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ADCY5-Related Dyskinesia: Comments on Characteristic Manifestations and Variant-Associated Severity

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We have been gratified by the spate of publications on ADCY5-related dyskinesia, including that of Chang and colleagues,[1] since we first identified the causative gene.[2] This heightened awareness will enable expansion of the spectrum of mutations and definition of the range of manifestations. These objectives depend on the accuracy of new reports and completeness of literature reviews. The article by Chang and colleagues omits data and includes multiple statements of novelty or first description of genotypes, phenotypes, and treatment responses that are inaccurate. Although unique findings are criteria in publication, given the difficulty of proving "first," "only," and "novel," some journals have disallowed such pronouncements.

Table 1 and Supporting Table 1 nicely summarize findings on multiple patients, including cases with p.R418W and p.A726T from our earlier publications.[2,3] However, the titles of these tables imply they are comprehensive tallies of all cases published to date, yet they completely ignore the 15 new families we described in detail in 2015,[4] even though they cite this publication. Not only do those 3 multigenerational and 12 single-case families (26 total cases) represent a sizeable proportion of published cases, but 4 affected individuals in 1 family carry a pathogenic variant, p.M1029K, not mentioned by Chang and colleagues.

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Although they indicate they are the first to describe a p.R418Q mutation, we had already documented this variant in 3 patients, 1 of whom was shown in a video.[4,5] The omissions in these tables are of great concern, as they are likely to serve as a basis for future literature reviews of ADCY5-related dyskinesia.

The authors' identification of a patient with a p.R418G mutation further supports our hypothesis of a mutational hot spot at this residue.[4] Although they acknowledge that the small number of families evaluated limits the ability to determine genotype-phenotype correlations, they suggest that p.R418Q and p.R418G may result in milder disease than p.R418W. In our much-larger cohort, we found that, with the exception of p.A726T, which causes a distinctive mild form of disease in 2 multigenerational families, a broad range of disease severity is seen with other pathogenic variants, including p.R418W and p.R418Q. An important caveat is the somatic mosaicism we detected in ~43% of de novo cases sometimes resulted in considerably milder disease.[4] Chang and colleagues do not mention mosaicism as a possible contributor to phenotypic variability – an omission that might lead readers to give families incorrect prognoses and recurrence risks.

Developing efficacious treatments requires identification of larger patient cohorts, and thus we are pleased this article describes 7 additional cases of ADCY5-related dyskinesia and supports our proposed list of important clues to diagnosis, including axial hypotonia and choreoathetosis during wakefulness and sleep.[4,5] However, we urge caution regarding claims of therapeutic benefit. Although the authors suggest they are the first to describe improvement with clonazepam, we previously described response to clonazepam in several patients,[4] but have found mixed benefit in larger cohorts and over time. The fluctuating course in many patients complicates these determinations and necessitates prolonged observation to accurately determine efficacy.

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