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# Molecular Identification of Human Sporotrichosis in Korea

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**Background:** Sporotrichosis is a common deep mycosis caused by the *Sporothrix schenckii* complex. Until 2016, no molecular studies had been conducted on these fungi, and all the included strains were reported as *S. schenckii*. However, investigations conducted in northeast China, Japan, and India revealed that *S. globosa* was the most prevalent *Sporothrix* species, whereas *S. schenckii sensu stricto* was reported very rarely.

**Objective:** To investigate the accurate prevalent causative species of sporotrichosis among strains reported as *S. schenckii* in Korea.

**Methods:** We isolated strains of *Sporothrix* spp. Prevalent in Korea from fungus collection centers or private collections and reviewed the available literature on molecular studies of strains from this region. We found five *S. schenckii* (1998-2016) and three *S. globosa* (2016-2018) strains. Ribosomal DNA internal transcribed spacer (ITS) sequences of these strains were compared with those of the *S. schenckii* complex strains.

**Results:** The ribosomal ITS sequences of the eight strains were 100% identical with that of *S. globose*. No *S. schenckii sensu stricto* was found. In addition, a study on the molecular analysis of Korean *S. schenckii* published by Ishizaki et al. (2004) demonstrated that the eight strains were of the mitochondrial subtype group B (*S. globosa*). Thus, all the 16 strains examined within the Korean *S. schenckii* complex were determined to be *S. globosa*.

**Conclusion:** In summary, *S. globosa* is the causative species within the tested Korean sporotrichosis cases reported between 1998 and 2018. Based on our analyses, *S. globosa*, and not *S. schenckii*, may be the predominant species in Korea.

**Key Words:** Sporotrichosis, *Sporothrix globosa*

## INTRODUCTION

Sporotrichosis is a subcutaneous or systemic fungal infection caused by the *Sporothrix schenckii* complex. Under ordinary circumstances, *Sporothrix* infection occurs via traumatic inoculation of the skin or subcutis. *S. schenckii* has been considered the sole species causing all types of sporotrichosis in humans[1]. In 2007, Marimon et al.[2] reported the following six species of *S. schenckii* complex based on phenotypic and genotypic analyses: *S. schenckii sensu stricto*, *S. globosa*, *S. brasiliensis*, *S. luriei*, *S. mexicana*, and *S. pallida* (*S. albicans*). Ishizaki et al.[3] investigated 357 Japanese isolates of *Sporothrix* via restriction fragment length polymorphism (RFLP) analysis of mitochondrial DNA (mtDNA) and discovered only 15 isolates belonging

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to group A (*S. schenckii*; 4.2%), with all other isolates belonging to group B (*S. globosa*; 342/357, 95.8%). Liu et al.[4] and Yu et al.[5] demonstrated that in northeast China, all of the sporotrichosis-causing *S. schenckii* complex strains were *S. globosa*.

Since 1970, a total of 521 cases of sporotrichosis were published within 31 reports in Korea, and all those cases were reportedly caused by *S. schenckii*[6-36]. No molecular studies were conducted until 2016, and *S. schenckii* was long believed to be the causative species of sporotrichosis in Korea. Kim et al.[37,38] reported three cases of human sporotrichosis caused by *S. globosa* and suggested that this fungus is the only causative organism of sporotrichosis in Korea. To clarify the causative pathogen, the current study aimed to collect strains of *Sporothrix* prevalent in Korea and analyze them using ribosomal DNA internal transcribed spacer (ITS) sequences.

# MATERIALS AND METHODS

## 1. Fungal isolates

This study included five and three clinical isolates reported as *S. schenckii* (1998-2016) and *S. globosa* (2016-2018), respectively, in Korea (Table 1). These strains were isolated from fungus collection centers or private collections. The isolates were cultured on potato dextrose agar (PDA; Difco™ Becton, Dickinson and Company, Sparks, USA) and incubated at -80℃. In addition, eight Korean strains described before in 2003 by Ishizaki et al. were included[39] (Table 2).

## 2. DNA extraction and amplification

The *Sporothrix* spp. strains were sub-cultured on PDA for

**Table 1.** *Sporothrix* spp. strains found in South Korea

| No | Year | Area | Source | Reported as | rDNA ITS |
|---|---|---|---|---|---|
| 1 | 1998 | Gwangju | Human skin | *S. schenckii* | *S. globosa* |
| 2 | 2009 | Gwangju | Human skin | *S. schenckii* | *S. globosa* |
| 3 | 2009 | Gwangju | Human skin | *S. schenckii* | *S. globosa* |
| 4 | 2015 | Gyeungju | Human skin | *S. schenckii* | *S. globosa* |
| 5 | 2016 | Gyeungju | Human skin | *S. schenckii* | *S. globosa* |
| 6 | 2016 | Daegu | Human skin | *S. globosa* | *S. globosa* |
| 7 | 2018 | Daegu | Human skin | *S. globosa* | *S. globosa* |
| 8 | 2018 | Daegu | Human skin | *S. globosa* | *S. globosa* |

**Table 2.** Mitochondrial DNA analysis of *Sporothrix schenckii* from South Korea, as isolated by Ishizaki et al.[39]

| No | Year | Area | Source | Reported as | mtDNA type (Type/Group) | rDNA ITS |
|---|---|---|---|---|---|---|
| 1 | <2003 | Korea | Human skin | *S. schenckii* | 4/B | *S. globosa* |
| 2 | <2003 | Korea | Human skin | *S. schenckii* | 4/B | *S. globosa* |
| 3 | <2003 | Korea | Human skin | *S. schenckii* | 4/B | *S. globosa* |
| 4 | <2003 | Korea | Human skin | *S. schenckii* | 4/B | *S. globosa* |
| 5 | <2003 | Korea | Human skin | *S. schenckii* | 4/B | *S. globosa* |
| 6 | <2003 | Korea | Human skin | *S. schenckii* | 5/B | *S. globosa* |
| 7 | <2003 | Korea | Human skin | *S. schenckii* | 5/B | *S. globosa* |
| 8 | <2003 | Korea | Human skin | *S. schenckii* | 5/B | *S. globosa* |

at least 2 weeks at 28℃. Then, genomic DNA was directly extracted and purified from the fungal colonies using the QIAmp DNA Mini Kit (Qiagen, Hilden, Germany). Approximately 1 mg of fresh filamentous mycelia were scraped and incubated overnight at 56℃ in 1.5 mL microcentrifuge tubes containing 180 μL of animal tissue lysis buffer and 20 μL of proteinase K. Additional lysis buffer (200 μL) was added and mixed by pulse vortexing for 15 s, and the solution was then incubated at 70℃ for 10 min. Next, 200 μL of ethanol was added to the sample after which it was vortexed and briefly centrifuged. The sample mix was then carefully added to a QIAmp Mini column and centrifuged for 1 min. After switching on the vacuum pump, wash buffer (AW1 and AW2; 500 μL each) was added and the sample was centrifuged twice. Subsequently, 100 μL of elution buffer was added to the sample mixt, after which the sample was incubated for 5 min at room temperature (20~25℃) and centrifuged for 1 min. The total volume of the final extraction product was approximately 100 μL, which was preserved at -20℃ until use.

DNA was amplified using polymerase chain reaction (PCR) with the primer pair ITS1 (5'-TCCGTAGGTGAACCTGCGG-3') and ITS4 (5'-TCCTCCGCTTATTGATATGC-3'). The PCR mixture consisted of 15 μL of 2× PCR premix, 1 μL of the DNA template, 2 μL of ultrapure water, and 1 μL of each primer (10 pmol/μL). The cycling conditions were as follows: 5 min at 95°C for initial denaturation; 30 cycles of 30 s at 95℃, 30 s at 60℃, and 1 min at 72℃ for amplification; and 10 min at 72℃ for extension. The PCR product quantities were determined using agarose gel electrophoresis, and the products were then purified using a purification kit (Bioneer, Daejoon, Korea).

## 3. Sequencing

Automated sequencing was performed at Macrogen (Seoul, Korea), and ribosomal DNA (rDNA) ITS sequences were

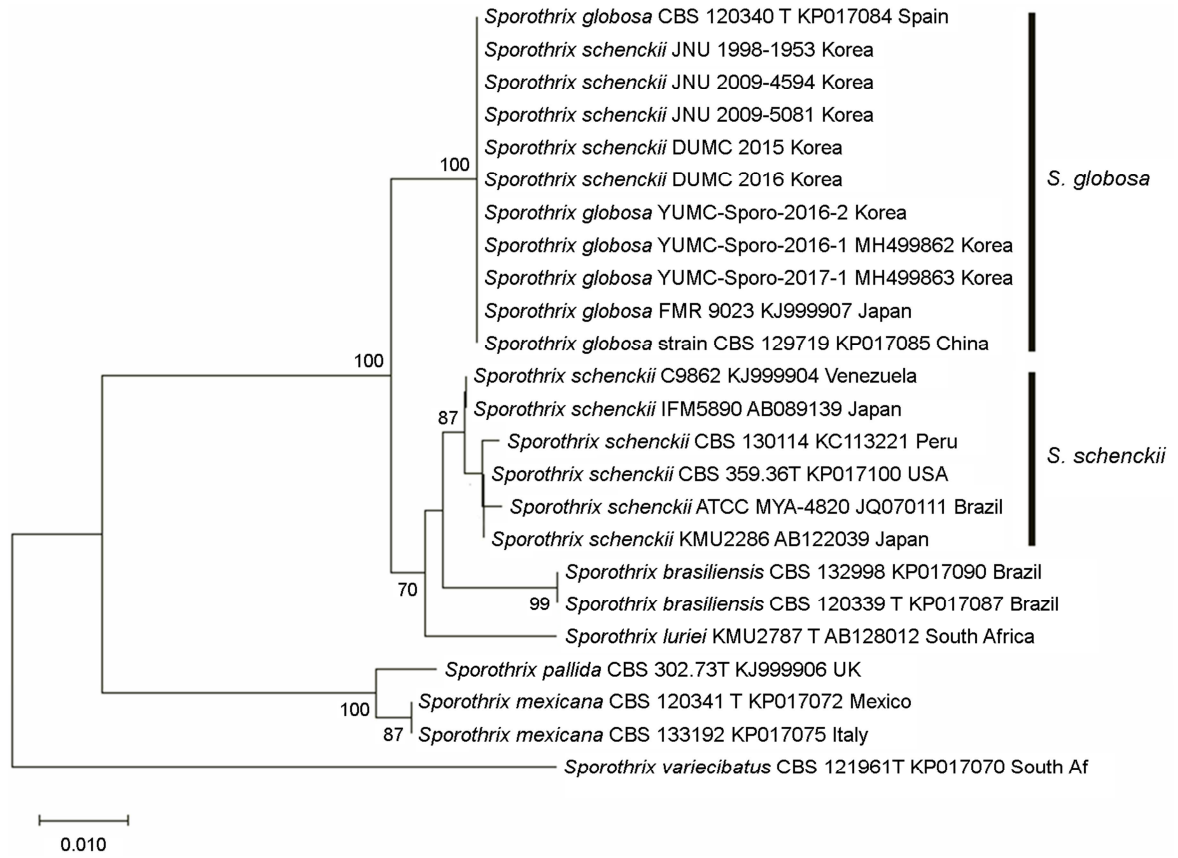


**Fig. 1.** Neighbor-joining tree based on sequences of ITS *Sporothrix schenckii* complex, including Korean isolates. The percentage of replicate trees in which the associated taxa clustered together in the bootstrap test (1,000 replicates) is shown next to the branches[40-43].

compared with those of the the *S. schenckii* complex strains using BLAST®.

### 4. Phylogenetic study

The ITS sequences of the Korean isolates were compared with those of the *S. schenckii* complex strains available in GenBank. Evolutionary history was inferred using the neighbor-joining method in MEGA X[40-43]. Evolutionary distances were computed using the Kimura 2-parameter method. All positions containing gaps and missing data were eliminated (complete deletion option).

## RESULTS

The ribosomal ITS sequence BLAST search revealed that all the five strains initially reported as *S. schenckii* and the three strains of *S. globosa* were 100% identical to *S. globosa*. *S. schenckii sensu stricto* was not detected. The phylogenetic tree of the rDNA ITS sequences showed that six well-defined pathogenic species and all clinical isolates from South Korea were clustered into the *S. globosa* group (Fig. 1).

The mtDNA analysis of eight *S. schenckii* strains isolated from South Korea by Ishizaki et al.[39] in 2004 were identified as being mitochondrial type 4 and 5, which belong to group B (*S. globosa*). Therefore, our molecular identification revealed that all 16 strains of the Korean *S. schenckii* complex actually belonged to *S. globosa*.

## DISCUSSION

Sporotrichosis is a common deep mycosis and was previously considered to be caused solely by the *S. schenckii* complex strains. However, with the decline in the rural population and improvements in mechanized agriculture and personal hygiene due to industrialization, the incidence of sporotrichosis cases has been decreasing[10].

In 2000, *Sporothrix* isolates were classified into 24 mtDNA types (types 1~24) based on RFLP patterns, and Ishizaki et al.[3] classified these types phylogenetically into Groups A (types 1~3, 11, 14~19, 22, and 23) and B (types 4~10, 12, 13, 20, 21, and 24). Later, using molecular analyzes, such as ITS, and markers, such as β-tubulin, chitin synthase, and calmodulin, *S. schenckii* was identified as a species complex comprising the species *S. schenckii sensu stricto*, *S. globosa*, *S. luriei*, *S. brasiliensis*, *S. mexicana*, and *S. pallida*[44]. Analysis of the phenotypic characteristics and molecular identities revealed that *S. schenckii sensu stricto*, *S. globosa*, *S. luriei*, and *S. brasiliensis*, which are grouped into *S. schenckii sensu lato*, show phylogenetic proximity with each other, whereas *S. mexicana* and *S. pallida* are placed in highly remote positions. Furthermore, the phylogenetic tree indicated that *S. mexicana* and *S. pallida* share a common ancestor (Fig. 1)[44].

**Table 3.** Distribution of *Sporothrix* species in East Asia (modified from Moussa et al.[47] and Ishizaki et al.[3])

| Nation | Reported cases | Sequenced isolates (%) | | |
|---|---|---|---|---|
| | | Total | *S. globosa* | *S. schenckii* |
| Japan | 555 | 42 | 41 (97.6) | 1 (2.4) |
| | | 357[3] | 342 (95.8) | 15 (4.2) |
| China | 4,482 | 689 | 685 (99.4) | 4 (0.6) |
| India | 2,983 | 14 | 14 (100) | 0 (0) |
| Korea | 521 | 16 | 16 (100) | 0 (0) |

Zhang et al.[45] reviewed the literature data from Asia-including China, India, and Japan-wherein there were 4,275 reported cases of sporotrichosis, whereas sequenced isolates comprised of only 140 strains. Of those, 139 (99.3%) were classified as *S. globosa*, and only one was identified as *S. schenckii*. In Japan, Ishizaki et al.[3] analyzed 357 *Sporothrix* isolates using RFLP analysis of mtDNA and revealed that most species (342/357) belonged to group B (*S. globosa*) and very few (15/357) belonged to group A (*S. schenckii*). More than 4,000 cases of sporotrichosis were reported throughout most of the Chinese provinces, with the largest number of cases occurring in northeast China[46]. *S. globosa* (685/689, 99.4%) was the most prevalent, and *S. schenckii* (4/689, 0.6%) was very rare in China[47]. In India, sporotrichosis cases have been reported to cluster within the sub-Himalayan region in the northeast states, and the 14 sequenced isolates were all found to be *S. globosa*[46,47]. The number of reported cases and sequenced isolates are listed in Table 3. In Asia, *S. globosa* is the predominant endemic species, whereas *S. schenkii* is extremely rare and S. *brasiliensis* has not been reported[47].

In Korea, prior to 2016, based on morphological studies, *S. schenckii* was reportedly the causative species of sporotrichosis[6-36]. Recent case reports by Kim et al.[37,38] in South Korea revealed three causative organisms to be *S. globosa* by molecular studies. To confirm the causative species of sporotrichosis within South Korea, we collected strains and reviewed the literature[39]. Our study, to some extent, identified sixteen causative species as *S. globosa* using rDNA ITS sequencing and mtDNA types.

*S. globosa* is endemic to Asia, and Moussa et al.[47] suggested a hypothesis of an India-China-Japan belt for *S. globosa* prevalence. Our research supports the statistical probability that *S. globosa* is the predominant species in Korea and that Korea should also be included in this proposed belt[45-47].

The limitations of the current study include the small sample size (16 strains), collection within a short period of time (1998-2018), and the lack of causative species sourced from the environment. Further studies examining more *Sporothrix* strains from fungus collection centers should be conducted. Because sporotrichosis commonly occurs in mammals mostly through "sapronosis" (caused by organisms of the environment rather than a living host) or "zoonosis" (transmitted from animals to humans), there is also a need to investigate and isolate *Sporothrix* spp. from surrounding environments[48]. Studies integrating other human pathogens as well as environmental species should be performed.

To conduct a comprehensive overview of the causative species of sporotrichosis, we need to sequence all the strains that have been reported in Korea. Despite 521 cases being reported in Korea, only eight strains were adequately stored, whereas most of them were discarded. To perform more optimal studies in the future, fungal strains should be collected and stored within well-controlled settings for adequate long-term preservation. Therefore, a collection center that guarantees a state of quality and maintenance of all regulations concerning biosafety is urgently needed in Korea.

In Brazil, *S. brasiliensis* reportedly caused an epidemic zoonosis affecting domestic cats[44]. New causative species, such as *S. braziliensis*, could be imported into Korea due to globalization. Therefore, a range of sporotrichosis infections, particularly those in cats, should be monitored.

In conclusion, as previously considered, *S. schenckii* is not a unique causative species of sporotrichosis in Korea. We identified that the 16 strains of sporotrichosis reported in Korea since 1998 belonged to *S. globosa*. Nowadays, there are several methods available to confirm sporotrichosis species, such as direct morphological examination, fungal culture, and molecular biology diagnosis[44]. Thus, it is critical that we carefully observe and examine samples from *Sporothrix* infections.

## CONFLICT OF INTEREST

In relation to this article, we declare that there is no conflict of interest.

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