

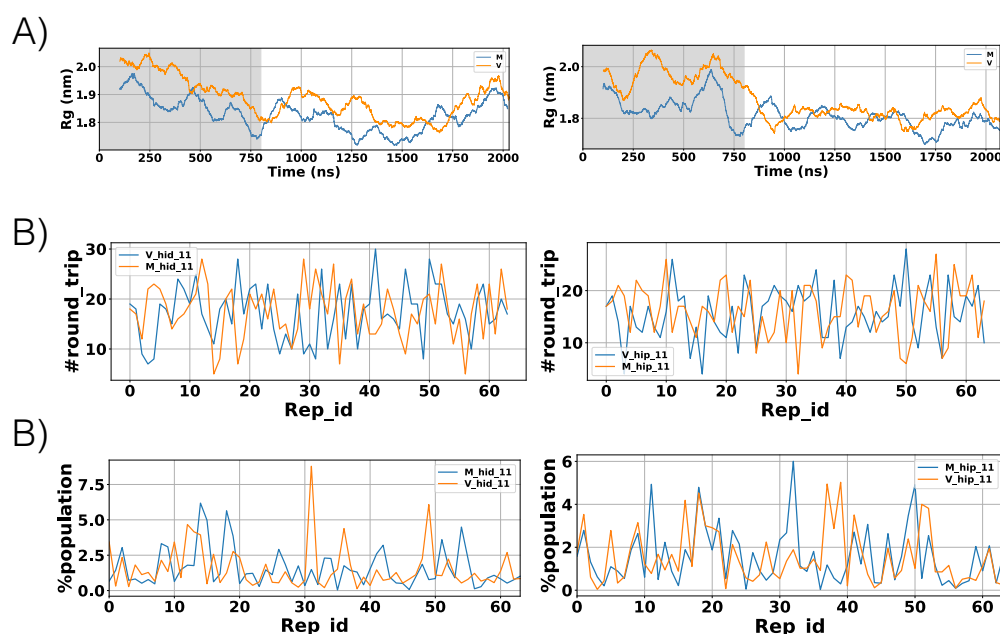
# Mechanism underlying conformational effects of a disease-associated hydrophobic-to-hydrophobic substitution on an intrinsically disordered region

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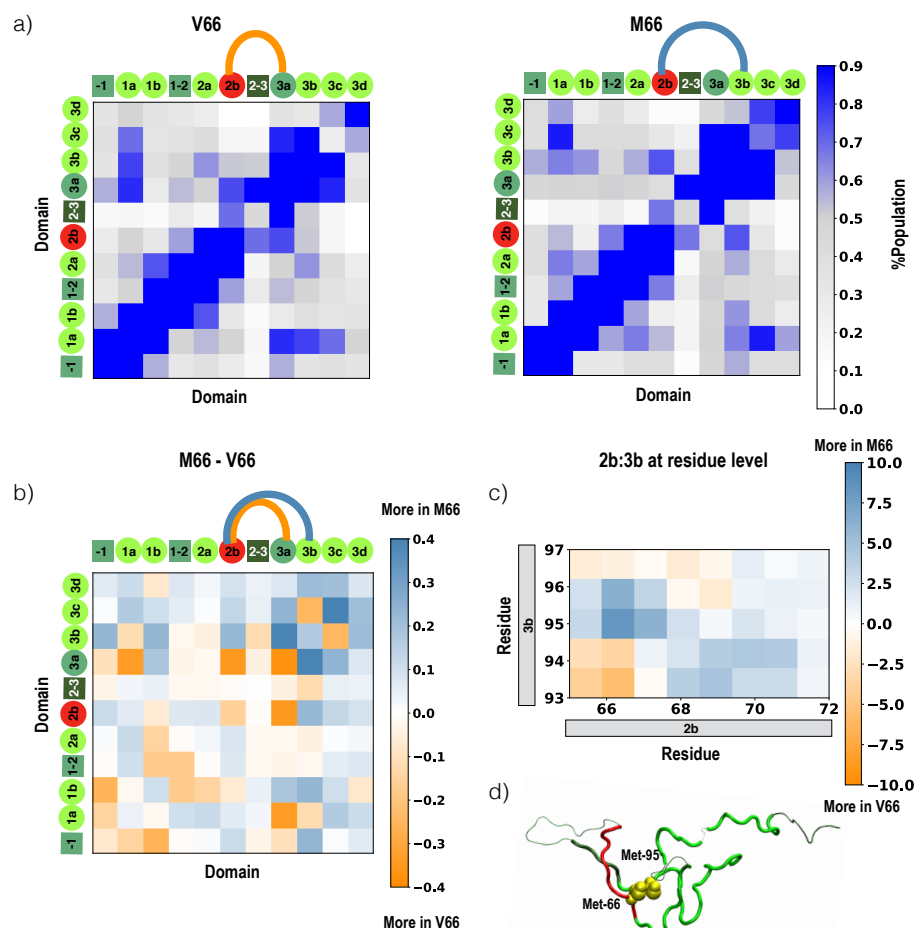
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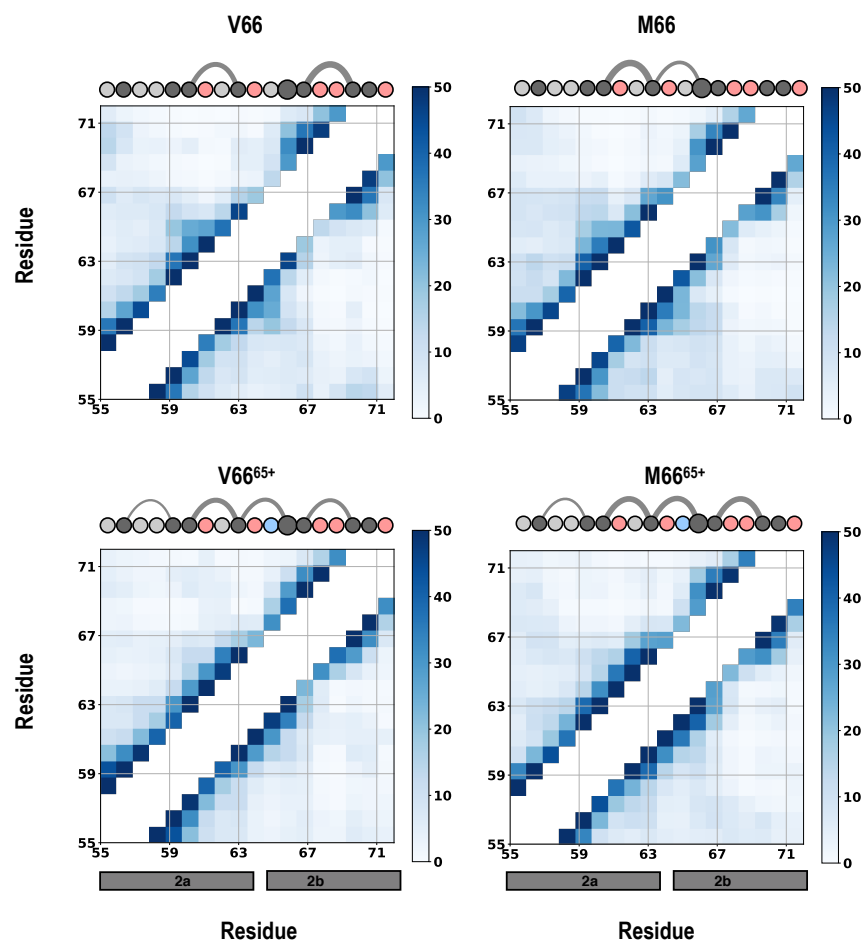
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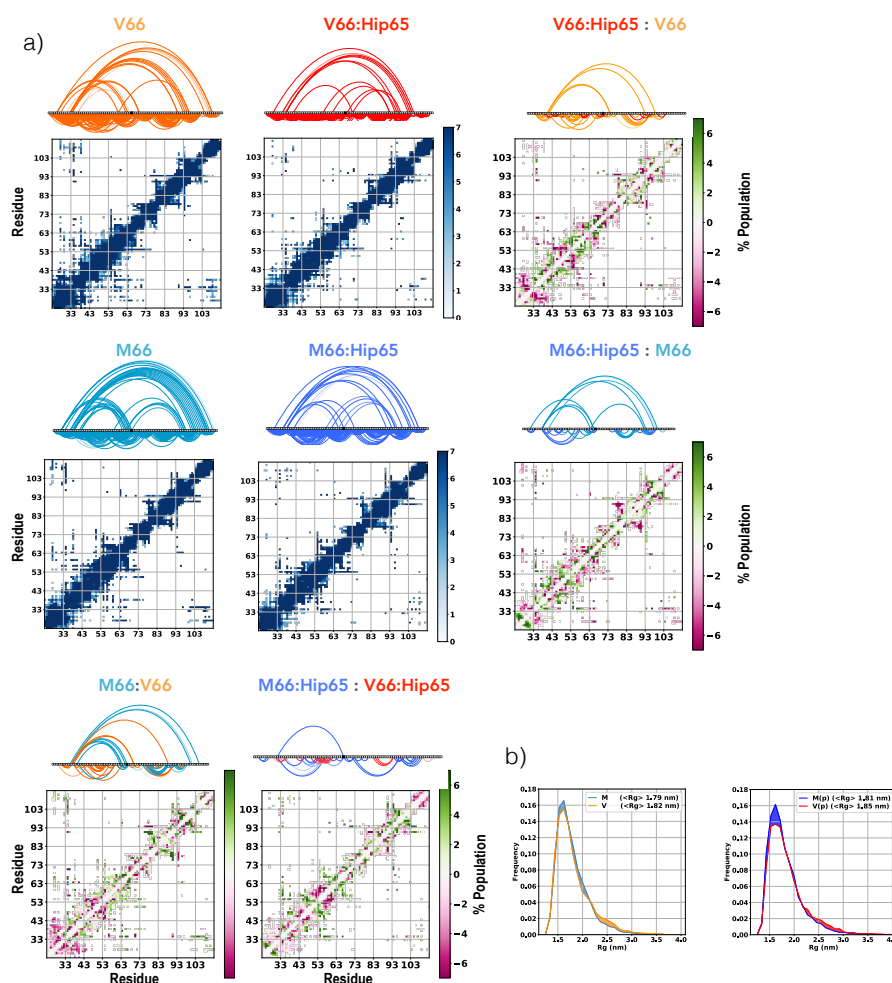
**S1 Fig. Mixing of replicas during the simulation.** Time series of blocked Rg distribution and number of round trips completed by each replica for protonated His65 and neutral His65.



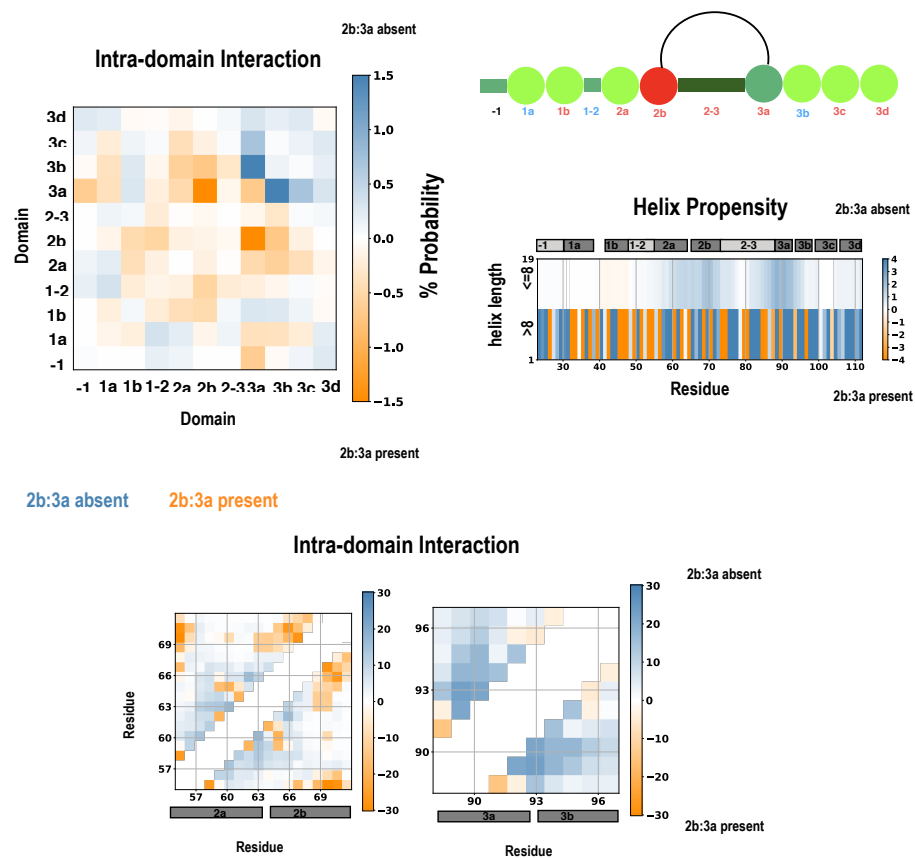
**S2 Fig. Simulation predicted secondary structure properties.** a) Difference in helix length (top) and beta length (bottom) for each residue. In agreement with the experiment, we find higher tendency of forming longer helix at SNP domain and Janus domain. V66 has higher tendency of forming beta at Janus domain. b) Helix length distribution at each residue when 66 is in the helix region of ramachandran map (methods)



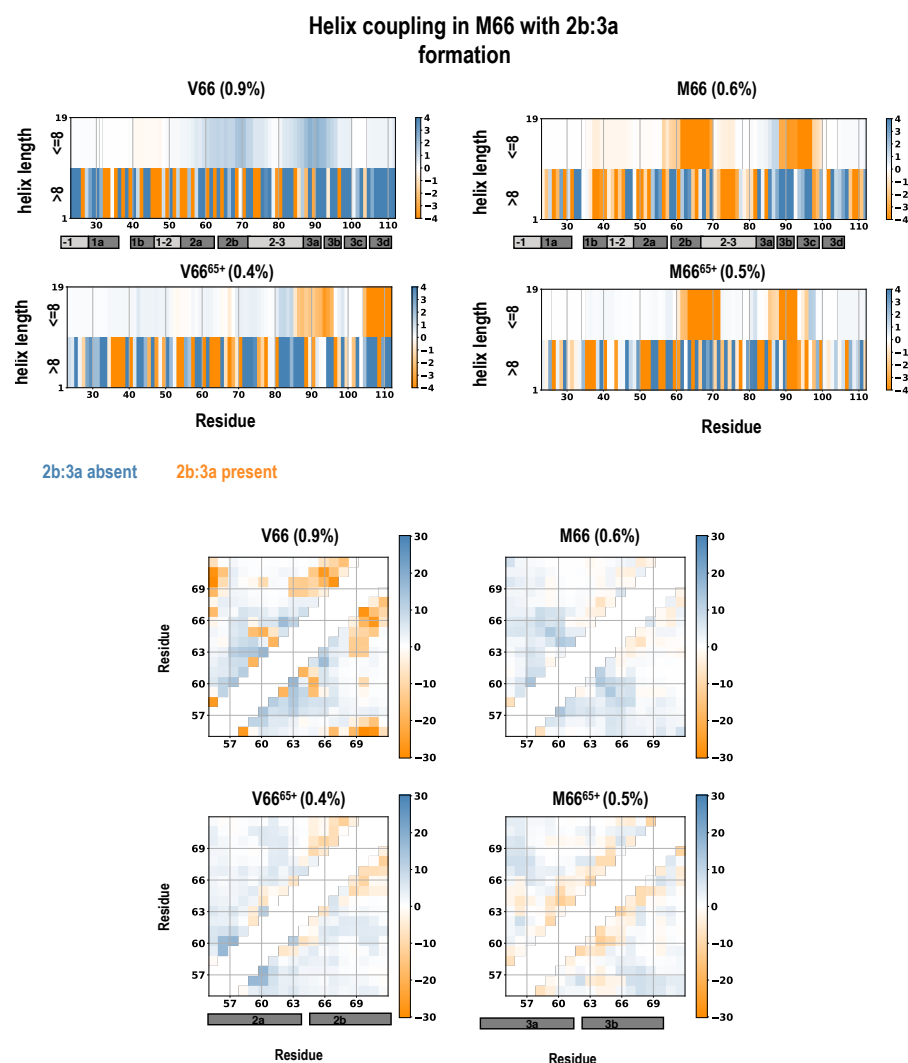
**S3 Fig. Intra-domain contacts at domain 2.** Weight of contact formed at every residue pair. M66 forms strong contact at residue M66:F63, whereas V66 forms strong contact at residue I67:L70.



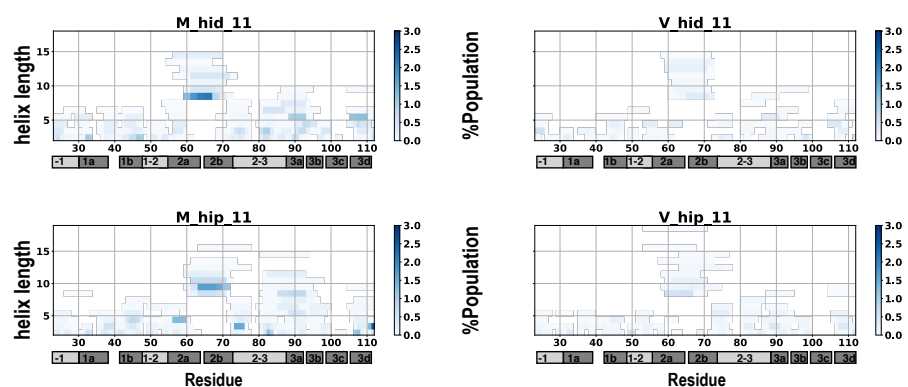
**S4 Fig. Linear networks of transient tertiary contacts.** a) The backbone tertiary-contact network is made for V66 and M66, with each residue serving as a node in the network, as described in Methods. A contact is formed if the C $\alpha$  atoms of two residues are within .85nm of each other. If the two residues forming contact are more than 24 residues apart the edge is drawn on the top of the node, otherwise the edge is drawn at the bottom of the node. Backbone interactions serve as edges between individual network nodes; the thickness and the transparency of the edge corresponds to the strength of the contact. Contacts observed in 37 or more replicas are only visible. Gain of protonation states loses contacts formed from x2 region for both V66 and M66.



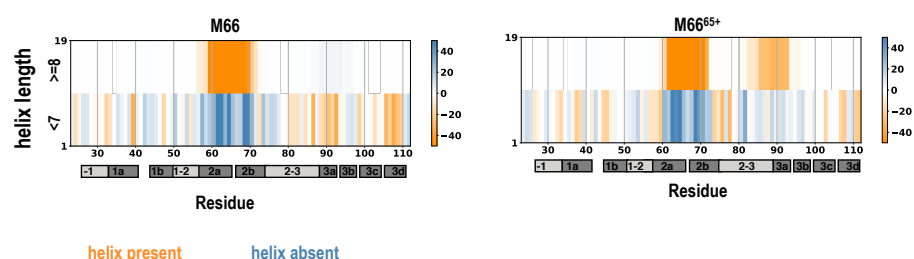
S5 Fig. 2b:3a contact formation in V66.



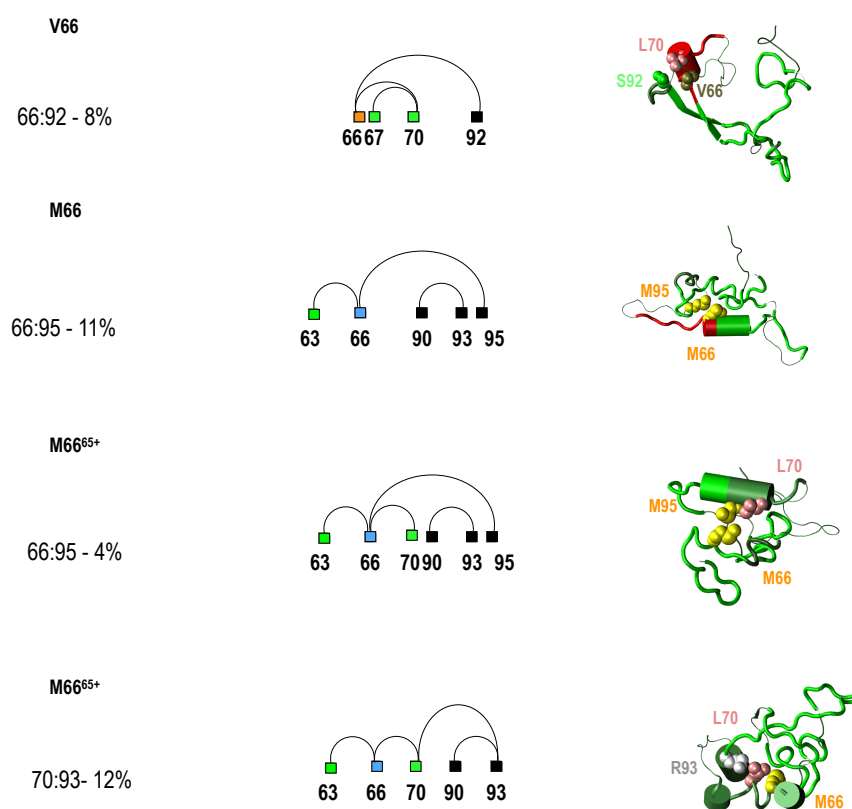
S6 Fig. 2b:3a contact formation in all four simulations



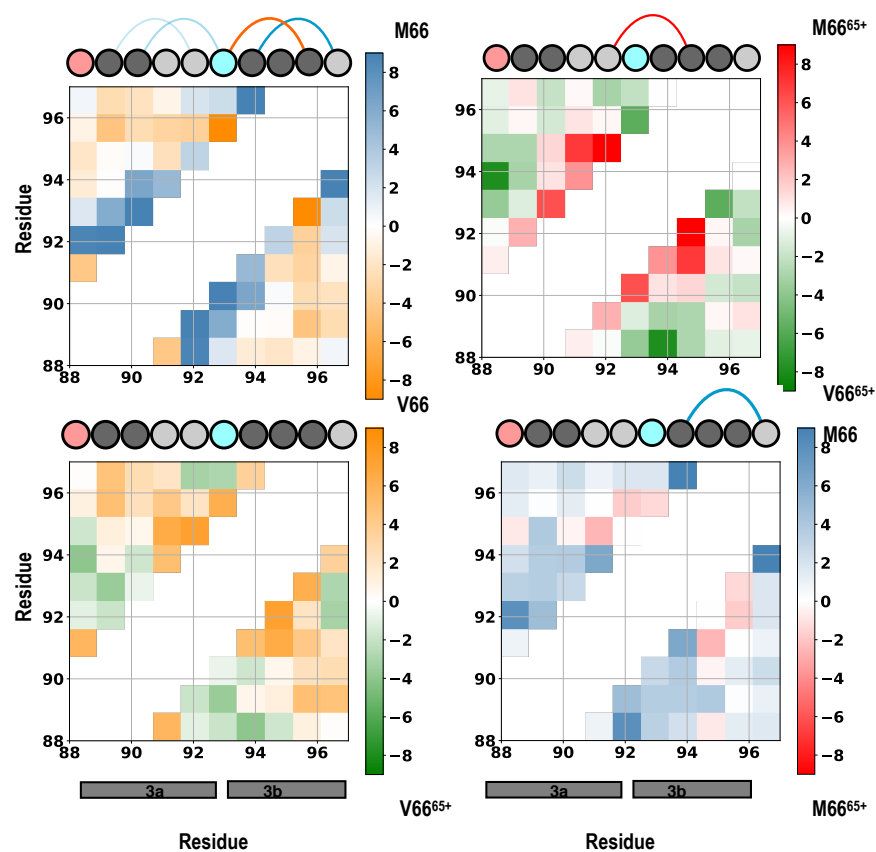
S7 Fig. Helix coupling at domain 2a:2b and 3a.



S8 Fig. Helix coupling at domain 2a:2b and 3a.



S9 Fig. Secondary structure and long range contacts coupling in prodomain.



S10 Fig. Difference in Intra-domain contacts at domain 3.