

Evolutionary Perspective of Fungal Pathogenic Genes

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ABSTRACT

Fungal pathogenesis has been vastly investigated in recent years and the phylogenetic studies of fungal genome reveal that unique genes are responsible for pathogenesis. It has been found that the pathogenesis is caused by genes responsible for DNA repair, vegetative growth and sporulation. In the recent past, studies on filamentous pathogenic fungi playing an important role in establishing a pathogenic relationship with the host was well described.

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1. INTRODUCTION

Fungal pathogenesis has steadfastly progressed in recent years and phylogenetic studies reveal that unique genes are responsible for pathogenesis (Schafer, 1994). Several genes are involved in DNA repair, vegetative growth and sporulation which further augment the role of pathogenesis. In the recent past, studies on filamentous pathogenic fungi playing an important role in establishing a pathogenic relationship with the host was well described (Cao Y et al. 2012). The effect on growth conditions in budding yeast and *Candida albicans* are known to be highly similar and so these characteristic features are shared between pathogenic and non-pathogenic fungi (Gary et al., 2011). Many existing programs for automated gene prediction and annotation are not perfect and need to be improved which would allow us to better predict the pathogenesis in fungi. Follow-up of manual annotation is necessary to improve the accuracy of automated annotation especially for the proteins specific to fungal pathogenesis. With recent studies on the interactions of the proteins reveal pathogenic pathways specific to cancer in human, there is a hope that identifying better functional candidates are needed. With Invasive fungal infections (IFI) most often seen and studied in immunocompromised patients, there is a major cause of morbidity and mortality. However, there still remains much uncertainty and controversy regarding the best methods for establishing the diagnosis of these infections (Ascioglu S et al 2002). The development of new tools in molecular biology in the recent years and narrowing down to whole genome sequences has revolutionized research on pathogenic fungi. The computational approaches to study the fungal genome have further promoted to identify and compare the pathogenic factors which afflict human health (Tierney L et al 2012). Such advances have led to characterization of pathogenic agents pinpointing at the genomic level so that underlying mechanism of pathogenesis could be well comprehended. A comprehensive fungal genome database similar to yeast (<http://www.yeastgenome.org>) would overcome the limitation of searching umpteen proteins through redundant databases. Several diverse virulent factors like DNA repair proteins, metabolic proteins, cancer proteins, GSTs (Glutathione S-transferases), sporulation proteins, vegetative

growth proteins that holds a potential cause human fungal diseases have been existing which we have annotated. To complement this, we have earlier addressed evolutionary and phylogenetic questions in closely related pathogenic fungi using a compendium of database of pathogenic genes and interactions of those proteins implicated in fungal pathogenesis ~ Fungome (Gudimella R et al. 2010). The web-server is to be renewed and established to study if a candidate falls in the pathogenic fungi and its line of evolution (<http://www.bioclues.org/fungome/>). We complement the use of such webserver to predict its extent of pathogenicity if a protein is extracted as a query. Our annotation was examined to identify candidate genes involved in host range determination, infection-related morphogenesis, and virulence. Such open source repository of all fungal pathogenic proteins we believe, would allow the researchers to focus on functional characterization of candidate genes specific to fungal pathogenesis. We also showed that the fungome integrates genes specific to human cancers across diverse strains by elucidating the functionality and sub-cellular localization of selected proteins related to signaling cascades to understand a particular disease. For example, characterization of proteins involved in the fungi from putative or hypothetical function to some known function can be introduced to study such candidates in details. Here we discuss couple of case studies:

1.1 Case:1

What makes nonpathogenic fungi anchor some genes present in pathogenic fungi? (Gary et al., 2011). All DNA repair genes Msh6, Msh3, msh2, Msh1, Msh5 were shown to have motifs, DNA binding regions and chains that are known to have more conservation when compared to Baker's yeast and other non-pathogenic fungi. However phylogram analysis shows divergence (fig 1 a-c). Although other genes like GST, MAPK, and BRCT are identified as pathogenic genes, the latter doesn't have much similarity with non-pathogenic fungi. The relations shown in the figures concur with motifs and as most recurring residues in multiple sequence alignment. This may be purely a phylogenetic change shown while anchoring those genes. These relations also clarify the way non-pathogenic and pathogenic fungi share genes and hereafter these may change during the fungal survival in various conditions, making them as pathogenic.

1.2 Case:2

Are any of these pathogenic genes essential? Does a nonpathogenic fungus undergo pathogenesis during evolution? Yes, genes like DNA repair and vegetative are more essential in any type of fungi showing the relativity while some budding yeast and candida albicans are known to show great similarity in almost all types of genes. Hyphae development and sporulation are most important characteristic features of fungi which are shared between pathogenic and non-pathogenic. Pathogenic fungi like *Cryptococcus neoformans* change its morphology from normal yeast like to pseudohyphal morphology (a less virulent form) by accumulating mutations in genes involved in RAM/MOR pathway which are additionally needed for morphogenesis and regress to normal yeast by counter mutation (Magditch DA et al., 2012). While interactions existing within these organisms are involved in activities of pathogenic proteins, we would ask if there are any non-essential genes of non-pathogenic bacteria showing counterparts sitting in pathogenic bacteria. Our current results may not conclude this but we believe some non-essential genes would be sitting as counterparts in pathogenic bacteria. We hope our webserver would match the annotation.

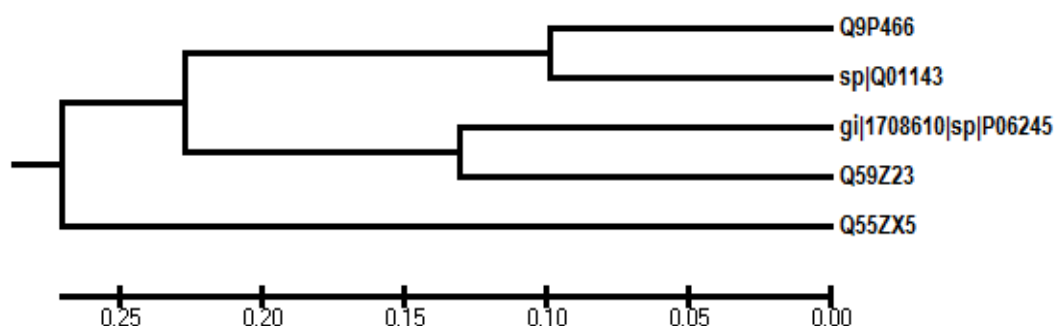


Figure 1. cAMP dependent protein kinase with non-pathogenic fungi

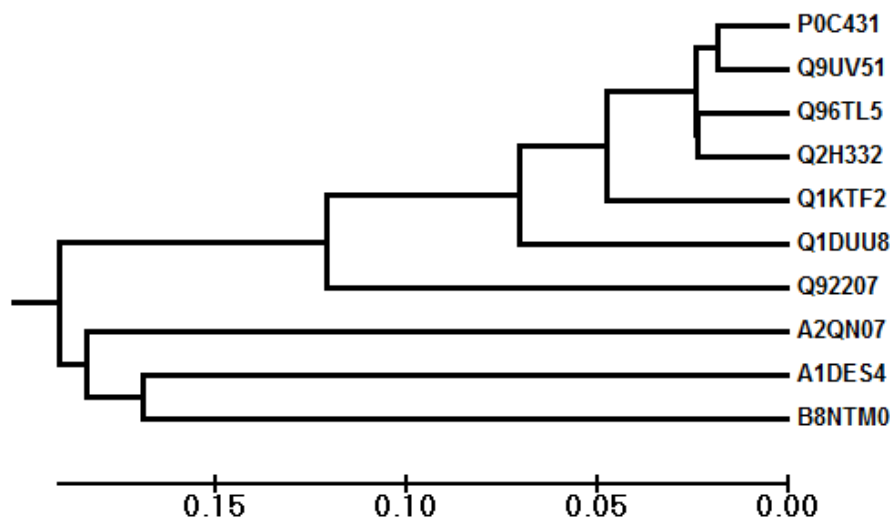


Figure 2. MAPK in pathogenic fungi (no non-pathogenic fungi hits)

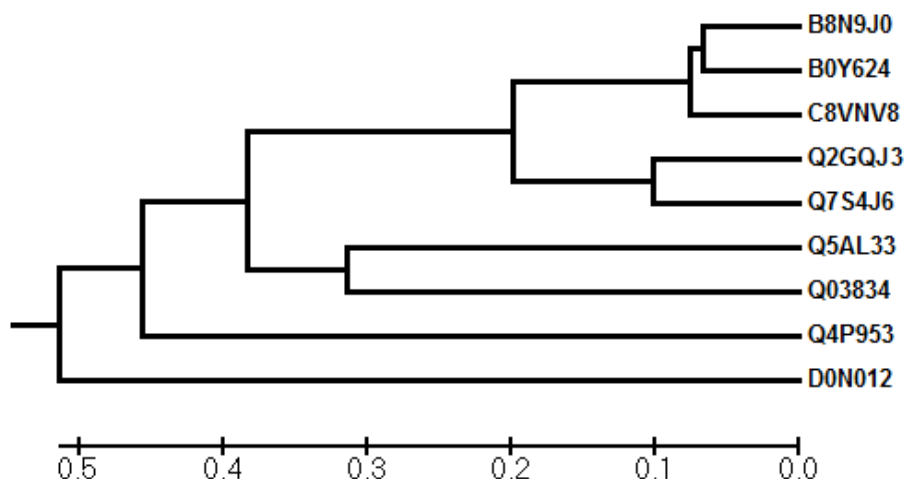


Figure 3. MSH6 relation with non-pathogenesis

2. FUTURE DIRECTION

The study of fungal pathogenesis is complex and rapidly evolving. Because Fungi have evolved through several specific evolutionary mechanisms here describe a few evolutionary mechanisms and properties of the non-pathogenic genes undergoing pathogenesis during evolution, it is equally important to understand any fungal infection. This information will have great promise of providing rapid and in depth understanding about host pathogen interactions in the way responsible for pathogenesis. This would also allow us to validate specific genes in wet lab aiming to develop a rapid diagnostic kit which can detect early stage of infections.

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