Different genetic causes of short stature in a family

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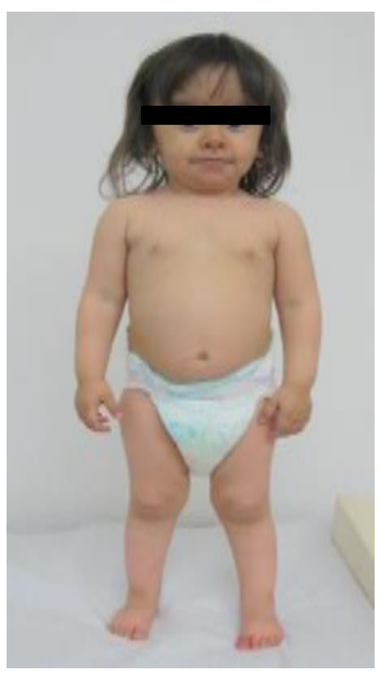
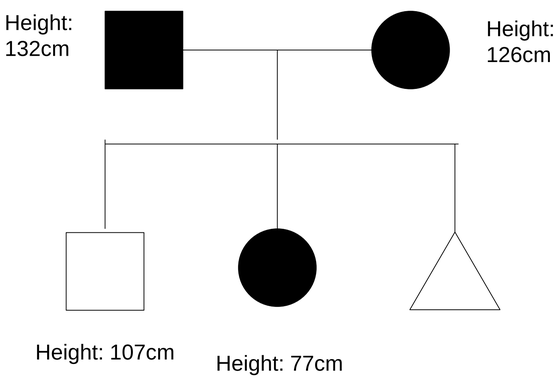
Background

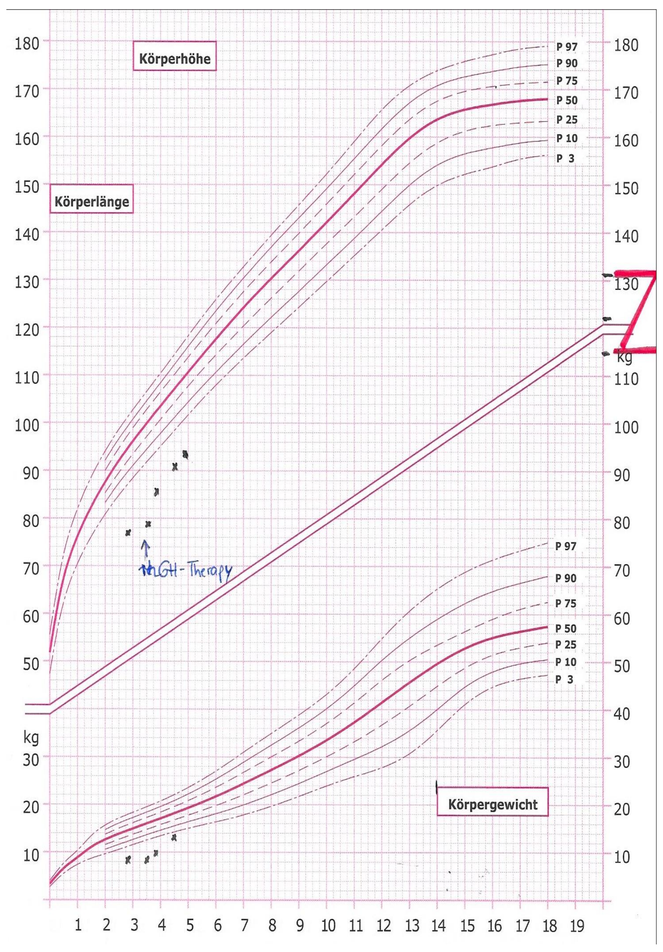
The differential diagnosis of short stature is extremely wide and difficult. It includes both primary skeletal disorders and secondary causes such as growth hormone deficiency. The most common endocrine cause of growth disorders in childhood is growth hormone deficiency (GHD). The rare monogenic forms of GHD are inherited as autosomal dominant or recessive traits and manifest as isolated deficiency or in combination with other hormone deficiencies. Here, we report on a three-year-old girl with a severe growth retardation (height 77cm, -5,6 SDS). She is the child of non-consanguineous parents from northern Iraq, who also showed short stature (mother`s height: 126cm, fathers height: 132cm)

Objective

We aimed to investigate the etiology of short stature in the family by using laboratory and genetic tests (Sanger and whole-exome sequencing).







Methods and Results

First baseline screening tests at age of three showed:

- X-ray analysis of the left hand: retarded bone age (1.6 years)
- Basal serum Insulin Growth Factor-1 (IGF-1): <25µg/L
- Basal serum IGF-Binding Protein-3 (IGFBP-3): <0,5µg/L
- Thyroid function tests, calcium, phosphate and urine analyses were within normal range
- 2-plane cranial MRI showed an empty Sella

Pharmacological stimulation tests with Arginine (maximum of GH-peak after 45min: 1,28µg/L) and Clonidine (maximum of GH-peak after 60min: 0,77µg/L) revealed a complete GH deficiency.

Genetic investigations were performed:

- Sanger sequencing of *GH1* revealed a heterozygous mutation (c.291+1 G>A) leading to aberrant splicing in our patient and her father that has been already described in other patients with autosomal dominant GHD (Ariyasu *et a*l. 2013, Cogan *et al.* 1995)
- The mother does not carry this mutation; however, subsequent trio whole-exome sequencing identified a *de novo* heterozygous mutation in *COL1A2* (c.2565+1 G>A) in her, but not in the child. This mutation is described to cause Osteogenesis imperfecta Type IV.
- The mutation in GH1 was not detected by exome sequencing due to low coverage

Summary of identified variants

Gene	Variants	Zygosity			MAF*	Disorder (OMIM)	Classification
		Index	Mother	Father			
GH1	Chr17:61995377, NM_000515.4, c.291+1G>A	**het**	WT	**het**	0	growth hormone deficiency, isolated, type II (#173100)	pathogenic
COL1A2	chr7:94052431, NM_000089.3, c.2565+1G>A	WT	**het**	WT	0	Osteogenesis imperfecta, type IV (#166220)	pathogenic

* MAF: minor allele frequency in GnomAD database

Conclusions

Our patient and her father have an isolated GHD Type II with a heterozygous mutation in *GH1* gene identified by Sanger Sequencing. Surprisingly this mutation could not be found by performing trio whole-exome sequencing which revealed the cause of short stature of the mother (OI Type IV). This case shows that a combination of a careful medical history, physical examination, laboratory investigations and new technologies like exome sequencing can help to make a correct diagnosis.