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Case Report

TENM4 gene mutation in a case of unilateral essential tremor

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ABSTRACT

Essential tremor (ET) is a prevalent hyperkinetic movement disorder of clinical practice. The exact aetiopathogenesis of ET is unknown. Genetics has shown a proven role in approximately 50% cases of ET. Different loci of genes are associated with ET, but wide-scale validation into generalized population is lacking. This is primarily due to biodiversity in genetic milieu in different population, environmental factors as well as detection of newer mutations. In this case we described a 19 year old male presenting with progressive hand tremors without familial history and tried to explore genetics for aiding the diagnosis.

1. Introduction

Essential tremor (ET) is a globally prevalent hyperkinetic movement disorder with unknown aetiology. The prevalence of ET is 1% which increases to 5% with advancing age> 65 years.[1] The spectrum of ET has expanded to non-motor features (REM-sleep behaviour disorder, cognitive decline, sensory dysfunction, dysautonomia, depression).

The most important risk factor for ET lies in positive family history and old-age. The usual mode of inheritance pattern is autosomal dominant, however complex modes of inheritance are also observed. The role of genetics in ET has been demonstrated from detection of newer genetic variants from different family cluster, studies in twins, and the emerging naive variants derived from candidate gene association studies(CGASs) and genome wide association studies(GWASs).[2] Scattered studies on exome sequencing have reported association of certain genes with familial ET (ETM, FUS, HTRA2, TENM4, LINGO1, SORT1, ANO3, SCN11A, NOTCH2NLC, NOS3, KCNS2, HAPLN4, USP46, CACNA1G, SLIT3, CCDC183, MMP10, and GPR151), but it was observed in only singular families implicating private polymorphisms.[3] Transcriptomic studies and imaging studies in ET have emphasised the concept of cerebellar pukinjopathy-related genetics.[4]

2. Case Description

The 19-year-old-man born of non-consanguineous marriage presented with insidious-onset tremulousness of right hand for 5 years. Initial shakiness while holding pen during writing gradually progressed to affect activities of daily living. Emotional stress and anxiety increased the tremulousness, while it subsided with sleep. There was no complain of limb weakness, posturing, slowness, pain, numbness, difficulty in walking/speaking/swallowing/hearing or vision. There was no history of headache, convulsion, memory loss, cognitive decline or similar illness in his family. There is no history of head injury, thyroid disorder or any significant drug history or substance abuse. He is a strict vegan, without history of addiction or high-risk behavior. His bowel and micturition habits were regular. His general examination was unremarkable. Nervous system examination was normal except for presence of coarse postural tremor in

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right hand of predominant 3-6 Hz of greatest amplitude at wrist joint involving flexion-extension movements with mild rest tremors, without intentional component. (Figure 1) There was no evidence of tremor elsewhere in the body. There was no evidence of dystonia, bradykinesia, rigidity or ataxia. Other system examination were normal.

His blood investigations showed normal haemogram including peripheral blood picture, normal renal, liver, thyroid and parathyroid functions with normal electrolytes and blood glucose levels. Kayser Fleischer ring was absent along with negative screening for Wilson's disease. His serological tests were negative for Hepatitis-B, Hepatitis-C and HIV-1,2. Magnetic resonance imaging(MRI) of brain was non-significant except for presence of mega cisterna magna. Patient improved with propranolol therapy (40 mg sustained release twice daily dosing) at 2 months.(Figure 1) Genetic exome sequencing was performed which detected heterozygous missense variant in TENM4 gene in exon 19[NM_001098816.2c.2689C>T;p.Arg897Cys].

3. Discussion

This patient presented with progressive unilateral isolated postural tremor of right hand and clinically labelled as early-life onset essential tremor and worked-up for treatable etiologies. A differential of young-onset Parkinson's disease was considered in view of asymmetric hand but other components (prominent rest/re-emergent tremor, bradykinesia, rigidity or hypomimia) were absent. Structural and metabolic causes were negative. In this case, genetic testing aided the diagnosis of TENM4 gene related ET. Tremor can be unilateral or markedly asymmetric in 5% cases of ET.[5] The diagnosis of ET can be compared with dystonic tremor or enhanced physiological tremor. A vast heterogeneity in clinical spectrum, lack of stringent diagnostic criteria and non-availability of specific biomarkers leads to uncertainity in diagnosing ET. The role of genetics is emphasized hereby to aid the diagnosis. Newer genetic loci are being clustered as possible candidates in ET.

TENM4 or ODZ4 is a member of teneurin family mostly distributed in cerebellum. TENM4 gene resides in long arm of chromosome 11 and encodes for trans-membrane protein-4, responsible for neuronal plasticity and signaling. It guides proper homophilic matching between neuronal synapses guiding neural orientation. It also helps in regulating oligodendrocytic differentiation and cellular process formation and myelinating central small-diametered axons.[6] Clinically, TENM4 gene has been associated with some neuropsychiatric disorders like bipolar disease, schizophrenia, autism and neurological disorder like ET. Hor and colleagues observed c.4324 G>A mutation(located at NHL-repeat/β propeller domain) in TENM4 gene in Spanish ET families, which was critical step for homophilic interaction of TENM1 and TENM4 to influence cellular recognition, adhesion strengthening, and neuronal pathfinding.[7] They also found that the TENM4 gene is associated with hereditary essential tremor-5 (ETM5), an autosomal dominant neurological disorder characterized by postural tremors of arms, head, leg, trunk, voice, jaw and facial muscles.Subsequently, Houle et al detected multiple rare missense variants in patients of ET but it lacked significant association in Canadian population.[8] Furthermore, studies by Yan et al and Chao et al did not find an association of TENM4 gene mutation for patients of ET in Chinese population.[9,10]

Figure 1: Video 1 showing coarse postural tremor in right hand of 3-6 Hz of greatest amplitude across wrist joint involving flexion-extension movements with mild rest tremors, without intentional component; Video 2: Follow-up video showing improvement in tremor

4. Conclusion

ET is an important hyperkinetic movement disorder of daily practice. The pathogenesis of ET is yet to be understood and explored. Repeated epigenetic perturbations in the form of de-novo mutations and diverse heterogeneity in population genomics could explain the poor yield of genetics in ET. A multi-corpus collaboration study is required for better exploration of genetics in ET.

5. Source of Funding

None.

6. Conflict of Interest

None.

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