Pathogenic mutations and variants in KSR2 in a cohort of obese children

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Background
Kinesin suppressor of Ras 2 (KSR2) gene codes for a scaffold protein modulating intracellular pathways that involve MEK/ERK cascade and AMPK signaling. KSR2 is mainly expressed in the brain and plays an important role in energy balance regulation, and KSR2 mutations were reported to be associated with obesity and insulin resistance in mice and humans1,2. In transfected cells, several KSR2 mutations lead to impaired glucose and fatty acid oxidation1. Fatty acid oxidation (FAO) was showed to improve under metformin treatment1.

Patients and methods
In n=88 children with suspected monogenic obesity, genetic panel analysis for known mutations in obesity-causing genes including the KSR2 gene (transcript ID ENST00000425217) was performed. In total, five heterozygous KSR2 variants were identified. We evaluated genotype interacting allele frequency of the variants according to gnomAD (AF), pathogenicity according to in silico prediction tools (PP-2: Polyphen-2, MT: Mutation Taster, Align GVGD, SIFT) and ACMG classification, as well as phenotype of variant carriers.

Results

In Patient 1, who showed early-onset obesity, two heterozygous variants were detected. Corresponding variants have been previously reported in obese subjects and variant p.Asp294GlU lead to reduced glucose and FAO in transfected cells1. Patient 1 underwent sleeve gastrectomy at age of 21 years (red dot in figure 1), with postoperative impressive BMI improvement (preoperative BMI 50.8 kg/m², postoperative BMI 34.8 kg/m²). Metformin therapy was interrupted after adverse gastrointestinal effects. Patient 1 showed postoperative dyslipidemia with no further metabolic abnormalities.

Patient 2 showed early-onset obesity. At age of 17, hypertension, dyslipidemia and impaired glucose tolerance were diagnosed. The patient’s father showed this variant and a BMI of 41.4 kg/m², while the mother did not show the variant and had a BMI of 40 kg/m². The same variant was previously reported in one obese patient and was shown to lead to reduced AMPK binding and impaired glucose and FAO, which improved under metformin1. Patient 2 started metformin treatment at age 17 years. Follow up is pending.

In Patient 3 early-onset obesity despite diet restriction was observed. No metabolic abnormalities were observed. A novel maternally inherited heterozygous KSR2 variant was detected. The patient’s mother showed a BMI of 33.7 kg/m². The patient’s father, not carrying the variant, had a BMI of 26.2 kg/m².

Discussion
This is the first case study in obese patients with KSR2 variants since the initial study by Pearce et al. 20131. KSR2 variants seem to be more frequent among obese children than previously suggested. We present three patients with probably disease-causing variants, and further six patients showing a variant which has been associated with higher BMI.1 Causality and penetrance of KSR2 variants for the obesity phenotype should be clarified through evaluation of allelic frequency, in silico prediction tools, family history and if possible, through functional cell studies. Metformin treatment and bariatric surgery may be therapeutic options in affected patients. For deeper understanding of pathogenic mechanisms in KSR2 related human obesity and evaluation of therapeutic approaches, further studies are needed.

References

1Pearce et al., Cell 2013; 155(4):765-77, 2transcript ID ENST00000425217
2Costanzo-Garvey et al., Cell Metab. 2009; 10(5) 366-78.
3Turcotte et al., Nat Genet. 2018; 50(1):26-41

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Poster presented at: