Fungal Infections Could Be Linked to Genetic Mutations

BY MARY ANN MOON

Genetic mutations that impair dectin-1 function have been tied to susceptibility to fungal infection in two families, according to two separate reports.

In the first study, genetic assessments were performed in a large, consanguineous Iranian family to determine whether a mutated gene was responsible for their nonsyndromic fungal infections, noted Dr. Erik-Oliver Glocker of Royal Free Hospital and University College London and his associates.

The index patient was a 19-year-old man who had had oral candidiasis since the age of 3 years but was otherwise healthy. This patient had a brother with intermittent thrush throughout his childhood and adolescence, and then suddenly died at age 19 of meningitis that proved to be caused by *Candida* species.

The mother of both boys, aged 50 at the time of the study, had had vaginal candidiasis since age 42. Her adult sister also had had oral and vaginal candidiasis since childhood, and their brother had had dermatophytosis since childhood. Both of this man's daughters, who both died suddenly at age 15, were given postmortem diagnoses of invasive candidal meningoencephalitis. Blood samples were obtained for DNA analysis from 36 family members and were compared with those from 50 healthy Iranian blood donors and 180 healthy white donors of other nationalities.

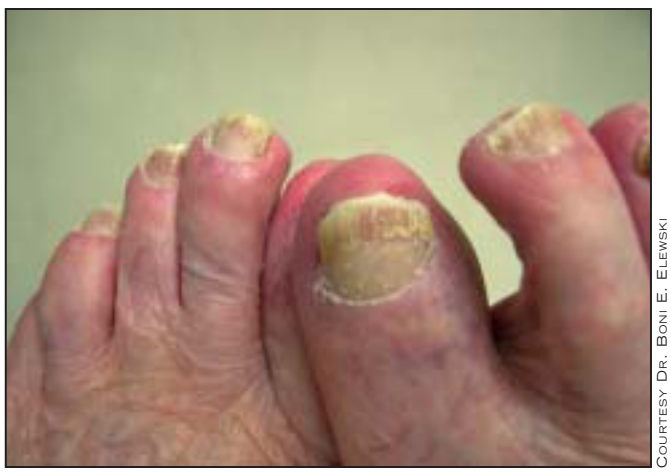
A previously unknown mutation in the CARD9 gene was found in 4 affected patients and 18 other relatives, but not in any of the control samples. The CARD9 gene "plays a central role in antifungal defense by receiving signals from several antifungal pattern-recognition receptors and stimulating proinflammatory responses," the investigators noted.

"Our study shows that a homozygous point mutation in CARD9 … is associated with a susceptibility to fungal infections," Dr. Glocker and his colleagues wrote. The mutation impairs the function of dectin-1, a transmembrane pattern-recognition receptor that senses the beta-glucan component of fungal cell walls (N. Engl. J. Med. 2009;361:1727-35).

In the second study, genetic analyses were performed on mononuclear cells from a patient with recurrent vulvovaginal and oral or esophageal candidiasis, as well as on cells from four relatives. The patient's two sisters had chronic onychomycosis; one of them also had recurrent vulvovaginal candidiasis. Their mother had chronic onychomycosis, and their father had transient onychomycosis.

The index patient had been found to have defective cytokine production in response to stimulation with *C. albicans* and with beta-glucan, indicating a potential defect in dectin-1 recognition, according to Bart Ferwerda, Ph.D., of Radboud University, Nijmegen, the Netherlands, and his associates.

The researchers identified a homozygous mutation that caused defective surface expression of dectin-1. This apparently caused an impaired cytokine response by monocytes and macrophages but did not affect the normal killing of *C. albicans* by neutrophils (N. Engl. J. Med. 2009;361:1760-7). Neither Dr. Glocker nor Dr. Ferwerda reported any financial conflicts of interest. ■



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Fungal infections, such as onychomycosis, have been traced back to genetic mutations found in families.