ELSEVIER

CrossMark

Urologic Oncology: Seminars and Original Investigations 33 (2015) 331.e1–331.e7

UROLOGIC ONCOLOGY

Original article

Genetic variations in genes involved in testosterone metabolism are associated with prostate cancer progression: A Spanish multicenter study

Luis Alberto Henríquez-Hernández, Ph.D.[a,b,c,*], Almudena Valenciano, B.D.[b], Palmira Foro-Arnalot, Ph.D., M.D.[d], María Jesús Álvarez-Cubero, Ph.D.[e,f], José Manuel Cozar, Ph.D., M.D.[g], José Francisco Suárez-Novo, M.D.[h], Manel Castells-Esteve, M.D.[h], Pablo Fernández-Gonzalo, M.D.[i], Belén De-Paula-Carranza, M.D.[i], Montse Ferrer, Ph.D., M.D.[j], Ferrán Guedea, Ph.D., M.D.[k], Gemma Sancho-Pardo, Ph.D., M.D.[l], Jordi Craven-Bartle, Ph.D., M.D.[l], María José Ortiz-Gordillo, Ph.D., M.D.[m], Patricia Cabrera-Roldán, Ph.D., M.D.[m], Juan Ignacio Rodríguez-Melcón, M.D.[a,b], Estefanía Herrera-Ramos, B.D.[n,o], Carlos Rodríguez-Gallego, Ph.D.[n], Pedro C. Lara, Ph.D., M.D.[a,b,c]

[a] *Radiation Oncology Department, Hospital Universitario de Gran Canaria Dr. Negrín, Las Palmas, Spain*
[b] *Instituto Canario de Investigación del Cáncer, Las Palmas, Spain*
[c] *Clinical Sciences Department, Universidad de Las Palmas de Gran Canaria, Las Palmas, Spain*
[d] *Institud d'Oncologia Radioteràpica, Hospital de la Esperanza, Parc de Salut Mar, Barcelona, Spain*
[e] *Laboratory of Genetic Identification, Legal Medicine and Toxicology Department, Facultad de Medicina, Universidad de Granada, Granada, Spain*
[f] *GENYO, Pfizer-University of Granada-Andalusian Government Centre for Genomics and Oncological Research, Granada, Spain*
[g] *Department of Urology, Hospital Universitario Virgen de las Nieves, Granada, Spain*
[h] *Department of Urology, Hospital Universitari de Bellvitge, L'Hospitalet de Llobregat, Spain*
[i] *Radiation Oncology Department, Onkologikoa, Guipuzcoa, Spain*
[j] *Health Services Research Group, Institut de Recerca Hospital del Mar (IMIM), Barcelona, Spain*
[k] *Department of Radiation Oncology, Institut Català d'Oncologia (ICO), L'Hospitalet de Llobregat, Spain*
[l] *Radiation Oncology Department, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain*
[m] *Radiation Oncology Department, Hospital Universitario Virgen del Rocío, Sevilla, Spain*
[n] *Department of Immunology, Hospital Universitario de Gran Canaria Dr. Negrín, Las Palmas, Spain*
[o] *Department of Medical and Surgical Sciences, Universidad de Las Palmas de Gran Canaria, Las Palmas, Spain*

Received 25 February 2015; received in revised form 20 March 2015; accepted 8 April 2015

Abstract

Background: Prostate cancer (PCa) is an androgen-dependent disease. Nonetheless, the role of single nucleotide polymorphisms (SNPs) in genes encoding androgen metabolism remains an unexplored area.

Purpose: To investigate the role of germline variations in cytochrome P450 17A1 (*CYP17A1*) and steroid-5α-reductase, α-polypeptides 1 and 2 (*SRD5A1* and *SRD5A2*) genes in PCa.

Patients and methods: In total, 494 consecutive Spanish patients diagnosed with nonmetastatic localized PCa were included in this multicenter study and were genotyped for 32 SNPs in *SRD5A1, SRD5A2,* and *CYP17A1* genes using a Biotrove OpenArray NT Cycler. Clinical data were available. Genotypic and allelic frequencies, as well as haplotype analyses, were determined using the web-based environment SNPator. All additional statistical analyses comparing clinical data and SNPs were performed using PASW Statistics 15.

This work was subsidized by Grants from the Instituto de Salud Carlos III, Madrid, Spain (Ministerio de Economía y Competitividad, Spain), ID: PI12/01867 and PI13/00412; and Instituto Canario de Investigación del Cáncer, Canary Islands, Spain (ID: ICIC-GR-F-14/11). Almudena Valenciano received a Grant from the Instituto Canario de Investigación del Cáncer (ICIC).

* Corresponding author. Tel.: +34-92-845-0927; fax: +34-92-844-9805.
E-mail address: luis.henriquez@ulpgc.es (L.A. Henríquez-Hernández).

http://dx.doi.org/10.1016/j.urolonc.2015.04.003

Results: The call rate obtained (determined as the percentage of successful determinations) was 97.3% of detection. A total of 2 SNPs in *SRD5A1*—rs3822430 and rs1691053—were associated with prostate-specific antigen level at diagnosis. Moreover, G carriers for both SNPs were at higher risk of presenting initial prostate-specific antigen levels >20 ng/ml (Exp(B) = 2.812, 95% CI: 1.397–5.657, P = 0.004) than those who are AA-AA carriers. Haplotype analyses showed that patients with PCa nonhomozygous for the haplotype GCTTGTAGTA were at an elevated risk of presenting bigger clinical tumor size (Exp(B) = 3.823, 95% CI: 1.280–11.416, P = 0.016), and higher Gleason score (Exp(B) = 2.808, 95% CI: 1.134–6.953, P = 0.026).

Conclusions: SNPs in *SRD5A1* seem to affect the clinical characteristics of Spanish patients with PCa.

Keywords: SNP; *SRD5A1*; *SRD5A2*; *CYP17A1*; Prostate cancer; OpenArray

1. Introduction

Prostate cancer (PCa) is an androgen-dependent disease [1]. The synthesis of testosterone is mediated by the enzyme 17-hydroxylase/17,20-lyase, encoded by *CYP17A1* gene. Dihydrotestosterone (DHT) is considered the active metabolite of testosterone. Testosterone is converted into DHT through the 5α-reductase pathway, thus conditioning tumor availability of the hormone and subsequent tumor development and progression [2].

Single nucleotide polymorphisms (SNPs) are simple genetic variations in the DNA sequence, which modify the efficacy of encoded enzymes [3]. Genetic alterations in the testosterone metabolism pathway are expected to alter hormonal homeostasis and likely influence PCa development and progression.

The association between *CYP17A1* gene polymorphisms and PCa is controversial [4–6]. Although it has been suggested that some polymorphisms in *CYP17A1* are associated with PCa risk [7] and survival [8], it is not clear how SNPs in this gene affect clinical variables of PCa such as tumor size, prostate-specific antigen (PSA) levels, or Gleason score. In any case, *CYP17A1* is considered an important factor for PCa progression and has become a new therapeutic target. Thus, abiraterone acetate is a new drug very active in the treatment of certain PCa through specific *CYP17A1* blockade [9], although the role of SNPs in *CYP17A1* in response to abiraterone acetate has not been explored.

The 5α-reductase enzymes are encoded by the steroid-5α-reductase, α-polypeptide 1 (*SRD5A1*) and steroid-5α-reductase, α-polypeptide 2 (*SRD5A2*) genes. The role of *SRD5A1* and *SRD5A2* polymorphisms in PCa has been little studied, although it has been shown positive associations of several *SRD5A1* and *SRD5A2* variations as independent predictors of PCa outcome in terms of biochemical recurrence [10]. Anyhow, *SRD5A1/A2* are also therapeutic targets, and the specific blockade of these enzymes with dutasteride or finasteride has shown to decrease the production of DHT using 5α-reductase inhibitors, thus, decreasing the incidence of clinically localized PCa [11,12].

At a clinical level, tumor size, Gleason score, and pretreatment serum level of PSA are the most important prognostic factors [13]. Nonetheless, although these are key factors that affect the outcome, the heterogeneity in clinical behavior requires the expansion of knowledge about the disease [14].

As the presence of genetic variations in the androgen biosynthesis and metabolism genes may alter hormone bioavailability, we hypothesized here that certain polymorphisms in the testosterone synthesis pathway may be important to define the biological characteristics of the disease, possibly influencing the classic prognostic factors of PCa. For the first time, we conducted a study to explore the association between germline variations in *SRD5A1/2* and *CYP17A1* and PCa progression in a cohort of Spanish white patients with PCa.

2. Materials and methods

2.1. Patients

A total of 601 patients with nonmetastatic localized PCa were initially included in the study. The patients were recruited from 4 different regions of Spain, as has been previously published [15]. As genotypic and allelic frequencies vary among subjects from these regions, and Andalusian patients showed the greatest differences [15,16], we excluded these subset of patients from further analyses to avoid bias. Patients who were initially operated were also excluded to form a homogenous group of patients with PCa. Thus, 494 subjects were included in the present study. All patients were of Spanish origin and provided written informed consent before blood sample collection. The study was approved by the Research and Ethics Committee of each institution that participated in the study: Hospital Universitario de Gran Canaria Dr. Negrín (Las Palmas de Gran Canaria), Hospital de la Esperanza. Parc de Salut Mar (Barcelona), Hospital Universitari de Bellvite (L'Hospitalet de Llobregat), Onkologikoa (Guipuzcoa), Institut Català d'Oncologia (L'Hospitalet de Llobregat), and Hospital de la Santa Creu i Sant Pau (Barcelona).

Clinical tumor size (cT), initial PSA value, and Gleason score were analyzed for all PCa. cT was assessed by digital rectal examination, followed by transrectal ultrasonography and magnetic resonance imaging; PSA serum levels were assessed by chemiluminescence in an Architect i2000