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Research Article

JOURNAL OF BIOINFORMATICS AND SYSTEMS BIOLOGY

ISSN: 2688-5107

Control of Expression Level in Human Genes: Observations with Apoptosis Genes and Genes Involved in B cell Development

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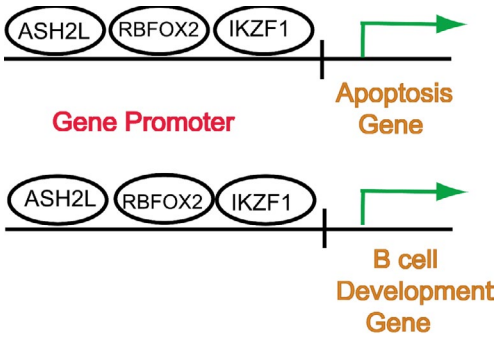
Abstract

To understand the way a gene functions in development, one needs to know about the gene product's functional capabilities, the tissues where it is located, and the level of its expression. It is now widely accepted that transcription factors can affect the level of gene expression, but the results emphasize the need for further clarification. The study described here was carried out to determine whether the amount of a transcription factor bound in the promoter region might be directly related to the level of the gene's expression. The study was focused on a population of human genes involved in apoptosis, a pathway known to be affected by the transcription factor Ikaros (IKZF1 gene). For each apoptosis gene, information was accumulated about its expression level and about the level of IKZF1 binding in the promoter. The two measurements were then compared and interpreted to identify instances where the amount of IKZF1 binding is related to the level of gene expression. A similar analysis was carried out with genes involved in B cell development, also a gene population influenced by IKZF1. The results identified gene groups, each containing 3-8 genes, in which the expression level was related to IKZF1 binding in the promoter, a result that supports the idea that promoter bound IKZF1 can affect the level of gene expression. A further study was performed to examine the secondary, non-IKZF1 transcription factors bound in the promoters of apoptosis and B cell development genes. Prominent amounts of RBFOX2, ASH2L and TAF1 were observed in both populations suggesting IKZF1-rich promoters may resemble each other in their content of other transcription factor binding sites as well.



Graphical Abstract

Keywords: gene expression, transcription factor, promoter, IKZF1, apoptosis, B cell development

Introduction

Control of gene expression is one of the most actively studied areas of molecular biology today, and this has been the case for more than half a century. The effort has been highly productive. As a result, we now have an advanced understanding of regulatory control as it occurs in a wide variety of organisms including humans. Relevant features uncovered include the role of transcription factors, enhancers, epigenetic modifications, and the way chromatin architecture

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Citation: Jay C. Brown. Control of Expression Level in Human Genes: Observations with Apoptosis Genes and Genes Involved in B cell Development. Journal of Bioinformatics and Systems Biology 5 (2022): 108-115.

Received: July 11, 2022
Accepted: July 20, 2022
Published: July 29, 2022

Jay C. Brown, J Bioinform Syst Biol 2022
DOI:10.26502/jbsb.5107038

can affect gene expression [1-4]. A neglected area, however, has been an identification of factors that affect the quantitative level of expression. Studies have addressed whether a gene is on or off but avoided the issue of whether expression is high, medium, or low. It is expected that the same factors that affect expression will also affect the level of expression, but one would like to have additional information about how such functions operate.

The study described here was designed to confront the issue of expression level directly. The goal was to test the role of a promoter bound transcription factor with the level of gene expression. Analysis was focused on a single transcription factor, Ikaros (IKZF1) and a population of 56 human genes involved in apoptosis, a system whose function is known to be affected by IKZF1 [5]. For each apoptosis gene, two values were identified, (1) the level of expression and (2) the amount of IKZF1 bound at the promoter. The values were then plotted, and the plots were interpreted to indicate whether IKZF1 was affecting expression of a gene and if so then whether the effect was to potentiate or repress the level of expression. A similar analysis was carried out with 64 human genes involved in B cell development, a function also known to be regulated by IKZF1 [6-8]. The results identify several groups of genes in which promoter bound IKZF1 is correlated with the level of gene expression.

Materials and Methods

Gene databases

The study was performed beginning with two human gene populations, one of genes involved in apoptosis (Supplementary Table 1) and the other of B cell development genes (Supplementary Table 2). Apoptosis and B cell development genes were derived beginning with those reported by Jourdan et al. [5] and Calonga-Solis et al. [9], respectively. Transcription levels were derived from the GTEx Portal of RNA-seq results as reported in the UCSC Genome Browser (version hg38; https://genome.ucsc.edu/). ChIP-seq results for IKZF1 and control transcription factor binding to the gene promoter were obtained for GM12878 cells by way of the Integrated Genome Browser (https://igv.org/app/). Secondary, non-IKZF1 transcription factor binding sites were retrieved from the ENCODE Transcription Factor ChIP Clusters data base by way of the UCSC Genome Browser. For each gene reported, the list of TF binding sites from ENCODE was examined visually, and the number of binding sites was counted. The counts were used to identify the three most prevalent binding sites which were reported as TF rank 1-TF rank 3. Gene functions were retrieved from GeneCards (https://www.genecards.org/).

Table 1: Properties of apoptosis genes in proposed regulatory groups

Gene group	Gene	Chr	Gene Length (kb)	TF rank 1	TF rank 2	TF rank 3	Gene function
1	CASP1	11	9.7	IKZF1	TAF1	ZBTB33	apoptosis effector
	BIRC7	20	4.6	RBM39	ASH2L	SP1	inhibits apoptosis
	CASP4	11	25.7	ASH2L	EP300	REST	apoptosis effector
	CASP6	4	14.8	RBFOX2	AGO1	TAF1	apoptosis effector
	CASP10	2	38.5	CHD4	KDM1A	HDAC1	apoptosis effector
	BCL2L10	15	3.5	YY1	HDAC6	ZFX	regulates apoptosis
2	BCL2A1	15	10.3	IKZF1	MTA3	MLLT1	regulates apoptosis
	TNFRSF10B	8	48.9	IKZF1	RBFOX2	HDAC1	TNF receptor
	AIFM1	23	38.4	IKZF1	RBFOX2	RNF2	induces apoptosis
	CASP7	10	51.7	CTBP1	DPF2	IKZF1	apoptosis effector
	CASP8	2	53.1	IKZF1	ASH2L	RBFOX2	apoptosis effector
3	BCL2L2	14	9.4	IKZF1	PHF8	ASH2L	regulates apoptosis
	BCL2L1	20	59.5	IKZF1	RBFOX2	ASH2L	regulates apoptosis
	TNFRSF1A	3	17.9	IKZF1	MAX	REST	TNF receptor
	TNFSF1A	12	13.3	IKZF1	RBFOX2	HDAC1	TNF family cytokine
	TNFRSF11B	8	28.3	IKZF1	KDM4A	EZH2	TNF receptor
4	BAX	19	6.9	RBFOX2	HDAC1	IKZF1	regulates apoptosis
	FAS	10	23.7	TAF1	IKZF1	EZH2	TNF receptor
	FADD	11	4.1	RBFOX2	RNF2	MYC	regulates apoptosis

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DOI:10.26502/jbsb.5107038

Data analysis

Data were recorded with RStudio and Excel. Results were analyzed and rendered graphically with SigmaPlot 14.5.

Results

Experimental strategy

The goal of the project described here was to test the idea that binding of a transcription factor in the promoter region of a gene might affect the quantitative level of the gene's expression. It was expected this might be the case as transcription factors (TF) are known to affect whether a gene is expressed or not. It is reasonable therefore to consider that the same factors that affect on vs. off might also affect the degree of on. Also, the resources needed to carry out the test are readily available. The results of RNA-seq studies yield the required information about gene expression levels and ChIP-seq results provide promoter binding information. After accumulating the above information, the study involved plotting the level of gene expression (RNA-seq results) against the amount of promoter bound TF (ChIP-seq results) to determine if the plot indicates a relationship between the two values.

Apoptosis results

A plot of the apoptosis data yielded the expected result (Fig. 2a). The plot showed that the range examined was well-populated with points corresponding to individual apoptosis genes. For instance, of 56 apoptosis genes in the database, 43 are present in the plot. Red lines suggest the identify of genes that might be related to each other because their expression level is linearly related to IKZF1 level in the promoter. The genes between BCL2A1 and CASP8 are an example. Expression of these genes is inversely related to the level of IKZF1 bound to the promoter indicating that IKZF1 is acting repressively with the genes. For further analysis, a name was assigned to each of the four gene groups identified (Groups 1-4; see Fig. 2a). Only repressive relations are noted (red lines), but other groups including activating groups can be observed and are considered viable interpretations like the ones

Table 2: Properties of B cell development genes in proposed regulatory groups

Gene group	Gene	Chr	Gene Length (kb)	TF rank 1	TF rank 2	TF rank 3	Gene function
1	BACH2	6	370.4	EZH2	RBFOX2	EP300	control transcription
	RUNX2	6	222.8	TAF1	FOS	TAF7	transcription factor
	PTPRC	1	118.4	MTA3	ATF7	MLLT1	protein phosphatase
	MRE11	11	78.6	ZFX	SMAD5	HDAC1	DNA repair
	NHEJ1	2	91.5	KDM1A	EP300	HDAC2	DNA repair
	GAB1	4	137.8	ASH2L	RBFOX2	RBBP5	adaptor protein
	CREBBP	16	155.7	RBFOX2	DPF2	TAF1	histone acetylation
	RPA2	1	23.1	RBFOX2	HNRNPLL	L3MBTL2	DNA repair
2	TLR1	4	8.5	IKZF1	MLLT1	MEF2B	pathogen recognition
	POU2F2	19	46.5	EZH2	SMC3	PCBP1	transcription factor
	TRAF1	9	26.8	IKZF1	RBFOX2	ASH2L	TNF receptor subunit
	JAK1	1	234.5	RBFOX2	HDAC2	RBBP5	protein tyr kinase
	PRKACA	19	26.1	RBFOX2	ZBTB7A	TAF1	protein kinase A
3	IL4	5	8.7	IKZF1	GATAD2B	DPF2	cytokine
	BATF	14	24.5	IKZF1	RCOR1	ZNF217	transcription factor
	TRAF1	9	26.8	IKZF1	RBFOX2	ASH2L	TNF receptor subunit
	ELF1	13	87.4	ASH2L	HDAC1	CHD1	transcription factor
4	DCLRE1C	10	49.5	RBFOX2	DPF2	IKZF1	DNA repair
	CD86	3	65.8	IKZF1	DPF2	CBX5	T cell activation
	TRAF1	9	26.8	IKZF1	RBFOX2	ASH2L	TNF receptor subunit
	TCF3	19	43.3	RBFOX2	KDM4A	BRD4	transcription factor
5	RUNX1	21	261.5	IKZF1	MTA3	ZBED1	transcription factor
	RUNX3	1	65.5	MLLT1	IKZF1	DPF2	transcription factor
	NFKB1	4	115.9	TAF1	RBFOX2	IKZF1	transcription factor
	NBN	8	51.3	IKZF1	ATF2	EP300	DNA repair
	RELA	11	9.3	IKZF1	ASH2L	RBFOX2	NFKB subunit

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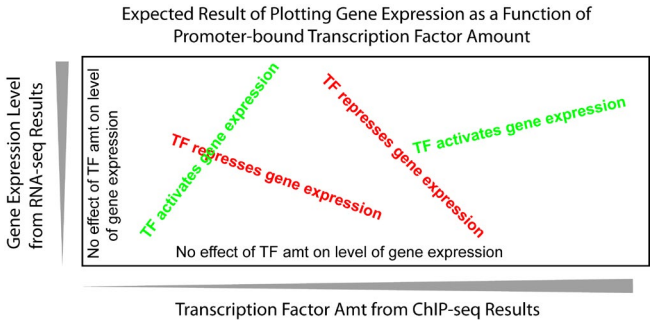

Figure 1: Graph showing the expected result when gene transcription level (y axis) is plotted against the amount of transcription factor bound in the promoter (x axis). Points with a negative slope (red text) indicate the transcription factor is acting to repress transcription. A positive slope (green text) is expected if the transcription factor is acting to potentiate expression. Data points near the axes (black text) are expected if the transcription factor has little effect on transcription.

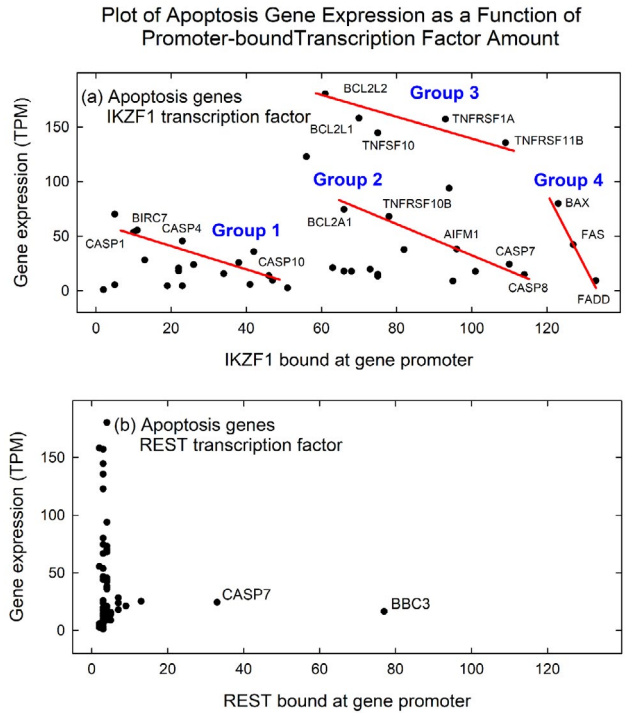

Figure 2: Graph showing the level of apoptosis gene expression plotted against the level of promoter bound IKZF1 (a) and REST (b). Note that most genes are in the dynamic range of the IKZF1 plot indicating their expression is affected by the presence of IKZF1. In contrast, most genes in the REST plot are in the range expected if the transcription factor has little effect on gene expression.

suggested. A control experiment was performed in which ChIP-seq results from the transcription factor REST were substituted for IKZF1 (Fig. 2b). REST was considered to be an appropriate control transcription factor as it has not been implicated in regulation of apoptosis genes. Results demonstrated that few apoptosis genes are found in the same range of the plot observed for IKZF1 genes. Two are CASP7 and BBC3 (see Fig. 2b). The results are interpreted to indicate that other transcription factors do not have the same influence on apoptosis gene expression as IKZF1. Together the experimental and control studies suggest the identification of several apoptosis gene groups (Fig 2a) in which promoter bound IKZF1 is related to the level of gene expression

B cell development genes

A similar analysis was carried out with genes in the B cell development database. Fig. 3a shows a plot of gene expression against IKZF1 promoter binding for 59 of the 64 B cell development genes. As in the case of apoptosis genes, groups are suggested in which gene expression is related to IKZF1 binding (Groups 1-5). Among the B cell development genes, two groups contain genes in which IKZF1 is interpreted to exert a repressive effect on transcription level (Groups 2 and 4) while in the other three groups IKZF1 is activating (Groups 1, 3 and 5). A control study was performed in which the transcription factor SMC3 was substituted for IKZF1, and the results were plotted against gene expression. The results demonstrated little evidence of genes with the same expression/transcription factor values observed with IKZF1 (Fig. 3b). As with the apoptosis genes, the results with B cell development genes are interpreted to suggest the existence of specific gene groups in which expression is related to IKZF1 binding in the promoter.

Transcription factor binding sites in the promoters of expression group member genes Identification of apoptosis genes related by their response to IKZF1 suggested group members might be related in other ways that would be revealing

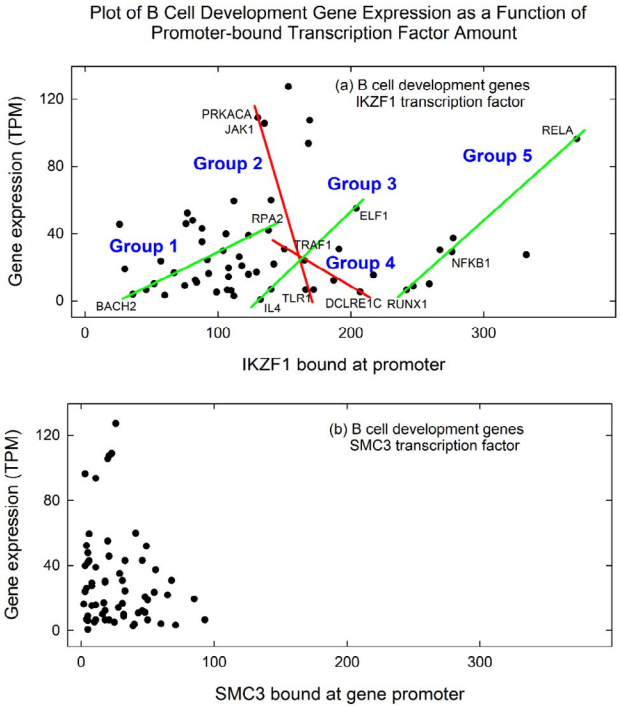

Figure 3: Graph showing the level of B cell development gene expression plotted against the level of promoter bound IKZF1 (a) and SMC3 (b). Note that most genes are in the dynamic range of the IKZF1 plot indicating their expression is affected by the presence of IKZF1. In contrast, most genes in the SMC3 plot are in the range expected if the transcription factor has little effect on gene expression.

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DOI:10.26502/jbsb.5107038

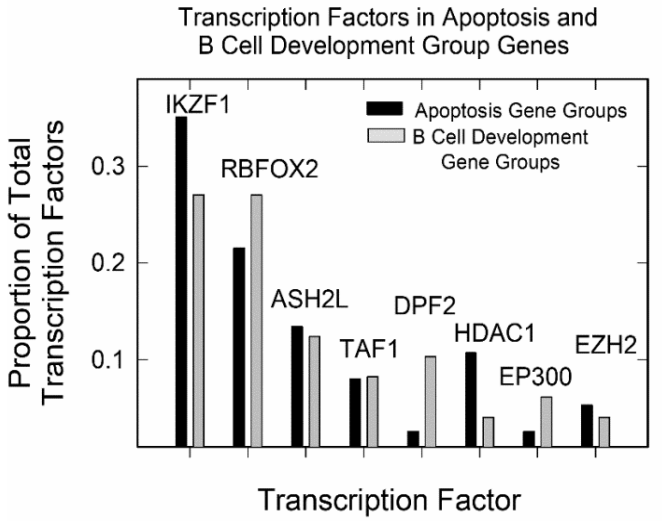

Figure 4: Plot comparing the transcription factor binding sites in apoptosis and B cell development genes. The plot includes all TF binding sites in the two gene populations, 57 for apoptosis genes and 78 for B cell development. Note the similarity observed in the proportion of IKZF1, RBFOX2, ASH2L, TAF1 and EZH2 in the two gene populations.

about the control of their expression. Additional information about gene group members was therefore accumulated and compared. Features examined were gene chromosome, gene length, gene function, and the presence of non-IKZF1 binding sites in the promoter. The latter measure involved rank ordering TFs according to their binding site abundance in the promoter. TFs with higher rank were those that have greater abundance. Information accumulated about apoptosis group genes was also accumulated for B cell development genes.

Apoptosis gene groups

The results with apoptosis group genes show little similarity in chromosome or gene length (Table 1). For instance, no two genes are on the same chromosome in groups 2, 3 and 4. This result was expected and suggests much of the information relevant to control of gene expression is present in the local area of the gene. Some evidence of grouping by gene function was evident (Table 1). For instance, four of the six genes in group 1 encode caspases (i.e. CASP1, CASP4, CASP6 and CASP10). Three of the 5 genes in group 3 encode proteins involved in tumor necrosis factor function.

The role of TFs other than IKZF1 was probed by examining the abundance of their binding sites in apoptosis gene promoters. Binding site abundance was rank ordered beginning with data from ENCODE as described in Materials and Methods. The top three TFs are reported for each apoptosis gene (Table 1). As expected, IKZF1 had the highest abundance among rank 1 TFs with 10 of the 19 genes in the aggregate of the four apoptosis groups. A greater diversity was observed among rank 2 and 3 TFs. Among 15 rank 2 TFs, for instance, only two were represented more than once.

B cell development gene groups

As in the case of the apoptosis genes, genes in B cell development groups show little evidence of similarity in chromosome or gene length (Table 2). B cell development genes are enriched, however, in gene functions including transcription control and DNA repair. For example, 3 of 8 group 1 genes encode aspects of DNA repair (Table 2). Three of five group 5 genes are TFs.

Comparison of TFs in apoptosis and B cell development gene promoters

The availability of rank ordered TF binding sites in apoptosis and B cell development promoters made it possible to compare binding sites in the two gene populations. While both populations were found to be enriched in IKZF1 binding sites in the promoter, one could now ask whether there was a similarity in less abundant TF binding sites as well. An analysis was performed beginning with all 57 binding sites recorded in grouped apoptosis genes (i.e., ranks 1-3), and the same binding sites (78) for B cell development genes. For each binding site present, the number was counted, expressed as a proportion of the total and the proportion plotted.

Results for the 8 most abundant TFs are shown in Fig. 4. They demonstrate a similarity between apoptosis and B cell development in 5 of the 8 TFs in the plot (i.e., IKZF1, RBFOX2, ASH2L TAF1 and EZH2). B cell development gene promoters are enriched in DPF2 and EP300 while apoptosis genes are enriched in HDAC1. The results are interpreted to emphasize the similarities in the apoptosis and B cell development gene promoters. The similarity in IKZF1 (Fig. 4) was expected as the gene populations were selected because of their response to IKZF1. The other four similarities are novel and suggest that high abundance of one of the five TFs in the promoter is correlated with high abundance of the others.

Discussion

A reliable strategy was employed here for exploring how the level of gene expression is controlled. Plot the level of gene expression against the level of promoter bound TF, and if a relationship exists, then the plot should reveal it. In the study described here, the chances of success were increased by the use of gene populations, apoptosis genes and B cell development genes, whose function was known to be influenced by IKZF1 [5-7]. The study also benefitted from the availability of information about the level of gene expression and about the extent of transcription factor binding at the promoter.

The results yielded a gratifying number of genes in which expression was related to IKZF1 promoter binding, 43 of 56 in the case of apoptosis genes and 59 of 64 for B cell development. This finding supports the view that IKZF1 has an important role in controlling the genes of the two systems examined. Also, the method proved very good in discriminating regulation due to IKZF1 from that of the control transcription factors, REST in the case of apoptosis genes and SMC3 for B cell development. A significantly greater number of responsive genes were identified

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DOI:10.26502/jbsb.5107038

with IKZF1 compared to the control TFs (see Figs. 2 and 3). The method therefore suggests itself for a role in future studies aiming to distinguish active from inactive TFs for a specific gene population.

It was expected that this study would reveal the observed abundance of IKZF1 binding sites in the promoters of apoptosis and B cell development genes. The two gene populations were chosen for study because of their dependence on Ikaros. Not expected, however, was the observed similarity in non-IKZF1 TF binding sites such as RBFOX, ASH2L and TAF1 (Fig. 4). The result suggests that similar gene regulatory elements may be found in genes in the same functional system [12]. Use of such similar control mechanisms may be an asset in integrating the elements of a functional pathway during evolutionary adaptation.

It was also unexpected to note the relative homogeneity in the most abundant TF in both the apoptosis and B cell development gene populations (10 of 19 genes in the case of apoptosis genes and 10 of 26 in B cell development). The result suggests there may be a special significance attached to the most abundant TF in the genes examined. Possibilities include specificity for co-factor binding or interaction with enhancers. The observation is an intriguing one that justifies further investigation.

Competing interests

The authors declare that there are no conflicts of interest.

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DOI:10.26502/jbsb.5107038

SUPPLEMENTARY FILES

Supplementary Table 1: All apoptosis genes used in this study: 56 genes

Gene	Gene expression[a]	IKZF1 ChIP-seq signal[b]	REST ChIP-seq signal[c]
AIFM1	38.2	96	4
APAF1	8.9	189	5
BAD	66.7	427	3
BAK1	35.9	42	4
BAX	80	123	3
BBC3	16.5	144	77
BCL2	23.8	173	7
BCL2A1	74.5	66	3
BCL2L1	180.4	61	4
BCL2L10	9.7	47	3
BCL2L11	17.9	66	7
BCL2L12	20.9	22	4
BCL2L13	19.7	73	3
BCL2L14	4.6	19	2
BCL2L2	158.1	70	2
BID	37.7	82	4
BIK	23.9	26	3
BIRC2	46.5	808	3
BIRC3	43.6	175	4
BIRC5	13.4	75	3
BIRC6	17.8	68	4
BIRC7	55.5	11	2
BMF	14.3	172	4
BNIP3	73	429	4
BNIP3L	122.8	56	3
BOK	70.2	5	4
CASP1	53.6	10	3
CASP10	13.9	46	5
CASP2	3	325	3
CASP3	21.2	63	9
CASP4	45.6	23	4
CASP5	5.5	5	3
CASP6	25.8	38	3
CASP7	24.3	110	33
CASP8	14.9	114	3
CASP9	28.3	13	7
CFLAR	68	277	4
CYCS	93.9	94	4
DIABLO	18.1	22	185
ENDOG	15.1	75	5
FADD	9.4	133	3
FAS	42.3	127	4
FASLG	5.8	41	2
HRK	4.6	23	248
HTRA2	44	254	3
NAIP	1	2	3
PMAIP1	25.3	184	13
TNF	9	95	4
TNFRSF10A	12.6	172	3
TNFRSF10B	68	78	4
TNFRSF10C	2.6	51	2
TNFRSF10D	17.7	101	3
TNFRSF11B	135.6	109	3
TNFRSF1A	157.1	93	3
TNFSF10	144.6	75	3
XIAP	15.7	34	5

[a] TPM; NIH Genotype-Tissue Expression Project, Version 8, August 2019.

[b] ChIP-sep signal p-value; GM12878 cells; downloaded from IGV, experiment

ENCSR874AFU, accession ENCFF678BHT.

[c] ChIP-seq signal p-value; GM12878 cells; downloaded from IGV, experiment

ENCSR000BGF, accession ENCFF898SKK.

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DOI:10.26502/jbsb.5107038

Supplementary Table 2: All B cell development genes used in this study: 64 genes

Gene	Gene expression[a]	IKZF1 ChIP-seq signal[b]	SMC3 ChIP-seq signal[c]
BACH2	3.7	36	40
BATF	6.6	140	4
CD40	42.7	533	6
CD86	11.9	187	46
CHEK2	8.8	75	5
CREBBP	38.7	123	11
CUX1	30.6	191	68
DCLRE1C	5.1	207	10
E2F3	12.1	83	18
E2F6	9.8	259	32
ELF1	54.8	204	20
ERCC1	51.7	639	49
ETS1	93.5	168	11
GAB1	24.1	92	33
IKBKB	42.9	508	46
IKZF2	10.7	84	43
IL15	4.9	99	25
IL4	0.5	132	5
INPP5D	27.2	332	8
JAK1	107.3	169	21
JAK3	16	93	2
MAP3K14	19.3	108	85
MDC1	39.6	106	3
MRE11	16.4	67	31
NBN	37.1	277	56
NFKB1	29	276	8
NHEJ1	18.7	30	50
PARP1	59.2	112	6
PIK3R1	59.7	140	41
PMS2	14	108	28
POU2F1	11	1095	48
POU2F2	6.4	172	93
PRKACA	108.8	130	23
PRKDC	25.9	116	4
PTPRC	9.9	52	16
RAD50	16.8	129	17
RELA	96.2	370	3
RELB	29.6	104	18
RPA1	34.9	88	29
RPA2	41.7	138	5
RPA3	20.5	118	48
RUNX1	8.5	247	32
RUNX2	6.3	46	21
RUNX3	6.3	242	18
SMAD3	30.1	267	18
SMAD7	47.7	81	5
SP1	45.3	26	21
SPI1	23.3	57	55
SUPT5H	105.4	135	20
SWAP70	42.8	88	33
TCF3	30.5	150	31
TGFB1	127.3	153	26
TGFBR1	21.6	142	65
TLR1	6.4	166	11
TLR5	6.3	107	50
TLR6	2.6	112	39
TLR9	3.1	60	71
TNFRSF8	3.9	526	60
TNFSF13	45.7	76	21
TNFSF13B	6	110	5
TRAF1	23.8	165	3
TRAF2	15.5	123	11
TRAF3	15.1	217	8
XRCC4	52	77	4

[a] TPM; NIH Genotype-Tissue Expression Project, Version 8, August 2019.

[b] ChIP-seq signal p-value; GM12878 cells; downloaded from IGV, experiment

ENCSR874AFU, accession ENCFF678BHT.

[c] ChIP-seq signal p-value; GM12878 cells; downloaded from IGV, experiment

ENCSR000DZP, accession ENCFF179PKD.