# Reply to: "Neurodevelopmental Gene-Related Dystonia: A Pediatric Case with *NAA15* Variant"

We thank Yubero and colleagues for commenting on our recently published letter describing the manifestation of adult-onset dystonia-parkinsonism in association to a pathogenic *NAA15 de-novo* nonsense variant.[1] Variants in *NAA15*, a gene involved in post-translational protein modifications via N-alpha-acetylation, have previously been shown to result in typical (neuro-)developmental disorder traits such as intellectual disability, behavioral disturbances, and craniofacial dysmorphisms ("Intellectual developmental disorder, autosomal dominant 50, with behavioral abnormalities"; MIM:617787).[2,3] Yubero and colleagues have now identified an additional carrier of a (likely) pathogenic nonsense variant in *NAA15* who demonstrated dystonia as a leading clinical phenotype, thus confirming that abnormal (especially dystonic) movements can be part of the phenotypic spectrum of *NAA15*-related diseases. These aggregate findings, considered together with observations in large cohorts of individuals with *NAA15*-associated conditions,[2,3] highlight that *NAA15* may be considered one of the many genes implicated in brain development whose mutational changes can give rise to (1) "classical" neurodevelopmental phenotypes without dystonia, (2) dystonia coexisting with neurodevelopmental features (ie, complex dystonia), or (3) seemingly isolated dystonia with no or only minor, difficult-to-recognize developmental comorbidity.[4] Low rates of reported movement disorders in previous publications on *NAA15* disease subjects could be due to underdiagnosis. Therefore, we strongly agree with the proposition from Yubero and colleagues that patients presenting with intellectual disability and related traits, particularly if associated with rare neurodevelopmental gene variants, should be carefully screened for the expression of movement abnormalities, including dystonia. We note though that our recently published case with *NAA15* variant displayed movement-disorder characteristics markedly different from those reported in association to the *NAA15* alteration detected by Yubero and colleagues: their identified patient had limb dystonia with onset at the age of 3 years and no other movement disorders, whereas our individual manifested dystonia-parkinsonism in late adulthood.[1] Although Yubero and colleagues point out that many pediatric-onset neurodevelopmental movement disorders can worsen later in life, we really want to stress that our case had no movement disorders before the age of 46 years. This raises importance questions regarding variable expressivity and reduced penetrance of movement-disorder symptoms in the context of *NAA15* variants. Why do some individuals with *NAA15*-related disorders manifest late-onset combined movement disorders and some others childhood-onset dystonia, whereas the majority of cases do not seem to express abnormal movements at all (including the variant-positive mother of Yubero and colleagues` patient)? Variant-specific effects, environmental influences, endogenous protective factors, multigenic inheritance, as-yet-undiscovered molecular determinants, or simply stochastic variations may play role.[4] We hope that future multimodal research efforts will be able to clarify these mechanisms not only for *NAA15*-associated dystonia but also for other genetically determined movement disorders, which would have important implications for prognostication, treatment, and potentially preventive measures.

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## Data Availability Statement

Data available on request from the authors.

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