

Molecular Epidemiology of antifungal resistant *Trichophyton* species in Singapore

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Introduction

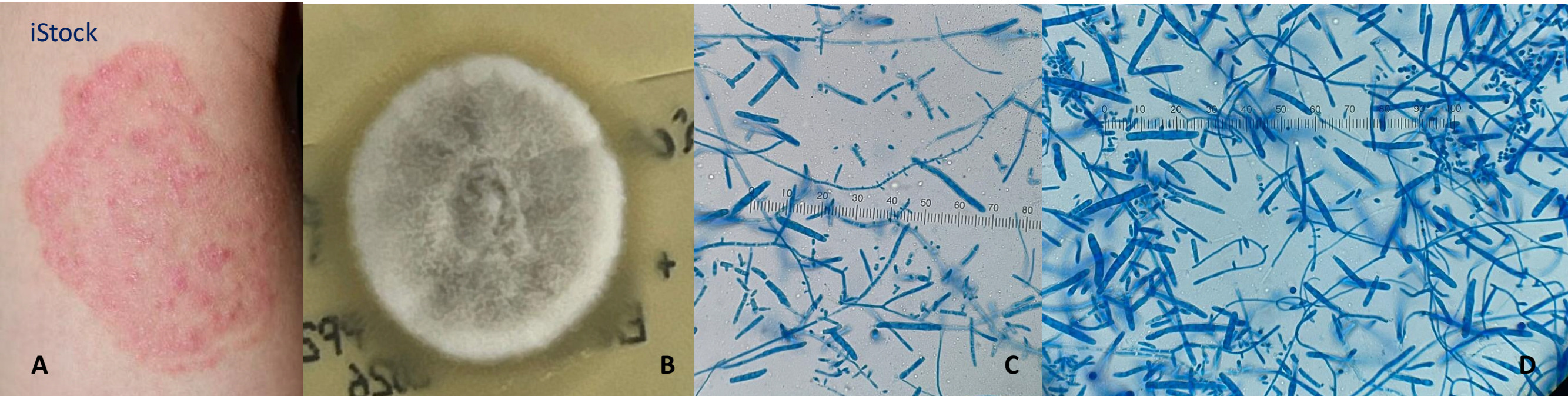
- Dermatophytosis is one of the most common superficial fungal infections, e. g. “ringworm”, “tinea”, “athlete’s foot”
- About 20-25% of global population is affected; global treatment costs US\$500 million/year
- Members in *Trichophyton*, *Microsporum* and *Epidermophyton* are common, major pathogens.
- Increased prevalence and widespread dissemination of difficult to treat dermatophytosis such as terbinafine resistant *Trichophyton indotineae*, pose significant burden to global public health.
- *T. indotineae*, a lineage in the *T. mentagrophytes* complex, is spreading globally from South Asia and Iran and has now been reported from 28 countries.
- Reports of *Trichophyton* infections have increased substantially in Singapore, but their genetic relationship and mechanisms of antifungal resistance are not well studied.

Objectives

- I. Microbiological and genomic approach to study the genetic relationships of *Trichophyton* isolates and to determine the possible transmission pattern in Singapore
- II. To measure the AST profiles toward various antifungal agents and to characterize the molecular mechanisms associated with resistance

Material and Methods

- 87 isolates were collected, including 62 isolates from National Skin Centre (NSC), Singapore and 25 from Singapore General Hospital (SGH) .
- Isolates were from patients with clinical presentation of tinea corporis or tinea cruris.
- They were identified by routine microbiological methods (images below).
- Antifungal susceptibility tests for 8 antifungal drugs by CLSI interpretations.
- Whole Genome Sequencing performed based on 150bp PE reads on Illumina platforms at Noveogene Ltd.
- Genomic data was analysed using suites of software: FastQC, Trim Galore, SPAdes, BLAST+; BWA, samtools, GATK, FastTree; reads mapped to reference genome [GCA_023065905.1] for variants.



Clinical image and macro- and microscopical features of *Trichophyton* spp.

Results

- Out of 83 isolates with quality genome data, 48 belonged to *T. indotineae*, 23 belonged to *T. interdigitale* and 12 were *T. rubrum* based on phylogenetic inference using ITS rRNA (Figure 1).
- Missense variants in signature loci were screened from 48 *T. indotineae* isolates.
- At squalene epoxidase (SQLE), F397L (n=25) was the most frequent mutation, followed by A448T (n=8) in *T. indotineae* (Figure 2A)
- At the cytochrome P450 sterol 14 α -demethylase (CYP51b), Y444H (n=15) was the most frequent mutation, followed by G445S (n=6) (Figure 2B).
- Isolates of *T. indotineae* had low genetic polymorphisms (24-894 SNPs) and could be introduced into Singapore multiple times. They cannot be differentiated by year and hospitals (Figure 3).
- When compared to the global isolates, they can be differentiated into 4 genetic groups previously recognized, confirming a clonal transmission globally (Figure 3).
- Clustering of several Singaporean isolates could indicate the persistence and circulation of pathogens in the community.

Figure 1 Phylogenetic placement of *Trichophyton* isolates (in red and blue) in Singapore when compared with international isolates based on ITS rRNA

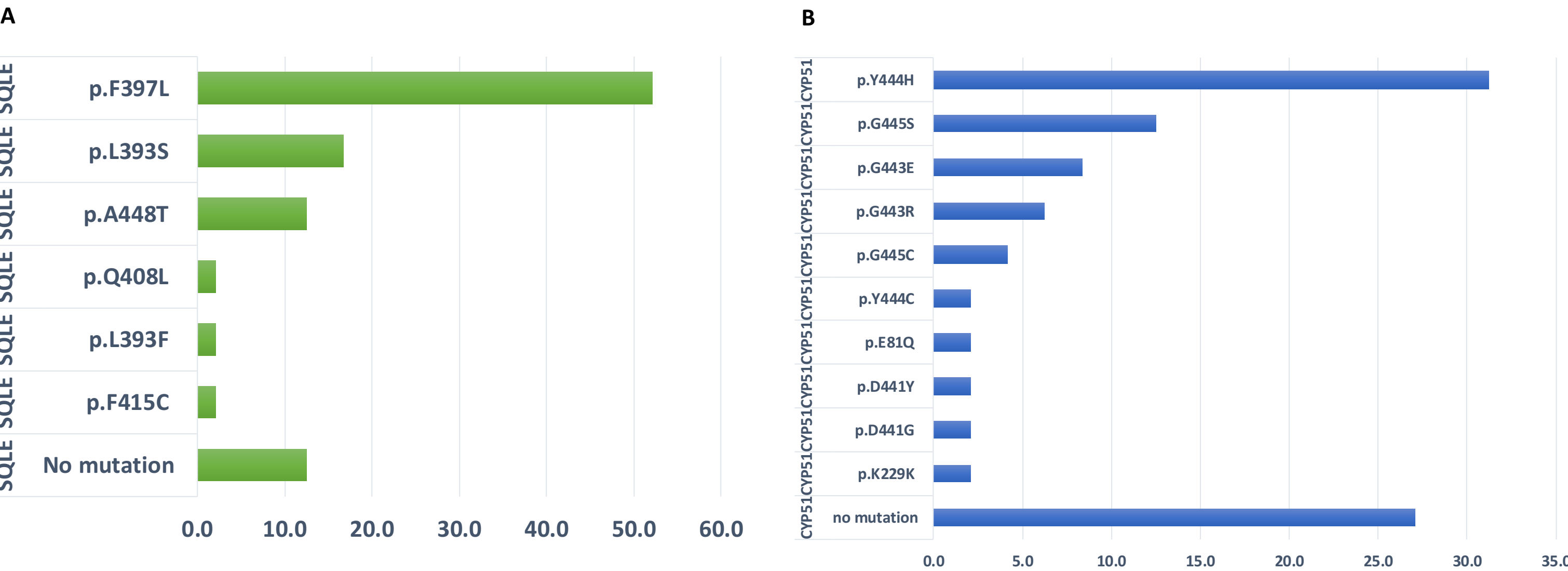
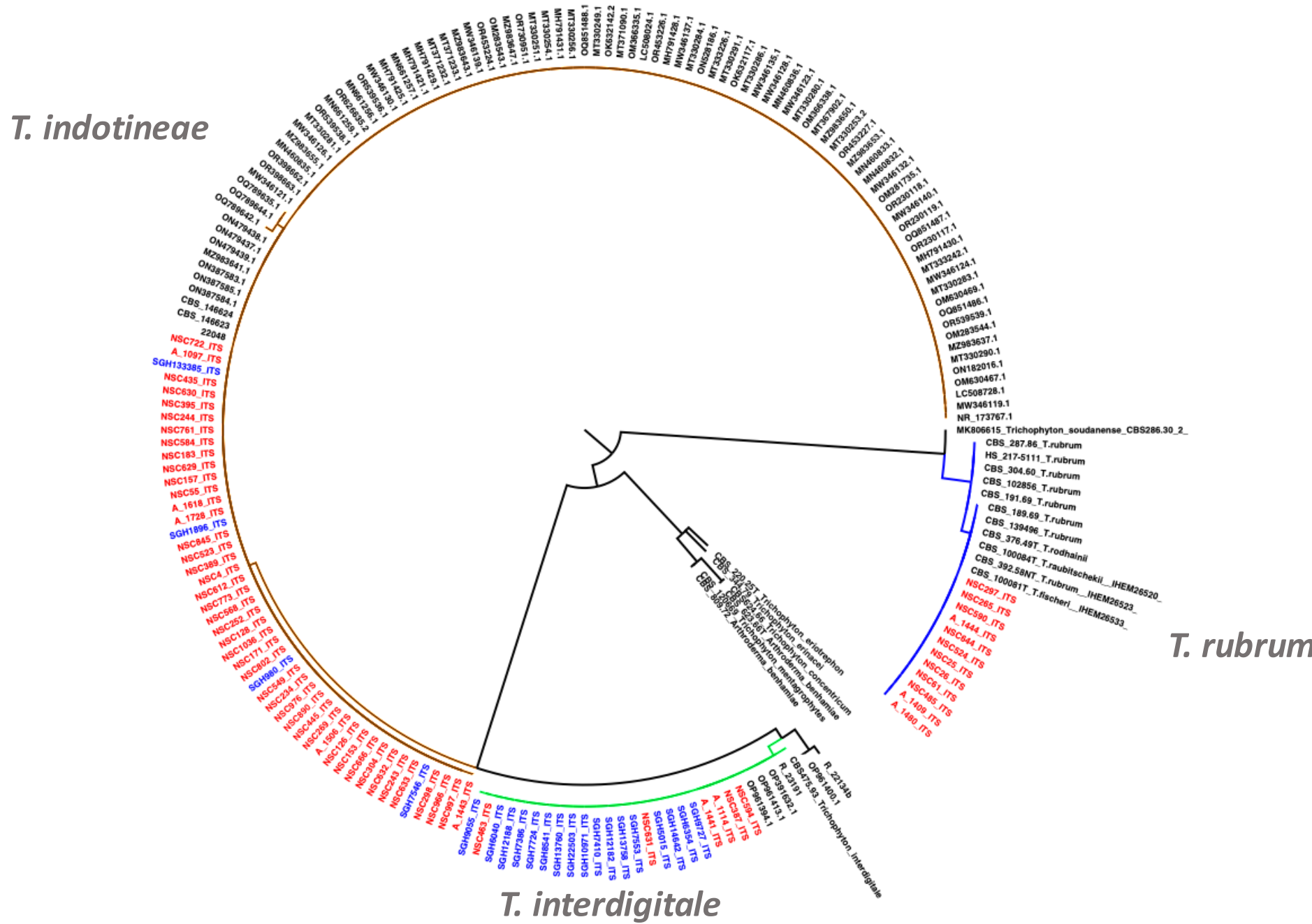
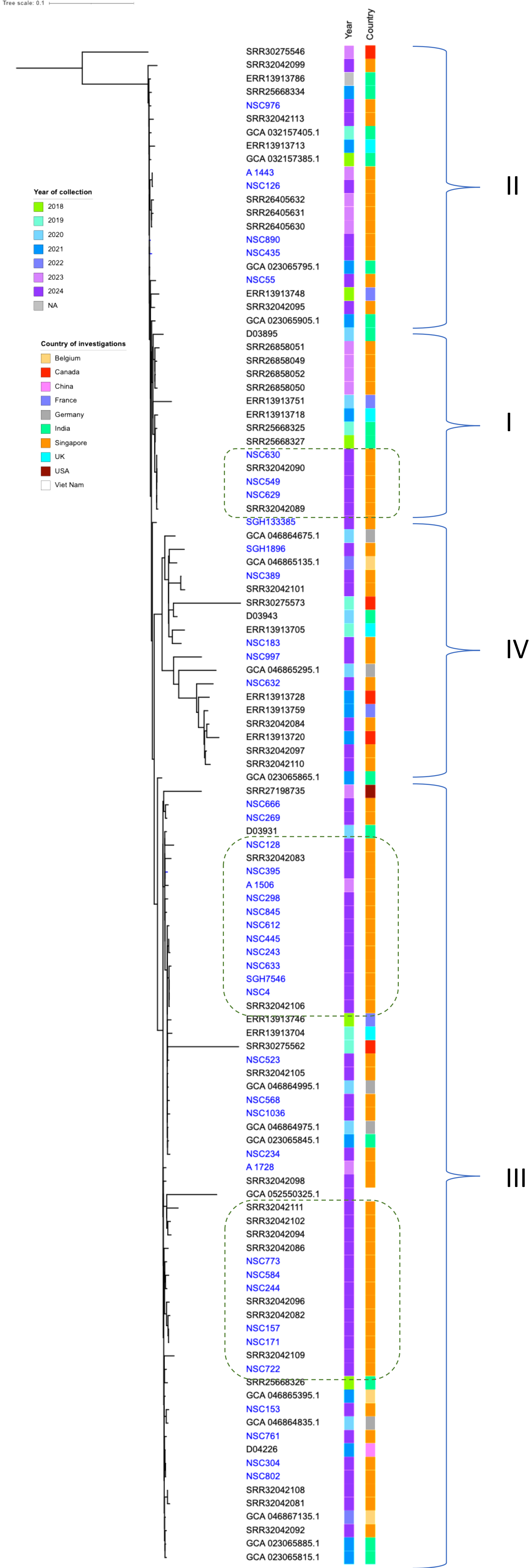


Figure 2 A, B. Frequency (%) of *SQLE* and *CYP51B* mutations in *T. indotineae* isolates.

Figure 3. Phylogenetic relationships between *T. indotineae* in Singapore and selected global isolates based on maximum likelihood analysis of genomic SNPs. Clusters I-IV recognised in previous study. (Samples sequenced in this study in blue)



Conclusion

- ❖ Our study illustrated the presence and circulation of terbinafine resistant *T. indotineae* in Singapore. Active surveillance is necessary to contain *T. indotineae* and to better understand the epidemiology of this emerging dermatophyte.

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