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Unifying RSV Evolutionary Dynamics and Epidemiology Through Phylodynamic Analyses

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Abstract : Introduction: Human respiratory syncytial virus (hRSV) is the leading cause of severe respiratory tract infections in infants under the age of two. Genomic substitutions and related evolutionary dynamics of hRSV are of great influence on virus transmission behavior. The evolutionary patterns formed are due to a precarious interplay between the host immune response and RSV, thereby selecting the most viable and less immunogenic strains. Studying genomic profiles can teach us which genes and consequent proteins play an important role in RSV survival and transmission dynamics. Study design: In this study, genetic diversity and evolutionary rate analysis were conducted on 36 RSV subgroup B whole genome sequences and 37 subgroup A genome sequences. Clinical RSV isolates were obtained from nasopharyngeal aspirates and swabs of children between 2 weeks and 5 years old of age. These strains, collected during epidemic seasons from 2001 to 2011 in the Netherlands and Belgium by either conventional or 454-sequencing. Sequences were analyzed for genetic diversity, recombination events, synonymous/non-synonymous substitution ratios, epistasis, and translational consequences of mutations were mapped to known 3D protein structures. We used Bayesian statistical inference to estimate the rate of RSV genome evolution and the rate of variability across the genome. Results: The A and B profiles were described in detail and compared to each other. Overall, the majority of the whole RSV genome is highly conserved among all strains. The attachment protein G was the most variable protein and its gene had, similar to the non-coding regions in RSV, more elevated (two-fold) substitution rates than other genes. In addition, the G gene has been identified as the major target for diversifying selection. Overall, less gene and protein variability was found within RSV-B compared to RSV-A and most protein variation between the subgroups was found in the F, G, SH and M2-2 proteins. For the F protein mutations and correlated amino acid changes are largely located in the F2 ligand-binding domain. The small hydrophobic phosphoprotein and nucleoprotein are the most conserved proteins. The evolutionary rates were similar in both subgroups (A: 6.47E-04, B: 7.76E-04 substitution/site/yr), but estimates of the time to the most recent common ancestor were much lower for RSV-B (B: 19, A: 46.8 yrs), indicating that there is more turnover in this subgroup. Conclusion: This study provides a detailed description of whole RSV genome mutations, the effect on translation products and the first estimate of the RSV genome evolution tempo. The immunogenic G protein seems to require high substitution rates in order to select less immunogenic strains and other conserved proteins are most likely essential to preserve RSV viability. The resulting G gene variability makes its protein a less interesting target for RSV intervention methods. The more conserved RSV F protein with less antigenic epitope shedding is, therefore, more suitable for developing therapeutic strategies or vaccines.

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