Meta Gene 2 (2014) 283–298

Contents lists available at ScienceDirect

Meta Gene

PSMA6 (rs2277460, rs1048990), *PSMC6* (rs2295826, rs2295827) and *PSMA3* (rs2348071) genetic diversity in Latvians, Lithuanians and Taiwanese

Tatjana Sjakste [a,*], Natalia Paramonova [a], Lawrence Shi-Shin Wu [b], Zivile Zemeckiene [c], Brigita Sitkauskiene [d], Raimundas Sakalauskas [d], Jiu-Yao Wang [e], Nikolajs Sjakste [f,g]

[a] *Genomics and Bioinformatics, Institute of Biology of the University of Latvia, Miera str. 3, LV2169, Salaspils, Latvia*
[b] *Institute of Biomedicine, Tzu-Chi University, Tzu-Chi, Taiwan*
[c] *Department of Laboratory Medicine, Medical Academy, Lithuanian University of Health Sciences, Kaunas, Lithuania*
[d] *Department of Pulmonology and Immunology, Medical Academy, Lithuanian University of Health Sciences, Kaunas, Lithuania*
[e] *Division of Allergy and Clinical Immunology, College of Medicine, National Cheng Kung University, Tainan, Taiwan*
[f] *Faculty of Medicine, University of Latvia, Riga, Latvia*
[g] *Latvian Institute of Organic Synthesis, Riga, Latvia*

ARTICLE INFO

Article history:
Received 26 February 2014
Revised 11 March 2014
Accepted 17 March 2014
Available online 17 April 2014

Keywords:
PSMA3
PSMA6
PSMC6
Proteasome
SNP
Genetic diversity
Human population

ABSTRACT

PSMA6 (rs2277460, rs1048990), *PSMC6* (rs2295826, rs2295827) and *PSMA3* (rs2348071) genetic diversity was investigated in 1438 unrelated subjects from Latvia, Lithuania and Taiwan. In general, polymorphism of each individual locus showed tendencies similar to determined previously in HapMap populations. Main differences concern Taiwanese and include presence of rs2277460 rare allele A not found before in Asians and absence of rs2295827 rare alleles homozygotes TT observed in all other human populations. Observed patterns of SNPs and haplotype diversity were compatible with expectation of neutral model of evolution. Linkage disequilibrium between the rs2295826 and rs2295827 was detected to be complete in Latvians and Lithuanians ($D' = 1$; $r^2 = 1$) and slightly disrupted in Taiwanese ($D' = 0.978$; $r^2 = 0.901$).

Abbreviations: LV, Latvian population; LT, Lithuanian population; TW, Taiwanese population; UPS, ubiquitin–proteasome system; SNP, single nucleotide polymorphism; TF, transcription factor; TFBS, transcription factor binding site; T2DM, type 2 *diabetes mellitus*; HapMap-CEU, NorthWestern Europeans; HapMap HCB, Han Chinese; HapMap JPT, Japanese; HWE, Hardy–Weinberg equilibrium; LD, linkage disequilibrium.

* Corresponding author. Tel.: +371 29716053; fax: +371 67944988.
E-mail address: tanja@email.lubi.edu.lv (T. Sjakste).

http://dx.doi.org/10.1016/j.mgene.2014.03.002

Population differentiation (F_{ST} statistics) was estimated from pairwise population comparisons of loci variability, five locus haplotypes and *PSMA6* and *PSMC6* two locus haplotypes. Latvians were significantly different from all Asians at each of 5 SNPs and from Lithuanians at the rs1048990 and *PSMC6* loci. Lithuanian and Asian populations exhibited similarities at the *PSMC6* loci and were different at the *PSMA6* and *PSMA3* SNPs. Considering five locus haplotypes all European populations were significantly different from Asian; Lithuanian population was different from both Latvian and CEU.

Allele specific patterns of transcription factor binding sites and splicing signals were predicted *in silico* and addressed to eventual functionality of nucleotide substitutions and their potential to be involved in human genome evolution and geographical adaptation. Current study represents a novel step toward a systematic analysis of the proteasomal gene genetic diversity in human populations.

Introduction

The ubiquitin-proteasome system (UPS) is the major nonlysosomal proteolytic pathway affecting crucial intracellular processes. UPS deregulation has been implicated in the efficiency of the immune response, ageing, inflammatory and many pathological processes (Sorokin et al., 2009; Willis et al., 2010; Zemeckienė et al., 2013).

UPS components possess potential to be a therapeutic target for treatment of several diseases (Bedford et al., 2011).

Importance of proteasomes in both normal and pathological processes triggers interest for search of sequence variations in the proteasomal genes to be associated with human pathologies including cardiovascular disorders (Alsmadi et al., 2009; Banerjee et al., 2008; Barbieri et al., 2008; Bennett et al., 2008; Ozaki et al., 2006; Sjakste et al., 2007b), *diabetes mellitus* (Sjakste et al., 2007a, 2007b), autoimmune diseases (Sjakste et al., 2004, 2010, in press; Trapina et al., 2009), children obesity (Kupca et al., 2013), cancer and its outcome (Bachmann et al., 2010). However, these associations could significantly vary in different ethnic populations as it was shown for coronary artery disease (Wang et al., 2013).

No systematic analysis has been done until now to evaluate the proteasomal gene genetic diversity in humans on population level. It appears that genotyping of the *PSMB5* gene single nucleotide polymorphism (SNP) in four American ethnic groups (Wang et al., 2008) and the 14q13.2 microsatellite polymorphism in Latvian and Finland populations (Kalis et al., 2002; Sjakste et al., 2007a) are the only studies directly addressed to that objective. Case/control disease association studies could provide significant information on population diversity. The rs1048990 of the *PSMA6* gene was widely genotyped during the last decade in several European and Asian populations for association with cardiovascular disorders, type 2 diabetes mellitus and other pathologies and their outcome (Table 1 and Wang et al. (2013) for references). Several SNPs located within and upstream the *PSMA6* gene as well as within the *PSME1*, *PSME2* and *PSMA3* genes were genotyped in Latvians on susceptibility to different pathologies (Kupca et al., 2013; Sjakste et al., 2007b, in press; Trapina et al., 2009). HapMap and PERLEGEN projects (http://www.ncbi.nlm.nih.gov/snp/) provide significant information on the genetic diversity of many individual loci in different ethnic populations; however this information is based on analysis of very small subject groups, more detailed studies are necessary.

In the current study five SNPs belonging to the *PSMA6* (rs2277460 and rs1048990), *PSMC6* (rs2295826 and rs2295827) and *PSMA3* (rs2348071) genes, have been genotyped on genetic diversity in Latvian (LV), Lithuanian (LT) and Taiwanese (TW) populations to evaluate extent of diversity and population differentiation. Allele specific patterns of transcription factor binding sites (TFBSs) and splicing signals were predicted *in silico* to reveal a potential of nucleotide substitutions in proteasomal genes to be important for human genome evolution and adaptation.