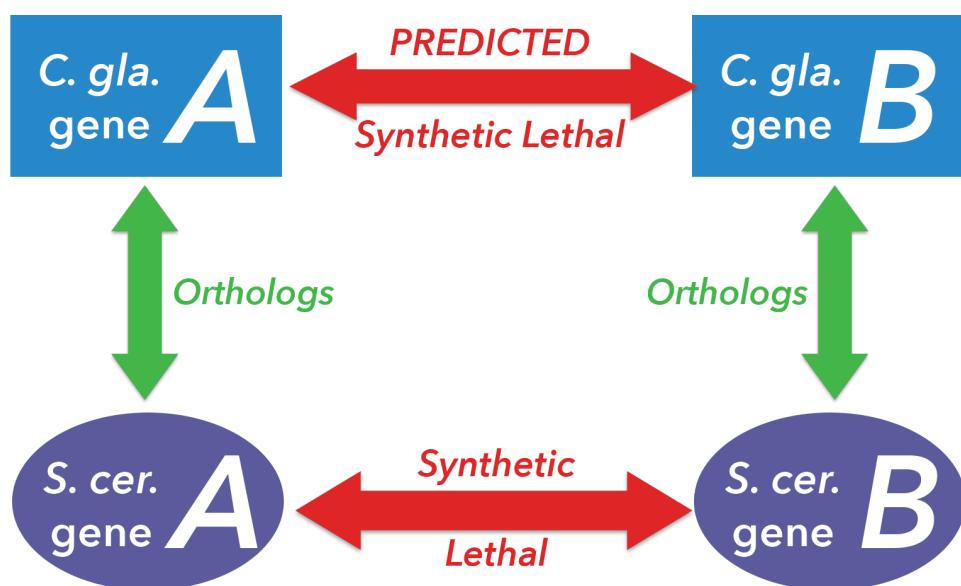


Using *S. cerevisiae* Orthologs of *Candida glabrata* Genes to Predict Fungal Pathogen Biology

Antifungal agents such as azoles are used to treat infections with *Candida* species. Unfortunately, the opportunistic fungal pathogen *C. glabrata* possesses a relatively high intrinsic resistance to azoles, and also becomes resistant toazole treatment quickly.

Mitochondrial dysfunction and loss of the mitochondrial genome have been proposed as mechanisms by which *C. glabrata* acquires azole resistance. To exploit the loss of mitochondrial function in resistant *C. glabrata* isolates, researchers may be able to target proteins or pathways that become essential only when the mitochondrial genome is absent. This is based on the idea of synthetic lethality—a type of genetic interaction where the loss of two or more nonessential genes in combination results in cell inviability.

Genetic interactions such as synthetic lethality are richly documented for the budding yeast *S. cerevisiae*, but not as much for many other fungal species. By examining known genetic interactions in *S. cerevisiae*, we can predict synthetic lethal relationships in *C. glabrata* and other fungal pathogens.



If conserved, these synthetic lethal interactions may reveal future antifungal targets for use against azole-resistant strains in the clinic. Using known synthetic lethal interactions in the *S. cerevisiae* genome allows prediction of potentially conserved synthetic lethal interactions for mitochondrial genes in *C. glabrata*.

1. Obtain a list of all genes encoded in the mitochondrial genome of *C. glabrata*:

- On the CGD homepage (<http://www.candidagenome.org>), open the Search tab in the yellow toolbar and select Advanced Search.

Candida Genome Database

Home Search GBrowse JBrowse Sequence GO Tools Literature Download Community

BLAST
GO Term Finder
GO Slim Mapper
Text Search
Primers
PatMatch
Advanced Search

GFP-labeled Dam1 Complex proteins in DAPI-stained nuclei
Courtesy of Laura Burack and Judy Berman, University of Minnesota

New and Noteworthy

C. lusitaniae strain CBS 6936 sequence and BLAST datasets now available at CGD

The sequence and annotation of *C. lusitaniae* strain CBS 6936, described in Durrens et al. (2017), has been made available at CGD. We provide downloads for sequences, chromosomal features, gff files and protein domain predictions. In addition, *C. lusitaniae* CBS 6936 is included among the datasets searchable by our multi-species BLAST tool. The sequence and annotation were obtained by CGD from NCBI.
(Posted February 27, 2018)

About CGD

CGD Curation News

- In Step 1 of the Advanced Search, select **Candida glabrata CBS138** as your strain.
- In Step 2, check the “**Select all chromosomal features**” checkbox.
- In Step 3, specify that that you are looking for mitochondrial genes by selecting “**mito_C_glabrata_CBS138**” as the chromosome.

Advanced Search:	
Step 1: Select strain (REQUIRED) • Select a strain to limit search results Candida glabrata CBS138  	
Step 2: Select chromosomal feature (REQUIRED) • Select one or more feature types <input type="checkbox"/> ORF <input type="checkbox"/> repeat_region <input type="checkbox"/> autocatalytically_spliced_intron <input type="checkbox"/> retrotransposon <input type="checkbox"/> blocked_reading_frame <input type="checkbox"/> snRNA <input type="checkbox"/> centromere <input type="checkbox"/> snoRNA <input type="checkbox"/> long_terminal_repeat <input type="checkbox"/> tRNA <input type="checkbox"/> multigene_locus <input type="checkbox"/> telomeric_repeat <input type="checkbox"/> ncRNA <input type="checkbox"/> not_in_systematic_sequence <input type="checkbox"/> pseudogene <input type="checkbox"/> rRNA <input checked="" type="checkbox"/> Select all chromosomal features 	
Step 3: Narrow results (OPTIONAL) • Select search criteria to return specific types of genes. Results will match all selected criteria. • Select search criteria by clicking on a checkbox, filling in a dialog box, or selecting a menu option. • Select or unselect multiple options for Chromosomes and GO terms by pressing the Control (PC) or Command (Mac) key while clicking. Annotation/sequence properties: Is a feature that is AND <input type="checkbox"/> Alternatively_spliced <input type="checkbox"/> Dubious <input type="checkbox"/> Uncharacterized <input type="checkbox"/> Verified <input type="checkbox"/> not_physically_mapped <input type="checkbox"/> transposable_element_gene <input type="checkbox"/> Merged/Split <input type="checkbox"/> Deleted <input type="checkbox"/> Deleted_from_Assembly_20 <input type="checkbox"/> Deleted_from_Assembly_21 The default search excludes Deleted features. Has introns (excluding UTR introns) <input type="checkbox"/> Yes <input type="checkbox"/> No AND Is on the following chromosome or contig sequence(s): AND (The "All" option includes unmapped features; to specifically exclude unmapped features, select each of the chromosomes of interest rather than "All") ChrJ_C_glabrata_CBS138 ChrK_C_glabrata_CBS138 ChrL_C_glabrata_CBS138 ChrM_C_glabrata_CBS138 mito_C_glabrata_CBS138 	

- Click on “Search”. A results page will follow, listing out 37 features in the *C. glabrata* mitochondrial genome.
- Scroll to the bottom of the page and click on the “**Download All Search Results**” link.

CaglfMt30	tRNA: Uncharacterized	tL(UAA)4mt	Mitochondrial leucine tRNA, has UAA anticodon	mito_C_glabrata_CBS138:17616 to 17697 GBrowse	Relative Coordinates	Chromosomal Coordinates
				Noncoding_exon 1 to 82	17,616 to 17,697	
Sort by : Systematic Name <input style="float: right;" type="button" value="Go!"/>						
Analyze gene list: further analyze the gene list displayed above or download information for this list						
Further Analysis:	GO Term Finder Find common features of genes in list	GO Slim Mapper Sort genes in list into broad categories	View GO Annotation Summary View all GO terms used to describe genes in list			
Download:	Download All Search Results Download all the data retrieved by this query	Batch Download Download selected information for entire gene list. Available information types include Sequence, Coordinates, GO annotations, Phenotype.				
Result Page : 1 2 Next						

2. Use FungiDB to find *S. cerevisiae* orthologs of *C. glabrata* mitochondrial genes:

- Open the FungiDB homepage (<http://fungidb.org/>). In the “Search for Genes” box, open the “Annotation, curation and identifiers” section and click on “List of ID(s)”.



The screenshot shows the FungiDB homepage with a dark header bar. The header includes the FungiDB logo, release information (Release 62, 9 Mar 2023), a site search bar, and links for My Strategies, Searches, Tools, My Workspace, Data, About, Help, Contact Us, and a user account icon labeled "My Organism".

The main content area is divided into two columns. The left column, titled "Search for...", contains a sidebar with expand/collapse buttons and a filter dropdown. It lists categories under "Genes": Annotation, curation & identifiers (with "List of IDs" highlighted by an orange arrow), Epigenomics, Function prediction, Gene models, Genetic variation, Genomic Location, Immunology, Orthology and synteny, Pathways and interactions, Phenotype, Protein features and properties, Protein targeting and localization, Proteomics, Sequence analysis, and Structure analysis. The right column, titled "Overview of Resources and Tools", features a "Getting Started" section with links to Take a Tour, Getting Started (which is currently active), Search Strategies, Genome Browser, Transcriptomic Resources, Phenotypic Data, Analyze My Data, Downloads, and Help. Below this is a "SITE SEARCH" section with a screenshot of the search results page.

- Using your exported file from CGD, copy and paste the ORF names of the *C. glabrata* mitochondrial genes into the box. Click on “Get Answer”.

Gene ID input set

Enter a list of IDs or text:

Upload a text file: No file chosen
Maximum size 10MB. The file should contain the list of

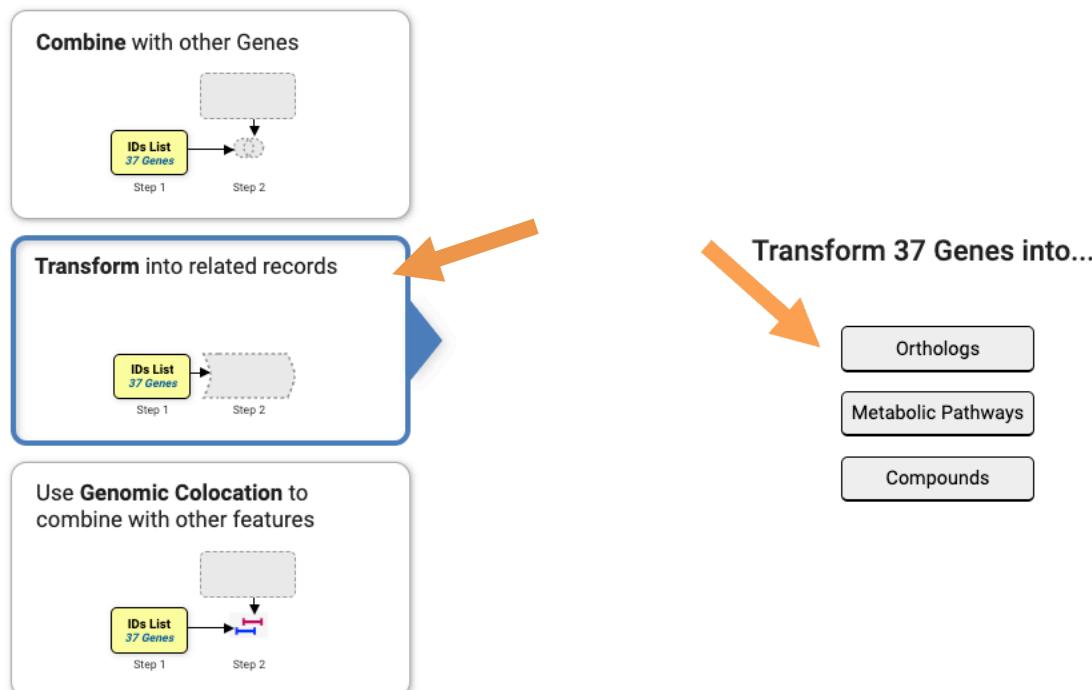
Upload from a URL:

The URL should resolve to a list of IDs

- In the Search Strategy panel, click on the “Add Step” button. In the resulting pop-up window, click on “Transform into related records” and then on the right select “Orthologs.”



Add a step to your search strategy [?](#)



- In the “Organism” list, type in “cerevisiae” to search and then select “Saccharomyces cerevisiae S288C”, and then hit “Run Step”.
- 12 orthologs in *S. cerevisiae* will be returned. Download this list by clicking on the “Download” link on the top right side of the table.

Gene Results								Genome View	Analyze Results			
Advanced Paging												
Gene	ID	Transcript	Organism	Genomic Location (Gene)	Product Description	Input Ortholog(s)	Ortholog Group	Paralog count	Ortholog count	Download	Add to Basket	Add Columns
Q0130	Q0130-t26_1	S. cerevisiae S288c	KP263414:46,723..46,953(+)	F0 ATP synthase subunit c	CaglMp10	OG5_126818		0	78	Download	Add to Basket	Add Columns
Q0045	Q0045-t26_1	S. cerevisiae S288c	KP263414:13,818..26,701(+)	cytochrome c oxidase subunit 1	CaglMp04, CaglMp07	OG5_128358		1	43	Download	Add to Basket	Add Columns
Q0070	Q0070-t26_1	S. cerevisiae S288c	KP263414:13,818..23,167(+)	intron-encoded DNA endonuclease aif5 alpha	CaglMp04, CaglMp07	OG5_128358		1	43	Download	Add to Basket	Add Columns
Q0105	Q0105-t26_1	S. cerevisiae S288c	KP263414:36,540..43,647(+)	cytochrome b	CaglMp03	OG5_128504		1	31	Download	Add to Basket	Add Columns
Q0120	Q0120-t26_1	S. cerevisiae S288c	KP263414:36,540..42,251(+)	intron-encoded RNA maturase bl4	CaglMp03	OG5_128504		1	31	Download	Add to Basket	Add Columns

- In the download options menu, select “**Tab- or comma-delimited (openable in Excel) – choose a pre-configured table**”. Set the Download Type as **Tab-delimited (.txt) file**, then hit **Get**. Open the text file, copy and paste all the data into an Excel sheet and go to Data/Text-to-column. Using the tool, select your delimiter as “tab” and hit finish. Now you will have a first column of gene IDs for pasting into YeastMine.

3. Import the *S. cerevisiae* orthologs into YeastMine:

- Open the YeastMine homepage. You can access YeastMine from SGD by opening the Analyze tab and selecting **Gene Lists**, clicking the YeastMine link in the upper right corner of the homepage, or by entering in the URL:<https://yeastmine.yeastgenome.org>

- Open the file of *S. cerevisiae* orthologs that you downloaded earlier. To import these orthologs into YeastMine, copy and paste all entries in the **Gene ID** column of the text file into the “**Analyse**” box. Then, click on the purple “**ANALYSE**” button.

- A disambiguation page will be shown confirming your matches. 12 results should be shown. Name your gene list something descriptive, such as: “**List 1: S. cerevisiae orthologs**”. Click on the green “**Save a list of Genes**” button.

4. In YeastMine, find all synthetic lethal interactions for the *S. cerevisiae* orthologs by using the Gene → Interaction query:

- Return to the YeastMine homepage: <https://yeastmine.yeastgenome.org>
- In the “popular templates” toolbar in the middle of the page, open the **INTERACTIONS** tab and select the query **Gene → Genetic Interactions**.

[Read more](#)

Query for interactions:

- Gene → Complex + Details
- Gene → Genetic Interactions
- Gene → Physical Interactions
- Literature → Interaction
- Complex → Details + Participants

[» More queries](#)

popular templates

- Check the “**constrain to be IN**” checkbox. This allows you to input a list of genes. From the dropdown menu, select the list of *S. cerevisiae* orthologs you saved earlier in part 3. Click on the green **Show Results** button.

Gene → Interaction
Retrieve all interactions for a specified gene.

Gene

LOOKUP: act1

constrain to be IN saved Gene list List 1: S. cerevisiae orthologs

Show Results **Edit Query**

[web service URL](#) [Perl | Python | Ruby | Java \[help\]](#) [export XML](#)



- The results table contains all genetic interactions for the list of *S. cerevisiae* orthologs you inputted. To filter for only **synthetic lethal** interactions, find the **Interaction Detection Methods Identifier** column. At the top of this column is a set of small blue icons. Click on the rightmost **View Column Summary** icon, which looks like a bar graph.

Trail: Query
Gene → Genetic Interactions
Retrieve all genetic interactions for a specified gene.

[Manage Columns](#) [Manage Filters](#) [Manage Relationships](#)

Showing 1 to 25 of 70 rows

Gene Primary DBID	Gene Standard Name	Gene Systematic Name	Gene Sgd Alias	Gene Name	Interaction Detection Methods Identifier	Count
S000007260	COX1	Q0045	cytochrome c oxidase subunit 1 OXI3	Cytochrome c Oxidase	Synthetic lethality	26
S000007260	COX1	Q0045	cytochrome c oxidase subunit 1 OXI3	Cytochrome c Oxidase	Synthetic lethality	23
S000007260	COX1	Q0045	cytochrome c oxidase subunit 1 OXI3	Cytochrome c Oxidase	Synthetic lethality	11
S000007260	COX1	Q0045	cytochrome c oxidase subunit 1 OXI3	Cytochrome c Oxidase	Synthetic lethality	5
S000007260	COX1	Q0045	cytochrome c oxidase subunit 1 OXI3	Cytochrome c Oxidase	Synthetic lethality	2
S000007260	COX1	Q0045	cytochrome c oxidase subunit 1 OXI3	Cytochrome c Oxidase	Synthetic lethality	1

7 Interaction Term Identifiers

Filter values

Interaction Term Identifier Count

Dosage Rescue 26 RA1/YEL023 synthetic lethality experiment name
Synthetic Rescue 23 Deutscher D, et al. 2006)-16941010-synthetic lethality
Synthetic Lethality 11 Deutscher D, et al. 2006)-16941010-synthetic lethality
Phenotypic Suppression 5 Deutscher D, et al. 2006)-16941010-synthetic lethality
Dosage Lethality 2 Deutscher D, et al. 2006)-16941010-synthetic lethality
Phenotypic Enhancement 2 Deutscher D, et al. 2006)-16941010-synthetic lethality
Synthetic Growth Defect 1 Deutscher D, et al. 2006)-16941010-synthetic lethality

Filter Download data

Deutscher D, et al. (2006)-16941010-Synthetic Lethality

genetic

BAT2/COX1/PUT1 triple lethal in synthetic rich m

- A window summarizing all entries for this column will open. Check the entry for **Synthetic Lethality** and hit Filter.
- The table now contains only synthetic lethal interactions. To save the interactors into a gene list, click on the **Save as List** button and select the entry **Gene > Interactions > Participant 2**. Give your list a descriptive name such as “**List 2: Synthetic lethal interactors, S. cerevisiae**”.

Showing 1 to 9 of 9 rows

Gene Primary DBID	Gene Standard Name	Gene Systematic Name	Gene Sgd Alias	Gene (1 Gene)	Gene > Organism (1 Organism)	Gene > Interactions > Details (9 Interaction Details)	Gene > Interactions > Participant 2 (9 Genes)	Gene > Interactions > Details > Experiment > Interactant Detection Methods (1 Interaction Term)	Gene > Interactions > Details > Experiment (1 Interaction Experiment)	Experiment Name	Details interactionType
S000007260	COX1	Q0045		cytochrome c oxidase subunit 1 OXI3						Deutscher D, et al. (2006)-16941010-Synthetic Lethality	genetic
S000007260	COX1	Q0045		cytochrome c oxidase subunit 1 OXI3	Cytochrome c Oxidase	S. cerevisiae	genetic interactions	inversible	Bait		
										Synthetic Lethality	
										Deutscher D, et al. (2006)-16941010-Synthetic Lethality	genetic

Create List Add to List

- Access your new gene list by clicking on the **Lists** link in the top purple toolbar. Make sure that the **View** tab is open (see arrows).

SGD YeastMine Search and retrieve S. cerevisiae data with YeastMine, populated by SGD and powered by InterMine.

Last Updated on: Apr-14-2018 Contact Us Video Tutorials Help Log in

Home Templates Lists QueryBuilder Tools Regions Data Sources API MyMine

Upload | View Search: e.g. act1 GO

Lists

View your own and public lists, search by keyword and compare or combine the contents of lists. Click on a list to view graphs and summaries in an analysis page, select lists using checkboxes to perform set operations. Click 'Upload' above to import a new list.

Filter: Reset Actions: Union | Intersect | Subtract | Asymmetric Difference | Copy Delete Options: Show descriptions Show Tags

You are not logged in. Log in to save lists permanently and to mark items as favourites ★.

List 2: Synthetic lethal interactors, S. cerevisiae 9 Genes List 1: S. cerevisiae orthologs 11 Genes All Curated Macromolecular Complexes 594 Molecular Complexes

- Export the list of synthetic lethal interactors by clicking on the **Export** button, and then on the **Download file** button.

List Analysis for List 2: Synthetic lethal interactors, S. cerevisiae (9 Genes)

Manage Columns Manage Relationships Generate Python code Export Save as List

Showing 1 to 9 of 9 rows

Gene Primary DBID	Gene Systematic Name	Gene Organism . Short Name	Gene Standard Name	Gene Name
S00000773	YEL047C	S. cerevisiae	FRD1	Fumarate ReDuctase

A. fischeri NRRL 181 (13) A. flavus NRRL3357 (15) A. fumigatus Af293 (13) A. gambiae (6) A. nidulans FGSC A4 (16) A. niger ATCC 1015 (18) C. albicans SC5314 (7) C. albicans WO-1 (7) C. dubliniensis CD36 (7) C. elegans (21) C. gattii VGII R265 (10) C. gattii WM276 (12) C. lusitaniae (1) C. neoflavus (1) C. neoflavus JEC21 (10) C. neoflavus H99 (10) C. neoflormans var. neoflormans JEC21 (10) C. parapsilosis CDC317 (7) C. posadasii C735 delta SW0gp (11) D. melanogaster (30) D. rerio (21) I. galbarta CBS 138 (10) H. capsulatum G166AR (12) H. capsulatum NAM1 (12) H. sapiens (20) M. musculus (20) M. oryzae 70-15 (12) N. crassa OR74A (12) R. norvegicus (22) S. cerevisiae (6) S. pombe (8) T. marmeffei ATCC 18224 (16) U. maydis 521 (12)

View homologues in other Mines: FlyMine D. melanogaster x

5. Import the *S. cerevisiae* synthetic lethal interaction genes into FungiDB for further analysis:

- Open the FungiDB homepage (<http://fungidb.org/>). Similar to part 2 of this exercise, in the **Search for Genes** box, open the **Annotation, curation and identifiers** section and click on Gene ID(s).
- Copy and paste all of the systematic *S. cerevisiae* gene names (YEL047C, YKL141W, etc.) from the downloaded list obtained in part 4 of this exercise. Hit **Get Answer**.
- To the right of the Gene Results table, click on the **Analyze Results** button. Select **Gene Ontology Enrichment** and run an enrichment for Biological Process.

The screenshot shows the FungiDB Gene Results page. At the top, there are three tabs: 'Gene Results' (selected), 'Genome View', and 'New Analysis'. Below the tabs, a message says 'Analyze your Gene results with a tool below.' A large box contains a 'Gene Ontology Enrichment' visualization. This visualization features a large blue 'GO' logo in the center, surrounded by a network of smaller circles representing biological processes. An orange arrow points to the 'Gene Ontology Enrichment' box. On the far left, there is a vertical bar with the text 'Hide organism filter'.

- Are the results surprising? Remember that these *S. cerevisiae* genes have synthetic lethal interactions with mitochondrial genes. Do the results suggest any biological processes that, if disrupted, might possibly inhibit mitochondria-defective *C. glabrata* clinical isolates?
- Use the “Transform by Orthology” function to convert the *S. cerevisiae* genes into *C. glabrata* orthologs. These *C. glabrata* genes are predicted to have synthetic lethal interactions with *C. glabrata* mitochondrial genes.