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Correspondence

Novel *GNAL* mutation in an Indian patient with generalized dystonia and response to deep brain stimulation

Mutations in *GNAL* have been associated with cranio-cervical dystonia (DYT-GNAL) [1]. The dystonia most often progresses to involve other regions, particularly the face and laryngeal muscles and less commonly the trunk, arm and lower limbs. The clinical phenotype in *GNAL*-related dystonia appears to be similar to that caused by mutations in *THAP1* [2].

We are reporting a 53 year-old lady with progressive dystonia caused by a novel mutation (p.Cys429Tyr variant) in *GNAL* gene, which has not been described in the literature to the best of our knowledge.

A 53-year-old lady presented to us with a six-year history of involuntary turning of the neck. Family history was negative for any neurological disorder. She had no exposure to drugs or toxins and there was no history of encephalitis or head injury. Her cranial magnetic resonance imaging (MRI) was normal. On examination, she had left laterocollis with an elevation of left shoulder. She had no tremors and her "Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS)" score was twenty two (Laterocollis:2, duration:4 × 2 = 8, effect of sensory trick; 2, shoulder elevation: 2, range of motion: 4, and time: 4) at initial presentation. She was initially treated with tablets of trihexyphenidyl (2mg three times daily for 3 months), levodopa + carbidopa (100 + 25 mg four times daily for 3 months) and baclofen (10 mg daily for 2 months) with minimal response. Subsequently, she was injected with Onabotulinumtoxin type A (200 units) with good response. She continued receiving botulinum toxin injections for a year, and her cervical dystonia improved significantly, but her dystonia progressed to involve the trunk and legs (See video segment 1). She also had a mild degree of camptocormia.

Supplementary video related to this article can be found at https://doi.org/10.1016/j.parkreldis.2019.01.011.

Considering the progression in dystonia, custom targeted clinical exome sequencing (MedG CNLV2) was performed to identify genetic mutation explaining the clinical condition of the patient. DNA extracted from the blood sample was used to perform targeted gene capture using a custom capture kit. The libraries were sequenced to mean > 80-100X coverage on the Illumina sequencing platform. The sequences obtained were aligned to the human reference genome (GRCh37/hg19) and analyzed to identify variants relevant to the clinical indication.

On analysis, a rare heterozygous missense variation in exon 12 of the *GNAL* gene that results in the amino acid substitution of Tyrosine for Cysteine at codon 429 (chr18:11881043G > A; c.1286G > A; p.Cys429Tyr; NM_182978.3; NG_033866.1) was detected (Fig. 1). The missense variant was predicted to be damaging by *in silico* prediction tools (PolyPhen, LRT, SIFT and Mutation Taster 2). Further, the observed variant was also absent in ethnically matched control individuals [MedGenome database (n = 6028)] and in the population databases [1000 genome, ExAC or GnomAD]. The variant was present in the G-alpha domain of the protein and the reference codon was conserved across species. Mutations affecting the same domain have been previously reported. The observed missense variant was validated by 'Sanger sequencing' in the proband. We also tried to test the family members, but there were no siblings or living relatives to be contacted. She underwent bilateral Globus pallidus internus (GPi) deep brain stimulation (DBS) and at one-year follow up (See 2video segment 2), her dystonic posturing of neck (TWSTRS decreased from 22 to 7), legs and trunk had improved significantly (See video segment 2). Post operatively she did not require botulinum toxin injections.

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The first report identifying *GNAL* mutation included 28 dystonia patients from eight families who had predominantly craniocervical form of dystonia with onset of symptom typically in the neck [1]. The symptom onset usually occurs in adulthood, although pediatric onset has also been reported [3]. The majority of the affected patients have disease progression to other muscle groups, including the larynx, and in some cases it progresses to generalized disease as observed in our patient.

Another interesting feature in our patient was significant improvement in symptoms following GPi DBS. Ziegan and colleagues reported first *GNAL* mutation-positive dystonia patient who underwent bilateral GPi DBS with excellent response at 5-year follow-up [4]. Carecchio et al. reported a novel *GNAL* mutation causing asymmetric dystonic tremor and a jerky cervical phenotype in two cases from an Italian family responding well to GPi DBS [3]. Recently, Sarva et al. also published a study describing three dystonia patients with *GNAL* mutation and all had amelioration of severe cervical dystonia symptoms after DBS; although cranial (including speech) and limb dystonia did not improve [5]. Furthermore, in one patient neck dystonia improved, but left arm dystonia continued to progress and was significantly worse 8 years after DBS. In contrast, our patient had significant improvement in dystonic posturing of neck, legs and trunk.

To summarize, we found a new pathogenic mutation (p.Cys429Tyr variant) for DYT-GNAL in our patient. We also observed significant improvement of dystonia in her body regions (including the rarely affected truncal region) other than the neck by GPi deep brain stimulation.

The manuscript has been prepared according to the ethical norms of the institute and the journal. The patient consented to the publication of the videos and that this includes online publications.

Authors' Roles

1. Research project: A. Conception, B. Organization, C. Execution; 2. Statistical Analysis: A. Design, B. Execution, C. Review and Critique; 3. Manuscript: A. Writing of the first draft, B. Review and Critique

Sanjay Pandey (SP): 1A, 1B, 2A, 2B, 3A, 3B

Charulata Savant Sankhla: 1A, 1B, 2A, 2B, 3A, 3B

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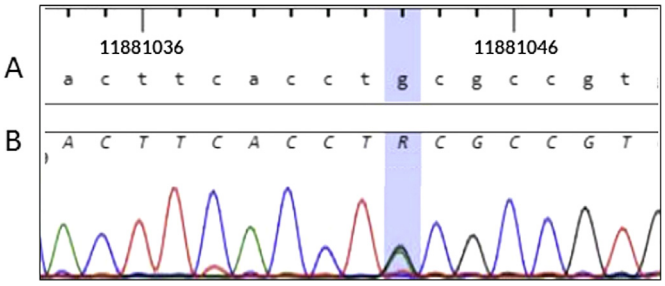

Fig. 1. Sequence chromatogram and alignment of the DNA reference sequence (A). The DNA sequence of the proband (B) shows heterozygous variation in exon 12 of *GNAL* gene (chr18:11881043G > A; c.1286G > A; p.Cys429Tyr; NM_182978.3; NG_033866.1). The protein isoform is NP_892023.1.

Vedam L Ramprasad: 1A, 2B, 3A, 3B
Thenral S Geetha: 1A, 2B, 3A, 3B

Roles of the authors

Sanjay Pandey and Charulata Savant Sankhla contributed in writing the first draft and revision. Vedam L Ramprasad and Thenral S Geetha contributed in revision of the first draft.

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Sanjay Pandey
Department of Neurology, Academic Block, Room No 503, Department of Neurology, Govind Ballabh Pant Postgraduate Institute of Medical Education and Research, New Delhi, 110 002, India

Charulata Savant Sankhla*
Department of Neurology, P D Hinduja National Hospital, Mumbai, Maharashtra, India
E-mail address: charusankhla@gmail.com.

Vedam L. Ramprasad, Thenral S. Geetha
MedGenome Labs, Bangalore, India

* Corresponding author. Department of Neurology, P D Hinduja National Hospital, Mumbai, Maharashtra, India.