Supplementary Table 1. *Cis*-regulatory changes between Saccharomycete species in the genes of the membrane protein regulon.

A

systematic name	gene name	$R_{Sc/Sp;cis}$[a]	$R_{Sk/Sp;cis}$[b]	$R_{Sb/Sp;cis}$[c]	annotation[d]
YGR213C	RTA1	-4.40	-3.06	-2.04	Member of the fungal lipid-translocating exporter (LTE) family of proteins
YOR134W	BAG7	-2.00	-2.68	-0.96	Rho GTPase activating protein
YPL149W	ATG5	-0.76	-2.57	-1.23	Involved in autophagy and the Cvt pathway
YBR203W	COS111	-2.30	-2.29	-1.93	Protein required for resistance to the antifungal drug ciclopirox olamine
YNR059W	MNT4	-0.01	-1.98	N/A	Putative alpha-1,3-mannosyltransferase
YBR005W	RCR1	-1.44	-1.36	-1.35	Protein of the ER membrane involved in cell wall chitin deposition
YMR020W	FMS1	-1.22	-1.35	0.71	Polyamine oxidase, converts spermine to spermidine
YGR212W	SLI1	-1.18	-1.21	0.29	N-acetyltransferase, confers resistance to the sphingolipid biosynthesis inhibitor myriocin
YGR121C	MEP1	-1.24	-1.08	-0.07	Ammonium permease
YLR350W	ORM2	-1.04	-0.76	-0.28	Controls membrane biogenesis by coordinating lipid homeostasis with protein quality control
YDR319C	YDR319C	0.22	-0.53	N/A	Ortholog of the FIT family of proteins involved in triglyceride droplet biosynthesis
YML118W	NGL3	-1.43	-0.33	0.57	Putative endonuclease
YLR120C	YPS1	-0.65	-0.28	N/A	Aspartic protease, member of the yapsin family of proteases involved in cell wall growth and maintenance
YGL166W	CUP2	-0.53	-0.25	-0.50	Copper-binding transcription factor
YGL185C	YGL185C	-0.76	-0.24	-0.61	Putative protein with sequence similarity to hydroxyacid dehydrogenases
YDL010W	GRX6	-0.12	-0.22	-0.54	*Cis*-golgi localized monothiol glutaredoxin that binds an iron-sulfur cluster; involved in the oxidative stress response
YPL057C	SUR1	-0.78	-0.20	-0.12	Probable catalytic subunit of a mannosylinositol phosphorylceramide (MIPC) synthase; involved in sphingolipid biosynthesis
YMR097C	MTG1	-0.09	-0.12	-0.13	Putative GTPase peripheral to the mitochondrial inner membrane
YLR257W	YLR257W	0.06	-0.11	0.71	Putative protein of unknown function
YDL234C	GYP7	-0.17	-0.10	-0.30	GTPase-activating protein for yeast Rab family members; involved in vesicle mediated protein trafficking
YKL159C	RCN1	-0.73	-0.01	-1.13	Protein involved in calcineurin regulation during calcium signaling
YHL027W	RIM101	0.35	0.09	N/A	Transcriptional repressor involved in response to pH and in cell wall construction
YLR414C	PUN1	-0.62	0.23	-1.34	Plasma membrane protein with a role in cell wall integrity
YNL192W	CHS1	-0.02	0.26	0.29	Catalyzes the transfer of N-acetylglucosamine (GlcNAc) to chitin
YMR316W	DIA1	0.04	0.56	-1.27	Involved in invasive and pseudohyphal growth
YGL006W	PMC1	-0.24	0.63	N/A	Vacuolar Ca2+ ATPase involved in depleting cytosol of Ca2+ ions
YNL003C	PET8	0.78	0.68	0.97	S-adenosylmethionine transporter of the mitochondrial inner membrane
YMR096W	SNZ1	-1.44	0.78	N/A	Protein involved in vitamin B6 biosynthesis
YBR287W	YBR287W	1.41	0.96	0.89	Protein of unknown function
YGR268C	HUA1	1.63	1.23	N/A	Cytoplasmic protein containing a zinc finger domain with sequence similarity to that of Type I J-proteins

YJL171C	YJL171C	0.06	1.35	0.46	GPI-anchored cell wall protein of unknown function; induced in response to cell wall damaging agents
YNR010W	CSE2	1.89	1.89	2.24	Subunit of the RNA polymerase II mediator complex
YLR194C	YLR194C	1.87	2.14	1.44	Structural constituent of the cell wall attached to the plasma membrane by a GPI-anchor; upregulated in response to cell wall stress
YNR064C	YNR064C	-0.95	N/A	-3.61	Epoxide hydrolase, member of the alpha/beta hydrolase fold family
YOR385W	YOR385W	-1.62	N/A	-1.65	Putative protein of unknown function
YGL183C	MND1	-0.12	N/A	0.15	Protein required for recombination and meiotic nuclear division
YLR054C	OSW2	0.15	N/A	1.05	Protein of unknown function proposed to be involved in the assembly of the spore wall
YGR288W	MAL13	0.86	N/A	N/A	MAL-activator protein, part of complex locus MAL1
YER185W	PUG1	-0.81	N/A	N/A	Plasma membrane protein with roles in the uptake of protoprophyrin IX and the efflux of heme
YHR139C	SPS100	0.12	N/A	N/A	Protein required for spore wall maturation
YMR040W	YET2	-0.22	N/A	N/A	Protein of unknown function that may interact with ribosomes
YKL218C	SRY1	3.01	N/A	N/A	3-hydroxyaspartate dehydratase, deaminates L-threo-3-hydroxyaspartate to form oxaloacetate and ammonia
YPR198W	SGE1	3.26	N/A	N/A	Plasma membrane multidrug transporter of the major facilitator superfamily
YGL051W	MST27	-3.00	N/A	N/A	Putative integral membrane protein, involved in vesicle formation
YCR007C	YCR007C	-0.66	N/A	N/A	Putative integral membrane protein
YER184C	YER184C	0.00	N/A	N/A	Putative zinc cluster protein
YLR438C-A	LSM3	1.12	N/A	N/A	Lsm (Like Sm) protein; involved in mRNA decay

B

	S. cerevisiae-S. paradoxus	***S. kudriavzevii-S. paradoxus***	***S. bayanus-S. paradoxus***
number of genes	47	33	30
$\Sigma R_{Sx/Sp;cis}$	-13.75	-9.94	-9.31
$p(\Sigma R_{Sx/Sp;cis})$[d]	0.006	0.014	0.007
$p(\Sigma \mathrm{sign}[R_{Sx/Sp;cis}])$[e]	0.043	0.029	0.070

[a] The $\log_2$ of the ratio of expression of the *S. cerevisiae* allele and that of the *S. paradoxus* allele in the interspecific hybrid.

[b] The estimated effect of *cis*-regulatory variation between *S. kudriavzevii* and *S. paradoxus*, based on expression measurements in interspecific hybrids between each species and *S. cerevisiae*. N/A, missing data.

[c] The estimated effect of *cis*-regulatory variation between *S. bayanus* and *S. paradoxus*, based on expression measurements in interspecific hybrids between each species and *S. cerevisiae*. N/A, missing data.

[d] Significance of a one-sided resampling test relative to the genomic null for an extreme value of the sum of the estimated effects of *cis*-regulatory variation between the indicated species and *S. paradoxus*.

[e] Significance of a one-sided resampling test relative to the genomic null for an extreme value of the sum of the signs of estimated effects of *cis*-regulatory variation between the indicated species and *S. paradoxus*.