IWGSC webinar 28th Oct 2021

Interaction between wheat cis- and trans-factors in shaping regulatory networks related to evolution and adaptation

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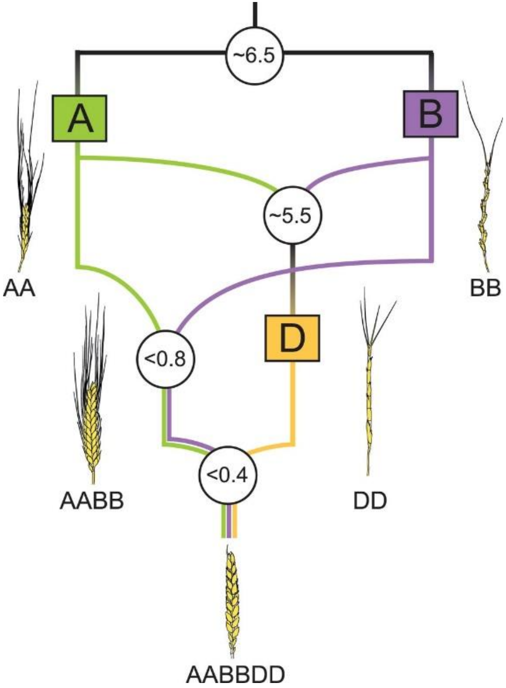
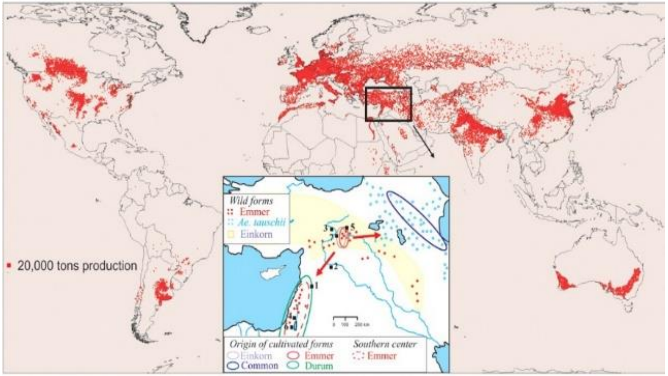
Origination and spread of common wheat





Polyploid wheat

High adaptability

Genome plasticity and success of polyploid

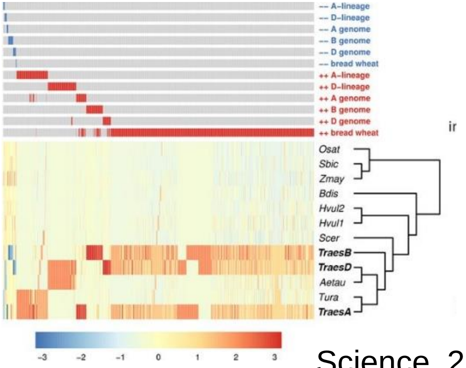
REVIEW

Genome Plasticity a Key Factor in the Success of Polyploid Wheat Under Domestication

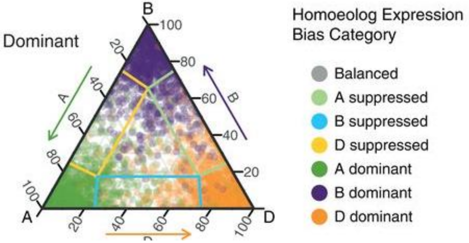
Jorge Dubcovsky* and Jan Dvorak

Science, 2007

Subgenome specific gene family expansion and transcription



Science, 2018a



Science, 2018b

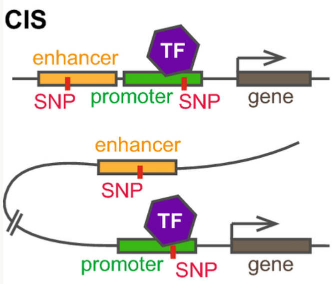
Plasticity: gene sequence vs. gene regulation

VS

Cis- and trans-regulation

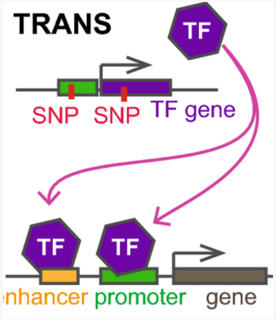
Cis-elements

- Promoter
- Enhancer

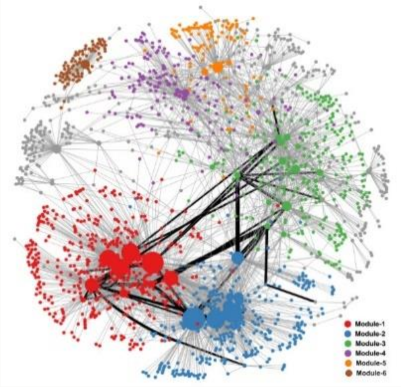


Trans-acting factors

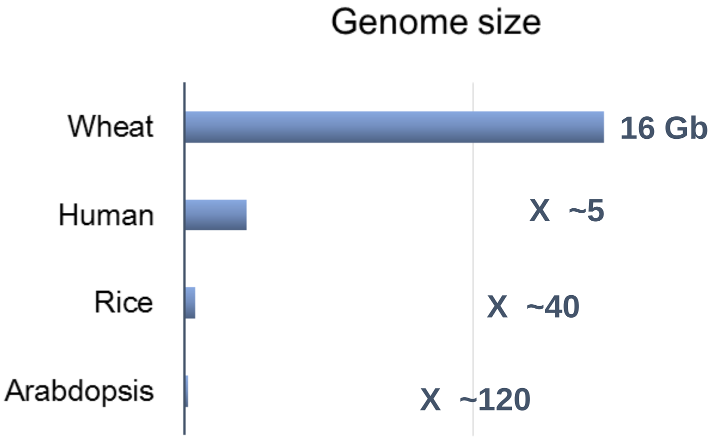
- Transcription factor
- Epigenetic factor



Regulatory network



Challenge: large and complex genome

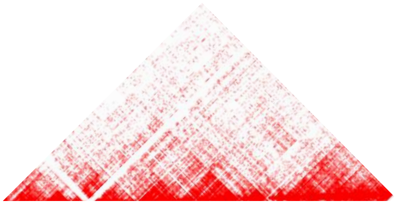


Arabidopsis

10 kb genome window in Arabidopsis

Wheat

1000 kb genome window in wheat



chr1A :40M-50M
Abundant distant regulation

Epigenomic Strategies

- **Detecting cis-elements and subgenome divergent regulation**

  1) The bread wheat epigenomic map reveals distinct chromatin architectural and evolutionary features of functional genetic elements. ***Genome Biol*** 2019,20, 139

  2) The epigenomic atlas delineates the specificity of subgenome-divergent development and stress responses encoded in wheat regulatory elements. ***Plant Cell*** (2021) 33, 865

- **Profiling trans-factor binding**

  Evolutionary rewiring of the wheat transcriptional regulatory network by lineage-specific transposable elements ***Genome Research*** 2021, doi:10.1101/gr.275658.121

Cis-elements and subgenome divergent regulation

1、 Identify regulatory elements (REs)

Challenge： large genome size

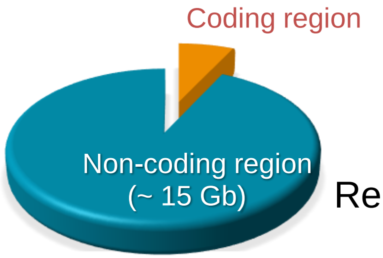
2、 Construct regulatory network

Challenge： assign target gene to enhancer

3、 Detect subgenome regulatory divergence

Challenge： integration of multi-omics data

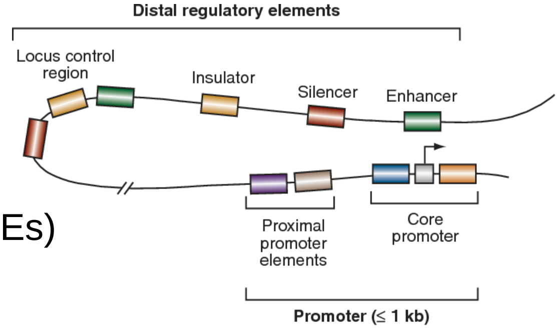
1. Define DNA regulatory elements: principle



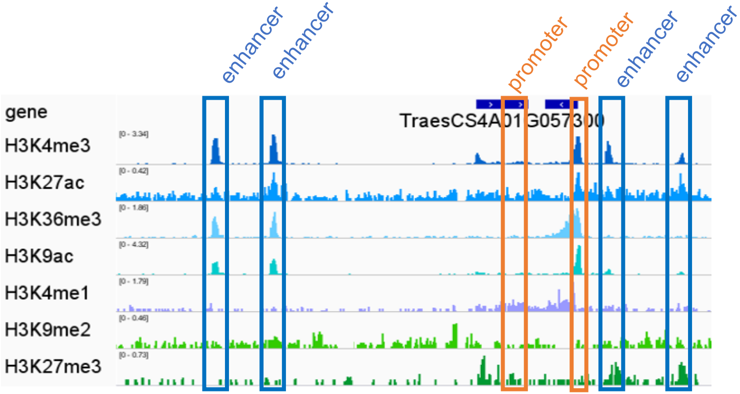
Functional gene

↕

Regulatory elements (REs)

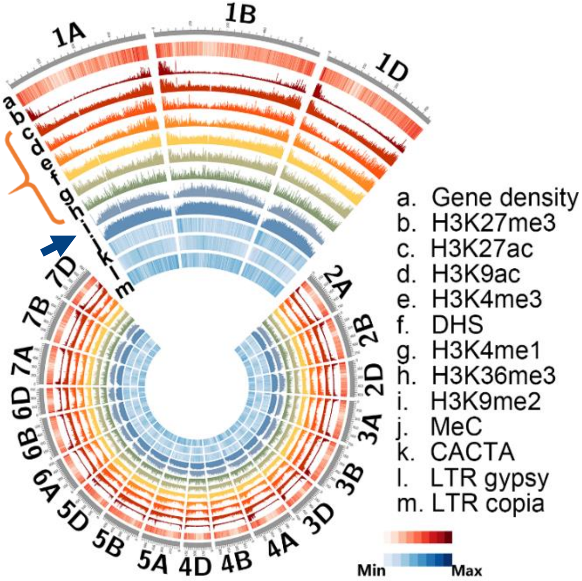


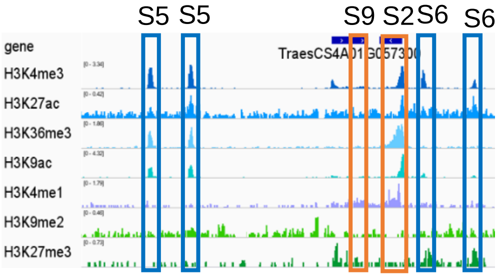
REs

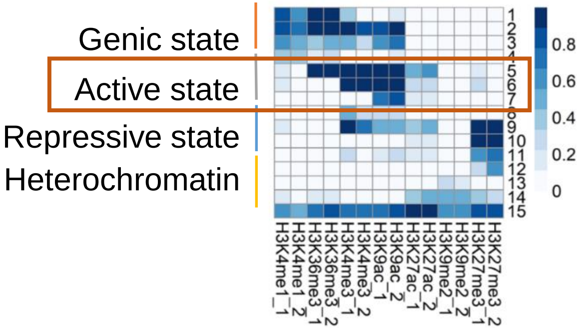


Define REs based on combinatorial histone marks

1. Define DNA regulatory elements







Histone modification: ChIP-seq

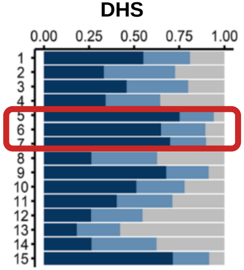
Chromatin accessibility: DHS-seq (DNase I-hypersensitive site sequencing)

DNA methylation: BS-seq

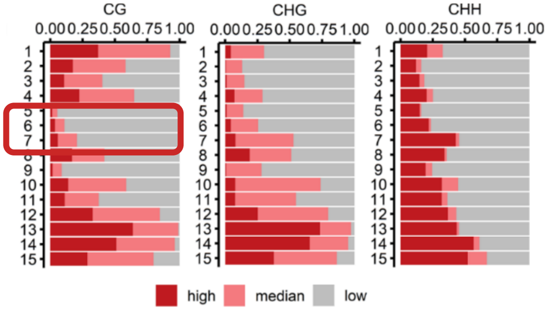
Genome Biology (2019)

Sequence and epigenetic features of REs

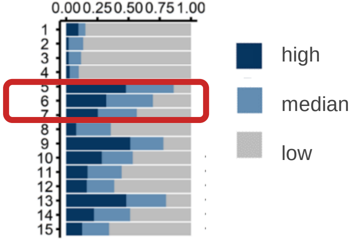
Open chromatin



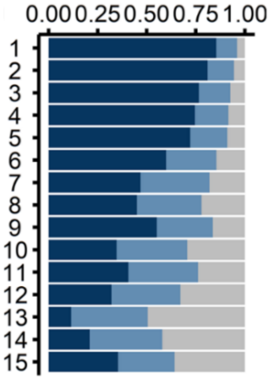
DNA methylation



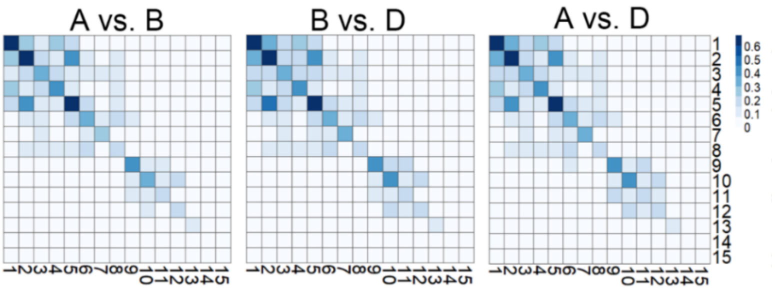
CpG island



Sequence conservation

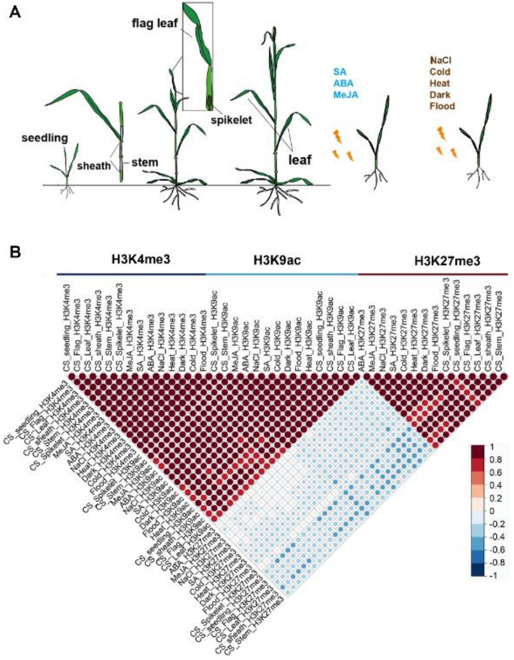


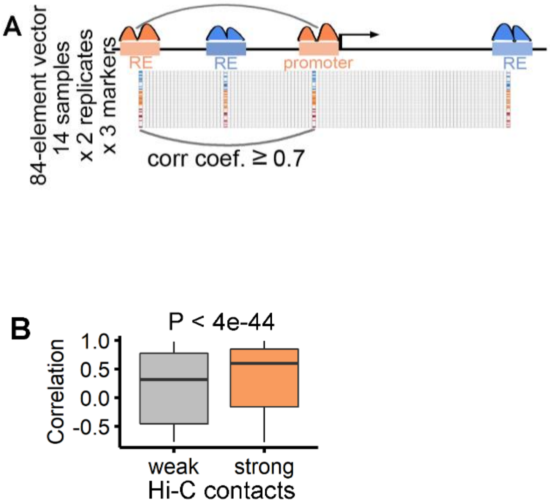
Epigenetic conservation



Sequence and epigenetic conservation → Functional importance

2. Assign target gene to enhancer: principle

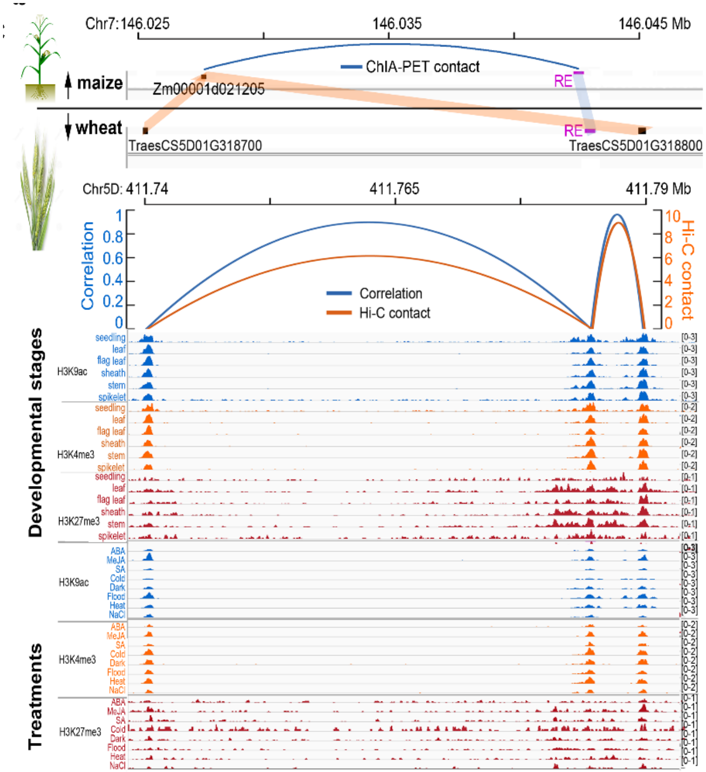




Assign target to enhancers via correlating epigenetic patterns with promoters

- ➢ Correlation based: functional interaction
- ➢ Hi-C based: physical interaction

2. Assign target gene to enhancer: principle

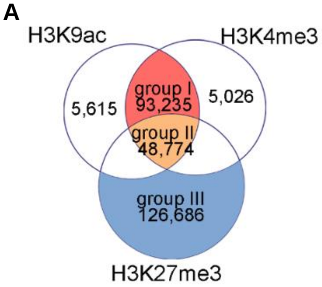


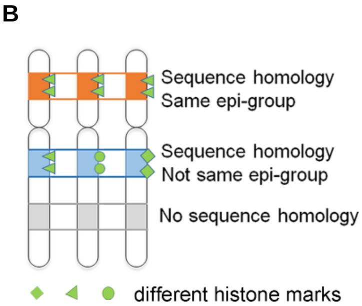
A total of 79,501 genes targeted by 223,976 distal REs

The Plant Cell （2021）

3. Subgenome divergent regulation

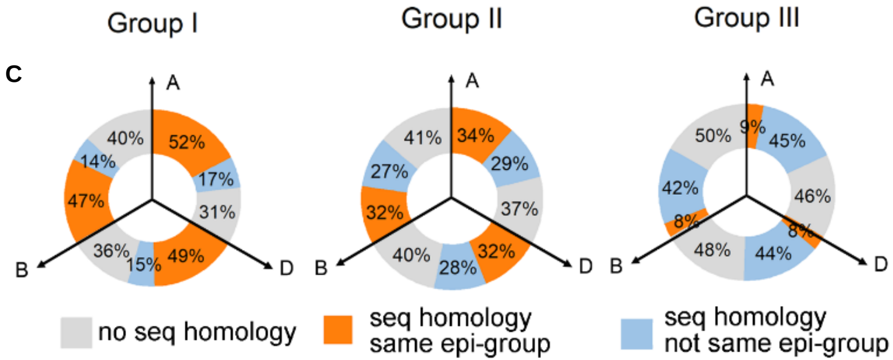
epi-groups of RE





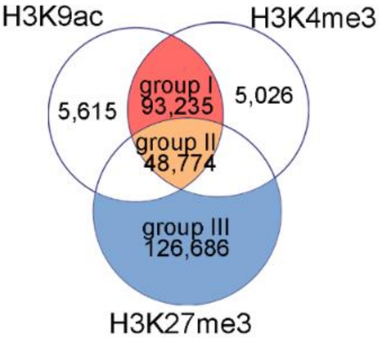
Epi-group III

- ➢ Marked by H3K27me3 only
- ➢ Preferentially localized to subgenome divergent regions

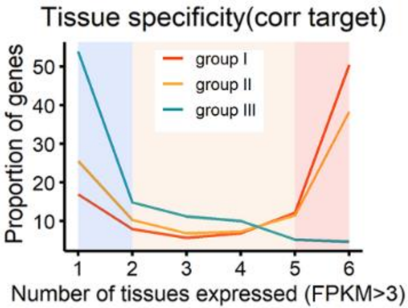


3. Subgenome divergent regulation: tissue specificity

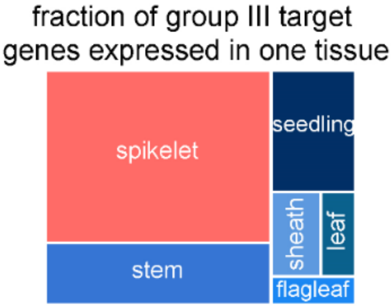
Subgenome divergent REs target spikelet-specific genes



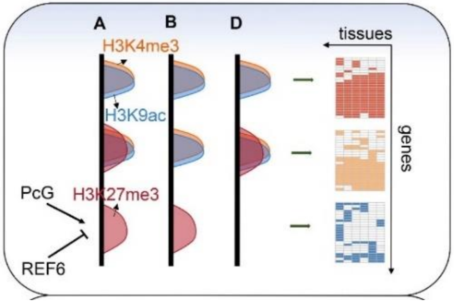
A



B

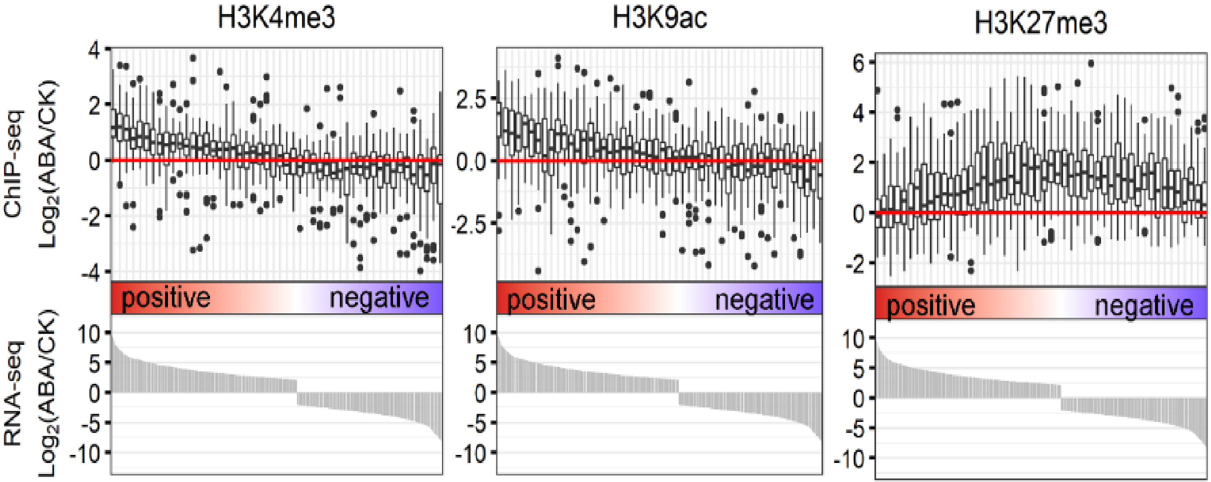


C



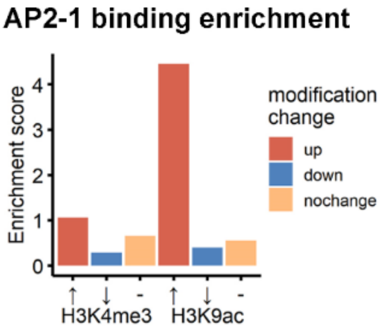
3. Subgenome divergent regulation: stress responses

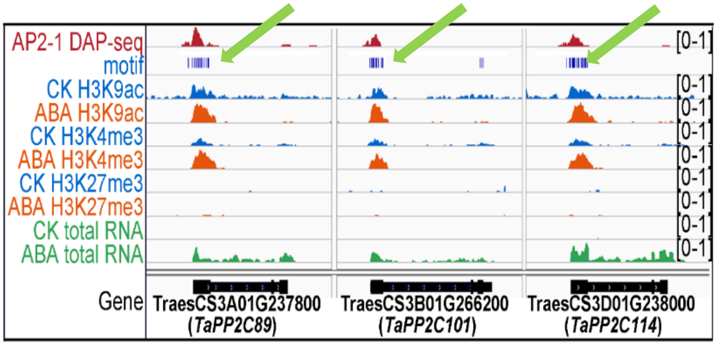
H3K4me3 and H3K9ac positively associated with stress responses



3. Subgenome divergent regulation: stress responses

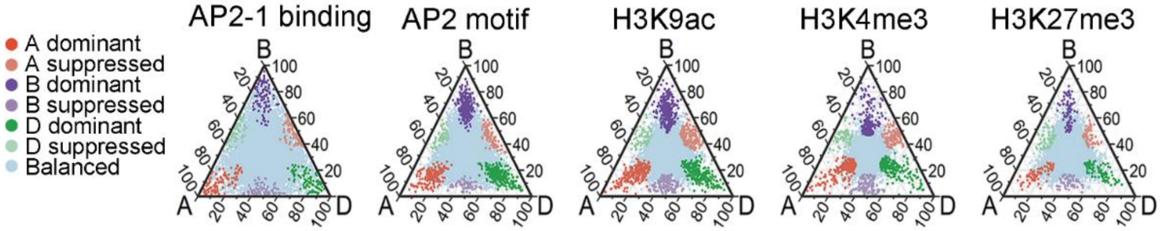
Predict stress responsive cis- and trans-elements based on quantitative epigenomic changes



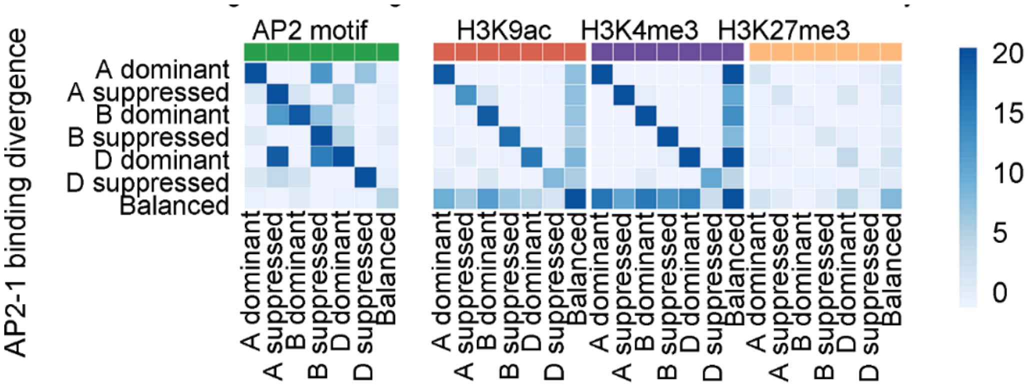


Quantitative association of subgenome divergent epigenetic modification, cis-/trans-elements

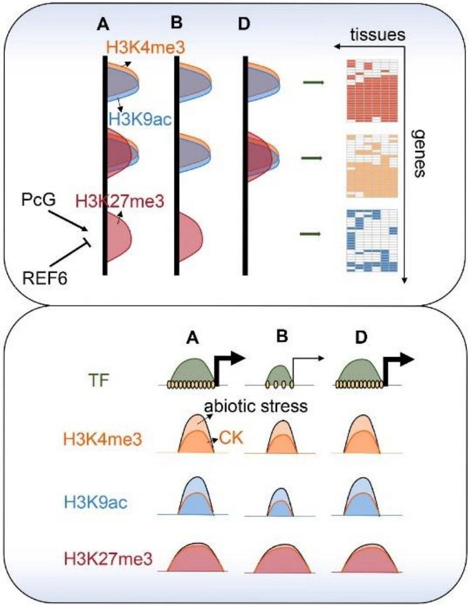
Subgenome divergence: cis-element density, AP2 binding, epigenetic marks

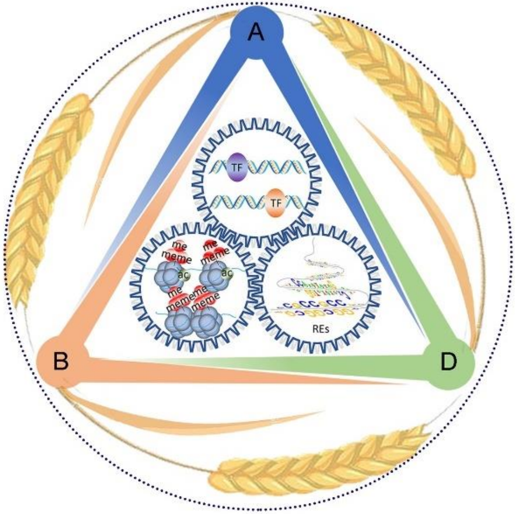


Coordinated divergence



Model





The Plant Cell **（2021）**

- Coordination between sequence contexts, epigenetic factors, and transcription factors in regulating subgenome divergence
- Quantitative epigenomic strategies facilitate mechanism study

Epigenomic Strategies

- **Detecting cis-elements and subgenome divergent regulation**

  1) The bread wheat epigenomic map reveals distinct chromatin architectural and evolutionary features of functional genetic elements. ***Genome Biol*** 2019,20, 139

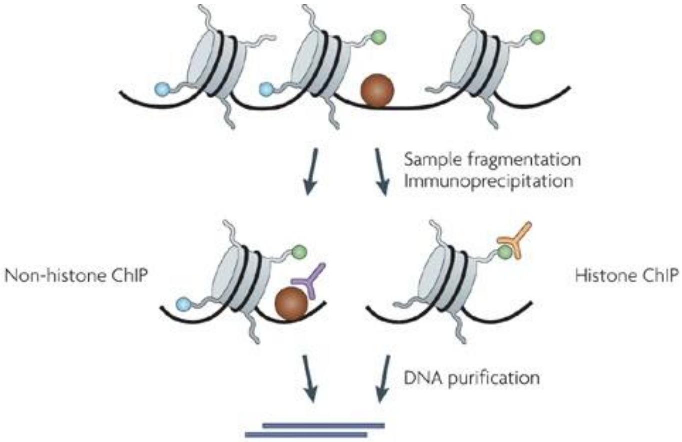
  2) The epigenomic atlas delineates the specificity of subgenome-divergent development and stress responses encoded in wheat regulatory elements. ***Plant Cell*** (2021) 33, 865

- **Profiling trans-factor binding**

  Evolutionary rewiring of the wheat transcriptional regulatory network by lineage-specific transposable elements ***Genome Research*** 2021, doi:10.1101/gr.275658.121

Strategies detecting trans-regulation

ChIP-seq vs. DAP-seq



ChIP-seq:

In vivo TF or tag antibody

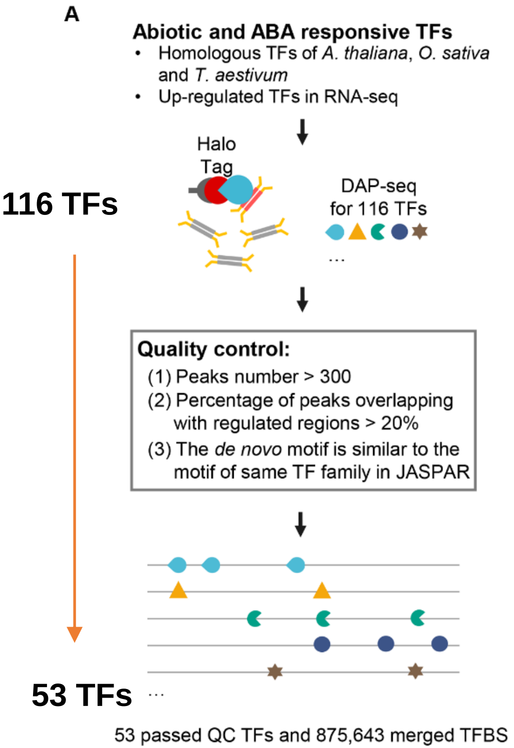
Depending on antibody or transgenic line

DAP-seq:

In vitro expressed TF-tag

Bartlett et al. Nat Protoc 2017

DAP-seq profiling of responsive TFs



116 TFs

Abiotic and ABA responsive TFs

- Homologous TFs of *A. thaliana*, *O. sativa* and *T. aestivum*
- Up-regulated TFs in RNA-seq

Quality control:

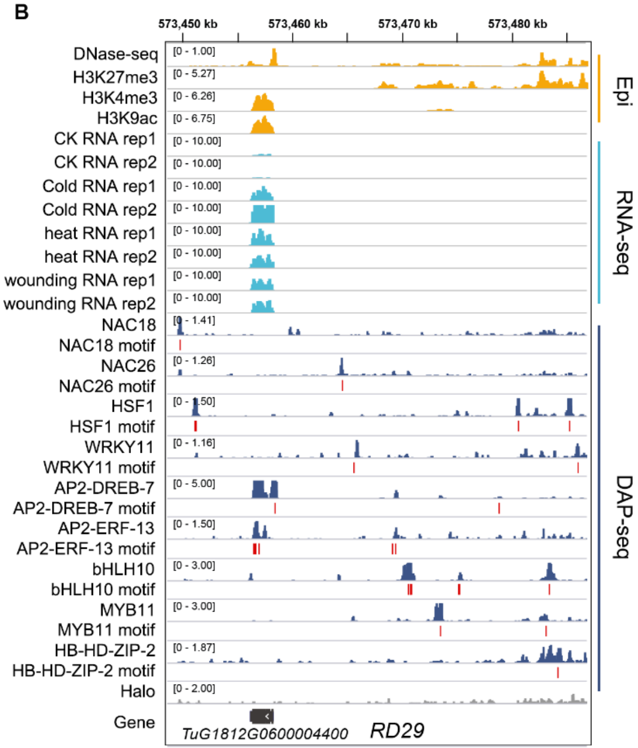
(1) Peaks number > 300

(2) Percentage of peaks overlapping with regulated regions > 20%

(3) The *de novo* motif is similar to the motif of same TF family in JASPAR

53 TFs

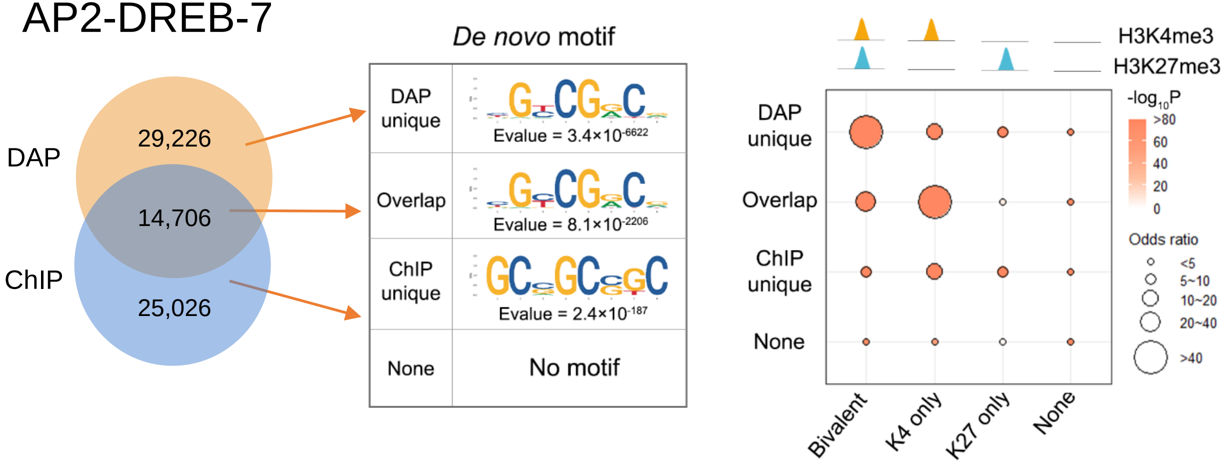
53 passed QC TFs and 875,643 merged TFBS



DAP-seq vs. ChIP-seq

Enrichment of DAP-seq peaks in bivalent chromatin regions

AP2-DREB-7

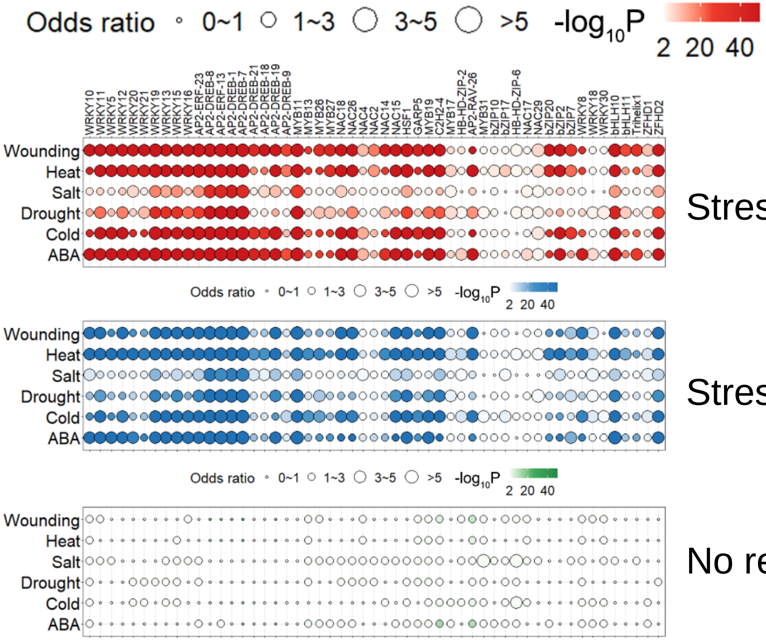


DAP-seq

- ➢ binding potential
- ➢ ”prepared” for changes

TFBS preferentially target stress response genes

Enrichment of TF targets (<10 kb) in stress-responsive genes

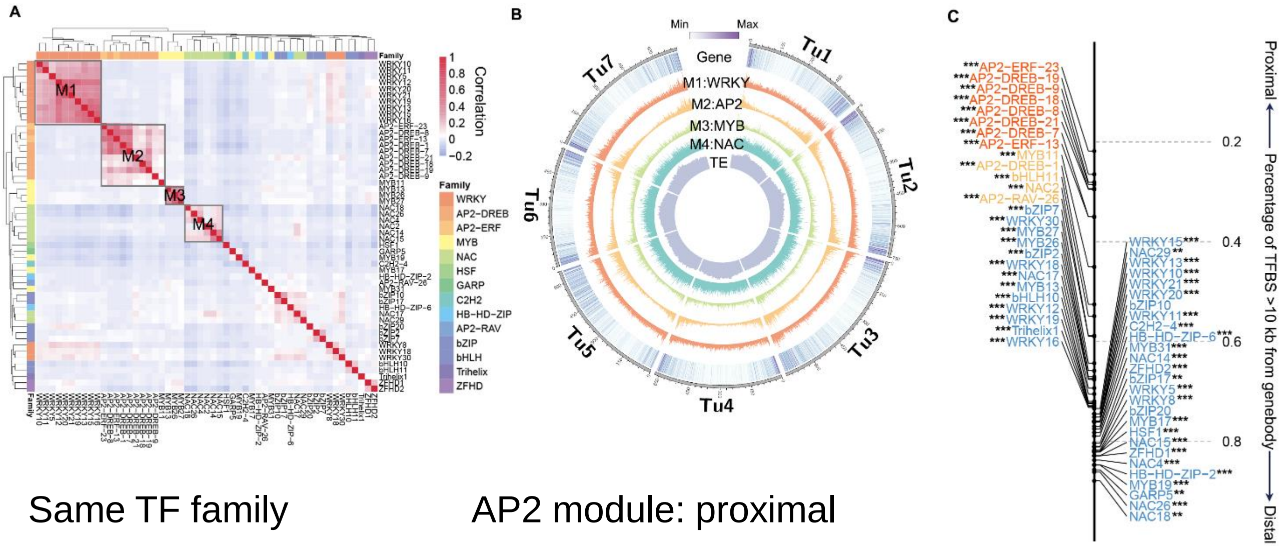


Stress-induced

Stress-repressed

No response

Gene-proximal and distal TF clusters



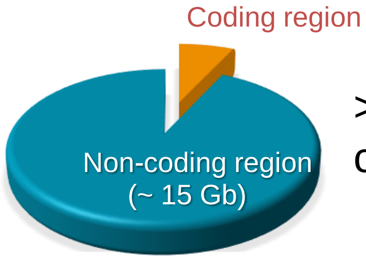
Same TF family

Same binding cluster

AP2 module: proximal

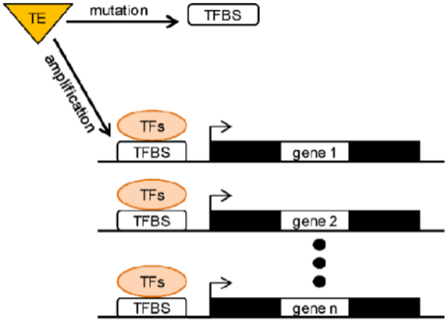
NAC module: across the chromosomes

TE burst in Triticeae



>80% non-coding region
composed of TEs and repeats

Function?



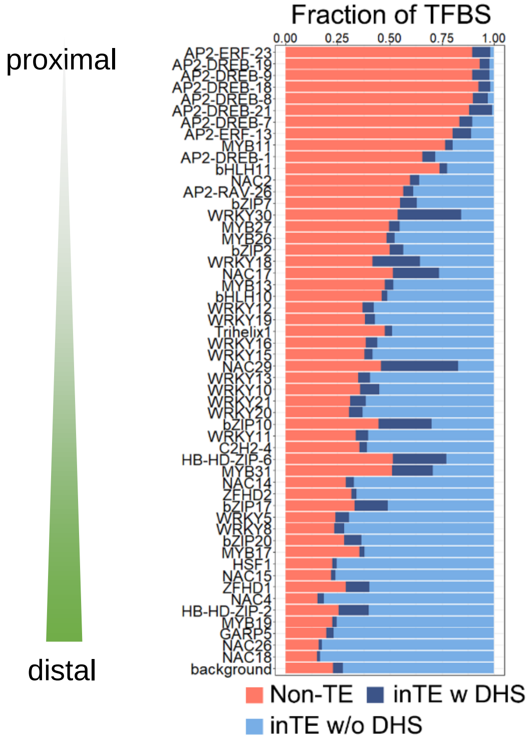
TE-derived transcription factor binding

- **Extent?**
- **Evolutionary process?**

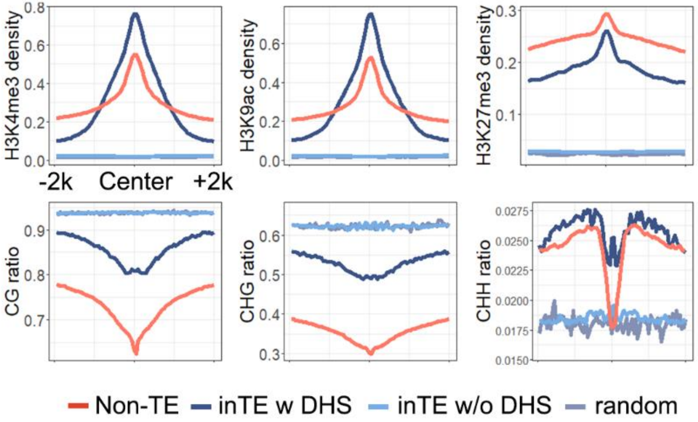
Review by Wei et al, 2015, Science China

Jordan et al, Genome Biol. 2020

Gene distal TFBS preferentially embedded in TEs



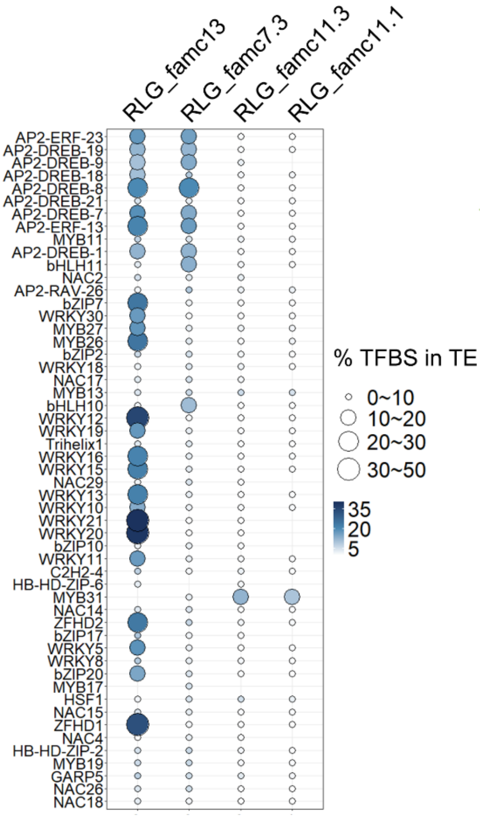
epigenetic activity

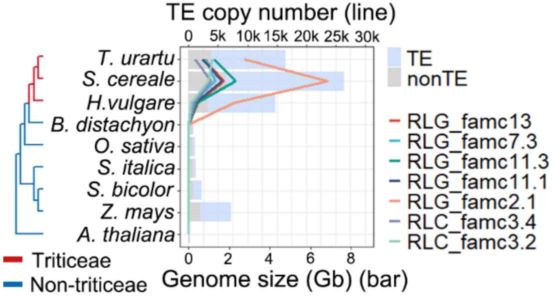


40,807 TFBS inTE w DHS

regulatory epigenetic signature

Specific TE subfamily contributed to TF binding

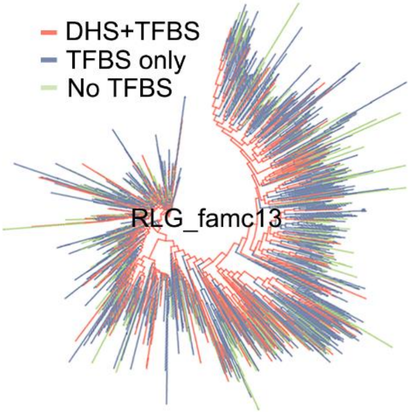




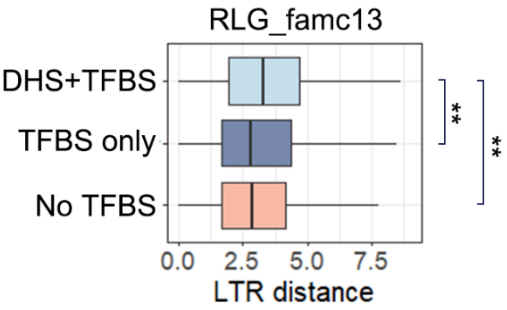
- LTR-Gypsy family 13 is the largest contributor
- majority TE-embeded binding are Triticeae specific

TE-embeded TFBS are relatively ancient

No single origin

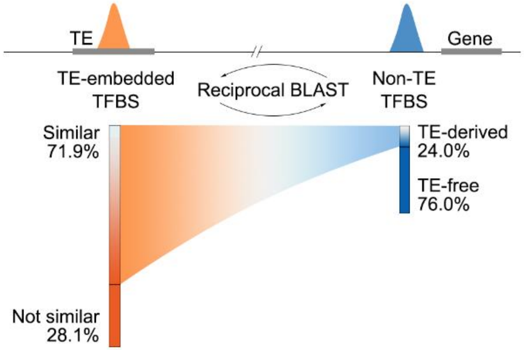


TE-TFBS in DHS are ancient



The degeneration of TEs subjected to a long-term evolutionary selection to evolve to TFBS

nonTE TFBS derived from TE-embeded TFBS

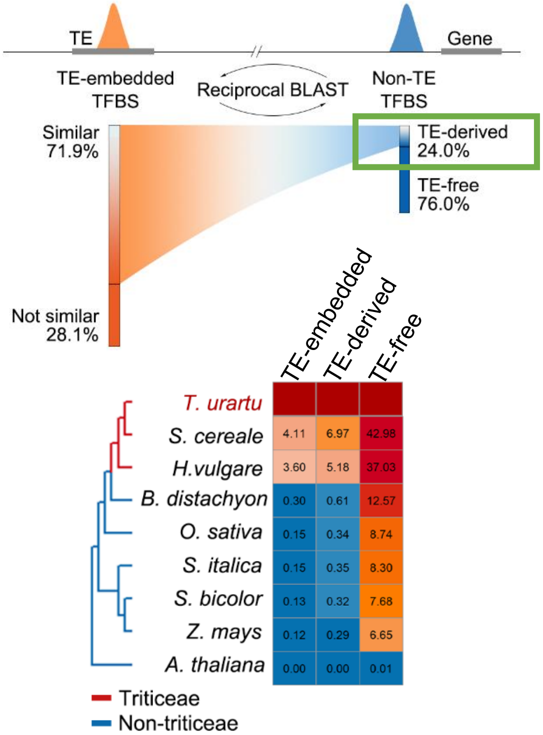


reciprocal sequence comparison

TE-embedded TFBS

vs. non-TE TFBS

nonTE TFBS derived from TE-embeded TFBS



	TE-embedded	TE-derived	TE-free
T. urartu			
S. cereale	4.11	6.97	42.98
H.vulgare	3.60	5.18	37.03
B. distachyon	0.30	0.61	12.57
O. sativa	0.15	0.34	8.74
S. italica	0.15	0.35	8.30
S. bicolor	0.13	0.32	7.68
Z. mays	0.12	0.29	6.65
A. thaliana	0.00	0.00	0.01

reciprocal sequence comparison

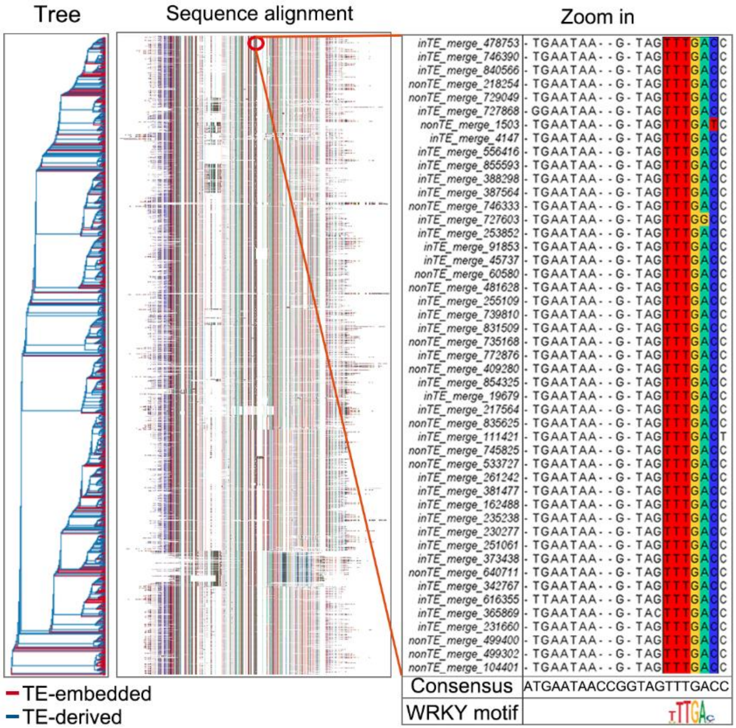
TE-embedded TFBS

vs. non-TE TFBS

Triticeae-specific
transposition and expansion

nonTE TFBS derived from TE-embeded TFBS

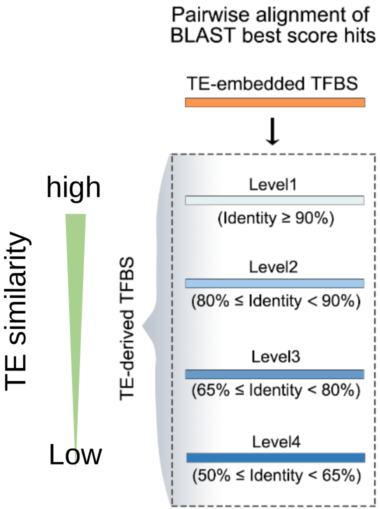
Alignment of homologous TE-embeded and TE-derived TFBS



inTE_merge_478753	-TGAATAA--G-TAGTTTGACC
inTE_merge_746390	-TGAATAA--G-TAGTTTGACC
inTE_merge_840566	-TGAATAA--G-TAGTTTGACC
nonTE_merge_218254	-TGAATAA--G-TAGTTTGACC
nonTE_merge_729049	-TGAATAA--G-TAGTTTGACC
inTE_merge_727868	-GGAATAA--G-TAGTTTGACC
nonTE_merge_1503	-TGAATAA--G-TAGTTTGATC
inTE_merge_4147	-TGAATAA--G-TAGTTTGACC
inTE_merge_556416	-TGAATAA--G-TAGTTTGACC
inTE_merge_855593	-TGAATAA--G-TAGTTTGACC
inTE_merge_388298	-TGAATAA--G-TAGTTTGACC
inTE_merge_387564	-TGAATAA--G-TAGTTTGACC
nonTE_merge_746333	-TGAATAA--G-TAGTTTGACC
inTE_merge_727603	-TGAATAA--G-TAGTTTGGCC
inTE_merge_253852	-TGAATAA--G-TAGTTTGACC
inTE_merge_91853	-TGAATAA--G-TAGTTTGACC
inTE_merge_45737	-TGAATAA--G-TAGTTTGACC
nonTE_merge_60580	-TGAATAA--G-TAGTTTGACC
nonTE_merge_481628	-TGAATAA--G-TAGTTTGACC
inTE_merge_255109	-TGAATAA--G-TAGTTTGACC
inTE_merge_739810	-TGAATAA--G-TAGTTTGACC
inTE_merge_831509	-TGAATAA--G-TAGTTTGACC
nonTE_merge_735168	-TGAATAA--G-TAGTTTGACC
inTE_merge_772876	-TGAATAA--G-TAGTTTGACC
nonTE_merge_409280	-TGAATAA--G-TAGTTTGACC
inTE_merge_854325	-TGAATAA--G-TAGTTTGACC
inTE_merge_19679	-TGAATAA--G-TAGTTTGACC
inTE_merge_217564	-TGAATAA--G-TAGTTTGACC
nonTE_merge_835625	-TGAATAA--G-TAGTTTGACC
inTE_merge_111421	-TGAATAA--G-TAGTTTGACT
nonTE_merge_745825	-TGAATAA--G-TAGTTTGACC
nonTE_merge_533727	-TGAATAA--G-TAGTTTGACC
inTE_merge_261242	-TGAATAA--G-TAGTTTGACC
inTE_merge_381477	-TGAATAA--G-TAGTTTGACC
inTE_merge_162488	-TGAATAA--G-TAGTTTGACC
inTE_merge_235238	-TGAATAA--G-TAGTTTGACC
inTE_merge_230277	-TGAATAA--G-TAGTTTGACC
inTE_merge_251061	-TGAATAA--G-TAGTTTGACC
inTE_merge_373438	-TGAATAA--G-TAGTTTGACC
nonTE_merge_640711	-TGAATAA--G-TAGTTTGACC
inTE_merge_342767	-TGAATAA--G-TAGTTTGACC
inTE_merge_616355	-TTAATAA--G-TAGTTTGACC
inTE_merge_365869	-TGAATAA--G-TACTTTGACC
inTE_merge_231660	-TGAATAA--G-TAGTTTGACC
nonTE_merge_499400	-TGAATAA--G-TAGTTTGACC
nonTE_merge_499302	-TGAATAA--G-TAGTTTGACC
nonTE_merge_104401	-TGAATAA--G-TAGTTTGACC
Consensus	ATGAATAACCGGTAGTTTGACC

Ongoing spread of TE-embedded TFBS to non-TE TFBS

TEs contribute to ongoing regulatory expansion



TE similarity

high

Low

Pairwise alignment of BLAST best score hits

TE-embedded TFBS

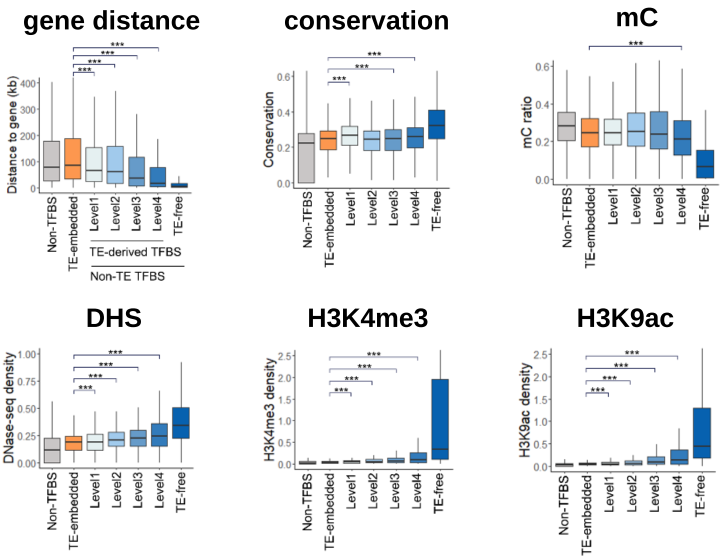
TE-derived TFBS

Level1
(Identity ≥ 90%)

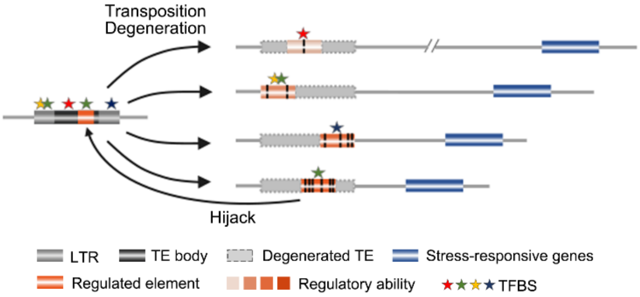
Level2
(80% ≤ Identity < 90%)

Level3
(65% ≤ Identity < 80%)

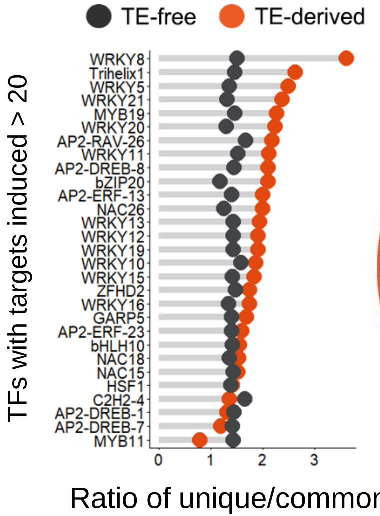
Level4
(50% ≤ Identity < 65%)

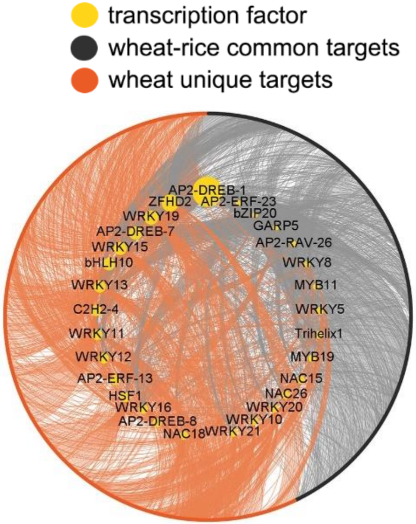


Rewiring of the gene regulatory network by TE-derived TFBS



TEs rewired the regulatory network





Incorporation of new stress-responsive genes by TE-derived TFBS

Summary

1. Detecting cis-elements and subgenome divergent regulation

- Coordination between REs, epigenetic factors, and transcription factors in regulating subgenome divergence
- Quantitative epigenomic strategies applied for mechanism study

Genome Biol 2019,20, 139
Plant Cell (2021) 33, 865

2. Profiling trans-factor binding

- High plasticity of the wheat stress response regulatory network
- Importance of TEs in promoting ongoing regulatory innovation

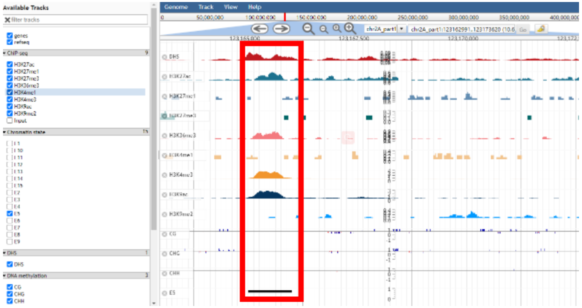
Genome Research 2021, doi:10.1101/gr.275658.121

Data resource 1

Detecting cis-elements and subgenome divergent regulation

http://119.78.67.240/cs_epigenome

species	varieties	tissues	treatments	sequencing types	details
Triticum aestivum	Chinese Spring	seedling	/	ChIP-seq	H3K4me1
					H3K4me3
					H3K9ac
					H3K9me2
					H3K27ac
					H3K27me1
					H3K27me3
					H3K36me3
					Input
				DNase-seq	DHS
				BS-seq	DNA methylation
				mRNA-seq	expression



enhancer

http://119.78.67.240/dynamic_epigenome

species	varieties	tissues	treatments	sequencing types	details
Triticum aestivum	Chinese Spring	flag leaf	/	ChIP-seq RNA-seq	H3K4me3 H3K9ac H3K27me3 total RNA
		leaf			
		seedling			
		sheath			
		spikelet I			
		spikelet II			
		stem			
		/	NaCl		
			Cold		
			Dark		
			Flood		
			Heat		
			MeJA		
			ABA		
			SA		
		seedling	/	DAP-seq	AP2-1-A
					AP2-1-D
					Halo

RE-target genes

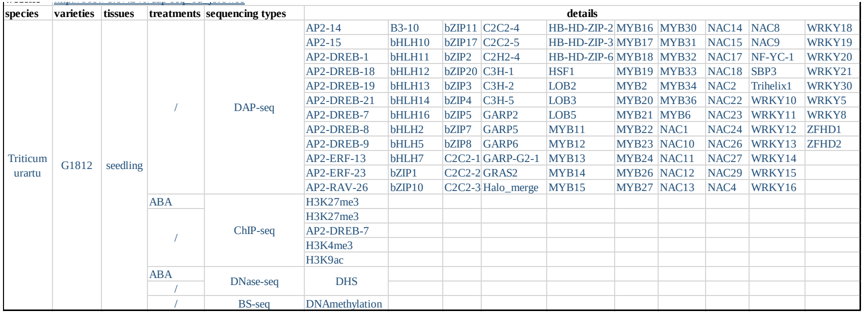
Genome Biol 2019,20, 139

Plant Cell (2021) 33, 865

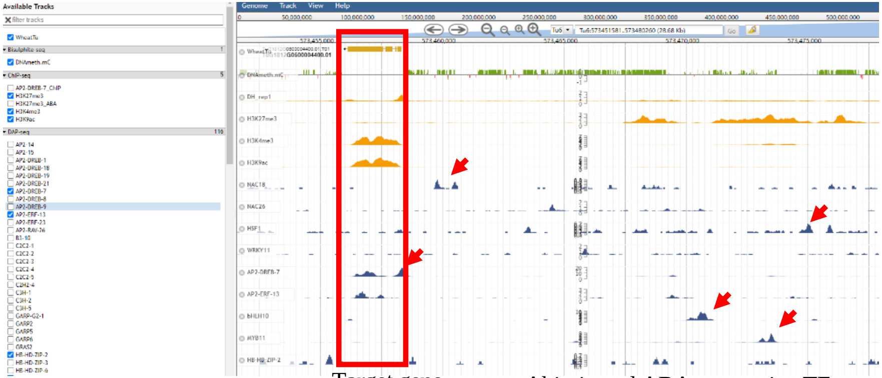
Data resource 2

Profiling trans-factor binding

http://119.78.67.240/dap-seq_Tu_jbrowse/



species	varieties	tissues	treatments	sequencing types	details									
Triticum urartu	G1812	seedling	/	DAP-seq	AP2-14	B3-10	bZIP11	C2C2-4	HB-HD-ZIP-2	MYB16	MYB30	NAC14	NAC8	WRKY18
					AP2-15	bHLH10	bZIP17	C2C2-5	HB-HD-ZIP-3	MYB17	MYB31	NAC15	NAC9	WRKY19
					AP2-DREB-1	bHLH11	bZIP2	C2H2-4	HB-HD-ZIP-6	MYB18	MYB32	NAC17	NF-YC-1	WRKY20
					AP2-DREB-18	bHLH12	bZIP20	C3H-1	HSF1	MYB19	MYB33	NAC18	SBP3	WRKY21
					AP2-DREB-19	bHLH13	bZIP3	C3H-2	LOB2	MYB2	MYB34	NAC2	Trihelix1	WRKY30
					AP2-DREB-21	bHLH14	bZIP4	C3H-5	LOB3	MYB20	MYB36	NAC22	WRKY10	WRKY5
					AP2-DREB-7	bHLH16	bZIP5	GARP2	LOB5	MYB21	MYB6	NAC23	WRKY11	WRKY8
					AP2-DREB-8	bHLH2	bZIP7	GARP5	MYB11	MYB22	NAC1	NAC24	WRKY12	ZFHD1
					AP2-DREB-9	bHLH5	bZIP8	GARP6	MYB12	MYB23	NAC10	NAC26	WRKY13	ZFHD2
					AP2-ERF-13	bHLH7	C2C2-1	GARP-G2-1	MYB13	MYB24	NAC11	NAC27	WRKY14	
					AP2-ERF-23	bZIP1	C2C2-2	GRAS2	MYB14	MYB26	NAC12	NAC29	WRKY15	
					AP2-RAV-26	bZIP10	C2C2-3	Halo_merge	MYB15	MYB27	NAC13	NAC4	WRKY16	
			ABA	ChIP-seq	H3K27me3									
			/		H3K27me3									
					AP2-DREB-7									
					H3K4me3									
					H3K9ac									
			ABA	DNase-seq	DHS									
			/											
			/	BS-seq	DNAmethylation									



Target gene

Abiotic and ABA responsive TFs

Genome Research 2021, doi:10.1101/gr.275658.121

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2021

Thanks for your attention

Welcome to our website

bioinfo.cemps.ac.cn/zhanglab

Relevant Publications

1. Jia J[#]*, Xie Y[#], Cheng J[#], Kong C[#], Wang M, Gao L, Zhao F, Guo J, Wang K, Li G, Cui D, Hu T, Zhao G*, Wang D*, Ru Z*, **Zhang Y***, Homology-mediated Inter-chromosomal Interactions in Hexaploid Wheat Lead to Specific Subgenome Territories Following Polyploidization and Introgression. ***Genome Biology*** (2021) 22(1):26

2. 2. Wang M [#], Li Z[#], Zhang Y[#], Zhang Y[#], Xie Y, Ye L, Zhuang Y, Lin K, Zhao F, Guo J, Teng W, Zhang W, Tong Y, Xue Y*, **Zhang Y***, The epigenomic atlas delineates the specificity of subgenome-divergent development and stress responses encoded in wheat regulatory elements. ***Plant Cell*** (2021) (2021) 33(4), 865

3. Li Z[#], Wang M[#], Lin K[#], Xie Y[#], Guo J, Ye L, Zhuang Y, Teng W, Ran X, Tong Y, Xue Y, Zhang W* and **Zhang Y***, The bread wheat epigenomic map reveals distinct chromatin architectural and evolutionary features of functional genetic elements. ***Genome Biology*** (2019) 20(1), 139

4. Zhang Y-Y, Li Z, Zhang Y-E, Lin K, Peng Y, Ye L, Zhuang Y, wang M, Xie Y, Guo J, Teng W, Tong Y, Zhang W*, Xue Y*, Lang Z*, **Zhang Y*.** Evolutionary rewiring of the wheat transcriptional regulatory network by lineage-specific transposable elements ***Genome Research***（2021）,doi:10.1101/gr.275658.121