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CASE REPORT

Wu Type GRIA3 Mutation Associated X-Linked Syndromic Intellectual Developmental Disorder: A Case Report

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Abstract

Background: A Wu type X-linked syndromic intellectual developmental disorder is caused by mutations in the GRIA3 gene This disorder is characterised by autistic features, hyporeflexia, intellectual disability and facial dysmorphism. **Case report:** The patient, a 4 year old male child, came with chief complaints of runny nose and tooth ache for 5 days. There was a past history of frequent falls, myoclonic jerks, tongue fibrillation, shudder attacks and delayed developmental milestones. The child at presention did not have myoclonic jerks or frequent falls. Family history is significant for maternal aunt presenting with similar complaints. On examination, protruding tongue, depressed nasal bridge, high arched palate, short fingers, right eye divergent squint, cafe-au-lait spot on the right knee, deep tendon reflexes- sluggish on both upper and lower limbs, power of 3/5 and hypotonia was observed in all four limbs with plantar- extensor bilaterally. **Conclusion:** On DNA testing, a missense mutation of GRIA 3 gene was noted. He was treated on a multi-disciplinary approach and was admitted in a special school where occupational therapy, speech therapy, behavioural therapy and physiotherapy was given.

Keywords: Intellectual disability, Refractory seizure, delayed developmental milestones, multidisciplinary approach

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Introduction

Wu type X linked GRIA 3 mutation associated Intellectual Developmental Disorder is a rare, X-linked syndrome characterised by mild to severe ID caused by mutations in the GRIA3 gene (1).This disorder is characterised by autistic features, hypotonia, hyporeflexia, ID and facial dysmorphism [1]. The phenotype is X-linked recessive. In some cases, GRIA 3 mutations can also occur de novo [2]. Here we present a case of Wu type X linked syndrome which had manifested with developmental delay. This is the 20th case ever reported of GRIA 3 mutation causing ID.

Case report

A four year old male child born of a non-consanguineous marriage came with complains of runny nose and right upper anterior tooth pain for the past five days for Paediatric opinion and oral rehabilitation.

He had a history of frequent falls at two years of age, fell down four times in 10 months while walking and running, sudden muscle jerks (three episodes within six months at two years of age for which there was no hospitalisation done prior and the child is not on any antiepileptic drugs), involuntary movements of the upper extremities which occur during normal activities without impairment of consciousness (shudder attacks) and history of not attaining age appropriate milestones.

He was born at term with a birth weight of 2.7 kg and cried immediately after birth. He was not admitted to the neonatal intensive care unit and there was no history of neonatal seizures. There was no significant antenatal history.

Developmental history

GROSS MOTOR MILESTONE

Head control	eight months
sitting with support	one year
standing without support	one year nine months
walking without support	two years

Fine motor milestones:

Mature pincer grasp	three years
scribbling	three years six months

Language milestones: Bisyllables at four years

Social milestones: Shares toys and group play at four years

In summary, moderate global developmental delay was present with a developmental age of two and a half years at the chronological age of four years.

Family history:

The maternal aunt has Intellectual Disability (ID) and Seizures. Phenotypically, she has a depressed nasal

bridge, short fingers and a café au lait spot on her abdomen. Parents are normal. Informed consent for publication was obtained from the parents of the patient.

Examination

Weight- (11.6kgs= -2 to -3 SD), head circumference (46cm= -2 to -3 SD),

The child is conscious, mouth open and tongue protruding out with depressed nasal bridge, high arched palate, short fingers, right eye divergent squint, cafe-au-lait spot on the right knee.

Oral examination- Dental caries present in all upper teeth and 74, 75, 73, 84, 85 according to the Federation Dentaire Internationale notation tooth numbering system of primary teeth.

B/L pupils- Equal, round, reactive to light. Hypotonia was observed in all four limbs with power of grade 3 in ech limb.

The biceps, triceps, knee and ankle reflexes were diminished bilaterally with extensor plantar response bilaterally.

Investigation:

DNA test report: GRIA3 gene (glutamate ionotropic receptor AMPA type 3) on Exon 13, hemizygous, variant of unknown significance - chrX:g.123464886G>A which results in amino acid substitution p.Glu700Lys gene was done using whole mitochondrial exome sequencing - targeted gene sequencing and confirmation via Sanger sequencing of exon 13. Average Sequencing depth – 208. *Average on target sequencing depth – 118.88*. This was done because the maternal aunt was diagnosed with X linked ID because of GRIA3 mutation.

SPINAL MUSCULAR ATROPHY MUTATION DETECTION - mutation not detected.

DNA test report of the parents-mother (asymptomatic)- similar GRIA3 gene detected(heterozygous), using targeted gene sequencing and confirmation via Sanger sequencing of exon 13. This was absent in the normal father.

DNA test report of the *affected aunt* - similar GRIA3 gene detected (heterozygous), was detected using whole mitochondrial exome sequencing - targeted gene sequencing and confirmation via Sanger sequencing of exon 13.

MRI Brain with MRS	no significant abnormality detected.
EEG	no epileptiform waves
EMG	Normal
Thyroid function tests-	
TSH	5.35, - (0.8 – 8.2 µg/dL)
Total T3	174.0 - (105 – 245 µg/dL)
Total T4	9.89 (7.8- 16.5 µg/dL)
Total CPK	150 (25 – 172 U/L)

Management

Child is treated in a multi-disciplinary approach at a special school in Chennai, where the child is given the following therapies every month since 2 years of age.

Occupational therapy:
Joint compression
Neutral warmth
Proprioceptive and vestibular input
Hand-eye coordination

Speech and language therapy:

For the initial 6 months, child was taught to match primary colours and shapes, match common fruits and vegetables with their names.

6 months later child was taught on:

Comprehension of body parts

Following simple one step command

Physiotherapy: given intermittently to improve the muscle tone and power.

Total mouth rehabilitation under general anaesthesia was done for the child three months later after visiting our OPD.

Discussion

GRIA3 gene codes for GLUA 3 subunit which is a part of the AMPA receptor (AMPAR) subunit. In the brain, this GLUA 3 heterodimerises with GLUA 2 forming a Calcium impermeable AMPAR. The GLUA3_R660T mutant as said by Sun et al [3], decays the mini Excitatory Post Synaptic Current (mEPSC) at AMPAR.

Philips et al [4] noted that a missense mutation in c.1888G > C (p.Gly630Arg) causing substitution of Arginine instead of glycine (neutral) in one of the familial variants. This caused a decreased inotropic glutamate receptor function associated with moderate ID as these mEPSCs are essential for long term potentiation for forming memory.

Patients with missense mutations (p.Arg631Ser) which lies right next to glycine, is associated with dysmorphic facies [5]. Chinoyobu et al [6] reported a copy number gain in Xq25 which showed reduced GRIA3 transcripts in both the carrier mother and her affected son. But the carrier mother was not affected because the skew was found only in the lymphocytes and not in the brain.

In addition to some of the usual features of this illness as mentioned above, Trivisano et al [1] reported hypothyroidism. The mutation observed in this case was a hemizygous missense variant c.2359 G > A (p.Glu787Lys), and Bipolar disorder was noted by Gecz et al. [7]. Among seizure types, myoclonic seizures were most common [8], [9]. Other types included absence seizures, GTCS, non-convulsive status epilepticus [1] and atonic seizures of which most are refractory to treatment.

ID with increased awake time of sleep wake cycle [10] was reported by Davies et al. They hypothesized that there is a progressively increasing wake cycle as the child grows, due to AMPAR sensitizing the retina to light (retino-hypothalamic pathway) and abundance of AMPAR in the supra chiasmatic nucleus.

Exaggerated startle reflex and chorea [8] were reported by Piard et al who on sequencing found out a missense variant c.2477G > A; p.(Gly826Asp) which affected the transmembrane AMPAR.

Bonnet et al [11] reported inguinal hernia and Philippe et al [12] reported ectopic testes, scoliosis, pain insensitivity, pes planus and micro-penis.

In our case, a missense variation in the exon 13 of the GRIA3 gene that results in the amino acid substitution of lysine for glutamic acid at codon 700 in the patient, with a similar gene detected in the mother in heterozygous condition indicating that the mother is an asymptomatic heterozygous carrier of uncertain significance. Other mutations reported in other studies include duplications deletions translocations [13]. Both duplications and deletions seem to cause reduced synthesis of GLUA 3 [14].

Conclusion

Early detection of genetic diseases helps in better management of the patient. In this case, refractory seizures and facial dysmorphism should clue into a rare genetic of illness. Genetic testing and counselling paves a way to the early detection and management of syndromic children. Physicians in this case, should treat the child in a multidisciplinary approach which symptomatically helps in well-being of the child.

Conflicts of interest

The authors declares that they do not have conflict of interest.

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References

1. Trivisano M, Santarone ME, Micalizzi A, Ferretti A, Dentici ML, Novelli A, Vigevano F, Specchio N. GRIA3 missense mutation is cause of an x-linked developmental and epileptic encephalopathy. Seizure. 2020 Nov 1;82:1-6.
2. Necpál J, Winkelmann J, Zech M, Jech R. A de novo GRIA3 variant with complex hyperkinetic movement disorder in a girl with developmental delay and self-limited epilepsy. Parkinsonism & Related Disorders. 2023 Jun 1;111.
3. 1;Sun JH, Chen J, Ayala Valenzuela FE, Brown C, Masser-Frye D, Jones M, Romero LP, Rinaldi B, Li WL, Li QQ, Wu D. X-linked neonatal-onset epileptic encephalopathy associated with a gain-of-function variant p. R660T in GRIA3. PLoS Genetics. 2021 Jun 23;17(6):e1009608.
4. 2;Philips AK, Sirén A, Avela K, Somer M, Peippo M, Ahvenainen M, Doagu F, Arvio M, Kääriäinen H, Van Esch H, Froyen G. X-exome sequencing in Finnish families with Intellectual Disability-four novel mutations and two novel syndromic phenotypes. Orphanet journal of rare diseases. 2014 Dec;9:1-3.
5. Wu Y, Arai AC, Rumbaugh G, Srivastava AK, Turner G, Hayashi T, Suzuki E, Jiang Y, Zhang L, Rodriguez J, Boyle J. Mutations in ionotropic AMPA receptor 3 alter channel properties and are associated with moderate cognitive impairment in humans. Proceedings of the National Academy of Sciences. 2007 Nov 13;104(46):18163-8.
6. 3;Chiyonobu, T., Hayashi, S., Kobayashi, K., Morimoto, M., Miyanomae, Y., Nishimura, A., Nishimoto, A., Ito, C., Imoto, I., Sugimoto, T. and Jia, Z., 2007. Partial tandem duplication of GRIA3 in a male with mental retardation. American Journal of

Medical Genetics Part A, 143(13), pp.1448-1455.

7. Gécz J, Barnett S, Liu J, Hollway G, Donnelly A, Eyre H, Eshkevari HS, Baltazar R, Grunn A, Nagaraja R, Gilliam C. Characterization of the human glutamate receptor subunit 3 gene (GRIA3), a candidate for bipolar disorder and nonspecific X-linked mental retardation. Genomics. 1999 Dec 15;62(3):356-68.
8. Piard J, Béreau M, XiangWei W, Wirth T, Amsallem D, Buisson L, Richard P, Liu N, Xu Y, Myers SJ, Traynelis SF. The GRIA3 c. 2477G> A variant causes an exaggerated startle reflex, chorea, and multifocal myoclonus. Movement Disorders. 2020 Jul;35(7):1224-32.
9. Rinaldi B, Ge YH, Freri E, Tucci A, Granata T, Estienne M, Sun JH, Gérard B, Bayat A, Efthymiou S, Gervasini C. Myoclonic status epilepticus and cerebellar hypoplasia associated with a novel variant in the GRIA3 gene. neurogenetics. 2022 Jan 1:1-9.
10. 4;Davies B, Brown LA, Cais O, Watson J, Clayton AJ, Chang VT, Biggs D, Preece C, Hernandez-Pliego P, Krohn J, Bhomra A. A point mutation in the ion conduction pore of AMPA receptor GRIA3 causes dramatically perturbed sleep patterns as well as intellectual disability. Human molecular genetics. 2017 Oct 15;26(20):3869-82.
11. Bonnet C, Leheup B, Béri M, Philippe C, Grégoire MJ, Jonveaux P. Aberrant GRIA3 transcripts with multi-exon duplications in a family with X-linked mental retardation. American Journal of Medical Genetics Part A. 2009 Jun;149(6):1280-9.
12. Philippe A, Malan V, Jacquemont ML, Boddaert N, Bonnefont JP, Odent S, Munnich A, Colleaux L, Cormier-Daire V. Xq25 duplications encompassing GRIA 3 and STAG 2 genes in two families convey recognizable X-linked intellectual disability with distinctive facial appearance. American Journal of Medical Genetics Part A. 2013 Jun;161(6):1370-5.
13. Philips AK, Sirén A, Avela K, Somer M, Peippo M, Ahvenainen M, Doagu F, Arvio M, Kääriäinen H, Van Esch H, Froyen G. X-exome sequencing in Finnish families with Intellectual Disability-four novel mutations and two novel syndromic phenotypes. Orphanet journal of rare diseases. 2014 Dec;9:1-3.
14. Soto D, Altafaj X, Sindreu C, Bayés À. Glutamate receptor mutations in psychiatric and neurodevelopmental disorders. Communicative & integrative biology. 2014 Jan 30;7(1):e27887.