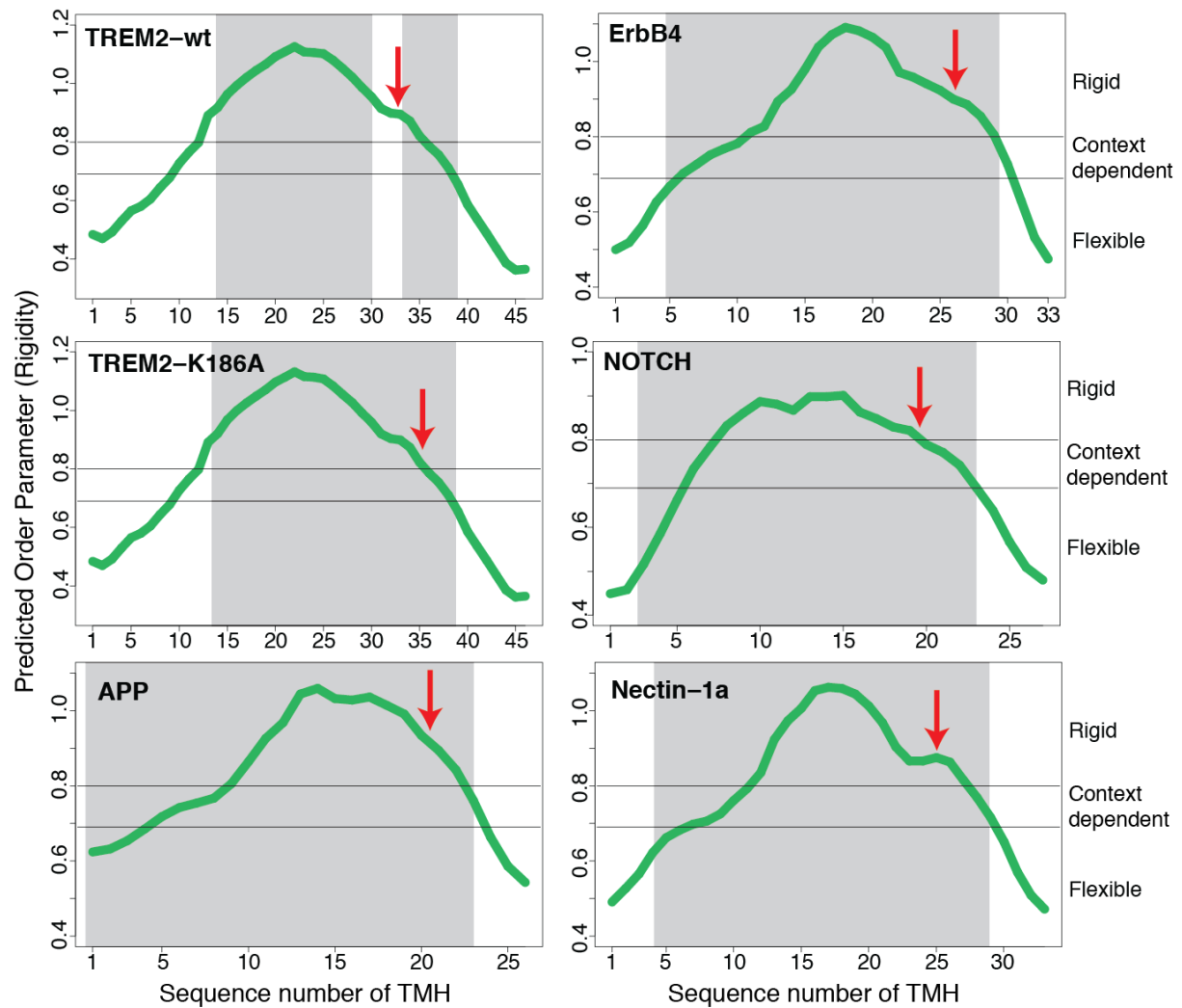


Appendix to:

γ -Secretase cleavage of the Alzheimer risk factor TREM2 is determined by its intrinsic structural dynamics

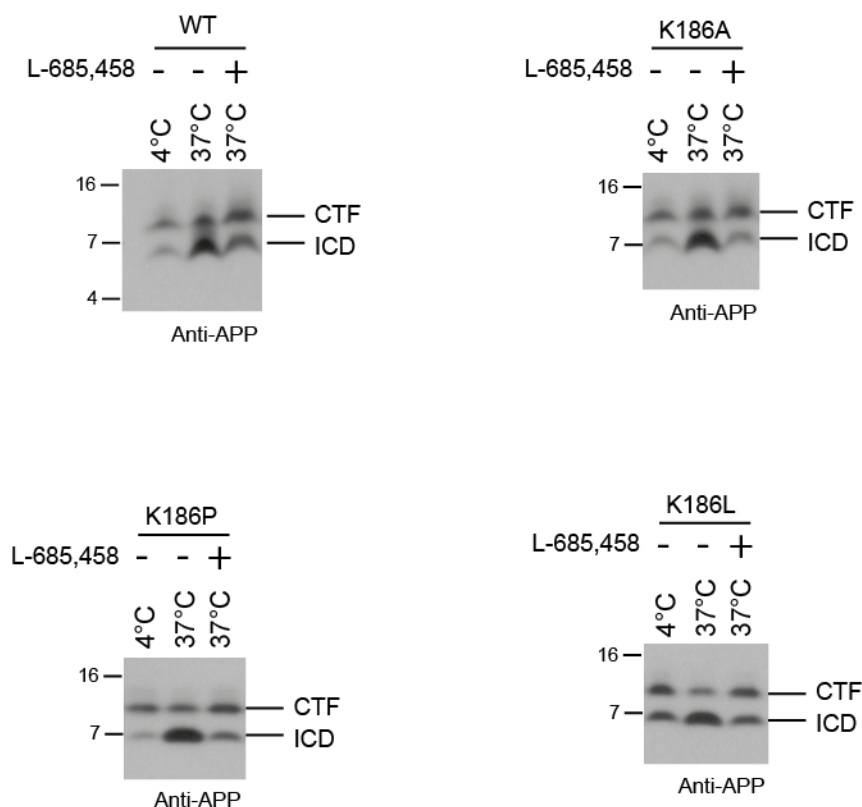
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Appendix Figure S1 - Estimation of TMH dynamics of various γ -secretase substrates.

Sequence-based prediction of the order parameter (= rigidity) of selected proteins using the MemBrain online server (Yin *et al*, 2018). The position of the ϵ cleavage site of γ -secretase is taken from (Beel & Sanders, 2008) and is indicated by a red arrow. Grey shaded areas indicate predicted α -helical regions in each case. These patterns clearly show that initial γ -secretase cleavage takes place at approximately 3 residues distance from the C-terminal end of substrate helices where predicted order parameters are low. In the TREM2-TMH case, this distance is larger due to helix destabilization induced by the presence of K186 in the membrane. The regular 3-residue pattern can again be observed for the TREM2-TMH K186A variant.



Appendix Figure S2 - Immunoblot analysis of samples used for mass spectrometry.

As a positive control for the mass spectrometric data shown in Fig. 5 immunoblot analyses of corresponding samples were conducted. Inhibition of APP ICD formation upon γ -secretase inhibition could be confirmed in all cases.

Appendix References

Beel AJ, Sanders CR (2008) Substrate specificity of gamma-secretase and other intramembrane proteases. *Cell Mol Life Sci* 65: 1311-1334

Yin X, Yang J, Xiao F, Yang Y, Shen HB (2018) MemBrain: An Easy-to-Use Online Webserver for Transmembrane Protein Structure Prediction. *Nanomicro Lett* 10: 2