Figure S1.

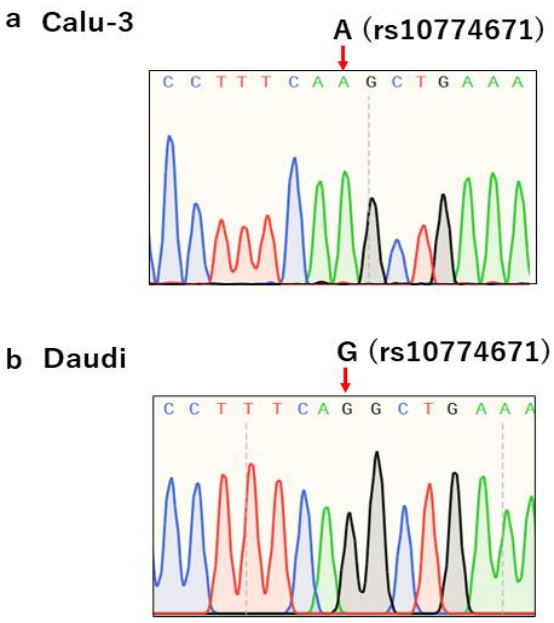

Fig. S1. Genotyping of the rs10774671 SNP. SNP genotyping of Calu-3 cells (a) and Daudi cells (b).

Figure S2.

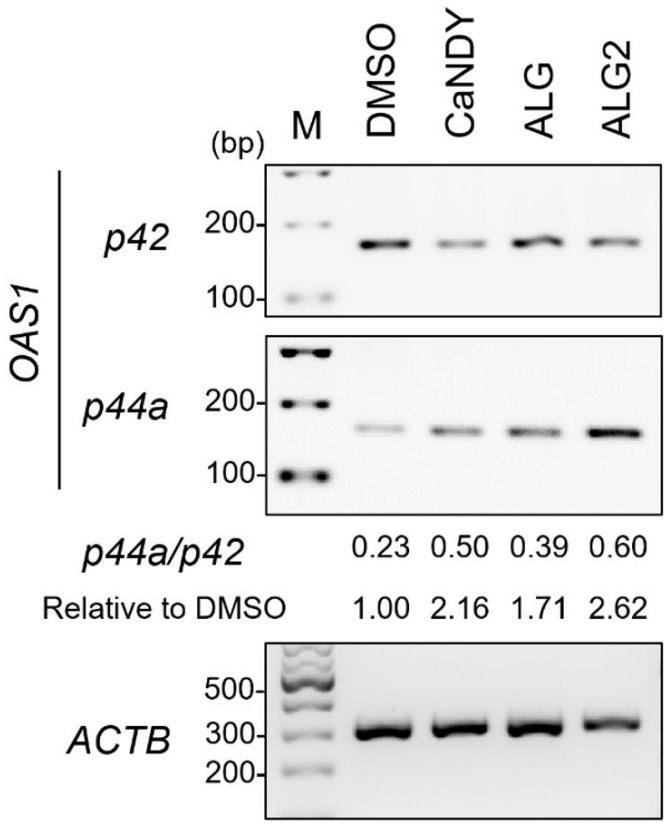

Fig. S2. CLK inhibitors affect the OAS1 alternative splicing profile. RT-PCR of OAS1 alternative splicing in Calu-3 cells. Calu-3 cells were treated with 0.1% DMSO, 10 μM CaNDY, 10 μM ALGERNON (ALG), or 10 μM ALGERNON2 (ALG2) for 18 h, and extracted RNAs were analyzed using RT-PCR. p44a/p42 indicates fold-change in the *p44a*/*p42* ratio upon densitometry. Relative values to DMSO conditions are presented together.

Figure S3.

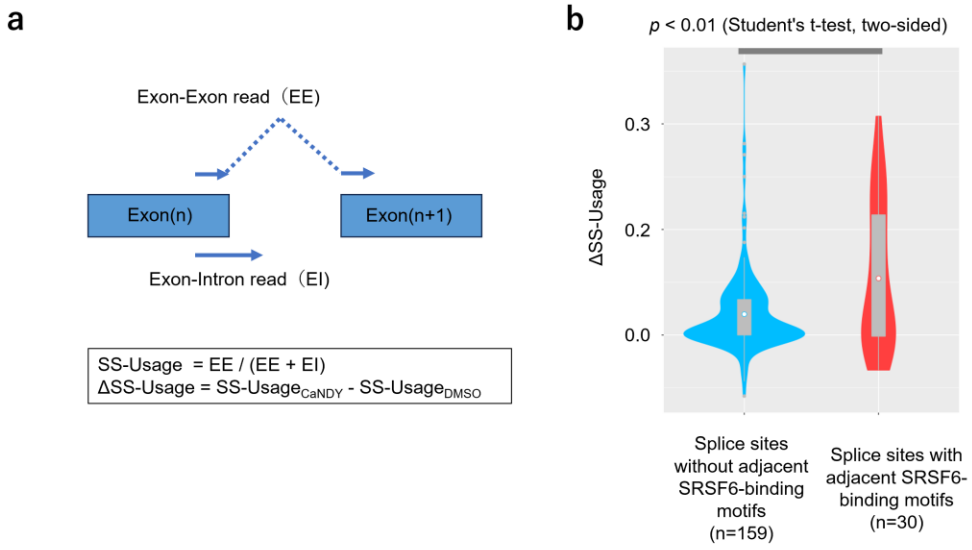

Fig. S3. Relationship between SRSF6 binding adjacent to the 5′ splice site and enhanced splice site (SS) usage under CaNDY treatment. (a) Conceptual diagram for calculating SS usage based on the Exon–Exon read and Exon–Intron read counts from RNA-seq results. (b) Violin plot for Δ SS-Usage for SS without and with SRSF-binding motifs around 5′ splice sites; 5′ splice sites were used when the introns were located immediately before the terminal exons; the SS-Usage$_{DMSO}$ was < 0.25. Positions -10 to + 20 of the 5′ splice sites were applied for the motif search. To determine SRSF6 binding sites, a motif described on the ESEfinder 2.0 website [16] was used with 3.0 as the threshold.

Figure S4.

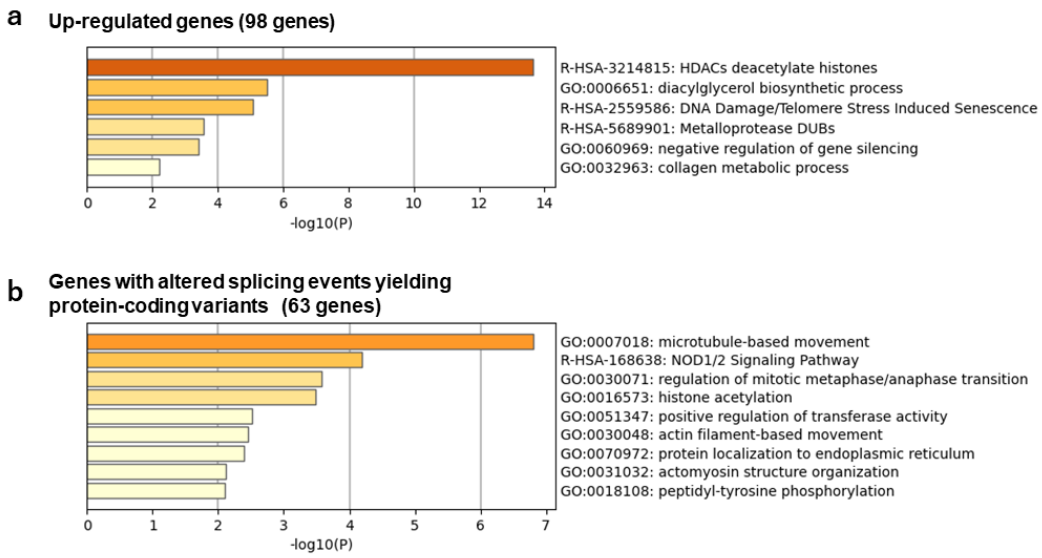

Fig. S4. Pathway analysis for CaNDY-affected genes. Pathway analyses for 98 differentially upregulated genes (a) and 63 differentially alternative spliced genes (b) in CaNDY-treated Calu-3 cells. For the differentially alternative spliced genes, the splicing events that promote productive forms were applied (see Methods for details). These analyses were performed with the Metascape web server [18].

Figure S5.

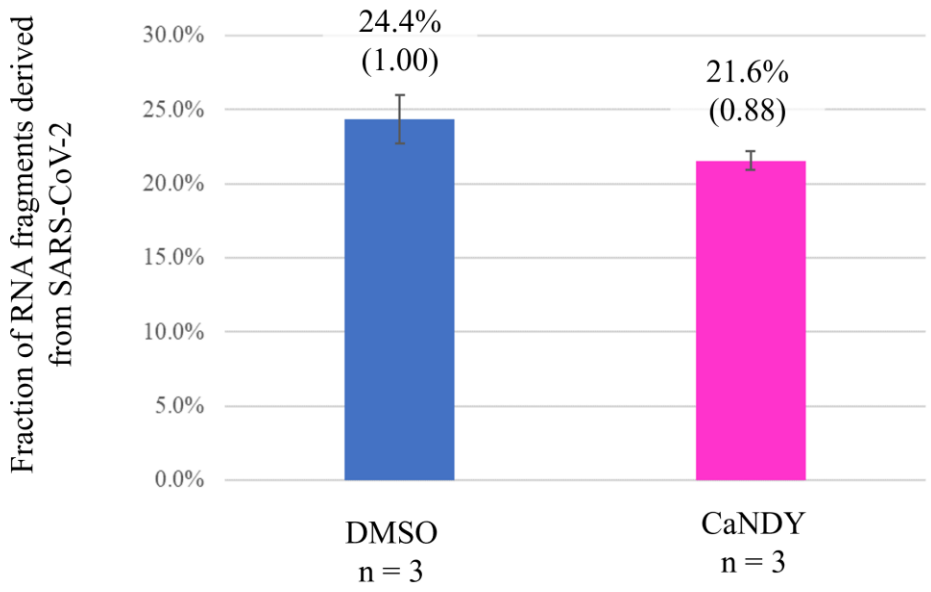

Fig. S5. Bar plot for the fraction of RNA fragments derived from SARS-CoV-2 calculated with RNA-seq data. Values in parentheses represent the relative amount of viral reads to the DMSO conditions. Error bars show the range of standard deviation.

Figure S6.

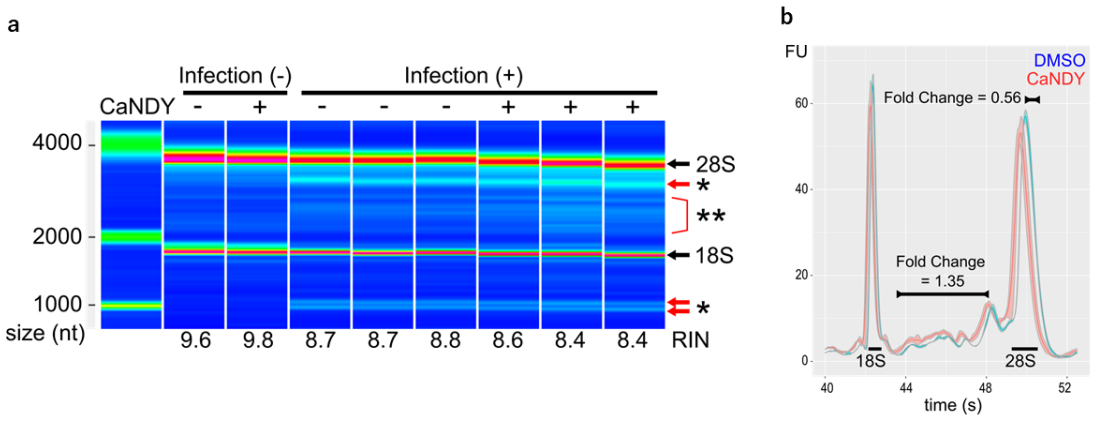

Fig. S6. RNA degradation in SARS-CoV-2-infected cells. (a) Gel image based on the results of the Bioanalyzer analysis. (b) Line graphs for fluorescence units according to migration times. Solid lines: mean values, ribbons: range of standard errors.

Figure S7.

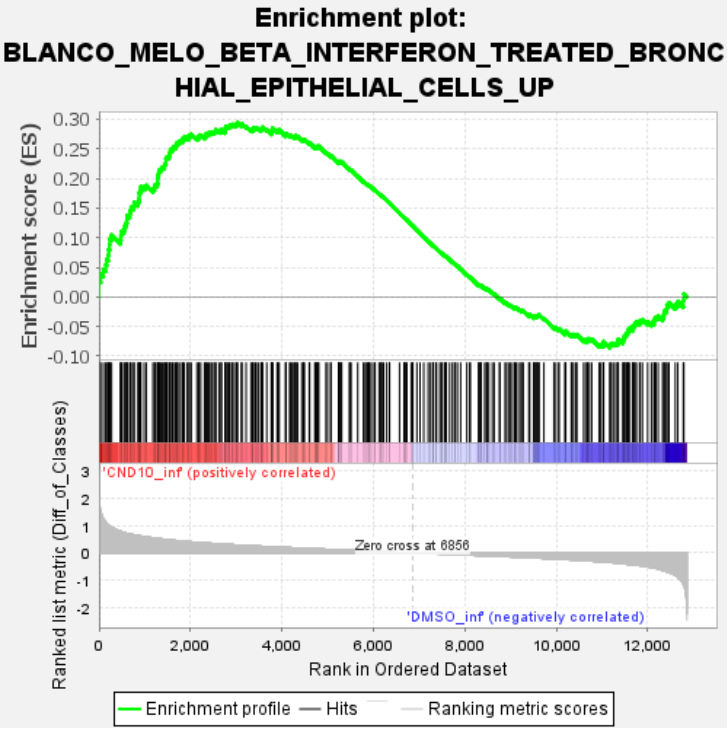

Fig. S7. Gene Set Enrichment Analysis (GSEA) results [19]. A gene ranking from SARS-Cov-2-infected Calu-3 cells with CaNDY pre-treatments versus the infected cells without CaNDY pre-treatments was used. A gene set named "BLANCO_MELO_BETA_INTERFERON_TREATED_BRONCHIAL_EPITHELIAL_CELLS_UP" [4] showed the normalized enrichment score (NES) 1.31 and p-value < 0.05.

Figure S8.

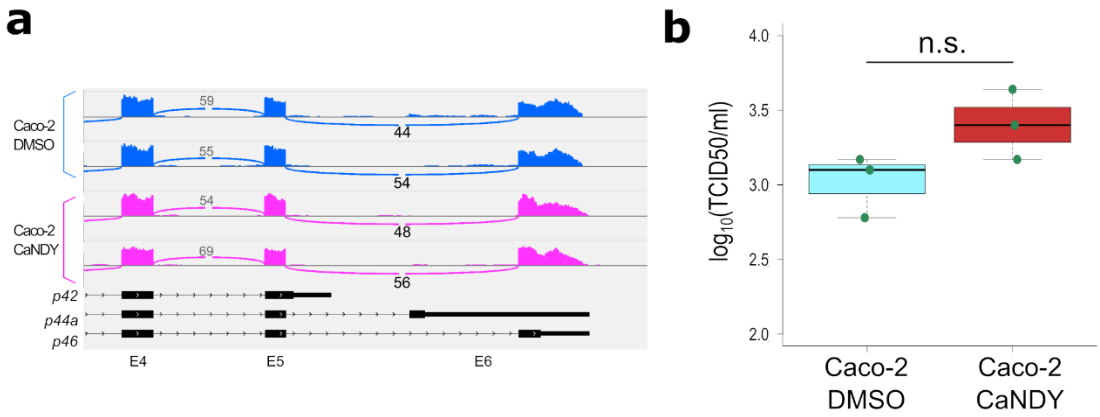

Fig. S8. CLK inhibitor exerts a non-significant effect on Caco-2 cells. **a,** RNA-Seq results in Caco-2 cells, indicated by a Sashimi plot for a region covering *p42*, *p44a*, and *p46*, treated with 0.1% DMSO or 10 µM CaNDY for 24 h. **b,** Box plots showing logarithm translated virus titers of Caco-2 cells. Center line, median; box limits, upper and lower quartiles; whiskers, 1.5× interquartile range; n.s., not significant; $p \geq 0.05$ by two-sided Student's *t*-test.

Figure S9.

```
CLUSTAL O(1.2.4) multiple sequence alignment


OAS1.p46        MMDLRNTPAKSLDKFIEDYLLPDTCFRMQINHAIDIICGFLKERCFRGSSYPVCVSKVVK    60
OAS1.p44a       MMDLRNTPAKSLDKFIEDYLLPDTCFRMQINHAIDIICGFLKERCFRGSSYPVCVSKVVK    60
OAS1.p42        MMDLRNTPAKSLDKFIEDYLLPDTCFRMQINHAIDIICGFLKERCFRGSSYPVCVSKVVK    60
                ************************************************************

OAS1.p46        GGSSGKGTTLRGRSDADLVVFLSPLTTFQDQLNRRGEFIQEIRRQLEACQRERAFSVKFE    120
OAS1.p44a       GGSSGKGTTLRGRSDADLVVFLSPLTTFQDQLNRRGEFIQEIRRQLEACQRERAFSVKFE    120
OAS1.p42        GGSSGKGTTLRGRSDADLVVFLSPLTTFQDQLNRRGEFIQEIRRQLEACQRERAFSVKFE    120
                ************************************************************

OAS1.p46        VQAPRWGNPRALSFVLSSLQLGEGVEFDVLPAFDALGQLTGGYKPNPQIYVKLIEECTDL    180
OAS1.p44a       VQAPRWGNPRALSFVLSSLQLGEGVEFDVLPAFDALGQLTGGYKPNPQIYVKLIEECTDL    180
OAS1.p42        VQAPRWGNPRALSFVLSSLQLGEGVEFDVLPAFDALGQLTGGYKPNPQIYVKLIEECTDL    180
                ************************************************************

OAS1.p46        QKEGEFSTCFTELQRDFLKQRPTKLKSLIRLVKHWYQNCKKKLGKLPPQYALELLTVYAW    240
OAS1.p44a       QKEGEFSTCFTELQRDFLKQRPTKLKSLIRLVKHWYQNCKKKLGKLPPQYALELLTVYAW    240
OAS1.p42        QKEGEFSTCFTELQRDFLKQRPTKLKSLIRLVKHWYQNCKKKLGKLPPQYALELLTVYAW    240
                ************************************************************

OAS1.p46        ERGSMKTHFNTAQGFRTVLELVINYQQLCIYWTKYYDFKNPIIEKYLRRQLTKPRPVILD    300
OAS1.p44a       ERGSMKTHFNTAQGFRTVLELVINYQQLCIYWTKYYDFKNPIIEKYLRRQLTKPRPVILD    300
OAS1.p42        ERGSMKTHFNTAQGFRTVLELVINYQQLCIYWTKYYDFKNPIIEKYLRRQLTKPRPVILD    300
                ************************************************************

OAS1.p46        PADPTGNLGGGDPKGWRQLAQEAEAWLNYPCFKNWDGSPVSSWILLAESNSADDETDDPR    360
OAS1.p44a       PADPTGNLGGGDPKGWRQLAQEAEAWLNYPCFKNWDGSPVSSWILLMRQRLREVRSLAQG    360
OAS1.p42        PADPTGNLGGGDPKGWRQLAQEAEAWLNYPCFKNWDGSPVSSWILLVRPPASSLPFIPAP    360
                ********************************************* .    .

OAS1.p46        RYQKYGYIGTHEYPHFSHRPSTLQAASTPQAEEDWTCTIL-----      400
OAS1.p44a       HQLTSG----------------------GNGIQAQWTLKPVLMSLC     384
OAS1.p42        LHEA------------------------------------------     364
```

Fig. S9. Multiple alignment of *OAS1* splicing isoform amino acid sequences; calculated with Clustal Omega [20].

Figure S10.

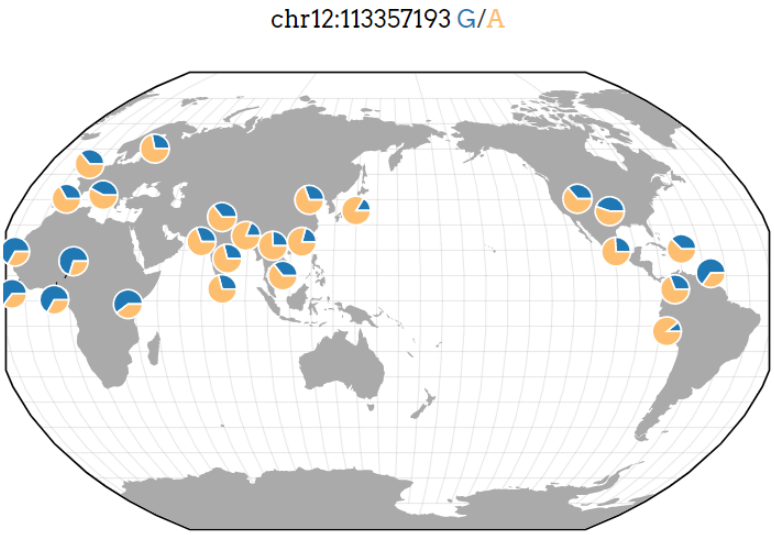

Fig. S10. Allele frequency of the rs10774671 SNP. World map showing the relationship between the location and allele frequency of the SNP. The position in the hg19 genome is shown. The map was obtained from the Geography of Genetic Variants (GGV) browser [21].