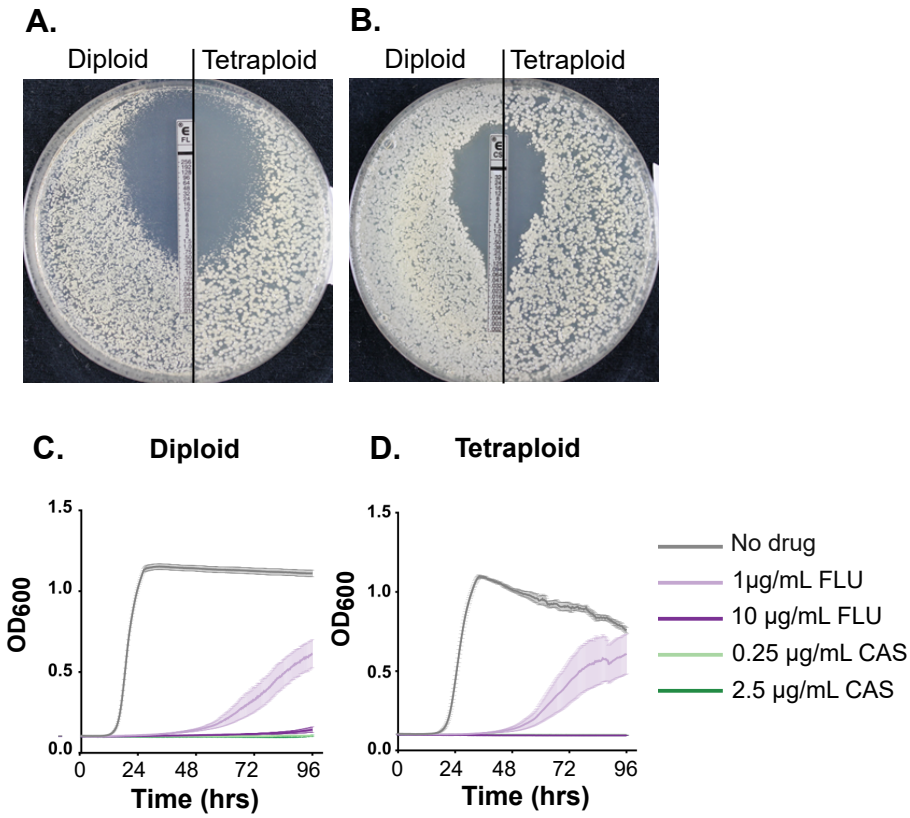


Figure S1: E-test and growth curves can quantify antifungal drug minimum inhibitory concentrations.
A). Diploid and tetraploid fluconazole MIC. The minimum inhibitory concentration (MIC) was determined using a standardized Biomerieux FLU e-test strip for 24hrs at 30°C. The size of the diameter in addition to the concentration of the strip where growth stops is indicative of the minimum inhibitory concentration.

B) Diploid and tetraploid caspofungin MIC. The minimum inhibitory concentration (MIC) was determined using a standardized Biomerieux CAS e-test strip for 24hrs at 30°C.

C) Diploid 96-hr growth curve. The growth curves, shown as average diploid optical density (OD_{600}) across at least 8 biological replicates is plotted over the course of 96hrs. Each line represents a different treatment, gray- no drug (Casitone), lavender- 1µg/mL FLU, dark purple-10µg/mL FLU, light green- 0.25 µg/mL CAS and dark green- 2.5 µg/mL CAS is plotted, with the average and error bars representing the SEM across the 8 replicates.

D) Tetraploid 96-hr growth curve. Same as A, testing at least 8 tetraploid isolates per condition.

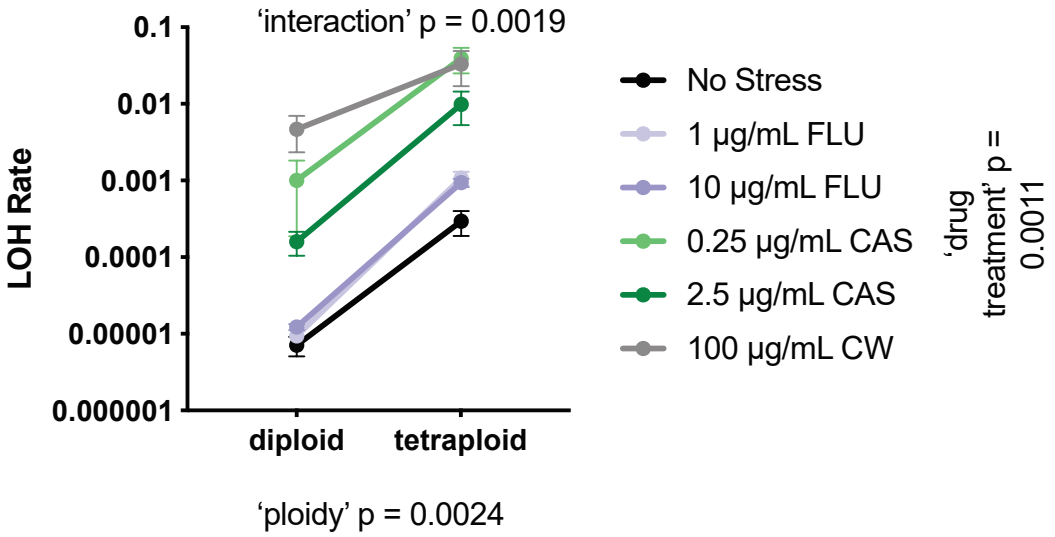


Figure S2: Two-Way ANOVA testing interaction between 'drug treatment' and 'ploidy' of Loss-of-heterozygosity measurements.

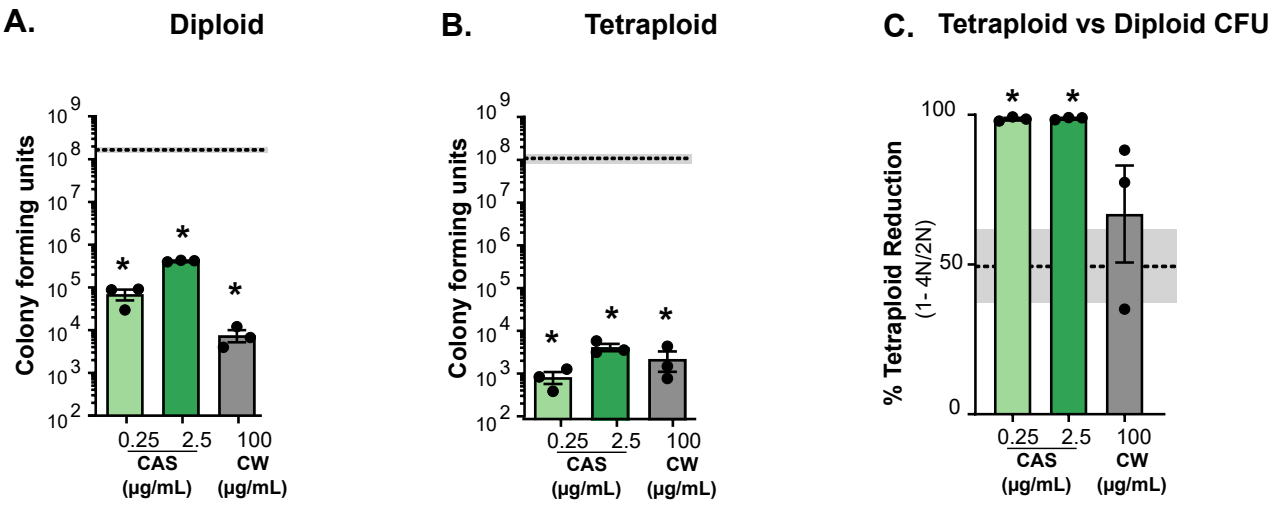
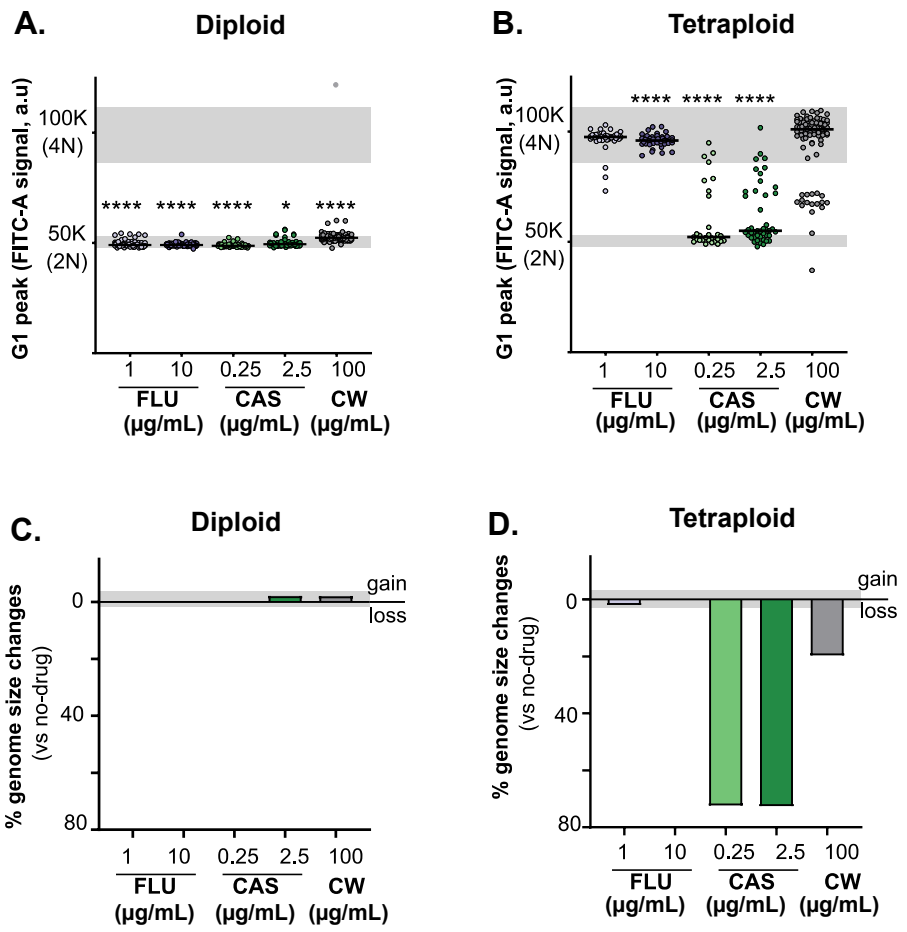


Figure S3: Diploids and Tetraploids are sensitive to antifungals.
A) Diploid colony forming units following 24hrs of exposure with no drug (dashed line). 0.025 ug/mL or 2.5 µg/mL caspofungin ('CAS', light and dark green bars) and 100µg/mL calcofluor while ('CW', gray). The bars represent mean of at least 3 independent experiments (black symbols) and the error bars are +/-SEM. The dashed line and shaded box represent the mean, +/- SEM of CFUs obtained in no drug treatment. Asterisks indicate the drug treatments that differ significantly from no drug treatment (*, $p < 0.05$; ** $p < 0.01$; unpaired Mann-Whitney U-tests).

B) Tetraploid colony forming units. Analysis was performed same as A.

C) The percent reduction of tetraploid CFUs relative to diploid CFUs was determined. Data is displayed and analyzed similarly to (A).



Supplemental Figure S4: Caspofungin and calcofluor white induce large-scale genome size changes in tetraploid *C. albicans* after 120hrs of exposure.

A) Diploid genome size measured after 120hrs of drug exposure using flow cytometry with the G1 peak plotted in a.u (arbitrary units). The gray lines represent the mean of the diploid no-drug control (n = 166), +/- 1 SD and the tetraploid no-drug control (n = 128), +/- 1 SD. Each symbol represents the genome size average of 10,000 events from one culture (1 µg/mL FLU, n = 69, 10 µg/mL FLU, n = 72, 0.25 µg/mL CAS, n = 48, 2.5 µg/mL CAS, n = 47, 100 µg/mL CW, n = 96). The bold line represents across all samples. Asterisks indicate statistical significant compared to the no-drug control diploid (*p < 0.05, ****p <0.0001; Mann-Whitney U-test).

B) Tetraploid genome size**.** Analysis and visualization same as (A). Each symbol represents to genome siza average of 10,000 events from one culture, (1 µg/mL FLU, n = 47, 10 µg/mL FLU, n = 47, 0.25 µg/mL CAS, n = 39, 2.5 µg/mL CAS, n = 44, 100 µg/mL CW, n = 66). The bold line represents across all samples. Asterisks indicate statistical significant compared to the no-drug control diploid (*p < 0.05, ****p <0.0001; Mann-Whitney U-test).

C) Quantification of diploid genome size changes. The percentage of diploid samples (from A) that show genome size changes after 120hrs was calculated as any sample that was 2-standard deviations above (gains) or below (losses) the mean of the no-drug diploid control (dashed line and gray shading).

D) Quantification of tetraploid genome size changes. Analysis and vizualozetion same a (C),

Strain	Genotype	References
Diploids		
MH84	*MTLα/α; ura3::imm434::URA3/ura3::imm434; iro1::IRO1/iro1::imm434; his1Δ::hisG/his1Δ::hisG; leu2Δ/leu2Δ; GAL1/gal1Δ::SAT1*	(Hickman et.al. 2015)
MH297	*MTLa/α; HIS4Δ::NAT/his4-G929T*	This Study
Tetraploids		
MH128	*MTLα/α/a/Δ; ura3Δ/ura3Δ/URA3/URA3, HIS1/HIS1/his1Δ::hisG/his1Δ::hisG; LEU2/LEU2/leu2Δ/leu2Δ; ENO1-GFP:NAT/ENO1/ENO1/ENO1; gal1Δ/gal1Δ/gal1Δ/GAL1;*	(Hickman et. al 2015)
MH296	MTLa*/alpha1Δ-alpha2Δ/MTLa1Δ-a2Δ/alpha*; *ura3Δ::λimm434/ura3Δ::λimm434/URA3/ura3*; *ade2::hisG/ade2::hisG/ADE2/ade2gal1::hisG/gal1::hisG/GAL1/gal1*; *his4Δ::NAT/his4-G929T/HIS4Δ::NAT/his4-G929T*	This study

Table S1: Strains used in this study.

		Reversion Rate (10^{-10})				
			Fluconazole		Caspofungin	
Strain	Ploidy	No drug	1 ug/mL	10 ug/mL	0.25 ug/mL	2.5 ug/mL
MH297	diploid	3.94 (±1.58) n=3	3.88 (±0.72) n=3	1.56 n=3	n.d.	63 n=1
MH296	tetraploid	11.9 (±6.86) n=3	9.45 (±3.91) n=3	20.06 (±6.50) n=3	10.15 n=1	23.3 n=1

Table S2: his4-G929T reversion rates in diploid and tetraploid *C. albicans.* The reversion rates were determined by fluctuation analysis using Luria- Delbruck Method (Luria S, Delbrück M 1943) and are shown above with the standard deviation in parenthesis. The 'n' value represents the number of independent experiments in which reversion events were detected.