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Ethnic Variation in Allele Distribution of the Androgen Receptor (AR) (CAG)_n Repeat

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Abstract

The androgen receptor (AR) is important in reproductive organ development, as well as tissue homeostasis of the pancreas, liver, and skeletal muscle in adulthood. The trinucleotide (CAG)_n repeat polymorphism in exon 1 of the AR gene is thought to regulate AR activity, with longer alleles conferring reduced receptor activity. Therefore, the evaluation of the allelic distribution of the AR (CAG)_n repeat in various ethnic groups is crucial in understanding the interindividual variability in AR activity. We evaluated ethnic variation of this AR polymorphism by genotyping individuals from the multiethnic Hyperglycemia and Adverse Pregnancy Outcome study cohort. We genotyped 4421 Caucasian mothers and 3365 offspring of European ancestry; 1494 Thai mothers and 1742 offspring; 1119 Afro-Caribbean mothers and 1142 offspring; and 780 Hispanic mothers and 770 offspring of Mexican ancestry from Bellflower, California. The distributions of (CAG)_n alleles among all 4 ethnic groups are significantly different ($P < .0001$). Pairwise tests confirmed significant differences between each pair of ethnicities tested ($P < 10^{-28}$). The relative AR (CAG)_n repeat length in the different groups was as follows: Afro-Caribbean (shortest repeat lengths and greatest predicted AR activity) < Caucasian < Hispanic < Thai (longest repeat length and lowest predicted AR activity). Significant interethnic differences in the allele frequencies of the AR exon 1 (CAG)_n polymorphism exist. Our results suggest that there may be potential ethnic differences in androgenic pathway activity and androgen sensitivity.

Keywords

Polyglutamine repeat; X-linked; polymorphism; HAPO; pregnancy

The human androgen receptor (AR) gene is located on chromosome Xq11.2–q12 and codes for a protein with 3 major functional domains: the N-terminal transactivation domain, the DNA-binding domain, and the androgen-binding domain. The protein functions as a steroid hormone-activated transcription factor, which signals through classical and nonclassical signaling pathways (Katzenellenbogen and Katzenellenbogen, 1996; Rahman and Christian,

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2007). AR is expressed in many tissues during development and adulthood, influencing an enormous range of physiologic processes including organ and tissue growth and differentiation, cognition, muscle hypertrophy, bone density, and insulin levels (Gelman, 2002).

The *AR* gene contains a highly polymorphic (CAG)_n repeat in exon 1 encoding a glutamine tract in the N-terminal transactivation domain of the protein, which becomes active only after AR binds to its ligand (Palazzolo et al, 2008). The polyglutamine tract length is inversely correlated to the transcriptional competence of the receptor, with longer tracts being associated with lower levels of AR-mediated transcription in both normal and disease states (Beilin et al, 2000; Buchanan et al, 2004; Harada et al, 2010).

Expansion of the *AR* (CAG)_n beyond the normal range (>38 repeats) causes spinal and bulbar muscular atrophy (SBMA), also known as Kennedy disease, which is an X-linked recessive form of spinal muscular atrophy. The expansion of *AR* (CAG) repeat has been implicated in SBMA either through loss of normal AR function, which induces neuronal degeneration, or through the pathogenic AR, which acquires a toxic property, thereby damaging motor neurons (Katsuno et al, 2006). Interestingly, some populations of affected individuals display a variety of endocrinologic symptoms including gynecomastia, infertility, androgen insensitivity, and increased incidence of type 2 diabetes (Mariotti et al, 2000), which would indicate a global disruption of AR function.

AR (CAG)_n repeats within the normal range (10–36 repeats) are associated with numerous endocrine cancers, male and female infertility, and many other neurological and endocrine conditions (Palazzolo et al, 2008; Wu et al, 2008; Chatterjee et al, 2009; Ludwig et al, 2009; Shaik et al, 2009). There is a continuous relationship between *AR* (CAG)_n repeat length and metabolic traits in Caucasian men, where repeat number correlates negatively with AR sensitivity and positively with body fat, insulin levels, and leptin in healthy and diabetic men (Zitzmann et al, 2003). Additionally, testosterone and luteinizing hormone levels are higher in diabetic men with >24 repeats, reflecting reduced negative feedback through a less sensitive receptor (Stanworth et al, 2008). In women with polycystic ovary syndrome, a disorder diagnosed by hyperandrogenism, association between testosterone and insulin resistance may be modified by the (CAG)_n repeat polymorphism (Mohlig et al, 2006). Therefore, ethnic differences in allele distributions of this marker could have far-reaching impact on diverse conditions in men and women.

Here we report the allelic distribution of the (CAG)_n polymorphism in Caucasian, Afro-Caribbean, Hispanic, and Thai populations from the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) cohort. To examine this, we genotyped 14 833 mothers and neonates of these 4 ethnicities and tested for differences in allele distributions of the *AR* (CAG)_n repeat.

Materials and Methods

Participants

The HAPO study is a multiethnic, multicenter observational epidemiologic study assembled to investigate the associations of maternal glycemia with adverse pregnancy outcomes. HAPO study protocols were in compliance with the Helsinki Declaration and were approved by the institutional review boards at all centers. Written informed consent was obtained from all participants (HAPO Study Cooperative Research Group et al, 2008). The present study included Caucasian individuals of European ancestry from centers in the United Kingdom (Manchester and Belfast), Australia (Brisbane and Newcastle), and North America (Toronto); Thai individuals from Bangkok; Afro-Caribbean individuals from Barbados; and Hispanic individuals of Mexican ancestry. All Hispanic participants were enrolled at 1 field

center in Bellflower, California, and self-identified as white Hispanic. The Afro-Caribbean population represents Caribbeans of African origin, and all Afro-Caribbean participants were collected at 1 center in Barbados and self-identified as black. Other studies have shown that Barbadians of African descent have 89.8% West African ancestry and 10.2% European ancestry (Benn-Torres et al, 2008).

Genotyping

DNA was extracted from blood at the Northwestern Center for Genetic Medicine Genomics Core (Chicago, Illinois). DNA samples and 3 Centre d'Etude du Polymorphisme Humain (CEPH) control DNA samples were organized randomly in each quadrant of 384-well microtiter plates. The *AR* (CAG)_n repeat was amplified as previously described (Ackerman et al, 2010) with primers (forward [5'-NED-GTGC GCGAAGTGATCCAGAA-3'] and reverse [5'-TAGCCTGTGGGGCCTCTACG-3']). Polymerase chain reaction products were separated on the Applied Biosystems 3130XL capillary DNA sequence analysis system and genotypes were assigned using GENEMAPPER software v.4.0 (Applied Biosystems, Foster City, California). Visual examination of each chromatogram confirmed the genotype assignment.

Statistical Analysis

Pearson's χ^2 and Monte Carlo tests were performed on maternal genotypes to test for differences in allele distribution between ethnicities, with $P < .05$ considered statistically significant. χ^2 tests were performed on alleles with an expected count of greater than = in all populations. Monte Carlo tests were performed using all alleles in each population, with 10^8 iterations and 99.9% accuracy. The above statistical tests were performed using SPSS (version 17.0; SPSS Inc, Chicago, Illinois). Hardy-Weinberg equilibrium (HWE) tests were performed from each ethnicity on maternal genotypes with frequencies $>.05$ using the Genepop software package (Rousset and Raymond, 1995; Rousset, 2008).

Results

Characteristics of the HAPO Study participants and outcomes have been previously reported (HAPO Study Cooperative Research Group et al, 2008; HAPO Study Cooperative Research Group, 2009). The Caucasian population (4421 mothers, 3365 neonates) represented the largest group in this study, and the Hispanics (780 mothers, 770 neonates) were the smallest group. The numbers of samples and chromosomes genotyped for each center and ethnicity are given in Table 1. The ethnic distribution was 52.5% Caucasian, 21.8% Asian, 15.2% Afro-Caribbean, and 10.5% Hispanic.

Genotyping

The CEPH control samples genotyped with an 89.5% success rate and a plate-to-plate concordance of 99.5%. Two percent of the HAPO participant samples were selected randomly and regenotyped without knowledge of previously assigned genotypes. Among these, 99.9% concordance was observed. We obtained *AR* (CAG)_n genotypes for 90.6% of the samples. *AR* allele designations represent the number of repeats; for example, allele 6 (A06) has 6 CAG repeats. We identified 34 alleles at the *AR* (CAG)_n locus: A06 and A08–A40. The frequency of each allele varied widely across populations, and distribution of the alleles by ethnic group for mothers and neonates combined is presented in the Figure. The range of alleles differed among ethnicities, with the Thais and Caucasians having the largest range (6–40 repeats, 32 alleles total) and the Afro-Caribbeans having the smallest range (9–37 repeats, 24 alleles total). The Caucasians, our largest group (7786 individuals, 13 822 chromosomes), had the highest number of rare alleles (frequency $<.01$, $n = 18$), and the Afro-Caribbeans, our second smallest group (2261 individuals, 3933 chromosomes), had

the fewest rare alleles ($n = 6$). A20 through A23 were common to all ethnicities (frequency $>.05$). The most common CAG repeats were A18 in Afro-Caribbeans (.17), A21 in Caucasians (.19), A23 in Hispanics (.15), and A22 in Thais (.21). The mean CAG repeat lengths were Afro-Caribbean 19.6 ± 3.2 , Caucasian 21.9 ± 2.9 , Hispanic 22.6 ± 3.1 , and Thai 23.1 ± 3.3 . These results are slightly different than those published by Edwards et al (1992), and are likely due to differences in sample size, stringency of ethnic classification, and location of participant recruitment.

Statistical Analysis

Because the maternal and fetal genotypes are not independent (eg, neonates inherit 1 of the mother's alleles), all statistical tests were performed on maternal genotype only. The numbers of chromosomes and their corresponding frequencies for each allele used in the maternal χ^2 tests are presented in Table 2. All 4 ethnic populations were in HWE. Because of the large number of rare alleles in each ethnicity and the presence of population-specific alleles, we performed a Pearson's χ^2 test on all ethnicities together using only alleles A13–30, which revealed significant differences in allele distributions between the 4 ethnic groups ($P < .0001$; Table 3). These differences were confirmed using the Monte Carlo test on all alleles present in each population ($P < .001$). Separate χ^2 analyses were also performed for pairwise comparisons of ethnicities, for example, Caucasian vs Hispanic, for all 6 pairwise comparisons. For these tests we maximized the alleles used for each pair, because a slightly different subset of alleles qualified for the pairwise χ^2 analyses. These analyses confirmed that there are highly significant differences between each pair of ethnicities tested ($P < 10^{-28}$), even after adjusting for multiple testing (Table 3).

Discussion

We genotyped over 14 800 individuals (26 065 chromosomes) at the *AR* (CAG)_n locus in 4 ethnic groups from the HAPO cohort. This is the first study to document *AR* (CAG)_n allele frequencies in 4 populations of this magnitude.

Interethnic differences in the distribution of genetic polymorphisms and how these affect human susceptibility to various disorders, including the development of type 2 diabetes, have been documented (Chambers et al, 2009; Tan et al, 2010). In multiethnic studies on SBMA, the number of *AR* (CAG)_n repeats seen in affected individuals typically ranges from 35 to 57 repeats, but differs by ethnicity (Lund et al, 2001). Differences in the *AR* (CAG)_n allelic distribution, which are expected to result in population-based differences in androgen sensitivity, may be due to either natural selection of alleles by environmental factors or fixation of allele frequency through founder effects.

In this study, Caucasians had the highest number of rare alleles and Afro-Caribbeans had the fewest. This is likely because of different sample sizes for each population as well as the fact that the Afro-Caribbean group is an island population and may thus have a smaller effective population size. Interestingly, within our Caucasian, Hispanic, and Thai populations, there are a very small number ($<0.25\%$) of individuals with repeat lengths that fall within the disease range for SBMA (< 35 repeats). After sequencing individuals to confirm actual number of repeats, we had 19 mothers (9 Thai, 3 Hispanic, 7 Caucasian), 9 female neonates (3 Thai, 3 Hispanic, 3 Caucasian), and 1 male Caucasian neonate with 35–40 repeats. In addition, there are a number ($<2\%$) of individuals in each ethnicity with very short (< 12) repeats ($n = 28–61$). These very short repeats have been observed to contribute to phenotypes indicative of *AR* malfunction, indicating that repeat lengths on either side of the normal range are associated with impaired receptor function (McPhaul et al, 1991). This has been further corroborated by cell culture studies that have revealed a critical range (16–29 CAG repeats) for maintenance of the protein's stability and function (Buchanan et al, 2004).

Age of onset of puberty for both males and females varies by ethnicity (NHANES, 1997). These ethnic differences may be explained by differences in hormone levels or in hormone action in target tissues or potentially by the ethnic variation in the *AR* described here. Furthermore, these ethnic differences in *AR* (CAG)_n may also contribute to interindividual variation in terms of disease risk, disease severity, and drug response. Given the association between *AR* activity and (CAG)_n repeat length, our study suggests that an individual's response to androgen and androgenic therapies might vary based on *AR* (CAG)_n genotypes.

In conclusion, we have shown that there are significant ethnic differences in allele distribution of the *AR* (CAG)_n polymorphism. This finding provides insight into ethnic differences in normal reproductive processes, as well as predicting risk and severity for a number of diseases. Our study provides an important starting point for better understanding the molecular basis underlying ethnic differences in androgen sensitivity and underscores the importance of using large multiethnic cohorts to examine genetic variation at known disease loci.

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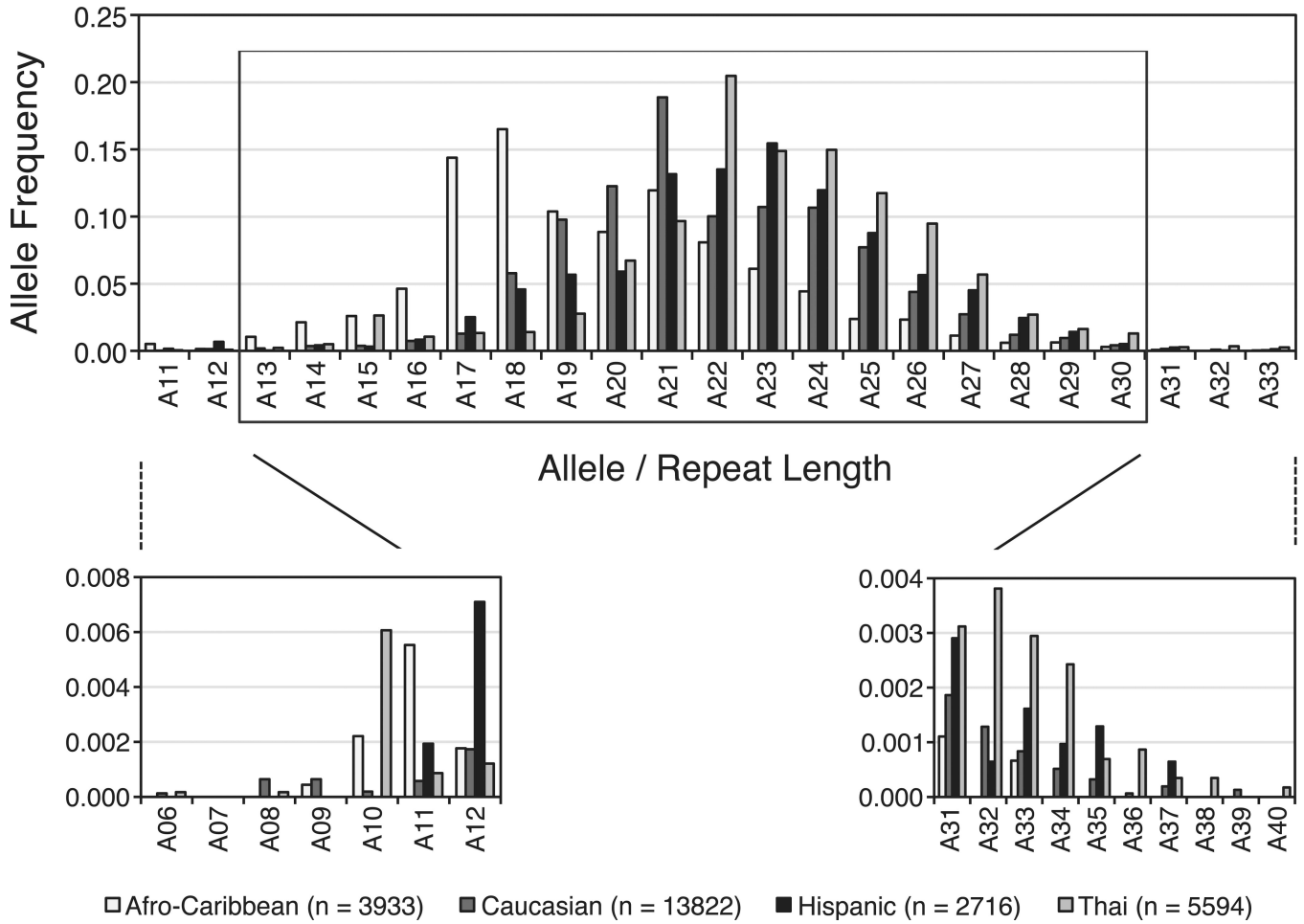


Figure.
 Distribution of $AR(CAG)_n$ alleles by ethnic group in the Hyperglycemia and Adverse Pregnancy Outcome study. Top panel: only alleles with a frequency $>.001$ are shown. The alleles within the inner box are the alleles used for the χ^2 analysis for all ethnicities. Lower left panel: individuals in each ethnicity with the lowest number of CAG repeats. Lower right panel: individuals in each ethnicity with the highest number of CAG repeats. White bars indicate Afro-Caribbean participants; dark gray, Caucasians; black, Hispanics; light gray, Thais. n = number of chromosomes.

Table 1
Maternal and neonate DNA samples by ethnicity successfully genotyped at the *AR* (CAG)_n locus

Center	Ethnicity	Mothers			Neonates			Total	
		No. Samples	No. Chromosomes	No. Samples	No. Chromosomes ^a	No. Samples	No. Chromosomes		
Belfast	Caucasian (United Kingdom)	1331	2662	1045	1537	2376	4199		
Manchester	Caucasian (United Kingdom)	982	1964	548	805	1530	2769		
Brisbane	Caucasian (Australia)	963	1926	703	1043	1666	2969		
Newcastle	Caucasian (Australia)	491	982	418	618	909	1600		
Toronto	Caucasian (North America)	654	1308	651	977	1305	2285		
	Total Caucasian	4421	8842	3365	4980	7786	13 822		
Bangkok	Thai	1494	2988	1742	2606	3236	5594		
Barbados	Afro-Caribbean	1119	2238	1142	1695	2261	3933		
Bellflower	Hispanic (North America)	780	1560	770	1156	1550	2716		
	Total	7814	15 628	7019	10 437	14833	26 065		

^aNeonate chromosome numbers are not 2n because this marker is on the X chromosome and approximately 50% of the neonates were male.

Table 2
 Number of chromosomes and their corresponding frequencies for each allele used in the maternal ² analyses^a

Allele	Caucasian			Afro-Caribbean			Thai			Hispanic		
	No. Chromosomes	Frequency	No. Chromosomes	Frequency	No. Chromosomes	Frequency	No. Chromosomes	Frequency	No. Chromosomes	Frequency	No. Chromosomes	Frequency
A13	23	.003	23	.010	4	.001	1	.001				
A14	37	.004	49	.022	15	.005	7	.004				
A15	36	.004	61	.027	65	.022	6	.004				
A16	72	.008	103	.046	29	.010	13	.008				
A17	114	.013	319	.143	34	.011	38	.024				
A18	520	.059	376	.168	33	.011	73	.047				
A19	882	.100	236	.105	80	.027	87	.056				
A20	1115	.126	193	.086	168	.056	90	.058				
A21	1631	.184	290	.130	271	.091	210	.135				
A22	904	.102	173	.077	544	.182	205	.131				
A23	965	.109	133	.059	402	.134	251	.161				
A24	950	.107	93	.042	396	.132	190	.122				
A25	663	.075	55	.025	335	.112	135	.087				
A26	390	.044	52	.023	260	.087	89	.057				
A27	226	.026	27	.012	139	.046	74	.047				
A28	110	.012	16	.007	72	.024	37	.024				
A29	88	.010	9	.004	43	.014	23	.015				
A30	40	.005	4	.002	36	.012	7	.004				
A31	15	.002	2	.001	12	.004	5	.003				
A32	11	.001	0	.000	10	.003	1	.001				

^aFrequency 5 No. chromosomes for each allele for a particular ethnic group/total No. chromosomes for that ethnic group.

Table 3

Results of the Pearson χ^2 analyses testing for differences in maternal allele distribution between ethnicities^a

Populations	Alleles Tested	No. Chromosomes Tested	df	χ^2 Value	P Value
All four ethnicities	A13-30	15 496	51	3215.9	<.0001 ^b
Afro-Caribbean vs Caucasian	A13-30	11 006	17	1716.7	<.0001 ^b
Afro-Caribbean vs Hispanic	A14-29	3756	15	750.0	<.0001 ^b
Afro-Caribbean vs Thai	A13-31	5162	18	1621.3	<.0001 ^b
Caucasian vs Hispanic	A14-30	10 334	16	203.1	1.86 × 10 ⁻³⁴
Caucasian vs Thai	A13-32	11 740	19	904.5	1.26 × 10 ⁻¹⁷⁹
Hispanic vs Thai	A14-29	4490	15	170.0	2.39 × 10 ⁻²⁸

^a Analyses were performed on maternal genotypes only.

^b Indicates P values beyond those generated by SPSS. The actual results returned are P = .000.