Side-Chain to Main-Chain Hydrogen Bonding Controls the Intrinsic Backbone Dynamics of the Amyloid Precursor Protein Transmembrane Helix

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SUPPORTING MATERIAL

Three Supplementary Figures provide additional information about the analysis of the MD simulations and a comparison of the DHX kinetics of the TM-C model peptides with unrelated TMDs with more average amino acid compositions.

Figure S1: Convergency of the simulations.

Figure S2: Definition of collective coordinates.

Figure S3: DHX kinetics of APP TM-C model peptides.

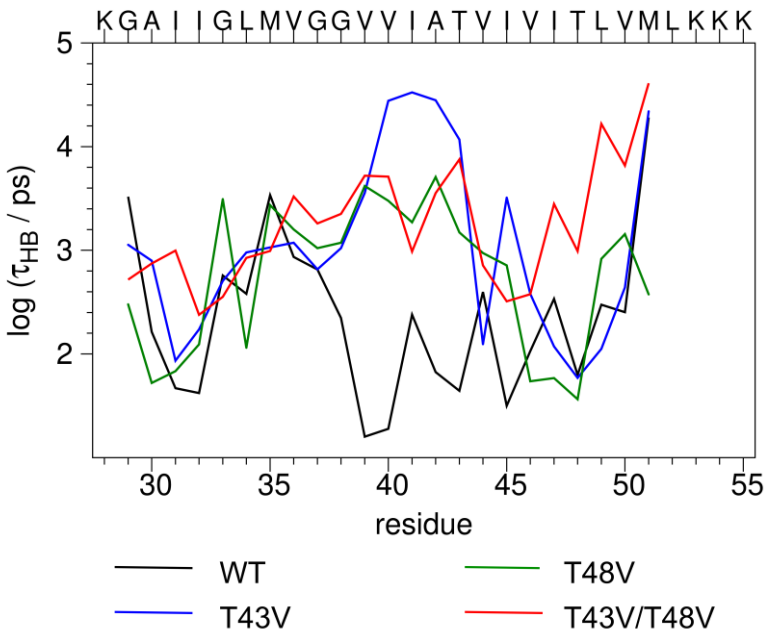

Figure S1. **Convergence of the simulations**. To estimate the statistical efficiency of the sampling of the backbone dynamics of the A28-55 model peptides (for sequence compare Fig. 1 A, the wild-type sequence is given on top), the time correlation function C(t) of the α-helical H-bonds was analyzed. The correlation function C(t) was constructed from the H-bond operator h(t) according to $C(t) = < h(0)\, h(t) >$, where h(t) = 1 if the H-bond is formed at time t, and h(t) = 0 otherwise. Brackets denote averaging over the whole 150 ns used for analysis. Using a standard geometry criterium (compare Methods), the H-bond is counted as "on" if the O(i) … H(i+4) distance is < 0.26 nm and the O(i) … H(i+4)-N(i+4) angle deviates not more than 60° from linear geometry. The autocorrelation time τ_{HB} was determined from a two-exponential fit of C(t) as the mean of slow and fast components weighted with the corresponding populations. Correlation times in the range from 100 ps to 5 ns indicate statistical inefficiencies (1) of $s = 2\, \tau_{HB} < 10$ ns. Only H-bonds at the fraying termini and in the locally unfolded turn between residues 40 to 43 of the T43V mutant have correlation times up to 30 ns. These long correlation times indicate incomplete sampling of the conformational space in these regions during our 150 ns analysis time. This incomplete sampling translates into large standard deviations around the site-specific block averaged properties shown in Fig. 2 which were determined from 30 ns time windows.

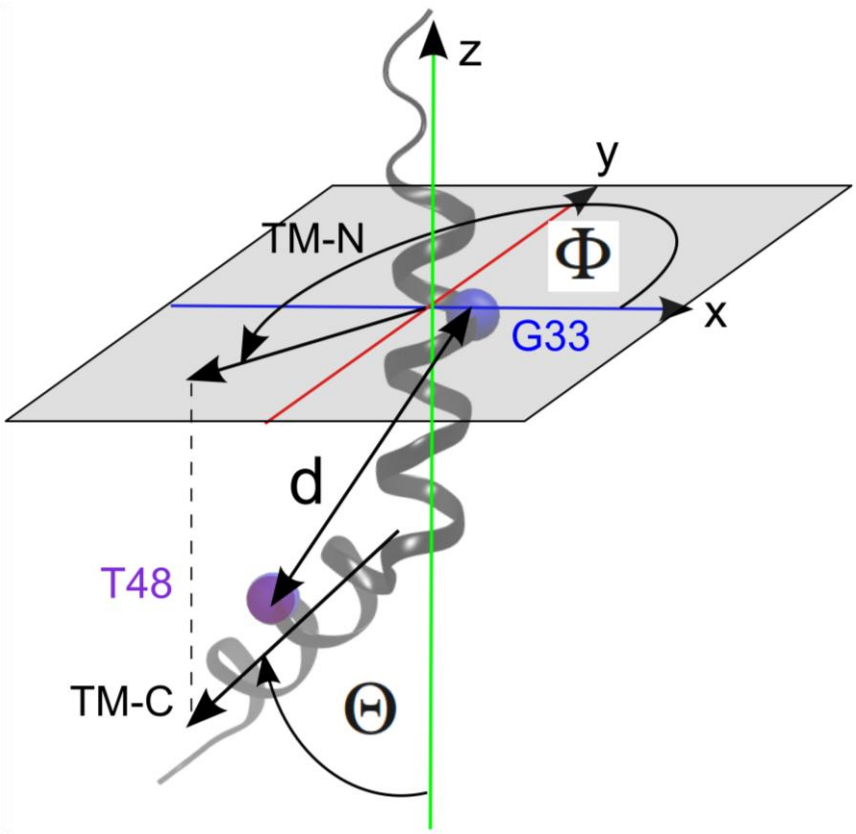

Figure S2. Definition of collective coordinates. Three coordinates characterize the movement of the C-terminal part (TM-C, compare Fig. 1 A) of the APP TMD relative to the N-terminal part (TM-N): bending angle Θ , rotation angle Φ, and interhelical distance d. The backbone atoms (C_α, C, N) of the N-terminal residues 30 – 36 were oriented with a rigid body fit to an ideal α-helix in z-direction. The center of mass of these atoms was translated to the center of the coordinate system and the whole helix was translated and rotated so that the C_α atom of residue G33 lies on the positive x-axis. The orientation of TM-C is characterized by the average orientation of vectors pointing from C(i) to N(i+4) (i = 44 … 47). This TM-C vector is projected onto the x-y plane perpendicular to the orientation of TM-N. The bending angle Θ is the angle between the negative z-axis and the TM-C helix vector, the rotation angle Φ of TM-C is determined with respect to the x-axis (which is the line between the center of the TM-N helix and the C_α of G33). The interhelical distance d is arbitrarily chosen as distance between the C_α atoms of residue G33 in TM-N and residue T48 in TM-C, respectively. Due to mutation induced distortions in the center of the helix, distances d and bending angles Θ are not correlated. As a consequence of these distortions standard routines for the determination of helix axes and bending angles do not work properly.

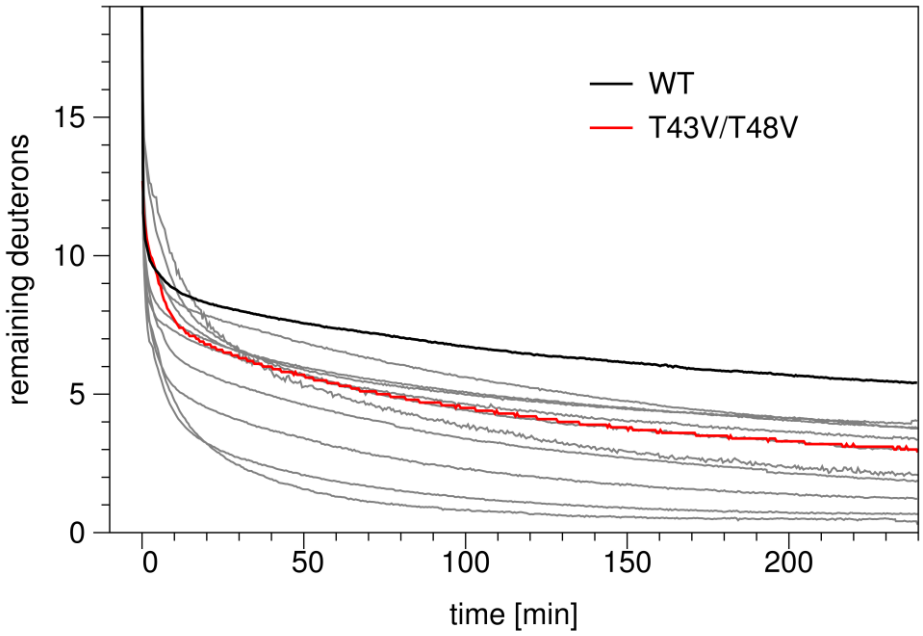

Figure S3. DHX kinetics of APP TM-C model peptides. Shown is a comparison of the DHX kinetics of wt A37-55 (black) and the T43V/T48V double mutant (red) to those of unrelated natural TMDs (grey) with more average amino acid compositions but identical hydrophobic length and terminal Lys tags (all data except those of T43V/T48V are taken from ref. (2)).

Supporting References:

1. Allen, M. P., and D. J. Tildesley. 1987. Computer Simulations of Liquids, Oxford University Press.
2. Pester, O., A. Götz, G. Multhaup, C. Scharnagl, and D. Langosch. 2013. The Cleavage Domain of the Amyloid Precursor Protein Transmembrane Helix does not Exhibit Above-Average Backbone Dynamics. ChemBioChem 14:1943-1948.