

Successful treatment of choreo-athetotic movements in a patient with an *EEF1A2* gene variant

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Abstract

Pathogenic variants in *EEF1A2*, a gene encoding a eukaryotic translation elongation factor, have been previously reported in pediatric cases of epileptic encephalopathy and intellectual disability. We report a case of a 17-year-old male with a prior history of epilepsy, autism, intellectual disability, and the abrupt onset of choreo-athetotic movements. The patient was diagnosed with an *EEF1A2* variant by whole exome sequencing. His movement disorder responded dramatically to treatment with tetrabenazine. To the best of our knowledge, this is the first report of successful treatment of a hyperkinetic movement disorder in the setting of *EEF1A2* mutation. A trial with tetrabenazine should be considered in cases with significant choreoathetosis.

Keywords

Epilepsy, genetics, autism, chorea, treatment

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Introduction

De novo variants in *EEF1A2* are associated with early infantile epileptic encephalopathy 33 (MIM# 616409) and autosomal dominant intellectual disability 38 (MIM# 616393). A de novo *EEF1A2* variant, p.G70S, was initially reported by De Light et al.¹ in a female with epileptic encephalopathy. Subsequently, 16 additional patients have been described in the published literature with 10 different de novo variants. Consistent clinical features include epilepsy/epileptic encephalopathy and global developmental delay/intellectual disability of varying severity (see Table 1). Autism or autistic features, behavioral abnormalities such as stereotypies or self-injurious behaviors, cerebral atrophy, microcephaly, and facial dysmorphism have also been reported in some patients. A recent conference report described abnormal movements in 14 patients with de novo variants in *EEF1A2*.⁹ Patients were noted to have focal or generalized epilepsy, chorea and/or dystonia, and developmental encephalopathy with neuroimaging features of global cortical volume loss and hypomyelination.

Case

The patient is a 17-year-old male born at term following a pregnancy complicated by maternal alcohol and substance

abuse. Development was delayed: he walked at age 18 months, requiring braces for support, and his first words were at age 4 years. Medical history includes strabismus status post surgery at age 1 year, hypothyroidism, asthma, gastroesophageal reflux disease, kidney dysfunction, ischemic stroke, and epilepsy well controlled on valproic acid. The patient had an episode of dystonia associated with antipsychotic treatment (haloperidol, aripiprazole) for bipolar disorder and aggression at age 9. Limited medical record

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Table 1. Summary of cases.

References	De Ligt ¹	Veeramah et al. ²	Nakajima et al. ³	Nakajima et al. ³	Lopes et al. ⁴	Lam et al. ⁵	Lam et al. ⁵	Lam et al. ⁵	Lam et al. ⁵	Lam et al. ⁵	Lam et al. ⁵	Lam et al. ⁵	Lam et al. ⁵	Inui et al. ⁶	Inui et al. ⁶	De Kovel et al. ⁷	Helbig et al. ⁸	Helbig et al. ⁸	This Report
Patient#	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	
Mutation	G70S	G70S	D252H	E122K	A92T	G70S	I71L	D91N	F98L	E122K	E124K	R423C	E122K	E122K	G70S	G70S	R266W	L246P	
GDD/ID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	nr	nr	+	+
Hypotonia	+	+	+	nr	nr	nr	nr	nr	nr	+	-	+	+	+	nr	nr	nr	+	+
Autism/autistic features	+	nr	+	+	+	nr	nr	nr	nr	-	-	nr	nr	nr	nr	nr	nr	+	+
Behavior abnormalities	nr	nr	+	+	+	nr	nr	nr	nr	nr	nr	+	nr	nr	nr	nr	nr	+	+
Abnormal movements	nr	nr	nr	nr	nr	nr	nr	nr	nr	nr	nr	+	nr	nr	nr	nr	nr	+	+
Ataxia/unstable gait	nr	+	nr	+	-	nr	nr	nr	nr	+	-	nr	nr	nr	nr	nr	nr	+	+
Microcephaly	-	+	+	+	nr	-	-	-	-	+	-	-	nr	nr	nr	nr	nr	-	-
Epilepsy	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Facial dysmorphism	-	nr	+	+	nr	-	+	+	+	+	+	+	+	+	nr	nr	nr	+	+

nr: not reported; GDD: global developmental delay; ID: intellectual disability.

documentation exists regarding the history of ischemic stroke. Magnetic resonance imaging (MRI) of the brain at ages 9 and 12 were normal. Family history is positive for bipolar disorder in his mother. Paternal family history is unknown. The patient has three healthy maternal half-siblings; ancestry is Caucasian.

He first presented to our institution at age 15 years 6 months for management of his seizures. The patient had a wide-based gait, balance impairment, and dysarthria. He demonstrated developmental skills at the 3- to 5-year level. At 2 months after his initial evaluation, he had the abrupt onset of severe choreo-athetotic movements affecting his face, arms, and trunk (see Supplemental Video). These movements dramatically affected his gait and resulted in use of a wheelchair. His speech, behavior, and short-term memory worsened as well. There was no acute preceding event or change of medication (benztropine 1 mg twice daily, valproic acid 500 mg twice daily, dextroamphetamine 5 mg once daily, diphenhydramine 50 mg every 6 h as needed, levothyroxine 31.25 mcg once daily, fluoxetine 20 mg once daily). Shortly thereafter, the patient was admitted twice to a psychiatric hospital because of anger issues and aggression, but did not require change of medication. He had another seizure after his 16th birthday and a third brain MRI was normal. Over the next several months, his condition worsened due to the involuntary movements and he was no longer able to feed or bathe himself. Gastrostomy (G) tube feeding was required for caloric support. His hyperkinetic movements failed to respond to benztropine 1 mg BID and valproic acid 500 mg BID.

Evaluation in a Pediatric Movement Disorders clinic at age 16 years and 4 months showed continuous choreo-athetotic movements of his face, trunk, and extremities. A trial with tetrabenazine (TBZ) 12.5 mg BID was initiated, which markedly improved his involuntary movements within 2 weeks. At his most recent follow-up visit (age 17 years), he was able to walk, feed himself, and use the bathroom independently. He continued to have antecollis and difficulties with gait, balance, and dysarthria, but was close to his baseline presentation.

Additional neurodiagnostic testing included a normal (fourth) brain MRI, single-nucleotide polymorphism (SNP) chromosomal array, Fragile X DNA testing, and mitochondrial DNA sequencing and deletion/duplication testing. A fasting lumbar puncture revealed a slightly low cerebrospinal fluid (CSF) glucose of 48 mg/dL (normal range 50–75); however, plasma-to-CSF glucose ratio (0.56) was not suggestive of GLUT1 deficiency. CSF lactate, pyridoxal phosphate, neurotransmitter metabolites, tetrahydrobiopterin, neopterin, 5-methyltetrahydrofolate, and succinyladenosine were all normal. CSF amino acids did not identify any abnormalities consistent with a metabolic disorder. Plasma amino acids showed elevated alanine and glycine, but were normal on repeat testing. Lactate, pyruvate, and urine organic acids were normal. In light of extensive negative work-up, whole

exome sequencing was performed using the methods previously described.¹⁰

Results identified a heterozygous missense variant, c.737T>C (p.L246P) in the *EEF1A2* gene (NM_001958.3). Targeted testing of the patient's maternal grandmother was negative; biological parental samples were not available to confirm a de novo occurrence in the patient.

Discussion

The defined *EEF1A2* abnormalities in this patient have not been previously reported in affected individuals, and it is absent from 138,632 exome/genome sequences in the Genome Aggregation Database (<http://gnomad.broadinstitute.org/>). The p.L246P variant is a semi-conservative amino acid substitution that occurs at a position that is evolutionarily conserved across species, and in silico analysis predicts that this alteration is likely damaging to protein structure/function.¹¹ It is located in domain II of the protein, which is involved in the binding of aminoacyl-tRNA. Pathogenic variants have been documented at nearby residues (e.g. p.D252H),³ supporting the functional importance of this region. We interpret this variant to be causative of the patient's neurodevelopmental impairments, epilepsy, facial dysmorphism, and movement disorder.

The *EEF1A2* gene encodes the eukaryotic translation elongation factor-1, alpha-2, which is critical for the GTP-dependent binding of aminoacyl-tRNAs to the ribosome during protein synthesis.¹² The genes which encode the two eEF1A isoforms are expressed ubiquitously during early development, but *EEF1A1* and *EEF1A2* are expressed in mutually exclusive somatic patterns around the time of weaning in juvenile mice. Complete homozygous loss of *EEF1A2* expression in mice gives rise to the "wasted" phenotype, in which the affected mice exhibit motor neuron disease with concomitant skeletal muscle atrophy leading to morbidity requiring euthanasia within 1 month of life.¹³

A recent article showed that the human pathogenic p.G70S eEF1A2 variant, introduced into mice via CRISPR mutagenesis, mimicked the wasted phenotype with the addition of a fatal audiogenic seizure phenotype.¹⁴ Furthermore, a mouse model which carried two copies of p.G70S exhibited an accelerated wasting phenotype requiring euthanasia at 18 days old. These data suggest that the p.G70S variant might confer a pathologic gain of function in addition to its loss of protein translation function. Nevertheless, it is recognized that the p.G70S mutation is in a physically and functionally remote location on the eEF1A2 protein relative to the p.L246P mutation identified in our patient. It remains unclear whether the neuropathologic phenotypes are a general consequence of human *EEF1A2* loss-of-function variants or correlate to mutations in distinct regions of the eEF1A2 protein.

Conclusion

Movement abnormalities associated with variants in *EEF1A2* are variable, including chorea, dystonia, unsteady gait, and/or ataxia. Our patient had an early history of ill-defined involuntary movements. Transient dystonic movements were reported with use of dopamine antagonists (age 9), and 6 years later he developed severe choreo-athetotic movements. The latter movements, we believe, are attributed to his underlying genetic mutation, although it is recognized that fluoxetine is associated with hyperkinesia in about 2% of children and adolescents and the patient has preceding history of prenatal drug exposure and reportedly a prior ischemic stroke. As described, his hyperkinetic movements dramatically responded to TBZ. TBZ depletes dopamine by inhibiting the vesicular monoamine transport of this neurotransmitter. TBZ is approved by the US Food and Drug Administration for treatment of chorea associated with Huntington disease; however, it has been shown to be effective for a large variety of hyperkinetic disorders.¹⁵ Practitioners must also consider the potential adverse central nervous system effects of TBZ that might be particularly concerning in patients with epileptic encephalopathy, specifically fatigue, sedation, depression, and falling. Based on this report, a trial with TBZ should be considered in those individuals with significant choreoathetosis and an *EEF1A2* mutation.

Declaration of conflicting interests

J.S.C. is a consultant for Invitae. H.S.S. is a consultant for TEVA pharmaceuticals. A.F. has received personal compensation in the form of consultant fees from Aevi Genomic Medicine, Vertex Pharmaceuticals, Stealth Biotherapeutics, BluebirdBio, and Calico Labs for services unrelated to the reported topic. The other authors declare that they have no competing interests.

Ethical approval

Our institution does not require ethical approval for reporting individual cases or case series.

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Informed consent

Informed consent was obtained from the subject's legal guardian to publish this case report and related video.

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Supplemental material

Supplemental material is available for this article online.

References

1. De Light J, Willemsen MH, Van Bon BW, et al. Diagnostic exome sequencing in persons with severe intellectual disability. *N Engl J Med* 2012; 20: 1921–1929.
2. Veeramah KR, Johnstone L, Karafet TM, et al. Exome sequencing reveals new causal mutations in children with epileptic encephalopathies. *Epilepsia* 2013; 7: 1270–1281.
3. Nakajima J, Okamoto N, Tohyama J, et al. De novo EEF1A2 mutations in patients with characteristic facial features, intellectual disability, autistic behaviors and epilepsy. *Clin Genet* 2015; 4: 356–361.
4. Lopes F, Barbosa M, Ameer A, et al. Identification of novel genetic causes of Rett syndrome-like phenotypes. *J Med Genet* 2016; 3: 190–199.
5. Lam WW, Millichap JJ, Soares DC, et al. Novel de novo EEF1A2 missense mutations causing epilepsy and intellectual disability. *Mol Genet Genomic Med* 2016; 4: 465–474.
6. Inui T, Kobayashi S, Ashikari Y, et al. Two cases of early-onset myoclonic seizures with continuous parietal delta activity caused by EEF1A2 mutations. *Brain Dev* 2016; 5: 520–524.
7. De Kovel CG, Brilstra EH, van Kempen MJ, et al. Targeted sequencing of 351 candidate genes for epileptic encephalopathy in a large cohort of patients. *Mol Genet Genomic Med* 2016; 5: 568–580.
8. Helbig KL, Farwell Hagman KD, Shinde DN, et al. Diagnostic exome sequencing provides a molecular diagnosis for a significant proportion of patients with epilepsy. *Genet Med* 2016; 9: 898–905.
9. Kruer M, Padilla-Lopez S, Helbig K, et al. Heterozygous de novo mutations in EEF1A2 Lead to an epileptic-dyskinetic encephalopathy. *Ann Neurol* 2016; 20: S296–S297.
10. Retterer K, Juusola J, Cho MT, et al. Clinical application of whole-exome sequencing across clinical indications. *Genet Med* 2016; 7: 696–704.
11. Soares DC, Barlow PN, Newbery HJ, et al. Structural models of human eEF1A1 and eEF1A2 reveal two distinct surface clusters of sequence variation and potential differences in phosphorylation. *PLoS ONE* 2009; 7: e6315.
12. NCBI Gene: EEF1A2 eukaryotic translation elongation factor 1 alpha 2 [Homo sapiens (human)], <https://www.ncbi.nlm.nih.gov/gene/1917#general-gene-info> (2018, accessed 9 March 2018).
13. Chambers DM, Peters J and Abbott CM. The lethal mutation of the mouse wasted (wst) is a deletion that abolishes expression of a tissue-specific isoform of translation elongation factor 1alpha, encoded by the Eef1a2 gene. *Proc Natl Acad Sci U S A* 1998; 8: 4463–4468.
14. Davies FC, Hope JE, McLachlan F, et al. Biallelic mutations in the gene encoding eEF1A2 cause seizures and sudden death in F0 mice. *Sci Rep* 2017; 7: 46019.
15. Jankovic J. Dopamine depleters in the treatment of hyperkinetic movement disorders. *Expert Opin Pharmacother* 2016; 18: 2461–2470.