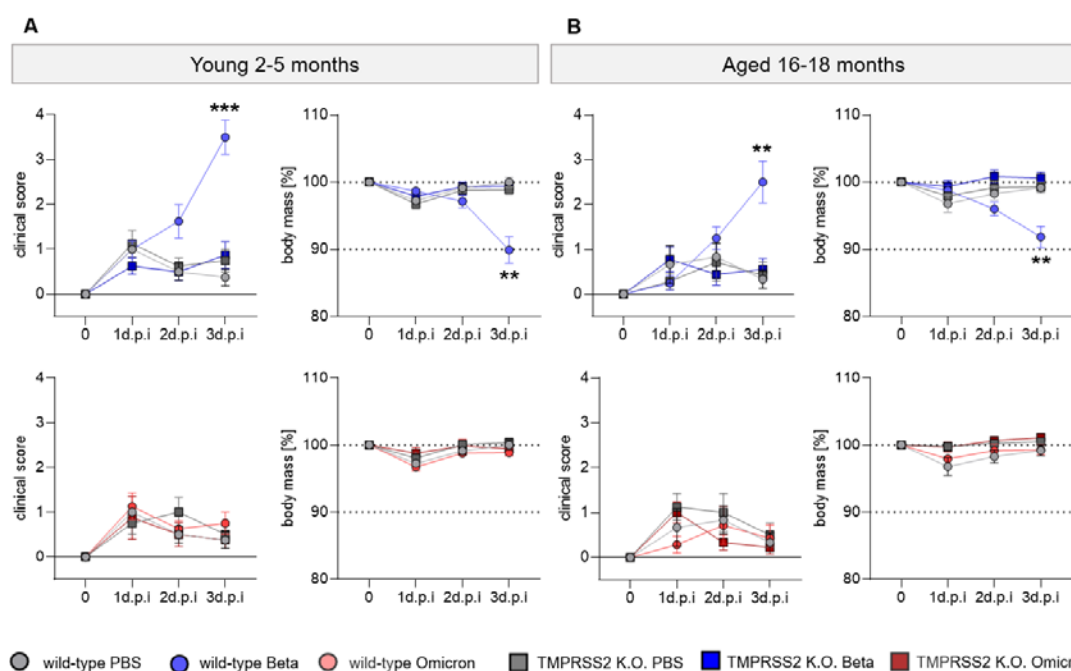


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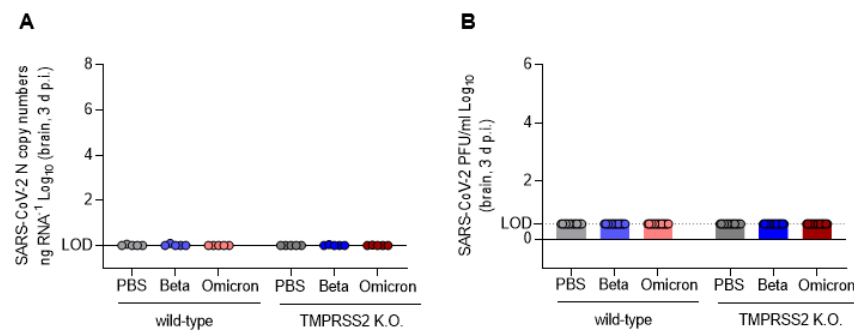
# TMPRSS2 is essential for SARS-CoV-2 Beta and Omicron infection

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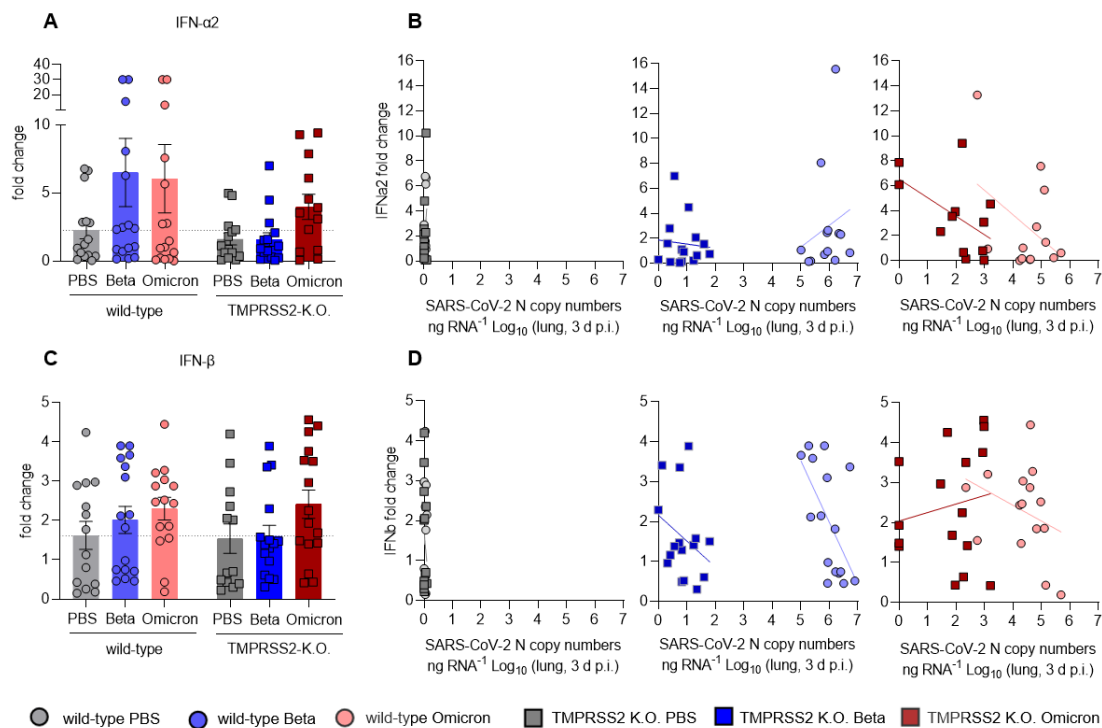
## Supplementary Materials:



**Supplementary Figure S1:** SARS-CoV-2 Beta and Omicron pathogenesis in young and aged mice. Wild-type and TMPRSS2 K.O. mice were intra-nasally infected with  $1 \times 10^4$  PFU of SARS-CoV-2 Beta or Omicron. Intra-nasal PBS-application was used as treatment control. **(A)** Young 2-5 months old mice show significantly altered clinical scores and body mass [%] for Beta infected wild-type mice at 3 dpi. Omicron infected young mice show no difference. Animal numbers: each group  $n=8$  **(B)** Aged 16-18 months old show equal changes in clinical scores and body mass. Significant increase in clinical score and reduction in body mass can be displayed for Beta infected wild-type mice. Omicron infection results in no changes in pathogenesis in aged mice. Animal numbers wt mice: PBS  $n=8$ ; Beta  $n=9$ ; Omicron  $n=8$ ; Animal numbers TMPRSS2 K.O. mice: PBS  $n=7$ ; Beta  $n=9$ ; Omicron  $n=9$  (A, B) Statistical significance for sequential body mass and clinical scores was calculated using Two-Way ANOVA with Geisser-Greenhouse correction and multiple comparison and correction for multiple comparisons following Tukey and are shown as mean  $\pm$  SEM (\*\* $p < 0.01$ , \*\*\* $p < 0.001$ ).



**Supplementary Figure S2:** Viral load and infectious-virus titers after infection with SARS-CoV-2 Beta and Omicron in brain tissue **(A)** SARS-CoV-2 N gene copy numbers as copy number/ng RNA Log<sub>10</sub> at 3 dpi with SARS-CoV-2 Beta (blue) and Omicron (red) in brain homogenates. **(B)** SARS-CoV-2 Beta and Omicron infectious-virus titer as PFU/ml Log<sub>10</sub> at 3 dpi in brain homogenates. Dotted lines indicate the limit of detection (LOD) for infectious-virus titers



**Supplementary Figure S3:** TMPRSS2 affects the Type I interferon response in SARS-CoV-2 infected mice. mRNA expression in isolated lung tissue of **(A)** IFNα2 and **(B)** IFNβ was detected in wild-type and TMPRSS2 K.O. mice intra-nasally infected with 1x10<sup>4</sup> PFU of SARS-CoV-2 Beta or Omicron and PBS respectively. The fold change was depicted as mean values ± SEM **(B, D)** Fold change of Type I interferon **(B)** IFNα2 and **(D)** IFNβ correlated to the SARS-CoV-2 N gene copy numbers as copy number/ng RNA Log<sub>10</sub> at 3 dpi with PBS (left) SARS-CoV-2 Beta (middle) and Omicron (right) comparing wild-type and TMPRSS2 K.O.