Hypersusceptibility to Azole Antifungals in a Clinical Isolate of Candida glabrata with Reduced Aerobic Growth

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Résumé en anglais	Petite mutations have been described in Saccharomyces cerevisiae and pathogenic yeasts. However, previous studies of the phenotypic traits of these petite mutants reported that they express azole resistance. We describe a clinical isolate of Candida glabrata with a striking association between increased susceptibility to azoles and respiratory deficiency. This isolate was obtained from a urine sample together with a respiration-competent C. glabrata isolate which exhibited azole resistance. The respiratory status of the two isolates was confirmed by cultivation on glycerol-containing agar and oxygraphy. Flow cytometry revealed the normal incorporation of rhodamine 123, and mitochondrial sections with typical cristae were seen by transmission electron microscopy for both isolates. Together, these results suggested a nuclear origin for the reduced respiratory capacity of the hypersusceptible isolate. The sterol contents of these isolates were similar to the sterol content of a reference strain. Sequencing of the ERG11 and PDR1 genes revealed that the sequences were identical in the two isolates, demonstrating their close relatedness. In addition to silent mutations, they carried a nonsense mutation in PDR1 that led to the truncation of transcription factor Pdr1p. They also overexpressed both PDR1 and one of its targets, CDR1, providing a possible explanation for the azole resistance of the respiration-competent isolate. In conclusion, in addition to azole resistance, which is a common feature of C. glabrata mitochondrial petite mutants, the mutation of a nuclear gene affecting aerobic growth may lead to azole hypersusceptibility; however, the mechanisms underlying this phenotype remain to be determined.
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