



CRYPTORCHIDISM – AN IMPORTANT MALE REPRODUCTIVE PATOLOGY IN DOGS AND CATS

TĂMAȘ ANCA, FŪR BEATRICE-RUTH, RANDON FONSECA MILA ROSE, MARC SIMONA, IGNA VIOLETA

University of Life Sciences "King Mihai I" from Timisoara, Faculty of Veterinary Medicine, 300645, No.
119 Calea Aradului, Timișoara, România
E-mail: simona.marc@usvt.ro

Cryptorchidism, a disorder of sex development, is a developmental abnormality characterized by the fail of descent of one or both testes to the scrotum, which has significant consequences for male health. With this bibliographic study, we aim to systematize the latest information on the possible genetic, epigenetic, and other causes of the occurrence. Other topics detailed are on testicular morphogenesis, clinical types of cryptorchidism, the main risks to male health- testicular tumors, such as seminomas and sertoliomas, or testicular torsion; methods of diagnosis (ultrasound, serum Anti-müllerian hormone level, molecular biomarkers). The incidence among dogs and cats is discussed along with treatment, prevention and medical perspectives on reducing the incidence. Cryptorchidism is considered to be a hereditary condition, with an increased number of familial cases in some dog breeds. Genetic studies suggest that several gene mutations, including *INSL3*, *RXFP2*, and *ESR1*, are implicated in the failure of the process of testicular migration. Recent genomic and epigenomic data suggests possible biomarkers associated with cryptorchidism. This condition not only affects males' health, but also limits their access to breeding and pedigree.

Keywords: cryptorchidism, testicular morphogenesis, biomarkers, epigenetic modifications

• Introduction

Testicular descent occurs in three main stages: first, the testes enlarge and the mesonephros regresses; second, androgens cause the anterior suspensory ligament to regress, allowing the testes to descend and in the third stage, the transinguinal migration takes place, hormonally dependent and guided by the gubernaculum testis.

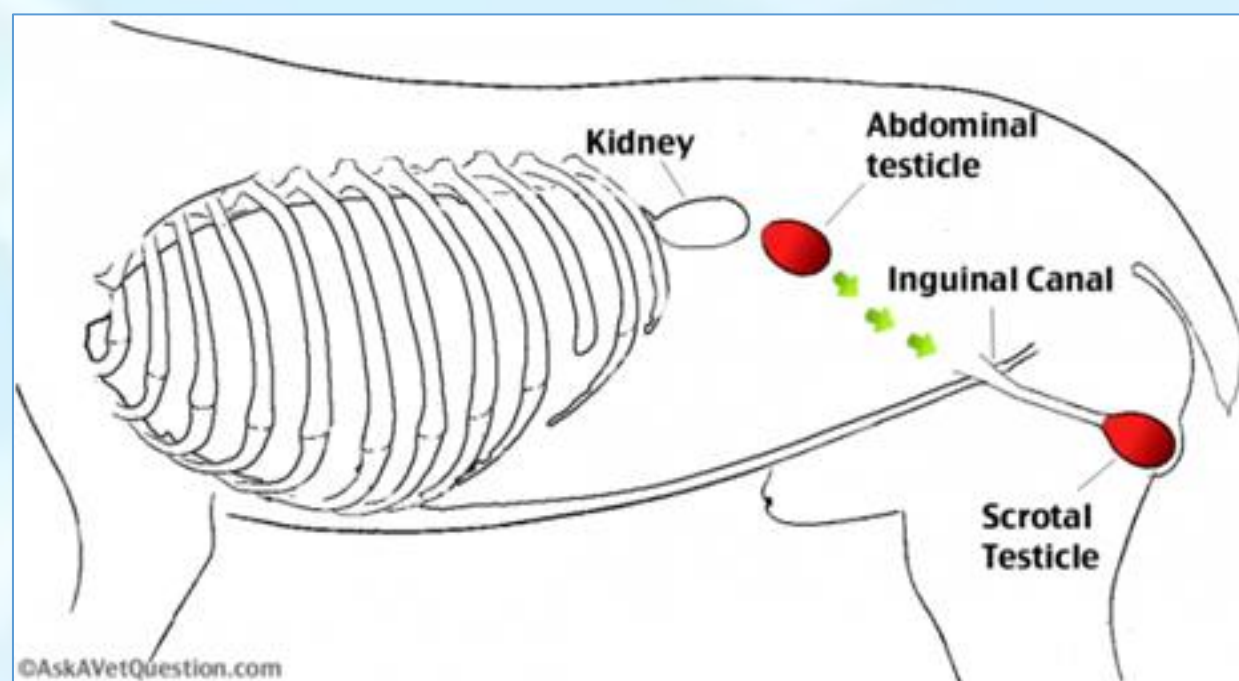


Fig.1 Main stages of testicular descent [22]

If this process is disrupted, cryptorchid testes may remain in the abdomen or inguinal canal, leading to infertility, testicular tumors, and torsion, with an incidence rate of 0.8–10% [3, 4, 13]. Furthermore, abdominally retained testes are exposed to higher body temperatures, which disrupt spermatogenesis and cause structural alterations in Sertoli cells [9, 11, 12, 13, 16].

• Material and method

There are many indicators that this is an inherited condition. Early signs of heredity were noted in Miniature Schnauzer families with cryptorchid cases [4] and in inbred dogs [18]. A study on 11,230 purebred puppies across 12 breeds found a higher cryptorchidism rate (24.1%) in offspring of suspected carriers compared to the general population (2.1%)[7]. Theories suggest multiple low-penetrance genes, modifier genes, and environmental factors play a role in cryptorchidism [14, 18, 20].

• Results and discussions

Studies highlight the role of *INSL3* gene and its receptor, *RXFP2*, in testicular descent, as evidenced by research in humans and mice. *RXFP2* shows high, tissue-specific expression in structures critical for testicular development and is regulated by the *SOX9* gene, essential for testicular formation [6]. In cryptorchid dogs, *RXFP2* expression is nearly absent in undescended testes but active in scrotal testes, suggesting its importance during fetal testicular descent [8].

Among genetic factors, the persistence of the cranial suspensory ligament, improper positioning of the gubernaculum bulb, and size discrepancies between the testis and inguinal canal and hormonal factors, including testosterone insufficiency, androgen insensitivity, Persistence Müllerian Duct Syndrome (PMDS), and hypothalamic or pituitary deficits, are also thought to disrupt normal testicular descent [2, 10, 18, 20].

References:

1. ABITBOL M., CHEVALLIER L. (2022) Document de cours de Génétique Moléculaire: Approche génétique de l'amélioration et de la santé des animaux domestiques. Polycopié. Maisons Alfort, Ecole Nationale Vétérinaire d'Alfort, Unité Pédagogique d'Éthologie, de Physiologie et de Génétique vétérinaires.
2. BOGATCHEVA N.V., FERLIN A., FENG S., et al. (2007) T222P mutation of the insulin-like 3 hormone receptor LGR8 is associated with testicular maldescent and hinders receptor expression on the cell surface membrane. Am J Physiol Endocrinol Metab 292(1), E138-144.
3. BIRCHARD SJ, NAPIER M. Cryptorchidism. Compend Contin Educ Vet. 2008 Jun;30(6):325-36; quiz 336-7. PMID: 18690608.
4. COX V.S., WALLACE L.J., JESSEN C.R. (1978) An anatomic and genetic study of canine cryptorchidism. Teratology 18(2), 233-240.
5. ENGLAND G., VON HEIMENDAH A. (2011) BSAVA Manual of Canine and Feline Reproduction and Neonatology, 2ème éd., Quedgeley, British Small Animal Veterinary Association.
6. FENG S., FERLIN A., TRUONG A., et al. (2009) INSL3/RXFP2 signaling in testicular descent. Ann N Y Acad Sci 1160, 197-204.
7. GUBBELS E.J., SCHOLTEN J., JANS S., ROTHUIZEN J. (2009) Relationship of cryptorchidism with sex ratios and litter sizes in 12 dog breeds. Anim Reprod Sci 113(1-4), 187-195.
8. HANNAN M.A., KAWATE N., KUBO Y., et al. (2015) Expression analyses of insulin-like peptide 3, RXFP2, LH receptor, and 3β-hydroxysteroid dehydrogenase in testes of normal and cryptorchid dogs. Theriogenology 84(7), 1176-1184.
9. HERNÁNDEZ-JARDÓN N., ROJAS-CASTAÑEDA J.C., LANDERO-HUERTA D., REYES-CRUZ E., REYNOSO-ROBLES R., JUÁREZ-MOSQUEDA MDL, MEDRANO A., REYES-DELGADO F., VIGUERAS-VILLASENOR RM. Cryptorchidism: The dog as a study model. Front Vet Sci. 2022 Sep 13;9:935307. doi: 10.3389/fvets.2022.935307. PMID: 36176705; PMCID: PMC9514118.
10. HUTSON J.M., HASTHORPE S., HEYNS C.F. (1997) Anatomical and functional aspects of testicular descent and cryptorchidism. Endocr Rev 18(2), 259-280.

Environmental factors may further increase cryptorchidism risk, with prenatal exposure to estrogen, phthalates, and pesticides among potential contributors. Additionally, various chemicals and medications have been implicated, highlighting the complex interaction between genetic, anatomical, hormonal, and environmental influences in the etiology of cryptorchidism. [15, 19, 21].

Species	Beginning of testicular descent	Testis within the inguinal canal	Testis within the scrotum
Cattle	15.8 cm CRL	22 cm CRL	40 cm CRL
Sheep	15 cm CRL	17.5 cm CRL	25 cm CRL
Pig	Day 65 p.c	Day 85-90 p.c	At birth
Horse	Day 45 p.c	Before birth	At birth
Dog	-	Day 3-4 p.p	Day 35-40 p.p
CRL – crown-rump length; p.c – post coitum; p.p – post partum			

Fig.2 Stages of testicular descend on different species [11]

• Conclusions

Cryptorchidism is a multifactorial condition, resulting from a complex interaction of genetic, hormonal, anatomical, and environmental factors.

Genetic studies highlight the importance of *INSL3* and its receptor *RXFP2*, both crucial for testicular descent. The low or absent expression of *RXFP2* in undescended testes in adults suggests a critical role in early development. Additional genes like *ESR1*, responsible for estrogen receptor activity, have been implicated in testicular migration.

Anatomical anomalies—such as the persistence of the cranial suspensory ligament, incorrect positioning of the gubernaculum, or disproportionate dimensions between the testicle and inguinal canal—further hinder normal testicular descent and increase susceptibility to cryptorchidism.

Hormonal and environmental influences also play a significant role. Hormonal disruptions, including testosterone insufficiency, androgen insensitivity, and hypothalamic-pituitary deficits, impair the descent process.

Environmental factors, like prenatal exposure to estrogen, phthalates, and pesticides, as well as exposure to certain chemicals and medications, have been shown to raise the risk of cryptorchidism. Together, these genetic and external factors underscore cryptorchidism's complex origin, reinforcing the importance of comprehensive research to clarify its mechanisms and improve management and prevention strategies.

11. HYTTTEL P, SINOWATZ F, VEJLSTED M, BETTERIDGE K. Essentials of domestic animal embryology. Elsevier Health Sciences; 2009. pp. 260-279. ISBN 978-0-7020-2899-1.
12. JOHNSTON S.D., ROOT KUSTRITZ M.V., OLSON P.S. (2001) Canine and feline theriogenology. Philadelphia, PA, Saunders.
13. KIM, E. P., SHIN, J.-H., KIM, W. H., & KIM, G. A. (2023). Integrated miRNA Changes in Canine Testis and Epididymis According to Age and Presence of Cryptorchidism. Animals, 13(8), 1390. https://doi.org/10.3390/ani13081390
14. KHAN F.A., GARTLEY C.J., KHANAM A. (2018) Canine cryptorchidism: An update. Reprod Domest Anim 53(6), 1263-1270.
15. KRISTENSEN D.M., HASS U., LESNÉ L., et al. (2011) Intrauterine exposure to mild analgesics is a risk factor for development of male reproductive disorders in human and rat. Hum Reprod 26(1), 235-244.
16. KURPISZ M., HAVRYLUK A., NAKONECHNYI A., CHOPYAK V., KAMIENICZNA M. (2010) Cryptorchidism and long-term consequences. Reprod Biol 10(1), 19-35.
17. MARSHALL L.S., OEHLERT M.L., HASKINS M.E., SELDEN J.R., PATTERSON D.F. (1982) Persistent Müllerian duct syndrome in miniature Schnauzers. J Am Vet Med Assoc 181(8), 798-801.
18. MIALOT J.-P. (1984) Pathologie de la reproduction chez les carnivores domestiques. Maisons Alfort, Editions du Point Vétérinaire NIELEN A.L., JANS S.L.L., KNOL B.W. (2001) Heritability estimations for diseases, coat color, body weight, and height in a birth cohort of Boxers. Am J Vet Res 62(8), 1198-1206.
19. PALMER J.R., HERBST A.L., NOLLER K.L., et al. (2009) Urogenital abnormalities in men exposed to diethylstilbestrol in utero: a cohort study. Environ Health 8, 37.
20. ROMAGNOLI S.E. (1991) Canine cryptorchidism. Vet Clin North Am Small Anim Pract 21(3), 533-544.
21. TOPPARI J., VIRTANEN H., SKARKEBAEK N.E., MAIN K.M. (2006) Environmental effects on hormonal regulation of testicular descent. J Steroid Biochem Mol Biol 102(1-5), 184-186.
22. https://vettohome.com/articles/ (Cryptorchidism, the main stages of testicular descent)