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Dermatophytes and mammalian hair: aspects of the evolution of *Arthrodermataceae*

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Abstract

Dermatophytes and other members of *Onygenales* are unique in their ability to degrade keratin, affecting hair and nails, and in the case of human hosts, causing skin infections. Subtillisins are essential proteases in keratin assimilation, and subtilisin-like protease 1 (SUB1) and SUB3–7 are specific for dermatophytes. *eIF2α* kinases are serine-threonine kinases that perform essential functions in response to infection, proteotoxicity, and nutrient scavenging. The relatively conserved nature of EIF2AK4 among fungi makes them potential evolutionary markers, which may contribute to a deeper understanding of dermatophyte taxonomy and evolution. This study aimed to assess the phylogeny of dermatophytes by examining the EIF2AK4 and SUB1 genes compared to the ITS gene marker. The phylogenetic trees generated from the EIF2AK4 and SUB1 genes exhibited a similar topology, which differed from that observed in the ITS tree. Our preliminary findings with a limited dataset suggest that the EIF2AK4 and SUB1 genes provide a reasonably correct reflection of the evolution of *Arthrodermataceae*. In addition, the study analyzed in vitro keratinolytic responses of 19 dermatophyte species using hairs of a broad range of mammals, including ancestral as well as derived species, as substrates. *Trichophyton mentagrophytes* and *Nannizzia gypsea* were the most active in degrading hair, while *Trichophyton verrucosum*, *Trichophyton tonsurans* and *Epidermophyton floccosum* showed low response. Hairs of *Hyracoidea* and *Rodentia* were most affected of all mammal hairs, while in contrast, bat hairs were difficult to degrade by nearly all tested dermatophyte species. Zoophilic species showed more activity than anthropophilic dermatophytes, but hair degradation profiles were not diagnostic for particular dermatophyte species.

Keywords *Arthrodermataceae* · Hair · *EIF2AK4* · *SUB1* · *Trichophyton* · Keratin

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Introduction

The family *Arthrodermataceae* classically has been divided according three ecological lifestyles, i.e. geophilic, zoophilic, and anthropophilic. Geophilic dermatophytes have a preference for terrestrial habitats producing their assimilative thallus and sexual states in soil. They live on keratinous animal debris, and are asymptomatically distributed in animal fur. Recent studies have shown a high prevalence of the ancestral geophilic genus *Arthroderma* in rodent populations (Moulíková et al. 2023; Gnat et al. 2022; Gallo et al. 2005). In humans and domesticated animals, they rarely cause infection (Moskaluk and Vande-Woude 2022). However, occasional invasion of keratinized tissues leads to acute dermatophytosis (tinea). Occupational exposition mainly involves gardeners and farmers (Chmel and Buchvald 1970; Dolenc-Voljč and Gasparič 2017). Indirect transmission to humans can also occur through domestic animals, although this is less likely (Moriello et al. 2017) (Fig. 1).

Zoophilic dermatophytes tend to have a closer association with the mammal host and less with the terrestrial habitat, leading to loss of sexuality (de Hoog et al. 2017a, b). Zoophilic species on domesticated hosts, when transmitted to humans or susceptible animals, may cause persistent, inflammatory infections, posing a significant risk to veterinary and public health (Weitzman and Summerbell 1995; Deng et al. 2008; Seyedmousavi et al. 2015) (Fig. 1). In agricultural settings, zoophilic dermatophytes have traditionally been common on livestock, such as cattle, with *Trichophyton verrucosum* being a primary veterinary health concern (Fawzi et al. 2023; Aghamirian et al. 2011). *Microsporum canis,* and *T. mentagrophytes* are the other commonly isolated dermatophytes from domesticated animals such as cats, dogs and rabbits (Seebacher et al. 2008; Zhang et al. 2019; Tang et al. 2021).

Members of the third, evolutionarily most advanced group, the anthropophilic dermatophytes such as *Microsporum audouinii* and *Trichophyton rubrum*, often cause

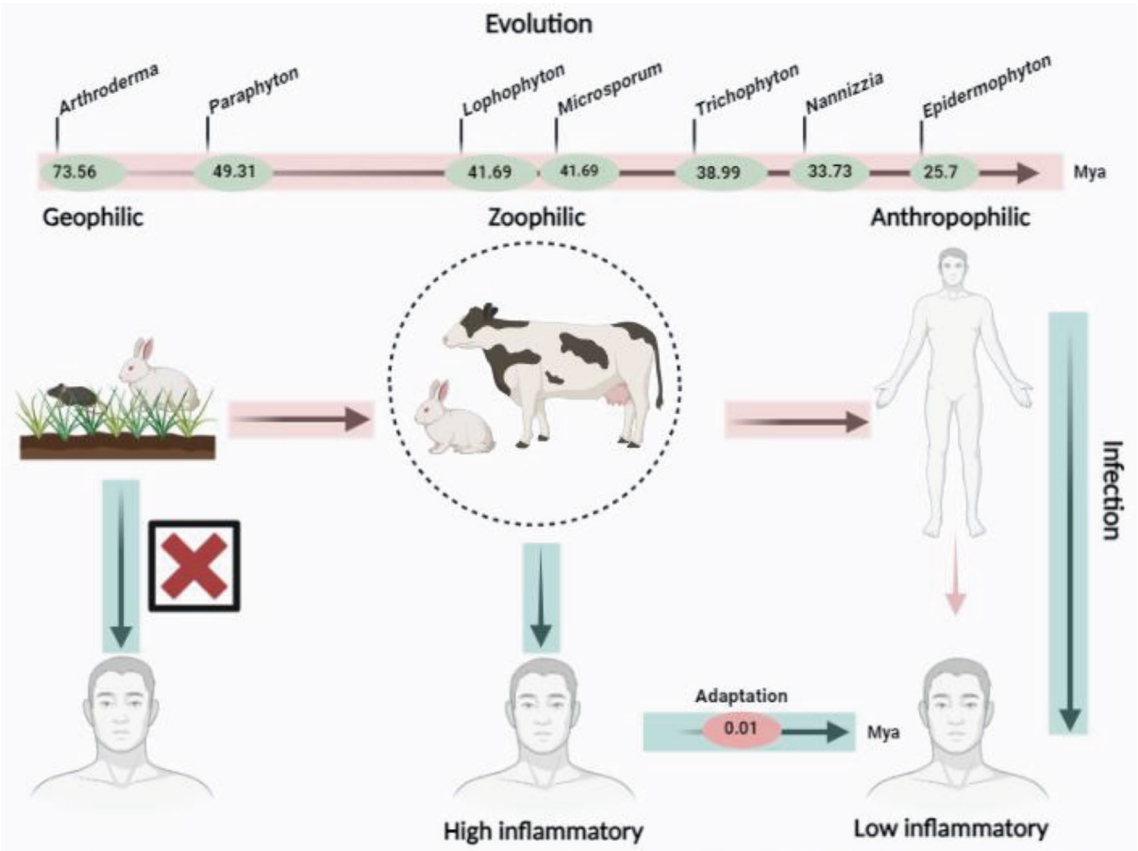

Fig. 1 Evolution of *Arthrodermataceae*. The family is classified ecologically into geophilic, zoophilic, and anthropophilic species. Anthropophilic species are primarily found in derived genera, while geophilic species are mostly in ancestral genera. However, via infection of non-preferred hosts, leading to high inflammation, adaptation, lowering inflammation, within shorter time frames is possible. Divergence times in Mya are based on Zhang et al. (2022). Adaptation to anthropophily is estimated at 0.01 Mya, signaling early domestication of wild animals

milder cutaneous disorders and may spread among families and schoolchildren (Donghi et al. 2011; Tartor et al. 2019). This group shows adaptation to the human host in their dispersal via skin flakes. Phylogenetic classifications of species in *Trichophyton* as well as in *Microsporum* underline that the transition from zoo- to anthropophilic lifestyles takes place within species complexes in a rather short timeframe (Tang et al. 2021) (Fig. 1), although most of these adaptations are observed in the derived genus *Trichophyton*. Some human-associated species such as *Trichophyton schoenleinii* are close to the animal host camel (Baghza et al. 2016). The inflammatory tinea capitis by this species has been common under poor living and sanitary conditions that are characteristics of rural communities in developing countries (Ayodele et al. 2021). The anthropophilic species *Epidermophyton floccosum* and *Trichophyton rubrum* rarely cause this type of infection (Chandra et al. 2021). They are more remote from zoophilic ancestors (Zhan et al. 2015) and possibly have adapted to the human host earlier in the past, by reducing their virulence.

Anthropophilic have their origin in domesticated animals, and the way back is highly exceptional (Brilhante et al. 2006). The main genera of anthropophilic dermatophytes are *Trichophyton*, *Epidermophyton*, and *Microsporum,* comprising about ten low-virulent dermatophytes (de Hoog et al. 2017a, b). *Trichophyton interdigitale*, *Epidermophyton floccosum* and particularly *Trichophyton rubrum* are common and widespread (Su et al. 2019; Moskaluk and VandeWoude 2022). It has been estimated that two-thirds of the global population will experience a dermatophyte infection at some point in life (Petrucelli et al. 2020). The anthropophilic species have adapted to human physiology and the immune system, resulting in mild immune responses and subtle clinical signs (White et al. 2014), but some cases are severe and long-lasting due to metabolic diseases, immune disorders, or corticosteroid therapy (Snell et al. 2016; Vaezi et al. 2018; Bishnoi et al. 2018). In immunosuppressed patients, dermatophyte infections can have atypical presentations with extensive lesions or even fatal outcomes (Wang et al. 2023). Individuals with inherited CARD9 deficiency are particularly vulnerable to severe dermatophytosis (Grumach et al. 2015). While deep and inflammatory infections are mostly associated with underlying diseases, there are also severe cases without apparent risk factors (Lanternier et al. 2013).

The relationship between humans and anthropophilic dermatophytes is highly dynamic; the spectrum of infecting agents is subject to continuous change. While in modern agriculture the problems with human infection from cattle have been minimized by better hygiene and less animal contact, and new dermatophyte problems have emerged. Zhan et al. (2015) described a shift in the prevalence of agricultural dermatophytes to pet-associated mycoses during the economic emergence of China. Among the recent infections, other than *M. canis* from cats, include *Trichophyton benhamiae* from guinea pigs (Ansari et al. 2021) and *Trichophyton erinacei* from African pygmy hedgehogs (Abarca et al. 2017; Čmoková et al. 2022). Of particular concern is the emergence of *Trichophyton indotineae* (Singh et al. 2018; Burmester et al. 2022; Jabet et al. 2022; Chowdhary et al. 2022). More than half of *T. indotineae* strains are highly virulent and resistant to the commonly used antifungal terbinafine (Ebert et al. 2020; Kong et al. 2021). This species shows poor response to oral terbinafine therapy, which is the primary treatment for moderate to severe dermatophytosis (Uhrlaß et al. 2022; Fattahi et al. 2021; Jabet et al. 2022; Rodr 2021). While primarily infecting humans, the presence of *T. indotineae* in domestic animals suggests the possibility of a host jump, potentially explaining its increased virulence (Jabet et al. 2022; Chollet et al. 2015). This challenges the assumption that the inappropriate use of steroid-containing antifungals alone is responsible for the emergence of *T. indotineae*.

In main traits, the above lifestyle classification matches with ribosomal phylogeny and this has led to a rearrangement of genera (de Hoog et al. 2017a, b). The early evolutionary success of dermatophytes was due to their secretion of keratinases, classified as serine proteases, serine metalloproteases, or metalloproteases, all contributing to hair degradation (Scott et al. 2004). Genes SUB1 and SUB3-7 are commonly detected in dermatophytes, but the panel of enzymes is often incomplete: *Microsporum canis* lacks SUB4-7 genes (Kaplan et al. 2020). SUB1 and SUB3 in *M. canis* are involved in adhesion to keratinized stratum corneum and virulence (Kaplan et al. 2020; Łagowski et al. 2021; Khalili et al. 2018). SUB1 and SUB2 can be amplified in all *T. verrucosum* strains, making SUB1 a potential evolutionary marker. Assuming that proteinases play an essential role in the ecological transition of geo-, zoo- and anthropophily, their phylogeny is expected to be associated in main traits with other markers, such as the ribosomal genes, and with fungal kinases which are known to be involved in crucial biological processes. Kinases have been shown to be important for organism's survival and are highly conserved across different taxonomic classes (Krishna and Kumar 2018). The mammal kinases EIF2AK1, EIF2AK2, EIF2AK3 and EIF2AK4 phosphorylate the same substrate which is the a subunit of eukaryotic translation initiation factor 2 (eIF2α), each responding to different stimuli (Assunção et al. 2020). In various microorganisms such as *Trypanosoma*, *Candida albicans*, and *Paracoccidioides brasiliensis*, eIF2 kinases play essential roles in differentiation, nutrient transport, morphogenesis, and infection establishment (Kamthan et al. 2012). Phylogenetic studies have demonstrated distinct clades and subclades within the eIF2 kinase family, with EIF2AK4 being the largest sequence and having a primitive origin in fungi and yeast (Krishna and Kumar

2018). Recently, the hypothetical EIF2AK2 gene was tested as a molecular marker for phylogenetic reconstruction of black yeast-like fungi (Assunção et al. 2020). Considering the significant functions of kinases in cellular mechanisms and their conservation throughout evolution, utilizing these molecules as markers can provide insights into fungal taxonomy and phylogeny. In this study, we aim to compare established ribosomal phylogeny with SUB1 and the novel gene EIF2AK4 across different genera of *Arthrodermataceae* for molecular diagnosis. Given the fact that dermatophytes are almost exclusively found and have their origin on mammals, we also investigated the interaction of a panel of dermatophyte species selected from the *Arthrodermataceae* phylogenetic tree and fur samples of a wide diversity of ancestral and derived mammal species.

Materials and methods

Strains and identification

Reference strains were obtained from the Centraalbureau voor Schimmelcultures (CBS, housed at Westerdijk Fungal Biodiversity Institute, Utrecht, Netherlands), and Belgian Coordinated Collections of Microorganisms, Scientific Institute of Public Health (BCCM/IHEM, Brussels, Belgium). Additional strains were kindly provided by P. Nenoff, R. Kano, M. Monod, S. Nardoni, H. van der Lee, P. Zhan, V. Hubka, and S. Hainsworth. In total, 97 strains of 29 species from*Arthrodermataceae* were analyzed for internal transcribed spacer region ITS-1 and ITS-4, EIF2AK4,and *SUB1* (Supplementary Table 1). Strains were cultured on Sabouraud's Glucose Agar (SGA; Oxoid,Hampshire, U.K.) for 1–2 weeks at 28 °C. DNA extraction and sequencing methods were performed according to Tang et al. (2021). Gel Extraction Kit (QIAquick, Hilden, Germany) was used for PCR product purification.

Development of PCR primers and amplification

Whole genome data of fourteen species (Table S2) in *Arthrodermataceae* were downloaded from the GenBank. Using XM_047748199.1 and XM_003236307.1 sequences, EIF2AK4 and SUB1 sequences were extracted from the whole genomes of the fourteen species. We used the website to design the primers (https://benchling.com/), and used Oligo Analysis Tool to check self-dimers. Primer pairs (Table S3) were designed in conserved regions to amplify EIF2AK4 (463 bp) and SUB1 (633 bp). PCR reactions were run in a thermal cycler (Applied Biosystems 2720 Thermal Cycler, CA, USA) in 50 µL volumes consisting of 10 µL PCR Buffer (Thermo Scientific, Waltham, MA, USA), 1 µL of 10 mM dNTPs, 0.5 µL Taq DNA polymerase (Thermo scientific, USA), 10 µM of each primer, 35.5 µL DEPC-treated water and 1 µL of 50–200 ng/µL DNA. PCR conditions for EIF2AK4 and SUB1 genes were as follows: 98 °C for 30 s, followed by 35 cycles at 98 °C for 10 s, 58 °C for 30 min, and 72 °C for 1 min, with an extension cycle of 72 °C for 10 min. PCR products were visualized on 3% agarose gel.

Phylogenetic and multilocus analysis

Sequences were edited and assembled with the BioEdit Sequence Alignment Editor program, manually corrected, and aligned using the MAFFT server (http://www.ebi.ac.uk/Tools/msa/mafft/) with default parameters, and MEGA (v7.0) was used to edit the sequences. A phylogenetic tree was generated using the maximum likelihood method with MEGA (v7.0) software with the general time-reversible as the evolutionary model with 1000 bootstrap replications. *Arthroderma uncinatum* strain CBS 119779 (NW 022983866.1) was used as the outgroup. The online tool ChartExpo™ (https://www.chartexpo.com/) was used to generate the Sankey diagram in Fig. 2.

In vitro keratinase activity

Keratin azure agar was prepared following Su et al. (2019). First, 5 mL of lower layer medium was sterilized and added to 15 mL tubes. The lower layer medium consisted of 2.5% agar, 0.05% $MgSO_4 \cdot 7H_2O$, 0.05% KCl, 0.05% K_2HPO_4, 0.01% $ZnSO_4 \cdot 7H_2O$, 0.01% $FeSO_4 \cdot 7H_2O$, 0.003% $CuSO_4$ and was in the 15 mL tubes. Once the medium solidified, 0.5 mL of the sterile second medium was added to the same tubes as the upper layer. The second medium contained 1% agar, 0.003% $CuSO_4$, 0.01% $FeSO_4 \cdot 7H_2O$, 0.01% $ZnSO_4 \cdot 7H_2O$, 0.05% $MgSO_4 \cdot 7H_2O$, 0.05% KCl, 0.05% K_2HPO_4, and 8 mg/mL keratin azure. Strains were inoculated from grown colonies on SGA plates into the tubes and then incubated at 28 °C for one month. The release of azure dye into the lower layer indicated keratinase production. The results include negative, weak, and positive (Fig. 4 and Table S4).

Hair analysis

Adequate amounts of hair were collected from 44 mammalian hosts classified in 11 orders. The human hairs were collected from the head of two adult volunteer individuals with different hair colors (black and blond), in addition to a sample of baby hair. Detailed information on the types of hair is provided in Table S5. Hair processing was done according to Al-Janabi et al. (2016). Collected hairs were

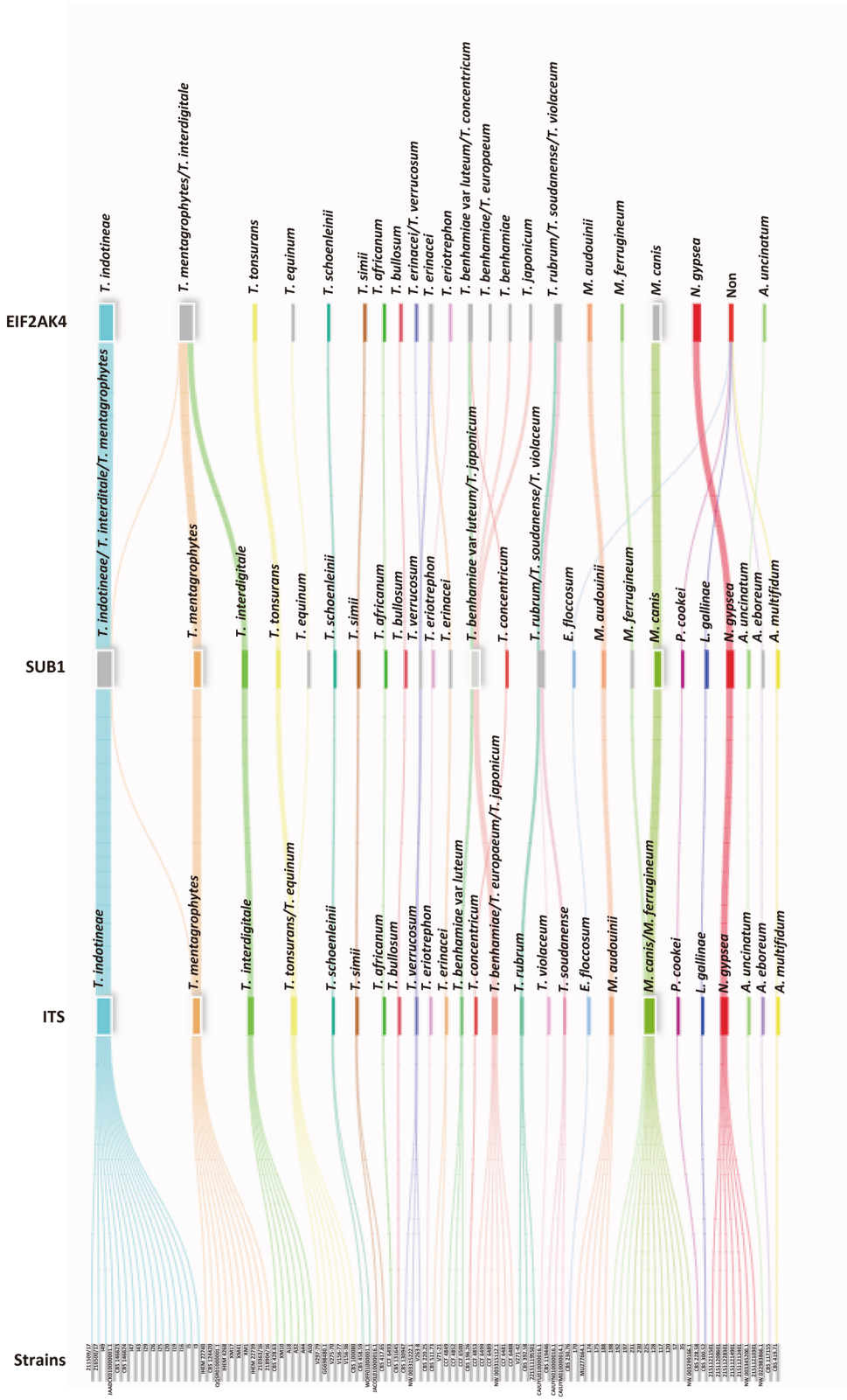

Fig. 2 Use the Sankey diagram to compare the congruence of the ITS, EIF2AK4, and SUB1 genes based on information gathered from the tree. The Sankey diagram was constructed with Chartexpo. The first column indicates strains. The second, third, and fourth column indicates strains are sorted into different species based on ITS, EIF2AK4 tree, and SUB1 tree. All strains from the same species are the same color. The Non indicated these strains cannot be amplified

cut into pieces of 1–2 cm length. Each type of mammalian hair was dispersed over 20 tubes and 5 mL of sterile MilliQ water was added, 2–3 drops of 10% yeast extract (Himedia, Mumbai, India) were added, and the tubes were sterilized at 121 °C for 15 min. After sterilization, 19 dermatophyte strains were added in different tubes (Fig. 4),

while one tube of each sample type was left blank. Affection of hair types was examined after 21 days of incubation at 28 °C.

Criteria of hair damage

A standard was set to judge the degree of hair damage inflicted by the dermatophyte, in numerical order according to severity (Fig. 3 and Table S4): no damage = 0, medulla damage = 1, cuticle damage = 2, hair perforation = 3,

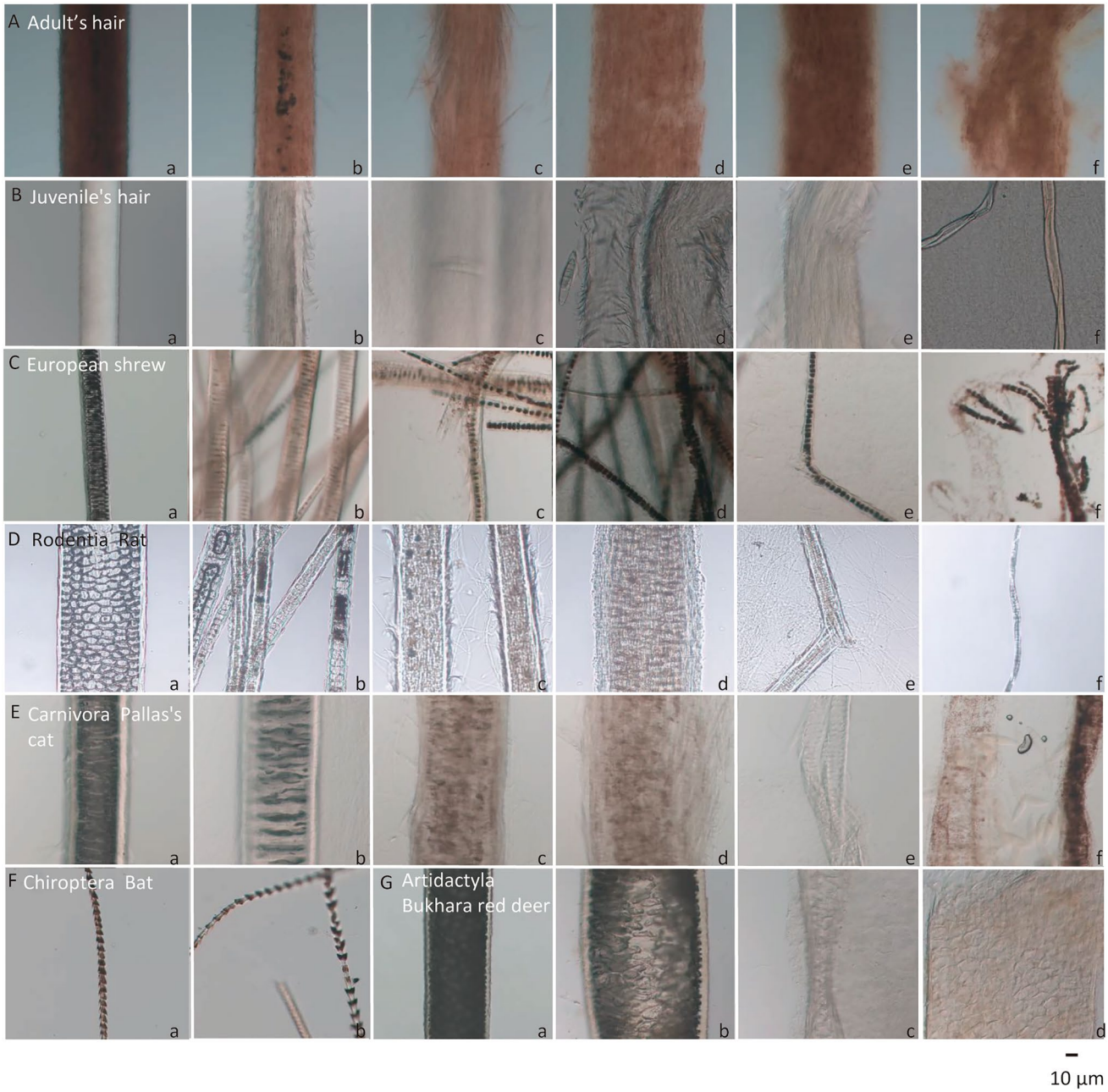

Fig. 3 Hair damage photos. Seven types of hair were selected. The pictures showed different degree of hair damage. All of **a** are normal hair as negative control. Adult's hair has six criteria. **A**(**b**–**f**) mean medulla damage, cuticle damage, hair perforation, loosen and fracture, respectively. **B**(**b**–**f**) mean cuticle damage, hair perforation, loosen, fracture and only shaft, respectively. **C**(**b**–**f**) mean medulla damage, cuticle damage, loosen, fracture and only medulla, respectively. **D**(**b**–**f**) mean medulla damage, cuticle damage, loosen, fracture and only shaft, respectively. **E**(**b**–**f**) mean medulla damage, cuticle damage, loosen, fracture and only medulla, respectively. **F**(**b**) means cuticle damage. **G**(**b**–**d**) mean medulla damage, loosen and fracture

Fig. 4 The heatmap of hair damage score. Hair damage grade values are colored along a white (low) to red (middle) to green (high) color scale. The first and second row means the total score of hair degraded by each strain and keratin azure degradation degree, respectively. It used white (low) to deeper purple (high) to represent. The left column is the total score of each mammal hair degraded by 19 strains. It used light brown (low) to deeper brown (high) to represent. This figure is based on Table S4

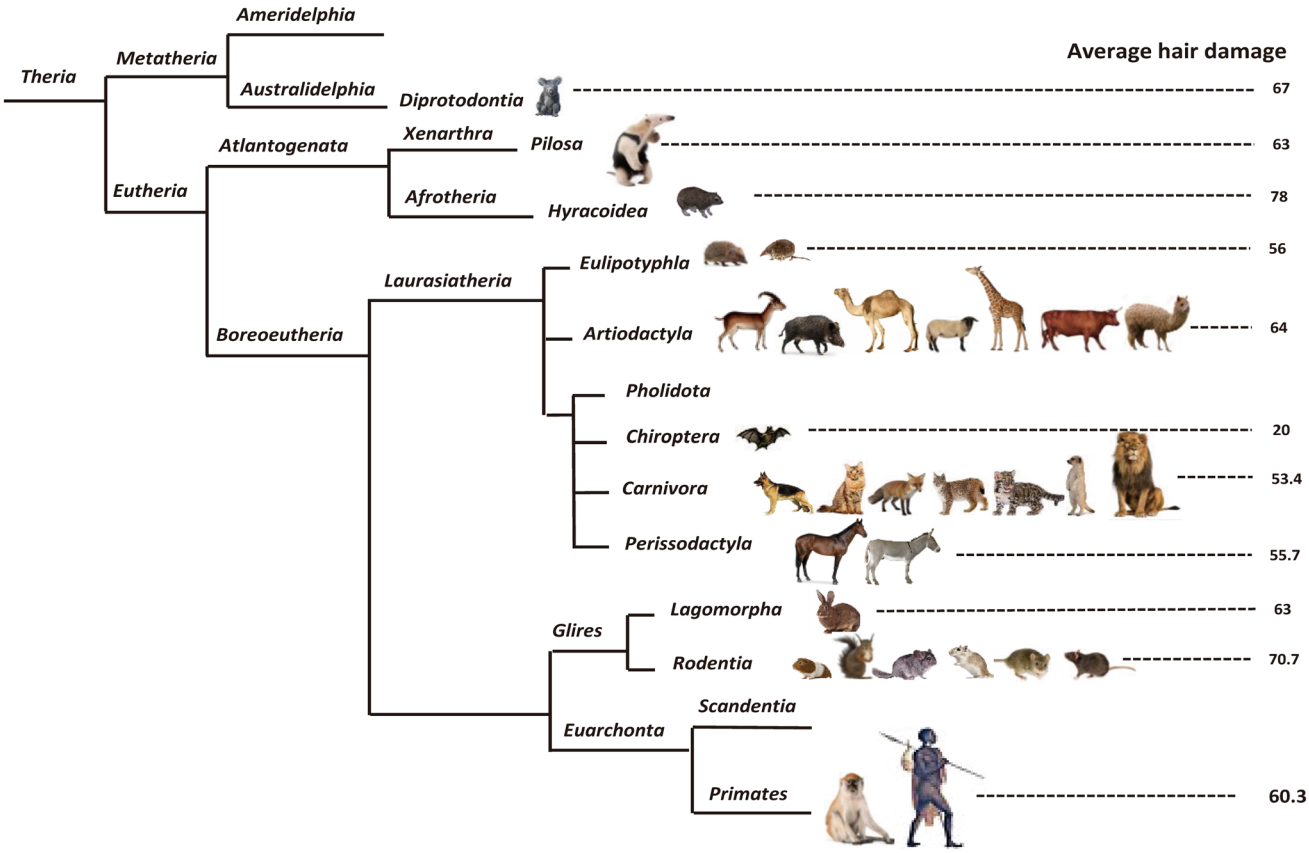

Fig. 5 Phylogeny of *Mammalia*. The value indicated average of hair degradation within each genus, allowing us to determine which genera have hair that is more easily degraded

loosening of fibers = 4, fracture = 5, only hair shaft remaining = 6. We calculated the sum of the degree of each strain to 44 kinds of hair and obtained the degradation ability of the strain. The sum of the degradation degree of each hair type is divided by the species number in the genus to get the average value for each mammal genus (Fig. 5), providing a graded overview of degrees of dermatophyte affection of mammal hair.

Results

Phylogeny of dermatophytes

The rDNA ITS sequences were used to construct a reference taxonomic overview of *Arthrodermataceae* (Fig. S1). Bootstrap support values above 80% are shown above the branches. The ITS tree includes six genera: *Epidermophyton*, *Lophophyton*, *Microsporum*, *Nannizzia*, *Paraphyton*, and *Trichophyton; Arthroderma uncinatum* is used as outgroup in this and in subsequent trees. In this overview, *Trichophyton* (BS support 96%) contains 16 species, of which 10 species have bootstrap support above 80%. *Microsporum* (BS support 99%) comprises three species with low bootstrap support. *Epidermophyton*, *Lophophyton*, *Nannizzia*, and *Paraphyton* each were included with a single species.

We evaluated the reliability of incorporating novel markers, in comparison with ribosomal phylogeny. Specifically, we developed a pair of new primers targeting the EIF2AK4 and SUB1 genes to investigate the evolution of *Arthrodermataceae*. Unfortunately, the whole genomes of *Epidermophyton*, *Lophophyton*, *Arthroderma eboreum*, *A. multifidum*, and *Paraphyton* were not available in the NCBI database, posing challenges in primer design. As a result, the EIF2AK4 primers could not be amplified from these genera. However, the SUB1 primers successfully amplified corresponding sequences from *Epidermophyton*, *Lophophyton*, and *Paraphyton*. Among the *Arthroderma* genus, only the whole genome of *Arthroderma uncinatum* was accessible in the NCBI database. Considering the significant intrageneric variability within the *Arthroderma* genus in *Arthrodermataceae*, the distances between its members exceeded the limits of successful amplification using the primer set designed for *A. uncinatum*. Nonetheless, the partial SUB1 gene of *Arthroderma multifidum* and *A. eboreum* could be amplified.

The EIF2AK4 and SUB1 primers successfully amplified all *Trichophyton* and *Microsporum* species as well as *Nannizzia gypsea*. *Trichophyton tonsurans* and *T. equinum* can be separated by EIF2AK4 (BS support 96%) (Fig. S1). The EIF2AK4 gene separates *T. interdigitale* and *T. mentagrophytes* from *T. indotineae* (BS support 98%), but the sequence with GenBank accession number JAADCK010000001.1 (*T. interdigitale*) is reidentified as *T. indotineae* based on our ITS, EIF2AK4 and SUB1 separate phylogenies (Fig. S1). While the IHEM 22740 strain was identified as *T. mentagrophytes* in the ITS and EIF2AK4 phylogenies, it was classified as either *T. indotineae* or *T. interdigitale* in the SUB1 phylogenies (Fig. S1). The EIF2AK4 phylogeny distinguishes the species in the *M. canis* complex (BS support 98%). This could also be achieved with SUB1, with the exception of one isolate that could not be amplified. In order to achieve optimal consistency of the three trees, we discarded this isolate from the comparison. The SUB1 gene was amplified in 99% of the strains included in the study. The topologies of the resulting EIF2AK4 and SUB1 trees were comparable to that of rDNA ITS (Fig. S1). The Sankey diagram shows that the connection lines of most strains are basically straight lines in the three genes (Fig. 2). Therefore, we reconstructed the seperate phylogeny of *Arthrodermataceae* using SUB1 and EIF2AK4 genes with high phylogenetic content in a similar set of samples. The taxonomic entities defined in earlier studies were well recognizable.

Degradation of non-human mammal hair by various dermatophytes

A set of dermatophyte species (Fig. 4) was used for in vitro digestion of hair samples from 42 widely different mammal species belonging to 11 genera. Hairs were collected from captive animals belonging to *Mammalia*, subclass *Theria* (Table S5). The five types of hair degradation, in five degrees of severity with category six being the total dissolution of the hair after 3 weeks incubation, is based on degradation of hair of *Homo sapiens* one-year-old child. In the summarized data below, animal hair types are arranged according to position of the respective orders in the phylogeny of *Mammalia* (Fig. 5).

Diprotodontia

Of this order, hairs of koala (*Phascolarctos cinereus*) were included. The unaffected medulla of koala hair is amorphous. Four types of hair damage were observed when incubated with strains of our dermatophyte panel. Most strains showed medulla damage (criterion 1), the medulla often disappearing and the hair eventually is locally filled with water (Fig. S1Ab). This type of hair damage was observed in the zoophilic species close to *T. verrucosum*, as well as in members of the anthropophilic *T. rubrum* group and *Epidermophyton floccosum*. In more advanced stages provoked by relatives of *T. mentagrophytes*, this leads to hair loosening (criterion 4) or hair fracture (criterion 5). Only *Trichophyton erinacei* remained entirely without hair damage. The sum of damage criteria over all test organisms applied on koala hair is 67 (Fig. 5).

Pilosa

Hair of the southern tamandua (*Tamandua tetradactyla*), also known as the lesser ant eater, showed amorphous medulla. Four degrees of hair damage were observed when incubated with strains of our dermatophyte panel (Fig. S2B). Most strains caused hair loosening (criterion 4) or fracture (criterion 5), but *Tamandua tetradactyla* hair was not damaged by *T. verrucosum*, *T. benhamiae*, *T. tonsurans*, and *Arthroderma flavescens* strains. The sum of damage criteria over all test organisms applied on *Tamandua tetradactyla* is 63 (Fig. 5 and Table S4).

Hyracoidea

Unaffected hair from yellow-spotted rock hyrax (*Heterohyrax brucei*) showed narrow medulla lattice. Four degrees of hair damage were observed (Fig. S2C). The hyrax hair was rather susceptible to fungal infection, almost all test strains causing hair fracture (criterion 5). Only *T. verrucosum* and *A. flavescens* strains remained without appreciable damage on hyrax hair (Fig. 4). The sum of damage criteria over all test organisms applied on hyrax hair is 78 (Fig. 5 and Table S4).

Eulipotyphla

Of the order *Eulipotyphla*, hairs of two animal species, European hedgehog (*Erinaceus europaeus*) and common shrew (*Sorex araneus*), were subjected to hair degradation test. There are different hair types in these two mammals. The medulla of hedgehog hair presents a globular structure (Fig. S2F). Five degrees of hair damage were observed (Fig. S2F). *Microsporum canis* caused only the medulla damage only (criterion 1). With increasing damage, which was particularly noted with *Trichophyton* species, the black granules gradually released the brown pigment, which finally became dispersed in the hair shaft with disappearance of the central medulla grains. The sum of damage criteria over all test organisms applied on European hedgehog hair is 47.

The medulla of the European shrew (*Sorex araneus*) presented a uniserial ladder structure (Fig. 3C). The shrew hair was particularly susceptible to infection by *Nannizzia gypsea*, which damaged the hair shaft but left the medulla

largely unaffected. The cuticle and cortex disappeared (criterion 6). Most strains led to hair fracture (criterion 5). The sum of damage criteria over all test organisms applied on shrew hair is 71 (Table S4).

Artiodactyla

Of the order *Artiodactyla*, hairs of eleven animal species were subjected to hair degradation test, i.e. Dorper sheep (*Ovis aries*), Bukhara red deer (*Cervus hanglu bactrianus*), Tarim red deer (*Cervus elaphus yarkandensis*), guneruk or giraffe gazelle (*Litocranius walleri*), Vicuña (*Vicugna vicugna*), Bactrian camel (*Camelus bactrianus*), goat (*Capra hircus*), pig (*Sus domesticus*), and cattle (*Bos taurus*). In cow hair, ovoid bodies are solid structures that are spherical to oval in shape, larger than pigment granules and with very regular margins. Five degrees of hair damage were observed (Fig. 4). *Trichophyton benhamiae* and *A. multifidum* yield no hair damage (criterion 0). Most strains showed hair fracture (criterion 5). The sum of damage criteria over all test organisms applied on *Bos taurus* is 71 (Table S4).

Bukhara red deer and goat hairs exhibit a wide medulla lattice (Fig. 3G). In deer hair, four degrees of hair damage were observed (Fig. 4). *Trichophyton verrucosum*, *T. indotineae*, *T. simii*, *M. canis*, *M. ferrugineum*, *L. gallinae*, *A. flavescens* and *E. floccosum* showed no hair damage (criterion 0). *Trichophyton violaceum*, *T. tonsurans*, *T, equinum*, *T. interdigitale* and *T. mentagrophytes* caused hair loosening or hair fracture (criterion 4 or 5). The sum of damage criteria over all test organisms applied on Bukhara red deer is 40 (Table S4). In goat hair, four degrees of hair damage were observed (Fig. 3). Only *T. simii* and *T. benhamiae* yield no hair damage, while *T. rubrum*, *T. interdigitale*, *T. mentagrophytes*, *T. erinacei* and *A. multifidum* showed hair fracture (criterion 5). The sum of damage criteria over all test organisms applied on goat hair is 55 (Table S4).

In *Artiodactyla*, hairs of vicuña and camels proved to be relatively vulnerable. In vicugna, four degrees of hair damage were observed (criteria 1, 2, 4, and 5). Only *T. benhamiae* caused medulla damage (criterion 1). *Trichophyton tonsurans* and *Microsporum ferrugineum* caused cuticle damage (criterion 2). The remaining strains caused hair loosening or fracture (criteria 4 or 5). The sum of damage criteria over all test organisms applied on vicuña hair is 81. In camel hair, only *A. multifidum* strain yielded cuticle damaged (criterion 2). The remaining strains presented hair loosening or hair fracture (criteria 4 or 5). The sum of damage criteria over all test organisms applied on camel is 87 (Fig. 3). The average degradation score of analyzed members of the order *Artiodactyla* is 64 (Fig. 4).

Perissodactyla

Of the order *Perissodactyla*, hairs of three animal species were subjected to hair degradation test, i.e. Somali wild ass (*Equus africanus somaliensis*), common horse (*Equus caballus*) and donkey (*Equus asinus*). Hair types from these animals all exhibited a contentious medulla. In this order, hair of Somali wild ass found to be resistant to degradation by dermatophytes. At the end of the incubation period, five degrees of damage were noted (criteria 0, 1, 2, 4, and 5); *Trichophyton equinum*, *T. mentagrophytes*, *T. simii*, *N. gypsea*, *M. canis* and *T. erinacei* presented hair fracture (criterion 5). *Paraphyton cookei* caused hair loosening (criterion 4). The remaining strains caused mild damage (criterion 1 or 2) or no damage. The sum of damage criteria over all test organisms applied on Somali wild ass hair is 39 (Table S4). In common horse hairs, five degrees of damage were observed (criteria 0, 1, 2, 4, 5; Fig. S2E). *Trichophyton rubrum*, *T. equinum*, *T. indotineae*, *T. simii*, *N. gypsea*, *P. cookei*, *M. canis*, and *A. flavescens* caused hair fracture (criterion 5), while *T. benhamiae*, *T. tonsurans*, *T. interdigitale* and *L. gallinae* showed no hair damage (criterion 0). The sum of damage criteria over all test organisms applied on horse hair is 55 (Table S4).

In the order *Perissodactyla*, hairs of the donkey were more vulnerable than those of related animal species. *Triochophyton tonsurans*, *T. equinum* and *Arthroderma flavescens* caused medulla damage (criterion 1), and *A. multifidum* caused cuticle damage (criterion 2). The remaining strains caused hair loosening or hair fracture (criterion 4 or 5). The sum of damage criteria over all test organisms applied on donkey hair is 71. The average of the *Perissodactyla* order hair damage degree is 55.7 (Fig. 4).

Rodentia

Of the order *Rodentia*, hairs of seven animal species were subjected to hair degradation test, i.e. Swinhoe's striped squirrel (*Tamiops swinhoei*), red squirrel (*Sciurus vulgaris*), guinea pig (*Cavia porcellus*), house mouse (*Mus musculus*), brown rat (*Rattus norvegicus*), short-tailed chinchilla (*Chinchilla chinchilla*), and Mongolian gerbil (*Meriones unguiculatus*). Uniserial ladder or wide aeriform lattice both types of medullae can be found in rodent hair (Fig. 3D). Dermatophytes usually invade cuticle, medulla and cortex, but are unable to perforate rodential hair. All six types of hair damage have been detected in brown rat hair (Fig. 3D). *Trichophyton tonsurans*, *T. equinum*, *M. canis* did not cause damage (criterion 0). The brown rat hair was particularly susceptible to infection by *T. simii*, which damaged the medulla and cortex but left the shaft unaffected (criterion 6). Most strains led to hair fracture (criterion 5). The sum

of damage criteria over all test organisms applied on rat is 68 (Table S4).

Hairs of striped squirrel (*Tamiops swinhoei*) and chinchilla were easily damaged than those of other rodent species. In striped squirrel, three degrees of hair damage were observed (criteria 0, 4, 5), while *T. equinum* and *E. floccosum* did not cause hair damage. The remaining species mostly caused severe hair damage (criteria 4, 5). The sum of damage criteria over all test organisms applied on striped squirrel hair is 83 (Table S4). The medulla of the chinchilla presented uniserial ladder structure. Two levels of hair damage were observed (based on criteria 4 and 5). All strains caused severe hair damage. The sum of damage criteria over all test organisms applied on chinchilla hair is 93 (Table S4).

Three degrees of hair damage were observed in guinea pig hair (criteria 1, 4, 5). *Trichophyton verrucosum*, *T. equinum*, *T. erinacei, Paraphyton cookei*, *Microsporum canis*, *Arthroderma flavescens*, *A. multifidum* and *Epidermophyton floccosum* caused medulla damage (criterion 1). The remaining strains caused hair loosening or hair fracture (criteria 4 or 5). The sum of damage criteria over all test organisms applied on guinea pig is 57. The average of damage on rodent hair is 70.7 (Fig. 5).

Chiroptera

In the order *Chiroptera*, a bat species (*Pipistrellus pipistrellus*) was tested. The structure of bat hair is completely different from the hairs of any other mammal. The cuticle pattern is simple with coronal petal-like scales which are triangular in shape and protrude from the hair shaft, and medulla is lacking (Fig. 3F). After incubation with dermatophyte strains, only two types of hair damage were observed (criteria 0, 2). *Trichophyton verrucosum*, *T. tonsurans*, *T. equinum*, *T. interdigitale*, *T. indotineae*, *N. gypsea*, *P. cookei*, *L. gallinae*, and *A. flavescens* were unable to cause bat hair damage. The remaining strains caused cuticle damage (criterion 2). The sum of damage criteria over all test organisms applied on bat hair is 20 (Table S4).

Carnivora

In the order *Carnivora*, nine species were investigated with hair degradation tests, i.e. Arctic fox (*Vulpes lagopus*), Carpathian lynx *(Lynx lynx carpathicus*), clouded leopard (*Neofelis nebulosa*), Pallas's cat (*Otocolobus manul*), Meerkat (*Suricata suricatta*), snow leopard (*Panthera uncia*), dog (*Canis familiaris*), cat (*Felis catus*), and lion (*Panthera leo*). Cat, lion, and dog hair tend to have a relatively wide medulla or uniserial ladder at mid-shaft (Fig. 3E). The medulla of fox, lynx, leopard and meerkat usually have a thick medulla taking more than half of the hair's diameter, with continuous patterns. Five degrees of hair damage were observed in Pallas's cat hair (criteria 0, 1, 4, 5, 6), and Fig. 3E(d) showing hair loosening. Dermatophytes without degradation effects were *T. tonsurans* and *A. multifidum*. *Trichophyton rubrum* caused hair fracture, and the medulla had disappeared (Fig. 3E(e)). *Nannizzia gypsea* damaged the hair shaft but left the medulla largely unaffected (Fig. 3E(f)). The cuticle and cortex had disappeared (criterion 6). The sum of Pallas's cat hair damage degree is 55 (Table S4).

Dog hair was difficult to degrade compared to that of other animals. Three degrees of hair damage were observed (criteria 0, 2, 4). *Trichophyton benhamiae*, *T. equinum*, *P. cookei*, *M. ferrugineum*, and *A. flavescens* caused hair loosening (criterion 4). The sum of damage criteria over all test strains applied on dog is 30 (Table S4). Hair of other members of the order carnivores, particularly those of clouded leopard were more easily damaged by dermatophytes. There are four degrees of hair damage in snow leopard hair (criteria 0, 2, 4, 5). *Trichophyton tonsurans* and *M. ferrugineum* were unable to cause damage in clouded leopard hairs. *Arthroderma multifidum* caused cuticle damage (criterion 2). The remaining strains caused hair loosening or hair fracture. The sum of damage criteria over all test organisms applied on clouded leopard is 76 (Table S4). The average of hair damage in the order Carnivores is 53.4 (Fig. 5).

Lagomorpha

In this order, we only used hair of the European rabbit (*Oryctolagus cuniculus*). Rabbit hair presented uniserial medulla. There were four types of hair damage (Fig. 4), whereby *T. erinacei* had no degradation effect. *Lophophyton gallinae*, *A. multifidum*, *A. flavescens*, *M. canis*, *M. ferrugineum*, and *E. floccosum* just showed medulla damage. The remaining strains were able to invade rabbit hair. The sum of damage criteria over all test organisms applied on rabbit hair is 63 (Fig. 5 and Table S4).

Primates

Hair from seven *primate* species were subjected to hair degradation tests (Fig. 4), taking human hair (adult and juvenile) as standards (Fig. 3A, B). In human hair, the medulla is amorphous in appearance or no discernable medulla is visible. The results of adult and juvenile hair degradation tests were different. The zoophile *Trichophyton verrucosum* degraded juvenile's but not adult's hair. However, another zoophile, *T. benhamiae* showed the opposite result. *Trichophyton rubrum* remained negative in both, while *T. indotineae* and *T. simii* were able to degrade human's hair strongly. *Trichophyton simii* caused the largest amount of damage, in children's hair leaving only the hair shaft. Frequently, pigmentation faded, black hair became brown after incubation with dermatophytes for 21 days. No color change

was observed in brown human children's hair. Hair perforation was most often (but not consistently) observed in children's hair but was weak in adult's hair.

The hair of red-bellied lemur (*Eulemur rubriventer*) is structurally very regular and well-defined (Fig. S1D) and showed three kinds of hair damage (Fig. 4), either limited to the medulla, or loosening and fracture of hair (criteria 1, 4, 5); perforation remained absent. Medulla damage was observed in *A. flavescens* only. The remaining strains caused hair loosening and fracture. The sum of damage criteria over all test organisms applied on *Eulemur rubriventer* is 82. The average of in *Primates* is 60.3 (Fig. 5).

Discussion

Phylogeny comparing time and function

The family *Arthrodermataceae* has been revised on the basis of conserved genes and multi-locus phylogenetic analyses. ITS, LSU, *BT2, RP 60S L1* and *TEF1* have been used as molecular markers for studies on phylogeny, taxonomy and evolution of *Arthrodermataceae* (Zhang et al. 2022; Zhan et al. 2018; de Hoog et al. 2017a, b). Despite insufficient resolution in the derived genus *Trichophyton*, the rDNA internal transcribed spacer is still in frequent use as a major barcoding marker. The search for novel marker genes has continued, resulting in genes that are usable for reconstructing phylogenies. In dermatophytes, ITS appeared to be more variable than *BT2* or *TEF1*, as shown in the example showing the diversity of the *T. mentagrophytes* complex (Uhrlaß et al. 2022). Taxonomy has primarily relied on phylogenetic relationships inferred from sequences of the ribosomal RNA gene internal transcribed spacer region. Nevertheless, there is no conclusive evidence that ITS analysis is superior to other genes in determining species boundaries (Kawasaki 2011). Kinases play crucial roles in cellular mechanisms, and the SUB1 gene specifically contributes to the process of keratin degradation. Hence, the ongoing search for novel markers with varying degrees of resolution is imperative. Supplementary genes are essential in confirming taxonomic decisions and establishing phylogenetic relationships among different clades.

Phylogeny currently is the prime character set in fungal taxonomy. Growth of knowledge means changing trees, as becomes obvious when comparing trees of any group of fungi with those produced a decade ago. Consequently, the progress of science leads to tsunamis of novel taxa, as well as species fragmentation into molecular siblings, and thus to nomenclatural and conceptual instability. However, this may be somewhat different in the dermatophytes, because the family *Arthrodermataceae* has a consistent evolution following its association with mammals. Due to this unique and consistent adaptive driver, the phylogeny of the *Arthrodermataceae* is remarkably reproducible: for example, trees based on ITS (Gräser et al. 2008), *TEF1* (Mirhendi et al. 2015) and *CAL* (Ahmadi et al. 2016) were similar in main traits. This led to a new phylogenetic classification of the dermatophytes, which reflected the course of evolution from geophilic to anthropophilic lifestyles (Gräser et al. 2008; de Hoog et al. 2017a, b).

Newly analyzed markers follow a similar pattern. The relatively conserved nature of *eIF2α* kinases in fungi makes them potential evolutionary markers, which may contribute to a deeper understanding of taxonomy and evolution. The present study indicated that EIF2AK4 can be used to complement phylogenetic studies of *Trichophyton*, *Microsporum*, and *Nannizzia* based on ribosomal and other conserved markers. Due to the unavailability of whole genomes of *Guarromyces*, *Epidermophyton*, *Lophophyton*, and *Paraphyton* in NCBI, appropriate primers have not yet been designed and amplification with the existing primers (Table S2) was mostly unsuccessful. Better results were obtained with the SUB1 primers, indicating a higher degree of conservation of the gene in this genus. Trees of ITS, EIF2AK4 and SUB1 had very similar topologies (Fig. 2), and correspondence of this set of independent genes was achieved. It may be concluded that the current phylogenetic system reflects the main traits of evolution in *Arthrodermataceae* and is likely to provide nomenclatural stability.

The evolution from geo-, via zoo- to anthropophilic dermatophyte lifestyles can be observed at two levels of diversity. The concept is generally applied at the family level, i.e. from the mainly geophilic ancestral genus *Arthroderma* until the prevalently anthropophilic genus *Trichophyton*, taking millions of years (Kandemir et al. 2022). In addition to this slow path of evolution at the generic level, a similar series of ecological steps probably can occur at a much higher speed within a single species complex. Tang et al. (2021) noted that different lifestyles were represented in the highly variable *T. mentagrophytes* complex. *Trichophyton mentagrophytes* is generally regarded as a zoophilic fungus, but Chollet et al. (2015) convincingly argued that the original strains came from humans, possibly after animal transfer, and the complex contains the low-virulent *T. interdigitale* as one of the human-adapted clones (Tang et al. 2021). The high-virulent novelty with as yet unknown origin, *Trichophyton indotineae*, emerged from this complex in epidemic proportions; this entity has repeatedly been detected in animals (Durdu et al. 2023).

The molecular approach allows a much higher level of distinction than morphology, which is blurred by pleomorphic growth and loss of vitality after prolonged culturing (Gräser et al. 2008). Species complexes such as *T. mentagrophytes* and *T. benhamiae* contain numerous genotypes, which may be largely clonal, some of which is recognized

as separate species (Čmoková et al. 2022). In such highly variable species complex we touch the limit of the level of genetic diversity that is still meaningful to be recognized. Tang et al. (2021) defined species as a community of genotypes with random sexual interaction with viable progeny, separated from the next species by a hybrid depression, and generally adapted to a particular habitat. The latter led to a recommendation to recognize clones as species only when they were ecologically or clinically significantly different, thus decreasing the value of phylogenetic distance as a prime parameter, following Gräser et al. (2008) and Tang et al. (2021) in the application of polyphasic taxonomy.

Physiology and phylogeny

We generally assume that all significant mycological knowledge dates back only a few decades, since the advance of DNA-based techniques. For most fungi this is certainly true, but much less in the case of the dermatophytes. Already in the nineteenth century, a remarkably good overview of the main dermatophyte species existed. Schönlein (1839) was the first to observe fungal hyphae in lesions of humans presenting with favus, which was a common disorder in his days (Monod and Lanternier 2022). This fungus was described as *Oidium schoenleinii* by Lebert, and is now known as *Trichophyton schoenleinii*. Gruby (1843) described *Microsporum audouinii* from human skin infections, and Malmsten (1848) *T. tonsurans* from tinea capitis.

Dermatomycology developed remarkably fast after the discovery of the fungal nature of skin infections, but technically, microbial taxonomy was still in its early days. Unfortunately, none of the materials of the species introduced in the nineteenth century has been preserved. To stabilize nomenclature for the future, we cannot return to the original type material. At present, we therefore apply only those names that have been re-established by the deposition of neotypes. A total of 26 dermatophyte names had been introduced in the nineteenth century (de Hoog et al. 2017a, b), of which currently six of the anthropophilic and zoophilic species have neotypes: *Lophophyton gallinae, Microsporum audouinii, Trichophyton mentagrophytes, T. quinckeanum, T. schoenleinii* and *T. tonsurans* (de Hoog et al. 2020). Thus, the majority of major anthropophilic species were already known in the nineteenth century. *Trichophyton rubrum* was the latest addition in 1910—which is somewhat exceptional because this is one of the prevalent species today. Possibly an earlier introduction was *T. rosaceum* (Sabouraud 1894), but this species has never been neotypified, just as *Microsporum felinae* (=*M. canis*?), and consequently these names have remained doubtful (de Hoog et al. 2020). Points of reference of the main species including the ones used in the present study are now unambiguous.

The early days of rDNA sequencing of dermatophytes started with a reduction of the number of recognized species, partly because numerous older names could not be verified due to of lack of material, but also because it was realized that strict application of culture methods led to overclassification (Gräser et al. 2008). Several biotypes, e.g. in the *Trichophyton rubrum* complex, were judged to represent a single species, effectively reducing the number of species, although some of these are now understood as recently adapted and distinguishable clones (Su et al. 2019). This makes the dermatophytes unique among the fungi, where improved methods along with exploration of unknown habitats lead to a multiplication of taxonomic novelties in most fungal groups (Quan et al. 2022). However, the main ecological concepts in dermatophytes, i.e. geo-, zoo- or anthropophilic, are difficult to link to particular species, since the label just reflects a prevalent source of isolation rather than establishment of intrinsic properties of the fungus. For this reason, we tested a set of representatives of dermatophyte phylogeny on a set of hairs from widely different mammals. Although the test set is as yet too small for statistically supported conclusions, it appears that the three ecological categories are not easily recognized experimentally.

Proteinases and hair degradation

The voluminous work on dermatophytes by Raymond Sabouraud (1910) has been very influential. It was the first overview of the family *Arthrodermataceae*, displaying a much larger diversity than had been recognized on the basis of clinical features alone. The dermatophytes are unique in the fungal Kingdom by the ability to degrade hard keratin by a specially designed family of seven serine endoproteases, subtillisins SUB1–7, aided by the fungalysins of metalloproteases, Mep1–5 (Zhan et al. 2018; Tartor et al. 2019). Excess of ammonium due to proteolysis is responsible for the characteristic mousy odour which can also be noticed in severe skin infections such as favus by *T. schoenleinii*. Secreted proteases are a critical virulence factor for dermatophytes.

Keratinolysis has been a major driver in dermatophyte evolution. Keratins are classified into two major types based on their secondary structure: α-keratin and β-keratin (Meyers et al. 2008). β-Keratin is rich in β-pleated sheets and is constructed from supramolecular fibrillar bundles, while α-keratin consists of α-helical-coil coils that self-assemble into intermediate filaments (Meyers et al. 2008). Keratinaceous materials, such as feathers, hair, bristles, and wool, typically contain a mixture of keratins including both α-keratin and β-keratin. For example, feathers are composed of 41–67% α-keratins, 33–38% β-keratin, and also amorphous keratin (Fraser et al. 2008), while α- and β-keratins are preferentially expressed in different feather parts. Other keratinaceous materials, such as hair, bristle,

and wool, consist mostly of α-keratins, matrix proteins, and minor amounts of β-keratins (Daroit et al. 2014). Hard keratins, which include hair and feathers, have diversified morphological structures and numerous disulfide bonds, making them insoluble in water, weak acid and alkaline solutions, and organic solvents. β-Keratin is more accessible for degradation by some keratinases than α-keratin because of its fibrillar structure and porosity, and its lower number of disulfide bonds. These structural differences may be important in understanding dermatophytes with different degradation abilities of mammal hair. In our study, we used keratin azure to monitor the degradation of β-keratin. Our tree of SUB1 largely follows the same path as shown by kinases, ribosomal and partial household genes (Fig. 2). Broadly, the tree displays an overabundance of geophilic species in ancestral position, via zoophilic species, and with anthropophilic in the most derived clades. Closer affiliation to the mammal host is accompanied by adaptive steps additional to loss of sexuality and macroconidial sporulation.

The special condition of the human host

Animals seem to be much better off in their interaction with dermatophytes than humans. They have protective fur, while humans are the mammal species with exposed skin. The degradation of mammal hair by the fungus is an essential theme in the evolution of dermatophytes. From the fungal perspective, a geophilic lifestyle seems like a highly efficient strategy, as it allows complete sexuality and recombination in the environment, and efficient distribution of conidia within a preferred habitat—thus avoiding waste of biomaterial by shotgun approaches such as airborne dispersal. No real interaction with the host is required, since the assimilative part of the life cycle is in the soil. Zoophilic species are mainly found on domesticated animals, with the sexual part of the life cycle being hampered, thus shifting the assimilative part of the life cycle more towards the host. *Homo sapiens* is one of the few near-naked mammals. Insufficient fur is present for asymptomatic or poorly symptomatic carriage, and the fungus needs infections to remain on the host. As infection of living tissue with active immunity is significantly different from digestion of dead hair, a higher degree of specialization is required. The human host carries a large number of adapted species (*T. rubrum, T. violaceum, T. soudanense, T. concentricum, T. interdigitale, T. indotineae, E. floccosum, M. audouinii, M. ferrugineum*), while, conversely, geo- and zoophilic species tend to have a wider host range of animal groups with more or less comparable fur properties. The increasing degree of specialization in the course of evolution, with concomitant loss of ascospores and differentiated conidia, is less beneficial for long term survival of the individual species.

As dermatophytes are nearly exclusively found in association with animals, with *L. gallinae* as one of the few examples on birds, the link between phylogeny and hair is key to understand the evolution of this fungal group. We tried to relate the phylogeny of the *Arthrodermataceae* with patterns of degradation by dermatophyte species of hairs obtained from mammals representing 11 orders of *Mammalia*. The degrees of hair degradation after 3 weeks incubation is presented in the form of a heatmap (Fig. 4). Clear species-specific patterns remained absent, and although the test set is limited, this suggests that types of hair degradation such as perforation are poorly diagnostic. Most significant hair destruction was achieved by the activity of *Trichophton interdigitale*, *T. mentagrophytes*, *T. simii*, and *N. gypsea*, and among these, *T. mentagrophytes* was the most active. *Nannizzia gypsea* preferably degraded the cuticle and left the medulla unaffected. *Trichophyton tonsurans*, *T. verrucosum*, and *E. floccosum* presented a weak ability to degrade hair; the latter species is mainly known from cutaneous tinea pedis and *T. tonsurans* is primarily associated with tinea capitis, with much less causing tinea corporis or tinea unguium (Hryncewicz-Gwóźdź et al. 2011). Infections within the hair shaft are referred to as endothrix, while when the dermatophyte is attached to the surface of the hair shaft, this condition is known as ectothrix (Dowd 2014). The pattern of fungal invasion affects the clinical appearance of the scalp lesion. In endothrix infections, the hair breaks off at or just below the opening of the follicle, resulting in a "black dot" appearance. In ectothrix infections, the hair typically breaks off 2–3 mm above the opening of the follicle, leaving short hair stumps (Warnock 2012). In the case of favus, caused by the *T. schoenleinii*, the hair remains intact, but the hair follicle and surrounding area is covered in a thick, waxy crust that resembles a honeycomb pattern. This is due to the intense fungal growth within the hair follicle. Endothrix and ectothrix types of hair invasion are not related to our grade system of hair degradation, because these two types can present hair loosening or hair fracture both (Peixoto et al. 2019; Anane et al. 2013). *Trichophyton verrucosum* degraded hair of cattle, donkey, and mouse, but did not degrade keratin azure, not being primarily adapted to invasion of human skin. The majority of species tested presented only a moderate ability to degrade hair. On the whole, zoophilic species had higher hair degrading abilities than anthropophilic species.

Based on our results, the hair of *Hyracoidea* and *Rodentia* appears to be the easiest to degrade by dermatophytes, while bat hair is the most difficult to degrade. However, Moulíková (2023) suggested that none of the zoophilic *Trichophyton* and *Microsporum* species they isolated from small wild rodents, nor did they isolate any geophilic dermatophytes outside of the genus *Arthroderma*. In contrast, our study found that *Trichophyton* and *Nannizzia gypsea* were highly

effective at degrading rodent hair. These findings suggest that in vitro measurements of dermatophyte hair degradation ability may not necessarily correlate with ability to infect hosts in the natural habitat. The ability of dermatophytes to degrade hair is likely influenced by both their secretion or proteases and on the structural characteristics of the hairs.

The structure of all mammalian hair mainly consists of three regions: inner medulla, cortex, and cuticle. Hair pigments may change from black to brown after dermatophyte invasion. In the case of *Eulemur rubriventer,* the hair medulla decreased and the cuticle was broken after incubation with dermatophytes. Lacarrubba et al. (2015) reported that hair appeared as empty bands at high magnification, which may be related to localized areas of fungal infection.

Any dermatophyte infection in vivo is initiated by direct contact of the pathogen and the target host. Arthroconidia adhere to keratinized tissues and begin their penetration process (Tainwala et al. 2011). Dermatophytes generate proteolytic enzymes which are essential in their life style, both in asymptomatic carriage and in infection. Degradation of keratin by dermatophytes is accompanied by an increase in the level of soluble proteins and peptides and the concentration of ammonium ions (Bohacz et al. 2020). The ammonia changes the initial pH in the host tissue from acidic (pH 5.0) to alkaline (pH 8.5), approximately within 72–96 h, producing an environment in which most of the known keratinolytic proteases of dermatophytes have optimal enzymatic activity (Ciesielska et al. 2021). Peter et al. (1976) found that the yellowing of wool in a mildly alkaline solution is thought to be caused by modifications to the cysteine residues (Norman 1976). This might explain why hair pigments may change from black to brown after dermatophyte invasion. Additional steps of adaptation are also associated with lipolysis (Su et al. 2019) and vitamins (Kandemir et al. 2020), as already suggested in ancient literature, but now elaborated in more detail with molecular support.

Conclusion

Based on our initial findings with a limited dataset, it appears that the EIF2AK4 and SUB1 genes provide a relatively accurate representation of the evolution of *Arthrodermataceae*. In our study, we also examined the keratinolytic responses of 19 dermatophyte species using various mammalian hairs as substrates. Our results indicated that *T. mentagrophytes* and *N. gypsea* were the most efficient at breaking down hair, while *T. verrucosum*, *T. tonsurans*, and *E. floccosum* exhibited a low response. Hairs from *Hyracoidea* and *Rodentia* were the most affected, while bat hairs proved challenging to degrade for almost all of the tested dermatophytes. Zoophilic species demonstrated more activity than anthropophilic dermatophytes, which matches with the reduction of virulence the the most derived, anthropophilic species.

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Declarations

Competing interests The authors have not disclosed any competing interests.

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