Objective: Candida auris is a multi-drug-resistant pathogen that poses a serious global threat to human health. The US Centers for Disease Control and Prevention has classified C. auris as an emerging threat to public health due to its clinical and economic impact and future projections of new infections over the next 10 years. Candida auris infections are difficult to treat since many isolates display high levels of resistance to fluconazole and exhibit variable resistance to amphotericin B and echinocandins. In this study, we performed comparative transcriptomics to understand the molecular mechanisms associated with azole resistance in C. auris environmental isolates.

Material and Methods: Two sets of environmental isolates including azole-resistant (n=2) and azole-susceptible (n=2) isolates were used for RNA-seq analysis. Pair-wise comparisons in edgeR were performed to compute the differentially expressed genes (DEGs) between the azole susceptible and resistant isolates. GO term enrichment analysis was performed using the ‘enrichGo’ function from the clusterProfiler package. Only GO categories with a q-value <0.05 were considered significant.

Results: Our data show significant enrichment of several functional categories, drug transport, MAPK pathway, as well as transcriptional reprogramming in azole-resistant strains compared to susceptible isolates. A total of 464 and 544 differentially expressed genes were identified in two azole-resistant isolates compared with the susceptible strain. A large number of multidrug transporter genes (CDR1, MDRI, HGT2, HGT7, HGT13, HGT1, and NAT) were differentially expressed between the two sets of genes. Interestingly, the average MIC for azole resistant C. auris isolates (ERG11) was observed in resistant isolates as compared with susceptible strain. Furthermore, resistant strain has two copies of ERG11 while susceptible isolate has only single copy of ERG11. Notably, MDG1 genes involved in the ergosterol biosynthesis pathway were found to be induced in azole-resistant isolates. These include HMG1, ERG1, ERG2, ERG6, ERG7, ERG9, ERG13, and ERG15. Furthermore, other multidrug transporters MDRI and SNQ2 responsible for azole resistance in other Candida species like C. glabrata also showed significant expression changes between the two sets of isolates. Furthermore, MDRI (glucose transporter) and NAT1 (N-acetyl-beta-D-glucosamine transporter) genes associated with azole and polypeptide resistance were found to be upregulated in the resistant isolate as compared with susceptible strain. Additionally, a Glycosylphosphatidylinositol (GPI)-anchored protein unique for C. auris, PIGQ was found to be overexpressed in resistant isolate. Importantly, we also identified several secreted aperoxide proteases (SAP1, SAP2, SAP3, and SAP4) to be downregulated between the two sets.

Conclusion: The present study identifies several gene families that are differentially expressed in azole resistant vs susceptible C. auris strains. These findings suggest that azole resistance in C. auris environmental isolates is influenced by changes in cell wall, lipid, and ergosterol biosynthesis. Overall, these data provide a framework for the mechanistic understanding of azole resistance mechanisms in C. auris environmental isolates.