Genome Aggregation Database Version 4—New Challenges of Variant Analysis in Movement Disorders

The occurrence of disease-associated variants in "healthy" controls is a well-established characteristic of inherited movement disorders.[1] A typical example of a pathogenic variant found in controls is *TOR1A* p.Glu303del underlying early-onset dystonia.[2] There are several explanations for why variants linked to monogenic movement disorders can be present in catalogs of "normal" genetic variations. First, such variants may be associated with reduced penetrance, that is, the phenomenon whereby a mutation carrier will not convert to a symptomatic patient; second, the variants may result in phenotypes with variable expressivity where the degree of clinical severity can have a mild end with underdiagnosis.[1] Large population genetic databases might not be screened for milder disease traits. Furthermore, the carriers of pathogenic variants may still be too young to display a disease phenotype at the time of sequencing.[1] Alternatively, the presence of a variant among controls can indicate its benign character. Available exome/genome sequencing-derived variant databases of individuals from the general population have been launched as useful resources for the assessment of the frequencies of studied genotypes in controls.[3] These databases are periodically updated, which can pose challenges for genetic analysts and movement disorder clinicians in interpreting the disease relevance of prioritized variants. In 2022, we examined monozygotic twins with suspected genetic dystonia. Patient 1 manifested dystonic movements at 6 months of age, along with psychomotor delay; his dystonia generalized with prominent cranio-cervical/truncal distribution (Video 1). Patient 2 developed oromandibular and cervical dystonia in childhood, with generalization during adolescence. Both patients also had sensorineural hypoacusis. Quad-based exome sequencing revealed a de novo heterozygous variant in *GRID2* in both twins, NM_001510.4:c.1966C > T, p.Leu656Phe; another amino-acid change at the same codon (p.Leu656Val) had previously been implicated in autosomal-dominantly transmitted (mostly ataxic) movement disorders with developmental delay and hearing impairment.[4,5] The variant was predicted to be deleterious (Combined Annotation Dependent Depletion score = 30), and it was absent from all controls available at the time of initial evaluation: in-house exomes (N = 20,000) and gnomAD, version 2.1.1 (N = 141,456). According to the criteria of the American College of Medical Genetics and Genomics, it was classified as "likely pathogenic" (PS2, PM2, PM5, and PP3) and considered a probable contributor to the phenotype of the twins, who were diagnosed with an atypical, dystonia-predominant manifestation of *GRID2*-related disease.[4,5] Surprisingly, reanalysis of the *GRID2* variant with data from the latest gnomAD release (November 1, 2023, version 4.0, https://gnomad.broadinstitute.org/) demonstrated that this alteration was now present in 7 heterozygous individuals of the database; gnomAD, version 4.0, contains sequencing data of 807,162 persons, providing an unprecedented wealth of genomic information. As of today, should we reclassify the *GRID2* variant as an innocuous polymorphism because it is seen "too frequently" in controls given the rarity of *GRID2*-related disorders? Or is it possible that 7 heterozygous carriers can be expected among >1 million control chromosomes in light of penetrance and expressivity variations in hereditary movement disorders? Similar questions may arise for many other listed movement disorder–associated mutations such as *ANO3*-p.Ala657Thr[6] (10 carriers in gnomAD, version 4.0) and *VPS16*-p.Arg647Ter[7] (5 carriers). Pathogenic loss-of-function variants, often absent from version 2.1.1, are now found at appreciable rates in gnomAD, version 4.0; for example, the pLI score of the dystonia-related gene *GNAL* decreased from 1.0 (version 2.1.1) to 0.0 (version 4.0). Although variant interpretation may become more

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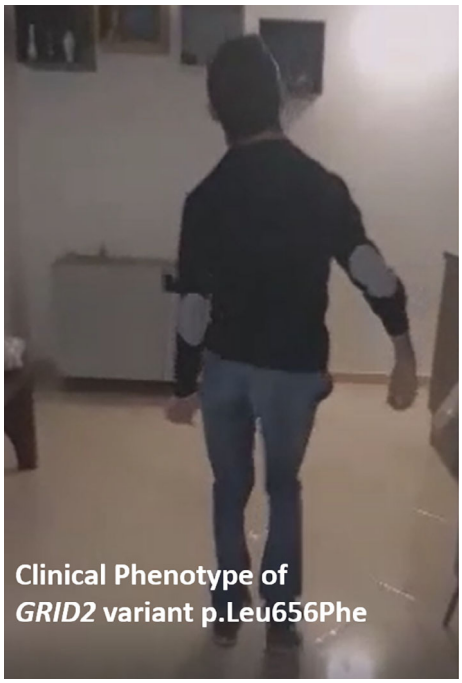

VIDEO 1. Video with captions showing the clinical features of patient 1 at the last evaluation (age: 31 years).
Video content can be viewed at https://onlinelibrary.wiley.com/doi/10.1002/mds.29797

difficult, we believe that the new gnomAD version offers great opportunities to estimate the true population frequency of movement disorder–linked variants. Fresh perspectives are open to the movement disorders community, enabling us to redefine prevalences of clinically determined variants and to better quantify their disease-causing potential. ■

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Data Availability Statement

Further detailed clinicogenetic information will be made available upon reasonable request by the corresponding author.

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