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Review Article

Review Article

New insights in dermatophyte research

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Abstract

Dermatophyte research has renewed interest because of changing human floras with changing socioeconomic conditions, and because of severe chronic infections in patients with congenital immune disorders. Main taxonomic traits at the generic level have changed considerably, and now fine-tuning at the species level with state-of-the-art technology has become urgent. Research on virulence factors focuses on secreted proteases now has support in genome data. It is speculated that most protease families are used for degrading hard keratin during nitrogen recycling in the environment, while others, such as Sub6 may have emerged as a result of ancestral gene duplication, and are likely to have specific roles during infection. Virulence may differ between mating partners of the same species and concepts of zoo- and anthropophily may require revision in some recently redefined species. Many of these questions benefit from international cooperation and exchange of materials. The aim of the ISHAM Working Group Dermatophytes aims to stimulate and coordinate international networking on these fungi.

Key words: dermatophyte phylogeny, taxonomy, zoonoses, CARD9, secreted protease, virulence.

Introduction

Despite the common presence of dermatophytes on the human host, contemporary research in this area is limited. One of the reasons is that disorders are generally superficial, often considered as an esthetic rather than a medical problem, and the dermatophytes are susceptible to most commonly used antifungals. The severe clinical pictures as seen in rural settings in developing countries have nearly disappeared due to improved hygienic standards and application of effective, low-cost treatment. However, changes in host conditions have led to changes in fungal floras and different transmission routes. Children with asymptomatic pet animals may become infected and be the source of zoonoses in classrooms which require immediate action. In addition, highly susceptible host populations exist in people with rare congenital immune disorders; infections then are highly

recalcitrant, with the fungus developing resistance *in vivo*. Consequently, a number of basic questions in dermatophyte research have changed considerably. At the host side there are major changes because of socioeconomic developments, while previously unrecognized immune disorders seem to be associated with some of the chronic and severe infections. Visible skin infections today are less tolerated than in the past, so that more precision is required in controlling infections and outbreaks, and then the small differences in antifungal susceptibility between species become important, requiring fine-tuned therapy. Molecular classification has revolutionized our vision on species definitions and relationships, and has questioned basic concepts as zoo- and anthropophily in dermatophytes, which has a profound impact on the study of virulence factors. These novel views in dermatophyte research are reviewed in the present paper.

Biodiversity

Dermatophytes are under study already since 1841, when David Gruby discovered the fungal nature of skin infections. Taxonomy is, however, a difficult area of research: diagnostic problems have remained ever since. Most dermatological routine laboratories still apply conventional methods for identification of etiologic agents of disease. By direct microscopic examination of potassium hydroxide (KOH) preparation or calcofluor white stain, the presence or absence of fungi can be assessed and histopathologic analysis performed, but it remains difficult to determine whether detected fungal elements are those of the main etiologic agent. Culturing is done with selective DTM agar containing cycloheximide and a phenol red pH indicator. False-negative results may be caused by limited vitality of the fungus due to, for example, antimycotic pretreatment, or to insufficient inoculum in the clinical sample. For experienced investigators, conventional methods work well to identify the main causative species,[1] but they have insufficient resolution for the less common taxa and for strains with atypical or reduced morphology.

On humans, about 10 species are prevalent. Older taxonomic studies have been misguided by variations in culture and micromorphology which has led to overclassification, far too many species having been distinguished.[2] It was expected that the molecular revolution would solve these problems and would enable precise and reproducible diagnostics, but unfortunately some significant, unexpected problems emerged. Species such as *Trichophyton rubrum* and *T. violaceum* are clinically different and very easy to distinguish in culture, but nevertheless they are molecularly very close, and the position of *T. soudanense* and *T. yaoundae* are difficult to distinguish from *T. violaceum* with standard barcoding genes. The distinction of zoophilic *T. equinum* from its anthropophilic counterpart *T. tonsurans* is still under debate.[3,4] Zoophilic and anthropophilic species of the *Microsporum canis* group are molecularly closer than expected, and are within the range of variability of the mating partners.[5] Thus, still a lot of fundamental work lies ahead of us.

Sexuality is one of the leading principles for species delimitation, as only members of the same species are able to produce fertile progeny. Heterothallism, that is, the production of sexual states by partners with different mating type genes, is common in the prevalently geophilic, ancestral genus *Arthroderma*,[6] but successful mating tends to get lost particularly in the evolutionarily recent, anthropophilic *Trichophyton* species. Mating partners can be phenotypically and clinically different, as in *T. benhamiae*.[7] Anthropophilic species that carry only a single mating type[8] are treated as preponderantly clonal species, and this interferes with genealogical concordance criteria of species affiliation which is based on recombination. If clonal species are recognized because they differ in clinical appearance, their distinction will be quantitative, using numerical distance in data sets as species criterion rather than sexuality.

Some significant taxonomic changes have been proposed (Table 1).[2] '*Trichophyton* anamorph of *Arthroderma benhamiae*' is now known as *Trichophyton benhamiae*. *Trichophyton interdigitale* is recognized as a strictly anthropophilic species with cottony colonies and reduced sporulation, while the related zoophilic strains (formerly '*T. interdigitale* var. *mentagrophytes*') are classified in a distinct species, *Trichophyton mentagrophytes*. *Trichophyton quinckeanum* was reinstated as a zoophilic dermatophyte on mice.

At the generic level, it has become apparent on the basis of several genetic data sets that *Trichophyton* in the classical sense was polyphyletic and could not be maintained as such. De Hoog et al.[2] restricted the genus to the phylogenetically most recent clade of *Arthrodermataceae* that prevalently contains anthropophilic taxa and species on domesticated animals. The ancestral, geophilic group is now referred to as *Arthroderma* (Table 2). This rearrangement also offered an opportunity to comply with new demands of nomenclature, where dual (sexual / asexual) naming of fungi has been abolished (article 59 in the International Code of Nomenclature for Algae, Fungi, and Plants[9,10]). Modern nomenclature primarily follows phylogenetic relationships. There is a fundamental flaw in this approach, in that trees are relative to and dependent on the sampled taxa and thus poorly predictive and unstable. This problem is less apparent in the dermatophytes because the basic structure of the tree is fixed: the anthropophilic species colonized the evolutionarily most recent host, that is, *Homo sapiens*, and thus should be at the top of the tree. The novel system[2]

Table 1. Overview of current species and species groups in genera prevalent in the routine clinical lab.

Epidermophyton floccosum-A	
Microsporum audouinii-A	
Microsporum canis-Z	
Microsporum ferrugineum-A	
Trichophyton benhamiae series	(*T. benhamiae*-Z, *T. concentricum*-A, *T. eriotrephon*, *T. verrucosum*-Z)
Trichophyton bullosum-Z	
Trichophyton mentagrophytes series	(*T. equinum*-Z, *T. interdigitale*-A, *T. mentagrophytes*-Z, *T. tonsurans*-A)
Trichophyton rubrum series	(*T. rubrum*-A, *T. soudanense*-A, *T. violaceum*-A)
Trichophyton simii series	(*T. quinckeanum*-Z, *T. schoenleinii*-A, *T. simii*-Z)

Note. A, anthropophilic; Z, zoophilic.

Table 2. Less prevalent and geophilic genera in the dermatophytes with currently accepted species.

Nannizzia	*Lophophyton*	*Paraphyton*
N. aenigmaticum-?	*L. gallinae*-Z	*P. cookei*-G
N. corniculata-G		*P. cookiellum*-G
N. duboisii-?		*P. mirabile*-Z
N. fulva-G		
N. gypsea-G		
N. incurvata-G		
N. nana-Z		
N. persicolor-Z		
N. praecox-?		
Arthroderma		
Arthroderma amazonicum-Z		
Arthroderma ciferrii-G		
Arthroderma cuniculi-G		
Arthroderma curreyi-G		
Arthroderma eboreum-Z		
Arthroderma flavescens-Z		
Arthroderma gertleri-G		
Arthroderma gloriae-G		
Arthroderma insingulare-G		
Arthroderma lenticulare-G		
Arthroderma melis-G		
Arthroderma multifidum-G		
Arthroderma onychocola-?		
Arthroderma phaseoliforme-G		
Arthroderma quadrifidum-G		
Arthroderma redellii-Z		
Arthroderma silverae-?		
Arthroderma thuringiensis-Z		
Arthroderma tuberculatum-Z		
Arthroderma uncinatum-G		
Arthroderma vespertilii-Z		

Note. A, anthropophilic; G, geophilic; Z, zoophilic; ?, ecology unknown because of rarity of the species.

now recognizes the genera *Arthroderma, Epidermophyton, Lophophyton, Nannizzia, Paraphyton,* and *Trichophyton,* which form unambiguously separate, statistically supported clades. The largest number of name changes is made in the geophilic genus *Arthroderma*. Note that the genera *Arthroderma* and *Nannizzia*, which earlier denoted sexual states of dermatophytes, now are considered regular genera, each species just having a single binomial.[10]

Secreted proteases

The genomes of dermatophytes comprise a broad repertoire of genes encoding hydrolytic enzymes, in particular proteases, which are highly similar from one species to another.[11,12] This repertoire is also similar to that of the remote genus *Aspergillus* species, with the difference that the genes encoding secreted endoproteases have expanded in dermatophytes. Twelve members encoding secreted subtilisins (S8 family in the MEROPS proteolytic enzyme database at http://merops.sanger.ac.uk), five members encoding secreted deuterolysins (M35 family) and five members encoding secreted fungalysins (M36 family) were recorded in dermatophytes.[12–14] Secreted proteases were *a priori* considered as virulence factors because these fungi are almost exclusively localized in keratinized tissues.

Like many other fungal species, dermatophytes produce various endo- and exoproteases during growth in a medium containing protein as sole nitrogen source.[14] Altogether, they allow the degradation of proteins into amino acids and short peptides which can be assimilated via transporters, and used as nutrients. At neutral or alkaline pH, dermatophytes secrete two major subtilisins, Sub3 and Sub4, and two major fungalysins, Mep3 and Mep4, as endopeptidases.[11,14,15] In addition, dermatophytes secrete aminopeptidases including leucine aminopeptidases (Lap1 and Lap2) and dipeptidyl-peptidases (DppIV and DppV) which showed similar activities to *A. fumigatus* orthologues.[16] Dermatophytes were also found to secrete a carboxypeptidase of the MEROPS M14A subfamily which is homologous to the human pancreatic carboxypeptidases A.[17] No orthologue enzyme exists in *Aspergillus*. In protein medium at acidic pH, dermatophytes secrete an aspartic protease of the pepsin family (Pep1) as endoprotease, as

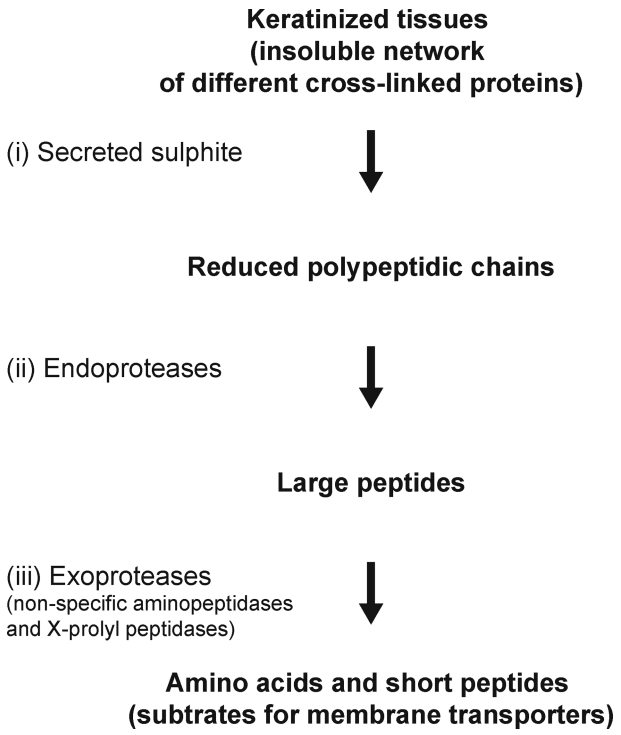

Figure 1. Diagram of hard keratin degradation by dermatophytes. Bottlenecks in the process: (i) Sulphite excretion to reduce sulphide bridges is mandatory to complement enzymatic activity. (ii) Large peptides with free ends on which exoproteases may act are produced by endoproteases. (iii) Proline cannot be bypassed by nonspecific aminopeptidases; in case of proline-rich proteins, degradation of peptide chains into amino acids and short (2-5-mer) peptides is achieved with the complementary action of prolylpeptidases.

well as exoproteases which are tripeptidyl peptidases of the sedolisin family (Seds), prolyl peptidases of the S28 family and carboxypeptidases of the S10 family.[14] Different from *Aspergillus*, dermatophytes have no gene encoding a secreted glutamic protease.

The inventory of proteases secreted by dermatophytes suggests basic mechanisms of extracellular proteolysis similar to those described in *Aspergillus* species at acidic and neutral pH.[18,19] Endoproteases produce large peptides with free ends on which the exoproteases may act to generate amino acids and short peptides. Then, trimming of large peptides from the N-terminus or the C-terminus needs the synergic action of two exopeptidases that are a nonspecific amino- or carboxypeptidase for which proline residues constitute roadblocks, and a prolyl peptidase (Fig. 1). This is a general rule in peptide degradation by microorganisms. For instance, Laps remove at neutral pH any amino acids from their N-terminus of peptides until an X-Pro sequence acting as a stop is encountered. However, the X-Pro sequences can be removed by DppIV, allowing Laps to access the next residue.[19] Likewise, at acidic pH, large peptides are digested into tripeptides by Seds. In this case, a Pro residue in the P1 or the P'1 position (position 3 or 4 relative to the peptide's N-terminus, respectively) constitutes a roadblock in sequential proteolysis, but, in a complementary way, X-X-Pro and X-X-X-Pro sequences can be removed by a prolyl peptidase of the S28 family, thus allowing further peptide trimming by Seds.[18]

One important common characteristic of dermatophytes is their ability to utilize compact hard keratin as a nutrient source. However, dermatophyte secreted proteases like other secreted endoproteases by fungi are incapable of degrading by themselves structures made of hard keratin.[20,21] Efficient keratin degradation by hydrolytic enzymes has to be accompanied by the simultaneous reduction of cysteine disulphide bridges, which are mainly responsible for the resistant nature of keratin.[20] During keratin degradation, dermatophytes and filamentous fungi were shown to excrete sulphite as a reducing agent.[22–24] In the presence of sulphite, disulphide bonds of the keratin substrate are directly cleaved to cysteine and S-sulphocysteine, and reduced keratin is accessible by secreted endo- and exoproteases. Genes encoding *Trichophyton rubrum* and *T. benhamiae* sulphite efflux pumps (Ssu1) were cloned and their heterologous expression in *Saccharomyces cerevisiae* resulted in a sulphite resistant phenotype of the yeast.[24] These transporters are homologous to the *S. cerevisiae* Ssu1 sulphite transporter allowing the yeast to resist to high sulphite concentration during wine fermentation.[25]

Sulphitolysis is an essential step in the digestion of compact keratinized tissues, which precedes the action of all proteases. *Trichophyton benhamiae* mutants in the gene encoding either Ssu1 and or cysteine dioxygenase, a cytoplasmic enzyme involved in conversion of cysteine into sulphite, were defective in their growth on hair and nails.[26]

In vivo secreted proteases

Until recently, the proteases secreted *in vitro* were considered as virulence factors. However, transcriptome analysis performed with RNA from guinea pigs infected by the dermatophyte *Trichophyton benhamiae* and proteomic analyses of proteins extracted from infected nail beds of patients with onychomycosis revealed that a particular subtilisin (Sub6) was the major protease during infection.[27–29] The gene encoding this protease, like others encoding proteases concomitantly secreted during infection (Sub 8, Sub10, and one member of the deuterolysin family), was not detected *in vitro*. In contrast, none of the genes encoding specific endo- and exoproteases involved in keratin digestion *in vitro* was found to be upregulated during infection. The sets of the 12 most highly expressed genes encoding proteases with a signal sequence only had the putative vacuolar aspartic protease gene *PEP2* in common during infection and in keratin medium.[29]

The results from *in vivo* experiments were found to be consistent with previous findings since Sub6 in *T. rubrum* was recognized 20 year ago as a major dermatophyte allergen, Tri r 2.[30] Tri r 2 was identified by its human immunoglobulin E (IgE) antibody-binding activity using a phage display library and sera from patients with high IgE antibody titers and IH (immediate-hypersensitivity) skin test reactions to a *Trichophyton* extract. Tri r 2 was found to induce dual immune responses by eliciting either immediate or delayed-type hypersensitivity skin test reactions in different individuals.[30–32]

In conclusion, the hypothesis that the proteases secreted by dermatophytes *in vitro* in a protein medium are virulence factors was not verified. Dermatophytes evolved from saprobic fungi in soil capable of degrading hard keratin in the process of recycling nitrogen. This can be concluded with a high degree of certainty. When in phylogenetic trees of the *Arthrodermataceae* as given by, for example, de Hoog et al.[2] the anthropophilic species are placed at the top, humans being the most recently evolved host, the geophilic *Arthroderma* species with complete (sexual / asexual) life cycles are found in an ancestral position. The saprobic phase has to be dissociated from a pathogenic phase acquired by some dermatophytes species. The emergence of multigenic families in highly specialized microorganisms is generally due to ancient gene duplication processes allowing adaptation to different environmental conditions. Some of the multiple members of protease families in dermatophytes are exclusively used for protein degradation while others, such as Sub6, likely have specific roles during infection.

Invasive dermatophytosis in immune competent patients

Dermatophytoses are generally known to be superficial with hyphae invading keratinized structures. However, rare cases of deep dermatophytosis have been recorded in human immunodeficiency virus (HIV) and immunosuppressed patients,[33,34] and several cases have been recently described in immunocompetent people in consanguineous families. These patients were found to bear homozygous mutations in the gene coding for the caspase recruitment domain-containing protein 9 (CARD9). Most reported cases of deep dermatophytosis in immunocompetent people were from North Africa.[35–37] A stop codon mutation in CARD9 (Q289*) was found in 15 patients from seven Algerian and Tunisian familie,[35] one patient of Egyptian origin with extensive skin and nail dermatophytosis[36] and recently from another patient in Algeria, with a brain abscess. Three missense mutations, R101C, R101L, and R70W were also detected in two Moroccan siblings, a patient in Brazil and a patient of Turkish origin in Belgium, respectively.[35,38,39]

CARD9 is an adaptator protein in the signaling pathway downstream from lectin receptors, such as dectin 1 and dectin 2 involved in the recognition of pathogenic fungi. Mainly in myeloid cells and involved in the stimulation of pro-inflammatory responses, CARD9 plays an important role in the innate immune response against fungal pathogens. CARD9-deficient cells showed low levels of interleukin 6 (IL-6) production after stimulation with zymosan, an agonist of dectin 1.[35]

Zoophilic dermatophytes and human transmission

Dermatophytes are classified into three ecological groups according to the source of metabolized keratin. Geophilic species are saprobes which subsist from keratin in soil, whereas anthropophilic and zoophilic species infect keratin-rich tissues on the living host, either human or animal, respectively. Zoophilic species can be transmitted to humans via direct contact and cause severely inflammatory infections. Most zoophilic species are adapted to one particular host, like *M. canis* to cats,[40] *T. verrucosum* to cattle,[41] or *T. erinacei* to hedgehogs.[42] Due to adaptation of the infecting agent to the host's immune system, animals mostly are asymptomatic carriers of dermatophytes.

Risks of infection depend on the prevalence of the zoophilic agent and the frequency of human-animal contact.[43] Accordingly, *M. canis* transmitted by cats and sometimes by dogs, which are very popular pet animals, is the most frequent zoophilic dermatophyte causing human infections in many parts of the world.[44–46] Two studies from Italy show high percentages (47%[47] and 100%[45]) of asymptomatic cats with *M. canis* colonization. For a few years the zoophilic dermatophyte *T. benhamiae* has been on the rise in central Europe, causing tinea corporis and tinea capitis infections in humans, mostly in children and young adults, after contact with pet guinea pigs.[48–52] Recently its incidence is comparable with that of *M. canis*.[51] In a study of 59 guinea pigs from pet shops in Berlin, Germany, the presence of this dermatophyte was analyzed.[53] Using the MacKenzie brush technique with sterile tooth brushes as well as FLOQSwabs™ (Copan Diagnostics, Italy) samples were taken and species identified with ITS sequencing, species-specific polymerase chain reaction (PCR), and culture. This study detected *T. benhamiae* on 93% of the guinea pigs. Most animals appeared healthy without any visible signs of infection. Only in 9% of the guinea pigs skin lesions were observed. All infected animals were obtained from commercial breeders, while all healthy animals in this study originated from private breeding of the shop owner. This suggests that hygiene standards and housing conditions may influence the incidence of dermatophyte infections.

Two types of *T. benhamiae* are known, which differ in ITS sequence and morphology.[7] The majority of recently emerging human infections in Europe are caused by the 'yellow type', while the 'white type' is rare on humans.[51] Interestingly, in the described study both the yellow and the white types of *T. benhamiae* were isolated. The distribution of the types was analyzed with a type-specific PCR and ITS-sequencing resulting in the presence of both types on the same guinea pigs in 50% of cases. This was surprising, because infections transmitted to humans are mainly caused by the yellow type of this pathogen. It can be speculated that the yellow type has a higher virulence than the white type.

To minimize the risk of infections with zoophilic dermatophytes (i) care should be taken to wash hands and other parts of the body directly after (pet) animal contact and (ii) pets, especially guinea pigs, should be analyzed for dermatophytes right after purchase.

Cooperation and future prospects

Dermatophyte research will benefit greatly from international cooperation as envisioned in the Working Groups initiated by the International Society for Human and Animal Mycology (ISHAM). These networks focus on particular themes in medical mycology and organise regular workshops which tend to culminate in joint publications on results af multidisciplinary studies. The dermatophytes were the focus of a 2017 special issue of *Mycopathologia*. Many members of the ISHAM Working group Dermatophytes contributed to 21 peer-reviewed articles on recent progress and prospects of research on the dermatophytes and dermatophytoses. The areas of study included genetics, virulence, prevalence, clinical and laboratory diagnosis, and therapy. A taxonomic reappraisal of the family *Arthrodermataceae* encompassed 13 new combinations based on multilocus sequencing.[2] A timely update described the whole genome sequences and transcriptomes of dermatophytes, transformation, and molecular toolkit for various gene manipulations.[54] The occurrence and prevalence of two mating loci in geophilic, zoophilic, and anthropophilic species were described in great detail.[6] A summary was given of genotyping approaches for the intra- and inter-strain differentiation included mitochondrial DNA analysis, RAPD (random amplification of polymorphic DNA), sequencing of the ITS or NTS (nontranscribed spacer) regions of rDNA, and microsatellite analysis.[55] A companion article highlighted host genetic loci likely to predispose to dermatophytic infections.[56] The clinical themes included changing epidemiology, socioeconomic factors, new drugs, and improved diagnosis based upon molecular tests.[57,58] Another article highlighted the challenges for the management of *Trichophyton rubrum* onychomycosis.[59] The nonfungal etiologies mimicking the typical dermatophyte lesion on the skin and their differential diagnosis were detailed with illustrations.[60] A differential diagnosis focus was also presented for dermatophytoses in animals.[61] The pros and cons of current drugs, new formulations, and drug delivery innovations for dermatophytes were covered in great detail.[62] The antidermatophytic properties of natural products although promising, are plagued by lack of standardized test methods.[63]

Dermatophyte diagnostics was covered with a reappraisal of the direct examination and culture methods given an enhanced role for the molecular diagnostics approaches some based upon commercial kits.[1] The promise of MALDI-TOF for the dermatophyte identifications and the problems and solutions for its implementations were covered.[64] The applications of PCR and real-time PCR as diagnostic tools for dermatophytoses of hair, skin, and nail were highlighted.[65] New pathogenic species of *Microsporum* and *Trichophyton* and the unusual clinical manifestations of the common dermatophytes were summarized.[66]

The role of dermatophyte transcription factors, proteins, and enzymes especially keratinases in host interactions was elucidated.[67] The continuing need for a good experimental model and the appeal of nude mice for pathogenesis studies[68] and the utility of mouse J774 macrophage-like cells as an *ex vivo* model were highlighted.[69] The role of acquired and innate immunity against dermatophytes was summarized with focus Th17 pathway and neutrophil extracellular traps (NETs).[70,71]

There remain many gaps in the understanding of the dermatophyte species spectrum, unique pathogenic attributes, clinical manifestations, and therapeutic responses. Renovated species delimitations may have an impact on antifungal susceptibility profiles, which therefore should be redetermined. Future investigations in many of these areas could receive a further boost by the availability of high-quality finished genomes of the representative species. The Working Group has finalized a list of the candidate species to be targeted for whole genome sequencing shortly.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and the writing of the paper.

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