Movement Disorders
CLINICAL PRACTICE

BRIEF REPORT

Dystonic Tremor as Main Clinical Manifestation of SCA21

Vidal Yahya, MD,[1,2] Claudio Baiata, MD,[3,4] Edoardo Monfrini, MD, PhD,[1,2] Sandrine Correia, RN,[3] Gloria Brescia, MSc, PhD,[5] Alessio Di Fonzo, MD, PhD,[1] and Elena Moro, MD, PhD[3,*]

Abstract: Background: Spinocerebellar ataxia type 21 (SCA21) is a rare inherited neurological disorder characterized by motor, cognitive, and behavioral disturbances, caused by autosomal dominant *TMEM240* variants.

Objectives: To identify the genetic cause of a dystonic tremor with autosomal dominant inheritance.

Methods: Six subjects of a multi-generational French family affected by tremor and dystonia were studied. Each patient underwent a comprehensive clinical assessment and a whole-exome sequencing analysis.

Results: All six subjects presented with early-onset prominent hand dystonic tremor and multifocal/generalized dystonia, secondarily developing mild cerebellar ataxia. The younger generation showed more pronounced cognitive and behavioral impairment. The known pathogenic *TMEM240* c.509C>T (p.P170L) variant was found in heterozygosis in all subjects.

Conclusions: Dystonic tremor can represent the core clinical feature of SCA21, even in absence of overt cerebellar ataxia. Therefore, *TMEM240* pathogenic variants should be considered disease-causing in subjects displaying dystonic tremor, variably associated with ataxia, parkinsonism, neurodevelopmental disorders, and cognitive impairment.

Spinocerebellar ataxia 21 (SCA21) is a rare early-onset, slowly progressive, autosomal dominant cerebellar ataxia, first described in a large French family in 2001.[1] So far, 63 cases and 24 families have been reported.[1–12]

Whole-exome sequencing (WES) and linkage analysis have allowed the identification of pathogenic variants in *TMEM240* as the cause of SCA21.[5] Seven pathogenic variants, with two being recurrent (p.P170L and p.G66R), have been reported to date.[8,9] *TMEM240* is expressed in mammal brains and might contribute to organize the cerebellar network.[13–16] Tmem240, the protein encoded by *TMEM240*, localizes at intracellular membranes, and its mutant forms are associated with autophagic-lysosomal degradation impairment in vitro.[14–17]

Besides cerebellar ataxia, cognitive impairment represents an important feature of SCA21. Additional rarely reported neurological features include tremor, bradykinesia, rigidity, pyramidal signs, myoclonus, dystonia, and oculomotor dysfunction. Neurodevelopmental abnormalities, psychiatric symptoms, and epilepsy have been reported as well.[2,3,8–11,18]

Here we report a multigenerational French family with six affected members presenting dystonic tremor as main clinical manifestation of SCA21.

Methods

Six members of a multigenerational family originating from North-East France have been evaluated at the Movement Disorders Center of the Grenoble Alpes University Hospital (Grenoble, France). Detailed medical histories were obtained.

[1]*Neurology Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy;* [2]*Dino Ferrari Center, Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy;* [3]*Division of Neurology, CHU of Grenoble, Grenoble Institute of Neurosciences, Grenoble Alpes University, Grenoble, France;* [4]*Neurology Unit, Foundation IRCCS San Gerardo dei Tintori, University of Milano-Bicocca, Monza, Italy;* [5]*Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy*

***Correspondence to:** Dr. Elena Moro, Division of Neurology, CHU of Grenoble, Grenoble Institute of Neurosciences, Grenoble Alpes University, Grenoble, France; E-mail: emoro@chu-grenoble.fr

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Vidal Yahya and Claudio Baiata contributed equally to this manuscript (co-first authorship).

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The affected relatives underwent a complete neurological exam and, when appropriate, neuropsychological tests. Three subjects underwent 3 T brain MRI, one ^{123}I-Ioflupane SPECT, and one brain CT.

After signed informed consent for genetic testing, peripheral blood was drawn by all evaluated relatives and DNA was extracted with standard methods. All underwent WES with the SeqCap EZ/Vchrom target enrichment kit (NimbleGen) on NextSeq500 (Illumina). Reads alignment and variant calling/annotation were performed using bwa mem and GATK. The candidate variant was validated with Sanger sequencing. The proband underwent genetic testing also for fragile X-associated tremor-ataxia syndrome (FXTAS).

Video 1. Dystonic tremor in subjects II-2, III-2, III-3.
Video content can be viewed at https://onlinelibrary.wiley.com/doi/10.1002/mdc3.14220

Results

The proband (subject II-2, Fig. 1A) is a 59-year-old woman affected by tremor and dystonia (Video 1). She came to our attention at the age of 54. Birth and psychomotor development were reported as normal. At age 5, she developed slowly progressive bilateral upper limb action tremor. A brain CT performed at the age of 37 years was normal. At that time, she was diagnosed with essential tremor (ET). Her tremor was partially responsive to ethanol and propranolol, whereas primidone resulted ineffective. At our first neurological exam (54 years), she displayed mild head tremor (no-no type) and moderate irregular postural and kinetic tremor with dystonic postures of both hands and right foot, as well as writer's cramp. Furthermore, mild ataxia of upper and lower limbs, clumsiness, and appendicular bradykinesia were observed. Rotigotine-responsive restless legs syndrome was also reported. Neuropsychological tests evidenced mild executive dysfunction and working memory impairment (MoCA score 29/30). Brain MRI displayed mild cerebellar vermis atrophy (Fig. 1B,C).

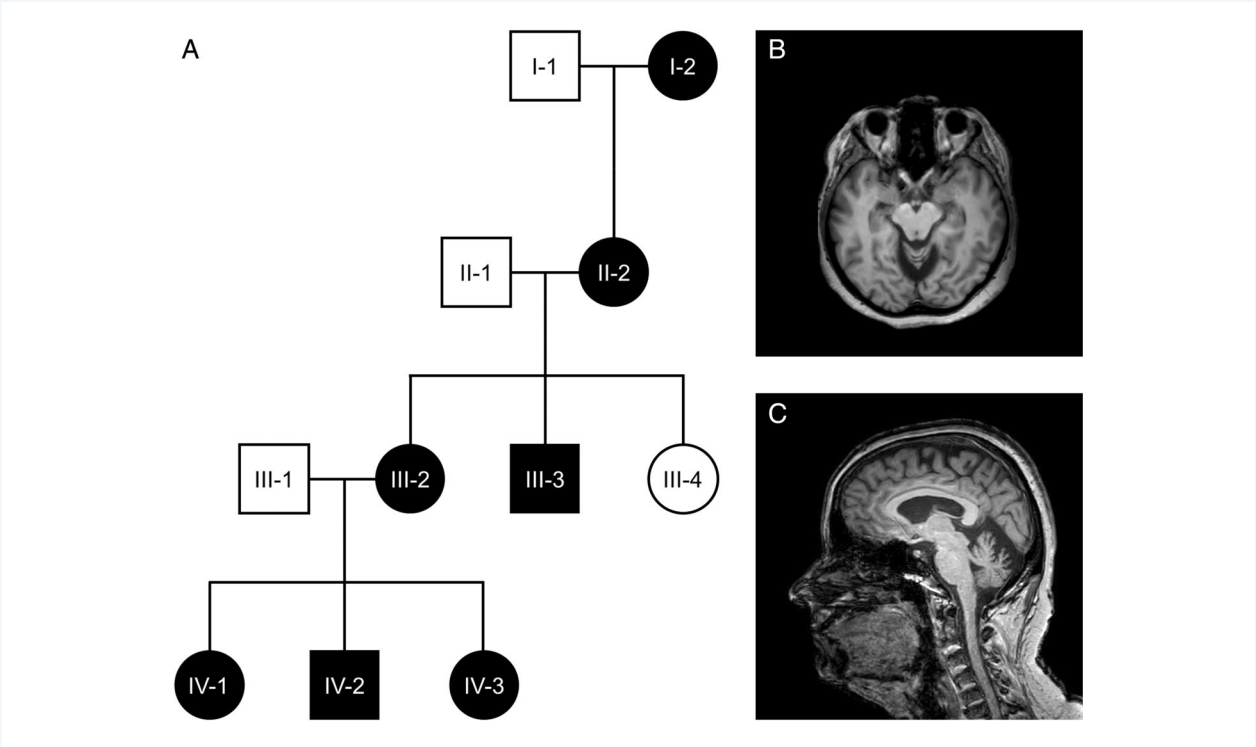

Figure 1. (**A**) Family pedigree. Black filling denotes affected individuals. (**B** and **C**) T1-weighted axial (**B**) and sagittal (**C**) brain MRI slices highlighting cerebellar vermis atrophy in subject II-2.

TABLE 1 *Clinical and instrumental findings of the six subjects*

Subject		II-2	III-2	III-3	IV-1	IV-2	IV-3
Sex		F	F	M	F	M	F
Age (years)	Onset	5	3	3	3	3	3
	Last control	59	34	30	12	7	7
Tremor (R/L), non resting	Head–Neck	+	−	+	−	−	−
	Upper limbs	+/+	+/+	+/+	+/+	+/+	+/+
	Lower limbs	+/−	+/+	−/−	−/−	−/−	−/−
Dystonic posture (R/L)	Neck	−	+	+	−	−	−
	Upper limbs	+/+	+/+	+/+	+/+	+/+	+/+
	Writer's cramp	+	+	+	+	+	+
	Lower limbs	+/−	−/−	+/+	−/−	+/−	−/−
Ataxic features	Limb ataxia	+	+	+	−	−	−
	Gait ataxia	+	+	−	−	−	+
	Dysarthria	−	−	+	−	−	+
	Dysphagia	−	+	+	−	−	+
	Oculomotor abnormality	−	Pursuit impairment	Slow saccades	Strabismus	−	Strabismus
	Maximal SARA	6	7	11	4	4	6
Parkinsonian features	Bradykinesia	+	+	+	−	−	−
	Resting tremor	−	+	−	−	−	−
Cognitive-behavioral features	PMD	−	−	+	−	+	−
	ASD	−	−	+	−	+	−
	Sleep disorder	RLS	−	Enuresis	Insomnia	OSAS, enuresis	−
	Executive dysfunction	+	+	−	−	−	−
	Attention deficit	+	+	+	ADHD	−	ADHD
	Language impairment	−	−	+	+	+	+
	MoCA score	29/30	29/30	NA	NA	NA	NA
Neuroimaging	Brain MRI	Cerebellar vermis atrophy	Normal	Ventricle enlargement	NA	NA	NA
	DAT-SPECT	NA	Normal	NA	NA	NA	NA
Treatment response	Good	Propranolol, ethanol, rotigotine	Propranolol, ethanol, topiramate	Botulinum toxin, trihexyphenidyl (not tolerated)	Melatonin	NA	NA
	Poor	Primidone	Levodopa, rotigotine, trihexyphenidyl, botulinum toxin	NA	NA	NA	NA

Clinical and instrumental findings of the six subjects.
Abbreviations: ASD, autism spectrum disorder; DAT-SPECT, dopamine transporter single photon emission computed tomography; F, female; L, left; M, male; MoCA, Montreal cognitive assessment; NA, non-available; OSAS, obstructive sleep apnea syndrome; PMD, psychomotor delay; R, right; RLS, restless legs syndrome; SARA, scale for the assessment and rating of ataxia.

The mother of the proband (subject I-2, Fig. 1A), who deceased at the age of 88 years, could not be evaluated. Yet, she apparently presented with tremor since her youth, and lately developed cognitive decline and gait impairment needing support to walk.

The proband had three children (III-2, III-3, III-4).

Subject III-2 is a 34-year-old female whose disease onset was at 3-year age with postural and kinetic tremor of upper limbs, which progressively worsened to involve lower limbs at the age of 8. EMG revealed a 6 Hz tremor. At 17 years, she was diagnosed with ET and propranolol was introduced with benefit. At 28 years, she came to our attention displaying postural and kinetic hand tremor alongside with dystonic posture of fingers, neck (right laterocollis and left torticollis), and writer's cramp. Intermittent resting tremor and mild appendicular bradykinesia were observed as well, alongside with slow and disrupted ocular pursuit, upper limbs ataxia, tandem gait inability, and fluid dysphagia. Trihexyphenidyl, rotigotine, levodopa, and botulinum toxin were ineffective whereas tremor improved with ethanol, topiramate, and propranolol. Interestingly, she reported a remarkable tremor improvement during her three pregnancies, while assuming no treatment. Neuropsychological tests revealed mild executive dysfunction and attention deficit (MoCA score 29/30). Brain MRI and ^{123}I-Ioflupane SPECT performed at age of 28 resulted normal.

Subject III-3 is a 30-year-old male. At the age of 3, he developed action tremor and was diagnosed with mild autism spectrum disorder (ASD) and speech developmental delay. At 25 years, he presented with mild postural and kinetic tremor of upper limbs, mild generalized dystonia affecting neck, trunk, and upper and lower limbs, and writer's cramp. Furthermore, upper limbs clumsiness and dysmetria, mild dysarthria, fluid dysphagia, and slow saccades were noted. Tandem gait was normal. Trihexyphenidyl was poorly tolerated while botulin toxin was effective on lower limbs' dystonia. Neuropsychological tests showed mild attentional deficit and verbal fluency impairment with an intact global functioning. Brain MRI performed at age of 25 showed mild lateral ventricles enlargement.

Subjects IV-1, IV-2, and IV-3, children of III-2, at the age of 3, developed bilateral postural and kinetic hand tremor with dystonic postures and writer's cramp alongside with a mild cerebellar involvement ranging from postural instability to dysarthria, dysphagia, and gait ataxia. They all presented language impairment requiring special education services. Subjects IV-1 and IV-3 were diagnosed with attention deficit hyperactivity disorder (ADHD) while subject IV-2 presented psychomotor delay (PMD) and ASD.

Further clinical and instrumental data are summarized in Table 1.

All evaluated patients underwent WES: the recurrent *TMEM240* variant c.509C > T, p.P170L (transcript NM_001114748.2) was identified in heterozygous state in all affected relatives and was classified pathogenic according to ACMG criteria PP5, PM2, and PP1. No other candidate variants in genes associated with dystonia were identified. The proband (subject II-2) was also tested for FXTAS, resulting negative. Further data on genetic analysis are available in Supplemental Material; Data S1.

Discussion

We have described a multi-generational SCA21 family with six members affected by childhood-onset dystonic tremor presenting as main clinical motor feature.

SCAs are a heterogenous group of hereditary neurodegenerative disorders affecting predominantly the cerebellum. However, neurodegeneration in SCAs may involve the whole central nervous system, consistently with their heterogeneous clinical features besides ataxia (eg, spasticity, parkinsonism, dystonia, chorea, tremor, cognitive impairment, sleep disorders).[19] Nevertheless, in SCAs with no radiological and pathological evidence of degeneration of brain structures other than the cerebellum, the origin of additional motor symptoms remains unclear, as in SCA12 and SCA14 which present predominantly with action tremor and dystonia, respectively.[20–22] Some studies suggest that cerebellar dysfunction itself may contribute to some manifestations, particularly tremor, dystonia, and cognitive dysfunction.[23–26] In this context, the wide phenotypic spectrum of SCA21 could be attributable to the diffuse expression of *TMEM240* in the brain as well as to the deleterious impact of these variants on the developing cerebellar network.

Dystonic tremor was the predominant motor feature at onset in all affected relatives. In particular, subjects II-2 and III-2 presented a bilateral upper limb dystonic tremor that was responsive to ethanol and propranolol. Their tremor was initially framed in an ET diagnosis; however, the finding of associated dystonic postures converted this diagnosis into dystonic tremor.[27] Similarly, another case with SCA21 presenting with ET and insidiously developing dystonic postures and mild ataxia had been reported by Camargo et al, 2021.[11] Thus, clinicians should be aware of this possible syndromic association and test for SCA21 patients with autosomal dominant history of action tremor and tremulous dystonic symptoms, even in absence of clear cerebellar ataxia.

Parkinsonism is reported as a typical manifestation of SCA2, SCA3, and SCA17, and extrapyramidal features have been reported as additional features of many other SCAs, in some cases with documented nigrostriatal degeneration and good response to dopaminergic therapy.[28,29] At the time of the study, the three eldest subjects presented bradykinesia and one of them (III-2) had rest tremor. Their poor response to levodopa and dopamine-agonists and the negative ^{123}I-Ioflupane SPECT in subject III-2 are compatible with a striatal impairment in absence of nigrostriatal degeneration, consistently with other observations of parkinsonism in SCA21 patients.[2,8] This hypothesis is supported by the robust expression of Tmem240 in caudate nuclei and putamina and by the relevant role of this protein in synaptic organization.[14,15] However, further molecular studies are needed to clarify the link between such motor manifestations and *TMEM240* dysfunction.

Intellectual disability and cognitive impairment represent frequent yet not obligatory features of SCA21, with an estimated overall frequency of 83%.[8] Consistently with the literature, the two elder patients (II-2 and III-2) displayed a mild cognitive decline characterized by executive dysfunction and working memory impairment. However, the four younger patients displayed more relevant cognitive disturbances since early infancy (ie, language impairment and

attention deficit). This "anticipation phenomenon" has been previously described,[1,9] however the little number of patients reported with SCA21 does not allow any speculation on possible pathogenetic mechanisms. Subjects IV-1 and IV-3 were diagnosed with ADHD and two male subjects (III-3 and IV-2) were diagnosed with PMD and ASD. While language impairment and ASD had already been associated with *TMEM240*-related disease,[3,5,9,12] ADHD may represent a novel clinical feature of this rare disease. A variant form of Tmem240, a transmembrane protein involved in synaptic function,[13,15] may play a key role in the genesis neurodevelopmental disorders (eg, ASD and ADHD) in these patients.[30,31] These cognitive disturbances may be framed as features of cerebellar cognitive affective syndrome (CCAS) or as signs of a more diffuse disruption of brain networks.[8,30,32–35]

In conclusion, this work strengthens the association of pathogenic *TMEM240* variants with dystonic tremor and highlights the importance of systematic re-evaluation of patients. Indeed, subjects previously diagnosed with ET, as in some of the cases reported here, later displayed other atypical symptoms such as dystonia, ataxia, or cognitive deficits. The remarkable phenotypic heterogeneity of SCA21, even among patients carrying the same genetic variant and among members of the same family, should stimulate the search of additional environmental and genetic factors that play a role in modulating the expression of the disease. Finally, we suggest to screen *TMEM240* in patients whose predominant clinical feature is dystonic tremor, variably combined with a multitude of additional neurologic manifestations including ataxia, parkinsonism, neurodevelopmental and cognitive disorders.[3,4,10,11]

Author Roles

(1) Research Project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript Preparation: A. Writing of the First Draft, B. Review and Critique.

V.Y.: 1C, 3A
C.B.: 1C, 3A
E.M.: 1A, 1C, 3B
S.C.: 2B, 2C
G.B: 1C
A.D.F.: 1A, 1C, 3B
E.M.: 1A, 1B, 1C, 3B

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Disclosures

Ethical Compliance Statement: The Direction for Clinical Research of Grenoble Alpes University Hospital approved this study. According to the policy of CHU Grenoble, all subjects signed an official form to consent for publication of their data. Written and informed consent was obtained by all patients prior to participation. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions. ■

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Supporting Information

Supporting information may be found in the online version of this article.

Data S1. Supplemental Material: Additional data on genetic analysis.