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A conserved cation binding site in the DNA binding domain of forkhead box transcription factors regulates DNA binding by FOXP2

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AUTHOR CONTRIBUTIONS

GM and NP contributed equally to this paper and can be considered as joint first authors

ABSTRACT

FOXP2 is a transcriptional repressor involved in development of the human brain and is the first gene product to be linked to the evolution of human speech. FOXP2 belongs to the FOX superfamily of proteins that share a common winged helix DNA binding domain – the forkhead domain. A divalent cation (Mg^{2+} or Ca^{2+}) has been identified bound to a group of highly conserved residues in a number of FOX forkhead domain crystal structures. This work aims to investigate the role of the conserved divalent cation binding site by studying both the structure and DNA-binding function of the FOXP2 forkhead domain when in the presence and absence of either cation (Mg^{2+} or Ca^{2+}). The presence of the cations does not significantly alter the structure of the apo-FOXP2 forkhead domain. However, when in the presence of a cognate oligonucleotide sequence, differences are observed upon addition of divalent cation. These differences occur both in the structure and in the thermodynamic DNA binding signature of the FOXP2 forkhead domain. The incorporation of molecular dynamics simulations together with the experimental data provides us with sufficient insight so as to propose a possible role for divalent cations in the regulation of DNA binding to FOX transcription factors.

Keywords: Transcription factors; Forkhead; DNA binding; FOXP2; divalent metal cation; transcriptional regulation

Abbreviations: CD: Circular dichroism; FHD: Forkhead domain; FOX: forkhead box