PERSPECTIVE

Androgen receptor polyglutamine repeat number: models of selection and disease susceptibility

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Abstract

Variation in polyglutamine repeat number in the androgen receptor (AR CAGn) is negatively correlated with the transcription of androgen-responsive genes and is associated with susceptibility to an extensive list of human disease. Only a small portion of the heritability for many of these diseases is explained by conventional SNP-based genome-wide association studies, and the forces shaping AR CAGn among humans remains largely unexplored. Here, we propose evolutionary models for understanding selection at the AR CAG locus, namely balancing selection, sexual conßict, accumulation-selection, and antagonistic pleiotropy. We evaluate these models by examining AR CAGn-linked susceptibility to eight extensively studied diseases representing the diverse physiological roles of androgens, and consider the costs of these diseases by their frequency and Þtness effects. Five diseases could contribute to the distribution of AR CAGn observed among contemporary human populations. With support for disease susceptibilities associated with long and short AR CAGn, balancing selection provides a useful model for studying selection at this locus. Gender-speciÞc differences AR CAGn health effects also support this locus as a candidate for sexual conßict over repeat number. Accompanied by the accumulation of AR CAGn in humans, these models help explain the distribution of repeat number in contemporary human populations.

Introduction

An applied understanding of the evolutionary forces shaping human health and disease susceptibility has profound medical implications, providing clinical insights and suggesting novel, testable hypotheses (Di Rienzo 2006; Nesse 2011). Robust integration of evolutionary theory with human medicine must continue to address topics whose resolution eludes research in each Þeld independently. In particular, identifying the extent and regions of the human genome most directly subjects to balancing selection (Andrés et al. 2009), and mutation-selection balance (Keller and Miller 2006; Haerty and Golding 2010b), and explaining the Ômissing heritabilityÕ of complex diseases(Kel-

balance (Haerty and Golding 2010b), as well as mediating notable potential for rapid, adaptive evolution (Birge et al. 2010).

Two well-studied human tandem-repeat polymorphisms are situated within the X-linked androgen receptor (AR) gene, which codes for a transcription factor that mediates binding of the androgens testosterone (T) and dihydrotestosterone. Androgens play an integral role in the organizational and ontogenic processes involved in sexual differentiation and male-sexual development during embryogenesis (Swerdloff et al. 1992; Chang et al. 2002), although the AR remains widely expressed in a range of tissues in both male and female adults (Ruizeveld de Winter et al. 1991). Among other functions, AR-mediated gene transcription is integral to skeletal (Kenny and Raisz 2003), muscular (Dillon et al. 2010), and nerve cell (Arnold and Breedlove 1985; Hammond et al. 2001) development and maintenance, and in the regulation of cognition and behav-

purity of repeats already present at that locus (e.g. Fig. 2 in Buschiazzo and Gemmell 2006).

Finally, the nature and magnitude of phenotypic effects and disease susceptibilities putatively associated with AR CAGn should vary within an individualÕs lifetime, suggesting the potential for antagonistic pleiotropic effects in any or all of the above models of selection. Traits linked to AR CAGn which favor mating success and fertility early in life may be in conßict with disease-associated costs later on (e.g. Summers and Crespi 2008; Carter and Nguyen 2011); these costs be may appear exaggerated in contemporary societies owing to increases in modal life span (Gurven and Kaplan 2007).

To evaluate these four non-exclusive hypotheses for explaining the distribution and variability in AR CAGn within and among human populations, we review eight of the best-studied diseases from a range of phenotypic classes putatively associated with AR repeat length, evaluate the evidence for and against associations between repeat length and disease, and appraise the relative strength and direction of selection for each disease. We also consider the health costs accompanying longer or shorter extremes in repeat number, the potential for sexual conßict arising from sex differences in the costs of, and the possible effects of antagonistic pleiotropy on, AR CAGn-associated disease. We conclude by discussing the accumulation of AR CAG repeat number in the human lineage in the context of human evolution and human disease susceptibility, and the potential role of AR CAGn as a component of the missing heritability of diseases linked to circulating androgen levels.

Methods

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We obtained data on the role of AR CAGn in human health and disease, using three online databases and one comprehensive review (Rajender et al. 2007) to compile a list of phenotypes and diseases with published, putative associations with AR CAG repeat length (Table S1). Database sources were the following: the AR Mutations Database (Gottlieb et al. 2004; ARDB; http://androgendb.mcgill.ca/, accessed 28 May, 2011), the online mendelian inheritance in man (OMIM) database (MIM ID*

against susceptibility alleles associated with typically Ôlate-onsetÕ diseases is likely greater than previously believed, as a result of marked variability in age at onset and a number of factors other than direct selection (e.g. effects on survival and reproduction of kin; Pavard and Metcalf 2007). Additionally, extensive allelic variability and the potential for rapid and reversible changes in tandem-repeat purity and number (Kashi et al. 1997) make exaggerated selection in short timescales a distinct possibility at the AR CAGn locus. While the prevalence of a number of the diseases discussed (e.g. osteoporosis, cardiac diseases, some types of cancer) in past populations has been difficult to estimate, data emerging from paleoepidemiological studies support the presence of these diseases in human history, although contributing environmental factors in those populations may have differed (Zimmerman 1993; Mays 1998; Faltas 2010). Factors with the capacity to modulate the severity or progression of a disease, such as diet or lifestyle, may play an important role in disease-related costs and are described further in Table 1 and Table S1.

Results

D[illegible] AR CAG

Spinal bulbar muscular atrophy

Spinal bulbar muscular atrophy (SBMA) shows an unequivocal relationship with AR CAGn. Patients with SBMA invariably have longer repeat number than is observed in the general population, typically between 38 and 62 repeats (La Spada et al. 1991; Amato et al. 1993; Brooks and Fischbeck 1995). Symptoms include late-onset muscular weakness and atrophy, frequently accompanied by androgen insensitivity and hypogonadism (Dejager et al. 2002; Palazzolo et al. 2008), believed to be a result of AR protein aggregation resulting in apoptosis of affected cells (Grierson et al. 1999; Ellerby et al. 2002; Vismara et al. 2009). Women may act as carriers of higher repeat number, experiencing mild if any symptoms of the disease, and toxicity appears to remain low even among women homozygous for high numbers of repeats (Mariotti et al. 2000; Greenland et al. 2004; Katsuno et al. 2010). Disease onset is typically later in life (30–60 years of age), although longer AR CAGn is predictive of earlier disease onset, which is often preceded by less severe symptoms including muscle fatigue and cramping (Atsuta et al. 2006). Despite the relatively rare nature of this disease (roughly 1/40 000 men), repeat numbers in the SBMA range bear formidable negative health effects. Risk of aspiration pneumonia (the most common cause of death in SBMA patients; Katsuno et al. 2010), muscle degeneration, and loss of mobility would likely have been strongly selected against under most ancestral conditions. The rescuing effect of a second less toxic allele with shorter repeat number in women, accompanied by the reduction in symptoms in homozygotes, means that the costs of high repeat number associated with this disease differ for men and women, conditions which would contribute to sexual conflict over AR CAG repeat length. There are no known fitness benefits associated with repeat numbers in the SBMA range.

Male infertility

The essential role of androgens in male virility and spermatogenesis (Collins and Chang 2002), and the association between SBMA and infertility (e.g. Arbizu et al. 1983) have led to a number of investigations into the differences in AR sensitivity arising from variations in CAGn and idiopathic male infertility (e.g. Table 1 and references therein). Repeat number at the AR CAGn among infertile patients has been variously found to be longer (e.g. Tut et al. 1997; Dowsing et al. 1999; Lim et al. 2000; von Eckardstein et al. 2001; Davis-Dao et al. 2007; Nenonen et al. 2010), shorter (Komori et al. 1999; Nenonen et al. 2010), or not significantly different (e.g. Dadze et al. 2000; Meyts et al. 2002; Thangaraj et al. 2002; Yong et al. 2003) from those of controls, with ethnic or population level differences potentially confounding the results. A large-scale meta-analysis provides good support for a link between longer AR CAGn and infertility (Davis-Dao et al. 2007), but the average contribution of each additional repeat to infertility has not been empirically demonstrated. Still, the actual difference between patients and controls is likely to underestimate the effect of repeat number, given the fact that an unknown proportion of patients with repeat numbers in the shorter, ÔnormalÕ range will be infertile because of other unknown causes (Davis-Dao et al. 2007). A non-linear relationship between infertility and AR CAGn has also been proposed, such that men with longer or shorter AR CAGn than the median (22–23 repeats) are at a 20% increased risk of infertility (Nenonen et al. 2010). If this pattern is true, then stabilizing selection around intermediate repeat frequency could arise from male infertility alone. Given the relative commonness of male infertility (estimated to be approximately 7%; Meacham et al. 2007), and the age-independent and thus potentially profound effects of AR CAGn on male lifetime reproductive success and fitness, longer (and possibly shorter) AR CAGn should be under strong selection from infertility in men.

Breast cancer

Endogenous androgen steroid levels have been recognized as modulating factors associated with breast cancer (BC) (Adams 1998; Ferro et al. 2002; Kaaks et al. 2005), and between 60% and 70% of BCs express the AR as well as androgen-dependent proteins (e.g. PSA and GCDFP-15; Sáez-Chico et al. 2007). *In vitro* studies support a

Table 1. Susceptibility for eight diseases putatively associated with AR exon 1 polyglutamine repeat number (AR CAGn).

Disease putatively associated with AR CAG	Disease prevalence	Age of onset	Susceptible sex	Health effects	Risk factors	References
Longer						
Spinal bulbar muscular atrophy	Rare	Mid–late reproductive	Males	Survival and reproduction	Androgens levels, pneumonia	1–8
Infertility	Common	Early reproductive	Males	Reproduction	Ethnicity, SHBG, epigenetics	9–20
Breast cancer	Very common	Late reproductive	Predominantly females	Survival	Other genes, hormone therapy, family history, parity	21–39
Osteoporosis, decrease BMD	Very common	Late reproductive	Both sexes	Survival	Age, gender, SHBG	40–45
Shorter						
Prostate cancer	Very common	Mid-Late reproductive	Males	Survival and reproduction	Androgen levels, other genes	46–73
Cardiac diseases	Very common	Mid reproductive	Both sexes	Survival	Diet, lifestyle	74–80
Colorectal cancer	Common	Mid-late reproductive	Both sexes*	Survival	Diet, gender, other genes/hormones	81–84
Cognition and behaviour disorders	Common	Pre-reproductive	Males	Survival?	Age, gender, environment	85–93

AR, androgen receptor; BMD, bone mass density; SHBG, sex hormone-binding globulin.

Diseases grouped by proposed direction of association, and prevalence is based on data from contemporary American society. ≤ 0.001/100 people = rare, 0.01–0.1/100 = common, and ≥ 0.1/100 = very common. Age of onset of disease pertains to the age at which health effects most likely become evident relative to reproductive age. Effects of disease on health and the sex most susceptible are described, and possible risk factor are provided based on the references provided.

*Direction of association with colorectal cancer may differ for each sex, see text.

References: 1. Amato et al. (1993). 2. Kazemi-Esfarjani et al. (1995). 3. Mariotti et al. (2000). 4. Dejager et al. (2002). 5. Greenland et al. (2004). 6 Atsuta et al. (2006). 7. Katsuno et al. (2010). 8. La Spada et al. (1991). 9. Asatiani et al. (2003). 10. Tut et al. (1997). 11. Thangaraj et al. (2002). 12. Dowsing et al. (1999). 13. Davis-Dao et al. (2007). 14. Komori et al. (1999). 15. Lim et al. (2000). 16. von Eckardstein et al. (2001). 17. Meyts et al. (2002). 18. Yong et al. (2003). 19. Lazaros et al. (2008). 20. Verhoeven et al. (2010). 21. Comings et al. (2003). 22. Chico et al. (2007). 23. Elhaji et al. (2001). 24. Ferro et al. (2002). 25. Giguère et al. (2001). 26. Goode et al. (2002). 27. Haiman et al. (2002). 28. Haiman et al. (2003). 29. Hao et al. (2010). 30. Iobagiu et al. (2005). 31. Kaaks et al. (2005). 32. Lillie et al. (2004). 33. Maclean et al. (2004). 34. Lazo Otón and Diamandis (1998). 35. Rebbeck et al. (1999). 36. Spurdle et al. (2005). 37. Suter et al. (2003). 38. Wang et al. (2005). 39. Yu et al. (2000). 40. Gennari et al. (2007). 41. Guadalupe-Grau et al. (2010). 42. Langdahl et al. (2003). 43. Limer et al. (2009). 44. Tofteng et al. (2003). 45. Zitzmann et al. (2001a, b). 46. Coetzee and Ross (1994). 47. Monroe et al. (1995). 48. Tilley et al. (1996). 49. Giovannucci et al. (1997). 50. Stanford et al. (1997). 51. Pettaway (1999). 52. Beilin et al. (2001). 53. Kittles et al. (2001). 54. Latil et al. (2001). 55. Panz et al. (2001). 56. Shibata et al. (2001). 57. Azzouni et al. (2002). 58. Chang et al. (2002). 59. Mononen et al. (2002). 60. Schatzl et al. (2002). 61. dos Santos et al. (2003). 62. Buchanan et al. (2004). 63. Gilligan et al. (2004). 64. Giwercman et al. (2004). 65. Zeegers et al. (2004). 66. Alvarado et al. (2005). 67. Forrest et al. (2005). 68. Freedman et al. (2005). 69. Platz et al. (2005). 70. Andersson et al. (2006). 71. Summers and Crespi (2008). 72. Lindstrom et al. (2010). 73. Kumar et al. (2011). 74. Hersberger et al. (2005). 75. Pausova et al. (2010). 76. Zitzmann et al. (2001a). 77. Alevizaki et al. (2003). 78. Lind et al. (2008). 79. Page et al. (2006). 80. Rexrode et al. (2008). 81. Slattery et al. (2005). 82. Gillessen et al. (2010). 83. Ferro et al. (2000). 84. Di Fabio et al. (2009). 85. Cheng et al. (2006). 86. Rajender et al. (2008). 87. Jonsson et al. (2001). 88. Westberg et al. (2009). 89. Manuck et al. (2010). 90. Fondon et al. (2008). 91. Yaffe et al. (2003). 92. Seidman et al. (2001). 93. Colangelo et al. (2007).

protective effect of androgens on hormone-independent BC-cell lineage proliferation (Di Monaco et al. 1995; Gatto et al. 1996; Szelei et al. 1997), and low premenopausal androgen levels have been associated with susceptibility to this disease (Adams 1998; Wang et al. 2000). Longer AR CAGn has been correlated with BC risk (Giguère et al. 2001; Haiman et al. 2002; Liede et al. 2003; Suter et al. 2003; but see Hao et al. 2010), younger age at onset (Rebbeck et al. 1999) and tumor aggressiveness (Yu et al. 2000) and grade (Elhaji et al. 2001; Maclean et al. 2004). Because the effects of AR CAGn on BC risk interact with a number of other factors, including nutrition (Kaaks et al. 2005), hormone treatment (Suter et al. 2003; Lillie et al. 2004), polymorphisms at other loci (Rebbeck et al. 1999; Suter et al. 2003), family history (Rebbeck et al. 1999; Haiman et al. 2002), and ethnicity (with Caucasians showing the highest risk and the longest average repeat number; Altekruse et al. 2007), it is difficult to infer the magnitude of selection against longer AR CAGn resulting from BC. Still, the high prevalence (lifetime risk approximately 12%; Altekruse et al. 2007) and variance in age at onset of the disease (Pavard and Metcalf 2007), and the importance of

alloparental care from post-reproductive women suggest that the Þtness costs of susceptibility to BC in ancestral environments could have been signiÞcant and could have contributed to the distribution in AR CAGn repeat number we see in contemporary populations. Although a positive relationship between repeat number and the occurrence and grade of BC has also been observed in men (Maclean et al. 2004), selection owing to disease susceptibility in this sex is unlikely to contribute to AR CAGn owing to the very low occurrence of this disease in men (approximately 0.13%; Altekruse et al. 2007).

Osteoporosis and bone mass density

The general role of androgens in bone metabolism, loss of bone mass in cases of hypogonadism, and reduction in bone turnover with testosterone treatment all lead to predictions for a decrease in bone mass density (BMD) and increase in osteoporosis (femoral neck BMD <0.56 g/cm^2) with longer AR CAGn (Zitzmann et al. 2001b; Zitzmann 2009). A relationship between polyglutamine repeat lengths among premenopausal (but not postmenopausal) women with lower BMD has been shown (Yamada et al. 2004), as has a relationship between BMD and AR CAGn on the longer of the two alleles in women, with significantly longer AR CAGn among female patients compared to controls (Langdahl et al. 2003). In healthy men, AR CAGn is a negative predictor of BMD, and the effect of age on bone loss is greater in subjects with longer repeat length ($\geq$22 repeats) compared to those with shorter repeat lengths (14–21 repeats; Zitzmann et al. 2001b). Several studies have reported the opposite, however, Þnding both a negative (Limer et al. 2009) or both positive and negative relationship between BMD, bone mineral content (BMC), and AR

(Monroe et al. 1995). Shorter AR CAGn repeat number has been associated with disease risk (Irvine et al. 1995; Panz et al. 2001; Andersson et al. 2006; but see Forrest et al. 2005), age at onset/diagnosis (Beilin et al. 2001; Latil et al. 2001; dos Santos et al. 2003), and prostate cancer grade, stage, metastasis and fatality resulting from the disease (Giovannucci et al. 1997; Hakimi et al. 1997; Shibata et al. 2001). Shortening of AR CAGn is also commonly associated with PC progression (Alvarado et al. 2005), and the AR itself has become a key target for therapeutic research (Berger et al. 2011). Additionally, ethnic differences in AR CAGn (like BC and osteoporosis) mirror racial susceptibility to prostate cancer, with men of African origin displaying the shortest CAGn and the highest incidence of prostate cancer, with the opposite being true of Asians (Figure S1; Edwards et al. 1992; Coetzee and Ross 1994; Pettaway 1999; Kittles et al. 2001; Panz et al. 2001). A 2004 meta-analysis conÞrmed a signiÞcant difference between cases and controls, although the differences do appear to be modest (<1 repeat difference between patients and controls; Zeegers et al. 2004).

In contrast to the patterns described above, the largest study to examine prostate cancer and AR CAGn (Lindstrom et al. 2010) did not detect any relationship between these two traits, nor did several other large-scale studies multi-ethnic cohort study (Mononen et al. 2002; Freedman et al. 2005). One explanation for the difference between earlier and more recent studies has been diagnostic technologies for identifying prostate cancer in its early stages. The

Colon and rectal cancer

Androgens regulate growth and differentiation in colon and rectal tissue, and there is support for an association between low testosterone levels and colon cancer in laboratory animals (Xiao et al. 2007; Gu et al. 2009). Studies in animals suggest a protective role of androgens in colon tumorigenesis (Ferro et al. 2002), and prostate cancer patients undergoing long-term androgen deprivation therapy were at a greater risk of developing colorectal cancer (Gillessen et al. 2010). While longer AR CAGn corresponds to the risk of colon cancer in men, longer repeat length appears to be protective in women (Slattery et al. 2005). Women with long repeat number in another polymorphic gene, the β-estrogen receptor, in addition to long AR CAGn, also had a higher risk of disease than women with shorter repeat numbers for both alleles (Slattery et al. 2005). It is worth noting that African American men show

men (Colangelo et al. 2007). Collectively, these data suggest that short AR CAGn may contribute to the risk of depression, particularly when testosterone levels are low.

The data described above suggest that men with shorter AR CAGn are more generally intelligent, violent, and aggressive, and less inclined toward depression, but that this relationship may be largely dependant on circulating testosterone levels. The modulating effect of AR CAGn is particularly intriguing, given the reciprocal relationship between dominance and testosterone; testosterone levels not only affect, but are also affected by, dominant social behavior (Mazur and Booth 1998). As a result, the psychological responses to competitive or goal-directed behavior may be mediated by testosterone, but the psychological costs and beneÞts of high or low testosterone levels may be greater for men with short AR CAGn. Based on these data, it is also interesting to consider a role of sexual selection for cognitive and behavioral traits of testosterone, which

Compelling evidence for disease risk accompanying AR CAGn at both long and short AR CAGn implies that balancing selection is involved in CAGn number distributions in human populations. To address this hypothesis, the sum beneÞts, costs, and susceptibilities of long AR CAGn diseases

(Stearns et al. 2010) may open up new possibilities for studying the evolutionary and functional context of accumulations at the AR CAGn, and for resolving some of the disease-associated consequences of their expansion (Haerty and Golding 2010a).

These kinds of advances may also provide powerful insights into the role of the AR CAGn in the missing heritability of complex diseases and phenotypes modulated by androgens. Tandem repeats such as the AR CAGn may be more informative than SNPs at the individual level owing to their functional role and greater standing genetic variation in human populations, but have been largely neglected in GWA studies owing to the statistical power and high-throughput assays required to incorporate them (Ku et al. 2010). Yet Þner-scale analyses of the genetic architecture of the human genome, including tandem repeats like the AR CAGn, are becoming an increasingly important goal in the pursuit of missing heritability for complex phenotypes and disease (Eichler et al. 2010).

A more comprehensive picture of the heritability of human disease susceptibility must also account for interactions between genes and between genes and the environment (Eichler et al. 2010; Stearns et al. 2010). As an evolvable, dynamic, yet robust, interface between cellular responses and the physiological and ecological environment, the endocrine system and its receptors are ideally situated to mediate a wide range of disease susceptibilities and health-related effects. Incorporating tandem repeats, particularly those with known functional roles like those found in the AR CAGn, into the current GWA study framework may unveil genetic and environmental interactions confounding current efforts to explain disease risk and etiology (Hannan 2010; Ku et al. 2010). While understanding the mechanistic and functional consequences of polymorphisms in tandem-repeat number are vital, the evolutionary forces upon which that genetic and functional variation is superimposed are inextricable from phenotypic and disease-associated manifestations. Applied as a component of more comprehensive GWA study design or therapeutically in relation to conventional (e.g. androgen supplementation or ablation) or novel (e.g. targeting instable repeats) personalized disease treatments, tandem repeats like the AR CAGn hold great promise for the effective identiÞcation and treatment of disease. In each case, the costs and beneÞts of polymorphisms in tandem-repeat number variation are fundamentally embedded in their evolutionary legacies.

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Literature cited

Ackerman, C. M., L. P. Lowe, H. Lee, M. G. Hayes, A. R. Dyer, B. E. Metzger, W. L. Lowe et al. is-3 -1sFw-415.8(uesponses)-5-41413.58460.3(in)-23

Atsuta, N., H. Watanabe, M. Ito, H. Banno, K. Suzuki, M. Katsuno, F. Tanaka, A. Tamakoshi, and G. Sobue. 2006. Natural history of spinal and bulbar muscular atrophy (SBMA): a study of 223 Japanese patients. Brain 129:1446–1455.

Azzouzi, A., B. Cochand-Priollet, P. Mangin, G. Fournier, P. Berthon, A. Latil, and O. Cussenot. 2002. Impact of constitutional genetic variation in androgen/oestrogen-regulating genes on age-related changes in human prostate. European Journal of Endocrinology 147:479–484.

Beilin, J., L. Harewood, M. Frydenberg, H. Mameghan, R. F. Martyres, S. J. Farish, C. Yue, D. R. Deam, K. A. Byron, and J. D. Zajac. 2001. A case–control study of the androgen receptor gene CAG repeat polymorphism in Australian prostate carcinoma subjects. Cancer 92:941–949.

Berger, M. F., M. S. Lawrence, F. Demichelis, Y. Drier, K. Cibulskis, A. Y. Sivachenko, A. Sboner et al. 2011. The genomic complexity of primary human prostate cancer. Nature 470:214–220.

Birge, L., M. Pitts, R. Baker, and G. Wilkinson. 2010. Length polymorphism and head shape association among genes with polyglutamine repeats in the stalk-eyed fly, Teleopsis dalmanni. BMC Evolutionary Biology 10:227.

Brooks, B. P., and K. H. Fischbeck. 1995. Spinal and bulbar muscular atrophy: a trinucleotide-repeat expansion neurodegenerative disease. Trends in Neurosciences 18:459–461.

Buchanan, G., M. Yang, A. Cheong, J. M. Harris, R. A. Irvine, P. F. Lambert, N. L. Moore et al. 2004. Structural and functional consequences of glutamine tract variation in the androgen receptor. Human Molecular Genetics 13:1677–1692.

Buschiazzo, E., and N. J. Gemmell. 2006. The rise, fall and renaissance of microsatellites in eukaryotic genomes. BioEssays 28:1040–1050.

Carter, A. J. R., and A. Q. Nguyen. 2011. Antagonistic pleiotropy as a widespread mechanism for the maintenance of polymorphic disease alleles. BMC Medical Genetics 12:160.

Castel, A. L., J. D. Cleary, and C. E. Pearson. 2010. Repeat instability as the basis for human diseases and as a potential target for therapy. Nature Reviews Molecular Cell Biology 11:165–170.

Chang, C. 2002. Androgens and androgen receptor: mechanisms, functions, and clinical applications. 1st edn. Kluwer Academic Publishers, Boston.

Chang, J. A., H. T. Nguyen, and T. F. Lue. 2002. Androgens in penile development, penile erection, and erectile dysfunction. In C. Chang, ed. Androgens and Androgen Receptor: Mechanisms, Functions, and Clinical Applications, 1st edn. pp. 283–298. Kluwer Academic Publishers, Boston, MA.

Cheng, D., C.-J. Hong, D.-L. Liao, and S.-J. Tsai. 2006. Association study of androgen receptor CAG repeat polymorphism and male violent criminal activity. Psychoneuroendocrinology 31:548–552.

Cherrier, M. M., and S. C. Craft. 2003. Androgens and cognition. In C. J.

nM., and S. D. 2011.Assoagaden and
28–:965
Hons ,M. 018 0 TDKempp(mauyen,)6251.Z(T.)-251.Zhoull, and E. 196006..

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C. 018 0 TD4(A.)-246.Kemppft(mauyen,)5049.7(and)-253.8(E.)-251.9(M.)-253.Wilarson. 19(298.)-253.Evolu(ation)-8.2(o-)]TJ 1.0353 -1.384 TD |
of Maiftatioy–393 0 TD4731

and number of androgen receptor CAG Repeats in normal men. Journal of Clinical Endocrinology and Metabolism 86:2585–2590.
Edwards, A., H. A. Hammond, L. Jin, C. T. Caskey, and R. Chakraborty. 1992. Genetic variation at Þve trimeric and tetrameric tandem repeat loci in four human population groups. Genomics 12:241–253.
Eichler, E. E., J. Flint, G. Gibson, A. Kong, S. M. Leal, J. H. Moore, and J. H. Nadeau. 2010. Missing heritability and strategies for Þnding the

androgen receptor CAG repeat polymorphism and risk of breast cancer in the NursesÕ Health Study. Cancer Research 62:1045–1049.

Haiman, C. A., S. E. Hankinson, I. D. Vivo, C. Guillemette, N. Ishibe, D. J. Hunter, and C. Byrne. 2003. Polymorphisms in steroid hormone pathway genes and mammographic density. Breast Cancer Research and Treatment 77:27–36.

Hakimi, J. M., M. P. Schoenberg, R. H. Rondinelli, S. Piantadosi, and E. R. Barrack. 1997. Androgen receptor variants with short glutamine or glycine repeats may identify unique subpopulations of men with prostate cancer. Clinical Cancer Research 3:1599–1608.

Hammock, E. A. D., and L. J. Young. 2005. Microsatellite instability generates diversity in brain and sociobehavioral traits. Science 308:1630–1634.

Hammond, J., Q. Le, C. Goodyer, M. Gelfand, M. TriÞro, and A. LeBlanc. 2001. Testosterone-mediated neuroprotection through the androgen receptor in human primary neurons. Journal of Neurochemistry 77:1319–1326.

Langdahl, B. L., L. Stenkjaer, M. Carstens, C. L. Tofteng, and E. F. Eriksen. 2003. A CAG repeat polymorphism in the androgen receptor gene is associated with reduced bone mass and increased risk of osteoporotic fractures. Calcified Tissue International 73:237–243.

Lascorz, J., A. Forsti, B. Chen, S. Buch, V. Steinke, N. Rahner, E. Holinski-Feder et al. 2010. Genome-wide association study for colorectal

Panz, V. R., B. I. Joffe, I. Spitz, T. Lindenberg, A. Farkas, and M. Haffejee. 2001. Tandem CAG repeats of the androgen receptor gene and prostate cancer risk in black and white men. Endocrine 15:213–216.

Pausova, Z., M. Abrahamowicz, A. Mahboubi, C. Syme, G. T. Leonard, M. Perron, L. Richer, S. Veillette, D. Gaudet, and T. Paus. 2010. Functional variation in the androgen-receptor gene is associated with visceral adiposity and blood pressure in male adolescents. Hypertension 55:706–714.

Pavard, S., and C. J. E. Metcalf. 2007. Negative selection on BRCA1 susceptibility alleles sheds light on the population genetics of late-onset diseases and aging theory. PLoS ONE 2:e1206.

Pearson, C. E., K. N. Edamura, and J. D. Cleary. 2005. Repeat instability: mechanisms of dynamic mutations. Nature Reviews Genetics 6:729–742.

Perrin, J. S., P.-Y. Herve, G. Leonard, M. Perron, G. B. Pike, A. Pitiot, L. Richer, S. Veillette, Z. Pausova, and T. Paus. 2008. Growth of white matter in the adolescent brain: role of testosterone Veillette,andDTf iln,55Thinthancie.35oS ONE

Suter, N. M., K. E. Malone, J. R. Daling, D. R. Doody, and E. A. Ostrander. 2003. Androgen receptor (CAG)n and (GGC)n polymorphisms and breast cancer risk in a population-based case-control study of young women. Cancer Epidemiology Biomarkers & Prevention 12:127–135.

Swerdloff, R. S., C. Wang, M. Hines, and R. Gorski. 1992. Effect of androgens on the brain and other organs during development and aging. Psychoneuroendocrinology 17:375–383.

Szelei, J., J. Jimenez, A. M. Soto, M. F. Luizzi, and C. Sonnenschein. 1997. Androgen-induced inhibition of proliferation in human breast cancer MCF7 cells transfected with androgen receptor. Endocrinology 138:1406–1412.

Thangaraj, K., M. B. Joshi, A. G. Reddy, N. J. Gupta, B. Chakravarty, and L. Singh. 2002. CAG repeat expansion in the androgen receptor gene is not associated with male infertility in Indian populations. Journal of Andrology 23:815–818.

Tilley, W. D., G. Buchanan, T. E. Hickey, and J. M. Bentel. 1996. Mutations in the androgen receptor gene are associated with progression of human prostate cancer to androgen independence. Clinical Cancer Research 2:277–285.

Tofteng, C. L., A. Kindmark, H. Brandstrom, B. Abrahamsen, S. Petersen, F. Stiger, L. S. Stilgren et al. 2003. Polymorphisms in the CYP19 and AR genes? relation to bone mass and longitudinal bone changes in postmenopausal women with or without hormone replacement therapy: the danish osteoporosis prevention study. Calcified Tissue International 72:276–