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Early Onset Obesity in a 4-Year-Old Female Found to Have Variants in Both the Single-minded Homolog 1 and SH2B Adaptor Protein 1 Genes

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IRB Number: N/A

Describe role of Submitting/Presenting Trainee in this project (limit 150 words): I, the submitting/presenting trainee, am a current Pediatric Endocrinology Fellow. I was the fellow working with Dr. De Luca in Endocrine Clinic when this patient presented for an appointment. I assisted in the laboratory evaluation of the patient and literature search regarding her genetic variants. We have submitted this abstract to the Pediatric Endocrine Soceity with the hope to present a poster at the annual meeting.

Background, Objectives/Goal, Methods/Design, Results, Conclusions limited to 500 words

Background: Childhood obesity is known to be multifactorial and heritable, with novel mutations continuously being described in many genes.

Objectives: We present a patient case with variants in 2 genes linked to early-onset obesity: Single-minded homolog 1 (SIM1) and SH2B adaptor protein 1 (SH2B1).

Results: A 3-year-old female was first evaluated by a geneticist for obesity and tall stature, both of which were first noted at 18 months of age. The geneticist obtained a 40-gene obesity panel and identified two heterozygous variants of unknown significance. The first is a p.Ala118Val change in the SH2B1 gene, and the second is a p.Arg235Leu change in the SIM1 gene. SH2B1 is a protein that enhances leptin activity. SIM1 is expressed in the paraventricular nucleus of the hypothalamus and regulates appetite and body weight. Genetic testing ruled out mutations of the MC4R gene. Her mother, who is not obese, was found with the same SH2B1 variant. Her father, who is reportedly obese, was not available for genetic testing. At 3 years and 11 months

old, the patient was evaluated at an endocrine clinic of another institution where she was found to have mildly elevated AST, IGFBP-3, insulin, and TSH levels. Blood glucose, IGF-1, leptin, and midnight cortisol were normal. A brain MRI revealed a mildly prominent anterior pituitary gland without lesion or mass. At 4 years and 2 months, she presented to our endocrine clinic seeking a second opinion. Her height was at the 99.95th percentile, weight at the 99.9th percentile, and BMI at the 99.97th percentile. Her mid-parental height is at the 50th percentile. Her physical exam was remarkable for acanthosis nigricans. She has a strong family history of type 2 diabetes mellitus. Additional laboratories showed a borderline-high ALT (42 U/L, 0-40), elevated insulin (36 uIU/mL, 0-19), IGF-BP3 (5190 ng/mL, 2169-4790), and triglycerides (275 mg/dL, 50-140). Blood glucose (87 mg/dL), HgbA1c (5.3%), and IGF-1 (138 ng/mL, 25-157) were normal. Her bone age was advanced (7 years and 5 months at a chronological age of 4 years 3 months).

Conclusions: This is the first case report of a child with early-onset obesity found to have genetic variants of both the SIM1 and SH2B1 genes. At age 4 years and 2 months, she is developing features of metabolic syndrome. We are exploring the feasibility of performing in vitro functional studies in order to determine the causal role of the identified genetic variants.