ABSTRACTS

6th International Symposium on Canine and Feline Reproduction

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6th Biennial EVSSAR Congress

European Veterinary Society for Small Animal Reproduction

"Reproductive biology and medicine of domestic and exotic carnivores"

University of Veterinary Sciences
9th – 11th July 2008
Vienna, Austria

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Inherited disorders of sexual development are important to identify, as they can cause infertility or sterility in specific breeds. Research is continually identifying new genes and pathways to consider in the pathogenesis of these disorders. This review updates an overview of normal sexual development (Meyers-Wallen 2006), providing specific examples in XX sex reversal, Persistent Mullerian Duct Syndrome and cryptorchidism, and discusses current methods used to identify causative mutations.

The process of sex determination is more complex in mammals than originally proposed. For example, it was hypothesized that testis determination was an active process while ovarian development occurred by default. Research now suggests that both testis- and ovarian-promoting pathways are active during the time of gonadal sex determination, antagonizing one another in the bipotential gonad. Furthermore, although SRY (sex determining region Y gene) is a testis determining factor, the autosomal gene, SOX9 (sex determining region Y- box9), also encodes an important testis determining factor. A new gene, R-spondin1 (RSPO1), probably acting in concert with the canonical pathway of the wingless-related protein family (WNT), may have a role in suppressing SOX9-mediated testis induction. The question is whether dysfunction in any of these causes SRY-negative XX sex reversal in any breed. Genome wide linkage disequilibrium analysis, fine mapping, and exon scanning of specific genes are used in a canine model to identify causative mutations of this disorder.

Internal genitalia development is dependent upon gonadal sex. For example, Mullerian Inhibiting Substance (MIS), secreted by the testis, is necessary for Mullerian duct regression in males. At the target organ, regression requires MIS receptors, components of the WNT pathway, and downstream transcriptional activators (Zhan et al 2006). Failure of Mullerian duct regression (Persistent Mullerian Duct Syndrome, PMDS) can result from disruption at any step. A mutation in a candidate gene in this pathway has been identified by exon scanning in a canine pedigree segregating the this disorder.

In male external genitalia, testosterone (T), secreted by the testis, provides the substrate for 5 alpha reductase to generate dihydrotestosterone (DHT), which masculinizes the urogenital sinus, genital tubercle and genital folds. Target organ response to T or DHT requires the androgen receptor (AR). For example, four factors have been identified to have a role in testis descent: T, AR, insulin-like peptide 3 (INSL3) produced by the testis, and the INSL3 receptor. However, mutations affecting these four cause only a small percentage of human cryptorchidism, so more genes are likely involved in testis descent (Virtanen et al 2007). Similarly, mutations causing canine cryptorchidism have not been identified. Association mapping is one approach to identifying the causative genes of this complex trait.

Small animal studies can identify new mutations, allowing us to eliminate these inherited disorders from breeding populations, while contributing to the understanding of mammalian sexual development and differentiation.

References
