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A rare case of Yhwag gene mutation causing developmental and epileptic encephalopathy

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Keywords
YWHAG, developmental and epileptic encephalopathy, neurocognitive disorder, autistic spectrum disorder, polymorphic seizures, Arnold-Chiari malformation type I, parietal dystrophy

ABSTRACT

Background: epileptic encephalopathy 56 or DEE is a rare disease characterized by early-onset treatment-refractory epilepsy accompanied by global developmental regression that has been shown to be caused by various mutations of the YWHAG gene.

Case presentation: We report a novel of a heterozygous mutation of YHWAG c.170G>A, p.(Arg57His), in a Caucasian male.

Conclusions: Our report further confirms that mutation of YWHAG results in developmental and epileptic encephalopathy.

BACKGROUND

Developmental and epileptic encephalopathy 56 (DEE 56)is a severe genetic disorder with early-onset, refractory, polymorphic seizures and developmental delay. YWHAG, known as the Tyrosine 3-Monooxygenase/ Tryptophan 5 Monooxygenase Activation Protein Gamma, was recently introduced in the international databases as responsible for the symptoms of epileptic encephalopathy type 56. [1-4]

It belongs to the 14-3-3 family of proteins and it is highly expressed in brain, skeletal muscle, and heart. The 7q11.23 deletion variant was found to cause Williams Beuren syndrome, which associates infantile spasms and cardiomegaly, this being a YWHAG related gene.

Multiple variants of the YWHAG gene have been reported to cause autistic spectrum disorder accompanied by epilepsy refractory to treatment, the causal relationship between these two being still inconclusive.

CASE PRESENTATION

We report a rare case of a Caucasian male with early onset epilepsy, autistic spectrum disorder, several brain malformations and scoliosis

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with the heterozygous mutation of YHWAG gene c.170G>A, p.(Arg57His). [1]

We present a 21-year-old male, born naturally after extended labor, having at birth a weight of 2950 grams, a length of 52 cm and normal head circumference. A double circular cord is mentioned, but it did not require resuscitation. He had a normal development until six months old. After that he presented infantile spasms and developmental delay.

At the age of 11 months in a febrile context, the child presented the first generalized tonic-clonic convulsion, and the diagnosis of epilepsy was established, recommending treatment with Valproic Acid, but the child continued to present tonic- clonic generalized seizures.

Topiramate was initially added, without significant improvement. After that Levetiracetam was added to valproic acid, but the seizures continued with a frequency of 1 to 3-4 episode per month. Clobazam was added, with a slight improvement in the frequency of epileptic seizures.

After that, the child was recommended ketogenic diet.

In that time the child's seizures stopped for 8 months and 3 weeks, being the longest period of absence of crises since the debut.

The crises returned, most of the time in the form of absences, sometimes accompanied by pallor and gestural automatisms, lasting 1-2 min, with constant progression towards generalized tonic-clonic seizure, these having a frequency of 1 episode every 3 weeks to a month.

Four years after, Clobazam was replaced by lamotrigine and carbamazepine, with a slight improvement in the frequency of epileptic seizures.

A combination of valproic acid, carbamazepine, lamotrigine and pregabalin managed to keep the seizures under control for about 1 year.

During this time, the child underwent permanent language development therapy and physical therapy.

At the age of 15, the child presented frequent, daily, polymorphic, generalized and focal seizures, which is why it was recommended to perform a brain MRI which revealed Arnold Chiari I malformation and focal cortical dysplasia, indicating neurosurgical intervention.

In 2019, the patient underwent a neurosurgical intervention for cortical dysplasia, but the epileptic seizures reappeared 5 days later.

Later it was decided to carry out a genetic test of total exon sequencing, supplemented by total genomic sequencing which revealed the YWHAG mutation. Patient's parents and sister did not present the mutation.

Discussion

Considering the negative family history for genetic diseases, the patient's genetic samples were tested for de novo variants of recessive inheritance

Sequence analysis using Whole Exome Plus identified a heterozygous missense variant YWHAG c.170G>A, p.(Arg57His).

This variant is absent in the international genetic databases. YWHAG c.170G>A, p.(Arg57His) affects an amino acid. The YHWAG mutation was previously described as an epileptic and neurodevelopmental encephalopathy presenting with generalized tonic-clonic seizures, global developmental delay and aspects of autistic spectrum disorder.

There have been reported different missense variants affecting the same codon as de novo in patients with epilepsy and developmental issues. [1,4,7-9]

YWHAG, Tyrosine 3- Monooxygenase/ Tryptophan 5 Monooxygenase Activation Protein Gamma, belonging 14-3-3 protein family affects several cellular processes implicated in neurological and cancer diseases. This protein is expressed in brain and skeletal muscle. The p value of YWHAG gene in the gnomAD variant database is 0.96. This value shows intolerance for loss-of-function variation. The observed reference population in gnomAD is 54 and the expected number is 159, showing a Z score of 2.95, which indicates the intolerance of missense variation. [1,5-7]

Until now, only de novo heterozygous missense YWHAG variants have been reported to be associated with developmental and epileptic encephalopathy 56, characterized by polymorphic early-onset seizures such as focal seizures with motor debut, myoclonic seizures, limb jerks, absences, generalized tonic-clonic seizures, febrile seizures, developmental delay, associated with behavioral abnormalities such as autism, deficit of attention with or without hyperactivity and anxiety. Other described features include scoliosis,

hyperlaxity of the joints, receptive and expressive language delay, hypotonic syndrome and different motor difficulties. [1,2,3,5-9]

Treatment and prognosis

In the present case, the patient required a complex therapeutic regimen of antiepileptics. Usually, epilepsy caused by YWHAG gene mutation requires complex combinations of antiepileptics including: valproic acid, levetiracetam, lamotrigine, carbamazepine, topiramate and lately stiripentol. Some of patients develop a phenomenon of tolerance to antiepileptic drugs, seizure control being obtained only for short periods of time. It is very important for patient to have multidisciplinary approach due to the particularity of each other's case. We believe that the main concern of the therapeutic team should be the early genetic diagnosis and the rigorous medicinal control of the seizures because it could allow the neuropsychomotor development of the patient and avoid the formation of a severe clinical picture. [1,2,3]

Conclusion

YWHAG c.170G>A, p.(Arg57His) is a highly pathogenic gene, that produces a genetic neurodevelopmental encephalopathy which requires a correct multidisciplinary approach where the main role is played by the specific neurological approach to epileptic manifestations. The risk of inheriting the variant and of being affected is 50%. We recommend genetic counseling for the patient and his family.

Abbreviations:
AD= autosomal dominant;
AR = autosomal recessive;
DEE= developmental and epileptic encephalopathy;
gnomAD = genome Aggregation Database;
gnomAD AC/AN = allele count/allele number in the genome Aggregation Database.

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