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Prevalence of Candida glabrata strains carrying transcription factor pdr1 mutations and mismatch repair gene msh2 mutations in bloodstream isolates from seven hospitals in Korea

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Background: Azole Resistance in *Candida glabrata* arises most commonly through overexpression of drug efflux pumps, which is achieved through a gain-of-function mutation of the transcription factor Pdr1. A recent report has shown that mutations in the mismatch repair gene (*MSH2*) may promote the acquisition of resistance to multiple antifungals. We investigated the prevalence of strains carrying Pdr1 and Msh2 mutations among bloodstream isolates of *C. glabrata* from Korean hospitals, and compared the results according to fluconazole resistance or multilocus sequence typing (MLST) genotypes.

Material/methods: A total of 108 *C*. *glabrata* bloodstream isolates were collected from seven hospitals from January to December 2014. *In vitro* antifungal susceptibility testing was performed using the broth microdilution method according to the CLSI M27-A. The isolates were genotyped using an MLST scheme of the internal regions of six housekeeping genes. *PDR1* genes were sequenced for all 108 isolates, and *MSH2* genes were sequenced for all fluconazole-resistant (FR) isolates, in addition to 92 fluconazole susceptible-dose dependent (FS) isolates.

Results: Of all 108 isolates, 11 (10.1%) were FR (MIC ≥ 64 μg/mL) and were also non-wild type for voriconazole (MIC ≥ 1 μg/mL). All isolates were susceptible to caspofungin and micafungin. Based on MLST, a total of 19 unique STs were identified in the 108 *C*. *glabrata* BSI isolates. Of these, ST 7 (52 isolates, 48.1%) was the most common type, followed by ST3 (28 isolates, 25.9%), ST22 (6 isolates, 5.6%), and ST10 (4 isolates, 3.7%). Of the 11 FR isolates, 6 were ST7, 4 were ST3, and 1 was ST55. All 11 FR isolates showed unique Pdr1 mutations (100%), while 97 FS isolates did not show any Pdr1 mutation (0%). Nonsynonymous mutations within *MSH2* were observed in 54.5% (6/11) of FR isolates and 69.5% (64/92) of FS isolates tested. Of all FR isolates, six ST7 isolates showed the same V239L mutation in Msh2, while the remaining five isolates did not show any Msh2 mutations. Of FS isolates tested, all 49 ST7 isolates showed the same V239L mutation in Msh2, all six ST 22 isolates showed the same E456D mutations, and all four ST10 isolates showed the same P208S mutation, while only 11.1% (3/27) of ST3 isolates showed nonsynonymous mutations.

Conclusions: Among Korean *C*. *glabrata* bloodstream isolates, ST7 and ST3 are the most common genotypes and FR isolates are also found among these two predominant genotypes. Pdr1 mutations are associated with acquisition of FR in *C*. *glabrata* isolates, while Msh2 mutations may occur depending on their genotypes, irrespective of FR.