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Notably increasing trend in azole-resistant Candida tropicalis in China (Aug. 2009 to July 2014): drug resistance mechanisms, molecular epidemiology and clinical azole consumption

Xin Fan*[1], Meng Xiao[1], He Wang[1], Yingchun Xu[2]

[1]*Peking Union Medical College Hospital; Department of Clinical Laboratory*

[2]*Peking Union Medical College Hospital*

Background: *C. tropicalis* is an important pathogen causing invasive candidiasis (IC). Furthermore, resistance to azoles, particularly to fluconazole, is increasingly being reported in this pathogen. To bring awareness to our domestic and international colleagues, we hereby explore the resistance mechanisms, molecular epidemiology, and any relationship between clinical azole consumption and increased resistance rate.

Material/methods: Between August 2009 and July 2014, non-duplicated 507 *C. tropicalis* isolates causing IC were collected from ten hospitals in China. The full-length *ERG11* gene of all clinical isolates studied were amplified and sequenced and aligned with reference wild-type *ERG11* gene sequence from *C. tropicalis* MYA-3404 (GenBank accession no. XM_002550939.1).A high discriminatory three-loci (ctm1, ctm3 and ctm24) microsatellite scheme was used for typing of all isolates collected. Clinical consumption of fluconazole and voriconazole was obtained and the Defined Daily Dose (DDD) measurement units were assigned to the data. The DDD per 100 patient-days in hospitals was used to measure time trends.

Results: Overall, 23.1% and 20.7% of isolates were non-susceptible to fluconazole and voriconazole, respectively. Two key mutations of the ERG11 gene were found, namely A395T and C461T, which resulted in amino acid substitution Y132F and S154F, respectively. Of the 65 fluconazole resistant isolates, these nucleotide mutations was detected in 83.1% (n=54) of the fluconazole-resistant isolates. All fluconazole susceptible and susceptible dose-dependent isolates carried wild-type ERG11 gene (Table 1). By using the three loci microsatellite scheme, 296 genotypes were identified amongst

the 507 isolates studied (Figure 1A). Four genotype clusters were observed to be associated with fluconazole non-susceptible phenotype. (Figures 1A-1E). The use of voriconazole was generally stable over five years. However, the use of fluconazole increased in the first three years, but decreased in the last two years. There was no significant correlation between the use of fluconazole or voriconazole and prevalence of azole non-susceptible isolates analysed by year (P>0.05).

Conclusions: Our findings show an unusual high-level of fluconazole and voriconazole resistance. Nucleotide mutations A395T and C461T in the ERG11 gene was the primary mechanism for azole-resistance. Continuous surveillance and molecular epidemiology study is still warranted, and if the trend persists, empirical therapeutic strategies for C. tropicalis invasive infections should be modified.

Table 1. Mutations in *ERG11* gene and fluconazole susceptible phenotypes amongst 507 *C. tropicalis* isolates

Nucleotide at sequence position		**Wild-type/non-wild-type sequences**	**No. of isolates**
359	**461**		
Fluconazole susceptible isolates (n=390)			
A	C	Wild-type	390
Fluconazole susceptible dose-dependent isolates (n=52)			
A	C	Wild-type	52
Fluconazole resistant isolates (n=65)			
A	C	Wild-type	11
T	T	Non-wild-type	35
W	Y	Non-wild-type	15
T	C	Non-wild-type	3
W	C	Non-wild-type	1

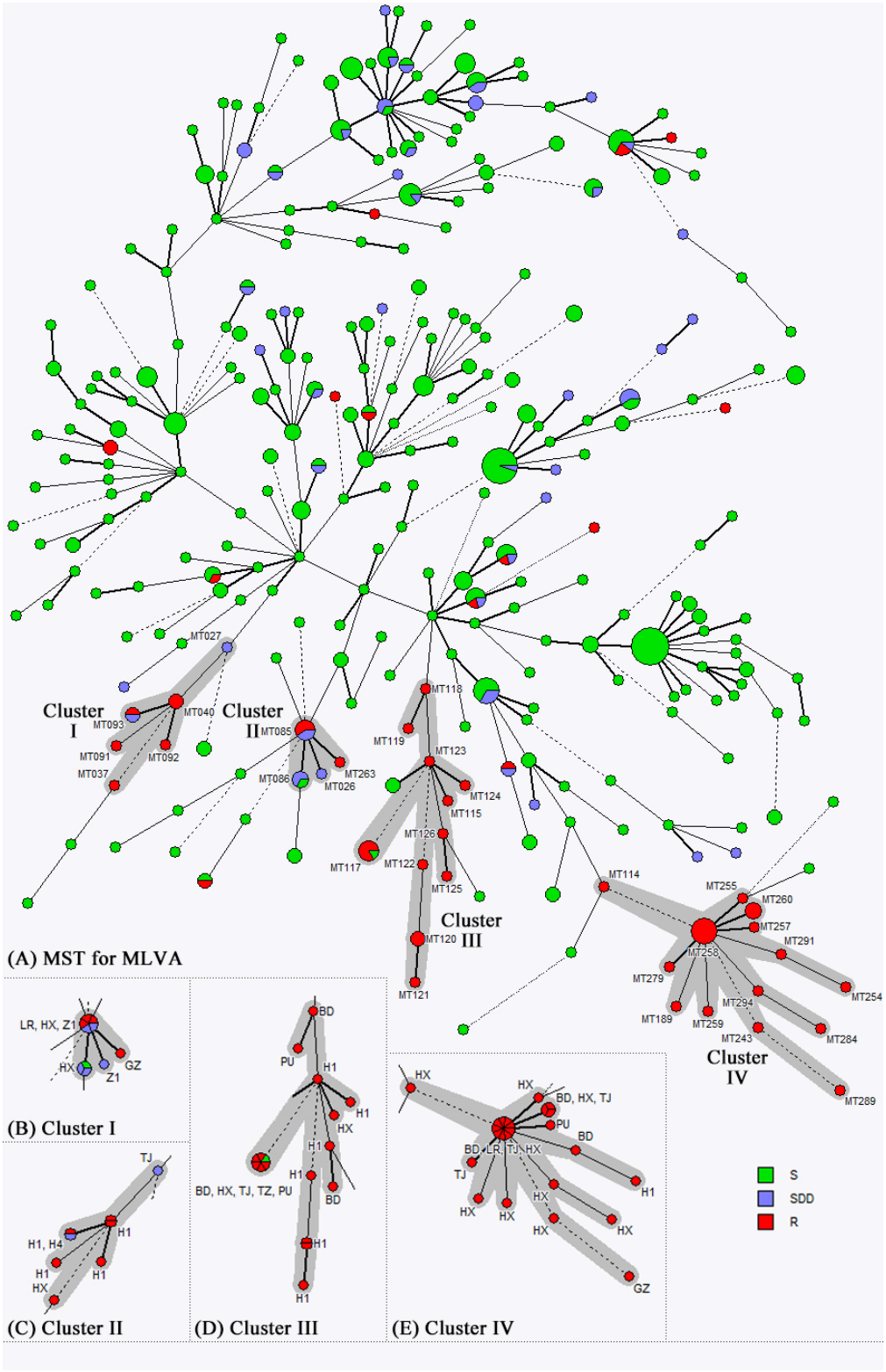

Figure 1. The minimum spanning tree (MST) draw by three-locus microsatellite genotyping results of 507 *C. tropicalis* isolates.