



On the Origin of *Candida auris*: Ancestor, Environmental Stresses, and Antiseptics

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ABSTRACT *Candida auris* has emerged as a serious threat to the health care settings. Advancements in molecular biology have provided several insights into the evolution of *C. auris* since it was first described in 2009. However, the simultaneous emergence of four different clades of the fungus at distinct geographical locations remains a mystery. The hypotheses already proposed by researchers fall short of explaining how and why *C. auris* emerged. In this article, we theorize that *C. auris* emerged from a common ancestor, subsequently migrated to specific geographical locations, and diversified genetically. This hypothesis is supported by genomic insights, historical events, and indirect scientific facts. *C. auris* adapted to humans at locations and times coinciding with the divergence from the most recent common ancestor, emerging almost simultaneously as an opportunist pathogen due to antiseptic practices. Future research will support or refute this hypothesis.

KEYWORDS *Candida auris*, emerging infection, epidemiology, evolution

The scientific community was unaware of the existence of *Candida auris* until 2009 when it was first reported as an agent of ear infection (1). Within the next decade, *C. auris* emerged as a “serious threat” to the health care settings and rapidly spread to more than 40 countries, resulting in multiple outbreaks with high mortality and multiple-drug resistance. Identification of the pathogen is difficult with routine diagnostic mycology, which adds to the problem (2). While we do not know the environmental niches of *C. auris* or how it has evolved as an opportunistic pathogen, we do know that this fungus commonly colonizes hospitalized patients (axilla, groin, and nares) (2). Nonetheless, definitive evidence of community transmission is lacking (3). To date, molecular analysis of global *C. auris* isolates have identified four distinct clades (clade I [South Asian], clade II [East Asian], clade III [South African], and clade IV [South American] [4, 5] with the possibility of a fifth clade from Iran [6]). The four distinct clades emerged almost simultaneously on different continents, but it is not known if all had a common ancestor (4).

Multiple hypotheses have been proposed to explain the emergence of *C. auris*. They include improved diagnostics (7), antifungal selection pressure (8), global warming (3), and human migration (9). Though each hypothesis addresses some aspects of the evolution of *C. auris*, none of them fully explain how and why *C. auris* emerged as a pathogen. The availability of molecular techniques has improved *C. auris* detection by overcoming the shortcomings of phenotypic identification. This alone cannot justify its emergence, as only six misidentified *C. auris* isolates were detected among 20,788 global *Candida* species isolates collected from 1997 to 2016 by the SENTRY Antifungal Surveillance Program (7). The theory that *C. auris* has been selected for by antifungal agents akin to azole-resistant *Aspergillus fumigatus* is also an insufficient explanation (8). The hot spots of *C. auris* do not coincide with areas of azole overuse or agriculture use. It also fails to account for the fitness costs associated with multidrug resistance (5). The third theory suggests that an overall increase in earth’s surface temperature

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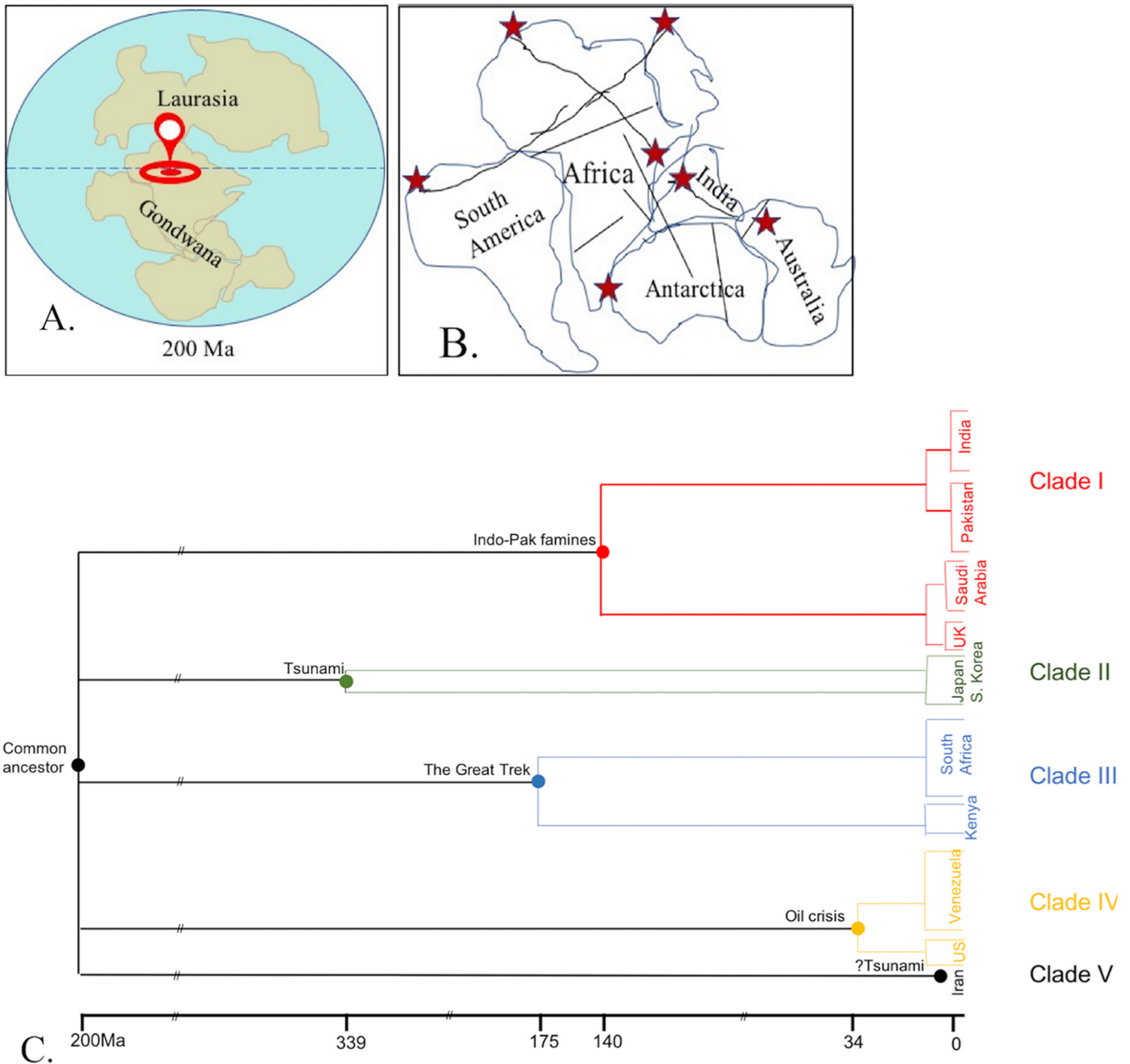


FIG 1 Diagrammatic representation of the possible location of the common ancestor of *C. auris* and the mechanism of its spread to specific geographical areas it emerged from. (a) The possible site of the common ancestor (as indicated by the red location pin) could be somewhere between the northern and central Sahara some 200 million years ago when the landmass of Earth consisted of Laurasia (Europe and North America) in the Northern Hemisphere and Gondwana (Africa, South America, India, Australia, and Antarctica) in the Southern Hemisphere. (b) The direction and extent of the major fault lineaments (indicated as interrupted lines), occurring secondary to tectonic activities of the Earth's crust, that could have served as possible routes for seeding of *C. auris* into the very regions it has been reported from (indicated by red stars). (c) Schematic timeline depicting the specific environmental disturbances coinciding with the most recent common ancestor of each clade of *C. auris* that could have precipitated the environment-to-human cross over of that clade at that particular place and time.

allowed thermotolerant *C. auris* to breach the environment-to-human interface (3, 10). This first occurred in the rural areas possibly via an intermediate avian host, and subsequently to health care settings via human migration to urban cities. Climatic change has been linked to the emergence of new infectious diseases, including mycoses in general and *C. auris* infection in particular (11). However, unlike *Candida glabrata* with a reservoir in seabirds (12), *C. auris* has neither been isolated from any bird (13) nor do the routes of bird migration support the reported pattern of its clade distribution (14). Rural amplification also demands a proven community transmission (3). The human migration theory can justify coexistence of multiple clades at certain places (9), but it

fails to clarify predominance of one clade at other places. Therefore, the origin of *C. auris* remains a mystery.

All theories proposed so far cannot explain the simultaneous emergence of different clades of *C. auris* around the world and its evolution as an opportunistic pathogen. Here we propose a hypothesis, connecting successive facts, which may explain the emergence of *C. auris*. We theorize the following: (i) There was a common ancestor of *C. auris* that was seeded into the areas where it has been reported (common ancestor). (ii) Significant environmental stresses coincided with divergence from the most recent common ancestor (TMRCA) and facilitated selection of each clade by breaching the environment-to-human interface (environmental stress). (iii) *C. auris* gained virulence and resistance traits while surviving silently on skin for years (stealth existence) and was selected for through the biased use of hand sanitizers in health care settings (antiseptic bias). We further propose that (iv) tsunamis played a role in the truncated evolution of clade II (tsunami-water cycling), thus contributing to the interclade differences.

Common ancestor. Several striking features, distinct from other *Candida* spp., raise the possibility of a common ancestor for the four clades of *C. auris*. However, the vast geographical distances between these clades questions the possible location of the common ancestor and its spread to distinct locations. Delving into the history of Earth, several missing links to the proposed common ancestor could be gathered. The Earth witnessed four major mass extinctions between 300 million years ago (Ma) and 170 Ma. The changing surface temperatures caused nearly all land species to go extinct, leaving behind few aquatic ecological niches where temperature changes were less steep (15). Molecular evolutionary studies of *C. albicans* isolates suggest that the *Candida* ancestor (possibly the ancestor of the CTG group containing *C. albicans*, *C. tropicalis*, *C. auris*) inhabited the Earth more than 800 Ma (16). It is possible that *C. auris*, forming part of an aquatic niche, survived through increasing temperatures (thermotolerance) via UV radiation-induced mutagenic changes (17) or overexpression of *HSP90* (5). So where could the reservoir of *C. auris* be? Around 250 Ma, the landmass of Earth consisted of a large continent named Pangea (meaning “all the landmass”) that later (~200 Ma) separated into two halves due to tectonic activities: Gondwana (present-day Africa, South America, India-Pakistan, Australia, and Antarctica) in the south and Laurasia (present-day North America and Europe) in the north (Fig. 1a) (18). The emergence of *C. auris* at three specific sites (South Africa, India-Pakistan, and Venezuela) suggests that their common ancestor was located in Gondwana, possibly somewhere in northern Gondwana corresponding to modern-day Saharan Africa (Fig. 1a). Sahara became a desert some seven million years ago before which it had widespread wetlands and lakes, a possible ideal niche for *C. auris*. The mass extinctions in Gondwana may have given *C. auris* the opportunity to flourish (15), forming a part of one of the aquatic ecosystems that survived. The spread of *C. auris* may be explained by how Gondwana broke into different continents owing to tectonic activities some 150 million years ago. These tectonic activities led to major fault lineaments (linear zones of geological fractures or bends), especially between northern and central Africa (Fig. 1b), leading to an easy seepage of water as rivers, streams, and lakes (19). We believe these geological events may have transported water ecosystems containing *C. auris* to distant parts of Gondwana. Not only do these fault lines correspond to present-day rivers in India, Pakistan, and South Africa, but also the strategic locations of these faults correspond to the present-day sites of clade-specific *C. auris* distribution (i.e., Tibesti lineament extending from northern Africa touching Spain to Kenya for clade III, Guinean-Nubian and Levant lineaments extending from Venezuela to Israel for clade IV) (19). *C. auris* might have also lodged “along” the way, as is speculated for the region that escaped desertification (present-day Brazil), which harbors *C. auris* (20). Nevertheless, as the continents drifted apart from Gondwana, India-Pakistan attained its present-day location by merging into Asia, South America joined with North America, while Australia and Antarctica separated out to form independent continents (18). Japan could have also received a *C. auris*-containing aquatic niche from Gondwana, which is believed to have formed a small part of the island country (21). Hence, *C. auris* was

“seeded” from the heart of Gondwana onto the very lands it has been documented from, i.e., India-Pakistan area (clade I), Japan (clade II), South Africa (clade III), and Venezuela (clade IV). Each clade was subsequently exposed to diverse environmental stresses over thousands of years leading to the differences seen today among the clades (5). The amplified fragment length polymorphism (AFLP)-derived minimum spanning tree placed African isolates of *C. auris* as a connecting link between closely related *C. haemulonii* and other clades (22). *C. haemulonii* was also isolated from a fish found in the Atlantic Ocean and seawater off the Portugal coast (5). These observations support the possible location of *C. auris*’ ancestor and its spread to the specific locations via these aquatic niches. We acknowledge that the great explorations of the Portuguese (23) during the 15th-17th centuries could have contributed to seeding of *C. auris*, as their travel itinerary coincides with the hot spots of South Africa, India, Australia, and Japan. However, this possibility does not support seeding of *C. auris* in Venezuela. Thus, our theory of the Gondwana common ancestor fits perfectly with how *C. auris* was seeded into specific geographical areas. However, its sudden emergence as a human pathogen in recent times is yet another mystery. To explain the sudden emergence, we propose that subsequent environmental stress has played an important role.

Environmental stress. Once seeded into the wetlands of these respective geographical areas, *C. auris* adapted to new ecological niches through various genetic and epigenetic changes. *C. auris* may have gained virulence and resistance traits from closely related species. Genomic studies revealed several orthologs of known virulence factors of *C. albicans* and *C. haemulonii* in *C. auris* (5, 24) and close relation to *C. lusitanae* on functional annotation (25). The subsequent environmental stress explains how and when each *C. auris* clade breached the environment-to-human interface. The “molecular clock,” the measure of evolutionary change in nuclear material and diversification from related species over time, suggests that the time to the most recent common ancestor (TMRCA) was 140, 339, 175, and 34 years for clades I, II, III, and IV, respectively (9). Though the clade-specific ancestors simultaneously reached their particular geographic locations many years ago, certain environmental imbalances at particular times caused clonal expansion of each clade in their respective region (Fig. 1c). Exactly 140 years ago, between 1880 and 1890, India and Pakistan (one country at the time) faced three major famines (26), which led to gradual drying of bodies of water over large areas and subsequent intensive cultivation on the semidry river banks. This incident would have exposed some humans to wetlands harboring *C. auris*, thus introducing it onto human skin, maybe as a mere colonizer. Further, relief measures sought from mainland Britain and the nearest colonial port in Saudi Arabia (27) explains the common clade I in India, Pakistan, Britain, and Saudi Arabia. Regarding the emergence of clade II, major earthquakes in Japan (1677) and South Korea (1681) (28) and the subsequent tsunamis could have introduced *C. auris* from the Sea of Japan to mainland humans, as they coincide with the TMRCA of clade II. The possible transition of clade III from the environment to humans in South Africa occurred some 175 years ago. Surprisingly, it coincides with the Great Trek of Africa (29) involving massive human migration during the 1835s to the 1845s. Clade IV, having a TMRCA of just 34 years breached the environment-human barrier most recently. The emergence of *C. auris* in Venezuela is concomitant with desperate attempts to save its crippling economy by extracting oil from offshore fields around 1985 to 1989 (30). Such activities could have disrupted the aquatic ecological niches (possibly harboring *C. auris*). Similar environmental stress has been proposed for the emergence of *Cryptococcus gattii* in the Pacific Northwest. The passage of contaminated ballast water owing to opening of the Panama Canal coincides with the TMRCA of *C. gattii* (31). Though our hypothesis of environmental stress causing an environment-to-human transmission has no strong evidence to support it, it does have strong support of historical events and may fill the missing links of how each clade of *C. auris* gained entry into the human reservoir at their respective time and place.

Stealth existence. The question remains, if *C. auris* has been part of the human mycobiome all these years (34 to 339 years), why was it never reported earlier? It possibly had a stealth existence because of inadequacies of diagnostic techniques, lack of

knowledge of the skin mycobiome, and absence of colonizing isolates in the collection of the SENTRY study (7). *C. auris* probably existed as a minute fraction of the skin mycobiome and even dispersed to involve nares and external ear. The question remains that if *C. auris*, fully equipped with resistance and virulence genes, was already surviving on human skin for many years in extremely small quantities, why did it suddenly create such a health care havoc? For this, we propose a possible explanation of antiseptic bias.

Antiseptic bias. Alcohol-based antiseptics perform best in the eradication of *C. auris* from skin (32, 33); however, their use is largely limited to the hands of health care workers as alcohol-based hand sanitizers and rubs. The body sites of patients are usually cleaned and decolonized using chlorhexidine, hydrogen peroxide, and non-alcohol-based antiseptics, which are not as effective against *C. auris* (32, 33), thus providing a growth opportunity for *C. auris* at these sites. One might argue that some resilience to these compounds is also exhibited by other species like *C. albicans* (32), so why is only *C. auris* biased by this? It is noteworthy that while planktonic stages of *C. auris* and *C. albicans* exhibit similar resilience to antiseptics, the biofilms of *C. auris* are much more resilient than those of *C. albicans* or *C. glabrata* to 0.5% chlorhexidine and 3% hydrogen peroxide (34). Surviving exposure to non-alcohol-based antiseptics and continuously being supplied from commensal sites (which were not exposed to hand sanitizers), *C. auris* might form biofilms and further replenish other colonizing sites. We believe that this antiseptic bias in the selection of antiseptic and choice of body site in the past decade has caused *C. auris* to emerge in health care settings and not as a community pathogen. Exposure to several broad-spectrum antimicrobials in critically ill patients may select for *C. auris* biofilms on skin, which can then gain access into the bloodstream via multiple invasive devices used in such patients.

The fact remains that unlike other clades, which cause invasive health care-associated infections and outbreaks, clade II is limited to infections of the ear. Clade II is also the least pathogenic and the least resistant clade despite being the oldest (35). We propose that the periodic tsunamis (>20 tsunamis in Japan; 3 in South Korea) since the TMRCA (28) might have brought the original seeded strains of *C. auris* to the mainland. Tsunamis have been implicated in increased fungal infections, be it invasive “tsunami lung” in a near-drowning Japanese patient (36) or emergence of *Cryptococcus gattii* in the Pacific Northwest (31). The ballast tank-tsunami hypothesis of *C. gattii* (31) gained popularity as the fungus was proven to be sexual where recombination was possible (37). Perhaps our theory of tsunami-water cycling will gain more impetus once a sexual phase is proven in *C. auris*. The observations that clade II has genomic relatedness to ancestral strains and lost subtelomeric sections responsible for adhesins (5) support the possibility of blunted evolution owing to local water cycling along the coasts. It is likely that a relatively low density of cells arrived on the mainland and they too were washed back into the sea via natural rain runoff or snow melt, thus hampering their coevolution with humans. Its access was limited to the external ear of divers and swimmers who entered such aquatic ecosystems and caused ear infection in the opportune host, like those on long-term antibiotics or with ear trauma (35). This theory of tsunami-coastal water cycling may be extrapolated to a *C. auris*-associated ear infection from Iran that has been proposed as the fifth clade (6). The initial primary seeding of *C. auris* in Iran remains enigmatic, and it may have been introduced into the Persian Gulf through trade and travel. The possibility exists that all four clades may have been introduced over time, allowing intra- and interclade transfer of genetic material (5). The increased number of tsunamis in Iran, occurring yearly since 2002 (38), may have caused rapid mixing of the old and new strains, thus giving rise to a strain similar to clade II in pathogenicity yet distinct enough to qualify as a novel clade. The fact that the 14-year-old Iranian patient (39) had no history of travel outside Iran but did have a history of frequent swimming suggests that she did not acquire *C. auris* from a distant land but that it was brought to her via water. The exact evolution of this fifth clade will become clearer as more isolates are subjected to molecular clock analysis.

C. auris, like a patient predator, had been lurking around from times immemorial. It kept adapting to the varied ecosystems that were presented to it, finally gaining access to the human host and causing the much-feared pathogenic switch.

Hypothesis testing. Future studies should aim to find evidence to prove or disprove our hypothesis. An attempt should be made to find the ancestral strains (from Sahara Desert lakes, lakes of Kenya, or wetlands of Brazil). A thorough whole-genome sequence-based comparison with contemporary strains would decipher the evolutionary attributes of different clades of *C. auris* and orthologs and paralogs within other *Candida* spp. Aggressive sampling of the wetlands and the skin mycobiome (especially targeting under nails, ear canal, nares) coupled with advanced deep sequencing techniques should be undertaken. Another study could compare the efficacy of alcohol and chlorhexidine in decolonizing patient bodies.

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