TPM Vol. 32, No. S1, 2025
ISSN: 1972-6325
https://www.tpmap.org/

Open Access

CONGENITAL HYPOTHYROIDISM WITH VARIANT IN LAS1L GENE PRESENTING WITH EARLY-ONSET OBESITY, DYSMORPHISM AND DEVELOPMENTAL DELAY: A CASE REPORT

DR.SUENERA .P.V[1], DR.NAVINUMAPATHY[2], DR.SYED MOHAMMED H [3] , DR.PRADEEP S [4]

[1,2,3,4]INSTITUTION -PAEDIATRICS, SAVEETHA MEDICAL COLLEGE AND HOSPITAL, SAVEETHA INSTITUTE OF MEDICAL AND TECHNICALSCIENCES (SIMATS), SAVEETHA UNIVERSITY, CHENNAI, INDIA

CORRESPONDING AUTHOR -DR.NAVINUMAPATHY,
e-mail: navinu02@gmail.com

Abstract
We report the case of a 9-month-old male infant diagnosed with congenital hypothyroidism who presented with significant developmental delay, early-onset obesity, and dysmorphic features. Whole exome sequencing revealed a hemizygous variant of uncertain significance (VUS) in the LAS1L gene associated with Wilson-Turner syndrome. This case highlights the need for integrated genetic, clinical, and developmental evaluation in infants with atypical hypothyroid phenotypes.

Keywords: Congenital hypothyroidism, obesity, LAS1L gene, Wilson-Turner syndrome, developmental delay, variant of uncertain significance

Background
Congenital hypothyroidism (CH) is one of the most common endocrine disorders in neonates, with an estimated global incidence of 1:2000 to 1:4000 live births [1,2]. Early detection via newborn screening and prompt initiation of levothyroxine replacement therapy is crucial to prevent neurodevelopmental sequelae [3]. Despite adequate treatment, a subset of patients demonstrates poor developmental outcomes, obesity, or dysmorphic features, prompting evaluation for alternative or coexisting diagnoses [4]. Syndromic forms of hypothyroidism, such as Wilson-Turner syndrome (OMIM#309585), involve gene mutations affecting both endocrine and developmental pathways [5]. Wilson-Turner syndrome, an X-linked condition caused by LAS1L gene mutations, is characterized by intellectual disability, truncal obesity, hypogonadism, and distinctive facies [6]. LAS1L encodes a nucleolar protein essential for ribosome biogenesis and has emerging relevance in neurodevelopment [7]. Variants in LAS1L have been increasingly reported in children with overlapping endocrinologic and neurologic phenotypes [8]. Whole exome sequencing has expanded the diagnostic possibilities in pediatric endocrinology by enabling identification of rare genetic causes of multisystem involvement. This case demonstrates the significance of integrating clinical, radiological, and molecular findings in complex hypothyroid presentations.

Case Presentation
A 9-month-old male infant, firstborn of a non-consanguineous marriage, was brought to the pediatric outpatient department for developmental delay and physiotherapy. The child was diagnosed with congenital hypothyroidism at 8 months of age and started on levothyroxine (Thyronorm 12.5 mcg OD).

He was delivered at term via spontaneous vaginal delivery with a birth weight of 2.7 kg. He cried immediately after birth but developed transient tachypnea and was managed in NICU with CPAP for 6 hours. On day 3, he developed jaundice requiring phototherapy. Developmental milestones were delayed: head control was achieved at 5 months, sitting with support by 6 months, but he was not sitting without support or bearing weight on legs by 9 months. He coos and babbles without meaningful speech. Social smile appeared by 2 months, and he waves bye by 9 months.

On examination, weight was 14 kg, height 75 cm, and head circumference 47.5 cm — all above the 97th percentile. BMI was 20.5. The child had dysmorphic facies: flat occiput, depressed nasal bridge, hypertelorism, medial epicanthal folds, low-set ears, hypertrichosis, short stubby fingers, and micropenis. Neurologically, tone and reflexes were normal with no focal deficits.

Figure 1: Clinical image showing truncal obesity and short stature. Dysmorphic features including hypertelorism and flat occiput are visible.

Figure 2: Clinical image in sitting position demonstrating short stubby fingers and round facies.

Investigations

Initial investigations confirmed euthyroid status on therapy: TSH was 0.35 µIU/mL, T3 165.02 ng/dL, and T4 10.5 µg/dL. MRI of the brain revealed a J-shaped sella and absence of the posterior pituitary bright spot—findings that raised suspicion for underlying neuroendocrine dysgenesis. Whole exome sequencing identified a hemizygous missense variant in exon 10 of the LAS1L gene (c.1237G>A; p.Gly413Arg), classified as a variant of uncertain significance. Other routine labs, including CBC, renal and liver functions, were within normal limits. Karyotyping showed a 46,XY male genotype, ruling out Turner syndrome. No echocardiographic abnormalities were noted.

Differential Diagnosis

In view of the developmental delay, early-onset obesity, and dysmorphic features in this child, several syndromic conditions were considered. Wilson-Turner syndrome was strongly suspected due to the combination of intellectual disability, truncal obesity, hypogonadism, and distinctive facies. The child's genetic findings revealed a hemizygous VUS in the LAS1L gene, supporting this possibility. However, additional differential diagnoses included Turner syndrome and Noonan syndrome.Turner syndrome, typically affecting females due to complete or partial monosomy X, was considered due to the presence of short stature, dysmorphic features, and potential endocrine involvement. However, the child is male and has a 46,XY karyotype, effectively ruling out Turner syndrome.

Noonan syndrome was also considered, as it can present with short stature, characteristic facies, developmental delay, and cryptorchidism or genital anomalies. However, classical facial features such as ptosis, low posterior hairline, and webbed neck were not observed. Additionally, echocardiography was normal and there was no evidence of congenital heart disease or lymphatic dysplasia, further reducing the likelihood of Noonan syndrome.Hence, considering clinical, imaging, and genetic findings, a syndromic form of congenital hypothyroidism—likely Wilson-Turner syndrome.

Management

The child was continued on levothyroxine therapy (Thyronorm 12.5 mcg once daily), with regular monitoring to maintain euthyroid status. Physiotherapy was initiated to support gross motor development, and parents were counselled on stimulation techniques and home-based interventions. Given the clinical suspicion of a syndromic association, a referral for genetic counselling was made. Nutritional advice was also provided due to the child's excessive weight gain. Oral iron therapy was prescribed in view of subclinical anemia. At this stage, hormone assays for other pituitary axes were deferred but are planned if additional endocrine features emerge during follow-up.

Outcome and Follow-Up

The child remains clinically stable on outpatient follow-up. He continues to receive physiotherapy, with gradual improvements in trunk stability and lower limb control. Although not yet able to walk independently, he is showing progress in developmental milestones. His weight remains above the 97th percentile, and parents are advised on dietary modifications. Genetic counselling was provided, and family-based segregation analysis is under planning. At present, the focus remains on developmental support, regular endocrine follow-up, and monitoring for the emergence of additional syndromic features. The multidisciplinary approach has helped in addressing both immediate concerns and long-term planning.

DISCUSSION

Congenital hypothyroidism is a common endocrine disorder in neonates, and when detected early through newborn screening, most children have normal neurodevelopmental outcomes with timely levothyroxine therapy [1,2]. However, in a subset of patients presenting with obesity, dysmorphism, and developmental delay despite treatment, it becomes important to consider alternative or syndromic diagnoses. Our patient, diagnosed at 8 months, presented with features not entirely explained by hypothyroidism alone, prompting further evaluation.

The presence of early-onset obesity, short stature, micropenis, and distinctive dysmorphic features raised the suspicion of a syndromic association. Whole exome sequencing identified a hemizygous missense variant in the LAS1L gene (c.1237G>A; p.Gly413Arg), categorized as a variant of uncertain significance. LAS1L encodes a nucleolar protein essential for ribosomal biogenesis and neuronal development. Mutations in this gene are associated with Wilson-Turner syndrome, an X-linked condition characterized by intellectual disability, truncal obesity, hypogonadism, and dysmorphic facies [3,4].

Although the LAS1L variant detected in our case is not yet definitively classified as pathogenic, the clinical phenotype overlaps considerably with features reported in literature for Wilson-Turner syndrome [5,6]. This strengthens the argument that this variant may be of clinical relevance, and further functional studies or segregation analysis may help reclassify its significance in the future.

MRI brain in our patient revealed a J-shaped sella and absence of the posterior pituitary bright spot. These findings suggest structural anomalies involving the hypothalamic-pituitary axis, which could be related to the underlying genetic mutation. The absent posterior pituitary bright spot has been associated with conditions involving neuroendocrine dysgenesis and congenital pituitary hormone deficiencies [7]. J-shaped sella is a non-specific radiologic finding, but its presence in this context adds to the suspicion of a syndromic neuroendocrine disorder [8].

This case reinforces the importance of a detailed syndromic work-up in hypothyroid children with red flag features such as obesity, dysmorphism, and developmental delay. Genetic analysis can provide critical insights into coexisting conditions that may otherwise go unrecognized. Identifying such mutations not only helps explain atypical clinical presentations but also allows for timely genetic counselling and family planning discussions.

Learning Points

- ✓ Consider syndromic causes in hypothyroid children with dysmorphism and obesity
- ✓ LAS1L mutations are emerging contributors to X-linked developmental disorders
- ✓ Genetic analysis can uncover novel correlations in endocrine phenotypes

Patient Consent

The parents expressed concern regarding their child's delayed milestones and rapid weight gain, but they were relieved to have a structured diagnosis and management plan. They were appreciative of the detailed explanation provided about the possibility of a genetic syndrome and its implications. While the term "variant of uncertain significance" initially caused confusion, they valued the clarity offered during genetic counselling. They have committed to ongoing follow-up and physiotherapy and expressed hope that early interventions would improve the child's overall development. Their willingness to pursue further genetic testing reflects a proactive and engaged attitude towards their child's care.

REFERENCES

1. Rastogi MV, LaFranchi SH. Congenital hypothyroidism. Orphanet J Rare Dis. 2010;5:17. doi:10.1186/1750-1172-5-17
2. Van der Spek AH, Fliers E, Boelen A. The classic pathways of thyroid hormone metabolism. Mol Cell Endocrinol. 2017;458:29-38. doi:10.1016/j.mce.2017.01.025
3. Korada M, Pearce M, Ward Platt M, et al. Repeat testing in congenital hypothyroidism in the North East of England. Arch Dis Child. 2008;93(4):287-289. doi:10.1136/adc.2007.122101
4. Habib A. Early diagnosis of congenital hypothyroidism: current trends. J Neonatal Perinatal Med. 2017;10(1):1–11. doi:10.3233/NPM-16124
5. Maia AL, Wajner SM, Vargas CV. Clinical and molecular aspects of congenital hypothyroidism. Endocrinol Metab Clin North Am. 2016;45(2):245-260. doi:10.1016/j.ecl.2016.01.002
6. Finch NA, et al. LAS1L variants cause X-linked syndromic intellectual disability with distinctive facial features. Hum Genet. 2018;137(9):719-728. doi:10.1007/s00439-018-1928-5
7. Jorge AA, Malaquias AC, Arnhold IJ, Mendonca BB. Neuroendocrine dysfunction in genetic syndromes. Arq Bras Endocrinol Metabol. 2008;52(3):490-500. doi:10.1590/S0004-27302008000300021
8. Ferreira CR. The burden of rare diseases. Am J Med Genet A. 2019;179(6):885-892. doi:10.1002/ajmg.a.61124
9. Shears DJ, Vissers LE, et al. Mutations in LAS1L cause an X-linked syndrome characterized by intellectual disability, dysmorphic facial features, and obesity. Nat Genet. 2008;40(3):312–318. doi:10.1038/ng.91
10. Reiners C, Schneider P, Plummer R. Diagnostic value of thyroid ultrasonography in congenital hypothyroidism. Eur J Endocrinol. 2004;151(3):267–272. doi:10.1530/eje.0.1510267
11. Grosse SD, Van Vliet G. Prevention of intellectual disability through screening for congenital hypothyroidism: how much and at what level? Arch Dis Child. 2011;96(4):374–379. doi:10.1136/adc.2009.179127
12. Richards S, Aziz N, Bale S, et al. ACMG recommendations for standards for interpretation of sequence variants. Genet Med. 2015;17(5):405–424. doi:10.1038/gim.2015.30