



REVIEWS

ANDROGEN RECEPTOR GENE AND ITS CLINICAL IMPORTANCE IN GYNECOLOGY, ONCOLOGY AND INFERTILITY

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ABSTRACT

This review presents the androgen receptor gene and its clinical importance in gynecology, oncology and infertility. A computerized literature search through Medline and PubMed was performed, applying the word " androgen receptor " cited between the years 1990 and 2009. The androgen receptor mediates androgen action, determining male sexual phenotypes and spermatogenesis. Constitutional mutations in the androgen receptor cause various forms of male pseudohermaphroditism. The androgen receptor CAG repeat length variations are associated with risk for some cancers, pelvic organ prolapsus, osteoporosis, hyperandrogenism in polycystic patients, metabolic syndrome and male infertility (Spinal bulbar muscular atrophy). Genetic diagnosis and research is becoming a standard requirement for the clinical practice of reproductive medicine, gynecology and oncology.

Keywords: AR protein, Infertility, Gynecology, Neoplasms

ANDROJEN RESEPTÖR GENİ VE JİNEKOLOJİ, İNFERTİLİTE VE ONKOLOJİ İÇİN KLİNİK ÖNEMİ

ÖZET

Bu derlemede androjen reseptör geni ve jinekoloji, onkoloji ve infertilite için klinik önemi araştırılmıştır. "Androjen reseptör" kelimesi girilerek Medline ve PubMed de yer alan ve 1990 ve 2009 yıllarını kapsayan literatürler gözden geçirilmiştir. Androjen reseptörü, spermatogenezi ve erkek seksüel fenotiplerini belirleyen androjen etkisini regüle eder. Androjen reseptöründeki konstitüsyonel mutasyonlar çeşitli formlardaki erkek psödohermafroditizmine yol açar. AR CAG tekrar uzunluğundaki varyasyonlar bazı kanserler, pelvik organ prolapsusu, osteoporoz, polikistik hastalarda görülen hiperandrojenemi, metabolik sendrom ve erkek infertilitesi ile ilişkilendirilmiştir. Reprodüktif tıp, jinekoloji ve onkolojinin klinik pratiğinde genetik araştırmalar, standart bir gereksinim olmaya başlamıştır.

Anahtar Kelimeler: AR proteini, Infertilite, Jinekoloji, Neoplaziler

INTRODUCTION

The androgen receptor (AR) gene for the androgen receptor is located on the X chromosome at Xq 11-12. The AR, also known as NR3C4 (nuclear receptor subfamily 3, group C, member 4), is a type of nuclear receptor which is activated by the binding of either of the testosterone or dihydrotestosterone to the C-terminal ligand-binding domain¹⁻².

The AR has three main functional domains: the transactivation domain (TAD), the DNA binding domain (DBD), and the ligand-binding domain (LBD).The AR gene was cloned in 1988³⁻⁶.

The AR mediates androgen action,determining male sexual phenotypes and the promotion of spermatogenesis. The two most important physiological androgens

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are testosterone and 5 α -dihydrotestosterone (DHT). Testosterone is crucial for the survival of the Wolffian duct and its subsequent development and differentiation into the epididymis, ductus deferens and seminal vesicles. DHT, a metabolite of testosterone, is involved in the development of the penis and scrotum. At puberty, androgens drive the initiation of spermatogenesis and the growth of accessory sex organs, including the prostate. All these androgen-dependent developmental processes culminate in successful spermatogenesis; thus, perturbation of any of these steps can result in spermatogenic failure. Abnormalities in the androgen signaling system result in many disturbances, ranging from changes in gender determination and sexual development to psychiatric and emotional disorders⁷.

ANDROGEN INSENSITIVITY SYNDROMES (AIS)

Constitutional mutations in the AR impair androgen - dependent male sexual differentiation to various degrees and cause various forms of male pseudohermaphroditism known as AIS. AR mutations that severely impair the amount, structure or function of the AR cause the well-known complete AIS (CAIS) (testicular feminizing syndrome), evidenced by the complete feminization of 46 XY individuals at birth. This condition has an incidence of 1 in 20000 to 1 in 60000 males and it is transmitted as an X-linked trait⁸⁻¹¹.

Mutations that do not completely disrupt AR function cause partial AIS (PAIS), in which various degrees of ambiguous genitalia occur, including partial labialscrotal fusion, hypospadias and gynaecomastia. Subtle mutations that result in minimal AR dysfunction lead to minimal AIS where depressed spermatogenesis occurs without any abnormalities in the secondary male sexual characteristics¹².

The development of the gonadoblastoma has been associated with a Y chromosome gene, in dysgenetic gonads. Codon 607 mutation in the DNA-binding domain of the AR gene in CAIS may be associated with an increased

risk of the early development of a germ cell tumour¹³⁻¹⁵.

Trinucleotide repeat disorders (trinucleotide repeat expansion disorders, triplet repeat expansion disorders or codon reiteration disorders) are caused by an expansion of repetitive three bases in the causative gene. In over half of these disorders the repeated codon is CAG, and codes for glutamine (Q). These diseases are commonly referred to as polyglutamine (PolyQ) diseases. The remaining disorders are classified as:

1) Non-polyglutamine diseases:

- 1) Fragile X syndrome (CGG repeat)
- 2) Myotonic Dystrophy (CTG repeat)
- 3) Friederich's Ataxia (GAA repeat)

2) Polyglutamine (PolyQ) diseases:

- 1) Spinal and bulbar muscular atrophy
- 2) Huntington's disease
- 3) Dentatorubralpallidoluysian atrophy (DRPLA)
- 4) Five spinocerebellar ataxias (SCAs 1, 2, 3, 6, 7).

These disorders are characterized by an autosomal dominant mode of inheritance (with the exception of spino-bulbar muscular atrophy which shows X-linked inheritance), midlife onset, a progressive course, and a correlation of the number of CAG repeats with the severity of disease and the age at onset. These disorders likely share a common pathogenesis caused by the gain of a toxic function of the expanded polyglutamine tract and neurodegeneration¹⁶.

DISEASES ASSOCIATED with AR CAG TRACT LENGTH VARIATION

The AR gene contains a polymorphic triple repeat sequence CAG in exon 1 with 9-36 repeats in the normal population, and displays ethnic dependence. The length of the CAG repeats varies among individuals and this polymorphism is believed to be related to AR transcriptional activity. A correlation between AR CAG repeat length and total risk, age at diagnosis, recurrence after surgery and aggressive growth has been reported for tumors of classical androgen target tissues (Table I).

**Table I.** Diseases associated with AR CAG tract length variation.

	Longer CAG tract	Shorter CAG tract
	(Reduced Androgen sensitivity)	(Increased Androgen sensitivity)
Direct Association	*SBMA	
Indirect Association	*Male infertility	*Prostate cancer
	*Female breast cancer	*Colon cancer
	*Endometrial cancer	*Oesophageal cancer
	*Pelvic organ prolapsus	*Hepatocellular carcinoma
		*Ovarian carcinoma
		*Hyperandrogenism in women

It is shown that fewer CAG repeats are associated with high intrinsic AR activity, increased severity and earlier age of onset of the androgen-regulated tumors and prostate, colon, hepatocellular, ovarian and oesophageal cancer or clinical hyperandrogenism in women. Whereas longer CAG tracts are associated with low AR activity and oligospermic infertility, pelvic organ prolapsus, endometrial and female breast cancer¹⁷⁻²³.

1) Spinal bulbar muscular atrophy (SBMA, Kennedy disease)

Expansion of the CAG tract > 40 repeats leads to spinal bulbar muscular atrophy, an adult onset, X-linked, fatal, neurodegenerative disease that also presents with low virilization and spermatogenic defects. The disease may show evidence of anticipation (increasing severity with succeeding generations accompanying further expansion of repeat length).

Current data is insufficient to conclude whether IVF patients who display AR CAG expansion may transfer infertility or premutation of neurodegenerative disease to their descendants. Based on Mendelian inheritance patterns, moderate CAG expansions in infertile men treated by ICSI would be vertically transmitted to female offspring. Should further elongation of the

repeat region occur in the male germline, it is conceivable that longer expansions could also be transmitted by ICSI and may lead to an increased incidence of male infertility and SBMA in succeeding generations. Screening of AR CAG repeat length can be recommended, at least in those populations where an association between repeat length and infertility could be established²⁴⁻²⁶.

2) Prostate Cancer (PC)

PC has a complex etiology; age, ethnicity, and family history are the most consistently reported risk factors associated with the disease. Androgen, acting through the AR is helpful in preserving the normal function and structure of the prostate. Studies have shown that fewer CAG repeats are associated with an increased risk as well as more aggressive forms of PC. Androgens are strong tumor promoters, and work with the AR to augment the effect of any carcinogens present and to stimulate cell division.

Epidemiological observations have shown that short CAG repeats are more frequently associated with higher transactivational function in the African-American population, which may explain racial differences in the incidence of prostate cancer. Among the Japanese, a short CAG repeat appears to predict a response to hormonal therapy, indicating a positive prognostic value and



good prognosis at the metastatic stage of prostate cancer. Several co-factors between ARs and the transcriptional complex have been cloned and reports indicate that steroid receptor co-activator 1 is correlated with the hormone-refractory progression of prostate cancer. Thus, ARs plays an important role in the progression of prostate cancer.

It has been shown that AR can be activated by neuropeptide, a ligand for G-protein coupled receptor, in the absence of androgen. The activation goes through the Src-tyrosine kinase pathway, and tyrosine kinase inhibitor is a potentially useful adjunctive therapy during androgen ablation. There is considerable evidence implicating the aberrant activation or "reactivation" of AR in the course of androgen-ablation therapy as a potential cause for the development of castration-resistant PC. Several new AR coregulators, including ARA70, 55, 54, 160 and 24, associated with LBD of AR, have been identified and the identification of factors or peptides that can interrupt androgen-mediated AR-ARA interactions have been suggested to be useful in the development of better antiandrogens for treating PC²⁷⁻²⁹.

3)Breast Cancer (BC)

In the breast, a higher risk and earlier onset of BC has been reported for carriers of BRCA1 mutations who also have long CAG repeats in the receptor gene. Decreased AR transactivational activity lowers androgen/estrogen balance, and may thereby effect functional hyperestrogenicity. This may promote the pathogenesis of BC. Hypotransactive ARs with long polyglutamine tracts may have a role in the initiation and/or progression of breast cancer^{30,31}.

4)Colorectal Carcinoma

Colorectal epithelial cells carrying AR alleles with shorter CAG repeat lengths may be more androgen-sensitive and therefore have a growth advantage³².

5)Hepatocellular Carcinoma (HC)

Worldwide, HC is more prevalent in men than in women, suggesting that sex hormones and/or X-chromosome-linked genes and AR

may be involved in hepatocarcinogenesis. Higher levels of androgen signaling, reflected by higher testosterone levels and 20 or fewer AR-CAG repeats, may be associated with an increased risk of HBV-related HC in men³³.

6)Oesophageal Carcinoma

Awan et al. examined the role of ARs and FGFs in oesophageal adenocarcinoma, where tumour incidence in males is higher, and found that AR expressed in the stroma of oesophageal adenocarcinomas may induce paracrine effects following stimulation by androgens (including tumour-derived), possibly via FGFs, including FGF-8b³⁴.

Two polymorphic triplet repeats-(CAG)(n) and (GGC)(n)-in the AR gene were evaluated as potential genetic susceptibility loci for oesophageal squamous cell cancer. Shorter lengths of these alleles have been found to be associated with increased risk for oesophageal squamous cell cancer¹⁹.

Studies with established tissue culture cell lines showed AR expression by RT-PCR, with stronger expression of AR in adenocarcinoma lines than in squamous carcinoma lines. The presence of AR in human oesophageal cancer is an impetus for further studies to assess anti-androgen therapy for treatment and or prevention of these tumors^{34,35}.

7)Endometrial Cancer(EC)

Androgen metabolism and actions are considered to play a very important role in the development and progression of the normal human endometrium and its disorders. 5alpha-reductases catalyze the conversion of testosterone to the bioactive and potent androgen, DHT. DHT may play more important roles than testosterone in the regulation of androgen action in EC, hormone-dependent human breast carcinoma, epithelial ovarian carcinoma and normal human endometrium, especially in the secretory phase, in which both AR and 5alpha-reductase are increased. Androgenic actions may be also regulated predominantly by serum testosterone and not by DHT in endometrial hyperplasia because of the



absence of 5 α -reductases in the site of its actions¹⁸⁻²¹.

The endometrium contains ARs and the androgens have antiproliferative properties in cultured EC cells. Larger CAG repeats of the AR gene give rise to a weaker transcriptional activity and have been found to be associated with endometrial carcinogenesis. The possible involvement of CAG and GGN tracts in the progression of EC is unknown. Studies suggest that short CAG or GGN repeats of the AR gene are associated with a more benign condition of traditional prognostic variables in EC^{36,37}.

8)Ovarian Cancer

Epidemiologic data suggest that aberrant androgen homeostasis may promote aggressive epithelial ovarian cancer biology. Hyperandrogenism results from both obesity and expression of polymorphic AR allelotypes harboring short CAG repeat sequences; both have been shown to independently correlate with poor overall survival in ovarian cancer. Short AR allelotypes and hyperandrogenism promote an aggressive epithelial ovarian cancer phenotype through inhibitory action of epidermal growth factor receptor (EGFR) signaling, and further studies are encouraged to investigate AR/EGFR antagonism in the treatment of ovarian cancers^{38,39}.

Recent studies have shown that BRCA1 may function as an AR coregulator or coactivator and play positive roles in androgen-induced cell death in cancer cells as well as other androgen/AR target organs. AR allele length affects the age of diagnosis of ovarian cancer, irrespective of BRCA mutation status. Ovarian cancer patients with or without BRCA mutation who carried a short AR allele, were diagnosed an average of 7.2 years earlier than patients who did not carry a short allele⁴⁰.

9)Head and Neck Tumors

Sex hormones may play an important role in the tumorigenic process of the head and neck. Shorter AR CAG repeat alleles have a protective effect for head and neck cancer development. But it has been reported that

short CAG repeat length (≤ 20) polymorphism is associated with poor prognosis in a subset of male patients with head and neck cancer and that AR gene microsatellite instability is uncommon in these tumors⁴¹.

10)Pelvic organ prolapsus

Last studies have showed that AR is also important for pelvic organ prolapsus. The increasing expression of AR in the tissue of the vaginal wall and cardinal ligament of the patients with pelvic floor dysfunction may play an important role in the etiology of pelvic organ prolapsus⁴².

11)Osteoporosis

Androgens play an important role in the maintenance of bone architecture and muscle mass and strength. The estrogen and androgen receptor genes are strong candidates for mediating the genetic influence on bone mass and the risk of osteoporosis. CAG repeat polymorphism in the first exon of the AR gene is associated with reduced bone mass and increased risk of osteoporotic fractures in women^{43,44}.

12)Hyperandrogenism in Polycystic Patients

There is an association between short CAG repeat length and the subset of anovulatory patients with low serum androgens, suggesting that the pathogenic mechanism of polycystic ovaries in these patients could be due to the increased intrinsic androgenic activity associated with short AR alleles⁴⁵. The AR gene CAG repeat polymorphism may contribute to the serum concentration of free testosterone in PCOS patients. A subset of PCOS patients with relatively longer CAG repeats (less AR activity) tended to show a higher serum androgen concentration⁴⁶. Increased hirsutism and decreased CAG repeat length within AR gene has been also demonstrated in polycystic women with normal testosterone levels. The expression of the estrogen receptor (ERs) as well as 5- α -reductases (SRD5A1-2 genes) activity was analysed in granulosa and theca cells and it is demonstrated that there are significant alterations in the expression of ER α and ER β in PCOS that may be related to



abnormal follicular development⁴⁷. Androgens influence androgenetic alopecia, hirsutism, and acne; the polymorphisms in CAG repeat length may affect the clinical course of patients with these cutaneous disorders.

13) Metabolic Syndrome

The AR gene CAG repeat polymorphism has been shown to modulate body fat mass and serum concentrations of insulin in men. It is hypothesized that shorter AR (CAG)(n) is associated with the metabolic syndrome or its components in women. But it is found that the AR (CAG)(n) is not a major determinant of the metabolic syndrome in women but it contributes to ovarian androgen production.

Shorter, more androgenic AR alleles with fewer CAG repeats are associated with lower HDL-C, but not with an increased risk for CHD or MI, which argues against a detrimental androgen effect on cardiovascular risk under physiologic conditions^{48,49}.

SELECTIVE ANDROGEN RECEPTOR MODULATORS(SARMs)

SARMs are a novel class of AR ligands, which bind to the AR and demonstrate osteo- and myo-anabolic activity; however, unlike testosterone and other anabolic steroids, these nonsteroidal agents produce less of a growth effect on prostate and other secondary sexual organs. With improved pharmacokinetic characteristics and tissue-selective pharmacological activities, SARMs are expected to greatly extend the clinical applications of androgens. SARMs provide therapeutic opportunities in a variety of diseases, including muscle wasting associated with burns, cancer and end-stage renal disease, male contraception, endometriosis, hypogonadism, functional limitations associated with aging and chronic disease, frailty and osteoporosis⁵⁰.

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