

The Androgen Receptor Gene in Androgen Insensitivity Syndromes

This study has used restriction fragment length polymorphism (RFLP) analysis of DNA for studying a large group of 52 patients with karyotype 46,XY and androgen insensitivity syndrome, considered as complete in 27 males having a female phenotype, and as partial in 25 males having ambiguous external genitalia. Endocrine investigation of these patients showed concomitantly high plasma testosterone and luteinizing hormone levels. The 52 patients were followed in 20 different clinics. Twenty-one were familial and 31 were isolated cases. Androgen-binding studies were performed from cultures of genital skin fibroblasts. Genomic DNA was prepared from peripheral blood leukocytes. DNA samples were studied by Southern blot analysis after digestion by 4 different restriction enzymes and hybridization with 3 cDNA probes covering the 3 domains of the androgen receptor. The informative relatives of the probands, ie, their mothers and unaffected brothers, were studied to the extent it was possible.

Androgen-binding studies revealed that androgen receptor-binding capacity was undetectable in the 27 patients with complete androgen insensitivity. In the 25 patients considered on a clinical and hormonal basis as having partial insensitivity, receptor-binding capacity ranged from 120 to 340 fmol/mg DNA (normal mean, 650 ± 200 fmol/mg DNA), with dissociation constants in the normal range of 0.5 ± 0.25 nM. Thus, androgen-binding studies did not sustain the clinical and hormonal evidence of partial androgen insensitivity.

No large DNA deletion was found in any of the 52 patients. This suggests that in these studies of androgen insensitivity syndromes, abnormalities of androgen receptor could be related to point mutations or to microdeletions, rather than to gross alterations of the receptor gene.

Heterozygosity in the mother was found in 3 of 14 families studied with the *HindIII* polymorphism, and in 12 of 25 families using the exon 1 CAG repeat polymorphism. This suggests that *HindIII* and exon 1 polymorphism studies would be of considerable help in prenatal diagnosis of androgen insensitivity in male fetuses and in identification of carrier females, at least for half of affected families.

Loebaccaro JM, Belon C, Chaussain JL, et al. Molecular analysis of the androgen receptor gene in 52 patients with complete or partial androgen insensitivity syndrome: a collaborative study. *Horm Res* 1992;37:54-59.

Editor's comment: *This genetic approach to the androgen insensitivity syndromes is a considerable work since it is based on multicenter clinical trials. It provides a complete and accurate biochemical study of androgen receptors in genital skin cells and studies of genomic DNA in white blood cells. The first and most important fact is that whatever the degree of clinical androgen insensitivity and lack of cellular androgen receptivity, no large genomic deletion has been found in the many patients studied. Thus, the microdeletions and/or point mutations responsible for androgen insensitivity are still to be elucidated. The second fact is that, even in these conditions, RFLP techniques allow for familial studies in both complete and partial androgen insensitivity syndromes, offering a reasonable chance to detect the carrier females after the study of one index case. Therefore, the possibility of prenatal diagnosis is offered. It is an important step in the complicated and difficult field of the genetics of androgen insensitivity syndromes.*