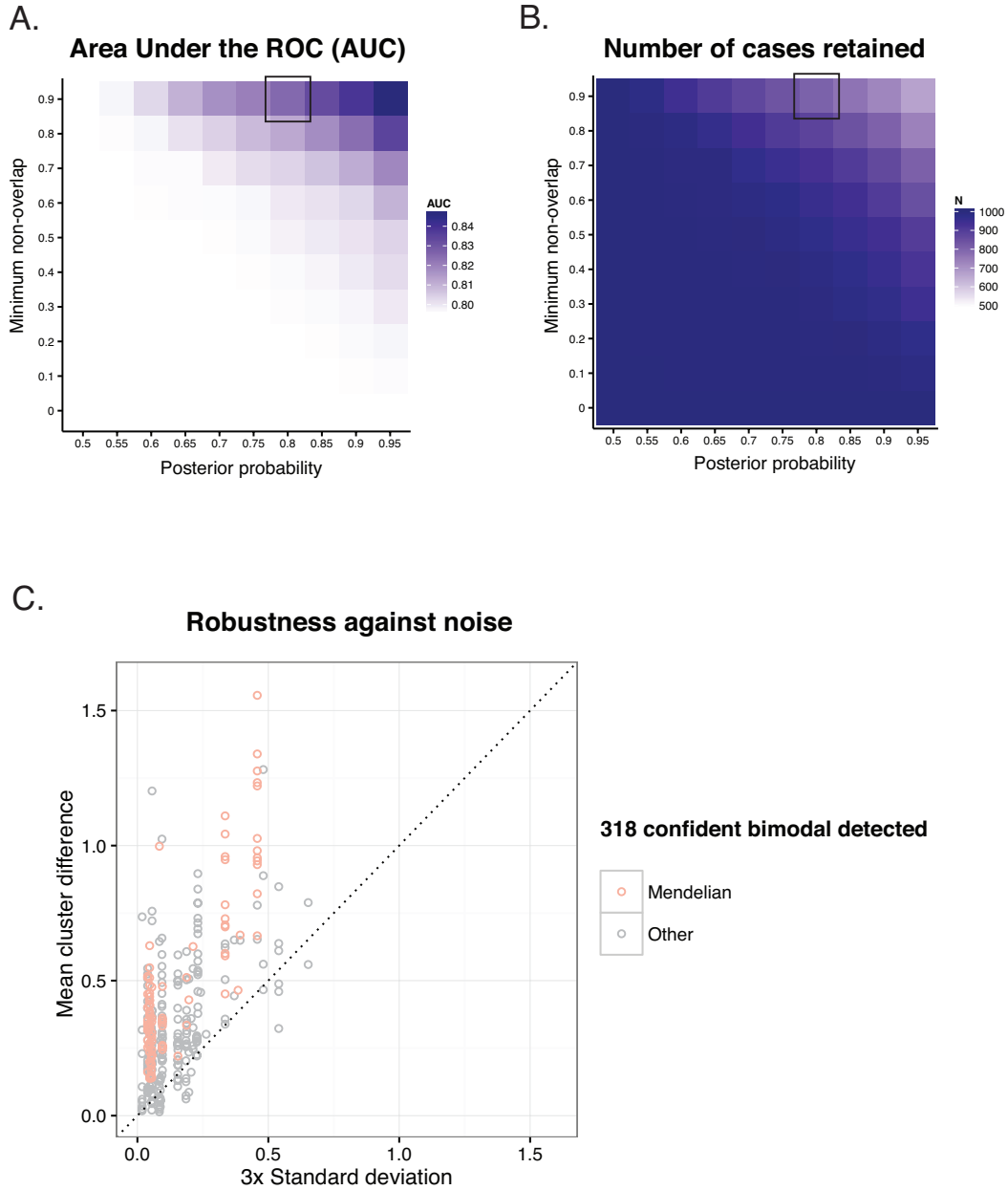


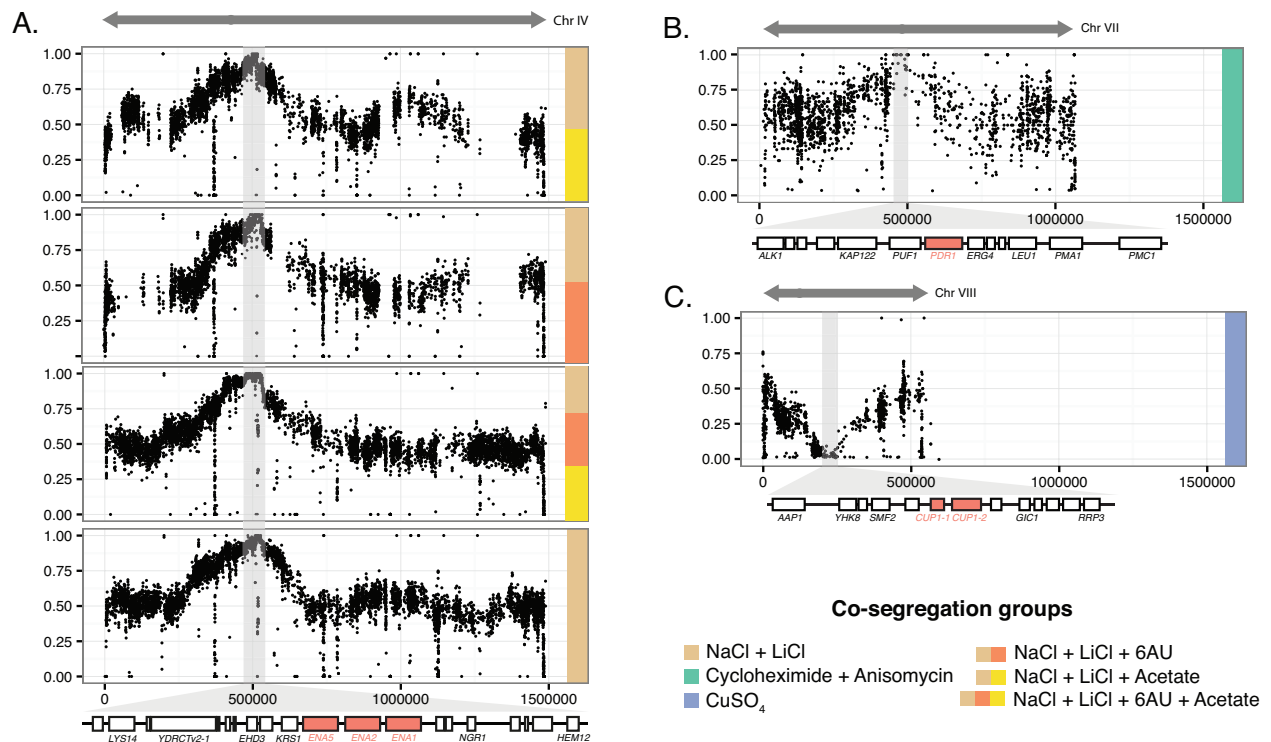
## **Supplemental information**

### **The hidden complexity of Mendelian traits across yeast natural populations**

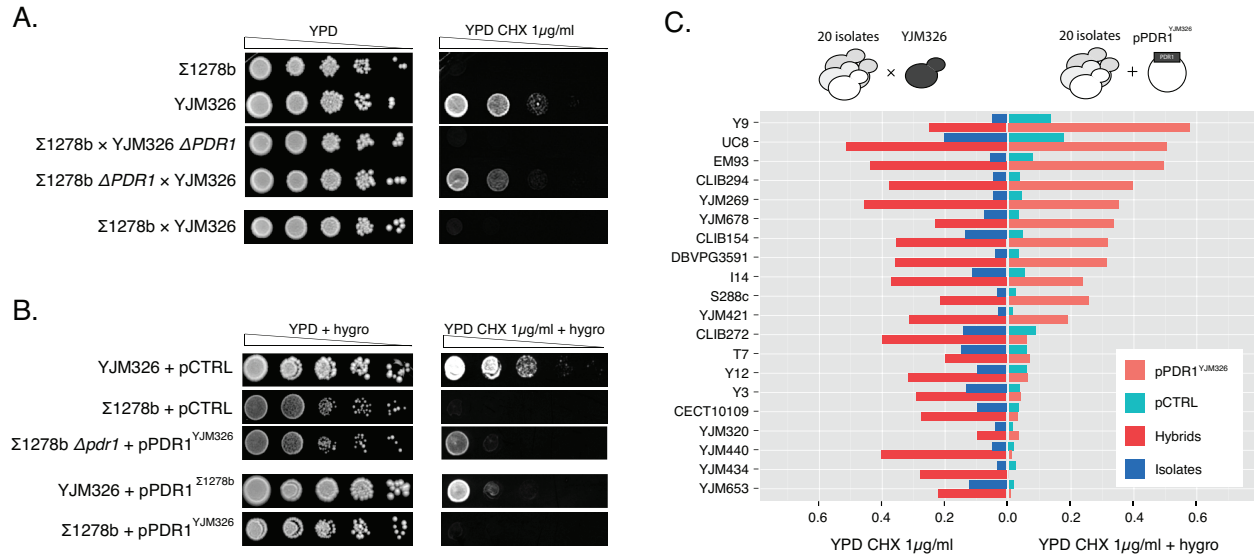
Jing Hou, Anastasie Sigwalt, Téo Fournier, David Pflieger, Jackson Peter, Jacky de Montigny,  
Maitreya J. Dunham and Joseph Schacherer



**Figure S1, related to Figure 1. Evaluation of detection power and robustness against noise.** (A) Evolution of area under the curve (AUC) with different combinations of parameters. X-axis: posterior probability cutoffs. Y-axis: minimum proportion of individuals passed the posterior probability cutoff *i.e.* non-overlapping between assigned clusters. (B) Number of cases that passed the threshold with different combinations of parameters. The axes are the same as indicated in (A) The cutoffs chosen for confident detection of bimodal distributions were highlighted. (C) Detected bimodal distributions were robust against noise. A total of 318 cases were detected as bimodal with the parental strains belong to distinct clusters using the cutoffs defined. Most cases showed mean fitness cluster difference (y-axis) higher than 3 times of standard deviation observed using replicates. Cases identified as Mendelian are in red.

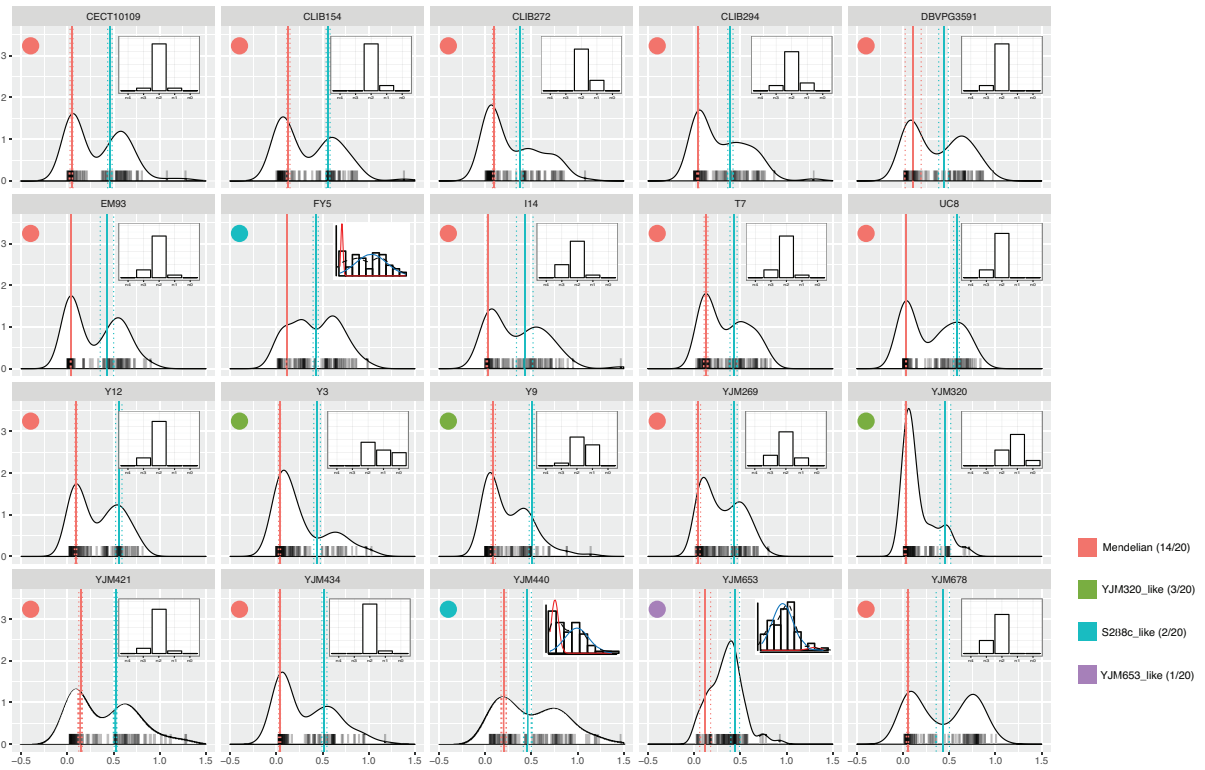


**Figure S2, related to Figure 1B. Identification of the genomic regions involved in identified Mendelian traits.** Bulk segregant analysis identified causal genomic regions in traits related to co-segregation with NaCl (A), cycloheximide and anisomycin (B) and copper sulfate (C). One chromosomal region 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  $\Sigma 1278b$ . Shaded areas correspond to regions with most skewed allele frequencies and genes with these regions are presented to scale.

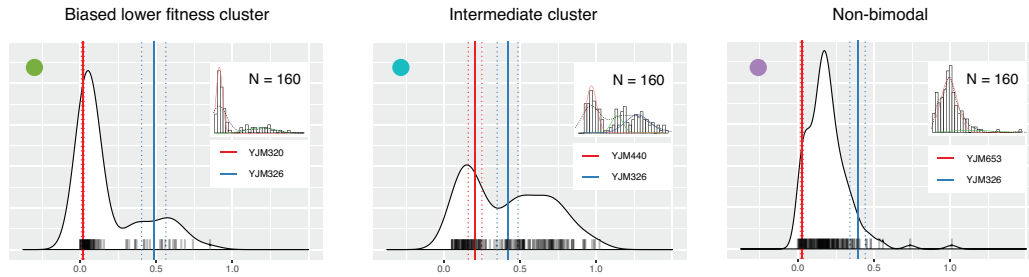


**Figure S3, related to Figure 3. Fitness comparison in strains with ectopic expression of  $PDR1^{YJM326}$  and in hybrid contexts.** (A) Reciprocal hemizygosity test for the candidate gene  $PDR1$ . Sensitive ( $\Sigma 1278b$ ) and resistant (YJM326) parental isolates as well as hybrids that are wild type or hemizygous for the  $PDR1$  gene are spotted in 5 dilutions onto YPD (left panel) and YPD CHX  $1\mu g/ml$  (right panel). Cells were grown for 48 hours at  $30^{\circ}C$ . (B) Ectopic expression of the resistance allele  $PDR1^{YJM326}$  confers drug resistance in the sensitive strain  $\Sigma 1278b$  only with deletion of  $PDR1$ . Growth of strains carrying empty control plasmid (pCTRL) or plasmids with the resistant (pPDR1<sup>YJM326</sup>) or sensitive (pPDR1 <sup>$\Sigma 1278b$</sup> ) allele was tested in the absence (left panel) or presence (right panel) of cycloheximide. All media were supplemented with  $200\mu g/ml$  of hygromycin to maintain plasmid stability. (C) 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<sup>YJM326</sup> (right panel). Strains are indicated on y-axis, with color codes correspond to different configurations (hybrid or plasmid).

A.



B.



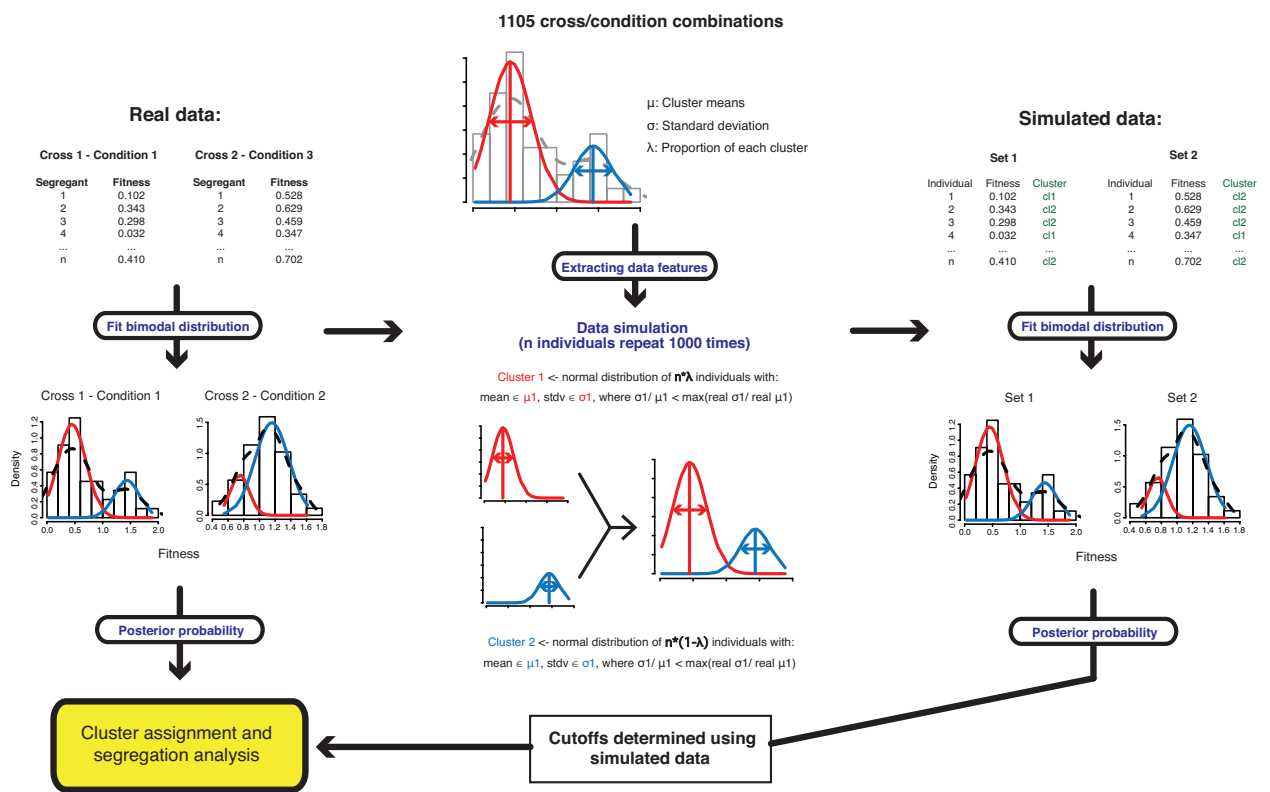
**Figure S4, related to Figure 4. Offspring fitness distribution related to drug resistance in 20 hybrid backgrounds.** (A) Distributions of 80 offspring (20 full tetrads) and the lethal phenotype segregation patterns (upper right side) in the presence of cycloheximide are presented for 20 isolates crossed with YJM326. Parental fitness values are indicated at vertical bars, with red corresponds to the sensitive isolate crossed and blue the resistant parent YJM326, and dotted lines representing  $\pm$  standard deviation ( $N = 4$ ). Different inheritance types are color-coded. In case of biased inheritance patterns, distributions and maximum likelihood cluster assignments are shown instead of segregation. (B) Additional offspring were tested for selected crosses with biased Mendelian patterns. Vertical bars indicates parental fitness values with dotted lines representing  $\pm$  standard deviation ( $N = 16$ ). A total of 160 offspring (40 tetrads) were tested.

## **Supplemental Experimental Procedures**

### **The hidden complexity of Mendelian traits across yeast natural populations**

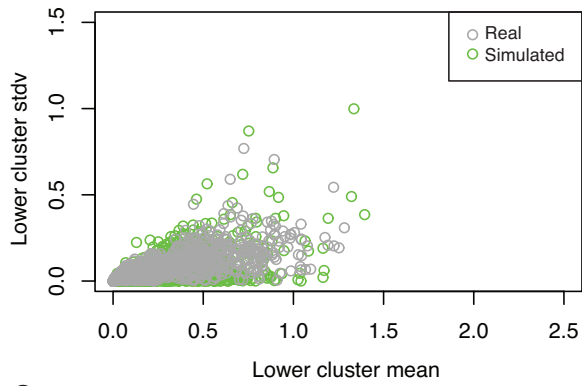
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## Workflow for data processing and simulations

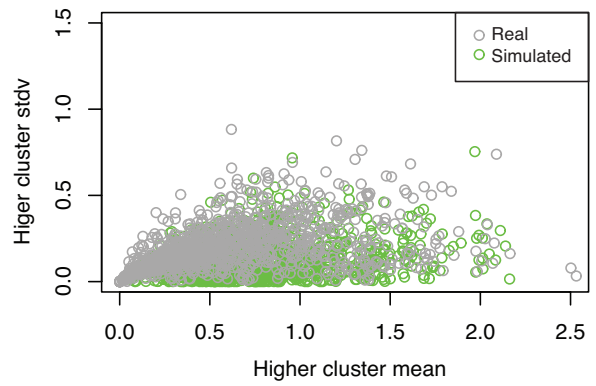


## Feature comparison of simulated dataset with the real data

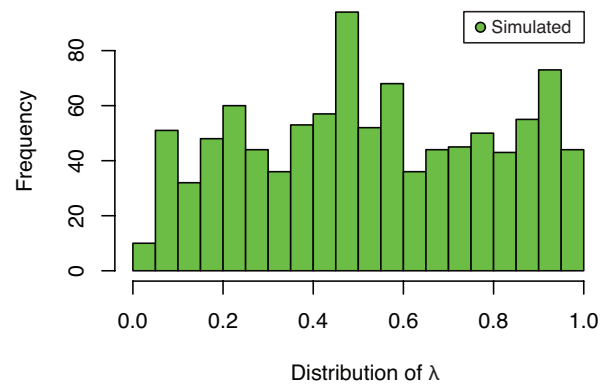
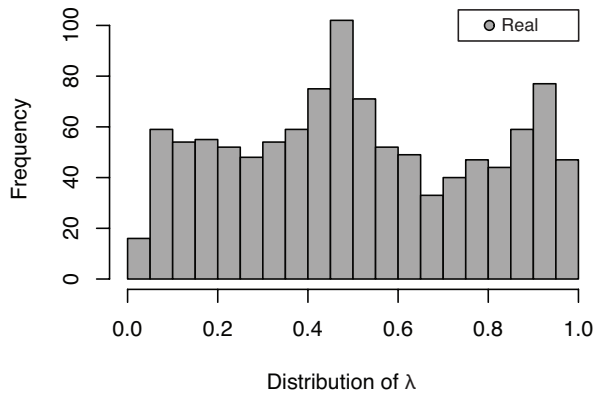
A.



B.



C.



(A) Lower cluster mean vs. lower cluster standard deviation.  $N_{\text{real}} = 1105$ ,  $N_{\text{simulated}} = 1000$ . (B) Higher cluster mean vs. higher cluster standard deviation. (C) Distribution of the proportion of lower fitness cluster.



## Origin and sequence divergence of strains used in this study

Strain	Source	Location	Crossed with YJM326	Estimated divergence to S288c (%)	References
BC187	Barrel fermentation	USA		0.37	Liti et al. 2009
YPS128	Soil beneath <i>Quercus alba</i>	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 <i>Quercus sp.</i>	USA		0.41	Schacherer et al. 2009
YPS163	Soil beneath <i>Quercus rubra</i>	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 <i>Quercus sp.</i>	North Carolina, USA		0.43	Schacherer et al. 2009
T7	Exudates <i>Quercus sp.</i>	Babler State Park, MO, USA	*	0.49	Schacherer et al. 2009

## Media compositions for conditions tested in this study

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