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Structural insights into the DDX11 helicase

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Helicases are essential and ubiquitous enzymes, playing a key role in a variety of processes in DNA and RNA metabolism. A subset of helicases play specialised and specific functions by resolving/remodelling a variety of atypical DNA structures, such as G-quadruplexes, triplexes, Holliday junctions, as well as displacement loops (D-loops and R-loops): among those a major role is played by the FeS family. Helicases containing FeS-clusters are ubiquitous but their exact mechanism of action is poorly understood; no structural information is available for some medically-relevant members of the family, like FANCJ, DDX11 and RTEL1.The combination of the intrinsic conformational flexibility, FeS cluster lability and size makes them challenging targets for structural biology.

DDX11 plays an important role in sister-chromatid cohesion, associates with the replisome and is involved in processing non-canonical nucleic acid structures. We have expressed and purified the human protein with an intact FeS cluster and carried out an extensive biochemical characterization. We have collected Cryo-EM data for the protein alone and in complex with a DNA fork: the apo structure is being refined at 3.5 Å resolution and a preliminary 5 Å structure in complex with a DNA fork has been determined. We can clearly see the path of the DNA fork bound to the helicase including the double helix, and the 5' single strand across the motor domains. Interestingly, in same regions the structure differs significantly from the AlphaFold model. These structures provide an essential framework to better understand the role of these enzymes.

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