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

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Background

Kinase suppressor of Ras 2 (*KSR2*) gene codes for a scaffold protein modulating intracellular pathways that involve MEK/BRAF 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 humans[1,2]. In transfected cells, several *KSR2* mutations lead to impaired glucose and fatty acid oxidation[1]. Fatty acid oxidation (FAO) was showed to improve under metformin treatment[1].

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, including allelic frequency of the variants according to gnomAD (AF_G), 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

Patient 1

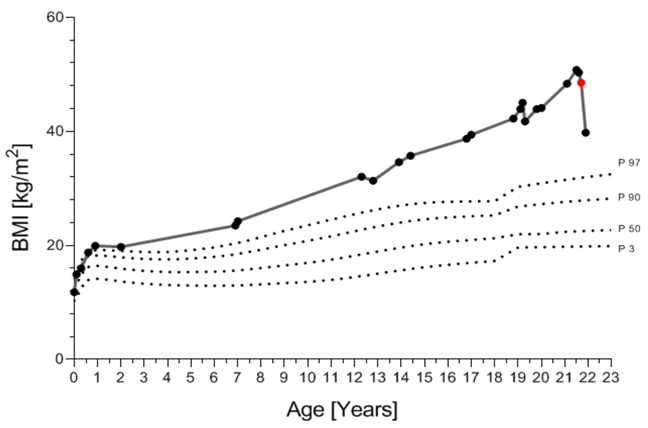

Figure 1: BMI curve in Patient 1.

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 cells[1]. 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.

- Variant: p.Arg224Trp/c.670C>T
- AF_G: 0.00003306
- *In silico* prediction: PP-2: damaging, MT: disease causing, Align GVGD: benign, SIFT: deleterious
- *In vitro* analysis: functional relevance[1]
- ACMG Class 3 (VUS)

- Variant: p.Asp294Glu/c.882C>G
- AF_G: 0.006814
- *In silico* prediction: PP-2: benign, MT: disease causing, Align GVGD: benign, SIFT: tolerated
- *In vitro* analysis: functional relevance[1]
- ACMG Class 3 (VUS)

Patient 2

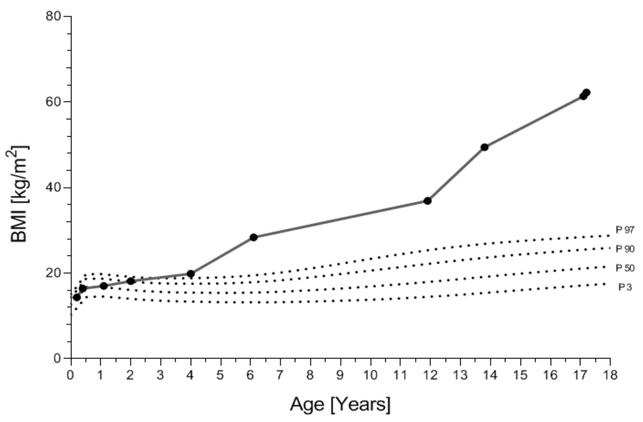

Figure 2: BMI curve in Patient 2.

Patient 2 showed early-onset obesity. At age of 17, hypertension, dyslipidemia and impaired glucose tolerance were diagnostified. 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 metformin[1]. Patient 2 started metformin treatment at age 17 years. Follow up is pending.

- Variant: p.Ala344Thr/c.1030G>A
- AF_G: 0.0001908
- *In silico* prediction: PP-2: benign, MT: polymorphism, Align GVGD: benign, SIFT: tolerated
- *In vitro* analysis: functional relevance[1]
- ACMG Class 3 (VUS)

Patient 3

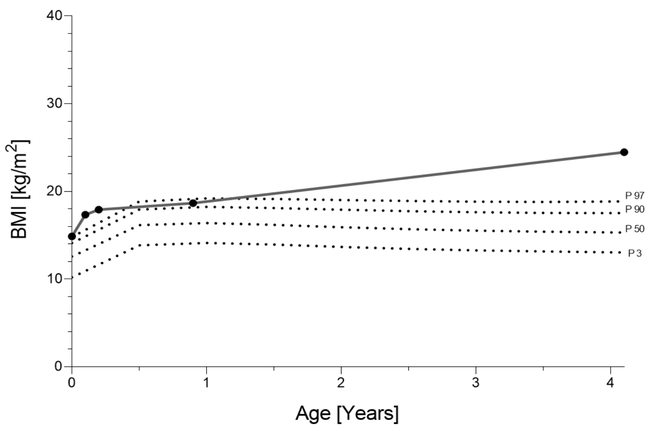

Figure 3: BMI curve in Patient 3.

- Variant: p.His536Tyr/c.1606C>T
- AF_G: 0.003335
- *In silico* prediction: PP-2: benign, MT: disease causing, Align GVGD: benign, SIFT: tolerated
- *In vitro* analysis: not available
- ACMG Class 3 (VUS)

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.

Further patients

- Variant: p.Arg525Gln/c.1574G>A
- AF_G: 0.007495
- *In silico* prediction: PP-2: benign, MT: disease causing, Align GVGD: benign, SIFT: tolerated
- *In vitro* analysis: functional relevance[1]

Six further patients showed the variant p.Arg525Gln, which was associated with higher BMI in a GWAS-study[3]. No significant difference in obesity prevalence between carriers of this variant and non-carriers was found in this study[3]. Obesity phenotype, in contrast to monogenic obesity, may develop in carriers of this variant only in concomitance with further disposing factors.

Discussion

This is the first case study in obese patients with *KSR2* variants since the initial study by Pearce et al. 2013[1]. *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[3]. 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

[1]*Pearce et al., Cell. 2013; 155(4):765-77, * transcript ID ENST00000339824*
[2]*Costanzo-Garvey et al., Cell Metab. 2009; 10(5) 366-78.*
[3]*Turcot et al., Nat Genet. 2018; 50(1):26-41*

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