ABSTRACT

Introduction: Long-term adverse symptoms of men who used oral finasteride against androgenic alopecia have been recently described as post-finasteride syndrome (PFS).

Aim: To determine whether (CAG)n-rs4045402 and (GGN)n-rs3138869 polymorphisms in the androgen receptor (AR) gene are implicated in PFS.

Methods: AR polymorphisms were studied according to PFS symptoms in 66 white participants (31.8% Italian, 28.8% American, and 39.4% other).

Main Outcome Measures: Symptoms were investigated by an ad hoc 100-item questionnaire and the Arizona Sexual Experience Scale and Aging Male Symptom Scale (AMS). (CAG)n and (GGN)n repeats were categorized as short ([CAG]9–19, [GGN]<23), medium ([CAG]20–24, [GGN]23), or long ([CAG]25–37, [GGN]>23).

Results: Median age was 32 years, duration of finasteride use was 360 days, and time from finasteride discontinuation was 1,053 days. We observed several frequency differences in symptoms according to (CAG)n and (GGN)n repeat numbers. Three AMS items were worse for medium (GGN)23 than for long (GGN)>23 carriers and one item was worse for short (GGN)<23 carriers. The AMS item for decrease in sexual desire or libido was worse for short (CAG)9–19 carriers than for medium (CAG)20–24 carriers. Through the ad hoc questionnaire, significant findings in (CAG)n and/or (GGN)n repeats were obtained for penile discomfort, loss of scrotal sensitivity, scrotal discomfort, less pubic hair, loss of perceived perineal fullness, increased sperm density, involuntary muscle spasms, loss of muscle tone, increased weight (>2 kg), increased skin dryness, and onset of symptoms after finasteride use.

Conclusion: This study showed that short and/or long (CAG)n and (GGN)n repeats had different frequencies according to symptoms reported by patients with PFS, likely reflecting the vast array of genes modulated by the AR. This study showed a U-curvilinear profile of (CAG)n repeats for skin dryness symptoms, where the two extremes exhibited a worse condition than medium repeats. Further studies are necessary to investigate the PFS pathophysiology using a precision medicine approach.

Cauci S, Chiriacò G, Cecchin E, et al. Androgen Receptor (AR) Gene (CAG)n and (GGN)n Length Polymorphisms and Symptoms in Young Males With Long-Lasting Adverse Effects After Finasteride Use Against Androgenic Alopecia. Sex Med 2017;5:e61-e71. Copyright © 2016, The Authors. Published by Elsevier Inc. on behalf of the International Society for Sexual Medicine. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Key Words: 5α-Reductase Inhibitor; Post-Finasteride Syndrome; Male Pattern Hair Loss; Androgenic Alopecia; Androgen Receptor; CAG Polymorphism; GGN Polymorphism; Erectile Dysfunction; Sexual Dysfunction; Loss of Libido; Finasteride Side Effects; Finasteride Safety
INTRODUCTION

Recent studies have described severe adverse effects in young men who used oral finasteride against androgenic alopecia (AGA) that persisted several months or years after finasteride discontinuation1−3 (a condition called post-finasteride syndrome [PFS]).4,5 A meta-analysis of clinical trials of finasteride on subjects with AGA showed that the toxicity information was very limited, of poor quality, and likely to be systematically biased.6

Finasteride inhibits 5α-reductase, the enzyme responsible for the reduction of testosterone into dihydrotestosterone. Finasteride against AGA (male pattern hair loss) is used at lower dosage (1 mg/d) than against benign prostatic hyperplasia (5 mg/d). Finasteride inhibits 5α-reductase type 2 and 3 enzymes much more strongly than the type 1 enzyme;7 therefore, finasteride can affect several different human tissues, such as the prostate, muscle, liver, kidney, brain, mammary gland, fronto cortex, skin, epidermis, pancreas, spleen, heart, testicle, stomach, dermis, small intestine, and adipose tissues.8,9,11

Finasteride use has several adverse effects, including erectile dysfunction, loss of libido, and smaller ejaculatory volume.5,10,12 A meta-analysis on the effects of 5α-reductase inhibitors found a significant pooled relative risk for sexual dysfunction in men with benign prostatic hyperplasia (2.56, 95% CI = 1.48−4.42) but no significant increased risk in men with AGA (1.21, 95% CI = 0.85−1.72).13

Recently, a clinical study described the main symptoms of subjects with PFS, including loss of penis sensitivity, decreased ejaculatory force, low penile temperature, smaller ejaculatory volume, anhedonia, lack of mental concentration, and loss of muscle tone or mass.4 In particular, an immunohistochemical study found increased levels of the androgen receptor (AR) in epithelial and stromal cells from the foreskin of eight men with PFS compared with healthy men.14

The expression level and amino acid protein sequence of AR can be affected by polymorphisms in its gene (AR).15 The most frequently studied polymorphisms of AR are two repeated nucleotide sequences: the (CAG)nCAA repeat nucleotide sequence, denoted as (CAG)n, encoding a polyglutamine stretch, and the polymorphic repeat (CGT)10GGG(GGT)4(GGC)n, denoted as (GGN)n, encoding a poly-glycine stretch. The two polymorphisms are included in the N-terminal of the AR protein and compose the transactivation domain of the nuclear receptor.16

The (CAG)n repeat length usually spans 9 to 36 repeat units, although the number varies among ethnic groups.17 Long (CAG)n repeats have been associated with decreased AR transactivation activity and weaker transcriptional potential than short repeats.18 CAG expanded repeats of at least 40 have been found in Kennedy disease, a neurodegenerative syndrome also characterized by androgen insensitivity.18−20 Long (CAG)n repeats have been associated with male infertility,21 although studies have been inconsistent.17,18,21 In contrast, a meta-analysis suggested that a shorter (CAG)n repeat polymorphism in Caucasians and Asians might increase the risk of prostate cancer compared with the longer (CAG)n repeat.22

The trinucleotide (GGN)n has been less investigated than the (CAG)n repeat polymorphism with respect to male androgenicity and infertility. Moreover, studies have not been very consistent.21 In an in vitro study, (GGN)n showed higher transcription than shorter or longer repeats.23 A meta-analysis found a correlation of long (GGN)n≥23 with testicular cancer.24

A recent molecular study (of 69 men with AGA and PFS, 91 men with untreated AGA, and 78 healthy men without AGA) focused on whether the two polymorphisms, (CAG)n-rs4045402 and (GGN)n-rs3138869, in the AR gene might play a role in the toxic long-term effects of finasteride.6 This study suggested that extreme repeats are a genetic predisposing factor for AGA development.

However, the pathophysiology of PFS remains largely unknown and detailed molecular events predisposing to specific long-term symptoms experienced by patients with PFS remain obscure.5

In our previous genetic study,6 we did not examine the relation of AR (CAG)n and (GGN)n polymorphisms with the single specific symptoms of subjects with PFS. In the present study, we explored this relation by three different questionnaires—the Arizona Sexual Experience Scale (ASEX),25 the Aging Male Symptom Scale (AMS),26 and our ad hoc 100-item questionnaire—for the clinical symptoms of 66 men with PFS. We also collected retrospectively the genetic data from our previous study to check whether less common repeat lengths of (CAG)n-rs4045402 and (GGN)n-rs3138869 polymorphisms might be related to the specific symptoms described by subjects with PFS.

METHODS

Subjects

Enrollment, inclusion, and exclusion criteria were previously described.4,6 Obese subjects (body mass index > 30.0 kg/m²) were excluded from this study because of the relation of fat body composition to androgens.27 According to the inclusion criteria, all participants were white.28 Moreover, because of the location of AR in the X chromosome, and to further confirm race, each participant was specifically asked to declare whether he had a white mother.6 None of the subjects declared homo- or bisexuality. The institutional ethical committee of each participating institution approved the study protocol (according to the Declaration of Helsinki), and all subjects signed a written informed consent.

This was an observational and retrospective study. We enrolled men (>18 and ≤50 years old) who used oral finasteride for AGA and had developed persistent adverse effects lasting for at least 6 months after drug discontinuation.4,6 Of 69 men initially enrolled,5 three were excluded for incomplete
questionnaires, leaving 66 subjects with PFS to be examined. Finasteride was used orally mostly at the dose of 1 mg/d, but some patients (to save money) broke a 5-mg pill into four parts (~1.25 mg/d) or broke a 1-mg pill into two parts (~0.5 mg/d).

Assessment of Symptoms and AR Polymorphisms

Three different questionnaires were used to evaluate adverse effects persisting longer than 6 months. We developed an ad hoc 100-item questionnaire to interview subjects with PFS about their demographic and clinical characteristics. In addition, participants filled out the ASEX25 reporting on their condition at the time of study (current ASEX) and retrospectively in addressing how they were before finasteride use (pre-ASEX) to rule out any sexual dysfunction before they started to use finasteride. However, because of possible recall bias for data before finasteride use, the pre-ASEX score was not used further to analyze the role of AR polymorphisms. The ASEX consists of five items with rating scales graded from 1 to 6 that quantify sex drive, arousal, penile erection, ability to reach orgasm, and satisfaction from orgasm, with higher scores indicating more severe sexual dysfunction.

Furthermore, participants filled out the 17-item AMS assessing androgenic dysfunction26,29 by three subscales for psychological, somatic, and sexual symptoms. Each item is graded from 1 (absent) to 5 (very severe); the total AMS score defines androgen deficiency as absent (score = 17–26), slight (score = 27–36), moderate (score = 37–49), or severe (score ≥ 50).26

The present inclusion criteria were a current ASEX total score corresponding to sexual dysfunction (total ASEX score ≥ 19 or any one item score = 5 or any three items with score ≥ 4)25 and/or AMS total score of least 27.4 Exclusion criteria included an ASEX score of at least 19 before finasteride use.4

For assessment of AR (CAG)n and (GGN)n polymorphisms, genomic DNA was extracted from blood or saliva samples, amplified, and sequenced as described previously.6

Statistical Analysis

AR (CAG)n and (GGN)n repeat lengths were divided into three quartiles—low quartile (<25th percentile, short repeats), interquartile (25th to 75th percentile, medium repeats), and high quartile (>75th percentile, long repeats)—and analyzed in a binary logistic regression model. For (GGN)n repeats, the central (GGN)23 repeat was found in more than 50% of subjects (44 of 66, 67%); therefore, short repeats (GGN)<23 and long repeats (GGN)>23 necessarily had a frequency lower than 25%.

The Kolmogorov-Smirnov test was adopted to assess the normal data distribution. Continuous data not normally distributed were expressed as median (25th to 75th percentile, interquartile range) and comparisons between groups were performed by Mann-Whitney U-test. Odds ratios (ORs) and 95% CIs were calculated to assess relative risks for binary (yes or no) variables, and the Pearson χ² or Fisher test was used to calculate the P value, as appropriate. Two-sided P values less than .05 were considered significant (P < .10 indicated a tendency). SPSS for Windows (IBM Corp, Armonk, NY, USA) was used.

RESULTS

Demographic characteristics and results from the ad hoc questionnaire, ASEX, and AMS are presented in Table 1. Subjects were enrolled a median of nearly 3 years after finasteride discontinuation and had used finasteride for 12 months.

Distribution of (CAG)n and (GGN)n repeat frequencies in the 66 subjects with PFS is illustrated in Supplementary Figures S1 and S2, respectively. Frequencies of subjects with short, medium, and long repeat lengths for the two polymorphisms were categorized: short = (CAG)9–19 (n = 18, 27.3%) and (GGN)<23 (n = 8, 12.1%); medium = (CAG)20–24 (n = 37, 56.1%) and (GGN) 23 (n = 44, 66.7%); long = (CAG)25–37 (n = 11, 16.7%) and (GGN)>23 (n = 14, 21.2%).

We did not find significant differences among the subgroups of (CAG)n and (GGN)n repeat lengths for age at enrollment, age at starting drug use, duration of finasteride use, period from drug discontinuation to study enrollment, and body mass index (Table 2). However, we observed a decreasing trend for duration of finasteride use and decrease of (CAG)n repeats with median values of 620 days for long (CAG)25–37, 450 days for medium (CAG)20–24, and 180 days for short (CAG)9–19 (short repeats showed a tendency to differ from medium repeats [P = .062], but the difference for short [CAG]9–19 vs medium to long [CAG]≥20 was significant [P = .045]).

Table 2 presents findings from the ASEX and AMS. The total scores of the ASEX and AMS did not differ with length of (CAG)n and (GGN)n repeats; however, we found differences for single items. For clarity, Table 2 presents only symptom items that showed a median number of points that differed statistically between at least two repeat length groups. ASEX item 5 (orgasm satisfaction) was worse in the long (CAG) 25–37 than in the short (CAG)9–19 subgroup (P = .040). Five AMS items showed differences among (CAG)n and/or (GGN)n subgroups. AMS item 5 (increased need for sleep and/or often feeling tired) was higher in the medium (GGN)23 than in the short (GGN)<23 group (P = .048). AMS items 9 (physical exhaustion or lacking vitality), 11 (depressive mood), and 12 (feeling that one has passed one’s peak) were worse in the medium (GGN)23 than in the long (GGN)>23 subgroup (P = .042, P = .036, and P = .044, respectively). In contrast, AMS item 17 (decrease in sexual desire/libido) was worse in the short (CAG)9–19 than in the medium (CAG)20–24 group (P = .028).

Tables 3 and 4 present data collected by the ad hoc questionnaire. Data were reported as binary variables, and only symptom items with at least one significant finding in relation to (CAG)n and/or (GGN)n repeats, respectively, were indicated.

Table 3 presents significant findings in relation to (CAG)n repeats. Scrotal discomfort was less frequent in the short
Table 1. Demographic characteristics, finasteride use, and symptoms of 66 subjects with post-finasteride syndrome

| Age (y), median (25th–75th percentile), range | 32 (27–39), 21–50 |
| BMI (kg/m²), median (25th–75th percentile), range | 23.9 (22.4–26.2), 17.3–29.9 |
| Nationality, n (%) |  |
| Italy | 21 (31.8) |
| United States | 19 (28.8) |
| Canada | 9 (13.6) |
| United Kingdom | 6 (9.1) |
| France | 3 (4.5) |
| Spain | 2 (3.0) |
| Bulgaria | 1 (1.5) |
| Hungary | 1 (1.5) |
| Sweden | 1 (1.5) |
| Australia | 1 (1.5) |
| Brazil | 1 (1.5) |
| Israel | 1 (1.5) |
| Educational level, n (%) |  |
| Elementary school | 1 (1.5) |
| High school | 15 (22.7) |
| College or university | 50 (75.8) |
| Marital status, n (%) |  |
| Single | 54 (81.8) |
| Married | 9 (13.6) |
| Divorced | 3 (4.5) |
| Age at starting finasteride (y), median (25th–75th percentile), range | 26 (22–31), 18–48 |
| Duration of finasteride use (d), median (25th–75th percentile), range | 360 (163–1,298), 17–3,650 |
| Discontinuation of finasteride (d), median (25th–75th percentile), range | 1,053 (560–2,043), 181–5,057 |
| Dosage used, n (%) |  |
| 1 mg/d | 46 (69.7) |
| 1.25 mg/d | 16 (24.2) |
| 0.5 mg/d | 4 (6.1) |
| Onset of symptoms, n (%) |  |
| During finasteride use | 59 (89.4) |
| After finasteride use | 7 (10.6) |
| ≤1 mo after discontinuation | 5 (7.6) |
| >1 mo after discontinuation | 2 (3.0) |
| Trend of symptoms after finasteride discontinuation, n (%) |  |
| Worsening | 38 (57.6) |
| Unchanged | 19 (28.8) |
| Improved | 9 (13.6) |
| Sexual symptoms, n (%) |  |
| Loss of penis sensitivity | 58 (87.9) |
| Decreased ejaculatory force | 54 (81.8) |
| Decreased penile temperature | 49 (74.2) |
| Decreased ejaculate volume | 47 (71.2) |
| Loss of scrotum fullness | 45 (68.2) |

(continued)
|                      | (CAG)9–19 repeats, short (n = 18) | (CAG)20–24 repeats, medium (n = 37) | (CAG)25–37 repeats, long (n = 11) | \( P \) value | Short vs medium | Long vs medium | Short vs long | \( P \) value | Short vs medium | Long vs medium | Short vs long |
|----------------------|-----------------------------------|-------------------------------------|-----------------------------------|----------------|----------------|----------------|---------------|----------------|----------------|----------------|---------------|
| Age (y)              | 34.5 (26.7–42.2)                  | 32.0 (26.5–37.5)                    | 31.0 (27.0–41.0)                  | .25            | .94            | .39            | 36.0 (30.7–38.7) | .18            | .25            | .95            |
| Age at starting Finasteride (y) | 29.7 (23.1–36.9)                  | 26.3 (21.9–30.6)                    | 24.4 (20.8–32.6)                  | .070           | .72            | .15            | 27.2 (25.6–32.9) | .24            | .31            | .58            |
| Duration of Finasteride use (d) | 180 (57–456)                      | 450 (168–2,115)                     | 620 (241–1,218)                   | .062           | .98            | .11            | 1,659 (105–2,671) | .20            | .70            | .29            |
| Discontinuation of Finasteride use (d) | 1,026 (536–2,286)                 | 1,073 (561–1,775)                   | 1,090 (617–2,128)                 | .80            | .100           | .96            | 561 (234–1,745)  | .23            | .54            | .088†         |
| BMI (kg/m²)          | 24.0 (22.1–26.7)                  | 23.7 (22.3–25.9)                    | 24.5 (22.7–26.9)                  | .51            | .39            | .79            | 25.8 (24.2–275)  | .29            | .85            | .37            |
| ASEX Total score     | 20.5 (17.7–24.0)                  | 21.0 (19.0–23.0)                    | 22.0 (20.0–23.0)                  | .86            | .45            | .65            | 23.0 (19.0–23.7) | .43            | .31            | .23            |
| Item 5, orgasm satisfaction | 3.5 (3.0–4.0)†                   | 4.0 (3.0–4.5)                       | 4.0 (4.0–5.0)                     | .25            | .21            | .040†         | 4.0 (3.0–5.0)  | .71            | .99            | .68            |
| AMS Total score      | 52.0 (47.5–54.7)                  | 52.5 (44.0–62.7)                    | 48.0 (42.0–64.0)                  | .84            | .96            | .89            | 52.0 (48.2–61.5) | .93            | .31            | .42            |
| Item 5, need for sleep and/or often feeling tired | 4.0 (2.0–4.0)                     | 3.0 (2.0–4.0)                       | 3.0 (3.0–4.0)                     | .18            | .52            | .50            | 2.5 (1.2–3.0)  | .30            | .25            | .39            |
| Item 9, physical exhaustion or lacking vitality | 3.5 (2.0–4.0)                     | 3.0 (2.2–4.0)                       | 3.0 (3.0–5.0)                     | .91            | .60            | .69            | 3.0 (3.0–4.0)  | .39            | .042†         | .41            |
| Item 11, depressive mood | 3.0 (2.0–3.2)                     | 4.0 (2.0–4.0)                       | 2.0 (3.0–3.0)                     | .27            | .32            | .60            | 2.5 (1.2–4.0)  | .31            | .036†         | .68            |
| Item 12, feeling that you have passed your peak | 3.5 (3.0–5.0)                     | 4.0 (3.0–4.7)                       | 3.0 (2.0–4.0)                     | .96            | .39            | .42            | 4.0 (3.0–4.0)  | .86            | .044†         | .106           |
| Item 17, decrease in sexual desire or libido | 5.0 (5.0–5.0)                     | 4.0 (4.0–5.0)                       | 5.0 (4.0–5.0)                     | .028           | .59            | .15            | 4.5 (4.0–5.0)  | .95            | .96            | 1.00           |

AMS = Aging Male Symptom Scale; ASEX = Arizona Sexual Experience Scale; BMI = body mass index.

*Continuous variables are reported as median (25th–75th percentile or interquartile range), and \( P \) values were evaluated by two-tailed Mann-Whitney U-test.

†Significant differences.

‡Nearly significant difference.
In this study, we examined for the first time in detail whether the specific symptoms experienced by men with PFS were related to the length of two trinucleotide repeats polymorphic sites located in the AR gene. The AR belongs to the superfamily of nuclear hormone receptors. Recent studies have evaluated sexual function recovery after testosterone replacement therapy in men with hypo- androgenic symptoms and patients with psychosomatic or psychiatric disorders but not in healthy control men older than 50 years. In our study, CAG and GGN polymorphisms were supposed to have a role in acute androgen deficiency, but not in healthy control men older than 50 years.

One study found a significant association of longer CAG repeats in the androgen receptor gene and age in men with prostatic symptoms. In the current study, we report the results of an analysis of the association of (CAG)n repeats with sexual symptoms in a group of men with PFS. In general, the results showed a significant association of longer (CAG)n repeats with higher symptom severity and more frequent complaints of sexual function disturbances.

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Table 4. Comparison of subgroups of patients with post-finasteride syndrome according to AR gene (GGN)n, short, medium, and long repeats*

|                      | GGN <23 repeats, short (n = 8) | GGN ≥23 repeats, medium (n = 44) | GGN ≥23 repeats, long (n = 14) | GGN short vs medium, OR (95% CI), P value | GGN long vs medium, OR (95% CI), P value | GGN short vs long, OR (95% CI), P value | GGN short vs medium + long, OR (95% CI), P value | GGN long vs medium + short, OR (95% CI), P value |
|----------------------|-------------------------------|----------------------------------|----------------------------------|------------------------------------------|------------------------------------------|------------------------------------------|-------------------------------------------------|-------------------------------------------------|
| Loss of scrotal sensitivity | 6 (75.0)                     | 30 (68.2)                        | 5 (35.7)                         | 1.40 (0.25–7.83), 1.00                   | 0.26 (0.07–0.92), 0.031†                  | 5.40 (0.78–37.5), 0.18                   | 1.97 (0.37–10.6), 0.70                           | 0.25 (0.07–0.85), 0.031†                          |
| Scrotal discomfort     | 2 (25.0)                      | 15 (34.1)                        | 0 (—)                            | 0.64 (0.12–3.59), 1.00                   | 0.012‡                                   | 0.12†                                    | 0.96 (0.17–5.26), 1.00                           | 0.014†                                           |
| Penile discomfort      | 3 (37.5)                      | 15 (34.1)                        | 1 (7.1)                           | 1.16 (0.24–5.53), 1.00                   | 0.15 (0.02–1.25), 0.08‡                  | 7.80 (0.65–93.8), 0.12                   | 1.57 (0.34–7.37), 0.68                           | 0.14 (0.02–1.20), 0.05†                          |
| Penile discomfort      | 3 (37.5)                      | 15 (34.1)                        | 1 (7.1)                           | 1.16 (0.24–5.53), 1.00                   | 0.15 (0.02–1.25), 0.08‡                  | 7.80 (0.65–93.8), 0.12                   | 1.57 (0.34–7.37), 0.68                           | 0.14 (0.02–1.20), 0.05†                          |
| Loss of pubic hair     | 5 (62.5)                      | 7 (15.9)                         | 3 (21.4)                          | 8.81 (1.70–45.6), 0.011†                | 1.44 (0.32–6.53), 0.69                   | 6.11 (0.90–41.1), 0.08§                   | 8.00 (1.64–39.0), 0.012§                          | 0.91 (0.22–3.80), 1.00                           |
| Loss of perceived perineal fullness | 8 (100)                     | 31 (70.5)                        | 8 (57.1)                          | 0.18†                                    | 0.56 (0.16–1.93), 0.51                   | 0.05‡,†,§                                  | 0.09†                                           | 0.44 (0.13–1.52), 0.20                           |
| Loss of muscle tone    | 7 (87.5)                      | 20 (45.5)                        | 7 (50.0)                          | 8.40 (0.95–74.1), 0.05†                 | 1.20 (0.36–4.00), 0.77                   | 7.00 (0.67–72.9), 0.17                   | 8.04 (0.93–69.5), 0.05§                          | 0.93 (0.28–3.01), 0.90                           |
| Increased skin dryness | 7 (87.5)                      | 11 (25.0)                        | 5 (35.7)                          | 21.0 (2.32–190), 0.001                   | 1.67 (0.46–6.05), 0.50                   | 12.6 (1.19–134), 0.03†                   | 18.4 (2.09–161), 0.002†                          | 1.05 (0.31–3.60), 1.00                           |
| Onset of symptoms after finasteride use | 1 (12.5)                     | 2 (4.5)                          | 4 (28.6)                          | 3.50 (0.27–44.7), 0.36                  | 8.40 (1.34–52.5), 0.026†                 | 0.42 (0.04–4.66), 0.62                   | 1.44 (0.15–14.1), 0.57                           | 6.40 (1.24–33.1), 0.034†                          |

OR = odds ratio.

*OR (95% CI) could not be determined because one group contained no subjects (0%) or all subjects (100%) for the specific variable.

†Significant values.

‡Nearly significant.

§Significant values.
found in Kennedy disease.\textsuperscript{20} In our patients with PFS, short (CAG)n repeats showed a greater decrease in sexual desire and libido (AMS item 17) than medium repeats, whereas long (CAG)n repeats were associated with worse orgasm satisfaction (ASEX item 5) than short repeats.

Furthermore, subjects with short (CAG)n repeats had scrotal discomfort and increased sperm density less frequently than those with medium or medium to long repeats. Curiously, involuntary muscle spasms were more frequent in the long (CAG)n than in the medium (OR = 6.3) and medium to short (CAG)<25 (OR = 5.5) subgroups.

In our study, body mass index did not differ according to (CAG)n subgroup. However, there were more subjects with PFS reporting increased weight after finasteride discontinuation in the long (CAG)n than in the medium (OR = 4.9) group. It is worth noting that Corona et al\textsuperscript{27} associated low testosterone with (CAG)22 repeats.\textsuperscript{37} The rationale of an U-pro

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decess to develop skin dryness after drug treatments. Our study found the highest androgen binding capacity in cytosol of fibroblasts and keratinocytes of human skin. One investigation on the in vivo concur with an in vitro study showing that ARs containing short and long (CAG)n stretches, respectively, displayed lower activity than the AR of median (CAG)22 repeats.\textsuperscript{35} The rationale of an U-profile is that AR is optimally functional with a medium length of the polyglutamine (and/or poly-glycine) stretch. Longer or shorter amino acid repeat stretches could modify optimal protein folding, leading to a suboptimal activity of the receptor protein.\textsuperscript{6,17,23,38,39} By extrapolation, this suggests that skin dryness after finasteride use might be due to decreased AR activity. Interestingly, a meta-analysis showed a non-linear association between AR CAG repeat length and risk of male subfertility.\textsuperscript{38}

In this study, subjects with PFS and long (GGN)\textgreater{}23 repeats had a better condition regarding physical exhaustion or lacking vitality, depressive mood, and the feeling of passing one’s peak than those with medium (GGN)23 repeats. In addition, subjects with PFS and long (GGN)>23 repeats less frequently had loss of scrotal sensitivity and scrotal discomfort but more frequently reported the onset of symptoms after finasteride discontinuation than those with medium (GGN)23 repeats.

Short (GGN)<23 carriers showed a better profile concerning need for sleep and/or often feeling tired than medium (GGN)23 carriers but were much more likely to report less pubic hair (OR = 8.8), loss of muscle tone (OR = 8.4), and increased skin dryness (OR = 21) than medium (GGN)23 carriers.

Overall, we found that the AR polymorphisms can affect several symptoms of PFS. To our knowledge, such specific associations have not been explored previously, which is the reason we cannot compare our results with those of other studies.

Our data showed that short and long (CAG)n and (GGN)n repeats correlate in an unpredictable way with several conditions related to male androgenicity; this could derive from the vast array of genes that are up- or down-modulated by the AR.\textsuperscript{16,40,41} The (CAG)n and (GGN)n polymorphisms also are likely to be in linkage disequilibrium with other polymorphic sites in the human genome, which in turn might determine the observed effects.\textsuperscript{40} In line with observations made by other investigators,\textsuperscript{39} the present findings suggest that the general belief associating long (CAG)n and (GGN)n repeats with a worse androgenic condition\textsuperscript{18} should be taken with caution.\textsuperscript{39} In general, investigations on the influence of AR polymorphisms on specific clinical features (ie, metabolic profile, bone density, and body composition) typically show very contradictory results.\textsuperscript{18,33} This could be due to the concomitant effect of AR-related genetic cofactors (apart from the two studied polymorphisms), which have not been fully explored thus far and which can exert an independent effect on clinical outcomes.\textsuperscript{10,44} It should be noted at this point that the dimension of complexity of the regulation and activities of nuclear receptors is being realized, and that tissue-specific effects and epigenetic changes occurring in a single individual can modulate the action of receptors.\textsuperscript{41,42} Therefore, many more investigations are needed to disclose the biological pathways relating molecular findings to phenotypes.\textsuperscript{41,43}

In our study, we decided to go beyond a simple categorization of (CAG)n and (GGN)n repeats as binary (ie, long or short), and we looked at three categories—short, medium, and long repeats—to obtain a better assessment of length variations relating to patients’ conditions. Indeed, U-profiles
have been observed in vitro, and a recent study reported that some markers of male reproductive function in fertile men show a curvilinear association with the CAG or GGN repeat length. To our knowledge, ours is the first clinical study showing that a U-profile for (CAG)n repeats is detectable for a specific human symptom (ie, increased skin dryness after finasteride use). However, it should be noted that for most of the examined symptoms, only one extreme of (CAG)n and/or (GGN)n repeats behaved differently from the medium length subgroup.

A limitation of this study is the limited number of subjects. Larger studies are warranted to substantiate the present finding in white and other ethnic groups. Larger investigations also could assess haplotypes comprising all the possible combinations of short, medium, and long (CAG)n plus short, medium, and long (GGN)n repeats. A general limitation of this study work is that some symptoms reported by patients with PFS could not be objectively determined. Furthermore, the retrospective design of our study did not allow a clinical assessment of these men before finasteride use. Future studies are necessary to assess the AR genetic profile and testosterone levels in subjects who developed PFS compared with subjects who did not develop adverse symptoms after using finasteride against AGA.

CONCLUSION

Causes and predisposing factors responsible for the development of long-term adverse side effects in young men who used low-dose finasteride against AGA remain an enigma. Several symptoms were in common in more than 70% of patients with PFS, but a plethora of other disturbances was reported by a minority of patients, with some clearly related and some not to androgenicity.

Our study showed that the length of two trinucleotide repeats in the AR gene contribute to the frequency of some specific symptoms reported by patients with PFS. The (CAG)n and (GGN)n polymorphisms were involved in two specific symptoms (ie, scrotal discomfort and increased skin dryness); for other symptoms, only one of the two polymorphisms was involved, which is likely a reflection of the complex modulation of AR activity. 

Our investigation using a precision medicine approach suggested genetic implications in symptoms of patients with PFS. Much more genetic and non-genetic research is necessary to elucidate the pathophysiological pathways leading to the onset and persistence of adverse effects in former finasteride users.

ACKNOWLEDGMENTS

We thank Giorgio Mazzon and Francesco La Marra for helping in subject recruitment. We are very grateful to Blase Billack (St John’s University, Queens, NY, USA) for critical revisions of this report, Francesca Migliozzi for reading the report, and to Elena De Mattia for technical support.

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Conflicts of Interest: None.

Funding: None.

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SUPPLEMENTARY DATA

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.esxm.2016.11.001.