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 *NR5A1*, *WT1*, 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 GTG 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*, *WT1*, *DMRT1*, *NR5A1* and *SOX9* were not identified.

Methods

- SALSA MLPA P185-C1 Intersex probemix and SALSA MLPA P334-A2 Gonadal Development Disorder probemix (MRC-Holland) were used for the MLPA assay and the aGH C*ytoScan*® 750*K (*Affymetrix®) assay was performed to confirm the results.

Results

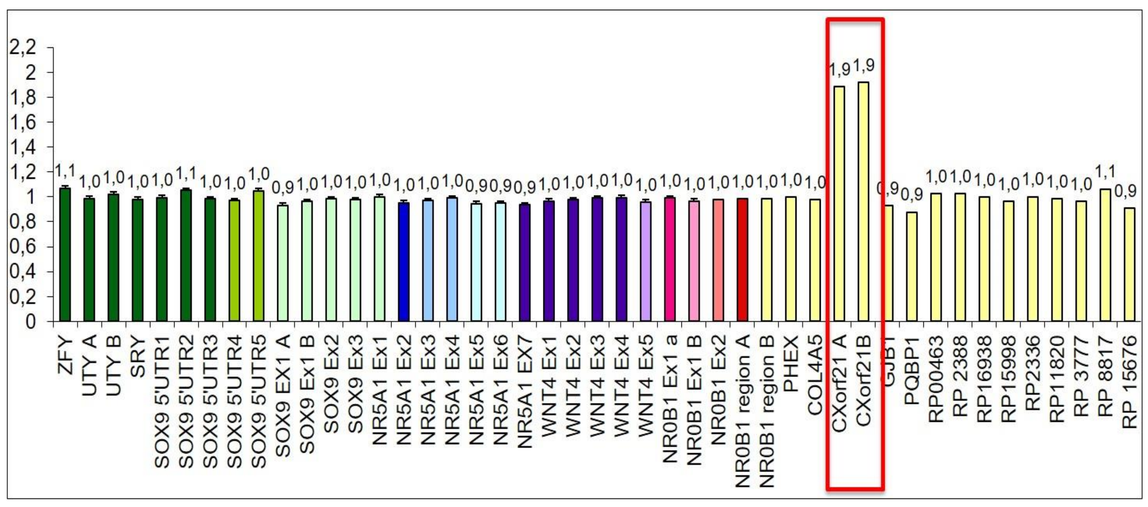

Figure 1: MLPA revealed the duplication of *CXorf21* probes at Xp21.2 [30,595,621-30,615,321] (arr[hg19]), but signals for *NR0B1* were normal.

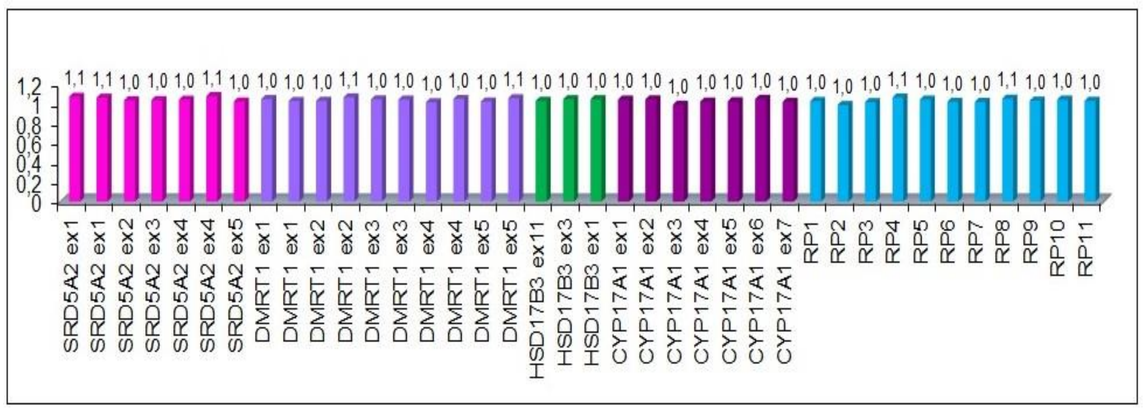

Figure 2: Probe signals for *DMRT1*, *CYP17A1*, *SRD5A2* and *HSD17B3* genes were normal.

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Figure 3: aGH analysis using software Chromosome Analysis Suite (ChAS - Affymetrix®) showed ≈ 277 kb duplication at Xp21.2 (arr[hg19] Xp21.2(30,580,693-30,857,187)x2). Consequently, *GK* gene is present in an extra dose and *TAB3* and *CXorf21* are partially duplicated.

Discussion and Conclusion

- The duplication includes *GK* gene in an extra dose and *TAB3* and *CXorf21* 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 *CXorf21* 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 *CXorf21* 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,* CXorf21 and *TAB3* on sex reversal.

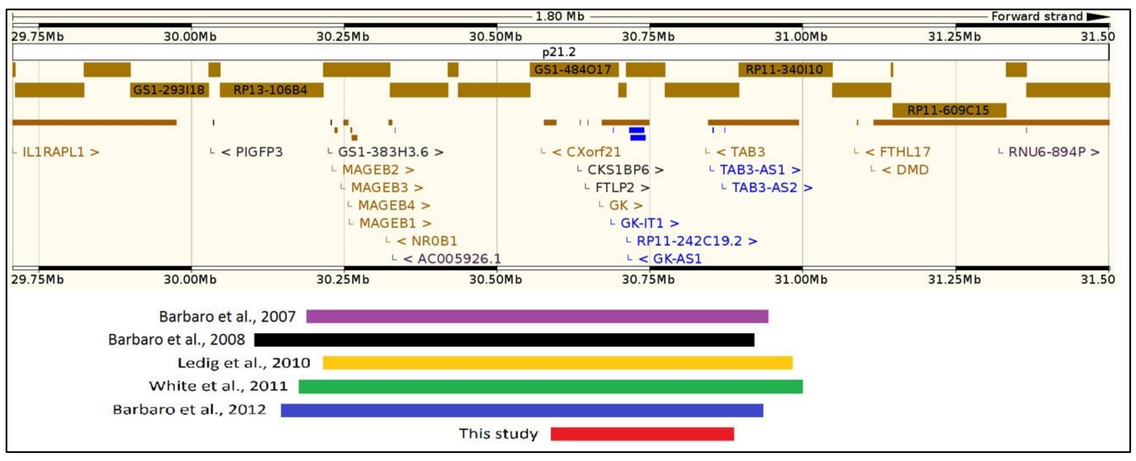

Figure 4: Comparison of *NR0B1* locus duplications. Representation from the Ensembl (GRCh37.p13) of the *NR0B1* locus.

References

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