



## Deciphering cellular functions of protein phosphatases by comparison of gene expression profiles in *Saccharomyces cerevisiae*

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**Expression profiles of protein phosphatase (PPase) disruptants were analyzed by use of Pearson's correlation coefficient to find profiles that correlated with those of 316 Reference Gene (RG) disruptants harboring deletions in genes with known functions. Twenty-six  $\Delta ppase$  disruptants exhibited either a positive or negative correlation with 94 RG disruptants when the  $p$  value for Pearson's correlation coefficient was  $>0.2$ . Some of the predictions that arose from this analysis were tested experimentally and several new  $\Delta ppase$  phenotypes were found. Notably,  $\Delta sit4$  and  $\Delta siw14$  disruptants exhibited hygromycin B sensitivity,  $\Delta sit4$  and  $\Delta ptc1$  disruptants grew slowly on glycerol medium, the  $\Delta ptc1$  disruptant was found to be sensitive to calcofluor white and congo red, while the  $\Delta ppg1$  disruptant was found to be sensitive to congo red. Because on-going analysis of expression profiles of *Saccharomyces cerevisiae* disruptants is rapidly generating new data, we suggest that the approach used in the present study to explore PPase function is also applicable to other genes.**

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[**Key words:** *Saccharomyces cerevisiae*; Protein phosphatase; Expression profile; Pearson's correlation; Phenotypic analysis; Hygromycin B; Congo red; Calcofluor white]

Reversible modification of proteins by covalent phosphorylation is a key regulatory mechanism for controlling diverse cellular processes including responses to extracellular stimuli, gene expression, and cell growth and division (1). In this form of regulation, a protein kinase (PKase) catalyzes the phosphorylation of a protein substrate, while a protein phosphatase (PPase) catalyses the dephosphorylation of the phosphorylated protein.

In eukaryotes, PPases are classified into three families (PPP, PPM and PTP) based on the structure of their catalytic domains (1). The PPP family includes the serine/threonine PPases, PP1, PP2A and PP2B subfamilies and a number of other PPases, such as the newly identified human PPases, PP4 and PP5 (1). The PPM family comprises Mg<sup>2+</sup>-stimulated PPases including PP2C, which also dephosphorylate phosphoserine and phosphothreonine residues (1). The PTP family includes protein tyrosine phosphatases (PTPases) that dephosphorylate phosphotyrosine residues of proteins and dual-specificity

phosphatases (DSPs) that can dephosphorylate phospho-serine, -threonine and -tyrosine residues in proteins (1).

When the nucleotide sequence of the entire *Saccharomyces cerevisiae* genome was determined in 1996, it predicted 117 PKase and 32 PPase genes among approximately 6000 genes (*Saccharomyces* Genome Database; SGD; <http://www.yeastgenome.org/>) (2). In an effort to identify the involvement of each PPase in various biological processes and to understand their roles in yeast physiology, we systematically constructed  $\Delta ppase$  disruptants, with the exception of the essential PPase genes, and undertook subsequent phenotypic analysis (2, 3). This led to the discovery of several new phenotypes. The  $\Delta yvh1$  disruptant was found to be cold sensitive for growth at 13 °C, the  $\Delta siw14$  disruptant was found to be sensitive to caffeine and the  $\Delta mpr150$  disruptant exhibited temperature-sensitive growth at 37 °C. Although the functions of most PPases are slowly becoming better understood, a more comprehensive functional analysis of all the PPases requires other genome-wide approaches.

In the present study, we attempted to determine cellular functions for the PPases by correlating expression profiles of all viable  $\Delta ppase$  disruptants with profiles for 316 Reference Gene (RG) disruptants missing genes with known functions. The analysis revealed that the expression profiles of some PPase disruptants exhibited significant similarity to those of some of the RG disruptants. Based on this similarity, we tested and confirmed new phenotypes for this subset of  $\Delta ppase$  disruptants.

Abbreviations: RG, Reference Gene; PPase, protein phosphatase; PKase, protein kinase; MAP, mitogen-activated protein; PCR, polymerase chain reaction; Cg, *Candida glabrata*.

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TABLE 1. List of reference disruptant (RD) strains.

Systematic name	Standard name	Systematic name	Standard name	Systematic name	Standard name	Systematic name	Standard name
YAL004w	–	YNL186w	DOT4	YDR034c	LYS14	YER019c-A	SBH2
YBL054w	–	YER088c	DOT6	YMR021c	MAC1	YHL034c	SBP1
YEL008w	–	YHR208w	ECA39	YJL030w	MAD2	YMR272c	SCS7
YEL020c	–	YAL059w	ECM1	YEL053c	MAK10	YMR305c	SCW10
YEL033w	–	YEL030w	ECM10	YDL056w	MBP1	YGR279c	SCW4
YER130c	–	YDR125c	ECM18	YKL093w	MBR1	YIL084c	SDS3
YFL052w	–	YLR228c	ECM22	YDL005c	MED2	YOR140w	SFL1
YLL054c	–	YHL030w	ECM29	YGL209w	MIG2	YMR190c	SGS1
YML081w	–	YBR176w	ECM31	YER028c	MIG3	YOR007c	SGT2
YMR269w	–	YHL043w	ECM34	YER001w	MNN1	YOR035c	SHE4
YMR293c	–	YDR385w	EFT2	YMR286w	MRPL33	YOL004w	SIN3
YNR063w	–	YPL037c	EGD1	YPR125w	MRS7	YGL208w	SIP2
YML003w	–	YHR193c	EGD2	YKL009w	MRT4	YKR101w	SIR1
YPR196w	–	YDR414c	ERD1	YHR039c	MSC7	YDL042c	SIR2
YEL001c	–	YMR202w	ERG28	YMR287c	MSU1	YLR442c	SIR3
YMR141c	–	YER044c	ERG28	YMR145c	NDE1	YDR227w	SIR4
YLR131c	ACE2	YLR056w	ERG3	YMR285c	NGL2	YGL213c	SKI8
YBL015w	ACH1	YGL012w	ERG4	YER002w	NOP16	YHR206w	SKN7
YAR015w	ADE1	YMR015c	ERG5	YEL062w	NPR2	YBR182c	SMP1
YLR028c	ADE16	YML008c	ERG6	YER072w	NRF1	YJR104c	SOD1
YOR128c	ADE2	YAL007c	ERP2	YDR043c	NRG1	YEL031w	SPF1
YDR216w	ADR1	YOR016c	ERP4	YJR062c	NTA1	YNL204c	SPS18
YMR282c	AEP2	YJR017c	ESS1	YHL020c	OP11	YKL020c	SPT23
YER017c	AFG3	YJL157c	FAR1	YAR044w	OSH1	YLR055c	SPT8
YER073w	ALD5	YMR029c	FAR8	YOR085w	OST3	YML034w	SRC1
YEL036c	ANP1	YER032w	FIR1	YER007w	PAC2	YBR112c	SSN6
YLL052c	AQY2	YLR342w	FKS1	YEL049w	PAU2	YLR452c	SST2
YHR013c	ARD1	YNL135c	FPR1	YDR440w	PCH1	YNL309w	STB1
YCR048w, YNR019w	ARE1, ARE2	YEL047c	FRDS1	YER059w	PCL6	YDR169c	STB3
YER069w	ARG5,6	YLL051c	FRE6	YLR266c	PDR8	YMR019w	STB4
YMR042w	ARG80	YMR232w	FUS2	YOR036w	PEP12	YKL072w	STB6
YML099c	ARG81	YBL016w	FUS3	YMR257c	PET111	YOR047c	STD1
YOR058c	ASE1	YGL254w	FZF1	YER058w	PET117	YLR362w	STE11
YJL170c	ASG7	YPL248c	GAL4	YOR017w	PET127	YHR084w	STE12
YKL185w	ASH1	YML051w	GAL80	YCR020c	PET18	YJR086w	STE18
YGL017w	ATE1	YER027c	GAL83	YMR026c	PEX12	YFL026w	STE2
YIL015w	BAR1	YMR307w	GAS1	YEL003w	PFD2	YJR117w	STE24
YPL161c	BEM4	YLR013w	GAT3	YKL043w	PHD1	YOR212w	STE4
YGR282c	BGL2	YEL009c	GCN4	YOR363c	PIP2	YDR103w	STE5
YER016w	BIM1	YDL226c	GCS1	YLR014c	PPR1	YDL159w	STE7
YNL271c	BNI1	YMR255w	GFD1	YEL060c	PRB1	YDR310c	SUM1
YBL085w	BOI1	YER040w	GLN3	YIL037c	PRM2	YAR003w	SWD1
YDR252w	BTT1	YER020w	GPA2	YPR191w	QCR2	YDR146c	SWI5
YGR188c	BUB1	YOR070c	GYP1	YKL113c	RAD27	YLR182w	SWI6
YMR055c	BUB2	YJL110c	GZF3	YDR004w	RAD57	YDR334w	SWR1
YOR026w	BUB3	YFL031w	HAC1	YGL058w	RAD6	YOR337w	TEA1
YAR014c	BUD14	YGL237c	HAP2	YOR101w	RAS1	YBR083w	TEC1
YOR078w	BUD21	YBL021w	HAP3	YNL098c	RAS2	YJR019c	TES1
YMR014w	BUD22	YEL056w	HAT2	YLR248w	RCK2	YBR240c	THI2
YJR092w	BUD4	YNL021w	HDA1	YMR182c	RGM1	YOL055c	THI20
YLR319c	BUD6	YMR284w	HDF1	YKL038w	RGT1	YOR009w	TIR4
YLR353w	BUD8	YOR237w	HES1	YLR039c	RIC1	YOR045w	TOM6
YGR041w	BUD9	YOR038c	HIR2	YEL024w	RIP1	YOL006c	TOP1
YMR275c	BUL1	YER055c	HIS1	YPL089c	RLM1	YLR234w	TOP3
YDR423c	CAD1	YML075c	HMG1	YER083c	RMD7	YJL164c	TPK1
YMR280c	CAT8	YJR147w	HMS2	YGR044c	RME1	YMR039c	TSP1
YHL038c	CBP2	YLR113w	HOG1	YDR257c	RMS1	YML124c	TUB3
YER061c	CEM1	YPR193c	HPA2	YMR234w	RNH1	YCR084c	TUP1
YOR028c	CIN5	YEL066w	HPA3	YER070w	RNR1	YMR223w	UBP8
YOR061w	CKA2	YDR399w	HPT1	YNL330c	RPD3	YGR184c	UBR1
YOR039w	CKB2	YPL015c	HST2	YEL054c	RPL12A	YLR024c	UBR2
YNL298w	CLA4	YOR025w	HST3	YMR242c	RPL20A	YPL139c	UME1
YPR119w	CLB2	YBL003c	HTA2	YHR010w	RPL27A	YDR207c	UME6
YGR109c	CLB6	YBL002w	HTB2	YER056c-A	RPL34A	YEL038w	UTR4
YOL016c	CMK2	YEL044w	IES6	YLR448w	RPL6B	YEL013w	VAC8
YKL190w	CNB1	YMR035w	IMP2	YHL033c	RPL8A	YEL051w	VMA8
YLR216c	CPR6	YDR123c	INO2	YER074w	RPS24A	YOR089c	VPS21
YMR025w	CSI1	YOL108c	INO4	YHR021c	RPS27B	YAL002w	VPS8
YMR264w	CUE1	YMR044w	IOC4	YHR031c	RRM3	YML076c	WAR1
YEL027w	CUP5	YBR245c	ISW1	YOR001w	RRP6	YOR043w	WHI2
YPL177w	CUP9	YBR245c, YOR304w	ISW1, ISW2	YGR056w	RSC1	YAL051w	YAF1
YKL096w	CWP1	YOR304w	ISW2	YMR030w	RSF1	YML007w	YAP1
YOR037w	CYC2	YMR294w	JNM1	YER050c	RSM18	YHL009c	YAP3
YOR065w	CYT1	YHR038w	KIM4	YOL067w	RTG1	YOL028c	YAP7
YNL314w	DAL82	YAR018c	KIN3	YOR014w	RTS1	YER024w	YAT2

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