Modeling Bird Flu Mutation Patterns and Cross-Species Transmission Using Sequence Analysis and a Novel Contrastive Learning and Influence-tree Graph Attention Network (CLIGAT)

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Avian influenza (Bird Flu) is a highly transmissive pathogen affecting over 166 million poultry and posing significant health risks to humans. Despite progress on surface proteins, differences between human and avian flu limit vaccine crossover. Internal proteins like the conserved NS1, which binds host proteins and increases viral replication, are promising targets for broader, cross-species flu intervention. Additionally, the 3D structure of viral-NS1 in complex with host-STAU2, an important feature of viral replication, remains unresolved. This study employs a two-part approach: (1) comparative analysis of 63 NS1 proteins to identify bird- and human-specific mutations and (2) development of a Contrastive Learning with Influence-Tree Graph Attention Network (CLIGAT) model to interpret how these mutations influence viral-host interactions. This study finds and maps 9 amino acid differences between bird and human NS1 variants and identifies R193Q as the strongest mutation (enhancing affinity), while S165F and I129T weakened viral affinity. CLIGAT achieved 98.9–99.2% accuracy in predicting these effects. In conclusion, three therapeutic targets are proposed, including residues 189–201 (linked to increased affinity), residues 162–168 (mutations that reduce affinity), and a potential allosteric site on Host-STAU2 (residues 446–470) that may destabilize viral-host interactions. Using contrastive learning and influence trees, this study improves the interpretability of 3D graph models by identifying direct (contact) and indirect interactions within the NS1-STAU2 complex. By constructing a novel 3D NS1-STAU2-RNA complex and understanding the effects of current mutations, these findings offer three potential intervention strategies to contain bird flu transmission.

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