Novel mutations in the SMN Tudor domain

Cuscó et al. report two type I SMA patients with subtle mutations in the SMN exon 3, a hot spot for mutations, supporting the view that the Tudor domain could have an important role in SMN function.

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Polygamy of the Tudors: New Tudor domain mutations of SMN cause spinal muscular atrophy

Commentary by Arthur H.M. Burghes, PhD

Spinal muscular atrophy (SMA) is caused by loss or mutation of the *SMN1* gene and retention of the *SMN2* gene. The genes differ by a single nucleotide, causing *SMN2* to produce insufficient levels of SMN protein for motor neurons. Ninety-five percent of SMA patients lack a detectable *SMN1* gene and 5% have various small mutations of *SMN1*. The following missense mutations have been reported: SMN G279V, Y272C, S261I, T274I, A2G. All these mutations disrupt SMN's ability to oligomerize. (Two additional mutations, P254L and G275S, have not yet been analyzed.) The disruption of oligomerization probably results in inefficient complex formation and subsequent degradation of the free SMN protein culminating in low SMN levels. The Tudor mutants were first described in Drosophila and so named because of defective germ cell development rendering the animals grandchildless. The Tudor protein has multiple repeated consensus amino acids called Tudor domains. These domains have been found in other proteins such as the Drosophila homeless and ovarian tumor genes, which are important in mRNA localization. The Tudor domain of SMN binds other proteins including the Sm proteins and has been extensively examined structurally. The E134K mutation in the Tudor domain of SMN does not affect oligomerization but does affect binding to Sm proteins. Additional patient mutations Q136E and I116F in the Tudor domain are reported in this issue of *Neurology* by Cuscó et al. The E134 and I116 amino acids are conserved through all species (the same amino acids or a conservative substitution). Interestingly, Q136 is conserved in all vertebrates except the frog where it is a histidine. Can these mutations be used to investigate the binding partners of SMN in motor neurons and understand SMN's structure?

The reason that low levels of SMN cause SMA is not understood. Do reduced SMN levels cause a defect in snRNP biosynthesis with motor neurons requiring large amounts of snRNPs? Alternatively, are high levels of SMN required for RNP assembly in mRNA transport/translation in motor axons and does this reduced level of SMN impair axon guidance or synaptic maintenance? The answer is not known but certainly the Tudor domain is critical for normal function of SMN and is found in proteins known to be important for mRNA localization.

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