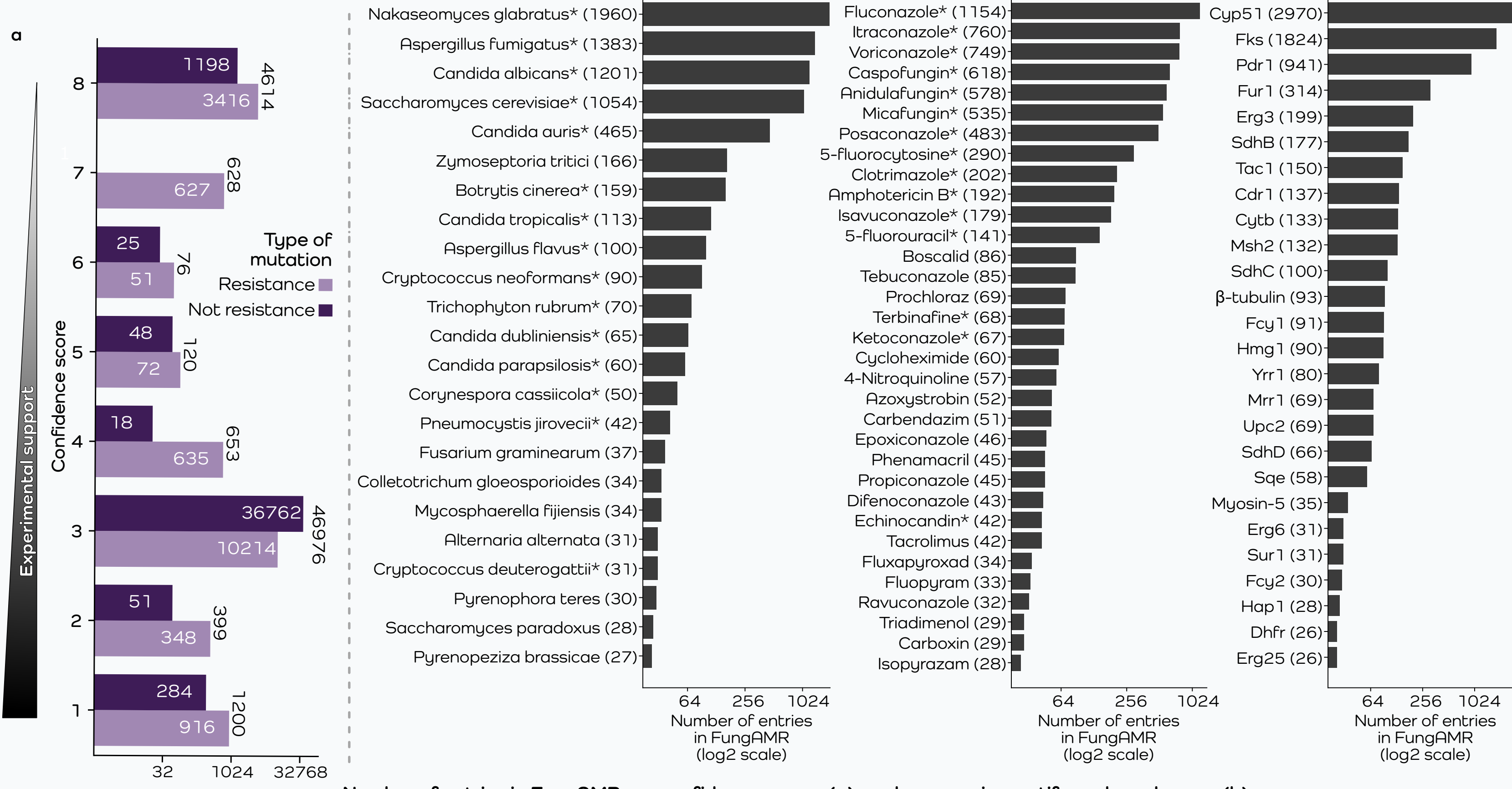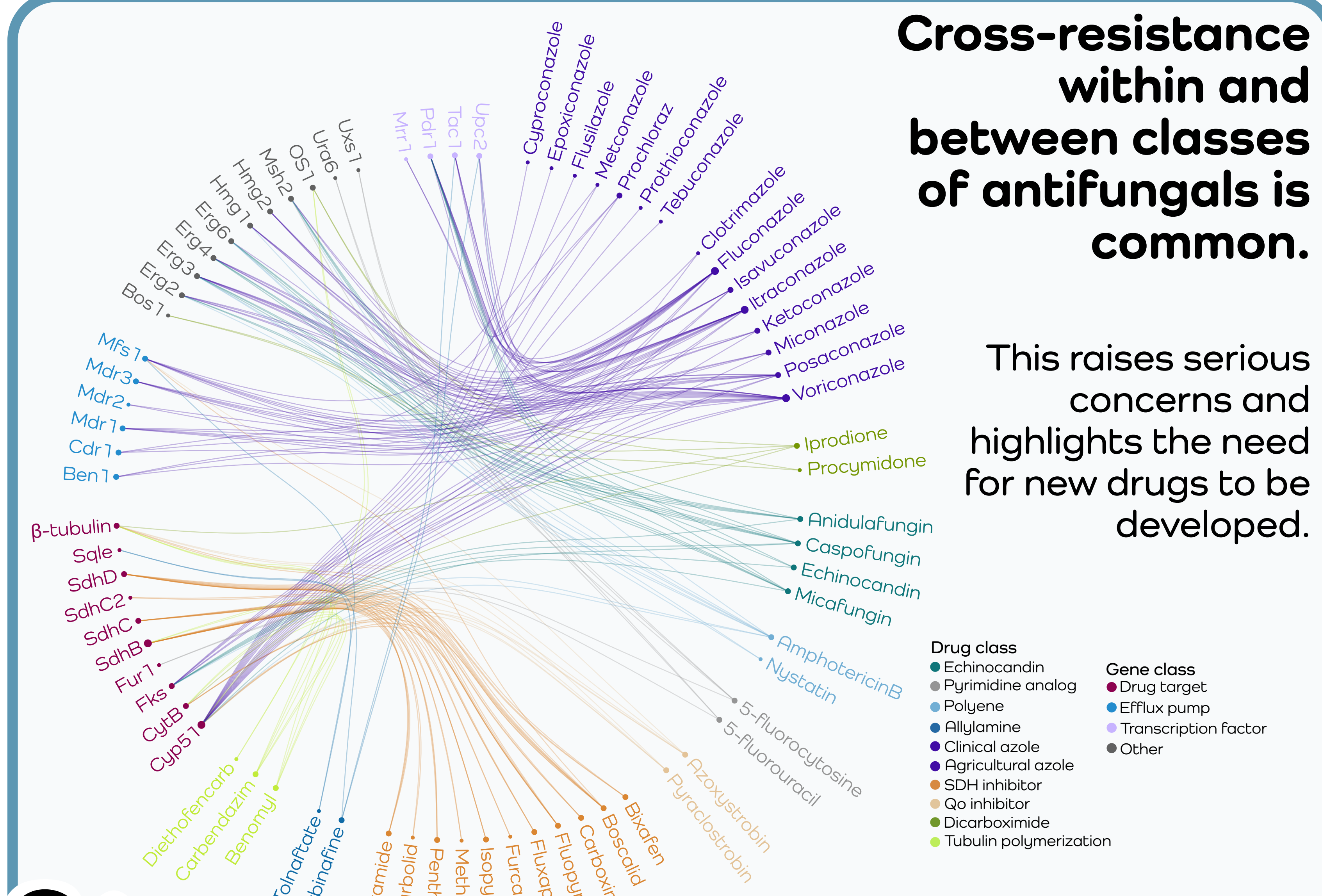# A comprehensive portrait of antimicrobial resistance mutations in fungi

Camille Bédard, Alicia Pageau, Anna Fijarczyk, David Mendoza-Salido, Alejandro J Alcañiz, Philippe C. Després, Romain Durand, Samuel Plante, Emilie M. M. Alexander, Francois D. Rouleau, Mathieu Giguère, Mégane Bernier, Jehoshua Sharma, Laetitia Maroc, Nicholas C. Gervais, Anagha C.T. Menon, Isabelle Gagnon-Arsenault, Sibbe Bakker, Johanna Rhodes, Philippe J. Dufresne, Amrita Bharat, Adnane Sellam, Domenica G. De Luca, Aleeza Gerstein, Rebecca S. Shapiro, Narciso M. Quijada, Christian R. Landry

Research on fungal AMR is skewed toward a few fungal species, genes and drugs, and many reported resistance mutations have little experimental support.
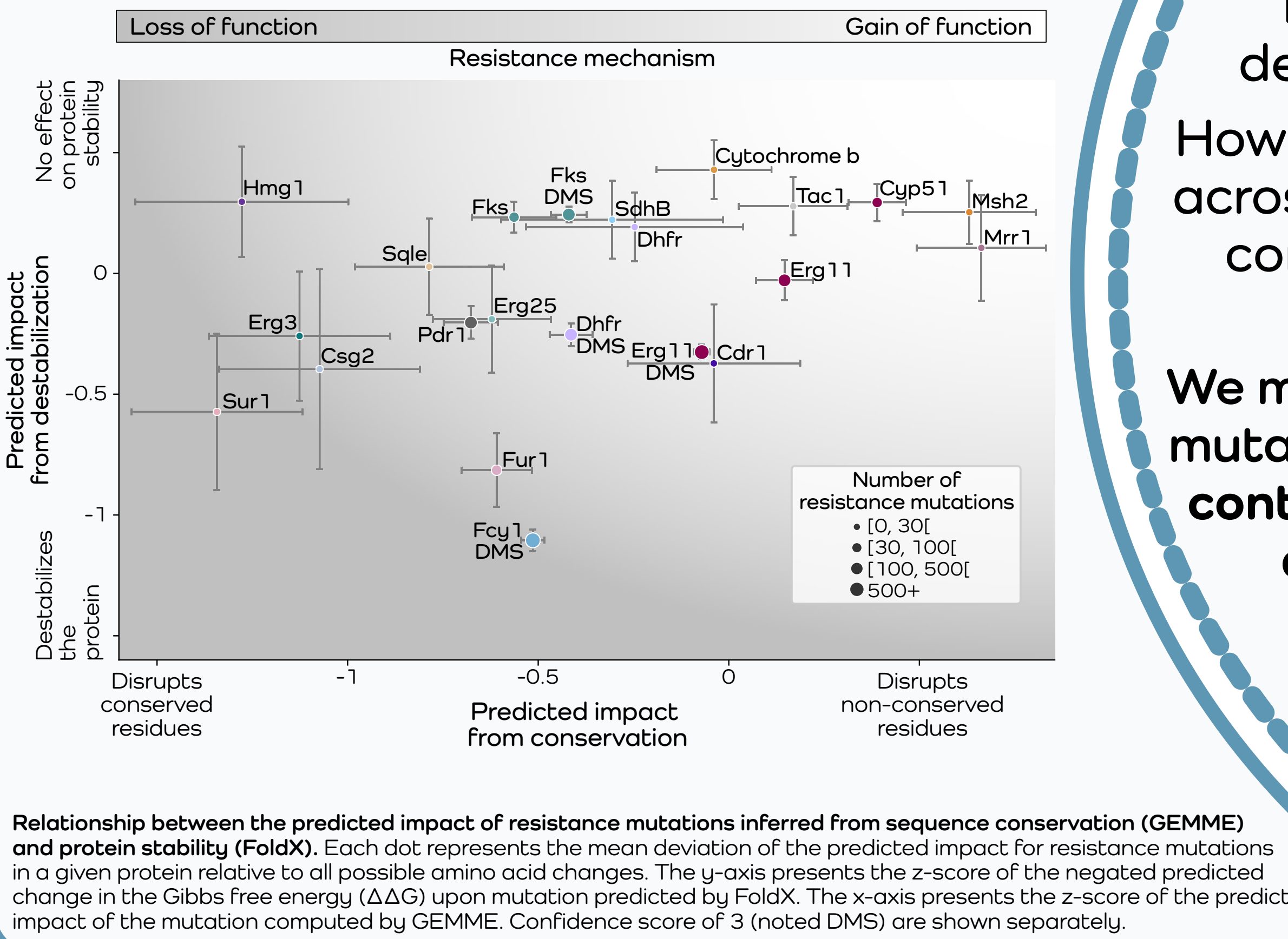

Number of entries in FungAMR per confidence scores (a), and per species, antifungals and genes (b).
a, Most entries come from high throughput experiments (confidence score of 3). Many remaining reports have limited experimental support. n = 54,666 entries.
b, Entries with a confidence score of 3 were excluded and cases with fewer than 25 reports are not shown to simplify the figure. * are of clinical interest. n = 7,690 entries.

Cross-resistance within and between classes of antifungals is common.

This raises serious concerns and highlights the need for new drugs to be developed.

Edgebundle plot of genes associated with at least one mutation conferring resistance to more than one clinical or agricultural antifungal. Only genes and drugs with more than 5 entries were included.

FungAMR

Fungal infections are a major public health problem and a threat to food security and biodiversity.

The widespread use of antifungals has led to the emergence of resistant fungal strains.

Diverse mechanisms of resistance have been described for all available classes of antifungals.

However, fungal AMR mutation reports are scattered across multiple studies. This limits the development of comprehensive genomic tools to interpret genetic variants.

We manually curated **462 papers** reporting fungal AMR mutations to create the FungAMR database. **FungAMR contains 54,666 carefully curated entries across 184 drugs for 92 fungal species. Every mutation is classified with the degree of evidence that supports its role in AMR.**

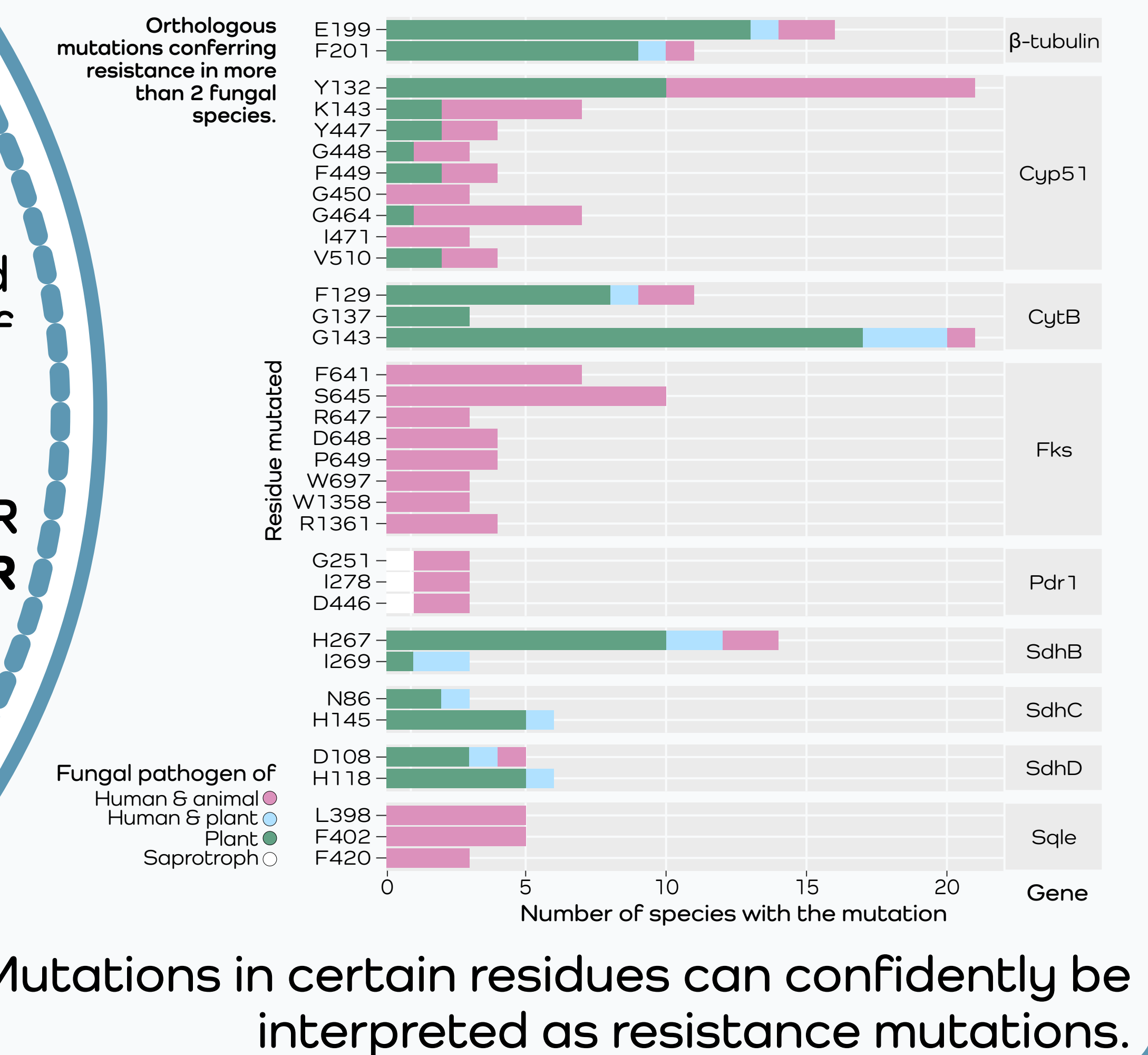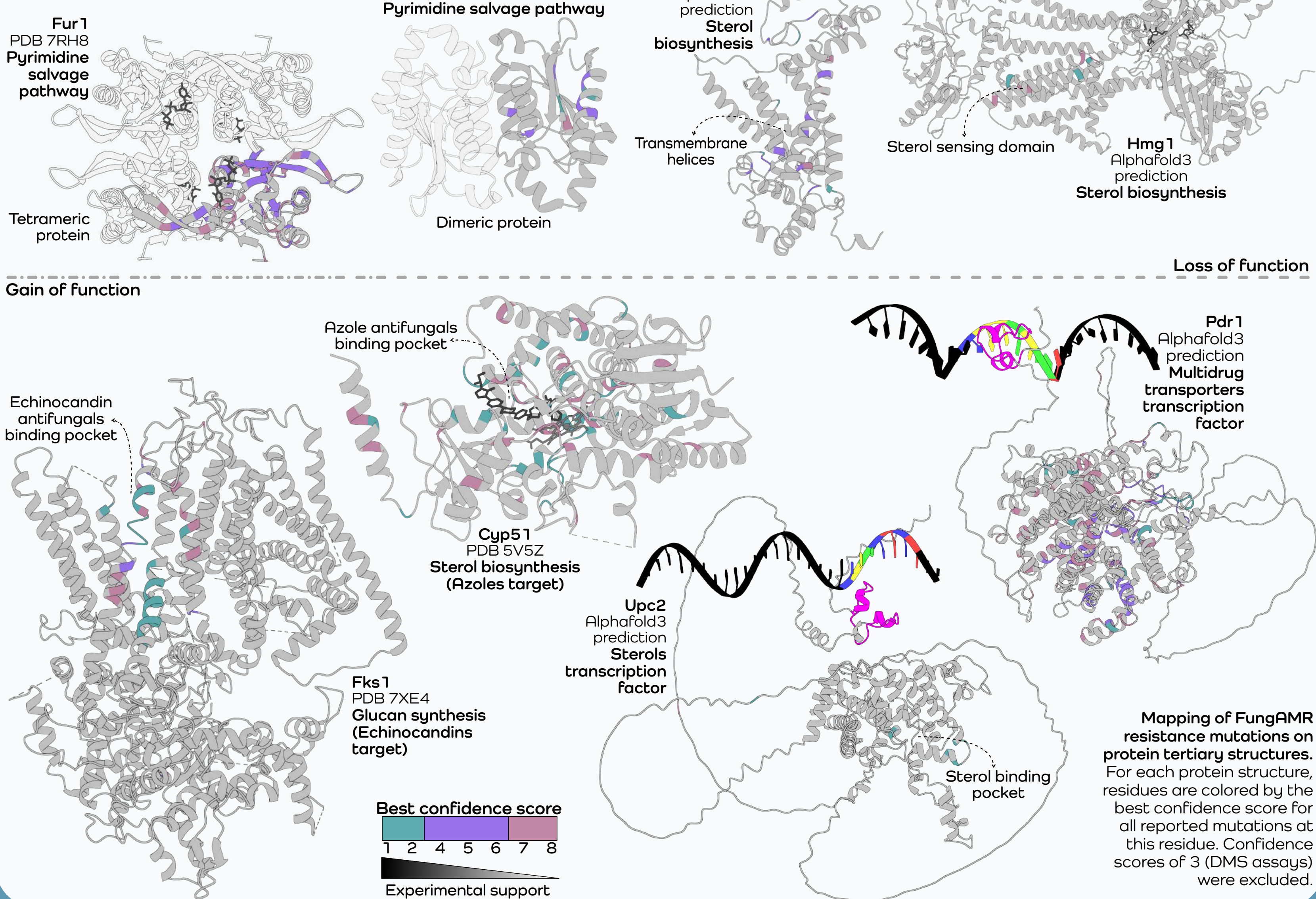This new resource illuminates the current state of knowledge on AMR for diverse genes across the fungal kingdom.

Variant effect predictors can be used to differentiate between loss of function and gain of function resistance mechanisms.

Relationship between the predicted impact of resistance mutations inferred from sequence conservation (GEMME) and protein stability (FoldX). Each dot represents the mean deviation of the predicted impact for resistance mutations in a given protein relative to all possible amino acid changes. The y-axis presents the z-score of the negated predicted change in the Gibbs free energy ($\Delta\Delta G$) upon mutation predicted by FoldX. The x-axis presents the z-score of the predicted impact of the mutation computed by GEMME. Confidence score of 3 (noted DMS) are shown separately.

There is a massive convergence in the mechanisms of resistance among fungi.

Mutations in certain residues can confidently be interpreted as resistance mutations.

Structural mapping can help interpret the impact of mutations in proteins involved in antifungal resistance.

Mapping of FungAMR resistance mutations on protein tertiary structures. For each protein structure, residues are coloured by the best confidence score for all reported mutations at this residue. Confidence scores of 3 (DMS assays) were excluded.

FungAMR can be used to screen for AMR mutations in fungal genomes.

To facilitate AMR screening, we developed ChroQueTas, a bio-informatic tool based on FungAMR. In an analysis of 144 published fungal genomes, ChroQueTas identified all AMR mutations reported by the initial authors, plus new AMR mutations that were not reported initially.

Practical example of AMR screening by using ChroQueTas and FungAMR. Phylogenetic comparaison of 144 published Zymoseptoria tritici genomes. The heatmap represents the positions within Cyp51 and are coloured when a mutation was identified.