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An Efficient Machine Learning Method to Identify Genetic Drivers of Avian Influenza Virus Adaptation to Humans

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Directional selection plays a major role in viral adaptation in different scenarios, such as resistance to antivirals or the emergence to new hosts. In this work we developed a method, based on a logistic regression model, to identify mutations subject to directional selection. We tested the model analyzing thousands of AIV (H5N1, H7N9) sequences from public datasets, to predict mutations facilitating the process of adaptation in host-switching. Additionally, the effect of predicted mutations in the viral fitness and viral infectivity of influenza mutant viruses was performed to validate the bioinformatics tools. We found mutations significantly associated with the emergence into humans in all AIV segments, being 238 and 62 mutations detected in H5N1 and H7N9, respectively. Most of them were located in the polymerase complex (PA, PB1 and PB2 genes). Interestingly, up to 18% of these mutations are known to be involved in AIV adaptive processes through host-switching. Related those influenza mutant viruses we reverted the candidate mutation driving human adaptation to avian state. Using reverse genetics, we introduced the mutations into human IAV (H3N2) backbone for each specific segment. We studied the infectivity of mutant viruses in ovo and in vitro at different times post infection compared to the wild-type virus. Three different cells lines were infected: A549 and HEK-293T as human cell lines and DF-1 as avian cell line. The results obtained in ovo showed that the most significant differences were observed in those viruses carrying the mutations in the PA, PB2, NP and PB1 segments. Regarding the in vitro study, we highlight that in the DF-1 cell line most of the mutant viruses reached higher titers at some point during the viral growth compared to the wild-type, enhancing viral growth in those mutant viruses with the mutations introduced in the viral polymerase and in the viral nucleoprotein. Consequently, the generated pipeline exhibits fastness and robustness in discerning manifestations of directional selection. Its application in AIV contexts suggests widespread adaptative trends in host-switching, thus exerting potential influence on all regions of the genome. Therefore, our results propose the efficacy of bioinformatics methodology designed to identify mutations crucial for host-switching.