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Harnessing the Intrinsic Disorder in Human Metapneumovirus for Therapeutic Development

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INTRODUCTION & AIM

Human metapneumovirus (hMPV) is a leading cause of acute respiratory infections in children, elderly adults, and immunocompromised patients. Despite its clinical significance, the structural landscape of hMPV proteins remains poorly characterized.

A key aspect of modern virology is the recognition of intrinsically disordered proteins (IDPs) and intrinsically disordered protein regions (IDPRs), which lack stable tertiary structures yet carry out essential functions such as viral replication, host-cell interaction, and immune evasion. These regions form part of the “dark proteome” and are increasingly being recognized as druggable targets, especially in viruses that exhibit rapid mutation and immune escape. This study aims to systematically map intrinsic disorder across the hMPV proteome (strain CAN97-83), identify potential disorder-based therapeutic targets, and explore their relevance in drug resistance and host adaptation.

METHOD

The complete proteome of *Human metapneumovirus* (strain CAN97-83) was retrieved from the UniProt database, comprising 9 proteins with a total of 4142 amino acids.

Intrinsic disorder in hMPV proteins was predicted using a multi-tool ensemble approach to ensure comprehensive coverage of both short and long disordered regions, as well as functional insights. The PONDR® VLXT algorithm was employed to detect short, flexible regions commonly associated with functional disorder such as molecular recognition motifs. IUPred2A predicted disorder based on the estimation of pairwise inter-residue interaction energies, effectively identifying both short and extended disordered regions. DISOPRED3 focused on locating long disordered stretches and disorder-related protein-binding regions.

A key component of this study was the application of ESpritz, which was used in three specialized modes trained on different experimental datasets—NMR, X-ray crystallography, and DisProt annotations. ESpritz provides binary disorder classification (ordered/disordered) and is particularly sensitive to context-dependent disorder under varying structural constraints. In addition, fiDPnn was used for the functional annotation of disordered regions, particularly those involved in molecular binding, interaction interfaces, and regulation, further enriching the biological relevance of predicted IDPRs.

Following disorder prediction, we performed a detailed statistical analysis to quantify and interpret the disorder landscape across the hMPV proteome. The percentage of disorder was calculated for each individual protein as well as for the overall proteome. Disordered segments were identified and categorized based on their lengths, particularly focusing on regions greater than 30 and 50 amino acids, as these are often associated with biologically functional IDPRs.

We then computed the mean segment length and standard deviation across all proteins to assess the variability and distribution of disordered regions. To ensure robustness, the results were aggregated and cross-compared across all prediction tools (PONDR®, IUPred2A, DISOPRED3, ESpritz, and fiDPnn), allowing us to identify consensus disordered regions with higher confidence.

Finally, we analyzed protein-specific disorder profiles to explore potential associations with known or predicted functional roles such as immune evasion, host receptor interaction, and viral replication control. These statistical insights were critical in prioritizing potential disorder-based therapeutic targets in the hMPV proteome.

RESULTS & DISCUSSION

General Disorder Statistics (NMR-based):

Metric	Value
Total % disorder	23.52%
Mean disorder segment length	12.33 ± 21.07
Proteins with >30-residue disordered region	33.33%
Proteins with >50-residue disordered region	22.22%
Total disordered segments	79

Table2. Protein-wise Disorder Summary:

UniProt ID	Protein Name	Length	% Disorder	Segments >1	>30	>50
SPQ6WB94	Glycoprotein G	219	83.56	3	1	1
SPQ8B9Q8	Fusion Protein F	294	68.7	8	3	1
SPQ6WB95	Phosphoprotein P	179	41.34	7	1	0
SPQ6WB97	Nucleoprotein N	187	33.15	5	0	0
SPQ6WBA1	Matrix Protein M	394	27.41	9	0	0
SPQ6WB98	M2-1 Transcription Antitermination Factor	539	16.69	9	0	0
SPQ6WB93	Large Polymerase Protein (L)	2005	11.42	31	0	0
SPQ6WB96	M2-2 Protein	71	11.26	2	0	0
SPQ6WB99	Small Hydrophobic Protein (SH)	254	7.09	5	0	0

The disorder landscape of the hMPV proteome, as predicted using multiple computational tools, reveals that several viral proteins harbor significant levels of intrinsic disorder, with strong implications for functional plasticity and therapeutic targeting (Table 1).

In particular, Glycoprotein G (SPQ6WB94) and Fusion Protein F (SPQ8B9Q8) emerged as top-ranking candidates in terms of overall disorder content (Table 2). Predictions made by fiDPnn—a deep learning-based tool designed to identify functionally relevant intrinsically disordered protein regions (IDPRs)—confirmed that both proteins possess extensive functional disordered regions, specifically associated with molecular recognition, binding interactions, and regulatory switching mechanisms.

SPQ6WB94 (G Protein)

fiDPnn predicted almost the entire sequence to be disordered, with long uninterrupted segments exceeding 30 residues. This aligns with its known role in host-cell attachment and immune modulation, where structural flexibility is advantageous for evading immune recognition. Such disordered regions may serve as molecular shields, mimicking host proteins or acting as decoys to interfere with immune surveillance.

SPQ8B9Q8 (Fusion Protein F)

While slightly less disordered overall, this protein still showed extensive IDPRs in its N-terminal and central regions, crucial for membrane fusion and host-cell entry. These regions are highly conserved yet structurally flexible, suggesting a mechanism for conformational adaptability during the fusion process. The functional disordered regions identified by fiDPnn may represent viable therapeutic targets, where stabilizing these dynamic regions could interfere with viral entry.

CONCLUSION & FUTURE WORK

This study provides the first comprehensive map of intrinsic disorder in the hMPV proteome, revealing a significant proportion of disorder, particularly in proteins involved in viral entry, transcription, and immune evasion. Intrinsic disorder is not random but strategically embedded in functionally critical proteins. Highly disordered proteins like Glycoprotein G and Fusion Protein F represent promising drug targets, especially for disorder-based therapeutic design.

Traditional structure-based inhibitors may be insufficient, and novel strategies targeting the dynamic, flexible nature of IDPs/IDPRs are necessary. Future research should combine this computational insight with experimental validation and drug screening assays against identified disordered targets to develop next-generation antivirals with higher resilience to mutational escape.

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