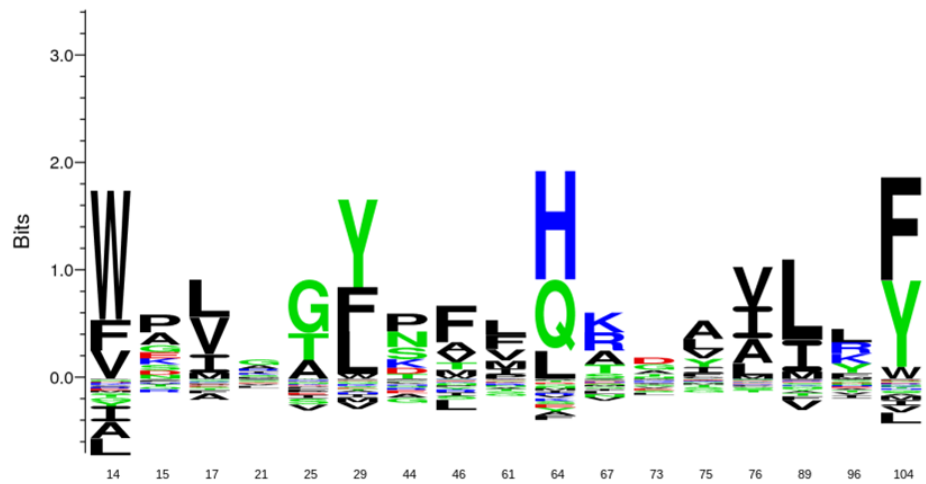**Supplementary Figure S1:** Nodes represent conserved residues and connections between the nodes describe co-evolution of residue pairs. The size of the nodes denote conservation. The positions of the nodes result from a distance scaling optimization (Brandes & Pich, 2009) in which layout distance are fit to shortest-path distances. The residues that form the shortest path are highlighted with colors.
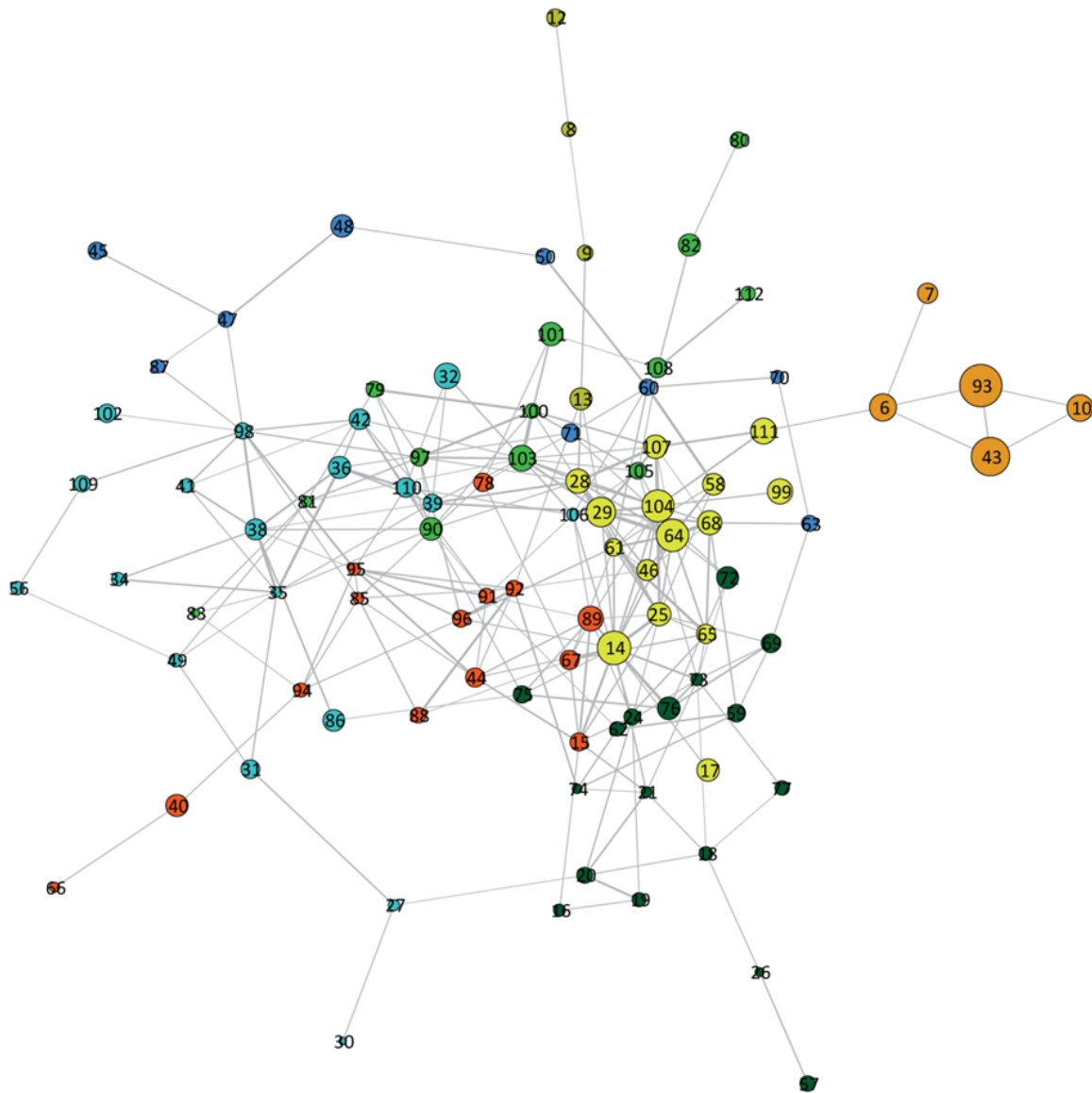
Supplementary Figure S2: Newman's clustering algorithm (Newman, 2004) is used to identify groups of residues that are structurally connected. The clustering algorithm reveals 8 communities with a modularity value of 0.51. The distinct groups are distinguished by color coding. The sizes of the nodes depict conservation and the edges between the nodes, where the thickness is based on the MI score, are drawn in gray.

Supplementary Figure S3: A histogram showing relative amino acid frequencies of selected nodes representing amino acids forming the shortest path from the MSA.