Supplementary information

Supplementary figure and table legends

Figure S1 - Workflow for data treatment procedure

Figure S2 - Feature comparison of simulated dataset with the real data

(a) Lower cluster mean *vs.* lower cluster standard deviation. $N_{real} = 1105$, $N_{simulated} = 1000$

(b) High cluster mean *vs.* lower cluster standard deviation.

(c) Distribution of the frequency of lower fitness cluster.

Figure S3 - Evaluation of detection power relative to case loss

(a) Evolution of area under the curve (AUC) with different combinations of parameters. X-axis: posterior probability cutoffs. Y-axis: Fraction of non-overlapping between clusters.

(b) Number of cases that passed the threshold with different combinations of parameters. X-axis: posterior probability cutoffs. Y-axis: Fraction of non-overlapping between clusters.

Figure S3 - Evaluation of detection power relative to case loss

(a-c) Bulk segregant analysis identified causal genomic regions in traits related to co-segregation with NaCl (a), cycloheximide and anisomycin (b) and copper sulfate (c). One chromosomal region with significantly skewed allele frequency was found in each cross, which is presented with color codes. Schematic representations of the chromosome involved are shown, with x-axis corresponding to chromosomal coordinates and y-axis to the allele frequency of the isolates crossed with Σ1278b. Shaded areas correspond to regions with most skewed allele frequencies and genes with these regions are presented to scale. See Figure S3 for additional mapping results.

Figure S5 - Functional validation of the gene involved in drug resistance

(a) Reciprocal hemizygosity test for the candidate gene *PDR1*. Sensitive (Σ1278b) and resistant (YJM326) parental isolates as well as hybrids that are wild type or hemizygous for the *PDR1* gene are spotted in 5 dilutions onto YPD (left panel) and YPD CHX 1µg/ml (right panel). Cells were grown for 48 hours at 30°C.

(b) Ectopic expression of the resistance allele $PDR1^{YJM326}$ confers drug resistance in the sensitive strain Σ1278b only with deletion of *PDR1*. Growth of strains carrying empty control plasmid (pCTRL) or plasmids with the resistant ($pPDR1^{YJM326}$) or sensitive ($pPDR1^{\Sigma1278b}$) allele was tested in

the absence (left panel) or presence (right panel) of cycloheximide. All media were supplemented with 200μg/ml of hygromycin to maintain plasmid stability.

Figure S6 - Fitness comparison in strains with ectopic expression of *PDR1*^{YJM326} and in hybrid contexts.

The fitness values for 20 isolates in the presence of cycloheximide were compared after hybridizing with the resistant isolate YJM326 (left panel) or after transformed with plasmid carrying the resistant allele pPDR1^{YJM326} (right panel). Strains are indicated on y-axis, with color codes correspond to different configurations (hybrid or plasmid).

Figure S7 - Offspring fitness distribution related to drug resistance in 20 hybrid backgrounds.

Distributions of 80 offspring (20 full tetrads) and the lethal phenotype segregation patterns (upper right side) in the presence of cycloheximide are presented for 20 isolates crossed with YJM326. Parental fitness values are indicated at vertical bars, with red corresponds to the sensitive isolate crossed and blue the resistant parent YJM326. Different inheritance types are color-coded.

Table S1. Origin and sequence divergence of strains used in this study

Table S2. Media compositions for conditions tested in this study

Supplementary references

Liti, G., Carter, D.M., Moses, A.M., Warringer, J., Parts, L., James, S.A., Davey, R.P., Roberts, I.N., Burt, A., Koufopanou, V.*, et al.* (2009). Population genomics of domestic and wild yeasts. Nature *458*, 337-341.

Schacherer, J., Shapiro, J.A., Ruderfer, D.M., and Kruglyak, L. (2009). Comprehensive polymorphism survey elucidates population structure of Saccharomyces cerevisiae. Nature *458*, 342-345.

Table S1.

Strain	Source	Location	Crossed with YJM326	Estimated divergence to S288c (%)	References
BC187	Barrel fermentation	USA		0.37	Liti et al. 2009
YPS128	Soil beneath *Quercus alba*	Pennsylvania, USA		0.53	Liti et al. 2009
DBVPG1106	Grapes	Australia		0.35	Liti et al. 2009
L-1374	Wine	Chile		0.36	Liti et al. 2009
378604X	Clinical sputum	Newcastle, UK		0.41	Liti et al. 2009
YJM975	Clinical isolate (Vaginal)	Bergamo, Italy		0.36	Liti et al. 2009
DBVPG6044	Bili wine	West Africa, Africa		0.60	Liti et al. 2009
Y55	Wine	France		0.54	Liti et al. 2009
CLIB192	Bakery	France		0.11	Schacherer et al. 2009
CLIB272	Beer	USA	*	0.23	Schacherer et al. 2009
CLIB382	Beer	Ireland		0.25	Schacherer et al. 2009
YJM145	AIDS patients	USA		0.37	Schacherer et al. 2009
YJM280	Peritoneal fluid	USA		0.35	Schacherer et al. 2009
YJM320	Blood	California, USA	*	0.32	Schacherer et al. 2009
YJM326	Human, clinical	California, USA		0.32	Schacherer et al. 2009
YJM421	Ascites fluid	USA	*	0.35	Schacherer et al. 2009
YJM434	Human, clinical	Europe	*	0.38	Schacherer et al. 2009
YJM440	Human, clinical	NA	*		Schacherer et al. 2009
YJM653	Human, clinical	NA	*		Schacherer et al. 2009
YJM678	Human, clinical	NA	*		Schacherer et al. 2009
CBS7960	Ethanol factory (sugar cane syrup)	São Paulo, Brazil		0.39	Schacherer et al. 2009
CECT10109	Prickly pear	Spain	*	0.31	Schacherer et al. 2009
DBVPG3591	Cocoa beans	NA	*	0.23	Schacherer et al. 2009
DBVPG6861	Poluted stream water	Tijuca forest, Rio de Janeiro, Brazil			Schacherer et al. 2009
EM93	Rotting fig	California, USA	*	0.14	Schacherer et al. 2009
YPS1000	Exudates *Quercus sp.*	USA		0.41	Schacherer et al. 2009
YPS163	Soil beneath *Quercus rubra*	USA		0.36	Schacherer et al. 2009
CLIB294	Distillery	France	*	0.25	Schacherer et al. 2009
CLIB413	Fermenting rice	China		0.33	Schacherer et al. 2009
K12	Sake	Japan		0.25	Schacherer et al. 2009
Y10	Coconut	Philippines		0.49	Schacherer et al. 2009
Y12	Palm wine	Ivory Coast	*	0.35	Schacherer et al. 2009
Y3	Palm wine	Africa	*	0.38	Schacherer et al. 2009
Y9	Ragi fermentation	Indonesia	*	0.34	Schacherer et al. 2009
YJM269	Red Blauer Portugieser grapes	Austria	*	0.38	Schacherer et al. 2009
CLIB154	Wine	Russia	*	0.21	Schacherer et al. 2009
I14	Vineyard soil	Italy	*	0.25	Schacherer et al. 2009
UC8	Wine	South Africa, Africa	*	0.28	Schacherer et al. 2009
WE372	Wine	South Africa, Africa		0.26	Schacherer et al. 2009
NC02	Exudates *Quercus sp.*	North Carolina, USA		0.43	Schacherer et al. 2009
T7	Exudates *Quercus sp.*	Babler State Park, MO, USA	*	0.49	Schacherer et al. 2009

Table S2.

Condition	Composition	Stress type
YPD	2% bactopeptone; 1% yeast extract; 2% glucose; 2% agar	Rich medium
YP acetate 2%	2% bactopeptone; 1% yeast extract; 2% acetate; 2% agar	Carbon sources
YP EtOH 2%	2% bactopeptone; 1% yeast extract; 2% ethanol; 2% agar	Carbon sources
YP glycerol 2%	2% bactopeptone; 1% yeast extract; 2% glycerol; 2% agar	Carbon sources
YP sorbitol 2%	2% bactopeptone; 1% yeast extract; 2% sorbitol; 2% agar	Carbon sources
YP galactose 2%	2% bactopeptone; 1% yeast extract; 2% galactose; 2% agar	Carbon sources
YP ribose 2%	2% bactopeptone; 1% yeast extract; 2% ribose; 2% agar	Carbon sources
YP xylose 2%	2% bactopeptone; 1% yeast extract; 2% xylose; 2% agar	Carbon sources
YPD formamide 4%	YPD; formamide 4%	Protein stability
YPD formamide 5%	YPD; formamide 5%	Protein stability
YPD EtOH 15%	YPD; ethanol 15%	Protein stability
YPD benomyl 200µg/ml	YPD; benomyl 200µg/ml	Subcellular organization
YPD benomyl 500µg/ml	YPD; benomyl 500µg/ml	Subcellular organization
YPD SDS 0.2%	YPD; SDS 0.2%	Membrane stability
YPD DMSO 6%	YPD; DMSO 6%	Membrane stability
YPD KCl 2M	YPD; KCl 2M	Osmotic stress
YPD NaCl 1M	YPD; NaCl 1M	Osmotic stress
YPD NaCl 1.5M	YPD; NaCl 1.5M	Osmotic stress
YPD $CuSO_4$ 10mM	YPD; $CuSO_4$ 10mM	Osmotic stress
YPD $CuSO_4$ 15mM	YPD; $CuSO_4$ 15mM	Osmotic stress
YPD LiCl 250mM	YPD; LiCl 250mM	Osmotic stress
YPD CHX 0.5µg/ml	YPD; cycloheximide 0.5µg/ml	Translation
YPD CHX 1µg/ml	YPD; cycloheximide 1µg/ml	Translation
YPD anisomycin 10µg/ml	YPD; anisomycin 10µg/ml	Translation
YPD anisomycin 20µg/ml	YPD; anisomycin 20µg/ml	Translation
YPD anisomycin 50µg/ml	YPD; anisomycin 50µg/ml	Translation
YPD caffeine 40mM	YPD; caffeine 40mM	Signal transduction
YPD caffeine 50mM	YPD; caffeine 50mM	Signal transduction
YPD 6AU 600µg/ml	YPD; 6-azauracile 600µg/ml	Transcription
YPD nystatin 10µg/ml	YPD; nystatin 10µg/ml	Sterol biosynthesis
YPD Mv 20mM	YPD; methylviologen 20mM	Oxydative stress

Figure S1.

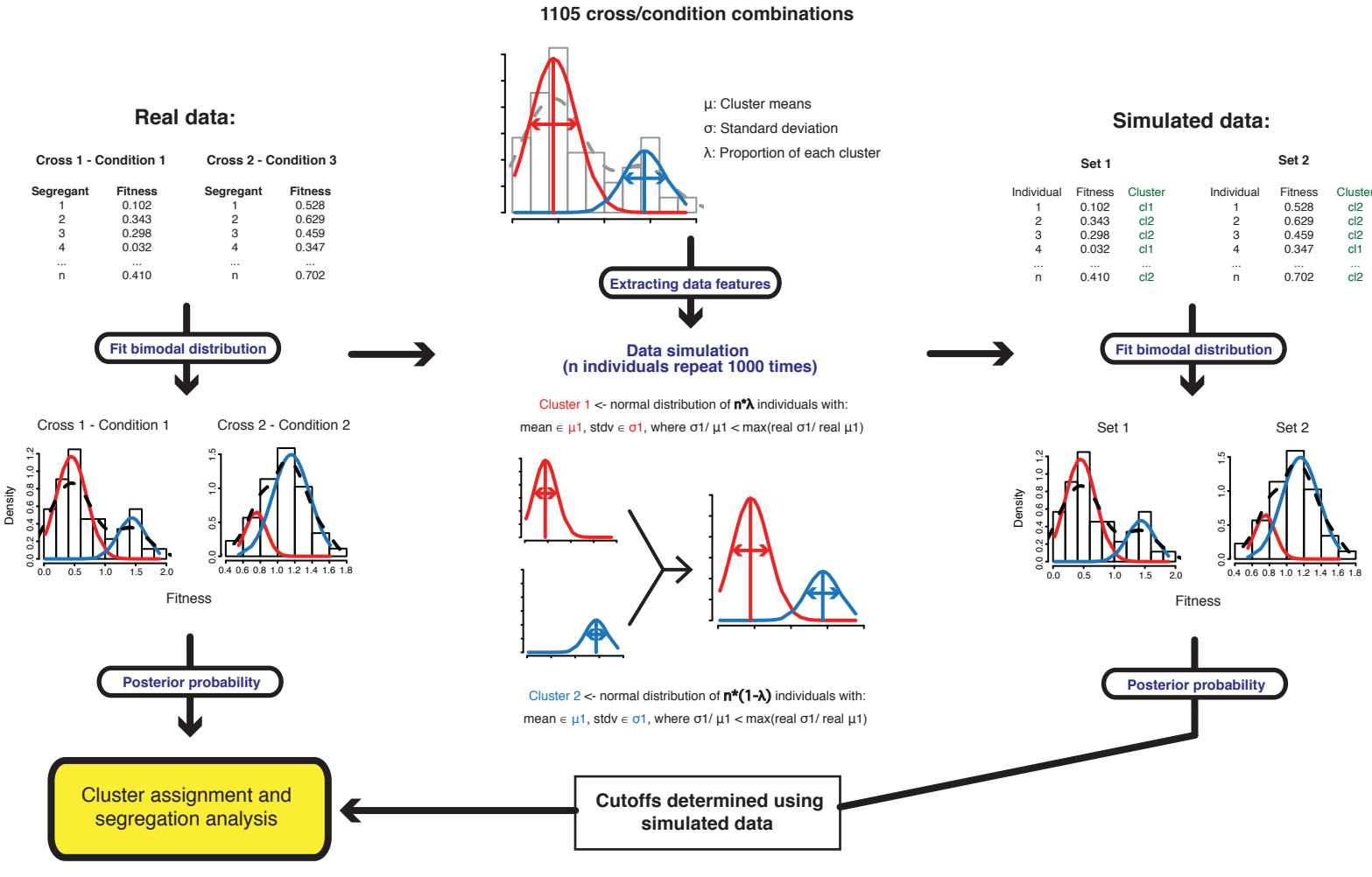

1105 cross/condition combinations
μ: Cluster means
σ: Standard deviation
λ: Proportion of each cluster
Real data:
Cross 1 - Condition 1
Segregant Fitness
1 0.102
2 0.343
3 0.298
4 0.032
... ...
n 0.410
Cross 2 - Condition 3
Segregant Fitness
1 0.528
2 0.629
3 0.459
4 0.347
... ...
n 0.702
Extracting data features
Fit bimodal distribution
Data simulation
(n individuals repeat 1000 times)
Cluster 1 <- normal distribution of n*λ individuals with:
mean ∈ μ1, stdv ∈ σ1, where σ1/ μ1 < max(real σ1/ real μ1)
Cluster 2 <- normal distribution of n*(1-λ) individuals with:
mean ∈ μ1, stdv ∈ σ1, where σ1/ μ1 < max(real σ1/ real μ1)
Simulated data:
Set 1
Individual Fitness Cluster
1 0.102 cl1
2 0.343 cl2
3 0.298 cl2
4 0.032 cl1
... ...
n 0.410 cl2
Set 2
Individual Fitness Cluster
1 0.528 cl2
2 0.629 cl2
3 0.459 cl2
4 0.347 cl1
... ...
n 0.702 cl2
Fit bimodal distribution
Cross 1 - Condition 1
Cross 2 - Condition 2
Density
Fitness
Set 1
Set 2
Density
Fitness
Posterior probability
Posterior probability
Cluster assignment and segregation analysis
Cutoffs determined using simulated data

Figure S2.

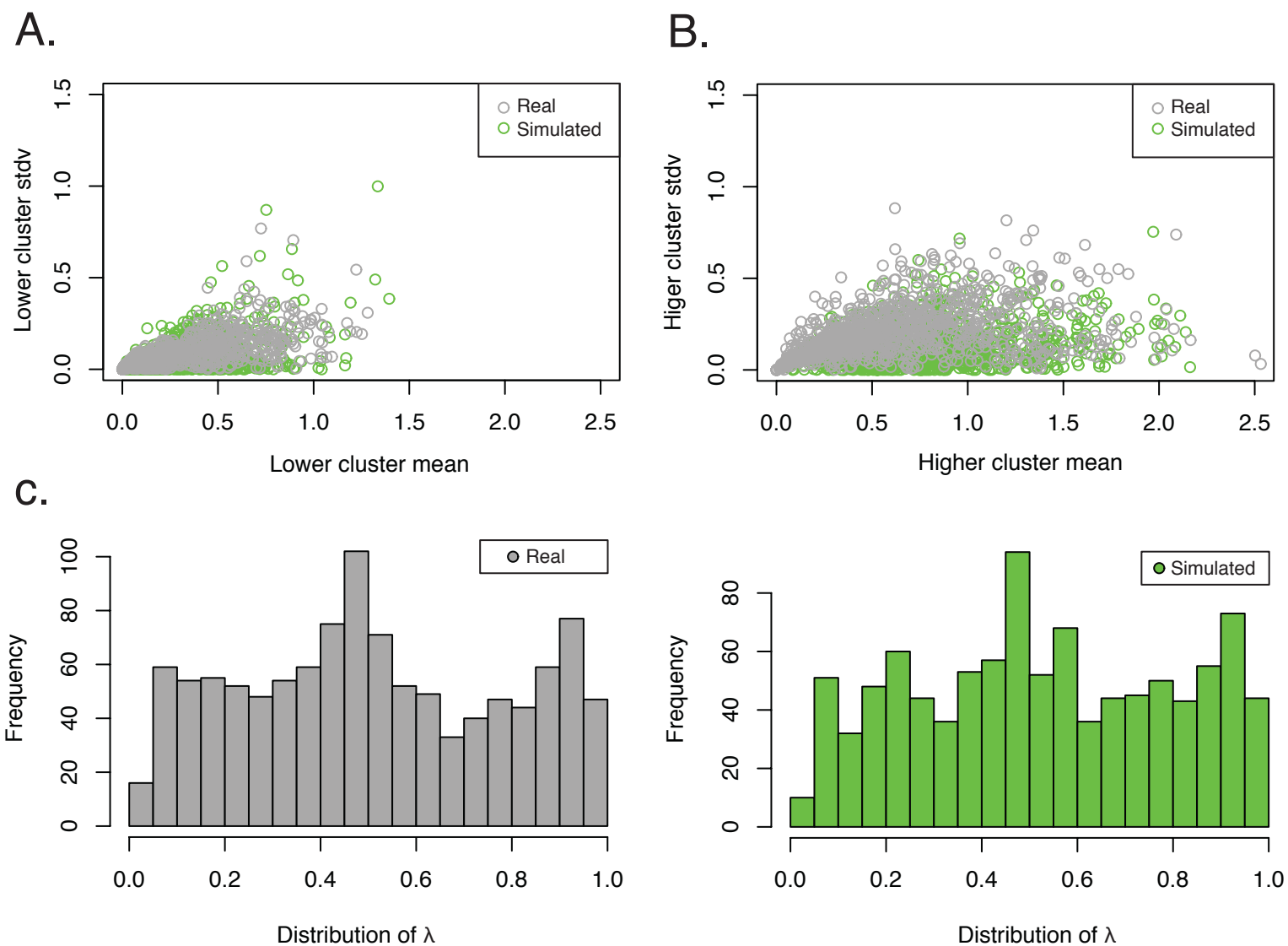

A.
Lower cluster stdv
Lower cluster mean
Real
Simulated
B.
Higer cluster stdv
Higher cluster mean
Real
Simulated
C.
Frequency
Distribution of λ
Real
Frequency
Distribution of λ
Simulated

Figure S3.

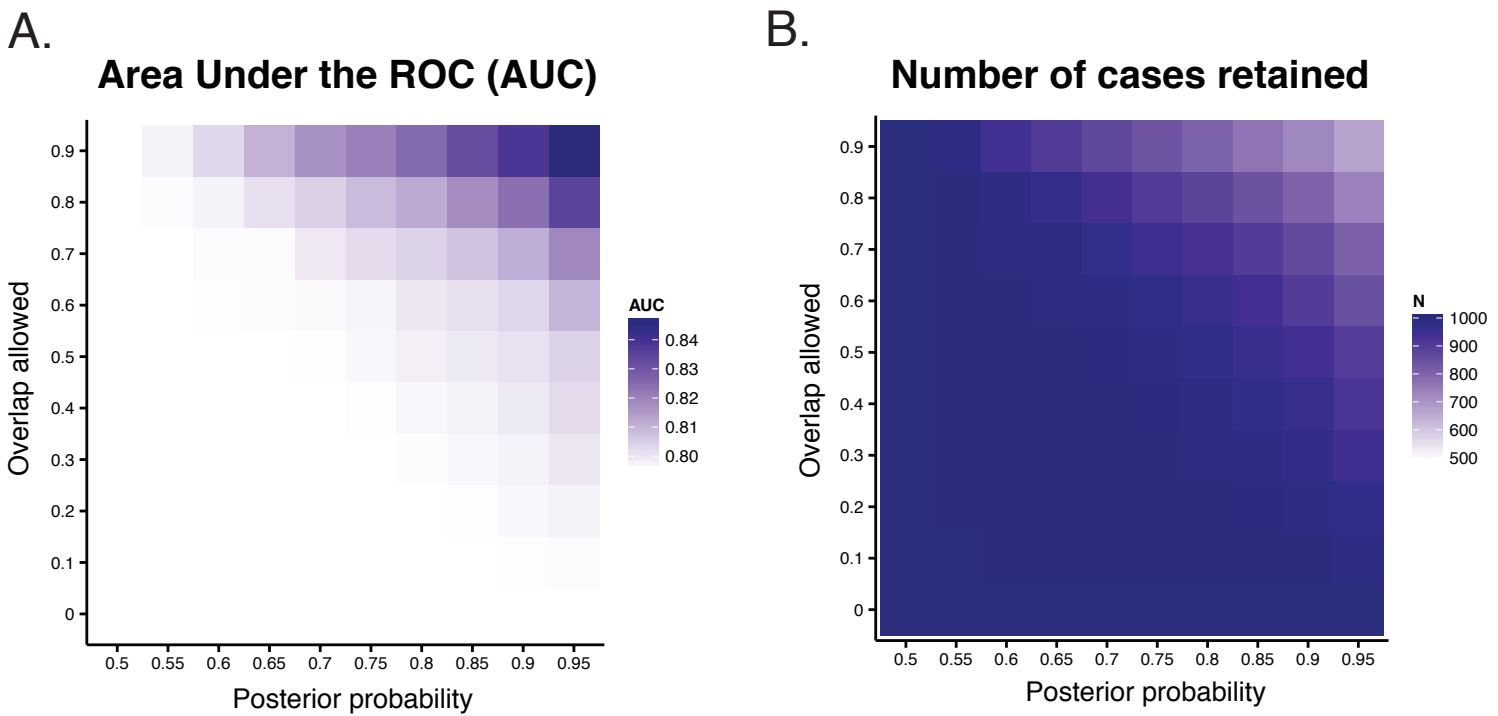

A.
Area Under the ROC (AUC)
Overlap allowed
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0.5 0.55 0.6 0.65 0.7 0.75 0.8 0.85 0.9 0.95
Posterior probability
AUC
0.84
0.83
0.82
0.81
0.80
B.
Number of cases retained
Overlap allowed
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0.5 0.55 0.6 0.65 0.7 0.75 0.8 0.85 0.9 0.95
Posterior probability
N
1000
900
800
700
600
500

Figure S4.

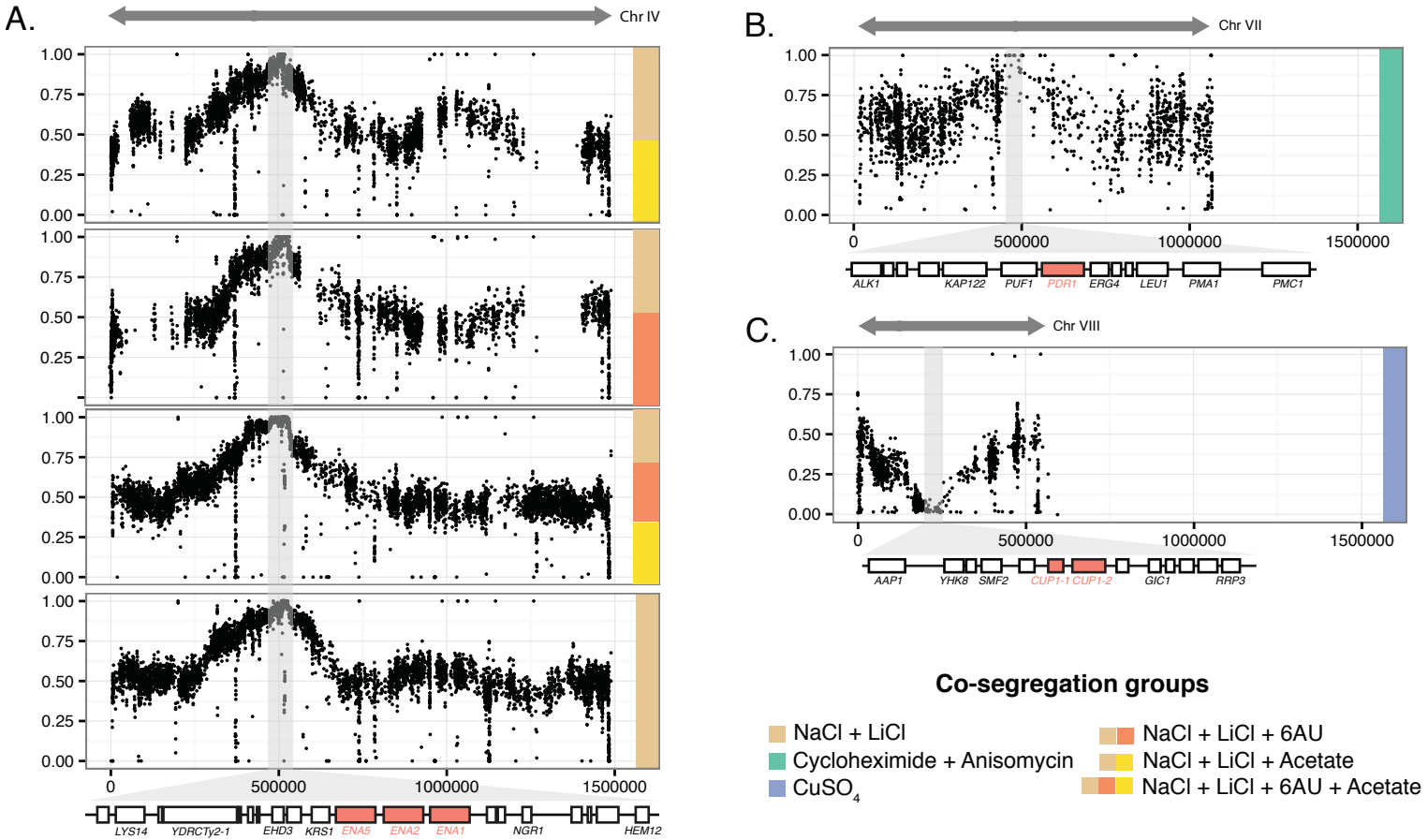

A.
Chr IV
1.00
0.75
0.50
0.25
0.00
0
500000
1000000
1500000
LYS14
YDRCTy2-1
EHD3
KRS1
ENA5
ENA2
ENA1
NGR1
HEM12
B.
Chr VII
ALK1
KAP122
PUF1
PDR1
ERG4
LEU1
PMA1
PMC1
C.
Chr VIII
AAP1
YHK8
SMF2
CUP1-1
CUP1-2
GIC1
RRP3
Co-segregation groups
NaCl + LiCl
Cycloheximide + Anisomycin
CuSO4
NaCl + LiCl + 6AU
NaCl + LiCl + Acetate
NaCl + LiCl + 6AU + Acetate

Figure S5.

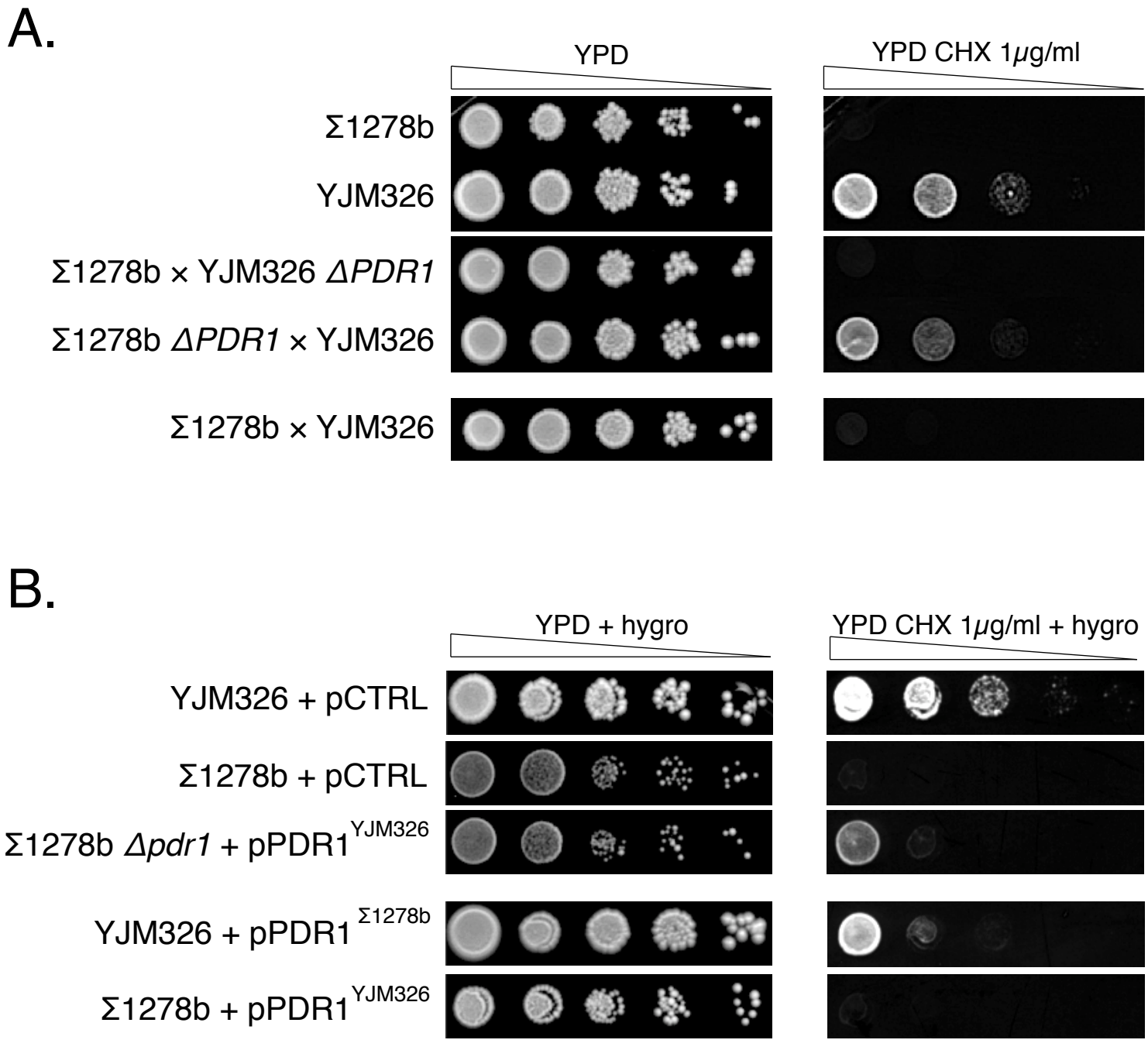

A.
YPD
YPD CHX 1μg/ml
Σ1278b
YJM326
Σ1278b × YJM326 ΔPDR1
Σ1278b ΔPDR1 × YJM326
Σ1278b × YJM326
B.
YPD + hygro
YPD CHX 1μg/ml + hygro
YJM326 + pCTRL
Σ1278b + pCTRL
Σ1278b Δpdr1 + pPDR1YJM326
YJM326 + pPDR1Σ1278b
Σ1278b + pPDR1YJM326

Figure S6.

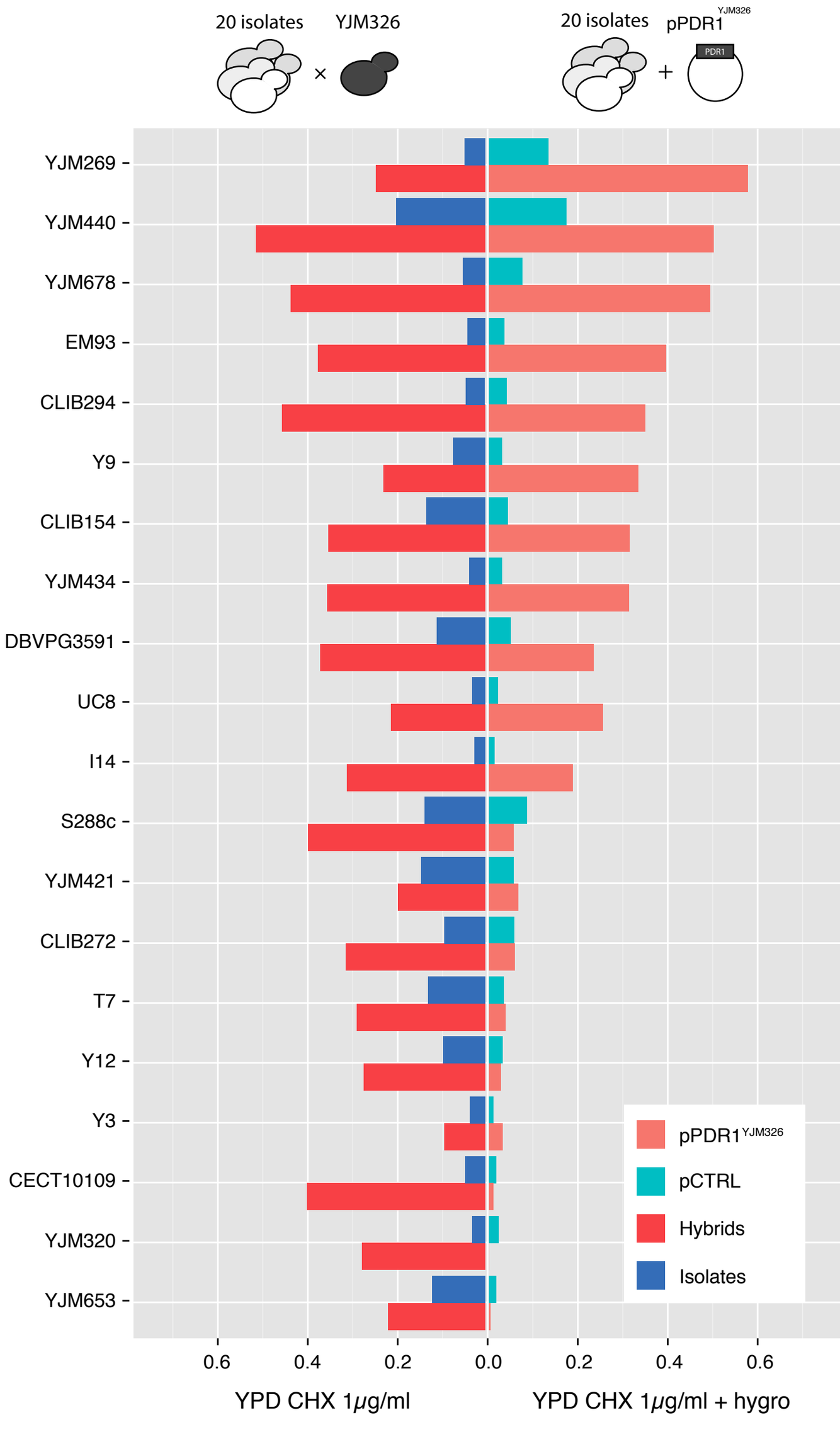
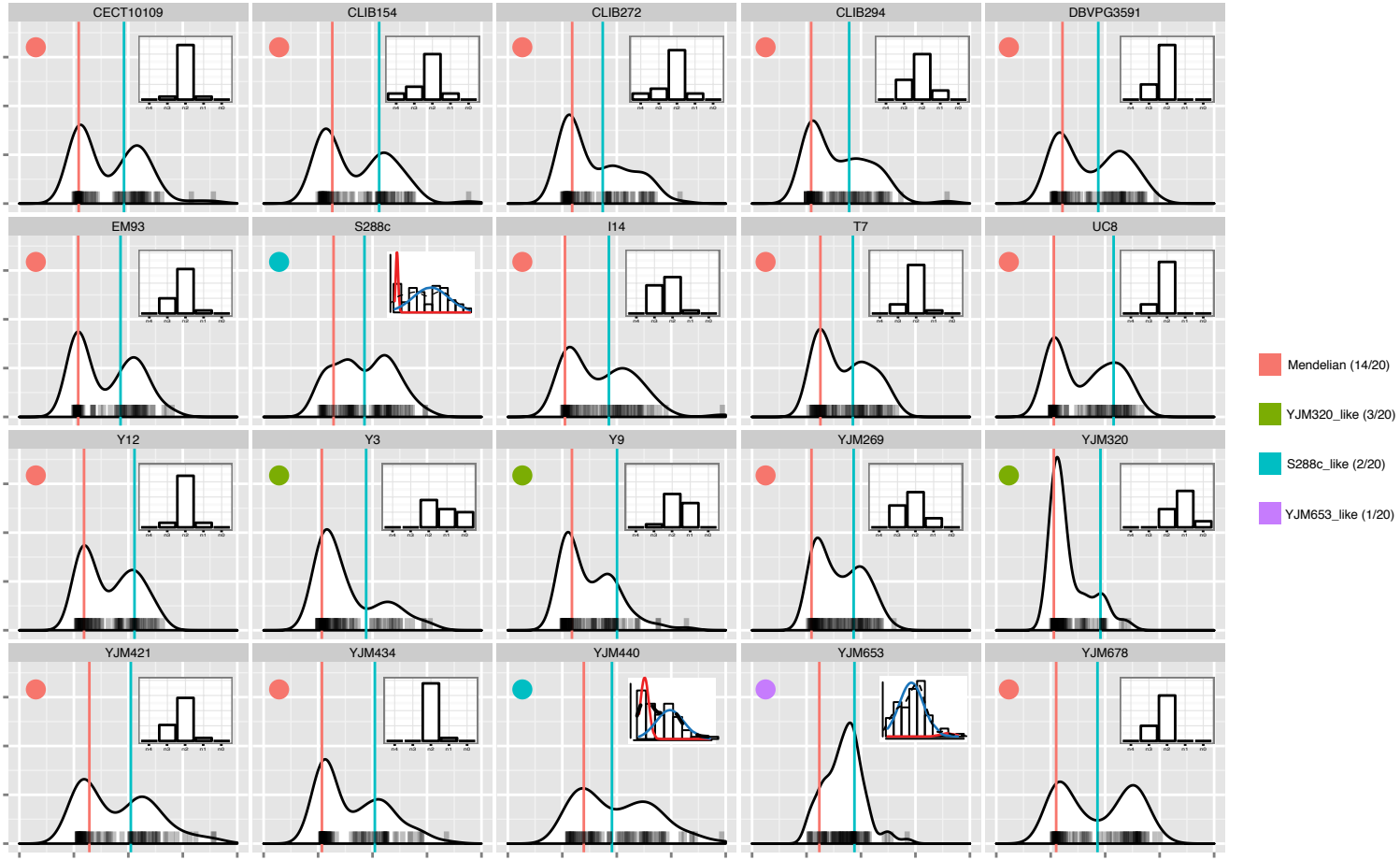

20 isolates
YJM326
20 isolates
pPDR1 YJM326
PDR1
YJM269
YJM440
YJM678
EM93
CLIB294
Y9
CLIB154
YJM434
DBVPG3591
UC8
I14
S288c
YJM421
CLIB272
T7
Y12
Y3
CECT10109
YJM320
YJM653
0.6
0.4
0.2
0.0
0.2
0.4
0.6
YPD CHX 1µg/ml
YPD CHX 1µg/ml + hygro
pPDR1 YJM326
pCTRL
Hybrids
Isolates

Figure S7.


CECT10109
CLIB154
CLIB272
CLIB294
DBVPG3591
EM93
S288c
I14
T7
UC8
Y12
Y3
Y9
YJM269
YJM320
YJM421
YJM434
YJM440
YJM653
YJM678
Mendelian (14/20)
YJM320_like (3/20)
S288c_like (2/20)
YJM653_like (1/20)