Habiby et al. (1) resolve a controversy concerning development of male sexual characteristics, in the process opening significant new areas for investigation. Their results indicate that the relationship between the hypothalamus and pituitary in male sexual development may be more complex than previously appreciated, and highlight significant issues regarding the role of the DAX1 gene product in female sexual differentiation.

The DAX1 gene (Dosage sensitive sex reversal - Adrenal hypoplasia congenita gene on the X chromosome, gene 1) was identified by positional cloning strategies after localization of the gene using DNA samples from patients with Xp21 contiguous gene syndromes that included adrenal hypoplasia congenita (AHC) (2, 3). Observation of intragenic DAX1 mutations in patients with AHC and hypogonadotropic hypogonadism (HH) clarified an earlier controversy: AHC and HH were due to alteration of a single gene product and were not due to deletion of two discrete, contiguous loci (2–4). The role of DAX1 in adrenal and pubertal development was all the more intriguing because of the similarity of the carboxy-terminal portion of the DAX1 protein with other nuclear hormone receptor superfamilies.

Since DAX1 maps to a region of the X chromosome that undergoes inactivation, a single copy is expressed in normal males and females. Loss of the DAX1 gene product by deletion or point mutation results in developmental abnormalities in the hypothalamic-pituitary-gonadal axis. Results of previous clinical studies of HH in patients with AHC were mixed regarding hypothalamic and/or pituitary origin (5–10). Some affected boys responded to pulsatile GnRH, others did not. Habiby et al. investigated two families with AHC and HH, and both had frameshift mutations in DAX1. Abnormal patterns of baseline gonadotropin levels were different in a postpubertal male in both families. One had no response to pulsatile GnRH and testosterone only rose to 39 ng/dl at the end of one week of treatment, a result interpreted by previous authors as a primary pituitary defect. The affected individual from the other pedigree responded normally to the initial pulse on day 1, with minimal responses on subsequent days, but a gradual rise in testosterone to 241 ng/dl during the week. These results indicated that he did not have absolute hypogonadotropic hypogonadism and suggested a mixed hypothalamic/pituitary defect. Investigations, carried out with identical clinical protocols on patients with very similar mutations, illustrate the marked phenotypic heterogeneity in this disorder. They show that DAX1 acts at both pituitary and hypothalamic levels to mediate pubertal development, resolving differences in previous studies.

Conclusions from these clinical investigations are supported by studies of DAX1 gene expression. Guo et al. observed amplification of DAX1 after reverse transcription of mRNA from human hypothalamus and pituitary, (11) observations that have been confirmed in the mouse (12).

If absence of functional DAX1 in males leads to HH, have any problems been associated with over-expression of this gene? DAX1 maps to the 160-kb dosage-sensitive sex reversal (DSS) critical region in Xp21. (13) and, since the gene product is a putative transcription factor, DAX1 is a candidate for the DSS gene. Patients with DSS have tandem duplications of Xp21 containing the DSS critical region, and, hence, the second copy of the gene is not subject to X inactivation. XX females with DSS duplications have normal phenotypes and normal fertility. XY genotypic males with DSS duplications and normal SRY have female or ambiguous genitalia. Whether the DAX1 gene or another gene in this portion of Xp21 is responsible for DSS remains to be determined.

The mouse may serve as a model for the investigation of DSS. The region of the X chromosome contiguous to DAX1 is syntenic between human and mouse (14). Therefore, if transgenic mice expressing multiple copies of this genomic region have a DSS phenotype, they will permit molecular genetic dissection of this region to determine whether DAX1 and DSS are identical, or whether another gene in the region is responsible for DSS.

The mechanism by which DAX1 ensures normal adrenal cortical and pubertal development remains to be determined. The sequence similarity with other members of this transcription factor superfamily resides in the carboxy-terminal half of the protein. While similarity in the amino-terminal half is not significant compared with most other family members, cysteines are arranged consistent with two zinc fingers, a structural motif important to many other members of the superfamily. The murine homologue of DAX1, Ahch, has each of these cysteines conserved, despite variability in the residues surrounding the cysteines, (12, 14) suggesting their functional importance.

A new orphan receptor, the short heterodimeric partner (SHP), has been identified and has its closest sequence similarity with DAX1 (15). Like DAX1, SHP has an unusual amino-terminal portion, and it is much shorter in SHP. The DAX1 protein has three and a half repetitions of an amino acid sequence in the NH2-terminal portion and this portion of the SHP protein has similarity with the repeat motifs, but is only a single repeat in length. The SHP protein appears to heterodimerize with other transcription factors to modulate their activity.

Perhaps DAX1 has properties similar to SHP, and, therefore, it may be the concentration of the DAX1 protein relative to its heterodimeric partners that influences its activity. Loss of DAX1 results in AHC and HH, and increased DAX1 leads to DSS and a female phenotype or ambiguous genitalia in XY genotypic males. DAX1 definitely is involved in male sexual development, because if there is too little then the patient has HH. Too much DAX1 may have a significant impact on the determination of phenotypic sex.

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