

## Female Development in Mammals by *Wnt-4* Signalling

Although differentiation of the testes and of male internal and external genitalia have long been known to be actively guided processes, it has been assumed that differentiation of the ovary and of female internal genitalia are "innate" processes that occur by default. Vainio et al demonstrated that in the mouse, ovarian and Müllerian duct differentiation are active processes influenced by the product of *Wnt-4*, a member of a family of extracellular, cysteine-rich glycoprotein signaling molecules (OMIM 603490). The latter influence a number of developmental processes, including normal renal development in the mouse.

*Wnt-4* also is expressed in the embryonic gonadal ridge, the undifferentiated fetal gonad, the fetal ovary (although downregulated in the fetal testis), and in mesenchyme of the Müllerian but not the Wolffian ducts. By crossbreeding animals heterozygous for inactivation of *Wnt-4*, these investigators developed fetuses and newborns that were homozygous for this defect (*Wnt-4*<sup>-/-</sup>).

The male offspring were phenotypically normal, but the female offspring were virilized. The ovary was deformed and the Müllerian ducts were absent. The single gonadal duct resembled an epididymis. The external genitalia of the female offspring were normal. The *Wnt-4*<sup>-/-</sup> female gonad appeared to synthesize and secrete androgens as it expressed both *HSD3B* and *CYP17*. The homozygous fetal ovary had far fewer oocytes than the normal ovary, suggesting that *Wnt-4* is necessary for oocyte maintenance. The investigators conclude that *Wnt-4* is important for normal fetal female sexual differentiation in the

mouse and, by inference, in other mammals, possibly including humans.

Vainio S, et al. *Nature* 1999;397:405-409.

**Editor's comment:** *This study demonstrates the essential role that Wnt-4 plays in Müllerian duct differentiation and ovarian function. It is of interest that in the Wnt-4<sup>-/-</sup> females, Müllerian duct inhibitor factor from the Sertoli cells was not necessary for regression of the Müllerian ducts!*

*It has been suggested that DAX1 (dosage sensitive sex reversal on the X chromosome—Xp21) may be important for ovarian differentiation. The role of DAX1 in sexual differentiation has been demonstrated by the sex reversal of 46,XY males in patients with duplication of this gene, thus suggesting that this transcription factor is involved in ovarian determination and repression of testicular function. Yu et al (Role of Ahch in Gonadal Development and Gametogenesis. Nature Genet 1998;20:353-357) generated a mouse model in which Dax1 has been inactivated. In these animals, ovarian differentiation and fertility are normal, but spermatogenesis and testosterone secretion in the male are disrupted. Thus, Dax1 affects testicular function in a dose-dependent manner; normally, it supports spermatogenesis and Leydig cell function, but when duplicated leads to inhibition of the testis-determining effects of SRY and SOX9. Embryologic sex differentiation becomes more complex as we learn more and more about gene control. We used to be able to explain sexual differentiation on a hormonal basis, but we cannot do this in 1999.*

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## COL9A3: A Third Locus for Multiple Epiphyseal Dysplasia

Multiple epiphyseal dysplasia (MED) refers to an autosomal dominant clinical phenotype characterized by mild to moderate short stature associated with painful joints and precocious osteoarthritis. Historically, MED has been divided into the severe (or Fairbank) form and the mild (or Ribbing) form, although the phenotypes merge to form a gradient of severity. MED is a genetically heterogeneous condition.

MED mutations were first found in the gene encoding cartilage oligomeric matrix protein, COMP. This locus, which also harbors mutations responsible for pseudoachondroplasia, was designated *EDM1*. It was clear soon after the *EDM1* locus was identified that, in some families, MED does not map to the *COMP-EDM1* locus.

A second locus, designated *EDM2*, was identified in 1996 through positional cloning. It encodes the alpha 2 chain of type IX collagen, an extracellular matrix protein of cartilage and skeletal growth plate. This led to the view that type IX collagen and COMP interact functionally in growing bones and that disturbances of this interaction occur in pseudoachondroplasia and MED.

The existence of a third *EDM* locus was anticipated from linkage studies that excluded *EDM1* and *EDM2* in some families with MED phenotypes. The genes encoding the other 2 chains of type IX collagen, *COL9A1* and *COL9A3*, were the strongest candidates. *COL9A3* has now been identified as *EDM3*. Paasilta et al first established linkage of a relatively mild form of MED to a genetic marker in *COL9A3*. They next demonstrated a mutation predicted to disrupt splicing of *COL9A3* mRNA transcripts, leading to deletion of 12 amino acids near the amino-terminal end of the collagen chain. The mutation resembles the *COL9A2* mutation found in other cases of MED. Not surprisingly, the manifestations are similar in the families with type IX collagen mutations.

Paasilta P, et al. *Am J Hum Genet* 1999;64:1036-1044.

**Editor's comment:** *It is now evident that genes encoding cartilage matrix proteins are a very rich source of mutations that cause human chondrodysplasias. This reflects the importance of these proteins to endochondral bone growth. Since these proteins interact with each other to form a functional extracellular matrix, it makes sense that disturbances of different elements of this matrix lead to relatively similar clinical*