Case Report

BIOMEDICAL Journal of Scientific & Technical Research

ISSN: 2574 -1241

DOI: 10.26717/BJSTR.2026.65.010224

A Ppp1r12a Gene Mutation in an Adolescent with Autism, Intellectual Disability and Polyorchidism

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ARTICLE INFO

Received: May 08, 2026

Published: May 18, 2026

Citation: Houang Muriel, Gerasimenko Anna-Gabriella, Nava Caroline and Faraj Sébastien. A Ppp1r12a Gene Mutation in an Adolescent with Autism, Intellectual Disability and Polyorchidism. Biomed J Sci & Tech Res 65(4)-2026. BJSTR. MS.ID.010224.

ABSTRACT

Background: Supernumerary testis (SNT) is a very rare condition. Here, we describe a 17-year-old adolescent with autism and an intellectual disability, as well as an SNT.

Patient: An adolescent was referred to us due to an increased, painless testicular volume. Ultrasound imaging revealed a right testis measuring 4 cm and a left testis measuring 3 cm, as well as a formation measuring 17.8 mm x 12.4 mm in contact with the head of the epididymis, accompanied by a hydrocele and dilated rete testis. Despite normal tumour markers and hormonal measurements, the diagnosis remained uncertain due to atypical imaging features. As it was not possible to confidently exclude a neoplastic process, surgical excision was performed. Histopathological examination of the paratesticular mass revealed normal testicular tissue with normal Leydig cells, an epididymis and seminiferous tubules showing evidence of different stages of spermatogenesis. There was no malignancy. Genome analysis revealed a pathogenic mutation in the PPP1R12A gene, leading to a diagnosis of Genito-Urinary and/or Brain Malformation Syndrome (GUBS) for this patient.

Conclusion: GUBS is usually associated with dysgenetic gonads. To our knowledge, this is the first reported case of polyorchidism associated with a PPP1R12A mutation, thereby expanding the phenotypic spectrum of GUBS.

Keywords: Polyorchidism; Variation in Sexual Development; Genito-Urinary and/or Brain Malformation Syndrome

Abbreviations: SNT: Supernumerary Testis; GUBS: Genito-Urinary and/or Brain Malformation Syndrome; MP: Myosin Phosphatase; ASD: Autism Spectrum Disorder; WGS: Whole-Genome Sequencing; PMDS: Persistent Müllerian Derivatives; PMDS: Primary Male Developmental Syndrome

Introduction

Protein phosphatase 1 regulatory subunit 12A (PPP1R12A) is a regulatory component of myosin phosphatase (MP) that modulates cell morphology and motility. Pathogenic variants in the PPP1R12A gene are associated with Genito-Urinary and/or Brain Malformation Syndrome (GUBS; OMIM #618820), an emerging condition characterised by brain malformations, urogenital anomalies and neurodevelopmental disorders of varying severity and combination. Since the initial report by Hughes, et al. [1], the literature has included 26 cases [1-10], displaying a phenotypic spectrum ranging from severe malformations, such as holoprosencephaly or acrania, to isolated variations in sex development or intestinal anomalies. Individuals with a 46,XY karyotype display variable degrees of genitourinary variation ranging from typical male genitalia [9,10] to hypospadias [1.3], cryptorchidism [2] to severe failure of virilisation resulting in

female gender assignment [1,2,4,5,8,9] (see table 1). Here, we present the first reported case of a 17-year-old male with autism spectrum disorder (ASD) and polyorchidism, who has otherwise normal gonadal function and hormone levels. Genetic testing identified a pathogenic nonsense variant (c.508C>T; p.Arg170*) in PPP1R12A, which expands the clinical spectrum of GUBS and suggests that PPP1R12A dysfunction affects testicular development beyond dysgenesis.

Table 1: Karyo: Karyotype, Digestive abnorm: Digestive abnormalities, Brain abnorm: Brain abnormalities, WES: whole genome sequencing, ND: not done, NA: not available, ADHD: attention deficit hyperactivity disorder.

Author	Karyo	PPP1R12A variant	Digestive Abnorm.	Genito- urinary description	Brain abnorm.	Developmental outcome	Ophtalmic findings
Hughes, et al. [1]	46,XX	c.2033_2034delCT, p.Ser678*	NA	NA	Syntelencephaly polymicrogyria; Chiari I	Intellectual disability; ADHD	Hypertelorism
Hughes, et al. [1]	46,XX	c.1415C>G, p.Ser472*	NA	NA	Semilobar holoprosencephaly; agenesis of corpus callosum	Intellectual disability	NA
Hughes, et al. [1]	46,XY	c.793-1G>A	NA	Renal asymmetry	Agenesis of corpus callosum; colpocephaly	ADHD and intellectual deficit	NA
Hughes, et al. [1]	46,XX	c.2232_2240delAC, p.Thr75Cysfs*8	NA	NA	Acrania with exencephaly	NA	Hypertelorism
Hughes, et al. [1]	46,XY	c.2739_2740delCT, p.Leu914Argfs*14	NA	Micropenis chordee; scrotal hypospadias; bilateral cryptorchidism uterus	Normal	Normal	NA
Hughes, et al. [1]	46,XY	c.1510CT, p.Arg504*	NA	Glandular hypospadias; chordee	Hydrocephalus; encephalocele; callosal dysgenesis; absent septum pellucidum; Chiari, cortical dysplasia; polymicrogyria; gray matter heterotopia	Global developmental delay; intellectual disability; autistic features	Stabismus; astigmatism; hyperopia; alternating esotropia
Hughes, et al. [1]	46,XY	c.2573G>A, p.Trp858*	blind shallow rectal cleft	Hypospadias Cryptorchidism uterus	Microcephaly; leukomalacia; opacified left tympanic cavity and mastoid air cells	Global developmental delay	
Hughes, et al. [1]	46,XY	c.2073dupA, p.Ser692Ilefs*2	Normal	Small uterus didelphys; bilateral gonadectomy	NA	Normal development	NA
Hughes, et al. [1]	46,XY	c.2698C>T, p.Arg900*	NA	Small genital Clitoral like bud ; urogenital sinus; vaginal opening; posterior fusion of labia majora	NA	NA	NA
Hughes, et al. [1]	46,XY	c.960dupA, p.Glu321Argfs*6	NA	Hypospadias cryptorchidism uterus; fallopian tube	Normal	Global developmental delay	NA
Hughes, et al. [1]	46,XY	c.1189delA, p.Thr397Hisfs*42	NA	Two streak gonads; rudimentary fallopian tubes; vaginal opening no uterus	Normal	Normal development	NA

Hughes, et al. [1]	46,XY	c.681dupT, p.Lys228*	Jejunal and ileal atresia	Normal appearing ovaries, fallopian tubes and uterus; posterior labial fusion, increased labial rugation and pigmentation	NA	Developmental delay; autism spectrum disorder	Stabismus; bilateral epicanthus inversus; right esotropia
Picard, et al. [2]	46,XY	c.2253del; p.Asp752Metfs*36	Proximal jejunal atresia; intestinal malrotation; narrowileum/ colon	Bilateral cryptorchidismute rus and fallopian tubes	NA	Normal development	NA
Picard, et al. [2]	46,XY	c.2741TA; p.Leu914*	Jejunal atresia type IIIB; multiple stenoses	Bilateral ovarian-position testes; uterus and fallopian tubes; atretic/ narrow vas deferens	NA	Learning difficulties	NA
Picard, et al. [2]	ND WES	c.2298C>A; p.Tyr766*	Small intestinalatresia involving jejunum and ileum	Cryptorchidism uterus and fallopian tubes	Cerebellar small size and cerebellar heterotopias	stillborn	Hypertelorism
Picard, et al. [2]	ND WES	Complex rearrangements in the first, non-coding, exon	Partial esophageal atresia	inguinal hernia containing a uterus and both testes on the same side typical of PMDS with transverse testicular ectopia	NA	NA	NA
Picard, et al. [2]	ND WES	c.2608C>T; p.Gln870*	NA	Bilateral cryptorchidism Müllerian remnants;	NA	Normal development	NA
Diao, et al. [3]	46,XY	c. 2666+3A>G	NA	Bilateral cryptorchidismSh ort penis; hypospadias;	Normal	NA	NA
Harris, et al. [4]	46,XY	c.3092A>T,p. Ter1031 LeuextTer71	Proximal jejunal atresia; perineal fistula	Unilateral palpable gonad penoscrotal transposition, hypospadias; uterus; unilateral renal agenesis	NA	NA	NA

Contreras -Capetillo et al. 2024	46,XY	c.1880del; p.Pro-627Leufs*4	Inguinal hernia	Small genital bud, unilateral inguinal gonad No Müllerian remnants	Temporal pseudocyst	Normal development	Hypertelorism
Tong, et al. [6]	ND	c.2533C>T, p.Arg845*	NA	Normal female genitalia	White matter softening; abnormal cerebellar signals; thinning of corpus callosum	NA	NA
Gomes, et al. [7]	46,XX	c.3092AT,p. Ter1031L euextTer71	Type III jejunal atresia; incomplete intestinal rotation; imperforate anus without fistula	Vaginal atresia; normal ovaries, fallopian tubes and uterus	Normal	Mild gross motor delay	None
Su, et al. [8]	46,XY	c.1186dupA; p.(-Thr396AsnfsTer17)	NA	bifid scrotum, perineal hypospadias normal Leydig and Sertoli cell function	Normal	NA	Normal
Tian, et al. [17]	46,XY raised as female	c.1551-2A>G (NM not specified)	NA	small genital bud, perineal hypospadias, non palpable gonads	slight enlargement of the bilateral lateral ventricles.	Normal at 3,5 y	NA
Tian, et al. [17]	46,XY raised as male	c.1551-2A>G (NM not specified)	NA	Unilateral inguinal testis well-developed penis, and scrotal hypospadias	slight enlargement of the bilateral lateral ventricles.	Normal at 3,5 y	NA
Saul, et al. [9]	ND WES	c.38A > G; p.(Gln13Arg)	Congenital jejunal atresia diagnosed prenatally, repared sugically	No anomaly	ectopic posterior pituary gland and interrupted pituary stalk	Normal	NA
Our patient	46, XY	c.508C>T, p.(Arg170*)	Unexplained chronic epigastric pain and vomiting, rectorragy	Polyorchidism Normal testicular function	No MRI	Autism complex neurodevelopmental disorder	Normal

Case Report

The patient is the second child of healthy, non-consanguineous French-Caribbean parents. His older brother had no known medical conditions and there was no notable family history. The patient was delivered by caesarean section at 34 weeks of gestation due to a breech presentation, following the premature rupture of membranes, after an otherwise uneventful pregnancy. His birth weight was 2,330 g (63rd percentile), his birth length was 45 cm (84thn percentile) and his head circumference was 33 cm (52nd percentile). The Apgar score was 10/10. The neonatal course was notable for hypotonia and

feeding difficulties; the mother reported needing to wake the infant for feeding. He achieved independent sitting before 9 months and began walking at 13 months. His expressive language was delayed, with bisyllabic words emerging at the age of three. Behavioural anomalies were prominent during childhood, including agitation, intolerance of frustration, aggressiveness and sleep disturbances. The patient benefited from psychomotor and speech therapy, and risperidone and melatonin were prescribed, providing good clinical control at the time of the last evaluation.

A neuropsychological assessment at age 12 confirmed ASD, with an ADOS score of 14 (cut- off = 8). WISC-V testing showed the following scores: VCI = 81, VSI = 105, FSIQ = 85, WMI = 91 and PSI = 86. Despite these challenges, he followed a mainstream education path and attended Year 9 with a dedicated teaching assistant at the age of 17.

The patient was referred to the paediatric endocrinology department due to increased, painless left testicular volume in a pubertal adolescent (Tanner 5). At the age of 17, his weight was 75.4 kg (+2 SD), his height was 183.4 cm (+1.8 SD); target height 177.5 cm, (+0.4 SD) and his body mass index was 22 kg/m^2 (+1.1 SD). His head circumference measured 58.5 cm (+1.5 SD). Penis length was normal, with good corpora cavernosa and no hypospadias. The right testicle measured 20 ml and the left 25 ml. Physical examination revealed joint stiffness (limited elbow xtension to 170° and ankle extension to 90°) and flat feet. Dysmorphic features included a flat facial profile, a depressed nasal bridge, down-slanting palpebral fissures, thick eyebrows with thinning of the lateral portions and broad fingers with persistent fetal pads. An ultrasound scan of the testicles showed that the right testicle measured 4 cm in length, while the left testicle measured 3 cm in length and was in contact with a 17.8 mm x 12.4 mm formation on the head of the epididymis, together with a hydrocele and a dilated rete testis (see Figure 1). Hormonal measurements and tumour markers were normal, with the following results: LH at 4.2 UI/L, FSH at 4.6 UI/L, testosterone level at 2.93 ng/ml (normal for Tanner stages 3-5), inhibin B at 305 pg/ml (normal pubertal range 100-390), and AMH at 3.92 ng/ml (normal range 2.6-76). LDH was 200 U/L (normal range 125-250), α-fetoprotein was 2.7 µg/L (normal range <10µg/L) and HCG was <1 U/L (normal range <5 U/L). Despite the normal tumour markers and hormonal measurements, the diagnosis remained uncertain due to the atypical imaging features, including a paratesticular mass associated with a hydrocele and a dilated rete testis. Given the inability to confidently exclude a neoplastic process, surgical excision was performed.

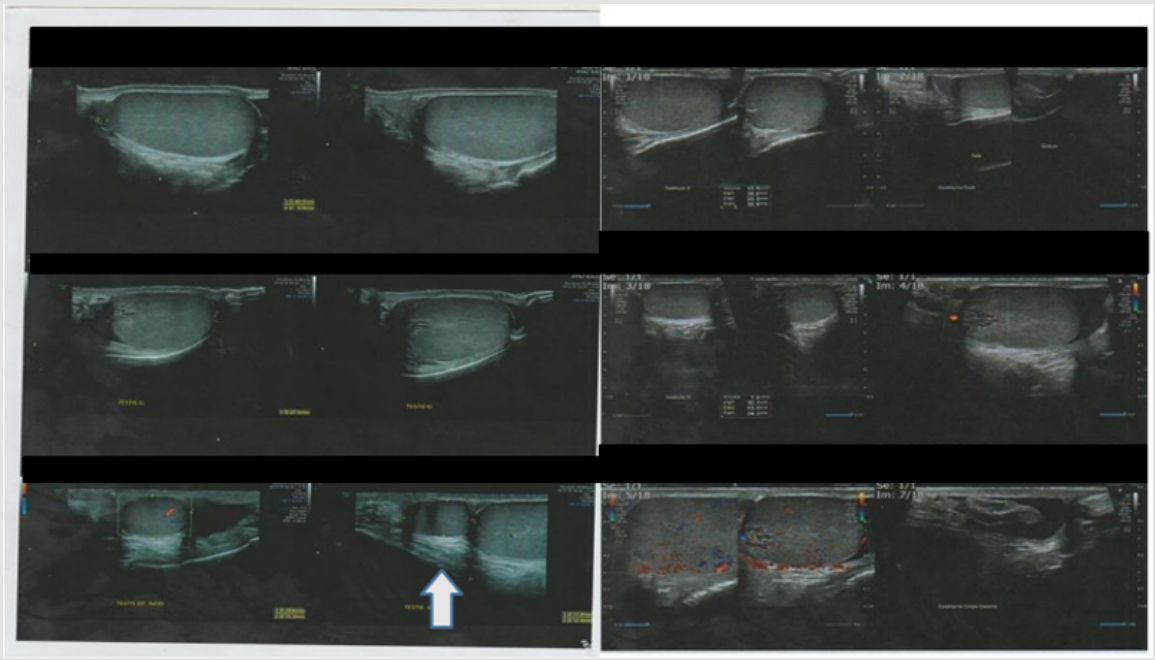

Figure 1: Ultra sound 1 Ultra sound 2
Ultrasound of the testicles : Ultrasound 1 : the right testicle is homogeneous and 4 cm in diameter ; the left testicle is slightly smaller at 3 cm. There si evidence of a formation measuring 17.8 x12.4 mm in contact with the head of the epididymis (white arrow), which was the same echostructure as the homogeneous testicle. Subsequent ultrasound (Ultrasound 2) shows normal vascularisation of the left testicle on the Doppler and anechoic reticular structures consistent with dilated rete testis.
Alt text : Two Ultrasounds Show The Left Supernumerary Testis And Dilated Rete Testis

Histopathological examination of the 3 x 1.5 cm paratesticular mass revealed a normal testis with normal Leydig cells and an epididymis measuring 3 cm in length, as well as seminiferous tubules showing evidence of different stages of spermatogenesis. There was no malignancy. Postoperative follow-up revealed that the patient still had an increased testicular volume, which was painless and soft. This was consistent with a lymphocele on ultrasound. Hormonal parameters remained within normal pubertal ranges: FSH 3.9 UI/L, LH 3.3 UI/L, testosterone 2.86 ng/ml, inhibin B 209 pg/ml (normal range 100–390), AMH 4.3 ng/ml (normal range 2.6-76), LDH 183 UI/L (normal range 125-250), HCG <2 UI/L (normal range <5 UI/L) and α-fetoprotein 3 µg/L (normal range <10 µg/L). Cardiac and abdominal ultrasounds, as well as ophthalmological and auditory examinations, were normal. Karyotype analysis revealed a normal male pattern (46, XY). SNP-array results were unremarkable. No pathogenic variants were found in MECP2, RAI1 or ARX, and FMR1 electrophoretic analysis was normal. Genome sequencing of the patient and his mother (father navailable) revealed a heterozygous variant in the PPP1R12A gene (NM_002480.3: c.508C>T, p.Arg170*). This nonsense variant, located in exon 4 of 25, is predicted to introducea premature stop codon, probably leading to the degradation of mRNA via nonsense-mediated decay (NMD), and consequently an absence of protein synthesis. This variant is absent from population databases (GnomAD v4) and has been reported as likely pathogenic in ClinVar (ID:3062288). Familial analysis showed the absence of this variant in the mother. According to the ACMG criteria, this variant is classified as 'likely pathogenic' based on PVS1 (a null variant in a gene where loss of function is a known disease mechanism) and PM2_Supporting (absent in controls).

Methods

Whole-genome sequencing (WGS) was performed using a duo-based approach at the "Laboratoire de Biologie Médicale Multi Sites SeqOIA" (https://laboratoire-seqoia.fr/). DNA was extracted from blood cells. Libraries were prepared using the Illumina DNA PCR-free Prep Tagmentation protocol. Paired-end (2 x 150 bp) sequencing was performed on a NovaSeq 6000® Flow Cell (Illumina®). The raw output was demultiplexed using bcl2fastq® (v2.20.0.422, Illumina®) and aligned to the GRCh38 reference genome with BWA-MEM2 (v2.2.1). Duplicates were marked using Picard MarkDuplicates (2.8.1) and the base quality was recalibrated using GATK4 (v4.1.9.0, Broad Institute). Small variants were identified using GATK4 (v4.1.9.0, Broad Institute) and annotated using SNPeff (v4.3t). Structural variants were identified using ClinSV (version 1.0.1) and WiseCandorX (version 1.2.4), and annotated using AnnotSV (version 3.0.7). An average depth of coverage of 37x was obtained for the proband and their mother. Variants were prioritised according to the ACMG guidelines [11].

Discussion

Polyorchidism, also known as supernumerary testis (SNT), is a very rare condition. Organ redundancy is well known in the adrenal glands, kidneys and spleen, but in the gonads it is very unusual. According to the Bergholz classification [12], there seem to be two types based on epididymal and vasal duplication. Type B corresponds to SNT with no vas deferens duct drainage. A meta-analysis of Bergholz (2009) [13] and a recent review by Balawender, et al. [14] of 279 published case reports from 2000 to 2021, mostly in adults, found that approximately 76% of SNTs were located in the scrotum and 24% were extra-scrotal. Of the testes located outside the scrotum, 87% were found in the inguinal canal and 13% in the abdominal cavity. SNT was mostly located on the left side (65% of cases). The most common symptom reported by patients was scrotal pain (31%). SNTs were incidentally diagnosed in 35% of reports during the treatment of unrelated conditions, such as inguinal hernias (15%), hydroceles (7%), or testicular torsion (7%), of the SNT itself or of the ipsilateral testis. Testicular torsion may be related to increased testicular mobility, altered gubernacular anchoring, and variable epididymal attachment. In 4% of cases, cancer was diagnosed in the SNT (seminoma, intratubular germ cell neoplasia, choriocarcinoma, teratoma, or embryonal carcinoma) [13]. Reported malignancies were associated with non-scrotal or dysgenetic gonads [15,16]. Scrotal SNTs are considered to be at low risk when associated with preserved vascularity and homogeneous parenchyma on ultrasound scans. Fertility appears comparable to that of the general population when SNT is scrotal and morphologically normal; 50-65% of individuals with polyorchidism demonstrate normal semen profiles and achieve paternity [17]. However, in Balawender's review [14], only nine patients underwent semen analysis, and five out of nine had low sperm concentration, abnormal morphology, or decreased motility. They Recommend orchidectomy for non-scrotal SNT and orchidopexy for boys and men of reproductive age with no radiological suspicion and normal hormonal and tumour marker measurements. For scrotal SNT, self-examination and follow-up with ultrasound and MRI scans of the abdomen and scrotum are recommended. The review also described nine cases of tetraorchidism, which probably corresponded to a bilobed testis, and two cases of pentaorchidism, with a bilobed testis on one side and three testicles on the other.

OMIM#618820: Genitourinary and/or Brain Malformation Syndrome (GUBS) is characterized by cerebral and urogenital anomalies associated with intellectual disability [1-10]. Brain malformations can range from moderate to severe within the holoprosencephaly spectrum, and can include dysgenesis of the corpus callosum, an absent septum pellucidum, Chiari malformations, cortical dysplasia/polymicrogyria, grey matter heterotopias, and leukomalacia. Urogenital anomalies range from hypospadias to sex reversal [9] in 46XY patients and are mostly caused by gonadal dysgenesis. This syndrome has been linked to mutations in the PPP1R12A gene [1]. This gene (MIM: 602021) encodes protein phosphatase 1 regulatory subunit 12A (PPP1R12A), which forms part of trimeric myosin phosphatase (MP) alongside protein phosphatase type 1 catalytic subunit (PP1C) and M20/21. Pathogenic variants in PPP1R12A prevent it from binding to PP1C, resulting in a non-functional MP. MP is a serine/thre-

onine-specific enzyme and a member of the protein phosphatase type 1 family. MP is known as the major regulator of smooth muscle contractility, mediating the dephosphorylation of the 20kDa myosin light chain. However, data also support its role in other non-contractile functions. PPP1R12A/MYPT1 and PP1C both localize to nuclear, mitochondrial, and plasma membrane fractions of cells [20] and are involved in a wide range of processes, including cytoskeletal processes, the control of cell proliferation and division, development, neurotransmitter release, neurodegenerative disorders, and insulin sensitivity.

In light of these functions, it is conceivable that the disruption of PPP1R12A during the early stages of gonadal development could interfere with the normal morphogenesis of the testes. This could lead to abnormal tissue partitioning or duplication, which could explain the occurrence of polyorchidism in this patient. Case reports associated with the PPP1R12A gene mutation (see Table 1) mostly describe sexual variation in the development of 46,XY patients with dysgenetic gonads and persistent Müllerian derivatives (PMDS), in five out of twelve cases [9]. These patients have low testosterone, AMH and inhibin B levels, as well as elevated FSH and LH levels. However, some patients have normal AMH measurements and an inguinal hernia containing a uterus and testes on the same side, as in typical PMDS with transverse testicular ectopia [2]. Nathalie Josso's team even suggested that myosin phosphatase could be involved in Müllerian regression independently of anti-Müllerian hormone (AMH). To our knowledge, this is the first time that polyorchidism with normal hormonal measurements has been described alongside a PPP1R12A gene mutation. This case report suggests that PPP1R12A-related disorders may encompass not only gonadal dysgenesis and primary male developmental syndrome (PMDS), but also structural anomalies in testicular development. No such association was identified in the genetic databases available, which supports the novelty of this observation. Conservative management is generally recommended for intra-scrotal supernumerary testes with normal imaging, hormonal profiles and tumour markers. In our case, however, the presence of atypical imaging findings and the inability to rule out malignancy justified surgical exploration and excision. Histopathological findings confirmed the lesion's benign nature, highlighting the diagnostic challenges in this case.

Conclusion

GUBS is usually associated with dysgenetic gonads. This case study broadens the phenotypic range of PPP1R12A-related disorders, demonstrating that they can present with polyorchidism and preserved gonadal function. It highlights the role of this gene in structural anomalies of testicular development. The case also emphasises the importance of considering a genetic evaluation for patients presenting with atypical testicular anomalies in conjunction with neurodevelopmental disorders.

Established Facts:

1. Polyorchidism is very rare, and has no known genetic cause.
2. Protein phosphatase 1 regulatory subunit 12A (PPP1R12A) is a regulatory component of myosin phosphatase (MP) that modulates cell morphology and motility.
3. PPP1R12A also has a non-contractile function and plays a role in development.
4. Genito-Urinary and/or Brain Malformation Syndrome (GUBS) is mostly associated with dysgenetic gonads and variations in sexual development and is due to PPP1R12A gene mutation.

Novel Insights:

1. We describe an adolescent with polyorchidism, autism and an intellectual disability, in whom genome analysis revealed a mutation in the PPP1R12A gene.
2. To our knowledge, this is the first reported case of polyorchidism associated with a PPP1R12A mutation, this expands the phenotypic spectrum of GUBS and highlights the role of this gene in structural anomalies of testicular development.

Statement of Ethics

Written informed consent was obtained from the mother for herself and her son for the genetic analysis, in accordance with the principles of the Declaration of Helsinki, the Council for International Organizations of Medical Sciences, Good Clinical Practice as described by the International Conference on Harmonisation guidelines, and applicable local regulations of Sorbonne University. Written informed consent was obtained from the mother of the patient for publication of the details of the medical case of her son and accompanying images.

Disclosure statement

The authors have no conflicts of interest to declare.

Funding sources

No funding was received for this paper.

Author contributions

MH collected the data, conceptualised the study and wrote the manuscript. AGG confirmed the GUBS diagnosis, collected the data and critically reviewed the manuscript. CN performed Duo-whole-genome sequencing (WGS) at the Laboratoire de Biologie Médicale Multi Sites SeqOIA, interpreted the variants and critically reviewed the manuscript. SF confirmed the SNT diagnosis and critically reviewed the manuscript.

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ISSN: 2574-1241

DOI: 10.26717/BJSTR.2026.65.010224

Houang Muriel. Biomed J Sci & Tech Res