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Gonadal mosaicism in GNAO1 causing neurodevelopmental disorder with involuntary movements; two additional variants

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ABSTRACT

Background: *GNAO1* encodes an alpha subunit of the heterotrimeric guanine nucleotide-binding proteins (G proteins). Mutations in *GNAO1* result in two clinical phenotypes: Early infantile epileptic encephalopathy 17 (EEIE17-OMIM #615473) and Neurodevelopmental disorder with involuntary movements (NEDIM-OMIM #617493). Both are inherited as autosomal dominant disorders and originate mainly as de novo. Only a few are reported as gonadal mosaicism.

Materials and methods: We recruited and retrospectively reviewed five patients from two families seen at King Faisal Specialist Hospital and Research Centre in Riyadh (KFSHRC).

Results: All patients presented with severe neurodevelopmental disorder, followed by progressive dystonia and hyperkinetic movements. In addition, none of the patients had seizures which was consistent with NEDIM phenotype. The specific diagnosis was not clinically entertained and was only found on whole exome sequencing (WES), which identified two variants (c.724-8G > A & c.709G > A). Both variants were previously reported as pathogenic de novo in patients with NEDIM, and one was reported as parental gonadal mosaicism.

Conclusion: We report these variants as additional variants in *GNAO1* gene that may be inherited as parental gonadal mosaicism. Both variants resulted in NEDIM with no observed clinical differences in the severity than the reported cases. This noticeable reported association between *GNAO1* gene associated disorders and gonadal mosaicism should be considered in reproductive genetic counselling of affected families. Furthermore, in view of these reports, more studies with prospective data collection to explore the association between *GNAO1* and gonadal mosaicism and the underlying mechanisms will be necessary.

1. Introduction

GNAO1 gene encodes Gαo, the α subunit of Go, a member of the Gi/o family of heterotrimeric G protein signal transducers. Go is the most abundant membrane protein in the mammalian central nervous system and plays a major role in synaptic neurotransmission and neurodevelopment (1). Gαo localizes ubiquitously throughout the brain with relatively high expression in hippocampus, striatum, and cerebellum (2). Mutation in *GNAO1* gene results in two clinical phenotypes; (EEIE17-OMIM #615473), and (NEDIM-OMIM #617493) (3). Both are inherited as autosomal dominant disorders and are caused mainly by de novo mutations.

The most common manifestations of NEDIM are hypotonia, developmental delay, spasticity, dystonia, and hyperkinetic movements with choreoathetosis. Before the first exacerbation of chorea, the motor syndrome typically appears nonspecific, and patients may be misdiagnosed with hypotonic or dyskinetic cerebral palsy (10–12). To date, four variants in *GNAO1* have been reported with parental gonadal mosaicism. Three variants are linked to NEDIM, and one variant caused EIEE17 (4,6,18,22). Here we report two additional variants (Table 2) in *GNAO1* associated with parental gonadal mosaicism among five patients with NEDIM. Both variants have been reported previously as pathogenic de novo mutations.

Abbreviations: NEDIM, Neurodevelopmental disorder with involuntary movements; EEIE17, Early infantile epileptic encephalopathy 17.

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Table 1
Phenotypic characteristic of five patients with disease-associated variants in GNAO1 gene.

Feature No.	Family I			Family II	
	I:1	I:2	I:3	II:1	II:2
Demographics					
Gender	Female	Female	Male	Male	Male
Current age	16 years	16 years	6 years	14 years	11 years
Age of onset	5 Months	5 Months	4 Months	Birth	Birth
Initial presentation	DD	DD	DD	Hypotonia	Hypotonia
Dystonia	Yes	Yes	Yes	Yes	Yes
Choreoathetosis	Yes	Yes	Yes	Yes	Yes
Dyskinesia	Yes	Yes	No	Yes	Yes
Stereotypic hand movements	Yes	Yes	Yes	Yes	Yes
Spasticity	Quadriplegia	Quadriplegia	Quadriparesis	Quadriplegia	Quadriplegia
Seizure	No	No	No	No	No
Speech	Anarthria	Anarthria	Anarthria	Delayed	Delayed
Thoracolumbar scoliosis	Yes	No	No	Yes	NA
Medications	Artane & Baclofen	None	None	NA	NA
Functional status	Wheelchair	Wheelchair	Spastic gait	Wheelchair	Wheelchair
Clinical examination					
Weight (kg)	28 (−6.1 SD)	33 (−4 SD)	17 (−1.9 SD)	16 (−5 SD)	NA
Height (cm)	150 (−1.9 SD)	139 (−2.8 SD)	111 (−1.6 SD)	119 (−2.4 SD)	NA
BMI	12.7	14.3	14.2	11.5	NA
Microcephaly	No	No	No	No	NA
Eye Exam	NA	NA	NA	Normal	NA
Laboratory workup and radiological imaging					
CK (24–192 U/L)	731	Normal	Normal	Normal	NA
Lactate mmol/l	Normal	NA	NA	2.7–4.4–1.5*	NA
EEG	Spikes, multiregional, maximum mid temporal. Intermittent slow activity, bitemporal	Spike, right and left anterior mid temporal. Intermittent slow activity, bitemporal	Bilateral temporooccipital intermittent slow activity	Bitemporal independent spikes/sharp wave more from the left side. Intermittent independent bitemporal delta slowing	NA
MRI	Normal	Normal	Normal	Normal	NA
Bone Scan *Z*-score/ SD	Osteopenia (−2.1)	Osteopenia (−2.0&-1.0)	NA	NA	NA
Alive	Yes	Yes	Yes	Yes	Yes

NA, Not Available, ID intellectual disability, DD developmental delay, * Values from initial to most recent, SD standard deviation.

Table 2
Molecular description of the variants in GNAO1 gene.

Feature No.	Family I			Family II	
	I:1	I:2	I:5	II:1	II:2
Variant	c.724-8G > A	c.724-8G > A	c.724-8G > A	c.709G > A (p.Glu237Lys)	c.709G > A (p.Glu237Lys)
Test	WES	Targeted	Targeted	WES	Targeted
Transcript	NM_020988	NM_020988	NM_020988	NM_020988	NM_020988
Exon	7	7	7	6	6
Type	Intronic Splice Site Acceptor Mutation			Missense	
ClinVar (Date of report/ Number of submissions)	Pathogenic (Sep 2021/3)			Pathogenic (Nov 2021/3)	
Allele origin	Germline			Germline	
Cytogenetic Location	16q12.2	16q12.2	16q12.2	16q12.2	16q12.2
Parent status	Negative			Negative	

WES whole exome sequencing.

2. Materials and methods

2.1. Institutional approval

This publication was approved by the Office of Research Affairs (ORA) at King Faisal Specialist Hospital and Research Centre-Riyadh (KFSHRC-R).

2.2. Patient data

We retrospectively reviewed all available clinical data and molecular findings on patients diagnosed with *GNAO1* mutation at King Faisal Specialist Hospital and Research Center (KFSH&RC) Riyadh.

2.3. Results (Table 1)

2.3.1. Family 1

Identical twin (I:1, I:2) born preterm at 34 weeks to a healthy consanguineous parents of Arab descent. They were admitted to neonatal intensive care unit shortly after birth due to prematurity for three weeks and discharged in good condition. They were noted to have delayed milestones since infancy. They walked around three years, followed by the occurrence of dystonic posturing of the lower limbs around four years and then progressing to upper extremities and face by age

Table 3
Previously reported variants in GNAO1 with their related phenotype.

No	Reference	Variant	Origin	Phenotype
1.	Law	Gly40Arg*	De novo	EIEE17
2.	Gawlinski	Gly45Glu*	De novo	EIEE17
3.	Nakamura	Asp174Gly*	De novo	Ohtahara syndrome
4.	Nakamura	191_197*	De novo	Ohtahara syndrome
5.	Nakamura	Gly203Arg*	De novo	EIEE17
6.	Nakamura	Ile279Asn*	De novo	Ohtahara syndrome
7.	Marce-Grau	Leu199Pro*	De novo	EIEE17
8.	Saitsu	Gly203Arg*	De novo	EIEE17
9.	Saitsu	Arg209Cys	De novo	NEDIM
10.	Saitsu	Ala227Val*	De novo	EIEE17
11.	Saitsu	Glu246Lys*	De novo	EIEE17
12.	Kulkarni	Arg209Cys	Gonadal mosaicism	NEDIM
13.	Kulkarni	Arg209Cys	Gonadal mosaicism	NEDIM
14.	Menke	Arg209His	De novo	NEDIM
15.	Menke	Arg209Leu	De novo	NEDIM
16.	Dhamija	Arg209His	De novo	NEDIM
17.	Ananth	Arg209His	De novo	NEDIM
18.	Ananth	Arg209Gly	De novo	NEDIM
19.	Ananth	Glu246Lys	Gonadal mosaicism	NEDIM
20.	Ananth	Glu246Lys	Gonadal mosaicism	NEDIM
21.	Ananth	Glu246Lys	De novo	NEDIM
22.	Ananth	Glu246Lys	De novo	NEDIM
23.	Talvik	Tyr231Cys*	De novo	Ohtahara syndrome
24.	Yilmaz	Glu233Pro	De novo	NEDIM
25.	Euroepiomics	Asn270His*	De novo	EIEE17
26.	Euroepiomics	Phe275Ser*	De novo	EIEE17
27.	Arya R	Gly203Arg*	De novo	EIEE17
28.	Bruun	Gly40Arg*	De novo	EIEE17
29.	Danti	Ser47Gly*	De novo	EIEE17
30.	Danti	Arg209Cys*	De novo	EIEE17
31.	Danti	Arg209Cys*	De novo	EIEE17
32.	Danti	c.723 + 1G > A	De novo	NEDIM
33.	Danti	Ile56Thr*	De novo	EIEE17
34.	Danti	Gly40Arg*	De novo	EIEE17
35.	Danti	Glu246Gly	De novo	NEDIM
36.	McKenna Kelly	Gly40Arg	De novo	NEDIM
37.	McKenna Kelly	Gly40Trp	De novo	NEDIM
38.	McKenna Kelly	Gly40Glu	Gonadal mosaicism	NEDIM
39.	McKenna Kelly	Gly40Glu	Gonadal mosaicism	NEDIM
40.	McKenna Kelly	Ser207Tyr	De novo	NEDIM
41.	McKenna Kelly	Arg209His	De novo	NEDIM
42.	McKenna Kelly	Arg209Cys	De novo	NEDIM
43.	McKenna Kelly	Ala221Asp	De novo	NEDIM
44.	McKenna Kelly	Tyr231Cys	De novo	NEDIM
45.	McKenna Kelly	Asp237Val	De novo	NEDIM
46.	McKenna Kelly	Ile279Asn	De novo	NEDIM
47.	McKenna Kelly	Tyr291Asn	De novo	NEDIM
48.	McKenna Kelly	Ile344del	De novo	NEDIM
49.	McKenna Kelly	Arg349_G352delinsQGCA	De novo	NEDIM
50.	Feng H (13,14)	Arg209His	De novo	NEDIM
51.	Feng H (13,14)	Arg209His	De novo	NEDIM
52.	Feng H (13,14)	Arg209His	De novo	NEDIM
53.	Feng H (13,14)	Arg209His	De novo	NEDIM
54.	Feng H (13,14)	Gly203Arg*	De novo	EIEE17
55.	Feng H (13,14)	Gly203Arg*	De novo	EIEE17
56.	Feng H (13,14)	Gly203Arg*	De novo	EIEE17
57.	Feng H (13,14)	Glu246Lys	De novo	NEDIM
58.	Feng H (13,14)	Glu246Lys	De novo	NEDIM
59.	Feng H (13,14)	Glu246Lys	De novo	NEDIM
60.	Feng H (13,14)	Glu246Lys	De novo	NEDIM
61.	Feng H (13,14)	Glu246Lys	De novo	NEDIM
62.	Feng H (13,14)	Gly42Arg	De novo	NEDIM
63.	Feng H (13,14)	Arg209Cys*	De novo	EIEE17
64.	Feng H (13,14)	Ile279Asp*	De novo	EIEE17
65.	Feng H (13,14)	Ile279Asp*	De novo	EIEE17
66.	Feng H (13,14)	Thr191_Phe197del*	De novo	EIEE17
67.	Feng H (13,14)	Arg209Gly	De novo	NEDIM
68.	Feng H (13,14)	Ala227Val*	De novo	EIEE17
69.	Feng H (13,14)	Tyr231Cys*	De novo	EIEE17
70.	Feng H (13,14)	Phe275Ser*	De novo	EIEE17
71.	Feng H (13,14)	Leu199Pro*	De novo	EIEE17
72.	Feng H (13,14)	Asp270His*	De novo	EIEE17
73.	Feng H (13,14)	Gly40Arg*	De novo	EIEE17
74.	Feng H (13,14)	Asp174Gly*	De novo	EIEE17
75.	Epi & Epi	Ile279Asp*	De novo	EIEE17
76.	Gerald	His371_372del*	De novo	EIEE17
77.	Sakamoto S (8)	Arg209Cys	De novo	NEDIM
78.	Schorling	Glu246Lys	De novo	NEDIM
79.	Schorling	Glu246Lys	De novo	NEDIM
80.	Schorling	Gly203Arg*	De novo	EIEE17
81.	Schorling	Gly203Arg*	De novo	EIEE17
82.	Ueda	Gly45Arg*	De novo	EIEE17
83.	Xiong	Gly203Arg*	De novo	EIEE17
84.	Yang X	c.724-8G > A	Gonadal mosaicism	DD & MD
85.	Yang X	c.724-8G > A	Gonadal mosaicism	DD & MD
86.	Yang X	c.136A > G(p.K46E)	De novo	West
87.	Yang X	c.687C > G(p.S229R)	De novo	West & MD
88.	Yang X	c.470 T > C (p.L157R)	De novo	West & MD
89.	Yang X	c.810C > A (p.N270K)	De novo	Ohtahara and MD
90.	Yang X	c.817G > T (p.D273Y)*	De novo	EIEE and MD
91.	Yang X	c.118G > C(p.G40R)	De novo	West
92.	Yang X	c.692A > G(p.Y231C)*	De novo	EIEE and MD
93.	Yang X	c.607G > A(p.G203R)*	De novo	EIEE and MD
94.	Yang X	c.736G > A(p.E246R)	De novo	DD
95.	Miyamoto S	c.724-8G > A	Gonadal mosaicism	NEDIM
96.	Retterer K	c.724-8G > A	De novo	NEDIM
97.	Retterer K	p.G203R	De novo	NEDIM

NEDIM Neurodevelopmental Disorder with Involuntary Movements, *EIEE17 Epileptic Encephalopathy, Early Infantile, 17.

five. This was followed by choreoathetosis and cervical dystonia resulting in left-sided intermittent torticollis with dystonic involuntary movements. Both twins had significant speech delay. On examination at eight years, their weight was below the 3rd percentile, height was on the 3rd percentile, and head circumference was appropriate for age. Extraocular movements were normal. They had spastic quadriplegia with hypertonia, more pronounced in the lower limbs as compared to upper limbs. Deep tendon reflexes were brisk, and planters were up going bilaterally. Initially, they were diagnosed with spastic diplegic cerebral palsy, but as dystonia became more evident, other diagnostic possibilities were entertained, including genetic causes. Twin B (I:2) was able to walk until the age of eight years, then she lost ambulation, whereas twin A (I:1) lost the ability to walk by 12 years. The dystonic involuntary movements partially responded to Artane, Baclofen, Clonazepam, and intermittent Botox injections. The third sibling was a baby boy (I:3), a product of full-term normal vaginal delivery without complications during pregnancy with a birth weight of 2.5 kg. He was discharged home as a normal newborn. By one year of age, the family noticed global developmental delay as he could not sit alone, had poor handgrip and linguistically, he could not babble. Socially, he interacted with his surroundings, and there were no concerns regarding hearing and vision. He sat at the age of 15 months, started to walk at 20 months of age, and started babbling at the age of 24 months. Currently, he is six years old and dependent on his mother for all daily activities. On examination, his growth parameters are appropriate for his age. He has some functional eye contact, responds to social smiles and is not communicating verbally except for babbling sounds. He has dystonic spastic posture with no hyperkinetic movements and his extraocular muscle movements are normal. Excessive saliva drooling is noted. Deep tendon reflexes were brisk, and planters were upgoing bilaterally. He has hypertonia in upper and lower extremities with the latter more severely affected and can walk with an ataxic spastic gait.

2.3.2. Family 2

Two siblings (II:1, II:2) delivered by normal vaginal delivery with uneventful antenatal and postnatal course. They were found to be floppy from birth. They started to reach objects by two years. They began to stand up and walk with support for a short distance by three years. They developed involuntary movement and dystonia associated with abnormal posturing by the age of four years. Speech delay was prominent and by five years, they only spoke a few words. On examination, they had generalized hypotonia, predominantly axial with normal reflexes till the age of three years. Then at the age of five years, they started to have spasticity and hyperreflexia more prominent in the lower limbs than in the upper limbs. The muscle bulk was decreased, and the power was 3/5 with dystonic hyperkinetic movements. Currently, both siblings have severe growth retardation and spastic dystonic posture with normal head circumference.

2.4. Molecular testing

In family I, Microarray-based comparative genomic hybridization, Array CGH + SNP was negative, and WES showed a heterozygous variant in *GNAO1* c.724-8G > A in all affected individuals. Whereas, in family 2, WES was performed for II:1 and revealed a heterozygous missense variant in *GNAO1*, c.709G > A (Glu237Lys). Further targeted mutation analysis confirmed the presence of the same variant in his sibling II:2. Both variants were not detected in the parental blood samples in both families, indicating gonadal mosaicism.

3. Discussion

To date, over 95 patients with *GNAO1* gene mutations have been reported in the literature (3–7,18,19,22); at least 39 patients with 21 unique variants are linked to EEIE17, 45 patients with 25 unique variants are linked to NEDIM, while four variants are linked to Ohtahara syndrome. The majority of variants are; missense in nature, few deletions, and one deep intronic splicing defect. Of these, four variants (Table 3) in nine cases have been reported with parental gonadal mosaicism. Three variants (p.E246K) in dizygotic twins and two variants p.R209H and c.724-8G > A in two sets of siblings were reported as a cause of NEDIM. In these six patients with NEDIM, all had motor and linguistic developmental delay. They also have developed progressive chorea and athetosis at the age of five years. One patient had a daily exacerbation of chorea that required intensive care admission and management. Two patients had improvement in the chorea with deep brain stimulation (4,6,24). One variant p.G40E was reported to cause EIEE17 in two adult brothers. Both had seizures that started in infancy, with significant findings in EEG and MRI imaging (22). In our view, instead of viewing *GNAO1* mutations as distinct phenotypes, we believe that they rather represent a clinical spectrum from a severe early-onset epileptic encephalopathy to a protracted neurodevelopmental delay with a movement disorder.

We describe here five patients from two families (See Fig. 1) with global developmental delay, hypotonia, spastic quadriplegia, and severe hyperkinetic movement disorder attributed to gonadal mosaicism, expanding the list of the mutations in *GNAO1* gene associated with this type of inheritance. Their phenotype was consistent with NEDIM. The oldest patient is 16, and the youngest patient is 6. None of our patients

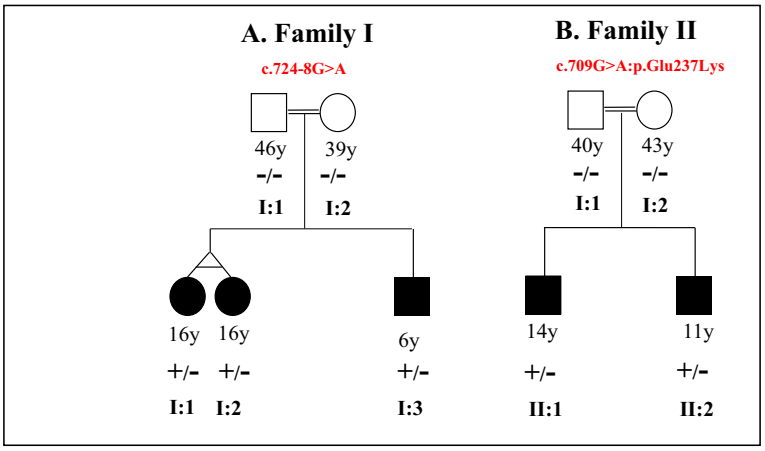

Fig. 1. Pedigrees of the two families with *GANO1*.

had clinical seizures, but they showed abnormal EEGs. Three patients presented in early infancy with hypotonia, whereas the other two had a normal initial neonatal period followed by global developmental delay at four and five months, respectively. The dystonia started in lower extremities and later extended gradually to the upper extremities and facial muscles. They all exhibited hyperkinetic movement with dystonia between four and seven years with partial response to pharmacotherapy. Eventually, they all lost the ability to ambulate as they grew older without triggering factors and became wheelchair-bound. They all demonstrated severe linguistic delay, but none had evidence of dysphagia. To date, they are all alive, and none of them have deep brain stimulation yet.

Using whole exome sequencing, two heterozygous variants have been detected in GNAO1 gene. The variants were not detected in parental blood samples from either family and all siblings are healthy. The presence of the same heterozygous variant in multiple children and its absence in both parents supports parental gonadal mosaicism. E237K variant was reported before in two patients with NEDIM (15,23). Also, this variant was reported in ClinVar database in an individual with microcephaly, seizures, and muscle weakness. The other variant c.724-8G > A has been reported by GeneDx in Clinvar as de novo in two presumably unrelated individuals with similar clinical features. In three recent reports, four additional patients with c.724-8G > A variant has been described in three families; two patients with germline mosaicism, one patient who inherited the variant from her mother with low-prevalent somatic mosaicism and one as de novo (24,25,28). This variant caused abnormal splicing of in-frame 6-bp intronic retention, leading to 2 amino acid insertion (p.Thr241_Asn242insProGln). Immunoblotting and immunostaining using wild type and mutant GNAO1 vectors showed no significant differences in protein expression level, but the cellular localization pattern of this mutant was partially shifted to the cytoplasm whereas WT was exclusively localized in the cellular membrane. Investigators suggested that this mutant might have a loss of function effect alongside with dominant negative effect predisposing to movement disorders without seizures (24). In some reports (22), parental somatic mosaicism has been observed in 6.6% - 8.3% of parents who had a child with a diagnosis of an apparently de novo monogenic developmental and epileptic encephalopathy caused by different genes (23,24,26,27). The level of mosaicism in their parents is widely correlated with the severity of disease and symptoms tend to appear in case with a mosaic rate of >10% (27). There is not enough evidence that *GNAO1* gene is associated with parental gonadal mosaicism more than the other genes; however, the association is significantly noticeable and should be considered when families are counselled about the recurrence risk and prenatal testing.

To conclude, we report two variants in *GNAO1* gene inherited as parental gonadal mosaicism. Both variants resulted in NEDIM with no observed clinical differences in the severity away from the reported cases. This noticeable reported association between *GNAO1* gene associated disorders and gonadal mosaicism should be considered in reproductive genetic counselling of affected families. Furthermore, in view of these reports, more studies with prospective data collection to explore the association between *GNAO1* and gonadal mosaicism and the underlying mechanisms will be necessary.

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Authors contributions

ZAM reviewed and summarized the literature and wrote the manuscript. MDS edited the manuscript and contributed to the clinical diagnosis and management of the patients.

Declaration of Competing Interest

The authors declare that they have no competing financial interests.

References

[1] L. Blumkin, T. Lerman-Sagie, A. Westenberger, et al., Multiple causes of pediatric early onset chorea-clinical and genetic approach, Neuropediatrics 49 (2018) 246–255, https://doi.org/10.1055/s-0038-1645884.
[2] P.F. Worley, J.M. Baraban, C. Van Dop, E.J. Neer, S.H. Snyder, Go, a guanine nucleotide-binding protein: immunohistochemical localization in rat brain resembles distribution of second messenger systems, Proc. Natl. Acad. Sci. U. S. A. 83 (1986) 4561–4565, https://doi.org/10.1073/pnas.83.12.4561.
[3] K. Nakamura, H. Kodera, T. Akita, et al., De novo mutations in GNAO1, encoding a Gαo subunit of heterotrimeric G proteins, cause epileptic encephalopathy, Am. J. Hum. Genet. 93 (2013) 496–505, 10.1016%2Fj.ajhg.2013.07.014.
[4] N. Kulkarni, S. Tang, R. Bhardwaj, S. Bernes, T.A. Grebe, Progressive movement disorder in brothers carrying a GNAO1 mutation responsive to deep brain stimulation, J. Child Neurol. 31 (2016) 211–214, https://doi.org/10.1177/0883073815587945.
[5] L.A. Menke, M. Engelen, M. Alders, V.J.J. Odekerken, F. Baas, J.M. Cobben, Recurrent GNAO1 mutations associated with developmental delay and a movement disorder, J. Child Neurol. 31 (2016) 1598–1601, https://doi.org/10.1177/0883073816666474.
[6] A.L. Ananth, A. Robichaux-Viehoever, Y.-M. Kim, A. Hanson-Kahn, R. Cox, G. M. Enns, J. Strober, M. Willing, B.L. Schlaggar, Y.W. Wu, J.A. Bernstein, Clinical course of six children with GNAO1 mutations causing a severe and distinctive movement disorder, Pediat. Neurol. 59 (2016) 81–84, https://doi.org/10.1016/j.pediatrneurol.2016.02.018.
[7] H. Saitsu, et al., Phenotypic spectrum of GNAO1 variants: epileptic encephalopathy to involuntary movements with severe developmental delay, Eur. J. Hum. Genet. 24 (2016) 129–134, https://doi.org/10.1038/ejhg.2015.92.
[8] S. Sakamoto, Y. Monden, R. Fukai, et al., A case of severe movement disorder with GNAO1 mutation responsive to topiramate, Brain Dev. 39 (2017) 439–443, https://doi.org/10.1016/j.braindev.2016.11.009.
[10] L. Blumkin, T. Lerman-Sagie, A. Westenberger, et al., Multiple causes of pediatric early onset chorea-clinical and genetic approach, Neuropediatrics 49 (2018) 246–255, https://doi.org/10.1055/s-0038-1645884.
[11] T.S. Pearson, R. Pons, R. Ghaoui, C.M. Sue, Genetic mimics of cerebral palsy, Mov. Disord. 34 (2019) 625–636, https://doi.org/10.1002/mds.27655.
[12] M.J. Malaquias, I. Fineza, L. Loureiro, L. Cardoso, I. Alonso, M. Magalhães, GNAO1 mutation presenting as dyskinetic cerebral palsy, Neurol. Sci. 40 (2019) 2213–2216, https://doi.org/10.1007/s10072-019-03964-7.
[13] H. Feng, B. Sjögren, B. Karaj, V. Shaw, A. Gezer, R.R. Neubig, Movement disorder in GNAO1 encephalopathy associated with gain-of-function mutations, Neurology 89 (2017) 762–770, 10.1212%2FWNL.0000000000004262.
[14] H. Feng, S. Khalil, R.R. Neubig, C. Sidiropoulos, A mechanistic review on GNAO1-associated movement disorder, Neurobiol. Dis. 116 (2018) 131–141, https://doi.org/10.1016/j.nbd.2018.05.005.
[15] F.R. Danti, S. Galosi, M. Romani, et al., GNAO1 encephalopathy: broadening the phenotype and evaluating treatment and outcome, Neurol. Genet. 3 (2017), e143, https://doi.org/10.1212/nxg.0000000000000143.
[18] S. Yilmaz, T. Turhan, S. Ceylaner, S. Gökben, H. Tekgul, G. Serdaroglu, Excellent response to deep brain stimulation in a young girl with GNAO1-related progressive choreoathetosis, Childs Nerv. Syst. 32 (2016) 1567–1568, https://doi.org/10.1007/s00381-016-3139-6.
[19] R. Dhamija, J.W. Mink, B.B. Shah, H.P. Goodkin, GNAO1-associated movement disorder, Mov. Disord. Clin. Pract. 3 (2016) 615–617, https://doi.org/10.1002/mdc3.12344.
[22] M. Kelly, M. Park, I. Mihalek, et al., Spectrum of neurodevelopmental disease associated with the GNAO1 guanosine triphosphate–binding region, Epilepsia 00 (2019) 1–13, https://doi.org/10.1111/epi.14653.
[23] H.C. Happ, G.L.A. Carvill, View on the genetics of developmental and epileptic encephalopathies, Epilepsy Curr. 20 (2020) (2020) 90–96, https://doi.org/10.1177/1535759720906118.
[24] S. Miyamoto, M. Nakashima, S. Fukumura, S. Kumada, H. Saitsu, An intronic GNAO1 variant leading to in-frame insertion cause movement disorder controlled by deep brain stimulation, Neurogenetics (2022), https://doi.org/10.1007/s10048-022-00686-5.
[25] X. Yang, X. Niu, Y. Yang, M. Cheng, J. Zhang, J. Chen, Z. Yang, Y. Zhang, Phenotypes of GNAO1 variants in a chinese cohort, Front. Neurol. 12 (2021), 662162, https://doi.org/10.3389/fneur.2021.662162.
[26] R.S. Mller, N. Liebmann, Larsen LHG, Parental mosaicism in epilepsies due to alleged de novo variants, Epilepsia 60 (6) (2019) e63–e66, https://doi.org/10.1111/epi.15187.
[27] C.T. Myers, G. Hollingsworth, A.M. Muir, et al., Parental mosaicism in “de novo” epileptic encephalopathies, N. Engl. J. Med. 378 (17) (2018) 1646–1648, https://doi.org/10.1056/nejmc1714579.
[28] K. Retterer, J. Juusola, M.T. Cho, et al., Clinical application of whole-exome sequencing across clinical indications, Genet. Med. 18 (7) (2016) 696–704, https://doi.org/10.1038/gim.2015.148.

Further readings

[9] X. Zhu, S. Petrovski, P. Xie, et al., Whole-exome sequencing in undiagnosed genetic diseases: interpreting 119 trios, Genet Med. 17 (2015) 774–781, https://doi.org/10.1038/gim.2014.191.

[16] M. Waak, S.S. Mohammad, D. Coman, et al., GNAO1-related movement disorder with life-threatening exacerbations: movement phenomenology and response to DBS, J. Neurol. Neurosurg. Psychiatry 89 (2018) 221–222, https://doi.org/10.1136/jnnp-2017-315653.

[17] C.M. Honey, A.K. Malhotra, M. Tarailo-Graovac, C.D.M. van Karnebeek, G. Horvath, A. Sulistyanto, GNAO1 mutation-induced pediatric dystonic storm rescue with pallidal deep brain stimulation, J. Child Neurol. 33 (2018) 413–416, https://doi.org/10.1177/0883073818756134.

[20] K. Ueda, F. Serajee, A.M. Huq, Exome sequencing identifying dual mutations in calcium signaling genes GNAO1 and ATP2B3 in a patient with early infantile epileptic encephalopathy, J. Pediatr. Neurol. 15 (2017) 183–186, https://doi.org/10.1055/s-0036-1597627.

[21] A. Benato, M. Carecchio, A. Burlina, et al., 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) 126 (2019) 739–757, https://doi.org/10.1007/s00702-019-02010-2.