*International Journal of Science and Healthcare Research*
*Vol.7; Issue: 2; April-June 2022*
*Website: ijshr.com*
*Case Study* *ISSN: 2455-7587*

# GRIN2B-Related Syndrome: A Rare Case Study of a Male Child and Insight into Physiotherapy Treatment

**Shruti Dnyaneshwar Ramekar[1], Pooja Kumari Mahaseth[2]**

[1]BPT Final Year Student, MGM School of Physiotherapy, Aurangabad, a Constitute Unit of MGMIHS, Maharashtra, India.
[2]Assistant Professor, MGM School of Physiotherapy, Aurangabad, MGMIHS, India.

Corresponding Author: Pooja Kumari Mahaseth

**DOI: https://doi.org/10.52403/ijshr.20220407**

## ABSTRACT

GRIN2B (Glutamate Ionotropic Receptor NMDA Type Subunit 2B) gene disorder is purely a neurodevelopmental disorder. It has a mild to profound intellectual disability, delayed development of speech along with motor skills. The GRIN2B gene majorly contributes to normal neuronal development in humans and is found on chromosome 12. The syndrome occurs when one of the two copies of the GRIN2B gene loses its normal function and as It plays a very important role in the transmission of signals in the brain.

Determine the psychological and neurological problems among GRIN2B-RELATED SYNDROME along with to Determine causes and risk factors of GRIN2B-RELATED SYNDROME. Also, to find the effectiveness of innovative physiotherapy treatment protocols for this rare condition. To Support Initiatives in the World aiming at improving Health and Wellbeing of GRIN2B-RELATED SYNDROME patients and Raise awareness of the role of Safety and Health culture and in protecting and enhancing children's physical and psychological development. Here, we summarize the current reports of disease-associated variants in *GRIN2B* from patients with several neurodevelopmental disorders, and discuss implications, highlighting the importance of functional analysis and precision therapies.

***Keywords:*** Developmental Delay; Intellectual Disability; Neurodevelopment Disorder; Physical Therapy.

## INTRODUCTION

GRIN2B (Glutamate Ionotropic Receptor NMDA Type Subunit 2B) gene disorder is purely a neuro-developmental disorder.It has a mild to profound intellectual disability, delayed development of speech along with motor skills. GRIN2B genes has very important role of controlling NMDAR (N-methyl-D-aspartate receptor) that is found in the family which is inotropic glutamate that mediates a slow, $Ca^{2+}$ permeable component of excitatory synaptic transmission in CNS System.[1]

The GRIN2B gene plays a crucial role in normal neuronal development and is important for learning and memory.The expeditious development of whole exome/genome sequencing technologies has given revolt to an unprecedented volume of data linking patient genomic variability to brain disorder phenotypes. Mutations in GRIN2B were distributed throughout the entire gene in several patients with various neuropsychiatric and developmental disorders.

The *GRIN2B* gene encoding the GluN2B subunit being implicated in many cases of neurodevelopmental disorders, which are psychiatric conditions originating in childhood and include language, and motor

learning disorders in autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD), developmental delay, epilepsy and other condition like Schizophrenia. Studies that provide functional analysis of variants are still lacking, however current analysis from the new variants that segregate with disease cases such as intellectual disability, developmental delay, ASD, or epileptic encephalopathies reveal altered NMDAR function.[2][3][4].

To date, fewer than 100 individuals have GRIN2B-related neurodevelopmental disorder /or child onset epilepsy is around 0.2%-1%.[2] Males and females of all races can be born with is variation. so far, we know of several hundred individuals are diagnosed from many different countries all around the world.[5]

Here, we summarize the current reports of disease-associated variants in *GRIN2B* from patients with several neurodevelopmental disorders, and discuss implications, highlighting the importance of functional analysis and precision therapies.

## CASE DESCRIPTION

A seven-year-old male was sent to the paediatrics physiotherapy department where his mother reported developmental delay along with difficulty in walking, communication, chewing food, drooling of saliva, tightness in right lower limb, seizures and screaming. A brief history was taken by the patient's mother where we found that the patient was delivered by a normal delivery and was discharged the next day. But after two days, the patient had fever and was kept in NICU for 3 days. After 4 months, the patient's family started noticing that he was not able to hold his neck similar to the children of his age group. But around seven months later, he was able to achieve his neck holding. At 13 months old, the patient suffered with diarrhoea and high fever due which he was admitted to the local children speciality hospital and was kept there for 3 days. The doctor suggested to stop feeding and put him on the oral supplementary. After 15 days, the patient again had the same episode as the previous and was again admitted for 3 days. In this duration, he lost 2-3 kg weight, but looking at his development delays and frequent episodes of fever and diarrhoea, the patient's family decided to take him to another doctor where the doctor suggested to take his MRI. After screening of MRI, the doctor was not able to draw any conclusion and decided to let him grow along with his achievement of milestones with the help of physiotherapy. By the age of 7, the patient was taken to several hospitals and several medication and therapies was done. Various doctors added him into different spectrum of diseases such as CP, Autism, Downs Syndrome, etc. but was not diagnosed exactly. During this period of time, the patient started to have frequent tonic-clonic seizures which lasted for 1-1.5 minutes once or twice a day or two.

### Patient's information

Subjective Examination: At present the patient is unable to sit on his own, unable to chew food, drooling of saliva, not trying to take things into his hands on his own and bears more weight on his left leg. He screams constantly and achieving minimal tripod sitting. Ophthalmic consultation reveals that the patient has altered retinal pigmentation in eyes. There is the presence of contracture in ankles. He refuses to speak and screams and gets easily scared.

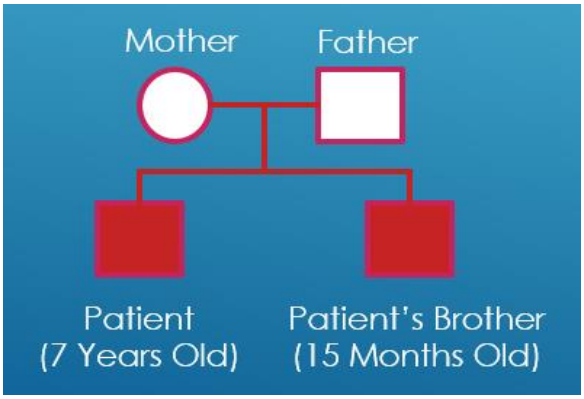


**Figure-1: Pedigree Chart**

**(a) (b) (c)**

**Fig. 2. Shows the posture of patient in a) Anterior, b) Lateral, c) Posterior views.**

## Clinical Findings

In the evaluation procedure, we found out that his developmental history the gross motor skills partially achieved in which he has gained control of his head along with rolling, sitting supported & unsupported pull to standing activities (supported & unsupported) achieved. In fine motor skills, he was able to hold the objects but he unwilling to form those activities. He was able to recognize his mother and strangers. He was able to speak monosyllables and bisyllables. His no visual fixation, tracking, scanning was achieved. There was partially closure of the lips. There was presence of right-side mouth deviation along with tongue protrusion. He was able to suck and swallow the food but he used to choke on some of the solid foods.

The patient was fully energetic and loves listening music, watching his favourite cartoons for not more than 2-3 minutes. The patient also loves foods which make sounds while eating. After more investigation, we found out that he has a history of seizures which lasts for 1-1.5 minutes once or twice a day. EEG reports suggested that he had epileptic encephalopathy. Where the seizures were tonic-clonic type, during the episodes, the patient has left side eye deviation along with tonic flexion of limbs. Ophthalmic consultation and further ophthalmic investigations reveal that the patient had altered retinal pigmentation in his eyes. DEXA scan revealed moderate osteoporosis in bilateral femoral neck. A molecular genetic testing revealed presence of GRIN2B gene- heterozygous developmental and epileptic encephalopathy.

Further examination reveals the head circumference 49 cm, no visual fixation, EOM normal, pupils NSRL, normal facial expressions, drooling of saliva, good volume of voice, variable tone in left upper limb, spasticity in right>left gastrocnemius muscle, right ankle contracture present. Deep tendon reflexes are brisk at bilateral knee and ankle. normal deep tendon reflex in upper limbs, wall standing is present and plantar flexors spine normal.

## INTERVENTION

Physiotherapy intervention goals include achieving patient's gross motor developmental milestones which include neurodevelopmental treatment (NDT) approach along with sensory integration. To make the patient calm and relax the patient was given relaxation at the beginning and at the end of the treatment to maintain the calmness throughout the session. he was also given music therapy in which his favourite song was played in background. to challenge the patients balance he was asked to perform reach outs activity with object of his interest, first while sitting on the mat and slowly progressing it to sitting on equilibrium board and updating it to Swiss ball. Proprioceptive input was given

by joint compression and weight bearing exercises. Trunk extension exercise was given on the Swiss ball. The therapeutic approach of using a trunk stabilizing pressure input orthosis (SPIO) in the context of the intensive rehabilitation program was designed to facilitate transitions like supine to sit, sit to stand, and half kneel to stand. The swing system was used to provide additional vestibular input. To manage mild scoliosis, child was also given opportunities to practise the functional movements like right side flexors of the trunk, rib cage mobilization, facilitation of the right-side flexors of the trunk, and hanging with upper trunk support. As the child started unsupported standing while wearing bilateral ankle-foot orthosis (AFO), a walker was used as aid for walking under close observation. He then practised standing on a balance board and stability disc with minimal support accompanied by multidirectional reaching while standing as well as pushing-pulling activities. He also practiced bouncing on a Swiss ball and trampoline with support and kicking a ball with ankle weight cuffs. Hence, the walking was practiced on the firm surface with the use of assistive orthosis and with walking harness with minimum support. The walking was then progressed by obstacle training to improve balance. and stair climbing was taught by holding onto railings with moderate supervision. And for drooling Oro motor exercises were given to improve oral facial tone, develop voluntary control of movement, and increase sensory awareness.

## DISCUSSION

This case study intends to find out the effectiveness of neurotherapeutic on GRIN2B gene disorder patients. The author, Chu Hu, mentioned in his article "GRIN2B Gene Homozygosity Syndrome: A Case Report and Literature Review" that clinical symptoms originating in childhood include language, motor, and learning disorders, autism spectrum disorder (ASD), and attention deficit hyperactivity disorder (ADHD) were associated with a rare genetic condition called homozygosity syndrome. The symptoms vary from person to person depending on which genes are working properly and which are not. This article will cover the clinical symptoms of the patient and discuss the similarities with the previous article by the same author on the same topic. Neurodevelopmental Approach along with Sensory integration has contributed in achieving motor skills of the patients. With progression physiotherapy sessions for, the patient was able to stand and walk with assistance for 15-20 steps in the corridor, bathroom, and stairs. He was also able to perform basic movements such as head nod and shoulder shrugs. We are hopeful that with continuous sessions, he will be able to stand independently. Significant improvement was noticed in patient's overall shoulder activities with mild assistance. Music therapy helped in maintaining his calmness and regulating his auditory deficits. Use of orthosis had great impact on improving his posture along with his movement. Oromotor exercises significantly reduced Drooling.

## CONCLUSION

Clinical features in the patient were consistent with the previous studies on GRIN2B gene syndrome. Developmental/ Behavioural characteristics like drooling, cortical blindness, abnormal movements, tics, Scoliosis, and episode of seizures, were found in the child. During and after the course of physiotherapy, at the initial stage of the sessions the patient had difficulty maintaining his balance but after few months he was able to stand and walk without support. there was significant improvement noticed in patients overall reaching activities. He was able to reach all overhead objects with mild assistance. Neurodevelopmental treatment along with sensory integration has contributed in achieving motor skills of the patients. Music therapy helped in maintaining patient calmness along with help in auditory input. Use of orthosis had great impact on in

improving posture along with movement. Drooling was significantly reduced by performing Oro fascial exercises. Improvement was observed in our case study.

**Limitation**

1. Less sample size.
2. Measurement was taken manually which may produce human errors.
3. Future research can be done.

**Future recommendations**

1. Increase overall duration of study.
2. Evaluation should be done by second therapist.
3. Increase number of parameters.

**Acknowledgement:**

I would like to thank all the participants for participating in research. I truly want to appreciate the subjects involved in my study and to mighty god. This study is self funded.

**Conflict of Interest:** We have no conflict of interest to declare.

**Source of Funding:** None

**REFERENCES**

1. Hu C, Chen W, Myers SJ, Yuan H, Traynelis SF. Human GRIN2B variants in neurodevelopmental disorders. Journal of pharmacological sciences. 2016 Oct 1;132(2):115-21.
2. Monyer H, Burnashev N, Laurie DJ, Sakmann B, Seeburg PH. Developmental and regional expression in the rat brain and functional properties of four NMDA receptors. Neuron. 1994 Mar 1;12(3):529-40.
3. Cohen S, Greenberg ME. Communication between the synapse and the nucleus in neuronal development, plasticity, and disease. Annual review of cell and developmental biology. 2008 Nov 10;24:183-209.
4. Hall BJ, Ripley B, Ghosh A. NR2B signaling regulates the development of synaptic AMPA receptor current. Journal of Neuroscience. 2007 Dec 5;27(49): 13446-56.
5. Myers SJ, Yuan H, Kang JQ, Tan FC, Traynelis SF, Low CM. Distinct roles of GRIN2A and GRIN2B variants in neurological conditions. F1000Research. 2019;8.
6. Stosser MB, Lindy AS, Butler E, Retterer K, Piccirillo-Stosser CM, Richard G, McKnight DA. High frequency of mosaic pathogenic variants in genes causing epilepsy-related neurodevelopmental disorders. Genetics in Medicine. 2018 Apr 1;20(4):403-10.
7. Lemke JR, Hendrickx R, Geider K, Laube B, Schwake M, Harvey RJ, James VM, Pepler A, Steiner I, Hörtnagel K, Neidhardt J. GRIN2B mutations in West syndrome and intellectual disability with focal epilepsy. Annals of neurology. 2014 Jan;75(1):147-54.
8. Pan Y, Chen J, Guo H, Ou J, Peng Y, Liu Q, Shen Y, Shi L, Liu Y, Xiong Z, Zhu T. Association of genetic variants of GRIN2B with autism. Scientific Reports. 2015 Feb 6;5(1):1-5.
9. Platzer K, Yuan H, Schütz H, Winschel A, Chen W, Hu C, Kusumoto H, Heyne HO, Helbig KL, Tang S, Willing MC. GRIN2B encephalopathy: novel findings on phenotype, variant clustering, functional consequences and treatment aspects. Journal of medical genetics. 2017 Jul 1;54(7):460-70.
10. Lemke JR. Predicting incidences of neurodevelopmental disorders. Brain. 2020 Apr 1;143(4):1046-8.
11. Vieira MM, Jeong J, Roche KW. The role of NMDA receptor and neuroligin rare variants in synaptic dysfunction underlying neurodevelopmental disorders. Current opinion in neurobiology. 2021 Aug 1;69:93-104.
12. Yoo HJ, Cho IH, Park M, Yang SY, Kim SA. Family based association of GRIN2A and GRIN2B with Korean autism spectrum disorders. Neuroscience letters. 2012 Mar 23;512(2):89-93.
13. Sapuppo A, Portale L, Massimino CR, Presti S, Tardino L, Marino S, Polizzi A, Falsaperla R, Praticò AD. GRIN2A and GRIN2B and Their Related Phenotypes.

Journal of Pediatric Neurology. 2021 May 21.

14. Kim JI, Kim JW, Park S, Hong SB, Lee DS, Paek SH, Han DH, Cheong JH, Kim BN. The GRIN2B and GRIN2A gene variants are associated with continuous performance test variables in ADHD. Journal of Attention Disorders. 2020 Sep;24(11):1538-46.

How to cite this article: Ramekar SD, Mahaseth PK. GRIN2B-related syndrome: a rare case study of a male child and insight into physiotherapy treatment. *International Journal of Science & Healthcare Research.* 2022; 7(2): 41-46. DOI: *https://doi.org/10.52403/ijshr.20220407*

******