



TBX3

**Ulnar-mammary syndrome (UMS)** is a rare autosomal dominant condition resulting from pathogenic variants in the *TBX3* gene, which, as other T-box transcription factors, has an important role in embryonic development.

*TBX3* haploinsufficiency results in variable phenotypic features including defects of ulnar ray, underdevelopment of apocrine and mammary glands and genital anomalies.

14-year-old boy

Neurodevelopmental consultation due to **learning difficulties**.

## PAST MEDICAL HISTORY:

- bilateral cryptorchidism surgically corrected
- bilateral clinodactyly of 4<sup>th</sup>-5<sup>th</sup> toes surgically corrected.

## FAMILY HISTORY

congenital bilateral agenesis of 3<sup>rd</sup> to 5<sup>th</sup> fingers and unilateral extension limitation of the arm

unilateral postaxial polydactyly  
learning difficulties

learning difficulties

learning difficulties  
short stature  
bilateral cryptorchidism  
hypogonadotropic hypogonadism  
mild dysmorphic features  
proximal interphalangeal joint deformity of the 5<sup>th</sup> finger

## PHYSICAL EXAMINATION:

**Dysmorphic features** (≠ from his brother):

- anteverted nostrils, mild micrognathia, long philtrum, thin vermilion of the upper lip, uvula cleft, macrodontia (central incisors);
- symmetrical nipple hypoplasia;
- proximal interphalangeal joint deformity of the 5<sup>th</sup> finger.

Anthropometric parameters: weight -0.27 SD, height +0.84 SD, BMI -1.27 SD.  
Prepubertal

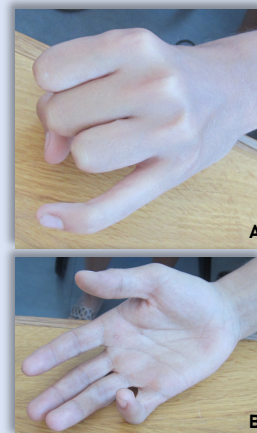


Fig.1 – 5<sup>th</sup> finger anomaly in index case (A) and his brother (B)

## NEURODEVELOPMENTAL EVALUATION (WISC III):

- Verbal IQ: extremely low
- Performance IQ: extremely low
- Full IQ: extremely low



## ENDOCRINOLOGICAL INVESTIGATION:

Anosmia was denied.



Total Testosterone: <0,1 nmol/L, LH <0,2 U/L, FSH 3,4 U/L  
Normal levels of other pituitary hormones.

**HYPOGONADOTROPIC  
HYPOGONADISM**

Bone age: delayed by 2 years compared to chronological age.

Brain MRI: normal pituitary gland and stalk.

**Testosterone treatment was started**  
Pubertal onset confirmed 9 months later.

## GENETIC INVESTIGATION:

- Karyotype: 46, XY
- Array: normal
- Fragile X molecular study: negative.
- NGS panel for hypogonadotropic hypogonadism: normal.
- NGS panel for intellectual disability detected a **likely pathogenic heterozygous variant c.880dup (p.Arg294Lysfs\*13) on *TBX3* gene**, which segregated in his brother and was inherited from the mother.

Although its dysmorphic and endocrine phenotypes are well described in UMS, intellectual disability is not mentioned in most literature.

As an extremely rare condition, more clinical features are to be described in the newly diagnosed cases. Intellectual disability, a common feature in this family, might be part of UMS spectrum and should be better characterized.