Humidity and low pH boost occurrence of Onygenales fungi in soil at global scale

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Abstract

Soils are important reservoirs for potential human pathogens and opportunistic fungi such as the dermatophyte or dimorphic fungi in the order Onygenales. In soils, these taxa are decomposers but many of them have the potential to cause respiratory and skin diseases in humans and, in some cases, systemic infections. Even so, the factors that determine the biogeography and ecology of order Onygenales remain largely undocumented. To address this knowledge gap, we surveyed members of Onygenales from topsoil fungal communities at 235 sites across six continents and provided a first global atlas. We retrieved 4.3% of the total fungal sequences (~420 Onygenales) across nine biomes ranging from deserts to tropical forests. This work advances our knowledge on the ecology and global distribution of order Onygenales and suggests the hypothesis that wet and acid soils support the larger proportions of these fungi, while their richness is constrained by aridity.

Keywords: Aridity, Fungi, Onygenales, soil-borne pathogens, soil communities

Introduction

The Fungal Kingdom is one of the most diverse groups of organisms in our planet (Hawksworth and Lücking 2017; Wu et al. 2019; Hyde et al. 2020). Many of these taxa are fundamental for supporting nutrient cycling, plant-soil mutualistic relationships and organic matter decomposition. However, others such as the opportunistic dimorphic fungi have the potential to cause important human diseases (Garcia-Solache and Casadevall 2010; Rodrigues et al. 2020; Casadevall 2020). Many of the most aggressive dimorphic fungal are Ascomycetes of the order Onygenales (Eurotiomycetes), which includes the spherule-forming *Coccidioides* spp. and yeast-forming fungi of the genera *Histoplasma*, *Paracoccidioides*, and *Blastomyces*. The same order also includes dermatophytes, the most common true pathogenic fungi causing superficial severe skin infections (e.g. *Trichophyton* spp.), as well as a number of non-pathogens.

Order Onygenales is also known to include emerging human pathogens due to increasing rates of immunosuppression from autoimmune disorders (Schwartz et al. 2019); moreover, unlike most fungal pathogens, may infect immunocompetent hosts, causing systemic mycoses with high case-fatality rates (Taylor 2014). This fungal order emerged around 150 million years ago (MYA) (Sharpton et al. 2009) and generally lives in animal burrows and as soil decomposers (Kollath et al. 2020) but, under certain environmental circumstances, they can also grow on human hosts (Van Dyke et al. 2019). They may enter in contact with humans through dust and air particles from soils surrounding our cities. Thus, learning more about the biogeography and ecology of order Onygenales can help us to develop new hypotheses to link their potential pathogenesis with human health.

Recently, species distribution models (SDM), which associate occurrence records with environmental variables that are expected to affect the species probability of persistence, have been increasingly applied to soil-dwelling fungi (Hao et al. 2020) and Onygenales in particular (Ocampo-Chavira et al. 2020) to estimate the environmental conditions that are most suitable for this particular group of fungi. However, despite these sound advances, our knowledge remain limited to local and regional scale (e.g. Ocampo-Chavira et al. 2020, Yamauchi et al. 2021) and we are lacking a systematic and comprehensive assessment of the global patterns and environmental factors associated with these important organisms in natural biomes at global scale.

To address this knowledge gap, we performed a global soil survey conducted in 235 natural ecosystems on six continents (Supplementary Figure S1). This database includes a

wide variety of bioclimatic regions (arid, temperate, tropical, continental and polar), covering ~73% of the environmental conditions found on Earth (Supporting Information; Egidi et al. 2019). To characterize Onygenales fungi in our survey, we used the ITS amplicon sequencing that, albeit encompassing a few limitations in terms of absolute quantification of the fungal ITS gene due to the hypervariable target region and primer choice (Nilsson et al. 2019), it is nowadays a predominant method to characterize diversity and structure of fungal communities in environmental samples (e.g. Alteio et al. 2021; Baldrian et al. 2021). We also generated the first global atlas for the current distribution of these fungi and used a suite of machine learning and statistical analysis to (i) identify the most dominant Onygenales taxa, and (ii) describe how their global distribution is influenced by climate and other important environmental factors. Besides, in this study, we do not make any claim on the pathogenesis associated with Onygenales, and focus on exploring the biogeography and ecology of these important soil-borne organisms aiming to provide the basic knowledge to develop future hypotheses on the linkages between these taxa and human health.

Materials and Methods

Global survey

Study sites and soil sampling

We used data from a global field survey (Egidi et al. 2019; Delgado-Baquerizo et al. 2020) to identify the distribution and ecological drivers of Onygenales taxa in soils from natural ecosystems worldwide. Briefly, bulk soils (top 7.5 cm) were collected from 235 ecosystems located in 18 countries from six continents (Supplementary Figure 1; Supplementary Table S1) and covered nine biomes (temperate, tropical and dry forests, cold, temperate, tropical and arid grasslands, shrubland and boreal) between 2003 and 2015. Locations were selected to provide a solid representation for most environmental conditions (for example, climate, soil, and vegetation types) found on Earth. Each location include composite soil samples from 5-10 soil cores. Composite samples were then sieved on arrival at the laboratory (2 mm mesh). Then, a portion of soil was immediately frozen at −20 °C for molecular analyses, and the rest of the soil was air-dried and stored for a month before physicochemical analyses.

Environmental factors

Our field global survey included 13 environmental variables, which were obtained either in the field or from satellites and databases: Aridity Index; precipitation seasonality (PSEA); mean annual temperature (MAT); mean diurnal temperature range (MDR); elevation; net

primary productivity (NDVI) index, 2003–2015 period; soil properties (texture [% of clay + silt], soil pH, total C, N and P concentrations and C: N ratio). Elevation and climatic variables, which include MAT, temperature and precipitation seasonality, were collected from the Worldclim database (https://www.worldclim.org; ~1 km resolution) (Hijmans et al. 2005). The aridity index (Food and Agriculture Organization, 1989) (AI, the ratio of precipitation to potential evapotranspiration) of each site was calculated using data interpolations provided by WorldClim (Zomer et al. 2006). To facilitate the interpretation of our results, we used 1 − AI as our surrogate of aridity (Delgado-Baquerizo et al. 2013). Soil properties (texture (% of clay + silt), pH and total organic C) were determined from topsoil (top 7.5 cm) samples collected from each location using standardized protocols (Maestre et al. 2012). To avoid biases associated with having multiple laboratories analyzing soils from different sites, all the samples were analyzed at the Universidad Rey Juan Carlos (Spain). Soil pH was measured with a pH meter in a 1:2.5 mass: volume soil and water suspension. The concentration of soil total organic carbon (C) was determined using a wet chemistry method (Anderson et al. 1993). Continent and ecosystems type were also included in the modelling.

Bioinformatics

The bioinformatics processing data is detailed in Egidi et al. 2019. Briefly, fungal diversity was determined by sequencing the Internal Transcribed Spacer (ITS) region 2 (Blaalid et al. 2013) with primers FITS7 (GTGARTCATCGAATCTTTG)/ITS4 (TCCTCCGCTTATTGATATGC) (Ihrmark et al. 2012) on an Illumina MiSeq platform (2 × 300 PE), and both positive and negative controls were included. All reads were quality filtered and dereplicated with the USEARCH pipeline, and low-quality bases were end-trimmed before merging. All the merged reads had an expected error < 0.5; the quality-filtered reads were clustered into operational taxonomic units (OTUs) of the length of 180 bp, at 100% similarity thresholds using UNOISE (Edgar 2016a). OTU identification was obtained against the UNITE fungal database (V7.2) (Abarenkov et al. 2016) using the SINTAX algorithm with a ≥ 80% probability threshold (Edgar 2016b). A ZymoBIOMICSTM Microbial Community DNA Standard has been used as positive control. After checking the distribution of sample sequencing depth (4,449–144,175, median: 46,481 reads), the OTU abundance table were rarefied without replacement to 4,449 sequences per sample. We examined whether the sampling effort was adequate to capture the fungal community richness by generating species accumulation plot using the ‘specaccum’ function in the R

package ‘vegan’ (v. 2.3-4; Oksanen et al., 2013), resulting in mostly saturated accumulation curve (Supplementary Figure S2) which is indicative of a satisfactory representation of the most common Onygenales members these communities harbor. As the main purpose was to focus on Onygenales (Eurotiomycetes), ITS sequences belonging to this order were filtered and used for downstream analysis. Each Onygenales OTU sequence ($n = 417$) was then searched against the GenBank repository using the BLAST function and ITS_RefSeq_Fungi database.

Statistical analyses

Random forest

We used the Random Forest (RF) model as described in (Delgado-Baquerizo et al. 2018) to identify the major significant environmental predictors explaining the variation of Onygenales according to environmental variables. The most common vegetation type (i.e. forest) in our database was included in our RF analysis as categorical variables with two levels: 1 (forest) and 0 (other ecosystem types). We also use the total fungal and bacterial richness, namely the total number of OTUs across the sampled sites, to test if changes in microbial composition influence Onygenales proportion (Delgado-Baquerizo, 2019). The importance of each predictor variable is determined by evaluating the decrease in prediction accuracy, i.e., increase in the mean square error between observations and OOB (out-of-bag) predictions, when the data for that predictor is randomly permuted. RF was implemented using the '*randomForest*' package V.4.6-14 in the R environment. In addition, to exclude possible confounding effects due to spatial autocorrelation of environmental variables, we repeated the correlation analysis between the main environmental variables and Onygenales richness (number of OTUs) and relative abundance, while controlling for space (e.g. latitude and longitude).

Correlation analyses

We then conducted a Spearman correlation analyses to evaluate the associations between the 13 environmental variables and the relative abundance and richness (i.e. number of OTUs) of Onygenales families and genera using the ‘ppcor’ package (Kim et al. 2015). Spearman rank correlations measure the strength and direction of association between two ranked variables. They do not require normality of data, and linearity is not a strict assumption of these

analyses. We used a false discovery rate approach to determine adjusted *P* values for all the correlations to control for spurious (false positives) correlations.

Distribution of richness of Onygenales fungi globally

A Random Forest regression analysis (Lahouar & Slama, 2015) was implemented to predict the distribution of richness of Onygenales fungi globally. We used the variables as follows: forest cover (land cover type from the MCD12Q1 V6 product for 2016 derived from the International Geosphere–Biosphere Programme classification; Loveland et al. 1999), net primary productivity (Normalized difference vegetation index; NDVI), soil C, pH, aridity, mean annual temperature, mean annual precipitation, mean diurnal range, precipitation seasonality, temperature seasonality and elevation and richness (number of Onygenales OTUs) data from 235 ecosystems with a range of richness between 1 and 24. The random forest model was constructed by finding the set of covariate combinations that most robustly predict the training samples. In particular, 999 numbers of trees and 999 replicates were used. To assess the accuracy of the predictions calculated from the random forest-based model, we calculated how much the parameter space of the predictors differed from the original dataset. We used the Mahalanobis distance of any multidimensional point of the dimensions given by the exogenous variables to the centre of the known distribution that we had previously calculated and the distance of any multidimensional point to the convex hull formed by the 235 ecosystem locations that were used in the model. We then used outlier identification to mask our results and provide more reliable predictions at the 0.9 quantile of the chi-squared distribution with eleven degrees of freedom to which each location belongs (Mallavan et al. 2010). The modelling approach was then validated by returning predicted values (x-axis) versus observed values (y-axis), following Piñeiro et al. (2008).

Results and Discussion

Using amplicon sequencing targeting the internal transcribed spacer (ITS) region, we identified 417 fungal OTUs belonging to the order Onygenales out of the 24,391 fungal OTUs found in our global survey. Using the number of reads as proxy to estimate the relative abundance of each Onygenales sequence in a given sample (Giner et al. 2016; Weiss et al. 2017), we found that these taxa represented between 0.1 and 14% of all the ITS sequences across the study samples, contributing to ca. 4.5% of the total reads identified as fungi (Figure 1a). Our results suggest that these organisms are likely a small but significant

component of soils in natural ecosystems worldwide. Besides, albeit in our global survey we reached a satisfactory representation of Onygenales members (Supplementary Figure S2), the diversity of taxa identified in this study may be constrained by the fungal taxa amplified with the primer pair used here and we are potentially underestimating the distribution of some lineages that are poorly amplified with commonly used ITS primers. Therefore, we envisage that future studies, including under-sampled regions of the world and ad hoc sequencing methodologies, will allow to better characterizing the Onygenales members of the global soil mycobiome.

On average, the sequences of Onygenales surveyed were dominated by Onygenaceae and Gymnoascaceae families, the first including the most dangerous dimorphic fungal species (Muñoz et al. 2018). A few genera were prevalent (Figure 1b; Supplementary Figure S3; Supplementary Table 2 for a complete list), which include the opportunistic genus *Chrysosporium*, known to cause skin as well as pulmonary infections (Gopal et al. 2020), and *Auxarthron*, *Spiromastix*, and *Gymnoascus*. Together, these OTUs accounted for almost a quarter (ca. 25%) of the retrieved ITS sequences classified as Onygenales. Many species of this group are considered to be of low pathogenic potential (Rizzo et al. 2014). In particular, *Spiromastix* and *Gymnoascus* include biotechnologically important extreme-resistant fungi, showing a high salinity and temperature tolerance (Zhou et al. 2016). Less frequent were dermatophytes such as *Microsporum* spp. Conversely, strains of *Emergomyces* and *Coccidioides* spp. that are accounted as the major contributors to the infections against patients with HIV/AIDS, and the Coccidioidomycosis (or 'Valley Fever') (Schwartz et al. 2018; McCotter et al. 2018; Gorris et al. 2021) that cause the majority of reported cases in the United States, were retrieved at the lowest percentage.

We then used the Random Forest (RF) machine learning approach to identify the most important predictors of the distribution of these organisms worldwide. As the complexity of diverse soils communities is known to be crucial in regulating humans and plants pathogens (Samaddar et al. 2021), we first explored whether total microbial (bacterial and fungal) diversity influenced the Onygenales proportion. We found that both fungal and bacterial assemblages had significant, albeit weak, positive association with soil Onygenales (Figure 2a,c), suggesting that the establishment and survival of these organisms might depend on even relatively small changes in soil communities.

Recently, it has been proposed that wet environments contribute to the ongoing expansion of the occurrence of currently known fungal pathogens in some areas of the Earth (Friedman and Schwartz 2019). Strikingly, we found that aridity, together with pH, were the

most important environmental predictors of the distribution of Onygenales worldwide (Figure 2a; Supplementary Figure S4). Significant associations ($P < 0.05$) were also obtained when controlling for spatial autocorrelation (i.e., using latitude and longitude as controlling matrix). Similar results were observed using non-parametric correlation analyses. We found that the increases in aridity had an overall negative effect on both richness (i.e. number of OTUs) and relative abundance when we focused on all Onygenales taxa, whereas no significant effects were detected at finer taxonomic levels with the exception of *Spiromastix* spp. (Figure 2b,c; Supplementary Figure S5). It is well known that some onygenalean fungi such as *Coccidioides* species are endemic to arid and semi-arid regions of North America, growing in sandy alkaline soils, rich in organic matter and salts; yet, they can also spread in nearly any type of desert soil, including those with low pH levels, tolerating soil temperatures ranging from -6.5 to 60.5 °C (Kollath et al., 2016). However, Onygenales may actually display different ecological preferences according to the phylogeny and can be classified as soil/oligotrophic, soil/keratinophilic, dung/agricultural, skin/nail, hair/feather, insect/pollen, halophilic/osmophilic, systemic and plant associated (Kandemir et al., 2020). It has been proposed a clear link between the capacity to tolerate or even prefer extreme environmental parameters and the emergence of opportunistic pathogenicity in the fungal Kingdom (Gostinčar et al., 2018). The evidences of our study suggest that wet and acid soils may support the spreading of "generalists", more competitive Onygenales taxa that are widely spread; conversely, dry and alkaline conditions favor the growth of "specialists" Onygenales such as *Coccidioides* spp. more restricted in specific regions, taking advantage over other microorganisms that cannot tolerate the extremes (del Rocío Reyes-Montes et al., 2016).

We also found that mean annual temperature (MAT) is positively associated with the richness of multiple taxa in the Ascosphaeraceae family as well as members of *Auxarthron* genus (Figure 2b). Yet, *Histoplasma*, a genus including members that has the potential to cause the serious human disease Histoplasmosis (Armstrong et al. 2018; Oladele et al. 2018), was found positively associated with MAT, even if it was recovered in low abundance in our dataset. It has been recently proposed that a gradual adaptation to increasing temperature caused by climate change could lead to an increase of fungi that can cause disease (Nnadi et al. 2021). In addition, climate change can bring major changes to the epidemiology of infectious diseases (Oaks et al. 1992; Patz et al. 1996), increasing the geographic range of pathogenic species or their vectors (De Crecy et al. 2009; Casadevall 2020).

Based on our global survey, we then generated the first global atlas that depicts the current distribution of the richness onygenalean fungi globally (Figure 3). Our results showed

that these fungi may have a global spread, even in those localities where they have been never reported (e.g. Russia, and Alaska) (Chaturvedi et al. 2020). In addition, in accordance with results of our multivariate analyses, we identified humid regions in the Northern Hemisphere, particularly sites in East Europe, as important hotspots of Onygenales distribution.

Conclusions

Taken together, our results based on a global survey provide a baseline understanding of dominant soil-borne Onygenales taxa identity, their occurrence and main environmental factors that drive their distribution in soils of natural ecosystems, highlighting that wet and acid soils are expected to support globally the largest proportions of these organisms. This evidence is the first contribution to understand the distribution and habitat preference of this systematic group that has potential human health implications. As anthropogenic activities continue to affect soil biodiversity in many ways, potentially influencing the balance and distribution of potential soil-borne human pathogens (Babič et al., 2020; Ferraresso et al. 2020), the risk of exposure and infections may increase in the future. Therefore, understanding the ecology, distribution, and diversity of Onygenales taxa, including potential pathogens, in natural environments where they occur may serve as a scientific basis to identify potential areas of risk. In addition, future work is necessary to identify the fine-scale distribution of these organisms in specific localities.

Data statement

The metadata associated with the global field survey are publicly available in Figshare (https://doi.org/10.6084/m9.figshare.11484747). Richness information that was used to implement the predictive model are publicly available in Figshare (https://figshare.com/articles/dataset/Untitled_Item/14776239).

Authors' contributions

C.C. developed the original idea of the analyses presented in the manuscript. M.D.-B. and B.K.S. put together the original global database. Statistical analyses, environmental modelling were done by C.C. Map was generated by E.G. The manuscript was written by

C.C. with contributions from L.S., E.G., B.K.S., and M.D.-B. All authors have read and agreed to the published version of the manuscript.

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Competing Interests

The authors declare no competing financial interests.

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Figures

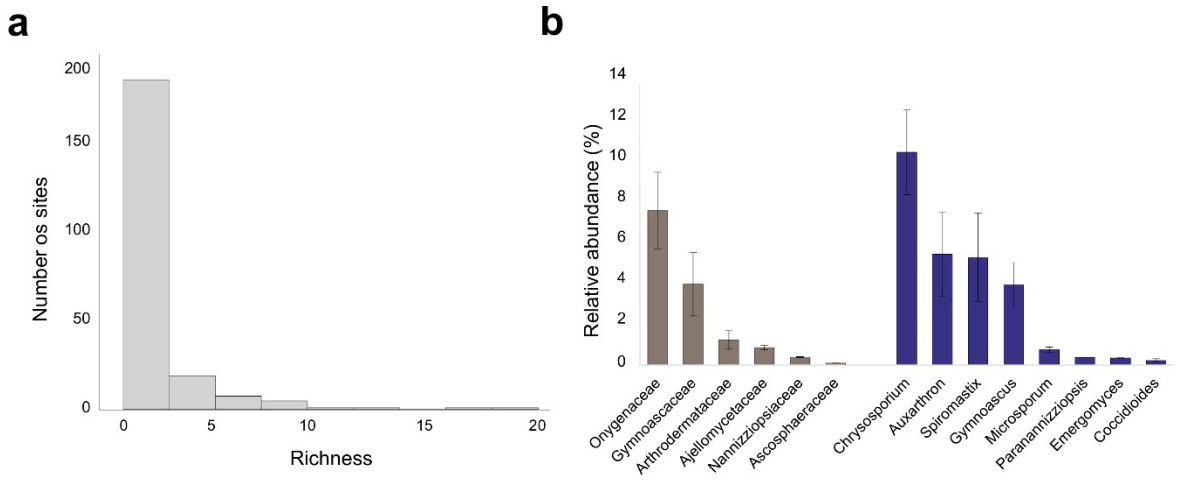

Figure 1. Relative abundance and identity of Onygenales worldwide. a) Distribution of the richness of total Onygenales across the 235 ecosystems surveyed. **b)** Relative abundance (percentage of all ITS sequences; mean ± standard error) of the most common Onygenales identified at family and genus level across all sites.
The standard error is calculated by dividing the standard deviation by the square root of number of measurements (number of taxa in a given family or genus) that make up the mean.

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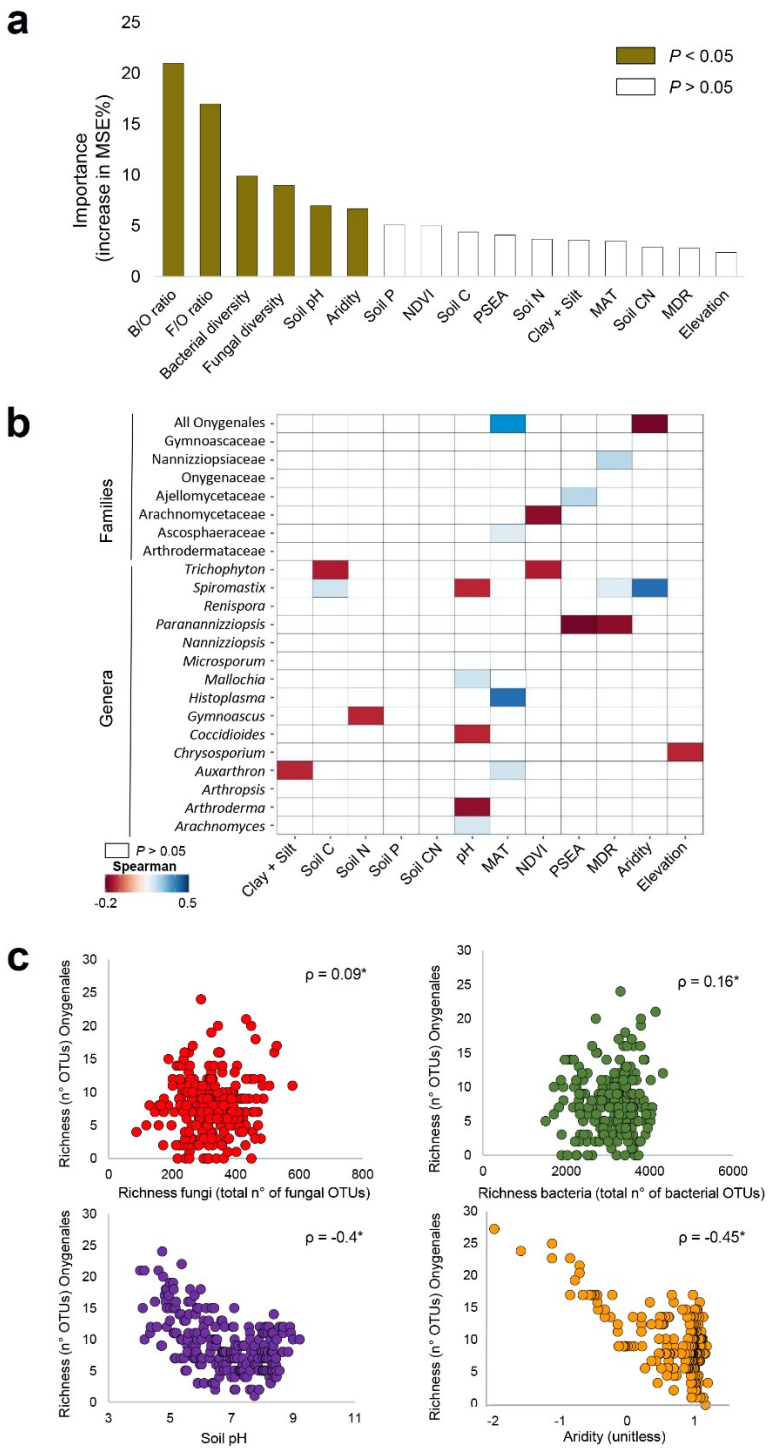

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529**Figure 2. Environmental factors associated with Onygenales richness (i.e. number of** 530**OTUs). a)** Random forest (RF) analyses identifying the importance of potential predictors of 531Onygenales richness. RF Importance = Increase in % mean square error. Coloured and white 532columns represent $P < 0.05$ and $P > 0.05$, respectively. MAT, mean annual temperature; 533MDR, mean diurnal temperature range; PSEA, temperature precipitation seasonality; NDVI, 534normalized difference vegetation index. B/O = bacteria to Onygenales ratio; F/O = fungi to 535Onygenales ratio. **b)** Spearman correlations between environmental factors and Onygenales 536richness ($n = 235$). Correlations with a false discovery rate adjusted $P > 0.05$ are excluded 537(plotted in white). **c)** Selected examples showing the relationship between environmental 538factors and Onygenales richness. Spearman correlation coefficients are shown in the upper 539part of each panel. *****, $P < 0.05$.

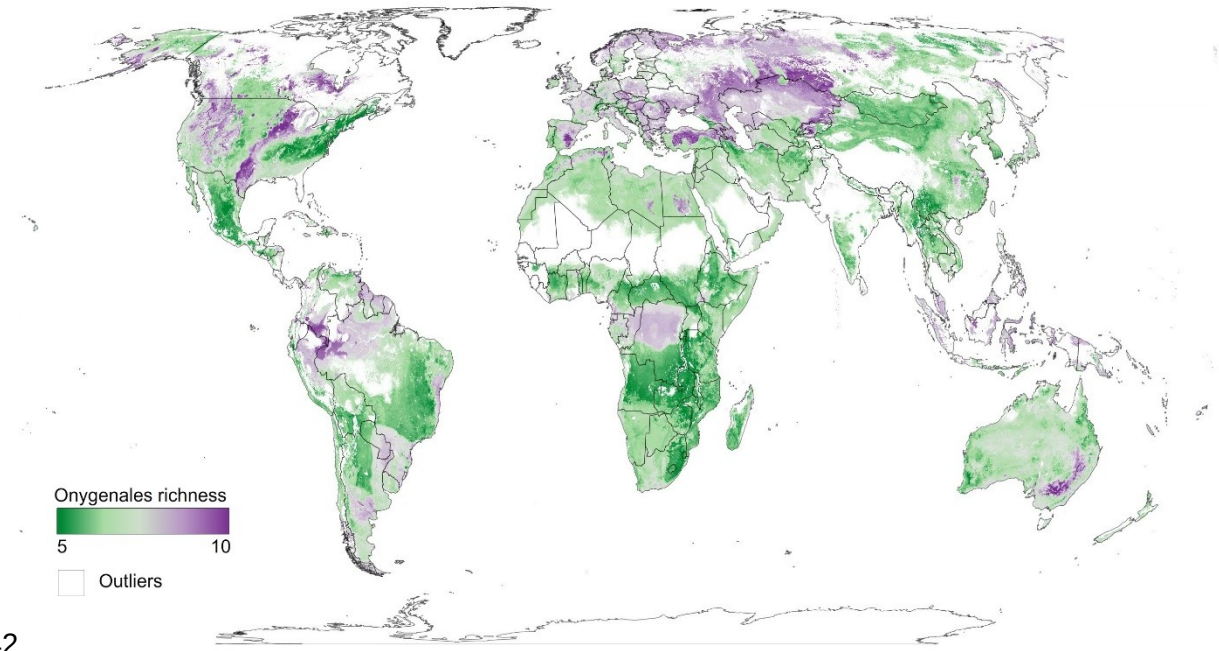

Figure 3. Predicted global distribution of Onygenales richness (i.e. number of OTUs) fungi in soil. The model performance with R = 0.89 and P < 0.001 in the validation of the modeling approach returning predicted values versus ground values. Outliers are calculated from the 0.9 quantile of the chi-square distribution with eleven degrees of freedom to mask areas of low reliability and provide more reliable predictions (see Materials and Methods).

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