A092 · Motif reuse across zinc finger proteins: Insights into function and evolution

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Zinc finger proteins (ZFPs) comprise a large, diverse class of proteins containing conserved zinc-binding domains that mediate recognition of DNA, RNA, and proteins. ZFPs play essential roles in regulation of gene expression and cellular homeostasis, and zinc finger domains have been widely exploited for genome editing, making them relevant for therapeutic development and protein engineering. However, despite their biological importance, we lack a fundamental understanding of the sequence features underlying zinc finger specificity and functional diversification, limiting our ability to predict zinc finger function and utilize these domains effectively. To investigate how zinc fingers are reused across proteins, we analyzed a nonredundant dataset of 1,400 ZFPs from the Protein Data Bank (PDB). We developed a computational pipeline to identify themes, or highly recurring sequence fragments, and focused on themes overlapping at least one zinc finger. We then examined how these themes are reused across proteins and how their reuse relates to function. Our results reveal patterns of zinc finger theme reuse across diverse proteins, providing insight into zinc finger evolution and the conservation of noncanonical features. For example, zinc-finger antiviral proteins and pre-mRNA splicing proteins show no obvious overall homology yet use the same theme to form a CCCH zinc finger. This observation is consistent with a modular, "mix-and-match" mode of zinc finger evolution. Overall, our results show that tracing theme reuse across protein families can uncover relationships between zinc finger sequence, structure, and function, potentially advancing our understanding of their evolution and guiding protein design efforts and therapeutic development.

Motif Reuse Across Zinc Finger Proteins: Insights into Function and Evolution.

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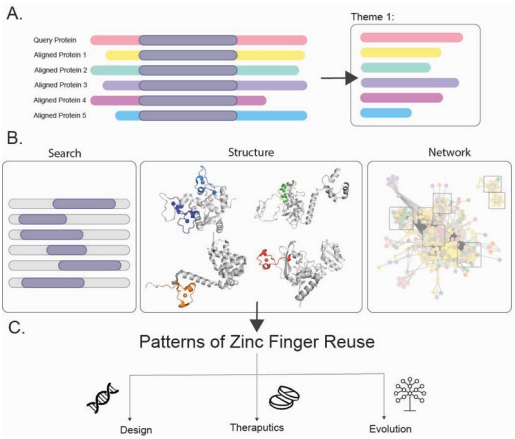

Figure 1. Computational pipeline for discovering zinc finger-related themes across diverse proteins. (A) ZFP sequences are analyzed to identify themes that can act as putative evolutionary building blocks. (B) Discovered themes are used to search other proteins for matching sequences and identify candidates with potentially conserved zinc finger structure and functional specificity. (C) These insights may guide protein engineering, therapeutic development, and studies of zinc finger evolution.