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A plain language summary of how some fungi samples that show resistance to antifungal medicines have changes in their genes

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Summary

What is this summary about?

Aspergillus fumigatus (shortened to *A. fumigatus*) is a fungus (plural: fungi) that can cause a serious infection in some people. *A. fumigatus* can become resistant to medicines known as azoles (isavuconazole, itraconazole, posaconazole, and voriconazole). This means they stop working and are not able to kill the fungus. Fungi can become resistant through changes in their genes, which are called mutations. Scientists looked at previously collected samples from people infected with *A. fumigatus* and found that 36 of the samples showed resistance to an azole. In 35 of these samples, scientists looked for mutations in 50 genes. These 50 genes are known to play a role in azole resistance and/or are important for fungal survival.

What were the results?

In total, 18 out of 36 samples (50%) showed resistance to isavuconazole only. Of these, 12 had mutations in 4 genes important for fungal survival (called *erg3C*, *erg2*, *erg7B* and *erg4B*). Mutations were found in 2 genes that are the most common causes of azole resistance (called *cyp51A* and *cyp51B*). The most common mutation, called *cyp51A* TR34/L98H, was found in 9 samples. Of these, 8 samples showed resistance to all 4 of the azoles tested.









What do the results of the study mean?

Studying mutations that make fungi resistant to medicines helps to make sure that people with fungal infections get treated with medicines that will work for them.

Who sponsored this study?

This study was sponsored by Pfizer Inc, New York, NY, USA.

How to say (double click sound icon to play sound)...

Aspergillosis: a-sperr-JILL-loe-sis 
Aspergillus fumigatus:
 a-sperr-JILL-uss few-mee-GAH-tuss 
Azole: AH-zole / a-zol 
Triazole: TRY-ah-zole / try-a-zol 
Isavuconazole: eye-za-voo-KON-a-zol 
Itraconazole: ee-tra-KON-a-zol 
Posaconazole: poe-sa-KON-a-zol 
Voriconazole: vo-ree-KON-a-zol 

Who is this article for?

This article may be suitable for healthcare professionals, scientists, and policy makers involved in prescribing and studying treatments for fungal infections. People who receive treatment for fungal infections and their families, caregivers and patient organizations may also find this article useful.

Where can I find the original article on which this summary is based?

You can read the original article, 'Isavuconazole nonwildtype *Aspergillus fumigatus* isolates from a global surveillance study display alterations in multiple genes involved in the ergosterol biosynthesis pathway not previously associated with resistance to other azoles', published in the journal *Mycoses* for a fee at:

<https://onlinelibrary.wiley.com/doi/abs/10.1111/myc.13267>

What is aspergillosis?

Aspergillosis is an infection of the body by the fungus (plural: fungi) *A. fumigatus*.

People who have a higher risk of contracting this serious infection include those with:

- Leukemia
- An organ or bone marrow transplant
- A weak immune system

People with aspergillosis may have shortness of breath, cough, wheezing, fever, or weight loss.

Resistance of *Aspergillus fumigatus* to some medicines

The main treatment for aspergillosis is a group of antifungal medicines called azoles. This group includes isavuconazole, itraconazole, posaconazole and voriconazole.

People with resistant infections have a higher chance of dying. *A. fumigatus* can become resistant to medicines, which means that the azoles are not able to kill the fungus. Fungi can become resistant to medicines through changes in their genes, which are called mutations.

- A gene is the basic unit of information containing the code of a protein. Proteins allow living things to grow and survive, and gives them different features
- Specific genes of *A. fumigatus* are named using letters and numbers. These are often written in italics

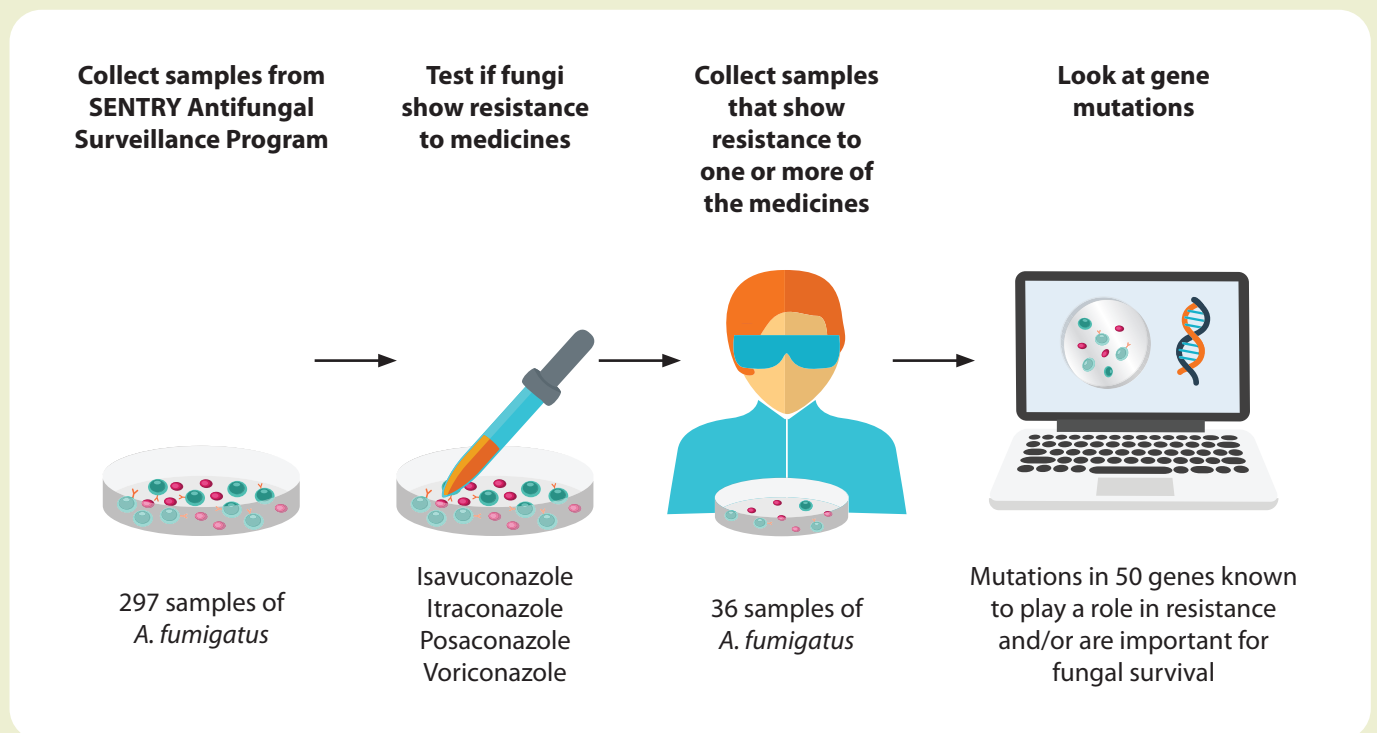
Studies called 'surveillance programs' collect samples from people who have fungal diseases, so scientists can study fungal resistance.

Why and how was the study carried out?

This study was done to identify and understand the genetic mutations in *A. fumigatus* that are involved in azole resistance. The SENTRY Antifungal Surveillance program is a long-running worldwide research project that has collected 297 samples from people infected with *A. fumigatus* from 2017 to 2018. Scientists tested these samples to see if the fungi showed resistance to isavuconazole, itraconazole, posaconazole, or voriconazole.

In total, 36 samples of *A. fumigatus* showed resistance to at least 1 of the azoles.

- In these samples, scientists looked at 50 genes that they know are involved in azole resistance and/or are important for fungal survival
- Scientists could not get gene information for 1 of the 36 samples, so they were only able to look at the genes in 35 samples

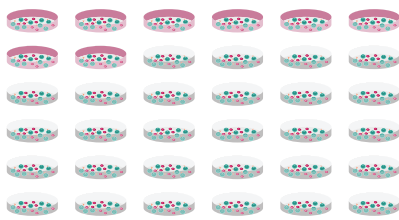


What were the results of the study?

Of the 36 samples, 18 out of 36 (50%) showed resistance to isavuconazole only, 5 out of 36 (14%) to itraconazole only, and 1 out of 36 (3%) to voriconazole only.

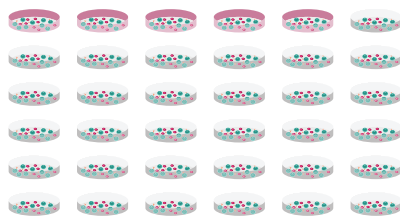
Samples and resistance results

Showed resistance to all 4 azoles



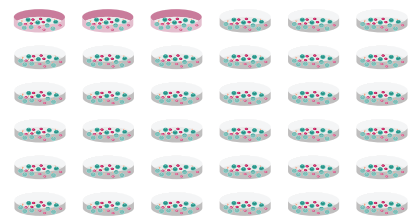
8 out of 36 samples (22%)

Showed resistance to itraconazole only



5 out of 36 samples (14%)

Showed resistance to isavuconazole and itraconazole



3 out of 36 samples (8%)

Showed resistance to isavuconazole only



18 out of 36 samples (50%)

Showed resistance to itraconazole and posaconazole



1 out of 36 samples (3%)

Showed resistance to voriconazole only



1 out of 36 samples (3%)



12 out of 18 (67%) samples were resistant to only isavuconazole, and had mutations in 4 genes that were important for fungal survival

erg3C *erg2* *erg7B* *erg4B*

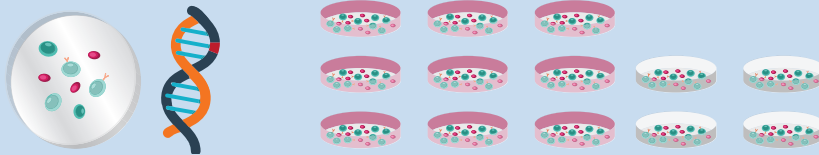


Mutations found in other genes that were important for survival

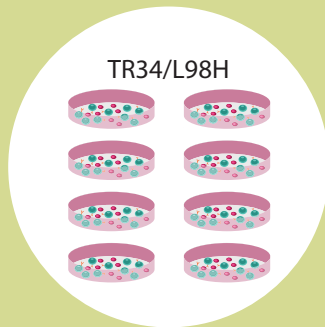
Afu8g06750 or *erg3B*

Mutations were found in 2 genes that are the most common cause of azole resistance (*cyp51A* and *cyp51B*). In total, 13 samples had a mutation in *cyp51A*. They all showed resistance to isavuconazole. The most common mutation (called *cyp51A* TR34/L98H) was found in 9 samples.

Resistance to medicines was found in 13 samples with *cyp51A* mutations.



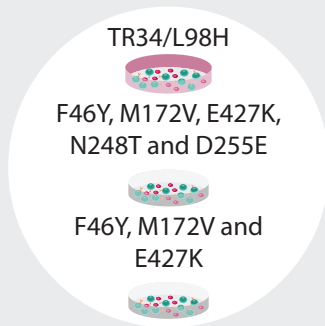
9 out of 13 samples (69%) had the *cyp51A* TR34/L98H mutation.



TR34/L98H

8 samples showed resistance to all 4 azoles:

- Isavuconazole
- Itraconazole
- Posaconazole
- Voriconazole



TR34/L98H

F46Y, M172V, E427K, N248T and D255E

F46Y, M172V and E427K

3 samples showed resistance to isavuconazole and itraconazole, including 1 sample with the TR34/L98H mutation



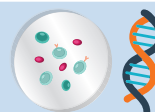
A9T

F46Y, M172V, E427K, N248T and D255E

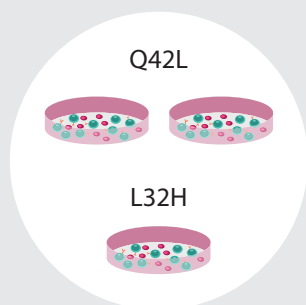
2 samples showed resistance to isavuconazole only, including 1 sample with 1 mutation and the other with 5 mutations

Samples are labeled with the name of the mutation in the *cyp51A* gene identified in each sample.

Resistance to medicines was found in 4 samples with *cyp51B* mutations.



1 sample showed resistance to voriconazole only



3 samples showed resistance to isavuconazole only

Samples are labeled with the name of the mutation in the *cyp51B* gene identified in each sample.

Mutations were also found in other genes important for fungal survival.

- A total of 9 samples had different mutations in a gene called *erg25*

What do the results of the study mean?

Studying fungi and learning about the mutations that make them resistant to medicines is important. This helps make sure that people with fungal infections resistant to the available medicines get treated with medicines that will work for them.

Fungi that showed resistance to only isavuconazole have mutations in several genes that should be studied further. Fungi with mutations in genes called *cyp51A* and *cyp51B* may be resistant to more than 1 azole. This means only some medicines will work in patients with these types of resistant fungi.

The study has certain limitations that should be considered:

- Scientists looked at 50 genes rather than looking at every fungal gene
- Scientists did not do any experiments looking at how the gene mutations may cause resistance
- This summary reports the results of a single study. The results of this study may differ from those of other studies. Healthcare professionals should make treatment decisions based on all available evidence, not on the results of a single study

Where can readers find more information on this study?

The original article titled 'Isavuconazole nonwildtype *Aspergillus fumigatus* isolates from a global surveillance study display alterations in multiple genes involved in the ergosterol biosynthesis pathway not previously associated with resistance to other azoles' was published in *Mycoses*.

The original article citation is: Castanheira *et al.* *Mycoses* 64(10), 1279–1290 (2021).

You can read the abstract of the original article at: <https://doi.org/10.1111/myc.13267>

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Financial & competing interests disclosure

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A full list of the authors' disclosures can be found in the original article.