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RESEARCH NEWS STORY

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Chiba University

Uncovering the Shield: Gene Duplication Behind Antifungal Resistance in *Madurella fahalii*

Research reveals how an extra gene allows a specific mycetoma-causing fungus to neutralize medication

Mycetoma, a devastating neglected tropical disease, often resists standard treatment with itraconazole when caused by the fungus *Madurella fahalii*. In a recent study, researchers from Japan identified the mechanism behind this resistance: an additional gene encoding a variant of cytochrome P450 14-α sterol demethylase. Using genetic engineering, protein modeling, and computer simulations, the team demonstrated how this second gene reduces treatment effectiveness, guiding the development of future effective therapies.

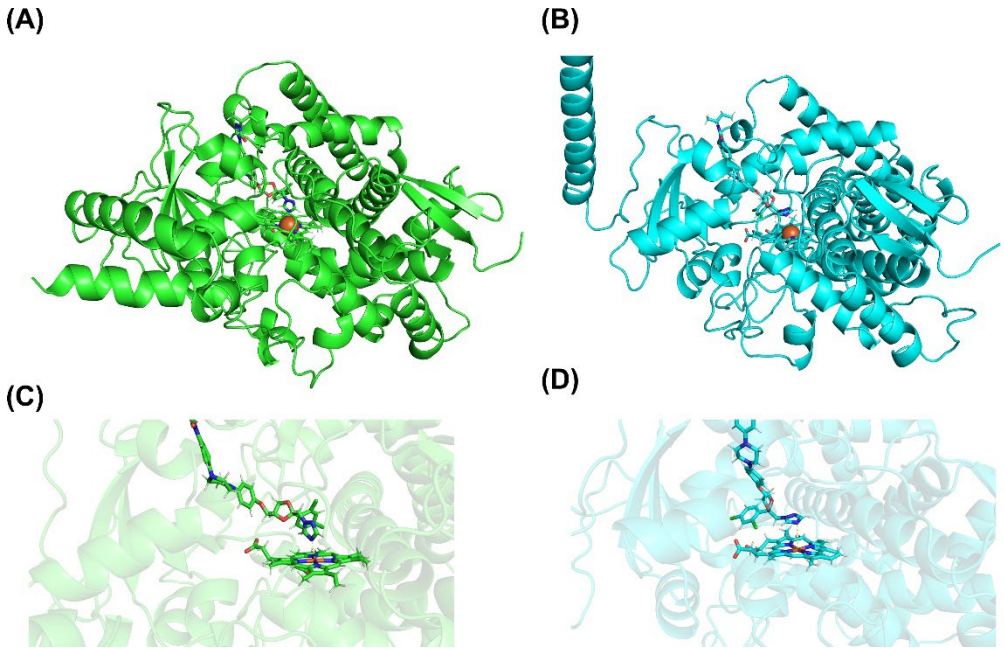

Image title: Key differences in protein structure that result in antifungal resistance
Image caption: Models of the proteins produced by *Madurella fahalii*: CYP51A (A and C) and CYP51A2 (B and D). In each panel, itraconazole and heme are illustrated in a stick representation in the upper and lower parts, respectively. (A) and (B) represent the overall structure of CYP51 proteins. In (C) and (D), the active centers of (A) and (B) were enlarged with their protein backbones made translucent, respectively.
Image credit: Associate Professor Takashi Yaguchi from Chiba University, Japan
Source link: https://journals.plos.org/plosntds/article?id=10.1371/journal.pntd.0012623

Mycetoma is a chronic and progressively debilitating disease that affects thousands of people living in tropical and subtropical regions, particularly those in low-resource settings. Characterized by painful swelling, skin nodules, and pus-discharging sinuses, the condition primarily affects individuals who come into frequent contact with soil, such as agricultural and manual workers. Despite its serious health and socioeconomic consequences, mycetoma has been largely overlooked by global medical research, resulting in limited diagnostic tools and few effective treatment options.

To treat the fungal form of mycetoma, known as eumycetoma, physicians have relied on itraconazole—an antifungal medication that targets a key fungal enzyme. However, cases caused by *Madurella fahalii*, a lesser-known fungal species, have repeatedly shown resistance to this drug, leaving patients with few alternatives. Until recently, the reasons behind this resistance remained poorly understood.

In an effort to address this knowledge gap, a research team led by Associate Professor Takashi Yaguchi from the Medical Mycology Research Center, Chiba University, investigated the molecular mechanisms behind itraconazole resistance in *M. fahalii*. In their latest study, published on March 27, 2025, in *PLOS Neglected Tropical Diseases*, the researchers used advanced genetic and biomolecular chemistry tools to uncover why this well-established treatment fails against *M. fahalii* but not other *Madurella* species. Other members of the research team included Dr. Isato Yoshioka from the Medical Mycology Research Center, Chiba University, Prof. Ahmed Hassan Fahal from Mycetoma Research Center, University of Khartoum, Prof. Satoshi Kaneko from the School of Tropical Medicine and Global Health, Nagasaki University, and Assistant Professor Wei Cao from the Research Institute for Science and Engineering, Waseda University.

Using genome sequencing and genetic engineering techniques, the researchers identified that, unlike its treatable cousin *M. mycetomatis*, *M. fahalii* possesses an additional gene encoding the enzyme cytochrome P450 14-α sterol demethylase (CYP51). This second copy of the *M. fahalii*-specific gene (*Mfcyp51A2*), which encodes the specific target of itraconazole, has key functional and structural differences compared to the gene common with *M. mycetomatis* (*Mfcyp51A1*), effectively neutralizing the drug's impact.

The team confirmed their discovery through multiple approaches. They demonstrated that both copies of the gene become more active when the fungus is exposed to itraconazole, with the unique *Mfcyp51A2* gene showing particularly strong activation—a typical defensive response. When the researchers transplanted these genes into yeast cells for further testing, cells carrying the *Mfcyp51A2* gene were markedly less susceptible to itraconazole compared to those with the standard gene version.

Additionally, computer simulations revealed that while itraconazole can bind to both versions of the enzyme, its interaction with the variant encoded by *Mfcyp51A2* is weaker, explaining why the drug becomes less effective against *M. fahalii* infections. "*This study represents the first report on the physiological characteristics of Madurella species using genetic engineering techniques*," remarks Dr. Yaguchi, "*These findings highlight the potential of molecular techniques in uncovering drug resistance mechanisms in neglected fungal pathogens*."

Overall, this work marks an important step forward in addressing a severe disease that primarily affects impoverished communities. By understanding how drug resistance develops at the molecular level, scientists can now work on targeted approaches to overcome it, bringing hope to thousands of patients worldwide who have limited access to specialized healthcare. "*Our findings will hopefully pave the way for more effective treatment strategies for eumycetoma caused by M. fahalii in the future,*" concludes Dr. Yaguchi, expressing optimism.

As mycetoma continues to pose challenges in regions with limited medical infrastructure, studies like this demonstrate the role of basic science in addressing real-world health problems. By exploring the genetic basis of treatment resistance, researchers are building the foundation for targeted, effective therapies that could benefit thousands worldwide.

About Associate Professor Takashi Yaguchi from Chiba University

Dr. Takashi Yaguchi is an Associate Professor at the Medical Mycology Research Center of Chiba University. He specializes in the collection, preservation, identification, and characterization of fungi that are pathogenic to humans. He has published over 300 papers on these topics. He is also a member of several academic societies, including the Mycological Society of America, the Japanese Society for Medical Mycology, and the Mycological Society of Japan.

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Reference:

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