Genes Nutr (2011) 6:397–402
DOI 10.1007/s12263-011-0221-2

RESEARCH PAPER

An update analysis of two polymorphisms in encoding ribonuclease L gene and prostate cancer risk: involving 13,372 cases and 11,953 controls

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Received: 8 June 2010 / Accepted: 28 March 2011 / Published online: 17 April 2011

Abstract Encoding ribonuclease L (*RNASEL*) is a ubiquitously expressed latent endoribonuclease involved in the mediation of antiviral and pro-apoptotic activities of the interferon-inducible 2-5A system. Although the relationship between *RNASEL* gene polymorphisms and prostate cancer (PCa) risk has been widely reported, results were somewhat controversial and underpowered. Now, we performed an update analysis of 14 publications evaluating the association between *RNASEL* R462Q and D541E polymorphisms and PCa risk. We conducted a literature search of PubMed database to identify all eligible articles that examined the association of *RNASEL* R462Q and D541E polymorphisms with PCa. Odds ratios (OR) with 95% confidence intervals (CI) were estimated to assess these association. R462Q showed a significantly elevated effect on Africans (QQ vs. RR: OR = 2.50, 95% CI = 1.28–4.87, $P_{\text{heterogeneity}} = 0.231$). In addition, PCa men who contain 462Q genotype had a higher Gleason score ≥ 7 (OR = 1.16, 95% CI = 1.05–1.28, $P_{\text{heterogeneity}} = 0.906$). On the other hand, D541E was associated with increased total PCa. In the stratified analysis by race, there was also significantly increased PCa in Africans and Caucasians, as well as in sporadic PCa studies (OR = 1.09, 95% CI = 1.04–1.15, $P_{\text{heterogeneity}} = 0.078$). Our update analysis showed evidence that *RNASEL* R462Q and D541E polymorphisms were associated with PCa risk. Still more well-designed studies should be performed to clarify the role of these two polymorphisms in the development of PCa.

Keywords *RNASEL* · Polymorphism · Prostate cancer · Gleason score · Development

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Introduction

Prostate cancer (PCa) remains the most commonly diagnosed solid tumor and the second leading cause of cancer deaths among men in USA (Jemal et al. 2009). Many factors are known to contribute to the risk of PCa, including diet, race/ethnicity, age, and sexual history (Hayes et al. 2000; Kolonel 2001; Chan and Giovannucci 2001); however, family history is the single most significant and reproducible risk factor, where men with two or three first-degree relatives with PCa had a 5- and 11-fold increased risk of developing PCa, respectively (Steinberg et al. 1990). Chronic inflammation may play a role in the etiology of PCa. Some epidemiological evidence suggests that sexually transmitted infections and prostatitis increase the risk of PCa, while aspirin and other anti-inflammatory agents have been inversely associated with this disease (Mahmud et al. 2004).

The encoding ribonuclease L (*RNASEL*) has recently been proposed as a candidate for the hereditary prostate cancer (HPC1) gene, which locates on chromosome 1q24-25 and comprises 741 amino acids. A strong candidate gene linked to the *HPC1* region is 2′-5′-oligoadenylate-dependent *RNASEL* (Grönberg et al. 1997; Xu et al. 2001), which is a constitutively expressed latent endoribonuclease mediating the antiviral and proapoptotic activity of the

interferon-inducible 2-5A system, and has been shown to play a role in regulating cellular viral defense, single-stranded RNA cleavage, tumor suppressor activities as stress-mediated apoptosis, cell proliferation, and regulation of protein synthesis (Le Roy et al. 2005; Xiang et al. 2003).

Several variants in *RNASEL* (E262X, 47delAAAG, R462Q, D541E) have been investigated in relation to familiar and sporadic PCa (Casey et al. 2002; Wiklund et al. 2004). Some families also carried relatively two common *RNASEL* variants: 1385G → A; rs486907 (resulting in the aminoacid substitution R462Q) and 1623T → G; rs627928 (resulting in the aminoacid substitution D541E) (Carpten et al. 2002). Both variants have been found to be significantly associated with PCa risk albeit with between-study variability in outcome. The R462Q polymorphism reduces the ability of cell to cause apoptosis in response to activation by 2-5A and causes a threefold reduction in enzymatic activity, whereas the D541E variant has similar enzymatic activity as wild-type *RNASEL* (Casey et al. 2002). Previously, Li and Tai (2006) performed a meta-analysis of the association of these two polymorphisms in *RNASEL* and PCa risk and found that compared with the genotype D/D, the E variant at the D541E polymorphism increases PCa risk by <2-fold in Caucasians. In the last 5 years, a number of new case–control studies have been published, so an update analysis is necessary to carry out.

So far, there are thirteen case–control studies in 11 articles (Wiklund et al. 2004; Agalliu et al. 2010; Robbins et al. 2008; Shea et al. 2008; Shook et al. 2007; Daugherty et al. 2007; Cybulski et al. 2007; Nam et al. 2005; Maier et al. 2005; Wang et al. 2002; Rökman et al. 2002) involving the role of R462Q polymorphism, and also thirteen studies in 11 articles (Wiklund et al. 2004; Robbins et al. 2008; Shea et al. 2008; Shook et al. 2007; Cybulski et al. 2007; Wang et al. 2002; Rökman et al. 2002; Beuten et al. 2010; Noonan-Wheeler et al. 2006; Nakazato et al. 2003) investigated the role of D541E polymorphism on the risk of PCa.

Taking into consideration of the extensive role of *RNASEL* in PCa, a more precise estimation of the association of R462Q and D541E polymorphisms in *RNASEL* and PCa risk is derived, we performed a meta-analysis of all eligible case–control studies.

Materials and methods

Publication search

We attempted to include all the case–control studies published to date on the association between *RNASEL* gene polymorphisms and PCa risk. Eligible studies were identified by searching the electronic literature PubMed for relevant reports (the range of publication years was from 2000 to 2011, using the search terms "*RNASEL*" or "ribonuclease L", "polymorphism" or "variant" and "prostate cancer" or "prostate"). A total of 70 articles were retrieved, of which 14 articles according to the inclusion criteria reported on studies examining the association between *RNASEL* R462Q and D541E polymorphisms and PCa risk.

Inclusion criteria

Inclusion criteria contains the following: (1) evaluation of *RNASEL* R462Q and/or D541E polymorphisms and PCa risk; (2) case–control studies; (3) genotype frequency was available; (4) the study was published in English language; (5) only the full-text manuscripts were included; and (6) Hardy–Weinberg equilibrium (HWE) of controls were more than 0.05.

Exclusion criteria

Major exclusion criteria are as follows: (1) no control population; (2) no available genotype frequency; (3) HWE of controls were less than 0.05; (4) if two or more studies used the same data or duplicated with each other, we included the latest one and excluded others; and (5) studies have not been published.

Data extraction

Data were extracted from each study by three authors (Yuan-Yuan Mi, Li-Jie Zhu, and Sheng Wu) independently according to the prespecified inclusion criteria. Data extracted from these articles included: first author's last name, year of publication, country of origin, research race, source of control (population-based, PB and hospital-based, HB), sample size (case/control), and HWE value of controls.

Statistical analysis

Odds ratios (ORs) with 95% confidence intervals (CIs) were used to measure the strength of the relationship between *RNASEL* R462Q and/or D541E polymorphism and PCa risk based on the genotype frequencies in cases and controls. In our analysis, we recognized 462Q or 541E as 'M', and R462 or D541 as 'W'. We explored the association between R462Q or D541E and PCa risk using three different models: allelic contrast (M vs. W), heterozygote comparison (MW vs. WW) as well as homozygote comparison (MM vs. WW) and dominant model (MM + MW vs. WW), respectively. Subgroup analysis was performed by race, source of case, Gleason score, and tumor stage. Different ethnic descents are categorized as Caucasian, Asian, African, and Mixed (if included population is not pure race). Source of case group contains familial and

sporadic origin in PCa. Familial PCa represents families in which there are two first-degree or one first-degree and two or more second-degree relatives with PCa. Disease aggressiveness was defined as "Low" (T category $<$ T2c and/or Gleason score $<$ 7) or "High" (T category $\geq$ T2c and/or Gleason score $\geq$ 7).

The fixed effects model (Mantel and Haenszel 1959) and the random effects model (DerSimonian and Laird 1986) were used to calculate the pooled OR. Heterogeneity assumption was evaluated with a chi-square-based Q test among the studies and at the same time, the statistical significance of the summary OR was determined with the Z test. A P value of more than 0.05 for the Q test indicated a lack of heterogeneity among the studies and fixed effects model was used, otherwise, random effects model was used. The departure of frequencies of *RNASEL* polymorphisms from expectation under HWE was assessed by χ^2 test in controls, $P < 0.05$ was considered significant. Publication bias was assessed with Egger's test (1997). All statistical tests for this meta-analysis were performed with Stata software (version 10.0; StataCorp LP, College Station, TX).

Results

Study inclusion

From all 70 abstracts retrieved through the search criteria in PubMed, 56 were excluded (including duplication, review, meta-analysis, case-only, and insufficient genotype). Finally, we identified 14 articles (29 case-control studies) to evaluate the association of *RNASEL* of R462Q and/or D541E polymorphisms with risk for PCa. Study characteristics were given in Table 1. According to the inclusion criteria, three case–control studies were excluded as their HWE was <0.05. (Shook et al. 2007; Beuten et al. 2010; Nakazato et al. 2003). Therefore, there were fifteen publications involving 13,372 cases and 11,953 controls. Control population included study participants with a normal digital rectal examination (DRE) and serum prostate-specific antigen (PSA) values of <4 ng/ml, as well as age-matched men, without individual or family history of cancer. For the R462Q polymorphism, Q% in Mixed (31.6%) or Caucasian (36.6%) was higher than in African (13.3%) in cases. There were 8 studies of Caucasian, 4 of African and one of Mixed population. Four studies referred to Gleason score and 3 studies about T stage in 3 different articles (Agalliu et al. 2010; Wang et al. 2002; Nakazato et al. 2003). Eight studied came from familial source and 7 from sporadic. For the D541E polymorphism, E% in Asian (66.3%) was higher than in Caucasian (55.2%) or African (34.5%) in cases. There had 9 studies of Caucasian, 3 of African and one of Asian. Ten studied came from familial source and 6 from sporadic. Just only one article (Nakazato et al. 2003) contained the detail in Gleason score and T stage. In another study (Larson et al. 2008), the author got Gleason score and T stage together as "Low-" or "High-" risk subgroups, which was excluded because of insufficient available data.

Table 1 Study characteristics from published studies on the relationship between two polymorphisms in RNASEL gene and prostate cancer

Author/year	Country	Race	Case/control		HWE of control		Source of control
			R462Q	D541E	R462Q	D541E	
Agalliu et al. (2010)	USA	Caucasian	965/1,237	–	0.137	–	PB
Beuten et al. (2010)	USA	Caucasian	–	156/227	–	0.368	HB
Robbins et al. (2008)	USA	African	243/296	243/296	0.95	0.495	HB
Shea et al. (2008)	USA	African	230/452	230/458	0.168	0.496	PB
Shook et al. (2007)	USA	Caucasian	430/484	–	–	0.187	HB
Shook et al. (2007)	USA	Caucasian	430/503	150/242	0.981	0.525	HB
Shook et al. (2007)	USA	African	68/145	68/146	0.633	0.661	HB
Daugherty et al. (2007)	USA	African	98/380	–	0.261	–	PB
Daugherty et al. (2007)	USA	Caucasian	1,116/1,344	–	0.235	–	PB
Cybulski et al. (2007)	Canada	Caucasian	737/511	737/511	0.625	0.344	PB
Noonan-Wheeler et al. (2006)	USA	Caucasian	–	150/170	–	0.198	HB
Nam et al. (2005)	Canada	Mixed	996/1,092	–	0.464	–	PB
Maier et al. (2005)	Germany	Caucasian	363/207	363/207	0.629	0.514	HB
Wiklund et al. (2004)	Sweden	Caucasian	1,622/796	1,563/791	0.432	0.199	PB
Nakazato et al. (2003)	Japan	Asian	–	101/105	–	0.138	PB
Wang et al. (2002)	USA	Caucasian	918/493	929/508	0.802	0.515	HB
Rökman et al. (2002)	USA	Caucasian	233/176	233/176	0.745	0.434	PB

Meta-analysis

In total, individuals carrying the QQ genotype did not have significantly increased risk of PCa in all three models (Table 2). However, stratified analysis by race, *RNASEL* R462Q polymorphism was strongly associated with PCa risk under homozygote comparison in African populations (OR = 2.50, 95% CI = 1.28–4.87, $P = 0.231$ for heterogeneity). In the subgroup analysis by source of case also, no association was detected in familial or sporadic PCa (Table 2). Interestingly, 462Q allele had a weekly higher percentage value than R462 allele in subgroup of Gleason score ≥ 7 (OR = 1.16, 95% CI = 1.05–1.28, $P = 0.906$ for heterogeneity, $P = 0.005$; Table 3).

In overall analysis, the 541E allele was associated with increased PCa risk compared with those with the D541 allele (OR = 1.04, 95% CI = 1.01–1.07, $P = 0.164$ for heterogeneity), as well as heterozygote comparison (OR = 1.07, 95% CI = 1.02–1.13, $P = 0.059$ for heterogeneity). Specifically, 541E significantly increased PCa risk in Caucasian and African race in several models, for example: in Caucasian, OR = 1.04, 95% CI = 1.01–1.07 for M versus W; in African, OR = 1.49, 95% CI = 1.11–2.00 for MW versus WW; Table 2. In the source of case subgroup, we found a weekly increased association between D541E polymorphism and sporadic PCa (OR = 1.09, 95% CI = 1.04–1.15, $P = 0.078$ for heterogeneity; Table 2).

Sensitivity analysis and bias diagnosis

We use sensitivity analysis to determine whether modification of the inclusion criteria of the meta-analysis affected the final results. Finally, no other single study influenced the summary OR qualitatively as indicated by sensitivity analysis. The Egger's test was performed to access the publication bias of literatures, which was used to provide

Table 2 Total and stratified analysis of two polymorphisms in RNASEL gene on prostate cancer

Variables	*N*	Case/control	M versus W		MM versus WW		MM + MW versus WW	
			OR (95% CI)	P_h	OR (95% CI)	P_h	OR (95% CI)	P_h
R462Q								
Total	13	8,019/7,632	1.00 (0.97–1.03)	0.322	1.02 (0.94–1.10)	0.217	0.99 (0.96–1.02)	0.932
Race								
Caucasian	8	6,384/5,267	0.99 (0.96–1.03)	0.733	0.99 (0.90–1.08)	0.643	0.99 (0.96–1.02)	0.912
African	4	639/1,273	1.10 (0.92–1.32)	0.056	2.50 (1.28–4.87)	0.231	1.03 (0.86–1.22)	0.433
Mixed	1	996/1,092	1.01 (0.89–1.16)	–	1.07 (0.80–1.43)	–	0.99 (0.84–1.18)	–
Source of case								
Sporadic	7	3,895/4,122	1.01 (0.97–1.05)	0.945	1.04 (0.92–1.16)	0.923	1.00 (0.97–1.04)	0.824
Familial	8	1,877/2,791	0.99 (0.84–1.17)	0.007	1.03 (0.69–1.56)	0.002	0.97 (0.92–1.02)	0.315
Variables	*N*	Case/control	M versus W		MW versus WW		MM + MW versus WW	
			OR (95% CI)	P_h	OR (95% CI)	P_h	OR (95% CI)	P_h
D541E								
Total	13	5,353/4,321	1.04 (1.01–1.07)	0.164	1.07 (1.02–1.13)	0.059	1.02 (1.00–1.05)	0.065
Race								
Caucasian	9	4,711/3,316	1.04 (1.01–1.07)	0.828	1.07 (1.01–1.13)	0.742	1.03 (1.00–1.05)	0.396
African	3	541/900	1.13 (1.01–1.26)	0.458	1.49 (1.11–2.00)	0.433	1.06 (0.96–1.17)	0.699
Asian	1	101/105	0.60 (0.39–0.92)	–	0.14 (0.04–0.52)	–	0.14 (0.04–0.48)	–
Source of case								
Sporadic	6	2,305/2,148	1.24 (0.87–1.76)	0.000	1.09 (1.04–1.15)	0.078	1.43 (0.97–2.10)	0.000
Familial	10	1,864/3,012	1.27 (0.98–1.65)	0.000	1.01 (0.72–1.42)	0.000	1.18 (0.83–1.68)	0.000

Table 3 Relationship between R462Q polymorphism in RNASEL gene and prostate cancer prognosis

RNASEL	Allele	Gleason ≥ 7	Gleason < 7	OR (95% CI)	P_h	*P*	Egger's test
R462Q	R	891	1,496				
	Q	435	644	1.16 (1.05–1.28)	0.906	0.005	$t = 0.81$, $P = 0.504$

statistical evidence of funnel plot symmetry. Ultimately, the results did not suggest any evidence of publication bias (data not show).

Discussion

RNASEL is a constitutively expressed latent endoribonclease that mediates the antiviral and proapoptotic activities of the IFN-inducible 2-5A system. There is a strong biological plausibility for the involvement of the *RNASEL* gene in PCa, since mutation carriers in this gene exhibited loss of heterozygosity and as a consequence were deficient in functional RNase L activity (Carpten et al. 2002). The rapid growth of *RNASEL* genetics creates countless opportunities for studies to explore this disease association. In the present meta-analysis, 13,372 cases and 11,953 controls concerning the R462Q D541E polymorphism in the protein kinase region of *RNASEL*, 5,353 cases and 4,321 controls concerning D541E polymorphism in the ribonuclease domain of *RNASEL* were included, respectively.

Although no significant associations were observed between R462Q polymorphism and the susceptibility to PCa in overall analysis, weak but significant relationship was detected in Africans. *RNASEL* R462Q polymorphism was implicated in up to 13% of PCa cases, with 3 times less enzymatic activity than the wild type, and an association among Caucasians and Africans with sporadic PCa risk was found (Casey et al. 2002). Our results suggested that *RNASEL* R462Q polymorphism was associated with PCa risk in African population rather than in Caucasians, which confirmed the hypothesis described above. Gleason score and T stage could be considered as prognostic factors in PCa, if Gleason score is more than 7 or T stage is higher than T2c, individuals must have a worse prognosis and PCa will show more aggressive. In our study, we found individuals who carried 462Q allele had a high percentage in Gleason $\geq$ 7, manifesting that R462Q polymorphism was partly related to PCa outcome. We did not find any association between T stage and PCa (data not show).

For D541E polymorphism, although this variant had similar enzymatic activity as wild-type *RNASEL* and could not influence its enzyme (Casey et al. 2002), whose function or mechanism has not been detected, a significant relationship with PCa was detected in Caucasians, the same as Li and Tai (2006); moreover, a new association between Africans and D541E polymorphism was observed in two genetic models. It is well known that sporadic and familial PCa have frequently quite different epidemiological and molecular peculiarities, clinical evolution and prognosis, so it is better to study these two kinds of PCa, respectively. Initially, researchers discovered the *RNASEL* gene is one of the major candidate genes for PCa, since mutations in this gene were linked to PCa in high-risk hereditary PCa families (Carpten et al. 2002). However, also poorly significant association was found in sporadic, but not in familial PCa and D541E polymorphism. The only Asian study (Nakazato et al. 2003) found decreased familial PCa risk in Japanese with the genotype EE. Larger studies involving a wider spectrum of Asian people are needed for a more definitive evaluation of the relationship between D541E polymorphism and PCa risk in Asians.

Several limitations of this meta-analysis should be addressed. First of all, there were only one Mixed case–control study about R462Q polymorphism and also one Asian population study about D541E polymorphism. Further, more new studies should focus on these two aspects. Second, the interactions between gene–gene, gene–environment, and even different polymorphic loci of the same gene may modulate PCa; future analysis may include these factors. Third, four studies referred to Gleason score and 3 studies about T stage about R462Q and one article contained the detail in Gleason score and T stage about D541E, the number of which was small; further studies should increase these relations to enlarge the subsequent meta-analysis. In spite of these, our meta-analysis also had four advantages. First, substantial number of cases and controls were pooled from different studies, which significantly increased statistical power of the analysis. Second, the quality of case–control studies included in the current meta-analysis was satisfactory based on our selection criteria. Third, the HWE of controls were all more than 0.05. Fourth, publication bias was not detected in all genetic models.

In summary, present update analysis found novel evidence that *RNASEL* R462Q or D541E polymorphism could increase PCa risk in Africans, moreover, R462Q polymorphism was associated with PCa prognosis. Further prospective studies with larger numbers of worldwide individuals are expected to examine associations between these two polymorphisms in *RNASEL* and PCa.

Conflict of interest The authors declare no conflict of interests.

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