RegulatorTrail: a web service for the identification of key transcriptional regulators

Tim Kehl[1,*], Lara Schneider[1], Florian Schmidt[1,2,3], Daniel Stöckel[1], Nico Gerstner[1], Christina Backes[1], Eckart Meese[1,4], Andreas Keller[1], Marcel H. Schulz[1,2,3], Hans-Peter Lenhof[1]

[1]Center for Bioinformatics, Saarland Informatics Campus, Saarland University, Saarbrücken, Germany
[2]Cluster of Excellence Multimodal Computing and Interaction, Saarland Informatics Campus, Saarland University, Saarbrücken, Germany
[3]Max Planck Institute for Informatics, Saarland Informatics Campus, Saarbrücken, Germany
[4]Human Genetics, Saarland University, Homburg, Germany

[*]To whom correspondence should be addressed. Email: tkehl@bioinf.uni-sb.de

Supplementary Table 1 – Alternative approaches

Name	Input	Output	Availability
TFACTS (14)	List of differentially expressed genes and collection of RTIs	Regulators with significantly over-represented target genes in the input list (p-value).	Webserver: http://www.tfacts.org/
DCGL v2.0 (15)	List of differentially expressed genes and collection of RTIs	Regulators with significantly over-represented target genes in the input list (p-value).	R-package: https://cran.r-project.org/web/packages/DCGL/DCGL.pdf
Regulator Impact Factors RIF1 + RIF2 (16)	A gene expression matrix with samples that belong to two groups and a collection of RTIs.	Impact score for each regulator.	-
Correlation set analysis (17)	A gene expression matrix and a collection of RTIs.	Regulators with a significant coherence between all target genes. (p-value)	-
REGGAE (18)	A gene expression matrix and a collection of RTIs	A prioritized list of influential regulators. (p-value)	Webserver: https://regulatortail.bioinf.uni-sb.de
TFRank (19)	A list of target genes (e.g. differentially expressed genes) and a collection of weighted RTIs in form of an adjacency list (network)	A prioritized / ranked list of influential regulators	Java implementation: http://web.tecnico.ulisboa.pt/aplf/code/tfrank/ + Adapted version of the algorithm in the Regulatory Snapshots webserver (22)
wPGSA (20)	A score list (e.g. fold-changes) and RTIs weighted by the number of experiments that confirm each RTI	A prioritized list of influential regulators (p-value)	Python script: https://github.com/eiryo-kawakami/wPGSA
MIPRIP (21)	A gene expression matrix and weighted RTIs in form of an adjacency matrix (network)	A list of significant regulators per target gene (p-value)	R-package: http://www.leibniz-hki.de/de/miprip.html
Regulatoy Snapshots (22)	Gene expression time series and RTIs in form of regulatory networks	Important regulatory modules	Webserver: http://kdbio.inesc-id.pt/software/regulatorysnapshots/

Table 1A: Overview of methods based on regulator-target interactions (RTIs).

Name	Input	Output	Availability
CENTIPEDE (23)	Matrix of read counts around candidate binding sites from DNaseI cut sites and/or histone marks	Posterior probabilities for all provided candidate binding sites to be true TF binding sites	R-package: http://centipede.uchicago.edu/
PIQ (24)	Bam file with DNaseI data, and a collection of PWMs	List of purely PWM based motif matches and a list of motif matches incorporating the DNaseI information as well as the corresponding scores	R-package: https://bitbucket.org/thashim/piq-single
MILLIPEDE (25)	Binned DNase data, TF binding information using PWM scores, optional: TF ChIP-seq labels	Probabilities for all candidate binding sites to be true TF binding sites	R-package: https://users.cs.duke.edu/~amink/software/millipede/
BinDNase (26)	Training data contains PWM scores for bound and unbound regions and DNaseI data, ideally in perBase resolution. Test data is composed of PWM scores and DnaseI data for all candidate regions	Probabilities for all candidate binding sites to be true TF binding sites	R-package: http://research.ics.aalto.fi/csb/software/bindnase/
HINT-BC (27)	BED file with regions of interest, e.g. DHS sites, a Bam file with DNaseI data, and optionally Bam files with histone mark data	A Bed file with all predicted TF-footprints and the related scores	Part of the Regulatory Genomics Toolbox http://www.regulatory-genomics.org/rgt/basic-introduction/
TEPIC (28)	Candidate regions for TF binding, e.g. DHS sites, a collection of PCMs, and a reference genome. Optionally, a wig file with DNaseI signal information	A file containing TF affinities calculated per peak and a file containing TF affinities calculated per gene	Bash and Python scripts as well as C++ code https://github.com/SchulzLab/TFAnalysis
PASTAA (29)	Ensembl IDs, Gene Symbols, or RefSeq IDs for Mouse or Human	List of TFs ranked according to the association with the input	Webserver: http://trap.molgen.mpg.de/cgi-bin/pastaa.cgi C++ Code: http://trap.molgen.mpg.de/PASTAA/

Table 1B: Overview of methods based on genome-wide transcription factor (TF) binding predictions.

Supplementary Table 2 – Expected runtimes

	Run 1 [ms]	Run 2 [ms]	Run 3 [ms]	Run 4 [ms]	Run 5 [ms]	Average runtime in *s*
Hypergeometric test	23724	23793	23644	23644	23577	**23.68**
Fisher's exact test	25281	25409	25485	25485	25140	**25.36**
Binomial test	247275	247336	247771	246396	246948	**247.15**
REGGAE	172959	172856	172620	172620	172665	**172.74**
REGGAE (without bootstrapping)	8645	8415	8402	8270	8058	**8.35**
RIF1	8338	8108	8272	8148	8174	**8.20**
RIF2	8194	8115	8346	8092	8229	**8.20**

Table 2A: Average runtime of all algorithms in Scenario 1 + 2. To perform the analyses, we used GSE10072 and calculated the expression differences for tumor and normal samples. We then selected the top 250 upregulated genes for each analysis. The analyses were performed using the entire RTI collection of Database V1 2016.

	Run 1 [ms]	Run 2 [ms]	Run 3 [ms]	Run 4 [ms]	Run 5 [ms]	Average runtime in *s*
Hypergeometric test	28619	28554	28643	28709	28651	**28.64**
Fisher's exact test	32003	31741	31793	32069	31710	**31.86**
Binomial test	250926	245165	243075	243993	244695	**245.57**
REGGAE	331289	331978	345028	344942	335938	**337.84**
REGGAE (without bootstrapping)	8470	8915	8731	8744	8337	**8.64**
RIF1	8425	8425	8280	8111	8320	**8.31**
RIF2	8474	8306	8305	8341	8473	**8.38**

Table 2B: Average runtime of all algorithms in Scenario 1 + 2. To perform the analyses, we used GSE10072 and calculated the expression differences for tumor and normal samples. We then selected the top 500 upregulated genes for each analysis. The analyses were performed using the entire RTI collection of Database V1 2016.

	Run1 [*s*]	Run2 [*s*]	Run3 [*s*]	Run4 [*s*]	Run5 [s]	Average runtime in *s*
TEPIC – all PSEMs	469	471	471	476	470	**471.4**
TEPIC – public PSEMs	263	263	262	264	262	**262.8**
INVOKE lasso penalty with performance measurement	422	410	441	404	431	**421.6**
INVOKE lasso penalty without performance measurement	205	*230*	*245*	*217*	*221*	***224***
INVOKE ridge penalty with performance measurement	106	104	105	105	104	**105**
INVOKE ridge penalty without performance measurement	*43*	*43*	*42*	*43*	*42*	***43***
INVOKE elastic net penalty with performance measurement	3441	3606	3467	3470	3533	**3503**
INVOKE elastic net penalty without performance measurement	*1683*	*1702*	*1738*	*1679*	*1772*	***1715***

Table 2C: Average runtime of all algorithms in Scenario 3 + 4. To perform the analyses, we used BLUEPRINT Sample S001S7. We calculated binding affinities using TEPIC and trained predictive models of gene expression using INVOKE.

Supplementary Table 3 – Methods for p-value adjustment

Method	Reference
Bonferroni	[S1.01]
Šidák	[S1.02]
Holm	[S1.03]
Holm- Šidák	[S1.02, S1.03]
Finner	[S1.04]
Hochberg	[S1.05]
Benjamini-Hochberg	[S1.06]
Benjamini-Yekutieli	[S1.07]

[S1.01] Bonferroni, Carlo E. Il calcolo delle assicurazioni su gruppi di teste. Tipografia del Senato, 1935.

[S1.02] Šidák, Zbyněk. "Rectangular confidence regions for the means of multivariate normal distributions." Journal of the American Statistical Association 62.318 (1967): 626-633.

[S1.03] Holm, Sture. "A simple sequentially rejective multiple test procedure." Scandinavian journal of statistics (1979): 65-70.

[S1.04] Finner, Helmut. "Some new inequalities for the range distribution, with application to the determination of optimum significance levels of multiple range tests." Journal of the American Statistical Association 85.409 (1990): 191-194.

[S1.05] Hochberg, Yosef. "A sharper Bonferroni procedure for multiple tests of significance." Biometrika 75.4 (1988): 800-802.

[S1.06] Benjamini, Yoav, and Yosef Hochberg. "Controlling the false discovery rate: a practical and powerful approach to multiple testing." Journal of the royal statistical society. Series B (Methodological) (1995): 289-300.

[S1.07] Benjamini, Yoav, and Daniel Yekutieli. "The control of the false discovery rate in multiple testing under dependency." Annals of statistics (2001): 1165-1188.

Supplementary Table 4 – REGGAE Parameters

Parameter	Value
Identifier level statistic	Shrinkage t-test
Upper-quantile filter	0.05
Enrichment method	Wilcoxon rank-sum test
Order of test set	decreasingly
Method to compute the influence of regulators	Pearson correlation
Scoring mode for influence scores	Absolute correlation
Method to adjust p-values	Benjamini-Yekutieli
Number of bootstrap replications	1000
Random seed	8938479563690567223
RTI collection	Entire collection V1 2016

Supplementary Table 5 – REGGAE Results

Rank	Regulator	#Targets	Score	Adjusted p-value	Mean correlation
1	FOSL2	968	27.07	4.88e-158	-0.319
2	CEBPA	861	26.16	7.70e-148	-0.328
3	ZBTB7A	917	25.58	1.76e-141	-0.318
4	SMAD1	780	25.49	1.35e-140	-0.317
5	GATA3	976	25.09	3.13e-136	-0.293
6	E2F6	983	24.14	3.92e-126	0.314
7	MITF	645	22.06	2.23e-105	0.355
8	FOXP1	813	21.92	4.92e-104	-0.294
9	TFAP2C	951	21.11	1.60e-96	-0.28
10	RXRA	802	20.81	7.42e-94	-0.277
11	CBX3	955	20.31	1.94e-89	0.301
12	BRCA1	741	19.6	3.03e-83	0.331
13	ATF2	925	18.98	4.00e-78	0.298
14	HEY1	941	18.92	1.37e-77	0.279
15	TP63	446	18.63	2.62e-75	-0.303
16	BCL11A	682	17.96	5.36e-70	-0.271
17	SP1	1018	17.62	2.49e-67	-0.231
18	RAD21	1017	16.91	5.14e-62	0.242
19	PBX1	624	16.8	2.85e-61	-0.268
20	KLF5	658	16.5	4.24e-59	-0.272
21	KDM5B	993	16.42	1.45e-58	-0.22
22	GRHL2	396	14.93	2.20e-48	-0.282
23	PRDM1	258	14.67	9.23e-47	-0.325
24	NANOG	922	14.49	1.31e-45	-0.232
25	ETV1	535	14.18	1.12e-43	0.318
26	NCOA1	419	13.64	1.97e-40	-0.3
27	RBL1	609	13.24	4.07e-38	0.280
28	NFIC	964	12.98	1.30e-36	-0.226
29	SMC1A	928	12.9	3.61e-36	0.246
30	CDK8	878	12.78	1.49e-35	0.244
31	ZMIZ1	860	12.67	5.94e-35	-0.214
32	RUNX1	964	12.59	1.64e-34	-0.219
33	ZNF750	415	12.51	4.32e-34	-0.258
34	ELL2	440	12.49	5.36e-34	-0.273
35	ATF1	750	12.39	1.98e-33	0.259
36	NIPBL	840	12.16	3.30e-32	-0.207
37	KLF4	384	12.1	6.60e-32	-0.271
38	STAT3	988	11.78	3.03e-30	-0.213
39	RB1	707	11.77	3.17e-30	0.254
40	SAP30	740	11.2	2.34e-27	0.255

41	AR	1010	10.84	1.23e-25	-0.214
42	PRAME	426	10.81	1.72e-25	0.279
43	ASUN	498	10.76	2.66e-25	0.283
44	YAP1	774	10.72	4.00e-25	-0.206
45	TBL1X	435	10.54	2.70e-24	-0.259
46	FOXM1	922	10.5	4.26e-24	0.227
47	CBFB	871	9.807	5.05e-21	0.241
48	NME1	232	9.66	2.10e-20	0.259
49	RCOR1	967	9.596	3.83e-20	-0.129
50	LIN9	247	9.546	6.09e-20	0.313
51	BCL6	892	9.502	9.13e-20	-0.219
52	LDB1	231	9.184	1.80e-18	-0.258
53	CTBP2	412	9.162	2.16e-18	0.261
54	HOXA4	741	9.142	2.55e-18	0.251
55	GATAD1	536	9.102	3.63e-18	0.263
56	CHD8	937	8.904	2.17e-17	-0.184
57	EREG	243	8.848	3.51e-17	-0.235
58	BCLAF1	806	8.815	4.66e-17	-0.157
59	NOTCH1	858	8.762	7.33e-17	-0.193
60	THAP1	392	8.714	1.10e-16	0.278
61	HDAC3	120	8.471	9.02e-16	-0.292
62	WRNIP1	588	8.146	1.37e-14	0.234
63	NCAPG	126	7.988	4.91e-14	0.343
64	RFX5	915	7.951	6.53e-14	0.201
65	E2F1	942	7.69	5.10e-13	0.207
66	EZH2	913	7.614	9.09e-13	0.184
67	APOBEC3B	164	7.549	1.48e-12	0.281
68	CEBPB	1024	7.324	7.97e-12	-0.177
69	TP73	241	7.114	3.68e-11	-0.223
70	TET3	95	7.026	6.85e-11	-0.305
71	RARG	189	6.918	1.45e-10	-0.255
72	GREB1	83	6.884	1.82e-10	0.323
73	RUNX3	969	6.819	2.83e-10	0.160
74	TCF4	361	6.783	3.59e-10	-0.199
75	SUMO2	944	6.592	1.30e-9	0.161
76	KDM6B	780	6.489	2.56e-9	-0.197
77	ING2	842	6.44	3.49e-9	-0.177
78	MAF	64	6.437	3.51e-9	-0.307
79	TET2	78	6.214	1.47e-8	-0.277
80	HOXB7	125	6.129	2.48e-8	0.272
81	VDR	632	5.947	7.60e-8	-0.188
82	SOX10	41	5.939	7.89e-8	0.343
83	SCLY	89	5.417	1.65e-6	0.221
84	ZNF143	971	5.329	2.64e-6	0.189

85	FOXO3	30	5.319	2.76e-6	-0.317
86	BRD3	755	5.283	3.32e-6	-0.158
87	LMNA	428	5.268	3.57e-6	-0.2
88	HDAC8	63	5.134	7.25e-6	0.302
89	GRHL1	36	5.053	1.10e-5	-0.339
90	JMJD6	84	5.045	1.14e-5	0.287
91	CHD2	966	4.946	1.88e-5	-0.132
92	E2F7	223	4.906	2.28e-5	0.240
93	SRF	975	4.863	2.79e-5	-0.175
94	GRHL3	37	4.599	1.02e-4	-0.314
95	KDM4C	791	4.583	1.09e-4	-0.205
96	ETV5	448	4.315	3.74e-4	0.224
97	REST	1006	4.277	4.40e-4	-0.101
98	BMI1	498	4.272	4.45e-4	0.204
99	MECP2	509	4.247	4.93e-4	0.186
100	TLE3	44	4.091	9.68e-4	-0.277
101	TFAP2A	953	4.007	0.001	0.125
102	SOX9	586	4.002	0.001	-0.171
103	FOXO1	385	3.982	0.001	-0.193
104	MAFF	894	3.96	0.002	0.165
105	ORC1	42	3.898	0.002	0.315
106	MBD2	72	3.809	0.003	-0.246
107	NCAPG2	48	3.783	0.003	0.298
108	TAF2	126	3.717	0.004	0.263
109	CREBBP	964	3.703	0.004	-0.034
110	RREB1	40	3.702	0.004	-0.28
111	MAFB	87	3.643	0.005	-0.242
112	PRKDC	108	3.608	0.006	0.249
113	CREB1	988	3.581	0.007	-0.099
114	AUTS2	59	3.568	0.007	-0.239
115	CDK9	868	3.565	0.007	-0.172
116	GABPA	970	3.542	0.008	0.116
117	NELFE	779	3.448	0.011	0.184
118	SP2	343	3.366	0.015	0.201
119	ZNF384	922	3.262	0.021	0.169
120	UBTF	756	3.062	0.041	-0.145
121	ELF1	995	2.978	0.054	-0.13
122	SUMO1	452	2.972	0.055	0.149
123	NR4A1	148	2.968	0.055	0.225
124	TERF1	226	2.919	0.064	0.231
125	DEK	147	2.855	0.078	0.230
126	GMEB2	238	2.846	0.079	-0.207
127	ELF5	71	2.833	0.082	-0.224
128	CDK7	799	2.805	0.089	-0.143

129	EHF	15	2.795	0.091	-0.286
130	BACH2	190	2.763	0.099	-0.203
131	OVOL2	21	2.759	0.099	-0.288
132	ASH2L	283	2.758	0.099	0.221
133	HLF	17	2.72	0.111	-0.21
134	PHF8	959	2.604	0.155	0.136
135	ZNF711	131	2.597	0.157	-0.136
136	YBX1	41	2.586	0.161	0.259
137	ZNF83	320	2.467	0.224	-0.221
138	MYB	867	2.463	0.225	-0.186
139	MBD1	4	2.447	0.234	-0.257
140	GTF2B	817	2.442	0.235	0.182
141	CBX8	14	2.403	0.259	0.313
142	BRIP1	7	2.402	0.259	0.333
143	YY1	1012	2.384	0.269	0.072
144	ETS1	955	2.333	0.307	0.154
145	NR3C1	980	2.279	0.352	-0.156
146	NCOA3	44	2.196	0.433	-0.259
147	ETV4	17	2.104	0.540	0.212
148	E2F4	991	2.102	0.540	-0.133
149	JUNB	658	2.1	0.540	-0.166
150	ZNF92	156	2.052	0.603	0.175
151	ARNT2	54	2.037	0.621	0.264
152	USF2	800	1.972	0.720	0.063
153	E2F8	228	1.965	0.728	0.224
154	CHD7	34	1.935	0.775	0.267
155	SPDEF	257	1.927	0.784	-0.177
156	SMAD3	730	1.924	0.786	-0.148
157	AREG	37	1.877	0.868	-0.175
158	ING4	2	1.867	0.883	-0.363
159	DNMT1	11	1.836	0.941	0.312
160	DDIT3	2	1.757	1	0.624
161	HECTD1	2	1.753	1	-0.379
162	PBX2	7	1.75	1	0.340
163	NFATC1	832	1.749	1	-0.184
164	WDHD1	1	1.721	1	0.763
165	DOT1L	1	1.708	1	0.593
166	RPA3	1	1.706	1	0.815
167	ZBTB33	718	1.703	1	0.118
168	DNAJC2	38	1.664	1	0.164
169	TTF2	109	1.656	1	0.229
170	MAX	1023	1.648	1	0.135
171	SFPQ	878	1.628	1	-0.109
172	PHF6	5	1.607	1	0.354

173	TCF7L2	987	1.564	1	-0.116
174	NFKB2	1	1.521	1	0.408
175	ZMYND11	5	1.507	1	-0.264
176	TAF7	805	1.476	1	0.172
177	TRRAP	190	1.453	1	0.218
178	POU3F2	110	1.438	1	0.192
179	FOSB	1	1.429	1	0.333
180	FANCD2	1	1.421	1	0.423
181	BDP1	392	1.42	1	0.085
182	NR2F6	1	1.364	1	-0.324
183	ZC3H8	57	1.357	1	0.232
184	TRIM24	1	1.335	1	0.325
185	DEAF1	1	1.334	1	-0.339
186	NFE2	850	1.33	1	-0.183
187	PURA	1	1.303	1	0.288
188	KDM6A	48	1.298	1	-0.198
189	MBD3	4	1.291	1	-0.255
190	PLSCR1	1	1.281	1	0.344
191	NOLC1	1	1.277	1	0.415
192	ELOF1	10	1.25	1	0.145
193	KAT5	180	1.229	1	-0.141
194	PARP1	2	1.227	1	0.315
195	SOX4	171	1.224	1	-0.109
196	BATF	804	1.208	1	0.112
197	HES1	1	1.2	1	-0.232
198	ELF3	1	1.152	1	-0.164
199	NR1H3	58	1.119	1	0.174
200	DVL1	1	1.082	1	0.281
201	ZNF486	19	1.077	1	-0.198
202	DYRK1A	21	1.074	1	0.166
203	HTT	10	1.064	1	-0.195
204	HNRNPK	1	1.048	1	-0.098
205	MYCN	42	1.038	1	-0.114
206	HMGA2	1	1.036	1	0.363
207	DLX3	1	1.027	1	-0.242
208	PLAU	1	1.008	1	0.189
209	RAD51	1	0.983	1	0.425
210	CDK2	4	0.956	1	0.352
211	ERG	1004	0.954	1	-0.146
212	MIA3	3	0.908	1	0.262
213	IRF2	101	0.894	1	0.203
214	WHSC1	2	0.850	1	0.300
215	ATF7	1	0.845	1	-0.244
216	RELA	985	0.842	1	-0.086

217	NKX2-2	1	0.837	1	0.220
218	RPA1	1	0.827	1	0.334
219	CBX4	15	0.821	1	0.245
220	NR2F1	792	0.808	1	0.172
221	SP3	20	0.808	1	-0.186
222	XRCC5	1	0.803	1	-0.256
223	UBP1	1	0.784	1	-0.327
224	KLF8	1	0.776	1	-0.219
225	ATF7IP	6	0.772	1	-0.166
226	GABPB1	1	0.738	1	0.312
227	FLII	29	0.706	1	-0.037
228	STAT5A	800	0.690	1	0.120
229	PIAS1	400	0.686	1	-0.151
230	LHX2	49	0.677	1	-0.142
231	CBX2	7	0.636	1	0.217
232	HDAC2	956	0.630	1	-0.078
233	BCL11B	1	0.619	1	-0.228
234	TEAD4	990	0.611	1	0.122
235	NFATC4	1	0.610	1	0.234
236	TEAD1	436	0.592	1	0.162
237	THRB	1	0.567	1	-0.202
238	ETS2	3	0.549	1	-0.248
239	ESRRG	1	0.523	1	0.211
240	BRD7	27	0.493	1	-0.117
241	ARRB1	12	0.492	1	-0.25
242	ZZZ3	257	0.473	1	0.157
243	ZNF395	3	0.473	1	-0.272
244	SRCAP	8	0.468	1	-0.223
245	HAND2	4	0.453	1	0.169
246	GLI2	596	0.433	1	-0.15
247	FOXO4	1	0.431	1	-0.171
248	ARNT	325	0.426	1	-0.17
249	REL	3	0.413	1	-0.236
250	GDNF	3	0.410	1	-0.085
251	NFE2L2	88	0.401	1	-0.126
252	ZNF350	1	0.381	1	-0.166
253	BRF2	232	0.377	1	0.158
254	EGFR	4	0.370	1	-0.169
255	KCNIP3	1	0.369	1	0.156
256	HIF1A	941	0.360	1	0.115
257	CBX7	4	0.346	1	-0.174
258	LTF	1	0.319	1	-0.232
259	DROSHA	11	0.299	1	0.161
260	ELF2	11	0.294	1	-0.228

261	NFKB1	222	0.280	1	-0.142
262	OLIG2	1	0.277	1	0.155
263	NR3C2	2	0.271	1	-0.273
264	AGO1	232	0.256	1	-0.187
265	MZF1	2	0.251	1	-0.202
266	TCFL5	1	0.232	1	0.201
267	EBF1	946	0.217	1	-0.163
268	NFYB	775	0.202	1	-0.052
269	DAND5	3	0.161	1	-0.064
270	ISL2	2	0.160	1	0.089
271	IRF5	40	0.157	1	-0.058
272	HIC1	1	0.140	1	0.012
273	HOXC10	1	0.138	1	0.184
274	CREM	1	0.122	1	0.173
275	NR5A2	28	0.106	1	0.159
276	NFIB	1	0.098	1	-0.237
277	FOXE1	3	0.083	1	-0.103
278	TP53BP1	17	0.081	1	0.076
279	TDRD3	6	0.062	1	0.252
280	PPARD	200	0.030	1	-0.004
281	NFATC2	3	0.019	1	0.106
282	TFE3	1	-0.004	1	0.129
283	ZIC1	1	-0.012	1	-0.147
284	PALB2	9	-0.014	1	0.226
285	SETD2	2	-0.02	1	-0.15
286	MAPK1	4	-0.028	1	0.104
287	HOXC13	1	-0.034	1	0.149
288	RFX2	20	-0.036	1	-0.194
289	WDR5	914	-0.06	1	-0.113
290	ETV7	1	-0.061	1	-0.117
291	DR1	30	-0.072	1	0.194
292	SNAPC1	7	-0.078	1	0.186
293	HOXC11	1	-0.092	1	0.125
294	PSIP1	14	-0.106	1	0.207
295	FOXD1	1	-0.132	1	0.129
296	AGO2	29	-0.132	1	0.024
297	SNAPC2	1	-0.174	1	-0.06
298	KDM5C	53	-0.185	1	-0.148
299	C17ORF96	9	-0.2	1	-0.055
300	RYBP	2	-0.23	1	0.096
301	ZIC2	1	-0.279	1	-0.107
302	CHD1	839	-0.298	1	0.148
303	SFMBT1	12	-0.318	1	0.141
304	EGR2	24	-0.319	1	-0.063

305	TFCP2	1	-0.32	1	0.205
306	TFDP1	2	-0.322	1	0.192
307	TERF2	2	-0.328	1	0.100
308	POLR2A	1002	-0.33	1	-0.143
309	PPARA	5	-0.333	1	-0.059
310	APEX1	1	-0.334	1	0.176
311	DNTTIP1	1	-0.336	1	0.133
312	DSCAM	2	-0.347	1	-0.139
313	EPAS1	50	-0.349	1	-0.104
314	BRD4	959	-0.352	1	-0.124
315	RUNX2	194	-0.354	1	0.147
316	POLR3G	4	-0.368	1	0.168
317	ARNTL	897	-0.369	1	-0.159
318	POU2F1	125	-0.378	1	-0.066
319	SPANXC	1	-0.384	1	-0.106
320	CIITA	45	-0.42	1	-0.056
321	TFAP2D	2	-0.424	1	-0.104
322	TOP2B	96	-0.431	1	0.027
323	HOXA5	7	-0.437	1	0.171
324	INO80	20	-0.441	1	-0.073
325	CKAP4	545	-0.459	1	-0.124
326	PPARGC1A	134	-0.462	1	0.170
327	CBFA2T3	3	-0.476	1	-0.093
328	KDM2B	1	-0.487	1	-0.15
329	BLVRA	1	-0.516	1	0.143
330	XRCC4	9	-0.519	1	0.081
331	HLTF	1	-0.531	1	0.084
332	MRE11A	57	-0.552	1	0.124
333	HOXA2	1	-0.556	1	-0.064
334	ZBTB24	2	-0.57	1	0.229
335	SLC6A4	2	-0.636	1	-0.122
336	ARHGEF7	9	-0.643	1	0.072
337	CDX1	1	-0.661	1	-0.175
338	DEC1	1	-0.688	1	-0.108
339	IRF9	2	-0.698	1	-0.115
340	HNF1B	11	-0.699	1	0.049
341	AFF4	704	-0.707	1	-0.003
342	SIRT3	1	-0.719	1	0.073
343	EWSR1	46	-0.72	1	0.130
344	SORBS2	1	-0.727	1	-0.061
345	TCF7L1	1	-0.751	1	-0.074
346	FABP4	1	-0.76	1	-0.121
347	HNRNPL	1	-0.805	1	-0.144
348	ARNTL2	1	-0.807	1	-0.028

349	CARM1	5	-0.841	1	0.128
350	SNAPC5	3	-0.845	1	0.157
351	PLAG1	29	-0.851	1	-0.119
352	HOXA13	2	-0.851	1	-0.03
353	CTNNB1	261	-0.875	1	0.167
354	FOXK1	4	-0.89	1	0.109
355	GLI1	7	-0.9	1	-0.08
356	TFF2	1	-0.901	1	0.100
357	RXRB	1	-0.904	1	-0.016
358	E2F2	7	-0.911	1	0.059
359	HOXA10	1	-0.93	1	0.084
360	ZNF148	1	-0.933	1	-0.087
361	MTA1	1	-0.947	1	-0.059
362	SALL2	1	-0.952	1	0.109
363	PES1	1	-0.962	1	-0.006
364	AFF1	227	-0.963	1	-0.165
365	ELL	11	-0.965	1	-0.183
366	ZC3H11A	28	-0.965	1	0.007
367	XRN2	139	-0.97	1	0.156
368	LIN54	139	-0.999	1	0.047
369	RXRG	1	-1.004	1	0.069
370	RPA2	1	-1.01	1	0.099
371	CEBPZ	16	-1.012	1	0.130
372	PCGF2	79	-1.043	1	0.014
373	PIAS4	11	-1.106	1	-0.052
374	HSF1	887	-1.109	1	0.123
375	GFI1	1	-1.114	1	-0.013
376	PRDM2	1	-1.132	1	0.020
377	MTF1	1	-1.132	1	0.043
378	CBX6	4	-1.154	1	0.089
379	ZFHX4	10	-1.176	1	0.129
380	GTF2I	567	-1.179	1	0.153
381	IRF8	14	-1.185	1	0.076
382	E2F5	2	-1.186	1	0.105
383	ZNF652	5	-1.199	1	0.034
384	FUBP1	1	-1.2	1	0.064
385	HMGA1	3	-1.202	1	0.078
386	FOXF2	51	-1.211	1	0.144
387	ELF4	1	-1.216	1	-0.025
388	CBX5	5	-1.226	1	-0.091
389	SCML2	180	-1.228	1	0.149
390	MEF2C	447	-1.231	1	0.166
391	BCL10	1	-1.244	1	0.007
392	DPPA3	2	-1.246	1	-0.038

393	ZNF281	3	-1.247	1	0.110
394	NR1H4	28	-1.264	1	0.036
395	CTBP1	263	-1.271	1	-0.159
396	ICE2	10	-1.279	1	0.068
397	HMBOX1	24	-1.302	1	-0.105
398	TFAM	1	-1.304	1	0.143
399	RLF	2	-1.307	1	0.031
400	T	147	-1.311	1	0.147
401	SOX11	50	-1.333	1	0.038
402	ZNF12	23	-1.351	1	0.218
403	NFYC	364	-1.358	1	-0.122
404	INSM1	51	-1.375	1	0.083
405	GLI3	6	-1.386	1	-9.85e-4
406	ASF1A	170	-1.395	1	-0.104
407	L3MBTL2	12	-1.396	1	0.073
408	NR5A1	8	-1.4	1	0.095
409	ZNF280D	255	-1.402	1	0.144
410	HSF4	1	-1.456	1	-0.023
411	ZNF84	21	-1.484	1	-0.021
412	KCNH8	23	-1.499	1	-0.04
413	KDM3A	165	-1.507	1	0.099
414	GPS2	19	-1.522	1	-0.076
415	ATRX	3	-1.532	1	0.068
416	ELK1	646	-1.537	1	0.100
417	BCOR	869	-1.547	1	0.142
418	ZFP42	95	-1.648	1	-0.172
419	SALL1	5	-1.671	1	0.041
420	SLC22A1	1	-1.692	1	-0.052
421	KMT2A	651	-1.708	1	-0.144
422	CLOCK	28	-1.727	1	-0.075
423	NRF1	919	-1.742	1	-0.092
424	ZKSCAN1	315	-1.747	1	0.154
425	ERCC3	184	-1.753	1	0.146
426	NR2C2	501	-1.764	1	-0.078
427	LMTK3	31	-1.782	1	-0.13
428	STAT6	36	-1.79	1	-0.07
429	HOXC8	4	-1.798	1	0.072
430	GBX2	11	-1.803	1	-0.055
431	CDX2	970	-1.81	1	0.064
432	SVIL	2	-1.847	1	-0.056
433	DACH1	138	-1.873	1	-0.149
434	SSRP1	73	-1.928	1	0.057
435	ZBTB10	106	-1.93	1	0.174
436	HSF2	4	-1.933	1	0.002

437	DCP1A	487	-2.001	1	0.146
438	ZFX	229	-2.044	1	0.139
439	EZH1	57	-2.09	1	-0.125
440	LEF1	74	-2.102	1	0.137
441	RBL2	328	-2.126	1	-0.101
442	HINFP	3	-2.17	1	0.080
443	SETDB1	709	-2.218	1	-0.026
444	SMAD2	355	-2.235	1	0.024
445	KAT2B	22	-2.249	1	-0.024
446	PRKCQ	29	-2.255	1	-0.129
447	NHLH1	39	-2.308	1	0.060
448	CCNT2	824	-2.342	1	0.015
449	MYC	1026	-2.353	1	0.134
450	STAT4	93	-2.371	1	0.031
451	HMGN3	793	-2.424	1	-0.083
452	TFAP4	442	-2.467	1	0.135
453	NR2F2	951	-2.476	1	0.092
454	TFEB	71	-2.484	1	-0.088
455	ONECUT1	30	-2.494	1	0.077
456	HDAC6	128	-2.503	1	-0.049
457	FOXH1	539	-2.505	1	0.102
458	WWTR1	145	-2.524	1	0.135
459	KAT8	111	-2.566	1	-0.13
460	MEIS1	58	-2.685	1	-0.092
461	HEYL	19	-2.692	1	0.007
462	LMO3	164	-2.744	1	-0.118
463	MYBL2	819	-2.812	1	0.148
464	ZNF274	101	-2.854	1	-0.074
465	TBP	993	-2.869	1	-0.127
466	GFI1B	30	-2.932	1	-0.07
467	TOP1	306	-2.954	1	0.048
468	ALKBH3	26	-2.988	1	-0.001
469	SMC3	959	-3.007	1	0.009
470	NFYA	821	-3.016	1	0.142
471	NOS2	12	-3.02	1	-0.005
472	FOXI1	46	-3.063	1	-0.094
473	SMARCB1	933	-3.074	1	0.101
474	HNF1A	23	-3.109	1	-0.067
475	TCF3	906	-3.141	1	0.068
476	NCOR2	337	-3.175	1	-0.122
477	ESRRA	225	-3.197	1	-0.051
478	ELK4	484	-3.245	1	-0.114
479	BACH1	653	-3.257	1	0.053
480	TP53	851	-3.282	1	-0.086

481	SOX17	40	-3.309	1	0.012
482	ASCL1	236	-3.326	1	0.090
483	RUNX1T1	672	-3.472	1	-0.137
484	GLYR1	17	-3.484	1	0.108
485	HIRA	130	-3.594	1	0.009
486	TAL1	968	-3.599	1	-0.074
487	TCF12	997	-3.632	1	0.059
488	FOXA3	81	-3.719	1	0.090
489	RNF2	255	-3.77	1	0.118
490	SIN3A	996	-3.796	1	-0.093
491	INTS3	686	-3.811	1	0.063
492	EED	113	-3.818	1	0.059
493	MXD3	27	-3.855	1	-0.038
494	HDAC1	870	-3.941	1	0.118
495	CYP27B1	17	-3.962	1	-0.045
496	CTCF	1022	-3.974	1	-0.037
497	LMNB1	744	-3.974	1	0.124
498	HOXC9	170	-4.038	1	0.108
499	SUPT5H	867	-4.049	1	-0.045
500	SALL4	104	-4.102	1	0.105
501	LYL1	175	-4.314	1	0.043
502	GTF3C2	228	-4.387	1	0.081
503	ICE1	636	-4.417	1	0.124
504	STAT2	574	-4.504	1	0.047
505	PRDM14	89	-4.519	1	0.042
506	C17ORF49	188	-4.521	1	-0.093
507	BRD1	703	-4.569	1	-0.117
508	TBX21	166	-4.693	1	0.031
509	AHR	210	-4.724	1	0.020
510	ARID3A	745	-4.739	1	-0.003
511	SIRT6	301	-4.762	1	-0.08
512	IRF4	931	-4.831	1	0.072
513	CSNK2A1	148	-4.863	1	0.101
514	IRF3	167	-4.898	1	-0.005
515	KDM5A	188	-4.983	1	-0.085
516	CDK12	99	-5.013	1	0.059
517	BRF1	339	-5.03	1	-0.068
518	CTCFL	919	-5.032	1	0.003
519	GTF2F1	799	-5.065	1	0.013
520	ERCC2	112	-5.089	1	-0.11
521	HMGN1	112	-5.199	1	0.039
522	E2F3	712	-5.226	1	0.149
523	ZNF263	941	-5.264	1	-0.07
524	TRIM28	995	-5.321	1	0.016

525	FOXA2	989	-5.357	1	0.068
526	JUN	1010	-5.373	1	-0.082
527	ELK3	362	-5.417	1	0.077
528	MTA3	786	-5.473	1	-0.15
529	KAT2A	247	-5.496	1	0.063
530	PADI4	98	-5.542	1	-0.114
531	PAF1	131	-5.571	1	-0.01
532	PAX6	218	-5.581	1	-0.076
533	GATA2	969	-5.599	1	-0.112
534	CHD4	151	-5.656	1	-0.03
535	ZNF76	173	-5.752	1	0.106
536	ESR2	289	-5.768	1	-0.06
537	JUND	1018	-5.773	1	-0.075
538	WT1	199	-5.852	1	0.072
539	TBL1XR1	791	-5.859	1	-7.94e-4
540	FOSL1	885	-6.022	1	0.125
541	PDX1	277	-6.065	1	3.50e-4
542	SP4	631	-6.084	1	0.082
543	FUS	211	-6.093	1	-0.015
544	EOMES	609	-6.226	1	0.110
545	ZNF217	354	-6.261	1	0.030
546	THAP11	153	-6.345	1	-0.113
547	SUPT20H	191	-6.352	1	0.034
548	BCL3	855	-6.361	1	-0.071
549	POLR3A	507	-6.385	1	-0.029
550	IRF1	951	-6.4	1	-0.074
551	SREBF1	557	-6.406	1	-0.107
552	SREBF2	236	-6.481	1	-0.033
553	SMARCA4	909	-6.492	1	0.013
554	MED12	328	-6.56	1	0.034
555	SMARCC1	867	-6.701	1	0.006
556	CUX1	851	-6.726	1	-0.007
557	STAT5B	350	-6.75	1	0.025
558	NKX3-1	375	-6.775	1	0.047
559	HNF4G	645	-6.791	1	0.129
560	SNAI2	903	-6.905	1	-0.057
561	DAXX	564	-6.959	1	-0.042
562	SMAD4	455	-6.985	1	-0.011
563	EHMT2	301	-7.056	1	-0.005
564	STAG1	886	-7.069	1	-0.054
565	EGR1	984	-7.205	1	-0.104
566	LMO2	320	-7.297	1	0.009
567	MED1	952	-7.385	1	-0.017
568	ZEB1	776	-7.407	1	-0.006

569	CPSF3L	507	-7.414	1	-0.022
570	MYH11	818	-7.418	1	-0.138
571	RBBP5	967	-7.422	1	0.052
572	DDX5	914	-7.429	1	0.026
573	TAF3	821	-7.482	1	-0.084
574	STAT1	992	-7.487	1	0.067
575	PROX1	192	-7.675	1	-0.056
576	SUZ12	420	-7.69	1	0.079
577	CDK6	351	-7.73	1	0.008
578	RBPJ	706	-7.755	1	-0.034
579	FOXP3	163	-7.764	1	-0.016
580	ZBTB17	503	-7.768	1	0.030
581	KAT7	760	-7.797	1	0.035
582	TCP1	453	-7.826	1	-0.042
583	BRD2	599	-7.916	1	-0.051
584	HCFC1	915	-8.076	1	0.061
585	KLF1	899	-8.233	1	0.004
586	ATF3	927	-20.45	1	-0.016
587	PAX5	914	-20.54	1	0.026
588	RAG2	867	-20.22	1	-0.018
589	OTX2	623	-16.67	1	-0.036
590	FOS	995	-16.96	1	-0.036
591	GATA1	980	-16.18	1	-0.026
592	NKX2-1	762	-14.74	1	0.056
593	MAFK	1010	-14.37	1	0.012
594	PBX3	952	-14.12	1	0.050
595	KDM4A	842	-14.64	1	0.030
596	CEBPD	803	-13.43	1	-0.03
597	XBP1	597	-13.87	1	0.045
598	RARA	834	-13.29	1	0.060
599	MEF2B	352	-13.74	1	-0.014
600	MYOD1	510	-12.56	1	-0.035
601	HOXA6	667	-12.7	1	0.004
602	GATA4	871	-12.05	1	0.075
603	NPAT	530	-12.23	1	0.061
604	MXI1	986	-12.01	1	-0.026
605	EP300	1022	-12.65	1	0.055
606	TCF21	290	-11.81	1	0.049
607	MAZ	970	-11.54	1	0.034
608	TAF1	1005	-11.71	1	0.006
609	MBD4	480	-11.57	1	-0.003
610	FOXP2	861	-11.31	1	-0.093
611	SOX2	605	-11.69	1	0.059
612	PPARG	839	-10.2	1	-0.101

613	FOXA1	1017	-10.43	1	0.042
614	FLI1	923	-10.98	1	-0.022
615	PGR	661	-10.97	1	0.003
616	BHLHE40	951	-10.39	1	0.081
617	USF1	1002	-10.68	1	0.086
618	KDM1A	618	-10.8	1	0.062
619	RING1	731	-10.96	1	-0.039
620	ING5	782	-10.48	1	0.082
621	GATA6	976	-10.56	1	0.098
622	JARID2	457	-9.195	1	0.038
623	BARX1	212	-9.714	1	0.061
624	NCOR1	561	-9.266	1	-0.046
625	HNF4A	1009	-9.104	1	0.050
626	ESR1	978	-9.884	1	-0.019
627	SMARCC2	751	-9.853	1	0.036
628	IKZF1	442	-9.8	1	-0.015
629	PRDM11	297	-9.212	1	-0.083
630	MEF2A	716	-9.703	1	-0.038
631	NELFA	612	-9.118	1	-0.057
632	ATF4	305	-9.377	1	0.009
633	KLF11	836	-8.336	1	-0.134
634	POU2F2	926	-8.296	1	-0.02
635	DMC1	386	-8.833	1	-0.034
636	PML	939	-8.536	1	-0.07
637	SIX5	589	-8.395	1	-0.027
638	SPI1	1003	-8.825	1	0.038
639	KMT2D	832	-8.434	1	0.083
640	TLX1	208	-8.992	1	0.074

Supplementary Table 6 – Top 15 Regulators – Associations to melanoma

Regulators	Adjusted p-value	Melanoma	Metastasis or tumor progression	Tumor suppressor gene	Oncogene
FOSL2	4.88e-158		[S4.01]		
CEBPA	7.70e-148		[S4.02]	[S4.03]	
ZBTB7A	1.76e-141	[S4.04]	[S4.02, S4.04]	[S4.05]	
SMAD1	1.35e-140	[S4.06, S4.07]	[S4.08]		
GATA3	3.13e-136	[S4.09]	[S4.10]		
E2F6	3.92e-126	[S4.11, S4.12]			
MITF	2.23e-105	[S4.13, S4.14]	[S4.13, S4.14]		[S4.13, S4.14]
FOXP1	4.92e-104	[S4.15]	[S4.16]	[S4.17]	
TFAP2C	1.60e-96	[S4.18]			
RXRA	7.42e-94	[S4.19, S4.20]	[S4.19, S4.20]		
CBX3	1.94e-89	[S4.21]	[S4.22]		
BRCA1	3.03e-83	[S4.23]	[S4.24, S4.25]	[S4.26]	
ATF2	4.00e-78	[S4.27]	[S4.27]	[S4.28]	[S4.28]
HEY1	1.37e-77	[S4.29, S4.30]			
TP63	2.62e-75	[S4.31]	[S4.32]	[S4.32]	

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Supplementary Table 7 – Macrophages

TF	Regression Coefficient	
HOXA3	0.148367202	[S6.01]
HLTF	0.089891363	[S6.02]
ETV5	0.078639561	[S6.03]
GMEB1	0.045548794	[S6.04]
HOXA5	0.04494131	[S6.05]
NRF1	0.039230003	[S6.06, S6.07, S6.08]
PAX2 (paralog of PAX5)	0.038496525	[S6.09]
ETS2	0.034375522	[S6.10]
ELF5	0.033069267	[S6.11]
NFATC1	0.032528012	[S6.12]
KLF4	0.025539592	[S6.13]
NKX2.5	0.025418796	[S6.14]
RAD21	-0.052709626	[S6.15]

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