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Case Report

BSCL2 Gene Mutation Causing Progressive Encephalopathy with or without Lipodystrophy, A Case Report from Pakistan

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Abstract

Celia's encephalopathy or Progressive encephalopathy with or without lipodystrophy (PELD) is a rare childhood neurodegenerative syndrome, that is autosomal recessive mendelian trait, It is Seipin protein associated encephalopathy and results in regression of developmental mile stones. We report a case with global developmental delay and hypertonia, hyperreflexia, recurrent infections and dyskinesia. The diagnosis was done by exome sequencing revealing mutation in the BSCL2 gene on chromosome 11q13. The cases was very rare and found to mimic other diseases that is why patient was investigated and reported. The study was done to identify report and manage such cases appropriately. The patient was investigated in OPD in 2021. Whole exome sequencing (WES) was done for diagnosis after taking appropriate blood sample. A protein change p.(trp323leufs*15) was identified due to homozygous frameshift elongation likely pathogenic on chromosome 11 in BSCL gene.p. (trp323leufs*15) creates a shift in reading frame starting at codon 323. The new frame ends in stop codon after 15 proteins downstream. This new variant is absent in genomAD and local database. This variant has also not been reported yet in clinVar. This variant is classified as likely pathogenic class 2 based on ACMG recommendations. Any patient was favoring symptoms and features should be investigated with whole genome sequencing to confirm the diagnosis.
Key words: Encephalopathy, BSCL2 gene, developmental regression, lipodystrophy.

Introduction

Lipodystrophy syndromes are rare disorders comprising a group with heterogeneous features including complete or incomplete deficiency of adipose tissue and a hormone secreted by adipose tissue, including subtypes consisting of congenital or acquired generalized lipodystrophy, and familial or acquired partial lipodystrophy.[1]

Patterns of these disorders are variable and keep changing in terms of appearance of features from the 1st to 7th decade and include mild disease with slow progression, abnormal gait with signs suggestive of pyramidal tract involvement, ranging from spasticity which may be mild to severe with increase reflexes in the lower limbs and inconsistent plantar responses which can be extensor some times and lower motor neuron involvement resulting in formation of pes cavus and other malformations of foot. The severity of disease is variable among families and even sometimes with in same family.

This approach to treat must be multidisciplinary, involving both pediatric neurologist and endocrinologists with expertise in lipodystrophies.[2] The therapeutic options are having two aspects that is the control of metabolic complications and fits. The treatment options under trials are dietary approach, i.e role of Metreleptin.[3,4] B*SCL2*Berardinelli-Seip congenital lipo- dystrophy 2gene was first identified in 200.[5] It is located on chromosome 11q13. BSCL2/seipin produces three transcripts of 2.2 kb, 1.8 and 1.6 kb. Seipin protein has three isoforms (1-3) that are 462, 398, and 287 amino acids long, respectively.

This gene is active in human body, particularly in nerve cells that control muscle movement (motor neurons) and in the brain. The gene is also active in adipocytes, which are the

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MN conceptualized the project and did the drafting, revision & writing of manuscript. WR did the literature search. SR performed the statistical analysis. NHB did the data collection.

major component of fatty (adipose) tissue. This mutation in this gene results in new splicing site as a result of which there is skipping of exon number seven leading to the formation of new protein, that is called seipin protein which is same as *BSCL2-008* transcript .

Mutations in BSCL2/seipin cause two distinct phenotypes.[6] Loss-of-function mutations are responsible for congenital generalized lipodystrophy type 2 (Berardinelli-Seip syndrome type Gain-of-function mutations or gain-of-toxic function mutations in seipin gene result in neurological disorders like Silver syndrome/spastic paraplegia and distal hereditary motor neuropathy type V. These disorders are currently being referred to as "seipinopathies". Patients with seipinopathies have heterogeneous symptoms and manifest both upper and lower motor neuron disruptions.

All of the patients were from Murica in south eastern Spain, and the transmission pattern of the disorder was compatible with autosomal recessive inheritance. The aim of study was to find the role of BSCL 2 gene and identify genetic basis of lipodystrophy with or without encephalopathy.

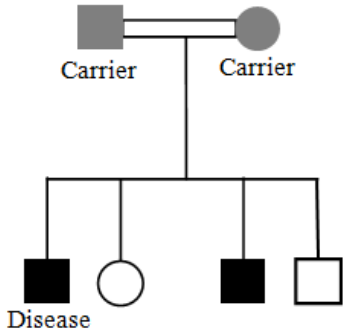
Case Report

Patient was born to a consanguineous family. My patient was a full term born male, and pregnancy was un event full throughout. In the first month of life, he presented with generalized hypotonia. One of his brother 9 years old also had similar complaints along with tonic seizures, which were managed with anti-epileptic medication in form of valproic acid, but his brother has not history of dystonia.

Patient was born to a consanguineous family. Few cases were reported from Murica in south eastern Spain in 2013. One case was reported from Iran. But no case from Pakistan is reported to date. BSCL2 is more common and severe form than BSCL1, with onset in the neonatal period or in early infancy, being more prevalent in Portugal, Lebanon, Norway, and the Middle East while BSCL 1 is found in afro American region.

The weight and height were 30 kg and 3.9 feet respectively and head circumference was 54 cm of patient.

Central nervous system examination revealed increase tone, exaggerated reflexes. There was no visceromegaly. Others systems were normal.



Family tree with proband.

Interpretation of Primary Finding

	Gene/OMIM	BSCL2/606158
	Genomic Coordinates (GRch38)	Chr11:62691317
	ID Transcript	NM_001122955.4
	HGVS nomenclature	c.967dup
	Protien Change	p.(Trp323Leufs*15)
	Location	Exon7of11
	Zygosity	Homozygous
	Function	Frameshift_elongation
	Impact	HIGH
	ClinVar	-
Allele Frequency	Local Database	-
	gnomAD	-
In silico Predictors	MetaSVM	-
	SIFT	-
	Mutation Assessor	-
	Ada-boost	-
	Clinical Significance	**Likely pathogenic (class 2)**
	ACMG Criteria	PVS1, PM2

HGVS= Human Genome Viariation Society; gnomAD= gnome Aggregation Database; ACMG= American College of Medical Genetics and Genomics; Class 1: Pathogenic; Class 2: Likely Pathogenic; Class 3: Variant of uncertain significance (VUS); Class 4: Likely benign; Class 5: benign

Whole genome sequencing report.

Routine lab studies were normal with MRI Brain revealing abnormal signals in bilateral putamen and head of caudate nuclei, periventricular and centrum semiovale with evidence of volume loss of heads of bilateral caudate nuclei resulting in dilatation of frontal horns suggestive of metabolic disorders. Electroencephalography was also done and it suggested diffuse encephalopathy and multiple epileptogenic areas.

Whole genome sequencing was done in 2021 which lead to diagnosis of diseaseand typical change on chromosome 11 leading to formation of BSCL gene lead to diagnosis.

The written consent was obtained from the family to publish the data concerning this case.

Discussion

Progressive encephalopathy is a rare diagnosis, with features similar to other neuro metabolic disorders. A mild phenotype having some characteristics similar to that seen in lipodystrophies is usually observed in most of the patients. Some of the patients may have raised triglycerides and enlarge liver but our patient had no hepatomegaly. In this study, we presented a case with developmental delay, who underwent wide neurological and metabolic studies but these were not diagnostic so we proceeded with genetic testing on the affected patient for definitive diagnosis, analysis of genome revealed a pathogenic homozygous variant in BSCL2 gene[7]. The same variant was detected in another affected sibling, while one male and female siblings were healthy.

The literature review reveled that disease is an extremely rare condition; Berardinelli was first to report a case of two year old girl from brazil with generalized congenital lipoatrophy in 1954. Later in 1959 three cases were reported by seip.[8]

Around 250 instances have been documented globally, with some ethnic groups like Latin Americans and Arabs reporting more cases than others (individuals of Portuguese and Norwegian ancestry). This is the first report of a Pediatric End-Stage Liver Disease patient from Pakistani population.

In rare genetic diseases identification of pathogenic mutation could increase the chances of final diagnosis, increase the efficacy of patient's management, counseling of affected families. However, the genetic diagnosis is difficult in Pakistan because of high cost and rarity of disease specifically when clinical features are overlapping with other neuro metabolic disorders and no alternative diagnostic approach available.

PELD is a severe neurodegenerative disorder characterized by developmental regression of motor and cognitive skills in the first years of life and often results in patient's death in the first decade of life. Exome sequencing is a reliable and rapid method for detection of the gene variants in Mendelian traits. Any patient having favorable history should be investigated and managed appropriately. All the cases must be reported to increase knowledge regarding the disease and genomic sequencing is best method to diagnose the suspected case.

Conflict of interest: None declared.

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