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The PathoYeastract database: an information system for the analysis of gene and genomic transcription regulation in pathogenic yeasts

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ABSTRACT

We present the PATHOgenic YEAst Search for Transcriptional Regulators And Consensus Tracking (PathoYeastract - http://pathoyeastract.org) database, a tool for the analysis and prediction of transcription regulatory associations at the gene and genomic levels in the pathogenic yeasts *Candida albicans* and *C. glabrata*. Upon data retrieval from hundreds of publications, followed by curation, the database currently includes 28 000 unique documented regulatory associations between transcription factors (TF) and target genes and 107 DNA binding sites, considering 134 TFs in both species. Following the structure used for the YEASTRACT database, PathoYeastract makes available bioinformatics tools that enable the user to exploit the existing information to predict the TFs involved in the regulation of a gene or genome-wide transcriptional response, while ranking those TFs in order of their relative importance. Each search can be filtered based on the selection of specific environmental conditions, experimental evidence or positive/negative regulatory effect. Promoter analysis tools and interactive visualization tools for the representation of TF regulatory networks are also provided. The PathoYeastract database further provides simple tools for the prediction of gene and genomic regulation based on orthologous regulatory associations described for other yeast species, a comparative genomics setup for the study of cross-species evolution of regulatory networks.

INTRODUCTION

Candida species are recognized as the 4th most common cause of nosocomial infections (1). Candidiasis is considered to be responsible for more than 400 000 life-threatening infections worldwide every year. The frequency and relative high mortality levels (up to 45% for *Candida glabrata*) of these infections (2) are generally attributed to the capacity of these pathogenic yeasts to efficiently develop multidrug resistance (MDR), to tolerate host defence mechanisms, to maintain high proliferative and repopulation capacity through biofilm formation, and to activate invasive growth related genes (3,4).

Since clinically evolved phenotypes can be seen as a long term genetic stabilization of the normal transient response to new environments (5), it is essential to understand the structure and functioning of the transcription networks regulating the early response to clinically relevant environmental changes, in *Candida* species, to be able to understand and circumvent the long term acquisition of virulence and drug resistance-related phenotypes. For example, MDR acquisition in clinical isolates is often related to the high expression levels of multidrug transporters (6,7), occurring as a consequence of point mutations in MDR-related transcription factors (TFs), including *C. glabrata* Pdr1 or *C. albicans* Tac1 and Mrr1 (8). Similarly other infection-relevant phenomena, such as biofilm formation or tissue invasion, also occur under the control of transcription factors such as *C. albicans* Efg1 and Cph1 (9) or Cph2, Tec1 and Czf1, respectively (10). However, the transcriptional control of infection-related phenomena appears to be much more complex than predicted. For example, it has been recently demonstrated that the carbon source in which *Candida* cells proliferate has deep impact in drug resistance and phagocytosis (11). Additionally, a significant number

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of clinical isolates, especially from non-*albicans Candida* species, that evolved to become drug resistant or virulent, have often been found not to display the 'typical' molecular markers associated to these phenotypes (3,12,13), showing that there is still a lot to learn in terms of the vast array of evolutionary paths that a fungal cell can undergo to reach a given infection-related phenotype.

The PathoYeastract database has been developed to provide researchers and clinicians working in the field of fungal infections with a tool to obtain a more complete understanding of the complex regulatory control that underlies the biology, pathogenicity and drug resistance capabilities of *Candida* species. Other important pathogenic yeasts, including those from the *Cryptococcus* and *Rhodotorula* genus, were not considered in PathoYeastract. This new information system follows the footsteps of the YEASTRACT (http://yeastract.com) database that has provided to the public up-to-date information on documented regulatory associations between TFs and target genes, as well as between TFs and DNA binding sites, in *S. cerevisiae* (14–17). However, it goes beyond YEASTRACT as it extends to pathogenic yeasts and provides the chance to run inter-species comparison of regulatory networks. Other databases focused on transcriptional regulation in yeasts and other organisms do exist, including TRANSFAC (18) or RSAT (19), but focus most of their analysis and predictive power on the understanding of promoter regions. Besides providing tools for promoter analysis in yeast, PathoYeastract is, to the best of our knowledge, the single information system that offers a complete integration of all the experimentally validated transcriptional regulatory data ever published for *C. albicans* and *C. glabrata*.

Side by side with the collected data, PathoYeastract offers an array of queries that enable users to extract the most out of the existing data. Specifically, tools are offered to predict the transcription factors that control a given transcriptional response, at the gene or at the genomic scales, suitable for the analysis of transcriptomics data. Moreover, bioinformatics tools to predict transcriptional associations based on the knowledge gathered for better known yeast species, including *S. cerevisiae* and *C. albicans* have also been devised, to compensate for the current lack of knowledge of similar processes in less well characterized yeast species, such as *C. glabrata*. These new tools provide the required backbone to be able to run cross-species comparison of transcription regulatory networks, which is expected to bring more light into the evolution of *Candida* species as competent human pathogens.

Data collection

In its first release, PathoYeastract gathers all available (and reliable) information on transcriptional associations for the two most prevalent of pathogenic *Candida* species: *C. albicans* and *C. glabrata*.

Basic information on gene and promoter sequence, amino acid sequence and a functional description for every *C. albicans* and *C. glabrata* genes/proteins were downloaded from the Candida Genome Database (http://candidagenome.org) (20). Promoter sequences were considered to be the first 1000 bp upstream of the START codon. Additionally, Gene Ontology terms associated to all the *C. albicans* and *C. glabrata* genes/proteins, and their hierarchy, were retrieved from the GO consortium database (21,22).

The genomes of *C. albicans* and *C. glabrata* are predicted to encode 163 and 117 transcription factors, respectively. An extensive literature survey was conducted to retrieve all the available information on associations between these transcription factors and their target genes. For each paper describing TF DNA binding results or transcription data, in the dependence of a TF, the data was collected based on the criteria used by the paper authors, validated by the review process. In each case, the experimental basis of the associations between TFs and target genes was included in the database. The underlying experimental evidence was also collected and classified as either *DNA Binding* or *Expression Evidence*. *DNA Binding Evidence* was considered to be provided through: experiments directly measuring the binding of the TF to the promoter region of the target gene (e.g. Chromatin ImmunoPrecipitation (ChIP), ChIP-on-chip, ChIP-seq and Electrophoretic Mobility Shift Assay (EMSA)); or the analysis of the effect on target-gene expression of the site-directed mutation of the TF binding site in its promoter region, as strongly suggesting an interaction of the TF with that specific target promoter. *Expression Evidence* classification was attributed to experiments such as the comparative analysis of gene expression changes occurring in response to the deletion, mutation or over-expression of a given TF, based on experimental techniques that include quantitative RT-PCR, microarray analysis, RNA sequencing or expression proteomics. In the case of *Expression Evidence*-based data the effect of the transcription factor in the target gene expression was registered as positive or negative, as it may help to discard indirect effects of TF expression. Specific gene expression levels are not included in PathoYeastract at this time. Based on this classification, PathoYeastract contains a total of 12 224 regulatory associations based on DNA-binding evidence and 24 752 on expression evidence, with some overlap. Altogether, PathoYeastract includes in its July 2016 release 2170 associations between TF and target genes in *C. glabrata*, including 1818 unique TF-target gene pairs, based in 76 different publications, and 34,806 associations between TF and target genes in *C. albicans*, including 26 473 unique TF-target gene pairs, based in 671 different publications.

Information on associations between transcription factors and TF binding sites in both *C. albicans* and *C. glabrata* was also gathered. In the *C. glabrata* case, 11 TF have been associated with a recognized consensus nucleotide sequence, predicted based on the use of motif finding algorithms and in some cases experimentally validated (e.g. Amt1 (23) and Pdr1 (24), using DNAse I footprinting assays). For *C. albicans*, a DNA binding motif has been appointed for 40 TFs, again most of which based only using bioinformatic predictions.

In all cases, the environmental condition in which the regulatory association was found to occur was included in the database, as the occurrence of these associations is extremely dependent on environmental stimuli. Published regulation data was found to be associated to a total of 995 different environmental conditions,

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which were then clustered into 12 groups, including: biofilm formation, carbon source quality/availability, cell cycle/morphology, human niche conditions, in vitro, ion/metal/phosphate/sulphur/vitamin availability, lipid supplementation, nitrogen source quality/availability, oxygen availability, pathogenicity, stress and unstressed log-phase growth (control). Each of these clusters is composed by sub-clusters to enable a finer filtering of the existing regulatory associations.

All TF-target gene or TF–TF binding site pairs included in the database are associated to at least one publication, whose reference and pubmed link is automatically provided.

Predicting gene and genomic regulation

The PathoYeastract database is equipped with several simple queries that aim at enabling its users to easily extract relevant information from the total underlying data. Those queries were built in a way as to respond to typical questions that a yeast biologist/research clinician may pose.

The simplest queries enable the user to obtain all the transcription factors that regulate a given gene or all the genes which are regulated by a given TF. This query can be set to rely on documented regulation data, herein coined 'documented regulation', or in prediction based on the occurrence of putative TF binding sites in the promoter region of the gene of interest, herein coined 'potential regulation'. This may be extremely useful when trying to predict the function of an uncharacterized target gene/TF. For example, the recently characterized *C. albicans* Qdr1–3 proteins, predicted to act as Drug:H+ Antiporters (DHA) of the Major Facilitator Superfamily, were shown to play instead overlapping roles in *C. albicans* virulence (25). Using the Search by TF query in PathoYeastract it is possible to predict all the TFs that may play a role in the control of the transcription of QDR genes (Figure 1). Interestingly, none of the Qdr encoding genes has been shown to be controlled by the *C. albicans* multidrug resistance transcription factors Tac1 or Mrr1. Surprisingly, these three genes are associated to a rather disparate set of transcription factors. Based on the PathoYeastract analysis, Qdr1 has been shown to be controlled by 17 different TFs, while Qdr2 is only known to be regulated by the Mcm1 TF, that regulates hyphal growth, and only three TF are known to control the expression of Qdr3: Mcm1, Hap43, related to the control of iron homeostasis, and Tbf1, an essential transcriptional activator that regulates ribosomal protein genes (Figure 1A). The transcriptional control of these homologous genes suggests, not only that indeed they play no direct role in drug resistance, but also strongly point to the hypothesis that they may serve more than paralogous roles. Indeed, the fact that *C. albicans* has three QDR genes in its genome sequence further suggests as much, especially, when compared to *C. glabrata* which exhibits only one QDR gene, *QDR2*, recently shown to play a role in azole drug resistance (26). Interestingly, using the search for TF query in PathoYeastract the *C. glabrata QDR2* gene can be seen to be solely regulated by Pdr1, as far as current knowledge goes, Pdr1 being the main regulator of azole drug resistance in this yeast species (Figure 1B).

Alternatively, using the 'Search for Genes' query it is possible to pinpoint all the genes that have been shown to be regulated by a given transcription factor. Keeping to the drug resistance case study, using this tool it is possible to observe that there are 399 genes known to be regulated by the *C. glabrata* Pdr1 TF, whereas there are only 45 genes known to be regulated by the *C. albicans* Tac1 TF (Figure 2). Interestingly, the list of genes whose expression is controlled by Pdr1 or Tac1 is also quite diverse in terms of associated functions, far beyond the classical targets, the multidrug efflux pumps of the ATP-Binding Cassette superfamily Cdr1 and Cdr2. Both lists include shared genes and functions, such as Hsp12, a stress resistance related protein chaperone, the Erg11 gene, the target of azole antifungal drugs, but also genes associated to central metabolic pathways. For example, *ADH1* and *SNZ1* were identified as targets of the Tac1 TF, being related to central carbon metabolism and vitamin B synthesis, respectively. This observation raises the possibility of either Tac1 playing additional roles in *C. albicans* biology or that Adh1 and Snz1 contribute somehow to drug resistance.

Analysing genome-wide expression data

One of the key uses of the regulatory data present in the PathoYeastract database is to predict the TF regulatory network that controls a given genome-wide expression remodelling. Specifically, the query 'Rank by TF' was designed to accept as input a list of genes, for example, the set of genes up-regulated in a given condition, as obtained by RNA sequencing or microarray analysis, providing as output the TFs that regulate the user's gene list, ranked by relative importance. For example, a recent study on the role of the *C. glabrata* Yap1 TF, a master regulator of the oxidative stress response in yeasts, provided a list of 70 genes which are up-regulated in *C. glabrata* cells exposed to stress induced by selenium, under the control of Yap1 (27). Using the 'Rank by TF' query to analyse the same list, it is possible to observe that besides Yap1, 14 other TFs play a role in the regulation of this gene list, suggesting that the network of TF responsible for the transcriptional remodelling occurring in these cells is much more complex than initially foreseen (Figure 3). The authors of the paper describing the role of Yap1 in the *C. glabrata* selenium response focused on the participation of some of the Yap1 homologs (27), however, TFs such as Pdr1, Skn7 or even the uncharacterized TFs encoded by ORF *CAGL0I07755g* (an homologue of the salt stress related *S. cerevisiae* Hal9 TF) or ORF *CAGL0G08844g* (an homologue of the cell wall stress related *S. cerevisiae* Asg1 TF) also appear highly ranked in this query, as they are required for the transcriptional control of >10% of the dataset in analysis. This result appears to suggest that selenium stress induces toxicity at several levels, beyond oxidative stress, thus activating an array of TF that control various biological functions required for *C. glabrata* cells to cope with selenium stress.

Predicting transcriptional regulation based on orthologous transcription regulatory networks in different yeast species

The fact that PathoYeastract comprises regulatory information on two *Candida* species enables the possibility to

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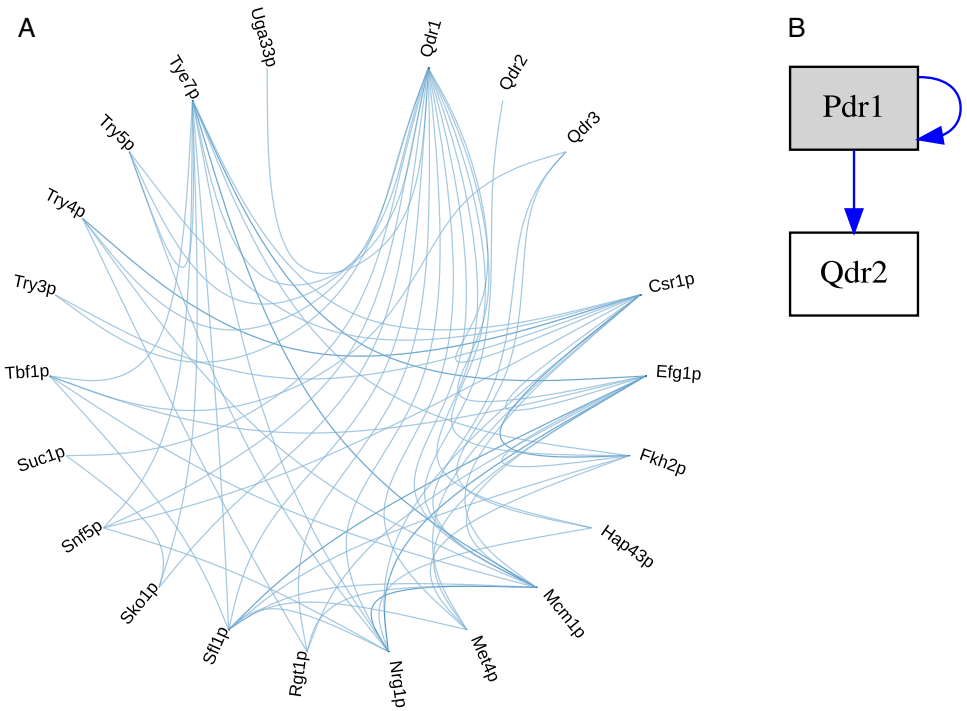

Figure 1. Regulation of the QDR genes in *C. albicans* (**A**) and in *C. glabrata* (**B**).

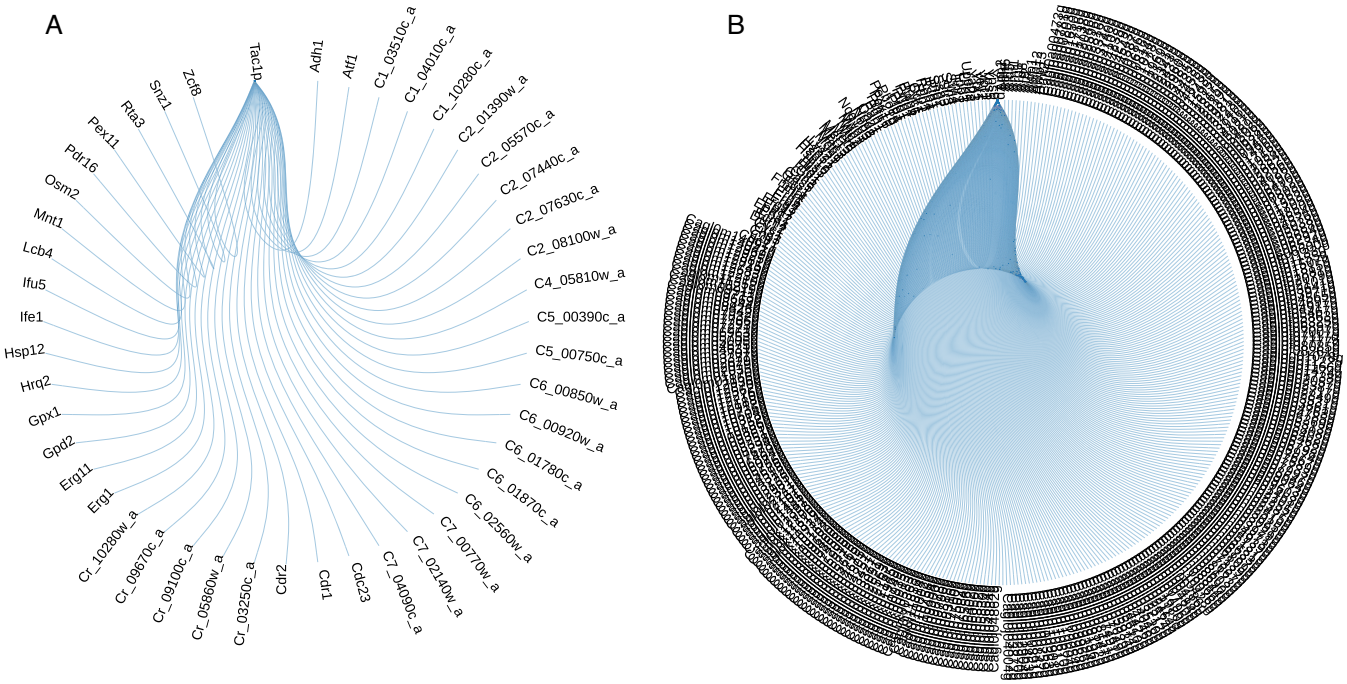

Figure 2. The Tac1/Pdr1 putative regulon in *C. albicans* (**A**) / *C. glabrata* (**B**) as obtained using the 'Search for target genes' in the PathoYeastract database.

run cross-species comparison in terms of regulatory associations. The potential of this approach is further increased when considering the ability to further access regulatory data on the model yeast *Saccharomyces cerevisiae* in the YEASTRACT database. Such a comparison can be made at the gene, but also genomic level.

Picking up the example above, focused on the regulation of the *C. glabrata QDR2* gene (26), the Search by TF query offers the possibility to predict the transcriptional control of this gene based on the transcription of their orthologous genes in either *C. albicans* or *S. cerevisiae* (Figure 4). Using this query it is possible to highlight the fact that, although *C. glabrata QDR2* gene is only known to be regu-

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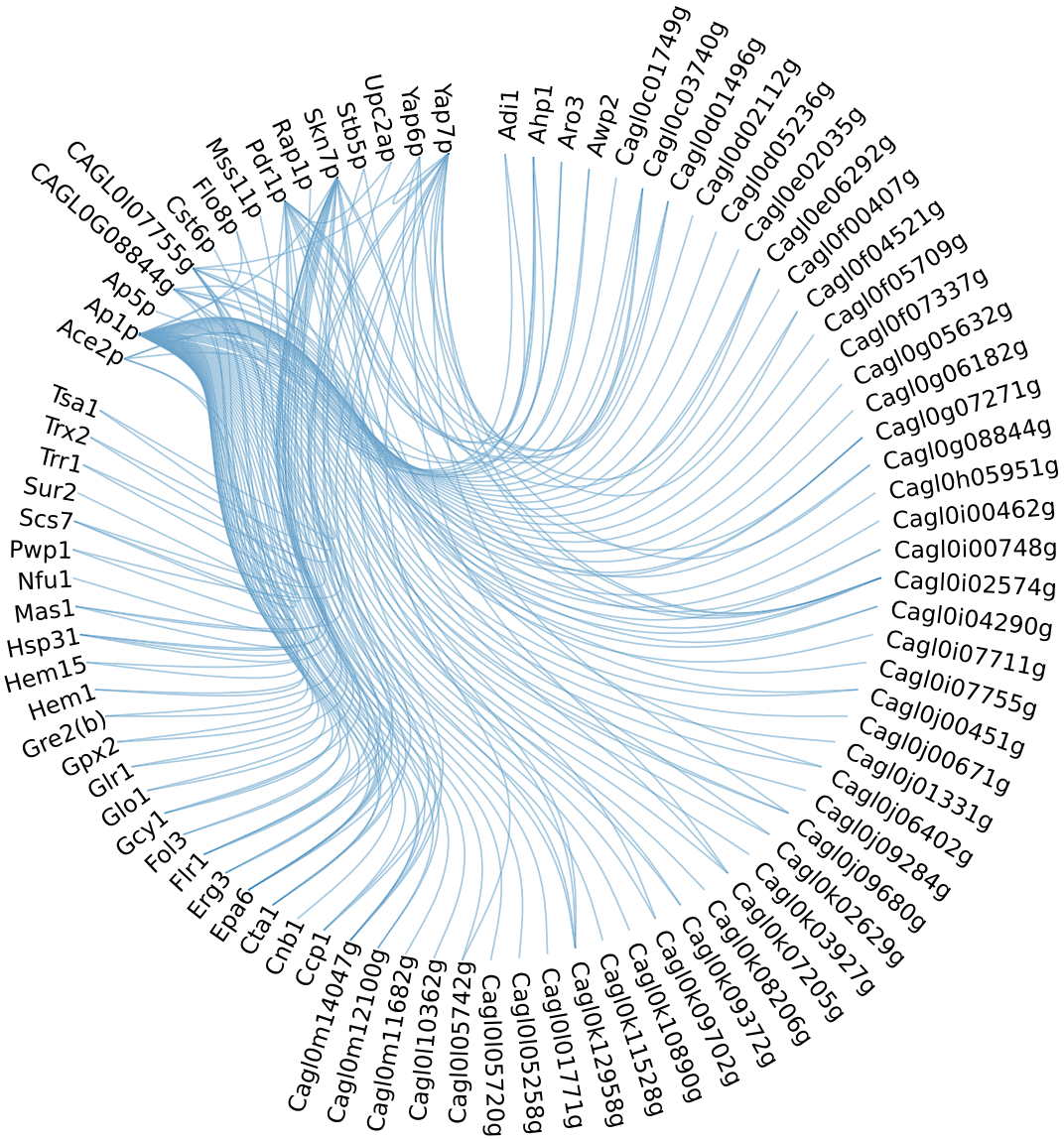

Figure 3. The TF regulatory network predicted to control the Yap1-dependent response to selenium stress in *C. glabrata*, based on the PathoYeastract 'Rank by TF' tool.

lated by a single TF, Pdr1, its homologs in *C. albicans* and *S. cerevisiae* are known to be regulated by 10 and 18 TFs for which there are orthologs in *C. glabrata*, respectively. This comparison may provide interesting clues, pointing out to which additional TFs may be involved in the regulation of the *C. glabrata QDR2* gene. Additionally, the comparison between the TF network that controls *QDR2* regulation in these three related yeast species may provide an interesting setup for the prediction of gene regulation evolution. In this case, the regulation of *QDR2* appears to have diverged significantly within the three species, as there is not a single TF known to be shared by the QDR genes in the three yeast species. It is important to point out, however, that the amount of data collected for the regulation of *QDR2* in *C. glabrata* is resumed to a single bibliographic reference, suggesting that many more regulators of the *C. glabrata QDR2* may still be uncovered. Nonetheless, the observed variability in terms of *QDR2* regulation within the three species appears consistent with the fact that the function of the *QDR2* gene appears also to have diverged within these yeasts (25,26,28–30).

FUTURE DIRECTIONS

The PathoYeastract team is committed to continue to offer updated, reliable and complete information on the field of transcriptional regulation in pathogenic yeasts to the international community working in the molecular basis of candidaemia and its prophylaxis and treatment. Furthermore, the possibility to run a systematic inter-species comparison of transcription regulatory networks in different yeast will continue to be developed, especially through the development of more complex dedicated tools and the extension of the PathoYeastract database to other relevant pathogenic

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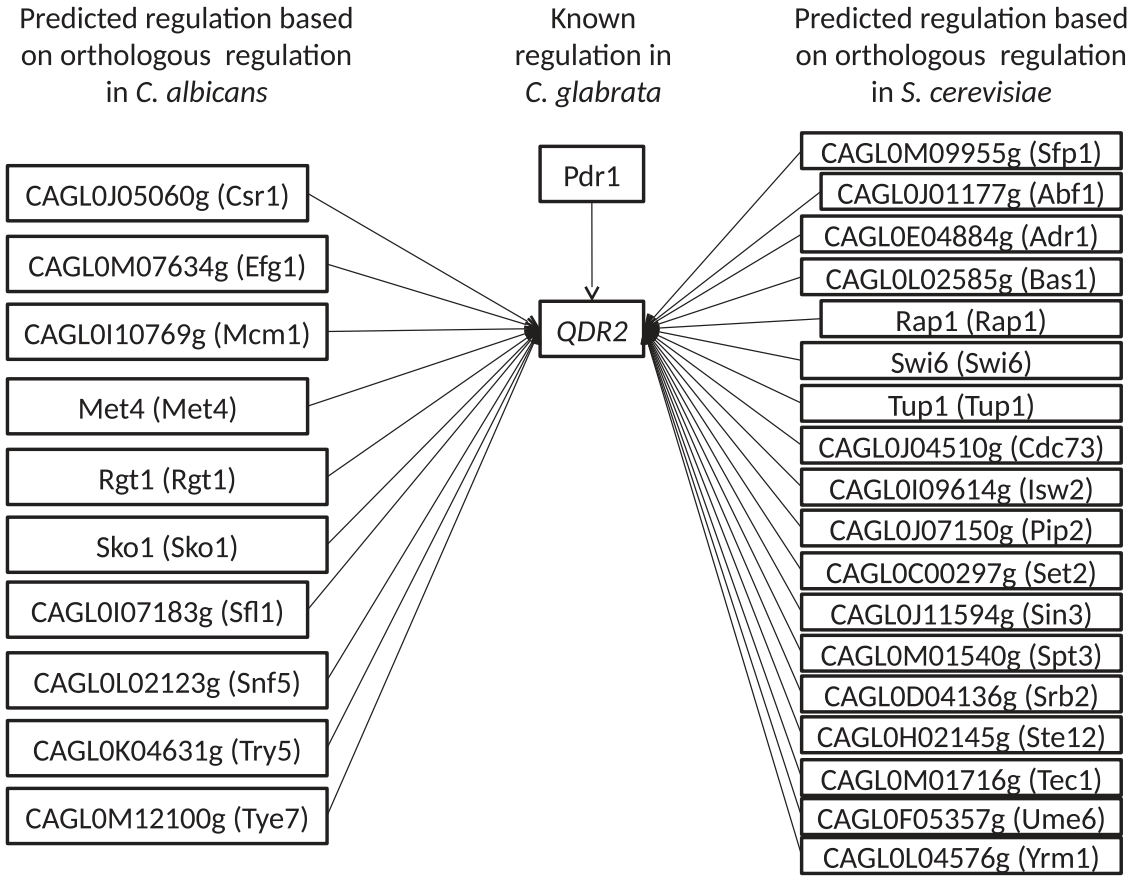

Figure 4. Prediction the TFs that regulate the *C. glabrata QDR2* gene, based on knowledge gathered in *C. glabrata* or on knowledge gathered for the regulation of orthologous genes in *S. cerevisiae* and *C. albicans*, as deposited in the PathoYeastract and YEASTRACT databases.

yeasts, including *Candida parapsilosis* and *C. dubliniensis*, but also *C. orthopsilosis*, *C. krusei* and *C. lusitaniae*.

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