

# CASE REPORTS

A CSPP1 VARIANT ASSOCIATED WITH METABOLIC DYSFUNCTION IN JOUBERT SYNDROME

## A CSPP1 variant associated with metabolic dysfunction in Joubert syndrome

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### Abstract

**Background:** Joubert syndrome is a genetically diverse ciliopathy defined by the presence of cerebellar vermis hypoplasia and the characteristic molar tooth sign on neuroimaging, often with neurological impairment. Pathogenic CSPP1 variants are identified in 3% of cases of Joubert syndrome. While some ciliopathies have been associated with metabolic dysfunction, this has not been described in cases of CSPP1-Joubert syndrome.

**Case Description:** We describe a 16-year-old Honduran mestiza female who has CSPP1-related Joubert syndrome and presented with insulin resistance, early-onset diabetes, dyslipidaemia, and metabolic dysfunction-associated steatotic liver disease. Importantly, she did not have the typical neurological manifestations of Joubert syndrome. Cerebellar magnetic resonance imaging demonstrated cerebellar vermis hypoplasia, which supported the diagnosis. Genetic testing identified a pathogenic heterozygous CSPP1 variant (c.3052C>T, p. Gln1018), supporting the diagnosis of CSPP1-related Joubert syndrome.

**Conclusion:** The case adds to the phenotypic spectrum of CSPP1-related Joubert syndrome, highlighting the possibility of a role for CSPP1 in metabolic homeostasis.

Further investigations are required to ascertain if mutations in CSPP1 contribute to metabolic dysfunction through ciliary or centrosomal-related mechanisms.

**Keywords:** Joubert syndrome, case report, CSPP1, diabetes, ciliopathy, primary cilium.

## Background

Joubert syndrome is a disorder with a genetic basis that manifests in cerebellar vermis hypoplasia and the characteristic “molar tooth sign” on neuroimaging, frequently with motor dysfunction and cognitive impairment. early-onset diabetes, dyslipidaemia, and metabolic dysfunction-associated steatotic liver disease (MASLD), in the absence of neurological features classically associated with JS. This case further broadens the phenotypic spectrum of CSPP1-related JS with implications pertaining to the potential role of CSPP1 in metabolic regulation.[1]

## Case Presentation

We present the case of a 16-year-old Honduran girl of mestizo background, born to non-consanguineous parents. She is the youngest of three siblings born to a 31-year-old mother and a 41-year-old father. Her pregnancy was unremarkable and was not exposed to teratogenic drugs/infections/radiation. She was born via an uncomplicated spontaneous vaginal delivery with a birth weight of 1.81 kg. There were no delays with developmental milestones. At 2 years of age, she began to lose fat progressively. Menarche occurred at age 11 years. Menstrual cycles were irregular, with menstrual bleeding lasting up to 15 days. Family history was significant for maternal hypertension and total thyroidectomy for hypothyroidism. Her father had hypertension and passed away at age 57 with lung cancer. In addition, second-degree maternal relatives had a history of diabetes and hypertension. She was previously evaluated by paediatric cardiology due to high Blood pressure. It was measured to be hypertensive (150/95 mmHg), and transthoracic echocardiography showed moderate left ventricular hypertrophy with a left

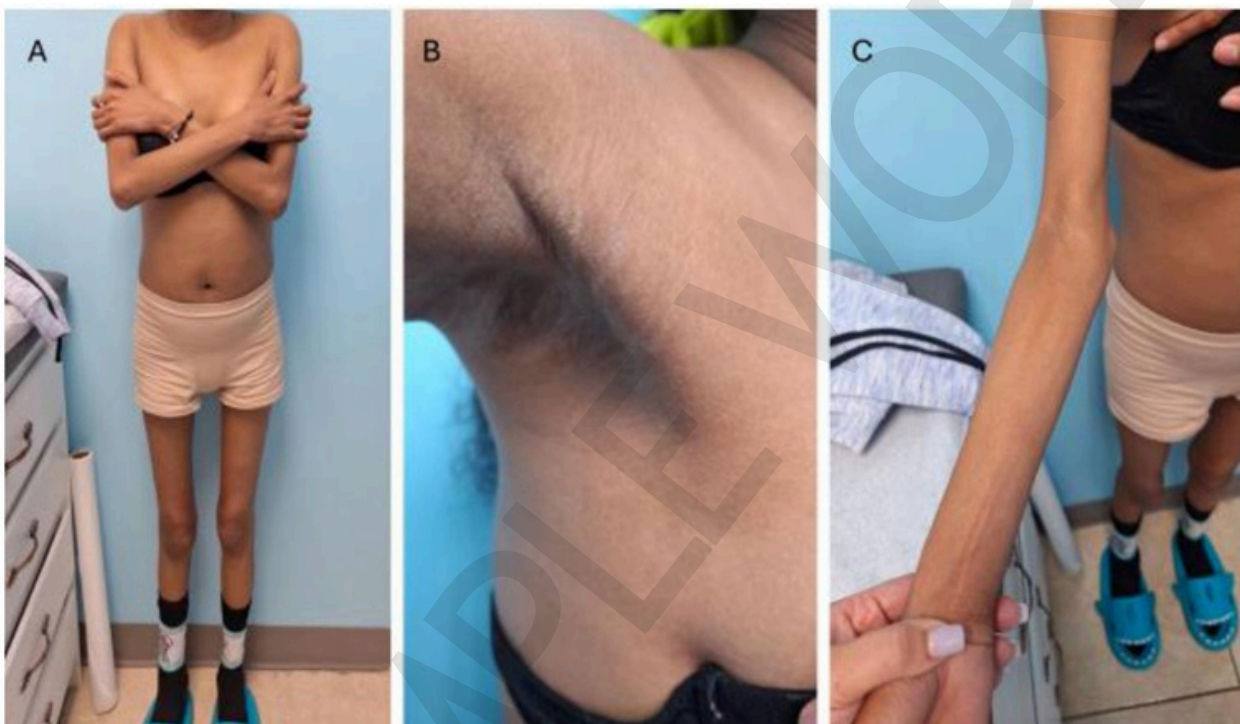
Pathogenic Variants in CPLANE1, CC2D2A, AHI1, CEP290, and TMEM67 account for approximately 6–9% of JS cases, while CSPP1 variants are responsible for about 3% of JS cases, which include kidney and liver disease, retinal dystrophy, chorioretinal colobomas, occipital encephalocele, and polydactyly, reflecting its broad clinical spectrum. We describe the case of a 16-year-old female patient with a novel pathogenic CSPP1 variant (c.3052C > T, p. Gln1018) who exhibited metabolic dysfunction [2],[3]

ventricular end-diastolic diameter of 42 mm and a left ventricular ejection fraction of 59.1%. The patient was evaluated for secondary causes of her hypertension. Sodium was 131 mEq/L, potassium was 4.1 mEq/L, and chloride was 99 mEq/L on serum electrolytes. Serum calcium measured 9.5 mg/dL, and phosphorus was 3.9mg/dL. Parathyroid hormone level was 17.7 pg/mL, and 24-h urinary cortisol was 37.57 µg/24 h. All these values were within normal limits, and the renal Doppler ultrasound was normal. The patient was started on amlodipine for the management of hypertension. The thyroid Doppler ultrasound showed a normal thyroid. Due to suspected thyroid dysfunction, she was referred to paediatric endocrinology for further evaluation. On clinical examination, the patient exhibited prominent supraorbital ridges, generalized lipoatrophy, and acanthosis nigricans at the neck, axillae, wrist, and groin (Fig. 1).

Further investigation revealed fasting blood glucose of 268 mg/dL, glycosylated haemoglobin (HbA1c) of 12.1%, fasting insulin levels of 78.4 µU/mL, C-peptide

which were 5.37 ng/mL, serum creatinine of 0.6 mg/dL, and an estimated glomerular filtration rate (eGFR) of 106 mL/min/1.73 m<sup>2</sup>. Lipid profile was significant for triglycerides of 459 mg/dL, total cholesterol of 237 mg/dL, high density lipoprotein (HDL) levels of 39 mg/dL, and low density lipoprotein (LDL) of 99 mg/dL. Liver function tests showed aspartate aminotransferase (AST) of 58 U/L and alanine aminotransferase (ALT) of 117 U/L. Total bilirubin was 0.80 mg/dL (direct bilirubin - 0.18 mg/dL; indirect bilirubin -

0.62 mg/dL). Hepatitis B surface antigen testing was negative. These laboratory findings, along with follow-up data, are summarized in Table 1. She was started on insulin therapy (18 units) immediately. Fenofibrate (160 mg daily) and omega-3 supplementation were added to treatment. Management of her diabetes and dyslipidaemia followed the American Diabetes Association Standards of Medical Care in Diabetes and the American College of Cardiology guidelines.



**Fig. 1:** Clinical features of a patient with Joubert syndrome associated with a novel CSPP1 variant; (A) generalized lipoatrophy, (B) acanthosis nigricans in the axilla, (C) acanthosis nigricans on the wrist.

At the 1-month follow-up visit, insulin therapy was adjusted with the initiation of insulin at 7–7.6 units before meals. Fasting blood glucose was 266 mg/dL, and HbA<sub>1c</sub> was 11%. Lipid profile showed total cholesterol of 277 mg/dL and triglycerides of 298 mg/dL. Liver function tests demonstrated AST at 66 U/L and ALT at 109 U/L. Serum creatinine was 0.5 mg/dL, with an eGFR<sub>m2</sub> of 128 mL/min/1.73. Leptin level was 2.1 ng/ml. Metformin was

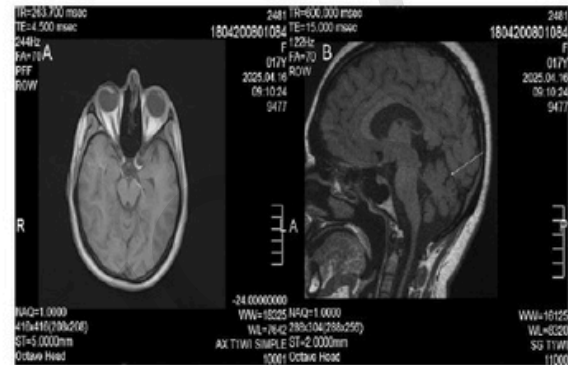
initiated at 500 mg twice a day. Vitamin E was added to the regimen, omega-3 supplementation was continued, and combined lipid-lowering therapy with rosuvastatin and fenofibrate was initiated.

During the subsequent appointment, there was an additional increase in insulin therapy to 30 units, part insulin at 10-10-10 units before meals, plus daily metformin 1000 mg. Lipid-lowering therapy was

modified to atorvastatin/fenofibrate (20/160 mg) because of elevated triglycerides (855 mg/dL) and total cholesterol (304 mg/dL). Both vitamin E and omega-3 supplementation were continued due to consistently elevated AST (155 U/L) and ALT (228 U/L). Magnetic resonance imaging (MRI) of the brain confirmed cerebellar vermis hypoplasia, which is consistent with JS (Fig. 2). Ophthalmologic

evaluation demonstrated bilateral astigmatism and myopia in the left eye. Imaging findings are summarized in Table 2. Due to failing to achieve glycaemic control, insulin therapy transitioned to a combination of insulin glargine-lixisenatide with an initial dose of 23 units and increased to 30 units later. As part of insulin adjusted to 8-8-7 units before meals.

**Fig. 2** Brain magnetic resonance imaging findings; (A) axial T1-weighted magnetic resonance imaging showing no evidence of the classic “molar tooth sign,” (B) sagittal T1-weighted magnetic resonance imaging demonstrating cerebellar vermis hypoplasia (white arrow)



**Table 1: Summary of initial and follow-up laboratory findings in a patient with CSPP1-related Joubert syndrome**

Parameter	Initial evaluation	First follow-up	Second follow-up
Electrolytes	Na: 131/K: 4.1/Cl: 99 (mEq/L)	-	-
Calcium and phosphorus	Ca: 9.5/P: 3.9 (mg/dL)	-	-
Endocrine evaluation	PTH: 17.7 (pg/mL); 24 h urinary cortisol: 37.57 (µg/24 h)	-	-
Renal function	Creatinine: 0.6 (mg/dL); eGFR: 106 (mL/min/1.73 m <sup>2</sup> )	Creatinine: 0.5 (mg/dL); eGFR: 128 (mL/min/1.73 m <sup>2</sup> )	-
Thyroid function	Free T4: 1.0 (ng/dL); TSH: 0.575 (mIU/L)	-	-
Autoimmune thyroid markers	Negative	-	-
Glucose metabolism	FG: 268 (mg/dL); HbA1c: 12.1%; insulin: 78.4 (µU/mL); C-peptide: 5.37 (ng/mL)	FG: 266 (mg/dL); HbA1c: 11%	-
Lipid profile	TC: 237/TG: 459/HDL: 39/LDL: 99 (mg/dL)	TC: 277/TG: 298 (mg/dL)	TC: 304/TG: 855 (mg/dL)

Liver function	AST: 58/ALT: 117 (U/L)	AST: 66/ALT: 109 (U/L)	AST: 155/ALT: 228 (U/L)
Bilirubin's	Total: 0.80/direct: 0.18/indirect: 0.62 (mg/dL)	-	-
Hepatitis screening	HBsAg: negative	-	-
Leptin	-	2.1 (ng/mL)	-
Autoantibodies (diabetes)	-	GAD-65 and islet cell antibodies: negative	-

*PTH parathyroid hormone, eGFR estimated glomerular filtration rate, T4 thyroxine, TSH thyroid-stimulating hormone, FG fasting glucose, HbA1c glycosylated haemoglobin, TC total cholesterol, TG triglycerides, HDL high-density lipoprotein, LDL low-density lipoprotein, AST aspartate aminotransferase, ALT alanine aminotransferase, HBsAg hepatitis B surface antigen*

**Table 2: Summary of imaging findings in a patient with CSPP1-related Joubert syndrome**

Imaging study	Findings
Transthoracic echocardiography	Moderate left ventricular hypertrophy; LVEF of 59.1%
Abdominal USG	Hepatomegaly with diffuse increased echogenicity; kidneys normal
Thyroid Doppler USG	Normal thyroid size and shape with diffuse heterogeneous echogenicity
Brain MRI	Hypoplasia of the cerebellar vermis
Renal Doppler USG	No evidence of renal artery stenosis or abnormalities

## Discussion and Conclusion

We present a case of a 16-year-old girl with a new pathogenic CSPP1 variant (c.3052C > T, p. Gln1018), who has metabolic dysfunction defined by insulin resistance, early onset of diabetes, dyslipidaemia, and MASLD. Although brain MRI results indicated hypoplasia of the cerebellar vermis, she had no neurological symptoms or developmental delay, which is atypical of CSPP1-related JS and is typically characterized by a heterogeneous phenotype and novel CSPP1 cases represent only about 9% of purely neurological Langdon-Down cases.

Additionally, mutations in CSPP1 have been associated with optic atrophy, nystagmus, oculomotor apraxia, and ptosis, the last of which is found in 51% of patients with JS with CSPP1 variants. Genotype-phenotype correlation in CSPP1 and other ciliopathies continues to be difficult, like with RPGRIP1L, MKS1, CPLANE1, CEP290 and TMEM231, where shared variants may also lead to clinically divergent phenotypes [4].

The disturbance of the functions has been associated with JS and the Jeune asphyxiating thoracic dystrophy; however, its effects on metabolic homeostasis have never been described. Since other ciliopathies, such as Alstrom syndrome, display insulin resistance and dyslipidaemia, perhaps CSPP1 could also be involved in metabolism-related pathways [5].

In our case, only a single heterozygous pathogenic variant in CSPP1 was identified, without detection of a second pathogenic allele. While this finding raises the possibility of a mild or atypical manifestation within JS, we acknowledge that cryptic second hits, such as copy number variants or deep intronic mutations, could not be ruled out. The patients were initially identified to have only one pathogenic heterozygous variant; a second cryptic mutation has been found in around 54% of cases after focused re-evaluation of the exome sequencing data. [6]. Previous studies have shown that individuals with two or more second-degree relatives affected by type 2 diabetes have an approximately 1.36-fold increased risk compared with those without such a family history [7].

A new meta-analysis shows that compared to individuals born at or over 2.5 kg, those born at less than 2.5 kg have an approximate 45% higher risk of developing type 2 diabetes, with a stronger association in females. [8]

This case adds to the phenotypic continuum of CSPP1-related Joubert syndrome, which raises the possibility of CSPP1's role in metabolic homeostasis. More work is needed to determine whether mutations in CSPP1 contribute to metabolic dysfunction through either ciliary or acentrosomal-related mechanisms, though these provide two interesting avenues to approach the study of metabolic dysregulation in this case.

## References

1. Reiter, J. F., & Leroux, M. R. (2017). Genes and molecular pathways underpinning ciliopathies. *Nature Reviews. Molecular Cell Biology*, 18(9), 533–547. <https://doi.org/10.1038/nrm.2017.60>
2. Bachmann-Gagescu, R., Dempsey, J. C., Phelps, I. G., O'Roak, B. J., Knutzen, D. M., Rue, T. C., Ishak, G. E., Isabella, C. R., Gordon, N., Adkins, J., Boyle, E. A., de Lacy, N., O'Day, D., Alswaid, A., Ramadevi A, R., Lingappa, L., Lourenço, C., Martorell, L., Garcia-Cazorla, À., ... Doherty, D. (2015). Joubert syndrome: a model for untangling recessive disorders with extreme genetic heterogeneity. *Journal of Medical Genetics*, 52(8), 514–522. <https://doi.org/10.1136/jmedgenet-2015-103087>
3. Vilboux, T., Doherty, D. A., Glass, I. A., Parisi, M. A., Phelps, I. G., Cullinane, A. R., Zein, W., Brooks, B. P., Heller, T., Soldatos, A., Oden, N. L., Yildirimli, D., Vemulapalli, M., Mullikin, J. C., NISC Comparative Sequencing Program, Malicdan, M. C. V., Gahl, W. A., & Gunay-Aygun, M. (2017). Molecular genetic findings and clinical correlations in 100 patients with Joubert syndrome and related disorders prospectively evaluated at a single center. *Genetics in Medicine: Official Journal of the American College of Medical Genetics*, 19(8), 875–882. <https://doi.org/10.1038/gim.2016.204>
4. Wang, S. F., Kowal, T. J., Ning, K., Koo, E. B., Wu, A. Y., Mahajan, V. B., & Sun, Y. (2018). Review of ocular manifestations of Joubert syndrome. *Genes*, 9(12), 605. <https://doi.org/10.3390/genes9120605>

5. Huang-Doran, I., & Semple, R. K. (2010). Knockdown of the Alström syndrome-associated gene *Alms1* in 3T3-L1 preadipocytes impairs adipogenesis but has no effect on cell-autonomous insulin action. *International Journal of Obesity* (2005) , 34(10), 1554–1558. <https://doi.org/10.1038/ijo.2010.92>
6. D'Abrusco, F., Serpieri, V., Taccagni, C. M., Garau, J., Cattaneo, L., Boggioni, M., Gana, S., Battini, R., Bertini, E., Zanni, G., Boltshauser, E., Borgatti, R., Romaniello, R., Signorini, S., Leuzzi, V., Caputi, C., Manti, F., D'Arrigo, S., De Laurentiis, A., Graziano, C., ... Valente, E. M. (2025). Pathogenic cryptic variants detectable through exome data reanalysis significantly increase the diagnostic yield in Joubert syndrome. *European journal of human genetics : EJHG*, 33(1), 72–79. <https://doi.org/10.1038/s41431-024-01703-x>
7. Smith, K. R., Meeks, H., Curtis, D., Brown, B. B., Kole, K., & Kowaleski-Jones, L. (2025). Family history of type 2 diabetes and the risk of type 2 diabetes among young and middle-aged adults. *Chronic Diseases and Translational Medicine*, 11(1), 46–56. <https://doi.org/10.1002/cdt3.147>
8. Knop, M. R., Geng, T.-T., Gorny, A. W., Ding, R., Li, C., Ley, S. H., & Huang, T. (2018). Birth weight and risk of type 2 diabetes mellitus, cardiovascular disease, and hypertension in adults: A meta-analysis of 7 646 267 participants from 135 studies. *Journal of the American Heart Association*, 7(23), e008870. <https://doi.org/10.1161/JAHA.118.008870>

SAMPLE WORK