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GNAO1-Related Disorder

Synonyms: *GNAO1*-Associated Disorder, *GNAO1*-Associated Epileptic Encephalopathy and Movement Disorder

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Summary

Clinical characteristics

GNAO1-related disorder encompasses a broad phenotypic continuum that includes hyperkinetic movement disorders and/or epilepsy and is typically associated with developmental delay and intellectual disability. Viewed by age of onset, three clusters in this continuum can be observed: (1) infantile-onset developmental and epileptic encephalopathy (DEE) with or without prominent movement disorder; (2) infantile- or early childhood-onset prominent movement disorder and neurodevelopmental disorder with or without childhood-onset epilepsy with varying seizure types; (3) later childhood- or adult-onset movement disorder with variable developmental delay and intellectual disability.

Epilepsy can be either DEE (onset typically within the first year of life of drug-resistant epilepsy in which developmental delays are attributed to the underlying diagnosis as well as the impact of uncontrolled seizures) or varying seizure types (onset typically between ages three and ten years of focal or generalized tonic-clonic seizures that may be infrequent or well controlled with anti-seizure medications).

Movement disorders are characterized by dystonia and choreoathetosis, most commonly a mixed pattern of persistent or paroxysmal dyskinesia that affects the whole body. Exacerbations of the hyperkinetic movement disorder, which can be spontaneous or triggered (e.g., by intercurrent illness, emotional stress, voluntary movements), can last minutes to weeks. Hyperkinetic crises (including status dystonicus) are characterized by temporarily increased and nearly continuous involuntary movements or dystonic posturing that can be life-threatening.

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Deaths in early childhood have been reported due to medically refractory epilepsy or hyperkinetic crises, but the phenotypic spectrum includes milder presentations, including in adults. As many adults with disabilities have not undergone advanced genetic testing, it is likely that adults with *GNAO1*-related disorder are underrecognized and underreported.

Diagnosis/testing

The diagnosis of *GNAO1*-related disorder **is established** in a proband with suggestive findings and a heterozygous pathogenic variant in *GNAO1* identified by molecular genetic testing.

Management

Treatment of manifestations: There is no cure for *GNAO1*-related disorder. Supportive care to improve quality of life, maximize function, and reduce complications can include multidisciplinary care by specialists in child neurology, adult neurology, neurosurgery, physical medicine and rehabilitation, physical therapy, occupational therapy, orthopedic surgery, speech-language therapy, and psychology.

Surveillance: Frequent evaluations by treating specialists are necessary to monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations.

Genetic counseling

GNAO1-related disorder is an autosomal dominant disorder most often caused by a *de novo* pathogenic variant. Individuals with severe *GNAO1*-related disorder phenotypes (i.e., DEE, severe developmental delay and/or intellectual disability, and/or an early-onset movement disorder) typically represent simplex cases (i.e., the only family member known to be affected) and have the disorder as the result of a *de novo* pathogenic variant; however, recurrence of severe *GNAO1*-related disorder phenotypes in affected sibs due to presumed parental germline mosaicism has been reported. Vertical transmission from an affected parent to an affected child has been reported in several families with the milder phenotype (i.e., later childhood- or adult-onset movement disorder with variable developmental delay and intellectual disability). Once the *GNAO1* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

GeneReview Scope

GNAO1-related disorder encompasses a broad continuum, including epilepsy and hyperkinetic movement disorders as prominent clinical phenotypes, but there is overlap in most affected individuals.

GNAO1-Related Disorder: Phenotypic Spectrum

Phenotype	MOI
Infantile-onset developmental & epileptic encephalopathy (DEE) [1] ± movement disorder	AD (*de novo*)
Infantile- or early childhood-onset movement disorder + neurodevelopmental disorder ± (non-DEE) epilepsy	AD (*de novo*)
Later childhood- or adult-onset movement disorder w/variable developmental delay & intellectual disability	AD (reported in 3 families)

AD = autosomal dominant; MOI = mode of inheritance

1. The international League Against Epilepsy defines DEE as an epileptic encephalopathy where the developmental impairment relates to the underlying etiology as well as uncontrolled epileptic activity.

Diagnosis

No consensus clinical diagnostic criteria for *GNAO1*-related disorder have been published.

Suggestive Findings

GNAO1-related disorder **should be considered** in individuals with the following clinical findings and family history.

Clinical findings

- **Epilepsy**
  - **Developmental and epileptic encephalopathy (DEE).** Early-onset (typically within the first year of life) drug-resistant epilepsy where developmental delays are attributed to the underlying diagnosis as well as the impact of uncontrolled seizures.
  - **Non-DEE epilepsy.** Later-onset focal seizures or generalized tonic-clonic seizures (ages 3-10 years). Seizures may be infrequent or well controlled with anti-seizure medications.
- **Movement disorder.** Most commonly presenting in infancy or early childhood consisting of **choreoathetosis** and **dystonia** with distinct risk for exacerbations of hyperkinetic movement disorder. Onset in later childhood and adulthood has been reported.
- **Axial hypotonia.** Typically present from birth or evident within the first few months of life.
- **Mild-to-profound intellectual disability** initially presenting as global developmental delay; reported in most but not all
- **Feeding difficulties,** most prominently in infancy

Family history. Because *GNAO1*-related disorder is typically caused by a *de novo* pathogenic variant, most probands represent a simplex case (i.e., a single occurrence in a family). Rarely, the family history may be consistent with autosomal dominant inheritance (e.g., affected males and females in multiple generations).

Establishing the Diagnosis

The diagnosis of *GNAO1*-related disorder **is established** in a proband with suggestive findings and a heterozygous pathogenic (or likely pathogenic) variant in *GNAO1* identified by molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include likely pathogenic variants. (2) Identification of a heterozygous *GNAO1* variant of uncertain significance does not establish or rule out the diagnosis.

Approach to molecular genetic testing in a child with developmental delay or an older individual with intellectual disability may begin with **chromosomal microarray analysis (CMA)**. Other options include use of a **multigene panel** or **exome sequencing**. Note: Single-gene testing (sequence analysis of *GNAO1*, followed by gene-targeted deletion/duplication analysis) is rarely useful and typically NOT recommended.

- **A multigene panel for epilepsy or movement disorders** that includes *GNAO1* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

- **Comprehensive genomic testing** does not require the clinician to determine which gene(s) are likely involved but may require relevant clinical details. **Exome sequencing** is most commonly used and yields results similar to an intellectual disability multigene panel, with the additional advantage that exome sequencing includes genes recently identified as causing intellectual disability, whereas some multigene panels may not. **Genome sequencing** is also possible.

  For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in *GNAO1*-Related Disorder

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
GNAO1	Sequence analysis [3]	98.5% [4]
	Gene-targeted deletion/duplication analysis [5]	1.5% [4, 6, 7]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Combined data from all published cases to date (See collected citations in Clinical Description.)
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications. Exome and genome sequencing may be able to detect deletions/duplications using breakpoint detection or read depth; however, sensitivity can be lower than gene-targeted deletion/duplication analysis.
6. One whole-gene deletion [Wirth et al 2022a] and one intragenic deletion [Krenn et al 2022] have been reported.
7. While not included in the percentages above, at least four contiguous gene deletions including *GNAO1* have been reported [Chang et al 2010, Apuzzo et al 2020, Yamamoto et al 2021, Lasa-Aranzasti et al 2022] (see Genetically Related Disorders).

Clinical Characteristics

Clinical Description

GNAO1-related disorder encompasses a spectrum of hyperkinetic movement disorders and/or epilepsy, typically associated with global developmental delay and intellectual disability.

To date, information on more than 200 individuals with *GNAO1*-related disorder have been published [Nakamura et al 2013, EuroEPINOMICS-RES Consortium et al 2014, Law et al 2015, Talvik et al 2015, Zhu et al 2015, Ananth et al 2016, Dhamija et al 2016, Gawlinski et al 2016, Helbig et al 2016, Kulkarni et al 2016, Marcé-Grau et al 2016, Menke et al 2016, Saitsu et al 2016, Yilmaz et al 2016, Arya et al 2017, Danti et al 2017, Schorling et al 2017, Bruun et al 2018, Honey et al 2018, Koy et al 2018, Okumura et al 2018, Waak et al 2018, Benato et al 2019, Kelly et al 2019, Malaquias et al 2019, Muir et al 2019, Schirinzi et al 2019, Arisaka et al 2020, Kim et al 2020, Yamashita et al 2020, Turro et al 2020, Akasaka et al 2021, Dzinovic et al 2021, Chaib et al 2022, Chopra et al 2022, Fung et al 2022, Krenn et al 2022, Krygier et al 2022, Liu et al 2022, Pérez-Dueñas et al 2022, Di Rocco et al 2023, Domínguez-Carral et al 2023, Galosi et al 2023, Gambardella et al 2023, Garofalo et al 2023, Hu et al 2023, Li et al 2023, Novelli et al 2023, Thiel et al 2023, Vasconcellos et al 2023]. The following description of the phenotypic features associated *GNAO1*-related disorder is based on these reports.

Epilepsy

Approximately half (50%-65%) of affected individuals have seizures and/or are diagnosed with epilepsy. While seizures may be refractory to anti-seizure medications (ASMs), some individuals have only a single seizure [Kelly et al 2019] or have only had seizures in the past [Axeen et al 2021].

Developmental and epileptic encephalopathy (DEE) is the most common epilepsy phenotype, occurring in 69% of individuals with epilepsy [Kelly et al 2019].

DEE. The onset of seizures in children with DEE can be as early as the first day of life and is typically within the first three months of life, consistent with an early-infantile DEE (often consistent with the previously termed Ohtahara syndrome) [Nakamura et al 2013, Kelly et al 2019, Axeen et al 2021]. Infantile-onset seizures often manifest as epileptic spasms or tonic seizures. Drug-resistant focal seizures can also have onset from birth. Infantile spasms syndrome and Lennox-Gastaut syndrome are also described in older infants and children, and in some as an evolution of early-infantile DEE.

Seizures in those with DEE are typically drug resistant. Individuals have global developmental delay, axial hypotonia, and feeding difficulties in infancy. Development of abnormal movements (chorea, choreoathetosis, dystonia, ataxia, hyperkinetic crises) is variable and can occur months to years after an established diagnosis of epilepsy.

There is no specific EEG abnormality associated with *GNAO1*-related disorder. The EEG in individuals with epilepsy is often abnormal with focal or multifocal spikes and features of encephalopathy such as background slowing and absence of normal awake and sleep features. EEG findings may suggest a specific electroclinical syndrome such as burst suppression in early-infantile DEE, hypsarrhythmia in infantile spasms syndrome, or slow spike-and-wave with Lennox-Gastaut syndrome.

Non-DEE epilepsy. Seizure onset is most often between ages three and ten years. Seizures are generalized tonic-clonic or focal. Some individuals have only a single seizure or well-controlled epilepsy on treatment with an ASM, which may contrast with their concurrent drug-resistant movement disorder. In this subset of individuals, other characteristic findings, including axial hypotonia, global developmental delay, early-onset feeding difficulties, and dyskinesia, precede seizure onset.

Developmental Delay and Intellectual Disability

During the first year of life, delay in motor development is significantly influenced by the severity of hypotonia. The more profound the hypotonia, the later the individuals achieve their motor milestones [Ananth et al 2016, Schorling et al 2017]. Severely affected individuals often lack head and/or trunk control and/or the ability to sit independently [Nakamura et al 2013].

Balance can be impaired due to axial muscular hypotonia, dystonic posturing of the neck, trunk, and extremities, and dyskinesia of the extremities. Although about 20% of individuals achieve independent ambulation, about 80% never do and depend on help for mobility [Saitsu et al 2016, Axeen et al 2021]. With the onset of involuntary movements, purposeful movements of the hands are often severely impaired.

Assessment of cognition is limited by the young age of many individuals and/or testing that typically depends on verbal communication and motor tasks [Kim et al 2020]. Therefore, formal tests of cognition can only be administered to individuals who have varying – but milder – degrees of disability. Recently, there have been attempts to assess cognitive impairment using an eye-tracking communication aid [Graziola et al 2021].

Despite the lack of expressive language, receptive language is often a relative strength [Graziola et al 2021, Domínguez-Carral et al 2023]. Some severely affected individuals can communicate with an eye-tracking communication aid or other communication aids [Axeen et al 2021, Graziola et al 2021, Thiel et al 2023].

The broad range of cognitive abilities in *GNAO1*-related disorder is highlighted by recent reports comparing individuals with a movement disorder phenotype and normal cognition or minimal intellectual disability [Krenn et al 2022, Liu et al 2022, Wirth et al 2022a, Galosi et al 2023, Thiel et al 2023] to individuals with DEE, who typically have severe to profound developmental delay and intellectual disability.

Movement Disorder

The vast majority of affected individuals have a hyperkinetic movement disorder [Kelly et al 2019, Schirinzi et al 2019, Axeen et al 2021]. The core features of the movement disorder are choreoathetosis and dystonia [Feng et al 2018], which can be severely disabling and painful. Complex motor stereotypies, ballism, myoclonus, facial dyskinesia, and ataxia have also been reported [Danti et al 2017, Axeen et al 2021].

Most individuals show a mixed pattern of persistent or paroxysmal dyskinesia that affect the whole body. Exacerbations of the hyperkinetic movement disorder, a characteristic feature, can occur spontaneously or can be triggered by intercurrent illnesses (e.g., febrile infections) as well as by emotional stress, excitement, voluntary movements, or change in position [Koy et al 2018]. They can last minutes, hours, days, or even weeks [Carecchio & Mencacci 2017].

Almost half of individuals experience prolonged exacerbations leading to life-threatening hyperkinetic crises (including status dystonicus), which are characterized by temporarily increased and nearly continuous involuntary movements or dystonic posturing. Accompanying problems can include impaired respiration, lack of sleep, dehydration, electrolyte imbalance, autonomic dysregulation, and rhabdomyolysis [Saini et al 2022]. These hyperkinetic crises often require intensive medical management (see Treatment of Manifestations). Response to oral and intravenous medications is often limited. Recovery may take weeks to months.

Cervical and oropharyngeal dystonia, with involvement of the laryngeal muscles, can lead to dysarthria (60%-80%) or even anarthria (20%-30%) [Axeen et al 2021, Wirth et al 2022a].

Chewing and swallowing are often impaired due to involuntary or dysfunctional tongue movements and weakness of the jaw muscles. A subset of individuals (20%-40%) need help with feeding as they can eat only very small portions or food with a soft consistency. Percutaneous endoscopic gastrostomy (PEG) or nasogastric feeding tube are often required (30%-50%) [Ananth et al 2016, Axeen et al 2021].

While the onset of movement disorders typically ranges from ages one to four years, some infants manifest movement disorders during the first weeks of life [Schirinzi et al 2019, Yang et al 2021]. In contrast, in some individuals with a milder phenotype, the movement disorder presents in the teens or adulthood [Wirth et al 2022a].

Individuals with symptom onset during early infancy and severe impairment of motor development are more likely to have hyperkinetic crises; in contrast, individuals with late onset and less severe motor impairment (i.e., are able to walk) and normal intellect or only mild intellectual disability appear to be at lower risk [Krenn et al 2022, Wirth et al 2022a, Thiel et al 2023].

Muscular Hypotonia

Significant axial hypotonia is often the first manifestation of *GNA01*-related disorder [Axeen et al 2021]. Hypotonia is mainly present in the neck and trunk, but also in the limbs, contributing to delays in motor development [Feng et al 2017, Wirth et al 2022a]. Some individuals have perioral hypotonia leading to insufficient closing of the mouth and reduced ability to chew solid food.

Other Common Features

Sleep disturbance, including difficulty with sleep initiation and sleep maintenance, is frequently reported and may be evident in infancy. It may or may not be related to concurrent epilepsy and movement disorder.

Gastrointestinal problems including constipation, gastroesophageal reflux disease, and vomiting are very common. Along with the lower intake of food in those with a movement disorder (see Clinical Description, Movement Disorder), these problems can lead to poor weight gain and malnutrition, which increase morbidity in cachectic individuals. Although often described, the coexistent problem of cachexia is not well understood.

Neuroimaging

While most individuals (particularly children younger than age five years) have a normal brain MRI [Schirinzi et al 2019], some individuals have nonspecific abnormalities such as cortical and cerebellar atrophy, white matter abnormalities, and altered densities of the thalami and globus pallidi [Ananth et al 2016, Axeen et al 2021].

Prognosis

It is unknown whether life span in *GNAO1*-related disorder can be normal.

Although a number of deaths in children have been reported [Nakamura et al 2013, Ananth et al 2016, Danti et al 2017, Koy & Cirak et al 2018, Xiong et al 2018, Kwong et al 2021, Yang et al 2021, Li et al 2023], there are also many reports of young adults with *GNAO1*-related disorder, demonstrating that survival into adulthood is possible [Benato et al 2019, Kelly et al 2019, Wirth et al 2022a]. Since many adults with disabilities have not undergone advanced genetic testing, it is likely that adults with *GNAO1*-related disorder are underrecognized and underreported.

Deaths reported due to neurologic disease include the following:

- **Epilepsy.** To date, at least six children have been reported to have died during early infancy in the setting of drug-resistant epilepsy [Nakamura et al 2013, Xiong et al 2018, Yang et al 2021].
- **Hyperkinetic crises with status dystonicus.** At least five individuals have been reported to have died during an exacerbation of their movement disorder, all of whom initially presented in the first year of life with hypotonia and developmental delay [Ananth et al 2016, Danti et al 2017, Koy et al 2018, Kwong et al 2021].

While immune dysfunction has not been described in individuals with *GNAO1*-related disorder, infections (including respiratory infections) can aggravate the movement disorder, often resulting in hyperkinetic crises with need for hospitalization. Dysphagia and/or seizures can also increase risk of aspiration-related events that may require admission to a hospital and respiratory support.

Genotype-Phenotype Correlations

More than 200 individuals with pathogenic variants in *GNAO1* have been reported in the literature to date.

To date, genotype-phenotype correlations have been described for several recurrent *GNAO1* variants: one splicing variant and variants at five hot spot residues (p.Gly40, p.Gly203, p.Arg209, p.Glu237, and p.Glu246). These recurrent variants account for approximately half of affected individuals reported to date [Kelly et al 2019, Schirinzi et al 2019] (see Table 2).

In addition, accumulating data may point to haploinsufficiency variants being associated with milder phenotypes, without epileptic encephalopathy or severe global developmental delay or intellectual disability [Krenn et al 2022, Wirth et al 2022a, Wirth et al 2022b, Galosi et al 2023, Thiel et al 2023].

Table 2. *GNAO1*-Related Disorder: Genotype-Phenotype Correlations

Variant	# of Persons	Clinical Characteristics		
		Epilepsy	Movement disorder (predominantly dystonia & chorea) [1]	DD/ID [2]
p.Gly40Arg [3]	8	All had DEE	Not a prominent feature	Profound global DD/ID
p.Gly40Trp [4]	2			
p.Gly40Glu [5]	2			
p.Gly203Arg [6]	25	All had DEE	Present in most to all; hyperkinetic crises common	Severe global DD/ID in 2; not stated in 9
p.Arg206Gln [7]	4 (from 1 family)	No seizures	Dystonia (onset at ages 15 yrs, 30 yrs, & 47 yrs, + 1 asymptomatic at 30 yrs); no chorea or hyperkinetic crises reported	No speech delay; motor delay NR; no ID
p.Arg209Cys [8]	19	Seizures mostly focal or generalized tonic-clonic; none had DEE	Present in most to all; hyperkinetic crises common	Moderate-to-severe global DD; mild-to-severe ID
p.Arg209His [9]	13	Seizures rare	Present in all; hyperkinetic crises common	Moderate-to-severe global DD; ID not stated
p.Arg209Leu [10]	3			
p.Arg209Gly [11]	1			
p.Arg209Pro [12]	1			
p.Cys215Tyr [13]	4 (from 3 families)	No seizures	Dystonia onset at age 3-6 yrs; no chorea; hyperkinetic crises in 1/4.	No speech delay; motor delay NR; mild ID in 3/4; no ID in 1/4 (person w/affected child)
p.Glu237Lys [14]	18	No seizures	Present in all; hyperkinetic crises common	Moderate-to-severe global DD; normal IQ for 1/10; not stated for 9/10
p.Glu246Lys [15]	18	Seizures in 2/18 (not DEE)	Present in most or all; hyperkinetic crises common	Severe global DD; ID varies (severe to profound); two persons assessed w/eye-tracking system had "normal fluid intelligence & lexical comprehension" [16]

Table 2. continued from previous page.

Variant	# of Persons	Clinical Characteristics		
		Epilepsy	Movement disorder (predominantly dystonia & chorea) [1]	DD/ID [2]
c.724-8A>G [17]	21 (from 18 families)	No seizures [18]	Present in all; hyperkinetic crises uncommon (observed in 1 person)	DD in 1st yr of life; most (not all) had ID, often mild

DD = developmental delay; DEE = developmental and epileptic encephalopathy; ID = intellectual disability; NR = not reported
1. Movement disorders are typically not the presenting manifestation. More often, initial presenting manifestations are seizures and/or hypotonia and developmental delay.
2. Not all reports provide this information. Of those that do, many do not distinguish between DD and ID.
3. Law et al [2015], de Kovel et al [2016], Danti et al [2017], Bruun et al [2018], Kelly et al [2019], Turro et al [2020], Yang et al [2021], Domínguez-Carral et al [2023]
4. Rim et al [2018], Kelly et al [2019]
5. Kelly et al [2019]
6. Nakamura et al [2013], Saitsu et al [2016], Arya et al [2017], Schorling et al [2017], Xiong et al [2018], Schirinzi et al [2019], Graziola et al [2021], Lee et al [2021], Yang et al [2021], Krygier et al [2022], Liu et al [2022], Domínguez-Carral et al [2023], Gambardella et al [2023], Li et al [2023], Novelli et al [2023], Thiel et al [2023]
7. Wirth et al [2022a]
8. Saitsu et al [2016], Danti et al [2017], Koy et al [2018], Waak et al [2018], Kelly et al [2019], Schirinzi et al [2019], Turro et al [2020], Dzinovic et al [2021], Graziola et al [2021], Kwong et al [2021], Chopra et al [2022], Pérez-Dueñas et al [2022], Domínguez-Carral et al [2023], Novelli et al [2023], Thiel et al [2023]
9. Ananth et al [2016], Dhamija et al [2016], Kulkarni et al [2016], Menke et al [2016], Blumkin et al [2018], Kelly et al [2019], Kim et al [2020], Akasaka et al [2021], Garofalo et al [2023], Hu et al [2023], Novelli et al [2023], Thiel et al [2023]
10. Menke et al [2016], Honey et al [2018], Chaib et al [2022]
11. Ananth et al [2016]
12. Domínguez-Carral et al [2023]
13. Wirth et al [2020], Wirth et al [2022a]
14. Koy et al [2018], Okumura et al [2018], Waak et al [2018], Schirinzi et al [2019], Turro et al [2020], Graziola et al [2021], Fung et al [2022], Domínguez-Carral et al [2023], Li et al [2023]
15. Ananth et al [2016], Helbig et al [2016], Saitsu et al [2016], Schorling et al [2017], Takezawa et al [2018], Waak et al [2018], Benato et al [2019], Kim et al [2020], Graziola et al [2021], Yang et al [2021],Thiel et al [2023]
16. Graziola et al [2021]
17. Yang et al [2021], Al Masseri & AlSayed [2022], Liu et al [2022], Miyamoto et al [2022], Wirth et al [2022a], Koval et al [2023], Novelli et al [2023], Vasconcellos et al [2023]
18. One of three affected family members reported by Vasconcellos et al [2023] had epilepsy; however, there was a family history of epilepsy in a deceased grandfather, who had no other reported manifestations of *GNAO1*-related disorder.

Prevalence

Approximately 200 individuals have been reported with *GNAO1*-related disorder to date. However, this disorder may be underreported, particularly given the recent reports of individuals with milder phenotypes [Wirth et al 2022a].

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *GNAO1*.

Contiguous gene deletions. Interstitial 16q12.2-q21 multigene deletions encompassing *GNAO1* have been reported in four individuals with seizures and one individual with a movement disorder [Lasa-Aranzasti et al 2022].

Differential Diagnosis

The phenotypic features associated with *GNAO1*-related disorder are not sufficient to diagnose this condition clinically.

Developmental and epileptic encephalopathy. All disorders with infantile-onset severe seizures, central hypotonia, global developmental delay, and severe intellectual disability should be considered in the differential diagnosis. See OMIM Phenotypic Series: Developmental and epileptic encephalopathy.

Dystonia. See Hereditary Dystonia Overview for genes associated with dystonia.

Movement disorder with epilepsy. Examples of other genes associated with both seizures and paroxysmal hyperkinetic, dystonic, and/or choreiform movement disorder phenotypes include the following [Papandreou et al 2020, de Gusmão et al 2021]:

- *ATP1A2*-related disorders (OMIM 182340)
- *ATP1A3*-related neurologic disorders
- *SLC2A1*-related glucose transporter type 1 deficiency syndrome
- *KCNA1*-related episodic ataxia type 1
- *KCNMA1*-related disorders (OMIM 600150)
- *ECHS1*-related mitochondrial short-chain enoyl-CoA hydratase 1 deficiency
- *PRRT2*-associated paroxysmal movement disorders
- *SCN8A*-related epilepsy with encephalopathy
- *TBC1D24*-related disorders

Management

No clinical practice guidelines for *GNAO1*-related disorder have been published.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *GNAO1*-related disorder, the evaluations summarized in Table 3 (if not performed as part of the evaluation that led to diagnosis) are recommended.

Table 3. *GNAO1*-Related Disorder: Recommended Evaluations Following Initial Diagnosis

System/Concern	Evaluation	Comment
Neurologic	Eval by pediatric or adult neurologist	• For evidence of DD/ID, epilepsy, & movement disorder • For those w/abnormal movements, eval by movement specialist is recommended. • Perform EEG if seizures are a concern. Distinguishing between dystonia & seizure can be a challenge. • Consider brain MRI if not previously performed.
Dysarthria	Communication assessment / speech-language therapy assessment	• For all persons w/speech delay, ensure hearing is normal. • Evaluate need for communication aids.
Development	Developmental assessment & cognitive function eval	• To incl motor, adaptive, cognitive, & speech-language eval • Eval for early intervention / individual education program
Neurobehavioral/ Psychiatric	Neuropsychiatric eval	Screening for behavior concerns incl sleep disturbances, ADHD, anxiety, &/or findings suggestive of ASD

Table 3. continued from previous page.

System/Concern	Evaluation	Comment
Musculoskeletal/ADL	Orthopedics / physical medicine & rehab / PT & OT eval	To incl assessment of: • Gross motor & fine motor skills • Mobility, ADL, & need for adaptive devices • Need for PT (to improve gross motor skills) &/or OT (to improve fine motor skills) • Orthopedics eval for scoliosis &/or joint deformity
Gastrointestinal/Feeding	Gastroenterology / nutrition / feeding team eval	• To incl eval of aspiration risk & nutritional status • Consider eval for gastrostomy tube placement in persons w/ dysphagia &/or aspiration risk.
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of *GNAO1*-related disorder to facilitate medical & personal decision making
Family support & resources	By clinicians, wider care team, & family support organizations	Assessment of family & social structure to determine need for: • Community or online resources such as Parent to Parent • Social work involvement for parental support • Home nursing referral

ADHD = attention-deficit/hyperactivity disorder; ADL = activities of daily living; ASD = autism spectrum disorder; MOI = mode of inheritance; OT = occupational therapy; PT = physical therapy
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

There is no cure for *GNAO1*-related disorder. Supportive care to improve quality of life, maximize function, and reduce complications can include multidisciplinary care by specialists in child neurology, adult neurology, neurosurgery, physical medicine and rehabilitation, physical therapy, occupational therapy, orthopedic surgery, speech-language therapy, and psychology (see Table 4).

Table 4. *GNAO1*-Related Disorder: Treatment of Manifestations

Manifestation/Concern	Treatment	Considerations/Other
Developmental delay / Intellectual disability	See Developmental Delay / Intellectual Disability Management Issues.	
Epilepsy	• Standardized treatment w/ASM by experienced child neurologist. Seizures can be drug resistant, w/those w/ongoing seizures reporting a mean of 3.1 medications trialed. [1] Treatment should be targeted toward the person's particular electroclinical syndrome or seizure type(s) (e.g., when present, epileptic spasms should be treated w/hormonal therapies [such as ACTH or prednisolone] or vigabatrin). • Persons w/refractory seizures may benefit from referral to epileptologist.	• Many ASMs may be effective; none has been demonstrated effective specifically for this disorder. • Use of benzodiazepines is often limited by tolerance & side effects. • Education of parents/caregivers • Obtain home videos of concerning events for clinician review. • Consider video EEG to distinguish abnormal movements from seizures if there is a diagnostic concern.
Movement disorders	• Orthopedics / physical medicine & rehab / PT & OT incl stretching to help avoid contractures & falls • Consider orthopedic aids (e.g., ankle-foot orthoses, walkers) to support & maintain ambulation.	• Because dystonia can lead to irreversible joint contractures, scoliosis, &/or hip dislocation, early initiation of regular PT is essential to maintain function & mobility &

Table 4. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
		prevent secondary orthopedic complications. • Consider need for positioning & mobility devices, disability parking placard.
	Dystonia & chorea: • Combination therapy is often necessary. • Consider treatment w/tetrabenazine, gabapentin, clonidine, trihexyphenidyl, oral baclofen. [2] • Benzodiazepines are often necessary as additional first-line therapeutics. Levodopa & ASMs (such as topiramate, valproate, levetiracetam) may have some additional efficacy in controlling hyperkinetic movements in some persons. [3] • Botulinum toxin injections should be considered for focal dystonia. • When movement disorders are drug resistant, incl during hyperkinetic crises, consider DBS of globus pallidus internus (target of choice in most persons), or subthalamic nucleus as well as pallidotomy, which can lead to substantial reduction of hyperkinetic movements. [4]	• Persons may benefit from referral to movement disorder specialist. • Parents / other care providers might consider maintaining movement disorder logs (time w/movement disorder symptoms / waking time) to estimate severity & treatment response.
Exacerbation of hyperkinetic movement disorder / Hyperkinetic crises	• Add or intensify pharmacotherapy, e.g., high doses of benzodiazepines, clonidine, chloral hydrate (if available) to induce sleep. Escalate to intravenous infusions of sedatives if needed. • If pharmacotherapy fails, consider emergency placement of DBS. [5] A few reports confirm sustained benefits from long-term DBS treatment. [6]	• Educate parents re risk of hyperkinetic crises & communicate emergency plan. • Avoid or treat triggers & risk factors (infection, electrolyte imbalances, or lack of sleep). • Early intervention is essential.
Dysarthria or anarthria	Speech-language therapy to assist in feeding skills & communication	Some persons may need communication devices.
Poor weight gain / Failure to thrive	• Feeding therapy • Nutritionists are important to assess calorie needs & ↓ risk of malnutrition. • Gastrostomy tube placement may be required for persistent feeding issues. • ↑ calorie intake if movement disorder is present.	Low threshold for clinical feeding eval &/or radiographic swallowing study when clinical signs or symptoms of dysphagia are present
Constipation	• Monitor for constipation. • Stool softeners, prokinetics, osmotic agents, or laxatives as needed	• Caused by neurologic dysfunction & poor intestinal motility, often accentuated by medication • Can trigger movement disorder
Gastroesophageal reflux disease	Proton pump inhibitors	Should be considered in eval of pain
Sleep disturbance	• Behavioral regulation • Pharmacotherapy	

Table 4. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Family/Community	• Ensure appropriate social work involvement to connect families w/local resources, respite, & support. • Coordinate care to manage multiple subspecialty appointments, equipment, medications, & supplies.	• Ongoing assessment of need for palliative care involvement &/or home nursing • Consider involvement in adaptive sports or Special Olympics.

ACTH = adrenocorticotropic hormone; ASM = anti-seizure medication; DBS = deep brain stimulation; OT = occupational therapy; PT = physical therapy
1. Axeen et al [2021]
2. Ananth et al [2016], Danti et al [2017], Waak et al [2018], Schirinzi et al [2019]
3. Schirinzi et al [2019]
4. Benato et al [2019]
5. Ananth et al [2016], Kulkarni et al [2016], Honey et al [2018], Waak et al [2018]
6. Koy et al [2018], Benato et al [2019]
1. Education of parents/caregivers regarding common seizure presentations is appropriate. For information on non-medical interventions and coping strategies for children diagnosed with epilepsy, see Epilepsy Foundation Toolbox.

Prolonged exacerbation of the hyperkinetic movement disorder requires hospitalization and, when severe, intensive care management. Infections or catabolic states are often triggers, while in some individuals, potential causes are unknown. The often poor nutritional status due to feeding problems can prolong hospital stays.

Although sudden unexpected death in epilepsy (SUDEP) has not specifically been reported in *GNAO1*-related disorder, generally recommended practices to reduce the risk of SUDEP include reduction in the frequency of generalized tonic-clonic seizures when possible, adherence to anti-seizure medication, and nocturnal supervision [Trivisano et al 2022].

While immune dysfunction has not been described in *GNAO1*-related disorder, infections can lead to hyperkinetic crises and need for hospitalization. Dysphagia and seizures can increase the risk of aspiration-related events, which may result in hospitalization for respiratory support.

Developmental Delay / Intellectual Disability Management Issues

The following information represents typical management recommendations for individuals with developmental delay / intellectual disability in the United States; standard recommendations may vary from country to country.

Ages 0-3 years. Referral to an early intervention program is recommended for access to occupational, physical, speech, and feeding therapy as well as infant mental health services, special educators, and sensory impairment specialists. In the US, early intervention is a federally funded program available in all states that provides in-home services to target individual therapy needs.

Ages 3-5 years. In the US, developmental preschool through the local public school district is recommended. Before placement, an evaluation is made to determine needed services and therapies and an individualized education plan (IEP) is developed for those who qualify based on established motor, language, social, or cognitive delay. The early intervention program typically assists with this transition. Developmental preschool is center based; for children too medically unstable to attend, home-based services are provided.

All ages. Consultation with a developmental pediatrician is recommended to ensure the involvement of appropriate community, state, and educational agencies (US) and to support parents in maximizing quality of life. Some issues to consider:

- IEP services:
  - An IEP provides specially designed instruction and related services to children who qualify.

- IEP services will be reviewed annually to determine whether any changes are needed.
- Special education law requires that children participating in an IEP be in the least restrictive environment feasible at school and included in general education as much as possible, when and where appropriate.
- Hearing consultants should be a part of the child's IEP team to support access to academic material.
- PT, OT, and speech services will be provided in the IEP to the extent that the need affects the child's access to academic material. Beyond that, private supportive therapies based on the affected individual's needs may be considered. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.
- As a child enters the teen years, a transition plan should be discussed and incorporated in the IEP. For those receiving IEP services, the public school district is required to provide services until age 21.

- A 504 plan (Section 504: a US federal statute that prohibits discrimination based on disability) can be considered for those who require accommodations or modifications such as front-of-class seating, assistive technology devices, classroom scribes, extra time between classes, modified assignments, and enlarged text.
- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a US public agency that provides services and support to qualified individuals. Eligibility differs by state but is typically determined by diagnosis and/or associated cognitive/adaptive disabilities.
- Families with limited income and resources may also qualify for supplemental security income (SSI) for their child with a disability.

Motor Dysfunction

Gross motor dysfunction

- Physical therapy is recommended to maximize mobility and to reduce the risk for later-onset orthopedic complications (e.g., contractures, scoliosis, hip dislocation).
- Consider use of durable medical equipment and positioning devices as needed (e.g., wheelchairs, walkers, bath chairs, orthotics, adaptive strollers).
- For increased muscle tone like in dystonia, consider involving appropriate specialists to aid in management of tone reduction by pharmacotherapy, or orthopedic procedures.

Fine motor dysfunction. Occupational therapy is recommended for difficulty with fine motor skills that affect adaptive function such as feeding, grooming, dressing, and writing.

Oral motor dysfunction should be assessed at each visit and clinical feeding evaluations and/or radiographic swallowing studies should be obtained for choking/gagging during feeds, poor weight gain, frequent respiratory illnesses, or feeding refusal that is not otherwise explained. Assuming that the child is safe to eat by mouth, feeding therapy (typically from an occupational or speech therapist) is recommended to help improve coordination or sensory-related feeding issues. Feeds can be thickened or chilled for safety. When feeding dysfunction is severe, an NG-tube or G-tube may be necessary.

Communication issues. Consider evaluation for alternative means of communication (e.g., augmentative and alternative communication [AAC]) for individuals who have expressive language difficulties. An AAC evaluation can be completed by a speech-language pathologist who has expertise in the area. The evaluation will consider cognitive abilities and sensory impairments to determine the most appropriate form of communication. AAC devices can range from low-tech, such as picture exchange communication, to high-tech, such as voice-generating devices. Contrary to popular belief, AAC devices do not hinder verbal development of speech, but rather support optimal speech and language development.

Surveillance

To monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations, the evaluations summarized in Table 5 are recommended.

Table 5. *GNAO1*-Related Disorder: Surveillance

System/Concern	Evaluation	Frequency
Feeding	• Measurement of growth parameters • Eval of nutritional status & safety of oral intake	At each visit
Gastrointestinal	Monitor for constipation.	
Respiratory	Monitor for evidence of aspiration, respiratory insufficiency.	
Neurologic	• Monitor those w/seizures as clinically indicated. • Assess for new manifestations such as seizures, changes in tone, & movement disorders.	
Development	Monitor developmental progress & educational needs.	
Neurobehavioral/ Psychiatric	Behavioral assessment for anxiety, attention, & aggressive or self-injurious behavior	
Musculoskeletal	Physical medicine, OT/PT assessment of mobility, self-help skills; clinical eval of hip & spine for those who are non-ambulatory &/or severely hypotonic	
Family/Community	Assess family need for social work support (e.g., palliative/respite care, home nursing, other local resources), care coordination, or follow-up genetic counseling if new questions arise (e.g., family planning).	

OT = occupational therapy; PT = physical therapy

Evaluation of Relatives at Risk

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Using *Caenorhabditis elegans* models of two specific *GNAO1* variants, researchers found that caffeine reduced abnormal movements [Di Rocco et al 2023]. This finding has not yet been explored with other variants, in other model systems, or in humans with *GNAO1*-related disorder.

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

GNAO1-related disorder is an autosomal dominant disorder most often caused by a *de novo* pathogenic variant. Individuals with a severe phenotype (i.e., developmental and epileptic encephalopathy, severe developmental

delay and/or intellectual disability, and/or early-onset movement disorder) typically represent simplex cases (i.e., the only family member known to be affected) and have the disorder as the result of a *de novo* pathogenic variant. However, recurrence of severe phenotypes in affected sibs due to presumed parental germline mosaicism has been reported [Kulkarni et al 2016, Schorling et al 2017].

Vertical transmission from an affected parent to an affected child has been reported in several families with milder phenotypes [Wirth et al 2022a].

Risk to Family Members

Parents of a proband

- Almost all probands reported to date with severe *GNAO1*-related disorder phenotypes whose parents have undergone molecular genetic testing have the disorder as the result of a *de novo* pathogenic variant or a pathogenic variant inherited from an unaffected, mosaic parent.
- Some probands with milder *GNAO1*-related disorder phenotypes have the disorder as the result of a pathogenic variant inherited from an affected parent.
- Molecular genetic testing is recommended for the parents of the proband to evaluate their genetic status and inform recurrence risk assessment.
- If the pathogenic variant identified in the proband is not identified in either parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
    - The proband has a *de novo* pathogenic variant.
    - The proband inherited a pathogenic variant from a parent with apparent germline (or somatic and germline) mosaicism * [Ananth et al 2016, Kulkarni et al 2016, Schorling et al 2017, Kelly et al 2019, Kim et al 2020, Yang et al 2021, Al Masseri & AlSayed 2022, Miyamoto et al 2022]. Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ cells only.

      * A parent with somatic and germline mosaicism for a *GNAO1* pathogenic variant may be mildly/minimally affected, although this has not been reported to date.

Sibs of a proband. The risk to the sibs of the proband depends on the genetic status of the proband's parents:

- If the *GNAO1* pathogenic variant present in the proband cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is slightly greater than that of the general population because of the possibility of parental germline mosaicism [Ananth et al 2016, Kulkarni et al 2016, Schorling et al 2017, Kelly et al 2019, Kim et al 2020, Yang et al 2021, Al Masseri & AlSayed 2022, Miyamoto et al 2022].
- If a parent of the proband is known to have the *GNAO1* pathogenic variant identified in the proband, the risk to the sibs of inheriting the variant is 50%.

Offspring of a proband

- Each child of an individual with *GNAO1*-related disorder has a 50% chance of inheriting the *GNAO1* pathogenic variant. Three individuals with milder phenotypes, including normal intellect and no seizures, have been documented to have had affected children [Wirth et al 2020, Wirth et al 2022a].
- Individuals with severe *GNAO1*-related disorder phenotypes are not known to reproduce.

Other family members. The risk to other family members depends on the genetic status of the proband's parents: if a parent has the *GNAO1* pathogenic variant, the parent's family members may be at risk.

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to parents of affected individuals.

Prenatal Testing and Preimplantation Genetic Testing

Once the *GNAO1* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **Asociación GNAO1 España**
  Spain
  Email: asociaciongnao1@gmail.com
  www.gnao1.es
- **Famiglie GNAO1**
  Italy
  www.gnao1.it
- **GNAO1 Tuki ry**
  Finland
  www.gnao1.fi
- **Mondo GNAO1 UK**
  www.mondo-uk.co.uk
- **Stitching GNAO1 NL**
  Netherlands
  Email: info@gnao1.nl
  www.gnao1.nl
- **The Bow Foundation**
  www.gnao1.org
- **American Epilepsy Society**
  aesnet.org
- **Canadian Epilepsy Alliance**
  Canada
  Phone: 1-866-EPILEPSY (1-866-374-5377)

canadianepilepsyalliance.org

- **Epilepsy Foundation**
  Phone: 800-332-1000; 866-748-8008
  epilepsy.com
- **National Institute of Neurological Disorders and Stroke (NINDS)**
  Phone: 800-352-9424
  Epilepsy and Seizures
- **GNAO1 International Registry**
  www.gnao1.org/gnao1-international-patient-registry

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. GNAO1-Related Disorder: Genes and Databases

Gene	Chromosome Locus	Protein	HGMD	ClinVar
GNAO1	16q13	Guanine nucleotide-binding protein G(o) subunit alpha	GNAO1	GNAO1

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for GNAO1-Related Disorder (View All in OMIM)

139311	GUANINE NUCLEOTIDE-BINDING PROTEIN, ALPHA-ACTIVATING ACTIVITY POLYPEPTIDE O; GNAO1
615473	DEVELOPMENTAL AND EPILEPTIC ENCEPHALOPATHY 17; DEE17
617493	NEURODEVELOPMENTAL DISORDER WITH INVOLUNTARY MOVEMENTS; NEDIM

Molecular Pathogenesis

GNAO1 encodes guanine nucleotide-binding protein G(o) subunit alpha, the alpha subunit of heterotrimeric guanine nucleotide-binding proteins o (Gαo). Heterotrimeric G proteins are a large family of signal-transducing proteins, essential for the function of G protein-coupled receptors (GPCRs). Together, the subunits α, β, and γ form the heterotrimeric G protein complex. Gα is responsible for binding to guanine nucleotides (GDP and GTP) and to cognate GPCRs [Savitsky et al 2020].

Gαo, the major G protein α subunit in the nervous system, is essential for nervous system development and functionality [Bromberg et al 2008, Solis & Katanaev 2017]. Gαo couples to inhibitory GPCRs such as α2-adrenergic, D2 dopamine, μ-opioid, somatostatin, and M2-muscarinic. The activation of GPCRs through GDP results in a release of Gßγ and Gα-GTP [Pierce et al 2002]. Gαo modulates the responsiveness of adenyl cyclase type 5 (AC5) to stimulatory Gαs/olf inputs by controlling the release of Gßγ [Muntean et al 2021], and therefore regulates the production of cyclic adenosine monophosphate (cAMP). The manifestations of movement disorders are caused by a reduced level of cAMP, as previously proven with *ADCY5* variants (see *ADCY5* Dyskinesia) that reduce the activity of AC5 [Carapito et al 2015, Chang et al 2016].

Mechanism of disease causation. Different molecular mechanisms explain the disease-causing mechanisms of different *GNAO1* variants.

Muntean et al [2021] proposed a model in which the majority of variants show loss-of-function behavior in transmission of GPCR signals from distinct mechanisms that affect the G protein cycle, including impairment in

binding to Gβγ and inability to promote downstream signaling. Furthermore, Muntean et al [2021] demonstrated that some variants also showed dominant-negative effects that interfered with the function of normal Gαo. They concluded that the combination of these two mechanisms disrupt the GPCR signaling.

Larasati et al [2022] showed that displacement of Gln205, which is critical for GTP hydrolysis, in *GNAO1* variants that affect codons Gly203, Arg209, or Glu246 accelerates GTP uptake and inactivates GTP hydrolysis. Although this leads to constitutive GTP binding by Gαo, the variants fail to adopt the activated conformation and display aberrant interactions with signaling partners. The deficit in binding and hydrolyzing GTP was also found in variants affecting the Gln52 codon [Solis et al 2021].

Table 6. *GNAO1* Pathogenic Variants Referenced in This *GeneReview*

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_029988.3 NP_066268.1	c.118G>C	p.Gly40Arg	See Genotype-Phenotype Correlations.
	c.118G>A	p.Gly40Arg	
	c.118G>T	p.Gly40Trp	
	c.119G>A	p.Gly40Glu	
	c.607G>A	p.Gly203Arg	
	c.617G>A	p.Arg206Gln	
	c.625C>T	p.Arg209Cys	
	c.625C>G	p.Arg209Gly	
	c.626G>A	p.Arg209His	
	c.626G>T	p.Arg209Leu	
	c.626G>C	p.Arg209Pro	
	c.644G>A	p.Cys215Tyr	
	c.709G>A	p.Glu237Lys	
NM_029988.3	c.724-8G>A	--	
NM_029988.3 NP_066268.1	c.736G>A	p.Glu246Lys	

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants. *GeneReviews* follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Chapter Notes

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Associated Neurologic Disease study (PI: Amy Viehoever) and is working to further describe *GNAO1*-related epilepsy.

Web pages:

- uvahealth.com/findadoctor/profile/erika-j-axeen
- braininstitute.virginia.edu/erika-axeen

Drs Thiel, Koy, and Axeen are actively involved in clinical research regarding individuals with *GNAO1*-related disorder. They would be happy to communicate with persons who have any questions regarding diagnosis of *GNAO1*-related disorder or other considerations. They may be contacted to inquire about review of *GNAO1* variants of uncertain significance.

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References

Literature Cited

Akasaka M, Kamei A, Tanifuji S, Asami M, Ito J, Mizuma K, Oyama K, Tokutomi T, Yamamoto K, Fukushima A, Takenouchi T, Uehara T, Suzuki H, Kosaki K. GNAO1 mutation-related severe involuntary movements treated with gabapentin. Brain Dev. 2021;43:576-9. PubMed PMID: 33358199.

Al Masseri Z, AlSayed M. Gonadal mosaicism in GNAO1 causing neurodevelopmental disorder with involuntary movements; two additional variants. Mol Genet Metab Rep. 2022;31:100864. PubMed PMID: 35782616.

Ananth AL, Robichaux-Viehoever A, Kim Y-M, Hanson-Kahn A, Cox R, Enns GM, Strober J, Willing M, Schlaggar BL, Wu YW, Bernstein JA. Clinical course of six children with GNAO1 mutations causing a severe and distinctive movement disorder. Pediatr Neurol. 2016;59:81-4. PubMed PMID: 27068059.

Apuzzo D, Cappuccio G, Vaisanen T, Alagia M, Pignataro P, Genesio R, Brunetti-Pierri N. Two cases of 16q12.1q21 deletions and refinement of the critical region. Eur J Med Genet. 2020;63:103878. PubMed PMID: 32045705.

Arisaka A, Nakashima M, Kumada S, Inoue K, Nishida H, Mashimo H, Kashii H, Kato M, Maruyama K, Okumura A, Saitsu H, Matsumoto N, Fukuda M. Association of early-onset epileptic encephalopathy with involuntary movements - case series and literature review. Epilepsy Behav Rep. 2020;15:100417. PubMed PMID: 33490948.

Arya R, Spaeth C, Gilbert DL, Leach JL, Holland KD. GNAO1-associated epileptic encephalopathy and movement disorders: c.607G>A variant represents a probable mutation hotspot with a distinct phenotype. Epileptic Disord. 2017;19:67-75. PubMed PMID: 28202424.

Axeen E, Bell E, Robichaux Viehoever A, Schreiber JM, Sidiropoulos C, Goodkin HP. Results of the first GNAO1-related neurodevelopmental disorders caregiver survey. Pediatr Neurol. 2021;121:28-32. PubMed PMID: 34139551.

Benato A, Carecchio M, Burlina A, Paoloni F, Sartori S, Nosadini M, d'Avella D, Landi A, Antonini A. Long-term effect of subthalamic and pallidal deep brain stimulation for status dystonicus in children with methylmalonic acidemia and GNAO1 mutation. J Neural Transm (Vienna). 2019;126:739-57. PubMed PMID: 31076915.

Blumkin L, Lerman-Sagie T, Westenberger A, Ben-Pazi H, Zerem A, Yosovich K, Lev D. Multiple causes of pediatric early onset chorea--clinical and genetic approach. Neuropediatrics. 2018;49:246-55. PubMed PMID: 29801190.

Bromberg KD, Iyengar R, He JC. Regulation of neurite outgrowth by G(i/o) signaling pathways. Front Biosci. 2008;13:4544-57. PubMed PMID: 18508528.

Bruun TUJ, DesRoches CL, Wilson D, Chau V, Nakagawa T, Yamasaki M, Hasegawa S, Fukao T, Marshall C, Mercimek-Andrews S. Prospective cohort study for identification of underlying genetic causes in neonatal encephalopathy using whole-exome sequencing. Genet Med. 2018;20:486-94. PubMed PMID: 28817111.

Carapito R, Paul N, Untrau M, Le Gentil M, Ott L, Alsaleh G, Jochem P, Radosavljevic M, Le Caignec C, David A, Damier P, Isidor B, Bahram S. A de novo ADCY5 mutation causes early-onset autosomal dominant chorea and dystonia. Mov Disord. 2015;30:423-7. PubMed PMID: 25545163.

Carecchio M, Mencacci NE. Emerging monogenic complex hyperkinetic disorders. Curr Neurol Neurosci Rep. 2017;17:97. PubMed PMID: 29086067.

Chaib H, Schoene-Bake JC, Saryyeva A, Jack T, Hartmann H, Krauss JK. DBS emergency surgery for treatment of dystonic storm associated with rhabdomyolysis and acute colitis in DYT-GNAO1. Childs Nerv Syst. 2022;38:1821-24. PubMed PMID: 35725943.

Chang CF, Li LH, Wang CH, Tsai FJ, Chen TC, Wu JY, Chen YT, Tsai AC. Identification of a submicroscopic 3.2 Mb chromosomal 16q12.2-13 deletion in a child with short stature, mild developmental delay, and craniofacial anomalies, by high-density oligonucleotide array-a recognizable syndrome. Am J Med Genet A. 2010;152A:2365-71. PubMed PMID: 20803649.

Chang FCF, Westenberger A, Dale RC, Smith M, Pall HS, Perez-Dueñas B, Grattan-Smith P, Ouvrier RA, Mahant N, Hanna BC, Hunter M, Lawson JA, Max C, Sachdev R, Meyer E, Crimmins D, Pryor D, Morris JGL, Münchau A, Grozeva D, Carss KJ, Raymond L, Kurian MA, Klein C, Fung VSC. Phenotypic insights into ADCY5-associated disease. Mov Disord. 2016;31:1033-40. PubMed PMID: 27061943.

Chopra M, Gable DL, Love-Nichols J, Tsao A, Rockowitz S, Sliz P, Barkoudah E, Bastianelli L, Coulter D, Davidson E, DeGusmao C, Fogelman D, Huth K, Marshall P, Nimec D, Sanders JS, Shore BJ, Snyder B, Stone SSD, Ubeda A, Watkins C, Berde C, Bolton J, Brownstein C, Costigan M, Ebrahimi-Fakhari D, Lai A, O'Donnell-Luria A, Paciorkowski AR, Pinto A, Pugh J, Rodan L, Roe E, Swanson L, Zhang B, Kruer MC, Sahin M, Poduri A, Srivastava S. Mendelian etiologies identified with whole exome sequencing in cerebral palsy. Ann Clin Transl Neurol. 2022;9:193-205. PubMed PMID: 35076175.

Danti FR, Galosi S, Romani M, Montomoli M, Carss KJ, Lucy Raymond F, Parrini E, Bianchini C, McShane T, Dale RC, Mohammad SS, Shah U, Mahant N, Ng J, McTague A, Samanta R, Vadlamani G, Valente EM, Leuzzi V, Kurian MA, Guerrini R. GNAO1 encephalopathy: broadening the phenotype and evaluating treatment and outcome. Neurol Genet. 2017;3:e143. PubMed PMID: 28357411.

de Gusmão CM, Garcia L, Mikati MA, Su S, Silveira-Moriyama L. Paroxysmal genetic movement disorders and epilepsy. Front Neurol. 2021;12:648031. PubMed PMID: 33833732.

de Kovel CGF, Brilstra EH, Van Kempen MJA, Van't Slot R, Nijman IJ, Afawi Z, De Jonghe P, Djémié T, Guerrini R, Hardies K, Helbig I, Hendrickx R, Kanaan M, Kramer U, Lehesjoki AEE, Lemke JR, Marini C, Mei D, Møller RS, Pendziwiat M, Stamberger H, Suls A, Weckhuysen S, Balling R, Barisic N, Baulac S, Caglayan HS, Craiu DC, Depienne C, Gormley P, Hjalgrim H, Hoffman-Zacharska D, Jähn J, Klein KM, Komarek V, LeGuern E, Lerche H, May P, Muhle H, Pal D, Palotie A, Rosenow F, Selmer K, Serratosa JM, Sisodiya SM, Stephani U, Sterbova K, Striano P, Talvik T, van Haelst M, Verbeek N, von Spiczak S, Weber YG, Koeleman BPC. Targeted sequencing of 351 candidate genes for epileptic encephalopathy in a large cohort of patients. Mol Genet Genomic Med. 2016;4:568-80. PubMed PMID: 27652284.

Dhamija R, Mink JW, Shah BB, Goodkin HP. GNAO1-Associated Movement Disorder. Mov Disord Clin Pract. 2016;3:615-7. PubMed PMID: 30838255.

Di Rocco M, Galosi S, Follo FC, Lanza E, Folli V, Martire A, Leuzzi V, Martinelli S. Phenotypic assessment of pathogenic variants in GNAO1 and response to caffeine in C. elegans models of the disease. Genes (Basel). 2023;14:319. PubMed PMID: 36833246.

Domínguez-Carral J, Ludlam WG, Junyent Segarra M, Fornaguera Marti M, Balsells S, Muchart J, Čokolić Petrović D, Espinoza I, Ortigoza-Escobar JD, Martemyanov KA, et al. Severity of GNAO1-related disorder correlates with changes in G-protein function. Ann Neurol. 2023;94:987-1004. PubMed PMID: 37548038.

Dzinovic I, Škorvánek M, Necpál J, Boesch S, Švantnerová J, Wagner M, Havránková P, Pavelekova P, Haň V, Janzarik WG, Berweck S, Diebold I, Kuster A, Jech R, Winkelmann J, Zech M. Dystonia as a prominent presenting feature in developmental and epileptic encephalopathies: a case series. Parkinsonism Relat Disord. 2021;90:73-8. PubMed PMID: 34399161.

EuroEPINOMICS-RES Consortium, et al. De novo mutations in synaptic transmission genes including DNM1 cause epileptic encephalopathies. Am J Hum Genet. 2014;95:360-70. PubMed PMID: 25262651.

Feng H, Khalil S, Neubig RR, Sidiropoulos C. A mechanistic review on GNAO1-associated movement disorder. Neurobiol Dis. 2018;116:131-41. PubMed PMID: 29758257.

Feng H, Sjögren B, Karaj B, Shaw V, Gezer A, Neubig RR. Movement disorder in GNAO1 encephalopathy associated with gain-of-function mutations. Neurology. 2017;89:762-70. PubMed PMID: 28747448.

Fung EL, Mo CY, Fung ST, Chan AY, Lau KY, Chan EK, Chan DY, Zhu XL, Chan DT, Poon WS. Deep brain stimulation in a young child with GNAO1 mutation - feasible and helpful. Surg Neurol Int. 2022;13:285. PubMed PMID: 35855141.

Galosi S, Novelli M, Di Rocco M, Flex E, Messina E, Pollini L, Parrini E, Pisani F, Guerrini R, Leuzzi V, Martinelli S. GNAO1 haploinsufficiency: the milder end of the GNAO1 phenotypic spectrum. Mov Disord. 2023. Epub ahead of print.

Gambardella ML, Pede E, Orazi L, Leone S, Quintiliani M, Amorelli GM, Petrianni M, Galanti M, Amore F, Musto E, Perulli M, Contaldo I, Veredice C, Mercuri EM, Battaglia DI, Ricci D. Visual function in children with GNAO1-related encephalopathy. Genes (Basel). 2023;14:544. PubMed PMID: 36980817.

Garofalo M, Beudel M, Dijk JM, Bonouvrié LA, Buizer AI, Geytenbeek J, Prins RHN, Schuurman PR, van de Pol LA. Elective and emergency deep brain stimulation in refractory pediatric monogenetic movement disorders presenting with dystonia: current practice illustrated by two cases. Neuropediatrics. 2023;54:44-52. PubMed PMID: 36223877.

Gawlinski P, Posmyk R, Gambin T, Sielicka D, Chorazy M, Nowakowska B, Jhangiani SN, Muzny DM, Bekiesinska-Figatowska M, Bal J, Boerwinkle E, Gibbs RA, Lupski JR, Wiszniewski W. PEHO syndrome may represent phenotypic expansion at the severe end of the early-onset encephalopathies. Pediatr Neurol. 2016;60:83-7. PubMed PMID: 27343026.

Graziola F, Garone G, Grasso M, Capuano A. Cognitive assessment in GNAO1 neurodevelopmental disorder using an eye tracking system. J Clin Med. 2021;10:3541. PubMed PMID: 34441836.

Helbig KL, Farwell Hagman KD, Shinde DN, Mroske C, Powis Z, Li S, Tang S, Helbig I. Diagnostic exome sequencing provides a molecular diagnosis for a significant proportion of patients with epilepsy. Genet Med. 2016;18:898-905. PubMed PMID: 26795593.

Honey CM, Malhotra AK, Tarailo-Graovac M, van Karnebeek CDM, Horvath G, Sulistyanto A. GNAO1 mutation–induced pediatric dystonic storm rescue with pallidal deep brain stimulation. J Child Neurol. 2018;33:413-6. PubMed PMID: 29661126.

Hu W, Fang H, Tang J, Zhou Z, Wu L. [Genetic analysis of a child with early onset neurodevelopmental disorder with involuntary movement and a literature review]. Zhonghua Yi Xue Yi Chuan Xue Za Zhi. 2023;40:385-9. PubMed PMID: 36972929.

Kelly M, Park M, Mihalek I, Rochtus A, Gramm M, Pérez-Palma E, Axeen ET, Hung CY, Olson H, Swanson L, Anselm I, Briere LC, High FA, Sweetser DA, Kayani S, Snyder M, Calvert S, Scheffer IE, Yang E, Waugh JL, Lal D, Bodamer O, Poduri A. Spectrum of neurodevelopmental disease associated with the GNAO1 guanosine triphosphate–binding region. Epilepsia. 2019;60:406-18. PubMed PMID: 30682224.

Kim SY, Shim YK, Ko YJ, Park S, Jang SS, Lim BC, Kim KJ, Chae JH. Spectrum of movement disorders in GNAO1 encephalopathy: in-depth phenotyping and case-by-case analysis. Orphanet J Rare Dis. 2020;15:343. PubMed PMID: 33298085.

Koval A, Larasati YA, Savitsky M, Solis GP, Good JM, Quinodoz M, Rivolta C, Superti-Furga A, Katanaev VL. In-depth molecular profiling of an intronic GNAO1 mutant as the basis for personalized high-throughput drug screening. Med. 2023;4:311-325.e7. PubMed PMID: 37001522.

Koy A, Cirak S, Gonzalez V, Becker K, Roujeau T, Milesi C, Baleine J, Cambonie G, Boularan A, Greco F, Perrigault PF, Cances C, Dorison N, Doummar D, Roubertie A, Beroud C, Körber F, Stüve B, Waltz S, Mignot C, Nava C, Maarouf M, Coubes P, Cif L. Deep brain stimulation is effective in pediatric patients with GNAO1 associated severe hyperkinesia. J Neurol Sci. 2018;391:31-9. PubMed PMID: 30103967.

Krenn M, Sommer R, Sycha T, Zech M. GNAO1 haploinsufficiency associated with a mild delayed-onset dystonia phenotype. Mov Disord. 2022;37:2464-6. PubMed PMID: 36273395.

Krygier M, Zawadzka M, Sawicka A, Mazurkiewicz-Bełdzińska M. Reflex seizures in rare monogenic epilepsies. Seizure. 2022;97:32-4. PubMed PMID: 35305402.

Kulkarni N, Tang S, Bhardwaj R, Bernes S, Grebe TA. Progressive movement disorder in brothers carrying a GNAO1 mutation responsive to deep brain stimulation. J Child Neurol. 2016;31:211-4. PubMed PMID: 26060304.

Kwong AK, Tsang MH, Fung JL, Mak CC, Chan KL, Rodenburg RJT, Lek M, Huang S, Pajusalu S, Yau MM, Tsoi C, Fung S, Liu KT, Ma CK, Wong S, Yau EK, Tai SM, Fung EL, Wu NS, Tsung LY, Smeitink J, Chung BH, Fung CW. Exome sequencing in paediatric patients with movement disorders. Orphanet J Rare Dis. 2021;16:32. PubMed PMID: 33446253.

Larasati YA, Savitsky M, Koval A, Solis GP, Valnohova J, Katanaev VL. Restoration of the GTPase activity and cellular interactions of Gαo mutants by Zn2+ in GNAO1 encephalopathy models. Sci Adv. 2022;8:eabn9350. PubMed PMID: 36206333.

Lasa-Aranzasti A, Cazurro-Gutiérrez A, Bescós A, González V, Ispierto L, Tardáguila M, Valenzuela I, Plaja A, Moreno-Galdó A, Macaya-Ruiz A, Pérez-Dueñas B. 16q12.2q21 deletion: a newly recognized cause of dystonia related to GNAO1 haploinsufficiency. Parkinsonism Relat Disord. 2022;103:112-4. PubMed PMID: 36096018.

Law CY, Chang ST, Cho SY, Yau EK, Ng GS, Fong NC, Lam CW. Clinical whole-exome sequencing reveals a novel missense pathogenic variant of GNAO1 in a patient with infantile-onset epilepsy. Clin Chim Acta. 2015;451:292-6. PubMed PMID: 26485252.

Lee J, Park JE, Lee C, Kim AR, Kim BJ, Park WY, Ki CS, Lee J. Genomic analysis of Korean patient with microcephaly. Front Genet. 2021;11:543528. PubMed PMID: 33584783.

Li Y, Chen H, Li L, Cao X, Ding X, Chen L, Cao D. Phenotypes in children with GNAO1 encephalopathy in China. Front Pediatr. 2023;11:1086970. PubMed PMID: 37705601.

Liu Y, Zhang Q, Wang J, Liu J, Yang W, Yan X, Ouyang Y, Yang H. Both subthalamic and pallidal deep brain stimulation are effective for GNAO1-associated dystonia: three case reports and a literature review. Ther Adv Neurol Disord. 2022;15:17562864221093507. PubMed PMID: 35509770.

Malaquias MJ, Fineza I, Loureiro L, Cardoso L, Alonso I, Magalhães M. GNAO1 mutation presenting as dyskinetic cerebral palsy. Neurol Sci. 2019;40:2213-6. PubMed PMID: 31190250.

Marcé-Grau A, Dalton J, López-Pisón J, García-Jiménez MC, Monge-Galindo L, Cuenca-León E, Giraldo J, Macaya A. GNAO1 encephalopathy: further delineation of a severe neurodevelopmental syndrome affecting females. Orphanet J Rare Dis. 2016;11:38. PubMed PMID: 27072799.

Menke LA, Engelen M, Alders M, Odekerken VJ, Baas F, Cobben JM. Recurrent GNAO1 mutations associated with developmental delay and a movement disorder. J Child Neurol. 2016;31:1598-601. PubMed PMID: 27625011.

Miyamoto S, Nakashima M, Fukumura S, Kumada S, Saitsu H. An intronic GNAO1 variant leading to in-frame insertion cause movement disorder controlled by deep brain stimulation. Neurogenetics. 2022;23:129-35. PubMed PMID: 35147852.

Muir AM, Myers CT, Nguyen NT, Saykally J, Craiu D, De Jonghe P, Helbig I, Hoffman-Zacharska D, Guerrini R, Lehesjoki AE, Marini C, Møller RS, Serratosa J, Štěrbová K, Striano P, von Spiczak S, Weckhuysen S, Mefford HC. Genetic heterogeneity in infantile spasms. Epilepsy Res. 2019;156:106181. PubMed PMID: 31394400.

Muntean BS, Masuho I, Dao M, Sutton LP, Zucca S, Iwamoto H, Patil DN, Wang D, Birnbaumer L, Blakely RD, Grill B, Martemyanov KA. Gαo is a major determinant of cAMP signaling in the pathophysiology of movement disorders. Cell Rep. 2021;34:108718. PubMed PMID: 33535037.

Nakamura K, Kodera H, Akita T, Shiina M, Kato M, Hoshino H, Terashima H, Osaka H, Nakamura S, Tohyama J, Kumada T, Furukawa T, Iwata S, Shiihara T, Kubota M, Miyatake S, Koshimizu E, Nishiyama K, Nakashima M, Tsurusaki Y, Miyake N, Hayasaka K, Ogata K, Fukuda A, Matsumoto N, Saitsu H. De Novo mutations in GNAO1, encoding a Gαo subunit of heterotrimeric G proteins, cause epileptic encephalopathy. Am J Hum Genet. 2013;93:496-505. PubMed PMID: 23993195.

Novelli M, Galosi S, Zorzi G, Martinelli S, Capuano A, Nardecchia F, Granata T, Pollini L, Di Rocco M, Marras CE, Nardocci N, Leuzzi V. GNAO1-related movement disorder: an update on phenomenology, clinical course, and response to treatments. Parkinsonism Relat Disord. 2023;111:105405. PubMed PMID: 37142469.

Okumura A, Maruyama K, Shibata M, Kurahashi H, Ishii A, Numoto S, Hirose S, Kawai T, Iso M, Kataoka S, Okuno Y, Muramatsu H, Kojima S. A patient with a GNAO1 mutation with decreased spontaneous movements, hypotonia, and dystonic features. Brain Dev. 2018;40:926-30. PubMed PMID: 29935962.

Papandreou A, Danti FR, Spaull R, Leuzzi V, Mctague A, Kurian MA. The expanding spectrum of movement disorders in genetic epilepsies. Dev Med Child Neurol. 2020;62:178-91. PubMed PMID: 31784983.

Pérez-Dueñas B, Gorman K, Marcé-Grau A, Ortigoza-Escobar JD, Macaya A, Danti FR, Barwick K, Papandreou A, Ng J, Meyer E, Mohammad SS, Smith M, Muntoni F, Munot P, Uusimaa J, Vieira P, Sheridan E, Guerrini R, Cobben J, Yilmaz S, De Grandis E, Dale RC, Pons R, Peall KJ, Leuzzi V, Kurian MA. The genetic landscape of complex childhood-onset hyperkinetic movement disorders. Mov Disord. 2022;37:2197-209. PubMed PMID: 36054588.

Pierce KL, Premont RT, Lefkowitz RJ. Seven-transmembrane receptors. Nat Rev Mol Cell Biol. 2002;3:639-50. PubMed PMID: 12209124.

Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17:405-24. PubMed PMID: 25741868.

Rim JH, Kim SH, Hwang IS, Kwon SS, Kim J, Kim HW, Cho MJ, Ko A, Youn SE, Kim J, Lee YM, Chung HJ, Lee JS, Kim HD, Choi JR, Lee ST, Kang HC. Efficient strategy for the molecular diagnosis of intractable early-onset epilepsy using targeted gene sequencing. BMC Med genomics. 2018;11:6. PubMed PMID: 29390993.

Saini AG, Hassan I, Sharma K, Muralidharan J, Dhawan S, Saini L, Suthar R, Sahu J, Sankhyan N, Singhi P. Status dystonicus in children: a cross-sectional study and review of literature. J Child Neurol. 2022;37:441-50. PubMed PMID: 35253510.

Saitsu H, Fukai R, Ben-Zeev B, Sakai Y, Mimaki M, Okamoto N, Suzuki Y, Monden Y, Saito H, Tziperman B, Torio M, Akamine S, Takahashi N, Osaka H, Yamagata T, Nakamura K, Tsurusaki Y, Nakashima M, Miyake N, Shiina M, Ogata K, Matsumoto N. Phenotypic spectrum of GNAO1 variants: epileptic encephalopathy to involuntary movements with severe developmental delay. Eur J Hum Genet. 2016;24:129-34. PubMed PMID: 25966631.

Savitsky M, Solis GP, Kryuchkov M, Katanaev VL. Humanization of drosophila Gαo to model GNAO1 paediatric encephalopathies. Biomedicines. 2020;8:1-16.

Schirinzi T, Garone G, Travaglini L, Vasco G, Galosi S, Rios L, Castiglioni C, Barassi C, Battaglia D, Gambardella ML, Cantonetti L, Graziola F, Marras CE, Castelli E, Bertini E, Capuano A, Leuzzi V. Phenomenology and clinical course of movement disorder in GNAO1 variants: results from an analytical review. Parkinsonism Relat Disord. 2019;61:19-25. PubMed PMID: 30642806.

Schorling DC, Dietel T, Evers C, Hinderhofer K, Korinthenberg R, Ezzo D, Bönnemann CG, Kirschner J. Expanding phenotype of de novo mutations in GNAO1: four new cases and review of literature. Neuropediatrics. 2017;48:371-7. PubMed PMID: 28628939.

Solis GP, Katanaev VL. Gαo (GNAO1) encephalopathies: plasma membrane vs. Golgi functions. Oncotarget. 2017;9:23846-7. PubMed PMID: 29844856.

Solis GP, Kozhanova TV, Koval A, Zhilina SS, Mescheryakova TI, Abramov AA, Ishmuratov EV, Bolshakova ES, Osipova KV, Ayvazyan SO, Lebon S, Kanivets IV, Pyankov DV, Troccaz S, Silachev DN, Zavadenko NN, Prityko AG, Katanaev VL. Pediatric encephalopathy: clinical, biochemical and cellular insights into the role of Gln52 of GNAO1 and GNAI1 for the dominant disease. Cells. 2021;10:2749. PubMed PMID: 34685729.

Takezawa Y, Kikuchi A, Haginoya K, Niihori T, Numata-Uematsu Y, Inui T, Yamamura-Suzuki S, Miyabayashi T, Anzai M, Suzuki-Muromoto S, Okubo Y, Endo W, Togashi N, Kobayashi Y, Onuma A, Funayama R, Shirota M, Nakayama K, Aoki Y, Kure S. Genomic analysis identifies masqueraders of full-term cerebral palsy. Ann Clin Transl Neurol. 2018;5:538-551. PubMed PMID: 29761117.

Talvik I, Møller RS, Vaher M, Vaher U, Larsen LHG, Dahl HA, Ilves P, Talvik T. Clinical phenotype of de novo GNAO1 mutation: case report and review of literature. Child Neurol Open. 2015;2:2329048X1558371-2329048X1558371.

Thiel M, Bamborschke D, Janzarik WG, Assmann B, Zittel S, Patzer S, Auhuber A, Opp J, Matzker E, Bevot A, Seeger J, van Baalen A, Stüve B, Brockmann K, Cirak S, Koy A. Genotype-phenotype correlation and treatment effects in young patients with GNAO1-associated disorders. J Neurol Neurosurg Psychiatry. 2023;94:806-15. PubMed PMID: 37225406.

Trivisano M, Muccioli L, Ferretti A, Lee HF, Chi CS, Bisulli F. Risk of SUDEP during infancy. Epilepsy Behav. 2022;131:107896. PubMed PMID: 33741238.

Turro E, Astle WJ, Megy K, Gräf S, Greene D, Shamardina O, Allen HL, Sanchis-Juan A, Frontini M, Thys C, Stephens J, Mapeta R, Burren OS, Downes K, Haimel M, Tuna S, Deevi SVV, Aitman TJ, Bennett DL, Calleja P, Carss K, Caulfield MJ, Chinnery PF, Dixon PH, Gale DP, James R, Koziell A, Laffan MA, Levine AP, Maher

ER, Markus HS, Morales J, Morrell NW, Mumford AD, Ormondroyd E, Rankin S, Rendon A, Richardson S, Roberts I, Roy NBA, Saleem MA, Smith KGC, Stark H, Tan RYY, Themistocleous AC, Thrasher AJ, Watkins H, Webster AR, Wilkins MR, Williamson C, Whitworth J, Humphray S, Bentley DR, Kingston N, Walker N, Bradley JR, Ashford S, Penkett CJ, Freson K, Stirrups KE, Raymond FL, Ouwehand WH, et al. Whole-genome sequencing of patients with rare diseases in a national health system. Nature. 2020;583:96-102. PubMed PMID: 32581362.

Vasconcellos LF, Soares VP, de Ricchezza LL. Dystonic cerebral palsy phenotype due to GNAO1 variant responsive to levodopa. Tremor Other Hyperkinet Mov (N Y). 2023;13:11. PubMed PMID: 37034444.

Waak M, Mohammad SS, Coman D, Sinclair K, Copeland L, Silburn P, Coyne T, McGill J, O'Regan M, Selway R, Symonds J, Grattan-Smith P, Lin JP, Dale RC, Malone S. GNAO1-related movement disorder with life-threatening exacerbations: movement phenomenology and response to DBS. J Neurol Neurosurg Psychiatry. 2018;89:221-2. PubMed PMID: 28668776.

Wirth T, Garone G, Kurian MA, Piton A, Millan F, Telegrafi A, Drouot N, Rudolf G, Chelly J, Marks W, Burglen L, Demailly D, Coubes P, Castro-Jimenez M, Joriot S, Ghoumid J, Belin J, Faucheux JM, Blumkin L, Hull M, Parnes M, Ravelli C, Poulen G, Calmels N, Nemeth AH, Smith M, Barnicoat A, Ewenczyk C, Méneret A, Roze E, Keren B, Mignot C, Beroud C, Acosta F, Nowak C, Wilson WG, Steel D, Capuano A, Vidailhet M, Lin JP, Tranchant C, Cif L, Doummar D, Anheim M. Highlighting the dystonic phenotype related to GNAO1. Mov Disord. 2022a;37:1547-54. PubMed PMID: 35722775.

Wirth T, Garone G, Kurian MA, Piton A, Roze E, Lin JP, Tranchant C, Cif L, Doummar D, Anheim M. Reply to: "GNAO1 haploinsufficiency associated with a mild delayed-onset dystonia phenotype". Mov Disord. 2022b;37:2466-7. PubMed PMID: 36533587.

Wirth T, Tranchant C, Drouot N, Keren B, Mignot C, Cif L, Lefaucheur R, Lion-François L, Méneret A, Gras D, Roze E, Laroche C, Burbaud P, Bannier S, Lagha-Boukbiza O, Spitz MA, Laugel V, Bereau M, Ollivier E, Nitschke P, Doummar D, Rudolf G, Anheim M, Chelly J. Increased diagnostic yield in complex dystonia through exome sequencing. Parkinsonism Relat Disord. 2020;74:50-6. PubMed PMID: 32334381.

Xiong J, Peng J, Duan HL, Chen C, Wang XL, Chen SM, Yin F. [Recurrent convulsion and pulmonary infection complicated by psychomotor retardation in an infant]. Zhongguo Dang Dai Er Ke Za Zhi. 2018;20:154-7. PubMed PMID: 29429466.

Yamamoto EA, Berry M, Harris W, Shahin MN, Wilson JL, Safarpour D, Raslan AM. Good response to deep brain stimulation in two forms of inherited chorea related to GNAO1 and neuroacanthocystosis with illustrative videos. Mov Disord Clin Pract. 2021;9:401-3. PubMed PMID: 35402648.

Yamashita Y, Ogawa T, Ogaki K, Kamo H, Sukigara T, Kitahara E, Izawa N, Iwamuro H, Oyama G, Kamagata K, Hatano T, Umemura A, Kosaki R, Kubota M, Shimo Y, Hattori N. Neuroimaging evaluation and successful treatment by using directional deep brain stimulation and levodopa in a patient with GNAO1-associated movement disorder: a case report. J Neurol Sci. 2020;411:116710. PubMed PMID: 32044685.

Yang X, Niu X, Yang Y, Cheng M, Zhang J, Chen J, Yang Z, Zhang Y. Phenotypes of GNAO1 variants in a Chinese cohort. Frontiers in Neurology. 2021;12:662162. PubMed PMID: 34122306.

Yilmaz S, Turhan T, Ceylaner S, Gökben S, Tekgul H, Serdaroglu G. Excellent response to deep brain stimulation in a young girl with GNAO1-related progressive choreoathetosis. Childs Nerv Syst. 2016;32:1567-8. PubMed PMID: 27278281.

Zhu X, Petrovski S, Xie P, Ruzzo EK, Lu Y-F, McSweeney KM, Ben-Zeev B, Nissenkorn A, Anikster Y, Oz-Levi D, Dhindsa RS, Hitomi Y, Schoch K, Spillmann RC, Heimer G, Marek-Yagel D, Tzadok M, Han Y, Worley G, Goldstein J, Jiang Y-H, Lancet D, Pras E, Shashi V, McHale D, Need AC, Goldstein DB. Whole-exome sequencing in undiagnosed genetic diseases: interpreting 119 trios. Genet Med. 2015;17:774-81. PubMed PMID: 25590979.

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