

**MS05-2-6 Target sequence recognition and gene regulation by Grainyhead/CP2 transcription factors**  
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**Abstract**

Recognition of and binding to specific target sequences on double-stranded (ds) DNA are the initial steps in gene regulation by transcription factors (TFs). In humans, TFs of the Grainyhead/CP2 family are involved in regulating a variety of genes both during embryogenesis and in different tissues of the adult organism. Based on their sequences these TFs are ordered in the Grainyhead-like subfamily comprising GRHL1, GRHL2 and GRHL3, and the CP2 subfamily comprising TFCP2, TFCP2L1 and UBP1. In earlier work, we biochemically analyzed dsDNA binding and determined crystal structures of the DNA-binding domains (DBDs) and oligomerization domains of GRHL1 and GRHL2. The structural basis of target DNA recognition by Grainyhead-like TFs was established by co-crystallizing the GRHL1 DBD with a dsDNA fragment centred around the core binding motif AACCGGTT (1). Unexpectedly, a recent survey of GRHL1-binding DNA motifs using neural networks identified target DNA sequences not containing the previously known core binding motif (Proft et al., unpublished). To extend this study, crystal structures of the DBDs of TFCP and TFCP2L1 from the CP2 branch of the larger protein family were determined. In addition, a structure of dsDNA-bound TFCP2L1 DBD was analyzed and binding parameters were measured by isothermal titration calorimetry (Wang et al., unpublished). These analyses indicated that the TFs of the Grainyhead/CP2 family share a common mode of DNA recognition by binding as apparent dimers to symmetric target sequences, forming specific hydrogen-bonded contacts in the major groove and less specific contacts in the minor groove of dsDNA that displays a largely unperturbed B-form structure. Although the DNA recognition is similar in Grainyhead and CP2 TFs, other aspects of their gene regulation mechanisms are expected to differ, because the N-terminal transactivation domains in both subfamilies are distinct.

**References**

1. Ming, Q., Roske, Y., Schuetz, A., Walentin, K., Ibraimi, I., Schmidt-Ott, K.M. & Heinemann, U. (2018) Structural basis of gene regulation by the Grainyhead/CP2 transcription factor family. *Nucleic Acids Res.* 46, 2082-2095.