Clinical Vignette

# A Novel Pathogenic Hemizygous Variant of *AP1S2* Gene in a Child with Dandy-Walker Malformation, Developmental Delay, and Autism

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## Abstract

There is a high degree of genetic and phenotypic heterogeneity for X-linked intellectual disability. Pettigrew syndrome is a rare X-linked syndromic intellectual disorder that presents with hydrocephalus with or without Dandy-Walker malformation (DWM), basal ganglia calcification, developmental delay, autism, and seizures. This is a report of a male child who presented at the age of 7.5 years with global developmental delay, autism, and behavioral disturbances. Ultrasound during the antenatal period in the third trimester had revealed hydrocephalus. Magnetic resonance imaging (MRI) of the brain after birth showed features of hydrocephalus and DWM. The chromosomal microarray was normal. Trio whole-exome sequencing (WES) revealed a novel hemizygous pathogenic variant c.286dup (p.Ser96LysfsTer4) [NM_001369007.1] in exon 3 of the *AP1S2* gene related to Pettigrew syndrome and the mother was found to be heterozygous for the same variant. Though hydrocephalus and DWM are etiologically heterogeneous, *AP1S2* gene-related Pettigrew syndrome should be considered in individuals who are found to have these intracranial anomalies with autism and intellectual disability.

***Keywords:*** Pettigrew syndrome, *AP1S2* gene, autism, Dandy-Walker malformation

## Introduction

Pettigrew syndrome is a rare X-linked intellectual developmental disorder (Cacciagli et al., 2014) with variable phenotypic features. Global developmental delay, facial dysmorphism, and hydrocephalus are common findings of this disorder. Dysmorphic features include macrocephaly/microcephaly, high forehead, anteverted large ears, strabismus, long nose, and micrognathia. Behavioral abnormalities, autism, and abnormal gait have been reported in some patients. Cerebral calcification, iron deposition in basal ganglia, and choreoathetosis are uncommon findings. *AP1S2* gene contains five exons and codes for adaptor protein-1 (Baltes et al., 2014). *AP1S2* gene pathogenic variants and their association with Pettigrew syndrome were first identified in 2006. Till now only nine pathogenic variants have been identified in the *AP1S2* gene (Huo Let al., 2019). All these pathogenic variants are either nonsense variants or splice variants.

## Clinical report

This male child, referred at the age of 7.5 years for evaluation of global developmental delay, autism, and behavioral disturbances, was born to a healthy non-consanguineous couple. The first and second pregnancies of the couple resulted in spontaneous abortions and one pregnancy was terminated due to unilateral hydrocephalus in the fetus. The boy was born by vaginal delivery with a birth weight of 3.5 kg. There was no history suggestive of teratogenic exposures or maternal comorbidities. The nuchal scan and detailed fetal anomaly scan were normal. A growth scan at 9 months of gestation revealed hydrocephalus (ventricular atrial diameter of 17 mm) in the fetus. Postnatally, ventriculoperitoneal (VP) shunt placement was done for hydrocephalus at the age of 3 months. There was no feeding difficulty or respiratory distress**.** The child had global developmental delay and autism and was not

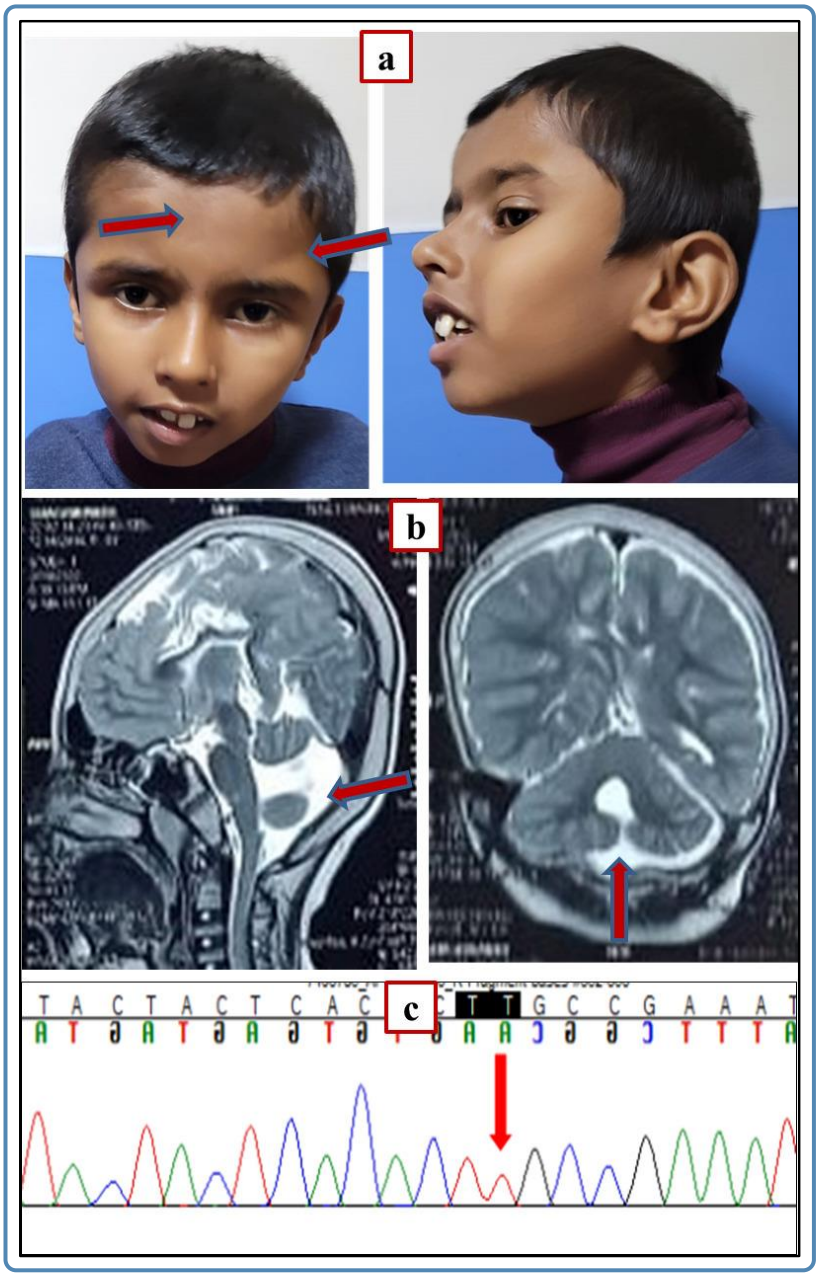


Figure 1 Clinical photographs depicting the facial, radiological, and genetic characteristics of the child

**Figure 1A**: Frontal and lateral view of the face showing dysmorphism in the form of a long face, depressed metopic suture and supraorbital ridges, flat forehead, low-set left ear, long nose, and a short philtrum

**Figure 1B**: MRI brain showing Dandy-Walker malformation

**Figure 1C**: Targeted Sanger sequencing confirmed presence of the hemizygous variant *c.286dup* in exon 3 of the *AP1S2* gene in the child

able to speak. He had not attained bladder and bowel control. There were no seizures or visual abnormalities. Hearing was impaired as per the parents. The mother was pregnant again and had been referred at around 8 weeks of gestation for prenatal genetic counselling.

On examination of the child, the head circumference was 48.5 cm ($5^{th}$-$10^{th}$ centile),

height was 122 cm (50th centile), and weight was 21 kg (25th-50th centile). There was craniofacial dysmorphism in the form of plagiocephaly, long face, depressed metopic suture and supraorbital ridges, flat forehead, low set left ear, long nose, and short philtrum (**Figure 1A**). The neck, chest, spine, and extremities were normal. The feet were flat. The child was not responding to sounds and there was no eye contact. There was hypotonia with normal deep tendon reflexes. Examination of other systems was normal. MRI brain was suggestive of communicating hydrocephalus with a Dandy-Walker malformation (**Figure 1B**). The electroencephalogram (EEG) was normal. The couple was counseled regarding the possibility of a genetic etiology. Differentials considered were either a copy number variation or a neurodevelopmental disorder with structural brain abnormalities.

Chromosomal microarray of the boy did not reveal any clinically significant copy number variants. Trio whole-exome sequencing (WES) revealed a novel hemizygous pathogenic variant (PM2, PVS1, PP3, PP4) c.286dup (p.Ser96LysfsTer4) [NM_001369007.1] in exon 3 of *AP1S2* gene related to Pettigrew syndrome. Targeted Sanger sequencing confirmed presence of the variant in hemizygous form in the child (**Figure 1C**) and revealed heterozygosity for the variant in the mother. The couple was counselled regarding the X-linked recessive inheritance of the disorder with a 50% risk of recurrence in each male offspring. They opted for prenatal genetic testing of the ongoing pregnancy and amniocentesis was done. Targeted testing of the *AP1S2* gene variant in the amniocyte DNA revealed absence of the variant in the fetus.

## Discussion

In 1973, Fried and Sanger first reported a Scottish family with X-linked mental retardation with hydrocephalus (Fried & Sanger, 1973). Later, multiple individuals with intellectual disability and Dandy-Walker malformation (DWM) with or without hydrocephalus were categorized under X-linked intellectual disability disorder and the condition was named Pettigrew syndrome (PGS) (Pettigrew et al., 1991; Cowles et al., 1993; Carpenter et al., 1999; Turner et al., 2003; Wakeling et al., 2002). *AP1S2* gene pathogenic variants and their association with Pettigrew syndrome were first identified in 2006 in families with intellectual disability and abnormal behaviour (Tarpey et al., 2006). Basal ganglia calcification is also one of the requisite findings to recognize this syndrome (Saillour et al., 2007; Borck et al., 2008; Cacciagli et al., 2014). Till now, there are only 58 patients who have been diagnosed with PGS caused by *AP1S2* mutation. Intrafamilial and interfamilial variable expressivity has been observed. Though facial dysmorphism is seen in many cases with PGS there are no specific dysmorphic features. Macrocephaly, long face, high forehead, protruding ears, strabismus, long nose, and small pointed jaw are some of the common facial features reported with PGS (Huo et al., 2019).

Imaging features of the brain may be normal in early childhood or affected individuals may have hydrocephalus, cerebellar/ posterior fossa anomalies (Strain et al., 1997), and/or iron and calcium depositions in the basal ganglia. Periventricular nodular heterotopia has also been reported. Based on imaging and brain pathology in Pettigrew syndrome, neurodegeneration begins with iron deposition. Serial imaging of the brain would be required to identify the same. Table 1 compares the clinical features in previously reported cases and our case. Female carriers are usually asymptomatic. Mild intellectual disability and iron deposition with neuroaxonal dystrophy in the basal ganglia leading to presenile dementia have been reported in a few carrier females. This could be due to skewed X inactivation (Pettigrew et al., 1991).

*AP1S2* gene has 5 exons and encodes the sigma-2 subunit of the heterotetrameric adaptor protein-1 (AP1) and plays a role in the assembly of endocytic vesicles and recognition of signals of transmembrane receptors (Baltes et al., 2014; Glyvuk et al., 2010). Till now 9 pathogenic loss-of-function variants (5 intronic variants and 4 exonic variants) have been reported (**Figure 2**). The variant identified in our patient is a novel variant. Intrafamilial and interfamilial variable expressivity are not explained by the type of pathogenic variants. Genotype-phenotype correlations are not well defined in this syndrome as there are only a few cases reported till now. Based on previous reports, those with nonsense mutations had a higher incidence of microcephaly; seizures were common in cases with splice site mutations. Our patient did not have microcephaly or seizures.

The recurrence risk estimation is by exact molecular diagnosis and carrier status of the mother. In our case as the mother was a carrier,

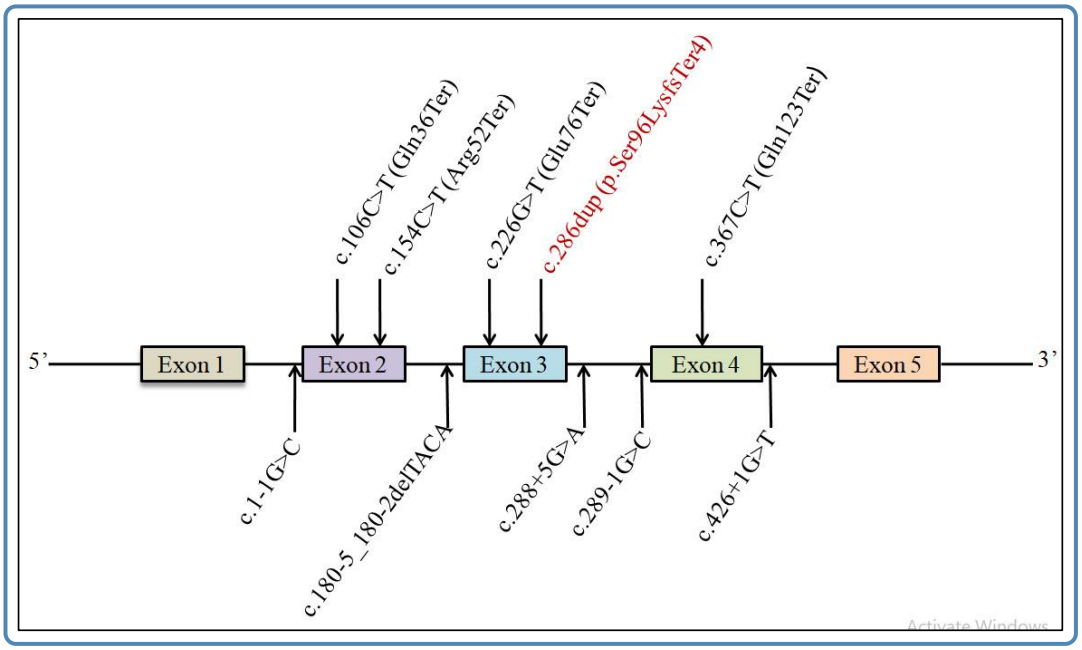


**Figure 2** Pathogenic variants reported in the *AP1S2* gene; the variant identified in our patient is shown in red font

the recurrence risk was 50% for each male offspring. If the mother is not a carrier for the disorder, the empiric recurrence risk due to gonadal mosaicism is not more than 1%. Preimplantation genetic diagnosis and assisted reproduction with use of donor ovum (for female carriers) are other available reproductive options.

## Conclusion

This case highlights that *AP1S2*-related Pettigrew syndrome, though a rare cause of X-linked intellectual disability, should be considered in cases with prenatal presentation of hydrocephalus and Dandy-Walker malformation, and postnatal presentation with autism and intellectual disability.

## Acknowledgments

The authors wish to thank the patient and family for their cooperation and for giving consent for photography.

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Table 1 Comparison of the clinical features of previously reported individuals with Pettigrew syndrome with those of our patient

| Clinical feature/finding | n-58 (% of previously reported patients) | Our patient |
|---|---|---|
| Motor developmental delay | 59% | + |
| Intellectual disability | 100% | + |
| Autism | 7% | + |
| Seizures | 82% | - |
| Aggressive behaviour | 52% | - |
| Self–abusive behavior | 48% | - |
| Facial dysmorphism | 52% | + |
| Microcephaly | 72% | - |
| Hypotonia | 53% | + |
| Abnormal gait | 26% | - |
| Hydrocephalus | 76% | + |
| Dandy-Walker malformation | 17% | + |
| Cerebral calcification | 12% | - |
| Iron deposition in basal ganglia | 9% | - |


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