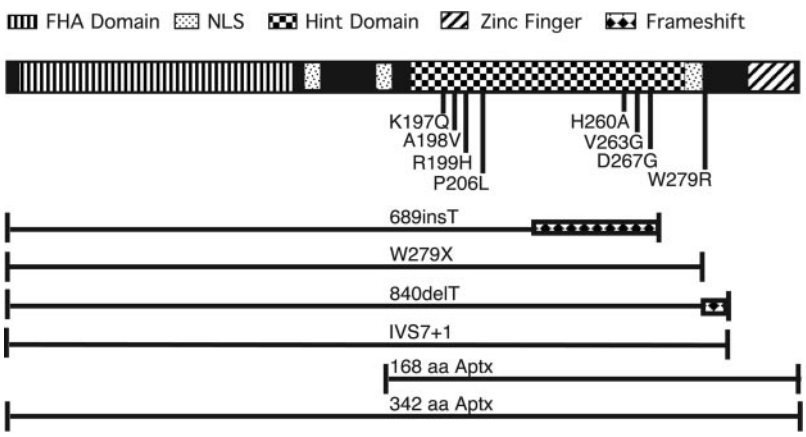
Papers of the Week

Enzyme's Hydrolase Activity Hints at Root of Disease ♦



The domain structure of Aprataxin and its disease-associated alleles.

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.

♦ See referenced article, *J. Biol. Chem.* 2005, **280,** 20927–20931