Unveiling the Molecular Landscape of Dandy-Walker Syndrome

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ABSTRACT

Dandy-Walker syndrome or Dandy-Walker Malformation (DWM) causes an upward rotation of the cerebellar vermis and hypoplasia, as well as cystic inflation of the fourth ventricle which affects one in every 5000 live births (MIM:220200). Motor impairments such as hypotonia, ataxia and delayed motor development are common in affected persons and roughly some have hydrocephalus and half have mental retardation. The main causes of this malformation are chromosomal anomalies, duplications, microdeletions and some de novo mutations in six genes. The two genetic loci 3q24 and 6p25.3 on human chromosomes have been identified that cause DWM. The related genes ZIC1 and ZIC4 are associated for developing cerebellum granule neurons precursor. The decrease expression of these GNPs could explain cerebellar hypoplasia due to deletion 3q24. It is important to distinguish DWM from malformations that have less severe cerebellar vermis hypoplasia, less noticeable or nonexistent upward vermis rotation, and frequently less posterior fossa fluid accumulation. Children with DWM have seizure and apnea and are hypotonic on physical examination which develop spasticity later. In this study, family from a PIMS hospital Islamabad Pakistan was examined. After a physical examination and magnetic resonance imaging, the proband was determined to have DWM. Sanger sequencing was used to examine the molecular underlying cause and pathogenic variant linked to the family's DWM. By examining the probands' sequencing results, we did not find any pathogenic missense, frameshift, or disease-causing mutations in the targeted gene ZIC1 that resulted in the hydrocephalous DWM. Further study should be suggested by performing Whole Exome Sequencing (WES) to characterize the molecular pathogenic variants that causes the malformation.

Keywords:

Dandy-Walker Syndrome, Dandy-Walker Malformation, Granule Neurons Precursor, Whole Exome Sequencing, Cerebellar Vermis Hypoplasia.

INTRODUCTION

The most prevalent congenital abnormality of the human cerebellum, Dandy-Walker syndrome (DWS), also known as Dandy-Walker Malformation (DWM), affects one in every 5000 live births (MIM:220200). Cyst development towards the base of the skull, enlargement of the fourth ventricle (a tiny channel that permits fluid to freely flow between the upper and lower sections of the brain and spinal cord), and partial or entire absence of the cerebellar vermis are the main symptoms of this syndrome (a region of the brain that connects the two cerebellar hemispheres) [6,8]. In addition to having a hypoplastic cerebellar vermis that faces away from the brainstem, DWM is distinguished by having a noticeably enlarged fourth ventricle in a bulging posterior skull [1]. Dandy and Blackfan were the first to describe the Dandy-Walker deformity [3].

It can be brought on by small deletions, chromosomal duplications and anomalies, as well as Mendelian diseases such craniocerebellocardiac syndrome [9,1]. Neurological symptoms like nystagmus, developmental delay, episodic tachypnea, seizures, dysarthria, hypotonia, ataxia and spasticity, as well as other abnormalities of the brain like agenesis or dysgenesis of the occipital encephalocele or corpus callosum, are frequently present in individuals with DWM [2,14]. The human DWM phenotypes caused by del3q24 and del6p25.3 are noticeably different, ranging from normal DWM and moderate cerebellar vermis hypoplasia (CVH), which is characterized by a smaller cerebellar vermis without the bulging of the fourth ventricle or posterior skull present in typical DWM [1,5]. Most of the cases of DWS are sporadic. Although the route of inheritance is yet unknown, it appears that first-degree relatives of DWS patients (such as siblings and particularly twins) have an elevated risk of having the disorder compared to the general population [4,20].

Several genes, including NID1, FGF17, FOXC1, LAMC1, ZIC1, and ZIC4, have been known to contain uncommon mutations [7,1]. On human chromosomes two genetic loci 3q24 and 6p25.3 that cause DWM have been identified here so far [11]. The related two genes ZIC1 and ZIC4 are found in the first of these loci. Both of the genes are widely addressed in the developing cerebellum along with granule neurons precursor (GNPs) [10,15]. Because ZIC1 is responsible for normal GNP generation while it has been proposed that decreased GNP production could explain cerebellar hypoplasia seen in the deletion (del) 3q24 DWM patients [12]. FOXC1, which is not expressed throughout cerebellar development but is found in the surrounding head mesenchyme regulates the secretion of numerous growth factors such as Tfg1 and Bmps is found in the second DWM locus [13].

Traditionally, posterior fossa cystic malformations have been classified as posterior fossa arachnoid cyst, mega cisterna magna, Dandy-Walker malformation, and Dandy Walker variant [16,19]. It might not be possible to distinguish the abnormalities precisely using imaging techniques [17]. The Dandy Walker malformation, variation, and mega cisterna magna are currently thought to represent a continuum of developmental abnormalities on a spectrum known as the Dandy Walker complex [18].

In this study, a family from Abbottabad visiting PIMS Islamabad hospital was examined. Using clinical evaluation and an MRI, the proband's Dandy-walker malformation was identified. Sanger sequencing was used to look at the molecular etiology, inheritance pattern, and causal variant of the Dandy-walker malformation in the family. The main objectives of this thesis were:

- To identify susceptible genes associated with Dandy-Walker syndrome in consanguineous family from Abbottabad, Pakistan.

- To search and identify novel variants associated with Dandy-Walker syndrome.
- Computational analysis of pathogenic disease associated variant and visualization in protein structure.

METHODOLOGY

From the PIMS hospital in Islamabad, clinical information and blood samples were gathered for this research. For a complete clinical investigation, clinical data, pedigree, photos, and recorded. For DNA extraction and molecular analysis, blood samples from family members were taken. When collecting samples from patients and family members, consideration was given to the history of the disease, the observed common phenotype, the inheritance pattern, the family history, the age of onset, consanguineous marriages in the family, and medical records. The targeted family, which consists of four family members, the parents, and the affected one, has a neurodegenerative condition. Blood samples (3-5 ml) from this family were taken in an EDTA tube. DNA was extracted by most commonly used method for extracting liquid-liquid DNA, phenol chloroform isoamyl alcohol, was employed to isolate the DNA from whole blood samples. Gel electrophoresis was used to evaluate the quantity and quality of the isolated DNA. Prime3 input was used to generate the primers for Sanger sequencing, and the reference sequence for ZIC1 was obtained from the Ensemble Genome Browser.

Table 1: Primers for PCR amplification of *ZIC1*

Primer	**Sequence**	**Length**	**TM**
ZIC1_F	5’-CCTTCAAGCTCAACCCCAGT- 3’	20bp	59.89°C
ZIC1_R	5’-CTGGGATGCGTGTAGGACTT- 3’	20bp	59.46°C

Table 2: *ZIC1* left and right primer attachment sequences

DNA Sequence	ATGCTCCTGGACGCCGGCCCCCAGTACCCAGCGATCGGCGTGACCACCTTTGGCGCGTCCCGCCACC ACTCCGCGGGCGACGTGGCCGAACGAGACGTGGGCCTGGGCATCAACCCGTTCGCCGACGGCATGG GCGCCTTCAAGCTCAACCCCAGTTCGCACGAGCTGGCTTCGGCCGGCCAGACGGCCTTCACGTCGCA GGCGCCAGGCTACGCGGCTGCTGCGGCCCTGGGCCATCACCATCACCCGGGCCACGTCGGCTCCTAT TCCAGCGCAGCCTTCAACTCCACGCGGGACTTTCTGTTCCGCAACCGGGGTTTTGGCGACGCGGCGG CGGCAGCCAGCGCACAGCACAGCCTCTTTGCTGCATCGGCCGGGGGCTTCGGGGGCCCACACGGCC ACACGGACGCCGGGGCCACCTCCTCTTCCCCGGGCTTCACGAGCAGGCTGCCGGCCACGCGTCGCCT AACGTGGTCAACGGGCAGATGAGGCTCGGCTTCTCGGGGGACATGTACCCGCGACCGGAGCAGTAC GGCCAGGTGACCAGCCCGCGTTCGGAGCACTATGCTGCGCCGCAGCTGCACGGCTACGGGCCCATG AACGTGAACATGGCCGCGCATCACGGCGCCGGCGCCTTCTTCCGCTACATGCGCCAACCCATCAAGC AAGAGCTCATCTGCAAGTGGATCGAGCCCGAGCAGCTGGCCAACCCCAAAAAGTCGTGCAACAAAA CTTTCAGCACCATGCACGAGCTAGTTACGCACGTCACCGTGGAGCACGTAGGTGGCCCGGAGCAGA GTAATCACATCTGCTTCTGGGAGGAGTGTCCGCGCGAGGGCAAGCCCTTCAAAGCCAAATACAAAC TGGTTAACCACATCCGCGTGCACACGGGCGAGAAGCCCTTTCCCTGCCCCTTCCCTGGCTGTGGCAA GGTCTTCGCGCGCTCCGAGAATTTAAAGATCCACAAAAGGACGCACACAGGGGAGAAGCCCTTCAA GTGCGAGTTTGAGGGCTGTGACCGGCGCTTCGCTAACAGCAGCGACCGCAAGAAGCACATGCACGT GCACACGAGCGACAAGCCCTATCTTTGCAAGATGTGCGACAAGTCCTACACGCATCCCAGTTCGCTG CGCAAACACATGAAGGTCCACGAATCCTCCTCGCAGGGCTCGCAGCCTTCGCCGGCCGCCAGCTCTG GCTACGAATCCTCCACGCCTCCCACCATCGTGTCTCCCTCCACAGACAACCCGACCACAAGCTCCTT ATCGCCCTCCTCCTCCGCAGTCCACCACACAGCCGGCCACAGTGCGCTCTCTTCCAATTTTAACGAAT GGTACGTTTAA

Using Bio Edit sequence alignment software, the data was analyzed after sequencing to confirm gene variations in other patients and members of the affected family, as well as to confirm the family's inheritance pattern, and a chromatogram of the sequence was created using Chromas.

RESULTS

The current study included a total of four members of a family from Abbottabad visiting PIMS hospital Islamabad, Pakistan. The family underwent a clinical examination, and the results were discussed with neurologists at the Department of Neurology in PIMS and Benazir Bhutto Hospital. Through family member interviews, a pedigree was created. In fourth generation, there were two individuals who were affected. One male (IV-1) and one female (IV-2) were identified as having the Dandy-Walker malformation phenotype at ages 7 and 3, respectively. While neither of the patients (IV-1 nor IV-2) were bedridden, they were unable to walk normally like young children.

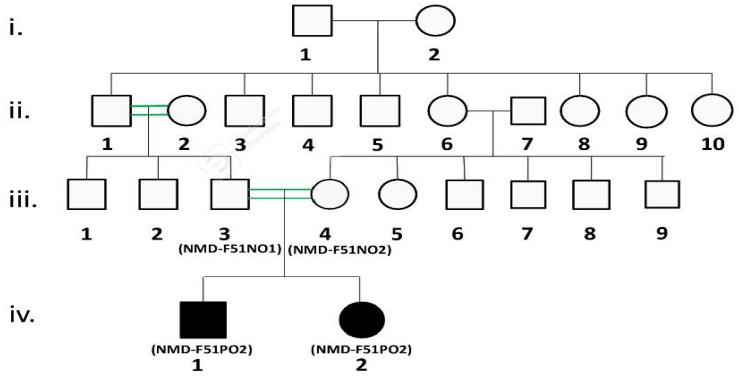

Figure 1: A pedigree of a consanguineous family with a Dandy-Walker malformation is shown, with a square denoting a male family member and a circle denoting a female member. Shaded circles/squares represent patients.

Table 3: Symptoms of the Dandy-Walker malformation patients. Yes = Present and No = Absent

Characteristics	IV.1	IV.2
Gender	**Male**	**Female**
Age (years)	7	3
Age of onset	After 1 Year	After 1 year
Symptom at age of onset	Developmental delay and intellectual disability	Developmental delay and intellectual disability
Progressive cognitive deficit	Yes	Yes
Sitting (unsupported)	Yes (up to 4 years)	Yes (up to 1.5 years)
Walking (unsupported)	No	No

Standing (unsupported)	No	No
Speech delay	No	Yes
Aggressive behavior	Yes	Yes
Self-injurious behavior	Yes	Yes
Infantile hypotonia progressing to hypertonia	Yes	Yes
Spasticity	No	No
Weakness (upper and lower limbs)	Yes	Yes
Muscles wasting (upper and lower limbs)	Yes	no
Increased deep tendon reflexes (upper and lower limbs, ankle jerk)	Yes	Yes
Babinski sign	Yes	Yes
Foot deformity	Yes (both feet)	Yes (both feet)
Impaired proprioception	Yes	Yes
Impaired vibration, pain and temperature sense	No	No
Impaired hearing and ptosis	No	No
Swallowing dysfunction	No	No
Seizures	Yes	Yes
Frequency of seizures	3 per week	1 per month
Cerebellar atrophy	Yes	Yes

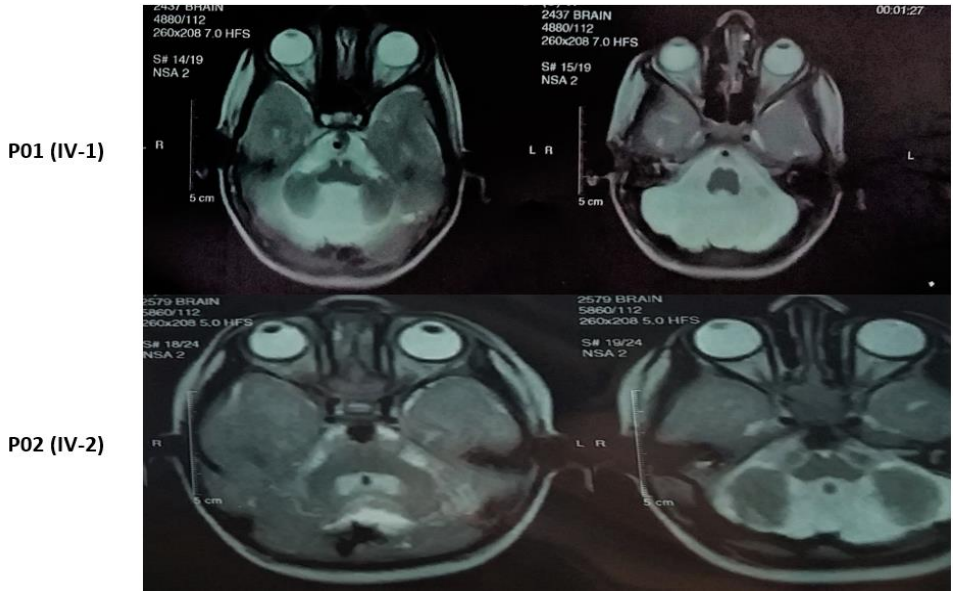

Figure 2: P01 (IV-1) MRI of the brain shows accumulation of CSF in the posterior fossa, also atrophy and hypoplasia of both cerebellar hemispheres and cerebellar vermis noted. **P02 (IV-2)** Finding of Brain MRI was there is evidence of increase extra axial CSF space is seen along bilateral cerebellar convexity as well as hypoplastic both cerebellar hemispheres and vermis. Findings were suggestive of cerebellar atrophy.

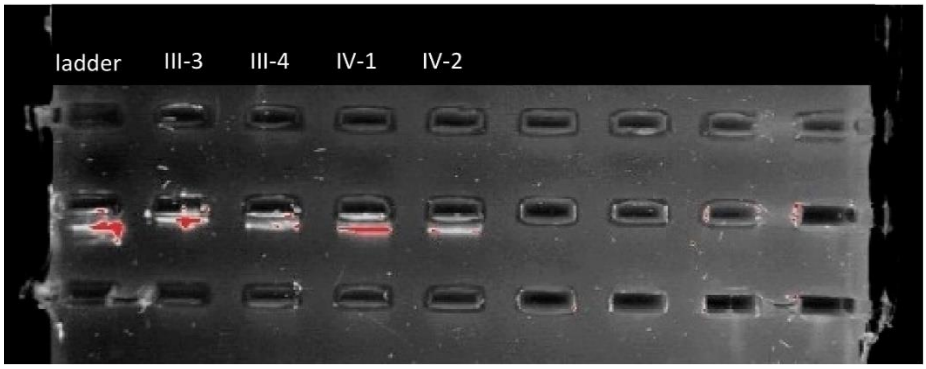

Figure 3: Agarose gel electrophoresis result of genomic DNA of III-3, III-4, IV-1 and IV-2.

PCR Amplification and Sanger Sequencing

ZIC1 was amplified by using

*ZIC1*_F: 5'-CCTTCAAGCTCAACCCCAGT-3' and

*ZIC1*_R: 5'-CTGGGATGCGTGTAGGACTT-3' primers.

At various annealing temperatures, primers were optimized and sequencing was performed in Microgen Inc. Korea.

Sanger Sequencing Analysis

For bioinformatics analysis, sequencing data was used. To verify the FASTA sequence, an online tool called BLAST was used (https://blast.ncbi.nlm.nih.gov). Using the Bio-Edit software, multiple sequence alignment for the ZIC1 sequence was carried out, with the reference sequence retrieved from (www.ensembel.org). In order to

evaluate the variant in additional family members and the pattern of inheritance of the pathogenic variant, the obtained file, an.ab1 file, was used to generate a chromatogram in the sequence alignment editor program Bio Edit.

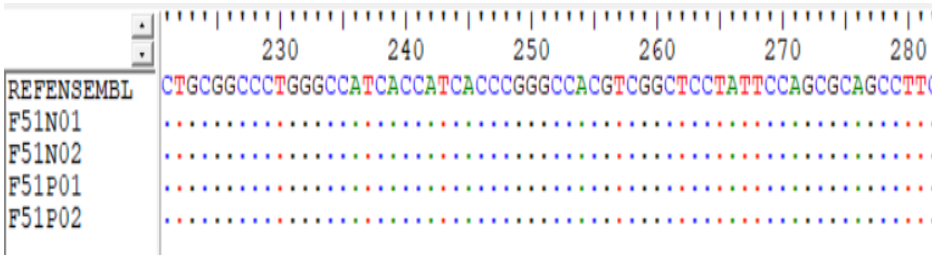

Figure 4: Gene ZIC1 multiple sequence alignment results of the Sanger sequencing

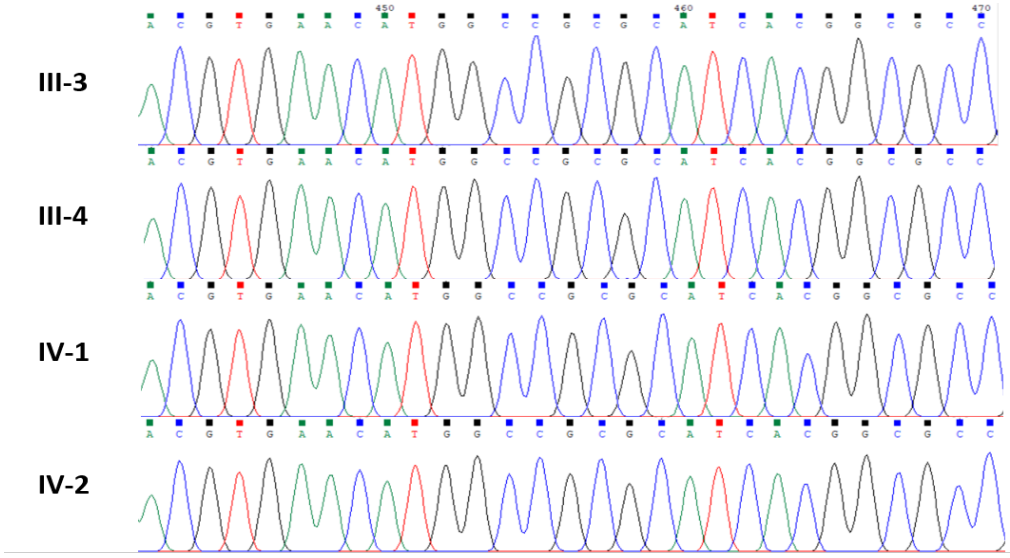

Figure 5: Sanger sequencing chromatograms for the four target family members. III-3 and III-4 are the normal members of the family (parents of the patients) and IV-1 and IV-2 are the patients of the target family. No mutation for the pathogenic variant was detected in the *ZIC1* gene which was sequenced through the Sanger sequencing. The chromatogram of the all four members showed that there is no heterozygous loss of the *ZIC1* gene.

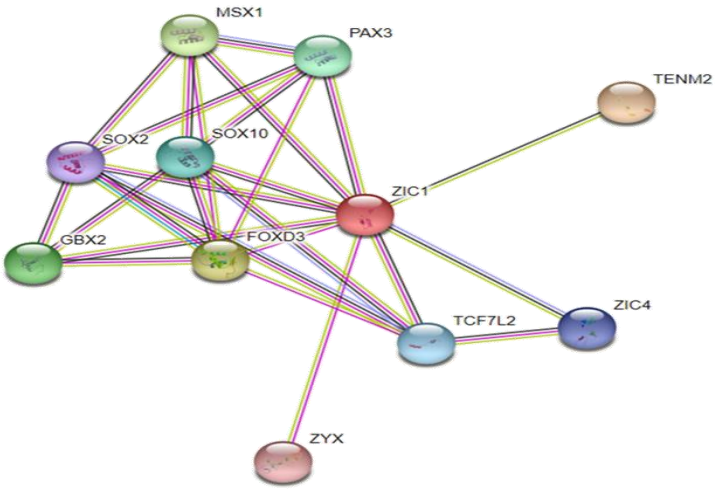

Figure 6: ZIC1 protein interactions with other proteins using the functional protein association network of STRING.

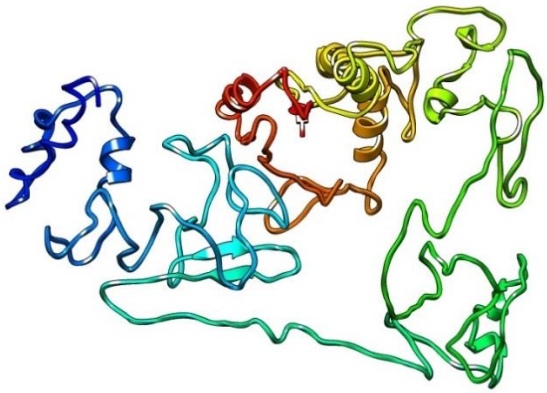

Figure 7: Protein model of the ZIC1 protein predicted by I-TASSER

DISCUSSION

DWM has a complex genetic grounding, and the genes that are involved are still widely undefined. According to [1] research, the heterozygous loss of ZIC1 and ZIC4 that results in DWM in those with 3q2 deletions, along with the low chance of clinical recurrence in humans and the varying expressivity reported in both humans and mice, lead researchers to hypothesis that changing loci may have an impact on the malformation. A 21-year-old female patient was studied by [7], and the findings of her FISH test indicated that she had an interstitial deletion of chromosome 3q23 to 3q25.1 in addition to the heterozygous deletion of ZIC1 and ZIC4 on 3q24. Following the discovery of the first significant DWM locus, recognized 6 children with 6p25 sub telomeric deletions, the second DWM locus, and (Aldinger et al., 2009) reported that DWM was caused by a variant in FOXC1 at 6p25.3.

In a male patient with a heterozygous deletion of distal 2q, a potential locus for DWM with an occipital cephalocele was discovered at 2q36.1 by linkage analysis reported by (Jalali et al., 2008) in 2008. Their family's inheritance pattern was autosomal dominant. In one study the coding areas of three DVL genes were sequenced in 480 adult Han Chinese controls and 176 stillborn or miscarried babies with neural tube defects (NTDs) or

Dandy-Walker malformation (DWM). The discovery of four rare mutations—DVL1 p.R558H, DVL1 p.R606C, DVL2 p.R633W, and DVL3 p.R222Q—indicates that these mutations, particularly DVL2 p.R633W, may be responsible for human neural diseases like NTDs and DWM by obstructing Wnt (Wingless-related integration site) signaling pathways (Liu et al., 2020). An ultrasound-detected DWM fetus in a case study by Sun Y et al. agreed to genetic testing, which revealed a micro-duplication of 12p13.33p11.1 and a microdeletion of 15q11.2 in a 750K single nucleotide polymorphism (SNP) array, as well as the karyotypic variant 46,XX,der(8)(8pter8q24::12p [3].

Fibroblast growth factors (FGFs) are important signaling molecules that work during the early vertebrate central nervous system's development. FGF17 and FGF8 have a crucial role in the patterning of the mid-hindbrain area with a complicated picture of spatiotemporal gene expression during the different phases of cerebellar development. A girl with severe growth retardation, seizures, and the classic Dandy-Walker malformation was found to have a de novo 2.3-Mb deletion of chromosome 8p21.2-p21.3 when Zanni G et al. performed gene expression analysis on blood lymphocytes and skin fibroblasts. Meanwhile, FGF17, which is located 1 Mb from the proximal deletion breakpoint, showed noticeably decreased levels. (Sun et al., 2021). It has been shown that transcriptional downregulation of the FGF17 gene is the first known cause of a cerebellar malformation in humans. According to Lida A. et al., a Japanese DWM patient had a novel intragenic 13.5-kb deletion in OPHN1 that affected exons 11 to 15 which is the first record of an OPHN1 deletion in a DWM patient from Japan [8].

In this study, we used Sanger sequencing to find a novel homozygous variant or heterozygous loss in a PIMS hospital Islamabad with symptoms of a Dandy-Walker malformation that first appeared in children. Two probands in the family had normal parents and were both diagnosed with DWM through MRI and their phenotype. The ZIC1 gene was targeted to find the novel mutations which is a good candidate gene for the malformation. By analyzing the sequencing results of probands we did not find any missense or frameshift mutation and disease-causing pathogenic variant in the targeted gene which was responsible for the hydrocephalous DWM. Whole Exome Sequencing should be performed to identify the pathogenic novel variant or heterozygous loss of the chromosome as reported previously in many studies.

CONCLUSION

A Dandy-Walker malformation was identified in a PIMS hospital Islamabad based on their clinical signs and symptoms and magnetic resonance imaging. Two patients and two healthy parents made up the family. We were unable to identify any pathogenic missense, frameshift, or disease-causing mutations in the targeted gene that caused the hydrocephalous DWM by analyzing the sequencing results of probands. We therefore recommend the whole exome or whole genome sequencing of the family for better understanding of the molecular characterization of the disease.

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