Genomic Instability of *Candida albicans* in Centromere Regions

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Background

- *Candida albicans* is a common opportunistic fungal pathogen of the human microbiome capable of large chromosomal rearrangements that confer drug resistance (e.g. i(5L)) (Figure 1).
- Antifungal resistance and limited classes of antifungal drugs pose severe threats for the treatment of fungal infections caused by *Candida* species.

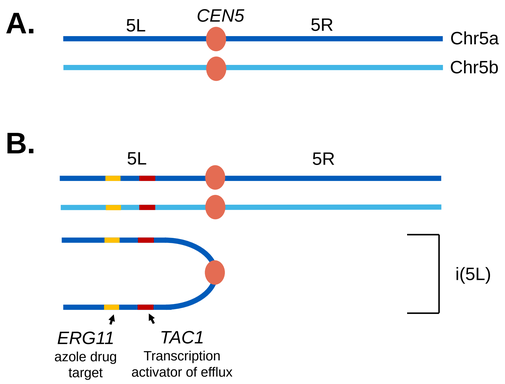

Figure 1: (A) The *C. albicans* genome is a heterozygous diploid as depicted by chromosome haplotypes (Chr5a and Chr5b) and has both left and right arms separated by a single centromere. **(B)** Schematic of homologous chromosomes and isochromosome 5L in aneuploid isolates. *ERG11 and TAC1*, genes that confer azole resistance, are present on all copies of Chr5L.

Methods

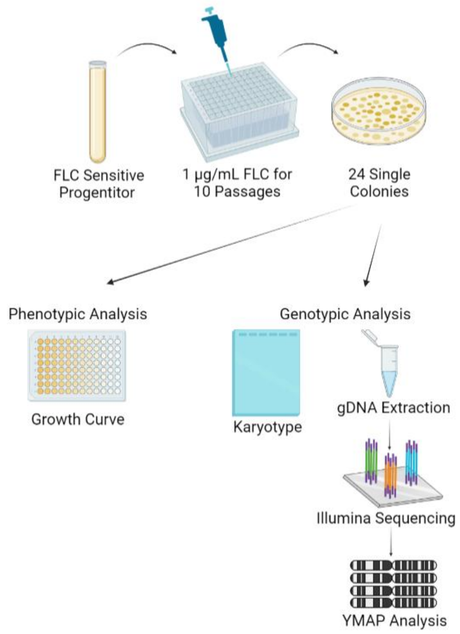

Figure 2: Experimental Layout

Isolates were derived from an in vitro evolution experiment under antifungal stress. Further phenotypic and genotypic analysis was used to establish the origin of the inversion leading to the observation of a novel isochromosome (i(5R)).

Comparative Fitness of Isolates Containing Isochromosomes

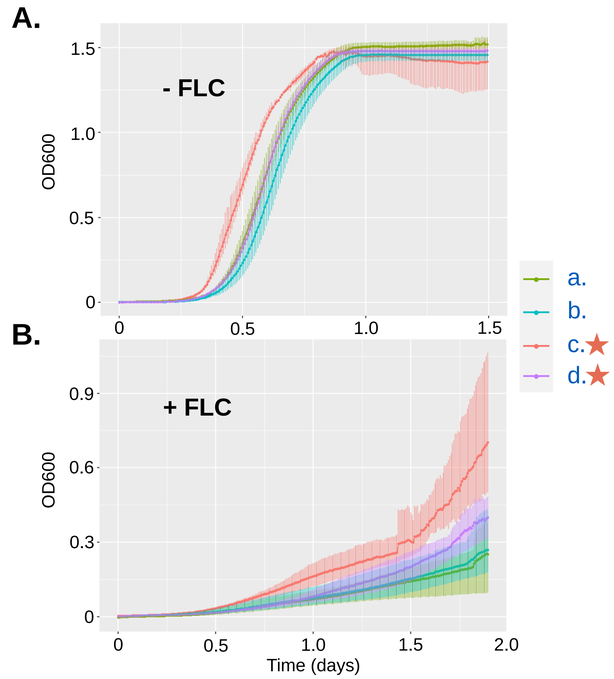

Figure 3: (A) Growth curves in the absence of drug comparing fitness of whole genome sequenced samples with isochromosomes. **(B)** Growth curves in the presence of 1µg/mL of fluconazole.

Model for Rearrangement of Full-length Chr5 into Isochromosomes

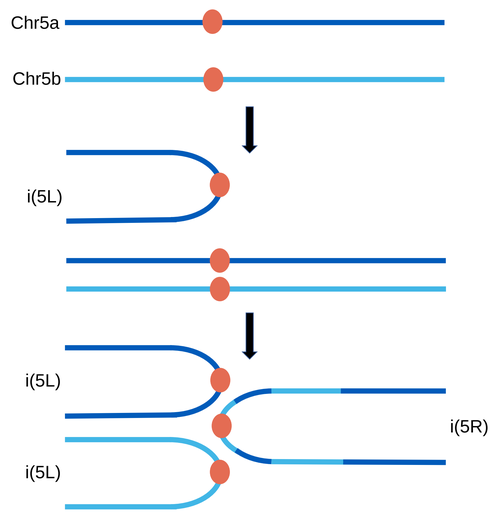

Figure 5: Chromosomal haplotypes are depicted as type Chr5a and Chr5b. An initial i(5L) is predicted to be formed followed by the second i(5L) from the other haplotype with synchronous i(5R) formation by recombination of the right arms of both Chr5 haplotypes. Consecutive degradation of the original chromosomes is expected to follow isochromosome formation.

Chr5 Rearrangement and Segmental Aneuploidy Detected by Single Colony Genomic Analysis

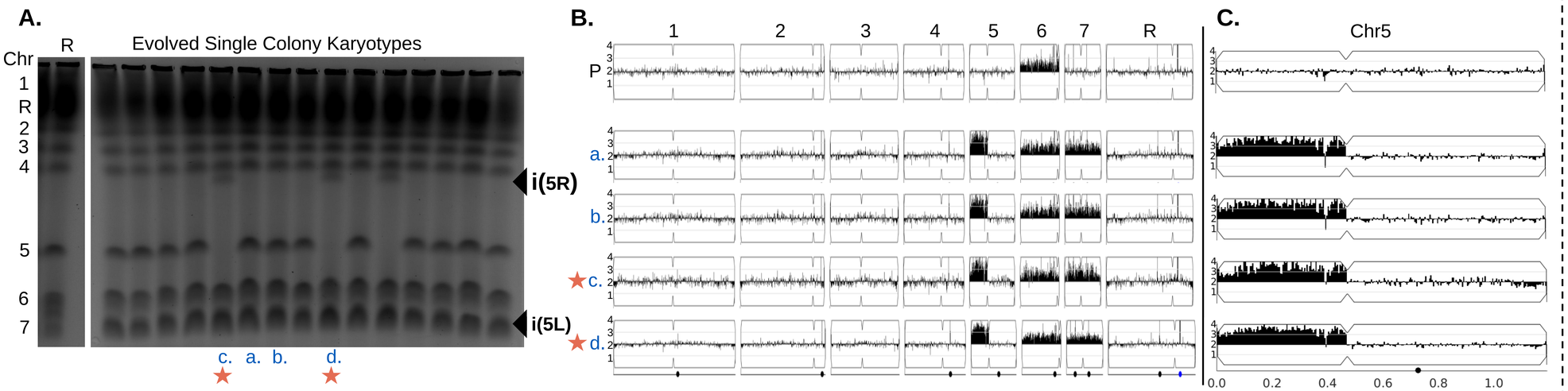

Figure 4: (A) Single colonies evolved by fluconazole and analyzed by **karyotype** gel (colony label, x-axis, chromosome number, y-axis, and R for reference strain) with the control strain on the left and the location of **i(5L)** and **i(5R)** on the right. **(B)** Visualization of **Illumina whole genome sequencing** data with chromosome copy number (y-axis), chromosome position (x-axis), and the progenitor (P) using Yeast Mapping Analysis Pipeline (YMAP). **(C)** Chr 5 is shown in closer detail with aneuploidy of the left arm represented by increased copy number.

Future Directions

- Conformation of i(5R) via Southern blotting
- MICs to assess drug resistance in cells with isochromosomes
- Single colony plating to compare colony size.

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References

https://z.umn.edu/references-go