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*Review*

# Genetics and Hormones in Testicular Descent*

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## ABSTRACT

**Testicular descent is an essential part of normal male sexual development. Any anomaly that disrupts normal testicular descent will be clinically evident as cryptorchidism. Several factors, such as Hoxa-10, epidermal growth factor (EGF), calcitonin gene-related peptide (CGRP), and hormones, especially androgens and insulin-like factor 3 (INSL-3), have been suggested as being regulators of testicular descent. Testicular descent from the lower pole of the kidney into the extra-abdominal scrotal sac is a two-stage process of transabdominal and inguino-scrotal migration. The transabdominal phase is androgen independent, whereas the inguinoscrotal phase depends on androgen action. Disruption of androgen action eg. by environmental anti-androgens are suspected as contributing to cryptorchidism. Estrogens can down-regulate INSL-3 production and thereby disturb testicular descent. Familial occurrence in some cases suggests a possible genetic background for cryptorchidism.**

**Key words:** cryptorchidism, testis, INSL-3, androgens, environment, genetics

## INTRODUCTION

Cryptorchidism, the most common congenital malformation in newborn boys, can occur as an isolated anomaly or may be associated with other congenital disorders. Cryptorchidism affects 1-9% of full term boys at birth and about 1% at three months of age[1]. Some reports have suggested substantial increase in the prevalence of cryptorchidism over the last few decades[2-4]. In most of the cases the aetiology of cryptorchidism remains unknown but several risk factors for cryptorchidism have been reported. Low birth weight adjusted to gestational age (small for gestational age) overrules all other risk factors and indicates a possible association with placenta malfunction. Possibly due to unsubstantial symptoms at birth, cryptorchidism is often considered a mild malformation but it is the best characterized risk factor for testicular cancer[5,6] and a serious risk factor for infertility[7,8].

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## TESTICULAR DESCENT

Development of the male genitalia is a complex series of events including a unique process of testicular descent occurring considerably late in pregnancy. The sexual dimorphic position of the gonads in mam-

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mals is dependent on the differential development of two ligaments during pregnancy: the caudal genitoinguinal ligament, or gubernaculum, and the cranial suspensory ligament (CSL). According to the biphasic model, two independent phases are seen in normal testicular descent. The outgrowth of the gubernaculum and the regression of CSL result in the transabdominal migration of the testes into the inguinal region. The subsequent descent of the testes to the scrotum is due to the shortening of the gubernacular cord and the outgrowth of the gubernacular bulb. The first (transabdominal) phase starts after 10 weeks of gestation when the gubernaculum starts to deposit extracellular matrix rich in glycosaminoglycans and hyaluronic acid and forms a cone-like structure at the caudal end of the gonad. Due to this swelling reaction, the gubernaculum becomes a ligamentous structure which anchors the developing testis close to the inguinal region during fetal growth. In the male fetus the gubernacular swelling is associated with androgen dependent regression of the cranial suspensory ligament (CSL) (Figure 1.) The second (inguinoscrotal) phase of testicular descent starts at around 26 gestational weeks when the gubernaculum begins to bulge through the inguinal canal. The gubernaculum reaches the scrotum by 35 gestational weeks and pulls the testis in its path before the gubernaculum shrinks to a fibrous remnant.

## HORMONES

A normal hypothalamo-pituitary-gonadal axis with normal androgen synthesis and action are commonly accepted as being essential for physiological testicular descent. This is supported by the findings that hypogonadotropic hypogonadism and androgen insensitivity often cause testicular maldescent. Moreover, a high percentage of cryptorchidism resolves spontaneously during the period of high serum gonadotropin and steroid hormone levels at the age of 1-3 months. It has been debated whether this postnatal surge of reproductive hormones has a biological effect since virilization does not occur in infants. Raivio et al[9] reported that androgen bioactivity at 3 months of age correlated with serum testosterone concentration and cryptorchid boys had reduced androgen bioactivity. In some studies, decreased serum testoterone levels together with reduced luteinizing hormone (LH) levels have been found[10,11]. The androgen effect is necessary but not sufficient alone for normal testicular descent. The first phase of testicular descent is successful even without androgens. Among androgen insensitivity patients, the testis is located in the inguinal region indicating that only inguinoscrotal descent has failed to occur. Although high androgen levels cause regression of the cranial suspensory ligament, no ovarian descent occurs in congenital adrenal hy-

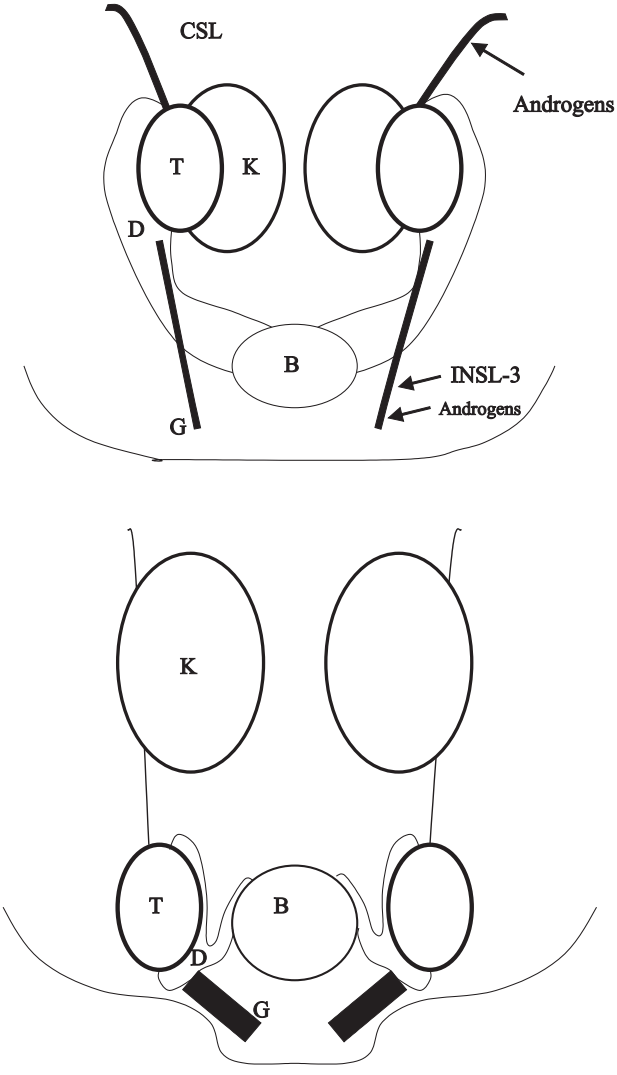


**Figure 1.** The theory of testicular descent is based on results from both human and experimental animals. At the indifferent stage the gonad is located next to the kidney (K). During the transabdominal phase between week 8 (upper illustration) and week 17 (lower illustration) of testicular descent, the testis (T) is anchored by the swollen gubernaculum (G) close to the inguinal region. Changes in the gubernaculum are regulated by INSL-3 and androgens. Regression of the cranial suspensory ligament (CSL) is androgen dependent. B= bladder, D=duct.

perplasia. The androgen action is mediated by androgen receptor, which contains stretches of polyglutamine. This polyglutamine is encoded by repeats of trinucleotide CAG, and progressive expansion of the CAG repeats in human AR caused a linear decrease of transactivation function[12]. However, CAG repeat length did not show any association with the risk for cryptorchidism.

Androgens might have a direct effect on the cremaster muscle[13] or the gubernaculum[14] but indirect mechanisms are also suggested. Hutson and his study group have shown a sex dependent masculinization of the genitofemoral nerve which releases calcitonin gene-related peptide (CGRP) into the gubernaculum and causes rhythmic contractions in rodents[15,16]. Cain et al[17] reported that supraphysiologic doses of epidermal growth factor (EGF) can reduce the incidence of antiandrogen-induced (flutamide) cryptorchidism in rats. They also reported that the EGF has no direct effect on Wolffian ducts or the fetal testis. EGF stimulates placental gonadotropin secretion[18] and it is possible that altered placental function explains the effects of EGF.

The male fetus is exposed to high levels of maternal estrogens during pregnancy and estrogen receptors (ER) are widely expressed in the male reproductive system[19]. In mice, ERα knockout (αERKO) caused infertility[20] but βERKO mice were fully fertile[21]. The aromatase knockout mouse (ArKO) has no circulating estrogens due to lack of functional aromatase enzyme. Fertility of initially fully fertile ArKO males decreases with advancing age[22,23]. In humans, only a few cases with ER or aromatase defects have been published and they all had normal male external genitalia with varying semen quality[24]. The role of estrogens in normal testicular descent is obscure. In rats, a single subcutaneous oestrogen injection on day 14 of pregnancy resulted in cryptorchidism in all male offspring[25]. An increased risk of cryptorchidism is associated with nausea during pregnancy, which is believed to be caused by high estrogen levels[26]. Moreover, mothers of cryptorchid boys had higher estradiol levels than control mothers during the first trimester[27] and Hadziselimovic[28] reported increased expression of placental estradiol in cryptorchid boys. In the mouse, maternal exposure to estrogens down regulates Insl-3 expression providing a possible mechanism for cryptorchidism[29,30].

The anti-Müllerian hormone (AMH) is a gonadal hormone secreted by Sertoli cells. AMH was thought to be a regulator of changes in the gubernaculum during testicular descent because lack of AMH often resulted in cryptorchidism in the inguinal region. However, Bartlett et al[31] showed that testicular descent was normal in AMH receptor-deficient mice. Thus, it seems that AMH is responsible in male fetuses for regression of the Müllerian ducts but changes in the gubernaculum are regulated by other factors. Hence, maldescent of the testes in humans with lack of AMH might be the result of an anatomical connection of the gonads to the persistent Müllerian ducts.

## ENVIRONMENTAL FACTORS

On the grounds of increased incidence of cryptorchidism in springtime[32-34], environmental factors have been suggested as affecting testicular descent. Probably this seasonal variation is associated with the circannual rhythm of hormonal action. In normal men, an increased secretion of luteinising hormone (LH), follicle stimulating hormone (FSH), testosterone and inhibin has been found in May-June, with a nadir in August[35,36]. A cyclical pattern might be induced by light or some other factors.

A theory of testicular dysgenesis syndrome (TDS) was presented by Skakkebaek[37]. According to the TDS theory, adverse changes in male reproductive health share the same risk factors. There is evidence that not only cryptorchidism and hypospadias but also testicular cancer and male infertility have a fetal origin. Low birth weight has been associated with testicular cancer, cryptorchidism, hypospadias and low sperm counts[38,39]. The increased risk of testicular cancer in cryptorhid patients remains regardless of treatment, and is also increased in contralateral testes of unilateral cases[5,40]. Testicular cancer patients have a reduced fertility already prior to the cancer diagnosis[41]. Both genetic and environmental factors, including endocrine disrupting chemicals, can contribute to the development of TDS[42]. This possibility is supported by findings showing that exogenous oestrogens and antiandrogens cause disorders of genital development in animals[43-45].

## GENES

A heritable background of cryptorchidism has been

suggested due to familial occurrence. Moreover, genetic syndromes might result in cryptorchidism and an increased probability for coexistence with other genital disorders has been reported. Weidner et al[46] screened risk factors for cryptorchidism and they reported that cryptorchidism was associated with hypospadias 3 times more often than expected, and an almost 4-fold increased risk of cryptorchidism was observed when an older brother had been cryptorchid as well.

Microdeletions of Y chromosome long arm (Yq) often result in improper spermatogenesis causing oligo- or azoospermia[47,48]. Microdeletions as a cause of cryptorchidism has also been investigated, and Foresta et al[49] reported microdeletions in the AZF region of Yq in 27.5% of cryptorchid males. This remains to be confirmed in other populations.

INSL-3, also known as relaxin-like factor (RLF), is a product of Leydig cells and is probably needed for normal testicular descent. Male mice mutant for INSL-3 were cryptorchid and showed improper development of the gubernaculum[50,51], whereas in female mice the overexpression of INSL-3 caused ovary descent[52]. The effect of INSL-3 can be augmented by AMH and dihydrotestosterone[53]. Thus, INSL-3 is an apparent regulator of testicular descent in rodents. The receptor for INSL-3 has been recently identified and named LGR-8 (leucine-rich repeat-containing G protein-coupled receptor 8) or Great (G protein-coupled receptor affecting testis descent)[54,55]. The correspondence between INSL-3 as ligand and LGR8/Great as receptor was suggested by the phenotype similarity between the *Great* mutant mice and the *Insl3* knockout mutants[51,56]. In humans several polymorphisms in the INSL-3 gene have been identified but mutations are rarely associated with cryptorchidism[57-60]. Likewise, Gorlov[61] reported nucleotide variations in LGR-8 cDNA but unique heterozygous mutation was identified only in one patient. In our own material we found only polymorphisms in LGR-8 gene[62]. In contrast, in a recent cohort of 87 ex-cryptorchid patients, Ferlin et al[63] found three heterozygous mutations in the INSL3 gene in four patients and one heterozygous LGR8/Great mutation in four patients (9.2%). The eight patients showed different phenotypes, ranging from bilateral cryptorchidism to retractile testes while the endocrine function of the testis was normal in all subjects suggesting that alterations of the INSL3-LGR8/Great system could be responsible, at least in part, for failure of the testicular descent. Thus far, there is no biological explanation as to how the heterozygous mutations could affect humans differently from mice that are normal when only one allele of the INSL-3 or LGR8 genes is missing[56].

Homeobox (HOX) genes seem to play a key role in the morphogenesis of the urogenital mesenchyma. Homozygous male mice mutated for Hoxa-10 gene exhibited cryptorchidism and gubernacular abnormalities and they also manifested defects in spermatogenesis[64]. Polymorphisms in exon 1 of Hoxa-10 gene have been found but no causative mutations have been identified until now in humans[65].

## CONCLUSION

Cryptorchidism is a common condition in newborn boys inducing fertility problems later in life if an appropriate treatment is not applied. Several risk factors for cryptorchidism have been described indicating multifactorial background. New candidate genes, like INSL-3 and Hoxa-10, have also been investigated but thus far, cryptorchidism has most often been associated with mutations of genes of androgen receptor or steroidogenic enzymes that are needed for androgen production or gene mutations leading to hypogonadotropic hypogonadism.

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