Ataxia-oculomotor apraxia syndrome 1 is a rare neurological disorder that results from loss of function mutations in the gene for Aprataxin. Normally, Aprataxin mediates protein-protein interactions with molecules that respond to DNA damage. However, the cellular phenotype of the disease does not appear to be associated with a major loss of this ability. Aprataxin contains three conserved domains, a forkhead-associated domain that mediates protein-protein interactions; a histidine triad domain that is similar to Hint, a universally conserved AMP-lysine hydrolase; and a C-terminal zinc finger domain. Mutations that cause the disease either appear in the histidine triad domain or truncate the protein N-terminal to a zinc finger.

Using novel fluorigenic substrates, Heather F. Seidle and colleagues investigated the link between Aprataxin inactivation and ataxia-oculomotor apraxia syndrome 1. They discovered that Aprataxin possesses intrinsic, active site-dependent AMP-lysine and GMP-lysine hydrolase activity that is dependent on the forkhead-associated domain for enzymatic activity and the zinc finger for protein stability. Biochemical analysis showed that eight reported disease-associated alleles are null or nearly null for the Hint active site. From their results, Seidle et al. conclude that the essential function of Aprataxin is the reversal of nucleotidylylated protein modifications and that all three domains contribute to the formation of a stable enzyme.

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