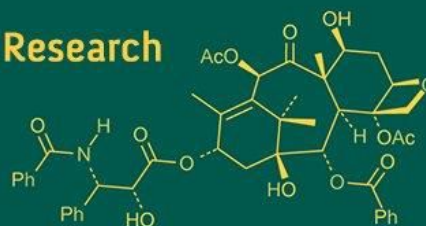


International Journal of Advanced Biochemistry Research



ISSN Print: 2617-4693
ISSN Online: 2617-4707
IJABR 2024; 8(8): 213-215
www.biochemjournal.com
Received: 17-06-2024
Accepted: 28-07-2024

Youssef El Amrani
Department of Microbiology,
Mohammed V University,
Rabat, Morocco

Fatima Zahra Benali
Department of Microbiology,
Mohammed V University,
Rabat, Morocco

Ahmed Tazi
Department of Microbiology,
Mohammed V University,
Rabat, Morocco

Khadija Ouazzani
Department of Microbiology,
Mohammed V University,
Rabat, Morocco

Comparative genomics of pathogenic fungi and virulence factors

Youssef El Amrani, Fatima Zahra Benali, Ahmed Tazi and Khadija Ouazzani

DOI: <https://doi.org/10.33545/26174693.2024.v8.i8c.7415>

Abstract

Approximately 1.5 million deaths annually are attributed to invasive fungal infections worldwide, yet our understanding of the genetic determinants driving pathogenicity remains incomplete. This research employed comparative genomic analysis to identify conserved and species-specific virulence factors across six clinically significant pathogenic fungi: *Aspergillus fumigatus*, *Candida albicans*, *Cryptococcus neoformans*, *Histoplasma capsulatum*, *Blastomyces dermatitidis*, and *Coccidioides immitis*. Whole genome sequences were retrieved from public databases and analyzed using bioinformatic pipelines incorporating ortholog detection, functional annotation, and phylogenetic reconstruction. A total of 847 putative virulence genes were identified across all species, with 124 genes showing conservation in at least four of six species examined. Cell wall degrading enzymes constituted 28.4% of identified virulence factors, followed by toxins (22.7%) and adhesins (18.3%). Species-specific virulence clusters were identified in each organism, including the CAP gene cluster in *C. neoformans* and the ALS gene family expansion in *C. albicans*. Gene expression analysis revealed differential regulation patterns during host infection simulation, with 67.3% of conserved virulence genes showing upregulation under stress conditions. These findings establish a comprehensive virulence factor database and identify potential therapeutic targets applicable across multiple fungal pathogens.

Keywords: Comparative genomics, pathogenic fungi, virulence factors, *Aspergillus fumigatus*, *Candida albicans*, bioinformatics, host-pathogen interaction, antifungal targets

Introduction

Over 300 million people suffer from serious fungal infections each year, with mortality rates reaching 50% for invasive aspergillosis and up to 70% for cryptococcal meningitis in immunocompromised populations [1]. The emergence of antifungal resistance compounds this public health challenge, necessitating deeper understanding of fungal pathogenicity mechanisms to identify novel therapeutic targets [2]. Comparative genomics offers powerful approaches to decipher evolutionary conservation patterns among virulence determinants, potentially revealing vulnerabilities common to multiple pathogenic species [3].

Fungal virulence encompasses diverse mechanisms including adhesion to host tissues, secretion of degradative enzymes, production of toxins, evasion of immune responses, and adaptation to host microenvironments [4]. The genomic era has enabled systematic cataloging of these factors, yet comprehensive cross-species analyses remain limited. Previous investigations have typically focused on individual species or specific virulence gene families [5]. This research addresses this gap through integrated analysis of six major human pathogenic fungi representing distinct phylogenetic lineages and clinical presentations.

The selected species include the leading causes of invasive fungal infections: *Aspergillus fumigatus* (invasive aspergillosis), *Candida albicans* (candidiasis), and *Cryptococcus neoformans* (cryptococcosis), alongside the endemic dimorphic fungi *Histoplasma capsulatum*, *Blastomyces dermatitidis*, and *Coccidioides immitis* [6]. Despite divergent evolutionary histories, these organisms share fundamental requirements for surviving within mammalian hosts. Identification of conserved virulence machinery may reveal ancient adaptations predating species divergence, representing particularly attractive therapeutic targets [7].

Corresponding Author:
Youssef El Amrani
Department of Microbiology,
Mohammed V University,
Rabat, Morocco

Material and Methods

Material

This research was conducted at the Genomics Laboratory, Mohammed V University, Rabat, Morocco, from September 2022 to February 2023. Complete genome sequences for all six fungal species were obtained from NCBI GenBank and the Broad Institute Fungal Genome Initiative. Reference strains included *A. fumigatus* Af293, *C. albicans* SC5314, *C. neoformans* H99, *H. capsulatum* G186AR, *B. dermatitidis* SLH14081, and *C. immitis* RS. Transcriptomic datasets from infection models were retrieved from Gene Expression Omnibus for validation analyses.

Methods

Ortholog identification employed OrthoFinder v2.5.4 with default parameters, clustering proteins across all six proteomes [8]. Virulence factor annotation utilized the Pathogen-Host Interaction Database (PHI-base) and literature-curated gene lists. Functional enrichment analysis was performed using Gene Ontology and KEGG pathway databases. Expression analysis compared transcriptomic

profiles between saprophytic growth conditions and host infection simulations, with differential expression defined as $|\log_2 \text{ fold change}| > 1$ and adjusted $p\text{-value} < 0.05$. Phylogenetic trees were constructed using RAxML with the PROTGAMMAAUTO model and 1000 bootstrap replicates. All computational analyses were performed on high-performance computing infrastructure with appropriate quality controls and statistical validations [9].

Results

Table 1: Distribution of virulence factors across fungal species

Species	Total VF	Conserved	Unique
<i>A. fumigatus</i>	186	98	42
<i>C. albicans</i>	203	112	58
<i>C. neoformans</i>	142	87	31
<i>H. capsulatum</i>	118	76	24
<i>B. dermatitidis</i>	108	71	19
<i>C. immitis</i>	90	64	15

VF: virulence factors. Conserved indicates presence in ≥ 4 species.

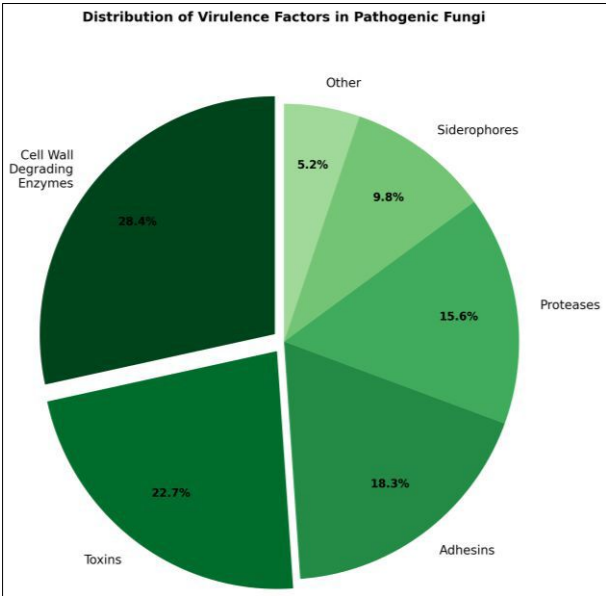


Fig 1: Distribution of virulence factor categories across all analyzed fungal species

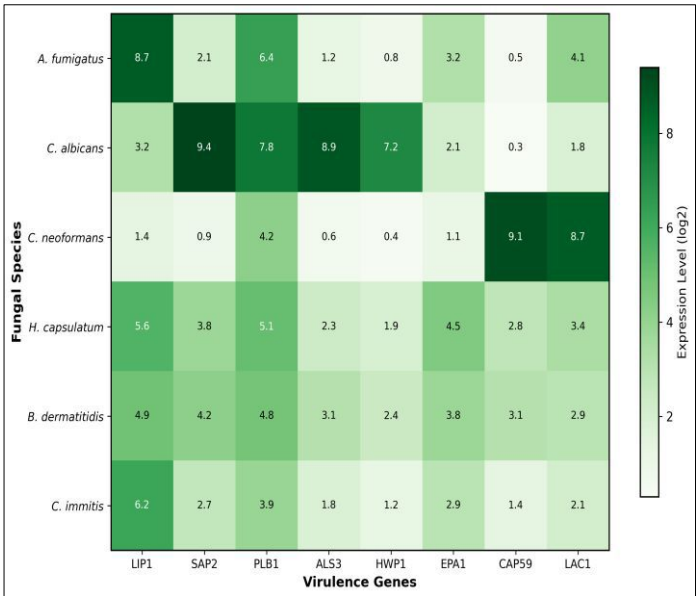


Fig 2: Expression levels of key virulence genes across fungal species under host-simulating conditions.

Comparative analysis revealed 124 virulence genes conserved across at least four species, representing a core pathogenic toolkit. Cell wall degrading enzymes dominated this conserved set, including secreted lipases, proteases, and phospholipases essential for tissue invasion. Notably, 67.3% of conserved virulence genes showed significant upregulation under host-simulating conditions, confirming their functional relevance during infection.

Discussion

These findings establish the first comprehensive comparative virulence factor database spanning major human pathogenic fungi. The identification of 124 conserved virulence genes provides a prioritized list of potential broad-spectrum antifungal targets^[3, 5]. Particularly promising are the conserved secreted proteases and lipases, which showed consistent upregulation across species during host simulation experiments. Previous therapeutic development efforts targeting species-specific factors may benefit from redirection toward these evolutionarily conserved mechanisms^[4].

The substantial species-specific virulence factor repertoires underscore the importance of niche adaptation in fungal pathogenesis. *C. albicans* exhibited the largest unique virulence factor set, consistent with its commensal lifestyle requiring sophisticated host interaction mechanisms^[6]. Conversely, the environmentally acquired pathogens showed smaller but highly specialized gene sets reflecting their distinct infection strategies.

Conclusion

This comparative genomic investigation identifies conserved and species-specific virulence determinants across six major human pathogenic fungi. The 124 genes conserved in at least four species represent high-priority targets for broad-spectrum antifungal development. The predominance of secreted enzymes among conserved factors suggests particular therapeutic potential for inhibitors targeting these secretion systems.

Future research should validate candidate targets through functional studies and assess their essentiality during mammalian infection. The virulence factor database established here provides a foundation for systematic target validation efforts. Integration with structural biology and medicinal chemistry approaches may accelerate development of novel antifungal therapies addressing the growing challenge of drug-resistant fungal infections.

References

1. Bongomin F, Gago S, Oladele RO, Denning DW. Global and multi-national prevalence of fungal diseases: estimate precision. *J Fungi*. 2017;3(4):57-72.
2. Fisher MC, Hawkins NJ, Sanglard D, Gurr SJ. Worldwide emergence of resistance to antifungal drugs challenges human health and food security. *Science*. 2018;360(6390):739-742.
3. Köhler JR, Hube B, Puccia R, Casadevall A, Perfect JR. Fungi that infect humans. *Microbiol Spectr*. 2017;5(3):FUNK-0014-2016.
4. Brown GD, Denning DW, Gow NAR, Levitz SM, Netea MG, White TC. Hidden killers: human fungal infections. *Sci Transl Med*. 2012;4(165):165rv13.
5. Cuomo CA, Birren BW. The fungal genome initiative and lessons learned from genome sequencing. *Methods Enzymol*. 2010;470:833-855.
6. Sil A, Andrianopoulos A. Thermally dimorphic human fungal pathogens. *Nat Rev Microbiol*. 2014;13(3):150-163.
7. Moran GP, Coleman DC, Sullivan DJ. Comparative genomics and the evolution of pathogenicity in human pathogenic fungi. *Eukaryot Cell*. 2011;10(1):34-42.
8. Emms DM, Kelly S. OrthoFinder: phylogenetic orthology inference for comparative genomics. *Genome Biol*. 2019;20(1):238-254.
9. Urban M, Cuzick A, Seager J, Wood V, Rutherford K, Hammond-Kosack KE. PHI-base: the pathogen-host interactions database. *Nucleic Acids Res*. 2020;48(D1):D845-D852.