

46,XX ovotesticular disorder of sex development: potential role of a 1.7 kb segment in 13q31.1 region

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Introduction

The origins of 46,XX ovotesticular DSD remain unclear in a substantial number of cases. Genetic tools such as Complete Genome Hybridization (CGH)-array can help identifying genes and loci involved in gonadal development and differentiation. We report the results of the extensive genetic investigations performed in a 15 years-old African adolescent with SRY-negative 46,XX ovotesticular DSD.

Methods

Clinical evaluation, imaging studies, surgical exploration, histological analysis and genetic investigations including CGH-array (Agilent, 1 million array, resolution 2.1 kb overall median probe spacing) were performed to characterize the origin of the DSD.

Case report & Results

The patient, who was raised as a boy, was addressed to our consultation at the age of 15 years. Tanner stages were B4 PH4. External genitalia showed a 4 cm-long phallic structure with penoscrotal hypospadias, completely fused labioscrotal folds, the right one with rugae and containing a palpable gonad, the left one smooth and empty. A common sinus led to the urinary bladder anteriorly and to a vagina posteriorly. Laparoscopy revealed on the right side a hemi uterus, a Fallopian tube and an intra-abdominal gonad. The later was removed: histology revealed an ovary without testicular tissue. Histology of the scrotal gonad was compatible with an ovotestis (Figure 1).

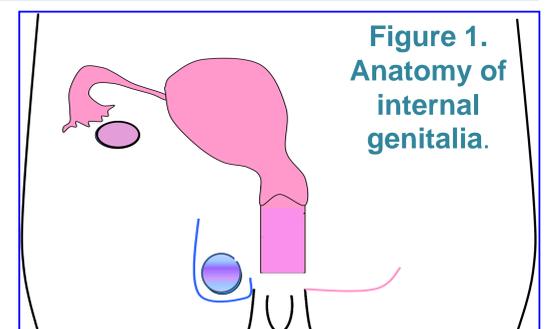
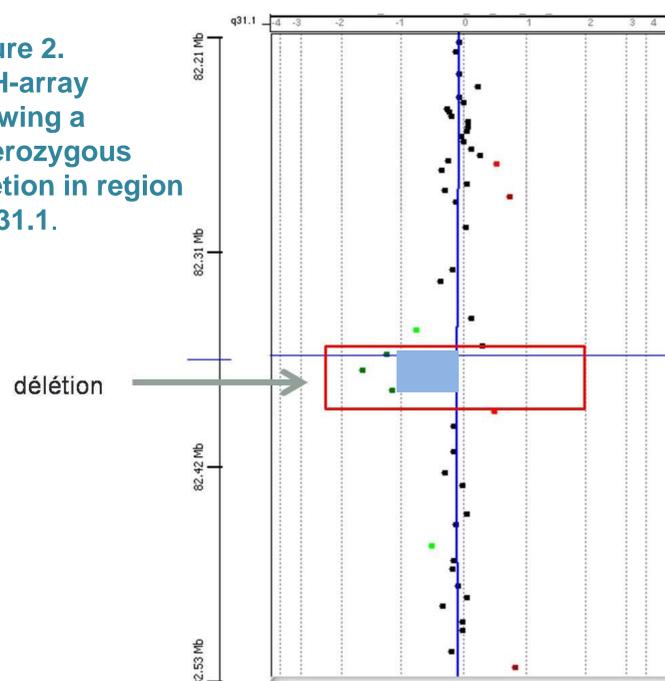


Figure 1. Anatomy of internal genitalia.

Leucocyte and scrotal fibroblast karyotype was 46,XX. No *SRY* could be detected in different tissues, including in leucocytes and gonadal tissue (PCR). Mosaicism and chimerism were excluded as well as *SOX9* duplication (MLPA), *WNT4* deletion (MLPA) and *R-spondin1* mutation (PCR).

Figure 2. CGH-array showing a heterozygous deletion in region 13q31.1.



CGH-array revealed a heterozygous deletion of 1.7 kb in region 13q31.1 between positions 81,270,158 and 81,287,901 bp (hg18) (Figure 2). This deletion was not present in the mother. This non-coding region is highly conserved between species (Figure 3).

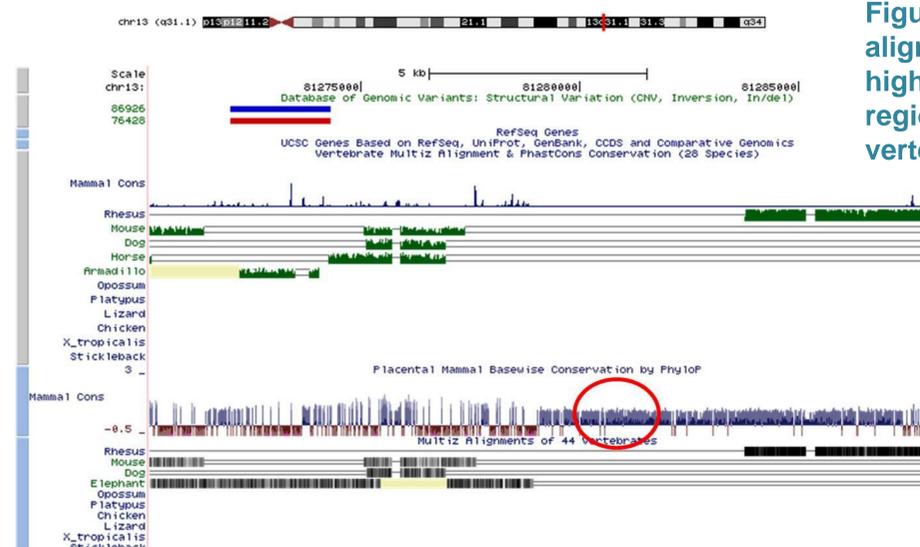


Figure 3. MultiZ alignment revealed a highly conserved region across 44 vertebrate species.

Discussion & Conclusion

Although our understanding of the molecular mechanisms driving sex determination has improved over the past decades, the genetic cause of the majority of patients diagnosed with ovotesticular DSD remain elusive suggesting that new genes or loci await discovery. The 1.7 kb deletion in 13q31.1 region discovered in our patient, contains a long intergenic noncoding RNA (linkRNA RP11-452B18.2-001)¹. The function of linkRNAs, defined as noncoding RNAs of more than 200 nucleotides, is not well-understood but they are suspected to be key regulators of diverse cellular processes². The high conservation of 13q31.1 sequence throughout vertebrates is a strong indicator of essential function. Indeed, conserved non-coding elements are probably required for tight control of genes during development³.

In conclusion, the discovery of a deletion in a highly conserved region of 13q31.1 in our patient suggests that this locus could be implicated in the pathogenesis of 46,XX ovotesticular DSD. The underlying suspected mechanism could be the perturbation of the action of a linkRNA implied in the regulation of genes orchestrating gonadal differentiation.

1 Vega Genome Browser release 56 - June 2014

2 Cabili M, Genes & Development, 2011

3 Gordon CT, J Med Genet, 2009