New concept on association of FGFR4 G388R, V10I polymorphisms and risk of cancer

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Abstract

Background: The correlation between G388R, V10I polymorphisms of fibroblast growth factor receptor (FGFR) 4 gene and risk of carcinoma has been investigated previously, but the results are contradictory.

Methods: Odds ratios (ORs) with 95% confidence intervals (95% CIs), in silico tools and immunohistochemical staining (IHS) were adopted to assess the association.

Results: Totally, 13,793 cancer patients and 16,179 controls were evaluated in the pooled analysis. When all the studies were summarized, we found that G388R polymorphism is associated with elevated susceptibility to cancer under homozygous comparison (OR = 1.21, 95%CI = 1.03 - 1.43, P = 0.020) and recessive genetic model (OR = 1.21, 95%CI = 1.04 - 1.41, P = 0.012). In stratification analysis by cancer type and ethnicity, similar findings were indicated in prostate cancer, breast cancer, and Asian descendants. Polyphen2 bioinformatics analysis showed that the G388R mutation is predicted to be possibly damaging to the protein function of FGFR4. IHS analysis indicated that the FGFR4 expression is increased in more advanced prostate cancer.

Conclusion: FGFR4 G388R polymorphism may be associated with cancer risk, especially in prostate cancer, breast cancer, and Asian descendants. Up-regulation of FGFR4 may be related to a poor prognosis in prostate cancer.

1 Background

Cancer remains a global threat to public health and poses a huge economic burden on society of both developing and developed countries nowadays. Breast cancer, colorectal cancer (CRC), prostate cancer, hepatocellular carcinoma (HCC), head and neck squamous cell carcinoma (HNSCC) are the most common cancers in the world. However, the etiology underlying cancer development is far from being comprehensively demonstrated (Torre et al., 2005). Gene mutation, such as single nucleotide polymorphism (SNP), has been indicated to have an impact on susceptibility of cancer in recent years (Shao et al., 2018; Zhang et al., 2019).

Fibroblast growth factor receptor 4 (FGFR4) is one member of the family of fibroblast growth factor receptors. It displays a variety of biological activities, including angiogenic and mitogenic activities. It can also transduce signals of more than 20 known ligands such as cell proliferation, differentiation and development (Wilkie et al., 1995; Powers et al., 2000). FGFR4 is highly activated in many types of solid tumors and hematological malignancies, in which it drives the development and progression of cancer as an oncogene (Tang et al., 2018). In addition, immunohistochemical evaluation showed that the strong expression of FGFR4 in malignant tumor cells was significantly correlated with the increase of clinical stage and tumor grade and the decrease of patients' survival rate (Gowardhan et al., 2005).

Recently, several studies have concentrated on the relationship between FGFR4 gene variant and the susceptibility of cancer (Chen et al., 2019; Li et al., 2017; Chou et al., 2017; Xiong et al., 2017; Wimmer et al., 2019). A common SNP rs351855, which leads to substitution of glycine by arginine at codon 388 in the domain of EGFR4 receptor (Gly388Arg, G388R), was reported to be associated with cancer risk. In 2017, previous meta-analysis assessed the EGFR4 G388R polymorphism and found that it was correlated with an elevated susceptibility of several cancers (Xiong et al., 2017). Since then, more case-control studies have appeared. Nevertheless, the correlation between FGFR4 G388R, V10I variants and susceptibility of carcinoma remains controversial. To comprehensively investigate the relationship between FGFR4 G388R, V10I variants and cancer risk, we conducted the present analysis based on all eligible studies and used online database and immunohistochemical staining (IHS) to further assess the expression of FGFR4 (Wimmer et al., 2019; Chen et al., 2019; Li et al., 2017; Chou et al., 2017; Sheu et al., 2015; Jiang et al., 2015; Ture et al., 2015; Gao et al., 2014; Shen et al., 2013; Heinzele et al., 2012; Yang et al., 2011; Batschauer et al., 2011; Ho et al., 2010; Tanuma et al., 2010; FitzGerald et al., 2009; Ho et al., 2009; Naidu et al., 2009; Nan et al., 2009; Ma et al., 2008; Mawrin et al., 2006; Spinola et al., 2005; Wang et al., 2004; Morimoto et al., 2003; Bange et al., 2002).

2 Methods

2.1 Literature identification

A comprehensive search of eligible publications relating the FGFR4 G388R, V10I polymorphisms and cancer risk was performed using PubMed, PMC database, Google scholar, and Chinese Wanfang database. The search terms were: ('FGFR4' OR 'fibroblast growth factor receptor 4') AND ('variant' OR 'mutation' OR 'polymorphism') AND ('cancer' OR 'carcinoma' OR 'malignant tumor'). The latest search was conducted in June 2 2020. The reference of related reviews and original articles as well as supplementary material was also evaluated to maximize the coverage of the present analysis.

2.2 Inclusion criteria and exclusion criteria

The inclusion criteria were as follows: (a) investigation of the relationship between FGFR4 G388R, V10I polymorphisms and risk of cancer; (b) cohort or case-control studies; (c) sufficient genotype information to calculate OR and 95% CI; (d) *P* value for Hardy-Weinberg equilibrium (HWE) of controls must more than 0.05. Articles that departed from HWE were removed. We also excluded studies with no control population. When repeated studies appeared, only the latest or largest articles were enrolled.

2.3 Data extraction

Two authors searched the research and extracted data from individual studies independently according to the inclusion criteria. Information collected from all eligible studies contain the name of first author, publication date, ethnicity of study location, source of control, number of genotyped cases and controls, *P* value for HWE of controls, genotyping method.

2.4 Statistical analysis

We adopted ORs with 95% CI to explore the correlation between FGFR4 G388R, V10I polymorphisms and risk of cancer. For G388R variant, five genetic models were carried out (allelic contrast, R vs. G; heterozygous model, RG vs. GG; homozygous model, RR vs. GG; dominant model, RR + RG vs. GG; recessive model RR vs. RG + GG). For V10I polymorphism, the five models were as follows: I vs. V; IV vs. VV; II vs. VV; II + IV vs. VV; II vs. IV + VV. Homogeneity of study was calculated by a chi-square based Q-test. *P* value > 0.05 indicated a lack of heterogeneity, the summary OR was evaluated by fixed-effects model (Mantel-Haenszel method). Otherwise, random effects model was employed. Begg's funnel plot and sensitivity analysis was conducted to assess the publication bias. Stratification analysis was applied to evaluate the impact of ethnicity and cancer type. All statistical analyses were conducted using Stata software (Stata Corporation, College Station, TX, version 11.0).

2.5 *In silico* and IHS analysis of FGFR4 expression

We employed online database to assess the promoter methylation level of FGFR4 in prostate cancer. Moreover, gene-gene interaction of FGFR4 was also evaluated by online database (<http://ualcan.path.uab.edu/analysis.html>). The Cancer Genome Atlas (TCGA) samples were also applied to investigate the effect of FGFR4 expression on overall survival (OS) time (<http://genomics.jefferson.edu/proggene/results.php>). The relationship between G388R, V10I polymorphisms and FGFR4 protein damaging was analyzed by Polyphen2 tools (<http://genetics.bwh.harvard.edu/pph2/>). Furthermore, we used IHS to test the tissue expression of FGFR4 in prostate cancer subjects recruited by our centers. Paraffin-embedded samples were stained with hematoxylin and eosin to confirm cancer. Tissue sections were dewaxed in xylene, dehydrated in alcohol and washed in phosphate buffer (PBS). Each slice was incubated overnight with rabbit anti-FGFR4 monoclonal antibody at 4 °C. After rinsing with PBS for 3 times, the slices were incubated with secondary antibody at room temperature for 30 minutes. PBS was used instead of primary antibody as negative control. The present study was approved by Ethics Committee of Changzhou No.2 People's Hospital and Affiliated Hospital of Jiangnan University.

3 Results

3.1 Characteristics of relevant studies

Totally, data were collected on 29,972 participants (13,793 cancer subjects and 16,179 controls) from 30 case-control studies on FGFR4 G388R polymorphism. The most common types of cancer were prostate cancer (6 studies, *n* = 4,610), breast cancer (6 studies, *n* = 3,008), hepatocellular carcinoma (HCC) (3 studies, *n* = 2,481), oral squamous cell carcinoma (OSCC) (2 studies, *n* = 2,396), colorectal cancer (CRC) (3 studies, *n* = 2,349), lung cancer (2 studies, *n* = 899) (Table 1). In subgroup analysis by ethnicity, 15 studies were based on European population, 13 studies on Asian descendant, 1 study on Latins, and 1 study on Africans. For FGFR4 V10I variant, 7 studies with 9,369 subjects (4,377 cases and 4,992 controls) were identified in total. 4 studies focused on Asian population (*n* = 5,055), 2 on Europeans (*n* = 4,087), and 1 on Africans (*n* = 227). In stratification analysis by cancer type, 2 studies concentrated on prostate cancer. There was only one study each on cervical cancer, OSCC, breast cancer, HCC, and skin cancer. Moreover, minor allele frequencies (MAF) from the main worldwide population were also investigated. For FGFR4 G388R polymorphism, global population, 0.300; African descendants, 0.110; Americans, 0.310; East Asians, 0.463; Europeans, 0.294; South Asians, 0.390 (Fig. 1A). For FGFR4 V10I variant, global population, 0.229; African descendants, 0.018; Americans, 0.320; East Asians, 0.1; Europeans, 0.180; South Asians, 0.210 (Fig. 1B).

3.2 Main results

The overall result showed that FGFR4 G388R variant was associated with elevated susceptibility to cancer under homozygous comparison (OR = 1.21, 95%CI = 1.03–1.43, $P_{\text{heterogeneity}} < 0.001$, *P* = 0.020) and recessive genetic model (OR = 1.21, 95%CI = 1.04–1.41, *P* value for heterogeneity < 0.001, *P* = 0.012, **Table 2**). In stratification analysis by cancer type, similar positive findings were indicated in prostate cancer (allelic contrast, OR = 1.17, 95%CI = 1.07–1.29, $P_{\text{heterogeneity}} = 0.183$, *P* = 0.001; heterozygous, OR = 1.16, 95%CI = 1.02–1.32, $P_{\text{heterogeneity}} = 0.714$, *P* = 0.025; dominant model, OR = 1.20, 95%CI = 1.06–1.35, $P_{\text{heterogeneity}} = 0.892$, *P* = 0.004, Fig. 2A) and breast cancer (allelic contrast, OR = 1.26, 95%CI = 1.13–1.41, $P_{\text{heterogeneity}} = 0.622$, *P* < 0.001; heterozygous comparison, OR = 1.25, 95%CI = 1.07–1.47, $P_{\text{heterogeneity}} = 0.186$, *P* = 0.005; homozygous comparison, OR = 1.73, 95%CI = 1.35–2.20, $P_{\text{heterogeneity}} = 0.960$, *P* < 0.001; recessive model, OR = 1.32, 95%CI = 1.14–1.54, $P_{\text{heterogeneity}} = 0.197$, *P* < 0.001; dominant model, OR = 1.46, 95%CI = 1.17–1.83, $P_{\text{heterogeneity}} = 0.986$, *P* = 0.001). In subgroup analysis by ethnicity, we observed that FGFR4 G388R variant was also correlated with increased risk to cancer in Asian descendants (RR vs. GG, OR = 1.29, 95%CI = 1.01–1.66, *P* value for heterogeneity < 0.001, *P* = 0.043; RR vs. RG + GG, OR = 1.28, 95%CI = 1.02–1.60, $P_{\text{heterogeneity}} < 0.001$, *P* = 0.034, Fig. 3A). For FGFR4 V10I polymorphism, no significant correlation was found when all studies pooled together (I vs. V, OR = 0.94, 95%CI = 0.85–1.04, *P* value for heterogeneity = 0.049, *P* = 0.227; IV vs. VV, OR = 0.97, 95%CI = 0.89–1.07, $P_{\text{heterogeneity}} = 0.169$, *P* = 0.601; II vs. VV, OR = 0.92, 95%CI = 0.72–1.17, *P* value for heterogeneity = 0.020, *P* = 0.488; II + IV vs. VV, OR = 0.95, 95%CI = 0.87–1.04, *P* value for heterogeneity = 0.147, *P* = 0.300, Fig. 2B; II vs. IV + VV, OR = 0.90, 95%CI = 0.74–1.11, *P* value for heterogeneity = 0.020, *P* = 0.328). Similar findings were indicated in subgroup analysis by cancer type. In stratification analysis by ethnicity, no positive association was identified in Asian population (II vs. IV + VV, OR = 0.85, 95%CI = 0.66–1.08, $P_{\text{heterogeneity}} = 0.021$, *P* = 0.184, Fig. 3B) and European descendants (II vs. IV + VV, OR = 1.08, 95%CI = 0.83–1.42, $P_{\text{heterogeneity}} = 0.825$, *P* = 0.563).

3.3 *In silico* and IHS analysis of FGFR4 expression

We used *in silico* tools to investigate whether the G388R and V10I mutation could affect the protein function of FGFR4. Polyphen2 bioinformatics analysis showed that FGFR4 G388R is predicted to be possibly damaging with a score of 0.700 to the protein function (Fig. 4A). Nevertheless, the V10I variation is predicted to be benign with a score less than 0.001 to the FGFR4 protein function (Fig. 4B). We also utilized online database to assess the expression of FGFR4 in prostate cancer participants. As described in Fig. 5A, the FGFR4 expression is elevated in prostate cancer, as compared to control. The Cancer Genome Atlas (TCGA) samples were also adopted to investigate the effect of FGFR4 expression on overall survival (OS) time. No significant difference on the OS time can be observed between the high FGFR4 expression group and low expression group ($P > 0.05$, Fig. 5B). In order to demonstrate the expression of FGFR4 in prostate cancer tissues, we applied IHS to evaluate its expression among prostate cancer patients in our centers. The feature distribution from prostate cancer volunteers has been provided in our previous article (Zhang et al., 2020). As described in Fig. 6, the expression of FGFR4 is up-regulated in more advanced cases, as compared to ones in early stage (T3 + T4 versus T1, $P < 0.05$). Moreover, the gene-gene correlation of FGFR4 was also assessed. At least 24 genes can participate in the interaction with FGFR4 (Fig. 7A). Among them, CORIN (corin, serine peptidase, Fig. 7B) is predicted to positively correlated with FGFR4.

3.4 Publication bias and sensitivity analysis

Begg's funnel plot was employed to investigate the publication bias. No evidence of asymmetry was observed for FGFR4 G388R ($t = -1.52$, $P = 0.140$, Fig. 8A) and V10I variant ($t = 0.07$, $P = 0.945$, Fig. 8B). Sensitivity analysis about FGFR4 G388R, V10I polymorphisms and risk of cancer was conducted by removing individual study in turn. No single study could influence the overall OR, which showed that the results of the above analysis for FGFR4 G388R (Fig. 8C) and V10I (Fig. 8D) polymorphisms are trustworthy.

4 Discussion

The etiology of cancer has not been totally elucidated. Clinically, single nucleotide polymorphisms can have various influences on the development of diseases, including cancer (Ding et al., 2018; Dai et al., 2019; Zhu et al., 2019). The association between FGFR4 G388R, V10I variants and susceptibility of cancer has been evaluated previously, but the results remain conflicting. Ma et al performed a case-control study and found that R allele of the G388R variant indicated a significant impact on the development and progression of prostate cancer in Japanese descendants (Ma et al., 2008). However, this conclusion could not be confirmed by the research of FitzGerald et al, who observed no positive correlation of the FGFR4 G388R, V10I polymorphism with the prostate cancer susceptibility in Caucasians or African Americans (FitzGerald et al., 2009). Xiong et al carried out a meta-analysis using the articles published before October 2016 to assess the effect of FGFR4 G388R variant (Xiong et al., 2017). It showed evidence that G388R variant was correlated with an elevated susceptibility of prostate and breast cancer, but with a reduced risk of lung cancer. In our analysis, all eligible studies based on inclusion criteria were included to extensively evaluate the association between FGFR4 G388R, V10I variants and susceptibility of cancer. We further adopted *in silico* and IHS analysis to confirm the above conclusion.

We performed a pooled analysis containing 9,416 cancer participants and 11,187 control subjects to investigate the relationship between FGFR4 G388R variant and susceptibility of cancer. When all the studies were pooled, we found that G388R polymorphism is associated with elevated risk to cancer. Furthermore, stratifying by type of cancer, we observed that this variant is correlated with prostate and breast cancer, but not with lung cancer. Our results are consistent with the studies conducted by Xu et al and Wei et al (Xu et al., 2011; Wei et al., 2018). In subgroup analysis by ethnicity, we also found that FGFR4 R-allele is correlated with an increased risk of cancer in Asian descendants. For FGFR4 V10I polymorphism, no significant relationship was indicated in both the overall and stratifying analysis. Moreover, *in silico* tool was applied to investigate whether the G388R and V10I mutation could affect the protein function of FGFR4. It showed evidence that G388R mutation, but not V10I, is predicted to be possibly damaging to the protein function of FGFR4. We further utilized TCGA samples to assess the expression of FGFR4 in prostate cancer participants. The FGFR4 expression is elevated in prostate cancer, as compared to control group. Nevertheless, no significant difference on the OS time can be identified between the high FGFR4 expression group and low expression group. In addition, we applied IHS to evaluate its expression among prostate cancer subjects in our centers. The expression of FGFR4 is increased in more advanced cases, which indicates that up-regulation of FGFR4 is related to a poor prognosis of prostate cancer.

There are some potential limitations in the present analysis should be interpreted. First of all, P value of heterogeneity is less than 0.05 in five genetic models when all studies pooled together to assess the FGFR4 G388R polymorphism. Although the Der Simonian and Laird method (random-effect model) was performed (DerSimonian et al., 1986), conclusion from the above analysis may be influenced by potential bias. Second, the number of eligible studies for FGFR4 V10I variant in present analysis remains insufficient for more comprehensive analysis. In subgroup analysis by cancer type, only two studies concentrated on prostate cancer. There was one study each on cervical cancer, OSCC, breast cancer, HCC, and skin cancer. Further research including more participants in various carcinomas are warranted to confirm this effect. Third, previous study demonstrated that FGFR4 G388R polymorphism was related to up-regulation of FGFR4 in breast cancer (Wei et al., 2018). Further functional experiments are required to conduct in prostate cancer to determine whether the G388R mutation is responsible for an increased expression of FGFR4. Importantly, at least 24 genes are involved in the interaction with FGFR4. Among them, CORIN (corin, serine peptidase) is predicted to positively correlated with FGFR4. Since few studies on their specific connection can be retrieved from online database, future *in vitro* studies are needed to ascertain these correlations in more detail.

5 Conclusions

In summary, our study showed that FGFR4 G388R polymorphism is associated with elevated risk to cancer, especially for prostate and breast cancer. R-allele of FGFR4 G388R variant is correlated with an increased risk of cancer in Asian descendants. The G388R mutation, but not V10I, is predicted to be possibly damaging to the protein function of FGFR4. Up-regulation of FGFR4 may be related to a poor prognosis in prostate cancer.

Abbreviations

CIs: confidence intervals; HNSCC: head and neck squamous cell carcinoma; HCC: hepatocellular carcinoma; OSCC: oral squamous cell carcinoma; CRC: colorectal cancer; HWE: Hardy-Weinberg equilibrium of controls; HB: hospital-based; IHS: immunohistochemical staining; MAF: minor allele frequencies; NA: not available; NHL: non-Hodgkin's lymphoma; ORs: odds ratios; OS: overall survival; PB: population-based; PCR-RFLP: polymerase chain reaction and restrictive fragment length polymorphism

Declarations

Availability of data and materials

All the data generated in the above research is included in the current manuscript.

Ethics approval and consent to participate

The present research was approved by Ethics Committee of Changzhou No.2 People's Hospital and Affiliated Hospital of Jiangnan University.

Consent for publication

Not applicable.

Competing interests

The authors declare no conflict of interest.

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Authors' contributions

Conceptualization, YYM, LZ, and LFZ; Methodology, ZZ, KX, and YYS; Resources, WZ, TP, and WY; Formal analysis, HW, and XLZ; Manuscript writing, ZZ, KX, and LFZ. All the authors have agreed to the submission of the manuscript.

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Tables

Table 1 Basic information of included studies for FGFR4 G388R, V10I variants and risk of cancer.

First author	Year	Origin	Cancer	Ethnicity	Source	Case	Control	Case			Control			HWE	Method
G388R								RR	RG	GG	RR	RG	GG		
Wimmer	2019	Germany	HNSCC	European	PB	284	123	12	84	188	8	60	55	0.114	PCR-RFLP
Chen	2018	Taiwan	Cervical cancer	Asian	HB	226	335	56	101	69	74	165	96	0.845	TaqMan
Li	2017	China mainland	Cervical cancer	Asian	HB	162	162	48	79	35	40	72	50	0.170	PCR-RFLP
Chou	2017	Taiwan	OSCC	Asian	PB	955	1191	206	524	225	334	596	261	0.873	TaqMan
Sheu	2015	China mainland	HCC	Asian	HB	289	595	57	150	82	122	314	159	0.146	TaqMan
Jiang	2015	China mainland	Breast cancer	Asian	NA	747	716	138	404	205	98	348	270	0.398	Snaps
Ture	2015	Turkey	Lung cancer	European	HB	124	100	11	47	66	6	46	48	0.242	PCR-RFLP
Gao	2014	China mainland	NHL	Asian	NA	421	486	115	189	117	75	240	171	0.541	PCR-RFLP
Shen	2013	China mainland	Gastric cancer	Asian	PB	304	392	62	124	118	72	188	132	0.724	Sequencing
Heinzle	2012	Austria	CRC	European	PB	85	1660	10	33	42	135	723	802	0.114	TaqMan
Yang	2012	China mainland	HCC	Asian	HB	711	740	144	351	216	132	361	247	0.996	TaqMan
Batschauer	2011	Brazil	Breast cancer	Latin	PB	68	85	3	26	39	3	35	47	0.249	PCR-RFLP
Ho	2010	UK	Prostate cancer	European	PB	397	291	32	182	183	24	117	150	0.860	TaqMan
Tanuma	2010	Japan	OSCC	Asian	HB	150	100	28	53	69	10	48	42	0.487	PCR-S
FitzGerald	2009	USA	Prostate cancer	European	PB	1254	1251	123	544	587	124	496	631	0.070	SNPlex
FitzGerald	2009	USA	Prostate cancer	African	PB	146	80	3	39	104	2	18	60	0.646	SNPlex
Ho	2009	Singapore	HCC	Asian	PB	58	88	14	17	27	20	38	30	0.241	Sequencing
Naidu	2009	Malaysia	Breast cancer	Asian	HB	387	252	36	172	179	15	105	132	0.322	PCR-RFLP
Nan	2009	USA	Skin cancer	European	PB	768	833	78	325	365	84	343	406	0.359	TaqMan
Ma	2008	Japan	Prostate cancer	Asian	HB	492	179	133	196	163	25	87	67	0.701	PCR-RFLP
Mawrin	2006	Germany	Glioma	European	HB	94	25	4	51	39	2	13	10	0.428	PCR-RFLP
Spinola	2005	Italy	Lung cancer	European	HB	274	401	22	104	148	40	168	193	0.699	Pyrosequencing
Spinola	2005	Italy	Breast cancer	European	HB	142	220	20	55	67	25	83	112	0.117	Pyrosequencing
Spinola	2005	Italy	CRC	European	HB	179	220	18	63	98	25	83	112	0.117	Pyrosequencing
Wang	2004	USA	Prostate cancer	European	PB	284	97	42	117	125	4	40	53	0.291	PCR-RFLP
Wang	2004	USA	Prostate cancer	European	PB	45	94	2	6	37	0	18	76	0.305	PCR-RFLP
Morimoto	2003	Japan	Sarcomas	Asian	NA	143	102	17	72	54	13	50	39	0.624	PCR-RFLP
Bange	2002	Russia	Breast cancer	European	PB	61	123	7	28	26	8	60	55	0.114	PCR-RFLP
Bange	2002	Germany	Breast cancer	European	PB	84	123	9	34	41	8	60	55	0.114	PCR-RFLP
Bange	2002	Italy	CRC	European	PB	82	123	7	38	37	8	60	55	0.114	PCR-RFLP
V10I								II	IV	VV	II	IV	VV		

Chen	2018	Taiwan	Cervical cancer	Asian	HB	227	335	61	105	61	76	168	91	0.927	TaqM:
Chou	2017	Taiwan	OSCC	Asian	PB	955	1191	228	514	213	326	580	285	0.391	TaqM:
Jiang	2015	China mainland	Breast cancer	Asian	NA	747	716	168	408	171	226	364	126	0.322	Snaps
Sheu	2015	China mainland	HCC	Asian	HB	289	595	64	160	65	144	300	151	0.835	TaqM:
Nan	2009	USA	Skin cancer	European	PB	753	821	41	251	461	43	271	507	0.390	TaqM:
FitzGerald	2009	USA	Prostate cancer	European	PB	1259	1254	72	405	782	65	447	742	0.827	SNPle
FitzGerald	2009	USA	Prostate cancer	African	PB	147	80	0	15	132	0	10	70	0.551	SNPle

HNSCC: head and neck squamous cell carcinoma; HCC: hepatocellular carcinoma; OSCC: oral squamous cell carcinoma; CRC: colorectal cancer; HWE: Hardy-Weinberg equilibrium of controls; HB: hospital-based; NA: not available; NHL: non-Hodgkin's lymphoma; PB: population-based; PCR-RFLP: polymerase chain reaction and restrictive fragment length polymorphism.

Table.2 Stratified analysis of FGFR4 G388R and V10I polymorphisms on susceptibility of cancer

Variables	N ^a	Case/	OR(95%CI) <i>P</i> _{heter} <i>P</i>	OR(95%CI) <i>P</i> _{heter} <i>P</i>	OR(95%CI) <i>P</i> _{heter} <i>P</i>	OR(95%CI) <i>P</i> _{heter} <i>P</i>	OR(95%CI) <i>P</i> _{heter} <i>P</i>
		Control	M-allele vs. W-allele	MW vs. WW	MM vs. WW	MM+MW vs. WW	MM vs. MW+WW
G388R							
Total	30	9416/11187	1.06(0.98-1.15) <0.001 0.123	0.99(0.90-1.09) 0.003 0.820	1.21(1.03-1.43) <0.001 0.020	1.03(0.94-1.14) <0.001 0.526	1.21(1.04-1.41) <0.001 0.012
Ethnicity							
Asian	13	5045/5338	1.12(0.99-1.26) <0.001 0.078	1.03(0.89-1.18) 0.011 0.715	1.29(1.01-1.66) <0.001 0.043	1.09(0.94-1.26) 0.002 0.247	1.28(1.02-1.60) <0.001 0.034
European	15	4157/5684	1.01(0.90-1.13) 0.013 0.876	0.94(0.81-1.09) 0.016 0.396	1.10(0.94-1.28) 0.198 0.238	0.97(0.84-1.12) 0.010 0.669	1.08(0.93-1.26) 0.296 0.306
African	1	146/80	1.14(0.66-1.98) - 0.635	1.25(0.66-2.38) - 0.496	0.87(0.14-5.33) - 0.876	1.21(0.65-2.25) - 0.544	0.82(0.13-5.00) - 0.828
Latin	1	68/85	0.97(0.57-1.64) - 0.905	0.90(0.46-1.73) - 0.743	1.21(0.23-6.31) - 0.825	0.92(0.48-1.75) - 0.799	1.26(0.25-6.46) - 0.780
Cancer Type							
Prostate cancer	6	2618/1992	1.17(1.07-1.29) 0.183 0.001	1.16(1.02-1.32) 0.714 0.025	1.60(0.98-2.61) 0.020 0.058	1.20(1.06-1.35) 0.892 0.004	1.56(0.92-2.65) 0.004 0.103
Cervical cancer	2	388/497	1.12(0.93-1.36) 0.178 0.225	1.06(0.77-1.45) 0.073 0.729	1.26(0.88-1.82) 0.209 0.211	1.12(0.83-1.51) 0.071 0.454	1.21(0.89-1.65) 0.756 0.228
OSCC	2	1105/1291	0.87(0.78-0.98) 0.188 0.019	0.97(0.79-1.18) 0.164 0.726	1.01(0.44-2.32) 0.046 0.984	0.90(0.75-1.09) 0.806 0.284	1.13(0.40-3.21) 0.008 0.820
HCC	3	1058/1423	1.04(0.93-1.16) 0.241 0.518	1.00(0.83-1.20) 0.127 0.991	1.09(0.86-1.37) 0.341 0.478	1.03(0.86-1.22) 0.139 0.769	1.09(0.89-1.33) 0.656 0.423
Breast cancer	6	1489/1519	1.26(1.13-1.41) 0.622 <0.001	1.25(1.07-1.47) 0.186 0.005	1.73(1.35-2.20) 0.960 <0.001	1.32(1.14-1.54) 0.197 <0.001	1.46(1.17-1.83) 0.986 0.001
Lung cancer	2	398/501	0.85(0.69-1.05) 0.587 0.138	0.79(0.60-1.05) 0.800 0.099	0.82(0.50-1.34) 0.312 0.435	0.80(0.61-1.04) 0.932 0.091	0.91(0.57-1.47) 0.267 0.704
CRC	3	346/2003	0.98(0.80-1.19) 0.691 0.820	0.89(0.67-1.17) 0.972 0.387	1.08(0.69-1.69) 0.521 0.730	0.92(0.71-1.19) 0.901 0.518	1.14(0.74-1.76) 0.496 0.551
Other cancers	6	2014/1961	0.96(0.74-1.24) <0.001 0.743	0.85(0.63-1.15) 0.003 0.301	1.04(0.67-1.63) 0.003 0.854	0.89(0.65-1.23) <0.001 0.496	1.13(0.78-1.64) 0.012 0.510
V10I							
Total	7	4377/4992	0.94(0.85-1.04) 0.049 0.227	0.97(0.89-1.07) 0.169 0.601	0.92(0.72-1.17) 0.020 0.488	0.95(0.87-1.04) 0.147 0.300	0.90(0.74-1.11) 0.020 0.328
Ethnicity							
Asian	4	2218/2837	0.93(0.79-1.10) 0.011 0.408	1.05(0.91-1.21) 0.140 0.493	0.87(0.62-1.22) 0.009 0.423	0.98(0.78-1.23) 0.049 0.844	0.85(0.66-1.08) 0.021 0.184
European	2	2012/2075	0.97(0.87-1.07) 0.407 0.516	0.92(0.80-1.05) 0.220 0.200	1.05(0.80-1.38) 0.994 0.728	0.93(0.82-1.06) 0.269 0.293	1.08(0.83-1.42) 0.825 0.563
African	1	147/80	0.81(0.35-1.84) - 0.609	0.80(0.34-1.86) - 0.598	NA	0.80(0.34-1.86) - 0.598	NA
Cancer Type							
Prostate cancer	2	1406/1334	0.93(0.82-1.06) 0.732 0.276	0.86(0.73-1.01) 0.861 0.067	1.05(0.74-1.49) - 0.780	0.88(0.75-1.03) 0.811 0.114	1.11(0.79-1.57) - 0.555
Cervical cancer	1	227/335	1.09(0.86-1.39) - 0.461	0.93(0.62-1.40) - 0.735	1.20(0.75-1.91) - 0.450	1.01(0.69-1.48) - 0.939	1.25(0.85-1.85) - 0.257
OSCC	1	955/1191	0.96(0.85-1.09) - 0.542	1.19(0.96-1.47) - 0.118	0.94(0.73-1.20) - 0.596	1.10(0.90-1.34) - 0.375	0.83(0.68-1.01) - 0.066
Breast cancer	1	747/716	0.75(0.65-0.87) - <0.001	0.83(0.63-1.08) - 0.165	0.55(0.40-0.74) - <0.001	0.72(0.56-0.93) - 0.012	0.63(0.50-0.79) - <0.001
HCC	1	289/595	1.02(0.83-1.24) - 0.870	1.24(0.87-1.76) - 0.228	1.03(0.68-1.55) - 0.880	1.17(0.84-1.63) - 0.349	0.89(0.64-1.25) - 0.499
Skin cancer	1	753/821	1.02(0.86-1.21) - 0.802	1.02(0.82-1.26) - 0.865	1.05(0.67-1.64) - 0.835	1.02(0.83-1.25) - 0.828	1.04(0.67-1.62) - 0.855

^a Number of comparisons

P_{heter} : P value of Q -test for heterogeneity test.

Figures

Figure 1

Minor allele frequencies of FGFR4 G388R (Figure A) and V10I (Figure B) variants in various races.

Figure 2

Forest plot of odds ratio for the association between FGFR4 G388R (Figure A) and V10I (Figure B) polymorphisms and susceptibility of cancer (dominant genetic model, fixed-effects) in subgroup analysis by cancer type.

Figure 3

Stratified analysis by ethnicity between FGFR4 G388R (Figure A), V10I (Figure B) polymorphisms and cancer risk (recessive genetic model, random-effects).

Figure 4

The relationship between G388R, V10I polymorphisms and FGFR4 protein damaging analyzed by Polyphen2 tools (black lines represent scores).

Figure 5

In silico analysis of FGFR4 expression in prostate cancer patients (A). Effect of FGFR4 expression level on prostate cancer participant's overall survival (OS) time (B).

Figure 6

Tissue expression of FGFR4 among prostate cancer participants. The expression of FGFR4 is increased in more advanced cancer, as compared to less advanced cases (T3 + T4 versus T1, $P < 0.05$).

Figure 7

Gene-gene interaction of FGFR4 in prostate cancer (A). CORIN (corin, serine peptidase, figure B) is predicted to positively correlated with FGFR4.

Figure 8

Begg's funnel plot analysis for FGFR4 G388R (A) and V10I (B) polymorphisms under dominant genetic model. Sensitivity analysis for FGFR4 G388R (C) and V10I (D) polymorphisms and risk of cancer. No evidence of publication bias was identified.