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·*Review*·

Phenotypic heterogeneity of mutations in androgen receptor gene

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Abstract

Androgen receptor (*AR*) gene has been extensively studied in diverse clinical conditions. In addition to the point mutations, trinucleotide repeat (CAG and GGN) length polymorphisms have been an additional subject of interest and controversy among geneticists. The polymorphic variations in triplet repeats have been associated with a number of disorders, but at the same time contradictory findings have also been reported. Further, studies on the same disorder in different populations have generated different results. Therefore, combined analysis or review of the published studies has been of much value to extract information on the significance of variations in the gene in various clinical conditions. *AR* genetics has been reviewed extensively but until now review articles have focused on individual clinical categories such as androgen insensitivity, male infertility, prostate cancer, and so on. We have made the first effort to review most the aspects of *AR* genetics. The impact of androgens in various disorders and polymorphic variations in the *AR* gene is the main focus of this review. Additionally, the correlations observed in various studies have been discussed in the light of *in vitro* evidences available for the effect of *AR* gene variations on the action of androgens. *(Asian J Androl 2007 Mar; 9: 147–179)*

Keywords: androgen receptor; androgen insensitivity; prostate cancer; breast cancer; CAG repeat; GGN repeat

1 Introduction

Androgens, upon testes differentiation, drive male secondary sexual differentiation and maturation. Androgens can be considered to function through an axis involving the testicular synthesis of testosterone, its transport to target tissues, and the conversion by 5α-reductase to the more active metabolite 5α-dihydrotestosterone (DHT). Both the androgens in humans, testosterone (T) and dihydrotestosterone (DHT), complex with the androgen receptor (AR) for their action but exert different biological functions. The receptor-testosterone complex signals differentiation of Wolffian duct during embryonic life, regulation of secretion of leutinizing hormone by hypothalamic-pituitary axis and spermatogenesis. The receptor-dihydrotestosterone complex promotes the development of external genitalia and prostate during embryogenesis and is also responsible for changes that occur at puberty in males [1]. Androgens are important not only for secondary sexual differentiation in males but also have numerous other functions in both males and females. Androgens promote the enlargement of the skeletal muscles [2] and affect human behavior [3], ag-

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gression [4] and libido [5]. Recent studies have also indicated that androgens inhibit the ability of some fat cells to store lipids by blocking a signal transduction pathway that normally supports adipocyte function [6]. All these studies emphasize multiple roles of androgens in the human body right from the embryonic stage to adulthood.

The *AR* gene has been mapped to the long arm (Xq11-12) of the X-chromosome [7]. The gene consists of eight exons and encodes a protein with 919 amino acid residues. Exon 1 of the gene consists of two polymorphic repeat (CAG and GGN) motifs, encoding variable lengths of polyglutamine and polyglycine stretches, respectively (Figure 1), in the N-terminal region (transactivation domain) of AR protein [7, 8]. The two repeat regions are separated by 248 amino acids of non-polymorphic sequence. CAG, a simple repeat, varies in length from eight to 35 repeats, while GGN, a complex repeat represented by $(GGT)_3GGG(GGT)_2(GGC)_n$, varies in length from 10 to 30 repeats [8]. The CAG repeat length and the AR transactivation potential are inversely correlated [9, 10]. In *in vitro* studies, *AR* alleles with more than 40 CAG repeats showed reduced transcription activity in comparison to the molecules with 25, 20 and no repeats [9, 10]. Therefore, it seems that the increased length of the CAG repeat should associate with decreased AR activity and hence the disorders related to the reduced androgen actions. Similarly, the deletion of GGN repeats also resulted in 30% reduction in transactivation potential [11]. However, it needs to be determined whether this trinucleotide repeat functions as a protein interaction domain and there is a direct correlation between the GGN repeat length and the AR transactivation function. If so, the increased GGN repeats should associate with the disorders related to higher androgen actions.

AR shares with other members of the nuclear receptors superfamily: a signature-structural and functional organization that includes an N-terminal transactivation domain (TAD), a central DNA-binding domain (DBD), a C-terminal ligand-binding domain (LBD), and a hinge region connecting the LBD and the DBD (Figure 1). Elucidation of the 3-D crystallographic structure of AR-LBD has established twelve α helices and four β strands arranged in two β sheets, which make a typical helical sandwich to form ligand-binding pocket [12]. The 12 helices of AR are folded into a three-layered sandwich. Helices H1/2, H3, H7 and H10/11 form two outer layers while inner layers consist of a ligand binding pocket and a non-ligand binding hydrophobic core (helices H4/5, H8 and H9). In addition to ligand binding, LBD is also involved in dimerization of the receptors, binding of specific ligands, and contains a ligand-dependent activation function (AF2) [4, 6, 7, 13]. Unlike many other nuclear receptors, the NTD of AR harbors one or more transcriptional activation function (AF1) and exhibits strong hormone-independent activity in isolation, but AR-LBD

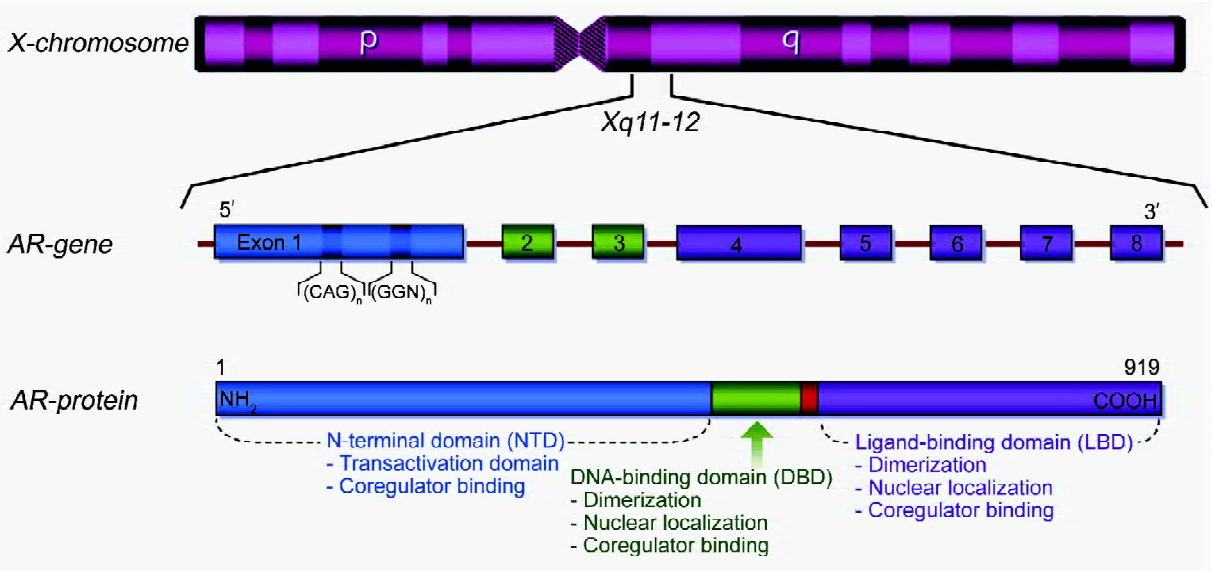

Figure 1. Genetic organization of the *AR* gene on the X-chromosome and major functional domains of the encoded protein.

in isolation exhibits only a weak hormone-dependent activity. The actions of AR are subject to modulation, either positively or negatively, by a number of co-regulators [8–10]. The NTD of AR is known to strongly interact with the LBD (N-C interaction) in a hormone-dependent manner [6, 14, 15] and this interaction is important for transcriptional regulation and interaction with coactivators [16].

Androgen pathways are integrated with several other pathways regulating metabolic processes in the human body. Therefore, the disturbances in the androgen pathways may lead to alteration not only in the secondary sexual differentiation but also in the physiology of numerous other organs. Further, the level of androgens differs dramatically between males and females, hence the differences in the incidence and course of many disorders between males and females may be attributed to the androgens. Therefore, the *AR* gene has been very well studied in a number of clinical conditions in addition to the reproductive disorders. In addition to the point mutations, *AR* gene has been a subject of interest because of the presence of two polymorphic trinucleotide repeats and diverse roles of androgens in the human body. Of the two repeats, CAG has been the most commonly studied, while GGN repeat has been less commonly studied because of technical problems in the amplification of GC rich region of this repeat. Different phenotypes associated with the *AR* gene mutations and trinucleotide repeat length polymorphisms, along with the underlying mechanisms and the phenotypic variations in the affected individuals will be the focus of this review.

2 *AR* gene in reproductive disorders

2.1 Androgen insensitivity

2.1.1 Androgens and androgen insensitivity

The end organ resistance to the androgens as a result of mutations in the *AR* gene results in mild to complete androgen insensitivity. The phenotypic features of complete androgen insensitivity syndrome (CAIS) are female external genitalia, usually with small labial folds, a short blind ending vagina, absence of Wolffian duct derived structures and prostate, gynecomastia, scanty pubic and axillary hair (Figure 2). The patients usually lack uterus and ovaries, however sometimes a rudimentary uterus may be present [17]. Usually testosterone levels are elevated at the time of puberty with or without elevated levels of leutinizing hormone (LH). Elevated testosterone levels also serve as substrate for estrogen synthesis, which results in further feminization in CAIS patients [18].

In partial androgen insensitivity syndrome (PAIS), several different phenotypes are evident (Figure 2), ranging from predominantly female phenotype (female external genitalia, pubic hair with or without clitoromegaly and partially to completely fused labia) through ambiguous genitalia to predominantly male phenotype with micropenis, perineal hypospadias and cryptorchidism [18]. The later phenotype is also termed as Reifenstein syndrome [18]. PAIS patients are assigned a grade (Figure 2) according to the severity of androgen insensitivity and affinity of the phenotype with male or female pattern. Individuals with MAIS usually have normal male genitals and internal male structures and during puberty may have breast enlargement, sparse facial and body hair, and small penis [19]. Some affected Individuals may also have impaired sperm production resulting in oligozoospermia or azoospermia [20].

2.1.2 AR gene in androgen insensitivity

A large number of mutations have been identified in the *AR* gene worldwide and are available at *AR* gene mutation database [21] (web: http://www.mcgill.ca/androgendb/). Of these, approximately 90% have been reported in androgen insensitivity. A significant number of these mutations have been supported by functional assays to result in lower ligand binding or transactivation potential of the mutant receptor molecule. Most of the mutations resulting in androgen insensitivity are the substitutions along with a low frequency of deletions/insertions. Structural–functional correlation of these mutations is now possible because of the availability of crystal structure for AR-LBD [12]. Although almost every kind of mutation has been reported in the *AR* gene, certain generalizations have been made [22].

One of the first mutations was a group in which single nucleotide substitutions resulted in the insertion of premature termination codon within the open reading frame of the *AR* gene. In different pedigrees, such mutations have been localized to each of the eight exons of the *AR* gene and associated uniformally with CAIS [22]. Mutations associated with normal androgen binding represent another relatively homogenous class of defects. Nucleotide sequencing in such patients localized the mutations to DBD, which associated with a broad range of androgen resistant phenotypes, including CAIS and

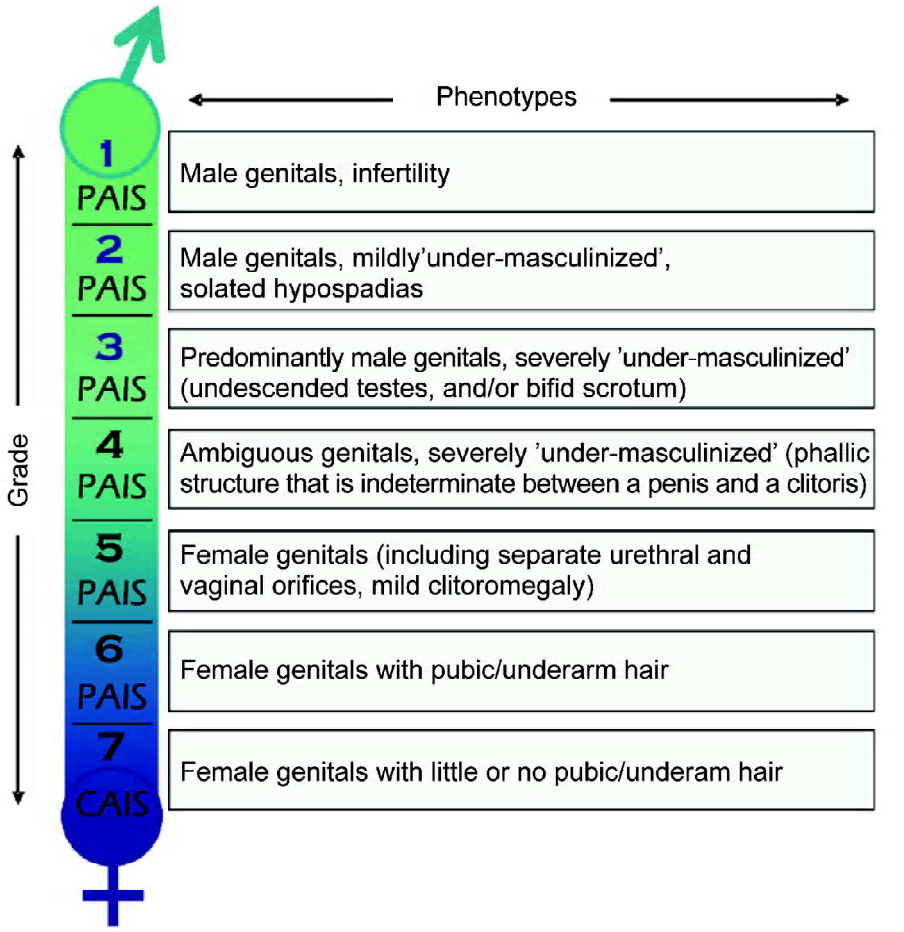

Figure 2. Scale showing the severity of androgen insensitivity. The highest grade is named CAIS while the lowest form is named as PAIS grade 1 or MAIS. All the intermediate forms are scaled to different PAIS grades.

PAIS [22]. Mutations that disrupt N and C-terminal interactions of AR protein form another category of *AR* mutations, which retain normal ligand binding [23]. The final category of mutations is associated with qualitative abnormalities of ligand binding such as alterations of ligand affinity, thermal instability of ligand-binding and rapid dissociation of ligand from the receptor protein. Uniformly, these defects have been traced to amino acid substitution mutations within the LBD of the receptor protein and associate with the entire range of androgen-resistant phenotypes [22, 24].

Correlations between the site of the mutation in the secondary structure of AR protein and the androgen insensitivity phenotype have also been sought. Most of the mutations in the α-helical and β-sheet regions of the receptor result in CAIS and those in turns and linker regions result in PAIS. Supporting this, our study on a familial case of CAIS revealed L859F mutations in helix 10 of the AR protein [25]. However, a general correlation is difficult to derive because some mutations in the α helices and β sheet regions associate with PAIS and those in turns and linker region are responsible for CAIS [21, 26].

2.2 Genital abnormalities

AR mutations in androgen insensitivity patients are known to associate with variable development of the Wolffian duct, micropenis, hypospadias and cryptorchidism [15, 27]. However, screening of the *AR* gene in patients with isolated cryptorchidism failed to find any

mutation [28, 29]. The study of *AR* gene for mutations has been lacking in isolated hypospadias.

To the best of our knowledge, until now four studies have examined the CAG repeat length in men with cryptorchidism. The earliest study on Japanese men (48 cryptorchid and 100 normal) suggested no significant difference between cases and controls [30]. However, Lim *et al*. [16] found that longer repeats were associated with severe genital abnormalities among men (n = 175) in the UK. In another study, Aschim *et al*. [31] analyzed both the CAG and GGN repeats in Caucasian men (51 hypospadiac, 23 cryptorchid and 201 controls). The study revealed no difference in the CAG repeat between cases and controls, but the GGN repeat was longer in patients with hypospadiasis and cryptorchidism in comparison to controls. Ferlin *et al*. [32] reported no difference between ex-cryptorchid men (n = 105) and controls (n = 115) in the mean and median values, and in the distribution of CAG and GGC repeats when considered independently. But the analysis of the joint distribution of CAG and GGC repeats showed that some combinations were significantly more frequent in men with bilateral cryptorchidism. In particular, men with a history of bilateral cryptorchidism more frequently presented the combination CAG = 21/ GGC = 18 and CAG ≥ 21/GGC ≥ 18.

2.3 Male infertility

2.3.1 Androgens, spermatogenesis and fertility

The germ cells are nurtured by Sertoli cells for their differentiation into sperms and Sertoli cells are in turn dependent on Leydig cells for androgens. Although germ cells themselves do not express *AR*, but are indirectly dependent upon androgens for their differentiation into sperms. Studies of a hypomorphic and conditional allele of the *AR* gene, have uncovered a dual post-meiotic requirement for AR activity during male germ cell differentiation [33]. Observations in *AR* hypomorphic animals demonstrated that terminal differentiation of spermatids and their release from the seminiferous epithelium is AR dependent and maximally sensitive to AR depletion within the testis. Cell-specific disruption of *AR* in Sertoli cells of hypomorphic animals further showed that progression of late-round spermatids to elongating steps is sensitive to loss of Sertoli cell *AR* function [33]. Considering this, AR appears to play a role in the final stages of sperm differentiation to attain elongated morphology, and hence point mutations in the *AR* gene are more likely to result in dysmorphic sperms (teratozoospermia or oligoteratozoospermia) rather than no sperms (azoospermia) [34].

2.3.2 AR gene in male infertility

2.3.2.1 AR mutations

Although hundreds of mutations have been reported in the *AR* gene in various disorders, only a few have been reported in male infertility [21] (web: http://www.mcgill.ca/androgendb/). Most of the mutations in infertile men resulted in the reduction of transactivation potential of the mutant protein. However, there has been no correlation between the type of mutation and the subtype of infertility (azoospermia, oligozoospermia or oligoteratozoospermia). Gln58Leu substitution was observed in one azoospermic and one oligoteratozoospermic male [35]. The specificity of these mutations and their ultimate role in male infertility are unclear because many of these mutations have been reported to exist in normal populations as well. A synonymous Glu211Glu mutation has been reported in both infertile and fertile males. The polymorphism showed ethnic difference as it occurs in 10–15% of Caucasians but not in Chinese men [36]. A 20% reduction in the transactivation potential of AR as a result of Gly214Arg substitution resulted in severe oligozoospermia, but the mutation was also observed in a fertile man [37].

Further, there have been reports of mutations showing no effect on AR activity in *in vitro* assays, but associated with infertility or even androgen insensitivity in certain other individuals [21]. A study on a large cohort of infertile males revealed Pro390Ser substitution in two oligozoospermic patients. Although *in-vitro* assays showed no gross change in the transactivation potential but the importance of the above residue in AR function was shown by the association of the proline replacement with CAIS. However, the phenotype in certain other mutations could well be correlated with the *in vitro* observations. Asn756Ser substitution caused 62% reduction in transactivation potential of AR resulting in severe oligozoospermia. Similarly, Met886Val substitution caused 50% reduction in transactivation resulting in oligozoospermia [38]. In our recent study, we sequenced the complete coding region of *AR* gene in a total 399 infertile men, including 277 azoospermic, 100 oligozoospermic and 22 oligoteratozoospermic individuals [34]. The study revealed no mutation in the *AR* gene in any of the infertile individuals demonstrating that the

AR gene mutations might contribute to a very low percentage of infertility.

2.3.2.2 CAG repeat polymorphism

CAG repeat has been extensively studied in male infertility in various populations, but the results vary greatly between populations. Increased CAG-repeat length was associated with male infertility in Japanese, American, Australian, English, Singaporean, French and Chinese populations but not in German, Belgian, Danish and Dutch populations [39]. Most of the studies on European populations demonstrated no significant differences in CAG repeat between cases and controls (Table 1) except two studies reporting longer repeats in infertile men [40, 41]. However, the combined analysis of data from all the studies showed no significant difference between fertile and infertile European males [42].

Although most of the studies on Asian populations showed increased repeat length to associate with infertility, some studies showed no association with male infertility (Table 1). Our study on infertile Indian men (280 azoospermic and 201 normozoospermic) revealed no significant difference in the mean length or the range of the repeat between azoospermic and normozoospermic men [43]. Later our finding was supported by another study from India [44]. Surprisingly, one study on Japanese infertile men showed an association of shorter CAG repeats with infertility [45]. Similarly, another study on Chinese infertile men showed the association of both the longer and shorter repeats with infertility. However, sample size in the later study was too small to interpret the findings conclusively. But the combined analysis of the data on Asian populations showed significantly longer repeats in infertile men [39]. Two studies on American populations showed increased repeat length in the infertile men [46, 47]. The studies on other populations showed varied correlation of CAG repeat with male infertility (Table 1).

2.3.2.3 GGN repeat polymorphism

Few studies have analyzed GGN repeat length polymorphisms in male infertility (Table 1). In contrast to the varied association of CAG repeat length polymorphisms, only three studies on GGN repeat have shown no correlation with male infertility [48–50]. Our recent analysis of GGN repeats in a large sample size (n = 595), including azoospermic, oligozoospermic and oligoteratozoospermic individuals, revealed no difference between infertile and fertile men [51]. Therefore, it appears that the variation in the length of this repeat does not affect the sperm count. However, sequence analysis of the GGN repeat region revealed that mutations in this region are common in both fertile and infertile men. [52]

Two studies analyzing both CAG and GGN repeats observed significant differences in the joint analysis but not when the two repeats were considered independently. Ferlin *et al*. [49] showed that the haplotypes with CAG = 21/GGC = 18 and CAG ≥ 21/GGC ≥ 18 repeats were associated with infertility while the haplotype with CAG ≥ 23/GGC ≤ 16 repeats provided protection against infertility in Italian men. In another study on Swedish men, haplotype with CAG < 21 and GGN = 23 combination of repeats was shown to confer lower risk of infertility to the carriers [50]. However, the significance of this observation is weakened by the fact that the two protective haplotypes in the above studies had almost the same number of GGC repeats but the CAG repeat number differed substantially (≥ 23 in the former but < 21 repeats in the later study).

2.4 Klinefelter's syndrome

The phenotype in Klinefelter's syndrome is highly variable, but generally includes testicular failure, androgen deficiency, small penis, sperm deficiency, tall stature, and characteristic cognitive differences, such as language-based learning disabilities and reading dysfunction [53, 54]. In an effort to study the factors influencing the phenotype in Klinefelter's syndrome patients, Zinn *et al*. [53] studied karyotype to detect mosaicism, genotyped microsatellite markers to determine parental origin of the supernumerary X-chromosome, and number of CAG repeats and methylation to look at X-inactivation ratio in a cohort of white and black Klinefelter's syndrome boys and men (n = 35). The study showed that the CAG repeat was the only factor influencing the phenotype in Klinefelter's syndrome. CAG repeat length and penile length were inversely correlated in the affected individuals. Given the inverse relation between CAG-repeat length and the AR-transactivation function, this finding is not surprising. However, further studies replicating these results would strengthen the association.

2.5 Maleness, libido and depression

Testosterone (T) levels decline linearly with age and approximately one fourth of elderly men have mild-to-moderate T deficiency [55]. Symptoms of profound T

Table 1. Published data on *AR* gene trinucleotide repeat variation in male infertility. NA, not available.

Population	Total Cases/ Controls	Category of infertile samples	CAG repeat	GGC/GGN repeat	Reference
Singaporean/ Chinese	153/72	Mixed	Longer in infertile men	No significant difference	[48]
Swedish	33/294	Mixed	No significant difference	NA	[261]
Japanese	41/48	Azoospermic	Longer in patients	NA	[262]
Australian	35/32	Mixed	Longer in patients	NA	[263]
Japanese	59/36	Oligozoospermic	Short in infertile men	NA	[45]
Belgian	223/181	Undergoing ICSI treatment	No significant difference	NA	[264]
German	180/53	Mixed	No significant difference	NA	[36]
German	119/22	Mixed	No significant difference	NA	[265]
UK	78/850	MAIS/infertility	Longer in patients	NA	[266]
French	37/50	Mixed	Longer in patients	NA	[40]
German	30/62	Azoospermic	No significant difference	NA	[267]
Japanese	30/51	Azoospermic	No significant difference	NA	[268]
Singaporean/ Chinese	120/87	Azoospermic	Slightly longer in patients	NA	[46]
American	95/55	Mixed	Slightly longer in patients	NA	[46]
American	69/45	Severe oligozoospermic	Longer in patients	NA	[47]
Indian	280/201	Azoospermic	No significant difference	NA	[43]
Danish	119/110	Mixed	No significant difference	NA	[42]
Dutch	75/70	Mixed	No significant difference	NA	[269]
Indian	183/59	Mixed	No significant difference	NA	[44]
Singaporean	70/55	Mixed	Longer repeats in patients	NA	[270]
German	217/131	Oligozoospermic	No significant difference	NA	[271]
Chinese	85/45	Mixed	Short and long repeats associated with infertility	NA	[272]
Finnish	192/149	Mixed	No significant difference	NA	[35]
Spanish	102/96	Azoospermia	Longer in infertile men	NA	[41]
Australian	105/93	Mixed	No significant difference	NA	[273]
Swedish	94/223	Mixed	NA	No significant difference	[51]
Italian	163/115	Mixed	No significant difference	No significant difference	[49]
Tunisian	129/98	Mixed	No significant difference	NA	[274]
Swedish	99/223	Mixed	No significant difference	No significant difference	[50]
Israeli	172/–	Mixed	Longer in oligoteratospermia	NA	[275]
Italian	29/91	Mixed	No significant difference	NA	[276]
Irish	66/77	Mixed	No significant difference	NA	[277]
Chinese		Mixed	No inference	NA	[278]
Turkish	47/32	Mixed	No significant difference	NA	[279]

deficiency in young adult men include loss of libido, dysphoria, fatigue, and irritability [5]. The development of depressive symptoms in men with mild T deficiency is not well studied but appears to be variable [56]. Seidman *et al*. [57] assessed the relation between AR isotype, total T level, and depression in a large community-based sample of middle-aged and elderly men (n = 1 000), to understand the role of CAG repeat length polymorphisms in the progression of the above symptoms. The study revealed that depression was inversely associated with total T in men with shorter CAG repeats but not in men with moderate and longer CAG repeat lengths. This observation is in accordance with the above discussion on the relation of androgens with the development of less libido, fatigue and dysphoria. It is possible that in the men with higher T level, the presence of shorter CAG repeats result in higher overall effects of testosterone to maintain libido, physical and mental health. In a similar study, Harkonen *et al*. [58] reported a direct correlation between CAG repeat length and depression in Finnish men.

2.6 Prostate cancer

2.6.1 Androgens in prostate development

Androgens are required for prostate development and normal prostate function [59]. Therefore, AR and the modulators of AR activity remain important in prostate cancer (PC). Approximately 80–90% of PC are dependent on androgens at initial diagnosis, and endocrine therapy of PC is directed towards the reduction of serum androgens and inhibition of AR [60]. However, androgen ablation therapy ultimately fails, and PC progresses to a hormone refractory state. *AR* is expressed throughout PC progression and persists in the majority of patients with hormone refractory disease [61, 62]. There are reports stating that *AR* proliferates in PC showing that androgens and *AR* are actively involved in PC progression [61].

2.6.2 AR gene in prostate cancer

2.6.2.1 AR mutations

Newmark *et al*. [63] first reported an *AR* mutation in a patient with PC. Thereafter, a number of mutations have been identified in the *AR* gene in PC (web: http://www.mcgill.ca/androgendb). The majority of the mutations are substitutions predominantly localized to the AR-LBD [61]. There are relatively few reports of tumors that contain multiple *AR* mutations. The effect of many of the identified mutations has not yet been investigated *in vitro* [61]. The most frequent functional consequences of *AR* mutations isolated from metastatic PC are the ability of anti-androgens and adrenal androgens to act as AR agonists. The *AR* T877A mutation allows the antiandrogens (hydroxyflutamide and cyproterone acetate) [64], DHEA [65], androstenediol [66], estradiol and progesterone [61, 67] to activate *AR* transcription. Excluding the *AR* T877A mutant, *AR* mutations that confer enhanced transcriptional sensitivity to adrenal androgens have been identified in up to 30% of metastatic PC samples [61]. The *AR* mutations reported in PC have been reviewed, along with their mechanisms, in detail by Heinlein and Chang [61].

2.6.2.2 CAG repeat polymorphisms

In a study on Australian (n = 50) and Chinese (n = 50) men without known prostate disease, CAG repeat length was not found to be related to the volume of the central zone of the prostate [68], considered to be the most hormonally sensitive prostatic region. Several studies have shown an association of shorter CAG repeats with prostate cancer, however, at the same time a number of studies have failed to link *AR*-CAG repeat number with sporadic or familial PC (Table 2). The majority of studies on Caucasian men showed an association of shorter repeats with PC risk [69–71]. Similarly the studies on Hispanic whites [72], non-Hispanic whites [73] and black Americans [74] also showed the association of shorter repeats with PC risk. However, an almost equal number of the studies reported no association of CAG repeat length with PC risk (Table 2). Out of the four studies analyzing the age at diagnosis, two reported that the shorter repeats were associated with younger age at diagnosis [69, 75], while the other two mentioned no correlation between the repeat length and the age at diagnosis [76, 77].

Unlike Americans, not much data has been generated for Asian and European populations. Studies on Asian populations showed no association (with grade or age at diagnosis) in Taiwanese men [78], shorter repeats in Japanese [79], Chinese [80] and Indian men [81, 82] with PC. Therefore, it seems that the shorter CAG repeats correlate with the increased risk of PC among Asians. The majority of studies on Europeans have shown no association of CAG repeat length with the disease risk [83–87]. One study showed the association of shorter CAG repeats with the disease risk but did not find any

Table 2. Published data on *AR* gene trinucleotide repeat variations in prostate cancer. NA, not available.

Population	Total cases/Controls	CAG repeat	GGN repeat	Reference
American	68/123	Shorter repeats more disease risk of 16 GGC repeats	Patients had least frequency	[93]
American	109/–	Shorter repeats associated with the younger age at onset but not with stage, PSA level	NA	[69]
American	587/588	Shorter repeats more disease risk	NA	[70]
American	301/277	Lesser disease risk for long repeats	More risk for men with ≤ 16 repeats.	[71]
American	59/370	16 and 17 repeats predominant in patients	≤ 14 repeats predominant in patients	[280]
American	57/169	Shorter repeats more disease risk	NA	[73]
American	582/794	NA	More PC risk for 23 GGN	[92]
Swedish	190/186 *AR* alleles (females)	Shorter repeats correlated with younger age at diagnosis, higher grade but not risk	repeats NA	[84]
UK	178/195	No correlation with disease risk, grade or stage	Long repeats increased the risk of relapse and death but not disease risk	[85]
French-German	132/105 controls, 85 affected/46 not affected familial cases	No significant difference	No significant difference	[83]
American	310 (BPH)/1041	Risk of surgery for BPH increased linearly with decreasing repeat length.	NA	[281]
American	449 (BPH)/449	Short repeats more risk for surgery	NA	[282]
Chinese	109/304	Shorter repeats more risk	Shorter repeat more risk	[80]
American	318 patients	After radical prostatectomy, recurrence was higher with ≤ 18 repeats	NA	[283]
American	270 Caucasian patients	No association with risk, grade or age at diagnosis	NA	[76]
South African	20 black/20 white patients/20 white controls/20 black controls	No strong correlation	NA	[284]
Australian	545/456	Shorter repeats associated with earlier age of diagnosis but not disease risk	NA	[285]
American	226/156	No significant difference	NA	[286]
American	140/70	No significant difference	No significant difference	[90]
American	82/145	Significantly shorter in patients	NA	[72]
American	300/300	No significant difference	No significant difference	[91]
American	404/211	No significant difference	Significantly shorter in patients	[89]
Finnish	461 (PC), 223 (BPH), 105 (familial PC)/574	No association with family history, disease stage, grade, age at diagnosis, PSA level or prognosis	NA	[88]

Table 2. Published data on *AR* gene trinucleotide repeat variations in prostate cancer. NA, not available. (continued)

Population	Total cases/Controls	CAG repeat	GGN repeat	Reference
American	103 high grade, 93 low grade tumor	No significant difference	NA	[287]
UK	265 patients	No association with age of onset, stage or grade	NA	[86]
American	151 patients	Short repeat associated with disease risk and its higher stage	NA	[74]
Japanese	88 (PC), 53 (BPH)	Shorter repeats associated with lower tumor grade and younger age at diagnosis but not with clinical stage or serum PSA level	NA	[79]
American	131 PC	Shorter repeats associated with the higher histological grade but not with risk or age at diagnosis	NA	[77]
Australian	190/190	No association	NA	[288]
Taiwanese	64/104	No association with disease risk, grade or age of diagnosis	NA	[78]
Brazilian	133/279	Shorter repeats associated with younger age of diagnosis but not disease risk	NA	[75]
American	118/567	No significant difference	NA	[289]
UK	28PC/56 BPH	No significant difference	No significant difference	[87]
American	460/460	No significant difference	NA	[290]
Indian	113PC/57BPH/133	Shorter repeats in PC patients and marginally short in BPH cases	NA	[81]
Indian	87/120	Shorter repeats in patients	NA	[82]

correlation with family history, disease stage or grade prostate specific antigen level or the age at diagnosis [88]. Similarly, studies from other populations showed varied correlation (Table 2). The above observation that the short CAG repeats should increase the risk of prostate cancer is further supported by the fact that the ethnic differences in prostate cancer incidence are inversely correlated to the predominant *AR*-CAG repeat length in each group, with Europeans having the lowest prostate cancer incidence and the longest *AR*-CAG repeats, whereas Asians and black Americans have the highest incidence and shortest CAG repeat length.

2.6.2.3 GGN repeat polymorphisms

Similar to CAG repeat, the studies on GGN repeat have documented varying association with PC risk. Short GGN repeat lengths have been found to be associated with increased PC risk [71, 80, 89]. These results are in contrast to the direct correlation observed between GGN repeat length and transactivation in transfection assays [9, 10]. However, an almost equal number of studies showed no correlation between GGN repeat and PC risk [83, 90, 91]. Similarly, our data from two case-control studies showed no correlation between GGN repeat length and PC risk (unpublished data). Another study found that longer GGN repeat lengths (GGN > 16) were associated with an increased risk of PC recurrence and death [85]. In a completely different observation, Platz *et al*. [92] found that PC risk was high in individuals with 23 GGN repeat in comparison to all others. In a combined analysis of GGN and CAG repeats on the American population, the subgroup with two shorter repeats (CAG < 22; GGN ≤ 16) had a two-fold elevation in odds relative to those with two longer repeats (CAG ≥ 22; GGN > 16) [71]. In a similar observation, Irvine *et al*. [93] reported an excess of American white patients with < 22 CAG and not-16 GGC repeats relative to the white controls. In both the studies, the disease associ-

ated haplotype consisted of CAG repeats less than 22, but there was no consistency in GGN repeat length. Therefore, the above haplotypes may be just a chance finding.

2.7 Testicular cancer

2.7.1 Androgens and testicular cancer

The incidence of the most common form of testicular cancer, that is, testicular germ cell cancer (TGCC), is highest shortly after puberty [94]. The sharp rise in the levels of gonadotropins, luteinizing hormone (LH), follicle stimulating hormone (FSH) and sex steroids suggest that either one or a combination of these endocrine factors might stimulate the progression of testicular cancer [95]. It has also been hypothesized that testicular dysgenesis syndrome, including TGCC, is a result of an imbalance in sex steroid action in favor of estrogens during the fetal period. The high level of estrogens and the high risk of testicular cancer in AIS patients strengthen the above hypothesis. Epidemiological studies have indicated that CAG length might also play a role in the risk of TGCC. The shorter repeats in the black Americans than Asians parallels with the low risk of TGCC in the former group [96].

2.7.2 AR gene in testicular cancer

Mutations in the *AR* gene imply a dramatic loss of receptor activity, but are extremely rare [97], and thus not likely to be involved in most TGCC cases. A *Pubmed* search using 'androgen receptor CAG repeat' and 'testicular cancer' found only three studies. All three studies were conducted on European populations. To our knowledge, only one study has undertaken sequencing of the complete coding region of *AR* gene (cases = 123, controls = 115), revealing mutations in three out of 123 (2.3%) patients [98]. Independent analysis of CAG and GGC repeats did not show any significant difference between cases and controls in this study. However, the joint distribution of the two repeats showed that the haplotype with CAG = 20/GGC = 17 repeats was significantly more frequent in testicular cancer patients with and without cryptorchidism. In the second study, Rajpert De-Meyts *et al*. [99] analyzed *AR*-CAG repeat on Danish men with germ cell neoplasia (cases = 102, controls = 110) and reported no correlation between CAG repeat length and germ cell neoplasia, type of the tumor and the severity of the disease. In another study on TGCC in Swedish patients (cases = 83, controls = 220) Giwercman *et al*. [100] found that the CAG and GGN repeat length polymorphisms as such were not associated with the risk of developing TGCC, however, the CAG numbers exceeding 25 were more common in patients with tumors that had no seminoma component. The length of this trinucleotide repeat also seemed to correlate with the presence or absence of metastases at diagnosis. Because the AIS patients with *AR* mutations often develop testicular tumors [101], it needs to be stressed that the *AR* gene is a suitable candidate for testicular cancer and more studies sequencing the *AR* gene should be conducted in the future. However, the failure of testes descendence in androgen insensitivity cases cannot be excluded as a possible cause of the disorder in this group of individuals.

2.8 Ovarian cancer

2.8.1 Androgens and ovarian growth

Androgens are produced by ovarian theca lutein cells, present in ovarian follicular fluid, and are one of the principal sex steroids of growing follicles [102]. There is emerging evidence that androgens may be associated with ovarian cancer risk [103]. Interestingly, the postmenopausal ovary is androgenic, as evidenced by 15-fold higher testosterone concentration in the ovarian vein in comparison to serum from peripheral veins [104]. AR is found in the normal surface epithelium of the ovaries [105], suggesting that the androgens are active in the organ. Most ovarian cancers express AR [106], and antiandrogens inhibit ovarian cancer growth [107], indicating that androgens have mitogenic effects on ovarian cells. Oral contraceptives, the most effective chemopreventive agent against the disease, suppress ovarian testosterone production by 35–70% [108]. In contrast, there is evidence that the *AR* gene may have an ovarian tumor suppressor function because *AR* mRNA and protein are down-regulated in ovarian cancer [105, 109].

2.8.2 AR gene in ovarian cancer

No study has reported the sequencing of *AR* gene in ovarian cancer. However, trinucleotide repeat analysis has been undertaken on few populations. The *AR*-CAG repeat in ovarian cancer has been studied in two ways, as a direct risk factor and as a modifier of the ovarian cancer risk conferred by the BRCA mutations. Among the ovarian cancer women without BRCA gene mutation, an almost equal number of studies on both European and American populations have shown an association between the longer CAG repeats and disease risk [110, 111] and

Table 3. Published data on *AR* gene trinucleotide repeat variation in ovarian cancer. NA, not available.

Population	Total Cases/ Controls	BRCA mutation carriers	CAG repeat	GGN repeat	Reference
Australian	319/853	No	No significant difference	NA	[247]
Italian	50/–	No	No association with the disease risk or age of onset	NA	[112]
American	179/–	Yes	Shorter repeats associated with early age at diagnosis	NA	[114]
Israeli	149/78	Yes	Shorter repeats associate with younger age at diagnosis but not disease risk	NA	[115]
Italian	121/100	No	No strong association but longer repeats posed more disease risk	NA	[110]
American	77/–	No	Shorter repeats, faster disease recurrence, and less survival but no association with age at diagnosis, stage or grade	NA	[113]
American	63/–	No	Shorter repeats, higher incidence of thrombocytosis	NA	[291]
American	987/1034	No	Both longer alleles- more disease risk	NA	[111]
Korean	111/–	Yes	Shorter repeats associated with early diagnosis but not disease risk	NA	[116]

no association between the two [112] (Table 3). A related study on American women [113] did not show any correlation between *AR* allelotype and age of diagnosis, stage or grade at ovarian cancer; however, they reported that patients with ≤ 19 CAG repeats had a shorter time to recurrence and overall survival [113].

All studies on BRCA mutation carriers consistently reported an earlier age at diagnosis with shorter repeat size [114–116], while two studies mentioning the age of diagnosis did not find any correlation of the repeat size with the age at diagnosis of ovarian cancer [112, 113]. Taking into consideration the contrasting results of the studies on ovarian cancer without BRCA mutations and the consistent association of CAG repeat in BRCA mutation carriers, it can be concluded that the CAG repeat length alone does not affect the risk of ovarian cancer, but a shorter repeat size may help the disease manifest at an early stage in the presence of BRCA mutation. Surprisingly, no study has been conducted on GGN repeat or joint analysis of CAG and GGN repeats in ovarian cancer patients.

2.9 Polycystic ovary syndrome

2.9.1 Androgens, folliculogenesis and ovulation

Polycystic ovary syndrome (PCOS) is an endocrine disorder characterized by abnormal androgen production and/or activity that leads to changes in the control of follicle development and maturation [117]. Evidences from non-human primates [118] and transsexual women [119] treated with high doses of androgens indicate that the characteristic ovarian morphology (ovary with numerous small follicular cysts), may be the result of direct, receptor-mediated androgen activity. In women with PCOS, this disruption often leads to chronic anovulation and subsequent infertility.

2.9.2 AR gene in PCOS

None of the studies on PCOS to date have undertaken sequencing of the *AR* gene. However, a few studies have analyzed CAG repeat in these patients and generated contrasting results. Mifsud *et al*. [120] reported no difference in the repeat length between cases (n = 91) and controls (n = 112) from Singapore, although all the women carrying the very shortest *AR*-CAG repeats belonged to the PCOS group. Similarly, a later study on Finnish women (cases = 106, controls = 112) showed no correlation between CAG repeat length and PCOS [121]. Perhaps the most striking evidence on the role of CAG repeat length as a mechanism of ovarian hyperandrogenism comes from a study on Spanish girls [122]. The authors did follow-up studies on girls with premature pubarche (n = 181) and found that the CAG repeat length is shorter in these girls compared to healthy controls (n = 124). They also showed that the girls developing ovarian hyperandrogenism post menarche had shorter mean repeat length than those with normal ovarian function. Hickey *et al*. [123] reported in Australian women (cases = 122, controls = 83) that the patients exhibited a greater

frequency of *AR* alleles with more than 22 CAG repeats. The results of the former two studies are supported by the *in vitro* assays showing higher activity of the *AR* alleles with shorter CAG repeats, while the results of the latter study are contradictory to this observation.

2.10 Endometrial cancer

2.10.1 Androgens, endometrium and endometrial cancer

Steroid hormones are thought to influence the origin and growth of endometrial tumors [124]. Estrogens induce cellular proliferation on endometrial cells, whereas androgens have an anti-proliferative effect on endometrial cells [125]. Although no *AR* mutant mice has yet been generated, a role for androgens has been suggested in the female estrogen receptor null mutant (ERKO), as androgens have been shown to increase the wet weight of the uterus of ERKO animals [126]. Studies have described an increase in androgens during the menstrual cycle and in the early pregnancy of women [127]. The *AR*, like its counterpart estrogen receptors (*ER*) and progesterone receptors (*PGR*) is expressed in endometrial cells [128], and appear to be upregulated by estrogen [129]. After menopause, the ratio of androgen to estrogen is high and the steroidal effect on the endometrium is predominantly androgenic [125, 130].

2.10.2 AR gene in endometrial cancer

None of the studies on endometrial cancer have attempted *AR* gene sequencing to date, but a few studies have analyzed CAG repeat length polymorphisms. However, these studies have produced contrasting results (Table 4) with few reporting the association of short repeats [131, 132], while others have shown the association of longer repeats with increased risk of the disease [124, 133, 134]. Most of the studies on Asian populations have shown the association of longer repeats with endometrial cancer [124, 133, 134]. These results fit the observation that androgens inhibit the endometrial cancer and hence women with longer *AR*-CAG repeats should be predisposed to endometrial cancer. In an altogether different observation, Hsieh *et al*. [135] reported a higher risk of developing endometriosis among Chinese women with 21 CAG-repeats. Out of the two studies conducted on European women, one has reported shorter repeats in patients [131], while the other reported no correlation between CAG repeat length and susceptibility to endometrial cancer or its clinical manifestation [136]. Other studies showed varied correlation (Table 4). Of the two studies on GGN repeat, one reported longer repeats to associate with the risk of endometrial cancer [137] while the other reported shorter repeats to associate with more benign condition of endometrial cancer

Table 4. Published data on *AR* gene trinucleotide repeat variations in endometrial cancer. NA, not available.

Population	Total Cases/ Controls	CAG repeat	GGN repeat	Reference
American/Japanese	29/–	Longer allele active in patients	NA	[124]
Israeli	79/44	Longer repeats in patients but repeat length did not correlate with disease stage, grade, reproductive history or age at diagnosis.	NA	[133]
Chinese	110/99	21 repeats more frequent in patients	NA	[135]
Japanese	58/289	Longer repeats in patients	NA	[134]
Italian	105/92	No association with disease risk or clinical manifestation	NA	[136]
Japanese	113/202	NA	Longer repeats associated with increased risk	[137]
Spanish	204/–	Shorter repeats associated with a more benign condition of traditional prognostic variables	Shorter repeats associated with a more benign condition of traditional prognostic variables	[131]
American	222/666, 137/411	Longer repeat lesser disease risk	NA	[132]

[131]. In the joint analysis of the two repeats, Rodriguez *et al*. [131] observed that the relationship between the short-short-CAG genotype and early stage remained significant only in the presence of the short-short-GGN genotype (43.9% *vs*. 0%).

2.11 Breast cancer

2.11.1 Androgens in breast development

Estrogen and progesterone act in an integrative fashion to stimulate normal female breast development. Estrogen receptor (*ER*), progesterone receptor (*PR*) and *AR* expression were observed in 100% (30/30) of gynecomastia cases [138] and breast cancer [139]. Further, it is well known that after menopause the level of androgens goes up and the level of estrogens drops. Multiple studies have reported a statistically significant increase in postmenopausal breast cancer risk with increasing levels of endogenous testosterone [139]. The study of premenopausal women [140] found no statistically significant differences between cases and controls in mean levels of testosterone. The disturbances in the level of these hormones in coupling with the polymorphisms in the receptor molecules may result in the altered physiology of the reproductive organs. Several studies conducted to examine the effects of androgens on the growth of *AR*-positive breast cancer cell lines have reported both inhibitory [141] and stimulatory [142] effects. In contrast to the prostate, where androgens act as mitogenic agents, in the breast the hormone probably acts as anti-mitogen and hence, a higher risk and earlier onset of breast cancer may be associated with long CAG repeats in the receptor gene.

2.11.2 AR gene in breast cancer

Very few studies have reported mutations in *AR* gene in men and women with breast cancer [21] (web: www.androgendb.mcgill.ca/). Wooster *et al*. [143] reported the first *AR* mutation (R607Q substitution) in two brothers with breast cancer and PAIS. Thereafter, Lobaccaro *et al*. [144] reported R608L substitution in a male with breast cancer. The only mutation reported till date in a woman with breast cancer is the splice site variant in the *AR* gene [145]. However, a significant number of studies have analyzed the nucleotide triplet repeat variations. *AR*-CAG repeat length polymorphism in breast cancer has been studied in two ways, as a risk factor for breast cancer by itself and as a risk factor in the background of *BRCA* mutations. All the studies on American women with breast cancer have shown a consistent association of increased CAG repeats with breast cancer risk to smaller or greater extent (Table 5), irrespective of the *BRCA* mutation carrier status. However, all the studies on Asian women showed no correlation between the disease risk and CAG repeat length [115, 146, 147]. Only one study showed early onset of disease in women with shorter repeats [115]. Similarly, all the studies on European men and women with breast cancer have shown no correlation with the disease risk [148, 149] or disease risk and age at onset [112, 149]. A study on Australian men reported increased CAG repeat in patients [150] while another two studies on Australian women reported no association with [151] and without BRCA mutation [152]. The contrasting outcome of the two studies on men [148, 150] may be because the Australian men carried a BRCA mutation [150], while the European men did not carry BRCA mutations [148].

Steroid hormone pathways regulate *BRCA1* expression [153]. Therefore, the allelic variation in *AR* gene may be involved in modification of *BRCA1*-associated breast cancer risk. Hence, few studies have analyzed *AR*-CAG repeat in the BRCA mutation carriers. In one of the earliest studies on breast cancer, Rebbeck *et al*. [154] found that women carrying at least one allele with ≥ 28 CAG repeats were at higher risk of breast cancer than those carrying shorter alleles. Women with at least one allele of ≥ 28, ≥ 29 or ≥ 30 repeats were diagnosed earlier by 0.8, 1.8, or 6.3 years, respectively, than women who did not carry at least one such allele. Thus, *AR* appeared to be a modifier gene for breast cancer risk in *BRCA*1 mutation carriers. But three later studies did not support this finding [112, 115, 151]. One reason for this contradiction may be the ethnic differences between the patients, given the fact that former study involved American patients while the later three studies involved Australian/British, Israeli and Italian women. Therefore, it can be concluded that *AR*-CAG repeat may be a risk factor for breast cancer by itself but it does not act as a modifier of the breast cancer risk associated with the *BRCA* mutations. Analysis of GGN repeat on American women showed association of longer GGN repeat with decreased risk of breast cancer [155] but till date no study has analyzed both the repeats jointly.

2.12 Preeclampsia

Preeclampsia is characterized by high blood pressure, swelling, sudden weight gain, headache, changes in vi-

Table 5. Published data on *AR* gene trinucleotide repeat variation in breast cancer. NA, not available.

Population	Patient's gender	Total Cases/ controls	Familial/ Sporadic	BRCA mutation carrier	CAGrepeat	GGN repeat	Reference
American	Women	165/139	Sporadic	Yes	Longer repeats-more risk and early diagnosis	NA	[154]
Australian	Women	368/284	Sporadic	No	No significant difference	NA	[152]
Irish	Women (≤ 65 years)	178/–	Sporadic/ familial	No	No association with age at presentation or family history	NA	[148]
Japanese	Female	90/–	Sporadic	No	Formation of the apocrine subtype in the presence of longer CAG repeats.	NA	[146]
UK	Men	59/79	Sporadic	No	No significant difference	NA	[148]
American	Female	133/–	Sporadic	No	Inverse correlation with histological grade and risk for death	NA	[292]
Canadian	Female (over 40)	111/248	Sporadic	No	Longer repeats more disease risk	NA	[293]
Canadian	Female	255/461	Sporadic	No	Less than 39 cumulative repeat size – lesser disease risk	NA	[294]
Israeli	Female (aged over 56 years)	122/66	Sporadic	Yes	No association with disease risk	No association with disease risk	[147]
Italian	Female	101+47/–	Familial	Yes	No association with disease risk or age at diagnosis	NA	[112]
Israeli	Female	149/78	Sporadic	Yes	Shorter repeat associated with early onset but not disease risk	NA	[115]
American	Female	727/969	Sporadic	No	No overall association but longer repeats may increase risk in positive family history	NA	[295]
American	Female	–/538	–	No	No association with mammographic density	NA	[296]
Canadian	Female	299/299	Sporadic	No	Shorter repeats – lesser disease risk	NA	[297]
American	Female	524/461	Sporadic	No	More disease risk for cumulative repeat size of ≥ 43	Less risk for cumulative repeat size ≥ 33	[155]
Finnish	Male	32/–	Sporadic	No	No association with the disease risk	NA	[149]
Australian	Male	41/–		No	Longer repeats more disease risk but no correlation with age at diagnosis	NA	[150]
American	Female	404/–	Sporadic	No	Longer repeats high mammographic density	NA	[298]
American	Female	239/249			Overall, no association but high risk in individual with longer repeats in positive family history	NA	[299]
Australia/ British	Female	604/–	Familial	Yes	No significant difference	NA	[151]

sion and the presence of protein in the urine associated with elevated androgen levels [156]. Saarela *et al*. [157] first examined children born after preeclamptic pregnancy (cases = 59, controls = 58) and found that they had significantly shorter *AR* polyglutamine tracts compared to the control children born to normotensive mothers. The study fits the *in vitro* observation that shorter CAG repeats confer higher AR activity. The difference was more pronounced in the subgroup of boys. Theoretically, knowing the location of the *AR* gene on the X-chromosome, also the preeclamptic mothers of the boys would be expected to have relatively short polyglutamine tracts. With this *priori* information and the evidence of the role of *AR* polyglutamine tract in androgen response, the authors investigated whether the length of *CAG* repeats is altered in an unrelated group of women with preeclampsia (cases =133, controls = 112). But no significant differences were observed between preeclamptic women and controls, however, the shortest CAG repeats were observed only in the preeclmaptic women.

2.13 Androgen levels in women

As discussed above, the pathophysiological roles of androgens in women are gaining increasing attention given its role in ovary function, PCOS, libido, diabetes, breast cancer, and so on. Further, as evidenced above, the level of androgens goes up after menopause [125, 130]. Parallel to the observation in men [158], the inhibitory feedback of AR may affect the serum level of androgens in women. To test this hypothesis, analysis on a cohort of Swedish premenopausal women (n = 270) revealed that women with relatively few CAG repeats displayed higher levels of serum androgens [159]. A later study on postmenopausal Brazilian women (n = 39) reported that the biallelic CAG repeat mean was significantly less in the cases with high level of androgens [160].

3 *AR* gene in neurological disorders

3.1 Spinal and bulbar muscular atrophy (SBMA)

Spinal and bulbar muscular atrophy (Kennedy's disease) is a disorder affecting specialized nerve cells that control muscle movement (motor neurons). The condition, which mainly affects males, is characterized by muscle weakness and wasting that usually begins in adulthood and worsens slowly over time. Muscle wasting in the arms and legs results in cramping, difficulty in walking and a tendency to fall. Certain muscles in the face and throat (bulbar muscles) are also affected, which causes progressive problems with swallowing and speech. Additionally, muscle twitches (fasciculations) are common. Some men with the disorder experience unusual breast development (gynecomastia) and may even be infertile. The sexual differentiation is normal in initial stages of life but the abnormalities appear with time [161]. The disorder is caused by abnormal increase in the *AR*-CAG repeat length [162]. The CAG repeat length in all the SBMA patients have been found to be above the average range and varies from 38–75 repeats [162] The abnormally expanded CAG repeat disrupts the normal function of motor neurons in the brain and spinal cord. These nerve cells gradually die, leading to the muscle weakness and wasting seen in this condition. People with a higher number of CAG repeats tend to develop signs and symptoms of SBMA at an earlier age 163].

Evidences suggested that aggregate formation and proteolytic processing of the AR protein can occur in a polyglutamine repeat length dependent manner and abnormal metabolism of the AR protein with expanded repeat is coupled to cellular toxicity [164]. Thus, the loss of function of the *AR* gene contributes to the androgen insensitivity in SBMA, the pivotal cause of neurode-generation has been believed to be a gain of toxic function of the pathogenic *AR* as a result of expansion of the polyglutamine tract [165]. Finally, it has been evidenced that Caspase-3 cleavage of an AR displaying an expanded poly-glutamine tract can play a role in the induction of neural cell death [166]. The correlation of the expanded CAG repeat with SBMA has been proven beyond doubts and multiple studies have consistently reported the CAG repeat expansion in SBMA patients with various ethnic backgrounds. Unlike most other trinucleotide repeat associated diseases, SBMA shows limited meiotic instability, and evidences so far indicate the absence of somatic repeat instability in adults [167]. Therefore, the determination of the CAG repeat length has been used for prenatal screening of the disorder in case of positive family history [168]. The determination of the CAG repeat length in the prenatal samples not only helps in detecting the risk but also helps in estimating the probable age of onset of the disease.

3.2 Alzheimer's disease

Hogorvorst *et al*. [169] reported that men with Alzheimer's disease (AD) had lower serum levels of total testosterone than control males, independent of po-

tential confounds. Also, many other reports have shown that testosterone exerts neuroprotective actions, against oxidative stress [170], apoptosis [171] and toxicity of β-amyloid [172]. A recent study has found an interaction between the apolipoprotein E 14 allele (APOE14) and AR and testosterone levels affecting the memory of mice [173]. Therefore, Lehmann *et al*. [174] examined the potential association of the *AR*-CAG repeat polymorphism separately in an Oxford cohort of men and women (cases = 49 women and 50 men, controls = 50 women and 50 men), both in early- and late-onset AD. The study showed that the shorter CAG repeats were associated with AD in men but not in women [174].

3.4 Schizophrenia

The *AR* gene is a potentially attractive candidate gene for schizophrenia for several reasons. First, gender comparisons in epidemiological surveys of schizophrenia have demonstrated consistently that women show a later age of onset (10–25 years for men and 25–35 years for women) [175], less severe manifestation and a slightly better course [176]. Second, an apparent excess of sex chromosome aneuploidies (XXY and XXX) have been reported in populations of patients with schizophrenia and schizophrenic sib-pairs are more often of the same than of the opposite sex [177]. Finally, in families that included at least two siblings with schizophrenia, Crow *et al*. [178] reported that male-male pairs shared alleles at the *AR* gene above the rate expected by chance, although a later study did not replicate this finding [179]. Tsai *et al*. [180] conducted an association study on schizophrenia in Taiwanese patients (cases = 225, controls = 247) to test the hypothesis that the *AR*-CAG repeat polymorphism was associated with susceptibility to schizophrenia and/or its onset. However, the study revealed no association of the repeat length with Schizophrenia or its age of onset in either sex.

3.5 Cognitive function

Several recent studies suggested that testosterone and other androgens might improve cognitive function in older men [181]. *AR* is expressed in the brain in areas critical for learning and memory such as the thalamus, hippocampus, and in the deep layers of the cerebral cortex [182, 183]. Therefore, Yaffe *et al*. [181] analyzed *AR*-CAG repeat in community dwelling American white men (n = 301) and found that longer CAG repeat length was associated with lower cognitive functioning in older white men.

The CAG repeat analysis for the three disorders discussed above have produced different results: short repeats associated with Alzheimer's disease, longer with decrease in cognitive function while no association was observed with schizophrenia. These disorders share many features such as memory loss and impaired thinking. Although, individually, no more than one study has addressed CAG repeat in the above disorders, the comparative analysis of CAG repeat in these disorders raises doubt about the associations observed. This observation warrants the need for classification of the subjects with various symptoms in subgroups and analysis of data thereafter.

3.6 Psychoticism

Psychoticism, characterized by externalizing behavior problems, including impulsivity, aggression, and nonconformity to social rules has been correlated with androgens [3]. Similarly, T administration to eugonadal men has psychiatric effects only in susceptible sub-populations [184]. Turakulov *et al*. [185] studied the *AR*-CAG repeat on an Australian population (781 males and 890 females) in Canberra. The study found a modest but statistically significant association of short repeats with high P scores (score used for psychoticism) for men but no significant association in women. Another study on Brisbane women (n = 588) supported the relationship between P scores and short CAG sequences, but the adolescent boys showed differences, which although small but tended to lie in the opposite direction [186]. The results of the above two studies on psychoticism have produced contrasting results and need validation.

3.7 Migraine

There is no gender difference in migraine occurrence prior to puberty; however, migraine develops in three times as many women than men during the adult years [187]. In many women, migraine worsens around the time of menstruation, and may cease altogether after menopause or during pregnancy [188]. In a study on Australian patients (cases = 275, controls = 275), CAG repeats length was found not to associate with migraine [189].

3.8 Criminal activities

From the twin and adoption studies, it was demon-

strated that genetic components as well as environmental factors might affect the development of antisocial behavior [190]. The androgen-related signaling molecules may be altered as a part of the neurobiological substrate of antisocial or violent criminal behavior for several reasons. First, testosterone has been linked to male aggression in several studies [191, 192]. Second, significant psychiatric symptoms, including aggression and violence, have been associated with androgen-related drug abuse [192]. Finally, through surveys of the general population, it has been demonstrated that antisocial personality disorder (ASPD), a psychopathy characterized by continual antisocial or criminal acts, is more common in males (4.2%) than in females (1.9%) [193]. Therefore, Cheng *et al*. [194] studied criminal Chinese males (146 extremely violent criminals and 108 normal controls) and found no association between CAG repeat length and violent convicts, although more of violent criminals than controls presented with the shorter (< 17) repeats. Therefore, the tendency to be criminal appears to be influenced much more by environmental factors than genetic. However, more studies on this aspect will bring forward the role of genetics in criminal behavior.

4 *AR* gene in the disorders of aero-digestive tract and digestive system

4.1 Head and neck cancer

Squamous cell carcinoma of the mucosa of the upper aerodigestive tract (oral cavity, larynx, oropharynx and hypopharynx) showed an impressive higher incidence of head and neck tumors in males compared to females [195]. Further, expression studies showed that laryngeal tumors were positive for AR [196]. These studies indicate that the relatively higher incidence of the disorder in males could be attributed to the androgens. Therefore, a study on Brazilian males (cases = 103, controls = 100) revealed an increased relative risk of head and neck cancer in men with a CAG repeat length > 20 [197]. Higher incidence of the disorder in men indicates that androgen and hence shorter CAG repeats should promote the disease, but the above study has produced contrasting results.

4.2 Esophageal cancer

The prognosis of esophageal cancer is worse in males than in females, possibly because of the difference in hormonal environments [198]. Worldwide, two-thirds of the disease occurs in men [199], suggesting that X-chromosome linked genes may be involved in the disease. A high proportion (22 of 29) of tumors analyzed by comparative genomic hybridization (CGH) revealed changes involving the X chromosome [200], including the site of the *AR* gene. With this background, Dietzsch *et al*. [201] by analysis on African males (29 patients and 109 controls), African females (14 patients and 59 controls) and Colored (black people) males (15 patients and 58 controls), reported that CAG triplet length did not differ significantly between cases and controls, but the short $(GGC)_n$ alleles were implicated in esophageal cancer in African males. When the two alleles were considered jointly, additional information on predisposition was gained, revealing two haplotypes (CAG > 21, GGC < 16) and (CAG < 21, GGC > 16) conferring a protective effect. The results are, however, contradictory to the observation that the incidence of the disorder is higher in males and the shorter GGN repeats should produce more active AR molecules.

4.3 Colorectal cancer

Androgens are essential for the regulation of cell growth and differentiation in several tissues, including colorectal tissue [202]. Clinical studies have found that women had different tumor locations than men [203], are more often associated with peritoneal metastases and poorly differentiated lesions [204], and have significantly increased 5-year survival rates in colorectal cancer [205]. Slattery *et al*. [206] on the basis of data from case-control studies of colon (1 580 cases and 1 968 controls) and rectal (797 cases and 1 016 controls) cancers reported association of increased number of CAG repeats with colon cancer among men, but not women. The same authors on the basis of a later study on colon (1 580 cases and 1 968 controls) and rectal (797 cases and 1 016 controls) cancer reported that men with low vitamin D intake or low levels of sunshine exposure, who had more than 23 CAG repeats of the *AR* gene had the greatest risk of colon cancer. Men with high levels of sunshine exposure were at reduced risk of developing rectal cancer if they had 23 or more CAG repeats than if they had fewer than 23 CAG repeats [207]. According to the survival rates in colorectal cancer between the two genders, androgens and hence shorter CAG repeats should promote colorectal cancer, but none of the above studies confirmed it.

5 *AR* gene in disorders related to general body health and fitness

5.1 Bone and mineral density

5.1.1 Androgens and bone metabolism

Hypogonadism results in low bone mass and significant increase in the risk of osteoporosis in both sexes. The estrogen and the androgen receptor genes are therefore obvious candidates for mediating the genetic influence on bone mass and risk of osteoporosis. Previously, many studies have reported associations between polymorphisms in the estrogen receptor gene and reduced bone mass and increased risk of osteoporotic fractures [208]. Subsequently, a significant number of studies have analyzed the *AR* gene in relation to bone and mineral density (BMD). Although no study has reported mutation in the *AR* gene, but trinucleotide repeats have been analyzed in multiple studies.

5.1.2 AR gene in BMD

Given the fact that androgens help in the development of bones and the maintenance of BMD [209], an inverse correlation is expected between CAG repeat length and BMD. Studies on European populations have produced all the three possible patterns: no correlation [210–212], inverse correlation [213, 214] and direct correlation [214] between *AR*-CAG repeat and BMD, but studies on Asian populations showed inverse correlation [215, 216]. If we look at all the studies irrespective of the origin, an almost equal number of studies on women have shown the inverse correlation [214–216] and no correlation [211, 212] between the CAG repeat length and BMD. Yamada *et al*. [216] observed the inverse correlation in premenopausal women but not in post-menopausal women. Out of four studies on men, two have shown no correlation [210, 217], one has shown inverse correlation [213] and still another has shown direct relation [214] between the CAG repeat length and BMD. None of the studies on BMD in men or women has analyzed GGN repeat (Table 6). Hence, the role of variation in this repeat remains inconclusive.

5.2 Arthritis

The incidence of rheumatoid arthritis (RA) is higher

Table 6. Published data on *AR* gene trinucleotide repeat variations in bone and mineral density. NA, not available.

Population	Gender	Total Cases/ Controls	CAG repeat	GGN repeat	Reference
Belgian	Men	273	No association with BMD at the hip, forearm or any of the biochemical markers of bone turnover.	NA	[210]
German	Men	110	Longer repeats faster age-dependent bone loss.	NA	[213]
Taiwanese	Women	168/–	Longer repeats associated with lower BMD and a significantly greater risk for osteoporosis at the femoral neck.	NA	[215]
Danish	Women	226/255	Length of the longer allele was negatively correlated with BMD of the lumbar spine and femoral neck	NA	[214]
Danish	Men	58/72	BMD of the lumbar spine, femoral neck and total hip was positively correlated with length of the repeat	NA	[214]
Finnish	Women	331/–	No association with baseline BMD, 5-year bone mineral density change, or fracture risk in early postmenopausal women	NA	[211]
Danish	Women	1792/–	No significant difference	NA	[212]
American	Men	75/16	No association with BMD or physical performance	NA	[217]
Japanese	Women	1101/–	Inverse correlation with BMD for the lumbar spine in premenopausal women but not in postmenopausal women.	NA	[216]

in women than in men (2:1 to approximately 3:1). This difference suggests an influence of reproductive and hormonal factors in the occurrence of the disease [218]. The role of androgens in the pathogenesis of RA has been discussed in multiple studies [219, 220]. In men, a number of studies have suggested an etiological role of lower serum testosterone levels in developing RA [219]. In view of the possible role of androgens in developing RA, Kawasaki *et al*. [221] conducted a study on Japanese men and women (cases = 90 men and 276 women, controls = 305 men and 332 women) and reported association of shorter CAG repeats with younger age of onset in men. A later study on a cohort of Greek women (cases = 158, controls = 193) showed that only women with long-long genotype had a 2-fold lower risk of osteoarthritis compared to individuals with short-short genotype. In women, when odds ratio were adjusted for age, sex, BMI, age of menarche, age of menopause, and grade of physical demand, it was observed that those with long-long genotype had a significantly increased risk for knee osteoarthritis compared to those with short-short genotype [222].

5.3 Obesity

In men serum testosterone concentrations were frequently found to have inverse correlations with body mass index (BMI), waist circumference, waist-hip-ratio (WHR), amount of visceral fat, serum levels of leptin, insulin and free fatty acids [223]. A study by Zitzmann *et al*. [224] on German men (n = 106) reported an association of short CAG repeats with protective parameters (low body fat mass and plasma insulin) and adverse parameters (low high density lipoprotein cholesterol concentrations). The results of this study fit the observation that the levels of androgens in the human body are inversely proportional to the body fat content and BMI.

5.4 Type 1 diabetes

It has been shown that androgen treatment prevents diabetes in non-obese diabetic mice [225]. Moreover, testosterone increased the circulating insulin levels [226]. Mice transgenic to expanded CAG triplet repeats were prone to diabetes [227]. Therefore it would be expected that expanded repeats would be associated with diabetes. In light of the above facts, Gombos *et al*. [228] investigated the association of CAG repeat polymorphism with type 1 diabetes (T1D) in a German population of affected sibling pair families (n = 120), nuclear families (n = 645) and cohorts of sporadic cases (n = 208) and controls (n = 1381). However, no significant difference in the distribution of CAG repeat alleles was observed between the patients and the controls.

5.5 Cardiac diseases

It has been suggested that the difference in the incidence of ischaemic heart disease between men and women is a result of sex steroids, as estrogens are believed to be protective in women [229] and androgen harmful in men. Several reports have shown that the androgens are atherogenic when administered to women in high doses [230], while androgenic steroids are believed to be responsible for premature cardiovascular disease in athletes [231]. Considering this, Alevizaki *et al*. [232] investigated coronary artery patients (n = 131) and reported short CAG repeats in more severe forms of the disease. Later, in two independent case-control studies on white men (N = 544), Hersberger *et al*. [233] showed no association of short CAG repeats with coronary heart disease or myocardial infarction.

5.6 Hepatocellular carcinoma

Hepatocellular carcinoma (HCC) is more prevalent in men than in women throughout the world [234]. Prospective studies have demonstrated a positive association between circulating levels of testosterone and HCC risk in relation to chronic HBV or HCV infection among men [235]. *AR* has been detected in both HCC and non-tumorous liver tissues from men and women [236]. Yu *et al*. [237] on the basis of their case-control study on Taiwanese women (cases = 238, controls = 354) demonstrated that the women harboring both *AR* alleles with more than 23 CAG repeats had an increased risk of HCC. A higher incidence of HCC in men suggests that higher androgens levels and hence shorter CAG repeats should associate with the disease risk, but the above study produced contradicting results.

5.7 Muscle development and strength

AR is highly expressed in skeletal muscles [236], with expression being upregulated in response to muscle overload [237]. Animal and clinical studies have indicated that the androgen-AR signaling pathway is required for both skeletal muscle development and increases in muscle mass, strength, and muscle protein synthesis in response to androgens [238]. Based on their two independent studies on white men and women (n = 294 men,

112 men and 90 women), Walsh *et al*. [239] suggested that greater number of CAG repeats associated with higher total fat free mass in men but not in women.

5.8 Lateralization and Handedness

It has been proposed that exposure to high levels of testosterone *in utero* results in decreased lateralization and an increased likelihood of left-handedness [240]. Conversely, Witelson and Nowakowski [241] proposed that low testosterone levels are associated with increased left-handedness. Two linkage studies have mapped the region for handedness to DXS990 [242] and between DXS993 and DXS991 [243]. The *AR* gene on Xp11 is therefore a strong candidate for influencing handedness. Taking the above facts into consideration, Medland *et al*. [244] demonstrated that in females the probability of left-handedness was greater in those with a greater number of CAG repeats while in males the risk of left-handedness was greater in those with fewer repeats.

5.9 Male pattern baldness

Finasteride is a drug used to treat male pattern baldness (MPB). It works by blocking the conversion of the male hormone testosterone to dihydrotestosterone; high levels of which are linked to baldness. Finasteride is not necessarily effective on all of the MPB patients. To know any factor, which correlates with the effectiveness of finasteride, Wakisaka *et al*. [245] analyzed the CAG and GGN repeat polymorphism in MPB patients. The study indicated that the smaller the number of repeats (CAG + GGC) the more effective was the drug.

5.10 Acne, hirsutism and alopecia

Similar to many other disorders, acne (pimples or zits on face, chest, *etc.* especially during puberty), hirsutism (male pattern of hair distribution in a female) and alopecia (lacking hair where it would normally grow, especially on the head) are thought to have their etiology in the androgens action. In the light of the above facts, Sawaya *et al*. [246], studied CAG repeats in androgen related disorders such as acne, hirsutism and androgenetic alopecia on American men (n = 48) and women (n = 60), revealing that shorter CAG repeat lengths were associated with these disorders in both males and females. The results of the study fit the experimental observations that shorter CAG repeats result in higher activity of the AR protein.

6 Variable association of *AR* gene variations with various disorders

From the above discussion it is clear that mutations in the *AR* gene are responsible for varied phenotypes including androgen insensitivity syndrome, male infertility, prostate cancer and breast cancer. Apart from point mutations, trinucleotide repeat polymorphisms in the *AR* gene have been correlated with numerous other disorders. Drastically different observations in mutation/polymorphism studies in the same disorders in different populations have been quite interesting. However, the factors contributing to the differences between the studies involving *AR* mutations and trinucleotide repeat polymorphisms have been different and remain scarcely known.

6.1 Trinucleotide repeat length polymorphisms

Triplet repeat length polymorphisms associate variably with the same disorder in different populations; showing direct, inverse or no association at all. The well-established differences in the CAG repeat length range between different populations is the first source of variations in the results. Americans and Asians have the shortest CAG repeats (8–30 and 11–31 repeats, respectively), while Europeans have the longest repeats (8–39 repeats). Apart from the ethnic differences, it is likely that the differing study designs may contribute to the differing results. For example, the contrasting results of two studies on ovarian cancer [110, 247] may be because of the differences in the selection of controls. In one study, the control samples were recruited from general population [247], while in the other, controls were recruited from women donating blood at the hospital from which the cases were identified [110]. In both the studies, the mean age of the controls was significantly lower than that of the cases. In particular, while the distribution of allele lengths was almost identical for both studies' case groups, the distribution of allele lengths between the two studies' control groups differed substantially.

Another factor contributing to the variations in the results of the studies on female subjects may be the variations in data analysis methods. The data analysis on female subjects becomes complex because of the presence of two *AR* alleles in each subject. The data on female subjects have been analyzed by taking the mean of two alleles [169], counting both the alleles independently [169] and taking into consideration the long-long,

long-short or short-short allele combinations for all the subjects [185]. The data analysis becomes further complex because of the phenomenon of X-inactivation. Most of the studies to date did not take X-inactivation into account; however, some studies mention the analysis by taking only the active *AR* alleles into consideration. The best method of data analysis is taking into consideration the X-inactivation pattern followed by analysis for the active alleles of all the cases.

To understand the mechanism by which the length of CAG repeats should contribute to various disorders and variability in the association studies, it is important to study the co-regulator milieu of AR. More than 70 proteins are known to interact with the AR protein [21]. The CAG repeat region is located in the AR domain that is known to interact with some AR co-regulators [248]. It is possible that variation in the CAG repeat length affects its interaction with co-regulator milieu. Transfection assays have demonstrated that the interaction between AR and the co-activator ARA24 decreases with increasing *AR*-CAG repeat length, resulting in decreased AR transactivation [249]. Similarly, *AR* alleles with shorter CAG repeats are better co-activated by members of the steroid receptor co-activators (SRC) family of co-regulators (SRC-1, transcriptional intermediary factor 2 [TIF-2], and SRC-3) [250]. Alternatively, polymorphisms in the promoters of AR target genes in combination with short *AR*-CAG alleles may contribute to the susceptibility to various disorders.

6.2 Single nucleotide mutations

In the *AR* gene it is not only the trinucleotide repeats that show varying associations with various disorders, but also the single nucleotide substitutions [21]. The study on phenotypic variation was conducted on patients with familial AIS, having received the X-linked *AR* mutation from their carrier mother and having it in all their cells. No phenotypic variation was observed in families with CAIS, except one family with coexistence of CAIS and PAIS cases sharing M780I substitution [251]. However, distinct phenotypic variation was observed in one-third of the families with PAIS. D695N substitution was reported in both, PAIS and CAIS. A645D mutation, with proven pathogenicity in PAIS and CAIS patients was also found to be present in a totally normal individual. Another interesting example is E211E mutation, which was reported in MAIS, PAIS, and CAIS, and also in 8% of the normal population. W751STOP mutation has been reported not only in PAIS, CAIS but also in prostate cancer patients [21] (www.androgendb.mcgill.ca/). The later observation seems more surprising if we look at the mechanism by which *AR* mutations contribute to androgen insensitivity and prostate cancer. Mutations in AIS are mostly loss of function mutations, while mutations in prostate cancer result in gain of function and broadened specificity of the receptor for the ligands. Therefore, we need to understand the mechanism by which *AR* gene contributes to the development of AIS or prostate cancer and the factors that influence the ultimate phenotype in *AR* mutations, before the variability in the phenotype can be satisfactorily explained.

Some studies have suggested the role of genetic background or modifiers, in varying manifestations of androgen insensitivity syndrome [26, 252, 253]. The nature and exact role of the so-called 'genetic background' remains largely unknown; however certain components of this background have been identified. Holterhus *et al*. [254] reported a family with four affected individuals, displaying strikingly different external genitalia: ambiguous (first brother), severe micropenis (second brother), slight micropenis (third brother) and micropenis and penoscrotal hypospadias (uncle). All had been assigned a male gender and shared the same mutation in the *AR* gene. Taking into account the well-documented individual and time-dependent variation in testosterone concentration in early fetal development, the authors concluded that their observations illustrated the potential impact of varying ligand concentrations on phenotypic variability in different AIS cases. In another study, a 5-α reductase 2 deficiency in genital skin fibroblasts of the subject was found to be the cause of the more severely impaired virilization in a family with R846H mutation [255]. Affected members of another family with *AR* gene mutation M771I [251] also showed phenotypic variation, ranging from a female to a Reifenstein phenotype. The M771I mutation introduced qualitative defects in AR and also resulted in decreased expression of the AR protein in Scatchard analysis of GSF [251] and in *in vitro* expression studies [256]. However, the phenotypic variability could not be satisfactorily explained.

Somatic mosaicism was first shown to play a role in variable expressivity with the identification of L172STOP mutation in a patient with PAIS [257, 258]. The mutation had previously been reported in a CAIS patient and showed absent ligand binding upon functional assays [258]. Even more intriguing was the fact that cells from

the PAIS individual exhibited measurable androgen-binding activity, although the stop mutation would be expected to preclude any AR activity. Sequencing of the gene in the mother's blood leukocytes showed that the patient had initially inherited the mutation from their mother, but some of the *AR* genes in their genital skin fibroblasts had reverted to normal [253]. In a related study using kinetic analysis, the authors identified two different *AR* alleles within a single biopsy, indicating the presence of a heterogeneous *AR* population resulting from the somatic mosaicism [259]. Their conclusion was that in these cases some of the mutant genes had undergone a back mutation to produce wild-type receptors [258, 259]. It will be interesting to see whether somatic mosaicism can be found in more than 20 cases of variable expressivity reported in AIS to date. Currently, only five cases of variable AIS phenotypes are confirmed to be caused by somatic mosaicism [253, 259].

7 Conclusion

Highly variable results have been generated in the association studies of triplet repeat polymorphisms with various disorders and similar variations have been reported in *AR* mutations as well. Studies on the disorders, except for male infertility, prostate cancer and breast cancer, lack support from multiple studies and hence it would be premature to make conclusions on the association of the *AR* gene with these disorders. The CAG repeat has been analyzed *in vitro* [9, 10] and hence the outcome of various studies should be analyzed in view of *in vitro* observations. However, GGN repeat has been comparatively less studied and most of the studies on GGN repeat lack *in vitro* evidences. Therefore, more *in vitro* investigations on GGN repeat are anticipated before the results of various association studies can be analyzed.

Furthermore, very few studies have analyzed CAG and GGN repeats jointly. Joint analyses have shown certain differences between the cases and controls in male infertility [49, 50], prostate cancer [71, 93], testicular cancer [98], endometrial cancer [131] and esophageal cancer [201]. The *AR*-CAG repeat may be in linkage disequilibrium with other polymorphisms, including the *Stu*I mutation [260] and the GGC (GGN) repeat in exon 1 [32, 49, 93], however, these associations need confirmation by *in vitro* methods using specific combinations of CAG and GGN repeats in *AR* constructs. Therefore, the joint analyses of major polymorphic sites in the *AR* gene will not only help in understanding the association of these polymorphisms with various disorders but also help in understanding the variability in the eventual phenotypes.

The variation in the eventual phenotypes between individuals sharing the same *AR* mutation has been interesting. Studies to date have suggested variation in embryonic androgens concentration, 5-a reductase 2 deficiency and somatic mosaicism in the androgen target tissues contributing to variable phenotype. But these variations cannot account for phenotypic variability in all the known cases. Polymorphism studies on *AR* interacting genes may further help to understand the phenotypic variability. Analyses of these *AR*-interacting genes will help in further uncovering the mechanism of phenotypic variability.

The role of *AR* in diverse phenotypes makes it an interesting candidate for prenatal screening. Prenatal screening has already been used in SBMA and androgen insensitivity in the families at high risk. Once the information on the potential effects of mutation(s) at each nucleotide position of the gene is clear, the screening of the *AR* mutations in prenatal samples may be helpful in preventing the transmission of the mutant X-chromosome to the coming generations. The assignment of the gender in the PAIS cases has been quite difficult and does not always depend on the type of the mutation. Individuals with the same mutation in *AR* gene have been raised both as males and females. The determination of the triplet repeat length and other polymorphisms in the gene along with the understanding of the mechanism of phenotypic variability will help in proper management and rearing of the sex in the cases of androgen insensitivity. In addition, determination of the number of CAG and GGN repeats in these samples will also help in determining the risk of prostate cancer, infertility, breast cancer or other disorders related to variations in the triplet repeats.

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