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Multiple structure-intrinsic disorder interactions regulate and coordinate Hox protein function.

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During animal development, Hox transcription factors determine fate of developing tissues to generate diverse organs and appendages. Hox proteins are famous for their bizarre mutant phenotypes, such as replacing antennae with legs. Clearly, the functions of individual Hox proteins must be distinct and reliable *in vivo*, or the organism risks malformation or death. However, within the Hox protein family, the DNA-binding homeodomains are highly conserved and the amino acids that contact DNA are nearly invariant. These observations raise the question: How do different Hox proteins correctly identify their distinct target genes using a common DNA binding domain? One possible means to modulate DNA binding is through the influence of the non-homeodomain protein regions, which differ significantly among Hox proteins. However genetic approaches never detected intra-protein interactions, and early biochemical attempts were hindered because the special features of "intrinsically disordered" sequences were not appreciated. We propose the first-ever structural model of a Hox protein to explain how specific contacts between distant, intrinsically disordered regions of the protein and the homeodomain regulate DNA binding and coordinate this activity with other Hox molecular functions.