

Estrogen Resistance Caused by a Mutation in the Estrogen-Receptor Gene in a Man

The authors describe a fully virilized, 28-year-old adult male with absence of a functional estrogen receptor. This disorder was characterized by: (a) tall stature and continuous linear growth throughout adult life (during childhood height pursued the National Center for Health Statistics 75th percentile while at the age of the report height was 204 cm, or +4.2 standard deviations [SD]); (b) unfused epiphyseal growth plates of the long bones and a wrist bone age of 15 years; (c) osteopenia; (d) increased serum concentrations of luteinizing hormone and follicle-stimulating hormone, and estradiol and estrone with normal levels of testosterone; (e) normal sperm number but decreased sperm viability; (f) mild glucose intolerance, hyperinsulinism and acanthosis nigricans; and (g) lack of effect of high-dose estradiol delivered transcutaneously on sexual characteristics, breast growth, or bone mineral density. The parents of this patient were second cousins. This autosomal recessive trait was associated with substitution of thymine for cytosine at codon 157 in exon 2 of the estrogen receptor gene, resulting in substitution of a stop codon (TGA) for arginine (CGA) at this position and a highly truncated estrogen receptor with no DNA- or hormone-binding domains.

This patient, when compared with his normal siblings and parents, demonstrates that: (1) estrogen activity is not essential for life, fetal development, postnatal growth, or virilization in the male; (2) heterozygous males and females with one defective estrogen receptor allele are normal; (3) estrogen is essential for complete epiphyseal maturation and fusion and for normal skeletal mineralization in the male; (4) estrogen is essential for regulation of gonadotropin secretion in the male;

and (5) estrogen may be necessary for normal insulin sensitivity and sperm viability.

Smith EP, et al. *N Engl J Med* 1994;331:1056-1061.

Editor's comment: This report clarifies earlier reports in which the importance of aromatization of androgen to estrogen in the regulation of gonadotropin secretion in the male had been questioned. Since the level of insulin-like growth factor 1 was normal in this subject, it is possible that the secretion of growth hormone is not dependent on estrogen action. Studies of endogenous and stimulated secretion of somatotropin in this subject would be of interest.

The phenotype of a homozygous female deficient for the estrogen receptor is unknown, but one might speculate that such an individual may be virilized in utero and during adolescence. Shozu et al¹ and Conte et al² report the occurrence of female pseudohermaphroditism and pubertal virilization in females with an abnormality in the gene encoding the P450 enzyme aromatase, leading to decreased estrogen production in utero and unopposed androgen activity. In these respects, females with aromatase deficiency resemble female spotted hyenas who have aromatase deficiency; these females are virilized and quite aggressive.³

Allen W. Root, MD

1. Shozu M, et al. *J Clin Endocrinol Metab* 1991;72:560-566.
2. Conte FA, et al. *J Clin Endocrinol Metab* 1994;78:1287-1292.
3. Yalcinkaya TM, et al. *Science* 1993;260:1929-1931.

The Small Nuclear Ribonucleoprotein-Associated Polypeptide N (SNRPN) Gene in Prader-Willi and Angelman Syndromes

Imprinting is the process by which differences in the phenotype of a specific disorder are expressed depending on whether the allele was paternally or maternally derived. Imprinting occurs during gametogenesis; it is heritable and reversible.

Prader-Willi syndrome (PWS) and Angelman syndrome (AS) map to chromosome 15q11-q13, and they represent 2 of the best examples of imprinting in humans. PWS is characterized by infantile hypotonia, mental retardation, hyperphagia, and small hands and feet. AS is characterized by severe mental retardation, absent speech, seizures, ataxic gait, and bouts of uncontrollable laughter.

In PWS, approximately 70% of patients have a deletion involving the paternally derived chromosome 15; almost all of the rest of PWS patients have maternal uniparental disomy (UPD) of chromosome 15. In contrast to PWS, AS is associated with a similar area of chromosome 15 deletion but on the maternally derived chromosome 15 and with paternal UPD. The study of the molecular similarities and clinical differences between these 2 syndromes has provided valuable information regarding the gene control mechanisms involved in imprinting.

The small nuclear ribonucleoprotein-associated polypeptide N (SNRPN) gene has been mapped to the 15q11-q13 region. It is known to display paternal allele-specific expression in mouse and to be expressed exclusively from the father's allele in human fetal brain (Reed et al). Following the localization of the SNRPN gene, Sutcliffe et al constructed a complete yeast artificial chromosome (YAC) containing the region commonly

deleted in PWS and AS (Lalande) in order to determine the molecular basis for PWS and AS.

Two genes, PAR-1 and PAR-5, were isolated and mapped distal to SNRPN. Both PAR-1 and PAR-5 were detected in cultured cells of AS deletion individuals but not in cells of PWS patients, suggesting that these 2 genes are expressed only from the paternal chromosome.

The fact that PAR-1, PAR-5, and the SNRPN gene are in close proximity led them to the suggestion that these genes lie in a domain, ie, a group of genes with similar genetic control, of imprinted transcription. The highest levels of expression of SNRPN were in brain. PAR-5 expression also was highest in brain, while PAR-1 expression was highest in skeletal muscle. This suggests tissue specificity of gene expression.

Reed ML, et al. *Nat Genet* 1994;6:163-167.

Sutcliffe JS, et al. *Nat Genet* 1994;8:52-58.

Lalande M. *Nat Genet* 1994;8:5-6.

Editor's comment: Imprinting is increasingly being recognized as a very important molecular mechanism. It appears to be involved in genetic control of growth and behavior, and in early development. Intensive investigation of the 15q12 region is showing important differences in gene expression between the maternally and paternally derived chromosomes. The expression is tissue specific, time-in-development specific, and strain specific.

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