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BRIEF REPORT

GNAO1 Mutations Affecting the N-Terminal α-Helix of Gαo Lead to Parkinsonism

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ABSTRACT: Background: Patients carrying pathogenic variants in *GNAO1* present a phenotypic spectrum ranging from severe early-onset epileptic encephalopathy and developmental delay to mild adolescent/adult-onset dystonia. Genotype–phenotype correlation and molecular mechanisms underlying the disease remain understudied.
Methods: We analyzed the clinical course of a child carrying the novel *GNAO1* mutation c.38T>C;p.-Leu13Pro, and structural, biochemical, and cellular properties of the corresponding mutant Gαo—*GNAO1*-encoded protein—alongside the related mutation c.68T>C;p.Leu23Pro.
Results: The main clinical feature was parkinsonism with bradykinesia and rigidity, unlike the hyperkinetic movement disorder commonly associated with *GNAO1* mutations. The Leu → Pro substitutions have no impact on enzymatic activity or overall folding of Gαo but uniquely destabilize the N-terminal α-helix, blocking formation of the heterotrimeric G-protein and disabling activation by G-protein-coupled receptors.
Conclusions: Our study defines a parkinsonism phenotype within the spectrum of *GNAO1* disorders and suggests a genotype–phenotype correlation by *GNAO1* mutations targeting the N-terminal α-helix of Gαo. © 2024 The Authors. *Movement Disorders* published by Wiley Periodicals LLC on behalf of International Parkinson and Movement Disorder Society.

Key Words: *GNAO1*; Gαo; G-protein-coupled receptors; parkinsonism; hypokinetic phenotype

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Pathogenic *GNAO1* variants were first associated with severe early-onset epileptic encephalopathy.[1] Subsequent patients were reported with a movement disorder–predominant phenotype.[2] *GNAO1* disorders are thus classified as "developmental and epileptic encephalopathy 17" (OMIM-615473) and "neurodevelopmental disorder with involuntary movements" (OMIM-617493). However, recent *GNAO1* variants were linked to milder adolescent/adult-onset dystonia.[3,4] As clinical presentations are very heterogeneous, *GNAO1* disorders seem to represent a continuous phenotypic spectrum rather than two distinct phenotypes.[4]

GNAO1 encodes for Gαo, the most abundant Gα subunit of G-proteins in the brain.[5] Gαo is one of the 16 Gα subunits expressed in humans that complex with Gβγ to constitute the main transducers of G-protein-coupled receptors (GPCRs).[6] Gαo transmits signals from multiple GPCRs[7] and the Frizzled receptors family.[8,9] Ligand-activated GPCRs act as guanine-nucleotide exchange factors for GDP-loaded Gα, dissociating the heterotrimer into Gα-GTP and Gβγ, both involved in signaling.[6] Gαβγ heterotrimers are restored by the GTPase activity of Gα, which can be enhanced by RGS (regulator of G-protein signaling) proteins.[10,11]

Pathogenic Gαo mutants have been described as loss-of-function,[12-14] gain-of-function,[12,15,16] or dominant-negative mutants.[12-14,16-18] These opposing features led us to propose that *GNAO1* pathogenic variants are neomorphic in nature[12,19] and to identify a strong neomorphic interaction with Ric8A/B.[20] Typically, mutants leading to the severe epileptic phenotype show higher Ric8A/B binding and loss of plasma membrane (PM) and Gβγ binding, although they can still engage GPCRs.[13,20,21]

Here, we report parkinsonism of a child carrying the novel mutation c.38T>C;p.Leu13Pro (L13P), expanding the phenotypic spectrum of *GNAO1* disorders. We further performed extensive characterization of the mutant Gαo alongside the related c.68T>C;p.Leu23Pro (L23P) mutation published recently.[3]

Patients and Methods

Patient data were collected in the framework of two studies: "German GNAO1 registry" and "Natural History of GNAO1-associated disorders." Trials were approved by the Ethics Committee of the University of Cologne (9-19280 and 21-1579, respectively). Caregivers gave informed consent prior to participating in the study and for publication of the video.

Patient's genetic evaluation and experimental methods are provided in Supplementary Material (Appendix S1).

Results

Clinical Course

The male full-term newborn was floppy without vigilance, without impairment in cardiorespiratory function. At 12 hours of age, he had a generalized seizure, recognized by apnea and cyanosis without abnormal movements. Electrocardiogram and echocardiography did not reveal cardiogenic causes of cyanosis. Subsequently, he showed repetitive generalized seizures, all manifested by apnea. The initial treatment with pyridoxine and phenobarbitone combination terminated the seizures on the third day of life. Repeated electroencephalograms (EEG) were normal. Phenobarbitone was stopped after 11 days, and the patient was discharged without medication.

During the first year of life, central hypotonia and delayed motor development were dominant clinical symptoms. Short episodes of perioral dyskinesia and limb choreoathetosis were reported as increased during febrile infections. Additional problems were hypersalivation, feeding problems, and speech development delay.

At 7 years of age, he suffered from two generalized tonic–clonic seizures. Video EEG over 48 hours was normal. Valproic acid was initiated.

A detailed comprehensive metabolic investigation was performed, which showed no abnormalities apart from a slight increase in phytanic acid. Brain magnetic resonance imaging performed at 12 days and at 5 and 8 years were normal. At 5 years, a heterozygote de novo *GNAO1* variant [NM_020988.3]:c.38T>C; p.L13P was identified through whole-genome sequencing (Supplementary Table S1).

The boy was presented to our center at 9 years and 10 months. Besides central hypotonia, he showed symptoms of parkinsonism, including camptocormia, bradykinesia, shuffling, small steps, unsteady gait, and postural instability. He also showed cervical dystonia, leading to torticollis and laterocollis, and distal limb dystonia, leading to intermittent toe walking. Other symptoms included swallowing difficulties with constant hypersalivation, motor restlessness, obstipation, and aggressive social behavior. Muscle strength was reduced to 4/5, and muscle reflexes were increased bilaterally with enlarged reflex zones and striatal toe. Language perception was adequate, whereas expression was severely dysarthric. The Gross Motor Function Measure-66 was 72.16 (68.83–75.49, 95% confidence interval), and the Burke–Fahn–Marsden Dystonia Rating Scale movement score was 6/120. Medication comprised valproic acid 22 mg/kg/day. A case video is shown in Video S1.

Because parkinsonism was not seen in the cohort we recently reported,[4] we further analyzed the Gαo L13P mutant to better understand its genotype–phenotype correlation. We also included L23P, as it was associated with a similar phenotype.[3]

Structural, Biochemical, and Cellular Analyses

Gα subunits contain a Ras-like domain (RD), an α-helical domain (AHD), and an N-terminal α-helix (αN).[22] We highlighted the singular position of Leu13 and Leu23 alongside 45 missense mutations reported in *GNAO1* patients.[4,23,24] Whereas *GNAO1* mutations spread over the RD and AHD (red colored, Fig. 1A), Leu13 and Leu23 reside in αN (blue colored, Fig. 1A), which contains residues essential for the Gα–Gβ interaction (Fig. 1B).[22,25] As Pro is known to destabilize α-helices,[26] both mutations are predicted to curve αN, misplacing residues implicated in Gβ binding (Fig. 1C–E). Conversely, these Leu → Pro substitutions are not expected to alter nucleotide binding and GTPase activity, which involved only RD and AHD.[27,28]

To challenge these predictions, we introduced the L13P and L23P mutations into a recombinant His_6-Gαo[29] and purified the mutants (Supplementary Fig. S1A,B). We then analyzed GTP loading using the nonhydrolyzable fluorescent analog BODIPY-GTPγS (Supplementary Fig. S1C–F).[29,30] As predicted, GTPγS uptake by L13P was indistinguishable from the wild type (Supplementary Fig. S1C,D). L23P, however, showed a slightly slower GTPγS loading (Supplementary Fig. S1E,F). We next determined GTP hydrolysis using BODIPY-GTP, a hydrolyzable GTP analog.[29,31] Both mutants presented hydrolysis curves very similar to the wild type (Supplementary Fig. S1G–J). Thus, we conclude that the biochemical

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properties of L13P and L23P are unlikely the cause of disease.

We then analyzed the interaction between Gαo variants and Gβγ using co-immunoprecipitation (co-IP) from N2a cells co-expressing Gαo^{G92}-GFP and HA-Gβ1γ3.[21] Contrary to the robust co-IP of HA-Gβ1γ3 by Gαo^{G92}-GFP wild type, the signal was vastly reduced for L13P and L23P (Fig. 1F). Quantification revealed a reduction of more than 90% in Gβ1γ3 binding by the mutants, comparable to the constitutively active Q205L control mutant (Fig. 1G). This effect was confirmed using the bioluminescence resonance energy transfer (BRET)-based Gβ3γ9-displacement assay (Supplementary Fig. S2A),[20] which showed a dramatic decrease in the ability of L13P and L23P to interact with Gβ3γ9 (Supplementary Fig. S2B). The lack of Gβγ binding implies an exclusion from GPCR signaling, a notion we tested using a BRET assay that monitors GPCR coupling by Gα in HEK293T cells (Fig. 1H).[20,32] As expected, Gαo^{G92}-GFP coupling to GPCR on activation was observed for wild type but not L13P, L23P, and Q205L (Fig. 1I; Supplementary Fig. S2C).

We then tested the subcellular localization of Gαo variants in N2a cells using immunostaining. In addition

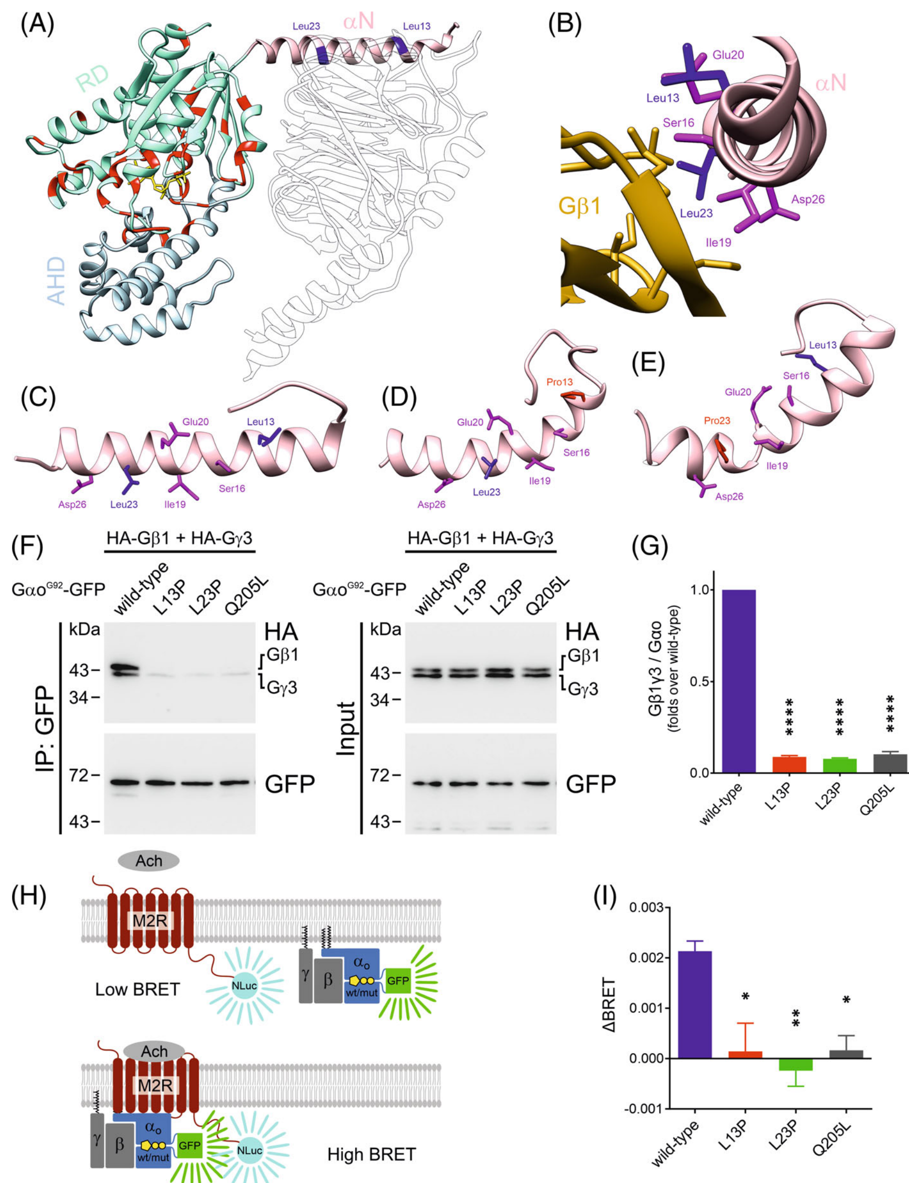

FIG. 1. (**A**) Gαo structure bound to Gβ1γ2 (translucent) and GDP (yellow). Pathogenic Gαo residues (red). (**B**) Gαo–Gβ1 interface (key residues in magenta). Predicted αN structures for (**C**) Gαo wild type, (**D**) L13P, and (**E**) L23P. (**F**) Western blot and (**G**) quantification of the co-immunoprecipitation of HA-Gβ1γ3 by Gαo^{G92}-GFP variants. (**H**) GPCR (G-protein-coupled receptor)-coupling assay and (**I**) quantification (ΔBRET). **P* < 0.05, ***P* < 0.01, and *****P* < 0.0001. Abbreviations: Ach, acetylcholine; AHD, α-helical domain; αN, N-terminal α-helix; IP, immunoprecipitation; M2R, M2 muscarinic acetylcholine receptor; RD, Ras-like domain. [Color figure can be viewed at wileyonlinelibrary.com]

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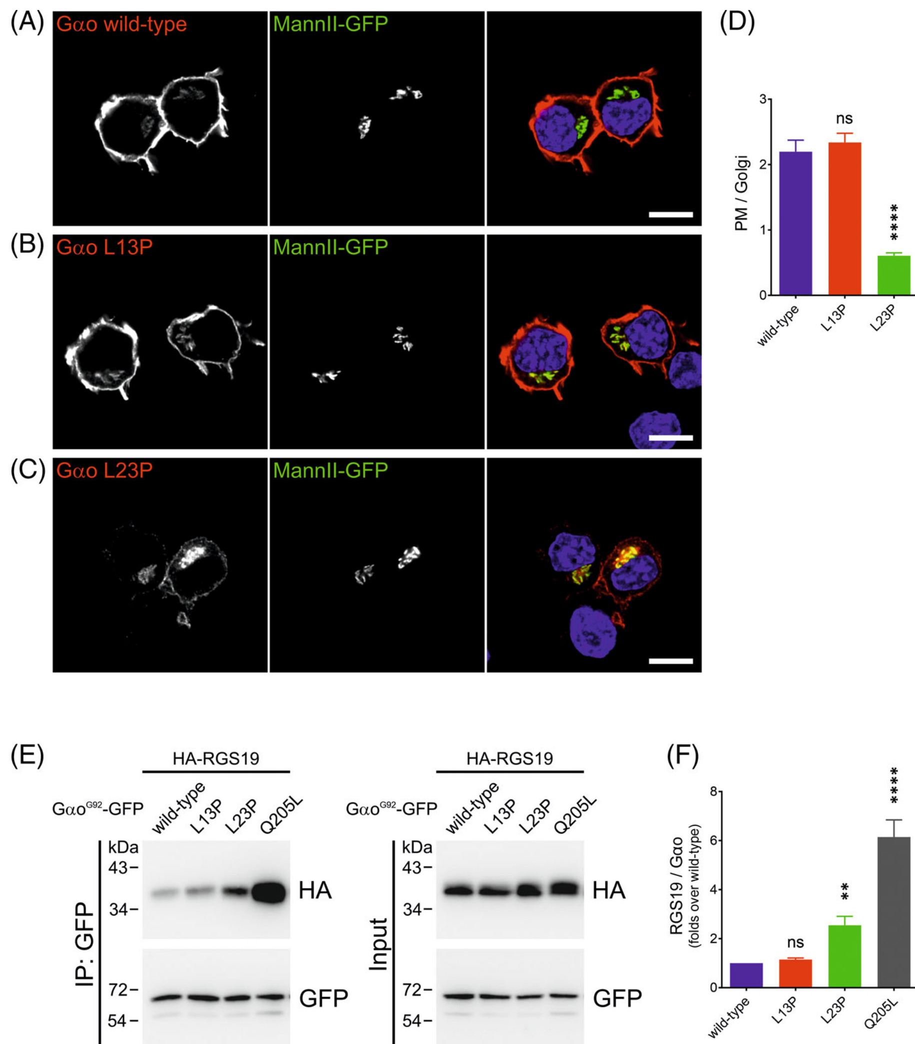

FIG. 2. Localization of (**A**) Gαo wild type, (**B**) L13P, and (**C**) L23P in N2a cells. MannII-GFP marked the Golgi. Scale bar: 10 μm. (**D**) Quantification of PM (plasma membrane)-to-Golgi fluorescence ratios. (**E**) Western blot and (**F**) quantification of the co-immunoprecipitation of HA-RGS19 by the Gαo^{G92}-GFP variants.**$P < 0.01$ and ****$P < 0.0001$. IP, immunoprecipitation; MannII, mannosidase II; ns, not significant. [Color figure can be viewed at wileyonlinelibrary.com]

to its PM localization, Gαo resides at the Golgi apparatus (Fig. 2A).[33,34] Intriguingly, L13P localized like Gαo wild type, whereas L23P displayed a weaker PM localization (Fig. 2A–C); quantification showed that the PM-to-Golgi ratio of L23P was ~3.5-fold lower than Gαo wild type and L13P (Fig. 2D). Gαo^{G92}-GFP wild type, L13P, and L23P (Supplementary Fig. S3A–C) showed the localization pattern similar to that of the nontagged Gαo variants (Fig. 2A–C).

All pathogenic *GNAO1* mutations analyzed so far impair the Gαo–RGS interaction.[5,12,16,20,21,24] RGS binds to GTP-loaded Gα via the RD and HD,[11,29] suggesting that the pathogenic Gαo mutants cannot adopt the proper active conformation. Because αN does not participate in RGS binding,[10,11] the Leu → Pro substitutions should not affect this interaction. Therefore, Gαo^{G92}-GFP wild type and L13P coprecipitated similar amounts of HA-RGS19 (Fig. 2E,F). L23P, however, showed a ~2.5-fold higher HA-RGS19 binding; Q205L reached a more than sixfold increase in the interaction (Fig. 2E,F). Finally, we tested whether the Leu → Pro substitutions induce the neomorphic Ric8A/B interaction[20] but found that GFP-Ric8A coprecipitated L13P and L23P as weakly as Gαo wild type (Supplementary Fig. S4).

Discussion

Here, we expand the phenotypic spectrum of *GNAO1* disorders by describing a child carrying a de novo L13P mutation. The symptoms showed striking similarities with those of a 28-year-old woman carrying the pathogenic L23P variant.[3] The initial symptoms of both were seizures but at different ages: neonatal seizures in our patient and seizures at 4 years in the L23P

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patient. Although tremor was not observed, they showed parkinsonism as the key feature, contrasting with the hyperkinetic movement disorder that defines the majority of *GNAO1* patients.[35] Both patients presented intellectual disabilities. Facial and cervical dystonia was also present in both, but central muscular hypotonia was seen only in our patient. Speech abilities also differed: the L23P patient had normal speech, whereas our patient presented dysarthria. Despite these differences, both patients represent a distinct phenotype within the spectrum of *GNAO1* disorders with core features of parkinsonism such as bradykinesia and rigidity. A related akinetic-rigid syndrome was diagnosed in patients carrying the *GNAO1* mutations c.737A>T; p.E246V and c.765dupT;p.N256*, and in 3 of 8 patients with c.724-8G>A;p.T241_N242insPQ.[3] Although the E246V and N256* mutants await characterization, the molecular defects of Gαo T241_N242insPQ differ from L13P and L23P.[16] Therefore, varying pathomechanisms may lead to parkinsonism.

At the molecular level, the Leu → Pro substitutions in αN severely impaired Gβγ binding and consequently GPCR-signaling. Conversely, Leu → Pro substitutions are not expected to affect Gαo′ enzymatic activity, a prediction fully validated for L13P. The slightly slower GTP uptake of L23P suggests a higher residency in the inactive GDP-bound state, which is at odds with its greater RGS19 interaction. As Gαo is activated at the Golgi in a Gβγ-independent manner,[33] this apparent contradiction could be the outcome of the increased Golgi localization of L23P.

Gα and Gβγ require each other for their PM localization[36]—the premise that is at odds with our finding that L13P localizes normally at the PM despite a poor Gβγ association. We recently demonstrated that Gαo localization is locally controlled by S-palmitoylation and that αN facilitates the PM targeting independently of Gβγ.[34] The Golgi accumulation of L23P resembles a Gαo construct lacking αN,[34] suggesting that the Leu13 → Pro substitution might impair S-palmitoylation at the PM.

In conclusion, we found that *GNAO1* mutations affecting the αN of Gαo lead to parkinsonism, offering a genotype–phenotype correlation. This phenotype is associated with the loss of heterotrimer formation and GPCR coupling by the Gαo variants, which uniquely retain the ability to adopt the active conformation. We propose that *GNAO1* should be considered for genetic testing in patients with hypokinetic phenotypes, in addition to those with the hyperkinetic movement disorder. ■

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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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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

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