SUPPLEMENTARY INFORMATION

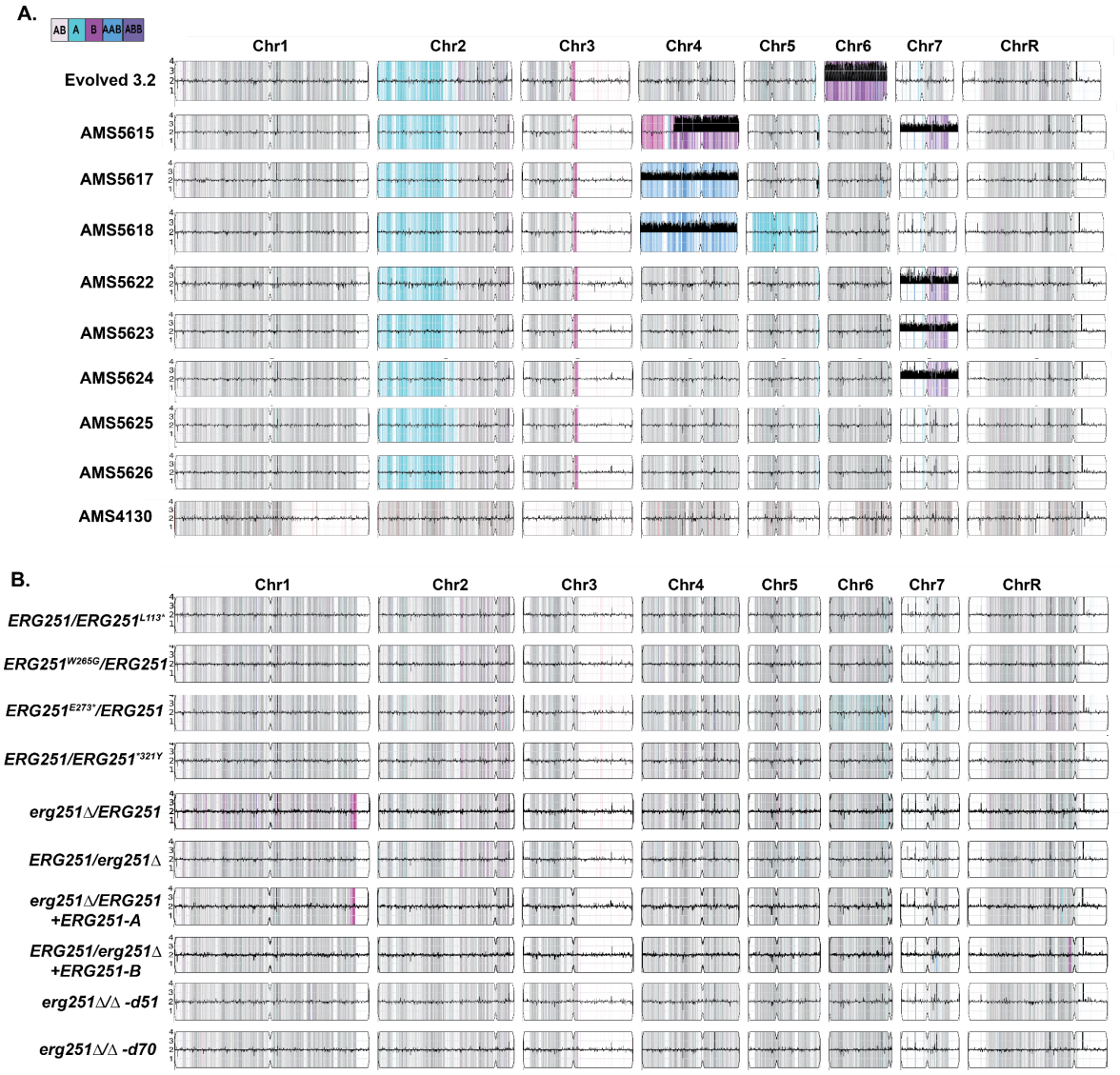

Fig S1. Whole genome sequencing analysis of FLC-evolved and engineered strains. **A.** *De novo* point mutations in *ERG251* often occur together with other aneuploidies. Representative whole genome sequencing (WGS) data of the FLC-evolved strains from Table 1: Evolved 3.2, AMS5615, AMS5617, AMS5618, AMS5622, AMS5623, AMS5624, AMS5625, AMS5626 and AMS4130 which acquired point mutations on *ERG251* during FLC evolution. **B.** The engineered *ERG251* mutants remain euploid. WGS data for all *ERG251* mutations engineered into the euploid SC5314 genetic background: the *ERG251* heterozygous point mutants (L113*, W265G, E273*, and *321Y), both heterozygous deletion strains of *ERG251*, two strains with complementation of the heterozygous deletion, and two independent homozygous deletions of *ERG251* (d51 and d70). **A&B** WGS data are plotted as the log2 ratio and converted to chromosome copy number (y-axis, 1-4 copies) as a function of chromosome

position (x-axis, Chr1-ChrR). Haplotypes are indicated by color: gray is heterozygous (AB), magenta is homozygous B, and cyan is homozygous A. The baseline ploidy was determined by propidium iodide staining (S1 Table).

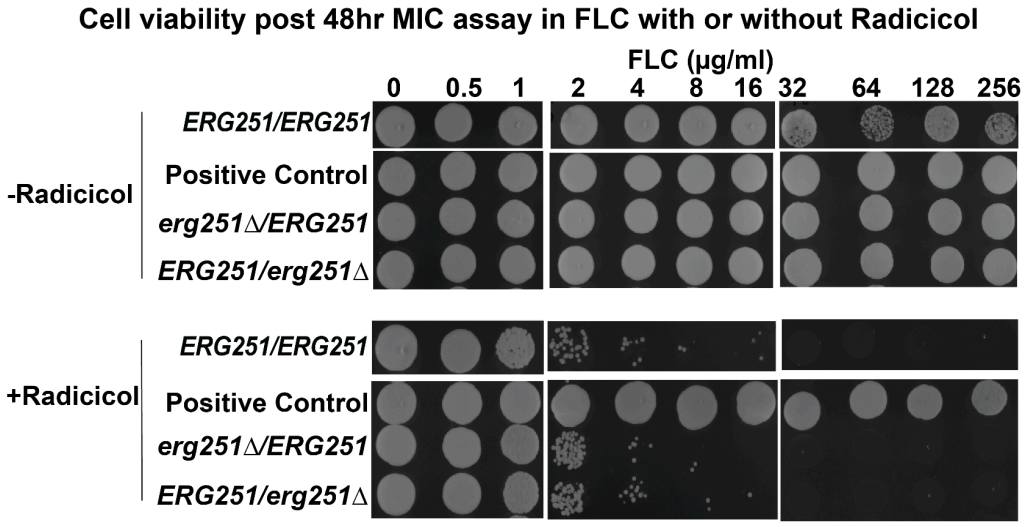

Fig S2. Radicicol, an Hsp90 inhibitor, blocks Erg251-driven tolerance and makes fluconazole fungicidal. Cells from the MIC assay at 48 hr in Fig 1D, with or without radicicol, were plated for viability on YPAD agar plates and imaged after 24 hr incubation. Wildtype SC5314 (*ERG251/ERG251*), a positive control strain known to be resistant to fluconazole (FLC), and both heterozygous deletion mutants of *ERG251* were tested. At least three biological replicates were performed.

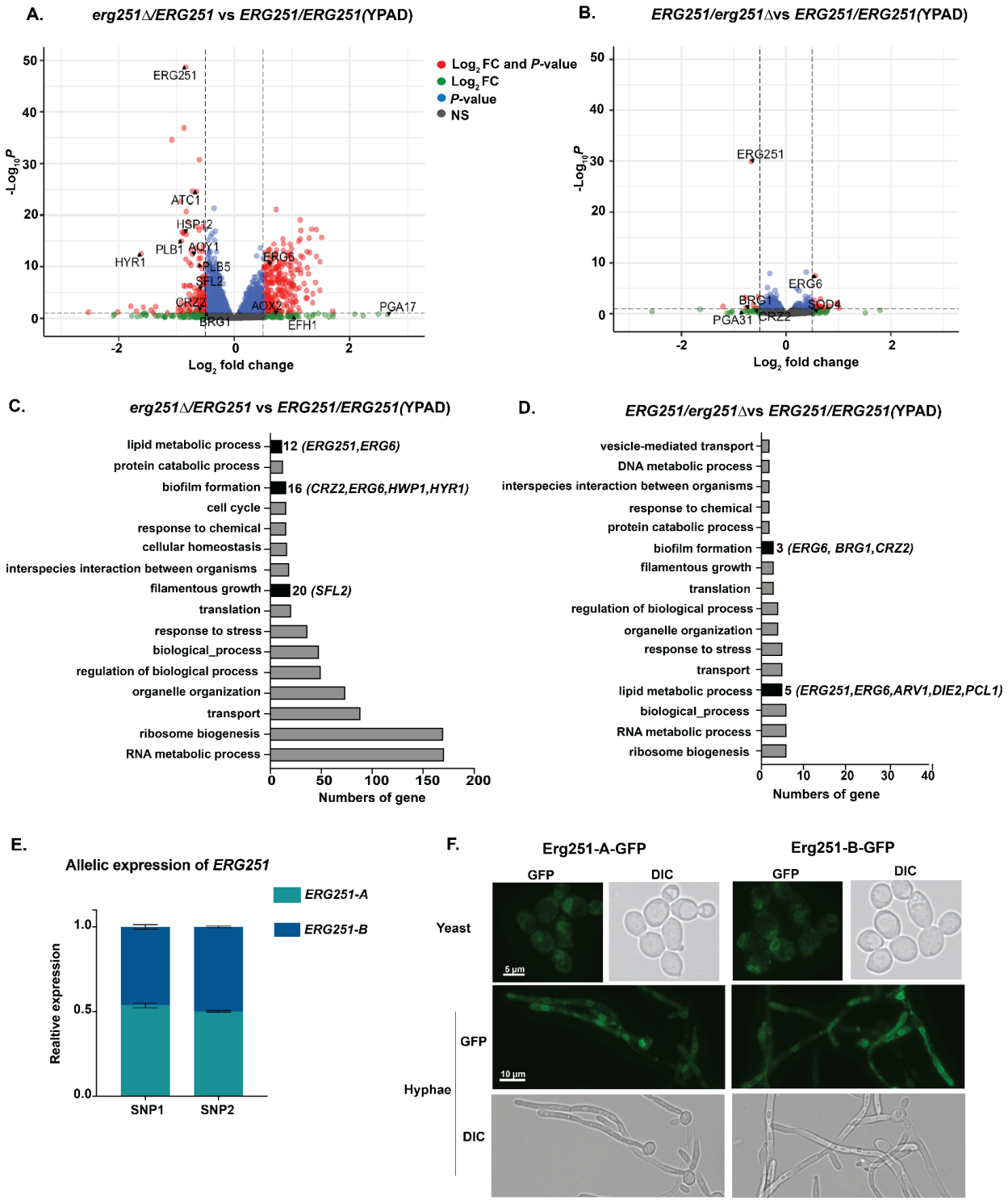

Fig S3. Heterozygous deletion of *ERG251-A* leads to a transcriptional response in filamentation regulation. Volcano plots for differentially expressed genes (log2 fold change ≥ 0.5 or ≤ -0.5 and adjusted *p*-value < 0.1) in the heterozygous mutants **(A)** *erg251Δ/ERG251* and **(B)** *ERG251/erg251Δ* in YPAD compared to the wildtype *ERG251/ERG251* in YPAD. Both the fold change and *p*-value are indicated. **C&D.** Gene

Ontology (GO) terms for genes differentially expressed in (C, S7 Table) *erg251Δ/ERG251* in YPAD and (D, S8 Table) *ERG251/erg251Δ* in YPAD compared to *ERG251/ERG251* in YPAD. **E.** Relative expression of *ERG251-A* and *ERG251-B* in the SC5314 background in YPAD. Relative expression was estimated using allelic RNA reads compared to overall reads at the two loci with polymorphisms in the *ERG251* gene (indicated as SNP1 and SNP2 above). Values are mean ± SEM calculated from three biological replicates. **F.** Subcellular localization of Erg251-A-GFP and Erg251-B-GFP in yeast and hyphal inducing conditions in SC5314 background. Yeast: scale bar, 5 μm; hyphae: scale bar, 10 μm.

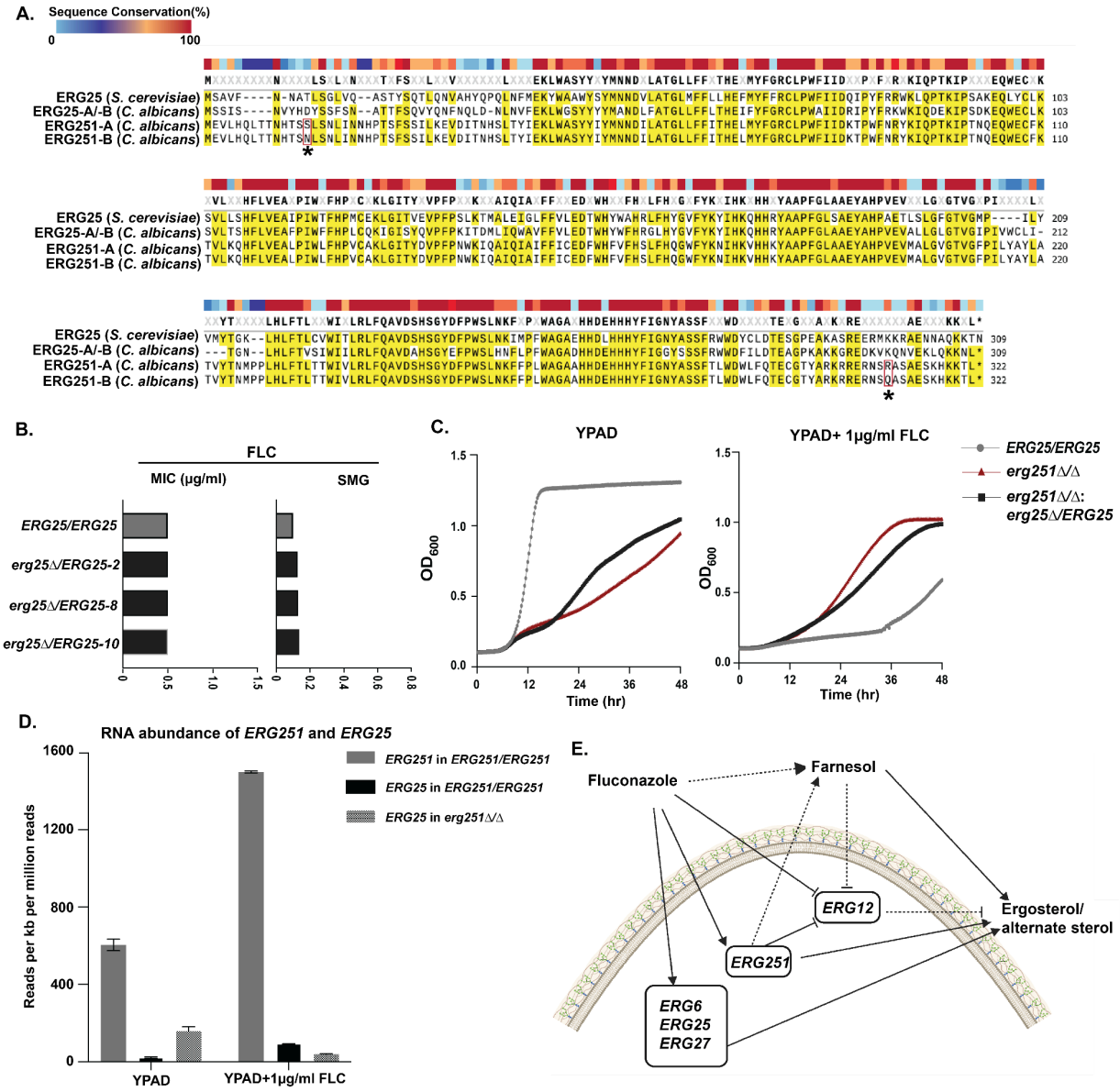

Fig S4. Erg251 is the major methyl sterol oxidase controlling drug susceptibility compared to its paralog Erg25. (**A**) Multiple sequence alignment for *ERG251-A*, *ERG251-B*, and *ERG25*-A/-B (no SNPs between A and B) from *C. albicans* and *ERG25* from *S. cerevisiae,* with yellow highlighting similarity among all four proteins. Colored blocks on the top indicate the sequence conservation. Asterisks (*) and red boxes indicate the locus of non-synonymous variation between *ERG251-A* and *ERG251-B* in *C. albicans.* **B.** FLC susceptibility determined by liquid microbroth dilution at 24hr MIC (left, μg/ml) and 48hr SMG (right, tolerance) in FLC for three *ERG25* heterozygous deletion mutants (*ERG25/erg25Δ-2, -8* and *-10*) in the SC5314 background with SC5314 (*ERG25/ERG25*) as the control. **C.** 48hr growth curve analysis of *erg25* heterozygous deletion strain in *erg251Δ/Δ* background (*erg251Δ/Δ: ERG25/erg25Δ*) in

YPAD (left) and YPAD+1µg/ml FLC (right) with SC5314 (*ERG25/ERG25*) and *erg251*Δ/Δ as the controls. The initial cell densities were OD_{600} of 0.001. MIC and SMG are not measurable for *erg251*Δ/Δ or *erg251*Δ/Δ*: ERG25/erg25*Δ given growth defects in YPAD. **B&C**: Minimum of three biological replicates were performed. **D.** RNA abundance of *ERG251* and *ERG25* in SC5314 (*ERG251/ERG251*), and *ERG25* in *erg251*Δ/Δ. RNA reads were normalised to transcript length and total RNA reads. Values are mean ± SEM calculated from three biology replicates. **E.** Predicted model for how FLC and farnesol impact the expression of *ERG* genes. In the wildtype, low concentrations of FLC promote the expression of most *ERG* genes, including *ERG6*, *ERG251*, *ERG25*, *ERG11* and *ERG27*, leading to the upregulation of ergosterol or/and alternate sterol biosynthesis. However, both low concentrations of FLC and Erg251 pose a negative regulation on Erg12, which may be achieved via farnesol which we predict inhibits *ERG12* [107]. Dashed lines indicate predicted relationships. Figure created in BioRender.com.

SUPPLEMENTARY TABLES

S1 Table. Strains used in this study.

S2 Table. Differentially expressed genes in *erg251*Δ/Δ in YPAD compared to wildtype in YPAD.

S3 Table. GO term analysis for differentially expressed genes in *erg251*Δ/Δ in YPAD compared to wildtype in YPAD.

S4 Table. Differentially expressed GPI genes in *erg251*Δ/Δ in YPAD compared to wildtype in YPAD.

S5 Table. Differentially expressed genes in *erg251*Δ*/ERG251* in YPAD compared to wildtype in YPAD.

S6 Table. Differentially expressed genes in *ERG251/erg251*Δ in YPAD compared to wildtype in YPAD.

S7 Table. GO term for differentially expressed genes in *erg251*Δ*/ERG251* in YPAD compared to wildtype in YPAD.

S8 Table. GO term for differentially expressed genes in *ERG251/erg251*Δ in YPAD compared to wildtype in YPAD.

S9 Table. Differentially expressed genes in *erg251*Δ*/ERG251* in FLC compared to wildtype in FLC.

S10 Table. Differentially expressed genes in *ERG251/erg251*Δ in FLC compared to wildtype in FLC.

S11 Table. Differentially expressed genes in *erg251*Δ/Δ in FLC compared to wildtype in FLC.

S12 Table. Primers used in this study.

S13 Table. *ERG251* SNPs from all FLC-evovled strains.

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