

## Reverse Genetics of Coronavirus

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Received: November 12, 2021; Accepted: November 26, 2021; Published: December 03, 2021

Citation: Li QK (2021) Reverse Genetics of Coronavirus. Diagn Pathol Open 6: S8-030.

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### About the Study

In addition to the SARS coronavirus, the complete genome sequences of six species in the coronavirus genus of the coronavirus family have been reported by the latest research. Their lengths range from 27,317 not for HCoV-229E to 31,357 not for the murine hepatitis virus-A59, establishing the coronavirus genome as the largest known among RNA viruses. The basic organization of the coronavirus genome is shared with other members of the Nidovirus order (the torovirus genus, also in the family *Coronaviridae*, and members of the family *Arteriviridae*) in that the nonstructural proteins involved in proteolytic processing, genome replication and subgenomic mRNA synthesis (transcription) are encoded within the 5'-proximal two-thirds of the genome on gene 1 and the structural proteins are encoded with the 3'-proximal one-third of the genome. Genes for the major structural proteins in all coronaviruses occur in the 5'-3' order as S, E, M and N. The precise strategy used by coronaviruses for genome replication is not yet known, but many features have been established. This chapter focuses on some of the known features and presents some current questions regarding genome replication strategy, the cis-acting elements necessary for genome replication, the minimum sequence requirements for autonomous replication of an RNA replicon and the importance of gene order in genome application.

Despite its unique property as the largest of the known plus-strand RNA genomes, the coronavirus genome shares with those of other plus-strand RNA viruses the properties of infectiousness and replication in the cytoplasm in close association with cellular membranes, many of the basic features of coronavirus genome

structures and replication have been described in recent reviews. With the advent of reverse genetics enabling site-directed mutagenesis of any part of the genome, many of the mechanistic features of coronavirus genome replication that could previously be learned only from direct manipulation of defective interfering RNA can now be examined in the context of the whole virus genome. The current knowledge of coronavirus genome structure and organization and the cis-acting elements in coronavirus replication and raise selected questions that we believe are important for approaching a better understanding of coronavirus genome replication.

It is anticipated that reverse genetics, which now enables an alteration of any part of the coronavirus genome, will facilitate examination of the cis and trans-acting elements in RNA replication and transcription within the context of the intact genome. These elements have until now been studied primarily in DI RNAs. In light of precedents established with many much smaller plus-strand RNA viruses of animals and plants, it would not be surprising to find novel long-distance RNA-RNA and protein-RNA interactions involving genome sequences not present in DI RNAs. Long distance interactions are hinted at in comparative studies of DI RNAs and sgmRNAs. What genes are important in regulation of replication and transcription and how important is gene order in these processes? These questions can now be rigorously analyzed. It is anticipated that one practical outcome of reverse genetics will be the development of safe coronavirus-based replicon vectors, not necessarily only those that become packaged, for vaccine and other biomedical uses. Still in waiting is the development of an *in vitro* virus replication system such as that used for poliovirus.