Reply to: "Clinical and Molecular Profiling in *GNAO1* Permits Phenotype–Genotype Correlation"

With great interest we read the recently published article by Lasa-Aranzasti et al on clinical and molecular profiling of *GNAO1*. The authors characterized the neurological phenotype and the molecular mechanisms caused by pathogenic Gαo identified in a cohort of patients with *GNAO1*-related disorders. They provided functional data underlying the proposed developmental and epileptic encephalopathy 17 and neurodevelopmental disorder with involuntary movement phenotypes.[1] Their study also included 1 patient exhibiting a rather mild phenotype with hyperkinetic movements (generalized chorea, myoclonus, and dystonia) associated with mild intellectual disability. The underlying mutation (p.Ile344del) was located at the end of protein and led the authors to the conclusion that milder phenotypes are correlated with splicing variants, previously hypothesized haploinsufficiency based on loss of function,[2] or variants at the end of the protein.

We report on a 34-year-old patient, who was referred to our movement disorders clinic to assess a 2-year-earlier-developed propranolol-resistant, myoclonic head tremor in the context of a cerebral palsy, which was prediagnosed due to delayed development of speech at age 4, despite the lack of a clear perinatal event. There was no history of epileptic seizures. At age 12 a slowly progressing action tremor of his right hand occurred, leading him to write with his left hand. He graduated regularly from secondary school and worked in logistics and later in farming. He performed skiing, hiking, and swimming without restraints.

At 32 years the tremor of his right hand had worsened, and he developed a myoclonic head tremor.

Our neurological examination at age 34 revealed segmental dystonia with predominant cervical dystonia with phasic abnormal rotation mainly to the left, laryngeal dystonia of the adductor type, slight postural tremor of the hands, and writing tremor with dystonic posture leading to an inability to write. His gait was mainly unaffected, showing only a reduced arm swing (Video 1).

His cognitive functions were slightly decreased, scoring 24/30 on the Montreal Cognitive Assessment test.

Brain magnetic resonance at age 32 demonstrated a slightly asymmetric ventricular system without further abnormalities. His family history (parents and four siblings) was negative for movement disorders or epilepsy.

Regarding the rather atypical presentation for cerebral palsy, we performed a trio-exome analysis that revealed a heterozygous de novo missense variant in *GNAO1* (NM_020988.3:c.4G > C,p.Gly2Arg), which was absent from control databases (in-house exomes, gnomAD version 4.0) and located in a highly mutation-constrained N-terminal region of *GNAO1*; the variant was classified as "likely pathogenic" according to American College of Medical Genetics and Genomics (ACMG), establishing the diagnosis of *GNAO*1-related dystonia with comparatively mild phenotype.

Although the consequence on protein function is unknown for the newly identified variant, our observation strengthens the proposition that missense amino-acid substitutions of *GNAO1* at the start of the *GNAO1*

Video 1. Video of the clinical examination of our patient showing normal gait with slightly reduced arm swing predominantly of the right arm (part 1), cervical dystonia with phasic abnormal rotation mainly to the left (part 2), laryngeal dystonia of the adductor type (part 3), and postural tremor with writing tremor of the right hand, compensated by relearned writing with the left hand (part 4/5).
Video content can be viewed at https://onlinelibrary.wiley.com/doi/10.1002/mds.30017

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Relevant conflicts of interest/financial disclosures: None of the authors have any conflicts of interest to disclose. No author has any financial disclosures related to the study.

Funding agency: No funding was received for this study.

Received: 22 July 2024; **Accepted:** 24 July 2024

Published online in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.30017

can also lead to less-severe clinical outcomes.[3] Our report contributes to an expansion of the catalog of *GNAO1* variation that produces attenuated clinical images with predominant dystonia, which may have important implications for better understanding of pathophysiology and future therapy development.

Acknowledgments: We thank the patient and his family for participating in the study. Open Access funding enabled and organized by Projekt DEAL.

Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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Response to Mortimer et al. "Clinical and molecular profiling in GNAO1 permits phenotype–genotype correlation"

We read with interest the contribution of Svec et al.[1] who described an additional patient suffering from *GNAO1-related disorder* caused by a de novo c.4G > G, p.Gly2Arg missense variant.

This patient developed a mild phenotype characterized by late-onset dystonia (>12 years) progressing slowly to segmental dystonia in adulthood (involving craniofacial regions and the upper limb). This case illustration is very similar to two patients harboring the genetic variants 16q12.2-q21 and I344del from our series,[2] and to many others reported by Wirth et al.[3] Importantly, patients with this phenotype received pallidal deep brain stimulation (DBS) with significant improvement in most cases.[2,3]

Another interesting observation in this patient was the combination of dystonia with other movement disorders such as tremor and myoclonus. Most patients described in our series, and others described previously,[2] showed that the main movement disorder in *GNAO1* is dystonia, combined with chorea, hypo/bradykinesia, myoclonus, tremor, or stereotypies.

As illustrated by Svec et al. and by our own work, it is common to misdiagnose individuals with *GNAO1* alterations as having cerebral palsy, especially in patients who present the NEDIM (Neurodevelopmental Disorder with Involuntary Movements) phenotype. In fact, *GNAO1* is one of the most common genetic disorders identified by exome sequencing in patients with cerebral palsy diagnosis.[4] Our work highlights that children with *GNAO1* defects experience motor exacerbations and related autonomic symptoms triggered by specific factors, which contrasts with the stable, non-progressive motor disturbances seen in cerebral palsy. Other studies have also emphasized non-epileptic paroxysmal neurological disorders, such as oculogyric crisis and dystonic crisis, together with symptom fluctuations, as red flags to differentiate classical cerebral palsy from cerebral palsy mimics, especially neurotransmitter and mitochondrial disorders.[5]

Mechanistically, the Gly2Arg mutation described by Svec et al. is predicted to cause a loss-of-function. The Gly2 in Gαo undergoes N-myristoylation, a lipid modification that is a prerequisite for the subsequent S-palmitoylation of Cys3.[6] As both lipidations are mandatory for the plasma membrane binding of Gαo,[5] a Gly2 substitution will render the protein cytosolic and excluded from G protein-coupled receptor (GPCR) signaling. The I344del loss-of-function variant from our study is also precluded from GPCR-coupling, although through a different mechanism.[2] Thus, it would be valuable to perform functional studies on the Gly2Arg

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Relevant conflicts of interest/financial disclosures: The authors declare no potential conflict of interest.

Received: 29 August 2024; **Accepted:** 30 August 2024

Published online in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.30018