Multiple pituitary hormone deficiencies and early onset obesity in two siblings with a mutation in the *MAGEL2*-gene

Ursula Kuhnle-Krahl [1], Moneef Shoukier [2], Christof Land [1], Christian Schaaf [3]

[1]Clinic for Paediatric Endocrinology, München-Gauting, Germany,
[2]Pränatal-Medizin, München, Germany,
[3]Universitätsklinikum Köln, Institute of Human Genetics, Germany

Paediatric Endocrinology München – Gauting Germany

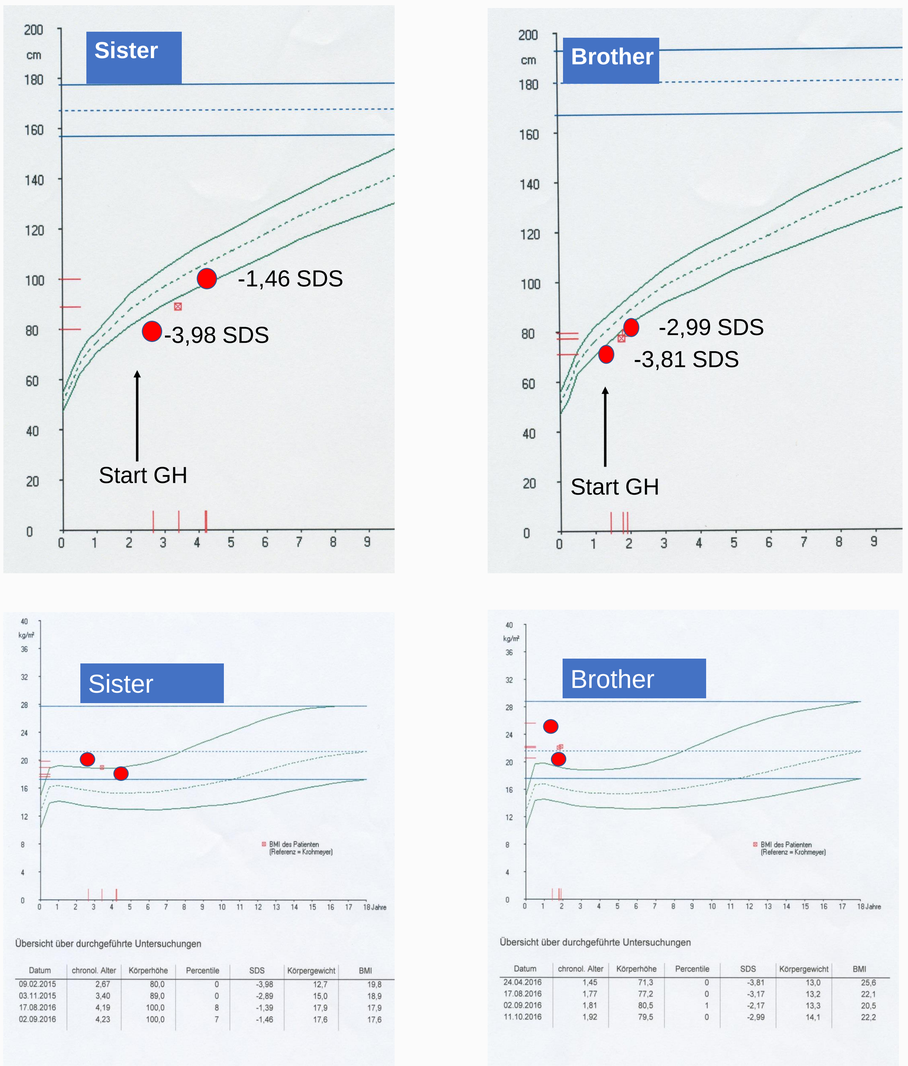
INTRODUCTION

The *MAGEL2*-gene has been identified to be one of the protein coding genes located within the Prader-Willi syndrome region on chromosome 15q11-13 (1). Mutations in the paternally imprinted *MAGEL2*-gene have been identified to cause a variety of symptoms overlapping the Prader-Willi-phenotype (2). Psychological and psychiatric problems are prominent features in the Prader-Willi syndrome as well as a variety of endocrine symptoms like short stature, hypogonadism and obesity. These symptoms are highly variable in the Prader-Willi syndrome as well as in individuals with a proven *MAGEL2* mutation (3). Most patients with a *MAGEL2* mutation have so far been identified through investigating individuals with Prader-Willi like symptoms and negative genetic findings. In contrast, the patients reported here have been referred to our endocrine clinic for the evaluation of short stature.

PATIENTS and METHODS

Two siblings from unrelated parents were referred at the age of 2 ½ and 1 ½ years for short stature and hypothyroidism.
The older sister was the first of the two siblings coming our institution for evaluation of short stature. At the age of 10 months she was started on 25 µg levothyroxine in her home country because of signs and symptoms described as 'myxedema'. She presented at the age of 2 ½ years with a height of -3.98 SDS and a BMI of 19.8 (>100th centile) (Fig. 1). Increased appetite was not reported. We documented developmental delay with in particular decreased fine motor skills and poor language abilities. The hormonal investigations are listed in Table 1. After initiation of growth hormone therapy the growth rate improved and at the age of 4 years and 2 months her height was at the 7th centile (-1.46 SDS). Similarly the BMI decreased to 17.6 (90th centile) (Fig. 2).
The younger brother came to us at the age of 1½ years. At the age of 1,4 years his height was -3.81 SDS and the BMI was 25.6 (>100th centile) and he was started on levothyroxine and growth hormone therapy in his home country. His growth rate improved and 6 months later his height SDS was -2,99, and the BMI 22.2 (still above 100th centile)(Fig. 1 and 2). Increased appetite is not reported, but increased thirst and increased diuresis was present. He was not able to walk unassisted. The hormone values are listed in Tab. 1.
In both children a MRI of the brain was performed. In the girl this was done abroad and diagnosed to be normal, whereas in the boy we found pathological findings with a small pituitary and an unvisable pituitary stalk. (Fig. 3).

RESULTS



Datum	chronol. Alter	Körperhöhe	Percentile	SDS	Körpergewicht	BMI
09.02.2015	2,67	80,0	0	-3,98	12,7	19,8
03.11.2015	3,40	89,0	0	-2,89	15,0	18,9
17.08.2016	4,19	100,0	8	-1,39	17,9	17,9
02.09.2016	4,23	100,0	7	-1,46	17,6	17,6

Datum	chronol. Alter	Körperhöhe	Percentile	SDS	Körpergewicht	BMI
24.04.2016	1,45	71,3	0	-3,81	13,0	25,6
17.08.2016	1,77	77,2	0	-3,17	13,2	22,1
02.09.2016	1,81	80,5	1	-2,17	13,3	20,5
11.10.2016	1,92	79,5	0	-2,99	14,1	22,2

Figure 1: Growth- and BMI charts of the two siblings

Parameter	Sister	Brother	Range
IGF-1	21.25	66.34	15-224 ng/ml
IGFBP-3	0.89	1.62	1.0-4.7 mg/L
ACTH	16.8	41.5	< 46 pg/ml
Cortisol	66.2	129.5	30.9-224.0 µg/ml
Prolaktin	361.4	455.8	58-473 ng/ml
Leptin	2.9	< 1	3.63-11.1 ng/ml
CT-Vasopressin	2.16	2.81	< 2.6 pmol/L
S-Osmolality	288	319	280-296 mOsmol/kg

Table: Hormonal values of the two siblings

RESULTS cont.

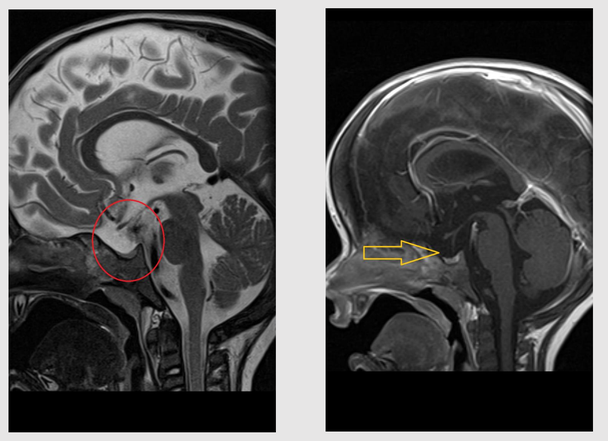
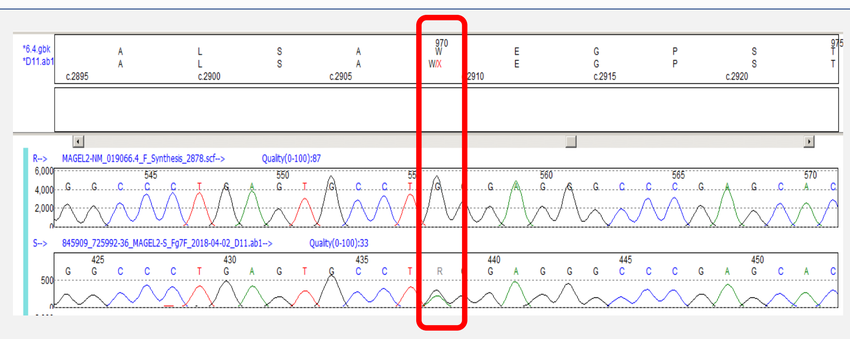
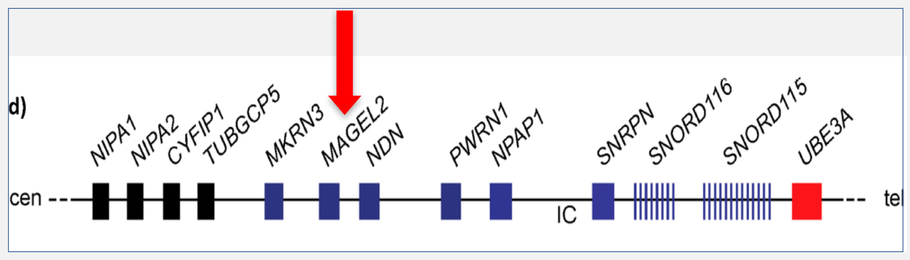


Figure 2: MRI of the brother showing small pituitary and small stalk

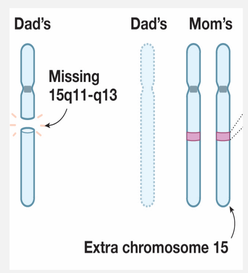


c.2909G>C; p.Trp970Ter

Figure 3: Mutation in the *MAGEL2-gene* identified in the two siblings



Prader-Willi syndrome is caused by deletions or uniparental disomy



Schaaf-Yang syndrome is caused by truncating mutations in the *MAGEL2* gene

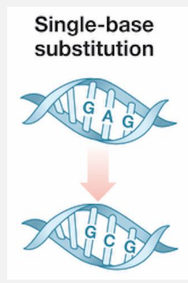


Figure 4: Comparison between Prader-Willi- and Schaaf-Yang syndrome.

- At least 5 genes, located in the PWS chromosomal region and expressed in the hypothalamus, have been identified, but their functions have not yet been understood completely.
- *MRKN3* (makorin 3), ***MAGEL2*** (*MAGEL*-like 2), *NDN* (necdin), *NPAP1* (nuclear pore associated protein 1), *SNURF-SNRPN* (*SNRPN* upstream reading frame – small nuclear ribonucleoprotein polypeptide N)
- The exact mechanisms by which these genes contribute to the development of early-onset obesity are still to be defined. Several other unknown genes are probably mutated, and this could explain the variability of the PWS phenotype.

Literature:
1. Prader-Willi syndrome. SB Cassidy et al.; Genet Med 2017

2. Truncating mutations of *MAGEL2* cause Prader-Willi phenotypes and autism. Christian P. Schaaf et al.; Nature Genetics 2013

3. The phenotypic spectrum of Schaaf-Yang syndrome – 18 new affected individuals from 14 families. Michael D Fountain et al. ; Genet Med 2016

4. Hormonal, metabolic and skeletal phenotype of Schaaf-Yang syndrome: a comparison to Prader-Willi syndrome. John M McCarthy et al.; J med Genet 2017

CONCLUSIONS

We investigated two siblings for short stature and we found multiple hormone deficiencies, like TSH, STH, ADH- and Leptin deficiency. As a cause we identified a stop codon mutation in the *MAGEL2*-gene in both children, a gene which has been identified within the Prader-Willi gene locus.
However, it was interesting to note that the hormone concentrations varied from day to day. This may indicate that there is no defective hormone synthesis but rather a defect in the regulation of hormone secretion. This could also explain the varying hormonal deficiencies which are found in the Prader-Willi syndrome.
Thus, it can be recommended that *MAGEL2* gene mutations should be included in the investigation of patients with multiple hormone deficiencies. Further research is needed to identify the mechanism of action by which the *MAGEL2*- gene is involved in the regulation of the hypothalamic-pituitary hormone secretion.

57ESPE 3--RFC15
Growth and syndromes (to include Turner syndrome)
Ursula Kuhnle-Krahl
Poster presented at: 57th ESPE 2018 Meeting ATHENS GREECE 27-29 September 2018
PosterSessionOnline.com