Androgen Insensitivity

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The androgen receptor (AR) protein regulates transcription of certain genes. Usually, this activity depends upon a central DNA-binding domain that permits the binding of androgen–AR complexes to regulatory DNA sequences near or in a target gene. The AR also has a C-terminal androgen-binding domain (ABD) and an N-terminal modulatory domain. These domains interact among themselves and with coregulatory, nonreceptor proteins to determine vector control over a gene’s transcription rate. The precise roles of these proteins are active research areas. Severe X-linked androgen receptor gene (AR) mutations cause complete androgen insensitivity, mild ones impair virilization with or without infertility, and moderate ones sometimes yield a wide phenotypic spectrum among sibs. Different expressivity may reflect variability of AR-interactive proteins. The family history must identify heterozygous XX females with sparse, delayed, or asymmetric pubic/axillary hair or delayed menarche and infertile XY maternal aunts or uncles. Mutation type and density vary along the length of the AR. N-terminal polyglutamine tract expansion limits AR transactivation, causing a form of mild androgen insensitivity. Analysis of ABD mutations that do not impair androgen binding or impair it selectively will illuminate its intradomain properties. For partial androgen insensitivity and mild androgen insensitivity, pharmacotherapy with certain androgens or other steroids may overcome some dysfunction of certain mutant ARs. Experience with this approach is limited; outcomes have been generally disappointing. Am. J. Med. Genet. (Semin. Med. Genet.) 89:210–217, 1999.

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INTRODUCTION

The X-linked intracellular androgen receptor (AR) is essential for androgen action, whether of testosterone (T) or of its 5α-reduced derivative, 5α-dihydrotestosterone (DHT). Hence, the AR is essential for normal primary male sexual development before birth (masculinization) and for normal secondary male sexual development around puberty (virilization). AR dysfunctions in XY individuals result in androgen insensitivity syndromes (AIS). Androgens also participate in female sexual development around puberty and in adult female sexual function. Therefore, androgens are involved in male and female reproduction, and AR mutations may interfere with reproduction in either sex, albeit much more subtly in females.

BASIC DIAGNOSIS OF ANDROGEN INSENSITIVITY SYNDROMES

The diagnosis of AIS is based on clinical findings, endocrine evaluation, and, whenever possible, family history. Mutation analysis of the AR gene (chromosomal locus Xq11-q12) is currently available on a research basis only. AIS can be subdivided into three phenotypes: complete androgen insensitivity syndrome (CAIS), partial androgen insensitivity syndrome (PAIS), and mild androgen insensitivity syndrome (MAIS). The diagnosis of CAIS usually is made on clinical findings and laboratory evaluations alone. The diagnosis of PAIS and MAIS may require, in addition, a family history consistent with X-linked inheritance.

Mutation analysis of the AR gene (chromosomal locus Xq11-q12) is currently available on a research basis only.

The clinical findings that permit a presumptive diagnosis of AIS include the following: absence of extragenital abnormalities, two nondysplastic testes, absent or rudimentary müllerian structures (i.e., no fallopian tubes, uterus, or cervix) and presence of a short vagina, undermasculinization of the external genitalia at birth, and impaired sper-
matogenesis and/or somatic virilization at puberty. The laboratory findings required for the diagnosis of AIS include the following: 46,XY karyotype, normal or increased synthesis of T by the tests, normal conversion of T to DHT, normal or increased luteinizing hormone production by the pituitary gland, and deficient or defective androgen-binding activity of genital skin fibroblasts.

SPECIAL DIAGNOSTIC CHARACTERISTICS OF ANDROGEN INSENSITIVITY SYNDROMES

AR mutations that severely impair the amount, structure, or function of the AR cause the phenotype of complete androgen insensitivity (CAI). Standard references quote rates of two to five per 100,000 for CAI. These estimates are derived from the number of otherwise normal girls whose inguinal hernias are discovered to contain normal testes. Subjects are born appearing unambiguously female because DHT-dependent masculinization of the external genital primordia is totally absent. They are typically not suspected of being abnormal until the onset of puberty, when breast development is normal, but pubic and axillary hair development is not. Menarche, initially considered late, never occurs. Müllerian duct regression, being androgen independent, is normal. Hence, these patients usually lack a uterus, oviducts, and the cervix. In theory, they also should lack the upper, Müllerian duct–derived portion of the vagina; however, many patients with CAI have satisfactory coitus without dyspareunia. Since Wolffian duct differentiation is T dependent, these subjects should lack vasa deferentia, epididymides, seminal vesicles, and ejaculatory ducts. Occasionally, however, rudimentary segments of the Müllerian duct or the Wolffian duct or both are found by ultrasonography or laparotomy. Their testes may or may not be inguinal.

Because all XY subjects with CAI are sterile (genetic lethals), one-third of their mutant alleles should represent new mutations. A recent report on single-case families with CAI or partial androgen insensitivity (PAI) gene mutations [Hiort et al., 1998a] found a de novo AR mutation rate of close to 30% (eight of 30), thereby affirming the theoretical expectation of 33% for an X-linked recessive genetic lethal [Hal-dane, 1935]. Thus, two-thirds of mothers of CAI subjects are heterozygous carriers of the mutant allele. Furthermore, because of random X-chromosome inactivation, such carriers may express their heterozygosity clinically by delayed, diminished, or asymmetric pubic and/or axillary hair and by delayed menarche [Kaufman et al., 1976]. The reason for delayed menarche is not entirely clear, but it has been recognized that females homozygous for 5α-reductase type 2 deficiency also have delayed menarche [Katz et al., 1995]. Since 5α-reductase type 2 is responsible for an important fraction of T→DHT conversion in some parts of the body, it follows that DHT deficiency or T excess or both contribute to delayed menarche. However, the effect of DHT deficiency can be mimicked by DHT resistance. Furthermore, by aromatization, T excess can generate estrogen excess. The latter mimics an androgen-resistant state. Thus, pubertal resetting of the gonadostat in heterozygous females may be delayed directly by DHT resistance or indirectly by an increased ratio of estrogen/androgen action.

Mild androgen insensitivity takes two phenotypic forms at puberty: in one, spermatogenesis and fertility are impaired; in the other, spermatogenesis is normal or sufficient to preserve fertility. In both, gynecomastia, high-pitched voice, sparse sex hair, and impotence may be noted. In the form where fertility is preserved, one presumes that the dysfunction of the mutant AR is sufficiently mild that it can be overcome by collaboration with the set of coregulatory proteins that is active in Sertoli cells. Such collaboration would permit the target genes necessary for spermatogenesis to be regulated properly. In the form where fertility is not preserved, one must conclude that the mutant AR is competent to masculinize or virilize most targets of androgen action and that its incompetence with regard to spermatogenesis cannot be rectified by collaboration with those coregulatory proteins that compose the transcriptional regulatory environment of Sertoli cells.

The great majority of families with CAI “breed true”; in other words, ef-
fected individuals depart little from the textbook phenotype of “complete tes-
ticular feminization” (as it used to be known).

In families with PAI, on the other hand, it is not uncommon for affected individuals to have frankly ambiguous external genitalia that are, nonetheless, predominantly masculine or predomin-
anty feminine. As may be expected, this can lead to opposite sexes of rearing [Rodien et al., 1996]. Indeed, for some mutations in the androgen-binding do-
main (ABD), such variable expressivity may be the rule, not the exception [Pinsky et al., 1996]. Furthermore, in rare families with PAI, the expressivity may vary markedly, from near-normal male to near-normal female.

Although experience with MAI families is limited, they appear to harbor relatively little phenotypic disparity. Nonetheless, between or among fami-
lies, the same mutation may be responsi-
ble for MAI or PAI. These consider-
ations of variable expressivity within or among families have great import for
taking a sophisticated family history. For instance, in the early differential dia-
gnosis of androgen resistance (insensi-
tivity) as a cause of apparently isolated hypospadias or azoospermia (no sperm production), it would be very helpful to know whether any maternally related females had delayed menarche, primary amenorrhea, delayed and reduced or absent sex hair (symmetrically or asym-
metrically), or even clitoromegaly with or without posterior labial fusion. Of course, the reciprocal would be true in the early differential diagnosis of phe-
otypic females with any of these pre-
senting signs.

STRUCTURE/FUNCTION RELATIONSHIPS OF THE ANDROGEN RECEPTOR PROTEIN AND GENE

Once transformed by binding an andro-
gen molecule, the AR acquires the ability to regulate the rate of transcription of genes whose expression is sub-
ject to androgenic control. To exert such regulation, a complex of an andro-
gen and an androgen receptor (an A-AR) must do three things: dimerize,
human AR. Among these functional assignments are a set of transactivation domains [Jenster et al., 1991, 1995; Chamberlain et al., 1996] and two putative dimerization zones [Langley et al., 1995].

In the ABD there is a striking preponderance of missense mutations and an equally striking concentration of them in and around those exons that putatively contribute to the androgen-binding pocket of the ABD (Fig. 3). In addition, a number of mutations have been reported that exhibit variable expressivity (i.e., mutations R855H and V866H in Fig. 3). The traditional explanation for such variable expressivity of an AR mutation is that the level or competence of coregulatory proteins acts as a genetic “background” factor in determining the overall clinical outcome [Pinsky et al., 1996; Rodien et al., 1996; Boehmer et al., 1997]. Recently, however, it has been appreciated that somatic mosaicism (more or less covert) may account for some variable expressivity [Boehmer et al., 1997; Holterhus et al., 1997]. In one study, three of the eight patients with de novo mutations had the mutation in only a fraction of the somatic cells [Hiort et al., 1998a]. The simplest origin of such mosaicism would be forward mutation of an inherited normal allele to a mutant allele in a subject with a negative family history. In a family with multiple affected individuals, however, a relatively mild clinical outcome could reflect back-mutation of an inherited mutation to a normal allele.

Kennedy syndrome is a spinobulbar motor neuronopathy associated with MAI. It is caused by expansion of the glutamine-coding (CAG)_{38-35} CAA

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**Figure 1.** A sample of coregulatory proteins that interact with different portions of the androgen receptor (AR) positively (coactivators), negatively (corepressors), or in an uncertain way (other proteins). The crosshatched rectangles in the left half of the AR represent the polyglutamine and polyglycine tracts in its N-terminal transactivation domain. The portion of the AR devoted to DNA binding is darkly stippled; that devoted to ligand binding is finely hatched. (An updated, referenced list of these coregulatory proteins, including novel AR interaction sites, is available from the authors by E-mail at MC33@musica.mcgill.ca or at the AR Gene Mutations Database Website: www.mcgill.ca/androgendb.)

**Figure 2.** A linear rendition of the major structure/function domains and putative subdomains of the androgen receptor. The solid portions of the interrupted lines below the androgen-binding domain indicate the most likely location of a given functional subdomain.
ANDROGEN INSENSITIVITY MUTATIONS

Premature termination, deletion, or insertion mutations

As substitution mutations

Location of splicing and untranslated region mutations

Location of intron mutations

Figure 3. Structure of the AR indicating the location of all exon and intron androgen insensitivity syndrome mutations. Δ, 1–4 bp deleted; ▽, 1–4 bp inserted; X, a termination codon at the site of the mutation or at the frameshifted codon identified by the number that follows; 0, a codon deletion; *, mutations in male breast cancer tissue. Mutations in normal type indicate complete androgen insensitivity (CAI). Mutations in italics indicate partial androgen insensitivity (PAI). Mutations in outline denote mild androgen insensitivity (MAI). Mutations that are underlined cause both CAI and PAI. Mutations in outline and underlined cause both PAI and MAI. Mutations in italic and underlined occur in both normal individuals and those with PAI.
tract in exon 1 of the AR to a total of $38$ (Fig. 4) [Andrew et al., 1997]. The MAI component reflects a loss of AR transcriptional regulatory activity by virtue of a pathologically expanded polyglutamine (polygln) tract. This loss may be intrinsic [Mhatre et al., 1993; Chamberlain et al., 1994; Kazemi-Esfarjani et al., 1995; McPhaul et al., 1997], it may reflect diminished intracellular steady-state levels of polygln-expanded AR [Choong et al., 1996; Brooks et al., 1997], or it may be both, depending on the cell type.

Gynecomastia is the single most common sign of MAI in spinobulbar muscular atrophy, and it is frequently the first [Beitel et al., 1998]. Decreased libido and impotence usually appear next. Testicular atrophy and infertility typically are last. Testicular atrophy represents impaired spermatogenesis and corresponds to oligospermia (reduced sperm production) or azoospermia on semen analysis. Because impotence, reduced libido, and impaired spermatogenesis appear relatively late, often between 40 and 50 years of age [Guidetti et al., 1986], males affected with Kennedy syndrome are usually fertile. In fact, in the cases summarized by Warner et al. [1990], 72% had children. In Singapore, otherwise normal males with 28 or more CAG repeats in their AR have been reported to have more than a fourfold increased risk of impaired spermatogenesis, and the more severe the spermatogenic defect, the greater the number with a long repeat [Tut et al., 1997]. It will be interesting to see if a similar observation can be made studying different ethnic populations.

Recently, infertility was reported to be associated with two different “silent” single nt polymorphisms [Hiort et al., 1998b; Wang et al., 1998]. Whether the association of each single nt alteration with male infertility is causal or coincidental remains to be defined. A third silent AR mutation now has been found in an individual with PAIS [Nordenskjöld et al., 1999]. In a recent report [Lumbroso et al., 1999], we have noted that missense mutations in the ABD region coding aa 785–800 are disproportionately associated with MAI and display distinctive ligand kinetics. Other mutation hot spots associated with specific AI phenotypes must be sought.

### PROSPECTS FOR THE THERAPY AND MANAGEMENT OF ANDROGEN INSENSITIVITY

As elaborated later herein, it is possible, in theory, to overcome the functional

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**Table 1. AIS mutations in the Database**

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<th>Type</th>
<th>Phenotype</th>
<th>Mutation</th>
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*AIS, androgen insensitivity syndrome.*

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**Figure 4.** Expansion of the trinucleotide repeat encoding polyglutamine (starting at residue 58 of the AR) is the cause of Kennedy syndrome (a form of spinobulbar motorneuronopathy associated with mild androgen insensitivity). The normal number (n) of repeats varies polymorphically from nine to 36. Kennedy syndrome occurs when n $\geq 38$. 

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**Table 1.** AIS mutations in the Database*
defects of certain mutant ARs by pharmacotherapy with appropriate androgens or other steroids. It may even be possible to increase the concentration of deficient, but otherwise normal ARs, simply by increasing the rate of synthesis or decreasing the rate of degradation. These statements are irrelevant for those with CAI or incomplete AI, who are irreversibly infertile.

Some missense AR mutations express androgen-binding defects that are conditional on being exposed to a particular type of androgen [Pinsky et al., 1984; Pinsky et al., 1985; Kaufman et al., 1990]. It follows that it may be possible to find, or design, a type of androgen (or steroid) that overcomes an androgen-binding problem that manifests only with a natural androgen. Likewise, there is evidence from somatic AR mutations in prostatic carcinoma that certain missense mutations not only permit the AR to bind unusual androgens or other steroids [Culig et al., 1993] promiscuously but also allow it to be activated by them [Taplin et al., 1995] in a manner that allows these unorthodox steroid receptor complexes to be effective in transcriptional regulation of certain androgen target genes. Therapeutic strategies based on such data could be useful for subjects with PAI reared as males and for those with the infertile form of MAI. In PAI, phallic growth is promoted before surgical reconstruction and after; conceivably, spermatogenesis could be promoted in testes that are brought into a reconstructed scrotum. Finally, in the absence of an intact sperm-transporting system, some form of sperm retrieval would be necessary for fertilization to occur.

In infertile subjects with MAI, promotion of spermatogenesis would be the main goal, and sperm retrieval would not be necessary in the context of an intact sperm-delivery system. Apart from the successful experience with mesterolone (1α-methylandrostan-17β-ol-3-one) in promoting spermatogenesis and fertility twice in one man with MAI [Yong et al., 1994], experience with long-term natural androgen pharmacotherapy is meager and its value unclear [Jukier et al., 1984; Price et al., 1984; McPhaul et al., 1991; Hiort et al., 1993]. This is notably disappointing, especially when laboratory studies indicate that a particular ABD mutation decreases androgen-binding affinity in a manner that theoretically should be normalized simply by provision of excess androgen. Failure of this therapeutic strategy implies that occupancy of the ABD by the androgen is only a superficial expression of mutant AR dysfunction: its core dysfunction is its failure to be activated to a competent transcriptional regulatory protein even when the androgen-binding pocket of the mutant AR is fully occupied.

**Experience with long-term natural androgen pharmacotherapy is meager and its value unclear.**

**REFERENCES**


