Aberrant protein N-terminal acetylation as a cause for congenital disease

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The major N-terminal (Nt) acetyltransferase NatA co-translationally acetylates nearly half of all human proteins at their N-termini. NatA consists of two core subunits; the catalytic subunit NAA10 and auxiliary subunit NAA15. In addition to NAA10´s evolutionarily conserved role as part of the NatA complex, there also exists a cellular population of monomeric NAA10. Monomeric NAA10 has been reported to regulate proteins both through lysine acetylation and in an acetyltransferase-independent manner. A variety of hereditary and *de novo* missense variants in the X-linked *NAA10* gene have been found to cause congenital disease in humans. Affected individuals display phenotypic heterogeneity, but phenotypes often include variable degrees of intellectual disability, developmental delay and cardiac anomalies. Importantly, the underlying disease mechanisms associated with pathogenic NAA10 variants are still poorly understood. In this project, we have investigated the biochemical profiles of novel and known NAA10 missense variants through immunoprecipitation and *in vitro* acetylation assays. While some missense variants appear to affect overall protein stability, some impair NAA10-NAA15 NatA complex formation and NatA mediated Nt-acetylation, and others appear to reduce monomeric NAA10 acetylation. Thus, different NAA10 missense variants are likely to affect different roles of the multifunctional NAA10 protein which may explain the heterogenous disease manifestations in affected individuals.
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