Novel *HIVEP2* Variant p.Q1248* is Associated with Developmental Delay: A Case Report

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Abstract

In this report, we describe a 5-year-old boy with global developmental delay who presented for medical genetic evaluation. We performed whole exome sequencing that revealed the involvement of a heterogenous variant p.Gln1248Ter (CAG > TAG): c.3742 C > T inherited de novo in exon 5 of *HIVEP2* (human immunodeficiency virus type I enhancer binding protein 2; NM_006734.3). The gene variant p.Q1248* is interpreted to be associated as a cause of the intellectual disability. We review pathomechanisms of *HIVEP2* and discuss the reasoning behind the pathogenicity of this novel variant. To the best of our knowledge, this the first reported case that demonstrates the p.Q1248* variant as pathogenic.

Keywords
- *HIVEP2* variant
- developmental delay
- whole exome sequencing

Introduction

HIVEP2 (human immunodeficiency virus type I enhancer binding protein 2), also referred to as MIBP1, ZAS2, ZNF40B, MBP-2, and Schnurri-2, is mapped to chromosome 6q23-q24. This gene plays a role in the function of immune system cells and helps to control the genes involved in brain growth and development. Inheritance is autosomal dominant. Mechanism of action of *HIVEP2* is through activation of somatostatin receptor (SSTR-2), a G-protein coupled receptor in the brain which links neurotransmitter release to somatostatin activity. This mechanism is hypothesized to cause disease due to loss-of-function resulting in haploinsufficiency of *HIVEP2*. The de novo loss-of-function can present with neurodevelopmental disorders characterized to be associated by intellectual disability and developmental delay.[1] On the basis of the role that *HIVEP2* has in the developing brain, and the deleterious nature and de novo occurrence of the variant, these genetic modifications are likely the cause of the patients' clinical manifestations. To date, a handful of patients have presented with de novo variants in *HIVEP2*.[2,3] Individuals with heterozygous de novo loss-of-function variants in *HIVEP2* present with neurodevelopmental disorders characterized by intellectual disability, developmental delay, hypotonia, mild dysmorphic features, and behavioral issues including autism spectrum disorder, hyperactivity, oppositional defiance, and anxiety (►**Table 1**).

Case Report

A 5-year-old male child presented to our clinic with global developmental delay. He was born out of a nonconsanguineous marriage and no prenatal or birth complications were reported. No significant physical findings were noted on examination. However, the patient demonstrated global developmental delays in speech, motor, and coordination with substantial language delay, limited expressive communication skills with seemingly fine receptive skills. Prior evaluation had revealed language disorder due to his difficulty in the acquisition and use of language, and this resulted in functional limitations, and low intelligence quotient (IQ). The Vineland Adaptive Behavior Scales, 3rd ed., revealed a low adaptive level with score 67 (normal–100 with standard deviation [SD] of 15). This test evaluates multiple domains like communication, daily living skills, socialization, and motor skills. The patient did not meet the cutoff for diagnosis for autism spectrum disorders (ASD) with the autism diagnostic interview-revised (ADI-R) assessment.

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Table 1 Clinical features of our patient with p.Q1248* variant and all the previously reported cases

Mutations	Dysmorphic features	Neurological features
c.3742 C > T p.(Gln1248*)	No significant features	Developmental delay, substantial language delay, limited expressive communication skills, intellectual disability
c.5737delGp. fs.15.p.(Gln1913*)	Upslanting palpebral fissures, small ears, high nasal bridge, thin upper lip, tapering fingers and radial deviation, hirsutism	Developmental delay, slurred speech, hypotonia, intellectual disability
c.C3556T p.(Gln1186*)	High forehead, widely spaced eyes, broad nasal root, small mouth	Developmental delay, language–unavailable, hypotonia, intellectual disability
c.C2827T p.(Gln943*)	Wide set eyes, broad nasal root and upturned nose, high arched palate	Developmental delay, language age equivalent to 15 mo, hypotonia, autism–unavailable, intellectual disability
c.G6475T p.(Gln2159*)	Mild retrognathia	Developmental delay, short sentences in speech, hypotonia, borderline intellectual disability, sensory disorder (processing), seizures
c.G2857T p.(Gln953*)	Elongated and narrow face	Developmental delay, no verbal speech, hypotonia, autism, intellectual disability, seizures
c.5614dupG fs.16p.(Gln1872*)	Low anterior hairline, epicanthal folds, dental crowding	Developmental delay, no verbal speech, hypotonia, autism, intellectual disability, seizures
c.G1189T p.(Gln397*)	Small hands and feet	Developmental delay, language limited to three words, hypotonia, intellectual disability–unavailable
c.6625dup fs.p.(Gln2209*)	High nasal bridge, broad mouth, flat philtrum, sacral dimple, finger webbing	Developmental delay, language–full sentences but difficult to understand, hypotonia, no autism, intellectual disability
c.3434delC fs.p.(Gln1145*)	Square face, broad forehead, strabismus, high nasal bridge, small ears, small teeth, microretrognathia	Developmental delay, language limited to sentences with three to four words, no autism, intellectual disability

Genetic testing for fragile X syndrome was normal. He was then evaluated using chromosomal microarray (CMA) which was unrevealing except for one deletion at 13q12, a deafness gene *GJB2* in the DFNB1 locus. The individual carries a single copy of the mutated gene which is insufficient to cause hearing loss as the inheritance pattern is autosomal recessive. In addition, mitochondrial sequence analysis and deletion testing of the entire mitochondrial genome showed no pathogenic variant associated with a disorder of mitochondrial metabolism. Subsequently, whole exome sequencing (WES) reported the involvement of a heterogeneous variant c.3742 C > T (p.1248*) in inherited de novo in exon 5 of *HIVEP2* (NM_006734.3). This variant was confirmed on Sanger's sequencing. Hundred percent of the coding region of the gene was covered at a minimum of 10× per technical description of the exome sequence, demonstrating good coverage. There was no indication of a multiexon deletion or duplication involving this gene observed in the exome sequencing data using laboratory developed bioinformatic approaches for deletion/duplication testing. Both the parents underwent genetic testing as part of a trio WES and do not harbor the p.Q1248* variant of the *HIVEP2*. The p.Q1248* was interpreted as pathogenic based on established American College of Medical Genetics (ACMG) guidelines for classification, consistent with the cause of intellectual disability reported in this individual.

Discussion

HIVEP2 provides instructions for making a zinc finger containing transcription factor that regulates the activity of multiple genes.[2] The *HIVEP2* is most abundant in the frontal cortex and hippocampus of the brain, where it binds to a TC-rich site in the somatostatin receptor (SSTR-2) promotor with the initiator-binding protein transcription factor 4 (tcf4). The resultant protein plays a role in the function of immune system cells, helps control the genes involved in brain growth and development and the process of bone remodeling. Additional roles in other bodily processes are proposed; however, not completely understood.[4] *HIVEP2* down-regulates transcription of both c-Myc (cell growth, differentiation, and apoptosis) and genes in the NF-κB pathway (synaptic activity, among other roles). Abnormal maturation and synaptic plasticity of hippocampal neurons can lead to behavioral and learning issues, such as learning, memory deficits, and anxiety in mice models.

The proposed mechanism of pathogenicity is haploinsufficiency as a result of new (de novo) mutations in early embryonic development or in reproductive cells in the parent during their formation. Hence, affected individuals can have no family history of the disorder. Other variants reported to date include missense, nonsense, and frameshift

variants. The p.Q1248* variant has neither been reported pathogenic nor benign. It is predicted to cause loss of normal protein function either through protein truncation or nonsense-mediated mRNA (messenger ribonucleic acid) decay. In addition, the Q1248* variant has not been observed in large population cohorts and not present in large population databases, such as ExAC (Exome Aggregation Consortium).[5]

Our patient underwent extensive testing for the cause of his global developmental delay. Standard genetic workup of fragile X testing and CMA proved negative. Thus, exome sequencing was employed as the next diagnostic test of choice. Using this approach, we were able to find the underlying root cause of this child's developmental delay and thus inform future natural history and recurrence risk for other family members.

Conflict of Interest
None declared.

References

1 Rauch A, Wieczorek D, Graf E, et al. Range of genetic mutations associated with severe non-syndromic sporadic intellectual disability: an exome sequencing study. Lancet 2012;380 (9854):1674–1682

2 Steinfeld H, Cho MT, Retterer K, et al. Mutations in HIVEP2 are associated with developmental delay, intellectual disability, and dysmorphic features. Neurogenetics 2016;17(03): 159–164

3 Nakao A, Miyazaki N, Ohira K, et al. Immature morphological properties in subcellular-scale structures in the dentate gyrus of Schnurri-2 knockout mice: a model for schizophrenia and intellectual disability. Mol Brain 2017;10(01):60

4 Srivastava S, Engels H, Schanze I, et al. Loss-of-function variants in HIVEP2 are a cause of intellectual disability. Eur J Hum Genet 2016;24(04):556–561

5 Lek M, Karczewski KJ, Minikel EV, et al; Exome Aggregation Consortium. Analysis of protein-coding genetic variation in 60,706 humans. Nature 2016;536(7616):285–291