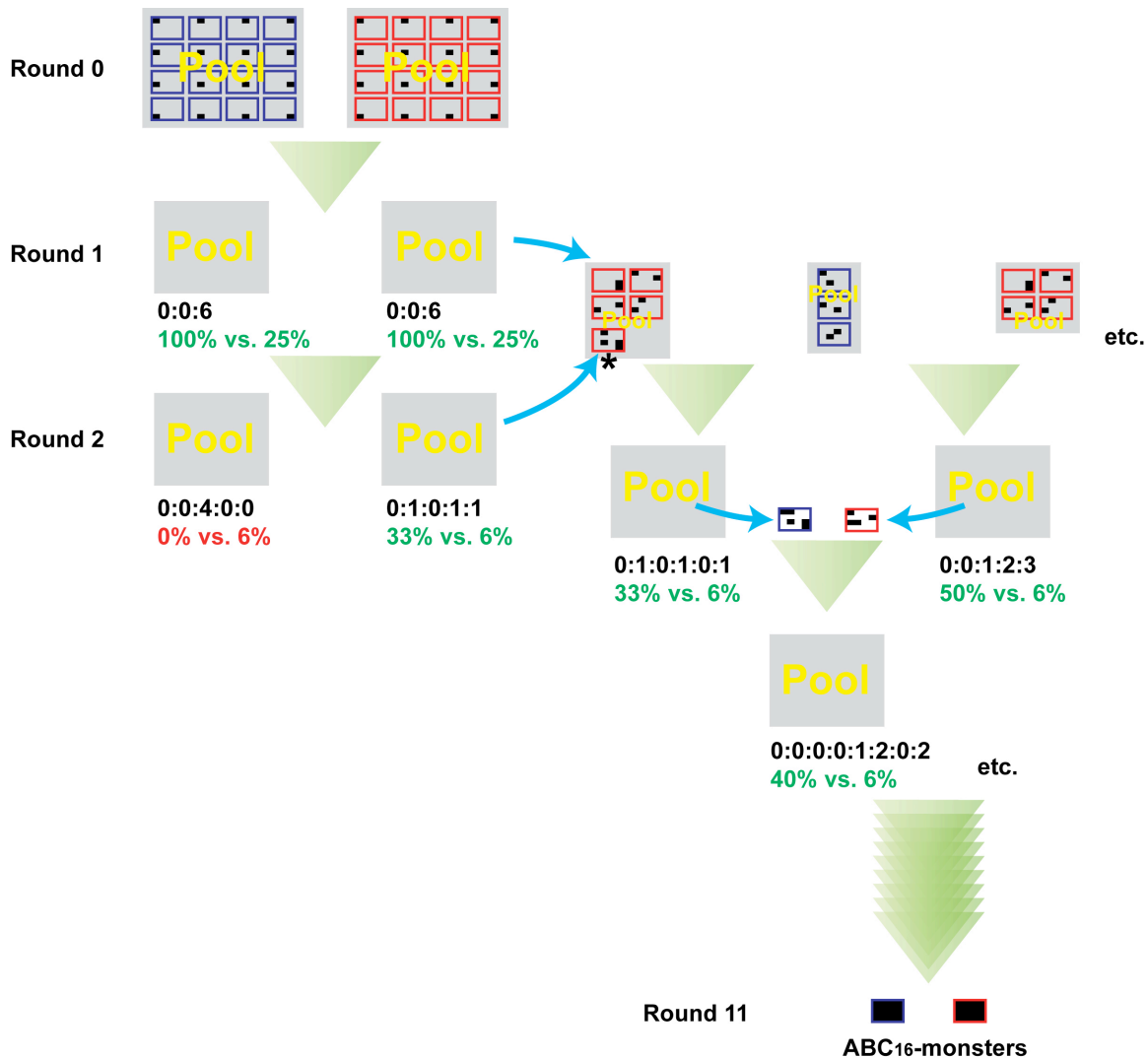
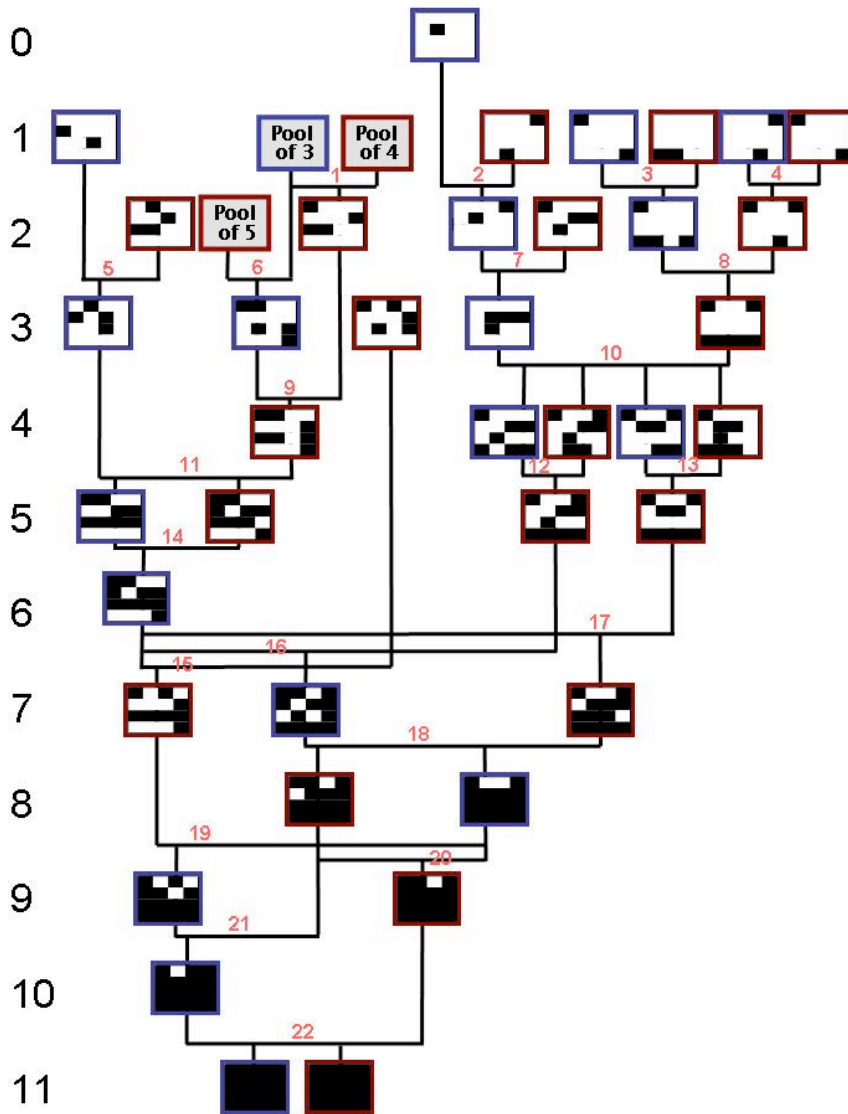


Supplementary Figure 1. The early phase of ABC₁₆-monster construction.



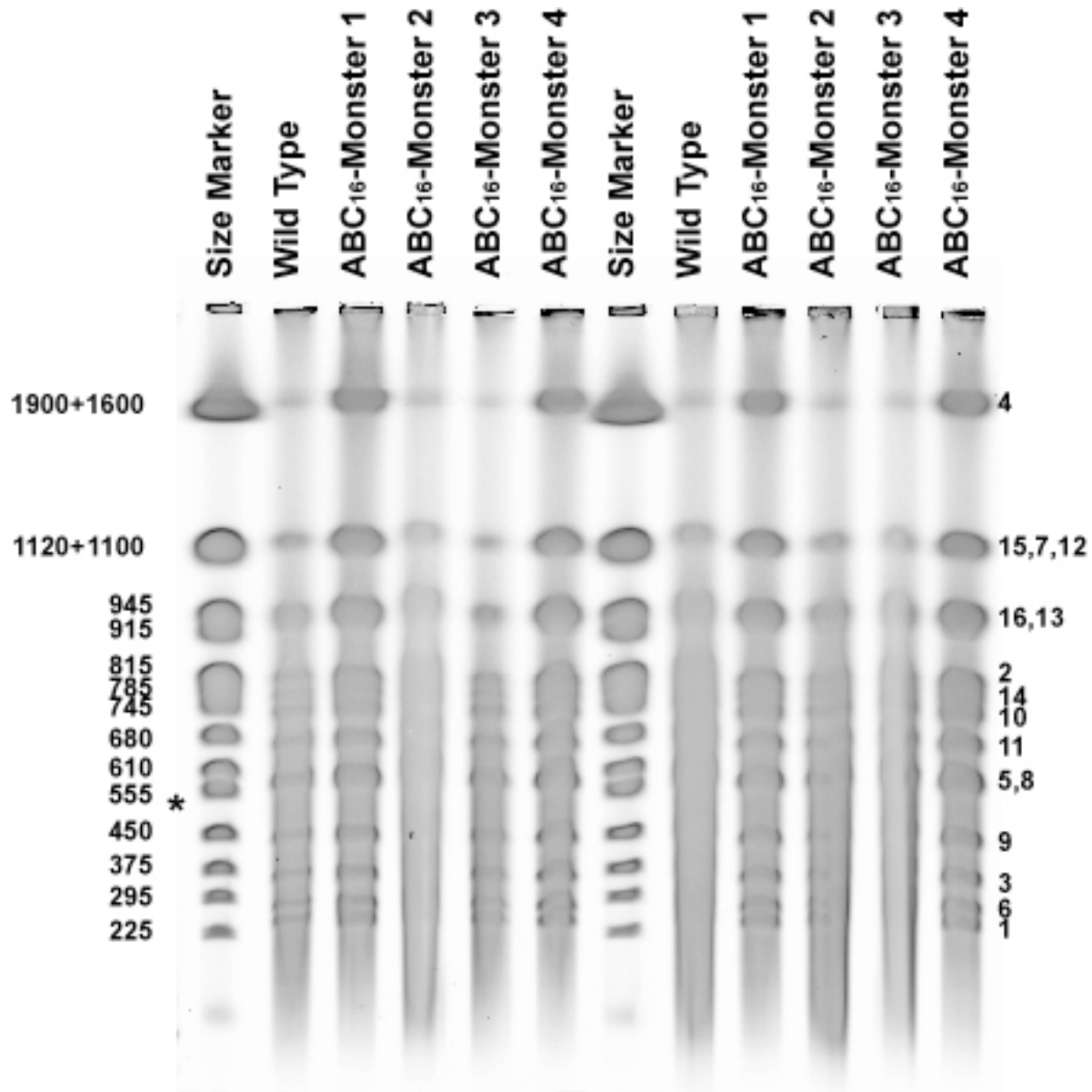
Each rectangle outlined in blue (*MATa* strains) or red (*MATα*) represents a strain. Positions of darkened rectangles within each strain rectangle indicate genes deleted within that strain. From left to right along each row, and descending from the top row, darkened positions correspond to *adp1Δ*, *snq2Δ*, *ycf1Δ*, *pdr15Δ*, *yor1Δ*, *vmr1Δ*, *pdr11Δ*, *nft1Δ*, *bpt1Δ*, *ybt1Δ*, *ynr070wΔ*, *yol075cΔ*, *aus1Δ*, *pdr5Δ*, *pdr10Δ*, and *pdr12Δ*. Green triangle indicates one round of the Green Monster process. Blue arrow indicates that strains were isolated from the resulting population from a Green Monster process. The one strain marked with asterisk was derived from the second round. Percentages refer to the experimentally determined fraction of sorted cells (left) and the expected fraction of unsorted cells (right) carrying the maximum theoretically achievable number of deletions in that round. Numbers of genotyped strains are shown above the percentages, starting from zero-deletion strains and ending with strains with the highest possible number of deletions. The rest of the lineage is shown in **Supplementary Fig. 2** online.

Supplementary Figure 2. The later phase of ABC₁₆-monster construction.



As in **Supplementary Fig. 1** online, each strain is indicated with a blue or red rectangle filled with darkened rectangles. The sexual cycling of the Green Monster process was performed in each round. The number of rounds experienced by strains since the initial single mutants is shown on the left. Strains without links to parental strains were obtained using *en masse* mating of pooled strains of opposite mating type. Number in red identifies the cross in this figure and in **Supplementary Table 2**.

Supplementary Figure 3. Karyotypes of ABC₁₆-monster and wild-type strains.



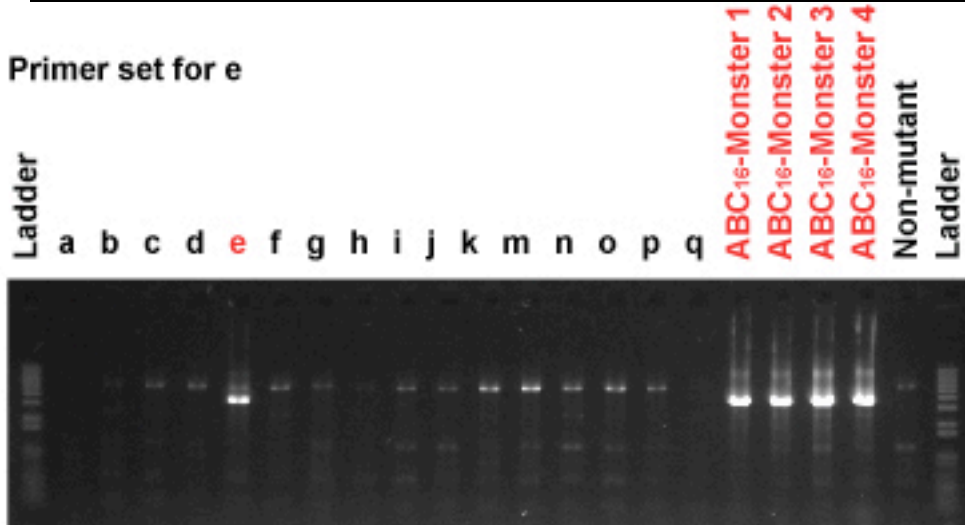
Genomic DNA samples were analyzed using pulsed-field gel electrophoresis. The identical samples were loaded twice. The band patterns were very similar for ABC₁₆-monster strains (1: RY0513, 2: RY0518, 3: RY0519, and 4: RY0523) and wild type (BY4741). The four ABC₁₆-monster strains were derived from slightly different branches of the lineage (**Supplementary Fig. 8** online). Size marker is NEB Yeast Chromosome PFG Marker, with band sizes in kb indicated on the left. Chromosome numbers for bands of our samples are indicated on the right.

In the experiment described in **Supplementary Fig. 4** online, amplification of the GFP cassettes for *yll048cΔ* and *ypl058cΔ* required a more robust enzyme than *Taq* polymerase. However, these loci are unlikely to be involved in translocation. Recombination between them would result in the loss of normal chromosomes 12 and 16 and the emergence of bands at 1480 kb and 542 kb. Although changes in the large size range may be difficult to detect, the 542-kb recombinant chromosome band is clearly absent around the asterisk.

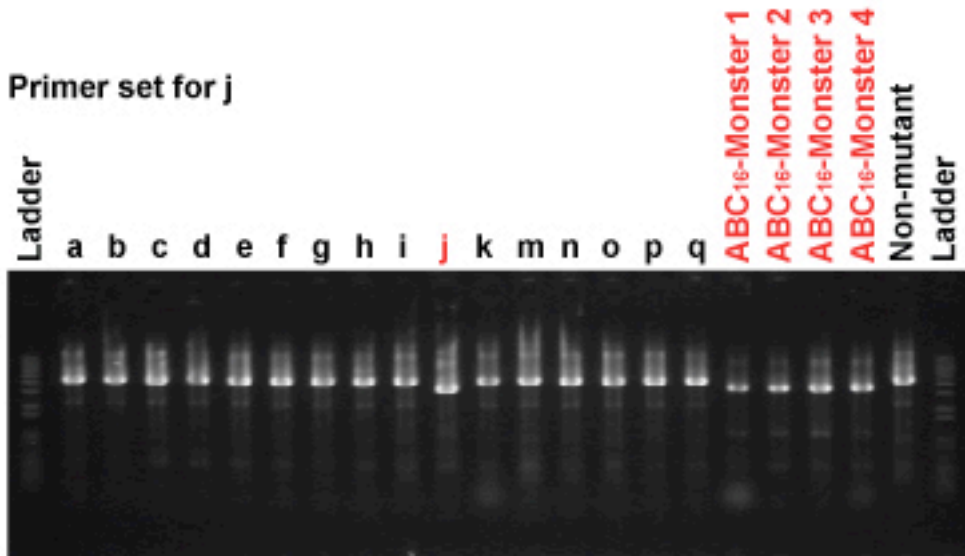
Supplementary Figure 4. Evidence for lack of recombination between GFP cassettes within four ABC₁₆-monster isolates.

		Strain															ABC ₁₆ -monsters				Non-mutant	
		Single-mutant ProMonsters															1	2	3	4		
Primer pair		a	b	c	d	e	f	g	h	i	j	k	m	n	o	p	q					
a		D	-	W	W	W	W	W	W	-	W	W	W	W	W	W	W	D	D	D	D	W
b		W	D	W	W	W	W	W	W	W	W	W	W	W	W	W	W	D	D	D	D	W
c		W	W	D	W	W	W	W	W	W	W	W	W	W	W	W	W	D	D	D	D	W
d		W	W	W	D	-	W	W	W	W	W	W	W	W	W	W	W	D	D	D	D	W
e		-	-	-	-	D	-	-	-	-	-	-	-	-	-	-	D	D	D	D	-	
f		W	W	W	W	W	D	W	W	W	W	W	W	W	W	W	W	D	D	D	D	W
g		W	W	W	W	W	W	D	W	W	W	W	W	W	W	W	W	D	D	D	D	W
h		W	W	W	W	W	W	W	D	W	W	W	W	W	W	W	W	D	D	D	D	W
i		-	-	-	-	-	-	-	-	D	-	-	-	-	-	-	D	D	D	D	-	
j		W	W	W	W	W	W	W	W	W	D	W	W	W	W	W	W	D	D	D	D	W
k		W	W	W	W	W	W	W	W	W	W	D	W	W	W	W	W	D	D	D	D	-
m		W	W	W	W	W	W	W	W	W	W	D	W	W	W	W	W	D	D	D	D	W
n		-	-	-	-	-	-	-	-	-	-	-	-	D	-	-	D	D	D	D	-	
o		W	W	W	W	W	W	W	W	W	W	W	W	W	D	W	W	D	D	D	D	-
p		-	-	W	W	W	W	W	W	W	W	W	W	W	W	D	W	D	D	D	D	W
q		W	W	W	W	W	W	W	W	W	W	W	W	W	W	W	D	D	D	D	D	-

Primer set for e



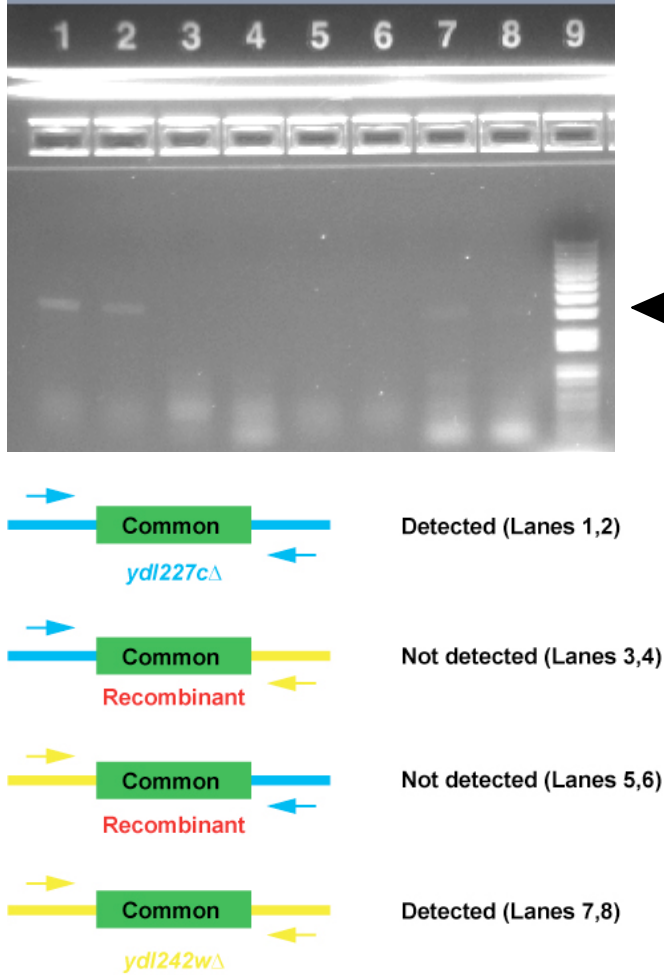
Primer set for j



Supplementary Figure 4 (continued).

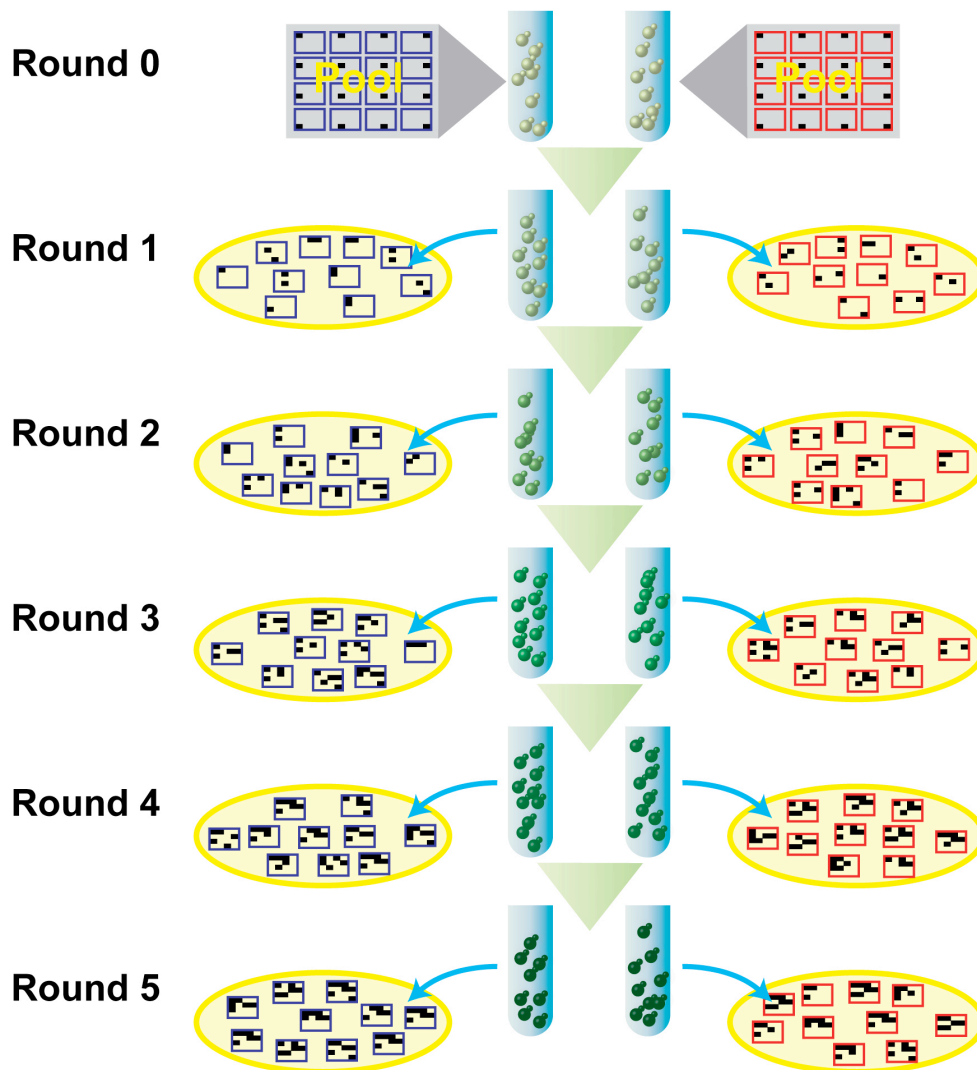
For each ABC transporter locus, primers were targeted to the flanking genomic regions to amplify the entire GFP cassette. Ectopic recombination between two GFP cassettes would be expected to affect our ability to detect the non-recombinant amplicons at the two corresponding loci. A non-mutant control (which has a GFP cassette in the unrelated *HO* gene), all 16 single-mutant ProMonsters, and four ABC₁₆-monsters were examined. The ABC₁₆-monster strains: isolate 1 (RY0513), isolate 2 (RY0518), isolate 3 (RY0519), and isolate 4 (RY0523) each differed slightly from the others in its construction lineage (**Supplementary Fig. 8** online). Deletions are indicated using codes: “a” for *ynr070wΔ*, “b” for *ygr281wΔ*, “c” for *ycr011cΔ*, “d” for *ydr135cΔ*, “e” for *yhl035cΔ*, “f” for *ydr011wΔ*, “g” for *yll015wΔ*, “h” for *yor011wΔ*, “i” for *ypl058cΔ*, “j” for *ykr103wΔ*, “k” for *yor153wΔ*, “m” for *yil013cΔ*, “n” for *yll048cΔ*, “o” for *yor328wΔ*, “p” for *yol075cΔ*, and “q” for *yde406wΔ*. When PCR was efficient (as in the test for j), bands of about 4-5 kb corresponding to the wild-type transporter sequences were also amplified (denoted ‘W’ in the table). Otherwise (as in the test for e), no bands or only background bands were amplified (denoted ‘-’ in the table). Bands of the correct size (about 3 kb) corresponding to the fragments containing the GFP deletion cassette (denoted ‘D’ in the table) were observed only when strains expected from previous genotyping to be deleted for a particular gene were tested with a primer set for that gene. Strain names for such strains are shown in red above the gels. The four ABC₁₆-monster samples all generated bands with all sixteen sets. This result is consistent with the absence of GFP-mediated chromosomal rearrangements. For example, in the gel (lower panel) for the ProMonster corresponding to j, the band for j of the ABC₁₆-monster is smaller than the band containing the intact open reading frame and consistent in size with a GFP-replaced locus. It is also clear from the PCR amplicon sizes that multimerization of the GFP sequence within the cassette, a formally possible mechanism for obtaining elevated fluorescence and thus surviving flow cytometric selection, was not observed. Amplification of the GFP cassette from two of the 16 loci (*yll048cΔ* and *ypl058cΔ*) required the Ex *Taq* enzyme (Takara). The need to change enzymes is likely due to these loci simply representing difficult amplicons, because we would expect to detect any rearrangements involving these loci by pulse-field gel electrophoresis analysis (see **Supplementary Fig. 3** online).

Supplementary Figure 5. Absence of GFP-mediated rearrangements between two nearby cassettes.



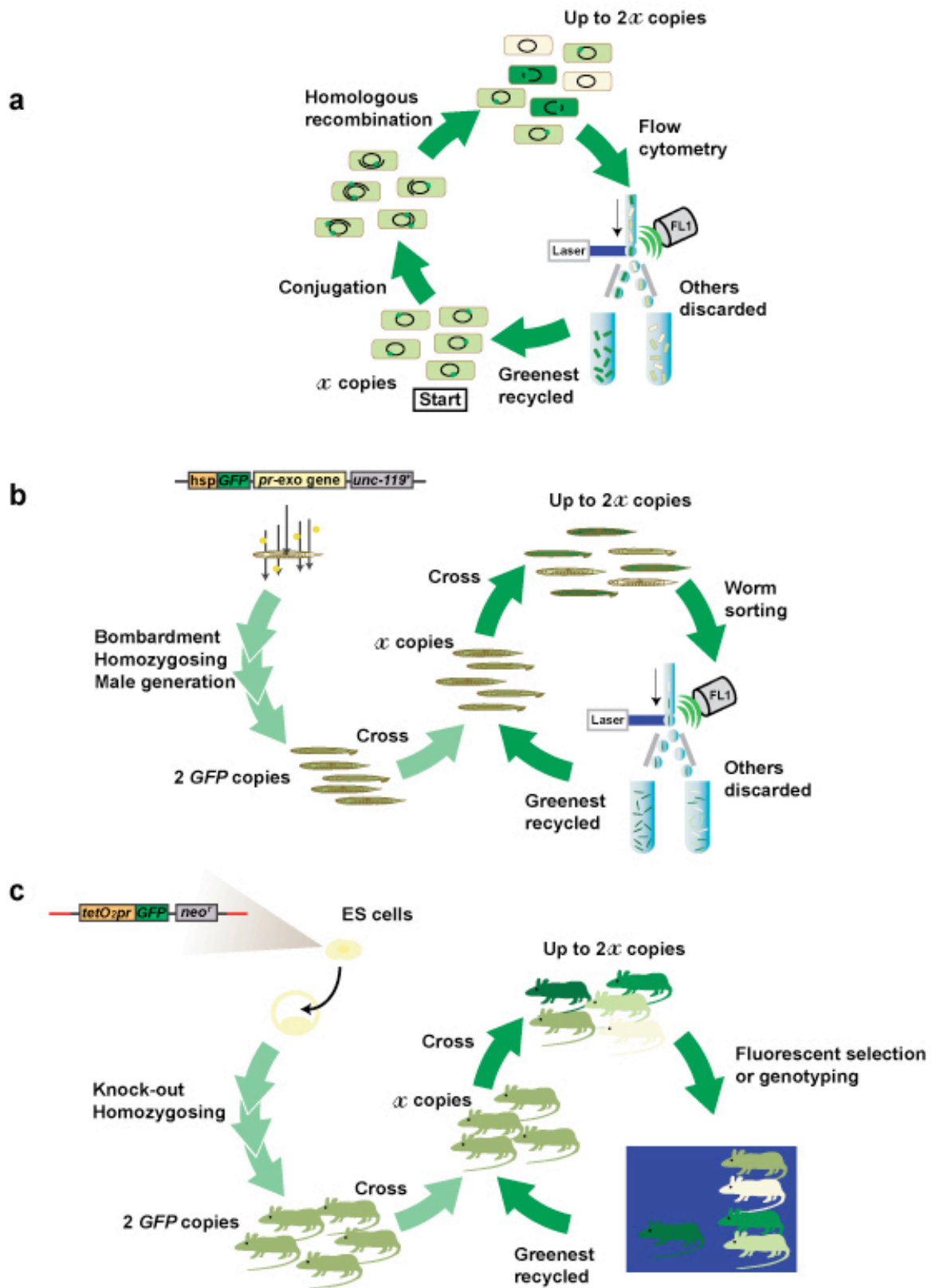
The possibility of frequent rearrangement involving nearby genes was examined using PCR for *YDL242W* and *YDL227C*. DNA samples each representing a mixture of haploid progeny derived from ~30,000 independent meiosis events were analyzed. The parental diploid had the genotype: *ydl227cΔ +/+ ydl242wΔ*. The four possible combinations for primers upstream and downstream of the two genes were used to detect any rearrangement. The gel shows results using the following primers: *YDL227C* upstream/*YDL227C* downstream (lanes 1 and 2), *YDL227C* upstream/*YDL242W* downstream (lanes 3 and 4), *YDL242W* upstream/*YDL227C* downstream (lanes 5 and 6), *YDL242W* upstream/*YDL242W* downstream (lanes 7 and 8). Lane 9 shows the 1 kb Plus ladder (Invitrogen). A >3 kb band (arrowhead) is expected for fragments spanning the GFP cassette. Only two representative PCR samples of the triplicates are shown. In this experiment, primer sets designed to detect a normal chromosome produced a band, whereas primer sets that would detect recombinant chromosomes never did. In the schematic diagram, PCR primers are indicated with arrows. Light blue and yellow lines denote sequences in the *ydl227cΔ* and the *ydl242wΔ* loci, respectively. The common GFP cassette sequence is shown in green.

Supplementary Figure 6. Schematic diagram of one implementation of the *en masse* variant of the Green Monster process.



Each strain is indicated with a blue or red rectangle filled with darkened rectangles as in **Supplementary Fig. 1** online. Green triangle indicates one round of the Green Monster process (i.e. mating, sporulation, and FACS sorting). Genotypes shown for colonies isolated on plates (yellow ovals) are from Series 1 data, using the first ten genotyped strains for each mating type from that round. Note that these sampled strains were genotyped solely to gauge progress of the *en masse* process, in contrast with the guided variant of the Green Monster process which uses controlled matings of genotyped strains to ensure representation of less-fit alleles.

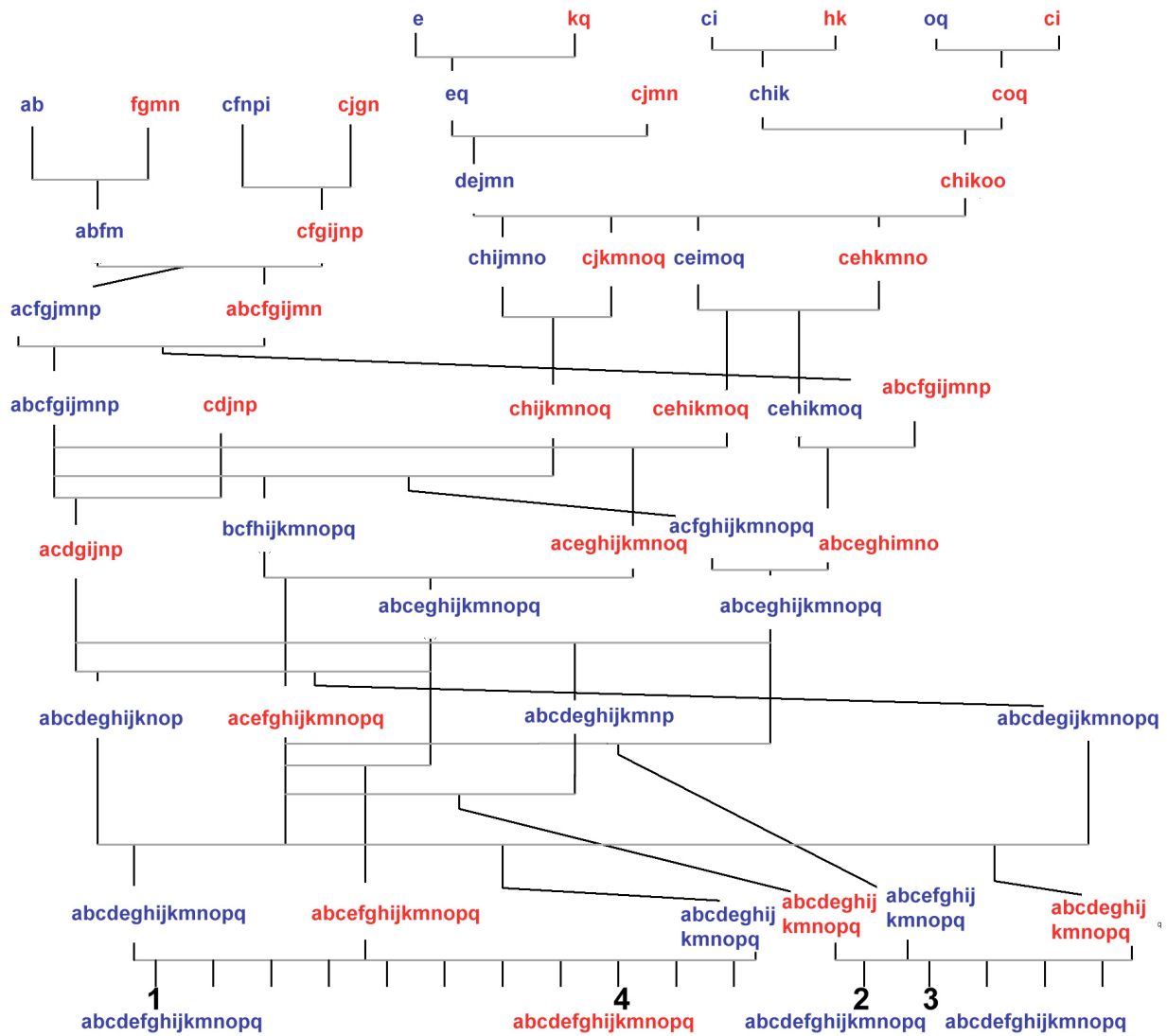
Supplementary Figure 7. Schemes for applying the Green Monster process in other species.



Supplementary Figure 7 (continued).

(a) *E. coli*. Genomic alterations in both F⁻ recipient cells and Hfr donor cells are marked with an identical GFP reporter (green tick mark) within the chromosome (black circle) under the control of an inducible (e.g., T7) promoter. Chromosomal fragments are conjugatively transferred from donor to recipient cells, with subsequent homologous recombination and spontaneous loss of one chromosome generating 0-GFP, 1-GFP, and 2-GFP cells. After flow-cytometric sorting, samples enriched for 2-GFP cells (F⁻ and Hfr cells) are used for the next round of the Green Monster process. **(b)** *C. elegans*. Although gene targeting is difficult in *C. elegans*, exogenous genes can be integrated to random locations in the genome, e.g., using bombardment with gold particles (yellow circles). The gene insertion cassette carries a GFP reporter with an inducible (e.g., heat-shock) promoter and an integration marker (e.g., *unc-119*⁺, where the target strain is an *unc-119(lf)* mutant). After homozygosing the insertion, a standard protocol is used to generate males (depicted with a hooked tail at right) for each single insertion strain. Gene insertion strains are pooled and mated *en masse* to generate heterozygotes for two of starting insertions. Progeny are crossed to generate a complex population of strains carrying zero to four insertions. Strains carrying four insertions should be the greenest and are selected using a worm sorter for the next cross. The number of insertions should grow in each round of the Green Monster process. **(c)** Mouse. Standard gene-targeting methods are used to generate knock-out mouse strains each carrying an identical *tetO₂-GFP* reporter in a targeted gene. *neo^r* is a neomycin-resistance marker for transfection of embryonic stem cells. ES cells with successful replacement are injected into blastocysts (yellow hollow circle), which when implanted becomes a chimeric mouse. Established knock-out mice are mated to combine deletion loci. Mating plugs prevent females from mating productively with multiple males. Therefore, ‘*en masse*’ mating is achieved via artificial insemination using pre-mixed sperm derived from several males. Doxycycline-fed mice can be efficiently screened for macroscopic fluorescence under a UV illuminator.

Supplementary Figure 8. Later part of the lineage of the ABC16-monsters.



Genotypes of the strains are indicated using codes: a for *ynr070wΔ*, b for *ygr281wΔ*, c for *ycr011cΔ*, d for *ydr135cΔ*, e for *yhl035cΔ*, f for *ydr011wΔ*, g for *yll015wΔ*, h for *yor011wΔ*, i for *yp1058cΔ*, j for *ykr103wΔ*, k for *yor153wΔ*, m for *yil013cΔ*, n for *yll048cΔ*, o for *yor328wΔ*, p for *yol075cΔ*, and q for *yde406wΔ*. Blue indicates a *MATa* strain; red indicates a *MATα* strain. The ABC₁₆-monster strains analyzed for detecting chromosomal rearrangements are indicated with 1, 2, 3, and 4.

Supplementary Table 1. Common Interpro entries in *S. cerevisiae*.This chart was obtained from http://www.ensembl.org/Saccharomyces_cerevisiae/Info/IPtop500 on 9/19/2009.Types for entries are defined in http://www.ebi.ac.uk/interpro/user_manual.html#type. Entries marked as families are indicated.

No.	Interpro ID	Interpro name	Number of genes	Interpro type (1: Family)
1	IPR011009	Protein kinase-like	132	
2	IPR003593	AAA+ ATPase - core	128	
3	IPR000719	Protein kinase - core	121	
4	IPR002290	Serine/threonine protein kinase	116	
5	IPR001245	Tyrosine protein kinase	112	
6	IPR008271	Serine/threonine protein kinase - active site	111	
7	IPR011046	WD40 repeat-like	108	
8	IPR001680	WD40 repeat	107	
9	IPR014001	DEAD-like helicase - N-terminal	90	
10	IPR000694	Proline-rich region	88	
11	IPR015820	Retrotransposon Ty1 A - N-terminal	80	
12	IPR001650	DNA/RNA helicase - C-terminal	79	
13	IPR011701	Major facilitator superfamily MFS-1	77	1
14	IPR012337	Polynucleotidyl transferase - Ribonuclease H fold	64	
15	IPR007114	Major facilitator superfamily	62	
16	IPR011545	DNA/RNA helicase - DEAD/DEAH box type - N-terminal	58	
17	IPR000504	RNA recognition motif - RNP-1	58	
18	IPR001138	Fungal transcriptional regulatory protein - N-terminal	56	
19	IPR009007	Peptidase aspartic - catalytic	53	
20	IPR007087	Zinc finger - C2H2-type	52	
21	IPR001841	Zinc finger - RING-type	47	
22	IPR015880	Zinc finger - C2H2-like	46	
23	IPR001806	Ras GTPase	45	1
24	IPR001584	Integrase - catalytic core	44	
25	IPR005225	Small GTP-binding protein domain	43	
26	IPR012336	Thioredoxin-like fold	43	
27	IPR013103	Reverse transcriptase - RNA-dependent DNA polymerase	42	
28	IPR005828	General substrate transporter	38	1
29	IPR005829	Sugar transporter superfamily	37	
30	IPR001969	Peptidase aspartic - active site	36	
31	IPR015424	Pyridoxal phosphate-dependent transferase - major region	35	
32	IPR003579	Ras small GTPase - Rab type	34	1
33	IPR009053	Prefoldin	34	
34	IPR013684	Miro-like	34	
35	IPR001993	Mitochondrial substrate carrier	34	1
36	IPR000357	HEAT	33	
37	IPR000104	Antifreeze protein - type I	33	1
38	IPR003439	ABC transporter related	33	
39	IPR013753	Ras	33	1
40	IPR003959	AAAATPase - core	33	
41	IPR013026	Tetratricopeptide region	33	
42	IPR002067	Mitochondrial carrier protein	32	1
43	IPR009057	Homeodomain-like	32	
44	IPR003663	Sugar transporter	32	1
45	IPR000992	Stress-induced protein SRP1/TIP1	31	1
46	IPR003577	Ras small GTPase - Ras type	31	1
47	IPR001849	Pleckstrin-like	29	
48	IPR009072	Histone-fold	29	
49	IPR011028	Cyclin-like	28	
50	IPR002048	Calcium-binding EF-hand	28	
51	IPR003578	Ras small GTPase - Rho type	26	1
52	IPR007219	Fungal specific transcription factor	26	
53	IPR005834	Haloacid dehalogenase-like hydrolase	25	
54	IPR010989	t-SNARE	25	
55	IPR004841	Amino acid permease-associated region	24	
56	IPR001452	Src homology-3	23	
57	IPR000533	Tropomyosin	23	1
58	IPR001142	Yeast membrane protein DUP	23	1
59	IPR001005	SANT - DNA-binding	23	
60	IPR002041	Ran GTPase	22	1
61	IPR006688	ADP-ribosylation factor	22	1
62	IPR011011	Zinc finger - FYVE/PHD-type	22	
63	IPR001440	Tetratricopeptide TPR-1	22	
64	IPR001623	Heat shock protein DnaJ - N-terminal	22	
65	IPR011032	GroES-like	21	
66	IPR004843	Metallophosphoesterase	21	
67	IPR000629	RNA helicase - ATP-dependent - DEAD-box type	21	
68	IPR002347	Glucose/ribitol dehydrogenase	21	1
69	IPR002110	Ankyrin	21	
70	IPR003960	AAAATPase - subdomain	21	
71	IPR013105	Tetratricopeptide TPR2	20	
72	IPR011511	Variant SH3	20	
73	IPR013154	Alcohol dehydrogenase GroES-like	20	
74	IPR004840	Amino acid permease	19	
75	IPR010920	Like-Sm ribonucleoprotein-related - core	19	
76	IPR013027	FAD-dependent pyridine nucleotide-disulphide oxidoreductase	19	
77	IPR002113	Adenine nucleotide translocator 1	18	1

78	IPR001394	Peptidase C19 - ubiquitin carboxyl-terminal hydrolase 2	18
79	IPR006670	Cyclin	18
80	IPR004762	Yeast amino acid permease	17
81	IPR011012	Longin-like	17
82	IPR006195	Aminoacyl-tRNA synthetase - class II	17
83	IPR013149	Alcohol dehydrogenase - zinc-binding	17
84	IPR001412	Aminoacyl-tRNA synthetase - class I	17
85	IPR001100	Pyridine nucleotide-disulphide oxidoreductase - class I	17
86	IPR000330	SNF2-related	17
87	IPR000795	Protein synthesis factor - GTP-binding	17
88	IPR001965	Zinc finger - PHD-type	17
89	IPR001878	Zinc finger - CCHC-type	17
90	IPR001395	Aldo/keto reductase	17
91	IPR000886	Endoplasmic reticulum targeting sequence	17
92	IPR000727	Target SNARE coiled-coil region	16
93	IPR002198	Short-chain dehydrogenase/reductase SDR	16
94	IPR006649	Like-Sm ribonucleoprotein - eukaryotic and archaea-type - core	16
95	IPR001757	ATPase - P-type - K/Mg/Cd/Cu/Zn/Na/Ca/Na/H-transporter	16
96	IPR001163	Like-Sm ribonucleoprotein - core	16
97	IPR004827	Basic-leucine zipper (bZIP) transcription factor	16
98	IPR008936	Rho GTPase activation protein	15
99	IPR001683	Phox-like	15
100	IPR014778	Myb - DNA-binding	15
101	IPR003954	RNA recognition - region 1	15
102	IPR008927	6-phosphogluconate dehydrogenase - C-terminal-like	15
103	IPR009060	UBA-like	15
104	IPR000608	Ubiquitin-conjugating enzyme - E2	15
105	IPR008984	SMAD/FHA	15
106	IPR000253	Forkhead-associated	15
107	IPR004161	Translation elongation factor EFTu/EF1A - domain 2	15
108	IPR014756	Immunoglobulin E-set	15
109	IPR010978	tRNA-binding arm	15
110	IPR000073	Alpha/beta hydrolase fold-1	15
111	IPR011704	ATPase associated with various cellular activities - AAA-5	15
112	IPR001023	Heat shock protein Hsp70	14
113	IPR008262	Lipase - active site	14
114	IPR006671	Cyclin - N-terminal	14
115	IPR006162	Phosphopantetheine attachment site	14
116	IPR013126	Heat shock protein 70	14
117	IPR001353	20S proteasome - A and B subunits	14
118	IPR001810	Cyclin-like F-box	14
119	IPR006186	Serine/threonine-specific protein phosphatase and bis(5-nucleosyl)-tetrakisphosphatase	14
120	IPR000626	Ubiquitin	13
121	IPR000182	GCN5-related N-acetyltransferase	13
122	IPR002917	GTP-binding protein - HSR1-related	13
123	IPR003095	Heat shock protein DnaJ	13
124	IPR013216	Methyltransferase type 11	13
125	IPR008985	Concanavalin A-like lectin/glucanase	13
126	IPR002409	Aflatoxin biosynthesis regulatory protein	13
127	IPR008979	Galactose-binding like	12
128	IPR006689	ARF/SAR superfamily	12
129	IPR001859	Ribosomal protein P2	12
130	IPR010987	Glutathione S-transferase - C-terminal-like	12
131	IPR003604	Zinc finger - U1-type	12
132	IPR007414	Protein of unknown function DUF468	12
133	IPR008991	Translation protein SH3-like	12
134	IPR000195	RabGAP/TBC	12
135	IPR000961	Protein kinase - C-terminal	12
136	IPR008250	E1-E2 ATPase-associated region	12
137	IPR002328	Alcohol dehydrogenase - zinc-containing	12
138	IPR008973	C2 calcium/lipid-binding region - CaLB	12
139	IPR001611	Leucine-rich repeat	12
140	IPR013078	Phosphoglycerate mutase	12
141	IPR013217	Methyltransferase type 12	12
142	IPR004839	Aminotransferase - class I and II	11
143	IPR001778	Pollen allergen Poa pIX/Phl pVI - C-terminal	11
144	IPR000759	Adrenodoxin reductase	11
145	IPR007086	Zinc finger - C2H2-subtype	11
146	IPR007125	Histone core	11
147	IPR004000	Actin/actin-like	11
148	IPR000387	Protein-tyrosine phosphatase - Tyr-specific/dual-specificity type	11
149	IPR000198	RhoGAP	11
150	IPR000008	C2 calcium-dependent membrane targeting	11
151	IPR011016	Zinc finger - variant RING-type	11
152	IPR000873	AMP-dependent synthetase and ligase	11
153	IPR009000	Translation elongation and initiation factors/Ribosomal - beta-barrel	11
154	IPR001411	Tetracycline resistance protein - TetB	11
155	IPR000836	Phosphoribosyltransferase	11
156	IPR005427	Salmonella/Shigella invasin protein C	11
157	IPR000571	Zinc finger - CCCH-type	11
158	IPR005824	KOW	11
159	IPR005479	Carbamoyl-phosphate synthase L chain - ATP-binding	11

160	IPR001487	Bromodomain	11	
161	IPR001763	Rhodanese-like	11	
162	IPR000679	Zinc finger - GATA-type	11	
163	IPR006025	Peptidase M - neutral zinc metallopeptidases - zinc-binding site	11	
164	IPR015590	Aldehyde dehydrogenase	11	
165	IPR003595	Protein-tyrosine phosphatase - catalytic	10	
166	IPR008917	Eukaryotic transcription factor - Skn-1-like - DNA-binding	10	
167	IPR013525	ABC-2 type transporter	10	
168	IPR004331	SPX - N-terminal	10	
169	IPR001632	G-protein - beta subunit	10	
170	IPR001357	BRCT	10	
171	IPR001917	Aminotransferase - class-II	10	
172	IPR000644	Cystathionine beta-synthase - core	10	
173	IPR000717	Proteasome component region PCI	10	
174	IPR003560	2,3-dihydro-2,3-dihydroxybenzoate dehydrogenase	10	1
175	IPR001140	ABC transporter - transmembrane region	10	
176	IPR001991	Sodium:dicarboxylate symporter	10	1
177	IPR002314	Aminoacyl-tRNA synthetase - class II (G - H - P and S)	10	
178	IPR001248	Permease for cytosine/purines - uracil - thiamine - allantoin	10	1
179	IPR001327	Pyridine nucleotide-disulphide oxidoreductase - NAD-binding region	10	
180	IPR005135	Endonuclease/exonuclease/phosphatase	10	
181	IPR002423	Chaperonin Cpn60/TCP-1	10	1
182	IPR013766	Thioredoxin domain	10	
183	IPR000420	Yeast PIR protein repeat	10	
184	IPR003594	ATP-binding region - ATPase-like	10	
185	IPR012681	Nucleobase cation symporter-1 - NCS1	10	1
186	IPR011332	Ribosomal protein - zinc-binding	10	
187	IPR006073	GTP1/OBG	10	
188	IPR006935	Restriction endonuclease - type I - R subunit/Type III - Res subunit	10	1
189	IPR011053	Single hybrid motif	10	
190	IPR002464	DNA/RNA helicase - ATP-dependent - DEAH-box type	10	with ≥10 42 members
191	IPR000103	Pyridine nucleotide-disulphide oxidoreductase - class-II	9	
192	IPR008950	GroEL-like chaperone - ATPase	9	
193	IPR008928	Six-hairpin glycosidase-like	9	
194	IPR009036	Molybdenum cofactor biosynthesis	9	
195	IPR000194	ATPase - F1/V1/A1 complex - alpha/beta subunit - nucleotide-binding	9	
196	IPR013922	Cyclin-related 2	9	1
197	IPR001984	Peptidase S16 - Lon protease	9	
198	IPR015891	Cyclophilin-like	9	
199	IPR002194	Chaperonin TCP-1	9	
200	IPR004087	K Homology	9	
201	IPR001202	WW/Rsp5/WWP	9	
202	IPR011598	Helix-loop-helix DNA-binding	9	
203	IPR000403	Phosphatidylinositol 3- and 4-kinase - catalytic	9	
204	IPR001356	Homeobox	9	
205	IPR011146	Histidine triad-like motif	9	
206	IPR006687	GTP-binding protein SAR1	9	1
207	IPR001509	NAD-dependent epimerase/dehydratase	9	1
208	IPR013130	Ferric reductase-like transmembrane component - N-terminal	9	
209	IPR006589	Glycosyl hydrolase - family 13 - subfamily - catalytic region	9	
210	IPR001214	SET	9	
211	IPR010993	Sterile alpha motif homology	9	
212	IPR000449	Ubiquitin-associated/translation elongation factor EF1B - N-terminal	9	
213	IPR000991	Glutamine amidotransferase class-I	9	
214	IPR009080	Aminoacyl-tRNA synthetase - class 1a - anticodon-binding	9	
215	IPR000243	Peptidase T1A - proteasome beta-subunit	9	1
216	IPR001844	Chaperonin Cpn60	9	1
217	IPR000277	Cys/Met metabolism - pyridoxal phosphate-dependent enzyme	9	1
218	IPR002685	Glycosyl transferase - family 15	9	1
219	IPR000767	Disease resistance protein	9	
220	IPR001270	Chaperonin clpA/B	8	1
221	IPR000583	Glutamine amidotransferase - class-II	8	
222	IPR006076	FAD dependent oxidoreductase	8	
223	IPR001433	Oxidoreductase FAD/NAD(P)-binding	8	
224	IPR011616	bZIP transcription factor - bZIP-1	8	
225	IPR001494	Importin-beta - N-terminal	8	
226	IPR015940	Ubiquitin-associated/translation elongation factor EF1B - N-terminal - eukaryote	8	
227	IPR006662	Thioredoxin-related	8	
228	IPR002130	Peptidyl-prolyl cis-trans isomerase - cyclophilin-type	8	
229	IPR004154	Anticodon-binding	8	
230	IPR002229	Blood group Rhesus C/E and D polypeptide	8	1
231	IPR012998	Glutamine amidotransferase - class I - active site	8	
232	IPR013121	Ferric reductase - NAD binding	8	
233	IPR004853	Protein of unknown function DUF250	8	
234	IPR001709	Flavoprotein pyridine nucleotide cytochrome reductase	8	
235	IPR004088	K Homology - type 1	8	
236	IPR013112	FAD-binding 8	8	
237	IPR010625	CHCH	8	
238	IPR006402	HAD-superfamily hydrolase - subfamily IA - variant 3	8	
239	IPR002942	RNA-binding S4	8	
240	IPR002952	Eggshell protein	8	

241	IPR002553	Clathrin/coatome adaptor - adaptin-like - N-terminal	8	
242	IPR009071	High mobility group box - HMG	8	
243	IPR006036	TrkA potassium uptake protein	8	1
244	IPR013120	Male sterility C-terminal	8	
245	IPR000089	Biotin/lipoyl attachment	8	
246	IPR011249	Metalloenzyme - LuxS/M16 peptidase-like - metal-binding	8	
247	IPR010916	TonB box - N-terminal	8	
248	IPR006046	Glycoside hydrolase family 13	8	
249	IPR011040	Neuraminidase	8	
250	IPR011043	Galactose oxidase/kelch - beta-propeller	8	
251	IPR001019	Guanine nucleotide binding protein (G-protein) - alpha subunit	8	1
252	IPR006047	Glycosyl hydrolase - family 13 - catalytic region	8	
253	IPR001026	Epsin - N-terminal	8	
254	IPR003656	Zinc finger - BED-type predicted	8	
255	IPR013809	Epsin-like - N-terminal	8	
256	IPR000910	High mobility group box - HMG1/HMG2	8	
257	IPR010929	CDR ABC transporter	8	
258	IPR000594	UBA/THIF-type NAD/FAD binding fold	8	
259	IPR002225	3-beta hydroxysteroid dehydrogenase/isomerase	8	
260	IPR004365	Nucleic acid binding - OB-fold - tRNA/helicase-type	8	
261	IPR001092	Basic helix-loop-helix dimerisation region bHLH	8	
262	IPR011013	Glycoside hydrolase-type carbohydrate-binding	8	
263	IPR001932	Protein phosphatase 2C-related	8	
264	IPR003107	RNA-processing protein - HAT helix	8	
265	IPR009038	GOLD	8	
266	IPR013057	Amino acid transporter - transmembrane	7	1
267	IPR001208	MCM	7	1
268	IPR006603	Cystinosis/ERS1p repeat	7	
269	IPR007502	Helicase-associated region	7	
270	IPR008254	Flavodoxin/nitric oxide synthase	7	
271	IPR000326	Phosphatidic acid phosphatase type 2-like	7	1
272	IPR000648	Oxysterol-binding protein	7	1
273	IPR006034	Asparaginase/glutaminase	7	1
274	IPR011766	Thiamine pyrophosphate enzyme - C-terminal TPP-binding	7	
275	IPR000348	emp24/gp25L/p24	7	
276	IPR006140	D-isomer specific 2-hydroxyacid dehydrogenase - NAD-binding	7	
277	IPR003608	MIR	7	
278	IPR006012	Syntaxin/epimorphin coiled-coil	7	
279	IPR000038	Cell division/GTP binding protein	7	1
280	IPR000637	HMG-I and HMG-Y - DNA-binding	7	
281	IPR009022	Elongation factor G - III and V	7	
282	IPR005024	Snf7	7	1
283	IPR000480	Glutelin	7	
284	IPR001461	Peptidase A1	7	1
285	IPR009078	Ferritin/ribonucleotide reductase-like	7	
286	IPR002860	Glycoside hydrolase - BNR repeat	7	
287	IPR000426	Proteasome alpha-subunit	7	
288	IPR011051	Cupin - RmC-type	7	
289	IPR005398	Tubby - N-terminal	7	
290	IPR000108	Neutrophil cytosol factor 2	7	
291	IPR002038	Osteopontin	7	1
292	IPR001804	Isocitrate/isopropylmalate dehydrogenase	7	1
293	IPR002109	Glutaredoxin	7	
294	IPR015413	Aminoacyl-tRNA synthetase - class I (M)	7	
295	IPR006596	Nucleotide binding protein - PINc	7	
296	IPR001926	Pyridoxal phosphate-dependent enzyme - beta subunit	7	
297	IPR000086	NUDIX hydrolase - core	7	
298	IPR002030	Mitochondrial brown fat uncoupling protein	7	1
299	IPR001313	Pumilio RNA-binding region	7	
300	IPR003903	Ubiquitin interacting motif	7	
301	IPR001958	Tetracycline resistance protein - TetA	7	1
302	IPR003892	Ubiquitin system component Cue	7	
303	IPR011054	Rudiment single hybrid motif	7	
304	IPR001594	Zinc finger - DHHC-type	7	
305	IPR011765	Peptidase M16 - N-terminal	7	
306	IPR012001	Thiamine pyrophosphate enzyme - N-terminal TPP binding region	7	
307	IPR011047	Quinonprotein alcohol dehydrogenase-like	7	
308	IPR011709	Region of unknown function DUF1605	7	
309	IPR001012	UBX	7	
310	IPR000883	Cytochrome c oxidase - subunit I	7	1
311	IPR005481	Carbamoyl-phosphate synthetase large chain - N-terminal	7	
312	IPR001312	Hexokinase	7	1
313	IPR014045	Protein phosphatase 2C - N-terminal	7	
314	IPR005819	Histone H5	7	1
315	IPR001199	Cytochrome b5	7	
316	IPR000640	Translation elongation factor EFG/EF2 - C-terminal	7	
317	IPR002123	Phospholipid/glycerol acyltransferase	7	
318	IPR002410	Peptidase S33 - prolyl aminopeptidase	7	1
319	IPR007863	Peptidase M16 - C-terminal	7	
320	IPR011060	Ribulose-phosphate binding barrel	7	
321	IPR015797	NUDIX	7	
322	IPR012000	Thiamine pyrophosphate enzyme - central region	7	

323	IPR003029	S1 - RNA binding	7	
324	IPR003395	SMC protein - N-terminal	7	
325	IPR004014	ATPase - P-type cation-transporter - N-terminal	7	
326	IPR011072	HR1 rho-binding repeat	6	
327	IPR007696	MutS III	6	
328	IPR006594	LisH dimerisation motif	6	
329	IPR014400	Cyclin - A/B/D/E	6	1
330	IPR008937	Ras guanine nucleotide exchange factor	6	
331	IPR001221	Phenol hydroxylase reductase	6	
332	IPR007109	Brix	6	
333	IPR006011	Syntaxin - N-terminal	6	
334	IPR005937	26S proteasome subunit P45	6	1
335	IPR003890	MIF4G-like - type 3	6	
336	IPR006085	XPG N-terminal	6	
337	IPR008971	HSP40/DnaJ peptide-binding	6	
338	IPR010996	DNA polymerase beta - N-terminal-like	6	
339	IPR000994	Peptidase M24 - catalytic core	6	
340	IPR003089	Alpha/beta hydrolase	6	
341	IPR001982	Homing endonuclease - LAGLIDADG/HNH	6	
342	IPR004046	Glutathione S-transferase - C-terminal	6	
343	IPR001164	Arf GTPase activating protein	6	1
344	IPR000815	Mercuric reductase	6	1
345	IPR004038	Ribosomal protein L7Ae/L30e/S12e/Gadd45	6	
346	IPR001419	HMW glutenin	6	1
347	IPR001251	Cellular retinaldehyde-binding/triple function - C-terminal	6	
348	IPR000306	Zinc finger - FYVE-type	6	
349	IPR000891	Pyruvate carboxyltransferase	6	
350	IPR013968	KR	6	
351	IPR002125	CMP/dCMP deaminase - zinc-binding	6	
352	IPR006204	GHMP kinase	6	
353	IPR001834	NADH:cytochrome b5 reductase (CBR)	6	1
354	IPR011335	Restriction endonuclease - type II-like - core	6	
355	IPR011498	Kelch repeat type 2	6	
356	IPR000340	Protein-tyrosine phosphatase - dual specificity	6	
357	IPR004820	Cytidyltransferase	6	
358	IPR002078	RNA polymerase sigma factor 54 - interaction	6	
359	IPR003010	Nitrilase/cyanide hydratase and apolipoprotein N-acyltransferase	6	
360	IPR004364	Aminoacyl-tRNA synthetase - class II (D - K and N)	6	
361	IPR004182	GRAM	6	
362	IPR000560	Histidine acid phosphatase	6	1
363	IPR008333	Oxidoreductase FAD-binding region	6	
364	IPR011658	PA14	6	
365	IPR001752	Kinesin - motor region	6	
366	IPR011702	Glutamine amidotransferase superfamily	6	
367	IPR003342	Glycosyl transferase - family 39	6	
368	IPR008273	Cellular retinaldehyde-binding/triple function - N-terminal	6	
369	IPR000219	DH	6	
370	IPR009020	Proteinase inhibitor - propeptide	6	
371	IPR001345	Phosphoglycerate/bisphosphoglycerate mutase	6	
372	IPR006581	VPS10	6	
373	IPR002375	Purine/pyrimidine phosphoribosyl transferase	6	
374	IPR000261	EPS15 homology (EH)	6	
375	IPR000408	Regulator of chromosome condensation - RCC1	6	
376	IPR001401	Dynammin - GTPase region	6	
377	IPR001247	Exoribonuclease - phosphorolytic domain 1	6	
378	IPR004367	Cyclin - C-terminal	6	
379	IPR006086	XPG I	6	
380	IPR000245	ATPase - V0 complex - proteolipid subunit C -	6	1
381	IPR006652	Kelch repeat type 1	6	
382	IPR011700	Basic leucine zipper	6	
383	IPR000432	DNA mismatch repair protein MutS - C-terminal	6	
384	IPR009001	Translation elongation factor EF1A/initiation factor IF2gamma - C-terminal	6	
385	IPR000047	Helix-turn-helix motif - lambda-like repressor	6	
386	IPR003958	Transcription factor CBF/NF-Y/archaeal histone	6	
387	IPR000804	Clathrin adaptor - sigma subunit/coatomer - zeta subunit	6	1
388	IPR008162	Inorganic pyrophosphatase	6	1
389	IPR002312	Aspartyl-tRNA synthetase - class IIb	6	
390	IPR008948	L-Aspartase-like	6	
391	IPR000960	Flavin-containing monooxygenase FMO	6	1
392	IPR013750	GHMP kinase - C-terminal	6	
393	IPR002478	PUA	6	with ≥6 80 members
394	IPR004299	Membrane bound O-acyl transferase - MBOAT	5	1
395	IPR001093	IMP dehydrogenase/GMP reductase	5	1
396	IPR004217	Zinc finger - Tim10/DDP-type	5	1
397	IPR004886	Glycolipid anchored surface protein GAS1	5	1
398	IPR000286	Histone deacetylase superfamily	5	1
399	IPR005482	Biotin carboxylase - C-terminal	5	
400	IPR002424	Insect alcohol dehydrogenase family	5	1
401	IPR006069	ATPase - P-type cation exchange - alpha subunit	5	1
402	IPR005556	SUN	5	1
403	IPR006896	Sec23/Sec24 trunk region	5	

404	IPR011006	CheY-like	5	
405	IPR003591	Leucine-rich repeat - typical subtype	5	
406	IPR002013	Synaptojanin - N-terminal	5	
407	IPR000467	D111/G-patch	5	
408	IPR002052	N-6 Adenine-specific DNA methylase	5	
409	IPR001553	RecA bacterial DNA recombination	5	1
410	IPR000591	Pleckstrin/ G-protein - interacting region	5	
411	IPR002524	Cation efflux protein	5	1
412	IPR000380	DNA topoisomerase - type IA - core	5	
413	IPR008351	JNK MAP kinase	5	1
414	IPR006121	Heavy metal transport/detoxification protein	5	
415	IPR008978	HSP20-like chaperone	5	
416	IPR003689	Zinc/iron permease	5	1
417	IPR005517	Translation elongation factor EFG/EF2 - domain IV	5	
418	IPR004045	Glutathione S-transferase - N-terminal	5	
419	IPR000695	H+ transporting ATPase - proton pump	5	1
420	IPR000651	Guanine nucleotide exchange factor for Ras-like GTPases - N-terminal	5	
421	IPR008968	Clathrin adaptor - mu subunit - C-terminal	5	
422	IPR000425	Major intrinsic protein	5	1
423	IPR006597	Sel1-like	5	
424	IPR001813	Ribosomal protein 60S	5	1
425	IPR000941	Enolase	5	1
426	IPR000793	ATPase - F1/V1/A1 complex - alpha/beta subunit - C-terminal	5	
427	IPR001046	Natural resistance-associated macrophage protein	5	1
428	IPR006084	DNA repair protein (XPGC)/yeast Rad	5	
429	IPR001305	DnaJ central region	5	
430	IPR003000	Silent information regulator protein Sir2	5	1
431	IPR003034	DNA-binding SAP	5	
432	IPR001222	Zinc finger - TFIIIS-type	5	
433	IPR002016	Haem peroxidase - plant/fungal/bacterial	5	1
434	IPR011038	Calycin-like	5	
435	IPR003607	Metal-dependent phosphohydrolase - HD region	5	
436	IPR009002	FMN-binding split barrel - related	5	
437	IPR000672	Tetrahydrofolate dehydrogenase/cyclohydrolase	5	
438	IPR005483	Carbamoyl-phosphate synthetase large chain	5	
439	IPR006575	RWD	5	
440	IPR011048	Cytochrome cd1-nitrite reductase-like - C-terminal haem d1	5	
441	IPR003347	Transcription factor jumonji/aspartyl beta-hydroxylase	5	
442	IPR008972	Cupredoxin	5	
443	IPR006068	ATPase - P-type cation-transporter - C-terminal	5	
444	IPR008918	Helix-hairpin-helix motif - class 2	5	
445	IPR002939	Chaperone DnaJ - C-terminal	5	
446	IPR001373	Cullin	5	
447	IPR001715	Calponin-like actin-binding	5	
448	IPR007484	Peptidase M28	5	
449	IPR001317	Carbamoyl-phosphate synthase - GATase region	5	
450	IPR014025	Glutaredoxin subgroup	5	
451	IPR001388	Synaptobrevin	5	
452	IPR000904	SEC7-like	5	
453	IPR000462	CDP-alcohol phosphatidyltransferase	5	1
454	IPR003613	U box	5	
455	IPR013720	LisH dimerisation motif - subgroup	5	
456	IPR007860	MutS II	5	
457	IPR007526	SWIRM	5	
458	IPR001310	Histidine triad (HIT) protein	5	1
459	IPR000232	Heat shock factor (HSF)-type - DNA-binding	5	
460	IPR006172	DNA-directed DNA polymerase B	5	1
461	IPR012110	Pyruvate decarboxylase/indolepyruvate decarboxylase	5	1
462	IPR006055	Exonuclease	5	
463	IPR013520	Exonuclease - RNase T and DNA polymerase III	5	
464	IPR009050	Globin-like	5	
465	IPR011074	Phosphatidylinositol transfer protein-like - N-terminal	5	
466	IPR000222	Protein phosphatase 2C - manganese/magnesium aspartate binding site	5	
467	IPR008957	Fibronectin - type III-like fold	5	
468	IPR013749	Phosphomethylpyrimidine kinase type-1	5	
469	IPR004861	Protein-tyrosine phosphatase - SIW14-like	5	1
470	IPR005946	Ribose-phosphate pyrophosphokinase	5	1
471	IPR015847	Exoribonuclease - phosphorolytic domain 2	5	
472	IPR010482	Integral peroxisomal membrane peroxin	5	1
473	IPR009079	Four-helical cytokine-like - core	5	
474	IPR000866	Alkyl hydroperoxide reductase/ Thiol specific antioxidant/ Mal allergen	5	
475	IPR000095	PAK-box/P21-Rho-binding	5	
476	IPR003152	PIK-related kinase - FATC	5	
477	IPR001431	Peptidase M16 - zinc-binding site	5	
478	IPR006539	Phospholipid-translocating P-type ATPase - flippase	5	1
479	IPR013740	Redoxin	5	
480	IPR015947	PUA-like	5	
481	IPR010997	HRDC-like	5	
482	IPR002523	Mg2+ transporter protein - CorA-like	5	1
483	IPR000569	HECT	5	
484	IPR001463	Sodium:alanine symporter	5	1
485	IPR004550	L-asparaginase - type II	5	1

486	IPR000399	TPP-binding enzymes	5	
487	IPR001882	Biotin-binding site	5	
488	IPR001609	Myosin head - motor region	5	
489	IPR008930	Terpenoid cyclases/protein prenyltransferase alpha-alpha toroid	5	
490	IPR000850	Adenylate kinase	5	1
491	IPR004160	Translation elongation factor EFTu/EF1A - C-terminal	5	
492	IPR000842	Phosphoribosyl pyrophosphate synthetase	5	
493	IPR001025	Bromo adjacent region	5	
494	IPR000223	Peptidase S26A - signal peptidase I	5	1
495	IPR002129	Pyridoxal phosphate-dependent decarboxylase	5	1
496	IPR000209	Peptidase S8 and S53 - subtilisin - kexin - sedolisin	5	
497	IPR004274	NLI interacting factor	5	
498	IPR000225	Armadillo	5	with ≥5
499	IPR015415	Vps4 oligomerisation - C-terminal	4	113 members
500	IPR003877	SPla/Ryanodine receptor SPRY	4	

Supplementary Table 2. Enrichment for deletions in the lineage leading to the ABC16-monsters.

The observed mean deletion number in each of Moflo-sorted samples is shown in green when it is larger than the expected number for the corresponding unsorted sample.

Deleted genes in *MATa* strains are highlighted with blue; deleted genes in *MATα* strains are highlighted with pink.

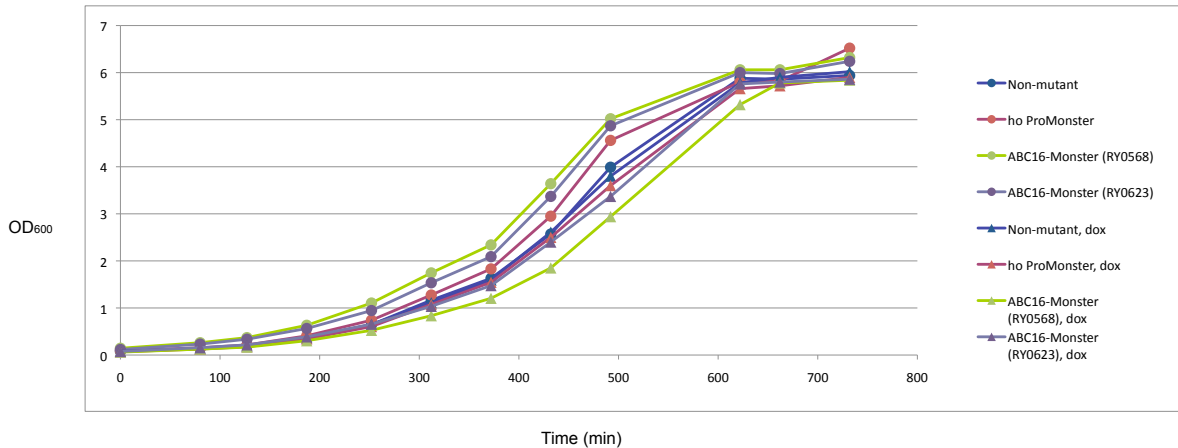
The same cross identification numbers are used in **Supplementary Fig. 2** online.

Cross	Deleted Genes in Parental Strain(s) 1	Deleted Genes in Parental Strain(s) 2	Deleted Genes in Selected Progeny Strain	Expected average deletion number for unsorted progeny	Observed average deletion number for genotyped sorted progeny	Standard error of the mean	Number of genotyped colonies
1	ADP1 YBT1 in one strain YOR1 YNR070W in one strain PDR11 YBT1 in one strain (three strains pooled)	YOL075C PDR12 in one strain ADP1 NFT1 in one strain NFT1 BPT1 in one strain SNQ2 BPT1 in one strain (four strains pooled)	ADP1 NFT1 BPT1 YBT1	2	3.7	0.3	3
2	VMR1	PDR15 PDR5	PDR15 VMR1	1.5	2.5	0.5	2
3	ADP1 PDR12	AUS1 PDR5	ADP1 AUS1 PDR5 PDR12	2	3.25	0.5	4
4	PDR15 PDR10	ADP1 PDR12	ADP1 PDR15 PDR10	2	3	N/A	1
5	YOR1 YNR070W	SNQ2 PDR11 BPT1 YBT1	SNQ2 YOR1 PDR11 YNR070W	3	3.5	0.2	6
6	YOL075C PDR12 in one strain (five strains pooled) ADP1 NFT1 in one strain NFT1 BPT1 in one strain SNQ2 BPT1 in one strain SNQ2 YBT1 YOL075C PDR12 in one strain	ADP1 YBT1 in one strain YOR1 YNR070W in one strain PDR11 YBT1 in one strain (three strains pooled)	ADP1 SNQ2 YBT1 YOL075C PDR12	2.2	3.2	0.3	14
7	PDR15 VMR1	ADP1 PDR11 NFT1 YBT1	VMR1 PDR11 NFT1 YBT1	3	3	1	2
8	ADP1 AUS1 PDR5 PDR12	ADP1 PDR15 PDR10	ADP1 PDR15 AUS1 PDR5 PDR10 PDR12	3.5	5.5	0.5	2
9	ADP1 SNQ2 YBT1 YOL075C PDR12	ADP1 NFT1 BPT1 YBT1	ADP1 SNQ2 NFT1 BPT1 YBT1 YOL075C PDR12	4.5	5.6	0.6	5
10	VMR1 PDR11 NFT1 YBT1	ADP1 PDR15 AUS1 PDR5 PDR10 PDR12	ADP1 PDR11 NFT1 YBT1 AUS1 PDR10 PDR12 ADP1 PDR15 PDR11 NFT1 YBT1 PDR5 PDR10 ADP1 PDR15 VMR1 PDR11 PDR10 PDR12 ADP1 VMR1 PDR11 YBT1 AUS1 PDR5 PDR10	5	5.4	0.3	14
11	SNQ2 YOR1 PDR11 YNR070W	ADP1 SNQ2 NFT1 BPT1 YBT1 YOL075C PDR12	ADP1 SNQ2 PDR11 NFT1 BPT1 YBT1 YNR070W YOL075C ADP1 SNQ2 YOR1 PDR11 NFT1 BPT1 YBT1 YNR070W PDR12	5.5	7.4	0.5	10
12	ADP1 PDR11 NFT1 YBT1 AUS1 PDR10 PDR12	ADP1 PDR15 PDR11 NFT1 YBT1 PDR5 PDR10	ADP1 PDR15 PDR11 NFT1 YBT1 AUS1 PDR5 PDR10 PDR12	7	6.9	0.3	14
13	ADP1 PDR15 VMR1 PDR11 PDR10 PDR12	ADP1 VMR1 PDR11 YBT1 AUS1 PDR5 PDR10	ADP1 PDR15 VMR1 PDR11 AUS1 PDR5 PDR10 PDR12	6.5	6.8	0.2	13
14	ADP1 SNQ2 PDR11 NFT1 BPT1 YBT1 YNR070W YOL075C	ADP1 SNQ2 YOR1 PDR11 NFT1 BPT1 YBT1 YNR070W PDR12	ADP1 SNQ2 YOR1 PDR11 NFT1 BPT1 YBT1 YNR070W YOL075C PDR12	8.5	8.75	0.9	4
15	ADP1 SNQ2 YOR1 PDR11 NFT1 BPT1 YBT1 YNR070W YOL075C PDR12	ADP1 YCF1 NFT1 YBT1 YOL075C	ADP1 YCF1 NFT1 BPT1 YBT1 YNR070W YOL075C PDR12	7.5	7.7	0.5	9
16	ADP1 SNQ2 YOR1 PDR11 NFT1 BPT1 YBT1 YNR070W YOL075C PDR12	ADP1 PDR15 PDR11 NFT1 YBT1 AUS1 PDR5 PDR10 PDR12	ADP1 SNQ2 PDR15 YOR1 PDR11 NFT1 YBT1 YOL075C AUS1 PDR5 PDR10 PDR12	9.5	10.6	0.3	16
17	ADP1 SNQ2 YOR1 PDR11 NFT1 BPT1 YBT1 YNR070W YOL075C PDR12	ADP1 PDR15 VMR1 PDR11 AUS1 PDR5 PDR10 PDR12	ADP1 PDR15 VMR1 PDR11 NFT1 BPT1 YBT1 YNR070W AUS1 PDR5 PDR10 PDR12	8.5	9.9	0.3	14
18	ADP1 SNQ2 PDR15 YOR1 PDR11 NFT1 YBT1 YOL075C AUS1 PDR5 PDR10 PDR12	ADP1 PDR15 PDR11 PDR11 NFT1 BPT1 YBT1 YNR070W AUS1 PDR5 PDR10 PDR12	ADP1 SNQ2 PDR15 YOR1 PDR11 NFT1 BPT1 YBT1 YNR070W YOL075C AUS1 PDR5 PDR10 PDR12 ADP1 PDR15 YOR1 VMR1 PDR11 NFT1 BPT1 YBT1 YNR070W YOL075C AUS1 PDR5 PDR10 PDR12	12	11.7	0.3	16
19	ADP1 YCF1 NFT1 BPT1 YBT1 YNR070W YOL075C PDR12	ADP1 PDR15 YOR1 VMR1 PDR11 NFT1 BPT1 YBT1 YNR070W YOL075C AUS1 PDR5 PDR10 PDR12	ADP1 YCF1 YOR1 VMR1 NFT1 BPT1 YBT1 YNR070W YOL075C AUS1 PDR5 PDR10 PDR12	11	11.7	0.2	24
20	ADP1 SNQ2 PDR15 VMR1 PDR11 NFT1 BPT1 YBT1 YNR070W YOL075C AUS1 PDR5 PDR10 PDR12	ADP1 PDR15 YOR1 VMR1 PDR11 NFT1 BPT1 YBT1 YNR070W YOL075C AUS1 PDR5 PDR10 PDR12	ADP1 SNQ2 PDR15 YOR1 VMR1 PDR11 NFT1 BPT1 YBT1 YNR070W YOL075C AUS1 PDR5 PDR10 PDR12	14	13.8	0.2	12
21	ADP1 YCF1 YOR1 VMR1 NFT1 BPT1 YBT1 YNR070W YOL075C AUS1 PDR5 PDR10 PDR12	ADP1 SNQ2 PDR15 VMR1 PDR11 NFT1 BPT1 YBT1 YNR070W YOL075C AUS1 PDR5 PDR10 PDR12	ADP1 YCF1 PDR15 YOR1 VMR1 PDR11 NFT1 BPT1 YBT1 YNR070W YOL075C AUS1 PDR5 PDR10 PDR12	13.5	13.4	0.3	12
22	ADP1 YCF1 PDR15 YOR1 VMR1 PDR11 NFT1 BPT1 YBT1 YNR070W YOL075C AUS1 PDR5 PDR10 PDR12	ADP1 SNQ2 PDR15 YOR1 VMR1 PDR11 NFT1 BPT1 YBT1 YNR070W YOL075C AUS1 PDR5 PDR10 PDR12	ADP1 SNQ2 YCF1 PDR15 YOR1 VMR1 PDR11 NFT1 BPT1 YBT1 YNR070W YOL075C AUS1 PDR5 PDR10 PDR12 ADP1 SNQ2 YCF1 PDR15 YOR1 VMR1 PDR11 NFT1 BPT1 YBT1 YNR070W YOL075C AUS1 PDR5 PDR10 PDR12	15	No sorting used	N/A	24

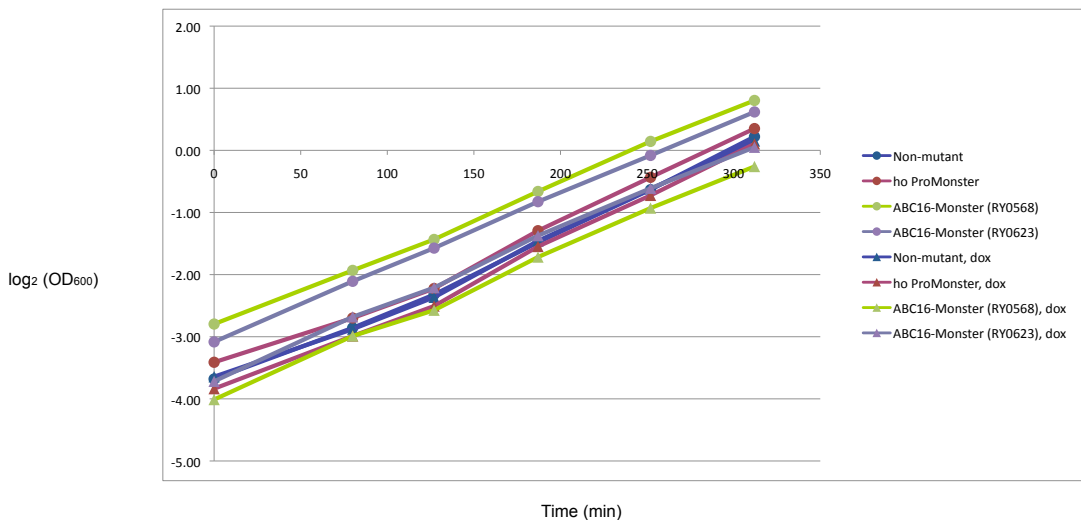
Supplementary Table 3. Growth of ABC₁₆-monsters in the presence of the inducer doxycycline.

For assessing the toxicity of GFP to cells, OD₆₀₀ of the cultures of GFP-induced cells and non-GFP-induced cells were measured over time. The cultures of GFP-induced cells were started from overnight cultures of already induced cells. The cultures of non-induced cells were never exposed to doxycycline. Non-mutant is a GMtoolkit-alpha strain not carrying any GFP cassette. *ho* ProMonster carries one GFP cassette in the *ho* deletion locus. Two ABC₁₆-monster strains are *MAT*alpha strains. The presence or absence of GFP expression was confirmed under the microscope.

Strain and induction condition	Time in minutes											
	0	80	127	187	252	312	372	432	492	622	662	732
Non-mutant	0.08	0.14	0.20	0.36	0.65	1.17	1.63	2.57	3.99	5.88	5.86	5.94
<i>ho</i> ProMonster	0.09	0.15	0.21	0.41	0.74	1.28	1.83	2.95	4.56	5.80	5.82	6.52
ABC ₁₆ -Monster (RY0568)	0.14	0.26	0.37	0.63	1.11	1.75	2.34	3.64	5.02	6.06	6.06	6.32
ABC ₁₆ -Monster (RY0623)	0.12	0.23	0.34	0.56	0.95	1.54	2.09	3.37	4.87	6.00	5.98	6.24
Non-mutant, dox	0.08	0.14	0.19	0.36	0.65	1.11	1.60	2.61	3.80	5.78	5.90	6.02
<i>ho</i> ProMonster, dox	0.07	0.13	0.18	0.34	0.61	1.08	1.55	2.50	3.60	5.66	5.72	5.90
ABC ₁₆ -Monster (RY0568), dox	0.06	0.13	0.17	0.30	0.53	0.84	1.21	1.85	2.94	5.32	5.78	5.84
ABC ₁₆ -Monster (RY0623), dox	0.08	0.16	0.22	0.39	0.66	1.04	1.48	2.40	3.37	5.76	5.80	5.86



Strain and induction condition	log ₂ (OD ₆₀₀) Values						Exponential growth rate	Dox effect (induced/uninduced)
	0	80	127	187	252	312		
Non-mutant	-3.68	-2.86	-2.32	-1.48	-0.63	0.22	0.013	1.0
<i>ho</i> ProMonster	-3.41	-2.70	-2.22	-1.29	-0.43	0.35	0.013	1.0
ABC ₁₆ -Monster (RY0568)	-2.80	-1.93	-1.43	-0.66	0.14	0.80	0.012	1.0
ABC ₁₆ -Monster (RY0623)	-3.08	-2.11	-1.57	-0.83	-0.08	0.62	0.012	1.0
Non-mutant, dox	-3.64	-2.88	-2.37	-1.46	-0.62	0.15	0.013	
<i>ho</i> ProMonster, dox	-3.84	-2.99	-2.51	-1.55	-0.72	0.10	0.014	
ABC ₁₆ -Monster (RY0568), dox	-4.01	-2.99	-2.57	-1.72	-0.93	-0.26	0.012	
ABC ₁₆ -Monster (RY0623), dox	-3.72	-2.68	-2.21	-1.37	-0.61	0.05	0.012	



Supplementary Table 4. Deletion numbers of strains during a Green Monster process with six loci.

Average deletion number and standard deviation are shown.

Sorted and unsorted strains were isolated and genotyped.

Genotyped strains were used in crosses in each round.

First round

Cross of yer042wDelta and ycl033cDelta

Sorted 2 ± 0

Unsorted 1.5 ± 0.5

Cross of ydl227cDelta and ydl242wDelta

Sorted 1.5 ± 0.5

Unsorted 0.8 ± 0.4

Cross of ykl069wDelta and yol118cDelta

Sorted 2 ± 0

Unsorted 1.1 ± 0.7

Second round

Cross of yer042wDelta ycl033cDelta and ydl227cDelta ydl242wDelta

Sorted 3.5 ± 0.5

Unsorted ND

Cross of yer042wDelta ycl033cDelta and ykl069wDelta yol118cDelta

Sorted 3.5 ± 0.7

Unsorted ND

Third round

Cross of yer042wDelta ycl033cDelta ydl227cDelta ydl242wDelta and yer042wDelta ycl033cDelta ykl069wDelta and yol118cDelta

Sorted 5.1 ± 1.1 4 out of 8 strains were 6-GFP strains.

Unsorted 3.3 ± 0.8

Supplementary Table 5. Composition of populations from the *en masse* Green Monster processes.

We note that two haploid-selected and induced samples in Round 4 contained many diploids, but these cells were eliminated by sorting, due to our focus on smaller cells ('events' with small forward scatter) originally designed to avoid cell aggregates.

*: These are cells that are resistant to both G418 (due to *KanMX4* in *GMToolkit-a*) and neuceothricin (due to *NatMX4* in *GMToolkit-α*) and are assumed to be diploids.

When 29 sorted cells from Round 3 that contained a deletion in *YBT1* were tested for the presence of the wild-type copy using PCR, none contained the wild-type *YBT1* sequence, indicating that these are haploids with only one chromosome for this locus.

ND: not determined due to test plate contamination.

Round	Sample	Series 1		Series 2		Series 3	
		Percentage of diploids*	n	Percentage of diploids*	n	Percentage of diploids*	n
0	Mated	14%	29	69%	13	28%	18
	Diploid-selected	100%	22	100%	17	100%	16
	Haploid-selected and induced (unsorted)	8%	24	0%	24	0%	24
1	Sorted	13%	24	4%	24	0%	24
	Mated	ND		ND		ND	
	Diploid-selected	100%	7	100%	15	100%	13
	Haploid-selected and induced (unsorted)	13%	24	0%	24	0%	24
2	Sorted	4%	24	0%	24	0%	24
	Mated	18%	22	28%	40	26%	31
	Diploid-selected	100%	30	100%	15	100%	21
	Haploid-selected and induced (unsorted)	0%	24	0%	23	0%	21
3	Sorted	0%	24	0%	24	0%	24
	Mated	38%	98	36%	151	37%	121
	Diploid-selected	100%	30	100%	21	100%	40
	Haploid-selected and induced (unsorted)	0%	24	0%	24	0%	24
4	Sorted	4%	24	0%	24	0%	24
	Mated	23%	99	24%	63	18%	100
	Diploid-selected	100%	92	100%	73	100%	45
	Haploid-selected and induced (unsorted)	42%	24	33%	24	0%	24
5	Sorted	0%	24	4%	24	6%	36

Supplementary Table 6. Statistical analysis of the *en masse* processes.

Mann-Whitney U tests were used to calculate p-values (1-tail for sorted vs. unsorted and 2-tail for comparison with the corresponding sorted sample of the previous round).

Round 0 corresponds to the initial ProMonster single mutants, which contain exactly one deletion.

One round is defined to start before mating and end after cell sorting.

SD: standard deviation.

Series 1

Round	Average deletion number				p-value				
	Unsorted	SD	Sorted	SD	Sorted vs. unsorted	Unsorted vs. sorted of the previous round	Sorted vs. sorted of the previous round		
1	1.1	0.6	1.8	0.4	0.0002		0.3	0.0000004	
2	1.5	0.9	3.0	0.8	0.000002		0.2	0.000001	
3	3.0	1.0	4.2	0.9	0.0001		1	0.00005	
4	4.2	1.0	5.3	0.7	0.0001		0.9	0.00003	
5	5.1	1.0	5.8	0.9	0.01		0.6	0.02	

Series 2

Round	Average deletion number				p-value				
	Unsorted	SD	Sorted	SD	Sorted vs. unsorted	Unsorted vs. sorted of the previous round	Sorted vs. sorted of the previous round		
1	1.0	0.8	1.7	0.4	0.0004		1	0.0000002	
2	1.4	0.7	3.2	0.7	0.000000009		0.04	0.00000002	
3	2.9	1.0	4.4	0.9	0.000005		0.2	0.00001	
4	3.4	0.9	5.4	0.9	0.00000003		0.0007	0.0003	
5	4.9	1.3	6.7	0.7	0.000009		0.2	0.00002	

Series 3

Round	Average deletion number				p-value				
	Unsorted	SD	Sorted	SD	Sorted vs. unsorted	Unsorted vs. sorted of the previous round	Sorted vs. sorted of the previous round		
1	0.7	0.6	1.9	0.3	0.00000001		0.02	0.000000003	
2	1.8	1.1	3.0	0.6	0.00004		0.6	0.00000002	
3	3.0	1.1	4.4	0.8	0.00004		0.8	0.0000001	
4	3.8	1.2	5.2	1.1	0.0001		0.05	0.006	
5	4.6	1.2	6.2	0.8	0.000002		0.08	0.0005	

Supplementary Table 7. Cumulative frequency of drugs for each drug-affected growth rate range.

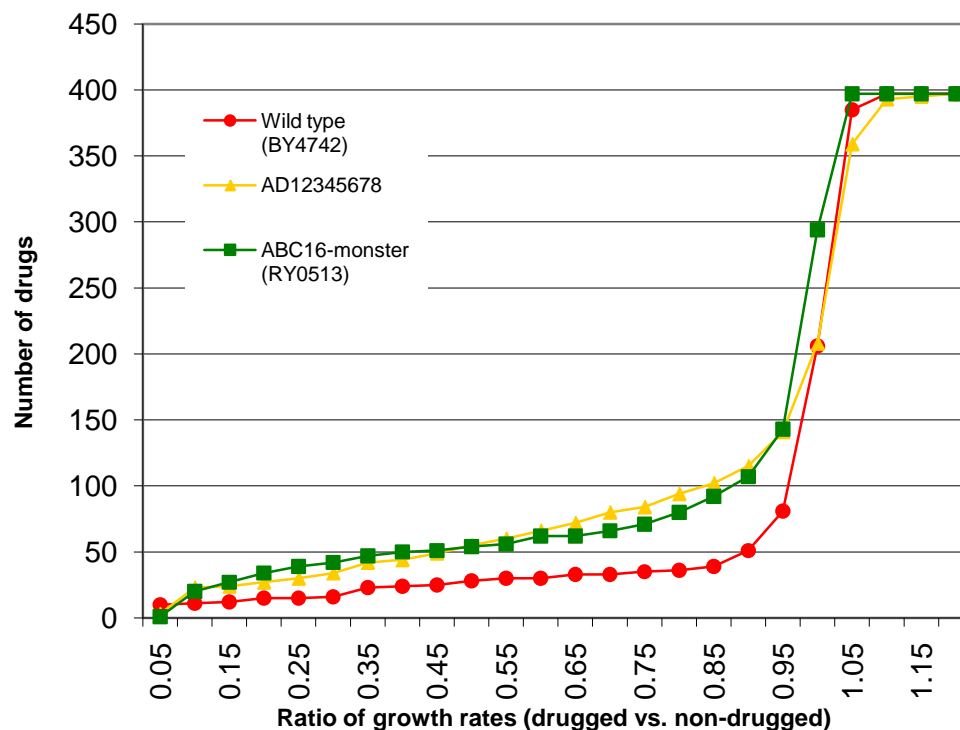
Exponential growth rate with drug relative to that without was calculated as a measure of sensitivity (resistance).

For varying cut-offs between <0.1 and <0.95 for this ratio (i.e., >90% to >5% inhibition of growth rate), both the ABC16-monster and AD12345678 were sensitive to roughly twice as many drugs as the wild type control.

More drugs strongly inhibited the ABC16-monster between the ratios 0.2 and 0.4.

The ABC16-monster was weakly sensitive (in the 0.95-to-1.0 range) to a large number of drugs,

Exponential growth rate of drugged relative to that of non-drugged	Wild type (BY4742)	AD12345678	ABC16-monster (RY0513)
0.05	10	3	1
0.10	11	23	20
0.15	12	24	27
0.20	15	27	34
0.25	15	30	39
0.30	16	34	42
0.35	23	42	47
0.40	24	44	50
0.45	25	49	51
0.50	28	55	54
0.55	30	60	56
0.60	30	66	62
0.65	33	72	62
0.70	33	80	66
0.75	35	84	71
0.80	36	94	80
0.85	39	102	92
0.90	51	115	107
0.95	81	141	143
1.00	206	208	294
1.05	385	359	397
1.10	397	393	397
1.15	397	395	397
1.20	397	397	397



Supplementary Table 8. Drug assay using drugs of the NIH Clinical Collection. The ratios of exponential growth rates with vs. without drug are shown. We note that clotrimazole, benidipine, cisapride, and perospirone had a large effect on the ABC16-monster and only a small effect on AD12345678. For comparison of ratios, we required different values to be at least 5% different, except in the comparison marked with asterisk, where even small differences were included.

Number	Drug	Wild type (BY4742)	Drug- hypersensi- tive strain (AD12345 678)	ABC16- monster (RY0513)	ABC16- monster more sensitive than AD123456 78 *	AD123456 78 more sensitive than wild type	ABC16- monster more sensitive than wild type	ABC16- monster more sensitive than AD123456 78	ABC16- monster as sensitive as AD123456 78	Neither sensitive, compared to WT	Mutant sensitive & ABC16- monster more sensitive than AD123456 78	Mutant sensitive & both strains comparabl e	Mutant sensitive & AD123456 78 more sensitive than ABC16- monster
1	lomeperazine dihydrochloride	0.94	0.05	0.05	0	1	1	0	1	0	0	1	0
2	clotrimazole	0.35	0.96	0.07	1	0	1	1	0	0	1	0	0
3	loratadine	0.09	0.05	0.07	0	1	1	0	0	0	0	0	1
4	naftopidil	0.85	0.05	0.05	0	1	1	0	1	0	0	1	0
5	nefazodone	0.82	0.05	0.05	0	1	1	0	1	0	0	1	0
6	efavirenz	0.51	0.05	0.07	0	1	1	0	0	0	0	0	1
7	aripiprazole	0.19	0.64	0.07	1	0	1	1	0	0	1	0	0
8	oxiconazole nitrate	0.29	0.41	0.07	1	0	1	1	0	0	1	0	0
9	indatraline	0.03	0.05	0.07	0	0	0	0	0	1	0	0	0
10	trifluoperazine dihydrochloride	0.03	0.05	0.07	0	0	0	0	0	1	0	0	0
11	honokiol	0.03	0.05	0.07	0	0	0	0	0	1	0	0	0
12	sertraline	0.03	0.05	0.07	0	0	0	0	0	1	0	0	0
13	bifonazole	0.03	0.05	0.07	0	0	0	0	0	1	0	0	0
14	pterostilbene	0.03	0.05	0.07	0	0	0	0	0	1	0	0	0
15	tegaserod maleate fluphenazine hydrochloride	0.03	0.05	0.07	0	0	0	0	0	1	0	0	0
16	hydrochloride	0.03	0.05	0.07	0	0	0	0	0	1	0	0	0
17	toremifene citrate	0.03	0.05	0.07	0	0	0	0	0	1	0	0	0
18	benidipine hcl	0.96	1.09	0.05	1	0	1	1	0	0	1	0	0
19	doxorubicin hydrochloride	0.46	0.31	0.08	1	1	1	1	0	0	1	0	0
20	telmisartan	0.33	0.40	0.09	1	0	1	1	0	0	1	0	0
21	tricalabandazole	0.14	0.31	0.11	1	0	1	1	0	0	1	0	0
22	epirubicin hydrochloride	0.79	0.29	0.12	1	1	1	1	0	0	1	0	0
23	idarubicin hcl	0.18	0.16	0.12	1	1	1	1	0	0	1	0	0
24	mesoridazine	0.34	0.17	0.12	1	1	1	1	0	0	1	0	0
25	ethinylestradiol	0.93	0.20	0.10	1	1	1	1	0	0	1	0	0
26	megestrol acetate	0.96	0.46	0.13	1	1	1	1	0	0	1	0	0
27	diphenylcyclopropenone tetraethylthiuram disulfide	0.46	0.35	0.16	1	1	1	1	0	0	1	0	0
28	disulfide	0.03	0.05	0.16	0	0	0	0	0	1	0	0	0
29	progesterone	0.90	0.34	0.15	1	1	1	1	0	0	1	0	0
30	ethylestrenol	0.93	0.24	0.15	1	1	1	1	0	0	1	0	0
31	3-deoxyadenosine	0.98	0.35	0.16	1	1	1	1	0	0	1	0	0
32	ketocanazole	0.49	0.27	0.20	1	1	1	1	0	0	1	0	0
33	latanoprost	0.99	0.23	0.16	1	1	1	1	0	0	1	0	0
34	lofepramine	0.90	0.39	0.19	1	1	1	1	0	0	1	0	0
35	carvedilol	0.99	0.43	0.18	1	1	1	1	0	0	1	0	0
36	cisapride	0.97	0.88	0.20	1	1	1	1	0	0	1	0	0
37	ezetimibe	1.03	0.05	0.21	0	1	1	0	0	0	0	0	1
38	idebenone	0.64	0.05	0.28	0	1	1	0	0	0	0	0	1
39	calcitriol	1.00	0.58	0.22	1	1	1	1	0	0	1	0	0
40	perospirone hcl	0.90	0.94	0.24	1	0	1	1	0	0	1	0	0
41	terbinafine hcl	0.31	0.50	0.33	1	0	0	1	0	1	0	0	0
42	calcipotriol	1.01	0.05	0.26	0	1	1	0	0	0	0	0	1
43	3-[3,5-dibromo-4-hydroxybenzoyl]-2-ethylbenzofuran	0.35	0.05	0.34	0	1	0	0	0	0	0	0	1
44	methyltestosterone	0.88	0.51	0.30	1	1	1	1	0	0	1	0	0
45	nifedipine	0.89	0.49	0.30	1	1	1	1	0	0	1	0	0
46	2h-indol-2-one,1,3-dihydro-1-phenyl-3,3-bis(4-pyridinylmethyl)	0.96	0.82	0.38	1	1	1	1	0	0	1	0	0
47	ifenprodil	0.92	0.56	0.31	1	1	1	1	0	0	1	0	0
48	enrofloxacin	0.93	0.51	0.38	1	1	1	1	0	0	1	0	0
49	finasteride	0.97	0.65	0.30	1	1	1	1	0	0	1	0	0
50	cervastatin na	0.60	0.34	0.41	0	1	1	0	0	0	0	0	1
51	artesunate	0.91	0.59	0.35	1	1	1	1	0	0	1	0	0
52	itraconazole	0.71	0.61	0.46	1	1	1	1	0	0	1	0	0
53	voriconazole	0.50	0.65	0.47	1	0	1	1	0	0	1	0	0
54	itavastatin ca	0.71	0.55	0.47	1	1	1	1	0	0	1	0	0
55	nimodipine	0.99	0.13	0.56	0	1	1	0	0	0	0	0	1
56	5-fluorocytosine	0.33	0.48	0.57	0	0	0	0	0	1	0	0	0
57	moxifloxacin hcl	1.00	0.63	0.54	1	1	1	1	0	0	1	0	0
58	am-251	1.07	0.49	0.69	0	1	1	0	0	0	0	0	1
59	exemestane	0.97	0.86	0.54	1	1	1	1	0	0	1	0	0
60	dolasetron mesylate	0.99	1.02	0.71	1	0	1	1	0	0	1	0	0
61	duloxetine hcl	0.64	0.54	0.71	0	1	0	0	0	0	0	0	1

62	pramipexole	1.01	0.53	0.59	0	1	1	0	0	0	0	0	1
63	nobiletin	0.91	0.90	0.57	1	0	1	1	0	0	1	0	0
64	diphenoxylate	1.01	0.83	0.58	1	1	1	1	0	0	1	0	0
65	carbamofur	0.42	0.59	0.76	0	0	0	0	0	1	0	0	0
66	tibolone	0.99	0.79	0.78	1	1	1	0	1	0	0	1	0
67	isradipine	0.97	0.18	0.60	0	1	1	0	0	0	0	0	1
68	rimcazole	0.31	0.66	0.80	0	0	0	0	0	1	0	0	0
69	phenothiazine	0.87	0.77	0.82	0	1	1	0	0	0	0	0	1
70	synephrine	1.03	0.99	0.82	1	0	1	1	0	0	1	0	0
71	nisoldipine	0.32	0.27	0.83	0	1	0	0	0	0	0	0	1
72	bicalutamide	0.98	0.65	0.66	0	1	1	0	1	0	0	1	0
73	nefinavir mesylate	0.99	0.70	0.67	1	1	1	0	1	0	0	1	0
74	ru 24969	1.01	1.06	0.86	1	0	1	1	0	0	1	0	0
75	nitazoxanide	0.95	0.99	0.66	1	0	1	1	0	0	1	0	0
76	medroxyprogesterone	1.00	0.90	0.87	1	1	1	0	1	0	0	1	0
77	stiripentol	0.94	0.88	0.88	0	1	1	0	1	0	0	1	0
78	corticosterone	1.02	0.95	0.89	1	1	1	1	0	0	1	0	0
79	tremulacin	1.02	1.03	0.90	1	0	1	1	0	0	1	0	0
80	desoximetasone	0.95	0.95	0.90	1	0	1	1	0	0	1	0	0
81	ketotifen fumarate	0.99	1.02	0.90	1	0	1	1	0	0	1	0	0
82	beta-estradiol	0.92	0.85	0.73	1	1	1	1	0	0	1	0	0
83	omeprazole	0.99	1.09	0.91	1	0	1	1	0	0	1	0	0
84	midazolam hcl	0.98	0.76	0.71	1	1	1	1	0	0	1	0	0
	methanesulfonamide, n-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride	1.01	1.05	0.92	1	0	1	1	0	0	1	0	0
85	nyl]-, dihydrochloride	1.01	1.05	0.92	1	0	1	1	0	0	1	0	0
86	vardenafil citrate	1.00	0.99	0.92	1	0	1	1	0	0	1	0	0
87	chlordiazepoxide dextrorpheniramine maleate	0.96	0.98	0.93	1	0	0	1	0	1	0	0	0
88	maleate	0.99	1.00	0.93	1	0	1	1	0	0	1	0	0
89	capsaicin	0.92	0.69	0.76	0	1	1	0	0	0	0	0	1
90	5-methoxytryptamine guanidine, n-cyano-n-(1,1-dimethylpropyl)-n-3-pyridinyl	1.00	1.03	0.94	1	0	1	1	0	0	1	0	0
91	pyridinyl	0.99	1.03	0.95	1	0	0	1	0	1	0	0	0
92	cgs 15943	0.87	0.77	0.77	0	1	1	0	1	0	0	1	0
93	19-nortestosterone	0.92	0.86	0.78	1	1	1	1	0	0	1	0	0
94	oxyphenonium bromide	0.99	1.03	0.95	1	0	0	1	0	1	0	0	0
95	7-nitroindazole	1.00	1.03	0.96	1	0	0	1	0	1	0	0	0
96	vecuronium bromide	0.99	1.16	0.96	1	0	0	1	0	1	0	0	0
97	i-694,247	0.99	1.00	0.96	1	0	0	0	1	1	0	0	0
98	beclomethasone	0.99	0.94	0.96	0	1	0	0	1	0	0	1	0
99	hmt	1.00	0.96	0.97	0	0	0	0	1	1	0	0	0
100	pinacidil monohydrate	0.96	1.02	0.97	1	0	0	0	1	1	0	0	0
101	cortisone	1.01	0.98	0.97	1	0	0	0	1	1	0	0	0
102	1-benzylimidazole	1.03	1.03	0.97	1	0	1	1	0	0	1	0	0
103	brucine	0.99	1.02	0.97	1	0	0	0	1	1	0	0	0
104	doxapram hydrochloride	1.01	1.02	0.97	1	0	0	0	1	1	0	0	0
105	secoisolariciresinol	1.02	0.98	0.97	1	0	0	0	1	1	0	0	0
106	diazepam	0.93	0.84	0.75	1	1	1	1	0	0	1	0	0
107	rolitetracycline	1.03	1.05	0.97	1	0	1	1	0	0	1	0	0
108	altanserin	1.00	1.00	0.75	1	0	1	1	0	0	1	0	0
109	lofexidine hcl	1.00	1.02	0.98	1	0	0	0	1	1	0	0	0
110	resveratrol	1.00	1.02	0.98	1	0	0	0	1	1	0	0	0
	benzo[a]phenanthridine-10,11-diol, 5,6,6a,7,8,12b-hexahydro-, trans	0.99	0.98	0.98	0	0	0	0	1	1	0	0	0
111	hexahydro-, trans	0.99	0.98	0.98	0	0	0	0	1	1	0	0	0
112	tramadol	1.01	1.02	0.99	1	0	0	0	1	1	0	0	0
113	cefixime trihydrate	1.02	1.04	0.99	1	0	0	0	1	1	0	0	0
114	raltitrexed	1.00	1.09	0.99	1	0	0	1	0	1	0	0	0
115	maltol	1.02	1.03	0.99	1	0	0	0	1	1	0	0	0
116	dactinomycin	0.97	1.01	0.99	1	0	0	0	1	1	0	0	0
117	cefdinir	1.02	1.03	0.99	1	0	0	0	1	1	0	0	0
118	3-pyridinemethanol	1.03	0.98	0.99	0	0	0	0	1	1	0	0	0
119	tryptoline	1.03	1.03	0.99	1	0	0	0	1	1	0	0	0
120	naproxen sodium	1.02	0.96	0.99	0	1	0	0	1	0	0	1	0
121	rofecoxib	1.00	1.01	0.82	1	0	1	1	0	0	1	0	0
122	dehydrocholic acid	1.02	1.03	0.99	1	0	0	0	1	1	0	0	0
123	anastrozole	1.02	1.05	0.99	1	0	0	1	0	1	0	0	0
124	homoveratrylamine mepivacaine hydrochloride	1.03	1.04	1.00	1	0	0	0	1	1	0	0	0
125	hydrochloride	1.01	1.09	1.00	1	0	0	1	0	1	0	0	0
126	ropivacaine hcl	1.02	1.05	1.00	1	0	0	0	1	1	0	0	0
127	trimebutine maleate	0.98	0.91	0.82	1	1	1	1	0	0	1	0	0
128	xanthinol nicotinate	1.03	0.99	1.00	0	0	0	0	1	1	0	0	0
129	tinidazole	1.00	1.01	1.00	1	0	0	0	1	1	0	0	0
130	cefaclor	0.98	1.03	1.00	1	0	0	0	1	1	0	0	0
131	6-aminoindazole 2-chloro-2-deoxyadenosine	1.02	1.04	1.00	1	0	0	0	1	1	0	0	0
132	deoxyadenosine	1.02	1.05	1.00	1	0	0	0	1	1	0	0	0
133	granisetron hcl	1.01	1.03	1.00	1	0	0	0	1	1	0	0	0
134	6-azauridine	0.98	1.00	1.00	0	0	0	0	1	1	0	0	0
135	nafadotride	1.00	1.07	1.00	1	0	0	1	0	1	0	0	0
136	zolmitriptan	1.02	1.03	1.00	1	0	0	0	1	1	0	0	0

198	trazodone hydrochloride benzeneacetone trile, alpha-[3-[[2-(3,4-dimethoxyphenyl)ethyl]methylamino]propyl]-3,4-dimethoxy-alpha-(1-methylethyl)-, (R)-	1.00	1.06	0.96	1	0	0	1	0	1	0	0	0
199	nifekalant hcl	1.01	0.99	0.96	1	0	0	0	1	1	0	0	0
200	rolipram	1.00	0.98	0.97	1	0	0	0	1	1	0	0	0
201	ipriflavone	1.02	1.02	0.92	1	0	1	1	0	0	1	0	0
202	pancuronium	1.00	0.91	0.92	0	1	1	0	1	0	0	1	0
203	epigallocatechin gallate	1.02	1.17	0.96	1	0	1	1	0	0	1	0	0
204	flvoxamine	0.98	1.06	0.96	1	0	0	1	0	1	0	0	0
205	cinanserin	0.94	0.86	0.96	0	1	0	0	0	0	0	0	1
206	letrozol	0.97	0.58	0.96	0	1	0	0	0	0	0	0	1
207	nateglinide	1.02	0.62	0.98	0	1	0	0	0	0	0	0	1
208	1h-cyclopenta[b]quinolin-9-amine, 2,3,5,6,7,8-hexahydro-, monohydrochloride	1.01	0.98	0.98	0	0	0	0	1	1	0	0	0
209	cefatrizine propylene glycol	0.88	0.93	0.97	0	0	0	0	1	1	0	0	0
210	cephalexin monohydrate	1.02	1.04	0.99	1	0	0	0	1	1	0	0	0
211	(-)-cotinine	0.99	1.02	0.99	1	0	0	0	1	1	0	0	0
212	atomoxetine hcl	0.99	0.97	0.97	0	0	0	0	1	1	0	0	0
213	tiagabine hcl	1.00	0.86	0.99	0	1	0	0	0	0	0	0	1
214	tosufloxacin tosylate	0.99	1.00	0.99	1	0	0	0	1	1	0	0	0
215	mestranol	1.01	0.97	0.99	0	0	0	0	1	1	0	0	0
216	docetaxel	0.97	0.89	0.92	0	1	1	0	1	0	0	1	0
217	nimetazepam	0.96	1.02	0.99	1	0	0	0	1	1	0	0	0
218	ramipril	1.00	0.97	0.93	1	0	1	0	1	0	0	1	0
219	1-(2-methyl-5-nitroimidazol-1-yl)-propan-2-ol	1.03	0.94	0.99	0	1	0	0	0	0	0	0	1
220	fempiverinium bromide	1.03	1.01	0.99	1	0	0	0	1	1	0	0	0
221	urapidil hydrochloride	1.04	1.04	1.00	1	0	0	0	1	1	0	0	0
222	l-glutamic acid, n-[4-[[[(2,4-diamino-6-pteridiny]methyl)methyl]amino]benzoyl]	0.98	1.01	0.98	1	0	0	0	1	1	0	0	0
223	zafirlukast	1.01	1.04	0.98	1	0	0	1	0	1	0	0	0
224	d-3-methoxy-n-methylmorphinan hydrobromide	1.03	0.42	0.93	0	1	1	0	0	0	0	0	1
225	indomethacin	1.02	1.00	0.98	1	0	0	0	1	1	0	0	0
226	troxipide	0.99	0.98	0.98	0	0	0	0	1	1	0	0	0
227	argatroban	0.99	1.02	1.00	1	0	0	0	1	1	0	0	0
228	tripelennamine hydrochloride	1.01	1.05	0.95	1	0	1	1	0	0	1	0	0
229	bisoprolol fumarate	0.98	0.99	0.99	0	0	0	0	1	1	0	0	0
230	piceid	0.98	1.01	1.00	1	0	0	0	1	1	0	0	0
231	glycine, n-[2-[(acetylthio)methyl]-1-oxo-3-phenylpropyl]-, phenylmethyl ester	1.01	0.99	1.00	0	0	0	0	1	1	0	0	0
232	benazepril hcl	0.98	0.72	0.99	0	1	0	0	0	0	0	0	1
233	nornicotine	0.96	0.96	0.95	1	0	0	0	1	1	0	0	0
234	temozolomide	0.98	1.00	0.99	1	0	0	0	1	1	0	0	0
235	alosetron hcl	0.93	1.00	1.00	0	0	0	0	1	1	0	0	0
236	phenelzine sulfate salt	0.90	1.02	1.00	1	0	0	0	1	1	0	0	0
237	famciclovir	1.00	1.01	0.99	1	0	0	0	1	1	0	0	0
238	benzeneacetic acid, 2-[(2,6-dichlorophenyl)amino]-, monosodium salt	1.05	1.01	1.00	1	0	0	0	1	1	0	0	0
239	pilocarpine hydrochloride	0.97	0.92	0.99	0	1	0	0	0	0	0	0	1
240	nizatidine	0.99	0.99	0.99	0	0	0	0	1	1	0	0	0
241	amlexanox	1.00	1.01	1.01	0	0	0	0	1	1	0	0	0
242	ozagrel hcl	0.96	0.98	0.95	1	0	0	0	1	1	0	0	0
243	triptolide	0.94	0.98	0.95	1	0	0	0	1	1	0	0	0
244	benzeneethanamine, n,alpha-dimethyl-n-2-propynyl	1.02	1.05	0.95	1	0	1	1	0	0	1	0	0
245	tfmpp	1.01	1.03	0.99	1	0	0	0	1	1	0	0	0
246	lidocaine	0.97	0.96	0.99	0	0	0	0	1	1	0	0	0
247	amfebutamone hcl	1.01	1.01	0.99	1	0	0	0	1	1	0	0	0
248	maprotiline hcl	1.03	1.00	1.01	0	0	0	0	1	1	0	0	0
249	ondansetron hcl	0.94	0.40	0.99	0	1	0	0	0	0	0	0	1
250	esomeprazole mg	1.01	1.04	1.01	1	0	0	0	1	1	0	0	0
251	ly 171883	0.98	1.07	0.96	1	0	0	1	0	1	0	0	0
252	galanthamine	0.98	0.91	1.00	0	1	0	0	0	0	0	0	1
253	diphenhydramine hydrochloride	1.01	1.02	1.00	1	0	0	0	1	1	0	0	0
254	picrotin - picrotoxinin	0.99	0.94	1.00	0	1	0	0	0	0	0	0	1
255		1.01	1.04	1.00	1	0	0	0	1	1	0	0	0

256	orlistat	0.97	1.02	1.01	1	0	0	0	1	1	0	0	0
257	alfuzosin	1.01	1.04	1.01	1	0	0	0	1	1	0	0	0
258	lamotrigine	1.06	1.03	1.01	1	0	0	0	1	1	0	0	0
259	pirenerone	1.01	1.02	0.95	1	0	1	1	0	0	1	0	0
260	ormetoprim	1.04	1.08	1.01	1	0	0	1	0	1	0	0	0
261	olmesartan medoxomil	1.01	0.99	1.02	0	0	0	0	1	1	0	0	0
262	penciclovir	1.01	1.00	0.95	1	0	1	0	1	0	0	1	0
263	loteprednol etabonate	0.97	0.83	0.95	0	1	0	0	0	0	0	0	1
264	tocainide	1.02	0.97	1.02	0	0	0	0	0	1	0	0	0
265	ud	1.04	1.02	1.00	1	0	0	0	1	1	0	0	0
266	ud	1.01	1.05	1.00	1	0	0	0	1	1	0	0	0
267	ud	1.01	1.02	1.00	1	0	0	0	1	1	0	0	0
268	ud	1.01	1.01	1.00	1	0	0	0	1	1	0	0	0
269	methyl paroxetine	0.92	0.49	1.02	0	1	0	0	0	0	0	0	1
270	zileuton	1.03	0.99	1.02	0	0	0	0	1	1	0	0	0
271	pidotimod	1.05	0.98	1.02	0	1	0	0	1	0	0	1	0
272	meropenem	1.05	0.98	1.02	0	1	0	0	1	0	0	1	0
273	pizotyline	0.86	0.27	1.00	0	1	0	0	0	0	0	0	1
274	lobeline hydrochloride	0.98	1.07	0.95	1	0	0	1	0	1	0	0	0
275	stavudine	1.00	0.98	1.02	0	0	0	0	1	1	0	0	0
276	losartan potassium (+)-3-hydroxy-n-methylmorphinan d-tartrate	1.01	1.04	1.02	1	0	0	0	1	1	0	0	0
277	tartrate	1.02	1.02	1.00	1	0	0	0	1	1	0	0	0
278	linezolid	1.03	0.93	0.95	0	1	1	0	1	0	0	1	0
279	famotidine	1.04	1.03	1.00	1	0	0	0	1	1	0	0	0
280	flumazenil	0.97	1.00	0.97	1	0	0	0	1	1	0	0	0
281	levosulpiride	0.99	1.01	1.02	0	0	0	0	1	1	0	0	0
282	pemoline	1.07	0.98	1.02	0	1	0	0	1	0	0	1	0
283	azelastine hcl	0.99	0.75	1.03	0	1	0	0	0	0	0	0	1
284	salbutamol sulfate 4-thiazolidinecarboxylic acid, 2-oxo-, (R)-	1.03	1.02	1.01	1	0	0	0	1	1	0	0	0
285	acid, 2-oxo-, (R)-	1.02	1.04	1.01	1	0	0	0	1	1	0	0	0
286	rosiglitazone maleate	0.96	0.94	0.97	0	0	0	0	1	1	0	0	0
287	rosiglitazone hcl	0.95	0.98	0.97	1	0	0	0	1	1	0	0	0
288	indinavir sulphate	1.00	1.06	0.97	1	0	0	1	0	1	0	0	0
289	phenprobamate	0.99	1.01	0.97	1	0	0	0	1	1	0	0	0
290	olanzapine	1.02	1.01	0.97	1	0	0	0	1	1	0	0	0
291	5-amino-2-hydroxy-benzoic acid l-ornithine, n5-[imino(methylamino)met	1.02	1.04	1.01	1	0	0	0	1	1	0	0	0
292	hyl]	1.03	1.06	1.01	1	0	0	0	1	1	0	0	0
293	metronidazole	1.02	1.01	1.01	0	0	0	0	1	1	0	0	0
294	oligomycin c	0.96	0.98	0.98	0	0	0	0	1	1	0	0	0
295	sr 57,227a memantine	1.01	1.01	1.02	0	0	0	0	1	1	0	0	0
296	hydrochloride	1.01	1.00	0.98	1	0	0	0	1	1	0	0	0
297	taxifolin-(+/-)	1.04	1.01	1.03	0	0	0	0	1	1	0	0	0
298	amisulpride	1.01	1.02	1.04	0	0	0	0	1	1	0	0	0
299	cpd00042823	1.01	0.98	1.02	0	0	0	0	1	1	0	0	0
300	taxifolin-(+)	1.03	1.02	1.04	0	0	0	0	1	1	0	0	0
301	zacopride	1.05	1.04	1.02	1	0	0	0	1	1	0	0	0
302	cefepodoxime proxetil	1.04	1.01	1.04	0	0	0	0	1	1	0	0	0
303	hyperoside	1.01	0.99	0.98	1	0	0	0	1	1	0	0	0
304	gr 89696 benactyzine	1.02	1.04	0.97	1	0	0	1	0	1	0	0	0
305	hydrochloride	1.01	1.01	0.97	1	0	0	0	1	1	0	0	0
306	roxatidine acetate hcl	1.03	1.01	0.97	1	0	1	0	1	0	0	1	0
307	viramune	1.03	1.03	0.98	1	0	0	0	1	1	0	0	0
308	nalbuphine	1.04	1.03	1.02	1	0	0	0	1	1	0	0	0
309	tropisetron hcl	1.02	1.05	0.99	1	0	0	1	0	1	0	0	0
310	delta1-hydrocortisone 21-hemisuccinate sodium salt	1.01	1.02	0.98	1	0	0	0	1	1	0	0	0
311	ranolazine	1.01	1.03	0.99	1	0	0	0	1	1	0	0	0
312	dihydrochloride	1.01	1.03	0.99	1	0	0	0	1	1	0	0	0
313	procarbazine hcl	0.98	1.01	0.99	1	0	0	0	1	1	0	0	0
314	fluticasone propionate	1.01	1.04	0.99	1	0	0	0	1	1	0	0	0
315	pefloxacin mesylate	1.02	0.91	0.99	0	1	0	0	0	0	0	0	1
316	3-hydroxy-1,2-dimethyl-4(1h)-pyridone	1.00	1.03	1.03	0	0	0	0	1	1	0	0	0
317	pioqilazone hcl	1.00	1.02	0.99	1	0	0	0	1	1	0	0	0
318	dichloroacetic acid	1.01	0.99	0.98	1	0	0	0	1	1	0	0	0
319	venlafaxine hcl	1.01	1.02	0.99	1	0	0	0	1	1	0	0	0
320	bupropion hydrochloride	1.02	0.99	0.99	0	0	0	0	1	1	0	0	0
321	actarit	1.08	0.97	1.05	0	1	0	0	0	0	0	0	1
322	bifemelane	0.91	0.31	1.03	0	1	0	0	0	0	0	0	1
323	oxaprozin	0.99	0.86	0.99	0	1	0	0	0	0	0	0	1
324	piroxicam	0.99	0.96	0.98	0	0	0	0	1	1	0	0	0
325	naltrindole	1.04	1.05	1.03	1	0	0	0	1	1	0	0	0
326	rifapentine	0.99	1.03	0.98	1	0	0	0	1	1	0	0	0
327	isoquercetrin	1.00	1.01	0.99	1	0	0	0	1	1	0	0	0
328	paroxetine	0.97	0.33	1.04	0	1	0	0	0	0	0	0	1
329	risperidone	1.01	1.07	1.00	1	0	0	1	0	1	0	0	0
330	icariin	1.04	1.03	1.00	1	0	0	0	1	1	0	0	0
330	10h-phenothiazine	0.19	0.05	1.04	0	1	0	0	0	0	0	0	1

331	moxonidine hcl	0.99	1.02	1.00	1	0	0	0	1	1	0	0	0
332	loxoprofen sodium	1.01	1.01	0.99	1	0	0	0	1	1	0	0	0
333	loxapine succinate	0.95	0.90	1.04	0	1	0	0	0	0	0	0	1
334	tranilast	1.01	1.04	1.00	1	0	0	0	1	1	0	0	0
	pantoprazole sodium												
335	salt	1.01	1.05	1.00	1	0	0	0	1	1	0	0	0
336	oxymetholone	0.83	0.05	1.00	0	1	0	0	0	0	0	0	1
337	levocetirizine	1.01	1.05	0.99	1	0	0	1	0	1	0	0	0
338	ornidazole	1.06	1.02	0.99	1	0	1	0	1	0	0	1	0
339	felbamate	1.01	1.02	0.99	1	0	0	0	1	1	0	0	0
340	diazoxide	1.01	0.99	0.99	0	0	0	0	1	1	0	0	0
341	acarbose	1.03	1.05	1.00	1	0	0	0	1	1	0	0	0
342	2,3-dideoxyinosine	1.04	1.04	1.00	1	0	0	0	1	1	0	0	0
343	raclopride	0.99	1.03	1.04	0	0	0	0	1	1	0	0	0
344	toradol	0.97	0.99	0.99	0	0	0	0	1	1	0	0	0
345	pramipexole hcl	1.01	1.05	1.00	1	0	0	0	1	1	0	0	0
346	milnacipran	0.99	1.00	0.99	1	0	0	0	1	1	0	0	0
347	terazosin	1.01	1.01	1.04	0	0	0	0	1	1	0	0	0
348	sumatriptan succinate	1.03	0.98	0.99	0	0	0	0	1	1	0	0	0
349	pentoxifylline	1.00	1.03	0.99	1	0	0	0	1	1	0	0	0
350	nicorandil	1.05	1.05	0.99	1	0	1	1	0	0	1	0	0
351	betaxolol hydrochloride	0.98	1.01	0.99	1	0	0	0	1	1	0	0	0
352	lamivudine	1.01	1.04	1.01	1	0	0	0	1	1	0	0	0
353	modafinil	1.03	1.03	1.01	1	0	0	0	1	1	0	0	0
354	vinorelbine bitartrate	1.04	1.12	1.00	1	0	0	1	0	1	0	0	0
355	dofetilide	1.04	1.05	1.00	1	0	0	0	1	1	0	0	0
356	glycopyrrolate	0.99	1.00	1.00	0	0	0	0	1	1	0	0	0
357	rutin	1.06	0.99	1.00	0	1	1	0	1	0	0	1	0
358	esmolol hydrochloride	1.01	1.05	1.01	1	0	0	0	1	1	0	0	0
359	montelukast na	1.02	0.97	1.00	0	0	0	0	1	1	0	0	0
	dexbrompheniramine												
360	maleate	1.03	1.00	1.00	0	0	0	0	1	1	0	0	0
361	2-(2-aminoethyl)pyridine	1.02	1.02	1.00	1	0	0	0	1	1	0	0	0
	1,1-dimethyl-4-												
	phenylpiperazinium												
362	iodide	1.01	1.02	1.00	1	0	0	0	1	1	0	0	0
363	physostigmine	1.03	1.01	1.00	1	0	0	0	1	1	0	0	0
364	azasetron	1.00	1.02	1.00	1	0	0	0	1	1	0	0	0
365	irbesartan	1.01	1.02	1.00	1	0	0	0	1	1	0	0	0
366	doxylamine succinate	0.96	1.02	1.00	1	0	0	0	1	1	0	0	0
367	lomifylline	0.98	1.02	1.01	1	0	0	0	1	1	0	0	0
	1h-imidazol-2-amine, n-												
	(2,6-dichlorophenyl)-4,5-												
368	dihydro	1.04	1.05	1.00	1	0	0	0	1	1	0	0	0
369	2,3-dideoxycytidine	1.02	1.02	1.00	1	0	0	0	1	1	0	0	0
370	topotecan hcl	1.03	0.89	1.02	0	1	0	0	0	0	0	0	1
371	fenoldopam mesylate	1.02	1.02	1.02	0	0	0	0	1	1	0	0	0
	6h-pyrido[2,3-												
	b][1,4]benzodiazepin-6-												
	one, 11-[[2-												
	[[diethylamino)methyl]-1-												
	piperidiny]acetyl]5,11-												
372	dihydro	1.05	1.06	1.00	1	0	0	1	0	1	0	0	0
373	escitalopram oxalate	0.98	1.03	1.02	1	0	0	0	1	1	0	0	0
	formoterol fumarate												
374	dihydrate	0.99	1.02	1.01	1	0	0	0	1	1	0	0	0
375	topiramate	1.03	1.01	1.02	0	0	0	0	1	1	0	0	0
376	2-chloroadenosine	1.02	1.03	1.01	1	0	0	0	1	1	0	0	0
377	cilastatin na	1.02	1.04	1.02	1	0	0	0	1	1	0	0	0
378	irsogladine maleate	1.03	1.00	1.02	0	0	0	0	1	1	0	0	0
379	torasemide	1.01	1.06	1.02	1	0	0	0	1	1	0	0	0
380	5-fluoro-2-pyrimidone	1.04	1.03	1.01	1	0	0	0	1	1	0	0	0
381	valsartan	1.02	1.06	1.01	1	0	0	0	1	1	0	0	0
382	milrinone	1.01	1.10	1.01	1	0	0	1	0	1	0	0	0
383	pravastatin sodium	0.99	0.73	1.03	0	1	0	0	0	0	0	0	1
384	rizatriptan benzoate	1.00	1.04	1.02	1	0	0	0	1	1	0	0	0
385	tadalafil	1.04	1.06	1.03	1	0	0	0	1	1	0	0	0
386	levetiracetam	1.03	1.06	1.03	1	0	0	0	1	1	0	0	0
387	miglitol	1.03	1.05	1.03	1	0	0	0	1	1	0	0	0
388	chlorpheniramine	1.00	1.02	1.02	0	0	0	0	1	1	0	0	0
	citalopram												
389	hydrobromide	0.99	0.97	1.02	0	0	0	0	0	1	0	0	0
390	ftorafur	1.00	1.02	1.03	0	0	0	0	1	1	0	0	0
391	itopride hcl	1.01	1.04	1.02	1	0	0	0	1	1	0	0	0
392	benproperine phosphate	0.87	0.91	1.03	0	0	0	0	0	1	0	0	0
393	rifaximin	1.03	1.05	1.02	1	0	0	0	1	1	0	0	0
394	pazufloxacin	1.02	0.99	1.04	0	0	0	0	0	1	0	0	0
395	sulfasalazine	1.05	1.07	1.05	1	0	0	0	1	1	0	0	0
396	indarubicin	1.03	1.04	1.04	0	0	0	0	1	1	0	0	0
397	enalaprilat	0.98	1.02	1.04	0	0	0	0	1	1	0	0	0
					246	121	122	104	215	232	74	31	60
					62%	30%	31%	26%	54%	58%	19%	8%	15%

Supplementary Table 9. IC50 value for each strain-drug combination (μM).

	<i>pdr5</i> Δ	<i>pdr10</i> Δ	<i>pdr11</i> Δ	<i>pdr12</i> Δ	<i>pdr15</i> Δ	<i>snq2</i> Δ	<i>ynr070w</i> Δ	<i>aus1</i> Δ	<i>yol075c</i> Δ
Fluconazole	37	59	66	61	67	61	63	64	64
Ketoconazole	1.5	1.9	1.8	1.9	1.9	1.9	1.6	1.9	1.8
Miconazole	0.17	0.22	0.16	0.20	0.21	0.20	0.20	0.20	0.20
Itraconazole	2	13	6	8	8	12	6	8	10
Tamoxifen	10	22	10	22	22	22	22	22	22
CCCP	17	17	18	19	17	7	15	16	19

	<i>adp1</i> Δ	<i>ycf1</i> Δ	<i>vmr1</i> Δ	<i>nft1</i> Δ	<i>bpt1</i> Δ	<i>ybt1</i> Δ	<i>yor1</i> Δ	Monster	Non-mutant
Fluconazole	62	34	61	64	64	63	67	1	60
Ketoconazole	1.9	1.7	2.1	1.7	1.5	1.9	1.7	0.01	1.7
Miconazole	0.20	0.29	0.15	0.19	0.31	0.21	0.33	0.01	0.20
Itraconazole	8	6	6	7	7	7	11	0.006	8
Tamoxifen	22	22	22	26	22	22	22	3.0	22
CCCP	19	17	18	21	16	14	19	5.1	14

Supplementary Table 10. Relative fitness values for the ABC16-monster and the multiplicative model based on single mutant relative fitness. Relative fitness was normalized to the fitness of non-mutant.

Miconazole

Concentration the non-mutant (μM)	ABC16 fitness normalized to the non-mutant fitness	Multiplicative model based on normalized single mutant fitness
6.0	0	546876
1.4	0.3	3645889
0.3	0.08	37
0.08	0.03	12
0	0.9	0.9

Tamoxifen

Concentration the non-mutant (μM)	ABC16 fitness normalized to the non-mutant fitness	Multiplicative model based on normalized single mutant fitness
40	0	0
17	0	1.5
7.6	1.1	2.8
3.3	1.0	7.9
0	1.0	0.4

Fluconazole

Concentration the non-mutant (μM)	ABC16 fitness normalized to the non-mutant fitness	Multiplicative model based on normalized single mutant fitness
60	0	1964956
13	0	0.8
2.8	0.005	2.7
0.6	1.0	3.4
0	0.8	0.6

CCCP

Concentration the non-mutant (μM)	ABC16 fitness normalized to the non-mutant fitness	Multiplicative model based on normalized single mutant fitness
60	0	0
14	0.2	0
3.5	0.8	0.08
0.8	0.7	0.01
0	1.0	0.001

Ketoconazole

Concentration the non-mutant (μM)	ABC16 fitness normalized to the non-mutant fitness	Multiplicative model based on normalized single mutant fitness
9.0	0.2	42154888
1.3	0	1.2
0.2	0	6.3
0.03	0	11
0	1.1	11

Valinomycin

Concentration the non-mutant (μM)	ABC16 fitness normalized to the non-mutant fitness	Multiplicative model based on normalized single mutant fitness
90	1.6	30
34	1.8	47
13	1.8	42
5.0	1.6	45
0	1.0	1.6

Itraconazole

Concentration the non-mutant (μM)	ABC16 fitness normalized to the non-mutant fitness	Multiplicative model based on normalized single mutant fitness
20	-0.3	20161239574
4.8	0.003	0.009
1.2	0.005	0.9
0.3	0.03	22468
0	0.9	1.8

Supplementary Table 11. Deletions not detected in diploid-selection mixtures or isolated and genotyped sorted cells in the *en masse* Green Monster processes.

NA: not applicable. ND: not determined.

	Round					
	0	1	2	3	4	5
Diploid-selection pool from Series 1	None	<i>ynr070w</i> Δ <i>yor1</i> Δ	<i>ynr070w</i> Δ <i>vmr1</i> Δ <i>pdr5</i> Δ	<i>ynr070w</i> Δ <i>yor1</i> Δ <i>vmr1</i> Δ <i>aus1</i> Δ <i>pdr5</i> Δ <i>ybt1</i> Δ <i>yol075c</i> Δ	ND	ND
Diploid-selection pool from Series 2	None	<i>ynr070w</i> Δ <i>pdr5</i> Δ <i>pdr15</i> Δ	<i>ynr070w</i> Δ <i>vmr1</i> Δ <i>aus1</i> Δ <i>pdr5</i> Δ <i>pdr10</i> Δ <i>pdr15</i> Δ	<i>ynr070w</i> Δ <i>vmr1</i> Δ <i>aus1</i> Δ <i>pdr5</i> Δ <i>pdr10</i> Δ <i>pdr15</i> Δ	ND	ND
Diploid-selection pool from Series 3	None	<i>pdr5</i> Δ	<i>ynr070w</i> Δ <i>vmr1</i> Δ <i>aus1</i> Δ <i>pdr5</i> Δ <i>pdr15</i> Δ	<i>ynr070w</i> Δ <i>vmr1</i> Δ <i>bpt1</i> Δ <i>aus1</i> Δ <i>pdr5</i> Δ <i>pdr10</i> Δ	ND	ND
Isolated and genotyped sorted cells	NA	<i>aus1</i> Δ	<i>aus1</i> Δ <i>pdr15</i> Δ	<i>vmr1</i> Δ <i>aus1</i> Δ <i>pdr5</i> Δ <i>pdr15</i> Δ	<i>vmr1</i> Δ <i>pdr5</i> Δ <i>pdr15</i> Δ	<i>vmr1</i> Δ <i>aus1</i> Δ <i>pdr5</i> Δ <i>pdr10</i> Δ

Supplementary Table 12. Drug concentrations used to characterize *ho* non-mutant control, the ABC16-monster (*MATa*), and sixteen single mutant strains. After learning the heightened sensitivity, the ABC16-monster was treated differently in the second round using lower concentrations for most drugs. The unit is μM . * indicates special ketoconazole concentrations used only for the *pdr5* Δ mutant. The solvent was dimethyl sulfoxide (DMSO) for all drugs.

	First round of assay					Second round of assay									
	All strains					ABC16-monster					The rest of the strains				
Valinomycin	0	5	13	34	90	0	50	100	200	400	0	50	100	200	400
Fluconazole	0	0.6	3	13	60	0	1	3	5	7	0	20	50	80	110
Tamoxifen	0	3	8	17	40	0	6	9	12	15	0	20	25	30	35
Miconazole	0	0.08	0.3	1.4	6	0	0.02	0.08	0.14	0.2	0	0.06	0.24	0.42	0.6
Itraconazole	0	0.3	1.2	5	20	0	0.01	0.04	0.07	0.1	0	2	8	14	20
CCCP	0	0.8	3	14	60	0	1	5	9	13	0	7	17	27	37
Ketoconazole	0	0.03	0.2	1.3	9	0	0.005	0.013	0.021	0.029	0	3	5	7	9
											0	1	2	3	4 *

Supplementary Table 13. List of primers.

Construction of universal tetO2pr-GFP deletion cassettes

Amplification of GFP

CGGGATCCATGAGTAAAGGAGAAGAAC
AGTCCGGGCCCTTATTTGTATAGTTCATCCATG

Amplification of ADHterm-tetO2-GFP-CYC1term

CAAGCTCCTCGAGTAATTCG
CATGATTACGCCAAGCTTG

Amplification of URA3

GCCGCTCGAGCTTTTCAATTCAATTCATC
GGGGTACCGGTAATAACTGATATAAT

Amplification of HphMX4

GCTCTAGAACATGGAGGCCCGAATACCC
AAGGAAAAAGCGGCCGCCAGTATAGCGACCAGCATTAC

Site-directed mutagenesis to introduce the S65T change in GFP

CACTTGCTACTACTTTCACTTATGGTGTTCAATGC
GCATTGAACACCATAAGTGAAAGTAGTGACAAGTG

Generation of the URA3 GFP deletion cassette

GGATCCCCGGGTTAATTAAGGCGCGCCAGATCTGTTTAGCTTGCCCAAGCTCCTCGAGTAATTCG
GGCGTTAGTATCGAATCGACAGCAGTATAGCGACCAGCATTACGTACCGGTAATAACTGATATAAT

Generation of the HphMX4 GFP deletion cassette

GGATCCCCGGGTTAATTAAGGCGCGCCAGATCTGTTTAGCTTGCCCAAGCTCCTCGAGTAATTCG
CAGTATAGCGACCAGCATTAC

Construction of GMToolkits

Amplification of KanMX4

GCTCTAGAAGCTTGCCTCGTCCCCGCCGGGTC
CACCGCTCGAGTCGACACTGGATGGCGGCGTTAG

Amplification of CMVpr-rtTA

CGGGGTACCCATGATTACGCCAAGCTTG
CATCGAGCTAGCCTTATACGATCCTCGCGCCCCCTAC

Generation of the CMVpr-rtTA KanMX4 fragment for integration

GGAAGACGATAAGGTTAAGATAAGTAGATAAGAGAATGATACGAGCATGATTACGCCAAGCTTG
GGAGTTAAGAAGTCTGAAGAACTCTGAAATAAACTTTTCGATTGACGACAGTCGACACTGGATGGCGGCGTTAG

Amplification of NatMX4

GCTCTAGAAGCTTGCCTCGTCCCCGCCGGGTC
CACCGCTCGAGTCGACACTGGATGGCGGCGTTAG

Amplification of STE3pr-LEU2

CGCGGATCCGTCGACCCAAGTTACCTAAGAGGTGTACGA
GACGTACAGTGGGCCCTTAAGCAAGGATTTTCTTAACTTCTTC

Amplification of CMVpr-rtTA

CATCGAGCTAGCCATGATTACGCCAAGCTTG
CATCGAGCTAGCCTTATACGATCCTCGCGCCCCCTAC

Generation of the CMVpr-rtTA NatMX4 STE3pr-LEU2 fragment for integration

GGAAGACGATAAGGTTAAGATAAGTAGATAAGAGAATGATACGAGCATGATTACGCCAAGCTTG
GCGAAATGGCGTGAAATGTGATCAAAGGTAATAAAACGTCATATTTAAGCAAGGATTTTCTTAACTTCTTC

Genotyping ABC transporter loci during the Green Monster assembly

ynr070w Δ

GCTTCTGAACAAGGGATTCATC

ygr281w Δ

GCTATACAAGAACAGGAAGAACG

ycr011c Δ

CGATTTACAGAACTTGCACAC

ydr135c Δ

CATAGTACGCTTGTATGCTGC

yhl035c Δ

GTAATAAATGTCAAATCGCTAGCTC

ydr011w Δ

CTCCTTCCATTGATTAGAGTTC

yil015w Δ

GTTGATCGTATTGTTTGCCTAG

yor011w Δ

CATACTTGAGAAGGCATTAGC

ypl058c Δ

CAACCATGGTACAAGGTAGTTCTC

yor153w Δ

CGTGGTACGATATCTGTTGAAC

ykr104w Δ

CGTATGTACGTTATATCTTCGTGC

ykr103w Δ

CCATAGCGTAAGTCTGGCGTTC

yil013c Δ

CCTTTTCTCATTAGTTCGTAAAC

yil048c Δ

GTGTGCGCATCTGCAAAGAACG

yol075c Δ

GCAGAAGTAGGCACAAGTGCTTGG

yor328w Δ

CACCTGCTGTCATCAGTACC

ydr406w Δ

CGTCATATGCAGTATTCAAGTATAC

Universal genotyping primer

CGAATTACTCGAGGAGCTTG

Test for recombination between GFP cassettes within ABC transporter loci

YCR011C

AGACAGGAAGTCGAGCGTGT

ATCTCGCTGCAGATGACCTT

YDR011W
GTTGAAGTGTGCGAGGTCA
TTTTGAGTCGAAACCCAAGG

YDR135C
CAAACAACGTTTCCACCTCA
AGTGCATTACCCCGCATAAG

YDR406W
GATCGGAAAGGGAGCATGTA
AAAAAGGCCGGTACGAGTTT

YGR281W
CAGGAAGAACGCATTTCCAT
CGTTGTCCAGTTTGCCTCAT

YHL035C
CGCCCCTGTTTTATTTTCAA
AAGAGGGCGAATCCTTCAAT

YIL013C
CCACATAGACGGCCACTTTT
TTTCTCGAACCTGGAATGCT

YKR103W
ACTGCAATTCAGGGTGTCC
CCAGTCTGAAAGCCGGTAAA

YLL015W
GGCTGCTATCCCACAATGTT
TTGCGAGTTGCGTTTATCTG

YLL048C
TGCCAGTCGCTTTTTCTTTT
TACAGGTGTGACCGATTGGA

YNR070W
GCGATACGGAATTGAGGTGT
TCATACCGGCAATGTTGAAA

YOL075C
CAAGTGCTTGGCAGTTTTCA
TTGAGGAGTTGTTGCGATGA

YOR011W
ACAGCCACAGCAGCTTACCT
TGTGGAGATCATCGGTTCAA

YOR153W
CACCCTTTGGACTCGTGATT
TCGCATTTTGGAGCAGTTTTG

YOR328W
GCTTTGTTCCACGGACTGAT
GCTAGGGCAGCAAGTTCATC

YPL058C
TCACGGTTCCTAACCTGGTC
TCCCCGCATAGACTTGAATC

Genotyping the second set of loci during the Green Monster assembly

yer042wΔ

AGTGTTGCAGAATCGAGAAGAG
TCATAAATAAGGGCACGTACAC

ycl033cΔ

AAGAATCCTTGGAGGCTTCAAC
GTCCACGATCTCAAACCCTTTC

ydl227cΔ

CTCTGTTCCCTCTCATATTTAC
CTACTCCAGCATTCTAGTTAAG

yol118cΔ

ACACATACCAGGATGCTTCTTC
GCTGACTAATTTGAAGCTATCG

ydl242wΔ

TCAAGCGTTATGTCTTCGACAC
GTTTCGATATTCGACATTTGC

ykl069wΔ

TAGCGACAGAGTGGTTCAATTC
TCAATTTGGCGAACAGGGAATG

Test for recombination between GFP cassettes within two nearby loci

YDL227C upstream

TGCAGAAGCTTGTTGAAGCA

YDL227C downstream

GGATCGAATCCCTCCAAAAT

YDL242W upstream

TCTTGGAACGAGGTCTGCTT

YDL242W downstream

GTGGAGGCTGTGGTGCTTAG