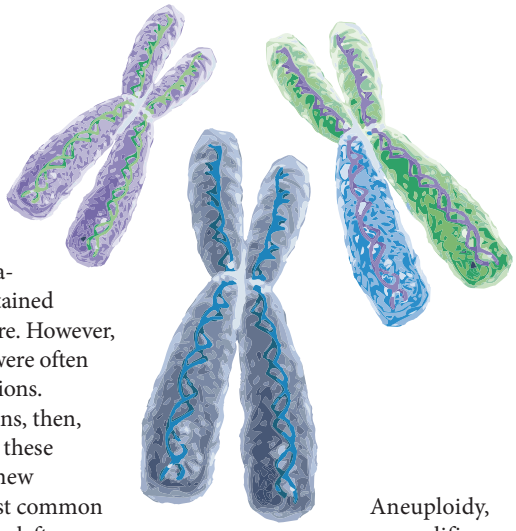
FUNGAL PATHOGENESIS

Varying for virulence



How has *Candida glabrata* become the second most prevalent yeast pathogen in humans? The answer almost definitely lies in its ability to rapidly change its genomic organization, and a report by Poláková *et al.* provides further insight into this phenomenon.

The authors analysed isolates of *C. glabrata* from randomly selected patients. When they investigated several coding and non-coding sequences, they found little variability between the isolates, so differences in gene sequence are not responsible for the increased virulence of *C. glabrata*.

At the chromosomal level, though, strong variations in structure were uncovered when the karyotypes were analysed. Large chromosome size polymorphisms were observed, derived from either translocation — reciprocal and non-reciprocal — of chromosome arms or interchromosomal duplication, which involved translocation of duplicated segments of 40–700 kb. In another type of structural change, new chromosomes were 'acquired'. Although small, these new chromosomes comprised a large (120–200 kb) segmental duplication that included a partial chromosome and the centromere region; viable telomeric chromosome ends were also present. Chimeric chromosomes were also formed from fusions of deleted parts of original chromosomes, often following a duplication event, and also contained a single active centromere. However, the new chromosomes were often lost over several generations.

Under what conditions, then, might *C. glabrata* retain these duplicated regions and new chromosomes? The most common duplications involved the left arms of chromosomes E and F, which contained several genes potentially involved in the interaction between *C. glabrata* and its host. Among the encoded gene products were ATP-binding cassette transporters, which are associated with resistance to several drugs, and secreted aspartyl proteases and a phospholipase B, both of which are potentially important for virulence. One strain of *C. glabrata* with an extra copy of part of chromosome F on a new chromosome could withstand almost ten times as much fluconazole than it could without this minichromosome. Similarly, the extra copy of a partial chromosome F was retained when this isolate was grown in medium containing azole, but was lost without this selective pressure, indicating that this chromosome is advantageous for growth in the presence of this antifungal agent.

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Aneuploidy, gene amplification and gene duplication are reportedly associated with drug resistance and virulence in certain other pathogens, but not in other yeasts. In fact, aneuploidy in *Saccharomyces cerevisiae* reportedly interferes with cell cycle progression, and this condition, along with changes in chromosome structure, is usually associated with pathological events in other eukaryotes. As an asexual species, however, *C. glabrata* does not need to preserve its genomic organization, and its ability to reshape its genome will undoubtedly present problems in our battle against this successful pathogen.

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ORIGINAL RESEARCH PAPER Poláková, S. *et al.* Formation of new chromosomes as a virulence mechanism in yeast *Candida glabrata*. *Proc. Natl Acad. Sci. USA* **106**, 2688–2693 (2009)