

# *Trichophyton mentagrophytes* ITS genotype VIII and *Trichophyton indotineae*: A terminological maze, or is it?

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## Introduction

There appears to be an ongoing epidemic of superficial dermatophytosis in India and neighbouring countries. The incriminated dermatophyte is anthropophilic considering the fact that it is primarily being transmitted from humans to humans. It has clearly dominated over *Trichophyton rubrum*, known to cause tinea pedis and onychomycosis worldwide, as well as tinea corporis and tinea cruris in India over many decades. This rather quick epidemiologic shift from *Trichophyton rubrum* to '*Trichophyton mentagrophytes*', documented as early as 2011, has been noticed for its propensity to frequently cause multidrug-resistant dermatophytosis in India and other countries. *Trichophyton mentagrophytes* ITS genotype VIII, the current predominant pathogen, has been confirmed by ribosomal deoxyribonucleic acid (rDNA) sequencing, considered the gold standard for determining a species besides the usual potassium hydroxide (KOH) positivity and culture characteristics. Unfortunately, the name of this dermatophyte has been wandering in a terminological maze with terms ranging from '*Trichophyton mentagrophytes*, *Trichophyton interdigitale*, *Trichophyton mentagrophytes/Trichophyton interdigitale* complex and finally, *Trichophyton mentagrophytes* ITS genotype VIII and *Trichophyton indotineae*. These terms have been used interchangeably by mycologists over the past few years and this lack of uniformity has confused practising dermatologists and has hampered evidence generation, collation and interpretation. This article aims to provide practising dermatologists with a simple explanation for these variably used terms over the past few years. The concluding message is that the two most recent terms, *Trichophyton mentagrophytes* ITS genotype VIII

and *Trichophyton indotineae*, refer to the same pathogen responsible for the recent epidemic of dermatophytosis in India and which is increasingly seen in other parts of the world, especially in Asia and Europe.

## Frequently used terms - then and now

Our aim here is to present a broad and simple overview of the myriad terms that have overwhelmed clinical dermatologists. It is interesting to delve into the recent few years of history of the terms used for the incriminated species under discussion. From 2008 to 2016, all strains within the species complex *Trichophyton mentagrophytes/Trichophyton interdigitale* were consistently classified as *Trichophyton interdigitale*, because the morphological differentiation between both species is very difficult and nucleotide polymorphisms within the internal transcribed spacer region of the ribosomal DNA are very rare compared to other fungal groups. Thus, sequences of dermatophytes stored in DNA databases across the world too were referred to as *Trichophyton interdigitale*, regardless of their anthropophilic or zoophilic nature. The taxonomy and nomenclature of dermatophytes were revised and the long-overdue clear distinction between zoophilic *Trichophyton mentagrophytes* and anthropophilic *Trichophyton interdigitale* was made in 2017.<sup>1</sup> During that period, Nenoff and Uhrlaß, taking a cue from the initial work by Heidemann *et al.* were describing various genotypes of what, according to the new classification, was *Trichophyton mentagrophytes*, by sequencing the Internal Transcribed Spacer (ITS) region of the rDNA and they described *Trichophyton mentagrophytes* ITS genotype VIII.<sup>2,3</sup> Such changes cannot be expected to be appreciated instantly because new concepts take time to be incorporated

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into mainstream literature. Even the most respected workers from India documenting squalene epoxidase gene (*SQLE*) mutations in their strains referred to them as *Trichophyton interdigitale* because the reference strains used for comparison from the database of the National Center for Biotechnology Information had also classified them as *Trichophyton interdigitale*.<sup>4</sup> The confusion was genuine and the need to update sequence databases was also spelt out.<sup>5,6</sup> The logical term, *Trichophyton mentagrophytes* ITS genotype VIII, found its place in mycology literature.<sup>7-11</sup> Amid this, a group from Japan described terbinafine resistance in two strains from an Indian and a Nepali patient, based on multigene phylogeny using high mobility group (HMG) and  $\alpha$  box genes in addition to the Internal Transcribed Spacer genes used by Nenoff. They introduced these strains, molecularly identical to *Trichophyton mentagrophytes* ITS genotype VIII, as a new species by the name *Trichophyton indotineae*.<sup>11</sup> Much water has flown under the bridge since the confusion began but it has been a logical one, and nobody is right or wrong in this terminological confusion.

### **Trichophyton mentagrophytes genotype VIII**

*Trichophyton mentagrophytes* and *Trichophyton interdigitale* cannot be differentiated from each other microscopically.<sup>12</sup> Macroscopically, however, some strains of the erstwhile *Trichophyton mentagrophytes variatio interdigitale* with white fluffy colonies may be distinguishable from *Trichophyton mentagrophytes* and *Trichophyton interdigitale* strains that show more granular thallus surface of the colonies. Therefore, molecular identification by polymerase chain reaction (PCR)-based sequencing of the rDNA is essential to distinguish one from the other. *Trichophyton mentagrophytes* genotype VIII is one of more than ten known and newly described genotypes or clusters within the *Trichophyton mentagrophytes/Trichophyton interdigitale* complex.<sup>2,3,13,14</sup> There are currently two genotypes (genotype I and II) within the anthropophilic species *Trichophyton interdigitale*, and 11 genotypes of zoophilic species *Trichophyton mentagrophytes*, including the ITS genotype VIII. The notable paradox, however, is that though the latter is classified as zoophilic according to the current classification, it is transmitted predominantly from a human being to another human being, making it anthropophilic in nature. It is rarely transmitted by animal sources, with only six such sequenced isolates in Poland, Iran and India.<sup>9</sup> Therefore, the rare possibility of an animal reservoir remains to be investigated. Though a mammoth task, the likelihood of millions of stray cattle, cats, dogs and rodents on the Indian subcontinent harbouring the infectious agent should be carefully looked into. The probability of this fungus having originated from the soil, primarily infecting animals who infect human beings, need to be looked into.<sup>3,15-17</sup> Also, a hypothesis of the so-called obligatory anthropization of the dermatophyte, needs to be disproved before coming to an educated conclusion.<sup>18</sup> The

evolution of the dermatophytes in question may have been geophilic at some point, later becoming zoophilic, with some of them undergoing a clonal expansion that adapts to the human skin.<sup>7</sup> The crux of the discussion, however, is that *Trichophyton mentagrophytes* VIII has adapted excellently to human skin and is easily transmitted to other humans. It also survives for presumably longer periods on inanimate surfaces and, hence, its transmission via fomites like clothes, bed linen and the surface of furniture and floor is a significant issue.

### **Trichophyton mentagrophytes ITS genotype VIII is now Trichophyton indotineae**

The current name of *Trichophyton mentagrophytes* genotype VIII has changed.<sup>11,19</sup> It is now considered a new species with the name *Trichophyton indotineae*.<sup>7</sup> This is the only genotype amongst the several existing ones, that has now been classified as a new species. The numerous genotypes present in a species complex are referred to as 'cryptic species' or 'molecular siblings.' While it is pointless to classify multiple genotypes as independent species, it is justifiable to do so with those which have a distinct disease-causing potential.<sup>20</sup> Such genotypes are also molecularly and phenotypically different within a species complex, as seen in this example. It has been recently proposed to refer to them as 'clonal offshoots'.<sup>20</sup> Therefore, *Trichophyton indotineae/Trichophyton mentagrophytes* ITS genotype VIII are 'clonal offshoots' of the *Trichophyton mentagrophytes/Trichophyton interdigitale* complex. The naming of this clonal offshoot as a species, therefore, has more practical than a scientific value.

Morphological differentiation between *Trichophyton mentagrophytes/Trichophyton interdigitale* and *Trichophyton indotineae* is difficult owing to significant similarities between these two species. *Trichophyton indotineae* shows fast-growing central beige stained, flat, in the periphery white colonies, similar to that of *Trichophyton mentagrophytes/Trichophyton interdigitale*. Microscopic features like round microconidia, cigar-shaped macroconidia, chlamydospores and spiral hyphae—are also the same in these species. Even positive Urease reaction is seen in some *Trichophyton indotineae* strains, though it is seen much more commonly in *Trichophyton mentagrophytes/Trichophyton interdigitale*.

Practising dermatologists who are not expected to be conversant with mycological nuances would be benefited by knowing that *Trichophyton mentagrophytes* ITS genotype VIII and the species *Trichophyton indotineae* are the same. They are molecularly identical, refer to the same pathogen with increased virulence, can cause widespread terbinafine resistance, and at times multidrug-resistant dermatophytosis, are linked with the abuse of topical steroid containing fixed-dose combination creams and erratic treatment with antifungal agents. The current confusion regarding the terms, therefore, may be attributed to the fact that the origin of the outbreaks (whether from an animal source or primarily

human-to-human transmission) has not been clearly established<sup>7</sup> and the current classification has not found uniform acceptance by the mycology community.

### **Trichophyton mentagrophytes genotype VIII/ Trichophyton indotineae not limited to the Indian subcontinent**

Taxonomy and terms change and evolve rapidly in the field of mycology.<sup>21-24</sup> *Trichophyton indotineae/Trichophyton mentagrophytes* ITS genotype VIII, notwithstanding the terminological confusion, is no longer restricted to the Indian subcontinent. Its presence as early as between 2004 and 2013 has been documented in India, Australia, Iran and Oman. A significant rise in the number of cases has been reported after 2014. Its presence in other countries is becoming a matter of interest for dermatologists far and wide. The scenario in the United Arab Emirates and other Middle East Asian countries appears to be identical.<sup>13,25</sup> It is thought that the disease has been introduced to Europe by migrants and travellers from India, Bangladesh, Pakistan, Bahrain, Libya, Saudi Arabia or Thailand.<sup>9</sup> The highest numbers are found in Germany with stray reports from France, Belgium and Switzerland.<sup>8,9,26-28</sup> Its presence has been noted in China too.<sup>29</sup> Indian dermatologists in certain parts of the country see many Indian patients coming from Africa and a majority of them give a history of steroid misuse as steroid-antifungal fixed dose combination creams are freely available over the counter there, as is seen in the Indian subcontinent and in the Middle East Asian countries.

We would like to reiterate that the epidemic of dermatophytosis in the Indian subcontinent needs more 'rational antifungal' stewardship and urgent, active intervention of the government in curbing the menace. We also propose to include dermatophytosis in the list of 'emerging infectious diseases' as well as 'neglected tropical diseases'. There is an unmet and urgent need for a drastic re-evaluation of policies related to manufacturing and sale of topical steroids and fixed dose combination creams containing antifungals and potent steroids in India. The Indian Association of Dermatologists, Venereologists and Leprologists has been an active crusader on this issue and has been prioritising curbing the menace of abuse and misuse of steroids among its multifarious activities. Active help of private practitioners, who constitute a vast majority of dermatologists, should be sought in fighting this menace. Finally, molecular diagnostics for detecting *Trichophyton indotineae* should be made more widely accessible to the community as this epidemic-like situation has wide ramifications due to its rampant spread and recalcitrance which, if detected early, can facilitate early, appropriate treatment.

#### **Declaration of patient consent**

Patient's consent is not required as there are no patients in this study.

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#### **Conflicts of interest**

There are no conflicts of interest.

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