The diverse genomes of *Candida auris*

Lancet Microbe 2024
Published Online
https://doi.org/10.1016/S2666-5247(24)00135-6

Candida auris is an emerging global public health threat and is classified as a WHO critical priority fungal pathogen, causing invasive candidiasis with a crude mortality of 45%.[1] The emergence, epidemiology, and evolution of *C auris* have been enigmatic, with multiple highly genetically distinct and clonal clades appearing simultaneously and even co-existing within single-hospital outbreaks.[2] First described in Japan in 2008, following a case of otomycosis in a 70-year-old woman,[3] *C auris* has now been identified in all major continents,[4] with infection rates that have surpassed those of other *Candida* spp in lower-middle income settings.[5] *C auris* has a highly adhesive, stress-tolerant, and environmentally persistent phenotype, and heterogeneity in traits such as aggregation suggest the clinical relevance of genotypic variation. Five clades of the pathogen have been described between 2009 and 2018. In addition, a new clade VI has recently been identified in Bangladesh[6] and Singapore,[7] with more new genotypes likely to follow. In this Comment, we discuss the diverse genomes of *C auris*, including their clade designations, ongoing efforts to predict genetic recombination, and the epidemiology and origins of *C auris*.

The six clades of *C auris* have been numbered but are sometimes still referred to by the geographical location in which they were originally discovered (I=South Asia, II=East Asia, III=South Africa, IV=South America, V=Iran, and VI=Bangladesh). Such geographical classifications have been discouraged because of ethical considerations[8] as they do not necessarily reflect clade origins. Although suggestions indicating the classification of clades to separate species are absent, such initiatives are plausible based on other reclassifications of lineages in pathogenic fungi.[9] Separate species designations can complicate the literature when biological differences are unclear, sampling reveals intermediate genotypes or groups, or hybrid or recombinant genotypes that overlap species boundaries are discovered. Conversely, clade classification is simple, facilitates communication, and allows expansion as new clades are identified or combination if recombinant isolates between populations are identified, without breaking expected species genetic boundaries. As such, the six recommended *C auris* clades can distinguish major and geographically overlapping populations, with future sub-clade designations useful for epidemiological tracking.

The six clades of *C auris* do not show the genetic hallmarks of recombination, hybridisation, or sexual cycle. Compelling evidence suggesting sexual recombination via population genetic tests is missing. Surprisingly, *C auris* appears to be clade-specific for its mating type locus (MTL; MTLa in clades I, IV and V and MTLα in clades II, III, and VI),[2,7,10] and hybrids have not been described despite the coexistence of clades with opposite MTL (clades I and III) in a single hospital setting and even within individual patients. Several essential components of the meiosis toolkit are missing or are pseudogenised for *C auris* clades I–IV and possibly other clades.[10] Although a sexual cycle in *C auris* appears unlikely, alternative lifecycle strategies might compensate for and contribute toward genetic diversity; for instance, these strategies could involve a parasexual cycle or horizontal gene transfer, both of which have been reported in and between other *Candida* species.

Genomic epidemiology has revealed key insights into the temporal and spatial dimensions of *C auris*. Whole-genome sequencing of 304 isolates belonging to four clades revealed a weak phylogeographic substructure, highlighting the ongoing international transmission of *C auris*,[2] which continues to spread within and between hospital wards and microevolves within patients despite continued antifungal drug exposure. For example, 133 isolates from ten outbreaks in the USA revealed transmission networks with Africa, South America, South Asia, and East Asia, indicating that multiple clades of *C auris* have been introduced into the USA, perhaps multiple times.[11] However, only 7% of these clinical cases showed clear evidence of being acquired through exposure to health-care settings abroad, suggesting that the outbreak or sequenced isolates cannot be traced to the index case.

Genomics has offered substantial insight into the epidemiology of *C auris*; however, the origins and time of emergence of each clade and of its most recent common ancestor remain speculative. The discovery of a new clade (VI) suggests that the population genetics of *C auris* is remarkably diverse and that a non-recent speciation event, or events, led to the genesis of each of these separate clades. Taxonomy and naming of these clades will lead to confusion and perhaps disagreement, although new opportunities for comparative genomics analyses and phenotypic screening might arise, which could provide

new insights into the evolutionary history of and trajectory for *C auris*.

HG and RAF are part of the Medical Research Council Centre for Medical Mycology at University of Exeter (MR/N006364/2; MR/V033417/1). HG is supported by a Medical Research Council Doctoral Training Grant MR/P501955/2. RAF is supported by a Wellcome Trust Career Development Award (225303/Z/22/Z). JR declares no competing interests.

*Hugh Gifford, Johanna Rhodes, *Rhys A Farrer*
r.farrer@exeter.ac.uk

MRC Centre for Medical Mycology, University of Exeter, Exeter EX4 4QD, UK (HG, RAF); MRC Centre for Global Disease Analysis, Imperial College London, London, UK (JR); Department of Medical Microbiology, Radboudumc, Nijmegen, Netherlands (JR)

1 Chen J, Tian S, Han X, et al. Is the superbug fungus really so scary? A systematic review and meta-analysis of global epidemiology and mortality of *Candida auris*. *BMC Infect Dis* 2020; **20:** 827.

2 Chow NA, Muñoz JF, Gade L, et al. Tracing the evolutionary history and global expansion of *Candida auris* using population genomic analyses. *mBio* 2020; **11:** e03364-19.

3 Satoh K, Makimura K, Hasumi Y, et al. *Candida auris* sp. nov., a novel ascomycetous yeast isolated from the external ear canal of an inpatient in a Japanese hospital. *Microbiol Immunol* 2009; **53:** 41–44.

4 Chybowska AD, Childers DS, Farrer RA. Nine things genomics can tell us about *Candida auris*. *Front Genet* 2020; **11:** 351.

5 Prayag PS, Patwardhan S, Panchakshari S, Rajhans PA, Prayag A. The dominance of *Candida auris*: a single-center experience of 79 episodes of candidemia from Western India. *Indian J Crit Care Med* 2022; **26:** 560–63.

6 Khan T, Faysal NI, Hossain MM, et al. Emergence of the novel sixth *Candida auris* clade VI in Bangladesh. *Microbiol Spectr* 2024; published online June 6. https://doi.org/10.1128/spectrum.03540-23.

7 Suphavilai C, Ko KKK, Lim KM, et al. Discovery of the sixth *Candida auris* clade in Singapore. *medRxiv* 2023; published online Aug 6. https://doi.org/10.1101/2023.08.01.23293435 (preprint).

8 Mayrianne Champagne A. Why scientists should not name diseases based on location. https://asm.org:443/Articles/2021/May/Why-Scientists-Should-Not-Name-Diseases-After-Plac (accessed March 28, 2024).

9 Hagen F, Khayhan K, Theelen B, et al. Recognition of seven species in the *Cryptococcus gattii/Cryptococcus neoformans* species complex. *Fungal Genet Biol* 2015; **78:** 16–48.

10 Muñoz JF, Gade L, Chow NA, et al. Genomic insights into multidrug-resistance, mating and virulence in *Candida auris* and related emerging species. *Nat Commun* 2018; **9:** 5346.

11 Chow NA, Gade L, Tsay SV, et al. Multiple introductions and subsequent transmission of multidrug-resistant *Candida auris* in the USA: a molecular epidemiological survey. *Lancet Infect Dis* 2018; **18:** 1377–84.