Cracking the Code of Combinatorial Stress: Genomic Innovation in Candida glabrata

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Candida glabrata is an emerging human fungal pathogen notable for its exceptional resistance to antifungal drugs and innate immune attack. Unlike other *Candida* species, *C. glabrata* thrives under combinatorial stresses, such as those encountered within macrophage phagolysosomes by deploying unique genomic adaptations. In this work we have combined, forward genetics, comparative genomics, and transcriptomic profiling to uncover the genomic basis of this stress resilience.
We have developed and exploited a functional mating system in *C. glabrata* to dissect heritable resistance traits through tetrad analysis of combinatorial stress-resistant mutants. Bulk segregant sequencing and SNP mapping of over 400 dissected tetrads have identified single-locus variants conferring high-level resistance to oxidative and osmotic stress combinations. Parallel time-resolved RNA-seq during combinatorial stress exposure reveals a distinct transcriptional program that is not simply additive, suggesting emergent regulatory mechanisms unique to stress synergy.
These genomic insights are further contextualized by *ex vivo* and *in vivo* assays demonstrating how combinatorial stress adaptation enhances immune evasion and virulence. Together, this data uncovers a combinatorial stress response (CSR) network in *C. glabrata* a potential reservoir of therapeutic and diagnostic targets. Highlighting the power of integrative genomics to illuminate pathogen evolution and genome plasticity under host-imposed pressures. It provides a model for how genomic innovation can drive clinical persistence and resistance, with broad implications for antifungal strategy development and understanding genome dynamics in fungal pathogens.