Parkinsonism and Related Disorders 23 (2016) 66–71

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

# Novel GNAL mutation with intra-familial clinical heterogeneity: Expanding the phenotype

Miryam Carecchio [a, b], Celeste Panteghini [a], Chiara Reale [a], Chiara Barzaghi [a], Valentina Monti [a], Luigi Romito [c], Francesco Sasanelli [d], Barbara Garavaglia [a, *]

[a] Molecular Neurogenetics Unit, IRCCS Neurological Institute C. Besta, Via L. Temolo 4, 20126 Milan, Italy
[b] Department of Pediatric Neurology, IRCCS Neurological Institute C. Besta, Via Celoria 11, 20133 Milan, Italy
[c] Department of Neurology, IRCCS Neurological Institute C. Besta, Via Celoria 11, 20133 Milan, Italy
[d] Department of Neurology, AO Ospedale di Circolo di Melegnano, Strada Pandina 1, 20070 Vizzolo Predabissi (MI), Italy

ARTICLE INFO

*Article history:*
Received 24 August 2015
Received in revised form
10 November 2015
Accepted 15 December 2015

*Keywords:*
GNAL
Dystonia
Tremor
Phenotype

ABSTRACT

*Introduction:* Mutations in *GNAL* have been associated with adult-onset cranio-cervical dystonia, but a limited number of cases have been reported so far and the clinical spectrum associated with this gene still needs to be fully characterized.
*Methods:* We identified an Italian family with adult-onset, dominantly-inherited dystonia whose members presented with different combinations of dystonia affecting the cervical, oro-mandibular and laryngeal regions associated with prominent tremor in some cases. Pure asymmetric upper limb dystonic tremor was present in one of the members and jerky cervical dystonia was also observed. A dedicate dystonia gene panel (Illumina) was used to screen for dystonia-associated genes and Sanger sequencing was performed to confirm results obtained and to perform segregation analysis.
*Results:* A novel single-base mutation in *GNAL* exon 9 (c.628G>A; p.Asp210Asn) leading to an amino-acidic substitution was identified and confirmed by Sanger sequencing. *In silico* prediction programmes as well as segregation analysis confirmed its pathogenicity. Clinically, no generalization of dystonia was observed after onset and DBS lead to an excellent motor outcome in two cases.
*Conclusion:* We report a novel *GNAL* mutation and expand the clinical spectrum associated with mutations in this gene to comprise pure asymmetric dystonic tremor and a jerky cervical phenotype partially mimicking DYT11 positive cases.



## 1. Introduction

In 2013, mutations in *GNAL* (DYT25) were identified in eight unrelated kindred with familial dystonia mainly affecting the cervical and cranial regions, with a tendency to spread to contiguous sites but with a low rate of generalization (11%) [1]. Subsequently, other studies in patients with familial and sporadic cervical dystonia individuated 14 additional pathogenic mutations, which are dominantly-inherited and show reduced penetrance [2–6]. The frequency of *GNAL* mutations ranges from 0.007% in a cohort of sporadic patients with adult-onset cervical dystonia to 15% in selected families with multiplex dystonia [1]. Moreover, segregation analysis of some *GNAL* mutations was not performed in a proportion of reported cases, raising doubts about the actual pathogenicity of some of these variants [7].

*GNAL* encodes guanine nucleotide-binding protein G(olf), subunit alpha [Gα(olf)], first identified as a G protein (guanine nucleotide-binding protein) that mediates odorant signaling in the olfactory epithelium. Gα(olf) couples dopamine type 1 receptors (D1Rs) of the direct pathway and adenosine A2A receptors (A2ARs) of the indirect pathway to the activation of adenylate cyclase type 5 and plays a key role in signal transduction within the olfactory neuroepithelium and basal ganglia, being predominantly expressed in striatal medium spiny neurons [1].

To date, adult-onset cervical dystonia, with or without superimposed tremor, seems to be the most common clinical phenotype associated with *GNAL* mutations. However, the full clinical spectrum of *GNAL* mutations is still largely to be explored as a limited number of cases have been published so far. Here we report a novel *GNAL* mutation in an Italian kindred showing phenotypic

* Corresponding author.
*E-mail address:* garavaglia@istituto-besta.it (B. Garavaglia).

http://dx.doi.org/10.1016/j.parkreldis.2015.12.012
1353-8020/

variability, including pure asymmetric upper limb dystonic tremor and a good response to DBS stimulation for cervical dystonia.

## 2. Materials and methods

### 2.1. Family description

The family reported herein is of Southern Italian origin and no consanguinity was documented (Fig. 1).

The index case (III:6) is a 59-year old male with cervical dystonia who first noticed a head turning to the left at age 36. Over the following years, a superimposed head tremor also appeared. Both cervical dystonia and tremor reached their peak within 4–5 years from the onset and then remained stable. Botulinum toxin injections were only partially beneficial and neither tetrabenazine nor levodopa were effective. At age 55 he underwent bilateral stereotactic Deep Brain Stimulation (DBS) targeting at the posteroventrolateral portion of the GPi using quadripolar electrodes (Medtronic, Minneapolis, MN, USA). Intraoperative macrostimulation and postoperative TC imaging verified correct placement of the electrode. DBS leads were connected to a battery-operated programmable pulse generator (Activa PC, Medtronic). Stimulation parameters at last follow-up were: Right GPi = 2.0 V, 90 μs, 130 Hz, - 8 + 9 (= - 0 + 1); Left GPi = 2.5 V, 90 μs, 130 Hz, - 1 case +. A substantial clinical improvement rated in 80–90% was referred by the patient. Burke-Fahn-Marsden Dystonia Scale (BFMDS) improved from 16/120 to 5/120 after surgery (67% improvement). Examination at age 59 (23 years after the onset) showed a mild cervical tilt to the left with some residual degrees of retrocollis and no head tremor at rest. A mild tremor was only detectable on extreme lateral rotation of the head. There was some dystonic posturing in the left arm when keeping it outstretched and arm swings were reduced on same side on walking (Video 1).

Supplementary video related to this article can be found at http://dx.doi.org/10.1016/j.parkreldis.2015.12.012.

The patient's younger sister (III:4) presented with isolated head tremor at age 42, followed by an abnormal head posture (left torticollis and retrocollis) after some years and by laryngeal dystonia (tremulous high-pitched voice). On examination at age 62, she showed left jerky torticollis with superimposed head tremor and a limited range of movements to the right along with tremor in the upper limbs, which was mainly visible when keeping arms flexed at the elbow; in this position, some dystonic posturing at the wrist junction was also detectable (BFMDS 12/120). The patient described the tremor as fluctuating and strictly asymmetrical, being more marked on the right side, although this feature was not visible when we examined her; the tremor intermittently impaired hand-writing. She reported she could ameliorate her head position by touching her chin with the hand. This patient was initially diagnosed with myoclonus dystonia due to DYT11 mutation, as she was found to carry a splicing variant (IVS3-3T > C) initially reported as a pathogenic mutation [8] but later classified as a polymorphism (rs17166384) with a minor allele frequency of 24% in the African population [9].

At age 62 the patient underwent a bilateral stereotactic DBS targeting at the posteroventrolateral portion of the GPi using quadripolar electrodes (Medtronic, Minneapolis, MN, USA). Intraoperative macrostimulation and postoperative TC imaging verified correct placement of the electrode. DBS leads were connected to two battery-operated programmable pulse generators (Activa SC, Medtronic). For both sides, a interleaving deep brain stimulation setting was programmed, according to the following parameters: Right GPi # 1 = 2.15 V, 60 μs, 125 Hz, - 1 case +; Right GPi # 2 = 2.20 V, 90 μs, 125 Hz, - 2 case +; Left GPi # 1 = 1.25 V, 60 μs, 125 Hz, - 0 case +; Left GPi # 2 = 2.00 V, 60 μs, 125 Hz, - 1 case +. After the implant, a rapid improvement (in two weeks) of cervical and laryngeal dystonia was obtained (Video 2). No parkinsonian or akinetic signs were present on examination.

Supplementary video related to this article can be found at http://dx.doi.org/10.1016/j.parkreldis.2015.12.012.

Subject III:5 is a 60-year-old man affected by Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) since age 48 and treated with Ig ev administration and steroids with improvement of motor weakness in the lower limbs. At age 43, he had a traumatic intracranial bleeding of the head of the left caudate nucleus and the anterior arm of internal capsula (24 × 14 mm on CT scan), which

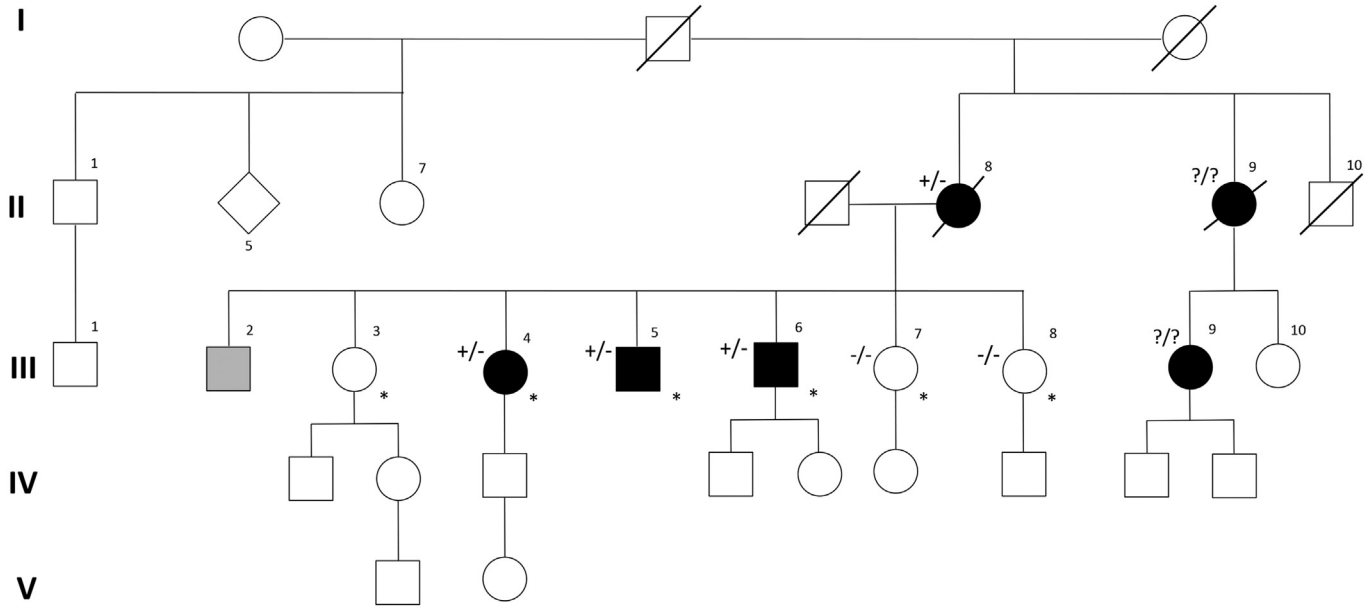


**Fig. 1.** Family pedigree. Filled symbols indicate affected individuals. Gray symbols with question mark indicate possibly affected individuals. Sequencing findings for the *GNAL* c.628G>A (p.Asp210Asn) mutation are indicated above and to the left of each symbol. Individuals marked with an asterisk were evaluated clinically.