6-year old girl with mutation in *DNMT3A* – a new overgrowth syndrome

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Background:

- Overgrowth disorders are a heterogeneous group of conditions characterized by increased growth and other clinical features
- Overgrowth may be apparent at birth and can be static or progressive
- The increased growth can be seen in combination with an increased weight and/or increased head circumference
- Many of the overgrowth syndromes are associated with an increased risk of malignancy

Methodology:

Standard DNA sequencing of all coding exons and flanking UTR's of *DNMT3A* was performed.

Objective and hypotheses:

- A 6 year old girl with accelerated growth rate was seen in paediatric outpatient clinic
- She was born at term, and her birth length was 55 cm long (+2,4 SD)
- At 6 years she was 134,4 cm tall (+3,7 SD) with a high growth rate at 8,9 cm/year
- Her growth rate was above the range for her family
- There were no signs of precocious puberty
- She had a bone age more than 3 years advanced
- She had cognitive impairment and slightly retarded motor development
- The only dysmorphic feature was heavy horizontal eyebrows

Figure 1. 6 year old girl with accelrated growth rate

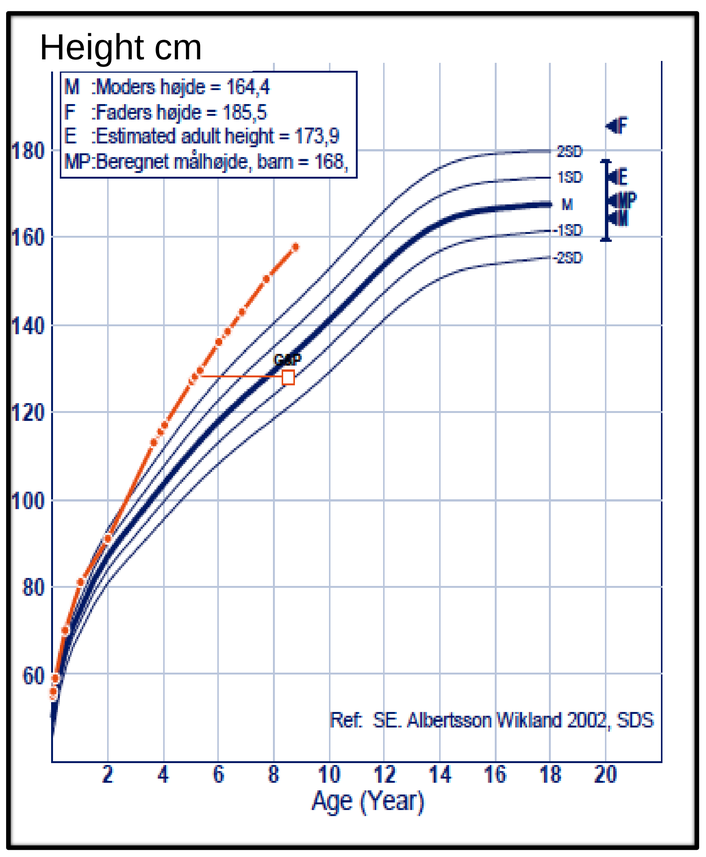

Figure 2. The girls height

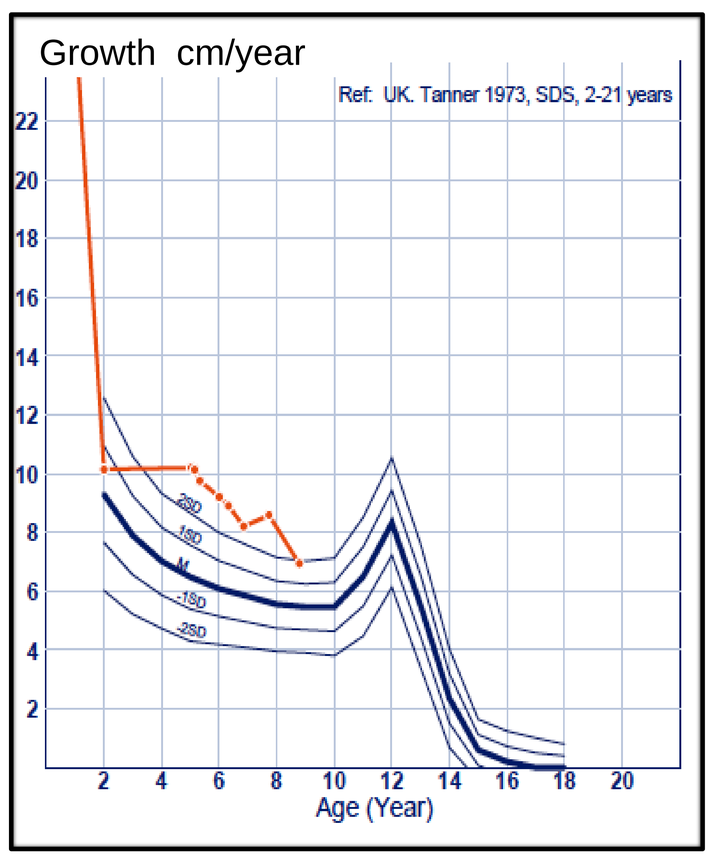

Figure 3. Growth Velocity

Results:

- A de novo mutation (*DNMT3A* c. 1232dup) was detected
- In 2014, Katrina Tatton_Brown et al reported the detection of 13 different *DNMT3A* mutations in 152 individuals with overgrowth phenotype
- A consistent phenotype was evident amongst the 13 individuals *with DNMT3A* mutations: distinctive facial appearance, tall stature and intellectual disability
- *DNMT3A* mutation is frequently found in acute myeloid leukemia and have also been reported in other hematological malignancies

Conclusions:

- In childhood, the differential diagnosis of increased growth includes normal variants, nutritional obesity, endocrinopathies, connective tissue disorders, sex chromosome abnormalities and overgrowth syndromes
- When assessing a child with tall stature and intellectual disabillity mutations in *DNMT3A* is important to consider
- In genereal, follow-up of children with overgrowth syndrome should be conducted due to the potential malignancy risk
- The *DNMT3A* related malignancy risk may be linked to a different mechanism and may not be present in patients with truncating mutations

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