TFEB explorer

https://tfeb.tigem.it/

A RESOURCE to study the effect of TFEB expression on the expression of genes of interest in three different species (human, mouse and rat) and to visualize already established TFEB direct targets and to predict others.

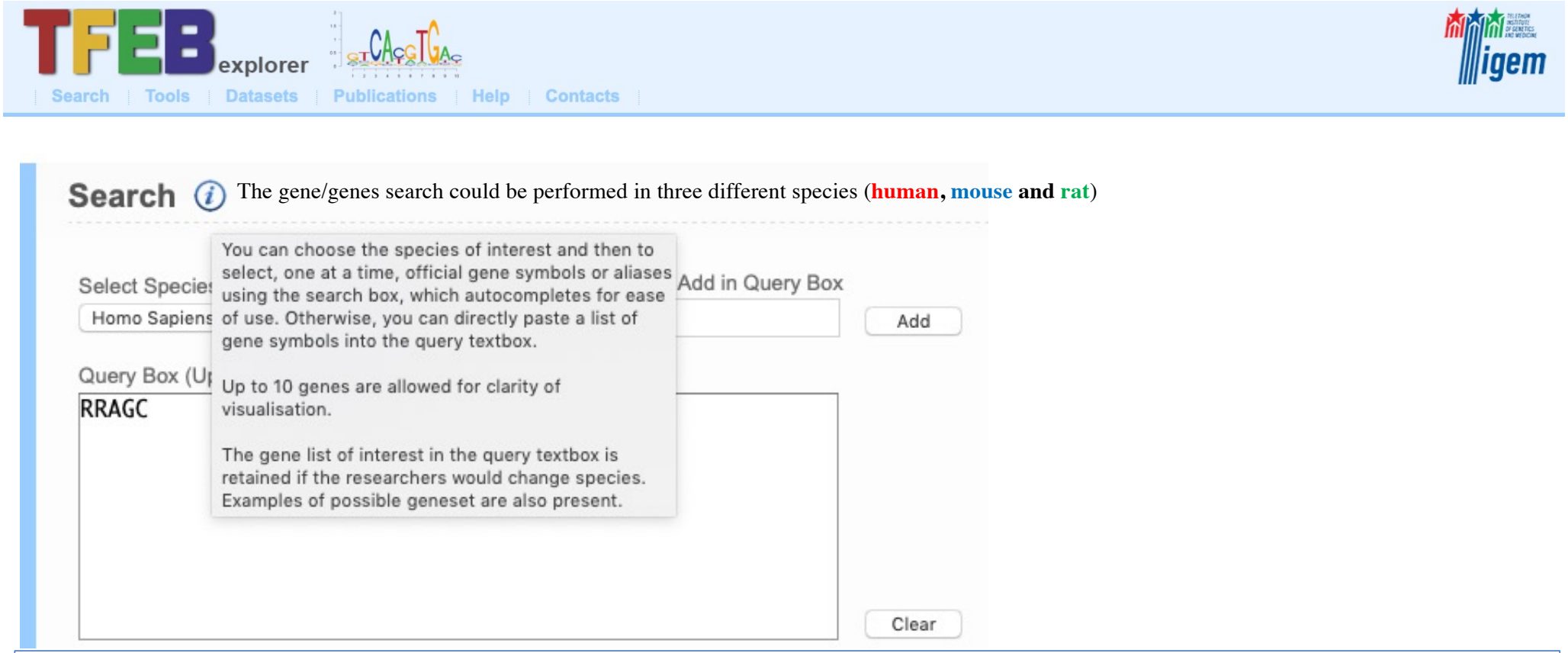
Data produced by Ballabio's and di Bernardo's lab at the Telethon Institute of Genetics and Medicine (TIGEM), Pozzuoli (NA), Italy.

Please contact:

Diego Carrella for web tool related enquiries.
Rossella De Cegli for methodological enquiries.
Diego di Bernardo as the project coordinator.

Browser compatibility

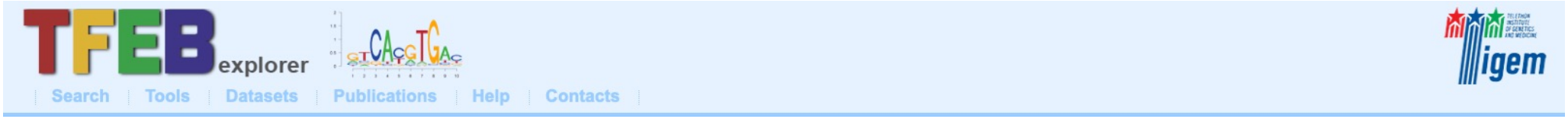
OS	Version	Chrome	Firefox	Microsoft Edge	Safari
Linux	Ubuntu 20.04	96.0.4664.45	94.0	n/a	n/a
MacOS	Mojave 10.14.6	96.0.4664.55	68.0.2	n/a	14.1.2
Windows	10	96.0.4664.45	94.0.1	96.0.1054.29	n/a



Overview

TFEBdb is a unique resource for those interested in understanding the effect of TFEB on a set of genes of interest.
The database offers an intuitive interface and results are displayed in an easy-to-interpret format offering information on the expression changes following inducible overexpression, knock-down and knock-out of TFEB across cell lines and species together with the experimental validated and bioinformatically predicted binding sites in the proximal promoter of the gene(s) of interest.

http://tfeb.tigem.it



The output of the query is displayed across different panels:

1. the "TFEB gene perturbation" section with the time series panel which reports the expression dynamics of the queried gene following inducible overexpression of TFEB in Hek293 cells (GSE98247), and the queried gene-TFEB network;

2. the "gene expression profile" panel, which shows whether the gene was significantly differentially expressed in any of the gene expression dataset included in TFEBdb, by reporting its False Discovery Rate (FDR), fold-change and the signed ratio (negative values colored in green for inhibition, and positive values colored in red for induction);

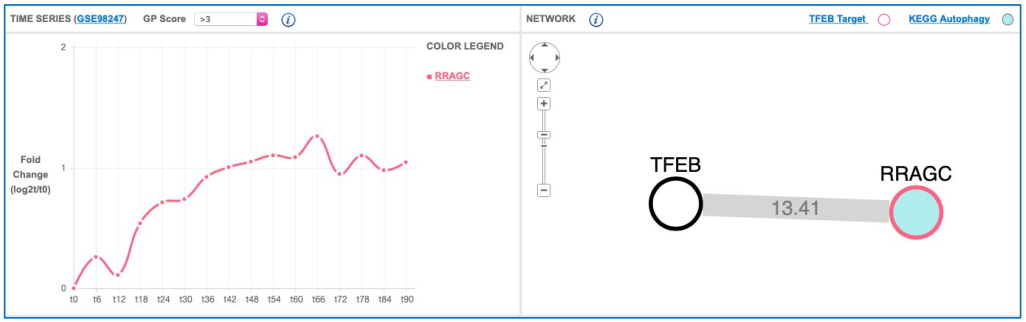
3. the "bioinformatic prediction of binding sites" panel reporting the predicted CLEAR motives in the proximal promoter of the gene;

4. the "experimental ChIP-seq" panel listing the chromosomal coordinated of ChIP-seq, confirmed binding sites in the promoter, if any.

TFEB gene perturbation

Expression dynamics of the queried gene following inducible overexpression of TFEB in Hek293 cells (GSE98247): the Tetracycline was removed at time 0h to induce TFEB expression and samples were collected every 6h up to 90h. The Time series include 16 time points.

The GP score: Gaussian process (GP) regression for estimating the continuous trajectories underlying in gene expression time-series.



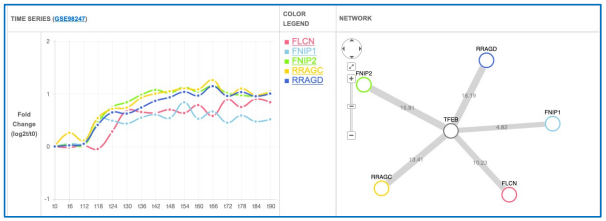
Gambardella, G., et al., Sci Adv, 2020. **6**(39).

NETWORK: Researchers can build TFEB network diagrams that are changing on the dynamic time-series data on their list of genes of interest. The nodes are the genes that are significantly perturbed (GP score >3), and the thickness of the arch is positively related to the experimental score.

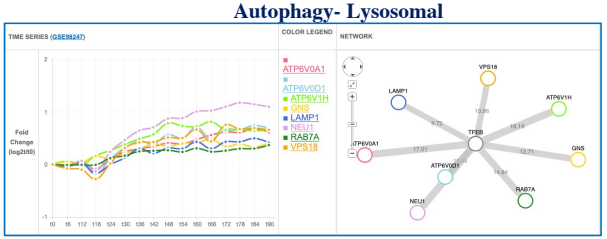
For each gene, on the nodes there is a link to https://www.genecards.org/, and an additional link is added for the genes belonging to the KEGG autophagy pathway, these nodes are colored in light blue. The TFEB targets established in Gambardella et al., 2020 are red circles.

2 TFEB network demo sets:

mTOR regulators



Autophagy- Lysosomal



Gene expression profile21

Is a gene of interest transcriptionally regulated by TFEB?

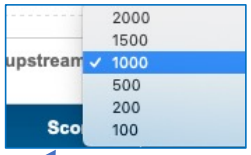
- The differentially expression of the gene X may be verified by looking at its expression in different gene expression dataset (microarrays) performed at TIGEM.

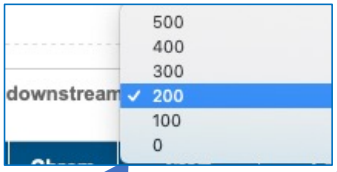
- This panel reporting its False Discovery Rate (FDR), the fold-change as signed ratio value (negative values colored in green for inhibition, and positive values colored in red for induction).

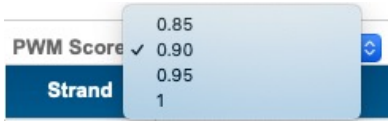
GENE EXPRESSION PROFILE FDR ✓ <5% ALL Background Legend Significant Down-Regulation Up-Regulation

Genesymbol	Experiment	FDR	Signed Ratio
RRAGC	TFEB HeLa - OE (GSE16267)	0.001584169	1.676950057
RRAGC	TFEB-GFP HeLa - OE (GSE73055)	1.44e-06	-1.362631813
RRAGC	TFEB-3xFLAG HeLa - OE (GSE73054)	1.05e-05	-1.396936467

Bioinformatic prediction of binding site



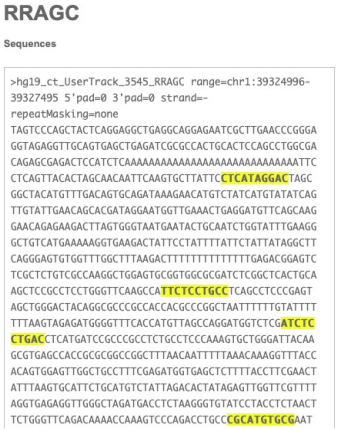




Genesymbol	Score	Binding Site	Chrom	Start	End	Strand	TSS Position	Promoter Sequence	View
RRAGC	0.9741982	GGCACGTGAC	chr1	39325549	39325558	-	-62	Promoter	IGV

It is possible to visualize the binding sites in **Integrative Genomics Viewer (IGV)** format

the CLEAR binding sites are highlighted



The sequences for all genes for three species were downloaded (from UCSC Genome Browser) 2000bp upstream and 500 bp downstream from the transcription start site (TSS).

Genome versions: **hg19** for human, **mm10** for mouse and **rn6** for rat.

For the determination of the binding sites, the package match-PWM by Biostrings was applied.

The position-weight matrix of the TFEB consensus binding sequence was identified using the Weeder tool 2.0.

The algorithm match-PWM establishes an enrichment score (PWM Score) for each sequence referred to the TFEB matrix.

The threshold used for each binding site predicted was the PWM Score greater than 0.85.

Experimental ChIP-seq

downstream ✓ 1000
5000
2500
1000
300

ChIP-seq HEK-293 (GSE98246) Upstream ✓ 1000 Downstream 1000

5000
2500
1000
300

Genesymbol	Chrom		End	TSS Position	View
RRAGC	chr1		39326057	0	IGV

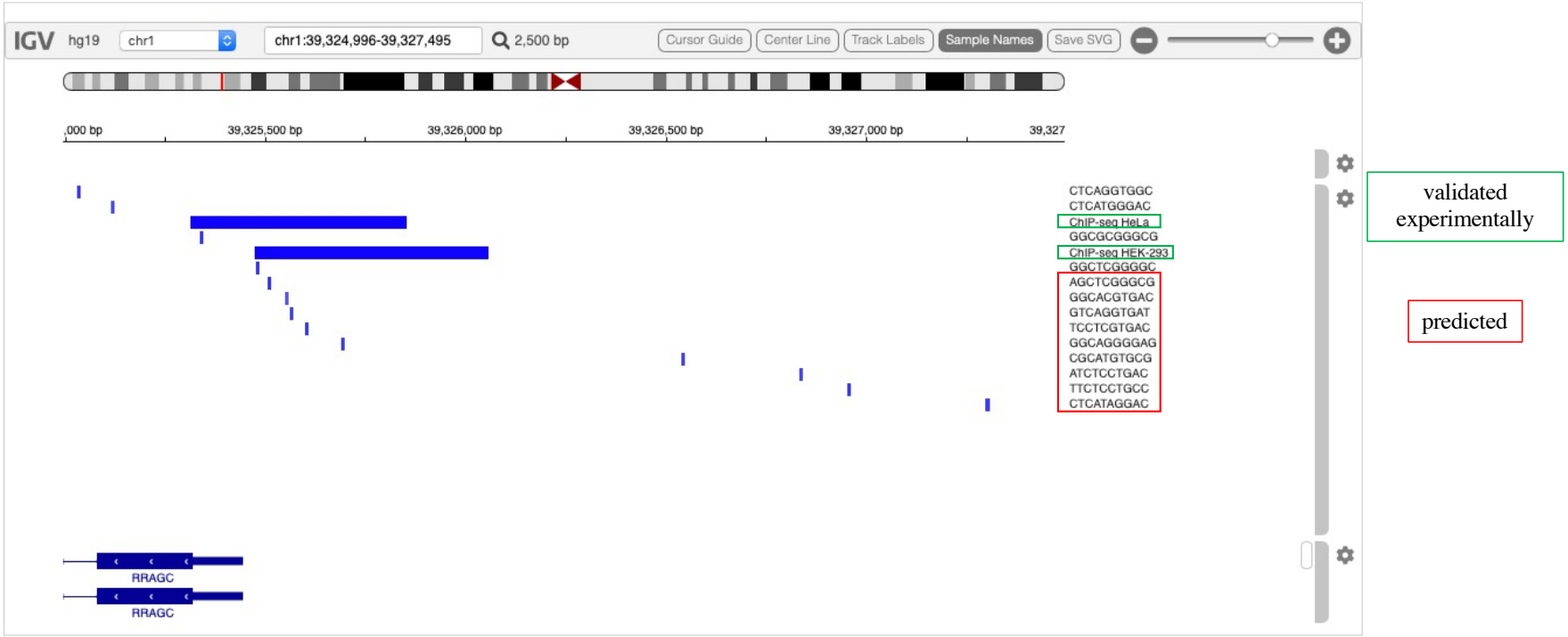
It is possible to visualize the binding sites in **Integrative Genomics Viewer (IGV)** format

ChIP-seq HeLa (Palmieri et al., HMG 2011 - ChIP-seq Palmieri HMG)

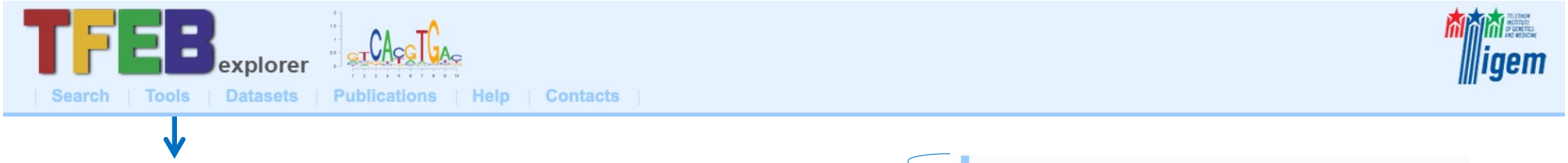
Genesymbol	Chrom	Start	End	TSS Position	View
RRAGC	chr1	39325313	39325853	0	IGV

- The TFEB binding to the promoter region could be assessed by Experimental evidence (ChIP-seq) performed in HeLa and Hek293 cells.
- For the ChIP-seq the genomic coordinates, the chromosome number and the distance from the TSS position are shown.

Visualization of Binding Sites and Experimental ChIP-seq



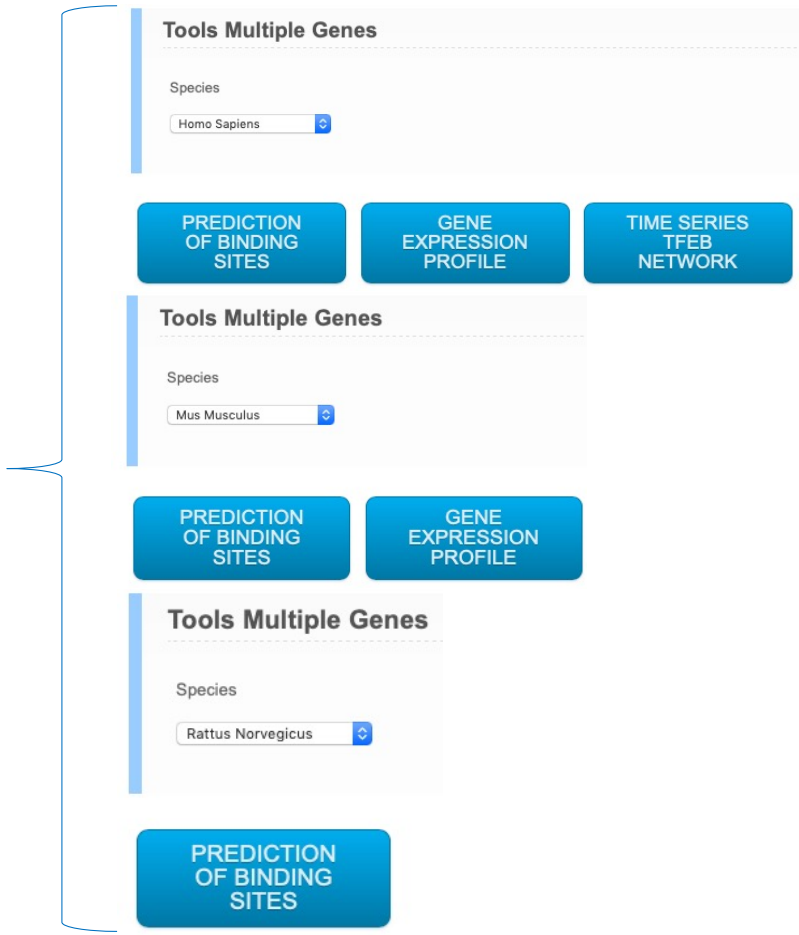
- The promoter region and the binding sites identified (both predicted and validated experimentally) are visualized in IGV format.
- The Integrative Genomics Viewer (IGV) is a high-performance, easy-to-use, interactive tool for the visual exploration of genomic data, and we decide to introduce it for a clearer visualization of all the binding sites found.



Tools Multiple Genes

- The effect of TFEB perturbation in the different GEPs and the bioinformatics prediction of the CLEAR binding sites could be performed on a LIST of genes of interest.
- The prediction of the TFEB binding sites could be performed in the promoter regions of three different species (human, mouse and rat), while the GEPs preset in the TFEBdb were not performed in rat.
- The results could be visualized and downloaded as csv file.

	A	B	C	D	E	F	G	H	I
1	genesymbol	number	score	sequence	chr	st	en	strand	tss_position
2	AIM2	6	0.9106459	GTCATCTGC(	chr1	159046773	159046782	-	-90
3	AIM2	6	0.9064245	CTCTCCTGAC	chr1	159046494	159046503	-	189
4	BATF2	12	0.9373479	GCCACGTGA	chr11	64764560	64764569	-	-51
5	BATF2	8	0.9001149	TTCATGTGA(	chr11	64757767	64757776	-	-26
6	CD68	13	0.9107337	CTCACATGCC	chr17	7482549	7482558	+	-256
7	CD68	13	0.9063909	CCCATGTGA(	chr17	7482750	7482759	+	-54
8	CD68	13	0.9005894	CTCACCTCAG	chr17	7482084	7482093	+	-720
9	CD68	13	0.9063909	CCCATGTGA(	chr17	7482750	7482759	+	-55
10	CD68	13	0.9005894	CTCACCTCAG	chr17	7482084	7482093	+	-721
11	CD68	13	0.9107337	CTCACATGCC	chr17	7482549	7482558	+	-255
12	CMPK2	7	0.9112235	GTCCCGTGA(	chr2	7007481	7007490	-	-723
13	EPSTI1	5	0.9021684	GCCACATGA(	chr13	43567435	43567444	-	-995
14	FXYD6	10	0.9180634	CCCACGTGA(	chr11	117748232	117748241	-	-39
15	FXYD6	12	0.9114422	GTCGCGTCA(	chr11	117748183	117748192	-	-445
16	FXYD6	10	0.9114422	GTCGCGTCA(	chr11	117748183	117748192	-	10
17	FXYD6	12	0.9180634	CCCACGTGA(	chr11	117748232	117748241	-	-494
18	HERC5	13	0.9005457	GTCCCGGGA	chr4	89378362	89378371	+	95
19	HERC5	13	0.9165983	ATCTCCTGAC	chr4	89377840	89377849	+	-427
20	IFI35	17	0.9314727	GGCATGTGA	chr17	41158752	41158761	+	11
21	IFI44L	5	0.9161246	GTCACCTCCC	chr1	79085163	79085172	+	-903
22	IFI6	4	0.949294	GTCACATGA(	chr1	27999159	27999168	-	-443
23	IFIH1	13	0.908285	CGCACCTGC(	chr2	163175059	163175068	-	151
24	IFIT1	9	0.9165983	ATCTCCTGAC	chr10	91151508	91151517	+	-794
25	IFIT3	7	0.9001577	GTTACGTGA	chr10	91092018	91092027	+	-217
26	IFIT3	7	0.9549224	GGCACGTGC	chr10	91091482	91091491	+	-753
27	IL18BP	10	0.9168183	GTCACTTGA(	chr11	71710828	71710837	+	-144
28	IL18BP	11	0.9168183	GTCACTTGA(	chr11	71710828	71710837	+	166
29	IL18BP	11	0.9200727	CTCAGGTGA	chr11	71709093	71709102	+	-864
30	IL4I1	15	0.926917	GACACCTGA(	chr19	50400544	50400553	-	-405



Sample Output

mTOR regulators in Homo Sapiens

https://tfeb.tigem.it/index.php?variable=RRAGC,RRAGD,FLCN,FNIP1,FNIP2,,&sp=Human

Autophagy-Lysosomal in Mus Musculus

https://tfeb.tigem.it/mouse10.php?variable=GNS,LAMP1,ATP6V0A1,ATP6V0D1,ATP6V1H,NEU1,VPS18,RAB7A,&sp=Mouse

Abbreviations

- TFEB: The transcription Factor EB
- CLEAR: Coordinated Lysosomal Expression And Regulation
- GP: Gaussian Process
- FDR: False Discovery Rate
- PWM: Position Weight Matrix
- GEPs: Gene Expression Profiles
- ChIP-seq: chromatin-immunoprecipitation followed by sequencing
- RMA: Robust Multiarray Average
- DMEM: Dulbecco's modified Eagle's medium

TFEB explorer

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All data present in the TFEB explorer are collected in these publications

TFEB Publications

1. *De Cegli R., Carrella D., et al., TFEBdb: An integrated database of genes regulated by the stress-responsive Transcription Factor EB.* (Under Revision)
2. Gambardella, G., et al., GADD34 is a modulator of autophagy during starvation. Sci Adv, 2020. 6(39). PMID: 32978159
3. Nnah, I.C., et al., TFEB-driven endocytosis coordinates MTORC1 signaling and autophagy. Autophagy, 2019. 15(1): p. 151-164. PMID: 30145926
4. Mansueto, G., et al., Transcription Factor EB Controls Metabolic Flexibility during Exercise. Cell Metab, 2017. 25(1): p. 182-196. PMID: 28011087
5. Calcagni, A., et al., Modelling TFE renal cell carcinoma in mice reveals a critical role of WNT signaling. Elife, 2016. 5. PMID: 27668431
6. Settembre, C., et al., TFEB controls cellular lipid metabolism through a starvation-induced autoregulatory loop. Nat Cell Biol, 2013. 15(6): p. 647-58. PMID: 23604321
7. Palmieri, M., et al., Characterization of the CLEAR network reveals an integrated control of cellular clearance pathways. Hum Mol Genet, 2011. 20(19): p. 3852-66. PMID: 21752829
8. Sardiello, M., et al., A gene network regulating lysosomal biogenesis and function. Science, 2009. 325(5939): p. 473-7. PMID: 19556463