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CASE REPORT

First Terbinafine-Resistant *Trichophyton indotineae* Isolates with Phe^{397}Leu and/or Thr^{414}His Mutations in Turkey

Murat Durdu · Hazal Kandemir · Ayşe Sultan Karakoyun · Macit Ilkit · Chao Tang · Sybren de Hoog

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Abstract Fungal infections of the skin, nails, and hair caused by dermatophyte species continue to be a worldwide concern. The increase in terbinafine-resistant superficial dermatophytosis has become a major concern over the last decade. In this report, we presented two cases of infection with terbinafine-resistant *Trichophyton indotineae*, the first diagnosis of this species in Turkey. One patient exhibited erythematous pruritic patches and plaques in the inguinal and gluteal regions, while the other patient showed annular erythematous scaly plaques in the bilateral posterior thigh and gluteal regions. One patient harbored a *CD36* mutation. Both strains harbored the same amino acid substitution in the squalene epoxidase gene, whereas one isolate had another unknown mutation. Clinical improvement was observed with resveratrol treatment in the patient with the *CD36* mutation but not in the other patient.

Keywords Resveratrol · Itraconazole · Terbinafin · *Trichophyton indotineae*

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M. Durdu (✉)
Department of Dermatology, Adana Dr. Turgut Noyan Application and Research Center, Başkent University Faculty of Medicine, Adana, Turkey
e-mail: sivandr@hotmail.com

H. Kandemir
Westerdijk Fungal Biodiversity Institute, Utrecht, The Netherlands

A. S. Karakoyun · M. Ilkit
Division of Mycology, Department of Microbiology, Faculty of Medicine, University of Çukurova, Adana, Turkey

C. Tang · S. de Hoog
Center of Expertise in Mycology, Radboud University Medical Center/Canisius Wilhelmina Hospital, Nijmegen, The Netherlands

Introduction

Dermatophyte infections have garnered renewed interest since the sudden emergence of a novel dermatophyte known as *Trichophyton indotineae*, a species with high virulence and strong terbinafine resistance [1]. This species is a member of the *Trichophyton mentagrophytes* complex, which comprises genotypes that are typically thought to have an animal origin [2] but are commonly transmitted by human hosts [3]. The fungus was first detected in India [4, 5] and has since spread rapidly to Southern Asia, Australia, and Europe [6]. A possible reason for its emergence can be the inappropriate use of antifungal creams with corticosteroids by the general public [7], which promotes antifungal resistance in the species. Patients typically show extensive skin and crural lesions, indicating significant virulence, which

indicates a recent animal host [8]. No specific animal host has been identified for *T. indotineae*, although Tartor et al. [9] reported an isolate from a cow in Egypt.

In general, affected patients are immunocompetent and do not have any underlying immune disorders. The cases presented in this report are the first from Turkey. One of the two patients described in this study had a mutation in the *CD36* gene, which encodes a membrane protein involved in fatty acid transport and scavenging receptors. As both strains of *T. indotineae* were terbinafine-resistant, we applied an alternative therapy with resveratrol. The course of events in these two cases is outlined below.

Case Presentation

Case 1

A 27-year-old man exhibited a fungal infection in the inguinal and gluteal regions that did not improve despite treatment with systemic terbinafine and itraconazole for the last 5 years. The patient was a doctor in the emergency department with no history of contact with animals. His symptoms began in the inguinal region and spread to the pubic and gluteal regions. The patient had been diagnosed with tinea cruris and had used topical antifungal agents—terbinafine (250 mg/day) for 6 months and itraconazole (2 × 100 mg/day) for 2 months. However, his symptoms continued to progress. Dermatological examination revealed scaly erythematous pruritic patches and plaques on the penis, scrotum, groin, pubic, and gluteal regions (Fig. 1a and b). KOH examination revealed dense hyphae and spores consistent with dermatophytosis. Histopathologically, fungal elements were observed only in the stratum corneum, without dermal invasion, which is compatible with superficial dermatophytosis. All lesions healed with high-dose fluconazole treatment (2 × 100 mg/day); however, when the drug was discontinued, the lesions recurred in the same regions. Additional skin scraping samples were collected for fungal culture. Although there was no history of other infections, a complete blood count and immunoglobulin levels were evaluated, and flow cytometry analysis was performed to detect possible immunosuppressive diseases in the patient; however, no pathology was found. The patient tested negative for HIV antibodies. Genetic testing revealed a heterozygous p. N220fs*4 variant in the *CD36* gene. Resveratrol tablets were recommended to the patient twice daily, and the clinical lesions resolved without further antifungal treatment (Fig. 1c and d).

Skin scraping samples were inoculated onto Sabouraud glucose agar plates (SGA; Merck, Darmstadt, Germany) containing 100 µg/ml chloramphenicol (Sigma-Aldrich, Steinheim, Germany) and 50 µg/ml gentamicin (Sigma-Aldrich). The plates were incubated at 28 °C for 14 d. DNA was extracted from fresh colonies using the Wizard® Genomic DNA Purification Kit (Promega, Madison, WI, USA), according to the manufacturer's instructions. The rDNA operon with the internal transcribed spacer (ITS) and D1–D2 region of the large subunit (LSU) were amplified using the primers ITS4–ITS5 and LR0R-LR5, respectively [10]. PCR amplicons were visualized on a 1.5% agarose gel, and sequencing was performed with the same primer pairs used for PCR amplification using Applied Biosystems BigDye Terminator version 3.1 (Thermo Fisher Scientific). The sequences were edited and assembled using Geneious R11 [11]. Phylogenetic analysis of ITS data was performed using maximum likelihood methods implemented in IQ-TREE software [12, 13]. The squalene epoxidase (*SQLE*) gene was amplified and sequenced using the primers described by Kong et al. [14]. The detected mutations and GenBank accession numbers of the sequences are listed in Table 2. Antifungal susceptibility testing was performed according to the EUCAST E. Def 9.3.1 protocol [15]. Isolates were deposited in the CBS reference collection under the accession numbers CBS 149165 and CBS 149166.

The fungus isolated from the clinical samples was cultured on SGA and was found to be consistent with *T. indotineae* based on ITS and LSU sequencing (Table 1 and Fig. 2). The isolate was resistant to fluconazole and terbinafine in vitro; additional antifungal susceptibility testing (AFST) data are listed in Table 2. Two non-synonymous mutations were found in *SQLE* (1189 T > C and 1240 T > C). A subculture was deposited in the CBS collection under the accession number CBS 149166.

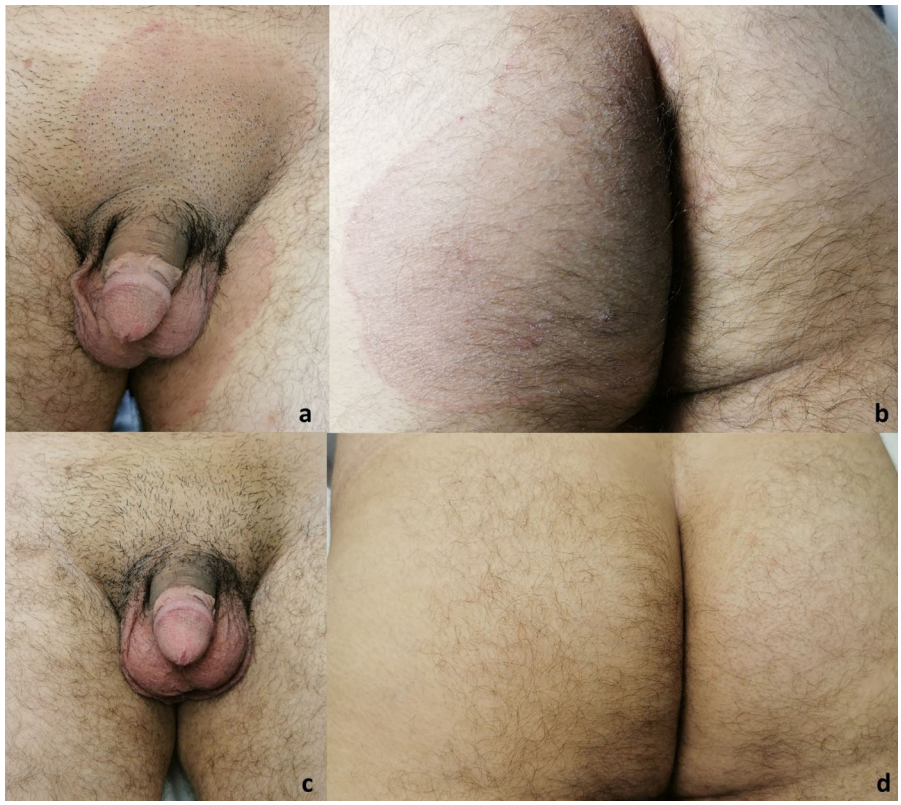

Fig. 1 Erythematous scaly plaques in (**a**) the penis, groin, and pubic region and (**b**) the gluteal region of a 27-year-old male patient and the clinical improvement with resveratrol treatment (**c** and **d**)

Table 1 GenBank accession numbers for the sequences and detected *SQLE* mutations

Case (CBS) numbers	GenBank accession numbers			Mutation(s)
	ITS	LSU	*SQLE*	
1 (149166)	ON528187	ON528577	ON863899	1189 T > C, 1240 T > C**
2 (149165)	ON528186	ON528576	ON863900	1189 T > C*

CBS Culture collection of the Westerdijk Biodiversity Institute; *ITS* internal transcribed spacer rDNA; *LSU* large subunit rRNA; *, $Phe^{397}Leu$; **, $The^{414}His$

Case 2

A 25-year-old woman exhibited a fungal infection in the bilateral posterior thigh and gluteal region; it had not responded to systemic terbinafine treatment for 2-years. There was no history of other recurrent infections, contact with animals, working in a warm environment, or use of immunosuppressive therapy. She was diagnosed with tinea corporis, and her symptoms did not improve despite topical and systemic terbinafine (250 mg/day for 6 months) treatment. Cutaneous examination revealed annular erythematous scaly plaques located in the anterior and posterior thighs and gluteal region (Fig. 3a and b). Blood immunoglobulin levels and complete blood counts were evaluated. Flow cytometric analysis was also performed, and no immunological defects were detected. The patient tested negative for HIV antibodies. Although hyphae and spores were observed in direct microscopic examination of the skin scraping

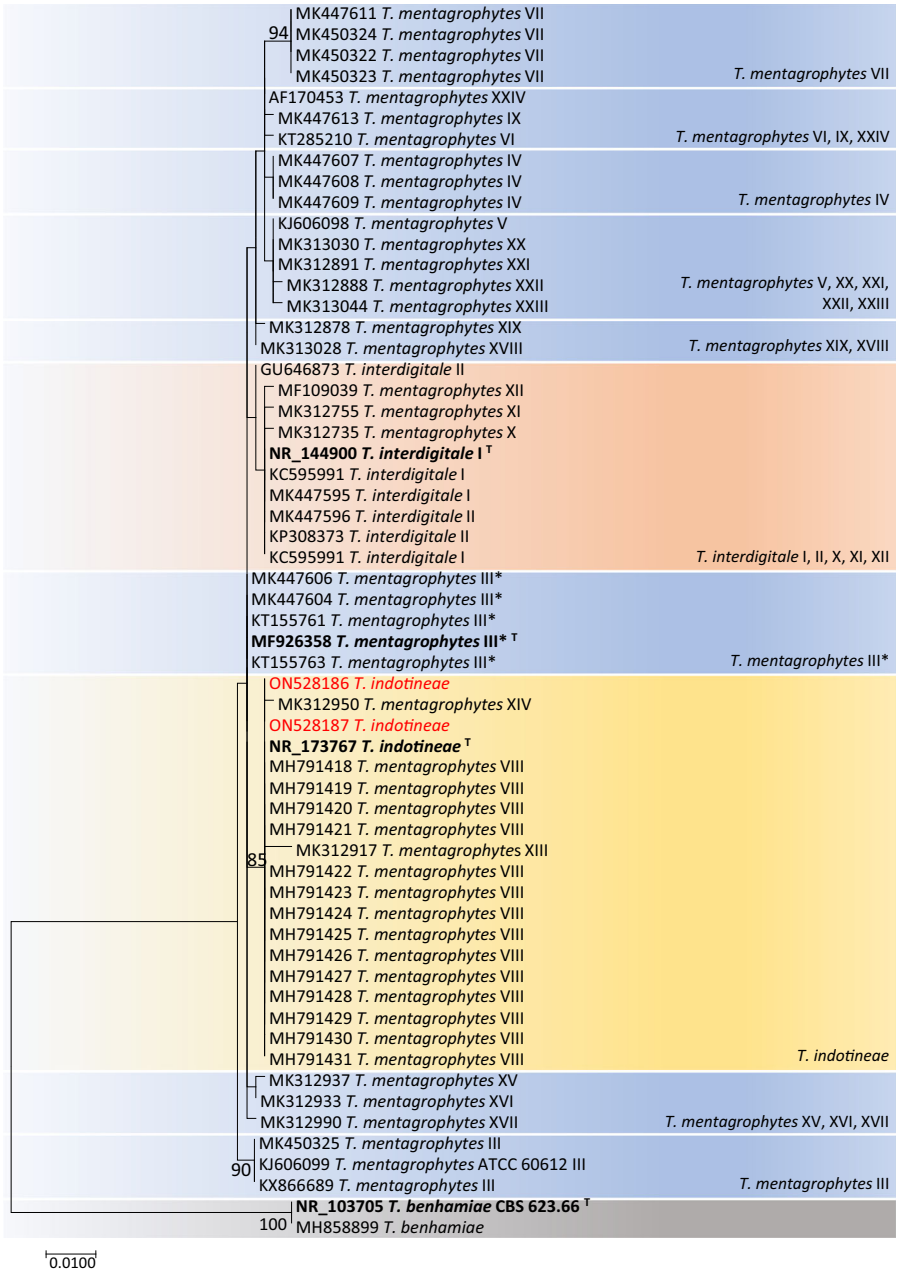

Fig. 2 Maximum likelihood phylogenetic analysis of *T. indotineae* ITS sequences. The names are used according to Nenoff et al. [16], Kano et al. [17], and Taghipour et al. [18]. Species affiliations on the right are given based on the supported ITS clades and MALDI-ToF MS data provided by Tang et al. [19]. According to this evaluation, genotypes VIII, XIII, and XIV are identified as *T. indotineae*. The two isolates presented in the current report are shown in red, and type strains are shown in bold. *ATCC*, American Type Culture Collection; *CBS*, Culture collection of the Westerdijk Biodiversity Institute; *DSM*, German collection of microorganisms and cell cultures; *IHEM*, Institute of Hygiene and Epidemiology-Mycology Laboratory; ^{T}, type strain

samples, histopathological examination was recommended to exclude invasive dermatophyte infection in the patient. A 4 mm punch biopsy sample was obtained for histopathological examination and was found to be compatible with superficial dermatophytosis. Genetic analysis could not be performed because

Table 2 Antifungal susceptibility results of the *Trichophyton indotineae* isolates

Case (CBS) numbers	MIC values (mg/L)							
	CPX	GSF	FLC	ITR	VRC	MCZ	TRB	KET
1 (149166)	0.25	2	16	0.031	0.125	1	> 16	0.125
2 (149165)	0.50	1	32	0.031	0.250	1	> 16	0.250

CBS Culture collection of the Westerdijk Biodiversity Institute; *CPX* ciclopirox; *GSF* griseofulvin; *FLC* fluconazole; *ITR* itraconazole; *VRC* voriconazole; *MCZ* miconazole; *TRB* terbinafine; *KET* ketoconazole

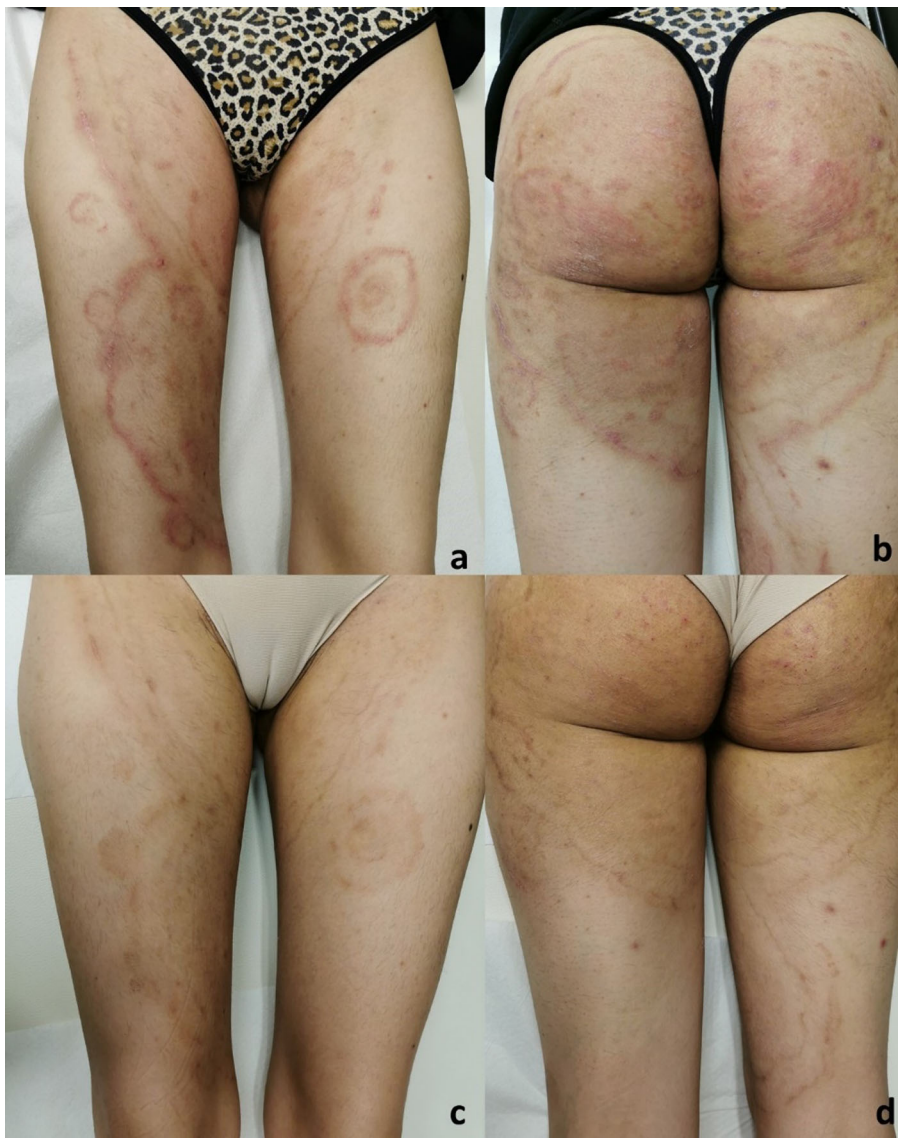

Fig. 3 Annular erythematous scaly plaques located in (**a**) the anterior and posterior thighs and (**b**) gluteal region of a 25-year-old female patient and the improvement with systemic itraconazole treatment (**c** and **d**)

of the lack of patient consent. The patient was treated with oral itraconazole (2 × 100 mg/day, 4 weeks), and the lesions resolved with post-inflammatory pigmentation (Fig. 3c and d). One month later, the patient returned with relapsed lesions on the same body parts. Since patient 1 responded well to resveratrol, the same treatment was recommended for this patient as well; however, no clinical improvement was observed. Therefore, systemic itraconazole treatment was initiated. No recurrence was observed after 2-months of systemic itraconazole treatment. The etiological agent isolated from clinical samples was cultured on SGA and was found to be consistent with *T. indotineae* based on ITS and LSU sequencing (Table 1 and Fig. 2). The isolate was resistant to fluconazole and terbinafine treatments in vitro; additional AFST data are listed in Table 1. A mutation was found in the *SQLE* gene (1189 T > C). A subculture was deposited in the CBS collection under the accession number CBS 149165.

Discussion

The identification of species in the *T. mentagrophytes* complex is highly controversial. Tang et al. [19] reported the emergence of a large number of ITS-based genotypes representing the species' host shift to humans after its probable origin from domesticated animals. The authors suggested restricting the naming of entities to those that are phenotypically different and clinically relevant. In accordance with the epidemiological data presented by Taghipour et al. [18], European, Asian, and Oceanian clusters of genotypes could be recognized, with different clinical predilections and distinct geographic locations in some, but not all, genotypes. The most deviant genotype was VIII, which was previously described as *T. indotineae*. A bootstrap-supported cluster of this species, also comprising the genotypes XIII and XIV, was formed in the ITS tree (Fig. 2). Genotypes XIII and XIV were listed by Taghipour et al. [18]; however, no information on these strains was provided. The two isolates reported in the present study were identical to the type strain of *T. indotineae* (ITS genotype VIII).

Herein, we presented the first two cases of superficial dermatophytosis caused by *T. indotineae* in Turkey. In both the cases, pronounced resistance to terbinafine was observed, a characteristic that has been noted since the first emergence of this species in India [4]. The most common causes of acquired resistance in dermatophytes are the combined use of antifungal creams containing steroids, non-adherence to the prescribed clinical course, treatment incompatibility, humid and warm living conditions, enhanced proliferation of dermatophytes, poor skin hygiene, repetitive contact with possible sources of infection, decreased hydration of the stratum corneum due to barrier function defects, and defective immune responses [20]. Although treatment compliance was good in both the patients, the *T. indotineae* infections were highly recalcitrant and relapsed when treatment was discontinued.

During the last decade, several outbreaks of multidrug-resistant dermatophytes have been reported in India [16]. Mycological studies during these outbreaks have revealed that the most common dermatophytes causing resistant infections in India are members of the *T. mentagrophytes* complex [1, 16, 21], followed by the *T. rubrum* complex [22]. *Trichophyton mentagrophytes* genotype VIII, currently known as *T. indotineae*, was first detected between 2004 and 2013 in India, later emerging in Australia, Iran, and Oman, and recently even emerging the USA and several European countries [6]. Cases outside India are sporadic. The crural prevalence of *T. indotineae* may enhance its distribution through sexual contact [23]. Neither of our patients had a history of travel to a hyperendemic region for *T. indotineae*.

Among the amino-acid substitutions in the *SQLE* gene that lead to terbinafine resistance, the most commonly encountered are $Phe^{397}Leu$ and $Leu^{393}Phe$ [24–27]. Resistant *Trichophyton* isolates have also been reported to show amino acid substitutions at positions Lys^{276}, Glu^{408}, Phe^{415}, His^{440}, and Ala^{448} [14, 25, 28–30]. To investigate resistance in our isolates, mutations were screened in the *SQLE* gene, which encodes the target enzyme of the drug. Both isolates obtained in the present study harbored a $Phe^{397}Leu$ substitution (T → C transition at position 1189), whereas the isolate from patient 1 had an additional $Thr^{414}His$ mutation (T→ C transition at position 1240) (Fig. 4). To the best of our knowledge, this mutation has not been previously reported in any terbinafine-resistant *T. indotineae* strains. As the isolate already harbors another substitution and the patient has a *CD36* defect, it is unclear whether this substitution enhances antifungal resistance.

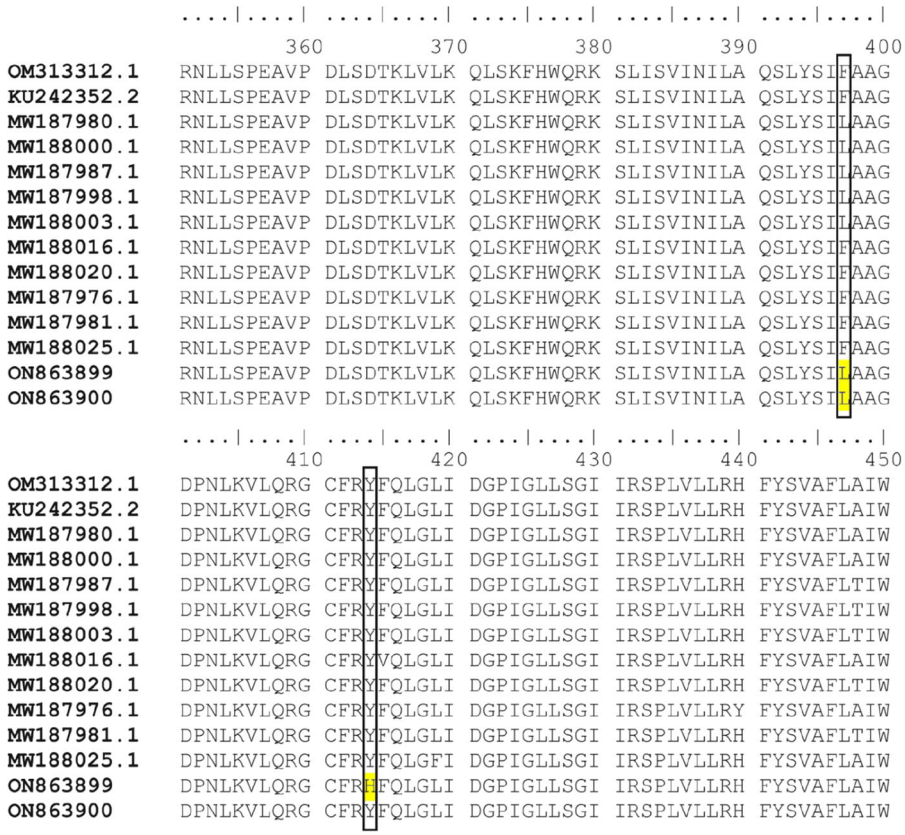

Fig. 4 Sequence alignment of the *SQLE* partial gene. Alignment was performed using CLUSTAL multiple sequence alignment in BioEdit. Sequences of two isolates (ON863899 and ON863900) were compared with those of *T. mentagrophytes* strain TIMM2789 (GenBank acc. no. KU242352.) and *T. interdigitale* isolate DK-Tinterdig-WT (GenBank acc. no. OM313312.1), as well as *SQLE* sequences of terbinafine-resistant *T. indotineae* strains (GenBank acc. no. MW187976, MW187980, MW187981, MW187987, MW187998, MW188000, MW188003, MW188016, MW188020, and MW188025) [14]. The amino acid substitutions that were found to be different in the two isolates are marked in yellow, and their positions are shown in black boxes

Remarkably, in such cases, in vitro resistance could not be clarified by the presence of any mutation in *SQLE* (wild-type) [31, 32]. Currently available data obtained from published studies clearly show that the Phe^{397}Leu mutation can cause terbinafine resistance by itself [24, 28, 31, 33]. Other mutations do not seem to increase minimum inhibitory concentration values for terbinafine resistance when they are found together with Phe^{397}Leu [24]. However, double mutants, Phe^{397}Leu and Ala^{448}Thr, have been reported to have combined terbinafine and increased fluconazole resistance [33]. Moreover, Taghipour et al. [24] reported a Leu^{393}Ser substitution together with Ala^{448}Thr in terbinafine-resistant *Trichophyton* isolates. These findings suggest that Leu^{393} mutations could also promote terbinafine resistance in dermatophytes. Nevertheless, mechanisms other than Phe^{397}Leu and Leu^{393}Phe may also lead to terbinafine-resistance; therefore, more studies are required to draw definite conclusions.

There are currently no guidelines for the management of terbinafine-resistant superficial dermatophyte infections. Posso-De Los Rios et al. [34] reported eight cases of terbinafine-resistant dermatophyte infections from Canada and outlined a clinical approach for such cases, with administration of fluconazole (400 mg/week for 12 weeks) or itraconazole (200 mg/day for 4 weeks) as the most important component. Although patient 2 responded well to systemic itraconazole treatment, patient 1 did not respond to itraconazole or fluconazole therapy. The lesions in patient 1 resolved

with high-dose fluconazole (200 mg/day) treatment but relapsed when the treatment was discontinued.

Genetic tests were performed on patient 1, revealing a mutation in the *CD36* gene. This gene encodes a glycoprotein ligand that can be found in different cell membrane structures and is involved in the membrane transport of lipids and fatty acids. The functions of the ligands vary according to the cell in which they are located. Ligands in platelets are involved in angiogenesis, whereas they act as pattern recognition receptors in phagocytic cells [35]. *CD36* recognizes fungal β-glucans [36] and binds to lipoprotein and lipid components [37]. The activation of *CD36 r*eceptors after contact with *Cryptococcus neoformans* and *Candida albicans* leads to the release of pro-inflammatory cytokines and chemokines from phagocytic cells [36]. In a study conducted in China, the frequency of *CD36* mutations varied according to the ethnic population [38]. *CD36* mutations also predispose individuals to malaria and attenuate experimental mycobacterial infections [39, 40]. Given these data, the enhancement of susceptibility to fungal infections is plausible.

Since the lesions recurred when antifungal therapy was discontinued in patient 1, who had the CD36 mutation, we started looking for an alternative treatment that might counteract this defect. Resveratrol is a stilbene phytoalexin found in certain plants, such as red grapes, peanuts, cranberries, and blueberries [41]. This molecule exhibits antifungal activity by inducing apoptosis in *C. albicans* [42]. In addition, resveratrol has been shown to inhibit different dermatophytes, such as *T. mentagrophytes*, *T. tonsurans*, *T. rubrum*, *Epidermophyton floccosum*, and *Nannizzia gypsea* [43]. In our patients, the response to resveratrol differed from that of the proven *CD36* deficiency. It remains unclear whether lesions were resolved due to the antifungal effect of or due to the defective *CD36* pathway. Nevertheless, the response to resveratrol treatment in the first patient, but not in the second, suggests a potential role of the *CD36* pathway. Further studies are needed to investigate the correlation between *CD36* pathway defects and dermatophyte infection.

In conclusion, due to the growing number of terbinafine-resistant *T. indotineae*, the high terbinafine-resistance in other dermatophyte species has not yet been clearly described. Therefore, terbinafine-resistance cannot be generated in unusual isolates that are probably clonal and exhibit higher MICs than global data, and the reasons behind this remain poorly understood. In addition, the observed and proposed epidemiological cut-off values can be misleading when applied to the rest of the world.

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Author Contributions All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by MD, HK, ASK, and CT. The first draft of the manuscript was written by MD, HK, MI, and SH, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Declarations

Conflict of interest The authors have no relevant financial or non-financial interests to disclose.

Ethical approval Ethical approval for this study was not required.

Consent to participate Informed consent was obtained from all individual participants included in the study.

Consent to publish The authors affirm that the human research participants provided informed consent for publication of the images in Figs. 1 and 3.

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