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CAV1 polymorphisms rs1049334, rs1049337, rs7804372 might be the potential risk in tumorigenicity of urinary cancer: A systematic review and meta-analysis

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ABSTRACT

Background As an integral membrane, Caveolin-1 (CAV1), is a pivotal component to make up the caveolae protein. It has been demonstrated to influence tumorigenicity, including bladder, colon, liver, stomach, breast and lung cancer. Several publications had illustrated the relationship of between CAV1 polymorphism and urinary cancer, but the results were not consistent. We performed a comprehensive meta-analysis to explore the associations and remove the fog.

Material and methods Extensive retrieve was performed in PubMed, Embase, Medline, Web of Science, CNKI, and Wanfang database up to September, 2018. Odds ratios (ORs) and 95% confidence intervals (CIs) were conducted to evaluate the overall strength of the associations in five genetic models, as well as in subgroup analyses, stratified by ethnicity, cancer type or source of control. Q-test, Egger's test and Begg's funnel plot were applied to evaluate the heterogeneity and publication bias. In-silico analysis was managed to demonstrate the relationship of polymorphism and CAV1 mRNA expression level.

Results 34 case-control studies with a total of 13,778 cancer cases and 20,581 healthy controls were enrolled into the meta-analysis. The polled result shown that an increased risk of rs1049334 polymorphism on urinary cancer were reveled in homozygote comparison model (MM vs. WW: OR = 1.240, 95% CI = 1.052–1.462, P = 0.011) and recessive comparison model (MM vs. MW + WW: OR = 1.198, 95% CI = 1.018–1.410, P = 0.030). What's more, rs17878467 polymorphism may play a protect role in the tumorigenesis of urinary cancer, shown in heterozygote comparison model (MW vs. WW: OR = 0.882, 95% CI = 0.78–0.999, P = 0.048). For rs7804372, the overall pooled results revealed a reducing risk in allelic contrast model (M vs. W: OR = 0.734, 95%CI = 0.544-0.99, P = 0.043), homozygote comparison model (MM vs. WW: OR = 0.532, 95% CI = 0.313–0.905, P = 0.020) and recessive comparison model (MM vs. MW + WW: OR = 0.580, 95% CI = 0.437–0.77, P < 0.001). In the stratified analyses by cancer types, the risk of PCa is downgrade by rs7804372 in all five genetic models. The GTEx in-silico analysis index that the polymorphism of CAV1 influence its mRNA expression by a dose-dependent effective of its mutant allele.

Conclusion rs1049334 polymorphismof CAV1 upgrade the risk of urinary cancer, while rs1049337 and rs7804372 polymorphisms may act as a protector of urinary cancer. Further large and well-designed studies in various populations are needed to confirm the results.

1. Introduction

Urinary cancer, especially renal cell carcinoma (RCC), bladder cancer (BCa) and prostate cancer (PCa), are a global pivotal epidemiological health concern. In the latest publication of cancer statistics, there are ~150,350 estimated new diagnosed cancer patients among bladder, kidney, renal pelvis, ureter and other urinary organs in both male and female, while another ~ 164,690 new diagnosed PCa in female, totally account for about 19% of all the new diagnosed cancers in 2018, USA [1]. In China, urinary cancer is also playing an important

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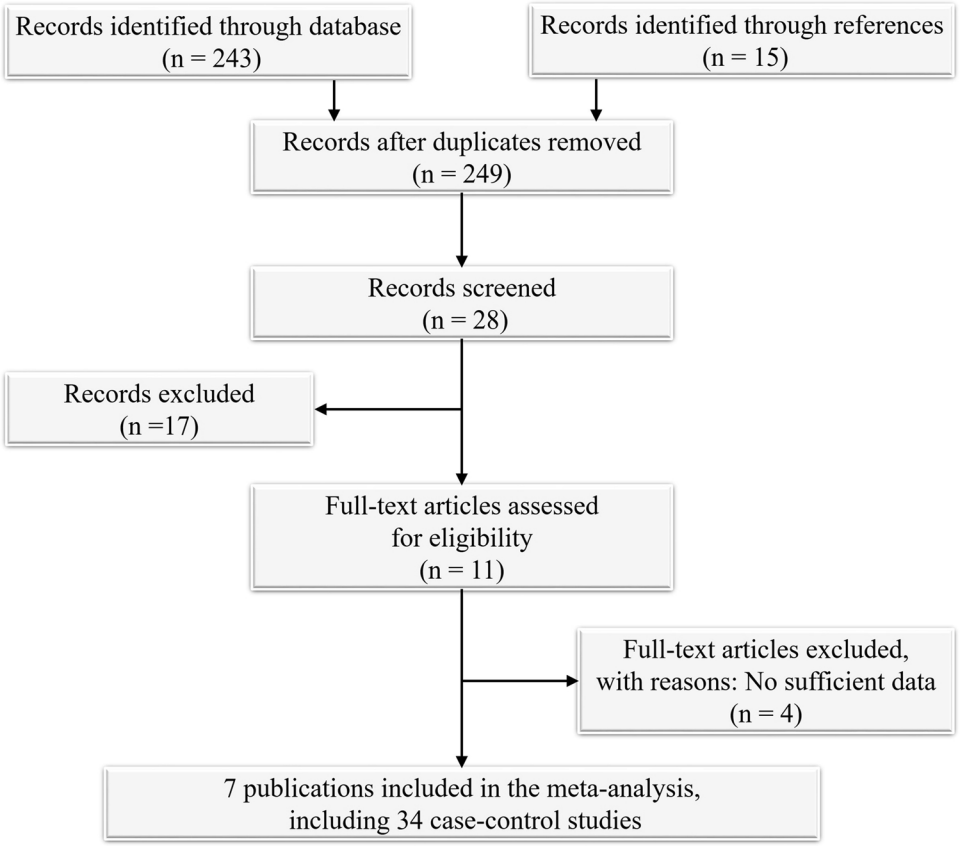

Fig. 1. Flow chart presenting the study selection procedure.

role in population health. PCa and BCa is the sixth and seventh most frequent cancer in Chinese female [2]. There are ~204,360 new diagnosed urinary cancers in 2014, account for about 5.65% of all new diagnosed cancers [3]. Well known, urinary cancer are multifactorial disease effected by genetic variants, aging, ethnicity, gender, smoking, androgen and etc. [1,4–9]. Genetic variants may be an important contributor to the risk of urinary cancer. Recently, several publications had reported the relationship between the polymorphism of genes and urinary cancer, including CASP3, MMP-9, HPGD, XRCC1, PSCA, AXIN1, CYP3A5 and CAV1 [10–16].

As an integral membrane, Caveolin-1 (CAV1), is a pivotal component to make up the caveolae protein. Caveolae protein could regulate cellular processes through numerous cell signaling and transport ways, the domains which is enriched of cholesterol and sphingolipids could to initiate caveolae-mediated endocytosis [17–19]. CAV1 has been demonstrated to influence tumorigenicity, including bladder, colon, liver, stomach, breast and lung [20–25]. Several publications also illustrated the influence of CAV1 polymorphisms in urinary cancer, but the result remained controversial. In the present study, we performed meta-analyses to evaluate and summarize the contribution of the CAV1 polymorphisms to urinary cancer susceptibility.

2. Methods

2.1. Literature search

We conducted a comprehensive literature search, using PubMed, Embase, Medline, Web of Science, CNKI, and Wanfang database, the latest updated date was September 2018. The following search terms were performed to retrieved the relevant articles: ((CAV1) OR (Caveolin-1) OR (Cell Growth-Inhibiting Protein 32)) AND (cancer OR tumor OR carcinoma OR neoplasms OR malignancy) AND (polymorphism OR mutation OR variant OR SNP OR genotype) AND (prostate OR bladder OR kidney OR renal OR Urinary tract). We also manually reviewed the references of retrieved articles or textbooks, to find out the potentially eligible articles. This study is performed according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement on reporting meta-analysis [26].

2.2. Inclusion and exclusion criteria

Inclusion criteria: 1) case–control or cohort studies; 2) evaluating the relationship between CAV1 polymorphism and urinary cancer risk; 3) results presented in odds ratios (ORs) with its 95% confidence intervals (CIs); 4) distribution of genotype in the cases and controls were available to extract directly or after calculating. Exclusion criteria: (1) systematic review, meta-analysis, case-report, or repetitive publications; (2) absence of genotype frequency; (3) publications accomplished on animals or cell lines.

2.3. Data extraction

Following a pre-specified, standardized form, two investigators independently assessed and extracted the data from each eligible studies, including the following information: the name of first author, publication year, country, ethnicity, sample size, genotyping method, allele and genotype frequencies in the cancer cases and healthy controls. In case of conflicting evaluations, disagreements were resolved through discussion and re-check between the authors.

2.4. Statistical analysis

ORs with corresponding 95% CIs was performed to measure the effect of CAV1 polymorphisms in five genetic models, allele contrast

Table 1
Details of enrolled studies for current meta-analysis and systematic review.

First author	Year	Ethnicity	Genotyping Method	Source of Control	Cancer Type	HWE	Cases			Controls		
							Size	W (%)	M (%)	Size	W (%)	M (%)
rs1049314												
Langeberg et al.	2010	Caucasian	ABI-SNPlex	PB	PCa	Y	1261	82.2%	17.8%	1245	83.5%	16.5%
Langeberg et al.	2010	African	ABI-SNPlex	PB	PCa	Y	144	70.1%	29.9%	79	70.9%	29.1%
Zhao et al.	2015	Asian	TaqMan	PB	RCC	N	1248	99.0%	1.0%	1440	98.9%	1.1%
rs1049334												
Langeberg et al.	2010	Caucasian	ABI-SNPlex	PB	PCa	Y	1269	92.2%	7.8%	1242	91.3%	8.7%
Langeberg et al.	2010	African	ABI-SNPlex	PB	PCa	Y	145	92.8%	7.2%	80	88.8%	11.3%
Zhao et al.	2015	Asian	TaqMan	PB	RCC	N	1248	64.4%	35.6%	1440	69.3%	30.7%
rs1049337												
Langeberg et al.	2010	Caucasian	ABI-SNPlex	PB	PCa	Y	1257	73.2%	26.8%	1239	71.2%	28.8%
Langeberg et al.	2010	African	ABI-SNPlex	PB	PCa	Y	144	92.7%	7.3%	80	91.3%	8.8%
Zhao et al.	2015	Asian	TaqMan	PB	RCC	N	1248	57.5%	42.5%	1440	56.7%	43.3%
rs12672038												
Bau et al.	2011	Asian	PCR	PB	BCa	Y	375	76.4%	23.6%	375	76.0%	24.0%
Wu et al.	2011	Asian	PCR	PB	PCa	N	250	76.2%	23.8%	500	76.3%	23.7%
Chang et al.	2013	Asian	PCR	PB	UUTC	N	218	74.5%	25.5%	580	76.5%	23.5%
Chang et al.	2014	Asian	PCR	PB	RCC	N	91	76.4%	23.6%	580	74.9%	25.1%
rs1997623												
Bau et al.	2011	Asian	PCR	PB	BCa	Y	375	99.3%	0.7%	375	98.8%	1.2%
Wu et al.	2011	Asian	PCR	PB	PCa	Y	250	99.0%	1.0%	500	98.4%	1.6%
Chang et al.	2013	Asian	PCR	PB	UUTC	N	218	97.0%	3.0%	580	98.1%	1.9%
Chang et al.	2014	Asian	PCR	PB	RCC	Y	92	98.4%	1.6%	580	99.0%	1.0%
rs3757733												
Bau et al.	2011	Asian	PCR	PB	BCa	N	375	74.4%	25.6%	375	75.5%	24.5%
Wu et al.	2011	Asian	PCR	PB	PCa	N	250	75.0%	25.0%	500	72.5%	27.5%
Chang et al.	2013	Asian	PCR	PB	UUTC	N	218	75.2%	24.8%	580	75.9%	24.1%
Chang et al.	2014	Asian	PCR	PB	RCC	N	93	77.4%	22.6%	580	75.7%	24.3%
rs3807987												
Bau et al.	2011	Asian	PCR	PB	BCa	N	375	59.7%	40.3%	375	78.1%	21.9%
Wu et al.	2011	Asian	PCR	PB	PCa	N	250	74.8%	25.2%	500	78.9%	21.1%
Chang et al.	2013	Asian	PCR	PB	UUTC	N	288	77.8%	22.2%	580	77.6%	22.4%
Chang et al.	2014	Asian	PCR	PB	RCC	N	92	87.0%	13.0%	580	77.4%	22.6%
rs3807992												
Bau et al.	2011	Asian	PCR	PB	BCa	Y	375	67.9%	32.1%	375	69.2%	30.8%
Wu et al.	2011	Asian	PCR	PB	PCa	Y	250	71.0%	29.0%	500	70.0%	30.0%
Chang et al.	2013	Asian	PCR	PB	UUTC	Y	218	71.1%	28.9%	580	69.2%	30.8%
Chang et al.	2014	Asian	PCR	PB	RCC	Y	92	73.9%	26.1%	580	70.1%	29.9%
rs7804372												
Bau et al.	2011	Asian	PCR	PB	BCa	Y	375	77.9%	22.1%	375	71.7%	28.3%
Wu et al.	2011	Asian	PCR	PB	PCa	Y	250	80.2%	19.8%	500	70.4%	29.6%
Chang et al.	2013	Asian	PCR	PB	UUTC	Y	218	79.1%	20.9%	580	71.6%	28.4%
Sugie et al.	2013	Asian	PCR-RFLP	PB	PCa	Y	134	68.3%	31.7%	86	53.5%	46.5%
Chang et al.	2014	Asian	PCR	PB	RCC	N	92	57.6%	42.4%	580	65.6%	34.4%

RCC: renal cell carcinoma; BCa: bladder cancer; PCa: prostate cancer; UUTC: upper urothelial tract cancer; HB: Hospital based; PB: Population based; HWE: Hardy Weinberg Equilibrium.

model (M vs. W), homozygote comparison model (MM vs. WW), heterozygote comparison model (MW vs. WW), dominant comparison model (MM + MW vs. WW), and recessive comparison model (MM vs. MW + WW) (WW, homozygotes for the wildtype allele; MW, heterozygotes; WW, homozygous for the mutant allele). The statistical significance of the ORs was determined with the Z-test, while the $\chi 2$ test was presented to assess the between-study heterogeneity [27]. Fixed effects model (the Mantel-Haenszel method) was used when the P value is more than 0.10 for the Q test; otherwise, the random effects model (the DerSimonian and Laird method) was adopted [28]. One-way sensitivity analyses were carried out to evaluate the stability of the pooled ORs, in which each individual study was removed from the meta-analysis to detect the effect of each individual data set on the pooled ORs. Moreover, we also conducted the Begg's funnel plots and Egger's test to evaluate the publication bias [29,30]. Hardy–Weinberg equilibrium (HWE) of controls was calculated by the $\chi 2$ test to compare the expected and actual genotype frequencies among the controls in each study. All the statistical tests in this meta-analysis were two-tailed, and *P*-values $\leq$ 0.05 were considered statistically significant.

2.5. In-silico analysis and Linkage disequilibrium (LD) analysis

In order to explore the influence of polymorphisms on CAV1, we replicated the association between the polymorphism and CAV1 expression levels using GTEx Analysis Release V6 (dbGaP Accession phs000424.v7.p2) data [31].

For LD analysis, data were extracted from the 1000 genomes Project comprising the polymorphisms in genes of CAV1 in the current study [32]. CHB (Han Chinese in Beijing, China), CHS (southern Han Chinese, China), CEU (Utah residents with Northern and Western European ancestry from the CEPH collection), JPT (Japanese in Tokyo, Japan) and YRI (Yoruba in Ibadan, Nigeria), ESN (Esan in Nigeria) were enrolled in the calculate project, analyses were performed with Haploview software, LD in each above-mentioned population was assessed by r^2 statistics.

3. Results

3.1. Characteristics of enrolled studies

According to the inclusion criteria, seven publications including

Table 2
Results of meta-analysis for CAV1 gene polymorphisms and urinary cancer susceptibility.

SNP	Genetic model	Analysis group	N	P_H	P_Z	Effects model	OR (95% CI)
rs1049314	M vs. W	Overall	3	0.836	0.272	Fixed	1.078 (0.943-1.233)
	MM vs. WW	Overall	3	0.721	0.406	Fixed	1.175 (0.803-1.721)
	MW vs. WW	Overall	2	0.325	0.444	Fixed	1.067 (0.904-1.259)
	MM + MW vs. WW	Overall	3	0.731	0.35	Fixed	1.078 (0.921-1.261)
	MM vs. MW + WW	Overall	3	0.646	0.398	Fixed	1.177 (0.807-1.717)
rs1049334	M vs. W	Overall	3	0.003	0.883	Random	0.976 (0.703-1.354)
	MM vs. WW	Overall	2	0.654	0.011*	Fixed	1.24 (1.052-1.462)
	MW vs. WW	Overall	3	0.004	0.98	Random	0.994 (0.595-1.658)
	MM + MW vs. WW	Overall	3	0.003	0.854	Random	0.966 (0.666-1.4)
	MM vs. MW + WW	Overall	2	0.724	0.03*	Fixed	1.198 (1.018-1.41)
rs1049337	M vs. W	Overall	3	0.686	0.131	Fixed	0.939 (0.866-1.019)
	MM vs. WW	Overall	2	0.516	0.418	Fixed	0.939 (0.807-1.093)
	MW vs. WW	Overall	3	0.967	0.048*	Fixed	0.882 (0.78-0.999)
	MM + MW vs. WW	Overall	3	0.816	0.068	Fixed	0.904 (0.811-1.007)
	MM vs. MW + WW	Overall	2	0.562	0.802	Fixed	0.982 (0.851-1.132)
rs12672038	M vs. W	Overall	4	0.884	0.858	Fixed	1.012 (0.886-1.157)
	MM vs. WW	Overall	4	0.921	0.92	Fixed	1.016 (0.743-1.389)
	MW vs. WW	Overall	4	0.843	0.866	Fixed	1.015 (0.852-1.209)
	MM + MW vs. WW	Overall	4	0.836	0.855	Fixed	1.015 (0.862-1.196)
	MM vs. MW + WW	Overall	4	0.936	0.944	Fixed	1.011 (0.744-1.373)
rs1997623	M vs. W	Overall	4	0.246	0.926	Fixed	1.022 (0.64-1.634)
	MW vs. WW	Overall	4	0.391	0.722	Fixed	0.912 (0.55-1.514)
	MM + MW vs. WW	Overall	4	0.308	0.897	Fixed	0.968 (0.594-1.578)
rs3757733	M vs. W	Overall	4	0.679	0.733	Fixed	0.977 (0.857-1.115)
	MM vs. WW	Overall	4	0.74	0.763	Fixed	0.956 (0.713-1.281)
	MW vs. WW	Overall	4	0.932	0.85	Fixed	0.983 (0.825-1.172)
	MM + MW vs. WW	Overall	4	0.822	0.786	Fixed	0.978 (0.83-1.151)
	MM vs. MW + WW	Overall	4	0.788	0.789	Fixed	0.962 (0.722-1.28)
rs3807987	M vs. W	Overall	4	< 0.001	0.644	Random	1.14 (0.655-1.984)
	MM vs. WW	Overall	4	< 0.001	0.646	Random	1.226 (0.514-2.924)
	MW vs. WW	Overall	4	< 0.001	0.38	Random	1.289 (0.732-2.27)
	MM + MW vs. WW	Overall	4	< 0.001	0.498	Random	1.246 (0.659-2.356)
	MM vs. MW + WW	Overall	4	0.003	0.619	Random	1.182 (0.612-2.284)
rs3807992	M vs. W	Overall	4	0.636	0.512	Fixed	0.959 (0.847-1.086)
	MM vs. WW	Overall	4	0.666	0.675	Fixed	0.943 (0.716-1.241)
	MW vs. WW	Overall	4	0.711	0.526	Fixed	0.946 (0.797-1.123)
	MM + MW vs. WW	Overall	4	0.684	0.492	Fixed	0.945 (0.804-1.11)
	MM vs. MW + WW	Overall	4	0.685	0.788	Fixed	0.964 (0.74-1.257)
rs7804372	M vs. W	Overall	5	< 0.001	0.043*	Random	0.734 (0.544-0.99)
	MM vs. WW	Overall	5	0.014	0.02*	Random	0.532 (0.313-0.905)
	MW vs. WW	Overall	5	< 0.001	0.408	Random	0.83 (0.533-1.291)
	MM + MW vs. WW	Overall	5	< 0.001	0.176	Random	0.75 (0.494-1.138)
	MM vs. MW + WW	Overall	5	0.299	< 0.001*	Fixed	0.58 (0.437-0.77)
	M vs. W	Prostate	2	0.649	< 0.001*	Fixed	0.571 (0.46-0.71)
	MM vs. WW	Prostate	2	0.432	< 0.001*	Fixed	0.325 (0.191-0.554)
	MW vs. WW	Prostate	2	0.894	< 0.001*	Fixed	0.603 (0.451-0.806)
	MM + MW vs. WW	Prostate	2	0.796	< 0.001*	Fixed	0.54 (0.41-0.712)
	MM vs. MW + WW	Prostate	2	0.487	< 0.001*	Fixed	0.398 (0.239-0.663)

P_H: P value of Q test for heterogeneity test; P_Z: means statistically significant ($P < 0.05$); RCC: renal cell carcinoma; BCa: bladder cancer; PCa: prostate cancer; UUTC: upper urothelial tract cancer; Note: Heterogeneity was considered to be significant when the P-value was less than 0.1. If there was no significant heterogeneity, a fixed effect model (Der-Simonian Laird) was used to evaluate the point estimates and 95% CI; otherwise, a random effects model (Der-Simonian Laird) was used. And the *Pz* was calculated based on the actual model adopted.

thirty-four case-control studies were enrolled in this meta-analysis [33–39]. The flow chart of study selection is shown in Fig. 1. The total of cancer cases and healthy controls were 13,778 and 20,581, respectively. The publication year of involved studies ranged from 2010 to 2015. Among these thirty-four studies, there are six upper urothelial tract cancer (UUTC) studies, six BCa studies, nine RCC studies and thirteen PCa studies. HWE test was conducted on the genotype distribution of the controls, eighteen studies did not deviate from the HWE. The characteristics of all included studies in the meta-analysis are presented in Table 1. In order to evaluate the quality of each enrolled study, we applied Newcastle-Ottawa Scale (NOS) [40], and fill the result in **Table S1**, the result of PRISMA2009 checklist was also listed to present our meta-analysis work **(Table S2)**.

3.2. Quantitative data synthesis

A summary of the meta-analysis findings of the correlation between *CAV1* polymorphisms and urinary cancer risk is provided in Table 2. An increased risk of rs1049334 polymorphism on urinary cancer were revealed in homozygote comparison model (MM vs. WW: OR = 1.240, 95% CI = 1.052–1.462, P = 0.011) and recessive comparison model (MM vs. MW + WW: OR = 1.198, 95% CI = 1.018–1.410, P = 0.030). What's more, rs17878467 polymorphism may play a protect role in the tumorigenesis of urinary cancer, shown in heterozygote comparison model (MW vs. WW: OR = 0.882, 95% CI = 0.78–0.999, P = 0.048). For rs7804372, the overall pooled results revealed a reducing risk in allelic contrast model (M vs. W: OR = 0.734, 95%CI = 0.544-0.99, P = 0.043) **(**Fig. 2**)**, homozygote comparison model (MM vs. WW: OR = 0.532, 95% CI = 0.313-0.905, P = 0.020) and recessive comparison model (MM vs. MW + WW: OR = 0.580, 95% CI = 0.437–0.77, P < 0.001). In the stratified analyses by cancer types, the risk of PCa is downgrade by rs7804372 in all five genetic models, allelic contrast model (M vs. W: OR = 0.571, 95%CI = 0.46–0.71, P < 0.001), homozygote comparison model (MM

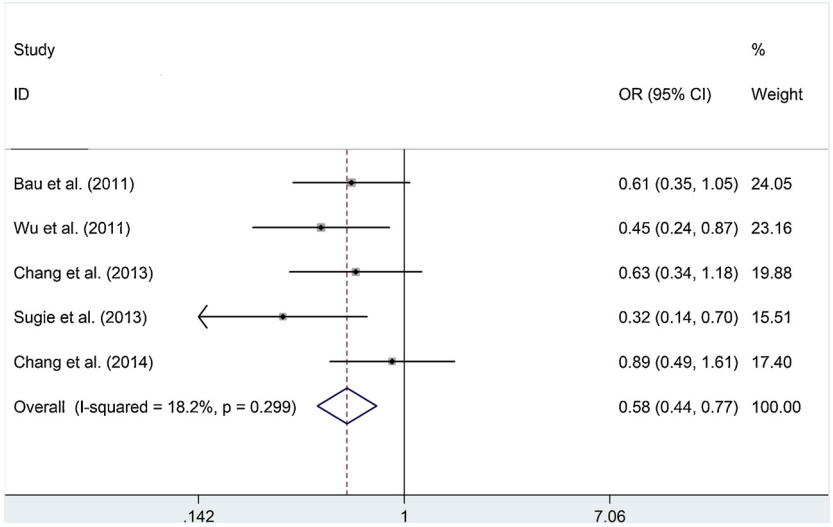

Fig. 2. Meta-analysis of the association between CAV1 rs7804372 polymorphism and urinary cancer risk (M vs. W).

vs. WW: OR = 0.325, 95% CI = 0.191-0.554, P < 0.001), heterozygote comparison model (MW vs. WW: OR = 0.603, 95% CI = 0.451–0.806, P < 0.001), dominant comparison model (MM + MW vs. WW: OR = 0.540, 95% CI = 0.410–0.712, P < 0.001) and recessive comparison model (MM vs. MW + WW: OR = 0.398, 95% CI = 0.239-0.663, P < 0.001). As to rs1049314, rs12672038, rs1997623, rs3757733, rs3807987 and rs3807992, there is no remarkable influence of them to the tumorigenesis of urinary cancer **(**Table 2**)**.

3.3. Sensitivity analysis

Sensitivity analysis was performed to assess the influence of each individual study on the overall result by removing it from the pooled analysis for each polymorphism. The analysis results suggested that no individual studies significantly affected the pooled ORs, indicating the result is robust **(Figure S1, S3, Table S3)**.

3.4. Publication bias

Publication biases within available research results might not be representative of all research results. Begg's funnel plot and Egger's linear regression test were performed to assess the publication biases of included studies. The shapes of the Begg's funnel plots did not reveal any evidence of obvious asymmetry under the dominant model **(Figure S2, S4)**. Egger's test also showed that there was no strong statistical evidence of publication bias under any polymorphism basic on M vs. W model. (rs1049314: $P =$ 0.228, rs1049334: $P =$ 0.35, rs1049337: $P =$ 0.64, rs12672038: $P =$ 0.536, rs1997623: $P =$ 0.536, rs3757733: $P =$ 0.626, rs3807987: $P =$ 0.286, rs3807992: $P =$ 0.168, rs7804372: $P = 0.849$,) **(Table S4)**.

3.5. In-silico analysis and LD analyses

According to the result on GTEx portal data, we found that the mutant allele leads to an increase expression of CAV1 mRNA in rs1049314 ($P = 6.0*10^{-14}$), rs1049334 ($P = 1.0*10^{-10}$), rs12672038 ($P = 2.4*10^{-9}$), rs3807987 ($P = 4.2*10^{-12}$), while the mutant allele of rs1049337 ($P = 9.5*10^{-9}$), rs1997623 ($P = 7.0*10^{-8}$), rs3757733 ($P = 3.8*10^{-6}$), rs3807992 ($P = 1.5*10^{-5}$), rs7804372 ($P = 2.8*10^{-6}$) result in a decrease expression of CAV1 (Fig. 3). LD analyses was performed to test the presence or absence of bins in the region containing these polymorphisms of *CAV1*, the results were presented in Fig. 4. In CEU, CHB, and YRI, significant LD was shown between rs3807987 and rs12672038, and among rs3757733, rs7804372, rs3807992 and rs1049314. For CHS, rs3757733, rs7804372, rs3807992 shown significant LD, as well as rs1262038 and rs1049314. As to JPT, rs3807987, rs12672038, rs3757733, rs7804372, rs3807992 and rs1049334 all shown LD with each other polymorphism. The ESN population only shown low LD between rs3757733 and rs7804372, rs3807992 and rs1049314.

4. Discussion

In solid tumors, CAV1 has detected to be overexpressed or variated to impact the process of tumorigenicity, but the effect is still controversial in epithelial tumors. The loss of CAV1 could promote the progress of tumor cell proliferation, progression, as well as angiogenesis. [41] Galbiati et al. [42] suggest that upregulation of caveolin-1 may result in the contact inhibition and negatively regulating the activation state of the p42/44 MAP kinase cascade to inhibit tumorigenesis. Volonte et al. [43] report that CAV1 could promote the premature senescence of human bronchial epithelial, and CAV1 expression is dramatically decreased in lung cancer patients, it means CAV1 has an inhibiting effect with lung cancer. However, Park et al. [44] report the upregulating of caveolin-1 RCC tissues during the chemotherapy of doxorubicin, caveolin-1 may provide a growth associated function to RCC cells, eventually might develop lung metastasis. Karam et al. [45] present that caveolin-1 over-expression leads to increased risk of aggressive PCa recurrence in both univariate and multivariate analysis. Pellinen et al. [46] report that caveolin-1 overexpression could promote tumorigenesis, through switching TGFβ signaling from tumor-suppressive to oncogenic in PCa.

According to the result from Biomuta database, about 45 unique polymorphisms had been recorded, while several of them have been illustrated to be associated with the tumorigenicity of urinary cancer [47]. Bau et al. [39] firstly reported the risk of CAV1 polymorphism on BCa in 2011, that rs3807987 shows an increase risk of BCa, while rs7804372 acts as a protector. On the contrast, Chang et al. [36] displayed an increased risk of RCC causes by the A allele of rs7804372. For rs1049314, rs1049334 and rs1049337, Langeberg et al. [38] suggested that they are not associated with the risk of PCa in both Caucasian and African, but a latest study conducted by Zhao et al. [35] revealed that rs1049334 predicts an upgrade risk of RCC. Due to the inconsistent result of the association between CAV1 polymorphisms and urinary cancer risk, our team comprehensively searched and recorded all eligible publications, and conducted a meta-analysis to remove the fog.

In the current study, we finally enrolled 7 eligible publications,

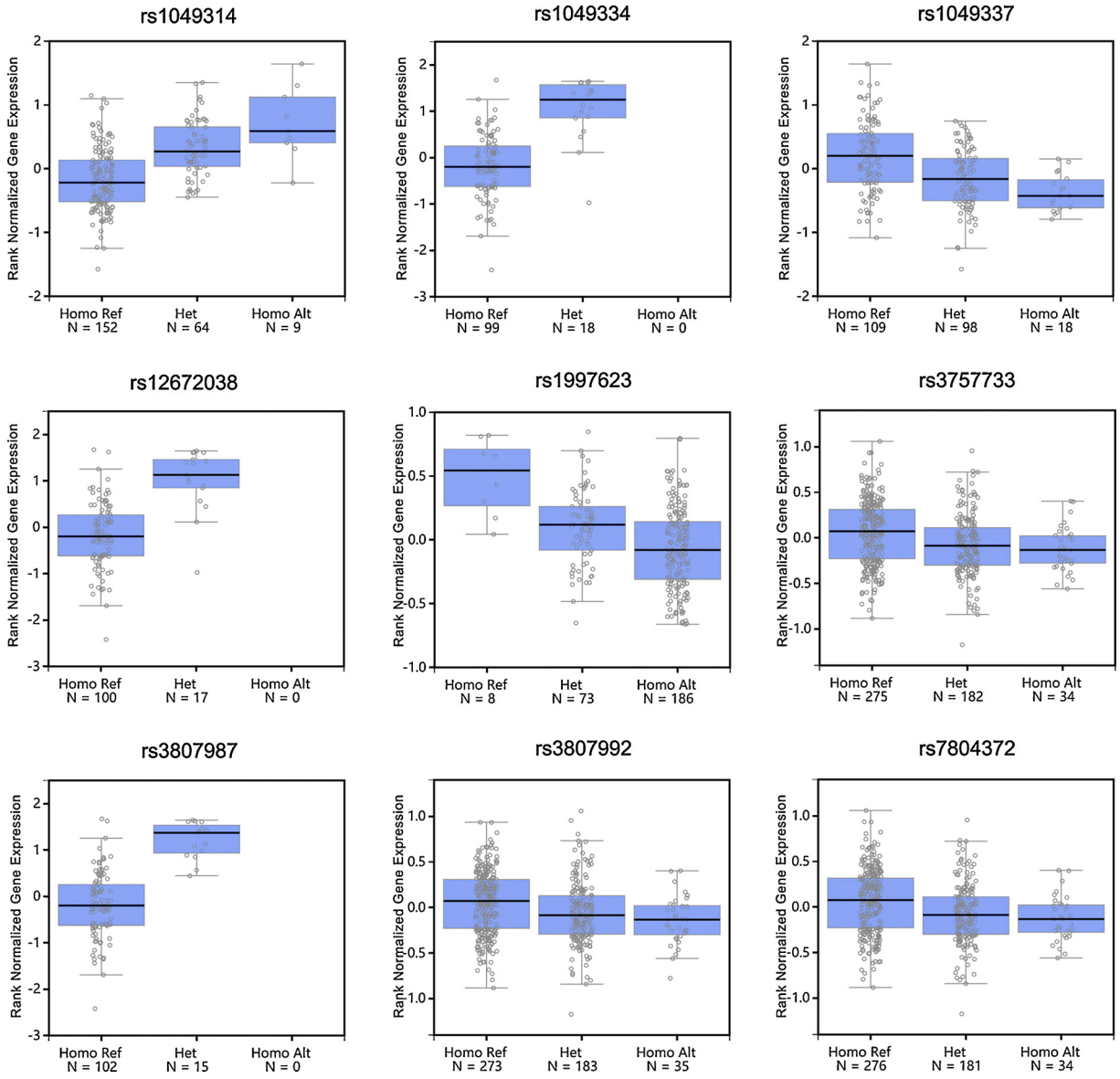

Fig. 3. In-silico analysis of CAV1 expression concerned to its polymorphisms and urinary cancer. CAV1 mRNA expression by eQTL analysis in Human tissues based on GTEx database. rs1049314 and rs1049337 detected in testis; rs1049334, rs12672038 and rs3807987 detected in lymphocytes; rs1997623 detected in aorta; rs3757733, rs3807992 and rs7804372 detected in musle-skeletal.

which concerned about the risk of urinary cancer influenced by CAV1 polymorphisms. The mutant AA genotype of rs1049334 causes an increasing risk of overall urinary cancer, as well as shown an upgrade risk in the subgroup analysis of PCa. As to polymorphism rs7804372, the homozygote model and recessive model also indicated the protect effect of mutant A allele and AA genotype. What's more, the heterozygote CT genotype of rs1049337 may also down regulate the risk of urinary cancer. The in-silico analysis by GTEx portal demonstrated that the mutant allele of rs1049314, rs1049334, rs12672038, rs3807987 lead to a dose dependent upgrade expression of CAV1 mRNA, while the mutant allele of rs1049337, rs1997623, rs3757733, rs3807992, rs7804372 show an opposite function. The result of LD analysis indicated that we should focused on the co-effective of different polymorphisms of CAV1 when assess whether affect the tumorigenesis of urinary cancer in the future study.

Results of current study about CAV1 polymorphisms and urinary cancer risk should be cautiously interpreted, because there are some limitations. Firstly, an insufficient capacity that slight effects on cancer susceptibility occurred, because of the small size of stratified analyses conducted by the cancer type, ethnicity, source of control. Secondly, confounding factors such as age, gender, smoking, and drinking was ignored, so we are unable to perform a further assessment of potential gene-environment interactions. Thirdly, we only enrolled publications written in English or Chinese, missing publications from other languages may cause potential bias.

In conclusion, we uncover that rs1049334 polymorphism of CAV1 upgrade the risk of urinary cancer, while rs1049337 and rs7804372 polymorphisms may act as a protector of urinary cancer. Further large and well-designed studies in various populations are needed to confirm our results.

Author contribution

S.F. and J.M. performed the literature search, data extraction, and statistical analysis and wrote the manuscript. J.M. and M.Z. supervised the literature search, data extraction, analysis, Z.H. and C.L. reviewed the manuscript.

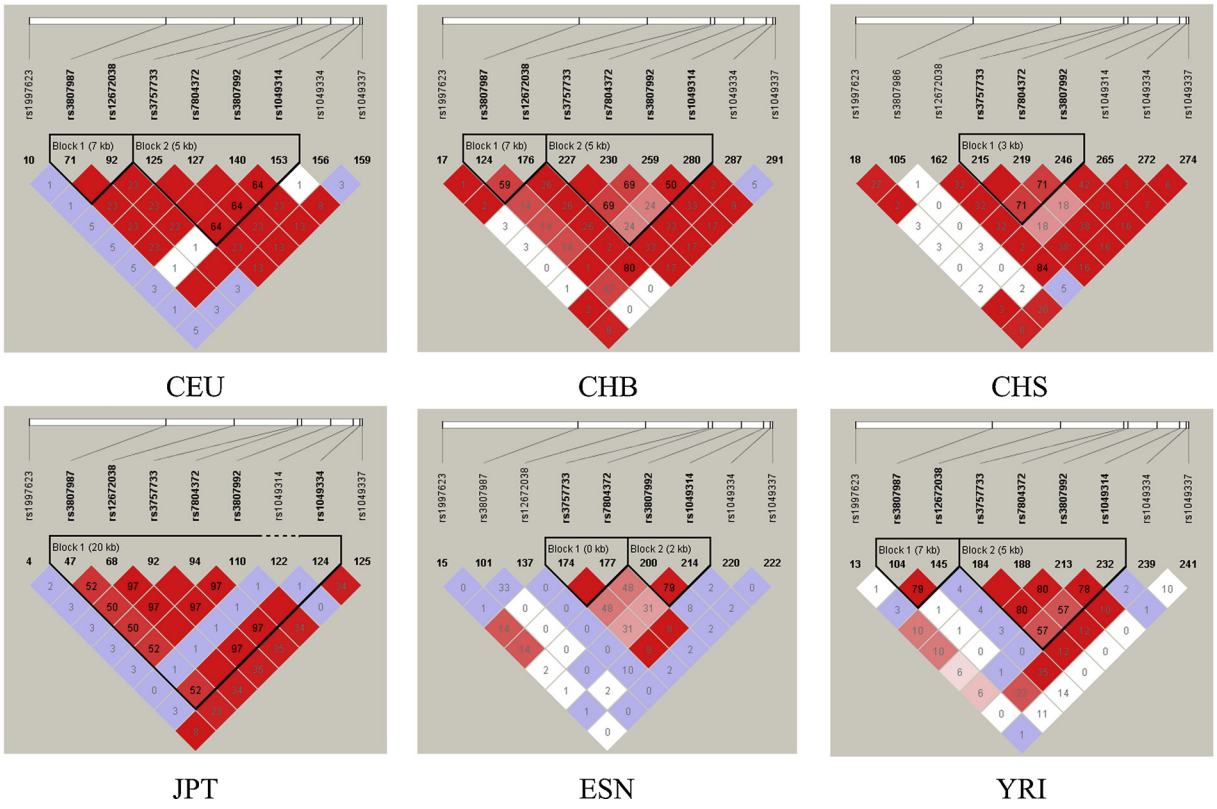

Fig. 4. Linkage disequilibrium analyses for CAV1 polymorphisms in populations from 1000 genomes Phase 3. The number of each cell represents r^2 and white color cells shows no LD between polymorphisms. Population descriptors: CEU: Utah residents with Northern and Western European ancestry from the CEPH collection; CHB: Han Chinese in Beijing, China; CHS: Southern Han Chinese, China; JPT: Japanese in Tokyo, Japan; YRI: Yoruba in Ibadan, Nigeria; ESN: Esan in Nigeria.

Competing interest

None.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.prp.2018.11.009.

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