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RESEARCH NOTE

Intraethnic variation in steroid-5-alpha-reductase polymorphisms in prostate cancer patients: a potential factor implicated in 5-alpha-reductase inhibitor treatment

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Introduction

Steroid-5-alpha-reductase inhibitors are commonly used in the treatment of benign prostatic enlargement and male alopecia with controversial results. Ethnic diversity is an important factor, accounting for interindividual variation in drug responsiveness. The aim of this study was to evaluate the genotypic distribution of 22 SNPs in steroid-5-alpha-reductase alpha polypeptides 1 and 2 in a set of 601 prostate cancer patients from four different Spanish regions. The genotyping was done in a Biotrove OpenArray NT Cycler. Twelve SNPs of 22 analysed were differentially distributed among the different regions. Since all subjects were Caucasian of Spanish origin, this result showed differences in genotype distribution among subject from the same ethnic origin. These observations were confirmed in cluster analysis, principal component analysis and in the differential distribution of haplotypes among the populations. Differences in distribution of genotypes within different populations of the same ethnicity could be an important factor responsible for the wide variety of pharmacological responses to steroid-5-alpha-reductaseinhibitors.

Prostate cancer (PCa) is a hormone-dependent tumour which needs androgens for disease initiation and progression

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(Huggins 1967). Although, testosterone (T) is the most abundant serum androgen, dihydrotestosterone (DHT) is the main prostate androgen. T is converted to DHT by the enzyme steroid-5-alpha-reductase (SRD5A) in the prostate, testes, hair follicles and adrenal glands (McConnell 1995). Since the discovery of the implications of SRD5A2 deficiency, it has been an increasing interest in the development of steroid-5-alpha-reductase inhibitors (5α-RI). Among several compounds, only two drugs have been FDA approved for clinical use: finasteride, which inhibits SRD5A2 and was approved for the treatment of benign prostatic enlargement (BPE) and male alopecia; and dutasteride, which inhibits SRD5A1 and SRD5A2 (approved for the treatment of BPE) (Edwards and Moore 2002; Andriole and Kirby 2003). Nowadays, dutasteride and finasteride do not prevent CaP, but merely temporarily shrink tumours that have a low potential for being lethal (Walsh 2010).

The enzymatic activity of SRD5A is highly modulated by single-nucleotide polymorphisms (SNPs) located in these genes (Giwercman *et al.* 2005; Cussenot *et al.* 2007). These genetic variations in key genes belonging to the androgen pathway seem to be important for the prostate response to androgens (Lindstrom *et al.* 2006). We have recently reported that differences in the distribution of genotypes within different populations of the same ethnicity could be an important confounding factor in association studies (Henriquez-Hernandez *et al.* 2013a).

We designed a study aimed to evaluate the genotypic distribution of 22 SNPs in SRD5A1 and SRD5A2 in a set of Spanish prostate cancer patients, to determine the homogeneity of the population and to disclose potential bias associated with the failure of 5α-RI when prescribed.

Materials and methods

A total of 601 patients with nonmetastatic localized prostate cancer were included in this study. Geographical distribution of patients was as follows (Henriquez-Hernandez *et al*. 2013a): 91 (15.14%) from Andalusia, 51 (8.48%) from Basque Country, 238 (39.60%) from Canary and 221 (36.77%) from Catalonia. All patients were of Spanish origin and all of them received written informed consent before sample collection. Ethnicity of patients was established until the second parental generation. This study was approved by the Research and Ethics Committee of each institution participant in the study.

DNA was isolated from 300 μL of whole-blood in an iPrep™ purification instrument using the iPrep™ PureLink™ gDNA Blood kit (Invitrogen, Life Technologies, Carlsbad, USA). DNA integrity was determined by NanoDrop ND-1000 (NanoDrop Technologies, Wilmington, USA).

SNPs were selected using data of individuals with European ancestry (CEU) from the HapMap Project (available at: http://www.hapmap.org). Pairwise linkage disequilibrium (LD) tagging was achieved with Haploview ver. 4.2 software (free downloaded from http://www.broadinstitute.org/scientific-community/science/programs/medical-and-population-genetics/haploview/haploview) (Barrett *et al.* 2005). The R^2 given by Haploview was >0.95 for all genes. Description of SNPs is provided in table 1 in electronic supplementary material at http://www.ias.ac.in/jgenet/.

The SNP genotyping was performed in a Biotrove OpenArray® NT Cycler (Applied Biosystems, Foster City, USA) following the instructions of manufacturer (Henriquez-Hernandez *et al.* 2013b). The fluorescence results were read using the OpenArray® SNP genotyping analysis software ver. 1.0.5 (Applied Biosystems). The genotyping analysis was performed using TaqMan Genotyper software ver. 1.0.1 (available at: http://www.invitrogen.com/site/us/en/home/Global/forms/taqman-genotyper-software-download-reg.html) using autocalling as the call method. The quality value of the data points was determined by a threshold above 0.95. Genotyping analysis was done for each population separately and it was done automatically without any manual assignment of genotypes as previously reported (Henriquez-Hernandez *et al.* 2013a). All the genotyped samples met the quality criteria and all samples were genotyped with the same batch of material and at the same time.

Genotype and allelic frequencies were determined using the web-based environment SNPator (SNP Analysis To Results, from the Spain's National Genotyping Center and the National Institute for Bioinformatics) (Morcillo-Suarez *et al.* 2008).

Principal component analysis (PCA) was done using SnpMatrix and XSnpMatrix classes and methods (Clayton 2012), implemented as an R package and available from Bioconductor (as of ver. 2.11; http://bioconductor.org). Nonsupervised hierarchical clustering of SNP in each population was done using MultiExperiment Viewer ver. 4.9 (available at: http://www.tigr.org).

Results

A total of 601 PCa patients were genotyped for 22 SNPs; 10 SNPs located in *SRD5A1* gene and 12 SNPs located in *SRD5A2* gene. Of the 13,222 possible determinations, 94.31% were successfully genotyped.

The genotypic and allelic frequencies are shown in table 1. The genotype distribution was different among the study populations in 12 of the 22 SNPs: rs166050, rs501999, rs518673, rs3822430, rs8192120, rs39848 (SRD5A1); and rs2208532, rs12470143, rs2281546, rs3754838, rs523349, rs9332975 (SRD5A2) (χ^2 test, table 1), showing a differential distribution of genotypes among populations.

A nonsupervised hierarchical cluster was performed to visualize the genotype distributions among the four populations. For SRD5A1, polymorphisms were distributed into three main clusters, each one with different numbers and identities of SNPs, suggesting heterogeneity among populations (figure 1 in electronic supplementary material, left panel). For *SRD5A2*, SNPs were distributed into two main clusters, very similar for Basque, Canary and Catalan populations,

Table 1. Genotype and allelic frequencies of *SRD5A1* and *SRD5A2* gene polymorphisms among the populations.

	Call rate	Genotype			Allele		Functional consequence	MAF
SRD5A1								
rs166050		AA	AG	GG	A	G	Intron variation	0.12
Andalusia	0.75	0.65	0.21	0.14	0.75	0.25		
Basque Country	0.98	0.52	0.42	0.06	0.73	0.27		
Canary	0.99	0.62	0.33	0.05	0.79	0.21		
Catalonia	0.94	0.57	0.37	0.06	0.76	0.24		
P value				0.025				
rs501999		CC	CT	TT	C	T	Intron variation	0.49
Andalusia	0.70	0.48	0.20	0.32	0.59	0.41		
Basque Country	1.00	0.29	0.49	0.22	0.54	0.46		
Canary	0.99	0.29	0.49	0.22	0.53	0.47		
Catalonia	0.98	0.30	0.43	0.27	0.51	0.49		
P value				0.003				
rs518673		AA	AG	GG	A	G	Intron variation	0.32
Andalusia	0.75	0.19	0.19	0.62	0.29	0.71		
Basque Country	1.00	0.16	0.37	0.47	0.34	0.66		
Canary	0.96	0.07	0.42	0.51	0.28	0.72		
Catalonia	0.96	0.10	0.40	0.50	0.30	0.70		
P value				0.006				
rs3822430		AA	AG	GG	A	G	Synonymous codon	0.30
Andalusia	0.77	0.37	0.24	0.39	0.49	0.51		
Basque Country	1.00	0.27	0.61	0.12	0.58	0.42		
Canary	0.97	0.33	0.51	0.16	0.58	0.42		
Catalonia	0.97	0.37	0.47	0.16	0.60	0.40		
P value				<0.001				
rs500182		GG	GT	TT	G	T	Intron variation	0.20
Andalusia	0.81	0.01	0.14	0.85	0.08	0.92		
Basque Country	1.00	0.02	0.18	0.80	0.11	0.89		
Canary	0.98	0.01	0.17	0.82	0.09	0.91		
Catalonia	0.99	0.01	0.18	0.81	0.10	0.90		
P value				0.961				
rs8192120		AA	AC	CC	A	C	Intron variation	0.43
Andalusia	0.80	0.14	0.22	0.64	0.25	0.75		
Basque Country	0.99	0.08	0.42	0.50	0.29	0.71		
Canary	0.97	0.10	0.42	0.48	0.31	0.69		
Catalonia	0.98	0.10	0.48	0.42	0.34	0.66		
P value				0.015				
rs4702378		CC	CT	TT	C	T	Intron variation	0.24
Andalusia	0.82	0.07	0.23	0.70	0.18	0.82		
Basque Country	1.00	0.06	0.20	0.74	0.16	0.84		
Canary	0.99	0.04	0.33	0.63	0.21	0.79		
Catalonia	0.99	0.06	0.33	0.61	0.23	0.77		
P value				0.304				
rs1691053		AA	AG	GG	A	G	NA	0.15
Andalusia	0.87	0.90	0.09	0.01	0.95	0.05		
Basque Country	1.00	0.90	0.08	0.02	0.94	0.06		
Canary	0.98	0.86	0.13	0.01	0.93	0.07		
Catalonia	0.99	0.85	0.15	0.00	0.93	0.07		
P value				0.341				
rs39848		CC	CT	TT	C	T	Downstream variant	0.43
Andalusia	0.70	0.32	0.22	0.46	0.43	0.57		
Basque Country	0.96	0.22	0.43	0.35	0.44	0.56		
Canary	0.97	0.11	0.50	0.39	0.36	0.64		
Catalonia	0.94	0.16	0.45	0.39	0.39	0.61		
P value				<0.001				
rs3797179		AA	AG	GG	A	G	Intron variation	0.12
Andalusia	0.70	0.00	0.17	0.83	0.09	0.91		
Basque Country	0.96	0.00	0.29	0.71	0.14	0.86		
Canary	0.99	0.05	0.25	0.70	0.17	0.83		
Catalonia	0.96	0.03	0.26	0.71	0.17	0.83		
P value				0.213				

Table 1 (*contd*)

	Call rate	Genotype			Allele		Functional consequence	MAF
SRD5A2								
rs2208532		AA	AG	GG	A	G	Intron variation	0.44
Andalusia	0.70	0.45	0.28	0.27	0.59	0.41		
Basque Country	0.99	0.20	0.42	0.38	0.41	0.59		
Canary	0.99	0.34	0.46	0.20	0.57	0.43		
Catalonia	0.92	0.28	0.54	0.18	0.55	0.45		
P value				0.001				
rs12470143		CC	CT	TT	C	T	Intron variation	0.37
Andalusia	0.81	0.45	0.24	0.31	0.57	0.43		
Basque Country	1.00	0.26	0.53	0.21	0.52	0.48		
Canary	0.99	0.32	0.51	0.17	0.57	0.43		
Catalonia	0.98	0.29	0.54	0.17	0.56	0.44		
P value				0.001				
rs2281546		GG	GT	TT	G	T	Intron variation	0.17
Andalusia	0.83	0.09	0.07	0.85	0.12	0.88		
Basque Country	1.00	0.00	0.27	0.73	0.14	0.86		
Canary	0.99	0.03	0.22	0.75	0.14	0.86		
Catalonia	0.99	0.02	0.25	0.73	0.14	0.86		
P value				0.001				
rs3754838		CC	CT	TT	C	T	NA	0.12
Andalusia	0.78	0.10	0.11	0.79	0.16	0.84		
Basque Country	1.00	0.00	0.23	0.77	0.12	0.88		
Canary	0.96	0.03	0.20	0.77	0.12	0.88		
Catalonia	0.98	0.02	0.20	0.78	0.12	0.88		
P value				0.010				
rs4952222		AA	AC	CC	A	C	Intron variation	0.04
Andalusia	0.85	0.00	0.01	0.99	0.01	0.99		
Basque Country	1.00	0.00	0.00	1.00	0.00	1.00		
Canary	0.99	0.00	0.00	1.00	0.00	1.00		
Catalonia	0.97	0.00	0.00	1.00	0.00	1.00		
P value				0.086				
rs7562326		CC	CT	TT	C	T	Intron variation	0.14
Andalusia	0.80	0.05	0.12	0.83	0.12	0.88		
Basque Country	1.00	0.00	0.23	0.77	0.12	0.88		
Canary	0.98	0.03	0.20	0.77	0.13	0.87		
Catalonia	0.97	0.02	0.21	0.77	0.12	0.88		
P value				0.321				
rs2300702		CC	CG	GG	C	G	Intron variation	0.45
Andalusia	0.81	0.28	0.34	0.38	0.45	0.55		
Basque Country	0.96	0.12	0.49	0.39	0.37	0.63		
Canary	0.99	0.21	0.47	0.32	0.44	0.56		
Catalonia	0.94	0.16	0.50	0.34	0.41	0.59		
P value				0.127				
rs4952197		AA	AG	GG	A	G	Intron variation	0.25
Andalusia	0.80	0.12	0.19	0.69	0.22	0.78		
Basque Country	0.99	0.04	0.28	0.68	0.18	0.82		
Canary	0.99	0.06	0.31	0.63	0.22	0.78		
Catalonia	0.97	0.06	0.36	0.58	0.24	0.76		
P value				0.117				
rs676033		CC	CT	TT	C	T	NA	0.35
Andalusia	0.81	0.57	0.31	0.12	0.72	0.28		
Basque Country	0.99	0.60	0.32	0.08	0.76	0.24		
Canary	0.99	0.50	0.39	0.11	0.70	0.30		
Catalonia	0.98	0.50	0.43	0.07	0.71	0.29		
P value				0.402				
rs523349		CC	CG	GG	C	G	Missense	0.35
Andalusia	0.78	0.55	0.27	0.18	0.68	0.32		
Basque Country	0.92	0.64	0.32	0.04	0.80	0.20		
Canary	0.71	0.18	0.52	0.30	0.45	0.55		
Catalonia	0.89	0.52	0.40	0.08	0.72	0.28		
P value				<0.001				

Table 1 (*contd*)

	Call rate	Genotype			Allele		Functional consequence	MAF
rs9332975		CC	CT	TT	C	T	utr variant	0.14
Andalusia	0.77	0.10	0.07	0.83	0.14	0.86		
Basque Country	1.00	0.00	0.26	0.74	0.13	0.87		
Canary	0.99	0.03	0.19	0.78	0.13	0.87		
Catalonia	0.98	0.02	0.20	0.78	0.12	0.88		
P value				0.002				
rs7594951		CC	CT	TT	C	T	Intron variation	0.11
Andalusia	0.75	0.84	0.10	0.06	0.89	0.11		
Basque Country	1.00	0.76	0.24	0.00	0.88	0.12		
Canary	0.99	0.77	0.20	0.03	0.88	0.12		
Catalonia	0.98	0.78	0.20	0.02	0.88	0.12		
P value				0.193				

MAF, minor allele frequency; NA, not available. Functional consequence and MAF are available at: http://www.ncbi.nlm.nih.gov/projects/SNP/. Differences in the genotype distribution were assessed by χ^2 test.

but clearly different from Andalusian population (figure 1 in electronic supplementary material, right panel). PCA was performed to identify global differences among populations. Components 1, 2 and 3 were responsible for the 43.7%, 22.6% and 15.3% of the variance for *SRD5A1*, respectively (cumulative percentage: 81.6%); and 48.8%, 33.2% and 9.1% of the variance for *SRD5A2* gene, respectively (cumulative percentage: 91.1%). The first component distinguished between the populations for both genes clearly showed the differences in the distribution of genotypes between the analysed populations (figure 1).

Haplotype analysis was performed in SNPator. For *SRD5A1* (chromosome 5), the haplotype GCCTATGGCA was only present among the Andalusian subjects. For *SRD5A2* (chromosome 2), there is a greater homogeneity in the distribution of haplotypes. The fact that the most frequent haplotypes were equal in all populations suggests a similarity between individuals of the same ethnicity.

Discussion

We have recently reported differences in the distribution of genotypes within different populations of the same ethnicity (Henriquez-Hernandez *et al.* 2013a), highlighting the importance of ethnic-specific differences in drug responsiveness (Yasuda *et al*. 2008; Ma and Lu 2011). In the present paper, we observed that genotype distribution of 12 of 22 SNPs were statistically different among the studied populations. The Spanish population is considered as Caucasian. However, the natural history of each subpopulation is different, and there is a high complexity in the Mediterranean migration processes that impact in the different population sources on the genetic composition of the Spanish population (Ambrosio *et al.* 2010). While Andalusian population seems to be originated by migrations from Arabian Peninsula, Fertile Crescent, Balkan region and North Africa (Ambrosio *et al.* 2010), Canary population has been influenced from Northwest Africa migration and European colonization (Rando *et al.* 1999). Differences among populations were also evident in haplotype analysis, suggesting that each gene need to be considered individually to find possible confounding variables that would be crucial for the interpretation of results. Neither ethnicity nor genetic endowment of patients is taken into account in clinical trials.

5α-RI arisen as a promise treatment for PCa prevention, as specific blocker of the enzyme responsible for the synthesis of DHT. We suggest here that SNPs located in *SRD5A1* and *SRD5A2* may be relevant factors to be considered when assessing the response to these drugs. Although, both genes encode for key enzymes in the conversion of testosterone into DHT and represent attractive targets for preventing prostate cancer development, they are expressed differentially in the prostate tissue. Thus, under normal physiologic conditions, SRD5A2 is preferentially expressed over SRD5A1 in the prostate (Thomas *et al.* 2005; Titus *et al.* 2005). In prostate cancer cells, however, the balance in expression of these genes shift toward predominant expression of SRD5A1 (Titus *et al.* 2005; Stanbrough *et al.* 2006), supporting a role for both enzymes in DHT bioavailability and carcinogenesis. However, the importance of androgens in early cancer initiation is emphasized by the fact that finasteride, a 5-AR type 2 inhibitor, and dutasteride, a dual 5-AR inhibitor targeting both 5-AR type 1 and type 2 enzymes, have been shown that the risk of prostate cancer incidence reduce by almost 23% (Thompson *et al.* 2003; Andriole *et al.* 2010). Since SRD5A1 and SRD5A2 are differentially expressed and are blockaded by different drugs, the role of SNPs in each gene should be studied intensely taking these biological peculiarities in to account. However, the fact that rs523349—a SNP clearly involved in the success of chemoprevention of CaP using 5-alpha-reductase inhibitors (Cussenot *et al.* 2007)—appeared differentially distributed in our study, reinforce our findings.

The present study has some limitations that should be noted. First, to blind the analysis, no clinical data of patients were available, i.e., there are no data about TNM staging, tumour grade, biochemical failure, or Gleason Score. Second, the study was focussed on SRD5A1 and SRD5A2,

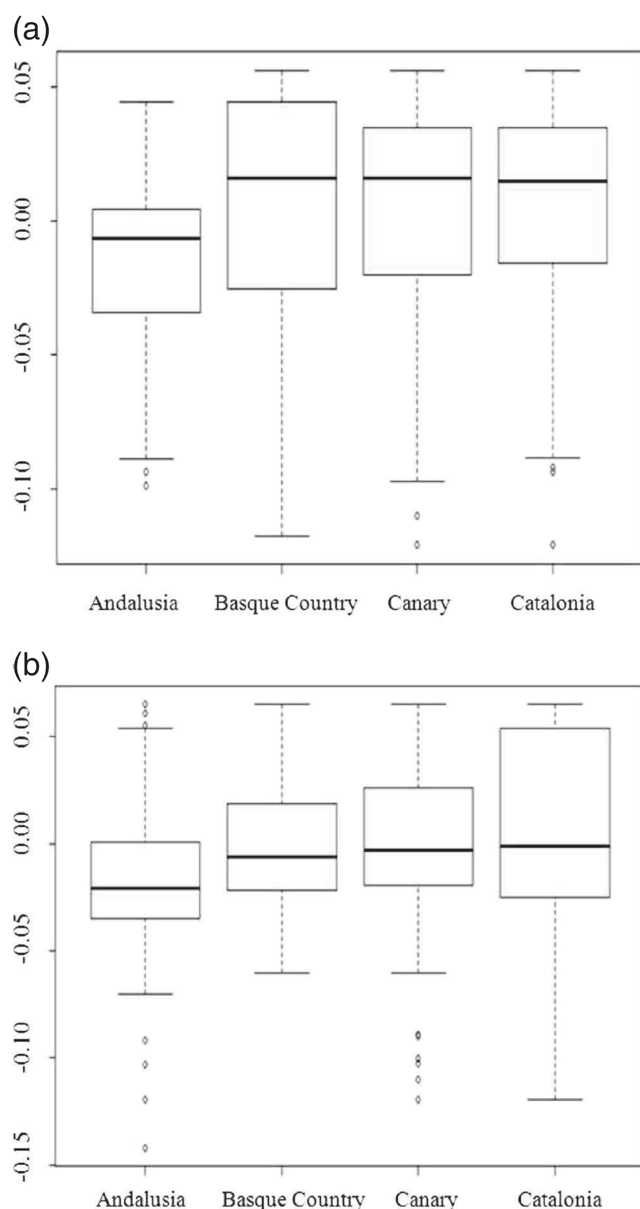

Figure 1. Box plot of component 1 among the different populations after PCA for (a) SRD5A1 and (b) SRD5A2.

ignoring possible associations with other genes and polymorphisms. Thus, the prostate cancer risk and aggressiveness conferred by certain SNPs located in 3 beta-hydroxysteroid dehydrogenase type II (HSD3B2) seem to be modified by SNPs located in SRD5A2 (Neslund-Dudas *et al.* 2007). In the same way, an association between SNPs in CYP17A1 (a gene encoding a key enzyme in the synthesis of androgens) and SRD5A2 has been suggested (Onen *et al.* 2007). Third, the number of subjects from different population varies widely. However, the fact that the main differences were not found in the population with the smallest number of patients (Basque Country, with 51 PCa) suggests that this limitation may not be decisive in the interpretation of results.

On the other hand, some advantages should be highlighted: (i) it includes a number of subjects sufficient to have reliable data on the distribution of these 22 SNPs in the PCa populations studied (especially for Canary and Catalonia); (ii) all subjects were male (which is the most interesting population since the 5α-RI are contraindicated in women), then avoiding the possible bias generated by the gender; and (iii) all the determinations (13,222 in total) were performed with the same methodology, with the same batch of chips and by the same investigator, thus minimizing biases from technical origin. All the analyses were automated and there was no manual assignment of genotypes in any case.

Conclusions

Differences in distribution of genotypes in SRD5A1 and SRD5A2 within different populations of the same ethnicity could be an important factor responsible for the failure of treatments based on 5α-RI. Our results suggest that genotypic endowment should be taken into account (especially in clinical trials including people from different ethnics) in assessing the effectiveness of these drugs.

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