# Monogenic obesity in children: focusing on *SH2B1* deletion

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## INTRODUCTION

**Genetic obesity is rare, and quite challenging for pediatricians in terms of early identification. SH2B1 is an important component in the leptin-melanocortin pathway and is found to play an important role in leptin and insulin signaling, and therefore in the pathogenesis of obesity and diabetes. Microdeletions in chromosome 16p11.2, encompassing the *SH2B1* gene, are known to be associated with obesity, insulin resistance, hyperphagia and developmental delay.**

## AIM

**Aim of our study is to report on a case series of young individuals with 16p11.2 microdeletions, including the *SH2B1* gene, and provide detailed information on BMI development and obesity-associated comorbidities.**

**In this way, we want to raise awareness of this syndromic form of obesity as a differential diagnosis of genetic obesity.**

## METHOD

- **inclusion criteria:**
  - **obesity (> 97th percentile for age and sex*) and**
  - **16p11.2 deletions, including the *SH2B1* gene, detected by MLPA**
- **Phenotype of 7 children**
  **(3 male; age range: 2.8 – 18.0 years)**
- **BMI-trajectories from birth onwards**
- **Screening for obesity-associated comorbidities**

*according to German reference data by Kromeyer-Hauschild et al.

## RESULTS

- **Deletion size range: 0.060 – 1,710 Mb**
- **Inheritance: de novo in 4 patients, in the rest paternal/maternal**
- **Phenotype: early onset obesity and variable, mild developmental delay (speech delay, motor delay, cognitive deficits, learning difficulties, ADHD, aggressive behavior)**

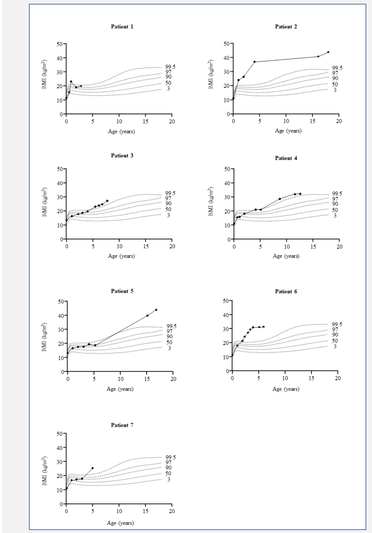


*Fig. 1. Individual BMI trajectories from birth of 7 children with microdeletions in chromosome 16p11.2, encompassing the SH2B1 gene.*

Table 1. Laboratory findings in patients with microdeletions in chromosome 16p11.2, encompassing the *SH2B1* gene.

| Patient | Age (years) | Sex | LEP [µg/L] (SDS) | bioLEP [µg/L] | Fasting insulin [mU/l] | fasting C-peptide [µg/l] | HbA1c [%] | Hepatic status* | Cholesterol [mg/dl] | Triglycerides [mg/dl] | HDL [mg/dl] | LDL [mg/dl] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 2.8 | male | n/a | n/a | n/a | n/a | n/a | normal | 153.0 | 291.0 | n/a | n/a |
| 2 | 18.5 | female | 64.8 (-2.5) | 69.3 | 33.0 | 3.9 | 5.4 | normal | 143.1 | 96.3 | 46.4 | 96.7 |
| 3 | 7.7 | female | 64.6 (+1.1) | 57.6 | 26.0 | 3.4 | 5.6 | NAFLD | 204.0 | 150.6 | 69.6 | 120.0 |
| 4 | 12.6 | female | 58.5 (-2.1) | 51.4 | 78.0 | 6.2 | 8.4 | NAFLD | 143.0 | 114.0 | 43.0 | 97.0 |
| 5 | 16.8 | female | 62.9 (-2.6) | 85.7 | 40.0 | 4.3 | 5.2 | NAFLD | 166.0 | 105.0 | 43.0 | 112.0 |
| 6 | 5.9 | male | 48.94 (-0.7) | 42.17 | 39.9 | 4.0 | 5.5 | NAFLD | 154.7 | 132.9 | 46.4 | 92.8 |
| 7 | 5.0 | male | 11.0 (-0.5) | n/a | 6.0 | n/a | 5.1 | normal | 168.0 | 56.0 | 56.0 | 101.0 |

**suspected NAFLD as assessed by liver enzymes and/or liver ultrasound*

*LEP: leptin, bioLEP: biologically active leptin, Hba1c: glycated haemoglobin A1c, NAFLD: non-alcoholic fatty liver disease, HDL: high-density lipoprotein, LDL: low-density lipoprotein, n/a: not available.*

## CONCLUSIONS

**Chromosomal microdeletions in 16p11.2, including the *SH2B1* gene, in children are associated with severe, early-onset obesity and comorbidities associated with insulin resistance.**

**Early genetic testing in suspicious patients and early screening for comorbidities is recommended.**

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