

Estimating the activity of transcription factors by the effect on their target genes

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Supplementary Material

Supplementary Figures

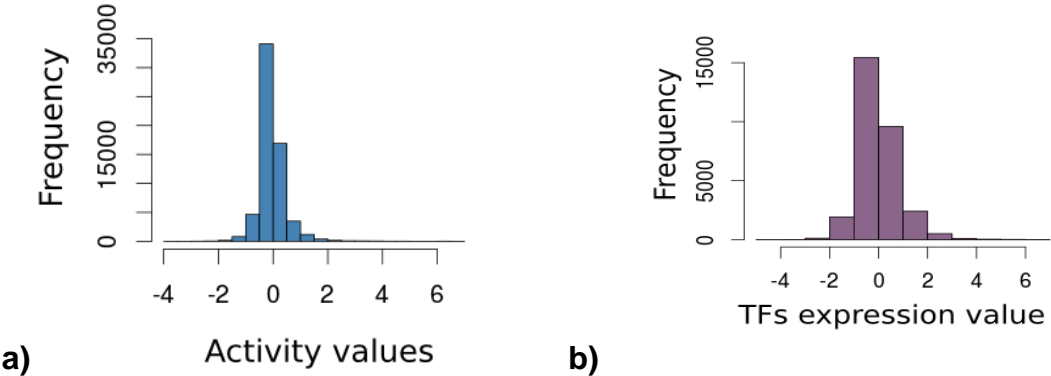


Figure S1: Distribution of activity (a) and TF-gene expression (b) over all transcription factors and investigated cell lines from the analyzed NCI-60 panel.

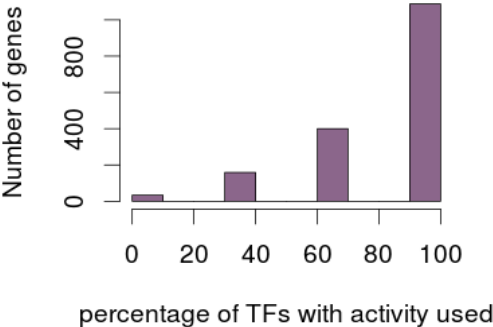


Figure S2: Most of the transcription factors were modelled using the activity definition when employing the model switch (here for 1682 target genes).

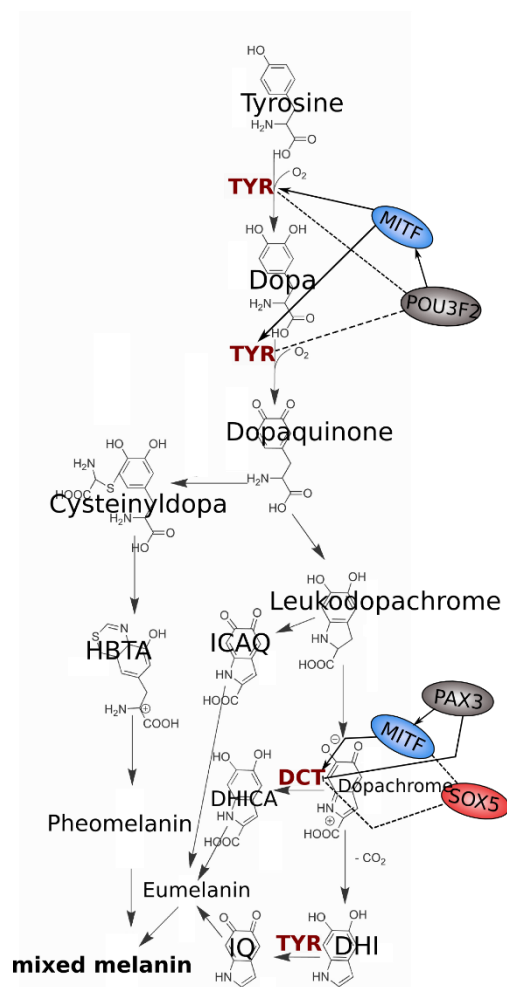


Figure S3: Melanogenesis and its regulators. TYR and DCT are the key enzymes of melanogenesis and they are regulated by MITF, POU3F2, PAX3 and SOX5. Melanocytes contain the skin pigment melanin produced by melanogenesis. This distinguishes them from the other analyzed cells. Genes TYR and DCT were highly up-regulated in the melanocytes of the NCI-60 panel. Melanin synthesis starts from tyrosine, processed by the pacemaker enzyme tyrosinase (TYR) which catalyzes the first two rate-limiting steps of melanin synthesis. Dopaquinone is transformed by autooxidation into dopachrome via leukodopachrome. Subsequent oxidation of dopachrome results in 5,6-dihydroxyindole (DHI) which is then further oxidized to indole-5,6-quinone (IQ) catalyzed by tyrosinase. Tyrosinase-related protein 2 (TRP2), also known as dopachrome tautomerase (DCT), converts dopachrome to 5,6-dihydroxyindole-2-carboxylic acid (DHICA) from which indole-2-carboxylic acid-5,6quinone (ICAQ) is produced using TRP1. Finally, oxidative polymerisation of IQ, DHICA and ICAQ leads to eumelanin. In the presence of glutathione or cysteine, dopaquinone can react with those amino acids yielding glutathionyldopa or cysteinyldopa, which are then further oxidized to 5-hydroxy 1,4-benzothiazinylalanine (HBTA). Pheomelanin is produced by oxidative polymerisation of HBTA (Chang, 2009). Under standard conditions, melanocytes produce eumelanin as well as pheomelanin resulting in a mixture of both melanin types (Lin and Fisher, 2007). The figure was produced according to the information from (Chang, 2009) using ChemBio Draw Ultra (www.cambridgesoft.com).

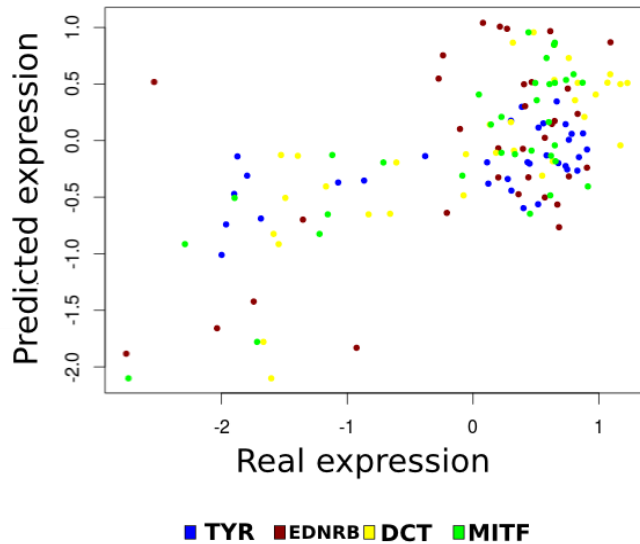


Figure S4: Scatterplot of predicted and measured transcript levels. For the four genes TYR, DCT, EDNRB and MITF the gene expression values were predicted for the 33 melanoma cell lines, which were not used for learning the model (fixed β -coefficients, learned from the data of the NCI-60 panel). Average of Pearson's correlation between all predicted and measured expression values was $r=0.64$.

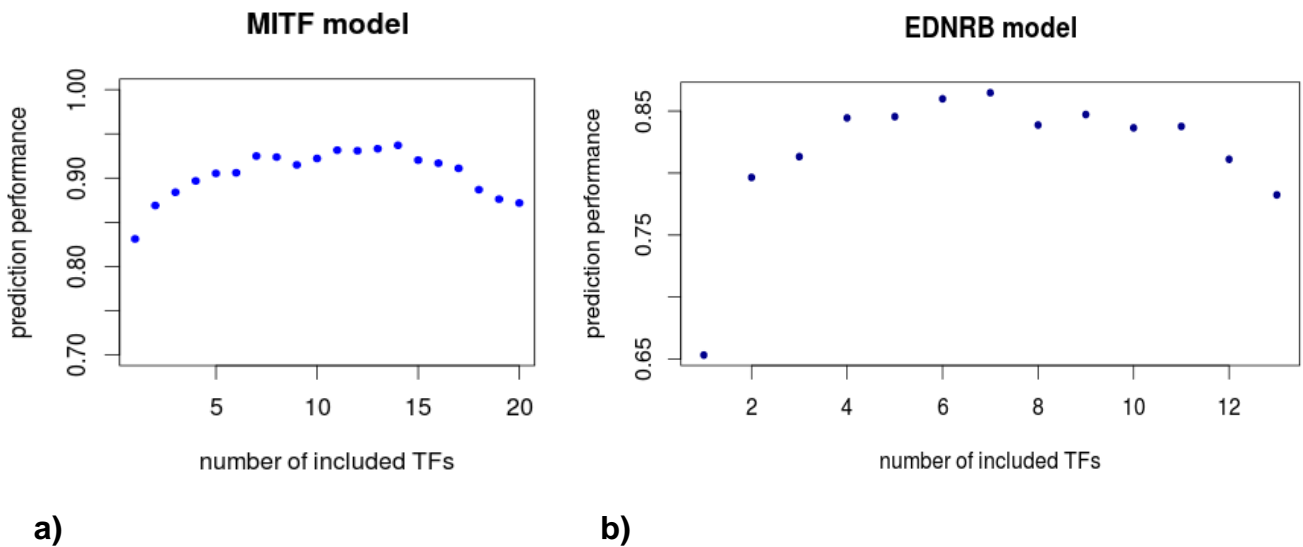


Figure S5: Tracking the prediction performance bottom-up to investigate the tendency of overfitting. For the genes a) MITF and b) EDNRB regulation models were set up to predict their gene expression. We constrained the models by the number of included TFs (betas unequal to zero) from 1 to the number of all putative TFs. The prediction performance was calculated using a leave-one-out cross-validation. Raising the number of non-zero betas improves the prediction performance until a plateau is reached, and the performance final decreases (overfitted model for higher numbers of non-zero betas).

Supplementary Method 1:

To restrict the number of parameters (β_t) for a model, further constraints were added. Each possible TF of a target gene (for which the model was set up) got a binary coefficient x_i , in addition to the TF's beta-coefficients. If the binary coefficient equaled zero, the according beta was forced to be zero and TF was not used for this model (formulas 2 and 3, below). For n possible regulators, the sum of the binary coefficients was set to r (formula 1). In our study, we used $r = 6$ (and $r = 3$ for analysis of section 3.4). A fixed variable called "Big M" with $M = 1000$ was needed to fulfill these criteria. Note that M was chosen large enough to not restrict the search space.

$$x_1 + x_2 + \dots + x_n = r \quad (1)$$

$$\beta_i - M \cdot x_i \leq 0 \quad (2)$$

$$\beta_i + M \cdot x_i \geq 0 \quad \text{for all } i = 1, \dots, n \quad (3)$$

References

Chang, T.S. (2009) An updated review of tyrosinase inhibitors, *International journal of molecular sciences*, **10**, 2440-2475.

Lin, J.Y. and Fisher, D.E. (2007) Melanocyte biology and skin pigmentation, *Nature*, **445**, 843-850.

Supplementary Table S1

TF	Number activity	Number gene expression	Total number	% Activity	Mean PCC r
ELK4	1	0	1	100	0.25
SATB1	3	0	3	100	0.34
HNF4G	2	0	2	100	0.41
HIC1	2	0	2	100	0.44
NEUROD1	3	0	3	100	0.44
ETV6	1	0	1	100	0.44
NR2C2	2	0	2	100	0.44
FOXA1,FOXA2,FOXA3	2	0	2	100	0.46
DMRT1	1	0	1	100	0.47
STAT4	6	0	6	100	0.48
GMNN	1	0	1	100	0.49
SRY	1	0	1	100	0.49
FOXA1	6	0	6	100	0.5
HNF4A,HNF4G	3	0	3	100	0.5
HOXC6	1	0	1	100	0.5
NFYB	6	0	6	100	0.5
STAT5A,STAT5B	6	0	6	100	0.5
ZNF148	7	0	7	100	0.51
PDX1	5	0	5	100	0.51
NR2F1,NR2F2	2	0	2	100	0.51
MXD1	1	0	1	100	0.51
NR5A2	5	0	5	100	0.52
NR0B2	2	0	2	100	0.52
GF11	8	0	8	100	0.52
MECOM	2	0	2	100	0.52
TFCP2	3	0	3	100	0.52
PKNOX1	1	0	1	100	0.52
ESRRB	2	0	2	100	0.53
SP1,SP3	5	0	5	100	0.53
HOXA13	3	0	3	100	0.53
REL,RELA	5	0	5	100	0.53
MESP1	5	0	5	100	0.53
ELF1	6	0	6	100	0.53
PAX2	1	0	1	100	0.53
HCFC1	1	0	1	100	0.54
CEBPG	11	0	11	100	0.54
SIX1	4	0	4	100	0.54
GLI3	4	0	4	100	0.55
NFE2	1	0	1	100	0.56
PITX2	4	0	4	100	0.56
MTA1	3	0	3	100	0.56
RXRβ	2	0	2	100	0.56
NR4A2	5	0	5	100	0.56
PPARα,RXRα	3	0	3	100	0.56

AHR	5	0	5	100	0.57
FOS,JUN	4	0	4	100	0.57
TFEB	2	0	2	100	0.57
LHX2	7	0	7	100	0.57
MSX2	2	0	2	100	0.57
TBX21	8	0	8	100	0.57
PURA	3	0	3	100	0.58
EPAS1	7	0	7	100	0.58
SIM2	2	0	2	100	0.58
RARA,RAR B,RARG	2	0	2	100	0.59
MYBL2	6	0	6	100	0.59
LEF1,TCF7, TCF7L1,TC F7L2	8	0	8	100	0.59
ESR1,ESR 2	4	0	4	100	0.59
DBP	4	0	4	100	0.59
NAB2	2	0	2	100	0.59
RUNX1,RU NX1T1	6	0	6	100	0.6
FOSL1,JUN	4	0	4	100	0.6
TLX3	2	0	2	100	0.6
FOXC1	2	0	2	100	0.6
PBX1,PKN OX1	2	0	2	100	0.61
ONECUT1	6	0	6	100	0.61
MBD1	4	0	4	100	0.61
GLI1	7	0	7	100	0.61
SMAD2	4	0	4	100	0.61
HHEX	2	0	2	100	0.61
USF1,USF2	4	0	4	100	0.61
RXRA,THR B	3	0	3	100	0.61
ZKSCAN3	3	0	3	100	0.61
IRF5	4	0	4	100	0.61
POU2F3	1	0	1	100	0.62
KLF13	1	0	1	100	0.62
BATF	4	0	4	100	0.62
IRF2	7	0	7	100	0.62
POU2AF1	2	0	2	100	0.62
NR1H2	2	0	2	100	0.62
MTF2	3	0	3	100	0.62
NFYC	5	0	5	100	0.62
NFATC3	6	0	6	100	0.63
MEF2C	8	0	8	100	0.63
SIX4	2	0	2	100	0.63
ZBTB33	2	0	2	100	0.63
FEV	3	0	3	100	0.63
CDX1	2	0	2	100	0.63
VAX2	1	0	1	100	0.64
MSX1	1	0	1	100	0.64
FOXO4	2	0	2	100	0.64
NR2F6	6	0	6	100	0.64

BCL6	7	0	7	100	0.65
EGR3	5	0	5	100	0.65
HNF1A,HN F1B	6	0	6	100	0.65
NR1H3,RX RA	9	0	9	100	0.65
KLF6	4	0	4	100	0.65
POU3F4	3	0	3	100	0.65
CBFB	4	0	4	100	0.65
ATF2	8	0	8	100	0.65
PBX2	3	0	3	100	0.65
OLIG2	3	0	3	100	0.66
POU4F2	1	0	1	100	0.66
ZNF217	4	0	4	100	0.66
ATF3	5	0	5	100	0.66
NFAT5	4	0	4	100	0.66
ETV1	6	0	6	100	0.66
LHX3	2	0	2	100	0.66
NEUROG3	2	0	2	100	0.66
FOXP1	10	0	10	100	0.67
NFKB2,REL B	3	0	3	100	0.67
NR1H4	6	0	6	100	0.67
FOXL2	7	0	7	100	0.67
SPDEF	3	0	3	100	0.67
HOXA9	2	0	2	100	0.67
SOX9	15	0	15	100	0.67
ASCL2	3	0	3	100	0.67
KCNIP3	1	0	1	100	0.67
GABPB1	3	0	3	100	0.67
ZNF350	1	0	1	100	0.67
BHLHE40	2	0	2	100	0.67
E2F2	6	0	6	100	0.67
POU1F1	3	0	3	100	0.67
GATA3	7	0	7	100	0.67
NR1H3	4	0	4	100	0.68
DACH1	4	0	4	100	0.68
GTF2I	4	0	4	100	0.68
NKX3-1	6	0	6	100	0.68
SMAD5	7	0	7	100	0.68
EHF	7	0	7	100	0.68
PHOX2A	3	0	3	100	0.68
NFE2L1	3	0	3	100	0.69
NR1I3	4	0	4	100	0.69
MTF1	3	0	3	100	0.69
ZEB2	6	0	6	100	0.69
NFIA,NFIB, NFIC,NFIX	4	0	4	100	0.69
NKX2-5	1	0	1	100	0.69
RREB1	2	0	2	100	0.7
FOXC1,FO XC2	1	0	1	100	0.7
ESRRG	4	0	4	100	0.7
NR1H2,RX	1	0	1	100	0.7

RA					
DMTF1	5	0	5	100	0.7
ERF	3	0	3	100	0.7
FO XK1	1	0	1	100	0.7
E2F5	3	0	3	100	0.7
MEIS2	4	0	4	100	0.7
LDB1	6	0	6	100	0.7
VDR	15	0	15	100	0.7
ARNT2	3	0	3	100	0.7
RORC	2	0	2	100	0.7
KLF2	3	0	3	100	0.7
TBX1	2	0	2	100	0.7
MLL	3	0	3	100	0.7
NR3C2	2	0	2	100	0.7
YAP1	5	0	5	100	0.7
NR2E1	3	0	3	100	0.71
LMX1B	1	0	1	100	0.71
SIX3	1	0	1	100	0.71
LMX1A	1	0	1	100	0.71
KLF11	3	0	3	100	0.71
ELF4	6	0	6	100	0.71
CITED2	5	0	5	100	0.71
HOXC8	2	0	2	100	0.71
SP4	3	0	3	100	0.71
ATOH1	3	0	3	100	0.71
YBX1	5	0	5	100	0.71
CHUK	3	0	3	100	0.72
SOX17	3	0	3	100	0.72
NHLH2	2	0	2	100	0.72
NR4A1	4	0	4	100	0.72
RFX2	1	0	1	100	0.72
SMARCA5	4	0	4	100	0.72
E2F8	1	0	1	100	0.72
SOX11	2	0	2	100	0.72
PTF1A	1	0	1	100	0.72
NR1I2,RXR A	1	0	1	100	0.72
CREB3	1	0	1	100	0.72
RFX1	1	0	1	100	0.72
ASH2L	4	0	4	100	0.72
EGR2	4	0	4	100	0.72
LITAF	3	0	3	100	0.72
CHD8	1	0	1	100	0.72
NRL	1	0	1	100	0.72
JDP2	4	0	4	100	0.73
PHF1	1	0	1	100	0.73
MLL4	1	0	1	100	0.73
NKX6-1	3	0	3	100	0.73
SATB2	2	0	2	100	0.73
NR1H4,RX RA	2	0	2	100	0.73
HOXB9	5	0	5	100	0.73
NR1I2	3	0	3	100	0.73
DNAJC2	2	0	2	100	0.73

MZF1	4	0	4	100	0.73
PROX1	6	0	6	100	0.73
CREB3L3	6	0	6	100	0.73
NRF1	2	0	2	100	0.73
NFAT5,NFATC1,NFATC2,NFATC3,NFATC4	1	0	1	100	0.73
SOX4	2	0	2	100	0.74
TCF21	3	0	3	100	0.74
BARX2	2	0	2	100	0.74
IRF7	3	0	3	100	0.74
RXRA,THRA	2	0	2	100	0.74
ARNTL2	3	0	3	100	0.74
CSDA	4	0	4	100	0.74
IRF9	2	0	2	100	0.74
NCOA2	3	0	3	100	0.74
ZBTB7B	4	0	4	100	0.74
E2F1,TFDP1	3	0	3	100	0.75
ERG,EWSR1	1	0	1	100	0.75
TFAP4	7	0	7	100	0.75
DLX5	2	0	2	100	0.75
FOSL2,JUN D	3	0	3	100	0.75
NFKB2	3	0	3	100	0.75
KLF3	1	0	1	100	0.75
PAX3	7	0	7	100	0.75
KLF10	4	0	4	100	0.75
GTF2IRD1	3	0	3	100	0.75
ETV2	3	0	3	100	0.76
NCOA1	3	0	3	100	0.76
PML	3	0	3	100	0.76
FOSL2,JUN	3	0	3	100	0.76
ZFHX3	2	0	2	100	0.76
FOXO1,PAX3	2	0	2	100	0.76
NPAS2	2	0	2	100	0.76
ATF5	3	0	3	100	0.76
MYF6	3	0	3	100	0.76
WDR5	2	0	2	100	0.76
MEF2D	5	0	5	100	0.76
THRA,THRB	1	0	1	100	0.77
DLX3	2	0	2	100	0.77
NR1D2	4	0	4	100	0.77
FOSL1,JUN B	1	0	1	100	0.77
CTCF	4	0	4	100	0.77
FOXE1	2	0	2	100	0.77
SPIB	2	0	2	100	0.78
T	2	0	2	100	0.78

MED1	2	0	2	100	0.78
OLIG1	4	0	4	100	0.78
TCF4	6	0	6	100	0.78
ONECUT2	3	0	3	100	0.79
TCF12	2	0	2	100	0.79
STAT2	2	0	2	100	0.79
SP2	1	0	1	100	0.8
PAX7	1	0	1	100	0.8
ISL1	3	0	3	100	0.8
EN1	1	0	1	100	0.8
BCL3	4	0	4	100	0.81
TCF15	1	0	1	100	0.81
ARX	1	0	1	100	0.81
SP7	2	0	2	100	0.81
ELK3	2	0	2	100	0.82
SOX15	1	0	1	100	0.82
MYF5	1	0	1	100	0.82
SOX7	1	0	1	100	0.83
RXRG	1	0	1	100	0.83
BACH1	1	0	1	100	0.83
LMO4	3	0	3	100	0.84
XBP1	1	0	1	100	0.84
KLF9	1	0	1	100	0.84
FOXD3	1	0	1	100	0.85
MLL,MLLT1	1	0	1	100	0.85
FOXN1	1	0	1	100	0.86
NR6A1	1	0	1	100	0.87
SOX5	3	0	3	100	0.89
TBX5	1	0	1	100	0.9
RFX5	1	0	1	100	0.93
CEBPD	19	1	20	95	0.57
RARA	16	1	17	94.1	0.66
RXRA	13	1	14	92.9	0.53
STAT5B	13	1	14	92.9	0.56
SMAD3	13	1	14	92.9	0.57
RBPJ	13	1	14	92.9	0.59
REL	13	1	14	92.9	0.69
FOSB	12	1	13	92.3	0.53
TWIST1	12	1	13	92.3	0.64
TCF3	11	1	12	91.7	0.68
REST	11	1	12	91.7	0.68
NFYA	10	1	11	90.9	0.61
PPARA,RX RA	10	1	11	90.9	0.63
FOS	19	2	21	90.5	0.59
MYB	9	1	10	90	0.56
TP53	63	7	70	90	0.6
USF2	9	1	10	90	0.61
TFAP2D	9	1	10	90	0.61
NFYA,NFY B,NFYC	9	1	10	90	0.63
SNAI1	9	1	10	90	0.69
NR2F1	9	1	10	90	0.69
TFAP2E	8	1	9	88.9	0.46

PAX6	8	1	9	88.9	0.53
IRF8	8	1	9	88.9	0.57
SMAD4	16	2	18	88.9	0.6
WT1	16	2	18	88.9	0.61
ATF1	8	1	9	88.9	0.61
KLF4	16	2	18	88.9	0.64
PGR	8	1	9	88.9	0.66
STAT6	8	1	9	88.9	0.66
IKZF1	8	1	9	88.9	0.68
ZEB1	8	1	9	88.9	0.76
CEBPA	23	3	26	88.5	0.58
JUN	30	4	34	88.2	0.64
MYOD1	7	1	8	87.5	0.55
GATA1	21	3	24	87.5	0.57
GATA6	7	1	8	87.5	0.57
CUX1	7	1	8	87.5	0.6
SMAD1	7	1	8	87.5	0.61
ETV5	7	1	8	87.5	0.61
NFIB	7	1	8	87.5	0.62
ATF4	7	1	8	87.5	0.66
HMGA1	7	1	8	87.5	0.66
FLI1	7	1	8	87.5	0.66
ESR2	21	3	24	87.5	0.66
E2F4	7	1	8	87.5	0.68
TCF7L2	19	3	22	86.4	0.64
ARNT2,HIF 1A	6	1	7	85.7	0.44
MBD2	6	1	7	85.7	0.5
RARA,RXR A	6	1	7	85.7	0.61
CEBPA,CE BPB,CEBP D,CEBPE,C EBPG	6	1	7	85.7	0.61
SOX2	36	6	42	85.7	0.61
HES1	6	1	7	85.7	0.64
HOXA10	6	1	7	85.7	0.65
ASCL1	6	1	7	85.7	0.66
THRA	6	1	7	85.7	0.67
GATA2	6	1	7	85.7	0.69
NR3C1	29	5	34	85.3	0.59
RELB	46	8	54	85.2	0.58
TP63	23	4	27	85.2	0.66
POU2F1	17	3	20	85	0.62
TFAP2B	11	2	13	84.6	0.52
PPARG	16	3	19	84.2	0.52
GATA4	16	3	19	84.2	0.57
ETS1	26	5	31	83.9	0.61
EGR1	46	9	55	83.6	0.59
GATA5	5	1	6	83.3	0.4
TFE3	5	1	6	83.3	0.53
NFIC	10	2	12	83.3	0.55
ZBTB16	5	1	6	83.3	0.56
STAT3	35	7	42	83.3	0.56

RUNX1,TR PS1	5	1	6	83.3	0.56
NFIA	5	1	6	83.3	0.58
ARNT	5	1	6	83.3	0.58
RORA	5	1	6	83.3	0.59
CEBPB	40	8	48	83.3	0.59
STAT5A	10	2	12	83.3	0.6
TP73	10	2	12	83.3	0.6
MEIS1	5	1	6	83.3	0.61
NKX2-2	5	1	6	83.3	0.67
MEF2A,ME F2B,MEF2 C,MEF2D	5	1	6	83.3	0.67
DDIT3	5	1	6	83.3	0.68
ZNF143	5	1	6	83.3	0.74
E2F1	24	5	29	82.8	0.64
NFATC1	9	2	11	81.8	0.65
ETS2	13	3	16	81.2	0.62
USF1	13	3	16	81.2	0.64
NFKB1,REL	17	4	21	81	0.57
PPARGC1A	17	4	21	81	0.57
RUNX1	21	5	26	80.8	0.55
SP1	82	20	102	80.4	0.6
TFAP2C	8	2	10	80	0.48
TAF1,TAF1 0,TAF11,TA F12,TAF13, TAF15,TAF 2,TAF3,TAF 4,TAF4B,T AF5,TAF6,T AF7,TAF7L, TAF8,TAF9, TAF9B,TBP	4	1	5	80	0.5
GLI2	4	1	5	80	0.54
FOXO1	16	4	20	80	0.56
NFKB1	20	5	25	80	0.56
RUNX3	4	1	5	80	0.6
HIF1A	28	7	35	80	0.6
GABPA,GA BPB1	4	1	5	80	0.6
ERG	8	2	10	80	0.64
POU3F1	4	1	5	80	0.64
FOXF1	4	1	5	80	0.65
NR1D1	4	1	5	80	0.65
EBF1	4	1	5	80	0.67
POU2F2	4	1	5	80	0.67
KLF5	4	1	5	80	0.69
TEAD4	4	1	5	80	0.71
NOTCH1	4	1	5	80	0.73
HSF4	4	1	5	80	0.73
RUNX2	15	4	19	78.9	0.6
CREB1	33	9	42	78.6	0.62
SRF	18	5	23	78.3	0.63

STAT1	25	7	32	78.1	0.59
ATF2,FOS, FOSB,FOS L1,FOSL2,J UN,JUNB,J UND	21	6	27	77.8	0.55
RARG	7	2	9	77.8	0.64
HNF4A	21	6	27	77.8	0.64
FOXA2	13	4	17	76.5	0.57
IRF1	13	4	17	76.5	0.65
SOX6	3	1	4	75	0.5
FOXO3	6	2	8	75	0.53
ELF3	3	1	4	75	0.54
SP3	24	8	32	75	0.55
PPARA	6	2	8	75	0.57
NFATC2	6	2	8	75	0.58
MEN1	3	1	4	75	0.59
HEY2	3	1	4	75	0.59
FOXA3	3	1	4	75	0.63
BHLHE41	3	1	4	75	0.63
CTNNB1	3	1	4	75	0.64
TBX3	3	1	4	75	0.64
KLF15	3	1	4	75	0.65
CLOCK	3	1	4	75	0.65
IRF4	6	2	8	75	0.66
CDX2	6	2	8	75	0.68
TEAD1	3	1	4	75	0.68
SNAI2	6	2	8	75	0.68
NFATC4	3	1	4	75	0.68
MEF2A	3	1	4	75	0.7
ARNTL	3	1	4	75	0.71
NR0B1	3	1	4	75	0.71
POU3F3	3	1	4	75	0.72
NFIL3	3	1	4	75	0.72
MAFB	3	1	4	75	0.72
PAX8	3	1	4	75	0.73
DLX2	3	1	4	75	0.75
AR	26	9	35	74.3	0.64
SPI1	23	8	31	74.2	0.56
TCF7L1	8	3	11	72.7	0.56
ELF5	8	3	11	72.7	0.57
JUND	8	3	11	72.7	0.6
LEF1	13	5	18	72.2	0.57
TFAP2A	23	9	32	71.9	0.58
TFAP2A,TF AP2B,TFAP 2C,TFAP2D ,TFAP2E	10	4	14	71.4	0.58
NFE2L2	5	2	7	71.4	0.61
NR2F2	5	2	7	71.4	0.7
HSF1	7	3	10	70	0.59
PAX5	7	3	10	70	0.62
MYC	37	16	53	69.8	0.62
MYCN	9	4	13	69.2	0.63

POU5F1	23	11	34	67.6	0.61
ETS1,ETS2	4	2	6	66.7	0.55
HLF	2	1	3	66.7	0.55
PPARD	8	4	12	66.7	0.55
CREM	6	3	9	66.7	0.57
MLXIPL	4	2	6	66.7	0.58
FOXP3	2	1	3	66.7	0.61
MAZ	4	2	6	66.7	0.62
FOSL1	4	2	6	66.7	0.62
E2F3	4	2	6	66.7	0.63
HAND2	2	1	3	66.7	0.63
FOXC2	2	1	3	66.7	0.63
ESR1	40	20	60	66.7	0.64
MITF	8	4	12	66.7	0.65
ZBTB7A	2	1	3	66.7	0.65
ESRRA	4	2	6	66.7	0.66
THRB	2	1	3	66.7	0.66
ATF2,JUN	2	1	3	66.7	0.67
NKX2-1	4	2	6	66.7	0.67
FOXM1	6	3	9	66.7	0.68
ETV4	6	3	9	66.7	0.68
TBP	2	1	3	66.7	0.68
ATF6	2	1	3	66.7	0.71
NCOA3	2	1	3	66.7	0.71
NR1H3,RXR A	2	1	3	66.7	0.71
MYOG	2	1	3	66.7	0.72
HSF2	2	1	3	66.7	0.72
OTX2	2	1	3	66.7	0.72
TRPS1	2	1	3	66.7	0.73
PITX1	2	1	3	66.7	0.76
SALL4	2	1	3	66.7	0.77
IRF9,STAT 1,STAT2	2	1	3	66.7	0.78
NFKB1,NF KB2,REL,R ELA,RELB	2	1	3	66.7	0.79
HNF1A	13	7	20	65	0.67
YY1	16	9	25	64	0.57
NFIX	5	3	8	62.5	0.62
GABPA	3	2	5	60	0.5
NR5A1	3	2	5	60	0.56
TCF7	9	6	15	60	0.59
E2F7	3	2	5	60	0.79
HNF1B	7	5	12	58.3	0.6
PBX1	6	5	11	54.5	0.62
EOMES	1	1	2	50	0.36
FOSL2	2	2	4	50	0.41
HOXA5	1	1	2	50	0.53
SREBF1	3	3	6	50	0.55
HEY1	1	1	2	50	0.6
ZBTB17	1	1	2	50	0.64
SREBF2	1	1	2	50	0.67
TGIF1	1	1	2	50	0.67

HOXD13	1	1	2	50	0.69
IRF3	3	3	6	50	0.69
TAL1	2	2	4	50	0.69
SOX10	4	4	8	50	0.7
NEUROG2	1	1	2	50	0.72
CTCFL	1	1	2	50	0.78
CRTC2	1	1	2	50	0.78
NFKB1,REL A	1	1	2	50	0.88
ELK1	7	8	15	46.7	0.55
CEBPE	3	4	7	42.9	0.59
POU3F2	2	3	5	40	0.65
KLF1	1	2	3	33.3	0.31
ZNF202	1	2	3	33.3	0.59
MAF	1	3	4	25	0.63
PRDM1	1	3	4	25	0.64
TBX2	0	1	1	0	0.31
RELA	0	1	1	0	0.66
POU4F1	0	1	1	0	0.79
DRAP1	0	1	1	0	0.93

Supplementary Table S2

Enriched gene groups (Gene Ontology Biological Process, except for gene groups annotated with "KEGG")	Probability (BH corrected)
Enrichments of target of activity modelled TFs (TOA)	
development	6.94e-021
morphogenesis	2.27e-019
regulation of transcription, DNA-dependent	4.42e-018
organogenesis	8.29e-018
regulation of transcription	1.33e-017
transcription, DNA-dependent	4.14e-017
transcription	3.35e-015
KEGG Cell cycle - Homo sapiens	6.79e-008
KEGG Cell Growth and Death - Homo sapiens	1.96e-006
response to external stimulus	5.94e-006
nucleotide and nucleic acid metabolism	1.54e-005
cell communication	3.35e-005
defense response	3.53e-005
immune response	4.12e-005
KEGG Complement andcoagulation cascades - Homo sapiens	8.05e-005
KEGG Immune System - Homo sapiens	8.05e-005
response to biotic stimulus	1.13e-004
antigen presentation	1.83e-004
cellular process	2.45e-004
cell surface receptor linked signal transduction	6.63e-004
regulation of cellular process	6.63e-004

regulation of biological process	1.27e-003
pattern specification	1.80e-003
antigen processing	4.31e-003
regulation of transcription from Pol II promoter	6.17e-003
neurogenesis	6.17e-003
negative regulation of transcription, DNA-dependent	6.17e-003
cell adhesion	6.36e-003
perception of biotic stimulus	6.76e-003
perception of pest/pathogen/parasite	6.76e-003
blood coagulation	7.56e-003
histogenesis and organogenesis	7.62e-003
negative regulation of transcription from Pol II promoter	7.62e-003
skeletal development	7.62e-003
transcription from Pol II promoter	8.34e-003
hemostasis	1.03e-002
histogenesis	1.03e-002
cell proliferation	1.15e-002
embryonic development	1.41e-002
response to pest/pathogen/parasite	1.41e-002
regulation of cell proliferation	1.41e-002
cell-cell signaling	1.70e-002
antigen processing, exogenous antigen via MHC class II	1.70e-002
antigen presentation, exogenous antigen	1.70e-002
striated muscle contraction	2.06e-002
KEGG Circadian rhythm - Homo sapiens	2.13e-002
KEGG Behavior - Homo sapiens	2.13e-002
rhythmic behavior	2.13e-002
regulation of cell growth	2.53e-002
synapse organization and biogenesis	2.85e-002
synaptogenesis	2.85e-002
embryonic development (sensu Animalia)	3.18e-002
cell motility	3.75e-002
circadian rhythm	3.75e-002
negative regulation of transcription	3.81e-002
response to light	4.59e-002
myeloid blood cell differentiation	4.65e-002
signal transduction	4.65e-002
extracellular structure organization and biogenesis	4.65e-002
extracellular matrix organization and biogenesis	4.65e-002
muscle development	4.74e-002
osteoclast differentiation	4.86e-002
gonad development	4.86e-002
Enrichments of targets of gene expression modelled TFs (TOGs)	
lipid biosynthesis	6.02e-003
cholesterol biosynthesis	2.89e-002
sterol biosynthesis	2.89e-002
Enrichments of target genes of TFs which activity didn't correlate the gene expression of the TF	
transmission of nerve impulse	8.64e-003
synaptic transmission	8.64e-003