NAA10-related disorder Arg83Cys

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Amino-terminal (Nt-) acetylation (NTA) is a common protein modification, affecting 80% of cytosolic proteins in humans. The human essential gene, NAA10, encodes for the enzyme NAA10, which is the catalytic subunit in the N-terminal acetyltransferase A (NatA) complex, also including the accessory protein, NAA15. The full spectrum of human genetic variation in this pathway is currently unknown. Here we reveal the genetic landscape of variation in NAA10 and NAA15 in humans. Through a genotype-first approach, one clinician interviewed the parents of 56 individuals with NAA10 variants and 19 individuals with NAA15 variants, which were added to all known cases (N = 106 for NAA10 and N = 66 for NAA15). Although there is clinical overlap between the two syndromes, functional assessment demonstrates that the overall level of functioning for the probands with NAA10 variants is significantly lower than the probands with NAA15 variants. The phenotypic spectrum includes variable levels of intellectual disability, delayed milestones, autism spectrum disorder, craniofacial dysmorphology, cardiac anomalies, seizures, and visual abnormalities (including cortical visual impairment and microphthalmia). One female with the p.Arg83Cys variant and one female with an NAA15 frameshift variant both have microphthalmia. The frameshift variants located toward the C-terminal end of NAA10 have much less impact on overall functioning, whereas the females with the p.Arg83Cys missense in NAA10 have substantial impairment. The overall data are consistent with a phenotypic spectrum for these alleles, involving multiple organ systems, thus revealing the widespread effect of alterations of the NTA pathway in humans.