**Table S1.** Pathogenic and non-pathogenic *Cryptococcus* species were identified through a literature review and the UniProt database

|  |  |
| --- | --- |
| **Pathogenic *Cryptococcus* Species** | **Non-pathogenic *Cryptococcus* Species** |
| *C. neoformans, C. gatti, C. gattii*VGI*, C. gattii*VGII*, C. gattii*VGIIb*, C. gattii*VGIV*, C. gattii*VGIV*/*VGIIIc*, C. gattii*CA1280*, C. gattii*EJB2*, C. deuterogattii, C. tetragattii, C. decagattii* | *C. amylolentus, C. bacillisporus, C. bacillisporus (*VGIII*), C. deneoformans, C. depauperatus, C. luteus, C. floricola, C. magnus, C. diffluens, C. liquefaciens, C. uniguttulatus, C. adeliensis, C. luteolus, C. curvatus, C. uniguttulatus, C. albidosimilis, C. randhawii, C. flavescens, C. albidus, C. laurentii, C. flavus, C. ater, C. wingfieldii, C. adeliensis, C. bestiolae, C. dejecticola,* and *C. heveanensis* |

**Table S2.** Pathogenic and non-pathogenic *Cryptococcus* species and their UniProt IDs and sequence lengths

|  |  |  |
| --- | --- | --- |
| ***Cryptococcus* Species** | **UniProt IDs** | **Sequence Lengths** |
| *C. neoformans* | E0XG22 | 185 |
| *C. gatti* | Q30H69 | 185 |
| *C. gattii*VGI | A0A0N9BA23 | 185 |
| *C. gattii*VGII | A0A1S6LQ30 | 185 |
| *C. gattii*VGIIb | A0A4P8XEH0 | 185 |
| *C. gattii*VGIV | A0A1S6LQ40 | 185 |
| *C. gattii*VGIV/VGIIIc | A0A894Z8G2 | 185 |
| **Non-Pathogenic Species** | **UniProt IDs** | **Sequence Lengths** |
| *C. wingfieldii* CBS 7118 | A0A1E3JEY3 | 530 |
| *C. depauperatus* CBS 7855 | A0A1E3J5N2 | 520 |
| *C. floricola* | A0A5D3AT58 | 530 |
| *C. amylolentus* CBS 6039 | A0A1E3I4Z3 | 530 |

**Table S3.** The Pfam IDs, protein family names, regions, and short names of the pathogenic and non-pathogenic *Cryptococcus* species

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| ***Cryptococcus* Species** | **PfamIDs** | **Protein Family Names** | **Regions** | **Short Name** |
| *C. neoformans* | PF01094 | Receptor family ligand binding region | 35-54 | ANF receptor |
| PF11735 | Cryptococcal mannosyltransferase 1 | 55-172 | CAP59 mtransfer |
| *C. gattii*VGI | PF01094 | Receptor family ligand binding region | 35-54 | ANF receptor |
| PF11735 | Cryptococcal mannosyltransferase 1 | 55-172 | CAP59 mtransfer |
| *C. gattii*VGIV*/*VGIII*c* | PF01094 | Receptor family ligand binding region | 35-54 | ANF receptor |
| PF11735 | Cryptococcal mannosyltransferase 1 | 55-172 | CAP59 mtransfer |
| *C. gattii* | PF11735 | Cryptococcal mannosyltransferase 1 | 55-180 | CAP59 mtransfer |
| *C. gattii*VGII | PF11735 | Cryptococcal mannosyltransferase 1 | 55-180 | CAP59 mtransfer |
| *C. gattii*VGIIb | PF11735 | Cryptococcal mannosyltransferase 1 | 55-180 | CAP59 mtransfer |
| *C. gattii*VGIV | PF11735 | Cryptococcal mannosyltransferase 1 | 55-180 | CAP59 mtransfer |
| **Non-Pathogenic Species** | **PfamIDs** | **Protein Family Names** | **Regions** | **Short Name** |
| *Cryptococcus wingfieldii* CBS 7118 | PF11735 | Cryptococcal mannosyltransferase 1 | 146-426 | CAP59 mtransfer |
| *Cryptococcus depauperatus* CBS 7855 | PF11735 | Cryptococcal mannosyltransferase 1 | 118-422 | CAP59 mtransfer |
| *Cryptococcus floricola* | PF11735 | Cryptococcal mannosyltransferase 1 | 146-426 | CAP59 mtransfer |
| *Cryptococcus amylolentus* CBS 6039 | PF11735 | Cryptococcal mannosyltransferase 1 | 145-425 | CAP59 mtransfer |

**Table S4.** Multiple sequence alignment of pathogenic *Cryptococcus* species with variant residues at specific positions

|  |  |  |
| --- | --- | --- |
| ***Cryptococcus*****Species** | **Position** | **Residues** |
| *C. gatti*, *C. gatti*-VGII, *C. gatti*-VGIIb, | 10 | Lysine |
| *C. neoformans*, *C. gatti*-VGIV/VGIIIc, *C. gatti*-VGI | 10 | Glutamine |
| *C. gatti*-VGIV | 10 | Arginine |
| *C. gatti*-VGIV, *C. gatti*, *C. gatti*-VGII, *C. gatti*-VGIIb, *C. gatti*-VGIV/VGIIIc, *C. neoformans* | 11 | Proline |
| *C. gatti*-VGI | 11 | Serine |
| C. gatti-VGIV, C. gatti, C. gatti-VGII, C. gatti-VGIIb, C. gatti-VGI, C. neoformans | 14 | Asparagine |
| C. gatti-VGIV/VGIIIc | 14 | Serine |
| *C. gatti*-VGIV, *C. gatti*-VGI | 15 | Alanine |
| *C. gatti*, *C. gatti*-VGII, *C. gatti*-VGIIb, *C. gatti*-VGIV/VGIIIc, *C. neoformans* | 15 | Serine |
| *C. gatti*, *C. gatti*-VGII, *C. gatti*-VGIIb, *C. gatti*-VGI, *C. gatti*-VGIV | 19 | Arginine |
| *C. gatti*-VGIV/VGIIIc, *C. neoformans* | 19 | Glycine |
| *C. gatti*-VGI, *C. gatti*-VGIV, *C. gatti*-VGIV/VGIIIc, *C. neoformans* | 20 | Arginine |
| *C. gatti*, *C. gatti*-VGII, *C. gatti*-VGIIb | 20 | Lysine |
| *C.gatti*, *C. gatti*-VGII, *C. gatti*-VGIIb, *C. gatti*-VGI, *C. gatti*-VGIV | 25 | Serine |
| *C. gatti*-VGIV/VGIIIc, *C. neoformans* | 25 | Alanine |
| *C. gatti*-VGI, *C. gatti*-VGIV, *C. gatti*-VGIV/VGIIIc, *C. neoformans* | 27 | Serine |
| *C. gatti*, *C. gatti*-VGII, *C. gatti*-VGIIb | 27 | Alanine |
| *C. gatti*-VGI, *C. gatti*-VGIV | 42 | Threonine |
| *C. gatti*, *C. gatti*-VGII, *C. gatti*-VGIIb, *C. gatti*-VGIV/VGIIIc, *C. neoformans*. | 42 | Valine |

**Table S5.** The pairwise distance matrix of the pathogenic and non-pathogenic species shows the relation of the species

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | ***C.* *gattii*VGIV** | ***C. gattii***  **VGI** | ***C. gattii*** | ***C. gattii*VGII** | ***C. gattii***  **VGIIb** | ***C. neoformans*** | ***C. gattii***  **VGIV/VGIIIc** | ***C. depauperatus* \_{outgroup}** | ***C. amylolentus* \_{outgroup}** | ***C. floricola* \_{outgroup}** |
| ***C. gattii* VGIV** |  |  |  |  |  |  |  |  |  |  |
| ***C. gattii* VGI** | 0.0108696722 |  |  |  |  |  |  |  |  |  |
| ***C. gattii*** | 0.0273989742 | 0.0329700192 |  |  |  |  |  |  |  |  |
| ***C. gattii* VGII** | 0.0273989742 | 0.0329700192 | 0 |  |  |  |  |  |  |  |
| ***C. gattii* VGIIb** | 0.0273989742 | 0.0329700192 | 0 | 0 |  |  |  |  |  |  |
| ***C. neoformans*** | 0.0273989742 | 0.0273989742 | 0.0273989742 | 0.0273989742 | 0.0273989742 |  |  |  |  |  |
| ***C. gattii* VGIV/VGIIIc** | 0.0329700192 | 0.0329700192 | 0.0329700192 | 0.0329700192 | 0.0329700192 | 0.0054200675 |  |  |  |  |
| ***C. depauperatus*\_{outgroup}** | 0.2030759883 | 0.1964753042 | 0.1834032227 | 0.1834032227 | 0.1834032227 | 0.2030759883 | 0.209720531 |  |  |  |
| ***C. amylolentus*\_{outgroup}** | 0.1769307082 | 0.1704998178 | 0.1704998178 | 0.1704998178 | 0.1704998178 | 0.1704998178 | 0.1704998178 | 0.1632005153 |  |  |
| ***C. floricola*\_{outgroup}** | 0.1834032227 | 0.1769307082 | 0.1769307082 | 0.1769307082 | 0.1769307082 | 0.1769307082 | 0.1769307082 | 0.1609303668 | 0.0075757938 |  |
| ***C. wingfieldii*\_{outgroup}** | 0.1834032227 | 0.1769307082 | 0.1769307082 | 0.1769307082 | 0.1769307082 | 0.1769307082 | 0.1769307082 | 0.1609303668 | 0.009478744 | 0.0018885747 |

**Table S6.** Predicted structures of pathogenic and non-pathogenic *Cryptococcus* species' Discrete Optimized Protein Energy scores and their template

|  |  |  |
| --- | --- | --- |
| **Template** | **DOPE scores** | **Pathogenic Species** |
| *C. neoformans* | -21230.12695 | *C. gatti* |
| -21215.10938 | *C. gatti-*VGI |
| -21230.12695 | *C. gatti-*VGII |
| -21230.12695 | *C. gatti-*VGIIb |
| -21346.68164 | *C. gatti-*VGIV |
| -21186.79297 | *C. gatti-*VGIV*/*VGIII*c* |
| **Template** | **DOPE scores** | **Non-Pathogenic Species** |
|  | -57770.63281 | *C. depauperatus* |
| *C. wingfieldii* | -58941.39453 | *C. floricola* |
|  | -59030.45703 | *C. amylolentus* |