

The primary manuscript provides a general outline of phenotypic conservation between *Saccharomyces cerevisiae* and *Candida albicans* transcriptional regulator orthologs. Below, we provide a listing of the specific phenotypes being compared, including an indication of the phenotype source (i.e. Data Sets S2 and S3 from this study as well as references from the existing literature). The data are split into two tables. Table 1 describes orthologs with a 1-to-1 relationship, and Table 2 describes orthologs with a 1-to-2 relationship that arose from the *S. cerevisiae* whole genome duplication.

Table 1. Phenotype conservation between *S. cerevisiae* and *C. albicans* transcriptional regulators with 1-to-1 orthology.

<i>S. cerevisiae</i> Gene	<i>C. albicans</i> Gene	Shared Phenotypes	Dissimilar Phenotypes	Comments
<i>Dissimilar Orthologs</i>				
<i>GAL4</i> [†]	<i>GAL4</i>		<i>Sc</i> : Galactose as C-source[1,2]*	
<i>ISW2</i>	<i>ISW2</i>		<i>Ca</i> : Fluconazole sensitivity ^{§*}	
<i>MBP1</i>	<i>ORF19.5855</i>		<i>Sc</i> : Base media growth impairment; Caffeine and Rapamycin resistant [3] ^{§*}	
<i>STB5</i>	<i>ORF19.3308</i>		<i>Sc</i> : Base media growth impairment and Caffeine sensitivity[4,5] ^{§*}	
<i>RTG1</i> [†]	<i>ORF19.4722</i>		<i>Sc</i> : Glutamate and Aspartate auxotrophy and Acetate as C-source[6], base SC medium growth impairment (lacks Glutamate and Aspartate) [§]	Orthology may be more complex than 1-to-1.
<i>Mixed Similarity Orthologs</i>				
<i>DPB4</i>	<i>ORF19.2088</i>	Base media growth impairment in liquid[3]* medium	<i>Ca</i> : Base media growth impairment on solid medium ^{§*}	
<i>ARG81</i>	<i>ORF19.4766</i>	Ornithine as N-source[7]*	<i>Ca</i> : Strong caffeine sensitivity ^{§*} ; <i>Sc</i> : Very weak caffeine sensitivity	
<i>BAS1</i>	<i>BAS1</i>	Adenine auxotrophy[8]*	<i>Sc</i> : YEPD growth impairment[3] ^{§*}	
<i>GLN3</i> [‡]	<i>GLN3</i>	Caffeine and Rapamycin resistance and Base SD medium growth impairment[9] ^{§*}	<i>Sc</i> : Base YEPD medium growth impairment[3] ^{§*}	
<i>HAP2</i> [†]	<i>ORF19.1228</i>	Non-glucose carbon source utilization[10]*	<i>Ca</i> : BPS sensitivity ^{§*}	
<i>TUP1</i>	<i>TUP1</i>	Flocculation[11,12]*	<i>Ca</i> : Fluconazole and Caffeine sensitivity; <i>Sc</i> : YEPD growth impairment[3] ^{§*}	Extensively characterized in both species and highly pleiotropic.
<i>ZAP1</i> [†]	<i>CSR1</i>	EDTA sensitivity[13] ^{§*}	<i>Sc</i> : Base media growth impairment[3] ^{§*}	
<i>HAP5</i> [†]	<i>HAP5</i>	Non-glucose carbon source utilization[10]*	<i>Ca</i> : BPS sensitivity ^{§*}	
<i>Similar Orthologs</i>				
<i>ARO80</i> [○]	<i>ARO80</i>	Isoleucine as N-source[14]*		<i>S. cerevisiae</i> phenotype is inferred based on expression profiling data.
<i>CYC8</i>	<i>SSN6</i>	Base media growth impairment[3] ^{§*} , etc.		Extensively characterized in both species and highly pleiotropic.

<i>S. cerevisiae</i> Gene	<i>C. albicans</i> Gene	Shared Phenotypes	Dissimilar Phenotypes	Comments
<i>DAL81</i> ^Ω	<i>ORF19.3252</i>	Base media growth impairment[5] ^{§*}		
<i>GAT1</i> [‡]	<i>GAT1</i>	Caffeine and Rapamycin resistance[9,15] ^{§*}		
<i>HCM1</i>	<i>HCM1</i>	Base media growth impairment[3] ^{§*}		Growth impairment is more severe in <i>C. albicans</i> mutant.
<i>MAC1</i>	<i>MAC1</i>	Metal homeostasis[16,17] ^{§*}		
<i>PHO2</i> [†]	<i>ORF19.4000</i>	Leaky adenine auxotrophy[18] ^{§*}		
<i>PHO4</i> [†]	<i>ORF19.1253</i>	Low phosphate sensitivity* [§]		
<i>RDS2</i>	<i>CWT1</i>	Calcofluor White sensitivity[4,19]		
<i>RGT1</i> [†]	<i>RGT1</i>	Glucose transport [20,21]		Function primarily inferred from regulatory data, not from phenotype.
<i>RIM101</i> [‡]	<i>RIM101</i>	Sensitivity to alkaline pH[22,23]*		Highly pleiotropic. Too many phenotypes to fully catalog.
<i>UPC2</i> [‡]	<i>UPC2</i>	Impaired anaerobic growth and sensitivity to Fluconazole[24-26] ^{§*}		Orthology may be more complex than 1-to-1 (not included in manuscript table).
<i>UGA3</i> [‡]	<i>ORF19.7570</i>	GABA as N-source[27]*		Orthology appears to be more complex than 1-to-1 (not included in manuscript table).
<i>SFL1</i> [‡]	<i>SFL1</i>	Invasive growth, flocculation, metal homeostasis[28-31] ^{§*}		Orthology appears to be more complex than 1-to-1 (not included in manuscript table).

[†] These genes are classified as orthologs using SYNERGY but are classified as “Best Hits” in CGD.

[‡] These genes are classified as orthologs in CGD but lacked a clear ortholog using SYNERGY.

[‡] Hand-annotated orthology

* *C. albicans* phenotype assayed in this study

[§] *S. cerevisiae* phenotype assayed in this study

^Ω *C. albicans* knockout isolates were not fully independent.

Table 2. Phenotype conservation between *S. cerevisiae* and *C. albicans* transcriptional regulators with 1-to-2 orthology.

<i>S. cerevisiae</i> WGD Genes	<i>C. albicans</i> Gene	Shared Phenotypes	Dissimilar Phenotypes	Comments
<i>Dissimilar Orthologs</i>				
<i>YML081W + RSF2</i>	<i>ORF19.5026</i>		<i>scYML081W</i> : Impaired growth on base media* [§]	The mutant phenotype of <i>scYML081W</i> was not reported in other high-throughput studies. (We verified that the strain was a valid knockout using primers, but it is possible that the phenotype results from extraneous mutations.)
<i>MET31 + MET32</i>	<i>ORF19.1757</i>		<i>scMET31+scMET32</i> : Methionine auxotrophy[32]*	Methionine auxotrophy is only seen in the double knockout.
<i>RLM1 + SMP1</i>	<i>RLM1</i>		<i>scRLM1</i> : Caffeine and Rapamycin sensitivity* [§] and Calcofluor White resistance[33]; <i>caRLM1</i> : Calcofluor White sensitivity*	No <i>scSMP1</i> deletion mutant was available to assay phenotypes.
<i>Mixed Similarity Orthologs</i>				
<i>CAD1 + YAP1</i>	<i>CAP1</i>	<i>scCAD1 + caYAP1</i> : Oxidative stress sensitivity[34,35]*	<i>scYAP1</i> : Fenpropimorph sensitivity* [§]	
<i>Similar Orthologs</i>				
<i>ACE2 + SWI5</i> [‡]	<i>ACE2</i>	<i>scACE2 + caACE2</i> : Cell separation defect[36,37]* [§]		The <i>scSWI5</i> regulator regulates homothallic switching[36].
<i>ACA1 + CST6</i>	<i>ORF19.6102</i>	<i>scCST6 + caORF19.6102</i> : Impaired growth on base media[3]* [§]		
<i>CUP2 + HAA1</i>	<i>CUP2</i>	<i>scCUP2 + caCUP2</i> : Copper sensitivity* [§]		
<i>SKN7 + HMS2</i>	<i>SKN7</i>	<i>scSKN7 + caSKN7</i> : H ₂ O ₂ sensitivity[31,38]*		

[‡] *scACE2* was identified as the ortholog of *caACE2* in CGD, but the WGD gene *scSWI5* was missed (both were missed by SYNERGY)

[†] These genes are classified as orthologs using SYNERGY but are classified as “Best Hits” in CGD.

[‡] These genes are classified as orthologs in CGD but lacked a clear ortholog using SYNERGY

**C. albicans* phenotype assayed in this study

[§] *S. cerevisiae* phenotype assayed in this study

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