Association of a common genetic variant in prostate stem cell antigen with cancer risk

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Submitted: 28 September 2012
Accepted: 6 January 2013
Arch Med Sci 2014; 10, 3: 425–433
DOI: 10.5114/aoms.2014.43736
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Abstract

Introduction: Polymorphisms in the prostate stem cell antigen (PSCA) gene have been hypothesized to increase the genetic susceptibility to cancers. The common sequence variation in PSCA rs2294008 (C>T) has been implicated in cancer risk. However, results of the relevant published studies were somewhat underpowered and controversial in general.

Material and methods: To evaluate the role of PSCA rs2294008 (C>T) genotype in global cancer, we performed a pooled analysis of all the available published studies involving 22,817 cancer patients and 27,753 control subjects.

Results: The results showed evidence that PSCA rs2294008 (C>T) was associated with increased total cancer risk in the overall comparisons. Stratified analysis by cancer type indicated that PSCA rs2294008 T is associated with increased risk of gastric cancer (OR = 1.24, 95% CI = 1.09–1.42, \( p_{\text{heterogeneity}} < 0.001, I^2 = 88.0\% \)) and bladder cancer (OR = 1.07, 95% CI = 1.04–1.11, \( p_{\text{heterogeneity}} = 0.108, I^2 = 55.0\% \)) by allelic contrast. Furthermore, in stratified analysis by histological types of gastric cancer, this PSCA variant showed significant associations with diffuse type (OR = 1.81, 95% CI = 1.16–2.81, \( p_{\text{heterogeneity}} < 0.001, I^2 = 88.9\% \)) but not intestinal type (OR = 1.29, 95% CI = 0.95–1.74, \( p_{\text{heterogeneity}} < 0.001, I^2 = 85.2\% \)) in a dominant genetic model. Similar results were found in Asian and European descendents and population-based studies.

Conclusions: In all, our meta-analysis suggests that PSCA rs2294008 (C>T) may play allele-specific roles in cancer development. Further prospective studies with larger numbers of participants worldwide should be performed in different kinds of cancer and other descendents in more detail.

Key words: prostate stem cell antigen, polymorphism, cancer risk, meta-analysis.

Introduction

The prostate stem cell antigen (PSCA) gene encodes a 123-amino-acid glycoprotein with 30% homology to stem cell antigen 2 (Sca-2), known as a cell surface marker of immature thymic lymphocytes [1]. It was initially identified as the prostate-specific cell-surface antigen over-expressed in prostate cancer, but its expression has subsequently been demonstrated in extraprostatic normal tissues including stomach, esophagus, bladder,
Pancreas and kidney [2–5]. In addition to prostate cancer, PSCA is also highly expressed in a proportion of other human solid tumors such as pancreatic, gestational trophoblastic and clear renal cell carcinoma [6–8]. In contrast, reduced PSCA expression was observed in head-and-neck squamous cell, esophagus and stomach tumors [3, 9]. It has been shown that PSCA is involved in a variety of tumor growth activities such as cell-proliferation inhibition and/or cell-death induction [10, 11], whereas the precise function of this gene remains unknown and controversial. Gu et al. reported that an up-regulated level of PSCA expression was associated with tumor stage, grade and androgen independence of prostate cancer. Conversely, reduced expression of PSCA was found in gastric intestinal metaplasia, a precursor lesion of intestinal-type gastric cancer [12]. In vitro studies indicated that PSCA affects survival of gastric cancer cells, because transfection of PSCA into PSCA-negative cells caused down-regulated cell proliferation [12]. In contrast, down-regulation of PSCA in a human bladder cancer cell line led to a reduction in cell growth, which was associated with activation of several immune signaling pathways [13]. Bahrenberg et al. [3] observed the reduced expression of PSCA in bladder cancer, whereas Amara et al. reported a contradictory result on the association of PSCA expression level and bladder cancer risk [14]. It appears that the role of PSCA in tumorigenesis is complex, involving protumorigenic and antitumorigenic functions in various contexts [15].

The PSCA rs2294008, located in the translation starting site which can regulate PSCA promoter activity, is a common genetic variant involved in a variety of studies. Recently, a study group reported findings of a 2-stage genome-wide association study (GWAS), which evaluated the association between rs2294008 single nucleotide polymorphism (SNP) and several histological types of gastric tumor [12]. Then, several independent case-control studies published the association between rs2294008 and other types of carcinoma including prostate cancer [16], bladder cancer [17, 18], upper gastrointestinal cancer [19], breast cancer [20] and colorectal cancer [21]. However, the association between PSCA rs2294008 (C>T) polymorphism and cancer risk is still controversial due to conflicting results from various studies. In this study, a meta-analysis based on 16,306 cancer patients and 17,962 control subjects [12, 16–29] was undertaken to evaluate the effect of PSCA rs2294008 (C>T) polymorphism on cancer risk.

Material and methods

Literature search and data extraction

PubMed database searches were performed using the following keywords: ‘PSCA’ or ‘Prostate stem cell antigen’, ‘polymorphism’ and ‘cancer’ (last search updated on Nov 1, 2012). We also screened references of the retrieved paper and review articles by a hand search. Included studies had to meet the following criteria: (a) information contained the evaluation of PSCA rs2294008 (C>T) polymorphism and cancer risk; (b) case-control studies; (c) involving information about available genotype frequency; (d) only full-text manuscripts were included. The major exclusion criteria were: (a) duplication of previous publications; (b) no available genotype frequency; (c) no control population; (d) study with a clear bias of accrual. Each of the database searches was performed by two of the reviewers to make sure published papers were not missed. Data were refined by the first author’s last name, year of publication, study population, ethnicity, genotyping methods, cancer type, sample size in cases and controls, source of control and so on.

Statistical analysis

Odds ratios (ORs) corresponding to 95% confidence interval (CI) were used to evaluate the strength of association based on genotype frequencies in cases and controls. We measured the association between PSCA rs2294008 (C>T) polymorphism and cancer risk by utilizing five genetic contrasts: the allelic contrast (T allele vs. C allele), the homozygote comparison (TT vs. CC), the heterozygote comparison (TC vs. CC), the dominant genetic model (TT + TC vs. CC) and the recessive genetic model (TT vs. TC + CC). The Statistical analysis was carried out by ethnicity, cancer type, source of control (population-based and hospital-based) and histological type. If the cancer type involved only one individual study, it was classified into the “other cancers” subgroup. Hardy-Weinberg equilibrium (HWE) of controls was tested with the Pearson χ² test for goodness of fit. We used the random effects model and fixed effects model to calculate the pooled OR. The heterogeneity assumption was calculated using a χ²-based Q test among the studies. A p-value more than 0.05 for the Q test indicated lack of heterogeneity [30]; thus the fixed effects model (Mantel-Haenszel method [31]) was used. Otherwise, the random effects model (DerSimonian and Laird method [30]) was used. The Z-test was used to examine the statistical significance of the summary OR and p < 0.05 was considered significant. Furthermore, I² values were also calculated to better determine the extent of heterogeneity between studies. As a guide, I² values of < 25% could be considered ‘low’, values of ~50% could be considered ‘moderate’ and values of > 75% could be considered ‘high’ [32]. We assessed publication bias using Egger’s test and p < 0.05 was considered
statistically significant [33]. All statistical analysis was performed using STATA software v 10.0 (Stata Corporation, College Station, TX, USA) and all the $p$ values were two sided.

**Results**

**Study inclusion**

A total of 18 studies (from 15 articles) [12, 16–29], which could meet all of the criteria, were included in this study. Genotype distribution of the control population was in line with HWE in each of the studies except for one study conducted in the Polish population [19]. Characteristics of the included studies are summarized in Table I. Among 18 eligible case-control studies, there were 22,817 cases and 27,753 control subjects concerning the PSCA rs2294008 (C>T) polymorphism. There were 11 studies of gastric cancer, three studies of bladder cancer and four studies of other cancers (including prostate cancer, esophageal cancer, breast cancer and colorectal cancer); in the subgroup of ethnicity, 11 were performed in an Asian population, and seven were in European descendants. Population-based controls were carried out in 11 studies. Polymerase chain reaction-restriction fragment length polymorphism (RFLP), the classical genotyping method, was performed in five comparisons. In addition, the GWAS was used in four comparisons.

**Quantitative synthesis**

In the overall analysis, a significant association was observed between the PSCA rs2294008 (C>T) and cancer risk in different genetic models: in the contrast of T allele vs. C allele (random-effects OR = 1.17, 95% CI = 1.08–1.27, $p_{\text{heterogeneity}} < 0.001$; homozygote comparison (random-effects OR = 1.35, 95% CI = 1.13–1.60, $p_{\text{heterogeneity}} < 0.001$; heterozygote comparison (random-effects OR = 1.24, 95% CI = 1.10–1.40, $p_{\text{heterogeneity}} < 0.001$, the dominant genetic model (random-effects OR = 1.28, 95% CI = 1.12–1.46, $p_{\text{heterogeneity}} < 0.001$, p < 0.001; recessive genetic model (random-effects OR = 1.18, 95% CI = 1.07–1.31, $p_{\text{heterogeneity}} < 0.001$, p = 0.001, $I^2$ = 70.1) (Table II). In the stratified analyses by cancer type, an increased risk was found between PSCA rs2294008 (C>T) polymorphism and gastric cancer risk in the allelic contrast (random-effects OR = 1.24, 95% CI = 1.09–1.42, $p_{\text{heterogeneity}} < 0.001$, p = 0.001, $I^2$ = 88.0), as well as the homozygote comparison (random-effects OR = 1.50, 95% CI = 1.09–2.07, $p_{\text{heterogeneity}} < 0.001$, p = 0.012, $I^2$ = 89.8), the heterozygote comparison (random-effects OR = 1.40, 95% CI = 1.15–1.70, $p_{\text{heterogeneity}} < 0.001$, p = 0.001, $I^2$ = 85.4) and the dominant genetic model (random-effects OR = 1.45, 95% CI = 1.16–1.81, $p_{\text{heterogeneity}} < 0.001$, p = 0.001, $I^2$ = 89.8) (Figure 1). However, in stratified analysis by histological types of gastric cancer, the PSCA variant showed significant associations with diffuse type (dominant genetic model: OR = 1.81, 95% CI = 1.66–2.01, $p_{\text{heterogeneity}} < 0.001$; recessive genetic model: OR = 1.49, 95% CI = 1.18–1.88, $p_{\text{heterogeneity}} < 0.001$, p = 0.009, $I^2$ = 88.9; recessive genetic model: OR = 1.11, 95% CI = 0.85–1.43, $p_{\text{heterogeneity}} = 0.001$, p = 0.443, $I^2$ = 72.7) (Figure 2, Table II).

There was also an association between increased risk of bladder cancer and PSCA rs2294008 (C>T) polymorphism in each of the genetic models: in allelic contrast (fixed-effects OR = 1.07, 95% CI = 1.04–1.11, $p_{\text{heterogeneity}} = 0.108$, p = 0.001, $I^2$ = 55.0), the homozygote comparison (fixed-effects OR = 1.15, 95% CI = 1.09–1.22, $p_{\text{heterogeneity}} = 0.190$, p < 0.001, $I^2$ = 39.8), the heterozygote comparison (fixed-effects OR = 1.07, 95% CI = 1.05–1.10, $p_{\text{heterogeneity}} = 0.241$, p < 0.001, $I^2$ = 29.7), the dominant genetic model (fixed-effects OR = 1.06, 95% CI = 1.04–1.09, $p_{\text{heterogeneity}} = 0.124$, p < 0.001, $I^2$ = 52.2), and the recessive genetic model (fixed-effects OR = 1.10, 95% CI = 1.04–1.16, $p_{\text{heterogeneity}} = 0.293$, p = 0.001, $I^2$ = 18.6). Similar results were also found in Asian descendants and population-based studies, with no significant association observed in the hospital-based studies (Table II). Furthermore, a positive association between this variant and cancer risk in the European population was observed in allelic contrast (random-effects OR = 1.14, 95% CI = 1.03–1.26, $p_{\text{heterogeneity}} < 0.001$, p = 0.009, $I^2$ = 79.7), homozygote comparison (random-effects OR = 1.32, 95% CI = 1.09–1.60, $p_{\text{heterogeneity}} < 0.001$, p = 0.005, $I^2$ = 77.5) and the recessive genetic model (random-effects OR = 1.22, 95% CI = 1.07–1.38, $p_{\text{heterogeneity}} = 0.017$, p = 0.002, $I^2$ = 61.2); the result did not change when excluding the study that was not in HWE.

**Publication bias**

We used Begg’s funnel plot and Egger’s test to evaluate the publication bias of literature. No evidence of publication bias could be found (T allele vs. C allele, t = 0.19, p = 0.853; TT vs. CC, t = 0.04, p = 0.966; TC vs. CC, t = –0.01, p = 0.992; TT+TC vs. CC, t = 0.19, p = 0.851; TT vs. TC+CC, t = 0.01, p = 0.989).

**Discussion**

The increasing growth of human genetics creates countless opportunities for studying disease association. Meta-analysis provides a quantitative method for combining the results from different studies.
Table I. Characteristics of studies of PSCA rs2294008 C>T polymorphism included in this meta-analysis

| First author | Year | Population | Ethnicity | Genotyping methods | Cancer type          | Sample size (cases/controls) | Source of control | $P_{\text{HWE}}$ | Frequency of T allele |
|--------------|------|------------|-----------|-------------------|----------------------|-----------------------------|-------------------|----------------|----------------------|
| Kim         | 2012 | Korea      | Asian     | MALDI-TOF         | Breast cancer        | 441/459                     | Hospital-based    | 0.324         | 0.49237              |
| Sala        | 2012 | Spain      | European  | Illumina technology | Gastric cancer      | 289/1515                   | Population-based  | 0.088         | 0.44026              |
| Smith       | 2012 | Scotland   | European  | TaqMan assays     | Colorectal cancer    | 388/493                    | Hospital-based    | 0.463         | 0.40264              |
| Fu          | 2012 | Spain      | European  | GWAS              | Bladder cancer       | 5,393/7,324                | Population-based  | 0.952         | 0.46348              |
| Zeng        | 2011 | Chinese    | Asian     | PCR-RFLP          | Gastric cancer       | 460/549                    | Population-based  | 0.493         | 0.270                |
| Song        | 2011 | Korea      | Asian     | PCR-RFLP          | Gastric cancer       | 3,245/1,700                | Population-based  | 0.130         | 0.516                |
| Joung       | 2011 | Korea      | Asian     | MALDI-TOF         | Prostate cancer      | 192/168                    | Hospital-based    | 0.963         | 0.47                 |
| Lochhead    | 2011 | Polish     | European  | Real-time PCR     | Gastric cancer       | 292/382                    | Population-based  | 0.011         | 0.518                |
| Lochhead    | 2011 | USA        | European  | Real-time PCR     | Gastric cancer       | 308/208                    | Population-based  | 0.832         | 0.5                  |
| Lochhead    | 2011 | USA        | European  | Real-time PCR     | Esophageal cancer    | 158/208                    | Population-based  | 0.832         | 0.5                  |
| Wang        | 2010 | Chinese    | Asian     | PCR-RFLP          | Bladder cancer       | 581/580                    | Hospital-based    | 0.508         | 0.266                |
| Ou          | 2010 | Tibetan    | Asian     | PCR-LDR           | Gastric cancer       | 196/246                    | Hospital-based    | 0.924         | 0.268                |
| Lu          | 2010 | Chinese    | Asian     | PCR-RFLP          | Gastric cancer       | 1023/1069                  | Population-based  | 0.166         | 0.253                |
| Wu          | 2009 | USA        | European  | GWAS              | Bladder cancer       | 5038/9,363                 | Population-based  | 0.418         | 0.447                |
| Wu          | 2009 | Chinese    | Asian     | PCR-RFLP          | Gastric cancer       | 1,710/995                  | Hospital-based    | 0.587         | 0.284                |
| Matsuo      | 2009 | Japan      | Asian     | TaqMan assays     | Gastric cancer       | 708/708                    | Hospital-based    | 0.638         | 0.376                |
| Study Group | 2008 | Japan      | Asian     | GWAS              | Gastric cancer       | 1,524/1,396                | Population-based  | 0.574         | 0.617                |
| Study Group | 2008 | Korea      | Asian     | GWAS              | Gastric cancer       | 871/390                    | Population-based  | 0.069         | 0.462                |

HWE – Hardy-Weinberg equilibrium of controls, RFLP – restriction fragment length polymorphism, GWAS – genome-wide association study.
Table II. Stratified analyses of the PSCA rs2294008 C>T polymorphism on cancer risk

| Variables                      | N<sup>a</sup> | Cases/controls | T allele vs. C allele | TT vs. CC | TC vs. CC | TT + TC vs. CC | TT vs. TC + CC |
|--------------------------------|---------------|----------------|----------------------|-----------|-----------|----------------|----------------|
|                                |               |                | OR (95% CI) | P<sub>heter</sub> | OR (95% CI) | P<sub>heter</sub> | OR (95% CI) | P<sub>heter</sub> | OR (95% CI) | P<sub>heter</sub> |
| Total                          | 18            | 22817/27753    | 1.17 (1.08–1.27) | < 0.001   | 1.35 (1.13–1.60) | < 0.001   | 1.24 (1.10–1.40) | < 0.001   | 1.28 (1.12–1.46) | < 0.001   | 1.18 (1.07–1.31) | < 0.001   |
| Ethnicity                      |               |                |           |           |           |           |           |           |           |           |           |           |
| Asian                          | 11            | 10951/8260     | 1.19 (1.05–1.36) | < 0.001   | 1.37 (1.00–1.88) | < 0.001   | 1.35 (1.12–1.63) | < 0.001   | 1.38 (1.11–1.70) | < 0.001   | 1.14 (0.96–1.35) | < 0.001   |
| European                       | 7             | 11866/19493    | 1.14 (1.03–1.26) | < 0.001   | 1.32 (1.09–1.60) | < 0.001   | 1.09 (0.92–1.30) | < 0.001   | 1.15 (0.97–1.37) | < 0.001   | 1.22 (1.07–1.38) | 0.017     |
| Cancer type                    |               |                |           |           |           |           |           |           |           |           |           |           |
| Gastric cancer                 | 11            | 10626/9158     | 1.24 (1.09–1.42) | < 0.001   | 1.50 (1.09–2.07) | < 0.001   | 1.40 (1.15–1.70) | < 0.001   | 1.45 (1.16–1.81) | < 0.001   | 1.21 (1.01–1.45) | < 0.001   |
| Bladder cancer                 | 3             | 11012/17267    | 1.07 (1.04–1.11) | 0.108<sup>c</sup> | 1.15 (1.09–1.22) | 0.190<sup>c</sup> | 1.07 (1.05–1.10) | 0.241<sup>c</sup> | 1.06 (1.04–1.09) | 0.124<sup>c</sup> | 1.10 (1.04–1.16) | 0.293<sup>c</sup> |
| Other cancers                  | 4             | 1179/1328      | 0.99 (0.90–1.08) | 0.099<sup>c</sup> | 0.99 (0.83–1.18) | 0.159<sup>c</sup> | 0.81 (0.59–1.12) | 0.041<sup>c</sup> | 0.86 (0.63–1.17) | 0.029<sup>c</sup> | 1.10 (0.95–1.28) | 0.784<sup>c</sup> |
| Source of control              |               |                |           |           |           |           |           |           |           |           |           |           |
| Hospital-based                 | 7             | 4216/3649      | 1.06 (0.90–1.25) | < 0.001   | 1.03 (0.74–1.44) | < 0.001   | 1.09 (0.89–1.34) | 0.001   | 1.09 (0.88–1.36) | < 0.001   | 1.00 (0.76–1.31) | 0.002     |
| Population-based               | 11            | 18601/24104    | 1.24 (1.14–1.36) | < 0.001   | 1.57 (1.28–1.92) | < 0.001   | 1.34 (1.15–1.57) | < 0.001   | 1.41 (1.39–1.66) | < 0.001   | 1.27 (1.15–1.41) | 0.001     |
| Histological types of GC       |               |                |           |           |           |           |           |           |           |           |           |           |
| Intestinal type                | 8             | 2775/5813      | 1.15 (0.94–1.40) | < 0.001   | 1.27 (0.84–1.92) | < 0.001   | 1.27 (0.98–1.65) | < 0.001   | 1.29 (0.95–1.74) | < 0.001   | 1.11 (0.85–1.43) | 0.001     |
| Diffuse type                   | 8             | 2218/5783      | 1.41 (1.17–1.71) | < 0.001   | 2.11 (1.25–3.57) | < 0.001   | 1.65 (1.09–2.51) | < 0.001   | 1.81 (1.16–2.81) | < 0.001   | 1.49 (1.18–1.88) | 0.014     |

<sup>a</sup> Number of comparisons; <sup>b</sup> p value of Q test for heterogeneity test (p<sub>heter</sub>); <sup>c</sup> random effects model was performed when p value for heterogeneity test < 0.05; otherwise, fixed effects model was used.
studies with the same topic, and for estimating and explaining their diversity [34–36]. Accumulating epidemiological and genetic evidence indicates that genetic variation is a significant component in cancer etiology and the overall goal of this meta-analysis is to combine the results of previous studies in order to achieve summary conclusions about a body of research. To the best of our knowledge, this can be considered as the first pooled analysis to explore the association between PSCA rs2294008 (C>T) polymorphism and overall cancer risk, containing about 22,817 cancer patients and 27,753 control subjects. We found that PSCA rs2294008 (C>T) polymorphism was associated with a significant increased risk of global cancer, especially bladder cancer and gastric cancer. Histopathological research has indicated that gastric cancer is not a single disease and it can be categorized into two major types: intestinal and diffuse. The intestinal-type tumors are found uniformly in geographic areas accompanied with a high incidence of gastric cancer, whereas the diffuse-type are found more predominantly throughout the world [37–40]. Sala et al. performed an EPIC-EURGAST study (based on 148 intestinal gastric cancer cases, 141 diffuse cases and 1515 control subjects) and found that PSCA is associated with both diffuse and intestinal gastric cancer in European [23]. However, our meta-analysis provided evidence that PSCA rs2294008 (C>T) is associated with susceptibility to diffuse type but not intestinal type gastric cancer, which is in line with the former GWAS study [12].

In addition, our results suggested that the effects of PSCA rs2294008 SNPs were stronger in the Asian population than in European descendants. Interestingly, the risk allele (T) frequency was somewhat more common in the Japanese and Korean populations than in the Chinese population. Furthermore, in the stratified analysis by source of control, a significant association between PSCA rs2294008 (C>T) polymorphism and increased cancer risk was observed in population-based studies in each genetic model. Some factors may influence these results. First, it is widely acknowledged that carcinogenesis is a multifactorial procedure induced by complex factors including genetic and environmental inter-
actions (such as dietary factors, age, toxins, radiation, and infectious agents), which indicates that a single factor might have little effect on cancer susceptibility [41]. Second, positive results appear to be published more quickly than articles with negative outcomes, which take longer time to be published (time-lag bias) [42]. Third, discrepancies among the distribution in different ethnicities between case and control populations could be a source of confounding when pooling studies. Furthermore, it is possible that the variant leads to carcinoma at this locus, but the combination of environmental factors or multiple genes [43] may predominate in the development or metastasis of cancer, with the association of the polymorphism not being observed.

Some limitations may exist in the present study. First of all, the numbers of eligible studies accumulated in our analysis may not be sufficiently large for a comprehensive analysis, especially for any given cancer (e.g. prostate cancer, esophageal carcinoma and bladder cancer). Second, our pooled analysis was predominantly based on unadjusted estimates. Thus, more precise analysis including individual information (including smoking, age and sex) should be further conducted if possible. Third, effects based on gene-environment and even different polymorphism loci in the same gene may alter gene expression and account for fluctuation in OR values. However, some key advantages in this present study should also be acknowledged. First, a substantial number of cancer patients and control subjects in this article were included from different studies; therefore, statistical power of the analysis could be significantly increased. Second, no evidence of publication bias was found in this article and quality of the case-control studies was uniformly good. Third, studies included in the meta-analysis strictly and satisfactorily met the selection criteria.

In conclusion, this pooled analysis showed evidence that PSCA rs2294008 (C>T) polymorphism was associated with increased cancer risk and this variant may play allele-specific roles in cancer development. Further prospective studies with larger sizes of unbiased-matched homogeneous participants and well-matched controls worldwide are required to evaluate the association.
between PSCA rs2294008 (C>T) polymorphism and cancer risk to establish more comprehensive conclusions.

Acknowledgments

This work was supported by the Science Development Foundation of Nanjing Medical University (2011NJMU086), the Society Development Foundation of Changzhou (CS2008917), the National Natural Science Foundation of China (81072085), The Key Laboratory Foundation of Suzhou (No: SZS201001).

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Association of a common genetic variant in prostate stem cell antigen with cancer risk

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