

Supplementary Data

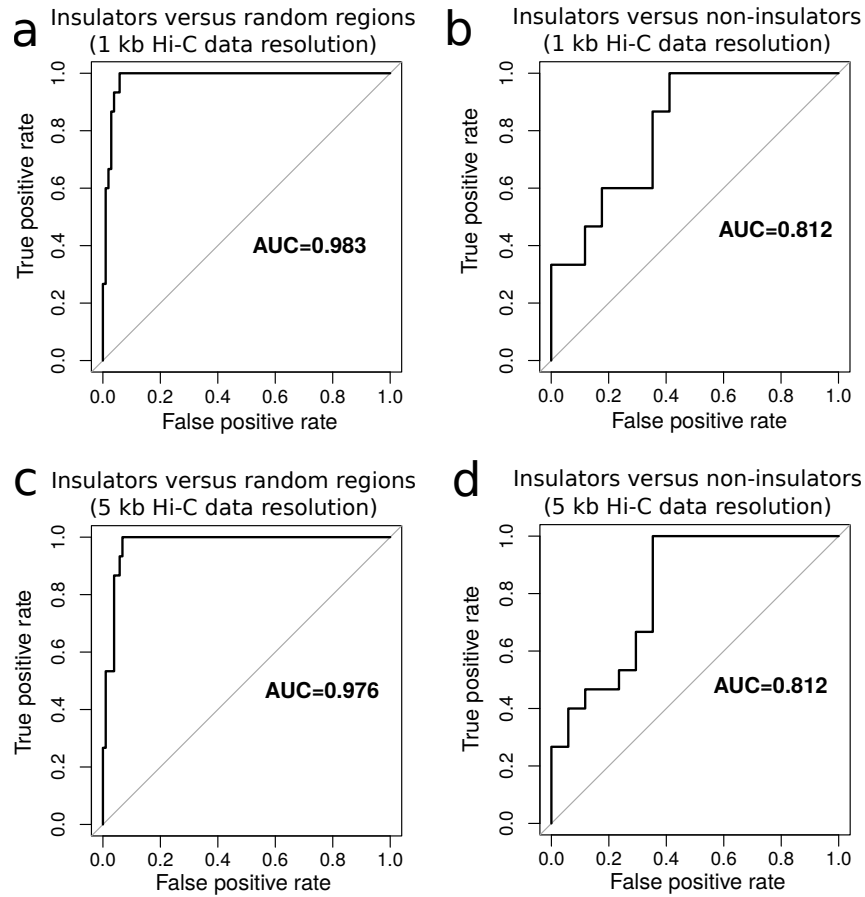


Figure S1: Predictions of enhancer-blocking assays for 1 and 5 kb resolutions. a) Receiver operating characteristic (ROC) curves of the prediction of insulating regions (positives) as compared to randomly drawn regions (negatives) at 1 kb resolution. Area under the ROC curve (AUC) is plotted. b) ROC curves of the prediction of insulating regions (positives) as compared to non-insulating regions (negatives) at 1 kb resolution. c) ROC curves of the prediction of insulating regions (positives) as compared to randomly drawn regions (negatives) at 5 kb resolution. d) ROC curves of the prediction of insulating regions (positives) as compared to non-insulating regions (negatives) at 5 kb resolution.

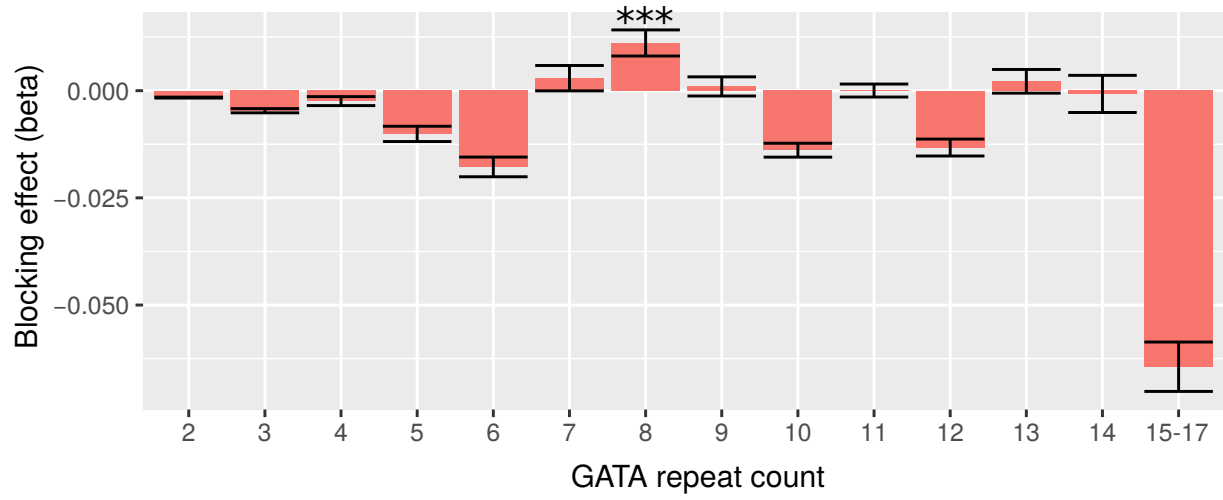


Figure S2: Blocking effects of GATA simple sequence repeats depending on the repeat count in human at 10 kb resolution and for 950-1000 kb distances.

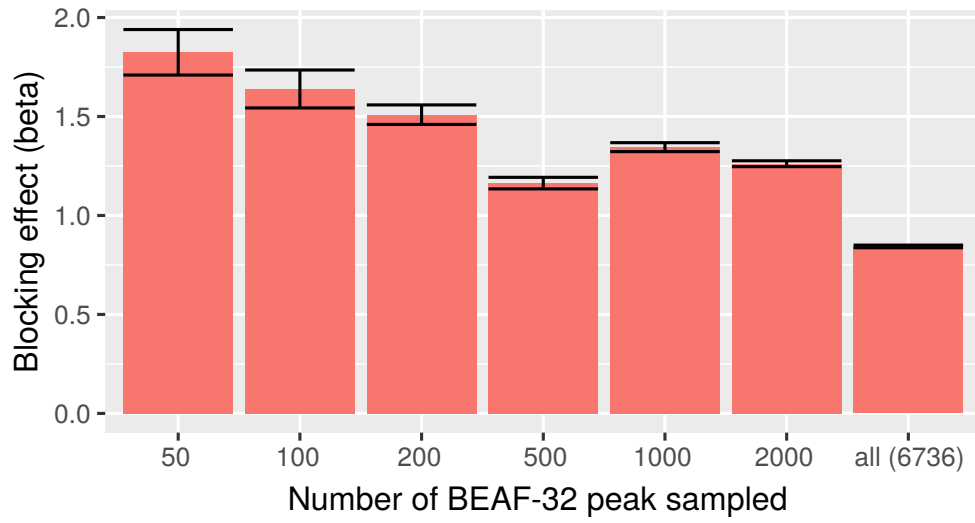


Figure S3: Blocking effect of BEAF-32 depending on the number of sampled ChIP-seq peaks. Analysis at 2 kb resolution in *Drosophila*.

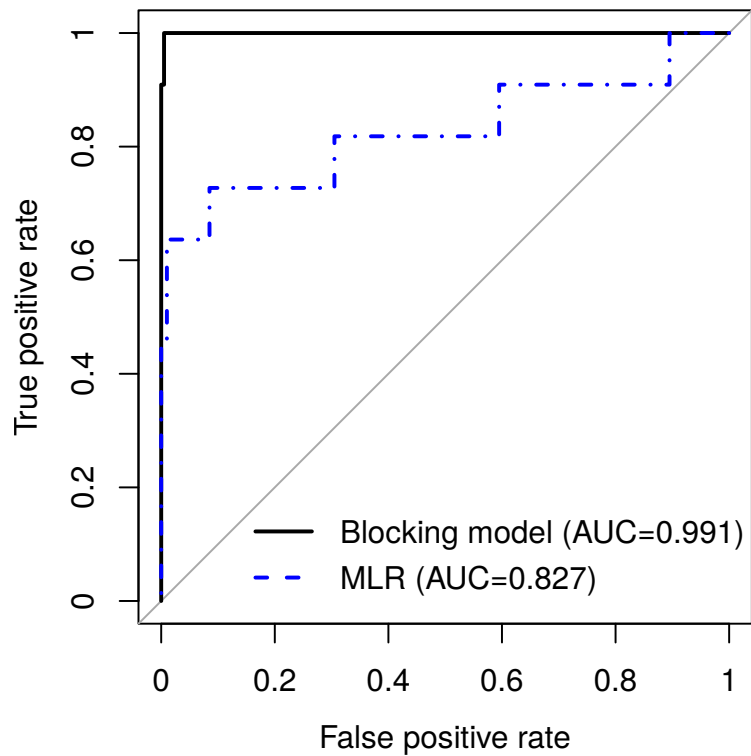


Figure S4: Receiver operating characteristic (ROC) curves of multiple logistic regression (MLR) and the blocking model to distinguish between known protein peaks (11 true positives) and random peaks (200 false positives). Absolute values of model betas are used to assess the effect of proteins on long-range contacts.

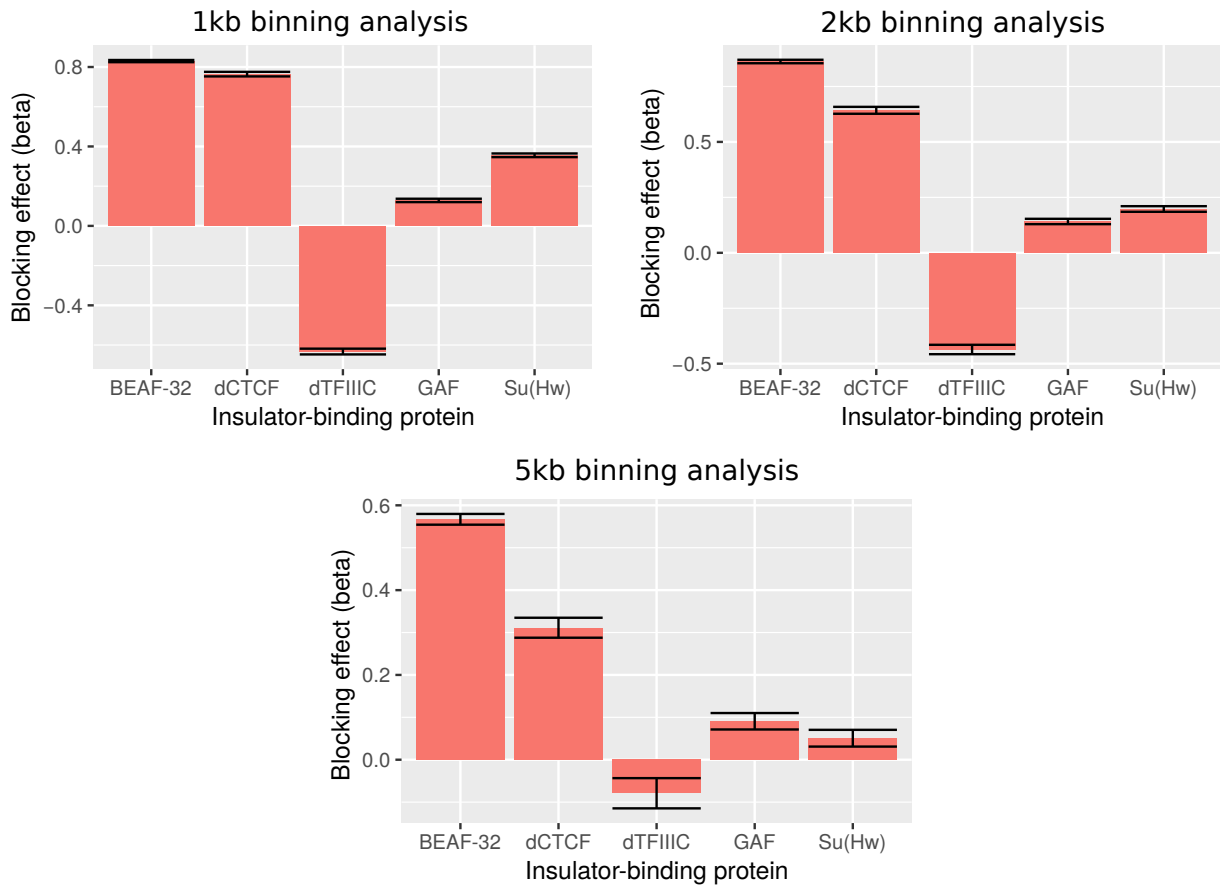


Figure S5: Blocking effects of insulator-binding proteins (IBPs) for different binning resolutions in *Drosophila*.

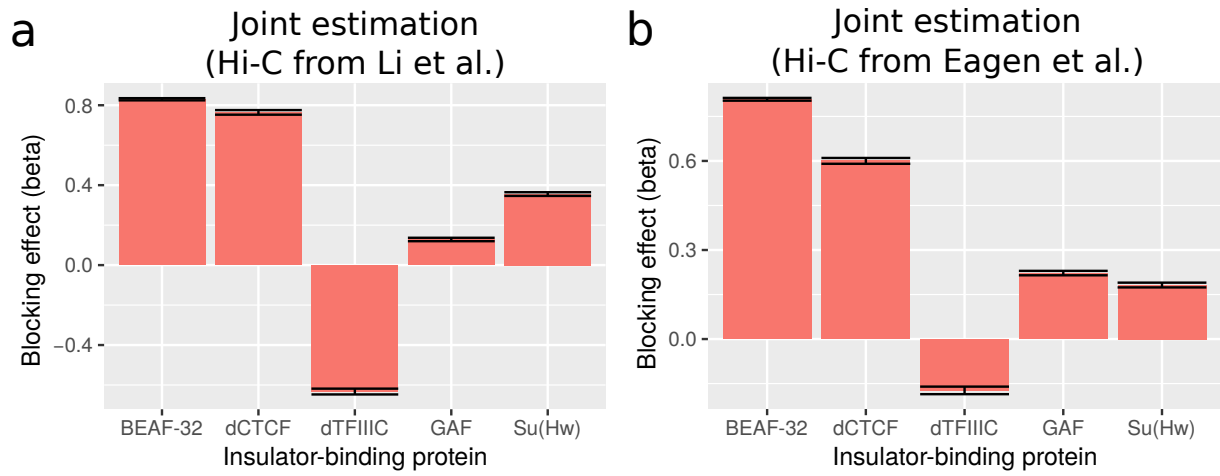


Figure S6: Blocking effects of insulator-binding proteins (IBPs) in *Drosophila* estimated from two different Hi-C data.

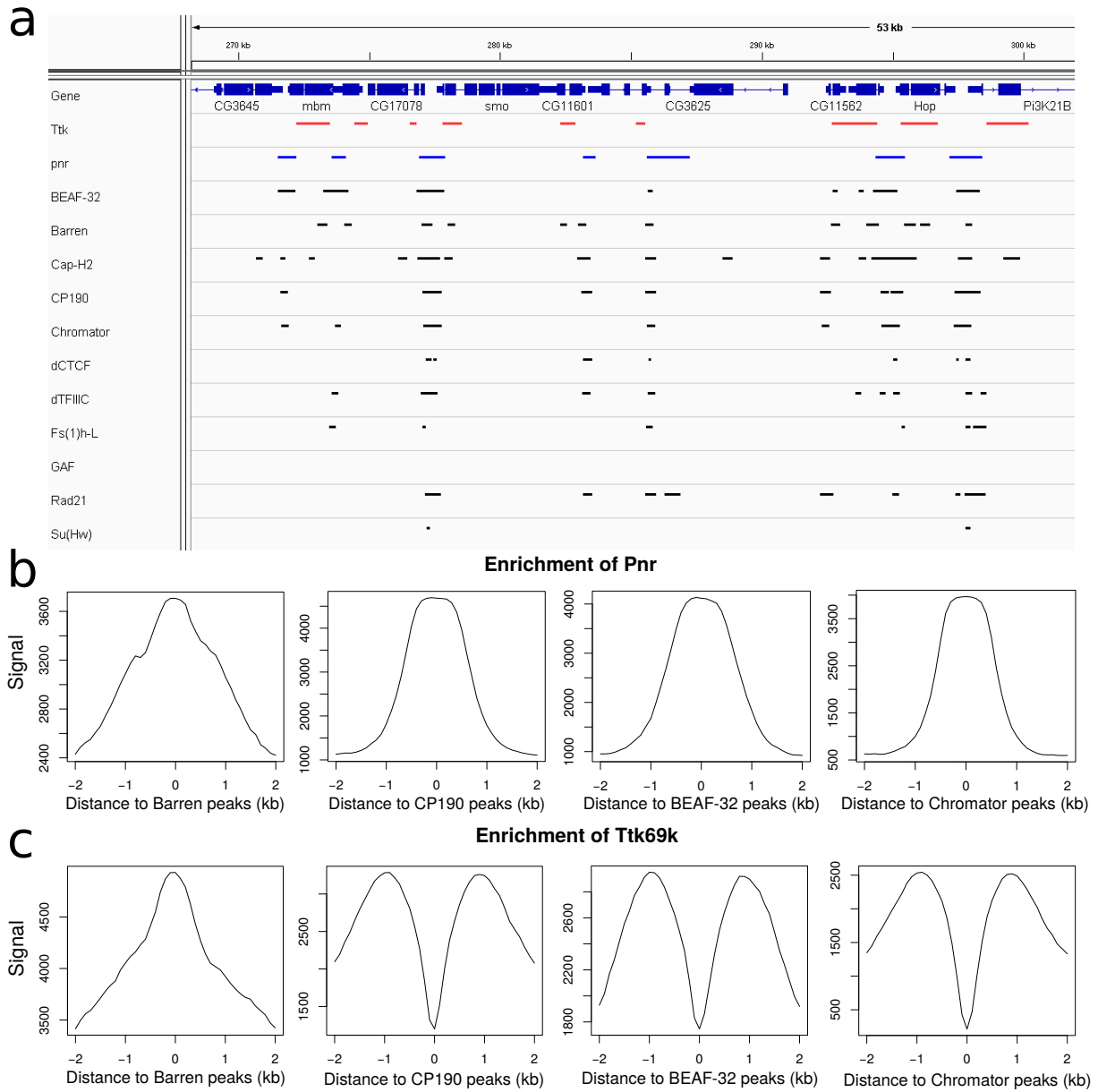


Figure S7: Colocalization of Pnr and Ttk69k with known architectural proteins. a) A genome browser view of Pnr and Ttk69k with known architectural proteins. b) Enrichment of Pnr at architectural protein peaks. c) Enrichment of Ttk69k at architectural protein peaks.

GATA repeat number	Beta	Standard Error	Z	p value
2	-0.006	0.0006	-10.55	4.91647830317279E-26
3	-0.055	0.0024	-22.73	2.06620518209449E-114
4	-0.024	0.0055	-4.43	9.33034970015101E-06
5-6	0.046	0.0081	5.65	1.57778907988474E-08
7-8	-0.008	0.0119	-0.70	0.4827496909
11-123	0.011	0.0100	1.13	0.2577483348

Table S1: Model betas of *Drosophila* GATA simple sequence repeats. Analysis at 2 kb resolution and for 20-50 kb distances.

GATA repeat number	Beta	Standard Error	Z	p value
2	0.013	8.86318829244965E-05	151.06	0
3	0.033	0.0003557116	93.38	0
4	0.038	0.0007036716	53.44	0
5	0.025	0.0011539619	21.27	1.9932908536974E-100
6	0.053	0.0014713421	35.70	4.55723899622072E-279
7	0.062	0.0018601317	33.44	3.45842495063154E-245
8	0.050	0.0019257774	25.85	2.66472092373179E-147
9	0.074	0.0014512988	51.01	0
10	0.071	0.0010661896	66.39	0
11	0.046	0.0009956774	46.18	0
12	0.038	0.0012535064	30.65	2.36704007855988E-206
13	0.042	0.0017541144	24.22	1.39923117425355E-129
14	0.047	0.0027698068	17.00	7.849994668352E-65
15-17	0.043	0.0037149771	11.67	1.86443740955706E-31

Table S2: Model betas of human GATA simple sequence repeats. Analysis at 10 kb resolution and for 100-250 kb distances.

GATA repeat number	Beta	Standard Error	Z	p value
2	-0.002	5.46123852711819E-05	-29.50	3.24053288057492E-191
3	-0.005	0.000250176	-18.70	5.16881150444874E-78
4	-0.002	0.0005330809	-4.56	5.10349653458264E-06
5	-0.010	0.0009108193	-11.07	1.82889335537025E-28
6	-0.018	0.0011700824	-15.20	3.5455797976855E-52
7	0.003	0.0015092428	1.93	0.0537410863
8	0.011	0.0015526436	7.17	7.51336216846802E-13
9	0.001	0.001139641	0.87	0.3836339734
10	-0.014	0.0008266659	-16.80	2.61447113005679E-63
11	0.000	0.0007720696	0.04	0.9681702841
12	-0.013	0.0010067703	-13.18	1.22115259786018E-39
13	0.002	0.0014072903	1.55	0.1206247202
14	-0.001	0.0022085452	-0.34	0.7314923455
15-17	-0.064	0.0029390948	-21.91	2.12936688286524E-106

Table S3: Model betas of human GATA simple sequence repeats. Analysis at 10 kb resolution and for 950-1000 kb distances.

Name	JASPAR code	Beta	Known Architectural Protein	Abundance	Name	JASPAR code	Beta	Known Architectural Protein	Abundance	Name	JASPAR code	Beta	Known Architectural Protein	Abundance
abd-A	MA0206.1	-0.24	No	8885	dve	MA0915.1	0.22	No	1741	ovo	MA0126.1	0.13	No	3199
Abd-B	MA0165.1	-0.07	No	11554	E5	MA0189.1	0.27	No	8208	pan	MA0237.2	0.08	No	5906
achi	MA0207.1	-0.47	No	3416	Ecr::usp	MA0534.1	-0.30	No	5468	pb	MA0238.1	0.12	No	9864
ai	MA0208.1	0.00	No	6545	Eip74EF	MA0026.1	-0.06	No	3092	PHDP	MA0457.1	0.32	No	12824
Antp	MA0166.1	-0.09	No	7400	Elba	MA0220.1	0.27	No	3424	Pita	MA0200.1	0.63	No	1537
ap	MA0209.1	-0.19	No	9148	ems	MA0219.1	0.00	No	7856	pnr	MA0536.1	0.59	No	7803
ara	MA0210.1	-0.19	No	8468	en	MA0220.1	0.37	No	10990	Pph13	MA0200.1	-0.11	No	9845
Awh	MA0167.1	-0.19	No	10170	Ets21C	MA0916.1	-0.60	No	1401	prd	MA0239.1	0.01	No	3199
bap	MA0211.1	0.14	No	3223	eve	MA0221.1	-0.40	No	7601	Ptx1	MA0201.1	-0.34	No	1245
bcd	MA0212.1	0.65	No	2331	exd	MA0222.1	0.09	No	4231	repo	MA0240.1	-0.03	No	8556
BEAF-32		0.13	Yes	5936	exex	MA0224.1	0.18	No	8491	ro	MA0241.1	-0.05	No	7743
Bgb::run	MA0242.1	-0.14	No	4664	fkh	MA0446.1	-0.25	No	11272	Rx	MA0202.1	0.18	No	10752
B-H1	MA0168.1	0.00	No	8596	ftz	MA0225.1	-0.14	No	10538	schlank	MA0193.1	0.00	No	3237
B-H2	MA0169.1	0.03	No	9021	GAF	MA0225.1	0.01	Yes	10367	Scr	MA0203.1	0.51	No	6504
brk	MA0213.1	0.43	No	2911	gcm2	MA0917.1	-0.46	No	1522	sd	MA0243.1	-0.15	No	5076
br	MA0010.1	-0.06	No	20321	Gsc	MA0190.1	-0.69	No	2437	Six4	MA0204.1	-0.08	No	2543
br(var.2)	MA0011.1	0.23	No	7265	gt	MA0447.1	0.05	No	1956	silbo	MA0244.1	-0.06	No	6651
br(var.3)	MA0012.1	0.33	No	12334	H2.0	MA0448.1	0.14	No	12408	siou	MA0245.1	0.20	No	9559
br(var.4)	MA0013.1	0.11	No	16448	hb	MA0049.1	-0.07	No	25953	slp1	MA0458.1	-0.15	No	12539
bsh	MA0214.1	0.30	No	8328	hbn	MA0226.1	0.07	No	12245	sna	MA0086.1	0.48	No	2555
btd	MA0443.1	-0.74	No	2956	HGTX	MA0191.1	0.01	No	11617	so	MA0246.1	0.22	No	2999
btm	MA0215.1	-0.30	No	8928	HHEX	MA0183.1	0.28	No	9177	Stat92E	MA0532.1	-0.12	No	6115
C15	MA0170.1	0.15	No	10974	hkb	MA0450.1	-0.04	No	2845	Su(H)	MA0085.1	-0.21	No	3909
cad	MA0216.2	-0.26	No	14203	h	MA0449.1	-0.13	No	1568	Su(Hw)		0.20	Yes	13929
caup	MA0217.1	0.29	No	6445	Hmx	MA0192.1	0.00	No	6450	tin	MA0247.2	-0.34	No	4859
Cf2	MA0015.1	-0.05	No	26370	hth	MA0227.1	0.10	No	3131	tlf	MA0459.1	-0.12	No	9997
CG11085	MA0171.1	0.31	No	6260	lbf		0.29	No	3586	Trl	MA0205.1	0.02	No	19732
CG11294	MA0172.1	-0.08	No	6829	ind	MA0228.1	-0.67	No	8848	Ttk69k		0.55	No	3484
CG11617	MA0173.1	0.55	No	5032	inv	MA0229.1	0.00	No	7061	tup	MA0248.1	-0.32	No	6848
CG15696-RA	MA0176.1	-0.15	No	12507	kni	MA0451.1	-0.50	No	4231	twi	MA0249.1	-0.28	No	4754
CG18599	MA0177.1	0.14	No	8900	Kr	MA0452.2	-0.05	No	5099	Ubx	MA0094.2	-0.24	No	8448
CG32105	MA0178.1	0.08	No	9392	lab	MA0230.1	0.28	No	8324	unc-4	MA0250.1	-0.48	No	8658
CG32532	MA0179.1	-0.04	No	11434	lbe	MA0231.1	0.05	No	6052	unpg	MA0251.1	0.17	No	11101
CG34031	MA0444.1	0.12	No	6329	lbi	MA0232.1	-0.22	No	7255	usp	MA0016.1	-0.38	No	1190
CG4328-RA	MA0182.1	-0.12	No	12208	Lim1	MA0194.1	0.33	No	6147	vis	MA0252.1	0.60	No	3179
CG9876	MA0184.1	0.17	No	10078	Lim3	MA0195.1	-0.47	No	9592	vnd	MA0253.1	-0.03	No	6194
cnc::maf-S	MA0530.1	-0.44	No	4014	lms	MA0175.1	-0.05	No	8975	Vsx1	MA0181.1	-0.41	No	11108
ct	MA0218.1	0.09	No	5491	M1BP		1.46	No	3646	Vsx2	MA0180.1	0.12	No	8443
Dbx	MA0174.1	0.17	No	12150	Mad	MA0535.1	-0.16	No	4228	vvl	MA0254.1	-0.06	No	6014
dCTCF		0.32	Yes	4155	mirr	MA0233.1	-0.02	No	9289	Zelda		-0.41	No	545
Deaf1	MA0185.1	-0.29	No	5345	NK7.1	MA0196.1	-0.14	No	9846	zen2	MA0257.1	0.00	No	9053
Dfd	MA0186.1	0.11	No	4208	nub	MA0197.2	-0.07	No	16871	zen	MA0256.1	-0.24	No	5867
Dll	MA0187.1	0.10	No	8537	oc	MA0234.1	0.00	No	2389	ZIPIC		-0.19	No	2351
dl	MA0022.1	0.00	No	4576	odd	MA0454.1	-0.19	No	2383	z	MA0255.1	-0.14	No	5137
dl(var.2)	MA0023.1	-0.22	No	3210	OdsH	MA0198.1	0.21	No	10250	ZW5		0.33	Yes	5252
D	MA0445.1	-0.19	No	10471	onecut	MA0235.1	0.10	No	10962					
DREF		0.07	Yes	8294	opa	MA0456.1	-0.09	No	1370					
Dr	MA0188.1	-0.16	No	4476	Optix	MA0199.1	-0.06	No	4057					
dTFIIIC		-0.05	Yes	3767	otp	MA0236.1	0.20	No	10548					

Table S4: Model betas of *Drosophila* DNA-binding protein motifs learned using the blocking model with Poisson lasso.

Name	JASPAR code	Beta	Known Architectural Protein	Abundance	Name	JASPAR code	Beta	Known Architectural Protein	Abundance	Name	JASPAR code	Beta	Known Architectural Protein	Abundance	
abd-A	MA0206.1	-0.71	No	8885	dve	MA0915.1	0.00	No	1741	ovo	MA0126.1	3.38	No	3199	
Abd-B	MA0165.1	2.20	No	11554	E5	MA0189.1	-0.22	No	8208	pan	MA0237.2	1.30	No	5906	
achi	MA0207.1	4.38	No	3416	Ecr::usp	MA0534.1	0.56	No	5468	pb	MA0238.1	3.13	No	9864	
ai	MA0208.1	0.00	No	6545	Eip74EF	MA0026.1	6.52	No	3092	PHDP	MA0457.1	4.75	No	12824	
Antp	MA0166.1	-0.12	No	7400	Elba	MA0220.1	1.89	No	3424	Pita		3.33	No	1537	
ap	MA0209.1	-0.79	No	9148	ems	MA0219.1	-1.73	No	7856	pnr	MA0536.1	1.88	No	7803	
ara	MA0210.1	-0.80	No	8468	en	MA0220.1	0.77	No	10990	Pph13	MA0200.1	0.00	No	9845	
Awh	MA0167.1	0.00	No	10170	Ets21C	MA0916.1	1.17	No	1401	prd	MA0239.1	0.00	No	3199	
bap	MA0211.1	5.24	No	3223	eve	MA0221.1	0.00	No	7601	Ptx1	MA0201.1	0.52	No	1245	
bcd	MA0212.1	2.42	No	2331	exd	MA0222.1	2.65	No	4231	repo	MA0240.1	0.00	No	8556	
BEAF-32		5.45	Yes	5936	exex	MA0224.1	0.57	No	8491	ro	MA0241.1	-1.48	No	7743	
Bgb::run	MA0242.1	0.93	No	4664	fkh	MA0446.1	0.77	No	11272	Rx	MA0202.1	0.00	No	10752	
B-H1	MA0168.1	3.16	No	8596	ftz	MA0225.1	0.75	No	10538	schlank	MA0193.1	6.88	No	3237	
B-H2	MA0169.1	1.77	No	9021	GAF		1.55	Yes	10367	Scr	MA0203.1	0.00	No	6504	
brk	MA0213.1	2.96	No	2911	gcm2	MA0917.1	4.25	No	1522	sd	MA0243.1	2.28	No	5076	
br	MA0010.1	-0.02	No	20321	Gsc	MA0190.1	5.63	No	2437	Six4	MA0204.1	3.67	No	2543	
br(var.2)	MA0011.1	2.54	No	7265	gt	MA0447.1	2.00	No	1956	silbo	MA0244.1	4.09	No	6651	
br(var.3)	MA0012.1	1.61	No	12334	H2.0	MA0448.1	0.65	No	12408	siou	MA0245.1	-2.31	No	9559	
br(var.4)	MA0013.1	0.91	No	16448	hb	MA0049.1	1.06	No	25953	slp1	MA0458.1	1.88	No	12539	
bsh	MA0214.1	0.00	No	8328	hbn	MA0226.1	0.00	No	12245	sna	MA0086.1	8.20	No	2555	
btd	MA0443.1	2.34	No	2956	HGTX	MA0191.1	0.52	No	11617	so	MA0246.1	2.89	No	2999	
btn	MA0215.1	0.89	No	8928	HHEX	MA0183.1	0.90	No	9177	Stat92E	MA0532.1	1.11	No	6115	
C15	MA0170.1	1.84	No	10974	hkb	MA0450.1	0.53	No	2845	Su(H)	MA0085.1	0.00	No	3909	
cad	MA0216.2	-0.06	No	14203	h	MA0449.1	1.11	No	1568	Su(Hw)		3.48	Yes	13929	
caup	MA0217.1	2.49	No	6445	Hmx	MA0192.1	0.00	No	6450	tin	MA0247.2	0.56	No	4859	
Cf2	MA0015.1	0.52	No	26370	hth	MA0227.1	2.98	No	3131	tlf	MA0459.1	0.66	No	9997	
CG11085	MA0171.1	1.88	No	6260	lbf		4.29	No	3586	Trl	MA0205.1	0.20	No	19732	
CG11294	MA0172.1	0.00	No	6829	ind	MA0228.1	1.02	No	8848	Ttk69k		1.28	No	3484	
CG11617	MA0173.1	3.73	No	5032	inv	MA0229.1	-1.00	No	7061	tup	MA0248.1	0.50	No	6848	
CG15696-RA	MA0176.1	-0.38	No	12507	kni	MA0451.1	1.59	No	4231	twi	MA0249.1	1.61	No	4754	
CG18599	MA0177.1	-0.79	No	8900	Kr	MA0452.2	0.00	No	5099	Ubx	MA0094.2	0.64	No	8448	
CG32105	MA0178.1	-2.12	No	9392	lab	MA0230.1	3.35	No	8324	unc-4	MA0250.1	0.00	No	8658	
CG32532	MA0179.1	0.00	No	11434	lbe	MA0231.1	0.13	No	6052	unpg	MA0251.1	0.11	No	11101	
CG34031	MA0444.1	0.00	No	6329	lbi	MA0232.1	-3.22	No	7255	usp	MA0016.1	2.44	No	1190	
CG4328-RA	MA0182.1	0.64	No	12208	Lim1	MA0194.1	0.00	No	6147	vis	MA0252.1	0.00	No	3179	
CG9876	MA0184.1	-0.57	No	10078	Lim3	MA0195.1	-1.86	No	9592	vnd	MA0253.1	1.95	No	6194	
cnc::maf-S	MA0530.1	0.00	No	4014	lms	MA0175.1	-0.48	No	8975	Vsx1	MA0181.1	0.00	No	11108	
ct	MA0218.1	4.61	No	5491	M1BP		8.65	No	3646	Vsx2	MA0180.1	-0.44	No	8443	
Dbx	MA0174.1	1.21	No	12150	Mad	MA0535.1	1.14	No	4228	vvl	MA0254.1	3.19	No	6014	
dCTCF		2.31	Yes	4155	mirr	MA0233.1	0.97	No	9289	Zelda		9.32	No	545	
Deaf1	MA0185.1	4.27	No	5345	NK7.1	MA0196.1	-3.88	No	9846	zen2	MA0257.1	0.00	No	9053	
Dfd	MA0186.1	-0.21	No	4208	nub	MA0197.2	0.26	No	16871	zen	MA0256.1	0.22	No	5867	
Dll	MA0187.1	1.45	No	8537	oc	MA0234.1	0.00	No	2389	ZIPIC		6.54	No	2351	
dl	MA0022.1	1.20	No	4576	odd	MA0454.1	0.85	No	2383	z	MA0255.1	2.55	No	5137	
dl(var.2)	MA0023.1	2.10	No	3210	OdsH	MA0198.1	1.03	No	10250	ZW5		7.79	Yes	5252.00	
D	MA0445.1	0.95	No	10471	onecut	MA0235.1	6.86	No	10962						
DREF		-0.49	Yes	8294	opa	MA0456.1	0.84	No	1370						
Dr	MA0188.1	3.11	No	4476	Optix	MA0199.1	2.18	No	4057						
dTFIIIC		4.68	Yes	3767	otp	MA0236.1	-0.33	No	10548						

Table S5: Model betas of *Drosophila* DNA-binding protein motifs learned using multiple logistic regression with lasso.

Interaction	Beta	Standard Error	Z	p value	Interaction	Beta	Standard Error	Z	p value
BEAF-32 x dCTCF	-0.17	0.07	-2.42	1.54E-02	GAF x Barren	0.14	0.07	1.85	0.0649537846
BEAF-32 x dTFIIIC	-0.52	0.10	-5.16	2.45E-07	GAF x Cap-H2	0.68	0.11	6.37	1.87E-10
BEAF-32 x GAF	-0.40	0.05	-7.86	3.76E-15	GAF x Chromator	-0.03	0.11	-0.24	0.8104822049
BEAF-32 x Su(Hw)	0.21	0.08	2.78	5.50E-03	GAF x CP190	0.67	0.06	11.65	2.43E-31
BEAF-32 x Barren	-0.40	0.06	-6.33	2.436121E-10	GAF x Fs(1)h-L	-0.34	0.07	-5.09	3.52E-07
BEAF-32 x Cap-H2	0.26	0.07	3.45	0.0005580305	GAF x Rad21	-0.06	0.01	-5.34	9.20E-08
BEAF-32 x Chromator	-2.32	0.04	-58.87	0	Su(Hw) x Barren	0.05	0.14	0.39	0.6981510779
BEAF-32 x CP190	0.76	0.05	16.25	2.15E-59	Su(Hw) x Cap-H2	-0.48	0.18	-2.72	0.0065023695
BEAF-32 x Fs(1)h-L	0.36	0.09	4.07	4.786944E-05	Su(Hw) x Chromator	3.39	0.13	25.15	1.39E-139
BEAF-32 x Rad21	0.16	0.02	8.04	9.17094E-16	Su(Hw) x CP190	-1.78	0.04	-45.96	0.00E+00
dCTCF x dTFIIIC	2.28	0.20	11.64	2.72E-31	Su(Hw) x Fs(1)h-L	-1.82	0.13	-13.76	4.47E-43
dCTCF x GAF	-0.56	0.07	-8.02	1.09E-15	Su(Hw) x Rad21	0.37	0.03	11.99	3.93E-33
dCTCF x Su(Hw)	0.07	0.08	0.91	0.3604072864	Barren x Cap-H2	0.78	0.08	10.34	4.43E-25
dCTCF x Barren	-0.14	0.14	-1.02	0.3064835317	Barren x Chromator	1.29	0.13	9.64	5.60E-22
dCTCF x Cap-H2	1.34	0.18	7.29	3.185281E-13	Barren x CP190	0.47	0.10	4.85	1.2130523695
dCTCF x Chromator	-0.03	0.14	-0.19	0.8487729677	Barren x Fs(1)h-L	-0.01	0.11	-0.12	9.01E-01
dCTCF x CP190	-0.87	0.06	-15.65	3.17E-55	Barren x Rad21	0.32	0.02	13.06	5.95E-39
dCTCF x Fs(1)h-L	-0.13	0.12	-1.04	3.00E-01	Cap-H2 x Chromator	-0.15	0.15	-1.03	3.04E-01
dCTCF x Rad21	-0.21	0.03	-7.35	1.914592E-13	Cap-H2 x CP190	-0.19	0.12	-1.65	9.88E-02
dTFIIIC x GAF	-0.68	0.07	-9.13	6.90E-20	Cap-H2 x Fs(1)h-L	0.21	0.17	1.24	2.14E-01
dTFIIIC x Su(Hw)	2.77	0.18	15.40	1.61E-53	Cap-H2 x Rad21	-0.22	0.02	-9.79	1.28E-22
dTFIIIC x Barren	-0.42	0.10	-4.29	1.754691E-05	Chromator x CP190	-1.68	0.07	-24.19	3.12E-129
dTFIIIC x Cap-H2	0.70	0.15	4.67	3.04E-06	Chromator x Fs(1)h-L	-0.28	0.19	-1.50	0.1342403806
dTFIIIC x Chromator	0.29	0.20	1.47	1.42E-01	Chromator x Rad21	0.33	0.04	8.19	2.60E-16
dTFIIIC x CP190	-2.33	0.11	-21.46	4.10E-102	CP190 x Fs(1)h-L	-0.53	0.12	-4.57	4.765758E-06
dTFIIIC x Fs(1)h-L	0.87	0.14	6.11	9.78E-10	CP190 x Rad21	0.43	0.02	17.85	3.13E-71
dTFIIIC x Rad21	-0.46	0.03	-13.93	4.12E-44	Fs(1)h-L x Rad21	-0.20	0.01	-21.33	6.40E-101
GAF x Su(Hw)	-0.12	0.07	-1.69	0.0915101024					

Table S6: Second-order interaction betas of *Drosophila* insulator-binding proteins and cofactors learned using negative binomial regression.

