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Human U2AF65 Recognizing the Major Polypyrimidine Splice Site Signal

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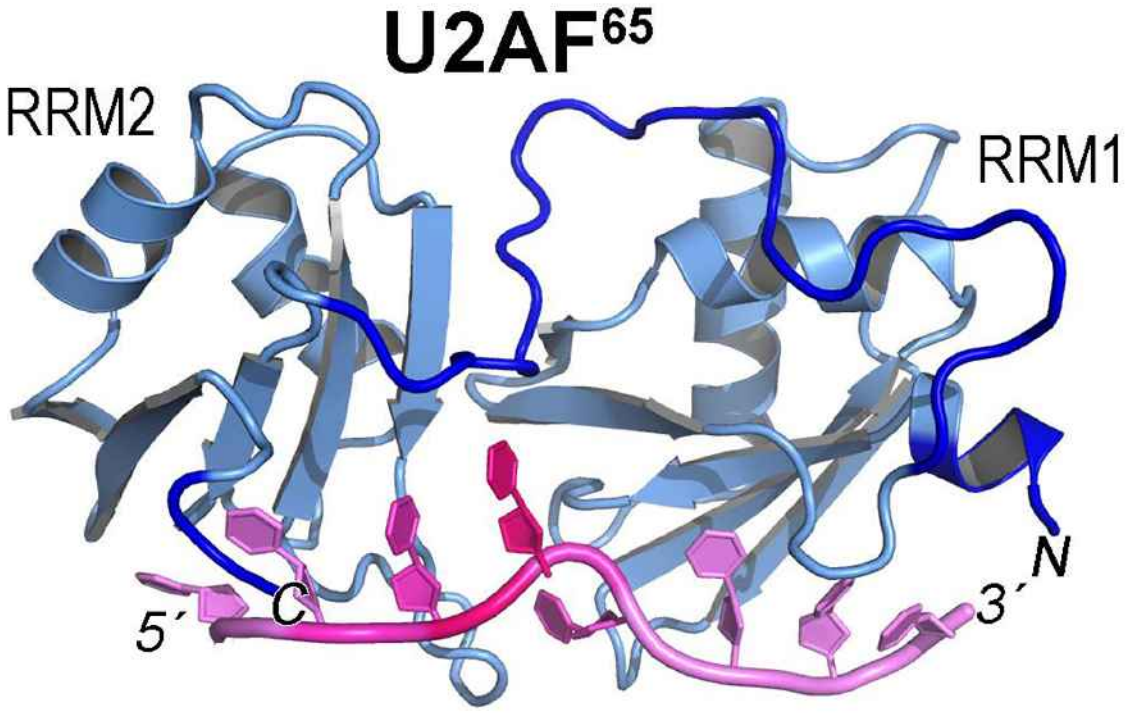
Disease-causing mutations often occur in the polypyrimidine (Py) tract splice site signals of human gene transcripts. The essential U2AF65 protein recognizes Py tracts near 3´ splice sites and initiates assembly of the splicing "machine", a megadalton complex comprised of approximately 100 proteins and five small nuclear RNAs. Our prior structures of a shortened U2AF65 variant reveal the basis for nucleotide interactions at subset of binding sites. How intact U2AF65 recognizes the Py tract splice site signal remains unknown to date. We determined a 2.0 Å resolution structure of intact U2AF65 recognizing an optimal, all-uridine Py tract. The new structure and complementary biochemical experiments reveal integral roles for main-chain atoms of the interdomain linker and residues surrounding two core RNA recognition motifs (RRM1 and RRM2) in recognition of the Py tract. The new U2AF65 structural information sheds light on the splicing defects caused by Py tract mutations in human genetic diseases. We test the U2AF65 structural relationship for a representative Py mutation that causes X-linked retinitis pigmentosa.



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