Mosaic structure of human coronavirus NL63, one thousand years of evolution

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Before the SARS outbreak only two human coronaviruses (HCoV) were known: HCoV-OC43 and HCoV-229E. With the discovery of SARS-CoV in 2003, a third family member was identified. Soon thereafter, we described the fourth human coronavirus (HCoV-NL63), a virus that has spread worldwide and is associated with croup in children. We report here the complete genome sequence of two HCoV-NL63 clinical isolates, designated Amsterdam 57 and Amsterdam 496. The genomes are 27,538 and 27,550 nucleotides long, respectively, and share the same genome organization. We identified two variable regions, one within the 1a and one within the S gene, whereas the 1b and N genes were most conserved. Phylogenetic analysis revealed that HCoV-NL63 genomes have a mosaic structure with multiple recombination sites. Additionally, employing three different algorithms, we assessed the evolutionary rate for the S gene of group Ib coronaviruses to be approximately $3 \times 10^{-4}$ substitutions per site per year. Using this evolutionary rate we determined that HCoV-NL63 diverged in the 11th century from its closest relative HCoV-229E.

type: journal paper/review (English)
date of publishing: 03-10-2006
journal title: J Mol Biol (364/5)
ISSN print: 0022-2836
pages: 964-73