Evolutionary Relationships, Phylogeographic Patterns, and a Hypothesis for Air- and Sea-driven Global Spread of Chromoblastomycosis by Etiological Fonsecaea Agents

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Abstract

Fonsecaea spp. is the most common pathogen underlying chromoblastomycosis. However, many aspects of its evolutionary history are not fully understood, and a timescale for its diversification is lacking . Here, we propose, explain, and validate the evolutionary relationships, transmission routes, and modes of transmission among pathogenic species of the genus Fonsecaea . we investigated the sequences of a total of 510 intra-ribosomal transcribed regions and 485 reported cases of eight strains of the genus Fonsecaea , that have spread epidemically worldwide, persisted, and diversified over 38.27 million years. This period coincides with the diversification of many filamentous fungi, and this evolution explains the diversity and origin of pathogenic species of Fonsecaea spp . , as well as the possible transmission routes. Fonsecaea pedrosoi originated in the Atlantic Ocean near Brazil, F. monophora originated in the Pacific Ocean near southern China, and F. nubica originated in the Indian Ocean near Madagascar. F. pugnacius originated and is endemic in the Atlantic Ocean near Brazil. We proposed the hypothesis that non-pathogenic environmental strains in the environment (Fonsecaea brasiliensis , F. multimorphosa , F. minima , and F. erecta) evolved into pathogenic strains (F. pedrosoi , F. pugnacius , F. nubica , and F. monophora) and spread globally with global tropical cyclone and ocean currents pathways. F. multimorphosa is potentially infectious to humans. The present study's results will greatly facilitate the prevention, treatment, and cure of Fonsecaea infections and give insight and reference to researchers in the field of fungal research, especially other pathogenic fungi and environmental fungi.

Introduction

Chromoblastomycosis (CBM) is a neglected, hard-curable, disabling, teratogenic, carcinogenic and progressive subcutaneous or cutaneous mycosis caused by traumatic inoculation with contaminated materials carrying inocula of the Herpotrichiellaceae family (Fungi; Dikarya, Ascomycota; saccharomyceta; Pezizomycotina; leotiomyceta; Eurotiomycetes; Chaetothyriomycetidae; Chaetothyriales (order)) (Breda et al., 2020). *Fonsecaea* spp. is the most common pathogen underlying CBM (Queiroz-Telles et al., 2017; Santos et al., 2021). At present, the *Fonsecaea* clade contains the clinically relevant species *F. pedrosoi* (Belda et al., 2020; de Andrade et al., 2020; Santos et al., 2007; Singh et al., 2006; Vicente et al., 2008), *F. monophora* (Campos-Macias et al., 2021), *F. nubica* (You et al., 2019) and *F. pugnacius* (Bombassaro et al., 2020). Infection by *Fonsecaea* spp. was first reported in 1911 in Brazil by Pedroso. Chromoblastomycosis caused by *Fonsecaea* spp. has been reported in countries including Argentina (Label et al., 2018), Venezuela (Paniz-mondolfi et al., 2008), Peru (Schwalb & Seas, 2020), China (Bao et al., 2018; You et al., 2019; Zhang et al., 2019; Shen et al., 2020; Chen et al., 2021), India (Varghese et al., 2016), the United States (Takei et al., 2007), Mexico (Carolina et al., 2015), Canada (Mourad & Haber, 2020), and Cuba (Badali et al., 2013). Molecular phylogenetic analyses have shown that several sibling species are involved. *Fonsecaea erecta* (Vicente et al., 2008; Vicente et al., 2017) and *F. minima* (Vicente et al., 2008) are commonly found in plant debris, while *F. brasiliensis* (Vicente & Orelis-Ribeiro et al., 2012) is involved in infection of both animals (e.g., strain CBS 119710 in mangrove crab) and plants. *F. multimorphosa* (Najafzadeh et al., 2011; Leao et al., 2017) can also infect both animals (e.g., strain CBS 980.96 in cat brain abscess) and plants.

Because of the inclination to research human infections and environmental organisms separately, our recognition of the evolutionary relationships and phylogenetic connections among *Fonsecaea* spp. is fragmentary. Few studies have combined strains from different sources and geographic origins; furthermore, sampling procedures are generally limited to short periods of time or small samples. Despite this information barrier, localized incidences of infection by *Fonsecaea* spp. are strongly associated with an environmental source, typically involving traumatic injection of plant material into patients' cutaneous or subcutaneous tissues. Moreover, traditionally, assumptions about distribution, abundance, and ecological niches were defined by the study of morphological features and infection case reports. However, characteristics used to distinguish between clinical and environmental *Fonsecaea* species are reported to overlap. Consequently, cryptic entities have been underappreciated during the taxonomic development of this genus. At present, molecular biological methods are important for diagnosing CBM. Multilocus sequencing enhances the reliable categorization and in-depth investigations of distribution and biodiversity.

An increasing number of endemic tropical diseases caused by prevalent fungi(Boekhout et al., 2021), bacteria, viruses, and parasites are expanding their geographical distribution(Tedersoo et al., 2021), while a large number of natural products of tropical biomes have excellent therapeutic efficacy and show promise for treating these diseases (Adegboye et al., 2021). This provides new possible treatment options for the large number of patients with severe illnesses (Khan et al., 2019) or very poor treatment results (Schwalb & Seas, 2020) who are currently widespread, because the complete cure of severe cases of *Fonsecaea* spp.-caused infections is a great challenge for clinicians and researchers (Santos et al., 2021). At present, the exact cost of CBM driven by etiological *Fonsecaea* agents is unknown, as there is no national surveillance mechanism in China to examine CBM in sentinel centers. Over the past century, large volumes of data have been gathered on a global basis, with hundreds of examples published in the past two decades alone. For example, the present study examined 238 articles containing case reports, case series, and outbreaks involving more than 485 cases. However, many aspects of the evolutionary history of *Fonsecaea* spp. are not fully understood, and a timescale for diversification is lacking. To understand the mechanisms for outbreak emergence, it is necessary to compare outbreak data with historical data on *Fonsecaea* spp. infections. Reinterpretation of historic data considering contemporary molecular phylogeny is thus necessary. In this study, we gathered pre-molecular literature that included interpretable case reports and geographic data. Strains from each of these locations were sequenced and identified, and the results compared with available published literature. Each of the detected species' frequencies was compared with the premise that their ranges in each region had remained mostly unchanged. Furthermore, molecular approaches were used to distinguish environmental and clinical isolates banked in the CBS culture collection (CBS-KNAW Fungal Biodiversity Centre, Utrecht, The Netherlands) over the last century, permitting phylogenetic analysis of human-pathogenic *Fonsecaea* spp. in relation to environmental- or animal-pathogenic species as well as to other species in Herpotrichiellaceae. This study provides a systematic and complete assessment of the molecular sequences of *Fonsecaea* spp. cases reported from 2000 to 2021 and published strains, describing phylogeographic patterns and evolutionary hypotheses in global transmission.

Materials And Methods

Research registration and ethics

The design of this study was composed of three parts: 1) collection of cases and strain genes of *Fonsecaea* spp. in China and abroad; 2) an exploration of the origin and transmission pathways of pathogenic *Fonsecaea* spp. strains collected in the laboratory; and 3) the temporal phylogenetic tree and haplotype network validation. The systematic review part strictly followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. The research plan was reviewed and approved by the National Health Service (NHS), and assigned the PROSPERO registration number: CRD42021275308.

Search strategy and inclusion criteria

Literature reviews included the selection of all articles addressing worldwide epidemiology of chromoblastomycosis that were published in different languages (including Chinese, English, French, Japanese, and Spanish) between 2000 and 2021. Searching work done from PubMed and the Chinese-language CNKI, SinoMed, and Wanfang databases. The search terms were (fungi[MeSH Terms]) AND (("*Fonsecaea*") OR ("*monophora*") OR ("*pedrosoi*") OR ("*multimorphosa*") OR ("*nubica*") OR ("*erecta*") OR ("*brasiliensis*") OR ("*minima*") OR ("*compacta*") OR ("*pugnacius*") OR ("*Trichosporum pedrosianum*") OR ("*Trichosporum pedrosoi*") OR ("*Hormodendrum pedrosoi*") OR ("*Hormodendroides pedrosoi*") OR ("*Rhinocladiella pedrosoi*") OR ("*Phialophora pedrosoi*") OR ("*Gomphinaria pedrosoi*") OR ("*Carrionia pedrosoi*") OR ("*Acrotheca pedrosoi*")) OR (("Medlar body") OR ("Medlar bodies") OR ("sclerotic bodies")) AND ((Chromoblastomycoses) or (Chromomycos*s) or ("Dermatitis Verrucosa")). All studies in this thorough evaluation met the major CBM diagnostic criteria: 1) A direct observation with 10% Potassium hydroxide revealed the presence of dark-colored, thick-walled muriform cells in a biological sample; and 2) fungal isolation was performed on Sabouraud dextrose agar, and *Fonsecaea spp.* was discovered using molecular analysis of strains taken from patients. Cultivation and DNA sequencing from culture verified the identity (Campos-Macias et al., 2021).

Fungal strains

All strains were kept in the CBS culture collection (https://wi.knaw.nl/) and PubMed's (https://www.ncbi.nlm.nih.gov/) reference collection under the name '*Fonsecaea*'. All type strains that were available were included. Data on *Fonsecaea* spp. used in this investigation were obtained from GenBank (https://www.ncbi.nlm.nih.gov/); the accession numbers of the sequences utilized are presented in Supplementary Table 1. Cultures originated from the Centraalbureau voor Schimmelcultures (CBS-KNAW Fungal Biodiversity Centre, Utrecht, The Netherlands, https://www.gbif.org/dataset/82dc5194-f762-11e1-a439-00145eb45e9a). Stock cultures were maintained on slants of Sabouraud's dextrose agar and Potato dextrose agar at 35°C. Strains are listed in Supplementary Table 1.

Genetic data analysis, dated phylogeny, and statistical analysis of collected strains

Genetic data analysis, dated phylogeny, and statistical analysis of the collected strains ribosomal internal transcribed spacer (ITS) sequences were collected using MEGA v. 11 ((Kumar et al., 2018)), Sequence were aligned using the ClustalW option and a neighbor-joining tree was estimated using the Kimura 2-parameter model plus gamma correction (K2 + G: 0.96), with 500 bootstrap replications. All temporal phylogenetic trees were built using the RelTime-ML method in MEGA v. 11 (Mello, 2018). Divergence times for *Cryptococcus gattii*, *Candida albicans*, *Aspergillus fumigatus*, and *Pyrenula anomala* are referenced on the website (http://www.timetree.org /search/goto_pairwise), and the searched divergence times were used as calibration time points for the molecular clock to infer evolutionary times. DnaSP v.6 (Rozas et al., 2017) on the Universitat de Barcelona server (http://www.ub.edu/dnasp/) was used to determine the extent of DNA polymorphism. All haplotype network models were constructed using PopART 1.7 (http://popart.otago.ac.nz/index.shtml; Clement et al., 2000). Categorical variables were compared with chi-square tests. Differences between groups were considered statistically significant if P-values were ≤ 0.05. Divergence times are reported in millions of years ago (Ma).

Results

Information on the characteristics of the collected global cases and strains

The study included a total of 498 CBM cases that were published. The worldwide distribution and prevalence of CBM cases are shown respectively in Fig. 1, while the main characteristics of CBM are illustrated by countries and continents as summarized in Supplementary Table 1. A total of 510 *Fonsecaea* spp. were evaluated, of which 44 were environmental plant, and four were animal. Data obtained on geographic origins and sources of isolation are listed in Supplementary Table 2. Regions with a high incidence of cases include Brazil, Venezuela, and Colombia (South America); Mexico, Cuba, and the United States (North America); China, India, Vietnam, and Japan (Asia); Madagascar (Africa); and France and the Netherlands (Europe). We compared the number of isolated *Fonsecaea* spp. strains with the number of reported cases of

chromoblastomycosis caused by this fungus in the same time period, showing the same trend. From 2000 to the first half of 2021, the number of reported cases and strains of *Fonsecaea* spp. infections were increased progressively, and both showed a consistent trend.

In each 4-year period, we found that the number of cases of the four pathogenic species increased over time, with the most pronounced increases in *F. pedrosoi* and *F. monophora*. *Fonsecaea pedrosoi* and *F. monophora* had the highest number of cases and isolated strains among patients.

Continent / region	Country	Sequenced isolates	F.pedrosoi	F.monophora	F.nubica	F.pugnacius	F. brasiliensis	F. erecta	F. minima	F.multimorph...
South America (316)	Argentina	3	3(100%)							
	Brazil	268	193(70%)	23(8%)	9(3%)	4(1%)	16(6%)	6(2%)	10(4%)	7(3%)
	Colombia	3	3(100%)							
	Costa Rica	12	10(83.3%)	2(17%)						
	Uruguay	4	1(25%)				2(50%)	1(25%)		
	Venezuela	14	14(100%)							
Asia (105)	China	82	3(4%)	59(72%)	19(23%)		1(1%)			
	India	6		6(100%)						
	Japan	10	10(100%)							
	Malaysia	2		2(100%)						
	Korea	1		1(100%)						
	Surinam	2	1(50%)		1(50%)					
	Thailand	2	1(50%)	1(50%)						
Oceania (4)	Australia	3	1(33%)	1(33%)						1(33%)
	Queensland	1								1(100%)
Africa (54)	Cameroon	1			1(100%)					
	Congo	2	1(50%)	1(50%)						
	Guinea	1		1(100%)						
	Libya	1	1(100%)							
	Madagascar	47	2(4.3%)	23(48.9%)	22(46.8%)					
	Mozambique	1	1(100%)							
Europe (9)	Czech Republic	2	1(50%)	1(50%)						
	England	1		1(100%)						
	France	2		1(50%)	1(50%)					
	Netherlands	3	1(33%)	1(33%)	1(33%)					
	Poland	1	1(100%)							
North America (35)	Cuba	9	5(56%)	4(44%)						
	Mexico	16	4(25%)	12(75%)						
	Puerto Rico	2	2(100%)							
	USA	8	2(25%)	6(75%)						
Total	32	510	268(51.7%)	147(28.6%)	54(10.6%)	4(0.8%)	18(3.5%)	8(1.6%)	10(2.0%)	9(1.8%)

Phylogenetic analysis revealed that the eight species of *Fonsecaea* spp. (*F. brasiliensis*, *F. multimorphosa*, *F. minima*, *F. erecta*, *F. pedrosoi*, *F. nubica*, *F. pugnacius*, and *F. monophora*) were clearly divided into eight major groups (Fig. 2). Most strains belonged to *F. pedrosoi, F. nubica*, and *F. monophora*. It is worth noting that among the *F. pedrosoi* strains, the Costa Rican and Brazilian strains have similar homology to those from Argentina, Brazil, Uruguay, Mexico, Venezuela, the United States, Puerto Rico, and China. Among *F. monophora* strains, the pathogenic strain from Guangdong, China has similar homology to both environmental and pathogenic strains from Guangdong, Nanjing, Shanghai, Shandong, and Taiwan (all from China), Japan, Korea, Malaysia, Vietnam, India, Costa Rica, Cuba, France, UK, Netherlands, Czech Republic, Kuwait, the United States, Africa, Guinea, and Brazil. Among the strains of *F. nubica*, those of

Madagascar are most similar to those of Mozambique, Cameroon, Congo, China, and Japan. *F. erecta* and *F. monophora* strains were isolated only from the environments of Australia, China, and Uruguay, while the other strains were mostly found in Brazil.

Divergence times of Fonsecaea spp. revealed by temporal phylogenetic tree

Using *Cryptococcus gattii* (divergence time: 723 Ma [626–806 Ma]), *Candida albicans* (divergence time: 590 Ma [480–713 Ma]), *Aspergillus fumigatus* (divergence time: 307 Ma [275–403 Ma]) and *Pyrenula anomala* (divergence time: 304.46 Ma [217–402 Ma]) as temporal reference standards, the divergence between the genera *Cladophialophora* and *Fonsecaea* was estimated at 94.15 Ma (the timetree figure is included in supplementary information). After 51.63 million years (around 38.27 Ma), *Fonsecaea* spp. began diversifying to survive in decaying organic matter, living plants, and animals (e.g., mangrove crab), with *F. brasiliensis* diverging first, followed by *F. multimorphosa* (around 21.30 Ma), *F. minima* (around 20.01 Ma), and *F. erecta* (around 19.11 Ma). A rough estimate of the divergence time of the globally epidemic *F. pedrosoi.* is around 17.41 Ma. The other main pathogenic species *F. pugnacius*, *F. nubica*, and *F. monophora* all diverged subsequently at ~8.23 Ma, ~1.64 Ma, and ~0.08 Ma, respectively (The timetree was included in supplementary information).

In the haplotype network model, the selected *Fonsecaea* sequences are all identified human-pathogenic and non-pathogenic species from Brazil (Fig. 3). Among the identified human-pathogenic species: *F. pedrosoi* has the greatest haplotype diversity (hap9, 12, 14, 15, 16, 17, 18, 19, 20, and 21). *Fonsecaea monophora*, *F. nibica*, and *F. pugnacius* are all closely related to *F. pedrosoi*. *Fonsecaea multimorphosa* has six haplotypes (hap5, 6, 7, 8, 9, and10), one of which (hap9) has the same sequence as that of *F. pedrosoi*. It is worth noting that *F. multimorphosa* also has a close evolutionary relationship to *F. pedrosoi*; although no human infection has been reported, infections of mammalian (e.g., cat) brains by *F. multimorphosa* have been reported (Leao et al., 2017).

Hypothesis on the origin and mode of dispersal of Fonsecaea spp.

Based on the dated phylogenetic tree and haplotype network model of the collected global *Fonsecaea* spp. gene sequences, we inferred the origin of the now globally prevalent pathogenic species of *Fonsecaea*. *Fonsecaeapedrosoi* may be from the marine area near Costa Rica, Colombia, or Brazil (including the eastern and northern waters of the Pacific Ocean and the northern waters of the Atlantic Ocean) (Fig. 4), as this region has the highest haplotype diversity of the *F. pedrosoi* gene and the highest number of haplotype genes. The haploid genotypes of Venezuela, Colombia, Uruguay, Argentina, Costa Rica, Mexico, the United States, Cuba, France, Netherlands, Congo, Libya, Madagascar, Australia, Thailand, Vietnam, China, and Japan can all be found in Brazil (Fig. 4). The origin of the pathogenic strain *F. nubica* appears to be in the ocean near Madagascar, and the strain has likely been spread by frequent Indian Ocean tropical cyclones or super typhoons (Fig. 5) to countries including China, Vietnam, France, Italy, Cameroon, and Brazil. *Fonsecaea monophora* strain likely originated in the maritime region near China (Fig. 6) and is now endemic to regions including southeastern China, India, Thailand, the Philippines, Madagascar, Australia, the United Kingdom, the United States, Mexico, Cuba, Costa Rica, and Brazil. *Fonsecaea pugnacius* originated and remains prevalent in the Atlantic Ocean near Brazil. Our predicted regions of origin of these pathogenic strains of *Fonsecaea* spp. are very similar to the global regions of origin of many tropical cyclones (Fig. 7). The transmission chain of this fungus is also very similar to the movement path of global tropical cyclones, so we hypothesize that the transfer path of tropical cyclones facilitates the global spread of the pathogen (Fig. 8).

In the absence of strain mutations, mycelia, spores, dormant bodies of *Fonsecaea* spp., or carriers containing the fungus are carried into the air with the onset of tropical cyclones in the northern hemisphere from June to October. The airborne fungus spreads randomly along the path of a tropical hurricane as the storm's path shifts. This fungus grows slowly and has a suitable temperature of 23–40°C (de Azevedo et al., 2015).

Discussion

Chromoblastomycosis (CBM) is a globally occurring mycosis caused principally by infectious strains of *Fonsecaea* spp. Despite their global distribution and increasing disease prevalence, the relationships to environmentally occurring strains and modes of global spread remain poorly understood. In this study, we combined data from a variety of sources (case reports, molecular data, and meteorological data) to provide a comprehensive assessment of and to derive a hypothesis for the evolution and transmission of infectious strains of *Fonsecaea* spp., the main causative agent of chromoblastomycosis.

Evolutionary relationships and divergences of infectious Fonsecaea spp. strains

Divergence time estimates indicated surprising antiquity of the major clades within *Fonsecaea*. Around 38.27 Ma, *Fonsecaea* spp. began diversifying to survive in decaying matter, living plants, and animals (e.g., mangrove crab), with *F. brasiliensis* diverging first. This was followed by divergences of *F. multimorphosa* (~21.30 Ma), *F. minima* (~20.01 Ma), and *F. erecta* (~19.11 Ma), but no human infection by these species has yet been reported. About 17.41 million years ago, a strain of *F. pedrosoi*, the main causative species of CBM, reported today in the vicinity of Costa Rica and Brazil, emerged and subsequently spread throughout the world. *Fonsecaea pugnacius, F. nubica*, and *F. monophora*, which are all in the clade subtended by the aforementioned *F. pedrosoi* strain, have all gradually diverged and been reported as infectious. These estimated divergence times are considerably earlier than previously recognized and coincide with the divergences of many other filamentous fungi (Beimforde et al., 2014; Kumar et al., 2017; Lücking et al., 2009; Riess et al., 2016; Steenwyk et al., 2019; Taylor & Berbee, 2006). This suggests that these pathogenic strains of *Fonsecaea* spp. should be more broadly infectious toward mammals in general, as they also coincide with the earliest known divergences within the hominin clade (Bramble & Lieberman, 2004; Wallis et al., 2008). The evolutionary relationships are supported by the haplotype network, where the three other identified human-pathogenic species (*F. monophora*, *F. nubica*, and *F. pugnacius)* are all most closely related to *F. pedrosoi*, the principal causative agent of CBM. It is worth noting that *F. multimorphosa* also has a very close evolutionary relationship to *F. pedrosoi* (Fig. 3); although no human infection has been reported, *F. multimorphosa* infection has been reported in cat brains, so it should be considered potentially infectious to humans as well.

Geographic origin and air/sea-driven dispersal of infectious Fonsecaea spp. strains

Combined analyses indicate that pathogenic *Fonsecaea pedrosoi* originated in the Atlantic Ocean near Costa Rica or Brazil and is now endemic worldwide (Fig. 4), *F. monophora* originated in the Pacific Ocean near southern China (Fig. 5), *F. nubica* originated in the Indian Ocean near Madagascar (Fig. 6), and *F. pugnacius* originated and is endemic in the Atlantic Ocean near Brazil. These predicted areas of origin of *Fonsecaea* variants are very similar to those of tropical cyclones (Fig. 7). The tropical oceans produce about 80 tropical storms per year, of which about two-thirds are severe (classified on a Saffir-Simpson intensity scale of 1 or higher). Almost 90% of storms form within 20° north or south of the equator (Britannica, 2022; National Hurricane Center and Central Pacific Hurricane Center National Oceanic and Atmospheric Administration, 2022), and CBM is also endemic in this region (Queiroz-Telles et al., 2017; Santos et al., 2021). Notably, the findings of DeLeon-Rodriguez et al., (2013) (DeLeon-Rodriguez et al., 2013) suggested that fogging of large fungal spore communities occurs during tropical hurricanes, and airborne fungi may remain viable after being carried aloft (Alsante et al., 2021; Mayer et al., 2020), where long-distance, transcontinental and even oceanic transport occurs. The fungal microbiota is a dynamic and underappreciated aspect of the lower oceanic layer, and the extensive flooding after mega-hurricanes can create ideal conditions (Barbeau et al., 2010) for the growth of molds such as *Fonsecaea* spp. (Bloom et al., 2009). Additionally, talaromycosis (penicilliosis) caused by invasive mycotic infection has been found to be highly associated with cyclones and floods during the tropical monsoon season (Narayanasamy et al., 2021).

Filamentous fungi and ascomycetes can grow in both natural and artificial seawater media. Salinity, water temperature, dissolved oxygen, and pH in seawater do not strongly affect growth of fungal communities, even of mycelia resting over long periods (Mouton et al., 2012; Manohar & Raghukumar, 2013; Rédou et al., 2015; Wijesekera et al., 2017; Grossart et al., 2019; Rojas-Jimenez et al., 2020). Fungi have been discovered in practically every marine ecosystem studied (Gladfelter et al., 2019; Grossart et al., 2019), including deep subsurface sediments (Rédou et al., 2014; Gladfelter et al., 2019; Vargas-Gastélum & Riquelme, 2020), coastal plankton (Taylor & Cunliffe, 2016), wood (Rämä et al., 2016; Lee et al., 2019; Rahaman et al., 2020), and marine animals (Wainwright et al., 2017; Amend et al., 2019) at depths ranging from the deep sea to surface waters (Amend et al., 2019). In addition, ascomycetes species are generally considered to be more tolerant of extreme environments (Rämä et al., 2016; Vargas-Gastélum & Riquelme, 2020). *Fonsecaea erecta* (strain 14A-2) was found in marine sponges in the South China Sea area (Qin et al., 2015). *Fonsecaea pedrosoi* has been found in very diverse environments including a babassu coconut shell (Marques et al., 2006), mouse passage soil (Najafzadeh et al., 2009), plant debris (Irinyi et al., 2015), and termite nests (Lima et al., 2020). *Fonsecaea monophora* has been found on fur seals (De Hoog et al., 2004), and a decaying babassu coconut shell (Vicente et al., 2014), while *F. brasiliensis* was found on mangrove crabs (Vicente & Orélis-Ribeiro et al., 2012).

As there seems to be a very strong correlation between tropical cyclones (hurricanes and typhoons) and the prevalence of the pathogenic fungus *Fonsecaea* spp., we conjecture that the widespread presence of this fungus in the ocean (from deep-sea sediments, decaying and living marine plants, and dead and living animals to microorganisms or floating material on the ocean surface), or zones close to the ocean, provides a source for the transmission of fungal pathogens including *Fonsecaea* spp. (both environmental and pathogenic strains). Frequent tropical cyclones provide a source of power and means of dispersing fungal pathogens. Small items such as fungal mycelia, spores, and dormant bodies can be transported by the tens of thousands in the air or on a carrier or container. Strong carrying capacity and lethality of tropical cyclones carrying *Fonsecaea*-containing materials, mixed with seawater and rainwater, can enable rapid long-distance transfer and wide seeding of highly durable pathogenic fungi across continents and even large oceans. Flooded target areas containing many injured and dead plants and animals provide good breeding environments for storm-dispersed fungi. In addition, the direction of ocean currents may further promote fungal dispersal by transporting floating rotting wood, marine microorganisms, and other propagation media carrying environmentally resistant fungal particles to new regions with suitable climatic conditions. The formation of the fungus like seeds in the global rapid spread and slow long-term spread of the mixed way. The mixture of faster and slower means of dispersal contributes to rapid global expansion of fungal communities. The combination of these factors has resulted in worldwide reports of infections and the isolation of globally occurring pathogenic *Fonsecaea* spp. and variants collected to date. In terms of genetic evolution of the strains, there is a mixture of primary and secondary strains, indigenous mutants, and exotic variants (across continents and oceans). Our findings indicate that *F. pedrosoi* has the most reported regional cases with strains in Brazil, *F. monophora* has the most reported cases near China, and *F. nubica* has the most reported cases in Madagascar, with haplotype networks of these three pathogenic species showing the greatest genotypic diversity. Our findings and proposed hypothesis for transmission have potentially important implications for better understanding not only the spread of invasive pathogenic fungi such as *Fonsecaea* spp., but hydrographic oceanic circulation, cloud dispersal, and fungal biogeographic dispersal science in general.

Conclusion

The data that could be collected so far may still be distant from the true picture of the genetic evolution and global modes and patterns of transmission of *Fonsecaea* spp., leading us to only roughly identify the regions of origin of the pathogenic fungi *F. pedrosoi*, *F. monophora*, *F. nubica*, and *F. pugnacius*. In this paper we propose, explain, and validate the evolutionary relationships, transmission routes, and modes of transmission among pathogenic species of the genus *Fonsecaea*. The results of the present study will give insight and reference to researchers in the field of fungal research, especially the global transmission mode and pattern of *Fonsecaea* spp.. This study represents a new breakthrough not only in relation to *Fonsecaea* spp., but also by providing a reference for examining the transmission mode, pathway and genetic evolution of other clinically relevant pathogenic fungi and environmental fungi, including the genera *Candida* (Boekhout et al., 2021), *Aspergillus*, *Cryptococcus*, and Zygomycetes (*Mucor*) and other environmental fungi (Devadatha et al., 2021).

Declarations

Statements and declarations

Competing interests:

The authors declare no conflicts of interests.

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Consent for publication All authors give their consent to publish this study in Fungal Diversity

Author contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by HuiWei Wang and WeiHua Pan. The first draft of the manuscript was written by HuiWei Wang and WeiHua Pan. All authors participated in the data analysis, manuscript editing process and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Availability of data and material

Data are partly presented in Supplementary Table 1, and 2. Data on *Fonsecaea* spp. used in this investigation were obtained from GenBank (https://www.ncbi.nlm.nih.gov/); Cultures originated from the Centraalbureau voor Schimmelcultures (CBS-KNAW Fungal Biodiversity Centre, Utrecht, The Netherlands, https://www.gbif.org/dataset/82dc5194-f762-11e1-a439-00145eb45e9a).This and all other relevant datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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Supplementary Tables

Supplementary Tables 1 and 2 are not available with this version.
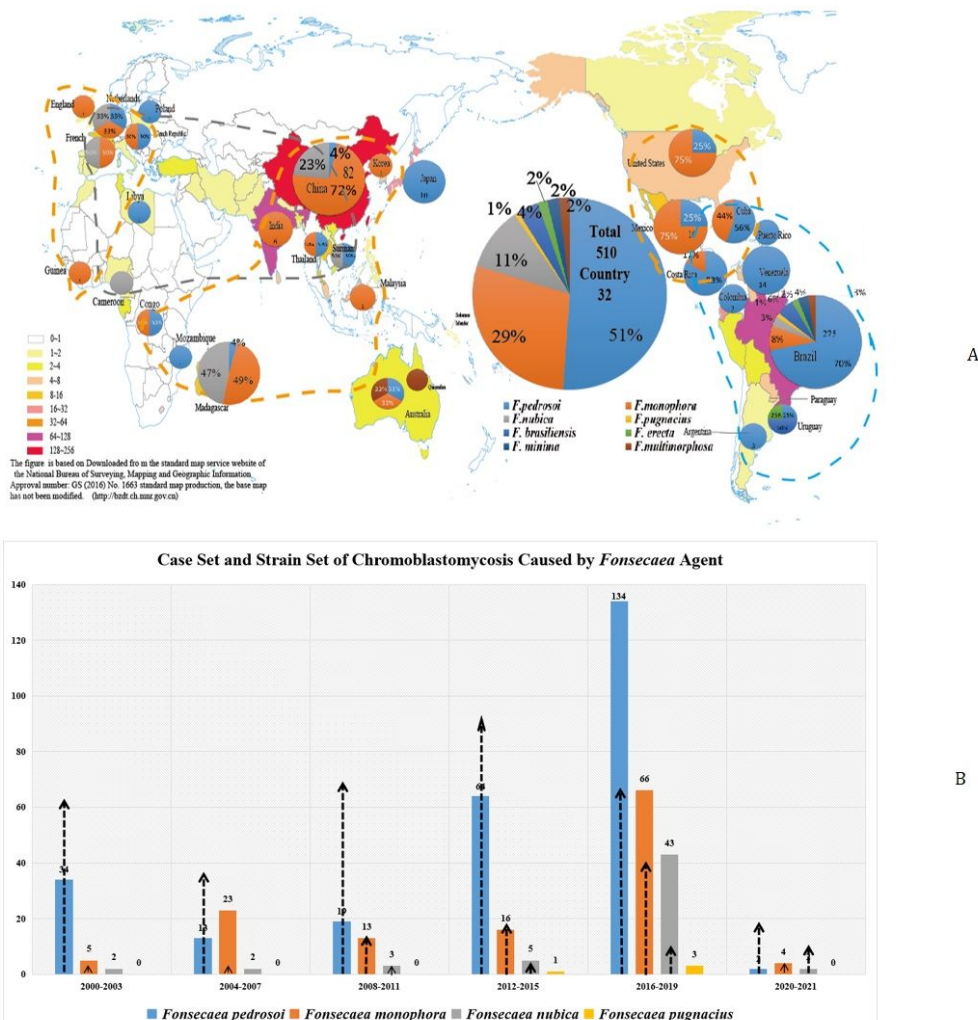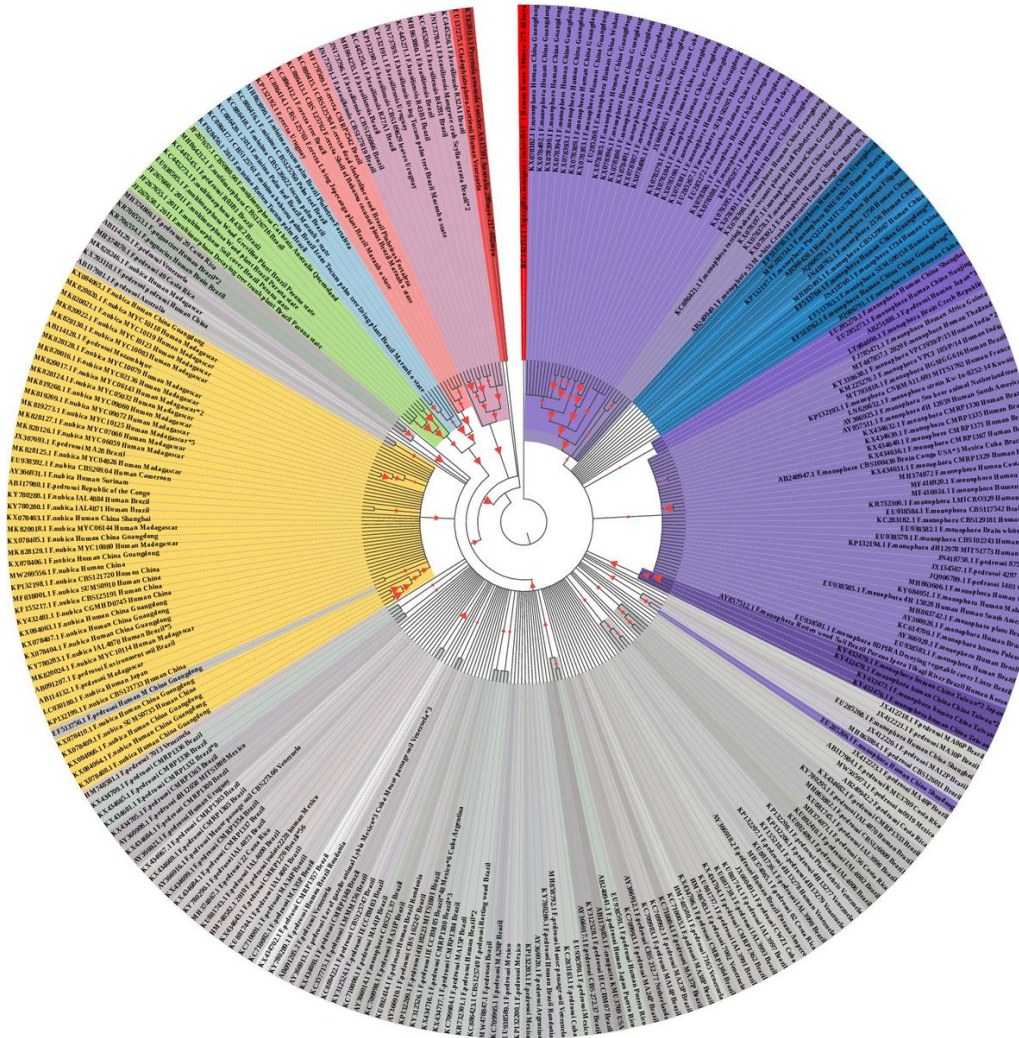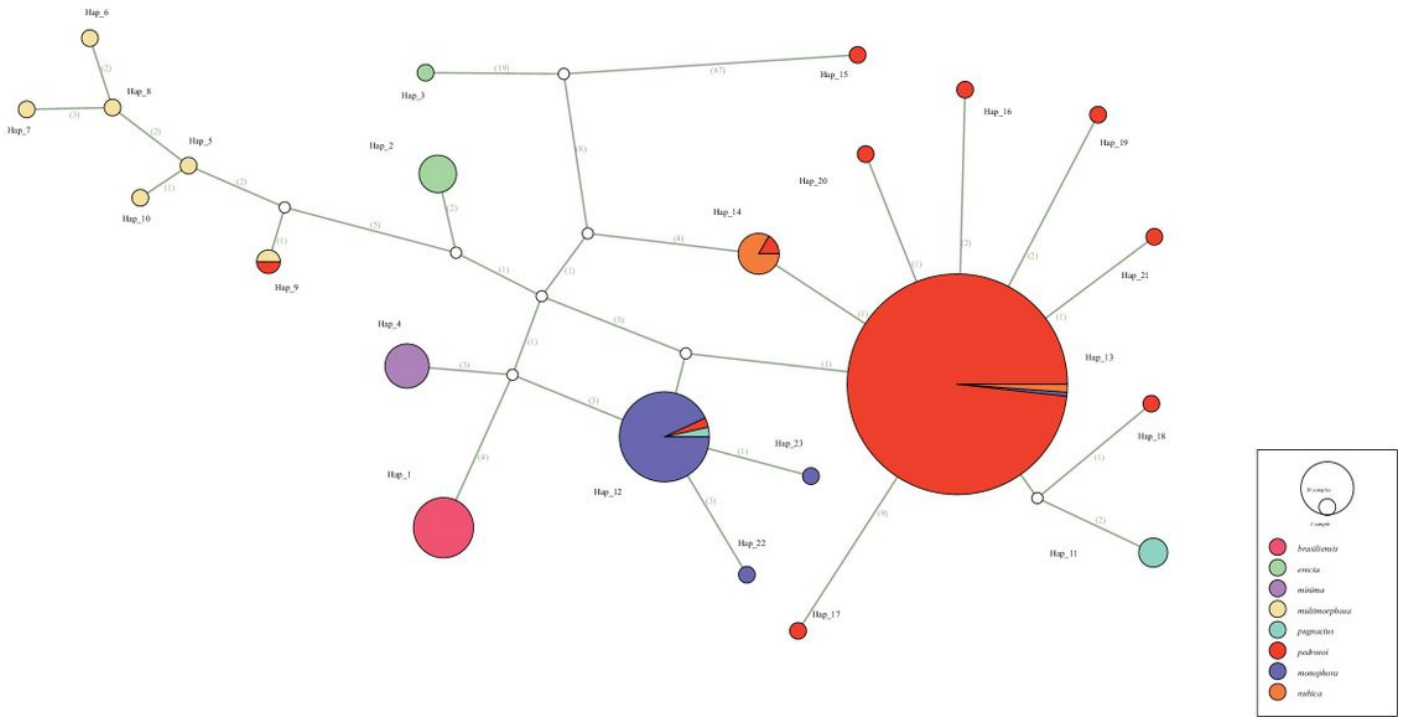
Figures

Figure 1

Fig.1b the plot is divided into groups at 4-year intervals, with the interval 20000-2021; the vertical coordinates are the count values (0-140), and the 4 colors represent the 4 species of *Fonsecaea* spp. The height of the bar graph represents the number of corresponding fungal species collected at 4-year intervals; the arrows indicate: the number of reported cases of the corresponding fungal species at 4-year intervals.

Figure 2

Global sequence phylogenetic tree. Each color category represents a strain of Fonsecaea spp. The subtle shades in each color category represent each collected strain of Fonsecaea spp. The red color represents a consistent reference fungus, The phylogenetic tree source is available at: https://itol.embl.de/tree/115232231116402164197047

Figure 3

Haplotype network using combined Ribosomal internal Transcribed Spacer (ITS) of Fonsecaea spp . sequence data from Brazil, with geographical distribution, gaps and missing data excluded. In combined ITS sequence data of Fonsecaea spp. Each color corresponds to a strain of fungal species. The size of the circle represents the number of matched samples
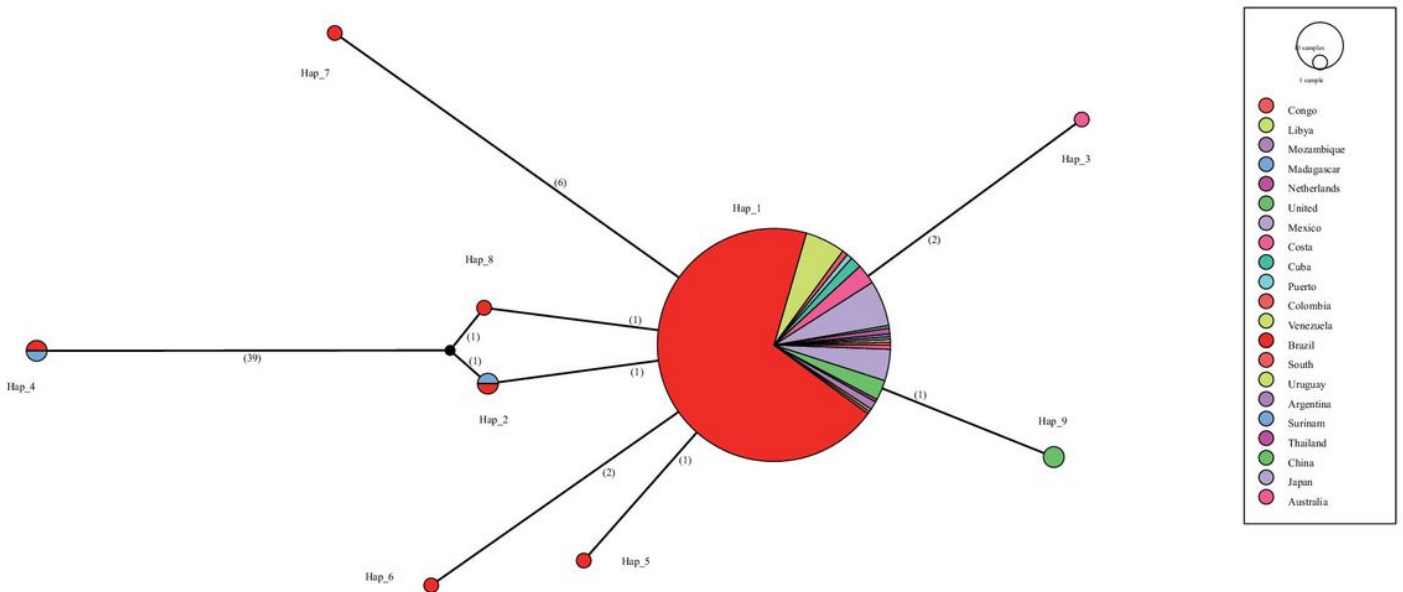
Figure 4

Global distribution pattern of the haploid network of Fonsecaea pedrosoi. Each color represents a country. The size of the circle represents the number of samples
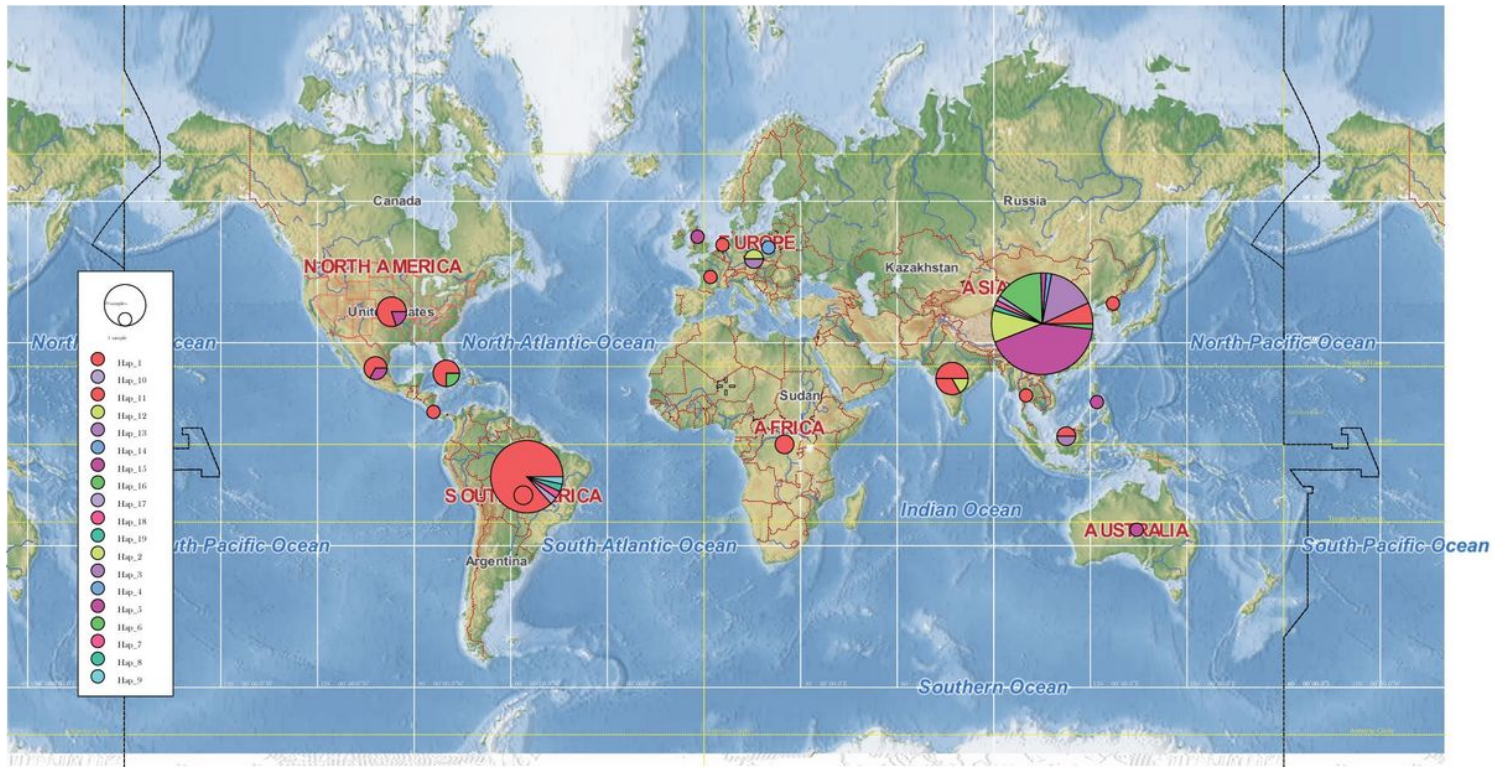
Figure 5

Global distribution pattern of the haplotype network of *Fonsecaea nubica*. Each color represents a haploid genetic subtype. The size of the circle represents the number of samples
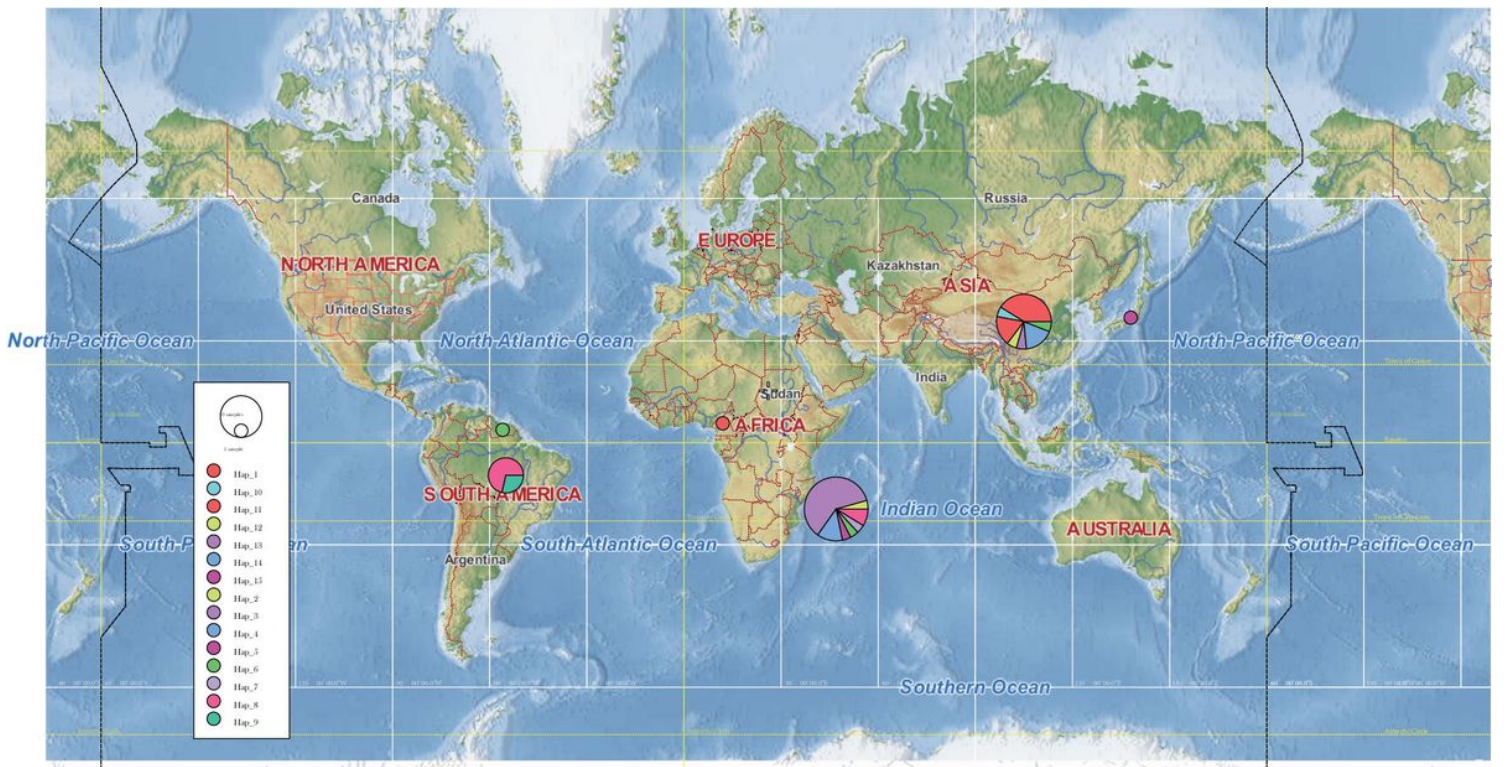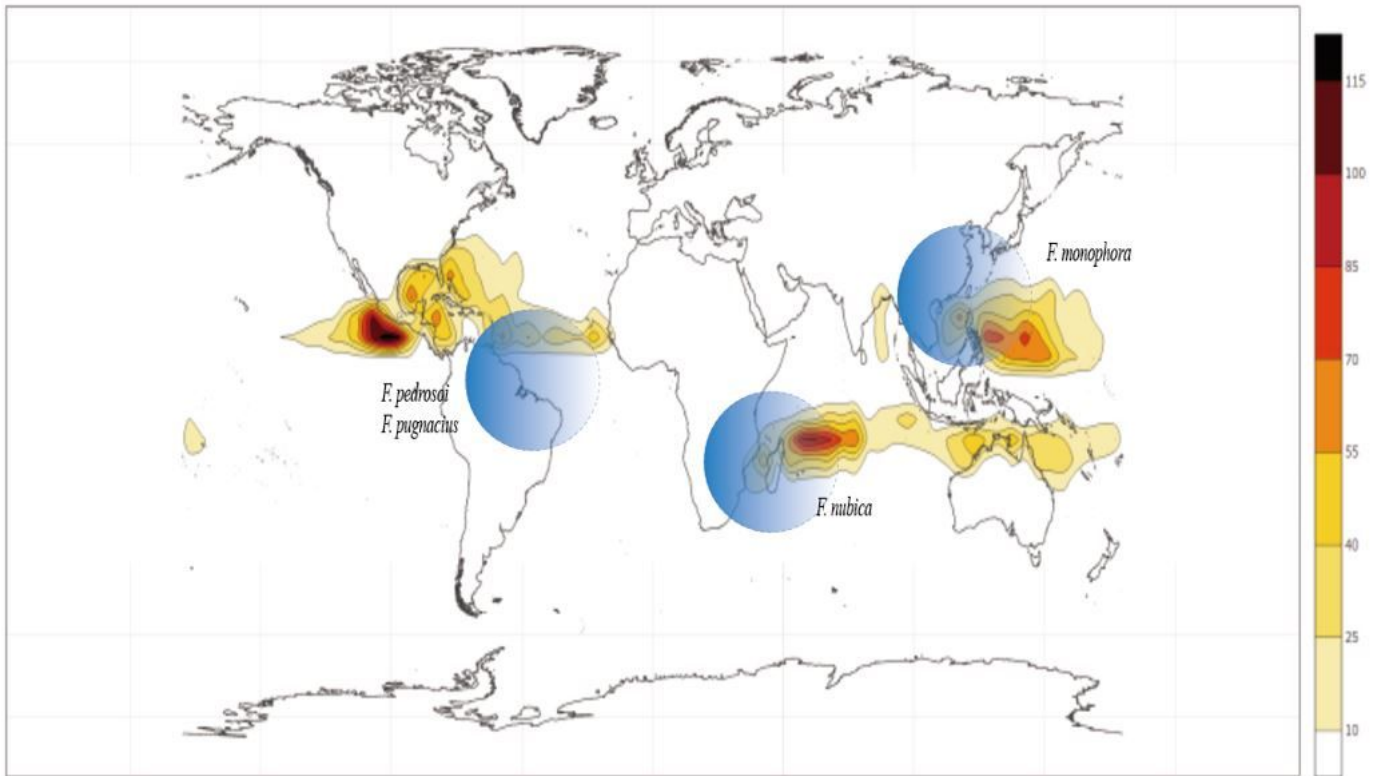

Figure 6

Global distribution pattern of the haplotype network of *Fonsecaea monophora*. Each color represents a haploid genetic subtype. The size of the circle represents the number of samples

Blue gradient circles: schematic diagram of the possible range of origin of pathogenic species

Map of the origin of tropical cyclones: https://chart-studio.plotly.com/~ToniBois/3306.embed

Figure 7

Hypothesis on the origin and global dispersal of strains of Fonsecaea spp. The blue gradient circles indicate the range of transmission origins of different strains of Fonsecaea spp. The colored contours indicate locations of the origins of tropical cyclones; darker red means more frequent origins of tropical cyclones
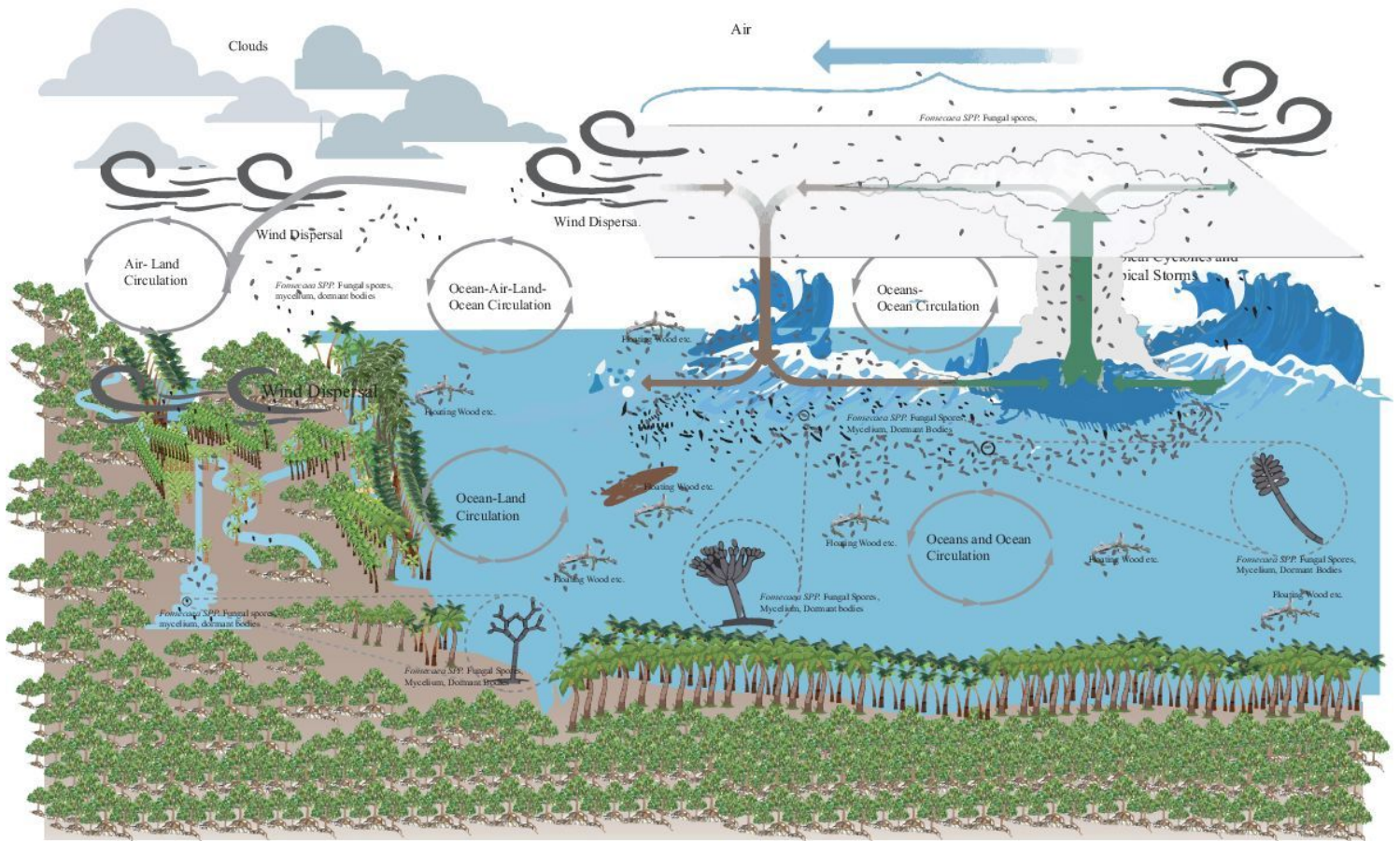
Figure 8

Graphical representation of our hypothesis for the global mode of dispersal of Fonsecaea spp.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- fonsecaeaquc194.pdf