Association Between ZFHX3 and PRRX1 Genes' Two Common Polymorphisms and Atrial Fibrillation Susceptibility in Asians

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Research

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Abstract

Background

One of the common sustained cardiac arrhythmia disorders is atrial fibrillation (AF), nowadays, results concerning the associations between ZFHX3/PRRX1 genes and AF has been widely reported. A meta-analysis to confirm above associations is necessary to be carried out in time.

Methods

The PubMed, Embase and Wanfang databases were conducted for searching, covering all publications before 20th July, 2020.

Results

Overall, seven articles including 3,674 cases and 8,990 healthy controls about ZFHX3 rs2106261 and 1045 cases and 1407 controls for PRRX1 rs3903239 were included. Odds ratio (OR)[95% confidence interval (CI)] was applied to assess the associations. Publication bias was calculated by both Egger's and Begg's tests. After calculated, we found that ZFHX3 rs2106261 polymorphism potential increased AF risk in Asians (for example: allelic contrast: OR [95%CI]: 1.39[1.31-1.47], $P < 0.001$). Similarly, stratified analysis by source of control and genotype method, also increased associations were detected (for example: allelic contrast: OR[95%CI] = 1.51[1.38-1.64], $P < 0.001$ for HB; OR[95%CI]: 1.31[1.21-1.41], $P < 0.001$ for PB; OR[95%CI] = 1.55[1.33-1.80], $P < 0.001$ for TaqMan; OR[95%CI] = 1.31[1.21-1.41], $P < 0.001$ for HRM). On the other hand, decreased relationship was observed between PRRX1 rs3903239 polymorphism and AF risk (C-allele vs. T-allele: OR[95%CI] = 0.83[0.77-0.99], $P = 0.036$; CT vs. TT: OR[95%CI] = 0.79[0.67-0.94], $P = 0.006$). No obvious evidence of publication bias was found.

Conclusions

In summary, our study suggested that ZFHX3 rs2106261 and PRRX1 rs3903239 polymorphisms had positive associations with AF risk, more large case-controls must be carried out to confirm above conclusions.

Background

Atrial fibrillation (AF) is one of the common forms of arrhythmia in clinics, about 1-2% incidence among adults worldwide[1, 2]. Previous studies have demonstrated that AF significantly increases the social and economic burden both in developed and developing countries[3]. AF is also a main cause of heart failure and stroke[4, 5]. A variety of structural heart diseases and systemic diseases are related to AF, including congestive heart failure, cardiomyopathy, pulmonary heart disease, essential hypertension, and hyperthyroidism[6, 7], while age, obesity, smoking, excessive drinking and drug use have also been contributed to the development of AF[6, 8]. So far, the exact pathogenesis of AF is still unclear. However, many evidences support that genetic factors play an important role in its occurrence and development[9]. In fact, common genetic variants (a multitude of single-nucleotide polymorphism, SNPs) associated with AF have been detected in Genome-wide association studies (GWAS)[10-12]: such as endothelial nitric oxide synthase 786T/C, CYP11B2 rs1799998, KCNE1 G38S, Caveolin-1 rs3807989[9, 13-15].

Two independent GWAS identified significant associations between rs2106261 and rs7193343 polymorphisms in zinc finger homeobox 3 (ZFHX3) gene and AF susceptibility in various populations of European ancestry[16, 17], which locates on chromosome 16q22 and encodes zinc finger homeobox 3. The specific contents were as follows: Benjamin et al.[16] indicated that rs2106261 SNP in ZFHX3 gene was associated with AF (OR = 1.19; $P = 2.76 \times 10^{-7}$), in the same period, Gudbjartsson et al.[17] assessed another SNP (rs7193343) in ZFHX3, which was confirmed to be related to AF in the Icelandic individuals (OR = 1.21, $P = 1.4 \times 10^{-10}$).

The paired related homeobox 1 (PRRX1) encodes a homeodomain transcription factor that is highly expressed in the developing heart[18]. In the PRRX1 knockout mouse model, fetal lung vascular development is impaired[19]. In addition, the expression pattern of PRRX1 in the mouse atria was evaluated. Compared with the right atrium, both proteins were overexpressed in the left atrium[20]. Above results suggested PRRX1 may play a vital role in heart disease, including AF. In a subsequent meta-GWAS, PRRX1 rs3903239 variant was associated with AF risk ($P = 8.4 \times 10^{-14}$) [21].

Taking into consideration of a more precise assessment of ZFHX3 rs2106261 and PRRX1 rs3903239 variants in AF risk, hence, we must first perform a meta-analysis of all eligible case-control studies to confirm[18, 22-27].

Methods

Identification and eligibility of relevant studies

The PubMed, Embase and Wanfang databases were selected, last search was updated on July 20, 2020, with the keywords containing 'ZFHX3' or 'zinc finger homeobox 3', 'PRRX1' or 'paired related homeobox 1', 'polymorphism' or 'variant' and 'atrial fibrillation'. After above search, a total of 96 publications were identified, of which 7 articles coincide following inclusion criteria.

The criteria for inclusion and exclusion

The research included in the analysis must meet all of the following conditions: (a) the study assessed the correlation between AF and ZFHX3 rs2106261 polymorphism and/or PRRX1 rs3903239 polymorphism; (b) unpaired case-control studies; (c) sufficient genotypes in cases and controls. The model number

was for each group. Therefore, the following exclusion criteria were also applied: (a) no control group; (b) no genotype frequency was available and (c) previous publications was repeated.

Data extraction

Two of the authors extracted all data independently, complied with the selection criteria. The following items were collected: author's name, ethnicity, year of publication, total or each genotype case/control number, original, source of control, genotyping methods and Hardy-Weinberg equilibrium (HWE) of controls.

Quality score assessment (NOS)

NOS was used to assess the quality of each study and evaluate all aspects of the methodology, including case selection, comparability between groups, and exposure determination. NOS has a total score of 0 to 9 stars. Research with a score greater than 7 is considered as high-quality study[28].

Statistic analysis

Based on the genotype frequencies of the cases and controls, the probability odds ratio (OR) with 95% confidence interval (CI) was used to measure the strength of association between the polymorphism of ZFHX3 rs2106261 polymorphism and PRRX1 rs3903239 polymorphism and AF. First to conduct a subgroup analysis stratified by race. The source of the control subgroup analysis was carried out in two categories: population-based (PB) and hospital-based (HB).

The statistical significance of OR was determined by Z-test. Using fixed effects model and random effects model to calculate the combined OR. The Q -test ($P \geq 0.10$) indicates that there is heterogeneity between including studies. If significant heterogeneity is detected, the random effects model (DerSimonian-Laird method) is used, but the fixed effects model (Mantel-Haenszel method) is selected [29, 30]. For ZFHX3 rs2106261, we investigated the relationship between genetic variants and AF risk in allelic contrast (A-allele *versus* G-allele), homozygote comparison (AA *versus* GG), dominant genetic model (AA+AG *versus* GG), heterozygote comparison (AG *versus* GG), and recessive genetic model (AA *versus* AG+GG). For PRRX1 rs3903239, C-allele vs. T-allele, CT vs. TT, CC vs. TT, CC+CT vs. TT and CC vs. CT+TT models was applied. Funnel plot asymmetry was assessed using Begg's test and publication bias was assessed using Egger's test [31]. The departure of frequencies of from expectation under HWE was assessed by χ^2 test in controls using the Pearson chi-square test ($P < 0.05$ was considered significant) [32]. All statistical tests for this meta-analysis were performed with Stata software (version 11.0; StataCorp LP, College Station, TX).

Gene interaction network of ZFHX3 and PRRX1 gene

In order to fully understand the role and potential and functional partners of ZFHX3 and PRRX1 in AF, respectively, String online server (<http://string-db.org/>) uses the gene-gene interaction network of ZFHX3 and PRRX1 genes [33] (Figure 10).

Results

Eligible studies

In total, eighty-six articles were collected from the PubMed, Embase and Wanfang databases. 89 articles were excluded (25-irrelevant articles, 4-systematic/Meta-analysis, 1-only case group, 23-supplement, 30-duplication and 6-no original numbers for case/control groups) (Figure 1). Finally, seven articles were identified in current analysis, including 3,674 cases and 8,990 healthy controls related to ZFHX3 rs2106261 polymorphism and 1045 cases and 1407 controls for PRRX1 rs3903239 polymorphism. The characteristics of each included study are listed in Table 1. In addition, the Minor Allele Frequency (MAF) reported from the five main worldwide populations in the 1000 Genomes Browser are checked (<https://www.ncbi.nlm.nih.gov/snp/>): African; European; East Asian; American and South Asian (Figure 2), which was similar with the average level in our current case and control groups.

Meta-analysis

ZFHX3 rs2106261 polymorphism and AF risk

In the overall analysis, significantly increased associations was observed in five genetic models in Asians: in the allelic contrast (OR[95% CI] = 1.39[1.31-1.47], $P_{\text{heterogeneity}} = 0.117$, $P < 0.001$, Figure 3A), the heterozygote comparison (OR[95% CI] = 1.37[1.18-1.59], $P_{\text{heterogeneity}} = 0.007$, $P < 0.001$, Figure 3B), AA vs. CC (OR[95% CI] = 1.96[1.73-2.21], $P_{\text{heterogeneity}} = 0.317$, $P < 0.001$, Figure 3C), the dominant model (OR [95% CI] = 1.49[1.30-1.70], $P_{\text{heterogeneity}} = 0.011$, $P < 0.001$, Figure 3D) and AA vs. AC +CC (OR[95% CI] = 1.70[1.52-1.90], $P_{\text{heterogeneity}} = 0.643$, $P < 0.001$, Figure 3E) (Table 2).

In the subgroup analysis by source of control, ZFHX3 rs2106261 A-allele or AA genotype acted as an risk factor in both HB and PB subgroups: HB (such as: A-allele *versus* C-allele: OR[95% CI] = 1.51[1.38-1.64], $P_{\text{heterogeneity}} = 0.302$, $P < 0.001$; AC *versus* CC: OR[95% CI] = 1.57[1.38-1.79], $P_{\text{heterogeneity}} = 0.156$, $P < 0.001$) and PB (such as: A-allele *versus* C-allele: OR[95% CI] = 1.31[1.21-1.41], $P_{\text{heterogeneity}} = 0.321$, $P < 0.001$; AC *versus* CC: OR[95% CI] = 1.17[1.04-1.30], $P_{\text{heterogeneity}} = 0.584$, $P = 0.007$) (Figure 3A,B, Table 2).

To detect whether the association were existed between genotype methods and ZFHX3 rs2106261 polymorphism, we carried out the next step. Several positive results were found in TaqMan [in the allelic contrast (OR = 1.55, 95% CI = 1.33-1.80, $P = 0.740$ for heterogeneity, $P < 0.001$ for significant), the heterozygote comparison (OR = 1.82, 95% CI = 1.46-2.27, $P = 0.668$ for heterogeneity, $P < 0.001$), AA vs. CC (OR = 2.06, 95% CI = 1.48-2.86, $P_{\text{heterogeneity}} = 0.884$, $P < 0.001$ for significant), the dominant model (OR[95% CI] = 1.87[1.52-2.30], $P_{\text{heterogeneity}} = 0.674$, $P < 0.001$) and AA vs. AC +CC (OR[95% CI] = 1.51[1.11-2.06], $P_{\text{heterogeneity}} = 1.000$, $P < 0.001$), High-Resolution Melt (HRM) [in the allelic contrast (OR = 1.31, 95% CI = 1.21-1.41, $P_{\text{heterogeneity}} = 0.647$, $P < 0.001$), the

heterozygote comparison (OR = 1.17, 95% CI = 1.04-1.30, $P = 0.584$ for heterogeneity, $P = 0.007$ for significant), AA vs. CC (OR = 1.81, 95% CI = 1.54-2.12, $P_{\text{heterogeneity}} = 0.417$, $P < 0.001$), the dominant model (OR = 1.29, 95% CI = 1.16-1.43, $P = 0.655$ for heterogeneity, $P < 0.001$) and AA vs. AC + CC (OR = 1.68, 95% CI = 1.45-1.94, $P_{\text{heterogeneity}} = 0.384$, $P < 0.001$ for significant) and Others (data not shown) (Figure 4, Table 2).

PRRX1 rs3903239 polymorphism and AF risk

Decreased associations were found in heterozygote comparison (OR[95% CI] = 0.83[0.77-0.99], $P_{\text{heterogeneity}} = 0.522$, $P = 0.036$, Figure 5A, Table 2) and dominant model (OR[95% CI] = 0.79[0.67-0.94], $P = 0.137$ for heterogeneity, $P = 0.006$, Figure 5B, Table 2).

Sensitivity analysis and publication bias

A Begg funnel chart and Egger test were performed to assess publication bias. The results did not show any evidence of publication bias (for example: A-allele *versus* G-allele, $t = 1.46$, $P = 0.205$ [Egger test]; $z = 1.2$, $P = 0.23$ [Begg test] for ZFHX3 rs2106261, Figure 6; C-allele *versus* T-allele, $t = 0.11$, $P = 0.933$ [Egger test]; $z = 0.0$, $P = 1.00$ [Begg test] for PRRX1 rs3903239, Figure 7, Table 3). A sensitivity analysis was performed to assess the impact of each individual study on the combined OR by removing individual studies one by one. The results suggested that no separate study significantly affected the overall OR for ZFHX3 rs2106261 (Figure 8).

Network of gene-gene interaction of ZFHX3 and PRRX1 gene, respectively.

The network of potential gene-gene interaction for ZFHX3 and PRRX1 genes was analyzed by String online webpage (<http://string-db.org/>) [33] (Figure 9). Each gene was shown ten significant related genes in the web of relationships.

Discussion

AF is considered to be the most common supraventricular arrhythmia, affecting up to 1% in the natural population[34, 35]. With the increase of age, the prevalence rate increases year by year, and the incidence of elderly cases (≥ 80 years) can reach 8%[36]. Many types of heart and medical diseases that increase the risk of AF over age, which included arterial hypertension, cardiomyopathies, obstructive sleep apnea and valve dysfunction[37, 38]. In addition, based on a recent meta-analysis of GWAS for AF[11], more than 100 AF risk genetic mutations and polymorphisms have been reported, indicating that genetics may participate in the mechanisms of AF. More and more studies have shown that genetic variation may promote to the pathophysiology of AF by altering the structure, proteins expression and function related to various cellular activities[39].

So far, several meta-analyses about gene polymorphisms and AF susceptibility have been published: such as chromosome 4q25 variants, CYP11B2 -344T>C, mink S38G, and so on[40-43]. A growing number of papers have pointed to polymorphisms from both ZFHX3 and PRRX1 genes. ZFHX3 rs2106261 and PRRX1 rs3903239 polymorphisms have been paid attention and have not reported through meta-analysis to clarify the associations to AF susceptibility.

Current analysis is the first evaluation to the associations among ZFHX3 rs2106261 and PRRX1 rs3903239 polymorphisms and AF risk involving 4719 cases and 10397 controls. The main results of our analysis are that we found increased relationships between ZFHX3 rs2106261 and AF risk, on the contrary, PRRX1 rs3903239 polymorphism acted as a protective factor in AF development. In other words, individuals carried A-allele of ZFHX3 rs2106261 polymorphism may have a high possibility to get AF; individuals taken along CC or CT genotype might have a decreased risk for AF, which can give us some warnings to reduce the incidence of AF: such as early detection, healthy life, pay more attention to the prevention. Different genes or variant polymorphisms in the same genes may play multifarious functions in the progress of AF, which should be explained above conclusions.

In addition, the online analysis system-String was applied to predict the potential and functional partners, which may help to expand the range of vision of related genes. Finally, ten genes were opened up. The first three highest score of association was CDKN1A (Score = 0.921), RUNX3 (Score = 0.918) and TGF β 1 (Score = 0.900). Several studies have been focused on CDKN1A and TGF β 1, not RUNX3, in the development of AF. Further studies should pay attention to above three potential related genes and their common polymorphisms and AF risk. On the other hand, the score of related genes for PRRX1 is general low, which should be proofed and indicated in the future research.

Although positive results were found, limitations in current study should also be discussed. Beginning, the literature included is relatively new, the number of published studies remains not sufficiently larger. Second, the interactions between gene-gene/gene-environment (other covariates including family history, age, sex, disease stage and lifestyle), and even variants polymorphisms in the same genes may regulate AF risk, which must be included in further studies. Third, there are several types of AF: such as persistent, permanent, pathologic, idiopathic and paroxysmal. If enough data for one concrete AF, we should classify to one subgroup and analyze the association for ZFHX3 rs2106261 and PRRX1 rs3903239 polymorphisms, which is better to offer a guide to precision in the clinic.

Conclusion

Our analysis illustrated the proof that ZFHX3 rs2106261 and PRRX1 rs3903239 polymorphisms were related with conspicuous AF risk for Asians. Therefore, following well-designed and larger studies, including information about gene-gene/gene-environment interactions are recommended to confirm above conclusions.

Abbreviations

AF, atrial fibrillation; ZFXH3, zinc finger homeobox 3; PRRX1, paired related homeobox 1, confidence intervals; HWE, Hardy–Weinberg equilibrium; OR, odds ratio.

Declarations

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Not applicable.

Author Contribution

L.W. conceived the study. M.C. searched the databases and extracted the data. W.Z. analyzed the data. L.W. wrote the draft of the paper. W.Z. reviewed the manuscript.

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Availability of data and materials

All the data generated in the present research is contained in this manuscript.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Tables

Table 1 Characteristics of studies of ZFHX3 and PRRX1 genes' two common polymorphisms and atrial fibrillation risk included in our meta-analysis

Author	Year	Country	Ethnicity	Case	Control	Case			Control			SOC	HWE	Genotype	NOS
ZFHX3 rs2106261						AA	AG	GG	AA	AG	GG				
Okubo	2020	Japan	Asian	289	287	46	143	99	32	109	146	HB	0.096	TaqMan	8
Zaw	2017	Japan	Asian	411	1765	54	182	175	151	725	889	HB	0.853	Illumina	8
Huang	2015	China	Asian	569	1996	99	237	233	216	869	911	PB	0.683	HRM	9
Huang	2015	China	Asian	641	1692	103	279	259	197	707	788	PB	0.048	HRM	9
Huang	2015	China	Asian	810	1627	128	369	313	149	726	752	PB	0.163	HRM	9
Liu	2014	China	Asian	593	996	110	299	184	99	446	451	HB	0.460	MassARRAY	8
Tomomori	2018	Japan	Asian	362	627	50	181	131	60	250	317	HB	0.298	TaqMan	8
PRRX1 rs3903239						CC	CT	TT	CC	CT	TT				
Kalinderi	2018	Greece	European	167	124	15	62	90	8	49	67	PB	0.809	RCR-RFLP	7
Okubo	2020	Japan	Asian	287	287	29	139	119	59	143	85	HB	0.935	TaqMan	8
Liu	2015	China	Asian	591	996	79	263	249	155	463	378	HB	0.503	MassARRAY	8

HB: hospital-based; PB: population-based; SOC; source of control; PCR-RFLP: polymerase chain reaction followed by restriction fragment length polymorphism; HRM: High-Resolution Melt; HWE: Hardy-Weinberg equilibrium of control group.

Table 2 Stratified analyses of ZFHX3 and PRRX1 genes' two common polymorphisms on atrial fibrillation risk

Variables	N	Case/	M-allele vs. W-allele	MW vs. WW	MM+MW vs. WW	MM vs. WW	MM vs. MW+WW
ZFHX3 rs2106261		Control	OR(95%CI) P_h P β	OR(95%CI) P_h P β	OR(95%CI) P_h P β	OR(95%CI) P_h P β	OR(95%CI) P_h P β
Total	7	3674/8990	1.39(1.31-1.47)0.117 0.000 41.1%	1.37(1.18-1.59)0.007 0.000 66.5%	1.49(1.30-1.70)0.011 0.000 63.6%	1.96(1.73-2.21)0.317 0.000 14.8%	1.70(1.52-1.90)0.643 0.000 0.0%
SOC							
HB	4	1654/3675	1.51(1.38-1.64)0.302 0.000 17.7%	1.57(1.38-1.79)0.156 0.000 42.5%	1.68(1.49-1.90)0.151 0.000 43.4%	2.20(1.82-2.66)0.388 0.000 0.7%	1.73(1.45-2.07)0.520 0.000 0.0%
PB	3	2020/5315	1.31(1.21-1.41)0.321 0.000 0.0%	1.17(1.04-1.30)0.584 0.007 0.0%	1.29(1.16-1.43)0.655 0.000 0.0%	1.81(1.54-2.12)0.417 0.000 0.0%	1.68(1.45-1.94)0.384 0.000 0.0%
Genotype							
TaqMan	2	650/914	1.55(1.33-1.80)0.740 0.000 0.0%	1.82(1.46-2.27)0.668 0.000 0.0%	1.87(1.52-2.30)0.674 0.000 0.0%	2.06(1.48-2.86)0.884 0.000 0.0%	1.51(1.11-2.06)1.000 0.000 0.0%
Other	2	1004/2761	1.47(1.21-1.80)0.068 0.000 70.1%	1.45(1.24-1.70)0.123 0.000 58.1%	1.59(1.19-2.12)0.057 0.002 72.4%	1.47(1.21-1.80)0.095 0.000 64.1%	1.86(1.50-2.32)0.279 0.000 14.5%
HRM	3	2020/5315	1.31(1.21-1.41)0.647 0.000 0.0%	1.17(1.04-1.30)0.584 0.007 0.0%	1.29(1.16-1.43)0.655 0.000 0.0%	1.81(1.54-2.12)0.417 0.000 0.0%	1.68(1.45-1.94)0.384 0.000 0.4%
PRRX1 rs3903239							
Total	3	1045/1407	0.82(0.63-1.07)0.023 0.147 73.5%	0.83(0.77-0.99)0.522 0.036 0.0%	0.79(0.67-0.94)0.137 0.006 49.7%	0.68(0.35-1.32)0.011 0.253 78.0%	0.75(0.42-1.31)0.023 0.310 73.5%

P_h : value of Q -test for heterogeneity test; P : Z-test for the statistical significance of the OR

Table 3 Publication bias tests (Begg's funnel plot and Egger's test for publication bias test)

Egger's test						Begg's test	
Genetic type	Coefficient	Standard error	t	P value	95%CI of intercept	z	P value
ZFHX3 rs2106261							
A-allele vs. G-allele	3.372	2.313	1.46	0.205	(-2.573- 9.317)	1.2	0.23
AG vs. GG	2.523	1.507	1.67	0.155	(-1.351- 6.398)	1.2	0.23
AA+AG vs. GG	2.744	1.543	1.78	0.133	(-1.223- 6.712)	1.2	0.23
AA vs. GG	1.671	0.977	1.71	0.148	(-0.840- 4.182)	1.2	0.23
AA vs. AG+GG	1.690	1.083	1.56	0.179	(-1.094- 4.475)	1.2	0.23
PRRX1 rs3903239							
C-allele vs. T-allele	1.034	9.771	0.11	0.933	(-123.117-125.186)	0.0	1.00
CT vs. TT	0.496	7.243	0.07	0.956	(-91.538-92.531)	0.0	1.00
CC+CT vs. TT	0.471	7.530	0.06	0.960	(-95.213-96.154)	0.0	1.00
CC vs. TT	0.251	3.834	0.07	0.958	(-48.468-48.971)	0.0	1.00
CC vs. CT+TT	0.290	4.031	0.07	0.954	(-50.938-51.519)	0.0	1.00

for ZFHX3 and PRRX1 genes' two common polymorphisms (rs2106261 and rs3903239)

Figures

Figure 1

A flowchart showing the search strategy applied to search related papers for ZFHX3 rs2106261 and PRRX1 rs3903239 polymorphisms and AF risk.

Figure 2

MAF for the gene polymorphisms among different ethnicity. Vertical line, MAF; Horizontal line, ethnicity type. EAS: East Asian; EUR: European; AFR: African; AMR: American; SAS: South Asian. A: rs2106261, B: rs3903239.

Figure 3

Forest plot of AF risk associated with ZFX3 rs2106261 polymorphism in all genetic models by source of control subgroup. The squares and horizontal lines correspond to the study-specific OR and 95% CI. The area of the squares reflects the weight (inverse of the variance). The diamond represents the summary OR and 95% CI. A: A-allele vs. C-allele; B: AC vs. CC; C: AA vs. CC; D: AA+AC vs. CC; E: AA vs. AC+CC.

Figure 4

Forest plot of AF risk associated with ZFH3 rs2106261 polymorphism in genotype method subgroup. A: A-allele vs. C-allele (fixed-model); B: A-allele vs. C-allele (random-model); C: AC vs. CC; D: AA+AC vs. CC (fixed-model); E: AA+AC vs. CC (random-model); F: AA vs. CC (fixed-model); G: AA vs. CC (random-model); H: AA vs. AC+CC.

Figure 5

Forest plot of AF risk associated with PRRX1 rs3903239 polymorphism in the whole analysis. A: heterozygote comparison; B: dominant model.

Figure 6

Begg's and Egger's tests for publication bias plot in all genetic models (ZFHX3 rs2106261 polymorphism). A: A-allele vs. C-allele; B: AC vs. CC; C: AA vs. CC; D: AA+AC vs. CC; E: AA vs. AC+CC for Begg's test. F: A-allele vs. C-allele; G: AC vs. CC; H: AA vs. CC; I: AA+AC vs. CC; J: AA vs. AC+CC for Egger's test.

Figure 7

Begg's and Egger's tests for publication bias plot in all two models (PRRX1 rs3903239 polymorphism). A: heterozygote comparison; B: dominant model.

Figure 8

Sensitivity analysis between ZFX3 rs2106261 polymorphism and AF risk (all five genetic models). A: A-allele vs. C-allele; B: AC vs. CC; C: AA vs. CC; D: AA+AC vs. CC; E: AA vs. AC+CC.

Figure 9

Human ZFH3 and PRRX1 genes interactions network with other genes obtained from String online server. At least 10 genes have been indicated to correlate with above two genes, respectively. A,C: network and ten related genes for ZFH3 gene; B,D: network and ten related genes for PRRX1 gene.