

The CHAIN program: forging evolutionary links to underlying mechanisms

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Proteins evolve new functions by modifying and extending the molecular machinery of ancestral proteins. Such changes show up as divergent sequence patterns, which are conserved in descendent proteins that maintain the divergent function. The CHAIN program (which is freely available at www.chain.umaryland.edu) uses Bayesian inference to identify conserved atomic interactions associated with protein functional divergence and thereby suggest plausible molecular mechanisms for experimental testing. This is illustrated by its application to the G protein alpha subunit.

The heterotrimeric G protein alpha subunit (Ga) functions as a molecular switch by cycling between inactive GDP-bound and active GTP-bound states. When bound to GDP, Ga interacts with high affinity to a complex of the beta and gamma subunits (Gbg), but when bound to GTP, Ga dissociates from this complex to activate downstream signaling pathways. Ga's state is communicated to other cellular components via conformational changes within its switch I and II regions. To identify key determinants of Ga's function as a signaling pathway molecular switch, the CHAIN program was used to infer the selective constraints that most distinguish Ga and closely related Arf family GTPases from distantly related translational and metabolic GTPases. The strongest of these constraints are imposed on seven residues within or near the switch II region. Likewise, constraints imposed on Ga but not on other, closely related molecular switches correspond to four nearby residues. These constraints can be explained by a proposed mechanism where an Arg-Trp pair senses the presence of bound GTP leading to conformational retraction of a nearby lysine and to disruption of an aromatic cluster, which together induce dissociation of Ga from Gbg.