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Packaging signal of SARS-CoV-2

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Selective genome packaging during viral assembly is a crucial step in the viral life cycle. The nucleocapsid (N) protein is thought to recognize the cis-acting packaging signal within viral genomic RNA, but the packaging signal of SARS-CoV-2 remains elusive. Here, we employed two complementary CLIP-seq techniques and mapped 22 regions interacting with SARS-CoV-2 N proteins. Using the virus-like particle and defective-interfering RNA systems, we discovered putative packaging elements clustered within the nsp12 polymerase-coding region. Synonymous point mutations revealed RNA sequences critical for triggering RNA packaging into virus particles. Furthermore, introducing these mutations to the full-length viral genome in a reverse genetics model impaired viral encapsulation and propagation without impacting viral RNA synthesis. Our study identifies the SARS-CoV-2 packaging signal residing within a highly conserved genome region, which may serve as therapeutic targets for current and future coronavirus outbreaks.