GNAO1 Haploinsufficiency Associated with a Mild Delayed-Onset Dystonia Phenotype

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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 nonprogressive 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]

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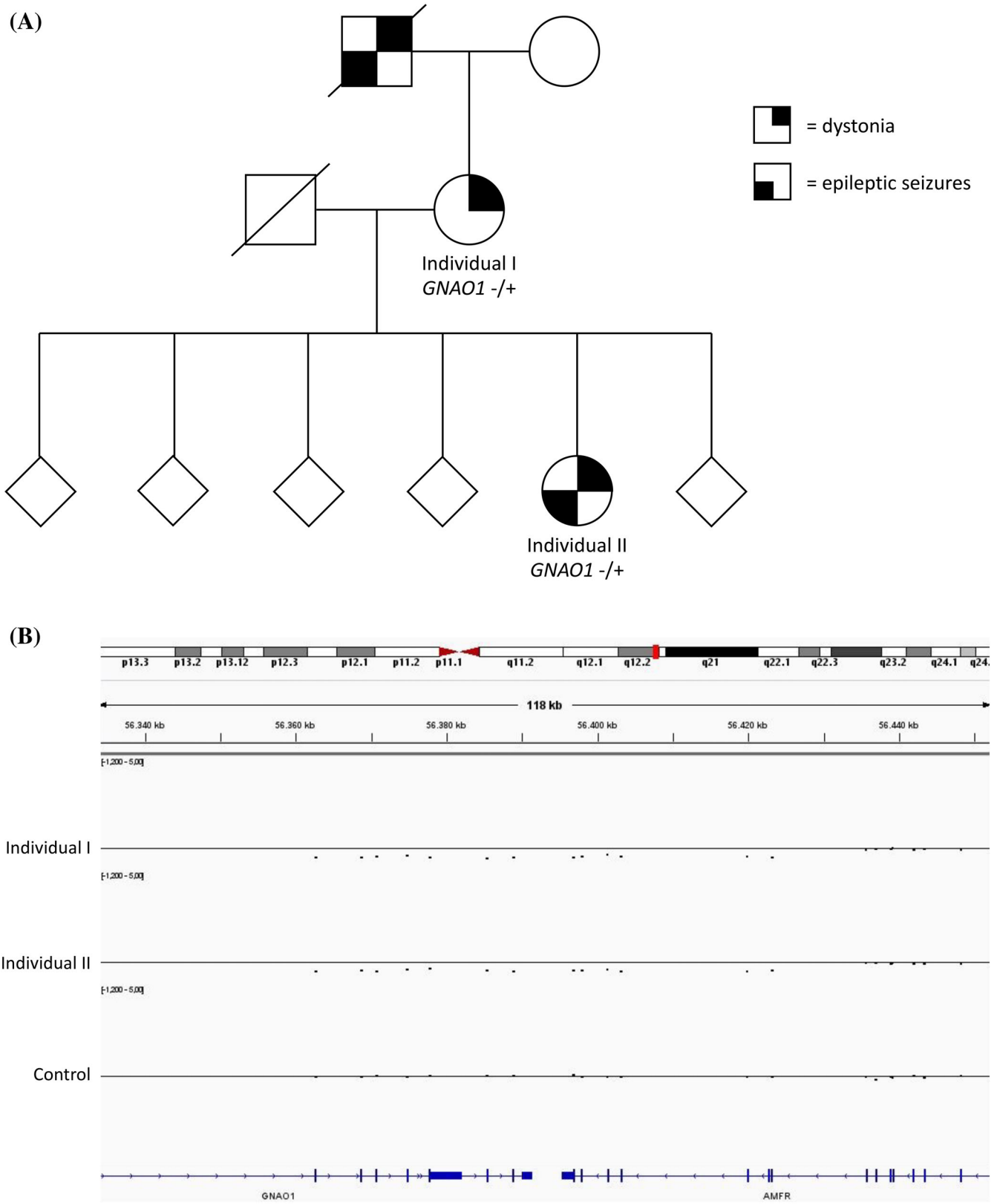

FIG. 1. (**A**) Pedigree drawing for the family with inherited 16q12.2 deletion affecting *GNAO1*. (**B**) Integrative Genomics Viewer(IGV) visualization of the detected deletion. The genes *GNAO1* and *AMFR* were included in the deletion interval; the latter gene has not been associated with a Mendelian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

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.

References

1. Wirth T, Garone G, Kurian MA, et al. Highlighting the dystonic phenotype related to GNAO1. Mov Disord 2022;37:1547–1554.
2. Nakamura K, Kodera H, Akita T, et al. De novo mutations in GNAO1, encoding a Galphao subunit of heterotrimeric G proteins, cause epileptic encephalopathy. Am J Hum Genet 2013;93:496–505.
3. Schirinzi T, Garone G, Travaglini L, et al. Phenomenology and clinical course of movement disorder in GNAO1 variants: results from an analytical review. Parkinsonism Relat Disord 2019;61:19–25.
4. Dzinovic I, Boesch S, Skorvanek M, et al. Genetic overlap between dystonia and other neurologic disorders: a study of 1,100 exomes. Parkinsonism Relat Disord 2022;102:1–6.
5. Zech M, Jech R, Boesch S, et al. Monogenic variants in dystonia: an exome-wide sequencing study. Lancet Neurol 2020;19:908–918.
6. Apuzzo D, Cappuccio G, Vaisanen T, et al. Two cases of 16q12.1q21 deletions and refinement of the critical region. Eur J Med Genet 2020;63:103878.
7. Landrum MJ, Chitipiralla S, Brown GR, et al. ClinVar: improvements to accessing data. Nucleic Acids Res 2020;48:D835–D844.

Author Roles

M.K. drafted the manuscript and was involved in clinical and genetic data interpretation. R.S. was responsible for clinical management of the patients. T.S. was involved in clinical and genetic diagnostic workup of the patients. M.Z. proposed and supervised the manuscript and performed genetic data analysis.

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