



Thomas Jefferson University  
Jefferson Digital Commons

---

Department of Pediatrics Faculty Papers

Department of Pediatrics

---

3-1-2021

## Phenotype Expression Variability in Children with GABRB3 Heterozygous Mutations.

Abdulhafeez M. Khair

Alana E. Salvucci

Follow this and additional works at: <https://jdc.jefferson.edu/pedsfp>

 Part of the [Pediatrics Commons](#)

[Let us know how access to this document benefits you](#)

---

This Article is brought to you for free and open access by the Jefferson Digital Commons. The Jefferson Digital Commons is a service of Thomas Jefferson University's [Center for Teaching and Learning \(CTL\)](#). The Commons is a showcase for Jefferson books and journals, peer-reviewed scholarly publications, unique historical collections from the University archives, and teaching tools. The Jefferson Digital Commons allows researchers and interested readers anywhere in the world to learn about and keep up to date with Jefferson scholarship. This article has been accepted for inclusion in Department of Pediatrics Faculty Papers by an authorized administrator of the Jefferson Digital Commons. For more information, please contact: [JeffersonDigitalCommons@jefferson.edu](mailto:JeffersonDigitalCommons@jefferson.edu).

# Phenotype Expression Variability in Children with GABRB3 Heterozygous Mutations

Abdulhafeez M. Khair\* and Alana E. Salvucci

Thomas Jefferson University, Sidney Kimmel Medical College, duPont Hospital for Children, Wilmington DE, USA

## ARTICLE INFO

### Article history:

Received: 13 November 2019

Accepted: 9 March 2020

### Online:

DOI 10.5001/omj.2021.27

### Keywords:

Receptors, GABA;  
gamma-Aminobutyric Acid;  
Mutation; Phenotype.

## ABSTRACT

*GABRB3* gene is a recently identified gene located in 15q12 chromosome and encodes for gamma-aminobutyric acid (GABA) receptor subunit beta-3 protein, which is linked to the GABAA receptor. The gene is believed to share a role in inhibitory GABAergic synapses, GABA iron-gated channel function, and possible cellular response to histamine. The  $\beta 3$  subunit is expressed in cerebral grey matter, thalami, hippocampi, and cerebellum, among other structures. Faulty *GABRB3* function is linked to several neurological disorders and clinical syndromes. However, the spectrum of such disorders is not yet well known. We present three case reports highlighting the potentially expanding clinical phenotype and variable expression in children with mutated *GABRB3* gene.

The *GABRB3* gene is a recently identified gene in a locus known with various clusters of major genes in the long arm of chromosome 15.<sup>1</sup> This 15q11-q13 locus is a known region of different genomic DNA deletions and duplications related to some neurodegenerative and neurodevelopmental disorders including, for example, Angelman syndrome and autism spectrum disorder (ASD).<sup>2,3</sup> Several gamma-aminobutyric acid (GABA) genes are mapped to the nearby 15q12 locus.<sup>4</sup> It is believed that any changes in the GABAergic signaling pathway are likely to result in several neurological disorders. However, the spectrum and extension of such clinical implications are yet to be unraveled. Our three reported cases do illustrate the likely wide variation in clinical phenotype in heterozygous *GABRB3* mutations.

## CASE REPORT

### Case one

A previously healthy male infant was thought to have a normal neurodevelopmental profile till the age of 20-month-old at presentation. He was born at term after an uneventful pregnancy and uncomplicated normal delivery. His family history was negative for any neurological or developmental disorders in close blood relatives. He was noted to have several worrisome observations around the

age of 20 months old, including progressive loss of consistent eye contact, consistently irritable mood with inconsolable high pitch cry, and worsening loss of prior vocabulary and speech abilities. He was described as more clumsy and noted to have more frequent falling than usual as he started walking around the age of one-year-old. Multiple family members noticed overall worsening with decreased interaction with family members and usual social cues. Because of the numerous concerning observations, his primary care physician initiated an urgent referral to the neurology specialist service. Upon evaluation by neurology service, he was found to be well-looking with no signs of acute illness. However, he had multiple abnormal neurological exam findings such as poor eye contact, irritable mood, diffusely decreased axial and appendicular tone, along with brisk deep tendon reflexes throughout all extremities. No nystagmus, cranial nerve palsies, striking abnormal facial features, or neurocutaneous signs were noted. No joint contractures or deformities were found. With this concerning neurological decline and abnormal physical exam, a brain magnetic resonance imaging (MRI) with magnetic resonance spectroscopy was completed and interpreted as an unremarkable study. Basic and targeted metabolic screening was obtained, including lysosomal, thyroid, amino acid, fatty acid, and immune disorders, which were all found to be negative. DNA genomic micro-array sequencing test was then done and showed heterogeneous de

\*Corresponding author: ✉drabboody@hotmail.com

novo p.L3101 pathogenic variant of *GABRB3*. Although his variant was not previously reported, it was thought to be pathological and likely represents the underlying etiology of his clinical symptoms and signs. The patient was started on an intensive rehabilitation program. Interestingly, his response to physical, occupational, and speech therapy services were positive and remarkable, and he continues to make developmental progress.

### Case two

An 18-month-old female infant presented to the emergency department for the first time with likely a brief febrile seizure. She was a product of an uneventful pregnancy, regular reassuring prenatal care, and spontaneous vaginal delivery at 38 weeks estimated gestational age. She attained all her motor and social developmental milestones within the normal range expected timelines with no regression. However, she was observed to have mild expressive speech delay as she was able to only say five to six words at the age of 18 months and could not combine words. Her family history included a cousin with childhood-onset epilepsy and another cousin with febrile seizures. Upon presentation to the emergency room, she had an apparent focal onset for her seizure with lateralized versive eye gazing, focal unilateral facial twitching, and unilateral body shaking. She was febrile with some upper respiratory symptoms but no other symptoms or signs of serious or central nervous system infection. Her exam was reassuring after recovering from the postictal period, and no focal neurological signs were elicited. Extensive infectious workup was negative. During hospitalization, she had two more similar seizures. Because of seizure recurrence and onset focality, she was ultimately diagnosed with a complex febrile seizure. She was temporarily started on levetiracetam because of seizure recurrence with anticipation of the need for only short-term course. Her electroencephalogram (EEG) study was normal. Her brain MRI demonstrated a borderline Chiari I malformation but was otherwise unremarkable and showed no evidence of hippocampal sclerosis or focal cortical dysplasia. Given the mild speech delay background, atypical clinical course for febrile seizures, and family history, genetic testing was then considered. Chromosome microarray revealed p.P54L heterozygous autosomal dominant pathogenic variant of *GABRB3*. A diagnosis of

generalized epilepsy with febrile seizures plus (GEFS+) was determined. Her seizures were well-controlled with levetiracetam and medication weaning is planned.

### Case three

This male patient was born full-term (40 weeks estimated gestational age) after a largely uncomplicated pregnancy and delivery with no neonatal resuscitation or critical care needs. He had normal behavioral and developmental progress up to near puberty age, and no major health comorbidities were noted. With a rather acute history, he presented at the age of 12 years old with an acute mental status change in the form of sudden onset of repeating certain phrases inappropriately outside the situational context. Other interesting behaviors were also observed, such as continuous scribbling and walking around in circles. Mental state examination revealed deficits in short-term memory and abstract thinking. However, physical and neurological exams were otherwise unremarkable. He was diagnosed preliminarily with acute encephalopathy. Complete blood count, chemistry profile, drug screening, and basic metabolic profile were all within normal limits. Head computed tomography scan was normal. As a part of medical evaluation, EEG was requested and showed near continuous spike and slow-wave complexes consistent with non-convulsive status epilepticus. Anti-seizure medications were initiated, and he showed a good initial response to the benzodiazepine trial with lorazepam and midazolam. However, his seizures were difficult to control over time, so detailed epilepsy evaluation, including genetic studies, was pursued. Epilepsy expanded panel was then obtained, which showed a p.R217C heterozygous autosomal dominant pathogenic variant of the *GABRB3* gene. His seizures remain difficult to control with standard anti-seizure drugs. Although his neuroimaging studies did not suggest any additional epilepsy risk, he is now undergoing further epilepsy surgery evaluations.

## DISCUSSION

Chromosome 15q11-13 is a complex genetic locus that encloses three GABAA receptor subunit (*GABR*) genes, *GABRB3*, *GABRA5*, and *GABRG3*. *GABRB3* gene encodes for a member of the ligand-gated ionic channel protein, which is one of the

subunits of a multi-subunit chloride channel that serves as the receptor for GABA, a major inhibitory neurotransmitter of the mammalian central nervous system.<sup>5</sup> Usually, both the wild-type and mutant  $\beta 3$  subunit-containing  $\alpha 1\beta 3\gamma 2$  GABAA receptors are attributed to impaired intracellular  $\beta 3$  subunit processing. It is believed that the  $\beta 3$  subunit is expressed in various neuromodulatory circuits in the cerebral cortex, hippocampus, and thalamic reticular nucleus, where they mediate phasic and tonic inhibition.<sup>6</sup> *GABRB3* gene mutation disorders continue to constitute a diagnostic challenge given the wide spectrum of linked clinical features and associated syndromes.<sup>7-10</sup>

The relationship between *GABRB3* mutations and traits of ASD has been studied in several systemic reviews, but results seem to be conflicting. Some studies have demonstrated that single-nucleotide polymorphisms (SNPs) in *GABRB3* have a statistically significant predictor value for development of ASD.<sup>11-13</sup> However, expression of *GABRB3* in a cohort of patients with ASD seems to be aberrant. A recent meta-analysis by Noroozi et al,<sup>14</sup> suggested that some *GABRB3* variants are not associated with increased risk of ASD. In fact, there is some evidence that different SNPs of GABA receptor B3, A5, and G3 subunit genes located on chromosome 15q11-q13 are not associated with the development of ASD in different ethnic populations.<sup>15</sup> Our first case testing showed a de novo pathological p.L3101 variant in the *GABRB3* gene. To our knowledge, this variant was never reported before in a cohort of patients with ASD and *GABRB3* mutations.

The contribution of *GABRB3* gene alterations to increased risk for febrile seizures in children is still not well understood. Across the spectrum of GEFS+, *GABRB3* mutations were found in a small group of patients. Mutations in *SCN1A* or *GABRG2* are better studied in GEFS+ cohort of patients.<sup>16</sup> In a recent review by Møller et al,<sup>17</sup> 416 patients with febrile seizures and early life epileptic encephalopathy were screened, identifying 22 patients with heterozygous mutations in *GABRB3*, including three probands from multiplex families. At the severe end of the clinical spectrum, *GABRB3* mutations are thought to be closely associated with early-onset epileptic encephalopathy, although *SCN8A* and *CDKL5* mutations are more prevalent.<sup>18</sup> Some recent reports suggest *GABRB3* is a potential etiological substrate

for severe myoclonic epilepsy of infancy, also known as Dravet syndrome.<sup>19</sup> Our reported second patient is thought to fit the diagnosis of GEFS+ as she continues to progress developmentally so far. Her overall clinical progress and good control of seizures with low-dose levetiracetam make the possibility of other epileptic encephalopathies less likely.

Whether there is a substantial correlation between alterations in the *GABRB3* gene and lower seizure threshold is an actively debated topic in the era of epilepsy epigenetics. The spectrum of possibly linked epilepsy syndromes is expanding, from more benign syndromes like childhood absence epilepsy to epileptic spasms and Lennox Gastaut syndrome. Recent studies suggested that impaired receptor localization to synapses is a common pathophysiological mechanism for *GABRB3* mutations, although the extent of impairment may be different among mutant subunits, leading to variable epilepsy-related phenotypes.<sup>20,21</sup> *GABRB3* mutations were also noted in children with unclassified epilepsy along with other genetic alterations after more utilization of epilepsy genetic panel testing. No specific seizure classification has been described, thus emphasizing the role of genetic heterogeneity. Whether *GABRB3* mutations can result in more severe phenotype and refractory epilepsy is not yet known. Our third reported patient is running a super refractory epilepsy clinical course and is currently under evaluation for possible epilepsy surgery consideration. Our patient had non-convulsive status epilepticus upon presentation, which has not been reported in patients with *GABRB3* alterations. A recent review of the genetics of pediatric intractable epilepsy did not consider *GABRB3* among the genetic mutations which are known to be associated with difficult-to-treat epilepsy.<sup>22</sup>

## CONCLUSION

GABAA receptor  $\beta 3$  subunits are widely expressed in the developing brain. Mutations in *GABRB3* gene appear to have a wide spectrum of clinical implications. We believe our three reported cases will add to the available knowledge about variations across both genotype and phenotype spectrum. More reports of this type will ultimately improve our understanding of how these genetic alterations are being translated into clinical manifestations for a wide range of neurological disorders, particularly in

the era of improved access and evolution of available genetic testing techniques and the whole future of precision-based medical care.

**Disclosure**

The authors declared no conflicts of interest. The authors confirm that patient identifiers have been omitted from the study and legal guardians have given a no objection verbal consent to the publication of general scientific data.

**REFERENCES**

1. Chen CH, Huang CC, Cheng MC, Chiu YN, Tsai WC, Wu YY, et al. Genetic analysis of GABRB3 as a candidate gene of autism spectrum disorders. *Mol Autism* 2014 Jun;5(1):36.
2. Battaglia A. The inv dup (15) or idic (15) syndrome (Tetrasomy 15q). *Orphanet J Rare Dis* 2008 Nov;3(1):30.
3. Pizzarelli R, Cherubini E. Alterations of GABAergic signaling in autism spectrum disorders. *Neural Plast* 2011;2011:297153.
4. Sutcliffe JS, Nurmi EL, Lombroso PJ. Genetics of childhood disorders: XLVII. Autism, part 6: duplication and inherited susceptibility of chromosome 15q11-q13 genes in autism. *J Am Acad Child Adolesc Psychiatry* 2003 Feb;42(2):253-256.
5. Goetz T, Arslan A, Wisden W, Wulff P. GABA(A) receptors: structure and function in the basal ganglia. *Prog Brain Res* 2007;160:21-41.
6. Farrant M, Nusser Z. Variations on an inhibitory theme: phasic and tonic activation of GABA(A) receptors. *Nat Rev Neurosci* 2005 Mar;6(3):215-229.
7. Bird LM. Angelman syndrome: review of clinical and molecular aspects. *Appl Clin Genet* 2014;7:93-104.
8. Gamsiz ED, Sciarra LN, Maguire AM, Pescosolido MF, van Dyck LI, Morrow EM. Discovery of rare mutations in autism: elucidating neurodevelopmental mechanisms. *Neurotherapeutics* 2015 Jul;12(3):553-571.
9. Papandreou A, McTague A, Trump N, Ambegaonkar G, Ngoh A, Meyer E, et al. GABRB3 mutations: a new and emerging cause of early infantile epileptic encephalopathy. *Dev Med Child Neurol* 2016 Apr;58(4):416-420.
10. Margolis SS, Sell GL, Zbinden MA, Bird LM. Angelman syndrome. *Neurotherapeutics* 2015 Jul;12(3):641-650.
11. Kim SA, Kim JH, Park M, Cho IH, Yoo HJ. Association of GABRB3 polymorphisms with autism spectrum disorders in Korean trios. *Neuropsychobiology* 2006;54(3):160-165.
12. Delahanty RJ, Kang JQ, Brune CW, Kistner EO, Courchesne E, Cox NJ, et al. Maternal transmission of a rare GABRB3 signal peptide variant is associated with autism. *Mol Psychiatry* 2011 Jan;16(1):86-96.
13. Warrier V, Baron-Cohen S, Chakrabarti B. Genetic variation in GABRB3 is associated with Asperger syndrome and multiple endophenotypes relevant to autism. *Mol Autism* 2013;4(1):48.
14. Noroozi R, Taheri M, Ghafouri-Fard S, Bidel Z, Omrani MD, Moghaddam AS, et al. Meta-analysis of GABRB3 gene polymorphisms and susceptibility to autism spectrum disorder. *J Mol Neurosci* 2018 Aug;65(4):432-437.
15. Mahdavi M, Kheirollahi M, Riahi R, Khorvash F, Khorrami M, Mirsafaie M. Meta-analysis of the association between GABA receptor polymorphisms and autism spectrum disorder (ASD). *J Mol Neurosci* 2018 May;65(1):1-9.
16. Goldberg-Stern H, Aharoni S, Afawi Z, Bennett O, Appenzeller S, Pendziwiat M, et al. Broad phenotypic heterogeneity due to a novel SCN1A mutation in a family with genetic epilepsy with febrile seizures plus. *J Child Neurol* 2014 Feb;29(2):221-226.
17. Møller RS, Wuttke TV, Helbig I, Marini C, Johannesen KM, Brilstra EH, et al. Mutations in GABRB3: from febrile seizures to epileptic encephalopathies. *Neurology* 2017 Jan;88(5):483-492.
18. Zhang Y, Lian Y, Xie N. Early onset epileptic encephalopathy with a novel GABRB3 mutation treated effectively with clonazepam: a case report. *Medicine (Baltimore)* 2017 Dec;96(50):e9273.
19. Le SV, Le PH, Le TK, Kieu Huynh TT, Hang Do TT. A mutation in GABRB3 associated with Dravet syndrome. *Am J Med Genet A* 2017 Aug;173(8):2126-2131.
20. Shi Y-W, Zhang Q, Cai K, Poliquin S, Shen W, Winters N, et al. Synaptic clustering differences due to different GABRB3 mutations cause variable epilepsy syndromes. *Brain* 2019 Oct;142(10):3028-3044.
21. Guazzi M, Striano P. GABA strikes down again in epilepsy. *Ann Transl Med* 2019 Feb;7(3):57.
22. Liu J, Tong L, Song S, Niu Y, Li J, Wu X, et al. Novel and de novo mutations in pediatric refractory epilepsy. *Mol Brain* 2018 Sep;11(1):48.