Endocrinology, Diabetes & Metabolism CASE REPORTS

R Gonsalves and others | SIM1 obesity and hypopituitarism

ID:20-0042;September2020
DOI: 10.1530/EDM-20-0042

# Severe early onset obesity and hypopituitarism in a child with a novel *SIM1* gene mutation

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## Summary

Single-minded homolog 1 (SIM1) is a transcription factor that plays a role in the development of both the hypothalamus and pituitary. *SIM1* gene mutations are known to cause obesity in humans, and chromosomal deletions encompassing *SIM1* and other genes necessary for pituitary development can cause a Prader–Willi-like syndrome with obesity and hypopituitarism. There have been no reported cases of hypopituitarism linked to a single *SIM1* mutation. A 21-month-old male presented to endocrinology clinic with excessive weight gain and severe obesity. History was also notable for excessive drinking and urination. Endocrine workup revealed central hypothyroidism, partial diabetes insipidus, and central adrenal insufficiency. Genetic evaluation revealed a novel mutation in the *SIM1* gene. No other genetic abnormalities to account for his obesity and hypopituitarism were identified. While we cannot definitively state this mutation is pathogenic, it is notable that SIM1 plays a role in the development of all three of the patient's affected hormone axes. He is now 6 years old and remains on treatment for his pituitary hormone deficiencies and continues to exhibit excessive weight gain despite lifestyle interventions.

## Learning points:

- Mutations in *SIM1* are a well-recognized cause of monogenic human obesity, and there have been case reports of Prader–Willi-like syndrome and hypopituitarism in patients with chromosomal deletions that contain the *SIM1* gene.
- *SIM1* is expressed during the development of the hypothalamus, specifically in neuroendocrine lineages that give rise to the hormones oxytocin, arginine vasopressin, thyrotropin-releasing hormone, corticotropin-releasing hormone, and somatostatin.
- Pituitary testing should be considered in patients with severe obesity and a known genetic abnormality affecting the *SIM1* gene, particularly in the pediatric population.

## Background

Single-minded homolog 1 (*SIM1*) gene mutations cause monogenic forms of obesity in humans (1, 2). Within the hypothalamus, SIM1 is a transcription factor expressed during the development of the paraventricular nucleus (PVN), anterior periventricular nucleus (aPV), and supraoptic nucleus (SON) (3). The PVN contains the melanocortin 4 receptor (MC4R), a key component of appetite regulation and energy homeostasis. Mutations in *SIM1*, which acts downstream of the MC4R, may contribute to obesity via alteration of the leptin-melanocortin-oxytocin pathway (4) or through regulation of energy balance (5).

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The PVN, aPV, and SON give rise to neuroendocrine cells that produce the hormones oxytocin, arginine vasopressin (AVP), thyrotropin-releasing hormone (TRH), corticotropin-releasing hormone (CRH), and somatostatin (3). Mice homozygous for a null allele of *SIM1* die shortly after birth and have hypocellular PVN and SON (3). Other studies have shown that *SIM1* heterozygous mice exhibit significantly decreased mRNA levels of CRH, TRH, and AVP (6). To our knowledge, there have been no cases of *SIM1* mutations resulting in hypopituitarism in humans.

Previous case reports have described children with early onset obesity and hypopituitarism found to have deletions in chromosome 6q16, which contains the *SIM1* gene (7, 8). These 6q16 deletions also contain the gene for POU Domain, class 3, transcription factor 2 (POU3F2), which acts in a cascade with SIM1 in the differentiation of neurons that produce AVP, TRH, and CRH (3). The hypopituitarism in these patients was largely attributed to the combination of *SIM1* and *POU3F2* deletions. We describe a patient with severe early onset obesity and hypopituitarism found to have a maternally inherited *SIM1* gene variant of uncertain significance which has moderate overlap with his clinical presentation.

## Case presentation

A 21-month-old male was referred to an outpatient pediatric endocrinology clinic by his general pediatrician due to abnormal weight gain and obesity. He was born full term and was appropriate for gestational age with a birth weight of 3880 g. Gestation was uncomplicated; however, at delivery he required emergent Cesarean section for fetal decelerations and received therapeutic hypothermia due to concern for hypoxic–ischemic encephalopathy. A brain MRI obtained after therapeutic hypothermia was unremarkable with normal midline structures and no evidence of hemorrhage.

Review of growth charts noted increasing weight percentiles from 21% at 6 weeks, 62% at 3 months, 80% at 5 months, 89% at 9 months, and 98% at 12 months (Fig. 1). Length and head circumference were normal and increasing appropriately throughout these time points. Mother reported a typical infant diet, though noted weight gain became more severe starting at approximately 12 months of age which is when he was started on whole milk. There was no noted polyphagia or lack of satiety. At the time of endocrine evaluation, his weight-for-length z-score was +4.9. Labs obtained by his pediatrician were significant for a low free T4 of 0.5 ng/dL (0.85–1.75)/6.44 pmol/L (10.9–22.5), with a normal TSH of 2.31 µU/mL

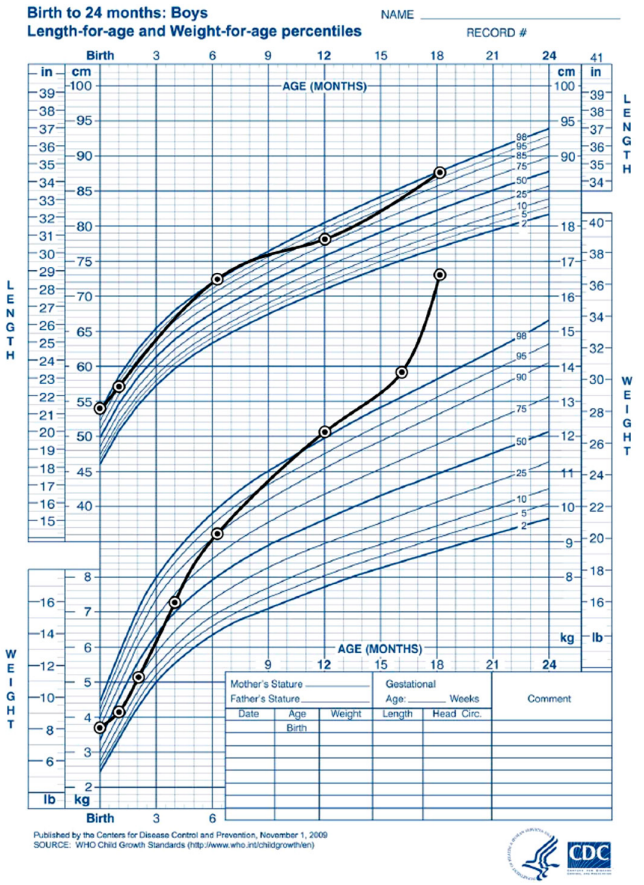


**Figure 1**
Patient growth chart at presentation.

(0.5–5.5), and otherwise unremarkable electrolytes and glucose. Additional history revealed significant polyuria and polydipsia, with greater than 10 wet diapers during the day and multiple overnight diaper changes. He drank approximately 10 ounces of water or milk every 2 h, and woke up in the middle of the night demanding his cup. He would only fall back asleep after drinking.

Family history was significant for obesity in the patient's mother. She has no additional medical issues, nor does she has symptoms suggestive of diabetes insipidus or adrenal insufficiency. Her thyroid function has been tested and is normal. The patient's father is overweight and has no known medical issues. The patient's maternal grandmother has type 2 diabetes and is overweight, but does not have any additional medical issues. The maternal grandfather and paternal grandparents do not have any significant medical issues. The patient does not have any siblings. There are no known pituitary abnormalities in the family.

Other than obesity, his physical exam was unremarkable. His eye exam was normal without

nystagmus. There were no features such as cleft lip, cleft palate, central incisor, or microphallus to suggest possible underlying hypopituitarism. There were no dysmorphic features associated with Prader–Willi syndrome such as small hands and feet, hypotonia, or almond-shaped palpebral fissures.

## Investigation

The results of his endocrine workup are detailed in Table 1, which contains both Conventional and International System (SI) of Units with reference ranges where applicable. A water deprivation test revealed partial diabetes insipidus (DI) after 20 h of fasting, with urine osmolality of 385 mOsm/kg (mmol/kg) when serum osmolality was 302 mOsm/kg (mmol/kg). Urine concentrated to 569 mOsm/kg (mmol/kg) after administration of desmopressin. Repeat thyroid function testing confirmed central hypothyroidism. A low-dose (1 µg) cosyntropin stimulation test revealed a baseline cortisol of 5 µg/dL (138 nmol/L), with 30-min level of 11.7 µg/dL (323 nmol/L) and 60-min level of 12.4 µg/dL (342 nmol/L), consistent with central adrenal insufficiency. Growth factors were normal. Brain MRI revealed a small anterior pituitary with no posterior pituitary visualized**.**

Genetic testing revealed a normal chromosomal microanalysis and Prader–Willi DNA methylation analysis. Whole-exome sequencing (Invitae) of the patient and both parents revealed a maternally inherited variant of uncertain significance in the *SIM1* gene: c.214C>T (p.Pro72Ser). Algorithms developed to predict the effect of missense changes on protein structure and function (SIFT, PolyPhen-2, Align-GVGD) all suggested the variant is likely to be tolerated, however, this has not been confirmed by published functional studies. Sanger analysis was not performed. This variant has not been reported in the literature in individuals with *SIM1*-related disease, however, is present in population databases (rs138378566, ExAC 0.03%).

## Treatment, Outcome and Follow-up

He was started on levothyroxine, hydrocortisone, and desmopressin for his pituitary hormone deficiencies, and remains on these medications at 6 years of age. His pattern of severe rapid weight gain continued despite multiple lifestyle interventions including daily physical activity, and dietary changes such as limiting sugary drinks, increasing vegetable intake, and instituting portion control. His linear growth has been appropriate, and height was at the 98th percentile with BMI z-score of +3.4 at his most recent endocrinology follow-up. The patient's growth chart through 6 years of age is provided in Fig. 2. There have been no signs of adrenarche or early puberty. Thyroid function is checked periodically, and levothyroxine has been adjusted to keep free T4 in upper half of the normal range. He has not had any additional pituitary testing. His most recent lipid panel and hemoglobin A1c were normal, however he recently developed mildly elevated transaminases and is being evaluated by gastroenterology for possible non-alcoholic fatty liver disease (NAFLD).

## Discussion

This patient was referred to endocrinology for early onset obesity and was subsequently discovered to have

**Table 1** Relevant endocrine laboratory values.

| Analyte | Conventional units | SI units |
|---|---|---|
| TSH | 2.41 µU/mL (0.5–5.5) | 2.41 mIU/L (0.5–5.5) |
| Free T4 | 0.5 ng/dL (0.85–1.75) | 6.44 pmol/L (10.9–22.5) |
| IGF-1 | 44 ng/mL (30–122) | 5.76 nmol/L (39.3–15.9) |
| IGFBP-3 | 2150 ng/mL (972–4123) | 282 nmol/L (127.3–540.1) |
| Completion of water deprivation test* | | |
| Urine osmolality | 385 mOsm/kg | 385 mmol/kg |
| Serum osmolality | 302 mOsm/kg | 302 mmol/kg |
| Serum sodium | 147 mEq/L (133–145) | 147 mmol/kg (133–145) |
| Low-dose cosyntropin stimulation test | | |
| Baseline cortisol | 5.0 µg/dL | 138 nmol/L |
| 30-min cortisol | 11.7 µg/dL | 323 nmol/L |
| 60-min cortisol | 12.4 µg/dL | 342 nmol/L |

Reference ranges provided in parentheses where applicable.
*Water deprivation test terminated after 20 h.
IGF-1, insulin-like growth factor 1; IGFBP-3, insulin-like growth factor binding protein-3; SI, International System of Units; TSH, Thyroid stimulating hormone.

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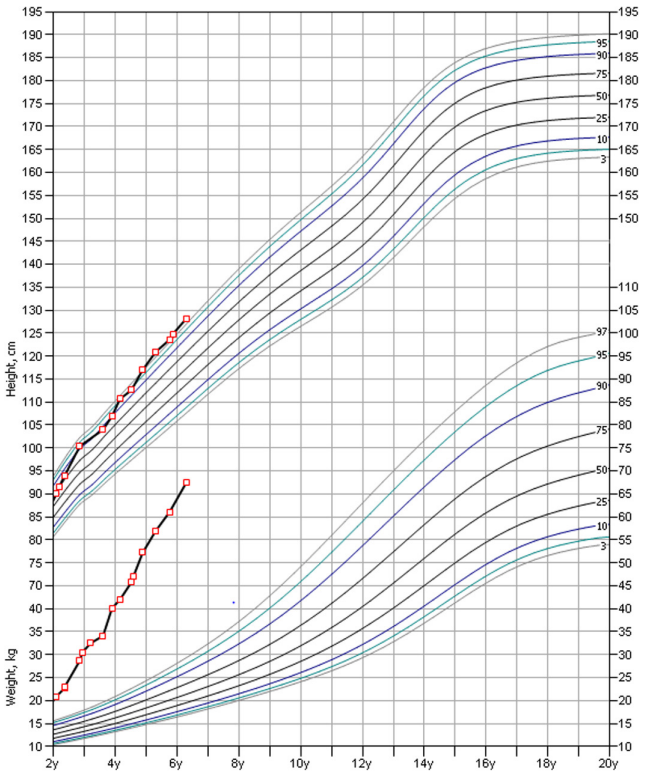


**Figure 2**
Patient growth chart at most recent endocrine encounter.

hypopituitarism. Genetic workup revealed a *SIM1* variant of uncertain significance that has moderate overlap with his phenotype. Izumi *et al* described a patient with features similar to Prader–Willi syndrome, but without the characteristic abnormality of chromosome 15. This patient had a deletion of chromosome 6q16 which contains the *SIM1* gene, and patients with similar deletions have also been reported to have a Prader–Willi-like syndrome (PWLS) (9). This patient was also diagnosed with hypopituitarism characterized by growth hormone deficiency, central hypothyroidism, partial adrenal insufficiency, and dysregulated AVP secretion. Brain MRI showed an anterior pituitary size at the lower end of normal with absent posterior pituitary bright spot. A patient with a similar chromosome 6q deletion resulting in PWLS and hypopituitarism was recently described by Rutteman *et al* (8). This patient had central hypothyroidism and adrenal insufficiency with partial DI and normal brain MRI. The combination of both *SIM1* and *POU3F2* deletions were suggested to be responsible for the obesity and hypopituitarism observed in these patients. While our patient shares similarities with these patients, he did not have any abnormalities in *POU3F2* or additional genes associated with pituitary development or function.

Our patient's mutation was inherited from his mother. She is obese; however, her obesity is less severe and occurred later in life. She additionally does not have any signs or symptoms to suggest hypopituitarism. It has been demonstrated that multiple *SIM1* variants cosegregate with obesity in extended family studies with variable penetrance (2). More recently, a variant in the C-terminal domain of *SIM1* (c.2133G>T; p.G715V) was described in two obese patients with varying clinical features (10). One patient had delayed milestones, behavioral issues, and visual motor deficits. The other patient with the same variant did not display any intellectual, behavioral, or visual motor deficits. Given the clinical heterogeneity observed in these and other patients with *SIM1*-related pathology, it was proposed that penetrance is likely due to additional genetic and environmental factors. While we cannot conclude our patient's specific mutation is responsible for his obesity and/or hypopituitarism, if it were indeed pathogenic, the well-described clinical heterogeneity of known pathogenic *SIM1* mutations may explain the difference in phenotype between the patient and his mother.

Our patient presented with obvious signs of diabetes insipidus but did not have any clinical signs or symptoms to suggest central hypothyroidism or adrenal insufficiency. Indeed, he did not have any issues typically associated with adrenal insufficiency and has not experienced any episodes of adrenal crisis since diagnosis. Besides weight gain, he had no constipation, hair loss, or poor growth velocity to suggest hypothyroidism. It is possible that a subset of patients with a *SIM1* variant and severe early-onset obesity may also harbor subtle pituitary deficiencies. It is also likely that many of these *SIM1* variants discovered in the context of obesity may not have an adverse effect on pituitary function. Regardless, it seems reasonable to have a high index of suspicion for hypopituitarism, especially hypothyroidism, adrenal insufficiency, and DI in patients with *SIM1* variants and severe early-onset obesity.

The *SIM1* mutations are a well-known cause of monogenic syndromic obesity, and the underlying pathophysiology remains to be fully understood. SIM1 is also closely tied to hypothalamic and neuroendocrine cellular development, and while we cannot conclude our patient's mutation is pathogenic, the fact that SIM1 plays a role in the development of his affected hormone axes is certainly noteworthy. If this variant is indeed pathogenic, the well described variable penetrance and expressivity of *SIM1*-related pathology may explain the phenotypic discrepancy between the patient and his mother with the same mutation. Ultimately, further studies, including functional analysis of this novel variant, are needed to

conclusively determine if it plays a pathogenic role in this patient's obesity and hypopituitarism.

**Declaration of interest**
The authors declare there is no conflict of interest that could be perceived as prejudicing the impartiality of this case report.

**Funding**
This case report did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

**Patient consent**
Written informed consent for publication of this case report was obtained from the patient's mother.

**Author contribution statement**
R G, O O, D N, and K A were involved in the clinical care of the patient and write-up of the manuscript. C K and G S were involved in the write up of the manuscript.

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**Received in final form** 14 July 2020
**Accepted** 11 August 2020