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Members of the DysTract Study Group are available as an online supplementary file.

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Reply to "Truncating *VPS16* Mutations are Rare in Early-Onset Dystonia"

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We thank Pott and colleagues for their letter confirming that loss-of-function variants in *VPS16* cause a new form of dominantly inherited dystonia. Using gene-based burden testing, we have recently determined a significant enrichment of heterozygous *VPS16* loss-of-function variants in 138 patients with generalized dystonia.[1] Five patients with *VPS16* nonsense and frameshift variants were identified as well as 1 case with a *VPS16*-involving microdeletion, giving an overall carrier rate of pathogenic *VPS16* variants of ~4%. Through collaboration with independent laboratories, we subsequently assembled a series of 19 patients with *VPS16*-associated dystonia.[1] These individuals displayed a strikingly similar presentation of generalized dystonia, most prominently affecting the upper body. Although early symptom onset was observed in the majority of cases, 2 patients (11%) first manifested dystonia after the age of 21 years, including 1 subject identified as part of the burden-analysis cohort. Pott et al report on the detection of a novel heterozygous *VPS16* frameshift variant in a patient with early-onset, upper-limb, truncal, and craniocervical dystonia, noting the clinical similarities with both our cases and *THAP1*-related disease.

Pott et al discovered 1 heterozygous loss-of-function variant in 114 patients with early-onset dystonia (0.9%), whereas in our burden-analysis cohort ~4% of patients were diagnosed with *VPS16*-associated dystonia.[1] Variant detection rates in genes may vary depending on the sequencing methodology used for screening and the population studied.[2,3] Two factors might explain discrepancies in the prevalence of *VPS16*-associated dystonia between the 2 cohorts. First, we had used whole-exome sequencing, including copy-number variant profiling, to identify *VPS16* variants in the burden-analysis cohort.[1] By contrast, Pott et al performed Sanger sequencing of the *VPS16* coding regions, which does not allow detection of certain variant types including microdeletions. Second, the burden-analysis cohort comprised patients with generalized dystonia who had already undergone extensive screening for variants in other dystonia-causing genes.[1] In contrast, Pott et al describe patients with early-onset dystonia without further information on what prior molecular testing had been undertaken in this cohort. When we assessed the frequency of *VPS16* loss-of-function variants in our entire sample of whole-exome sequenced individuals with early-onset dystonia (without extracting cases with mutations in other dystonia-causing genes - Zech et al[4] and unpublished data), a carrier rate of ~1% (6 of 505) was obtained, equaling the rate reported by Pott et al. As such, it is possible that *VPS16*-associated dystonia is rare in unselected, generic early-onset dystonia cohorts, but more frequent among a subgroup of patients with generalized dystonia in whom mutations in all other dystonia-causing genes have been excluded.

Potential Conflicts of Interest

Nothing to report.

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