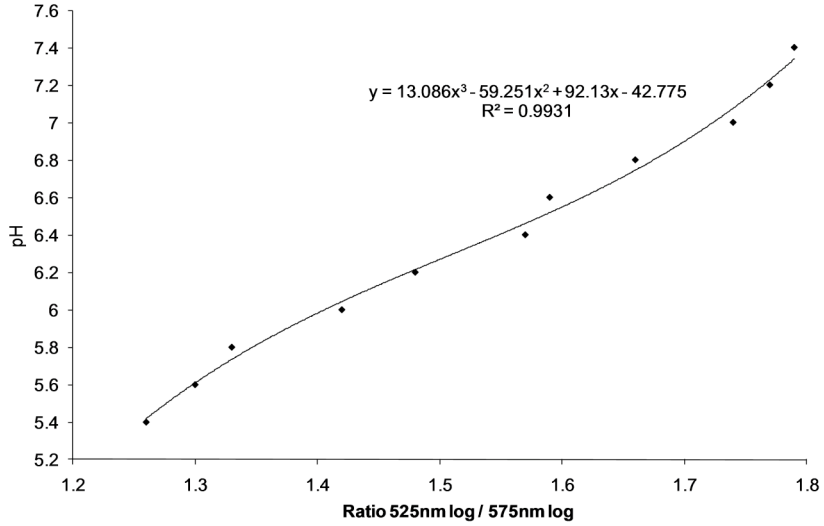

Figure S1. Sample calibration curve used to estimate absolute values of intracellular pH in yeast populations. Yeast cells were stained with CF-DA and incubated with amphotericin B in various buffers encompassing a range of pHs. Fluorescence emissions were measured with a flow cytometer.

Table S1: Functional characterizations of differentially expressed genes in strains carrying evolved alleles as compared to the progenitor strain. Analyses were performed using DAVID (13). Results with a false discovery rate (FDR) of less than 10% are presented.

***MDS3e*: Down-Regulated (91 genes)**

Gene Ontology Term	Count	%	PValue	Genes	List Total	Pop Hits	Pop Total	Fold Enrich.	FDR
Response to temperature stimulus	31	33.7	1.86E-22	YOR178C, YBR054W, YGR248W, YDR074W, YKL163W, YNL160W, YMR090W, YPR160W, YML100W, YBR117C, YLL039C, YMR250W, YMR105C, YJR096W, YMR169C, YFL030W, YAL061W, YDR406W, YIL066C, YBR072W, YBR169C, YLR258W, YLR178C, YBR214W, YGR088W, YML128C, YFL014W, YNL237W, YDR453C, YER150W, YHR087W	74	217	4882	9.42471	2.20E-19
Response to heat	24	26.1	4.56E-15	YOR178C, YDR406W, YBR054W, YKL163W, YNL160W, YIL066C, YBR169C, YLR258W, YMR090W, YPR160W, YML100W, YBR214W, YBR117C, YGR088W, YML128C, YFL014W, YNL237W, YLL039C, YMR250W, YDR453C, YER150W, YJR096W, YHR087W, YFL030W	74	203	4882	7.79976	5.37E-12
Monosaccharide metabolic process	18	19.6	6.31E-12	YOR178C, YPR184W, YMR323W, YGR043C, YGR248W, YGR256W, YGL156W, YLR258W, YPR160W, YBR117C, YER054C, YOR393W, YDL085W, YMR105C, YJR096W, YOR120W, YIL099W, YDL021W	74	136	4882	8.731717	7.45E-09
Carbohydrate catabolic process	15	16.3	1.07E-11	YPR184W, YMR323W, YGR248W, YGR043C, YGR256W, YGL156W, YPR160W, YBR117C,	74	84	4882	11.78089	1.26E-08

				YOR393W, YDL085W, YMR105C, YJR096W, YDL021W, YIL099W, YOR120W					
Alcohol catabolic process	11	11.9	2.76E-08	YBR117C, YMR323W, YOR393W, YGR043C, YGR248W, YDL085W, YGR256W, YMR105C, YJR096W, YOR120W, YDL021W	74	65	4882	11.16466	3.26E-05
Carbohydrate metabolic process	21	22.8	4.58E-08	YOR178C, YPR184W, YMR323W, YGR043C, YGR248W, YDR074W, YGR256W, YER096W, YGL156W, YLR258W, YML100W, YPR160W, YBR117C, YER054C, YOR393W, YDL085W, YMR105C, YJR096W, YOR120W, YIL099W, YDL021W	74	335	4882	4.135619	5.40E-05
Cellular carbohydrate metabolic process	20	21.7	1.67E-07	YOR178C, YPR184W, YMR323W, YGR043C, YGR248W, YDR074W, YGR256W, YGL156W, YLR258W, YML100W, YPR160W, YBR117C, YER054C, YOR393W, YDL085W, YMR105C, YJR096W, YOR120W, YIL099W, YDL021W	74	327	4882	4.035044	1.97E-04
Macromolecule catabolic process	23	25	1.62E-06	YOR173W, YPR184W, YGR248W, YDR074W, YGL156W, YLR258W, YER053C, YLR178C, YML100W, YPR160W, YBR214W, YER054C, YGR088W, YFL014W, YMR174C, YMR250W, YDR453C, YMR105C, YER150W, YMR169C, YER035W, YAL061W, YIL099W	74	496	4882	3.059231	0.001906
Cellular response to stress	24	26.1	3.53E-06	YDR406W, YBR054W, YKL163W, YNL160W, YIL066C, YBR169C, YLR258W, YMR090W, YML100W, YPR160W, YBR214W, YBR117C, YGR088W, YML128C, YFL014W, YNL237W, YLL039C, YMR250W, YDR453C, YER150W, YJR096W, YER035W, YHR087W, YFL030W	74	562	4882	2.817351	0.004165
Cellular catabolic process	25	27.2	3.95E-05	YOR173W, YGR248W, YGR043C, YDR074W, YGL156W, YML100W,	74	696	4882	2.369719	0.046559

				YPR160W, YER054C, YMR174C, YMR250W, YMR105C, YMR169C, YAL061W, YPR184W, YOR348C, YLR258W, YLR178C, YER053C, YBR214W, YLR438W, YGR088W, YFL014W, YDR453C, YER150W, YER035W					
Response to oxidative stress	7	7.6	0.001296	YKL026C, YGR088W, YFL014W, YDR453C, YMR250W, YJR096W, YOR120W	74	82	4882	5.631839	1.5186
Generation of precursor metabolites and energy	12	13	0.001671	YPR160W, YOR178C, YKL093W, YPR184W, YER054C, YMR323W, YOR393W, YDL085W, YMR105C, YLR258W, YDL021W, YIL099W	74	264	4882	2.998771	1.954101
Carbohydrate biosynthetic process	7	7.6	0.002617	YML100W, YOR178C, YPR184W, YDR074W, YMR105C, YER096W, YLR258W	74	94	4882	4.912881	3.045008
Sporulation resulting in formation of a cellular spore	10	10.9	0.005108	YOR178C, YER054C, YML128C, YDL222C, YLL039C, YNL194C, YER096W, YLR258W, YPR192W, YIL099W	74	220	4882	2.998771	5.862913
Alkaloid metabolic process	5	5.4	0.006306	YBR117C, YGR043C, YGR248W, YDL085W, YGR256W	74	50	4882	6.597297	7.192779

***MDS3e*: Up-regulated (47 genes)**

Gene Ontology Term	**Count**	**%**	**PValue**	**Genes**	**List Total**	**Pop Hits**	**Pop Total**	**Fold Enrich.**	**FDR**
Carbohydrate transport	4	8.7	0.002469	YDR345C, YMR011W, YHR092C, YHR094C	33	42	4882	14.08947	2.701808
Transmembrane transport	7	15.2	0.005094	YML123C, YDR345C, YMR011W, YHR092C, YHR094C, YBR296C, YMR319C	33	251	4882	4.1258	5.500594
Transport	16	34.8	0.006281	YNL095C, YDR345C, YOR049C, YJL012C, YBR296C, YMR319C, YPL019C, YPR194C, YAL067C, YML123C, YJR048W, YLL038C, YGR234W, YMR011W, YHR092C, YHR094C	33	1230	4882	1.924415	6.742447

***MKT1e*: Down-regulated (41 genes)**

Gene Ontology Term	Count	%	PValue	Genes	List Total	Pop Hits	Pop Total	Fold Enrich.	FDR
Peptide transport	4	10	1.54E-05	YPR194C, YKR093W, YJR152W, YJL212C	34	8	4882	71.79412	0.017518
Amine metabolic process	10	25	1.18E-04	YAL062W, YIR027C, YMR303C, YIR028W, YIR029W, YIR031C, YMR170C, YBR208C, YLR155C, YJR103W	34	301	4882	4.770373	0.134094
Heterocycle metabolic process	9	22.5	1.32E-04	YHR216W, YBR085W, YIR027C, YAR073W, YIR028W, YIR029W, YIR031C, YBR208C, YJR103W	34	237	4882	5.452718	0.150308
Amide transport	3	7.5	4.38E-04	YIR028W, YJR152W, YHL016C	34	5	4882	86.15294	0.496485
Cellular catabolic process	13	32.5	0.00128	YMR303C, YIR028W, YIR031C, YHL016C, YDL160C, YIR027C, YIR029W, YMR170C, YPR002W, YBR208C, YLR155C, YMR006C, YGL205W	34	696	4882	2.681964	1.446347
Cellular ketone metabolic process	9	22.5	0.003387	YAL062W, YMR303C, YIR031C, YMR170C, YBR208C, YPR002W, YLR155C, YGL205W, YJR103W	34	386	4882	3.347912	3.784685
Organic acid metabolic process	9	22.5	0.003728	YAL062W, YMR303C, YIR031C, YMR170C, YBR208C, YPR002W, YLR155C, YGL205W, YJR103W	34	392	4882	3.296669	4.158163

***MKT1e*: Up-regulated (182 genes)**

Term	Count	%	PValue	Genes	List Total	Pop Hits	Pop Total	Fold Enrich.	FDR
Mitochondrion organization	72	39.6	4.00E-50	YNL252C, YHR147C, YDR337W, YGR084C, YHR038W, YKR006C, YDR347W, YLR168C, YKL138C, YJL063C, YMR193W, YJR101W, YOR266W, YKL053C-A, YPL104W, YPL173W, YCR003W, YDR322W, YOR158W, YGR112W, YNL073W, YNL315C, YDR116C, YBR185C, YDL202W, YKL170W, YMR024W, YLL009C,	155	275	4882	8.246428	4.93E-47

				YGR076C, YGR165W, YBL038W, YCR071C, YHR116W, YHR024C, YLR069C, YDR175C, YNL284C, YDR405W, YGL129C, YGR062C, YJL180C, YML025C, YOR150W, YEL030W, YDR375C, YHL004W, YPR047W, YKR085C, YJR113C, YDR296W, YNL137C, YDR462W, YBR192W, YCR024C, YHR011W, YIL093C, YBL090W, YIL098C, YER058W, YJL116C, YBR146W, YPL040C, YMR158W, YJL096W, YGL143C, YNL185C, YDR237W, YPL189C-A, YLR312W-A, YHR091C, YOL023W, YMR188C					
Protein metabolic process	91	50	1.00E-09	YNL252C, YHR147C, YDR337W, YGR084C, YHR038W, YKR006C, YDR347W, YKL138C, YJL063C, YOL071W, YJL048C, YMR193W, YJR101W, YPL104W, YPR151C, YNL052W, YPL173W, YCR003W, YDR322W, YOR158W, YNL073W, YDR116C, YBR120C, YGL032C, YLR439W, YDL202W, YBR072W, YLR239C, YKL170W, YNL122C, YMR024W, YGR088W, YMR069W, YGR109W-B, YLL009C, YGL068W, YGL107C, YGR076C, YGR165W, YBL038W, YCR071C, YHR109W, YHR116W, YGL236C, YHR024C, YDR494W, YCL027W, YLR069C, YDR175C, YNL284C, YDR405W, YGL129C, YGR062C, YGL258W-A, YML025C, YOR150W, YEL030W, YHR015W, YKL087C, YLR121C, YHL004W, YPR047W, YKR085C, YJR113C, YNL137C, YDR462W, YCR024C, YHR011W, YIL093C, YIR039C, YPL097W, YNR044W, YBL090W, YER058W, YEL050C, YIL098C, YGR220C, YBR146W,	155	1699	4882	1.686996	1.24E-06

				YAL039C, YPL040C, YMR158W, YJL096W, YGL143C, YNL185C, YDR237W, YLR312W-A, YGL259W, YER150W, YHR091C, YOL023W, YMR188C					
Generation of precursor metabolites and energy	28	15.4	3.29E-08	YML120C, YIL070C, YPL252C, YLL041C, YDR175C, YKR046C, YOR065W, YPL132W, YOL071W, YJR048W, YDR375C, YNL111C, YEL024W, YNL052W, YHR011W, YGR112W, YDR116C, YBR185C, YMR145C, YMR267W, YMR118C, YJL089W, YGL068W, YGL107C, YGR165W, YOL152W, YMR188C, YHR116W	155	264	4882	3.340567	4.06E-05
Macromolecule biosynthetic process	78	42.9	1.31E-07	YNL252C, YHR147C, YDR337W, YGR084C, YHR038W, YKR006C, YDR347W, YKL138C, YJL063C, YMR193W, YJR101W, YPL104W, YNL052W, YPL173W, YCR003W, YDR322W, YOR158W, YNL073W, YDR116C, YBR120C, YGL032C, YLR439W, YDL202W, YKL170W, YMR024W, YNL122C, YGR109W-B, YGL068W, YLL009C, YGR076C, YGL107C, YGR165W, YBL038W, YCR071C, YHR116W, YGL236C, YDR494W, YCL027W, YLR069C, YDR175C, YNL284C, YDR405W, YGL129C, YGR062C, YML025C, YOR150W, YHR015W, YLR121C, YHL004W, YPR047W, YKR085C, YJR113C, YDR296W, YNL137C, YDR462W, YCR024C, YHR011W, YIL093C, YPL097W, YNR044W, YBL090W, YEL050C, YER058W, YGR220C, YBR146W, YAL039C, YHL024W, YPL040C, YJL089W, YMR158W, YJL096W, YGL143C, YNL185C, YDR237W, YLR312W-A, YHR091C, YOL023W, YMR188C	155	1473	4882	1.667854	1.62E-04

Gene expression	78	42.9	8.63E-06	YNL252C, YHR147C, YDR337W, YGR084C, YHR038W, YKR006C, YDR347W, YKL138C, YJL063C, YMR193W, YJR101W, YPL104W, YNL052W, YPL173W, YCR003W, YDR322W, YOR158W, YNL073W, YDR116C, YBR120C, YGL032C, YLR439W, YDL202W, YKL170W, YMR024W, YNL122C, YGL068W, YGR076C, YGL107C, YGR165W, YBL038W, YCR071C, YHR116W, YGL236C, YHR024C, YDR494W, YDR194C, YCL027W, YLR069C, YDR175C, YNL284C, YDR405W, YGL129C, YGR062C, YML025C, YOR150W, YHR015W, YLR121C, YHL004W, YPR047W, YKR085C, YJR113C, YDR296W, YNL137C, YDR462W, YCR024C, YHR011W, YIL093C, YPL097W, YNR044W, YBL090W, YGR150C, YEL050C, YER058W, YGR220C, YBR146W, YAL039C, YPL040C, YJL089W, YMR158W, YJL096W, YGL143C, YNL185C, YDR237W, YLR312W-A, YHR091C, YOL023W, YMR188C	155	1620	4882	1.516511	0.010635
Cellular biosynthetic process	87	47.8	1.61E-05	YNL252C, YHR147C, YDR337W, YGR084C, YHR038W, YKR006C, YDR347W, YKL138C, YMR095C, YJL063C, YDL244W, YMR193W, YJR101W, YPL104W, YNL052W, YPL173W, YCR003W, YDR322W, YOR158W, YNL073W, YDR116C, YBR120C, YGL032C, YLR439W, YDL202W, YPL172C, YLR239C, YKL170W, YMR024W, YNL122C, YGR109W-B, YLL009C, YGL068W, YGR076C, YGL107C, YDR511W, YGR165W, YBL038W, YCR071C, YHR116W, YGL236C, YDR494W, YPL252C, YJR122W,	155	1914	4882	1.431672	0.019875

				YCL027W, YLR069C, YDR175C, YNL284C, YDR405W, YGL129C, YGR062C, YML025C, YOR150W, YHR015W, YNL111C, YLR121C, YHL004W, YPR047W, YFL030W, YKR085C, YJR113C, YDR296W, YNL137C, YDR462W, YCR024C, YHR011W, YIL093C, YPL097W, YNR044W, YBL090W, YEL050C, YER058W, YGR220C, YBR146W, YAL039C, YHL024W, YPL040C, YJL089W, YMR158W, YJL096W, YGL143C, YNL185C, YDR237W, YLR312W-A, YHR091C, YOL023W, YMR188C					
Electron transport chain	11	6	4.39E-05	YOL071W, YMR118C, YML120C, YPL252C, YJR048W, YLL041C, YNL111C, YOR065W, YNL052W, YEL024W, YOL152W	155	68	4882	5.095066	0.054045

***MDS3e_MKT1e*: Down-regulated (128 genes)**

Gene Ontology Term	**Count**	**%**	**PValue**	**Genes**	**List Total**	**Pop Hits**	**Pop Total**	**Fold Enrich.**	**FDR**
Response to temperature stimulus	35	27.3	1.51E-21	YOR178C, YKL151C, YGR248W, YKL051W, YKL163W, YNL160W, YKL096W, YMR090W, YPR160W, YML100W, YBR117C, YKR091W, YBR056W, YDR001C, YLL039C, YMR250W, YIR038C, YMR105C, YMR169C, YJR096W, YAL061W, YAL062W, YCR019W, YIL066C, YBR169C, YLR258W, YLR178C, YBR214W, YGR088W, YML128C, YFL014W, YDR453C, YER150W, YHR087W, YBL078C	105	217	4882	7.499232	1.83E-18
Response to heat	30	23.4	3.51E-17	YOR178C, YKL151C, YKL051W, YKL163W, YNL160W, YKL096W, YMR090W, YPR160W, YML100W, YBR117C, YKR091W, YBR056W, YDR001C, YLL039C,	105	203	4882	6.871217	4.26E-14

				YMR250W, YIR038C, YJR096W, YAL062W, YCR019W, YIL066C, YBR169C, YLR258W, YBR214W, YGR088W, YML128C, YFL014W, YDR453C, YER150W, YHR087W, YBL078C					
Cellular catabolic process	38	29.7	3.18E-08	YOR173W, YMR303C, YGR043C, YGR248W, YLR164W, YIR031C, YHL016C, YPR160W, YML100W, YER054C, YDR001C, YMR174C, YIR029W, YMR250W, YIR038C, YMR170C, YMR105C, YMR169C, YLR155C, YAL061W, YPR184W, YEL011W, YIR028W, YOR185C, YOR348C, YLR258W, YNL202W, YLR178C, YBR214W, YLR438W, YIR027C, YGR088W, YFL014W, YDR453C, YER150W, YBR208C, YBL078C, YGL205W	105	696	4882	2.538533	3.86E-05
Cellular response to stress	32	25	2.86E-07	YKL151C, YKL051W, YKL163W, YNL160W, YKL096W, YMR090W, YPR160W, YML100W, YBR117C, YKR091W, YBR056W, YDR001C, YLL039C, YMR250W, YIR038C, YJR096W, YLR155C, YAL062W, YCR019W, YCR026C, YIL066C, YBR169C, YLR258W, YML058W-A, YBR214W, YGR088W, YML128C, YFL014W, YDR453C, YER150W, YHR087W, YBL078C	105	562	4882	2.647416	3.48E-04
Monosaccharide metabolic process	15	11.7	8.11E-07	YOR178C, YPR184W, YEL011W, YGR043C, YGR248W, YGR256W, YLR258W, YPR160W, YBR117C, YER054C, YDL085W, YMR105C, YJR096W, YDL021W, YIL099W	105	136	4882	5.128151	9.85E-04
Carbohydrate catabolic process	12	9.4	1.22E-06	YPR160W, YBR117C, YPR184W, YGR043C, YGR248W, YDR001C, YDL085W, YGR256W, YMR105C, YJR096W, YDL021W, YIL099W	105	84	4882	6.642177	0.001488
Carbohydrate metabolic	21	16.4	1.89E-05	YOR178C, YPR184W, YEL011W, YGR043C,	105	335	4882	2.914627	0.022932

process				YGR248W, YIR031C, YGR256W, YER096W, YLR258W, YPR160W, YML100W, YKL201C, YBR117C, YER054C, YDR001C, YBR056W, YDL085W, YMR105C, YJR096W, YIL099W, YDL021W					
Macromolecule catabolic process	26	20.3	2.77E-05	YOR173W, YGR248W, YML100W, YPR160W, YER054C, YDR001C, YMR174C, YIR038C, YMR250W, YMR170C, YMR105C, YLR155C, YMR169C, YAL061W, YPR184W, YEL011W, YOR185C, YLR258W, YLR178C, YBR214W, YGR088W, YFL014W, YDR453C, YER150W, YBL078C, YIL099W	105	496	4882	2.43725	0.033694
Cellular carbohydrate metabolic process	20	15.6	4.61E-05	YOR178C, YPR184W, YEL011W, YGR043C, YGR248W, YIR031C, YGR256W, YLR258W, YPR160W, YML100W, YKL201C, YBR117C, YER054C, YDR001C, YBR056W, YDL085W, YMR105C, YJR096W, YIL099W, YDL021W	105	327	4882	2.843745	0.056008
Alcohol catabolic process	8	6.3	4.10E-04	YBR117C, YGR043C, YGR248W, YDL085W, YGR256W, YMR105C, YJR096W, YDL021W	105	65	4882	5.722491	0.497505
Amine metabolic process	17	13.3	5.45E-04	YAL062W, YMR303C, YIR028W, YNL160W, YIR031C, YOR348C, YER096W, YMR090W, YLR438W, YIR027C, YIR029W, YMR250W, YMR170C, YBR208C, YLR155C, YMR169C, YJR103W	105	301	4882	2.625977	0.659894
Generation of precursor metabolites and energy	15	11.7	0.001275	YOR178C, YMR303C, YPR184W, YEL011W, YLR164W, YIR031C, YIL111W, YLR258W, YPR160W, YER054C, YDR001C, YDL085W, YMR105C, YDL021W, YIL099W	105	264	4882	2.641775	1.538854
Sporulation resulting in formation of a cellular spore	13	10.2	0.002278	YOR178C, YER096W, YKL096W, YLR258W, YNL202W, YPR192W, YER054C, YML128C, YDL222C, YDR001C,	105	220	4882	2.747446	2.732915

				YLL039C, YNL194C, YIL099W					
Alkaloid metabolic process	6	4.7	0.003944	YBR117C, YMR303C, YGR043C, YGR248W, YDL085W, YGR256W	105	50	4882	5.579429	4.688111
Amide transport	3	2.3	0.00431	YIR028W, YJR152W, YHL016C	105	5	4882	27.89714	5.113347
Cell differentiation	13	10.2	0.005487	YOR178C, YER096W, YKL096W, YLR258W, YNL202W, YPR192W, YER054C, YML128C, YDL222C, YDR001C, YLL039C, YNL194C, YIL099W	105	245	4882	2.467094	6.467174

***MDS3e_MKT1e*: Up-regulated (214 genes)**

Gene Ontology Term	**Count**	**%**	**PValue**	**Genes**	**List Total**	**Pop Hits**	**Pop Total**	**Fold Enrich.**	**FDR**
Mitochondrion organization	84	39.4	3.73E-58	YNL252C, YLR008C, YHR147C, YDR337W, YNL177C, YGR084C, YHR038W, YKR006C, YDR347W, YLR168C, YKL138C, YJL063C, YNL005C, YMR193W, YJR101W, YOR266W, YPL104W, YKL053C-A, YPL173W, YCR003W, YDR322W, YOR158W, YPL215W, YNL315C, YDR116C, YBL059C-A, YBR185C, YLR382C, YDL202W, YKL170W, YMR024W, YGR215W, YLL009C, YGR076C, YGR165W, YCR071C, YBR282W, YHR116W, YHR024C, YNR022C, YPR166C, YPR125W, YBR268W, YDR041W, YLR069C, YDR175C, YNL284C, YDR405W, YER050C, YGL129C, YJL180C, YML025C, YBR122C, YOR150W, YEL030W, YDR393W, YDR375C, YHL004W, YPR047W, YKR085C, YJR113C, YDR296W, YNL137C, YEL020W-A, YDR462W, YBR192W, YHR011W, YIL093C, YBL090W, YIL098C, YER058W, YOL033W, YBR146W, YPL040C, YMR158W, YJL096W,	185	275	4882	8.060698	4.71E-55

				YGL143C, YNL185C, YDR237W, YPL189C-A, YLR312W-A, YHR091C, YOL023W, YMR188C					
Macromolecule biosynthetic process	91	42.7	4.28E-08	YNL252C, YHR147C, YDR337W, YNL177C, YGR084C, YHR038W, YKR006C, YDR347W, YKL138C, YJL063C, YNL005C, YMR193W, YJR101W, YPL104W, YPL173W, YCR003W, YDR322W, YOR158W, YBR297W, YGR032W, YDR116C, YBR120C, YLR382C, YLR439W, YDL202W, YKL170W, YJR147W, YMR024W, YNL122C, YGR215W, YGL209W, YGR109W-B, YLL009C, YGL068W, YGR076C, YGL107C, YGR165W, YCR071C, YBR282W, YHR116W, YGL236C, YNR022C, YDR494W, YPR166C, YPL156C, YCL027W, YBR268W, YLR069C, YDR041W, YDR175C, YNL284C, YDR405W, YER050C, YGL129C, YMR319C, YML025C, YBR122C, YOR150W, YHR015W, YLR121C, YHL004W, YPR047W, YKR085C, YJR113C, YDR296W, YNL137C, YDR462W, YHR011W, YIL093C, YPL097W, YNR044W, YBL090W, YEL050C, YER058W, YGR220C, YBR296C, YBR146W, YOL033W, YAL039C, YPL040C, YMR158W, YJL096W, YGL143C, YNL185C, YDR237W, YLR312W-A, YGL125W, YHR091C, YOL023W, YMR316W, YMR188C	185	1473	4882	1.630289	5.40E-05
Protein metabolic process	100	46.9	5.79E-08	YHR147C, YDR337W, YNL177C, YGR084C, YHR038W, YDR469W, YNL005C, YMR193W, YJR101W, YPL104W, YPR151C, YPL173W, YOR158W, YCR003W, YDR322W, YLR439W, YLR382C, YDL202W, YNL122C, YJR147W, YGR215W, YGL209W,	185	1699	4882	1.553219	7.30E-05

				YGR165W, YJL046W, YCR071C, YGL236C, YPR166C, YBR268W, YDR041W, YPL072W, YDR175C, YER050C, YGL129C, YML025C, YBR122C, YOR150W, YLR121C, YJL117W, YKR085C, YDR462W, YHR011W, YNR044W, YER058W, YIL098C, YBR296C, YPL040C, YMR158W, YNL185C, YDR237W, YLR312W-A, YHR091C, YMR316W, YMR188C, YNL252C, YKR006C, YDR347W, YKL138C, YJL063C, YBR120C, YDR116C, YLR239C, YKL170W, YMR024W, YGR109W-B, YLL009C, YGL068W, YGR076C, YGL107C, YBR282W, YHR109W, YHR116W, YHR024C, YNR022C, YDR494W, YPL156C, YCL027W, YLR069C, YNL284C, YDR405W, YMR319C, YEL030W, YHR015W, YKL087C, YHL004W, YPR047W, YJR113C, YNL137C, YIL093C, YPL097W, YBL090W, YEL050C, YGR220C, YBR146W, YOL033W, YDR184C, YAL039C, YJL096W, YGL143C, YGL125W, YOL023W					
Gene expression	94	44.1	5.33E-07	YLR204W, YNL252C, YHR147C, YDR337W, YNL177C, YGR084C, YHR038W, YKR006C, YDR347W, YKL138C, YJL063C, YNL005C, YMR193W, YJR101W, YPL104W, YPL173W, YCR003W, YDR322W, YOR158W, YBR297W, YDR116C, YBR120C, YML080W, YLR382C, YLR439W, YDL202W, YKL170W, YJR147W, YNL122C, YMR024W, YGR215W, YGL209W, YGL068W, YGL107C, YGR076C, YGR165W, YCR071C, YBR282W, YHR116W, YGL236C, YHR024C, YOL080C, YNR022C, YDR494W,	185	1620	4882	1.531225	6.72E-04

				YDR194C, YPR166C, YPL156C, YCL027W, YBR268W, YLR069C, YDR041W, YDR175C, YNL284C, YDR405W, YER050C, YGL129C, YMR319C, YML025C, YBR122C, YOR150W, YHR015W, YLR121C, YHL004W, YPR047W, YKR085C, YJR113C, YDR296W, YNL137C, YDR462W, YHR011W, YIL093C, YPL097W, YNR044W, YBL090W, YGR150C, YER058W, YEL050C, YGR220C, YBR296C, YBR146W, YOL033W, YAL039C, YPL040C, YMR158W, YJL096W, YGL143C, YNL185C, YDR237W, YLR312W-A, YGL125W, YHR091C, YOL023W, YMR316W, YMR188C					
Cellular biosynthetic process	102	47.9	8.23E-06	YHR147C, YDR337W, YNL177C, YGR084C, YHR038W, YNL005C, YMR193W, YJR101W, YPL104W, YPL173W, YOR158W, YCR003W, YDR322W, YGR032W, YBR297W, YLR439W, YLR382C, YDL202W, YPL172C, YNL122C, YJR147W, YGR215W, YGL209W, YGR165W, YDR511W, YCR071C, YGL236C, YPR166C, YPL252C, YBR268W, YDR041W, YDR175C, YBR213W, YER050C, YGL129C, YML025C, YBR122C, YOR150W, YNL111C, YLR121C, YKR085C, YDR462W, YHR011W, YNR044W, YER058W, YBR296C, YPL040C, YMR158W, YNL185C, YDR237W, YLR312W-A, YHR091C, YMR316W, YMR188C, YNL252C, YKR006C, YDR347W, YKL138C, YMR095C, YJL063C, YKR071C, YDR441C, YBR120C, YDR116C, YLR239C, YKL170W, YMR024W, YGR109W-B, YLL009C, YGL068W, YGL107C, YGR076C,	185	1914	4882	1.40632	0.010377

				YBR282W, YHR116W, YNR022C, YDR494W, YPL156C, YJR122W, YCL027W, YLR069C, YNL284C, YDR405W, YMR319C, YHR015W, YHL004W, YMR062C, YPR047W, YJR113C, YDR296W, YNL137C, YIL093C, YPL097W, YBL090W, YEL050C, YGR220C, YBR146W, YOL033W, YAL039C, YJL096W, YGL143C, YGL125W, YOL023W					
Generation of precursor metabolites and energy	21	9.9	0.001999	YML120C, YNL177C, YBR238C, YIL070C, YPL252C, YHR011W, YFR033C, YDR116C, YDR175C, YBR185C, YMR256C, YMR145C, YMR267W, YJR048W, YGL068W, YGL107C, YDR375C, YGR165W, YNL111C, YHR116W, YMR188C	185	264	4882	2.09914	2.493083
Mitochondrial membrane organization	6	2.8	0.008237	YEL020W-A, YPR125W, YOR266W, YDR393W, YLR168C, YBR185C	185	34	4882	4.656916	9.908052

Table S2: List of genes whose expression is significantly affected by the epistatic interaction between *MKT1e* and *MDS3e* (FDR-corrected p-value < 0.01)**.**

Antagonistic Effect (114 genes)							
Gene ID	**p-value**	**Gene ID**	**p-value**	**Gene ID**	**p-value**	**Gene ID**	**p-value**
YML128C	5.4E-06	YEL024W	8.8E-05	YEL050C	2.1E-04	YOR205C	3.3E-04
YJR101W	5.7E-06	YBL043W	9.3E-05	YPR066W	2.2E-04	YMR090W	3.3E-04
YNL252C	6.2E-06	YOL084W	9.7E-05	YER093C-A	2.2E-04	YOL038W	3.3E-04
YDL222C	1.1E-05	YIL047C	1.0E-04	YDR453C	2.2E-04	YBR024W	3.4E-04
YDR116C	2.1E-05	YHR096C	1.0E-04	YDR034W-B	2.3E-04	YDR148C	3.4E-04
YOR120W	2.4E-05	YJL048C	1.2E-04	YCL033C	2.3E-04	YDR033W	3.5E-04
YNL137C	2.4E-05	YKR067W	1.2E-04	YBR150C	2.3E-04	YHR138C	3.5E-04
YPL172C	2.5E-05	YDL198C	1.2E-04	YBR054W	2.3E-04	YDR503C	3.5E-04
YCR020C	2.8E-05	YHR035W	1.2E-04	YDR511W	2.4E-04	YIL155C	3.5E-04
YDL202W	3.3E-05	YGR165W	1.2E-04	YBL059W	2.4E-04	YOR201C	3.6E-04
YLR439W	4.5E-05	YML030W	1.2E-04	YKR085C	2.4E-04	YLL041C	3.6E-04
YML120C	4.6E-05	YBL030C	1.2E-04	YIL089W	2.4E-04	YGL187C	3.6E-04
YEL059C-A	4.7E-05	YGR065C	1.3E-04	YKL150W	2.5E-04	YDR059C	3.8E-04
YMR056C	4.8E-05	YKR049C	1.4E-04	YGR138C	2.5E-04	YBR003W	3.8E-04
YBR044C	4.9E-05	YFL030W	1.5E-04	YIL136W	2.5E-04	YCR027C	3.9E-04
YPL040C	5.2E-05	YGR201C	1.5E-04	YMR271C	2.6E-04	YOL052C-A	3.9E-04
YGR088W	5.3E-05	YCR026C	1.6E-04	YER053C-A	2.7E-04	YGR138C	4.0E-04
YJL159W	5.5E-05	YDL183C	1.7E-04	YDR391C	2.7E-04	YGR021W	4.0E-04
YNL306W	5.7E-05	YLR289W	1.7E-04	YJL180C	2.7E-04	YNR020C	4.0E-04
YBR117C	5.8E-05	YNL160W	1.8E-04	YOR032C	2.8E-04	YKR039W	4.2E-04
YCR023C	6.1E-05	YLR069C	1.8E-04	YIL037C	2.8E-04	YDL227C	4.2E-04
YDR375C	6.9E-05	YJL070C	1.8E-04	YPL186C	2.8E-04	YOL048C	4.3E-04
YDR430C	7.0E-05	YMR293C	1.8E-04	YKL026C	2.9E-04	YHR022C	4.3E-04
YDL085W	7.1E-05	YML012W	1.8E-04	YDR115W	2.9E-04	YJR149W	4.3E-04
YJR080C	7.1E-05	YML087C	1.9E-04	YDR070C	3.1E-04		
YPL097W	7.3E-05	YNR040W	1.9E-04	YKR016W	3.1E-04		
YNL052W	7.5E-05	YGR070W	1.9E-04	YKL051W	3.2E-04		
YBL038W	7.7E-05	YHL029C	1.9E-04	YJR108W	3.2E-04		
YKL194C	8.1E-05	YCR019W	1.9E-04	YMR008C	3.2E-04		
YOR150W	8.2E-05	YNL004W	2.1E-04	YDL181W	3.3E-04		
Synergistic Effect (136 genes)							
Gene ID	**p-value**	**Gene ID**	**p-value**	**Gene ID**	**p-value**	**Gene ID**	**p-value**

YLL061W	7.8E-06	YPL086C	6E-05	YPR058W	0.000185	YHR053C	3.2E-04
YJL012C	1.0E-05	YDR322W	8E-05	YNR037C	0.000188	YDL082W	3.2E-04
YGL107C	1.1E-05	YGL232W	8E-05	YGR076C	0.000205	YMR193W	3.3E-04
YDR237W	1.1E-05	YPR035W	8E-05	YPR045C	0.000211	YNL258C	3.3E-04
YOR315W	1.2E-05	YBR294W	8E-05	YJL002C	0.000215	YMR033W	3.3E-04
YGR084C	1.2E-05	YMR024W	9E-05	YGL068W	0.000221	YIL098C	3.3E-04
YNL185C	1.2E-05	YPR047W	1E-04	YGR055W	0.000222	YER073W	3.4E-04
YBR146W	1.4E-05	YOR266W	1E-04	YER156C	0.000223	YML126C	3.4E-04
YGL129C	1.5E-05	YNR015W	1E-04	YDR390C	0.000227	YPL246C	3.4E-04
YGR234W	1.6E-05	YBL107C	1E-04	YGL253W	0.000233	YKL126W	3.5E-04
YPR002W	1.7E-05	YKL003C	1E-04	YOR323C	0.0002	YLR348C	3.5E-04
YBR093C	1.8E-05	YIL164C	1E-04	YHR132W-A	0.0002	YKL084W	3.6E-04
YMR062C	1.9E-05	YDR427W	1E-04	YBL061C	0.0003	YKL069W	3.6E-04
YGR150C	2.4E-05	YOR158W	1E-04	YGR020C	0.0003	YER081W	3.7E-04
YLR053C	2.4E-05	YGR233C	1E-04	YNL122C	0.0003	YDL007W	3.7E-04
YHR029C	3.0E-05	YNL217W	1E-04	YHR136C	0.0003	YJR113C	3.8E-04
YPR194C	3.0E-05	YIL093C	1E-04	YAR073W	0.0003	YJR075W	3.8E-04
YPL244C	3.1E-05	YDL237W	1E-04	YJL208C	0.0003	YJR064W	3.9E-04
YLR017W	3.2E-05	YKL195W	1E-04	YKL218C	0.0003	YGR148C	3.9E-04
YDR281C	3.5E-05	YGR275W	1E-04	YKR006C	0.0003	YPR118W	4.0E-04
YDR494W	3.7E-05	YBL022C	1E-04	YOR046C	0.0003	YFR030W	4.0E-04
YPL019C	3.9E-05	YMR064W	1E-04	YGL236C	0.0003	YIL009W	4.0E-04
YNR067C	3.9E-05	YLR155C	1E-04	YNR028W	0.0003	YPL208W	4.0E-04
YLR447C	4.1E-05	YJL191W	1E-04	YBR245C	0.0003	YLR239C	4.1E-04
YAR071W	4.8E-05	YIR029W	1E-04	YHR137W	0.0003	YER058W	4.2E-04
YKL087C	4.9E-05	YMR005W	1E-04	YFL031W	0.0003	YPL147W	4.2E-04
YBR296C	5.1E-05	YKL138C	2E-04	YDR345C	0.0003	YHR092C	4.3E-04
YBR263W	5.2E-05	YDR175C	2E-04	YLL018C	0.0003	YML091C	4.3E-04
YDR493W	5.3E-05	YNR022C	2E-04	YER072W	0.0003		
YHR011W	5.5E-05	YJL117W	2E-04	YDL045W-A	0.0003		
YCR071C	5.5E-05	YPL265W	2E-04	YMR011W	0.0003		
YJR048W	5.7E-05	YOR217W	2E-04	YNL213C	0.0003		
YOR184W	5.9E-05	YIR012W	2E-04	YIR031C	0.0003		
YJL217W	5.9E-05	YHR207C	2E-04	YHR128W	0.0003		
YML123C	6.0E-05	YMR039C	2E-04	YMR088C	0.0003		
YJL172W	6.4E-05	YMR318C	2E-04	YDR347W	0.0003		