Virilization of a girl at puberty due to a unique translocation of an abnormal duplicated Y-chromosome to a deleted chromosome 9 including the DMRT1 gene

Stefanie Graf1, Nijas Aliu2, Mazen Zeno3, Mafalda Trippet4, Christa E. Flück5

1Pediatric Endocrinology and Diabetology (Department of Pediatrics), Inselspital, Bern University Hospital, University of Bern, CH-3010 Bern, Switzerland
2University Clinic for Pediatrics, Human Genetics, Inselspital, Bern University Hospital, CH-3010 Bern, Switzerland
3Pediatric Surgery (Department of Pediatric Surgery), Inselspital, Bern University Hospital, University of Bern, CH-3010 Bern, Switzerland
4Institute of Pathology, Inselspital, Bern University Hospital, University of Bern, CH-3010 Bern, Switzerland
5Department of Biomedical Research, Inselspital, Bern University Hospital, University of Bern, CH-3010 Bern, Switzerland

The authors have nothing to disclose / corresponding author: stefanie.graf@insel.ch

Case report

- 11.5-year-old girl referred because of progressive clitoromegaly since 6 months
- **Physical exam:**
  - normal height (P10), overweight (BMI P90)
  - slight disproportions, no syndromic features
  - Pubertal stage: P5, B1-2, A1-2, rich bodily hair
  - External genitalia with a marked clitoromegaly (Fig. 1)
  - no gonads palpable
- **Imaging:**
  - Bone age: concordant to chronological age
  - Ultrasound:
    - normal adrenals and gonads
    - prepubertal uterus
    - no tumor found
  - MRI: normal adrenals and gonads
  - **24-h-urine-steroid profiling:**
    - high excretion of androgen metabolites
    - exclusion of any form of late-onset CAH
- **Chromosomal analysis:**
  - Karyotype 45,X (Fig. 2)

Objectives:

1. How to explain androgen excess at puberty in a 45,X girl?
2. Where is the Y-material hidden?
3. What to do with a suspected androgen secreting gonad in 45,X?

Material and Methods

- Expanded genetic exams in search of a hidden Y-chromosome including cytogenetic SRY-FISH analysis and Array-CGH
- Exploration of the gonads by laparoscopic and histopathological investigations

Results

1) Genetic analysis

- **FISH-Analysis** confirmed the presence of SRY-gene and showed a suspicious hybridization pattern (Fig. 2a & 2b)
- **Array-CGH-Analysis** revealed a terminal heterozygous deletion of 9p, monosity of X and a terminal duplication of Yp
- **45,X,ish der(9)(p11.2::9pter-9p23** plus a terminal heterozygote deletion 9p24.3-p23
- Resulting in a partial monosity 9p including 49 genes, e.g. the sex gene DMRT1 explaining a complete sex reversal phenotype

2) Laparoscopic gonadectomy – macroscopic findings

- Complete sex reversal phenotype – mixed gonadal dysgenesis

3) Histopathologic results

- Virilization at puberty in girls remains a challenge and can be more complex than routinely thought
- Several differential diagnosis must be considered including disorders of sex development (DSD) and tumors
- All efforts should be taken to find the underlying cause because ongoing virilization may result in irreversible bodily changes
- Repeat-and expanded biochemical and genetic workup can be necessary to solve complex cases
- Multiple genetic hits can manifest with unique, unsuspected phenotypes as shown in the presented case report