Ontogenesis of sex in mammals and its disturbances

Below is a short overview of sex determination, with some sex reversal syndromes. These syndromes are explicitly mentioned:

gene	inheritance	syndrome
RSPO1	AR	Palmoplantar hyperkeratosis with squamous cell carcinoma of skin and sex reversal
SRY (loss)	n.a.	XY female sex reversal
SRY (gain, e.g. translocation)	n.a.	XX male sex reversal
SOX9	AD	testicular feminization
AR	XR	testicular feminization

Mammalian sex determination depends on ***SRY* gene on Y chromosome**. Absence of Y chromosome will lead germ cells differentiate into oogonia and enter meiosis. Female sexual development can be thus seen to be a default pathway. It does not mean that no active genetic control is required. E.g. Wnt (wingless) signaling is required – if a Wnt signaling activator *RSPO1* is inactivated by mutation, a true hermaphroditism results with ovotestis development, persistence of both Mullerian and Woffian ducts and intermediate external genitalia. If *SRY* gene is present, its expression is self-activated in the somatic cells of the testis. *SRY* is a transcription factor, activating another transcription factor, *SOX9*. *SOX9* differentiate these cells into Sertoli cells. Loss of *SRY* causes XY female sex reversal. Translocation of *SRY* onto X chromosome causes XX male sex reversal. As Y chromosome contains genes necessary for spermatogenesis, these males have azoospermia. Mutation of *SOX9* causes campomelic dysplasia, where XY female sex reversal is combined with skeletal dysplasia (*SOX9* is necessary for mesenchyme condensation preceding cartilage formation and enchondral ossification).

Sertoli cells produce a lot of signaling molecules: Desert hedgehog is a morphogen differentiating peritubular myoid cells (high concentration) and Leydig cells (low concentration); **antimullerian hormone** is signaling apoptosis to Mullerian duct; prostaglandins turn germ cells into gonocytes (that later form spermatogonia). Leydig cells start to produce testosterone, which (in embryonic stage) control external genital development (penis, scrotum), stimulate survival of Wolfian duct (epididymis and efferent ducts), and stimulates regression of cranial ligament of testis, together with insulin-like 3 (another hormone from Leydig cells) that stimulates contraction of caudal gubernaculum (testis descend).

Leydig cells start to produce **testosterone** again in puberty (spermatogenesis, beard, pubic and axillary hair, balding, muscle growth etc.). Loss of function of androgen receptor causes androgen insensitivity syndrome called also testicular feminization (X linked recessive). In complete testicular feminization with no remaining function of androgen receptor, testis is formed and Muller ducts destroyed, but Wolfian duct also destroyed, testes undescended, and external genitalia female, overall female phenotype. Pubic and axillary hair is missing.