Movement Disorders
CLINICAL PRACTICE
LETTERS: GENOTYPE AND PHENOTYPE

Focal Head Tremor and *ZNF142*-Associated Neurodevelopmental Disorder

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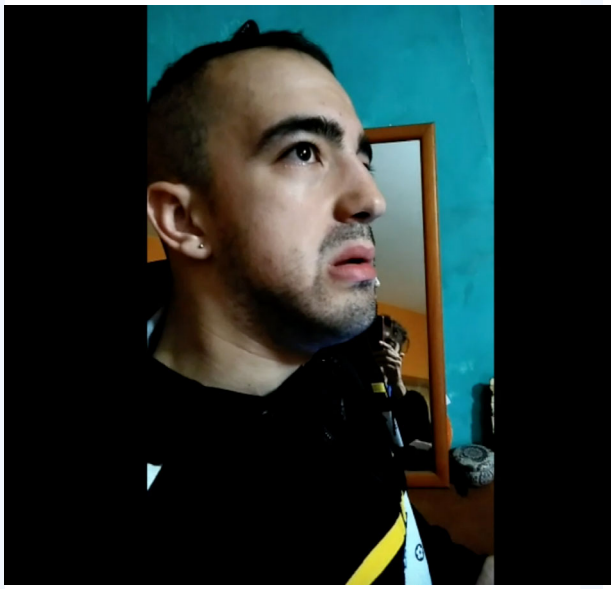
The zinc-finger protein (ZNF) superfamily is one of the largest groups of mammalian transcription factors and various disorders have been linked to disease-causing variants in *ZNF* genes. Recently, biallelic variants of *ZNF142* have been associated to a syndromic NEuroDevelopmental disorder with Impaired Speech and Hyperkinetic Movements (NEDISHM; MIM: 618425).

We here report on a patient of Italian origin with a homozygous single-nucleotide deletion (NM_001105537.2: c.3346del; p.Glu1116Asnfs⋆4) as a results of a 8.5 kb maternal uniparental disomy, which included *ZNF142*, and who has developed a focal tremor of the head as the only movement disorder.

This patient, who is currently 23 years old, has been previously included in a published series[1] but he did not have any movement disorders at the time of that report. He was born at term after an uncomplicated pregnancy. Motor developmental milestones were slightly delayed (age at sitting: 10 months; age at walking: 18 months) whereas the age at first word was of 3 years. Currently, he has a reduced vocabulary, but still produces a wide range of small phrases that can be at times difficult to understand. He is not able to write or read and has no comprehension of numbers. He has a moderate intellectual disability (WAIS Wechsler Adult Scale of Intelligence, IV; Total-IQ 36) and moderate-to-severe behavioral problems with social disorder, generalized anxiety disorder, and occasional aggressive behaviors towards his parents. He has never been exposed to dopamine-blocking agents or any other drugs potentially causing movement disorders. In the last year, he was noted to have tremor of the head that was particularly evident during episode of stress (Video 1A) and could be reduced by placing one hand over the left, lateral part of the neck. At examination, he did not have any sign of overt dystonia in the cervical region or elsewhere; a slight tremor of the neck in the primary position was observed soon after he got angry and that abolished when he fully turned the head to the right (Video 1B). He was managed with botulinum toxin injections (100 Units of Abo-Botulinum toxin into each



Video 1. (A) Slightly irregular "no-no" type of tremor; (B) slight head tremor in the primary position which abolished when the patient turns his head fully to the right, without signs of overt dystonia. It might be argued that a (dubious) head rotation is visible in the primary position at beginning of (B); however we note that (1) this is an inconstant feature as it is not present throughout the video, especially after the patient rotates his head to return in the primary position; (2) there are no patterned rotational movements of the head; and (3) there is no range-of-motion restriction on either side when turning the head. As such the, admittedly mild, and inconstant rotation of the head could be a compensatory habit to reduce the tremor. During (B), the patient shows the sensory trick that he uses to abolish the tremor and it is also possible to appreciate also the mild dysmorphic feature of this patient such as hypertelorism/wide nasal bridge and tele canthus.
Video content can be viewed at https://onlinelibrary.wiley.com/doi/10.1002/mdc3.13896

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Splenius Capitis), which was reported to be very beneficial by both the patient and his parents.

We have here reported a case with a rare syndromic neurodevelopment disorder due to biallelic *ZNF142* variants who, as part of the progression of his condition, has developed an isolated tremor of the head as the only movement disorder. His tremor has some features that would be in keeping with a dystonic type of tremor such as the presence of sensory trick and of a null point. However, according to the 2018 tremor classification, this type of tremor could not be labeled dystonic in the absence of overt dystonia and would therefore fall under the rubric of focal tremor of the head.[2,3] The current observation adds to previous claims arguing that most focal tremor of the head might be dystonic in nature.[4–6] Longitudinal observation of this and similar cases will show if these features (eg, sensory trick and null-points) might predict the development of overt dystonia.

Movement disorders have been reported in 36–56% in individual reports,[1,7] but they seem overall to account for a lower percentage of patients with biallelic variants of *ZNF142* (eg, ~25%; Table S1).[1,7–10] Movement disorders most commonly encompass tremor, ataxia, and dystonia, but also paroxysmal movement disorders akin to paroxysmal exercise-induced dystonia and episodic ataxia (Table S1). Clear genotype–phenotype correlations have not been established yet because, apart from few cases carrying missense variants and having a milder phenotype, most reported patients carry truncating variants (Table S1).[1,7–10] Moreover, in the absence of experimental information about the function and localization of *ZNF142*, it is difficult to speculate on exact genotype–phenotype correlations.

Given that information about patients with *ZNF142* variants are exceedingly scarce, it is important to collect new patients and to follow-up previously identified cases to define the phenotypic spectrum and natural history of the disorder.

Author Roles

(1) Data collection; (2) Manuscript Preparation: A. Writing of the first draft, B. Review and Critique.

R.E.: 1, 2A, 2B
C.S.: 1, 2B
M.R.: 2B
C.G.: 2B
P.B.: 2B

Disclosures

Ethical Compliance Statement: Institutional review board was not required for this work. Written informed consent was obtained from the patient's parent for the publication of his clinical data and videos. 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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Supporting Information

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

Table S1. Review of the *ZNF142* variants and of the movement disorders reported in all published cases.