46,XY Partial Gonadal Dysgenesis caused by an Xp21.2 interstitial duplication that does not encompass the NR0B1 gene

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Introduction
A portion of 160 kb at Xp21.2 was defined as dosage sensitive sex reversal, including NR0B1 and MAGEB genes, nonetheless, NR0B1 is considered the most likely candidate gene involved in XY gonadal dysgenesis if overexpressed. The excess of NR0B1 gene product seems to disturb testicular development by down regulating NRSA1, WTI, and SOX9. In spite of evidences reported in the literature, NR0B1 single duplication associated with XY gonadal dysgenesis is still to be demonstrated as a proof of its direct involvement in this condition. All the duplications already reported also contain at least some of the MAGEB genes, which are specifically expressed in the testis but whose function remains unknown.

Case report
The patient was referred for genetic assessment in the first month of life to evaluate genital ambiguity. She had a 0.5-cm phallus, a single perineal opening, partially fused labioscrotal folds and nonpalpable gonads (EMS = 4).

• Chromosome G-banding of the patient revealed 46,XY in 50 analyzed metaphases and FISH showed no 45,X cell line. Histopathological analysis of gonads revealed no gonadal tissue with mullerian and wolffian derivatives on the left and dysgenetic testis on the right. Mutations on SRY, WTI, DMRT1, NRSA1 and SOX9 were not identified.

Methods
• SALSA MLPA P185-C1 Intersex probemix and SALSA MLPA P334-A2 Gonadal Development Disorder probemix (MRCHolland) were used for the MLPA assay and the aGH CytoScan® 750K (Affymetrix®) assay was performed to confirm the results.

Results

Figure 1: MLPA revealed the duplication of Ckorf21 probes at Xp21.2 [30,595,621-30,615,321] (arr[hg19]), but signals for NR0B1 were normal.

Figure 2: Probe signals for DMRT1, CYP17A1, SRD5A2 and HSD17B3 genes were normal.

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Discussion and Conclusion
The duplication includes Gk gene in an extra dose and TAB3 and Ckorf21 partially duplicated, but it does not include NR0B1. The product of Gk gene present in extra copy is an enzyme involved in the glycerol metabolism. Both partially duplicated genes are located at the breakpoint: TAB3 coding the transforming growth factor is essential for the activation of the nuclear factor kappa B (NF-κB) pathway; and Ckorf21 encodes a hypothetical protein whose function is unknown. There are three hypotheses to consider regarding the genes that can be responsible for the phenotype: the duplication has caused the disruption of TAB3 and Ckorf21 genes at the breakpoint boundaries, therefore the pathogenic effect may have resulted from the haploinsufficiency of one of those genes or both; or, Gk can exert a dosage effect when in extra copy; or the pathogenic effect may outcome from both factors mentioned above.

To our knowledge this is the first description of Xp21.2 duplication resulting in gonadal dysgenesis with normal NR0B1 dosage (Figure 4). This study questions the well-accepted theory that NR0B1 is responsible for sex reversal in DSS region. Further studies are required to understand the roles of Gk, Ckorf21 and TAB3 on sex reversal.

Figure 4: Comparison of NR0B1 locus duplications. Representation from the Ensembl (GRCh38.p13) of the NR0B1 locus.

References