RESEARCH ARTICLE
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Integrative Protein–Protein Interaction Network Analysis and Druggability Assessment of the *Candidozyma auris* Proteome for Novel Drug Target Identification

ABSTRACT

Background: In pathogenic fungi, protein–protein interaction (PPI) analysis has high potential to identify proteins central to virulence and adaptation, which is particularly important for *Candidozyma auris*, a multidrug-resistant pathogen with high mortality, underscoring the urgent need for novel antifungal targets.

Methods: The *C. auris* proteome was retrieved from the STRING database to construct a PPI network. Proteins were ranked based on topological metrics including degree, betweenness centrality, closeness centrality, and eccentricity. The top 100 proteins were further filtered for non-homology to human and gut microbiome proteins. Essentiality was assessed via homologs in *C. albicans*, and proteins longer than 200 amino acids were evaluated for druggability using 3D structures through CavityPlus.

Results: The PPI network comprised 4214 nodes and 86 872 edges, exhibiting small-world properties and organized modular subnetworks. Analysis of the top 100 proteins showed a wide range of betweenness centrality, closeness centrality, and eccentricity, with divergent amino acid lengths. Subcellular localization was determined for 53% of the proteins. After filtering for non-homology and length, 15 novel proteins were prioritized for druggability, of which 3 (A0A2H0ZDG1, A0A2H0ZLN5, and A0A2H0ZVI9) were predicted as druggable based on available 3D structures. None of the selected proteins were essential according to *C. albicans* homologs. These results demonstrate that combining PPI topology, homology, and structural criteria can effectively narrow down potential antifungal targets.

Conclusion: Integrating PPI network analysis with homology filtering and 3D druggability assessment effectively identifies potential antifungal targets in *C. auris*. Nevertheless, the accuracy of such predictions highly depends on database completeness and interaction reliability.

Keywords: ***Candidozyma auris***, drug-target prediction, PPI network analyze

What is already known on this topic?

- Protein–protein interaction (PPI) networks are widely used to identify central or influential proteins that may serve as potential drug targets in pathogenic fungi.
- *Candidozyma auris* is a multidrug-resistant fungal pathogen with high mortality rates, creating an urgent need for new therapeutic strategies.
- Although PPI-based approaches have been applied in other fungal pathogens, comprehensive integration of topology, homology filtering, and structural druggability assessment for *C. auris* remains limited.

What this study adds on this topic?

- This study constructs a large-scale PPI network for *C. auris* and systematically ranks proteins using multiple topological metrics to identify central nodes.
- By integrating non-homology to human and gut microbiome proteins with essentiality screening and structural evaluation, it narrows thousands of proteins to a focused set of high-priority candidates.
- The study identifies 3 previously uncharacterized proteins as structurally druggable, demonstrating that a multi-criteria computational pipeline can effectively reveal promising antifungal targets in *C. auris*.

INTRODUCTION

Protein–protein interaction (PPI) network analyses are a critical tool for systems biology in the discovery of new drug targets, as these analyses assess not only individual proteins but also the holistic regulation of intracellular functions.[1] Topological analyses performed on the PPI network allow prioritization of potential drug-target proteins not only based on their high number of interactions (hubs) but also according to their strategic positions within the network.[2] Especially in the case of pathogenic microorganisms, numerous proteins that play central roles in virulence, signal transduction, and adaptation processes have been identified through PPI network analyses.[3-8] Studies on PPI network analysis in fungal pathogens have remained relatively limited so far due to persistent database constraints.[9] However, fungal pathogens pose a serious public health threat, as resistance is rising while only 4 classes of antifungal drugs are currently available. In this context, the discovery and development of new antifungal agents has become a major priority.[10]

Candidozyma auris (formerly *Candida auris*) is a rapidly spreading fungal pathogen that can cause invasive candidiasis, particularly among patients in

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intensive care units and those with prolonged hospital stays, and it exhibits multidrug resistance to antifungal agents.[11] Its placement in the "critical priority" category of the Fungal Priority Pathogens List published by the World Health Organization in 2022 clearly demonstrates the high public health risk posed by this species.[12] Clinical data[12] show that 30-day mortality rates in *C. auris* candidemia cases are remarkably high, ranging from 23% to 67%. This high mortality is thought to be associated with characteristics such as hospital-acquired colonization, biofilm formation, environmental persistence on abiotic surfaces, and a greater capacity for transmission compared to other *Candida* species.[13] In terms of treatment, 3 main classes of antifungal agents are currently commonly used for *C. auris* infections: azoles (particularly fluconazole), echinocandins, and amphotericin B.[14] However, there are significant limitations associated with these agents. Resistance to azoles in clinical isolates is reported to be as high as 80%-90%.[15] Although echinocandin resistance is still rare, it is showing an increasing trend, and cases of resistance to amphotericin B have also been reported worldwide.[16-18] In this context, the limited options for antifungal therapy and the slow progress of new drug development pose a major obstacle in the fight against *C. auris*.[19] The inadequacy of standard treatment classes and the rise of resistant pathogens provide a strong rationale for the development of "next-generation antifungals."[19]

In this context, PPI network analysis and related proteomic approaches have the potential to play a central role in the discovery of new antifungal targets. These tools enable the identification of novel drug-target proteins by analyzing the pathogen's core survival mechanisms.[20-22]

The aim of this study is to apply PPI network analyses to the *C. auris* proteome in order to identify protein drug targets that are species-specific and largely non-homologous to human proteins.

MATERIAL AND METHODS

Data Curation

For the computational analysis aimed at screening novel potential drug targets, the *C. auris* (CBS10913) proteome data were obtained from the STRING database (https://string-db.org/) via the STRINGapp in Cytoscape. The data included UniProt protein IDs, protein names, and amino acid sequences, as well as the corresponding gene names.

Network Analysis

All *C. auris* proteins with a confidence score >0.5 in the STRING database were imported via the STRINGapp. The proteins were analyzed using Network Analyzer[23] to calculate distributions of advanced network metrics, including degree, clustering coefficient, betweenness centrality, and closeness centrality. A multi-criteria score was applied based on network topology, incorporating betweenness (BC), degree (DC), closeness (CC), and eccentricity (EC), with respective weights of 0.4, 0.3, 0.2, and 0.1. Accordingly, this multi-criteria score was calculated using the following formula:

$$\text{Final score} = 0.4 \times [\text{BC}] + 0.3 \times [\text{DC}] + 0.2 \times [\text{CC}] + 0.1 \times [\text{EC}]$$

Homology Analysis

Amino acid sequences of the analyzed proteins were retrieved from Network Analyzer and prepared in FASTA file format. The online tool Pipeline Builder for Identification of Targets v3 (PBIT v3)[24] was then used to evaluate the homology of the *C. auris* proteome. The tool provides a pipeline to amino acid sequence comparison against the proteasome of humans and gut microbiota to support a non-homolog (<50% similarity) drug target selection. Possible human and human gut microbiota homology was also considered. A hundred proteins with the highest final score were analyzed for their non-homology characteristics against the proteasome of human and human gut microbiota using the PBIT v3 tool[24] (http://www.pbit.bicnirrh.res.in/drug_blast.php).

Essentiality and Druggability Analysis

Essentiality analysis was performed based on *C. albicans* using the Yeastract+ tool[25] (https://yeastract-plus.org/). For this analysis, homologous proteins in *C. albicans* were identified for the selected *C. auris* proteins.

Small proteins with fewer than 200 amino acids were excluded due to potential limitations in 3D structure and the likelihood of insufficient druggable cavities.[26] The possible subcellular localization and 3D structures (experimental or predicted) of the proteins were assessed using PBIT v3 and the UniProt database. The druggability scores of the most suitable proteins were then calculated based on their available 3D structures using the CavityPlus tool (http://www.pkumdl.cn:8000/cavityplus/#/).[27]

RESULTS

Candidozyma auris proteome in the STRING database contains a total of 5418 proteins, of which 5409 proteins with a confidence score >0.5 were included in the analysis. The resulting PPI network consisted of 4214 nodes and 86 872 edges, indicating a highly connected network with extensive interaction clusters within the proteome. The characteristic path length (3.274) and network diameter (8) support small-world properties, suggesting that biological signals can be transmitted rapidly across the network. Additionally, the clustering coefficient (0.419) indicates the presence of distinct functional submodules. Together with the low network density (0.010) and network heterogeneity (1.43), these metrics suggest that the network is sparse yet organized, as typically observed in biological systems, with certain proteins exhibiting pronounced hub characteristics. The network centralization (0.12) reflects a balanced distribution of interactions rather than the dominance of a single central node. Summary statistics for the corresponding STRING database are presented in Table 1. These overall metrics indicate that the proteome forms a

Table 1. Summary Statistics for the Used STRING Network

Summary Statistics	
Overall proteins (UniProt database *C. auris* reference: UP000230249)	5.41
Overall proteins (STRING database)	5.40
Number of nodes	4.21
Number of edges	86.87
Avg. number of neighbors	41.78
Network diameter	8
Network radius	5
Characteristic path length	3.27
Clustering coefficient	0.41
Network density	0.01
Network heterogeneity	1.43
Network centralization	0.12

well-structured PPI network, with critical points organized around hub proteins and modular subnetworks.

In the context of the topological evaluation of the PPI network, the top 100 proteins with the highest final scores ranged from 70.48 to 169.90 (Supplementary Table 1). Within this set, the values of BC, DC, CC, and EC ranged from 0.001 to 1, 233 to 541, 0.39 to 0.45, and 5, respectively (Table 2). The amino acid lengths of the selected proteins ranged from 200 to 1684 residues (Supplementary Table 1).

Subcellular localization of the selected proteins was unavailable for 47 (47%) proteins, while the remaining proteins were located in the nucleus (25, 25%), cytoplasm (12, 12%), and mitochondria (8, 8%).

After filtering for proteins with the highest final ranks, non-homology to human and human microbiota proteomes, and amino acid lengths greater than 200, 15 proteins were selected for assessment of druggability based on their available 3D structures (Table 3). Among these, based on the available predicted 3D structures, A0A2H0ZDG1 (Small ribosomal subunit protein uS4m), A0A2H0ZLN5 (Tr-type G domain-containing protein), and A0A2H0ZVI9 (Bystin) were considered druggable, whereas A0A2H0ZCF9 (Ribosome production factor 2 homolog) was classified as less druggable. No predicted 3D structures were available for 7 of the 15 selected proteins (46%) (Table 3). Comparison with essentiality analysis based on *C. albicans* proteome homology indicated that none of the selected *C. auris* proteins were essential (Table 3).

Table 2. Topological Evaluations for the First Hundred Proteins with the Highest Final Score

Topology	Min	Max	Mean
Final score	70.48	169.90	89.88
BC	0.001	1	0.005
DC	233	541	297.04
CC	0.39	0.45	0.4
EC	5	5	5

BC, betweenness centrality; CC, closeness centrality; DC, degree centrality; EC, eccentricity; Max, maximum; Min, minimum.

DISCUSSION

In this study, a PPI network analysis was performed using a total of 4214 nodes with a confidence cutoff >0.50 to identify highly interacting proteins within the *C. auris* proteome. The network analysis was complemented by homology assessment and druggability screening to select the most promising drug target candidates. Based on the network analysis, 100 proteins were initially selected according to their final scores. Of these, 23 (23%) and 27 (27%) were found to be non-homologous to human proteins and the human gut microbiome, respectively. Ultimately, a total of 15 (15%) novel proteins were selected based on their high final scores, non-homology to human and human gut microbiome proteins, and amino acid lengths greater than 200 residues, and were considered the most promising candidates for druggability analysis. Among the proteins with available predicted 3D structures (from UniProt), three—A0A2H0ZDG1, A0A2H0ZLN5, and A0A2H0ZVI9—were identified as druggable.

Studies on PPI networks in pathogenic fungi have been limited due to the persistent lack of available data. Of these, Das et al[28] identified 137 hyphae-associated proteins in *C. albicans*. In another study, a total of 139 proteins were reported to play significant roles during the course of infection.[29] Wang et al[30] predicted 4, 12, and 3 genes in *C. albicans* associated with adhesion, invasion, and host cell damage, respectively. Mukherjee et al[21] proposed YmL9 as a novel drug target in *Candida* spp. Similarly, Bappy et al[31] identified 3 proteins (XP_028890156.1, XP_028891672.1, and XP_028891858.1) as potential drug targets that are crucial for *C. auris* survival.

In this study, comparison of the top 100 high-ranking proteins with their *C. albicans* homologs revealed that none were essential proteins, and some essential proteins were represented with low ranks. Experimental and computational PPI datasets generated for *C. albicans* and other *Candida* species indicate that metabolic enzymes tend to be located at the periphery of the network, have fewer physical interactions, and that metabolism-related proteins are particularly underrepresented in databases such as STRING and BioGRID.[9] Furthermore, metabolic network analyses have shown that most essential reactions are associated with low-degree metabolites, meaning that the enzymes controlling these reactions naturally exhibit low connectivity in PPI networks. Proteomic and subtractive-proteomics studies conducted on *C. auris* support the same trend, reporting that critical pathogenesis- or metabolism-related proteins are represented with very few interactions in STRING-based networks, and that some essential proteins receive low rankings in network analyses due to incomplete data.[2]

In this study, unlike previous fungal PPI analyses that rely on druggability assessment based on similarity to drug

Table 3. Druggability and Flow Effect of the Most Appropriate Proteins

Uniprot IDs	Gene Name	Homolog Gene (Ca)*	Essentiality (Ca)*	Druggability
A0A2H0ZS53	B9J08_003087	C2_02630W_A	No	ND
A0A2H1A7B8	B9J08_000233	RPL7/CR_06120W_A	No	Undruggable
A0A2H0ZSM9	B9J08_003274	YML6/C7_00950W_A	No	Undruggable
A0A2H0ZTD5	B9J08_003560	C1_10470W_A	No	ND
A0A2H1A592	B9J08_000697	CR_00490W_A	No	ND
A0A2H0ZDG1	B9J08_005362	CR_04140W_A	No	Druggable
A0A2H0ZYF7	B9J08_001769	C2_02540W_A	No	ND
A0A2H0ZFE5	B9J08_005010	RPC40/C2_05340C_A	No	ND
A0A2H0ZNP1	B9J08_003530	C4_00660W_A	No	Undruggable
A0A2H0ZQC3	B9J08_001880	C3_07390C_A	No	ND
A0A2H0ZZZ1	B9J08_001128	C2_07680W_A	No	Undruggable
A0A2H0ZLN5	B9J08_003130	C2_04640C_A	No	Druggable
A0A2H0ZYV9	B9J08_001915	NOG1/C3_06030W_A	No	ND
A0A2H0ZVI9	B9J08_003872	ENP1/C7_03700C_A	No	Druggable
A0A2H0ZCF9	B9J08_005015	RPF2/C2_05230C_A	No	Less Druggable

ND, Not defined (no 3D structure available).
**Candida albicans*.

targets in DrugBank and similar databases, druggability analyses (Cavity analysis) was applied based on the 3D structures of the selected proteins using PBIT. The predictive accuracy of this approach will depend on the increasing availability of predicted or experimental 3D structures for *C. auris* proteome proteins in databases. In this study, it was observed that nearly half of the top-ranked proteins (n = 15) did not even have available predicted 3D structures.

Proteome data for fungal pathogens, particularly regarding protein–protein interactions within pathways, have been steadily improving over the past decade. The success of fungal PPI analyses in identifying new drug targets largely depends on comprehensive and accurate PPI databases; if the databases contain missing, erroneous, or low-confidence interactions, the resulting network topology will be flawed, hub proteins may be misidentified, and modular subnetworks may be underrepresented.[32,33] This can cause critical pathogenesis- or metabolism-related proteins to appear with low connectivity or incorrect rankings in the network, increasing the risk of errors in prioritizing drug targets. In particular, incomplete experimental data can lead to underrepresentation of metabolism- or virulence-related proteins in resources such as STRING or BioGRID, and essential proteins may appear with low ranks. Therefore, the accuracy of target discovery via PPI analysis is directly dependent on the coverage of the databases, the representation of the proteome, and the reliability of interaction data.[9,21]

A limitation of this study is the lack of compound suggestions for the identified proteins using cheminformatics approaches, as well as the absence of in-silico knockout data to validate the functional impact of these potential drug targets.

In conclusion, overall, this study highlights that while PPI network analysis combined with homology and druggability screening can effectively prioritize potential antifungal targets in *C. auris*, the reliability and predictive power of such analyses remain fundamentally dependent on the completeness, accuracy, and coverage of available proteomic and interaction data.

Data Availability Statement: The data that support the findings of this study are available on request from the author.

Ethics Committee Approval: Ethical approval was not required for this study, as all work was conducted entirely in silico.

Informed Consent: There is no involvement of human participants, human samples, or human-derived data; therefore, informed consent was not required.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – M.Ö.; Design – M.Ö.; Supervision – M.Ö.; Resources – M.Ö.; Materials – M.Ö.; Data Collection and/or Processing – M.Ö.; Analysis and/or Interpretation – M.Ö.; Literature Search – M.Ö.; Writing – M.Ö.; Critical Review – M.Ö.

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References

1. Kotlyar M, Fortney K, Jurisica I. Network-based characterization of drug-regulated genes, drug targets, and toxicity. *Methods*. 2012;57(4):499-507. **[CrossRef]**
2. Feng Y, Wang Q, Wang T. Drug target protein-protein interaction networks: A systematic perspective. *BioMed Res Int*. 2017;2017:1289259. **[CrossRef]**
3. Dai Y, Yu H, Yan Q, et al. Drug-target network study reveals the core target-protein interactions of various COVID-19 treatments. *Genes*. 2022;13(7):1210. **[CrossRef]**

4. Taghipour S, Zarrineh P, Ganjtabesh M, Nowzari-Dalini A. Improving protein complex prediction by reconstructing a high-confidence protein-protein interaction network of Escherichia coli from different physical interaction data sources. *BMC Bioinform*. 2017;18(1):10. **[CrossRef]**
5. Xue XY, Chen Z, Hu Y, Nie D, Zhao H, Mao XG. Protein-protein interaction network of E. coli K-12 has significant high-dimensional cavities: new insights from algebraic topological studies. *FEBS Open Bio*. 2022;12(7):1406-1418. **[CrossRef]**
6. Qian X, Yoon BJ. Comparative analysis of protein interaction networks reveals that conserved pathways are susceptible to HIV-1 interception. *BMC Bioinform*. 2011;12(suppl 1):S19. **[CrossRef]**
7. Mei S, Zhu H. AdaBoost based multi-instance transfer learning for predicting proteome-wide interactions between Salmonella and human proteins. *PLOS One*. 2014;9(10):e110488. **[CrossRef]**
8. Subbarayan K, Ulagappan K, Wickenhauser C, Bachmann M, Seliger B. Immune interaction map of human SARS-CoV-2 target genes: implications for therapeutic avenues. *Front Immunol*. 2021;12:597399. **[CrossRef]**
9. Schoeters F, Van Dijck P. Protein-protein interactions in Candida albicans. *Front Microbiol*. 2019;10:1792. **[CrossRef]**
10. Robbins N, Cowen LE. Antifungal discovery. *Curr Opin Microbiol*. 2022;69:102198. **[CrossRef]**
11. Du H, Bing J, Hu T, Ennis CL, Nobile CJ, Huang G. Candida auris: epidemiology, biology, antifungal resistance, and virulence. *PLOS Pathog*. 2020;16(10):e1008921. **[CrossRef]**
12. World Health Organization. WHO fungal priority pathogens list to guide research, development and public health action; 2022. Available at: https://www.who.int/publications/i/item/9789240060241. Accessed November 15, 2025.
13. Hayes JF. Candida auris: epidemiology update and a review of strategies to prevent spread. *J Clin Med*. 2024;13(22):6675. **[CrossRef]**
14. Chaabane F, Graf A, Jequier L, Coste AT. Review on antifungal resistance mechanisms in the emerging pathogen Candida auris. *Front Microbiol*. 2019;10:2788. **[CrossRef]**
15. Centers for Disease Control and Prevention (CDC). Infection prevention and control for Candida auris. Available at: https://www.cdc.gov/fungal/candida-auris/c-auris-infection-control.html. Accessed November 15, 2025.
16. Chowdhary A, Prakash A, Sharma C, et al. A multicentre study of antifungal susceptibility patterns among 350 Candida auris isolates (2009-17) in India: role of the ERG11 and FKS1 genes in azole and echinocandin resistance. *J Antimicrob Chemother*. 2018;73(4):891-899. **[CrossRef]**
17. Kordalewska M, Lee A, Park S, et al. Understanding echinocandin resistance in the emerging pathogen Candida auris. *Antimicrob Agents Chemother*. 2018;62(6):e00238-18. **[CrossRef]**
18. Kilburn S, Innes G, Quinn M, et al. Antifungal resistance trends of Candida auris clinical isolates in New York and New Jersey from 2016 to 2020. *Antimicrob Agents Chemother*. 2022;66(3):e0224221. **[CrossRef]**
19. Kriegl L, Egger M, Boyer J, Hoenigl M, Krause R. New treatment options for critically important WHO fungal priority pathogens. *Clin Microbiol Infect*. 2025;31(6):922-930. **[CrossRef]**
20. Bencurova E, Gupta SK, Sarukhanyan E, Dandekar T. Identification of antifungal targets based on computer modeling. *J Fungi (Basel)*. 2018;4(3):81. **[CrossRef]**
21. Mukherjee S, Kundu I, Askari M, Barai RS, Venkatesh KV, Idicula-Thomas S. Exploring the druggable proteome of Candida species through comprehensive computational analysis. *Genomics*. 2021;113(2):728-739. **[CrossRef]**
22. Kaltdorf M, Srivastava M, Gupta SK, et al. Systematic identification of anti-fungal drug targets by a metabolic network approach. *Front Mol Biosci*. 2016;3:22. **[CrossRef]**
23. Assenov Y, Ramírez F, Schelhorn SE, Lengauer T, Albrecht M. Computing topological parameters of biological networks. *Bioinformatics*. 2008;24(2):282-284. **[CrossRef]**
24. Chakraborty S, Askari M, Barai RS, Idicula-Thomas S. PBITV3: A robust and comprehensive tool for screening pathogenic proteomes for drug targets and prioritizing vaccine candidates. *Protein Sci*. 2024;33(2):e4892. **[CrossRef]**
25. Teixeira MC, Viana R, Palma M, et al. YEASTRACT+: a portal for the exploitation of global transcription regulation and metabolic model data in yeast biotechnology and pathogenesis. *Nucleic Acids Res*. 2023;51(D1):D785-D791. **[CrossRef]**
26. Gao M, Skolnick J. A comprehensive survey of small-molecule binding pockets in proteins. *PLOS Comput Biol*. 2013;9(10):e1003302. **[CrossRef]**
27. Xu Y, Wang S, Hu Q, et al. CavityPlus: a web server for protein cavity detection with pharmacophore modelling, allosteric site identification and covalent ligand binding ability prediction. *Nucleic Acids Res*. 2018;46(W1):W374-W379. **[CrossRef]**
28. Das S, Bhuyan R, Bagchi A, Saha T. Network analysis of hyphae forming proteins in Candida albicans identifies important proteins responsible for pathovirulence in the organism. *Heliyon*. 2019;5(6):e01916. **[CrossRef]**
29. Wang YC, Tsai IC, Lin C, et al. Essential functional modules for pathogenic and defensive mechanisms in Candida albicans infections. *BioMed Res Int*. 2014;2014:136130. **[CrossRef]**
30. Wang YC, Huang SH, Lan CY, Chen BS. Prediction of phenotype-associated genes via a cellular network approach: a Candida albicans infection case study. *PLOS One*. 2012;7(4):e35339. **[CrossRef]**
31. Bappy MNI, Robin TB, Prome AA, et al. Subtractive proteomics analysis to uncover the potent drug targets for distinctive drug design of Candidaauris. *Heliyon*. 2023;9(6):e17026. **[CrossRef]**
32. Mora A, Donaldson IM. Effects of protein interaction data integration, representation and reliability on the use of network properties for drug target prediction. *BMC Bioinform*. 2012;13:294. **[CrossRef]**
33. Peng X, Wang J, Peng W, Wu FX, Pan Y. Protein-protein interactions: detection, reliability assessment and applications. *Brief Bioinform*. 2017;18(5):798-819. **[CrossRef]**

Supplementary Table 1. Network topology and non-homology of the proteins with the highest final score

No	UniProt Code	Gene Name	BC	DC	CC	EC	AA length	HNH	GMNH	Final Score
1	A0A2H1A5H8	B9J08_000632	0.04276	541	0.453	5	150			162.91
2	A0A2H0ZHI4	B9J08_004769	0.03086	458	0.445	5	381			138.00
3	A0A2H0ZS53	B9J08_003087	0.02745	448	0.446	5	461	NH	NH	135.00
4	A0A2H0ZFP4	B9J08_004504	0.02383	420	0.433	5	1185	NH		126.60
5	A0A2H1A5C8	B9J08_000605	0.00660	393	0.423	5	132			118.49
6	A0A2H0ZWS6	B9J08_002533	0.01410	377	0.430	5	167			113.69
7	A0A2H0ZN47	B9J08_003349	0.03844	375	0.420	5	701	NH		113.10
8	A0A2H1A207	B9J08_001434	0.00347	367	0.410	5	234	NH		110.68
9	A0A2H0ZCD6	B9J08_004990	0.00377	360	0.419	5	249			108.59
10	A0A2H1A7B8	B9J08_000233	0.00265	354	0.405	5	266	NH	NH	106.78
11	A0A2H0ZKV5	B9J08_002813	0.02087	353	0.431	5	1051		NH	106.49
12	A0A2H0ZM86	B9J08_003023	0.00387	350	0.414	5	389			105.58
13	A0A2H0ZM70	B9J08_003313	0.00123	350	0.406	5	363		NH	105.58
14	A0A2H1A4U4	B9J08_000955	0.00332	334	0.409	5	127			100.78
15	A0A2H0ZYS2	B9J08_001870	0.00308	334	0.408	5	151			100.78
16	A0A2H0ZSM9	B9J08_003274	0.00167	332	0.409	5	247	NH	NH	100.18
17	A0A2H1A5Q2	B9J08_000699	0.00198	328	0.402	5	183			98.98
18	A0A2H0ZW29	B9J08_001974	0.00602	325	0.422	5	250		NH	98.09
19	A0A2H0ZP76	B9J08_004067	0.00181	325	0.409	5	223			98.08
20	A0A2H0ZTD5	B9J08_003560	0.00225	323	0.413	5	323	NH	NH	97.48
21	A0A2H0ZN64	B9J08_003677	0.00165	323	0.411	5	145		NH	97.48
22	A0A2H0ZP13	B9J08_003975	0.00222	323	0.408	5	262	NH		97.48
23	A0A2H0ZSF0	B9J08_003248	0.00104	322	0.404	5	142			97.18
24	A0A2H0ZQ99	B9J08_001822	0.00188	321	0.413	5	177			96.88
25	A0A2H1A2S6	B9J08_000203	0.00133	321	0.406	5	189			96.88
26	A0A2H1A7N8	B9J08_000346	0.00192	317	0.411	5	149			95.68
27	A0A2H1A592	B9J08_000697	0.00319	316	0.407	5	283	NH	NH	95.38
28	A0A2H0ZDG1	B9J08_005362	0.00171	316	0.404	5	468	NH	NH	95.38
29	A0A2H1A1L1	B9J08_001278	0.00171	314	0.406	5	200			94.78
30	A0A2H0ZDV4	B9J08_005510	0.00533	313	0.400	5	124			94.48
31	A0A2H1A814	B9J08_000192	0.00673	311	0.416	5	1167			93.89
32	A0A2H1A599	B9J08_000554	0.00295	309	0.412	5	140			93.28
33	A0A2H0ZLP7	B9J08_003127	0.00149	309	0.405	5	185	NH		93.28
34	A0A2H0ZVL8	B9J08_002473	0.00122	309	0.403	5	316		NH	93.28
35	A0A2H0ZE87	B9J08_005279	0.00400	308	0.415	5	115			92.98
36	A0A2H0ZM30	B9J08_003273	0.00137	308	0.410	5	145			92.98
37	A0A2H0ZGA2	B9J08_004689	0.00298	308	0.397	5	152			92.98
38	A0A2H1A5E3	B9J08_000771	0.00431	307	0.404	5	236			92.68
39	A0A2H0ZVC9	B9J08_002367	0.00358	307	0.405	5	191			92.68
40	A0A2H0ZCP9	B9J08_005099	0.00271	306	0.414	5	298		NH	92.38
41	A0A2H0ZFX1	B9J08_004574	0.00119	303	0.400	5	241			91.48
42	A0A2H0ZYF7	B9J08_001769	0.00480	301	0.411	5	1684	NH	NH	90.88
43	A0A2H0ZFE5	B9J08_005010	0.00622	300	0.410	5	334	NH	NH	90.58
44	A0A2H0ZDC5	RPS0	0.00204	300	0.412	5	264			90.58
45	A0A2H1A5Q8	B9J08_000711	0.00267	299	0.407	5	311		NH	90.28
46	A0A2H0ZHF9	B9J08_000604	0.00111	299	0.406	5	130			90.28
47	A0A2H0ZS54	B9J08_002605	0.00144	298	0.409	5	121	NH		89.98
48	A0A2H0ZE81	B9J08_005038	0.00815	297	0.414	5	308			89.69
49	A0A2H0ZNP1	B9J08_003530	0.00010	296	0.401	5	244	NH	NH	89.38
50	A0A2H1A6N0	B9J08_001046	0.00166	293	0.403	5	174			88.48

(*Continued*)

Supplementary Table 1. Network topology and non-homology of the proteins with the highest final score (Continued)

No	UniProt Code	Gene Name	BC	DC	CC	EC	AA length	HNH	GMNH	Final Score
51	A0A2H0ZN40	B9J08_003655	0.00010	293	0.404	5	156			88.48
52	A0A2H0ZCE7	B9J08_005005	0.00181	292	0.402	5	284	NH		88.18
53	A0A2H1A034	B9J08_001081	0.00114	289	0.403	5	137			87.28
54	A0A2H0ZTK4	B9J08_003596	0.00103	288	0.402	5	285			86.98
55	A0A2H0ZID0	B9J08_004238	0.00146	286	0.408	5	400			86.38
56	A0A2H1A5D1	B9J08_000698	0.00212	286	0.402	5	223			86.38
57	A0A2H1A705	B9J08_000107	0.00102	286	0.404	5	118			86.38
58	A0A2H0ZR79	B9J08_002772	0.00795	282	0.413	5	842			85.19
59	A0A2H0ZND6	B9J08_003755	0.00132	282	0.411	5	141			85.18
60	A0A2H0ZKN7	B9J08_002779	0.00114	281	0.402	5	132			84.88
61	A0A2H0ZW26	B9J08_002277	0.00142	280	0.402	5	120			84.58
62	A0A2H1A6P1	B9J08_001045	0.00878	279	0.422	5	1235			84.29
63	A0A2H0ZRL1	B9J08_002921	0.00010	279	0.398	5	155			84.28
64	A0A2H0ZVB4	B9J08_002384	0.00010	277	0.397	5	173			83.68
65	A0A2H0ZP19	B9J08_004006	0.00335	276	0.412	5	354	NH		83.38
66	A0A2H0ZGI3	B9J08_004761	0.00113	275	0.397	5	143			83.08
67	A0A2H0ZJ33	B9J08_004434	0.00138	274	0.392	5	263			82.78
68	A0A2H1A787	B9J08_000185	0.00010	274	0.391	5	188			82.78
69	A0A2H0ZC96	RPS1	0.00163	273	0.401	5	256		NH	82.48
70	A0A2H0ZCV5	B9J08_005153	0.00010	273	0.392	5	259			82.48
71	A0A2H1A6W9	B9J08_000064	0.00010	269	0.399	5	172			81.28
72	A0A2H0ZDF6	B9J08_005336	0.00183	261	0.405	5	165			78.88
73	A0A2H0ZM29	B9J08_002961	0.00010	261	0.395	5	204		NH	78.88
74	A0A2H0ZQC3	B9J08_001880	0.00010	259	0.401	5	242	NH	NH	78.28
75	A0A2H0ZZZ1	B9J08_001128	0.00010	259	0.398	5	293	NH	NH	78.28
76	A0A2H0ZK83	B9J08_004431	0.00010	257	0.404	5	254			77.68
77	A0A2H0ZCV1	B9J08_005150	0.00010	257	0.404	5	254			77.68
78	A0A2H1A3R4	B9J08_000091	0.00010	256	0.394	5	145			77.38
79	A0A2H0ZLN5	B9J08_003130	0.00586	255	0.392	5	963	NH	NH	77.08
80	A0A2H0ZPA8	B9J08_004073	0.00573	253	0.402	5	154			76.48
81	A0A2H0ZSJ0	B9J08_003288	0.00010	252	0.393	5	67			76.18
82	A0A2H0ZCQ8	B9J08_005110	0.00417	251	0.410	5	1156			75.88
83	A0A2H0ZVR3	B9J08_002508	0.00573	251	0.402	5	323		NH	75.88
84	A0A2H0ZMW6	B9J08_001686	0.00107	251	0.395	5	264			75.88
85	A0A2H0ZIY2	B9J08_004413	0.00010	251	0.379	5	199			75.88
86	A0A2H0ZS48	B9J08_003089	0.00010	249	0.394	5	135			75.28
87	A0A2H0ZJF3	B9J08_004222	0.00329	248	0.401	5	1639			74.98
88	A0A2H0ZTF1	B9J08_003605	0.00010	246	0.399	5	144			74.38
89	A0A2H0ZNZ0	B9J08_003634	0.00112	246	0.394	5	113			74.38
90	A0A2H1A3M0	B9J08_000090	0.00237	243	0.391	5	186			73.48
91	A0A2H0ZYV9	B9J08_001915	0.00117	243	0.376	5	637	NH	NH	73.48
92	A0A2H0ZVI9	B9J08_003872	0.00105	239	0.379	5	435	NH	NH	72.28
93	A0A2H0ZLX9	B9J08_003238	0.00644	237	0.405	5	430			71.68
94	A0A2H0ZK35	B9J08_002601	0.00010	237	0.400	5	220		NH	71.68
95	A0A2H0ZYM3	B9J08_001851	0.00010	237	0.391	5	204			71.68
96	A0A2H0ZCF9	B9J08_005015	0.00134	237	0.381	5	320	NH	NH	71.68
97	A0A2H0ZG69	B9J08_005382	0.00010	236	0.393	5	149			71.38
98	A0A2H0ZNX4	B9J08_003953	0.00010	235	0.393	5	208			71.08
99	A0A2H0ZD81	B9J08_004958	0.00109	234	0.390	5	165			70.78
100	A0A2H1A2B0	B9J08_000020	0.00710	233	0.403	5	543			70.48

BC, Betwenness centrality; DC, Degree centrality; CC, closeness centrality; EC, Eccentricity; HNH, Human non-homology; GMNH Gut microbiota non-homology; NH, non-homologous.