Research Article
Volume 17S:3, 2023
DOI: 10.3371/CSRP.2023.17.S3.100151

Clinical Schizophrenia & Related Psychoses

Open Access

Does Mutations of *DLG3* Gene Causes Mental Motor Retardation in Childhood?

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Abstract

Intellectual Disability (ID), formerly called Mental Retardation (MR) has heterogeneous environmental and genetic causes acting in various phases of pre and postnatal development. Current research has been directed to clarify the genetic base of what was accepted as idiopathic MR. Recently in literature many coding variants have been identified in MR in childhood, identification of non-pathogenic coding variants has so far been possible in only a few cases. In this study, we present two cases with Disc-large homolog 3 (*DLG3*) gene mutation in which the guanine position at position c.2267 was found to have adenine. *DLG3* is the first mental retardation gene directly linked to glutamate receptor signalling and trafficking, increasingly recognised as a central mechanism in the regulation of synaptic formation and plasticity in brain and cognitive development and known to be associated with X linked MR (XLMR). The second case in our study was diagnosed with atypical autism previously. The relationship between Autism Spectrum Diseases (ASD) and XLMR is still unclear, but we identified *DLG3* deletion, which appears to be the cause of mental impairment in this individual who was previously diagnosed with atypical autism. As a result of the whole Exom Sequence Analysis, the mutation detected as homozygous in *DLG3* gene is thought to cause the XLMR since the both two patients are male. New studies in the future will strengthen this thesis and enlighten the genetic etiology of MR and ASD in childhood.

Keywords: *DLG3* Gene • Mental Motor Retardation • Childhood

Introduction

Mental retardation (MR) or intellectual disability (ID) is the most common developmental disorder, with a prevalence of 1 to 3% in the worldwide population. They are diagnosed with developmental delay in early childhood and are defined by intellectual function below average (IQ <70). In more than half of the cases, the etiology is still unknown [1].

X-linked mental retardation (XLMR) is a highly heterogeneous disease that has identified more than 80 genes to date. XLMR has an estimated prevalence of 1 in 1,000 males, with fragile X syndrome accounting for 10 to 15% of cases, the prevalence of most other cloned X-linked genes being very low (0.5– 1.0%) with the exception of Aristaless X [2]. Mental retardation is defined as non-syndromic when cognitive dysfunction is the only distinctive feature and no other clinical, radiological or biochemical alterations are present.

Investigation of X-linked chromosome MR forms has led to the discovery of pathogenic gene variants and molecular pathways in MRI. The 2,3Disc-large homologous 3 (*DLG3*) gene (MIM300189) is found in Xq13.1 and encodes the synapse-related protein 102 (SAP102). It is the first identified gene that encodes the glutamate receptor that controls the postsynaptic system, the mutation causing XLMR. Only several families with a mutation in this gene have been reported to date. In this study we presented two idiopatic MR cases those we revealed DLG3 gene mutation which seem to be the cause of MR in these individuals [3-5].

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Received: 25 May 2023, Manuscript No. CSRP-23-99541**; Editor assigned**: 29 May 2023, Pre QC No. CSRP- 23-99541 (PQ); **Reviewed:** 02 June 2023, QC No. CSRP- 23- 99541 (Q); **Revised:** 06 June 2023, Manuscript No. CSRP-23-99541 (R); **Published:** 10 June 2023 **doi:** 10.3371/CSRP.MMWY.100151

Material and methods

Materials

Our first case is 5 years old male and family is of Turkish origin and consists of no other affected males in generations even showing X-linked recessive inheritance. *DLG3* gene validation analysis for first case was revealed DNA material mutation in *DLG3* gene of c.2267 G> A (p.Arg756Gln) sequence (Figure 1).

Standard karyotypes as well as *DLG3* gene mutation analysis were negative in all affected individuals of the family. All obligate carrier males are phenotypically normal. The male patient was born at term after a normal pregnancy, to healthy non consanguineous parents. Because of psychomotor delay, they were both sent to a school for special educational needs at the age of 2 and 5 years, respectively. The pro band speaks in short sentences with a poorly articulated, unclear speech. He has a severe MR with a WISC full-scale IQ of 40. He also exhibits behavioural problems requiring pharmacological therapy. He has epilepsy with severe convulsions requiring antiepileptic medications. The electroencephalography revealed severe epileptic pattern in this patient. He has normal vision and hearing and no dysmorphic features. Brain computed tomography scan was performed and was normal in result. The second case is 6 years old male and family is of Turkish origin and consists of no other affected males in generations even showing X-linked recessive inheritance. *DLG3* gene validation analysis for second case was revealed DNA material mutation in *DLG3* gene of c.2359G> A p. (Gly787Ser) sequence (Figure 2).

When 4-year-old, patient had delayed language development and had movement disorder. The patient was diagnosed with atypical autism. There is no consanguineous marriage between a healthy mother and father. He has limited communication skills with a slow and poor speech. He has a total IQ of 33. His behaviour is quiet and withdrawn. The physical and neurological examination of the proband was otherwise normal. There is no history of seizures, he has normal vision and hearing and no dysmorphic features. A brain computed tomography scan was performed and it was normal.

Methods

Method: Next Generation DNA Sequence Analysis (NGS)

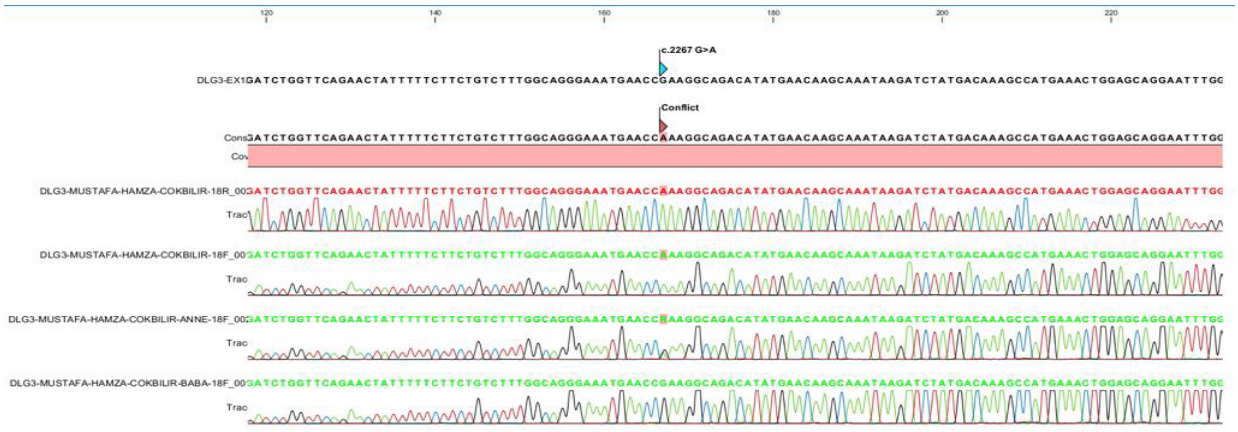

Figure 1. *DLG3* gene validation analysis for first case was revealed DNA material mutation in *DLG3* gene of c.2267 G> A (p.Arg756Gln) sequence.

Figure 2. *DLG3* gene validation analysis for second case was revealed DNA material mutation in *DLG3* gene of c.2359G> A p. (Gly787Ser) sequence.

Platform used: In the study; the 60MB exomes in humans (targeting 99% of the regions covering CCDS, RefSeq and gene code databases) were enriched using the Enriched "Agilent Sure Select Human All Exon V6" kit. The enriched library was sequenced with an average of 100X coverage on the Illumina next generation sequencing platform. Typically, 97% of the sequenced regions are> 10X.

Bioinformatics Analysis: In-house

Reference sequence: Bioinformatic analyzes were performed using the *GRCh37* / *hg19* genome alignment and regions with low coverage and variants with artifacts were excluded.

Reference databases: ClinVar (http://www.ncbi.nlm.nih.gov/clinvar/). The Human Gene Mutation Database (HGMD) (http://www.hgmd.cf) .ac.uk / ac / index.php), CentoMD® (https://www.centogene.com/digital-services/mutation-database-centomd.html), ExAc database (http://exac.broadinstitute.org) /)

Filters used: All disease-related variants reported in HGMD®, ClinVar or CentoMD® were considered in the evaluation, as well as variants with a small allele frequency (MAF) of less than 1% considered in the ExAc database. Intornic regions within +/- 20 bases of coding exons were also analyzed. When evaluating the variants, all possible inheritance patterns, as well as family history and clinical information, are considered. All identified variants are evaluated for pathogenicity and causality and are classified according to the following system. All variants related to the patient's phenotype have been reported, with the exception of benign or possibly benign variations.

Results

DLG3 gene validation analysis for first case was revealed DNA material mutation in *DLG3* gene of c.2267 G> A (p.Arg756Gln) sequence. In the validation study performed by Sanger sequence analysis; c.2267 G>A (p.Arg756Gln) variant was hemizygous at scans in the *DLG3* gene. The Fathers' *DLG3* gene c.2267 G> A (p.Arg756Gln) mutation was screened in situ. No mutation was detected at the scanned point in the validation study performed by Sanger sequence analysis. The Mothers' *DLG3* gene c.2267 G> A (p.Arg756Gln) mutation was screened in situ. In Sanger sequence analysis, c.2267 G> A (p.Arg756Gln) mutation was screened as heterozygous.

DLG3 gene validation analysis for second case was revealed DNA material mutation in *DLG3* gene of c.2359G> A p. (Gly787Ser) sequence. In the validation study performed by Sanger sequence analysis; C.2359G> A, p.Gly787Ser variant was hemizygous at scans in the *DLG3* gene. The fathers' *DLG3* gene was screened for c.2359G> A p. (Gly787Ser) mutation. In the validation study performed by Sanger sequence analysis; no mutation was detected in the scanned region. The mothers' *DLG3* gene for c.2359G> A p. (Gly787Ser) mutation It was screened. In the validation study performed by Sanger sequence analysis; at scanned points c.2359G> A, p.Gly787Ser variant was heterozygous.

Discussion

Synapse-associated protein *102 (SAP102)* belongs to the *SAP* subfamily of neuronal membrane associated guanylate kinase (*MAGUK*) proteins including; *SAP90* postsynaptic density (*PSD*) *95*, *SAP97/hDLG* and *Chapsyn110/PSD93*. SAP proteins are extensively expressed in the brain. *SAP102* is found in dendrites and axons and is abundant in the postsynaptic density as well as in the cytoplasm. *PSD95* and *PSD97* were predominant at later stages of brain

development, while *SAP102* was stabbed in early postnatal brain development. [6-8].

DLG3 is a known XLMR gene that encodes *SAP102* that is a member of the membrane-associated guanylate kinase (*MAGUK*) family of proteins. *MAGUKs* are a group of ionotropic scaffold proteins found at the Post Synaptic End (PSD) containing *PSD-95, PSD-93, PSD-97* and *SAP102* involved in the formation and plasticity of the stimulating synaptic terminals of neurons in the brain.

SAP102 has three tandem *PDZ (PSD-95* / Disk large / Zona occluded) domains at the amino terminus, the middle *SH3* (Src Homology 3) domain and an inactive carboxy terminal *GK* (Guanylate kinase) domain. In rats, *SAP102* is highly expressed in dendrites and axons in the hippocampus after fetal and early-late delivery, and decreases in 6 months while *PSD-95* and *PSD-93* expression increases with age [9-10].

DLG3 was the first *ID* gene associated with *NMDA* receptor mediated signalling and synaptic plasticity. Furthermore, significant reductions in *SAP102* levels increase the prevalence of filopodia, which is common in mouse models and *ID* patients [11]. *SAP102* has a critical role in early brain development is consistent with reports showing that loss-of function variants are associated with XLMR. *PSD-95* and *SAP102* have both overlapping and specific functions. Less serious phenotypic effects due to reductions in *SAP102* may be due to functional compensation by other *MAGUKs*. *SAP102* has been shown to compensate for some defects in *PSD-93/PSD-95* knockout neurons [12, 13].

In this study the results of the whole Exom Sequence Analysis, the mutation detected as hemisigot in *DLG3* gene is thought to cause the disease since the both two patients are male and this data is absolutely in agreement with previous studies in the literature.

The prevalence of autism is four times higher in males compared to females, and about 80% of cases express intellectual disability [14]. It is interesting that men have a higher prevalence and mental disability, just as characteristic for XLMR [15].

However, the relationship between autism and MR has not been identified yet. To date, over 90 genes underlying XLMR have been identified each of them contributing to the disease group with a small number of individual mutations [16].

Previous results in literature suggest that the *Xq11.1-q21.33* region is a plausible candidate region for autism spectrum disorders (ASD). In this site there are several candidate genes that affect neuronal function or may be genetically cause of XLMR [17-19].

In our study; the second case was diagnosed with atypical autism previously. The relationship between ASD and XLMR is still unclear, but we identified *DLG3* deletion, which appears to be the cause of mental impairment in this individual who was previously diagnosed with atypical autism.

Conclusion

As a result of the whole Exom Sequence Analysis, the mutation detected as hemizygous in *DLG3* gene is thought to cause the XLMR, since the both two patients are male. In our second case who previously diagnosed of atypical autism, we have identified *DLG3* deletion seem to be the cause of XLMR. This data is important to emphasize the genetical relationship between ASD and XLMR. New studies in the future will strengthen this thesis and enlighten the genetic etiology of mental retardation and ASD.

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How to cite this article: Huseyin Avni Solgun, Alper Ozkılıc, "Does Mutations of DLG3 Gene Causes Mental Motor Retardation in Childhood?". *Clin Schizophr Relat Psychoses* 17S3 (2023) doi: 10.3371/CSRP.MMWY.100151