Duplication of the region coding for this gene caused 46,XY individuals to develop as females, a situation that led to the hypothesis that DAX1 might be the ovary determining gene. However, its inactivation in mice does not impair ovarian development or other aspects of female differentiation, while it impairs spermatogenesis, suggesting that DAX1 is not an ovarian determining gene but rather plays a critical role in spermatogenesis. DAX1 acts as an anti-SRY factor in the process of gonadal sex differentiation and is upregulated by WNT4, its activation being mediated via the WNT/β-catenin pathway.

**FOXL2** is a member of a large family of forkhead/winged helix transcriptional factors. The FOXL2 gene is located on chromosome 3q23 (OMIM#605597). It is expressed in the gonads, pregranulosa and later in granulosa cells and is essential for granulosa cell differentiation and ovary maintenance. FOXL2 plays a role in the XX sex reversal phenotype of the polled intersex syndrome in goats, characterized by complete female to male sex reversal. More than 130 mutations in FOXL2 have been associated with a human congenital disease, the blepharophimosis-ptosis-epicanthus inversus syndrome (BPES). Mutations leading to a significantly shortened FOXL2 protein often cause BPES type I, which is characterised by eyelid abnormalities and premature ovarian failure, thus indicating a functional role in ovarian development or maintenance. Interestingly, inducible deletion of FOXL2 in adult ovarian follicles in the mouse model leads to immediate upregulation of testis-specific genes, including the critical SRY target gene SOX9 (located on chromosome 17q24.3-q25.1, OMIM#608160). It has been shown that ablation of FOXL2 results in somatic sex reprogramming of adult ovaries leading to testis development, thus implying that FOXL2 has an additional crucial role in maintaining femaleness, at least in mice.

R-spondins are a recently characterized small family of growth factors which are thought to play an essential role in ovarian development. R-spondins interact with β-catenin and may also synergize with WNT proteins, possibly through positive regulation of WNT4 signaling. R-spondin1 and FOXL2 act in two distinct cellular types during goat ovarian differentiation. This interaction appears critical for early genital development and ovarian determination. Mutations in the R-spondin1 (RSPO1) gene have been associated with 46,XX testicular DSD in the absence of the testis-determining gene SRY, as well as with ovotesticular DSD in a 46,XX individual. Palmoplantar hyperkeratosis, predisposition to squamous cell carcinoma of the skin, congenital bilateral corneal opacities, onychodystrophy and hearing impairment were additional findings in such cases. Therefore, the RSPO1 gene (located on chromosome 1p34.3, OMIM#609595) appears to be directly involved in ovarian determination.

**DISORDERS OF SEX DEVELOPMENT (DSD) IN THE 46,XX INDIVIDUAL (TABLE 2)**

A brief description of each condition is described below, with special emphasis on the pathophysiology and relevant advances in genetics.

**A. Disorders of gonadal (ovarian) development**

1. Ovotesticular DSD, previously named true hermaphroditism. It is a very rare disorder defined by the presence of both ovarian and testicular tissue in the same individual (Figure 4). In infancy the gonads appear to have normal ovarian tissue with numerous follicles and normal testicular tissue with seminiferous tubules containing germ cells. However, as time passes the ovarian tissue usually becomes functional and the testicular tissue regresses, becoming dys-