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 EEIE17 (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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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 (KFSH&RC).

2.2. Patient data

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

Table 1

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

| Feature No. | Demographics | Gender | Current age | Age of onset | Initial presentation | Dysxia | Choreoathetosis | Dyskinesia | Stereotypic hand movements | Spasticity | Seizure | Speech | Thoracolumbar scoliosis | Medications | Functional status | Clinical examination | Laboratory workup and radiological imaging |
|-------------|--------------|--------|-------------|--------------|---------------------|--------|----------------|-----------|---------------------------|------------|--------|--------|-----------------------|-------------|-------------------|---------------------|---------------------------------------------|
| Family I    | E1           | E2     | I:1         | I:2          | DD                  | Yes    | Yes            | Yes       | Yes                       | Quadrplegia| No     | Anarthria | No                    | Artane & Baclofen | Wheelchair        | Weight (kg) (6.1 SD) | CK (24–192 U/L) |
|             | I:3          |        | I:1         | I:2          | DD                  | Yes    | Yes            | No        | Yes                       | Quadrplegia| No     | Anarthria | No                    | NA           | NA                | 28 (6.1 SD)         | Normal |
| Family II   | II:1         | II:2   | II:1        | II:2         | DD                  | Yes    | Yes            | Yes       | Yes                       | Quadrplegia| No     | Anarthria | No                    | NA           | NA                | 150 (1.9 SD)         | Normal |
|             |              |        |             |              | DD                  | Yes    | Yes            | No        | Yes                       | Quadrplegia| No     | Anarthria | No                    | NA           | NA                | 12.7                | Normal |
|             |              |        |             |              | DD                  | Yes    | Yes            | No        | Yes                       | Quadrplegia| No     | Anarthria | No                    | NA           | NA                | 33 (4 SD)            | Normal |
|             |              |        |             |              | DD                  | Yes    | Yes            | No        | Yes                       | Quadrplegia| No     | Anarthria | No                    | NA           | NA                | 111 (1.6 SD)         | Normal |
|             |              |        |             |              | DD                  | Yes    | Yes            | No        | Yes                       | Quadrplegia| No     | Anarthria | No                    | NA           | NA                | 14.2                | Normal |
|             |              |        |             |              | DD                  | Yes    | Yes            | No        | Yes                       | Quadrplegia| No     | Anarthria | No                    | NA           | NA                | 11.5                | Normal |
|             |              |        |             |              | DD                  | Yes    | Yes            | No        | Yes                       | Quadrplegia| No     | Anarthria | No                    | NA           | NA                | 16 (5 SD)            | NA |
|             |              |        |             |              | DD                  | Yes    | Yes            | No        | Yes                       | Quadrplegia| No     | Anarthria | No                    | NA           | NA                | 119 (2.4 SD)         | NA |
|             |              |        |             |              | DD                  | Yes    | Yes            | No        | Yes                       | Quadrplegia| No     | Anarthria | No                    | NA           | NA                | 11.5                | NA |
|             |              |        |             |              | DD                  | Yes    | Yes            | No        | Yes                       | Quadrplegia| No     | Anarthria | No                    | NA           | NA                | 14.2                | NA |
|             |              |        |             |              | DD                  | Yes    | Yes            | No        | Yes                       | Quadrplegia| No     | Anarthria | No                    | NA           | NA                | 11.5                | NA |
|             |              |        |             |              | DD                  | Yes    | Yes            | No        | Yes                       | Quadrplegia| No     | Anarthria | No                    | NA           | NA                | 16 (5 SD)            | NA |
|             |              |        |             |              | DD                  | Yes    | Yes            | No        | Yes                       | Quadrplegia| No     | Anarthria | No                    | NA           | NA                | 119 (2.4 SD)         | NA |
|             |              |        |             |              | DD                  | Yes    | Yes            | No        | Yes                       | Quadrplegia| No     | Anarthria | No                    | NA           | NA                | 11.5                | NA |
|             |              |        |             |              | DD                  | Yes    | Yes            | No        | Yes                       | Quadrplegia| No     | Anarthria | No                    | NA           | NA                | 14.2                | NA |
|             |              |        |             |              | DD                  | Yes    | Yes            | No        | Yes                       | Quadrplegia| No     | Anarthria | No                    | NA           | NA                | 11.5                | NA |
|             |              |        |             |              | DD                  | Yes    | Yes            | No        | Yes                       | Quadrplegia| No     | Anarthria | No                    | NA           | NA                | 16 (5 SD)            | NA |

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. | Variant | Test | Transcript | Type | ClinVar (Date of report/ Number of submissions) | Allele origin | Cytogenetic Location | Parent status | Specialisation |
|-------------|---------|------|------------|------|-----------------------------------------------|---------------|---------------------|--------------|----------------|
| Family I    | E1      | c.724-8G > A | WES | NM_020988 | Intron Splice Site Acceptor Mutation | Germline | 16q12.2 | Negative | Intron Splice Site Acceptor Mutation | Germline |
|             | E2      | c.724-8G > A | Targeted | NM_020988 | Pathogenic (Sep 2021/3) | 16q12.2 | Negative | Negative | Intron Splice Site Acceptor Mutation | Germline |
|             | I:1     | c.724-8G > A | Targeted | NM_020988 | Pathogenic (Nov 2021/3) | 16q12.2 | Negative | Negative | Intron Splice Site Acceptor Mutation | Germline |
|             | I:2     | c.724-8G > A | Targeted | NM_020988 | Pathogenic (Nov 2021/3) | 16q12.2 | Negative | Negative | Intron Splice Site Acceptor Mutation | Germline |
| Family II   | II:1    | c.709G > A (p.Glu237Lys) | WES | NM_020988 | Missense Pathogenic | Germline | 16q12.2 | Negative | Intron Splice Site Acceptor Mutation | Germline |
|             | II:2    | c.709G > A (p.Glu237Lys) | Targeted | NM_020988 | Pathogenic (Nov 2021/3) | 16q12.2 | Negative | Negative | Intron Splice Site Acceptor Mutation | Germline |

WES, whole exome sequencing.
Table 3

Previously reported variants in GNAO1 with their related phenotype.

| No | Reference | Variant | Origin | Phenotype |
|----|-----------|---------|--------|-----------|
| 1  | Law       | Gly40Arg* | De novo | EIEE17    |
| 2  | Gawliński | Gly45Glu*  | De novo | EIEE17    |
| 3  | Nakamura  | Asp174Gly* | De novo | Syndrome |
| 4  | Nakamura  | 191_197*   | De novo | Syndrome |
| 5  | Nakamura  | Gly203Arg* | De novo | EIEE17    |
| 6  | Nakamura  | Ile279Asn* | De novo | NEDIM     |
| 7  | Marc-Grau | Leu199Pro* | De novo | EIEE17    |
| 8  | Saito     | Gly203Arg* | De novo | EIEE17    |
| 9  | Saito     | Arg209Cys* | De novo | NEDIM     |
| 10 | Saito     | Ala227Val* | De novo | EIEE17    |
| 11 | Saito     | Glu246Lys* | De novo | EIEE17    |
| 12 | Kulkarni  | Arg209Cys  | Gonadal | NEDIM     |
| 13 | Kulkarni  | Arg209Cys  | Gonadal | Mosaicism |
| 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 | NEDIM     |
| 20 | Ananth    | Glu246Lys  | Gonadal | Mosaicism |
| 21 | Ananth    | Glu246Lys  | De novo | NEDIM     |
| 22 | Ananth    | Glu246Lys  | De novo | NEDIM     |
| 23 | Talvik    | Tyr231Cys* | De novo | Syndrome  |
| 24 | Yilmaz    | Glu233Pro  | De novo | NEDIM     |
| 25 | Euroepiomics | Cys270His | De novo | EIEE17    |
| 26 | Euroepiomics | Phe275Ser* | De novo | EIEE17    |
| 27 | Arya R    | Gly203Arg* | De novo | EIEE17    |
| 28 | Brunu     | 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     | Gly246Gly  | De novo | NEDIM     |
| 36 | Mckenna   | Gly40Arg   | De novo | NEDIM     |
| 37 | Mckenna   | Gly40Trp   | De novo | NEDIM     |
| 38 | Mckenna   | Gly40Glu   | Gonadal | NEDIM     |
| 39 | Mckenna   | Gly40Glu   | Gonadal | Mosaicism |
| 40 | Mckenna   | Ser207Tyr  | De novo | NEDIM     |
| 41 | Mckenna   | Arg209His  | De novo | NEDIM     |
| 42 | Mckenna   | Arg209Cys* | De novo | NEDIM     |
| 43 | Mckenna   | Ala221Asp  | De novo | NEDIM     |
| 44 | Mckenna   | Tyr231Cys  | De novo | NEDIM     |
| 45 | Mckenna   | Asp237Val  | De novo | NEDIM     |
| 46 | Mckenna   | Ile279Asn  | De novo | NEDIM     |
| 47 | Mckenna   | Tyr291Asn  | De novo | NEDIM     |
| 48 | Mckenna   | Ile344del  | De novo | NEDIM     |
| 49 | Mckenna   | Arg349G352delinsGCA | De novo | NEDIM     |
| 50 | Feng H    | Arg209His  | De novo | NEDIM     |
| 51 | Feng H    | Arg209His  | De novo | NEDIM     |

Table 3 (continued)

| No | Reference | Variant | Origin | Phenotype |
|----|-----------|---------|--------|-----------|
| 52 | Feng H    | Arg209His | De novo | NEDIM     |
| 53 | Feng H    | Arg209His | De novo | NEDIM     |
| 54 | Feng H    | Gly203Arg* | De novo | EIEE17    |
| 55 | Feng H    | Gly203Arg* | De novo | EIEE17    |
| 56 | Feng H    | Gly203Arg* | De novo | EIEE17    |
| 57 | Feng H    | Gly246Lys  | De novo | NEDIM     |
| 58 | Feng H    | Glu246Lys  | De novo | NEDIM     |
| 59 | Feng H    | Glu246Lys  | De novo | NEDIM     |
| 60 | Feng H    | Glu246Lys  | De novo | NEDIM     |
| 61 | Feng H    | Glu246Lys  | De novo | NEDIM     |
| 62 | Feng H    | Gly42Arg   | De novo | NEDIM     |
| 63 | Feng H    | Arg209Cys* | De novo | EIEE17    |
| 64 | Feng H    | Ile279Asp* | De novo | EIEE17    |
| 65 | Feng H    | Ile279Asp* | De novo | EIEE17    |
| 66 | Feng H    | Thr191_Phe197del* | De novo | EIEE17    |
| 67 | Feng H    | Arg209Gly  | De novo | NEDIM     |
| 68 | Feng H    | Ala227Val* | De novo | EIEE17    |
| 69 | Feng H    | Tyr321Cys* | De novo | EIEE17    |
| 70 | Feng H    | Phe275Ser* | De novo | EIEE17    |
| 71 | Feng H    | Leu199Pro* | De novo | EIEE17    |
| 72 | Feng H    | Asp270His* | De novo | EIEE17    |
| 73 | Feng H    | Gly40Arg*  | De novo | EIEE17    |
| 74 | Feng H    | Asp174Gly* | De novo | EIEE17    |
| 75 | Epi & Epi | Ile279Asp* | De novo | EIEE17    |
| 76 | Gerald    | His371_372del* | De novo | EIEE17    |
| 77 | Sakamoto S | Arg209Cys | Ar* (8)  | 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 | DD & MD   |
| 85 | Yang X     | c.724-8G > A | Gonadal | Mosaicism |
| 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 | NEDIM & 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.P231C)* | 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 | NEDIM     |
| 96 | Retterer K | c.724-8G > A | De novo | NEDIM     |
| 97 | Retterer K | c.724-8G > A | p.G203R  | 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. Extracocular movements were normal. They had spastic quadriplegia with hypotonia, 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 (II:2) was able to walk until the age of eight years, then she lost ambulation, whereas twin A (II: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 (II: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. 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. 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 up going bilaterally. He has hypotonia 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 an 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 1, 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 EEIE17 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...
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 (14, 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-pen variance 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.

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