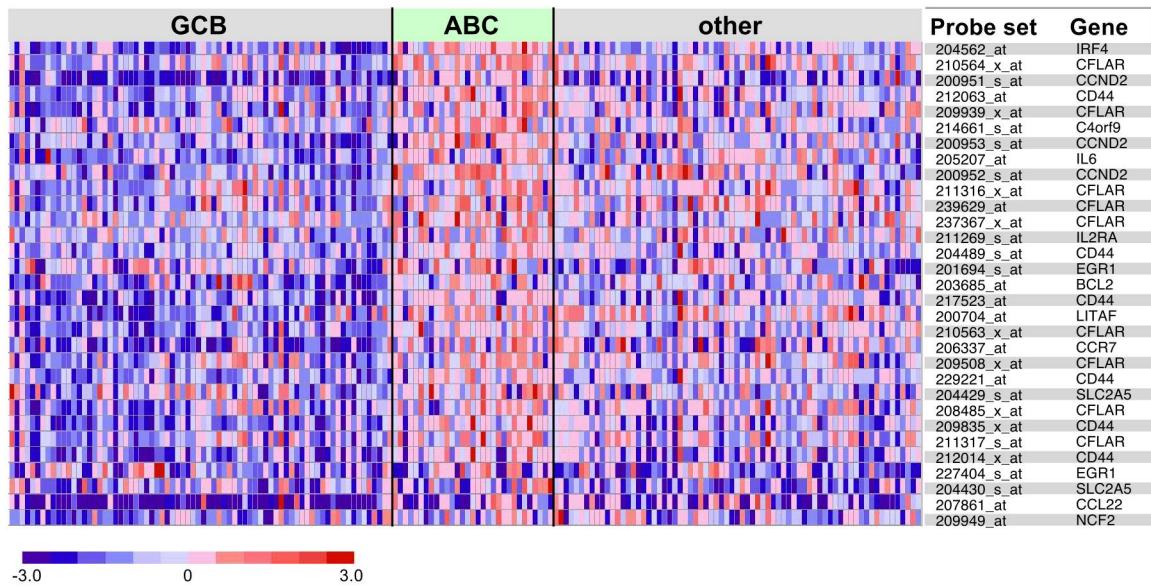
**Figure 2:** Differential expression of NF $\kappa$ B target genes in MLBCL vs. DLBCL. The results of the permutation analysis are listed in the corresponding table 2 below.



Affymetrix ID	Class	Score	99th percentile	Fold change	Name	description
201502_s_at	MLBCL	0.52	0.41	1.6	NFKBIA	nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha
204781_s_at	MLBCL	0.48	0.35	1.7	TNFRSF6	tumor necrosis factor receptor superfamily, member 6
208981_s_at	MLBCL	0.47	0.32	1.5	PCAM1	platelet/endothelial cell adhesion molecule (CD31 antigen)
205599_at	MLBCL	0.46	0.30	1.7	TRAFA1	TNF receptor-associated factor 1
201631_s_at	MLBCL	0.45	0.28	1.5	IER3	immediate early response 3
216252_x_at	MLBCL	0.45	0.27	1.8	TNFRSF6	tumor necrosis factor receptor superfamily, member 6
204780_s_at	MLBCL	0.44	0.26	1.8	TNFRSF6	tumor necrosis factor receptor superfamily, member 6
235116_at	MLBCL	0.44	0.25	2.0	TRAFA1	TNF receptor-associated factor 1
218335_x_at	MLBCL	0.41	0.23	1.3	TNIP2	A20-binding inhibitor of NF- $\kappa$ B activation-2
201426_s_at	MLBCL	0.39	0.22	1.3	VIM	vimentin
202071_at	MLBCL	0.39	0.22	1.5	SDC4	syndecan 4 (amphiglycan, ryudocan)
201473_at	MLBCL	0.38	0.22	1.4	JUNB	jun B proto-oncogene
202531_at	MLBCL	0.35	0.21	1.4	IRF1	interferon regulatory factor 1
207111_at	MLBCL	0.35	0.21	1.6	EMR1	egf-like module containing, mucin-like, hormone receptor-like sequence 1
215719_x_at	MLBCL	0.34	0.20	1.7	TNFRSF6	tumor necrosis factor receptor superfamily, member 6
206337_at	MLBCL	0.33	0.19	1.8	CCR7	chemokine (C-C motif) receptor 7
202644_s_at	MLBCL	0.32	0.19	1.5	TNFAIP3	tumor necrosis factor, alpha-induced protein 3
202643_s_at	MLBCL	0.3	0.18	1.4	TNFAIP3	tumor necrosis factor, alpha-induced protein 3
204790_at	MLBCL	0.3	0.18	1.4	SMAD7	MAD, mothers against decapentaplegic homolog 7 (Drosophila)
205114_s_at	MLBCL	0.29	0.17	1.6	CCL3	chemokine (C-C motif) ligand 3
205153_s_at	MLBCL	0.27	0.17	1.4	TNFRSF5	tumor necrosis factor receptor superfamily, member 5
205681_at	MLBCL	0.26	0.17	1.6	BCL2A1	BCL2-related protein A1
210563_x_at	MLBCL	0.25	0.16	1.4	CFLAR	CASP8 and FADD-like apoptosis regulator
209949_at	MLBCL	0.24	0.16	2.7	NCF2	neutrophil cytosolic factor 2 (65kDa, chronic granulomatous disease, autosomal 2)
205207_at	MLBCL	0.23	0.16	1.5	IL6	interleukin 6 (interferon, beta 2)
203233_at	MLBCL	0.23	0.15	1.3	IL4RA	interleukin 4 receptor
211862_x_at	MLBCL	0.23	0.15	1.3	CFLAR	CASP8 and FADD-like apoptosis regulator
208982_at	MLBCL	0.22	0.14	1.4	PCAM1	platelet/endothelial cell adhesion molecule (CD31 antigen)
212646_at	MLBCL	0.21	0.14	1.3	RAFTLIN	KIAA0084 protein
212312_at	MLBCL	0.19	0.13	1.3	BCL2L1	BCL2-like 1
221477_s_at	MLBCL	0.19	0.13	1.5	SOD2	superoxide dismutase 2, mitochondrial
204103_at	MLBCL	0.17	0.12	1.3	CCL4	MIP1beta
209939_x_at	MLBCL	0.16	0.12	1.3	CFLAR	CASP8 and FADD-like apoptosis regulator
202545_at	MLBCL	0.16	0.12	1.3	PRKCD	protein kinase C, delta
229221_at	MLBCL	0.16	0.11	1.3	CD44	CD44 antigen (homing function and Indian blood group system)
208983_s_at	MLBCL	0.15	0.11	1.3	PCAM1	platelet/endothelial cell adhesion molecule (CD31 antigen)
215223_s_at	MLBCL	0.15	0.11	1.5	SOD2	superoxide dismutase 2, mitochondrial
204430_s_at	MLBCL	0.14	0.11	1.4	SLC2A5	solute carrier family 2 (facilitated glucose/fructose transporter), member 5
207861_at	MLBCL	0.14	0.10	4.0	CCl22	chemokine (C-C motif) ligand 22
216945_x_at	MLBCL	0.13	0.09	1.3	PASK	PAS domain containing serine/threonine kinase
202859_x_at	MLBCL	0.12	0.08	1.4	IL8	interleukin 8
209795_at	MLBCL	0.11	0.07	1.3	CD69	CD69 antigen (p60, early T-cell activation antigen)
216841_s_at	MLBCL	0.1	0.06	1.4	SOD2	superoxide dismutase 2, mitochondrial
201041_s_at	MLBCL	0.1	0.06	1.4	DUSP1	dual specificity phosphatase 1
216598_s_at	MLBCL	0.07	0.04	1.3	CCL2	chemokine (C-C motif) ligand 2
206759_at	MLBCL	0.06	0.03	4.2	CD23A	Fc fragment of IgE, low affinity II, receptor for (CD23A)

**Table 2:** Permutation results corresponding to the analysis shown in Fig. 2

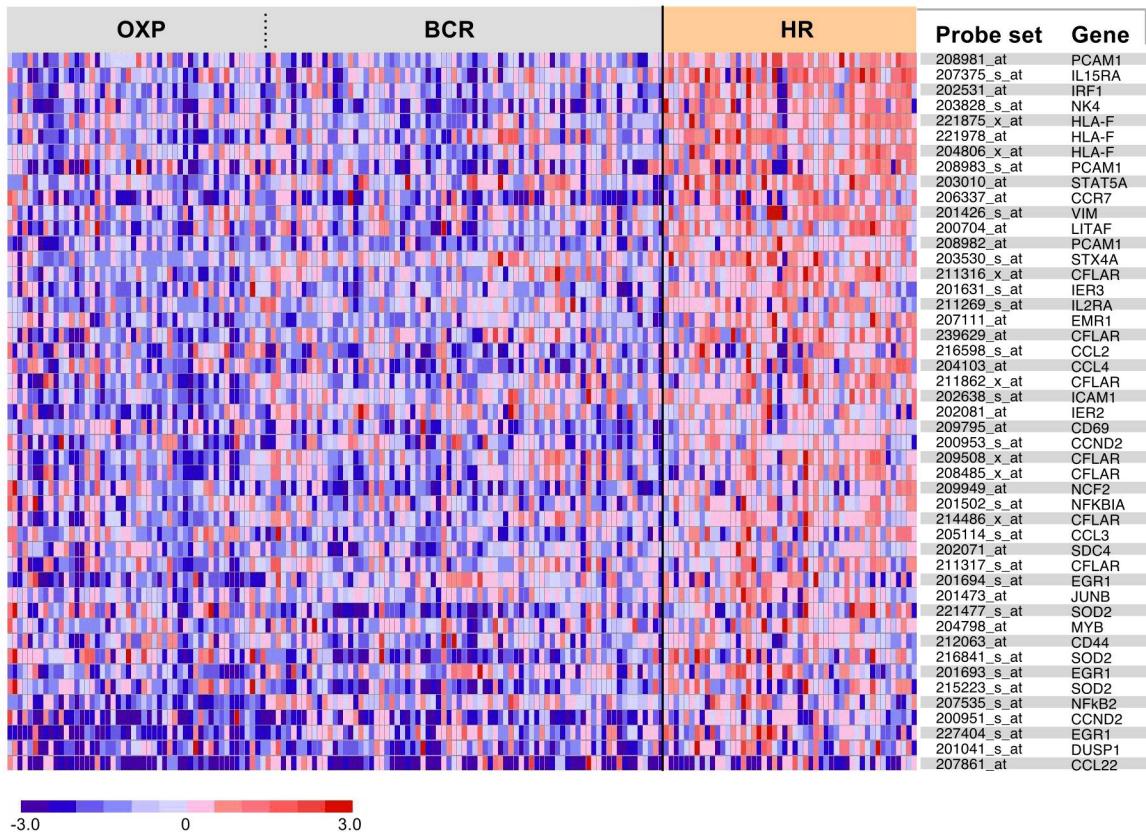
**Figure 3:** Differential expression of NFkB target genes in ABC-like DLBCL vs. non-ABC- like DLBCL. The results of the permutation analysis are listed in the corresponding table below.



Affymetrix ID	Class	Score	99th percentile	Fold change	Name	description
204562_at	ABC	0.51	0.46	2.3	IRF4	interferon regulatory factor 4
210564_x_at	ABC	0.46	0.37	1.4	CFLAR	CASP8 and FADD-like apoptosis regulator
200951_s_at	ABC	0.43	0.32	4.0	CCND2	cyclin D2
212063_at	ABC	0.43	0.29	1.7	CD44	CD44 antigen (homing function and Indian blood group system)
209939_x_at	ABC	0.42	0.28	1.8	CFLAR	CASP8 and FADD-like apoptosis regulator
214661_s_at	ABC	0.41	0.26	1.4	C4orf9	gene near HD on 4p16.3 with homology to hypothetical S. pombe gene
200953_s_at	ABC	0.40	0.25	1.8	CCND2	cyclin D2
205207_at	ABC	0.39	0.24	1.9	IL6	interleukin 6 (interferon, beta 2)
200952_s_at	ABC	0.34	0.23	1.5	CCND2	cyclin D2
211316_x_at	ABC	0.34	0.23	1.3	CFLAR	CASP8 and FADD-like apoptosis regulator
239629_at	ABC	0.32	0.22	1.4	CFLAR	CASP8 and FADD-like apoptosis regulator
237367_x_at	ABC	0.31	0.22	1.4	CFLAR	CASP8 and FADD-like apoptosis regulator
211269_s_at	ABC	0.30	0.21	1.4	IL2RA	interleukin 2 receptor, alpha
204489_s_at	ABC	0.29	0.20	1.7	CD44	CD44 antigen (homing function and Indian blood group system)
201694_s_at	ABC	0.28	0.20	1.5	EGR1	early growth response 1
203685_at	ABC	0.28	0.19	1.7	BCL2	B-cell CLL/lymphoma 2
217523_at	ABC	0.27	0.19	1.8	CD44	ESTs, Highly similar to CD44_HUMAN CD44 antigen precursor (Phagocytic glycoprotein I) (P-
200704_at	ABC	0.26	0.18	1.3	LITAF	LPS-induced TNF-alpha factor
210563_x_at	ABC	0.26	0.18	1.6	CFLAR	CASP8 and FADD-like apoptosis regulator
206337_at	ABC	0.24	0.17	1.7	CCR7	chemokine (C-C motif) receptor 7
209508_x_at	ABC	0.24	0.17	1.3	CFLAR	CASP8 and FADD-like apoptosis regulator
229221_at	ABC	0.22	0.16	1.6	CD44	CD44 antigen (homing function and Indian blood group system)
204429_s_at	ABC	0.22	0.16	1.3	SLC2A5	solute carrier family 2 (facilitated glucose/fructose transporter), member 5
208485_x_at	ABC	0.21	0.16	1.3	CFLAR	CASP8 and FADD-like apoptosis regulator
209835_x_at	ABC	0.20	0.16	1.7	CD44	CD44 antigen (homing function and Indian blood group system)
211317_s_at	ABC	0.19	0.15	1.3	CFLAR	CASP8 and FADD-like apoptosis regulator
212014_x_at	ABC	0.19	0.14	1.8	CD44	CD44 antigen (homing function and Indian blood group system)
227404_s_at	ABC	0.16	0.14	1.6	EGR1	EGR1
204430_s_at	ABC	0.15	0.13	1.5	SLC2A5	solute carrier family 2 (facilitated glucose/fructose transporter), member 5
207861_at	ABC	0.14	0.13	3.5	CCL22	chemokine (C-C motif) ligand 22
209949_at	ABC	0.12	0.12	1.3	NCF2	neutrophil cytosolic factor 2 (65kDa, chronic granulomatous disease, autosomal 2)

**Table 3:** Permutation results corresponding to the analysis shown in Fig. 3

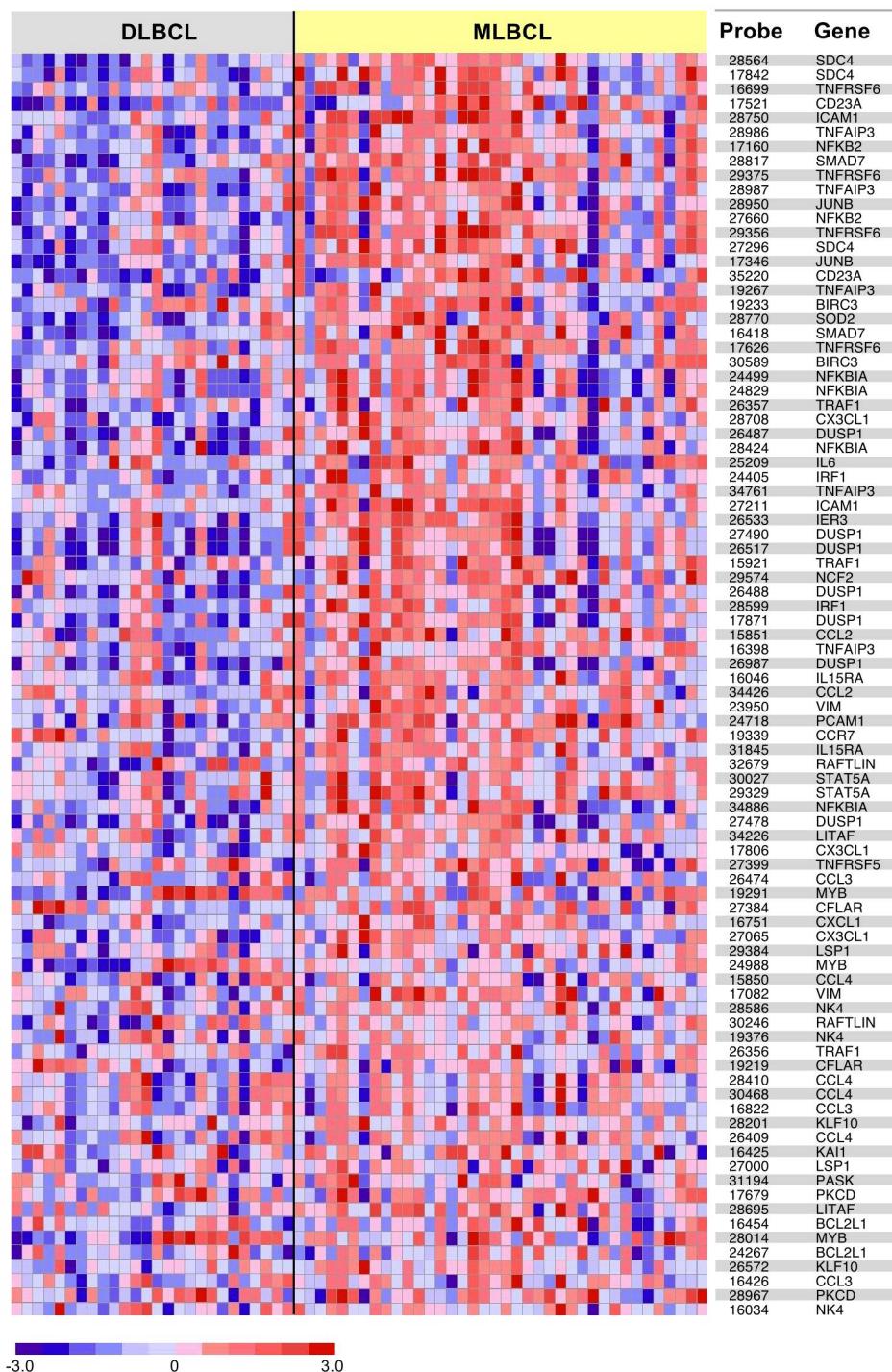
**Figure 4:** Differential expression of NF $\kappa$ B target genes in Host Response (HR) DLBCL vs. non-HR DLBCL. The results of the permutation analysis are listed in the corresponding table below.



Affymetrix ID	Class	Score	99th percentile	Fold change	Name	description
208981_at	HRS	0.74	0.38	1.8	PCAM1	platelet/endothelial cell adhesion molecule (CD31 antigen)
207375_s_at	HRS	0.69	0.32	1.8	IL15RA	interleukin 15 receptor, alpha
202531_at	HRS	0.62	0.27	1.7	IRF1	interferon regulatory factor 1
203828_s_at	HRS	0.62	0.24	2.7	NK4	natural killer cell transcript 4
221875_x_at	HRS	0.61	0.23	1.5	HLA-F	ESTs, Highly similar to A60384 MHC class I histocompatibility antigen HLA-F alpha chain Dev
221978_at	HRS	0.54	0.21	1.5	HLA-F	major histocompatibility complex, class I, F
204806_x_at	HRS	0.56	0.22	1.5	HLA-F	major histocompatibility complex, class I, F
208983_s_at	HRS	0.49	0.20	2.0	PCAM1	platelet/endothelial cell adhesion molecule (CD31 antigen)
203010_at	HRS	0.44	0.19	1.4	STAT5A	signal transducer and activator of transcription 5A
206337_at	HRS	0.4	0.17	2.3	CCR7	chemokine (C-C motif) receptor 7
201426_s_at	HRS	0.42	0.18	1.4	VIM	vimentin
200704_at	HRS	0.45	0.19	1.6	LITAF	LPS-induced TNF-alpha factor
208982_at	HRS	0.4	0.16	1.8	PCAM1	platelet/endothelial cell adhesion molecule (CD31 antigen)
203530_s_at	HRS	0.41	0.17	1.3	STX4A	syntaxin 4A (placental)
211316_x_at	HRS	0.4	0.17	1.4	CFLAR	CASP8 and FADD-like apoptosis regulator
201631_s_at	HRS	0.36	0.16	1.4	IER3	immediate early response 3
211269_s_at	HRS	0.35	0.15	1.4	IL2RA	interleukin 2 receptor, alpha
207111_at	HRS	0.3	0.14	1.6	EMR1	egf-like module containing, mucin-like, hormone receptor-like sequence 1
239629_at	HRS	0.35	0.14	1.5	CFLAR	CASP8 and FADD-like apoptosis regulator
216598_s_at	HRS	0.36	0.15	2.0	CCL2	chemokine (C-C motif) ligand 2
204103_at	HRS	0.36	0.16	1.6	CCL4	MP1beta
211862_x_at	HRS	0.29	0.14	1.4	CFLAR	CASP8 and FADD-like apoptosis regulator
202638_s_at	HRS	0.33	0.14	1.4	ICAM1	intercellular adhesion molecule 1 (CD54), human rhinovirus receptor
202081_at	HRS	0.29	0.13	1.3	IER2	immediate early protein = immediate early response 2 = ETR-101
209795_at	HRS	0.26	0.11	1.6	CD69	CD69 antigen (p60, early T-cell activation antigen)
200953_s_at	HRS	0.27	0.12	1.4	CCND2	cyclin D2
209508_x_at	HRS	0.28	0.13	1.3	CFLAR	CASP8 and FADD-like apoptosis regulator
208485_x_at	HRS	0.26	0.12	1.4	CFLAR	CASP8 and FADD-like apoptosis regulator
209949_at	HRS	0.27	0.13	1.7	NCF2	neutrophil cytosolic factor 2 (65kDa, chronic granulomatous disease, autosomal 2)
201502_s_at	HRS	0.25	0.11	1.3	NFKBIA	nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha
214486_x_at	HRS	0.25	0.10	1.3	CFLAR	CASP8 and FADD-like apoptosis regulator
205114_s_at	HRS	0.26	0.11	1.6	CCL3	chemokine (C-C motif) ligand 3
202071_at	HRS	0.24	0.10	1.3	SDC4	syndecan 4 (amphiglycan, ryudocan)
211317_s_at	HRS	0.23	0.10	1.4	CFLAR	CASP8 and FADD-like apoptosis regulator
201694_s_at	HRS	0.25	0.10	1.4	EGR1	early growth response 1
201473_at	HRS	0.26	0.12	1.3	JUNB	jun B proto-oncogene
221477_s_at	HRS	0.22	0.09	1.6	SOD2	superoxide dismutase 2, mitochondrial
204798_at	HRS	0.25	0.11	1.3	MYB	v-myb myeloblastosis viral oncogene homolog (avian)
212063_at	HRS	0.22	0.09	1.3	CD44	CD44 antigen (homing function and Indian blood group system)
216841_s_at	HRS	0.18	0.07	1.5	SOD2	superoxide dismutase 2, mitochondrial
201693_s_at	HRS	0.21	0.08	1.4	EGR1	early growth response 1
215223_s_at	HRS	0.22	0.09	1.8	SOD2	superoxide dismutase 2, mitochondrial
207535_s_at	HRS	0.19	0.08	1.3	NFKB2	nuclear factor of kappa light polypeptide gene enhancer in B-cells 2 (p49/p100)
200951_s_at	HRS	0.19	0.08	2.4	CCND2	cyclin D2
227404_s_at	HRS	0.19	0.08	1.7	EGR1	EGR1
201041_s_at	HRS	0.15	0.06	1.6	DUSP1	dual specificity phosphatase 1
207861_at	HRS	0.03	0.01	1.6	CCL22	chemokine (C-C motif) ligand 22

**Table 4:** Permutation results corresponding to the analysis shown in Fig. 4

**Figure 5:** Confirmation of the NF $\kappa$ B activation signature in MLBCL in an independent dataset. The full publicly available gene expression data set (provided as supplemental information with Ref.<sup>9</sup>, <http://llmpp.nih.gov/PMBL/>) encompassing 26 DLBCL (13 GCB-like and 13 ABC-like), and 38 MLBCL was included in the analysis. The permutation results are listed in table 5 (see next page).



Class	Score	99th percentile	Probe ID	Description
MLBCL	0.78	0.64	28564	IX670161*AA148737IHs.252189lsyndecan 4 (amphiglycan, ryudocan)
MLBCL	0.68	0.60	17842	IX670161*W60528IHs.252189lsyndecan 4 (amphiglycan, ryudocan)
MLBCL	0.64	0.55	16699	IX637171*N75066IHs.82359ltumor necrosis factor receptor superfamily, member 6
MLBCL	0.64	0.52	17521	IM150591*AA829959IHs.1416lFc fragment of IgE, low affinity II, receptor for (CD23A)
MLBCL	0.63	0.50	28750	IM242831*R77293IHs.168383lintercellular adhesion molecule 1 (CD54), human rhinovirus receptor
MLBCL	0.63	0.48	28986	IM594651-R70479IHs.211600ltumor necrosis factor, alpha-induced protein 3
MLBCL	0.61	0.43	17160	IX614981*AA256597IHs.73090lnuclear factor of kappa light polypeptide gene enhancer in B-cells 2 (p49/p100)
MLBCL	0.61	0.42	28817	IAF0101931*R82176IHs.100602lMAD, mothers against decapentaplegic homolog 7 (Drosophila)
MLBCL	0.61	0.42	29375	IX637171-AA282988IHs.82359ltumor necrosis factor receptor superfamily, member 6
MLBCL	0.6	0.41	28987	IM594651-R70479IHs.211600ltumor necrosis factor, alpha-induced protein 3
MLBCL	0.6	0.39	28950	INM_0022291*AA454711IHs.400124ljun B proto-oncogene
MLBCL	0.6	0.38	27660	IX614981*AA256597IHs.73090lnuclear factor of kappa light polypeptide gene enhancer in B-cells 2 (p49/p100)
MLBCL	0.59	0.38	29356	IX637171*AA293571IHs.82359ltumor necrosis factor receptor superfamily, member 6
MLBCL	0.59	0.38	27296	IX670161*W60528IHs.252189lsyndecan 4 (amphiglycan, ryudocan)
MLBCL	0.57	0.37	17346	INM_0022291*AA454711IHs.400124ljun B proto-oncogene
MLBCL	0.57	0.37	35220	IM150591*AA829959IHs.1416lFc fragment of IgE, low affinity II, receptor for (CD23A)
MLBCL	0.57	0.36	19267	IM594651*AA281660IHs.211600ltumor necrosis factor, alpha-induced protein 3
MLBCL	0.57	0.35	19233	IU458781*AA252610IHs.127799lbaculoviral IAP repeat-containing 3
MLBCL	0.53	0.35	28770	IY009851*AA488084IHs.372783lsuperoxide dismutase 2, mitochondrial
MLBCL	0.53	0.34	16418	IAF0101931*R82176IHs.100602lMAD, mothers against decapentaplegic homolog 7 (Drosophila)
MLBCL	0.52	0.34	17626	IX637171*N75066IHs.82359ltumor necrosis factor receptor superfamily, member 6
MLBCL	0.51	0.33	30589	IU458781-AA252610IHs.127799lbaculoviral IAP repeat-containing 3
MLBCL	0.5	0.32	24499	IM690431*AA809576IHs.81328lnuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha
MLBCL	0.49	0.32	24829	IM690431*AA489208IHs.81328lnuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha
MLBCL	0.49	0.31	26357	IU192611*R505341IHs.2134lTNF receptor-associated factor 1
MLBCL	0.49	0.31	28708	IU844871*R66139IHs.80420lchemokine (C-X3-C motif) ligand 1
MLBCL	0.49	0.30	26487	IX682771-W90037IHs.171695ldual specificity phosphatase 1
MLBCL	0.47	0.30	28424	IM690431*W56300IHs.81328lnuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha
MLBCL	0.47	0.29	25209	IM548941IHs.93913linterleukin 6 (interferon, beta 2)
MLBCL	0.46	0.29	24405	IK144541*AA766637IHs.80645linterferon regulatory factor 1
MLBCL	0.46	0.28	34761	IM594651-AA281660IHs.211600ltumor necrosis factor, alpha-induced protein 3
MLBCL	0.45	0.28	27211	IM242831*N68859IHs.168383lintercellular adhesion molecule 1 (CD54), human rhinovirus receptor
MLBCL	0.45	0.28	26533	INM_0038971*AA034912IHs.76095limmediate early response 3
MLBCL	0.45	0.28	27490	IX682771-AA149095IHs.171695ldual specificity phosphatase 1
MLBCL	0.44	0.27	26517	IX682771*W90037IHs.171695ldual specificity phosphatase 1
MLBCL	0.44	0.27	15921	IU192611*R71691IHs.2134lTNF receptor-associated factor 1
MLBCL	0.44	0.26	29574	IM320111*AA535007IHs.9491neutrophil cytosolic factor 2 (65kDa, chronic granulomatous disease, autosomal 2)
MLBCL	0.42	0.26	26488	IX682771-AA149095IHs.171695ldual specificity phosphatase 1
MLBCL	0.42	0.25	28599	IK144541*AA478043IHs.80645linterferon regulatory factor 1
MLBCL	0.42	0.25	17871	IX682771-AA149095IHs.171695ldual specificity phosphatase 1
MLBCL	0.42	0.25	15851	INM_0029821*AA425102IHs.303649lchemokine (C-C motif) ligand 2
MLBCL	0.41	0.24	16398	IM594651-R70479IHs.211600ltumor necrosis factor, alpha-induced protein 3
MLBCL	0.4	0.24	26987	IX682771*R27999IHs.171695ldual specificity phosphatase 1
MLBCL	0.39	0.24	16046	IU316281*AA054754IHs.12503linterleukin 15 receptor, alpha
MLBCL	0.36	0.23	34426	INM_0029821*R76806IHs.303649lchemokine (C-C motif) ligand 2
MLBCL	0.36	0.22	23950	I2195541*AI240349IHs.297753lvinmentin
MLBCL	0.35	0.22	24718	IM377801*AA713790IHs.78146lplatelet/endothelial cell adhesion molecule (CD31 antigen)
MLBCL	0.35	0.22	19339	IL315811IHs.1652lchemokine (C-C motif) receptor 7
MLBCL	0.34	0.22	31845	IU316281*AA054754IHs.12503linterleukin 15 receptor, alpha
MLBCL	0.34	0.21	32679	ID420431*AA243583IHs.79123lraft-linking protein
MLBCL	0.34	0.21	30027	IL411421*AA215499IHs.167503lsignal transducer and activator of transcription 5A
MLBCL	0.33	0.21	29329	IL411421*W009739IHs.167503lsignal transducer and activator of transcription 5A
MLBCL	0.32	0.20	34886	IM690431*AI281594IHs.81328lnuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha
MLBCL	0.32	0.20	27478	IX682771*AA149095IHs.171695ldual specificity phosphatase 1
MLBCL	0.32	0.19	34226	IU773961IHs.76507lipopolysaccharide-induced TNF factor
MLBCL	0.29	0.19	17806	IU844871*H17124IHs.80420lchemokine (C-X3-C motif) ligand 1
MLBCL	0.29	0.19	27399	IX605921*AA203290lICD40
MLBCL	0.29	0.19	26474	IM234521-W74288IHs.73817lchemokine (C-C motif) ligand 3
MLBCL	0.28	0.19	19291	IX660871*AA504350IHs.300592lv-myb myeloblastosis viral oncogene homolog (avian)-like 1
MLBCL	0.27	0.18	27384	IU970741*AA002262IHs.195175lCASP8 and FADD-like apoptosis regulator
MLBCL	0.27	0.18	16751	INM_001511*W42723IHs.7891chemokine (C-X-C motif) ligand 1 (melanoma growth stimulating activity, alpha)
MLBCL	0.26	0.17	27065	IU844871-H17124IHs.80420lchemokine (C-X3-C motif) ligand 1
MLBCL	0.25	0.17	29384	IK551881*AA743946IHs.56729lymphocyte-specific protein 1
MLBCL	0.24	0.17	24988	IM660871*AA836095IHs.300592lv-myb myeloblastosis viral oncogene homolog (avian)-like 1
MLBCL	0.24	0.17	15850	IU041301*H62864IHs.75703lchemokine (C-C motif) ligand 4
MLBCL	0.24	0.16	17082	IZ195541*AA131209IHs.297753limentin
MLBCL	0.23	0.16	28586	IM598071*AA458965IHs.943lnatural killer cell transcript 4
MLBCL	0.22	0.15	30246	ID420431*AA457047IHs.79123lraft-linking protein
MLBCL	0.22	0.15	19376	IM598071*N90140IHs.943lnatural killer cell transcript 4
MLBCL	0.21	0.14	26356	IU192611-R71691IHs.2134lTNF receptor-associated factor 1
MLBCL	0.2	0.14	19219	IU970741*AA281075IHs.195175lCASP8 and FADD-like apoptosis regulator
MLBCL	0.2	0.14	28410	IU041301*H62864IHs.75703lchemokine (C-C motif) ligand 4
MLBCL	0.2	0.13	30468	IU041301IHs.75703lchemokine (C-C motif) ligand 4
MLBCL	0.19	0.13	16822	IM234521*W74288IHs.73817lchemokine (C-C motif) ligand 3
MLBCL	0.18	0.13	28201	IS814391-H99660IHs.82173lTGFB inducible early growth response
MLBCL	0.18	0.13	26409	IU041301-N29753IHs.75703lchemokine (C-C motif) ligand 4
MLBCL	0.17	0.12	16425	IU207701*R479651IHs.323949lkangai 1 (suppression of tumorigenicity 6, prostate; CD82 antigen (R2 leukocyte anti
MLBCL	0.16	0.12	27000	IX551881*R766981IHs.56729lymphocyte-specific protein 1
MLBCL	0.15	0.12	31194	ID509251-AA427740IHs.79337lPAS domain containing serine/threonine kinase
MLBCL	0.15	0.11	17679	ID104951*AA005215IHs.155342lprotein kinase C, delta
MLBCL	0.15	0.11	28695	IU773961IHs.76507lipopolysaccharide-induced TNF factor
MLBCL	0.15	0.11	16454	I2231151*H09884IHs.305890IBCL2-like 1
MLBCL	0.14	0.10	28014	IX660871*AA768961IHs.300592lv-myb myeloblastosis viral oncogene homolog (avian)-like 1
MLBCL	0.14	0.09	24267	I2231151*N70813IHs.305890IBCL2-like 1
MLBCL	0.14	0.09	26572	IS814391*AA045731IHs.82173lTGFB inducible early growth response
MLBCL	0.12	0.09	16426	INM_0029831*R47893IHs.73817lchemokine (C-C motif) ligand 3
MLBCL	0.12	0.09	28967	ID104951*AA005215IHs.155342lprotein kinase C, delta
MLBCL	0.1	0.08	16034	IM598071*AA458965IHs.943lnatural killer cell transcript 4

**Table 5:** Permutation results corresponding to the analysis shown in Fig. 5

**Table 6:** Comparison between the NFkB target gene signatures in this series of MLBCls (34 MLBCls vs. 176 unselected DLBCLs) and an independent series of MLBCls (38 MLBCls vs. 26 selected DLBCLs [13 GCB and 13 ABC-like DLBCL])

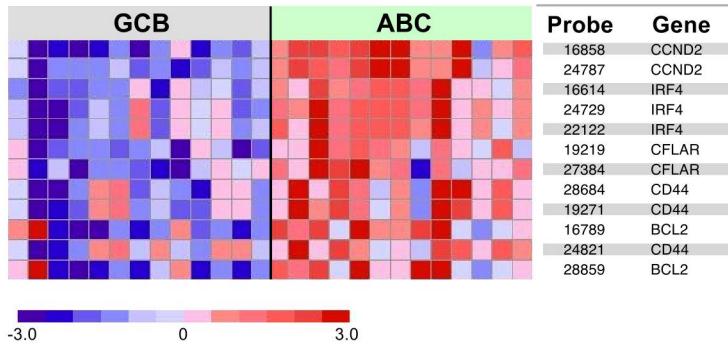
Gene name	This series	Independent series	Reference*
BCL2L1	✓	✓	1,2
CCL2	✓	✓	3
CCL3	✓	✓	1,2
CCL4	✓	✓	2
CFLAR	✓	✓	2
DUSP1	✓	✓	3
CCR7	✓	✓	1,2
CD23A	✓	✓	2
IER3	✓	✓	1
IL6	✓	✓	1,3
IRF1	✓	✓	1,2
JUNB	✓	✓	2,3
NCF2	✓	✓	1
NFKBIA	✓	✓	2,3
PASK	✓	✓	1
PCAM1	✓	✓	2
PKCD	✓	✓	1
RAFTLIN	✓	✓	1
SDC4	✓	✓	3
SMAD7	✓	✓	1
SOD2	✓	✓	3
TNFAIP3	✓	✓	2,3
TNFRSF5	✓	✓	2
TNFRSF6	✓	✓	1
TRAF1	✓	✓	1,2
VIM	✓	✓	1
CD44	✓		1,2
CD69	✓		2
CCL22	✓		1
IL4RA	✓		2
IL8	✓		2
SLC2A5	✓		1
BCL2A1	✓		1,2
ICAM1**		✓	1,2
IL15RA**		✓	1
STAT5A**		✓	1
MYB**		✓	2
NFKB2**		✓	1,2
NK4**		✓	3
LITAF		✓	1
LSP1		✓	1
KAI1		✓	2
KLF10		✓	1
BIRC3		✓	1,2

\*Source of genesets: (1) Geneset 1, Ref. <sup>2</sup>, (2) Geneset 2, Ref. <sup>4</sup> and Ref. <sup>3</sup>, (3) Geneset 3, Ref. <sup>5</sup>

\*\* The indicated NFkB targets are upregulated in HR DLBCLs <sup>1</sup> (Figure 4, Supplementary Information) and may not be well represented in the small independent comparison group of preselected GCB and ABC-like DLBCLs<sup>9</sup>.

Note: 2 genes (TNIP2 and EMR1) that were part of the Affymetrix-based MLBCl signature were not represented on the Lymphochip, and 2 genes (CXCL1 and CX3CL1) that were part of the Lymphochip-based MLBCl signature were not within the 15k MAD-filtered geneset.

**Figure 6:** Confirmation of the NF $\kappa$ B activation signature in an independent data set. The full publicly available gene expression data set (provided as supplemental information with Ref. <sup>9</sup>, , <http://lmp.nih.gov/PMBL/>) encompassing 26 DLBCL (13 GCB-like and 13 ABC-like) was included in this analysis. The permutation results are listed in table 7.



Class	Score	99th percentile	Probe ID	Description
ABC	1.42	1.06	16858	ID13639I*AA026336IHs.75586 cyclin D2
ABC	1.41	0.98	24787	ID13639I*AA831970IHs.75586 cyclin D2
ABC	1.19	0.90	16614	IU52682I*N33454IHs.82132 interferon regulatory factor 4
ABC	1.17	0.85	24729	IU52682I*AA743459IHs.82132 interferon regulatory factor 4
ABC	0.9	0.80	22122	IU52682I*AI087048IHs.82132 interferon regulatory factor 4
ABC	0.9	0.76	19219	IU97074I*AA281075IHs.195175 CASP8 and FADD-like apoptosis regulator
ABC	0.88	0.75	27384	IU97074I*AA002262IHs.195175 CASP8 and FADD-like apoptosis regulator
ABC	0.74	0.71	28684	IX56794I*AA283090IHs.169610 CD44 antigen (homing function and Indian blood group system)
ABC	0.69	0.69	19271	IX56794I*AA283090IHs.169610 CD44 antigen (homing function and Indian blood group system)
ABC	0.66	0.67	16789	IM14745I*W63749IHs.79241 B-cell CLL/lymphoma 2
ABC	0.64	0.64	24821	IX56794I*AA279047IHs.169610 CD44 antigen (homing function and Indian blood group system)
ABC	0.62	0.62	28859	IM14745I*W63749IHs.79241 B-cell CLL/lymphoma 2

Gene name	This series*	Independent series	Reference**
BCL2	✓	✓	2
CCL22	✓		1
CCND2	✓	✓	2
CCR7	✓		1,2
CD44	✓	✓	1,2
CFLAR	✓	✓	2
C4orf9	✓		1
EGR1	✓		3
IL2RA	✓		2
IL6	✓		1,3
IRF4	✓	✓	2
LITAF	✓		1
NCF2	✓		1
SLC2A5	✓		1

**Table 7:** Permutation results corresponding to the analysis shown in Fig. 6

**Table 8:** Comparison between the NF $\kappa$ B target gene signature in this series of ABC-like DLBCLs (vs. GCB and “other”) and an independent series of ABC-like DLBCLs (vs. only GCB)

\*In our data set, 40% of DLBCLs type as “other”, whereas the preselected independent series includes only “GC-type” and “ABC-like” DLBCLs (no “other” DLBCLs). These differences in the DLBCL groups may account for the higher number of differentially expressed NF $\kappa$ B target genes in our series.

\*\*Source of genesets: (1) Geneset 1, Ref. <sup>2</sup>, (2) Geneset 2, Ref. <sup>4</sup> and Ref. <sup>3</sup>, (3) Geneset 3, Ref. <sup>5</sup>

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