GNAO1 Haploinsufficiency Associated with a Mild Delayed-Onset Dystonia Phenotype

With great interest we read the manuscript recently published by Wirth and colleagues reporting 24 individuals with variants in *GNAO1* related to delayed-onset, dystonia-predominant phenotypes without encephalopathic features.[1] Based on the identification of two putative loss-of-function variants (including a nonsense alteration and a larger deletion containing *GNAO1*), the authors suggested that *GNAO1* haploinsufficiency may be a possible mechanism underlying comparably mild dystonic presentations with an age of onset beyond childhood.[1] By contrast, previous reports have associated *GNAO1* variants, both missense and loss-of-function variants, mostly with severe, infantile-onset encephalopathic, and neurodevelopmental disorders (with or without hyperkinetic movements).[2,3] A causal relation between *GNAO1* haploinsufficiency and dystonic conditions presenting to the adult neurology clinic remains to be confirmed.

Motivated by the findings of Wirth and colleagues, we reassessed our in-house dystonia cohort with 1100 index-case whole-exome sequencing data sets[4,5] for the presence of rare *GNAO1* variants. In addition to a set of four de novo missense changes causing previously published complex pediatric dystonia syndromes,[4,5] we observed a heterozygous interstitial deletion at 16q12.2 (61 kb) affecting the coding exons 4–8 of *GNAO1* (NM_020988.3) in 2 first-degree relatives (mother and daughter) with unresolved disease (Fig. 1). This copy-number variation, one of the smallest *GNAO1*-disrupting 16q12.2 microdeletions reported to date,[1,6,7] was initially considered to be of uncertain significance, as a relationship between heterozygous loss of *GNAO1* and our patients' phenotypes had not been established.

Individual I (mother) developed slowly progressive head tremor around the age of 40 years. There was no history of developmental delay or epileptic seizures. Neurological examination at age 53 revealed cervical dystonia with a marked phasic component and abnormal rotation toward the right side (45°). In addition, she showed dysarthria and dystonic posturing as well as myoclonic movements of shoulder-girdle muscles (left > right). Botulinum toxin injections were partially beneficial. Family history was positive for dystonia, with an affected father (unavailable for assessment) and an affected daughter.

Individual II (daughter) first reported dystonic symptoms at age 16 . Although early neurodevelopment was normal, she had learning difficulties in elementary school, requiring special needs education. At age 17, she experienced a generalized tonic–clonic seizure. Brain magnetic resonance imaging was normal, whereas electroencephalogram showed generalized spike–wave activity. Subsequently, she remained seizure-free under medication with lamotrigine. Neurological examination at age 20 showed cervical dystonia with a 30° leftward rotation and a pronounced phasic component; she also exhibited latero- and retrocollis.

Overall, our mother–daughter pair manifested familial non-progressive dystonia with onset in late adulthood/adolescence and only minor neurological comorbidity, presentations that are frequently observed in daily outpatient care and often remain genetically undiagnosed. Our report substantiates the recent observation that *GNAO1* loss-of-function variants can be associated with comparably mild dystonic phenotypes with or without comorbid epilepsy,[1] which has important implications for genetic testing and counseling. Moreover, our findings highlight a notable degree of intrafamilial variability in dominant *GNAO1*-mutated pedigrees, especially regarding age at dystonia onset and accompanying epileptic manifestations.

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Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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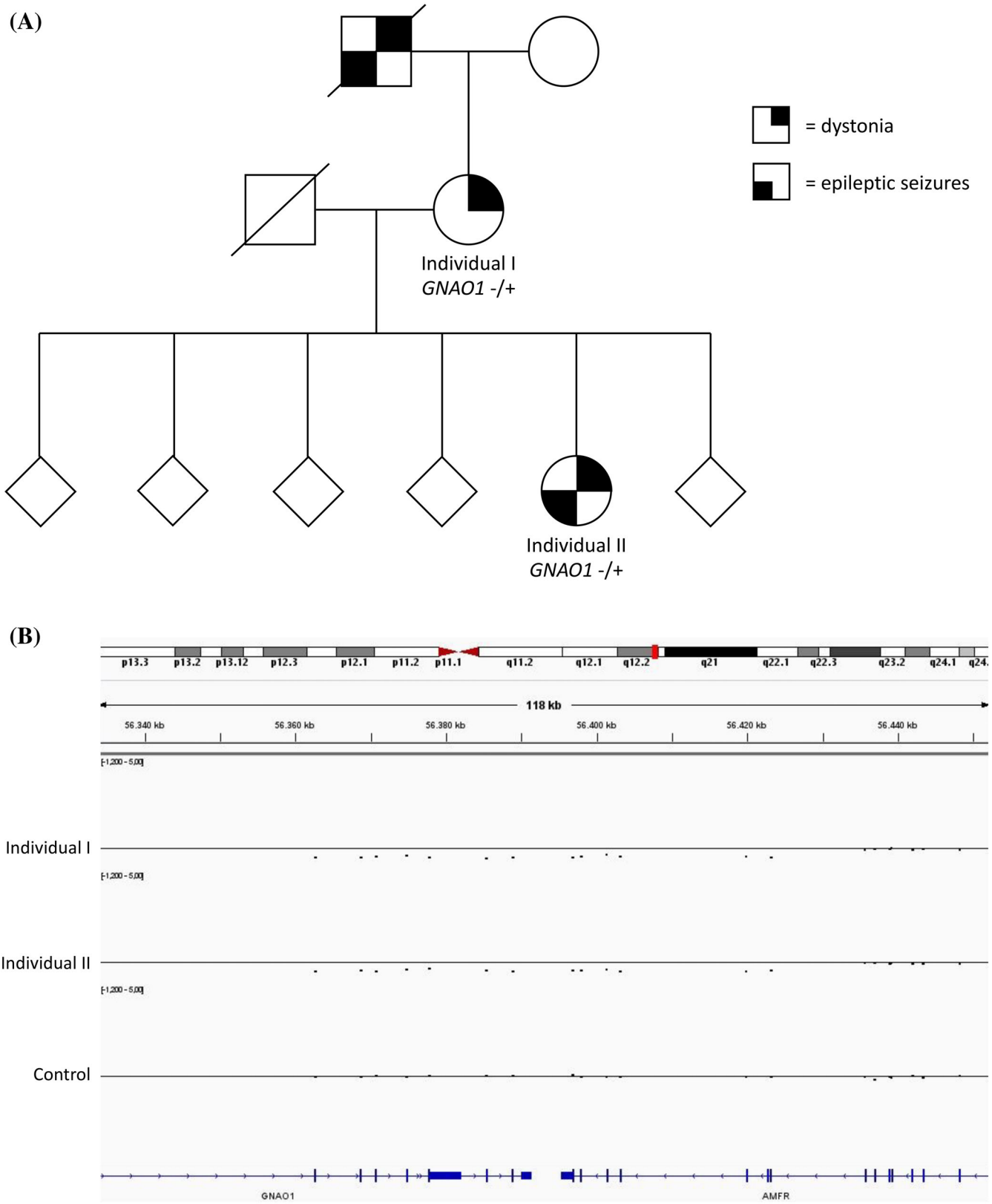

FIG 1. (**A**) Pedigree drawing for the family with inherited 16q12.2 deletion affecting *GNAO1*. (**B**) Integrative Genomics Viewer(IGV) visualization of the detected deletion. The genes *GNAO1* and *AMFR* were included in the deletion interval; the latter gene has not been associated with a Mendelian disorder. Copy-number variations in the patients' exome data were identified using the ExomeDepth algorithm. [Color figure can be viewed at wileyonlinelibrary.com]

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Reply to: "*GNAO1* Haploinsufficiency Associated with a Mild Delayed-Onset Dystonia Phenotype"

We read the letter written by Krenn et al.[1] regarding our recent article on the mild dystonic phenotype associated with *GNAO1* heterozygous variants.[2] The authors report on two first-degree relatives (mother and daughter) with delayed-onset dystonia and who carried a copy number variant (CNV) in *GNAO1*. The mother exhibited symptoms from the age of 40 years, focal cervical dystonia associated with head tremor, and then developed segmental dystonia with additional myoclonus. No encephalopathic features nor intellectual disability (ID) was reported. Her daughter showed nonprogressive focal cervical dystonia from the age of 16 years associated with learning difficulties in childhood and generalized tonic–clonic seizures. By reassessing the whole-exome sequencing (WES) data sets of a cohort of patients affected with dystonia, the authors identified a heterozygous interstitial deletion at 16q12.2 encompassing exons 4 to 8 of *GNAO1* (NM_020988.3) in the mother–daughter pair. Interestingly, this finding was initially ranked as a variant of unknown signification (VUS) and then reclassified in light of our recent article.[2]

Together with our results, these new findings are highly relevant in clinical practice. They highlight the importance of *GNAO1* CNV assessment facing patients presenting with autosomal dominantly inherited focal dystonia. Likewise, a very recent publication from Lasa-Aranzasti and colleagues identified a larger 16q deletion encompassing *GNAO1* in a patient showing mild ID associated with generalized dystonia.[3] *GNAO1* CNV may thus be an important cause of prominent dystonic phenotypes, which should be carefully searched for in patients exhibiting such a clinical presentation. In addition, these new reports further support that delayed-onset dystonia with no or little additional neurodevelopmental and neurological symptoms can be an underrecognized phenotype of *GNAO1*-related disorder. As highlighted,[1] autosomal dominantly inherited dystonia is not rare in movement disorder clinics. Our findings, taken together with those from Krenn and colleagues,[1] suggest that a substantial number of those cases could potentially be related to *GNAO1* likely pathogenic or pathogenic variants, which has important implications for genetic testing and counseling. *GNAO1* variants should be consequently searched for when the phenotype is compatible with the newly described *GNAO1*-related spectrum, which is reminding of *THAP1*-, *GNAL*-, or *KMT2B*-related dystonia.

The report provides further indication of the relationship between *GNAO1* haploinsufficiency and milder dystonic phenotypes without encephalopathic features. This question the current framework about genotype–phenotype correlations in *GNAO1*-related disorders: the hypothesis of loss-of-function variants causing epileptic encephalopathy and gain-of-function variants causing a neurodevelopmental syndrome with prominent dystonia is probably oversimplistic.[4,5] It also raises the question of the factors determining intrafamilial phenotypic variability and the differences in the clinical presentation between patients carrying loss-of-function variants. Further functional work assessing the specific impact of each mutation on the striatal cyclic adenosine monophosphate synthesis pathway, as well as neuroimaging studies of *GNAO1* carriers, might lead to a better understanding of these genetic, epigenetic, and environmental factors and to the refinement of genotype–phenotype correlations.

Data Availability Statement

Anonymized data pertaining to the research presented will be made available upon reasonable request from external investigators.

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