Review Article

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Association of *IRF6* rs2235371 Polymorphism with Non-Syndromic Cleft Lip/Palate: A Meta-analysis

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ABSTRACT

Background: The previous published data on the association between interferon regulatory factor 6 (IRF6) polymorphisms and non-syndromic Cleft Lip/Palate (NSCL ± P) risk remained inconclusive. The aim of this study was to conduct a meta-analysis to further assess the associations.

Methods: A comprehensive search in PubMed, EMBASE, Web of Science, and CNKI for all eligible studies up July 2021.

Results: A total of 23 studies with 6,161 cases and 8,919 controls were selected for this meta-analysis. Overall pooled analysis suggest a significant association between *IRF6 rs2235371* polymorphism and CL±P risk under all the five genetic models, i.e., allele (A vs. G: OR=0.754, 95% CI 0.628-0.905, P=0.002), homozygote (AA vs. GG: OR=0.621 95% 0.405-0.953, P=0.029), heterozygote (AC vs. GG: OR=0.619, 95% CI 0.485-0.791, P≤0.001), dominant (AA+AG vs. GG: OR=0.550, 95% CI 0.381-0.794, P=0.001) and recessive model (AA vs. AG+GG: OR=0.583, 95% CI 0.423-0.804, P=0.001). Subgroup analysis by ethnicity showed that rs2235371 was associated with NSCL±P risk in Asians.

Conclusion: This meta-analysis provides strong evidences that *IRF6* rs2235371 might be associated with risk of NSCL ± P.

Introduction

Cleft lip and cleft palate (CL ± P), also known as orofacial cleft are congenital malformations that comprise a large fraction of birth defects.[1] CL ± P is a common congenital malformation due to unknown etiological mechanisms.[2] According to epidemiological studies, maternal epilepsy, prenatal exposure to isotretinoin and nonsteroidal anti-inflammatories are extrinsic factors that increase the risk of CL ± P).[3] Overall, medicine intake during pregnancy increases the risk of CL ± P.[4] A complex interplay between genetic and environmental factors, including the interaction of cell growth, growth factors and receptors, the convergence ,and fusion of the facial and palatal processes, apoptosis, and adequate nutrient supply dictate the highly regulated process of craniofacial development).[5-7] The development of the craniofacial region is regulated by many genes including growth factors,[8,9] signaling molecules (e.g., WNT family, SHH and respective receptors),[10,11] and transcription factors (e.g., MSX, DLX, LHX, PRRX and BARX family genes and respective receptors).[12,13] Among these genetic factors, single nucleotide polymorphisms (SNPs) in the interferon regulatory factor 6 (IRF6) have been mostly investigated in their contribution to orofacial clefting.[14,15] In addition, a mutation in the *IRF6* gene is associated with the autosomal dominant van der Woude syndrome (VWS) or the related popliteal pterygium syndrome (PPS).

The human *IRF6* (OMIM # 607199) gene belongs to a family of transcription factors, which its function is related to the formation of connective tissue, for example, that of the palate. The IRF6 identified within the VWS critical region at 1q32-q41 contains ten exons and spanning approximately 20.5 kb. Some polymorphisms have been found in the IRF6, such as, 21082A/G (rs1800896), 2592C/A (rs1800872) and 2829C/T (rs1800871). Autosomal-dominant van der Woude syndrome is the most common Mendelian syndrome that has the cardinal signs of cleft lip with or without cleft palate (CL/P) and/or cleft palate only (CPO) with dental anomalies and pitted lips caused by mutations in this gene). In the past decade, a number of population-based case-control studies have shown the possible association of different *IRF6* polymorphisms with susceptibility of nonsyndromic cleft lip with or without palate (NSCL ± P). However, the results from these studies are dissimilar to some extent, but nevertheless intriguing, which may be owing to limitations in individual studies. To address this issue, we conducted a meta-analysis with subgroup analysis from all eligible studies, to obtain a more precise estimation of the association of *IRF6* rs2235371, rs2013162 and rs642961 polymorphisms with risk of NSCL ± P.

Materials and Methods

Publication Search: A comprehensive computer search was performed independently by two authors, in PubMed, Web of Knowledge, Web of Science, Embase, Scientific Information Database (SID), WanFang, VIP, Chinese Biomedical Database (CBD), and China National Knowledge Infrastructure (CNKI) database to collect the case-control studies that investigated the association between IR2 polymorphism with NSCL ± P risk up to September 05, 2019. Combinations of the following keywords were used in the search: (‘’Non-Syndromic Cleft Lip/Palate’’ OR ‘’Cleft Lip/Palate’’ OR ‘’Craniofacial’’ OR ‘’Van Der Woude Syndrome’’ OR ‘’VWS1’’) AND (‘’Interferon Regulatory Factor 6’’ OR ‘’IRF6’’) AND (‘’rs2235371’’ OR ‘’ 2829C>T’’ OR ‘’c.535G>A’’ OR ‘’p.Val179Ile’’ OR ‘’p.Val274Ile’’) AND (‘’rs2235375’’ OR ‘’c.382+27C>A’’ OR ‘’c.667+27C>A’’) AND (‘’Gene’’ OR ‘’Genotype’’ OR ‘’Allele’’ OR ‘’Polymorphism’’ OR ‘’ Single nucleotide polymorphisms’’ OR ‘’SNP’’ OR ‘’Variation’’ OR ‘’Mutation’’). We also manually searched and reviewed the

references of retrieved publications or review articles to identify more potential eligible studies. The whole search process was performed in English, Chinese, Russian and Portuguese. When overlapping data on the same cases were included in more than one publication, only the one with the larger sample size was selected. As the present study was a meta-analysis in which all data were extracted from published literature, Ethical approval or patient consent was not needed.

Inclusion and Excluding Criteria: The following inclusion criteria were used to select literature for the meta-analysis: 1) studies with case-control or cohort design; 2) studies focused on the association of IF2 polymorphisms with NSCL ± P risk; 3) studies contained at least two comparison groups (NSCL ± P patients and healthy subjects); 4) detailed data for estimation of odds ratio (OR) and 95% confidence interval (CI), as well as available genotype frequencies for both patients and healthy subjects. The major exclusion criteria were: 1) not relevant to *IRF6* polymorphisms or NSCL ± P; 2) no sufficient data reported; 3) case only studies or no controls; 4) linkage studies and family-based studies (twins, sibling and case-parent trios); 5) case reports, abstracts, comments, conference abstracts, editorials, reviews, meta-analysis; and 6) duplicated studies or data.

Data Extraction: Two authors performed data extraction independently using a standard form according to the inclusion criteria. When required, disagreements were resolved by discussion or consensus involving a third reviewer). The following data were collected from each study: first author's name, year of publication, ethnicity (Asian, Caucasian, African and mixed populations), country of origin, genotyping methods, numbers of cases and controls, frequencies of genotypes in cases and controls, minor allele frequency (MAF) in controls, and Hardy-Weinberg equilibrium (HWE) in controls. We contacted the corresponding authors by email to request the missing data if the publications did not report necessary data, as well as genotype frequencies. The ‘‘mixed’’ group means mixed or unknown populations. Moreover, when publications included a sample of more than one ethnicity or population, the data were extracted separately according to ethnicities.

Statistical Analysis: The strength of association between *IRF6* polymorphisms and NSCL ± P was estimated by odds ratios (ORs) with 95% confidence intervals (95% CIs). The significance of the pooled OR was determined using the Z-test and $P < 0.05$ was considered statistically significant. The pooled ORs were performed under all five genetic models, i.e., allele (B vs. A), homozygote (BB vs. AA), heterozygote (BA vs. BB), dominant (BB+BA vs. AA) and recessive (BB vs. BA+AA). Between-study heterogeneity was evaluated by using the Cochran Q-test, in which $P \leq 0.10$ indicated significant heterogeneity. Moreover, the I^2-value was used to quantify between-study heterogeneity (range of 0 to 100%: I^2 = 0-25%, no heterogeneity; I^2 = 25-50%, moderate heterogeneity; I^2 = 50-75%, large heterogeneity; I^2 = 75-100%, extreme heterogeneity). If obvious heterogeneity was observed among the studies, the random-effects model (the DerSimonian and Laird method) was applied to calculate the pooled OR and 95% CI. Otherwise, the fixed-effects model (the Mantel-Haenszel method) was adopted for the meta-analysis. A Hardy-Weinberg equilibrium (HWE) test in controls was tested using the chi-square test ($P < 0.05$). To explore potential sources of heterogeneity, we carried out subgroup analyses by ethnicity, source of controls, and HWE status. Sensitivity analysis was performed to evaluate the influence of every single study on pooled ORs and the stability of our results by sequential removal of individual studies. Subsequently, sensitivity analysis by excluding those studies HWE violating was performed to examine the stability of the results. The potential publication bias was estimated by the funnel plot, in which the standard error of log (OR)

of each study was plotted against its log (OR). An asymmetric plot suggests a possible publication bias. Using Egger's linear regression test, we examined funnel plot asymmetry, which relies on linear regression to estimate the OR on a natural logarithmic scale. For the interpretation of Egger's test, statistical significance was defined as $P < 0.05$. All of the statistical calculations were performed using Comprehensive Meta-Analysis (CMA) software version 2.0 (Biostat, USA). Two-sided $P < 0.05$ was considered statistically significant.

Results

The online databases presented 468 potentially relevant articles in the initial literature search. Two authors independently screened all titles and abstracts of the identified studies. After the first screening, 279 irrelevant and duplicate articles were excluded. Among the remaining articles, 12 explored other conditions instead of NSCL ± P; 5 reported incomplete data or sufficient genotype frequencies, 5 were review studies. Finally, a total of 23 case-control studies with 6,161 cases and 8,919 controls were selected. Characteristics of included studies are shown in Tables 1 and 2. All the included studies were published since 2005. All eligible studies were published in English, Chinese and Portuguese. The sample size in cases ranged from 20 to 284. Among them, eight studies were based on Asians (Iran, China, and India), six based on mixed population (Brazil and Mexico), five based on Caucasians (the USA, Austria and Turkey), and two were based on Africans (Egypt). Nine genotyping methods were applied in the included studies: AS-PCR, PCR-RFLP, TaqMan, MALDI-TOF, LDR, MassARRAY, Sequencing, Dot-blot and HRMA. The genotypes and minor allele frequency (MAF) distributions in the cases and controls are shown in Table 1. Moreover, the distribution of genotypes in the controls was in agreement with Hardy-Weinberg equilibrium (HWE) for all selected studies, except for six studies (Table 1).

Quantitative Data Synthesis: We pooled all the 23 case-control studies together to assess the overall association between *IRF6* rs2235371 polymorphism and NSCL ± P risk. Overall pooled analysis suggest a significant association between *IRF6 rs2235371* polymorphism and CL ± P risk under all the five genetic models, i.e., allele (A vs. G: OR = 0.754, 95% CI 0.628-0.905, P = 0.002), homozygote (AA vs. GG: OR = 0.621 95% 0.405-0.953, P = 0.029), heterozygote (AC vs. GG: OR = 0.619, 95% CI 0.485-0.791, $P \leq 0.001$), dominant (AA+AG vs. GG: OR = 0.550, 95% CI 0.381-0.794, P = 0.001) and recessive model (AA vs. AG+GG: OR = 0.583, 95% CI 0.423-0.804, P = 0.001). The studies were further stratified based on the ethnicity and country (China, Brazil and India). When stratified by ethnicity, a significant association between *IRF6 rs2235371* polymorphism and an increased risk of CL ± P was found in Asians under four genetic models, i.e., allele (A vs. G: OR = 0.705, 95% CI 0.571-0.871, P = 0.001), homozygote (AA vs. GG: OR = 0.570, 95% CI 0.363-0.896, P = 0.015), heterozygote (AC vs. GG: OR = 0.524, 95% CI 0.372-0.738, $P \leq 0.001$) and dominant (AA+AG vs. GG: OR = 0.590, 95% CI 0.444-0.785, $P \leq 0.001$), but not in Caucasians and mixed populations.

Sensitivity Analysis: To assess whether any individual study exerted undue influence on pooled ORs, "leave-one-out" sensitivity analysis was used by consecutively omitting one study each time for all subjects and subgroups. The sensitivity analysis for *IRF2* polymorphisms showed that no single study affected the pooled ORs significantly. Besides, we repeated sensitivity analysis by excluding those five studies that did not meet Hardy-Weinberg equilibrium (HWE). When these studies were excluded, the results were not changed in the overall population, indicating that our meta-analysis was statistically robust and reliable.

Publication bias: Begg's funnel plot and Egger's test were performed to assess the publication bias of the literatures.

Table 1. Characteristics of Studies Included in the Meta-Analysis

First Author/Year	Country (Ethnicity)	SOC	Genotyping Technique	Case/Control	Cases					Controls					MAFs	HWE
					Genotypes			Allele		Genotypes			Allele			
					GG	GA	AA	G	A	GG	GA	AA	G	A		
Zucchero 2004[17]	Multi-ethnic	NS	AS-PCR	132/370	75	50	7	200	64	163	162	45	488	252	0.340	0.628
Srichomthong 2005[18]	Thailand (Asian)	PB	PCR-RFLP	192/278	93	38	27	272	112	100	137	41	337	219	0.393	0.592
Jugessur 2008[19]	Norway (Caucasian)	PB	TaqMan	314/416	297	17	0	611	17	399	17	0	815	17	0.020	0.670
Ali 2009[20]	India (Asian)	PB	PCR-RFLP	323/214	252	65	6	569	77	141	66	7	348	80	0.186	0.830
Huang 2009[21]	China (Asian)	HB	PCR-RFLP	257/174	133	106	18	372	142	57	79	38	193	155	0.445	0.285
Tang 2009[22]	China (Asian)	HB	PCR-RFLP	66/96	30	31	5	91	41	34	50	12	118	74	0.385	0.330
Birnbaum 2009[23]	Central Europe (Caucasian)	PB	MALDI-TOF	442/952	435	7	0	877	7	913	39	0	1865	39	0.020	0.518
Pan 2010[24]	China (Asian)	HB	PCR-RFLP	127/115	69	40	18	178	76	47	60	8	161	69	0.300	0.054
Shen 2009[25]	China (Asian)	FB	Microarray	50/100	28	20	2	76	24	45	48	7	138	62	0.310	0.222
Carter 2010[26]	Ireland (Caucasian)	HB	AS-PCR	460/894	456	4	0	916	4	869	25	0	1763	25	0.014	0.671
Paranaiba 2010[27]	Brazil (Mixed)	PB	PCR-RFLP	177/126	159	18	0	336	18	113	13	0	236	13	0.051	0.541
Shi 2011[28]	China (Asian)	HB	LDR	173/154	82	69	22	233	113	63	71	20	197	111	0.360	0.999
Letra 2012[29]	Brazil (Mixed)	PB	TaqMan	311/281	283	26	2	592	30	245	34	2	524	38	0.067	0.498
Lu 2013[30]	China (Asian)	PB	AS-PCR	236/400	122	96	18	334	138	152	180	68	484	316	0.395	0.242
Song 2013[31]	China (Asian)	PB	MassARRAY	203/226	114	72	17	300	106	93	106	27	292	160	0.354	0.701
Zhou 2013[32]	China (Asian)	PB	PCR-RFLP	106/129	57	45	4	159	53	52	66	11	170	88	0.341	0.116
Gurramkonda 2013[33]	India (Asian)	NS	PCR-RFLP	189/190	152	36	1	340	38	164	25	1	353	27	0.071	0.964
Rathore 2014[34]	India (Asian)	HB	PCR-RFLP	25/25	14	11	0	39	11	2	22	1	26	24	0.480	≤ 0.001
Mijiti 2015[35]	China (Asian)	HB	DS	100/60	80	17	3	177	23	39	20	1	98	22	0.183	0.380
Ibarra-Arce 2015[36]	Mexico (Mixed)	NS	Dot-blot	100/100	12	88	0	112	88	13	86	1	112	88	0.440	≤ 0.001
Jafary 2015[37]	Iran (Asian)	NS	PCR-RFLP	107/100	97	10	0	204	10	74	26	0	174	26	0.130	0.135
Wu 2016[38]	China (Asian)	PB	DS	123/140	61	46	16	168	78	100	33	7	233	47	0.167	0.064
Xu 2016[39]	China (Asian)	NS	Microarray	104/300	54	44	6	152	56	114	134	52	362	238	0.396	0.247

SOC: Source of control; HB: Hospital based; PB: Population based; NS: Not Stated; PCR-RFLP: Polymerase chain reaction-restriction fragment length polymorphism; AS-PCR: Allele-specific PCR; DS: Direct sequencing; LDR: Ligase detection reactions; HRMA: High-resolution melting analysis; MAF: Minor allele frequency; HWE: Hardy-Weinberg equilibrium.

Table 2. Results of the Association of *IRF6* Polymorphisms with NSCL ± P Risk

Subgroup	Genetic Model	Type of Model	Heterogeneity		Odds Ratio				Publication Bias	
			I^2 (%)	P_H	OR	95% CI	Z_{test}	P_{OR}	P_{Beggs}	P_{Eggers}
rs2235371										
Overall	A vs. G	Random	72.32	≤ 0.001	0.712	0.600-0.846	-3.861	≤ 0.001	1.000	0.896
	AA vs. GG	Random	61.48	≤ 0.001	0.532	0.365-0.776	-3.272	0.001	0.790	0.721
	AC vs. GG	Random	79.14	≤ 0.001	0.582	0.453-0.747	-4.238	≤ 0.001	0.475	0.463
	AA+AG vs. GG	Random	91.91	≤ 0.001	0.506	0.346-0.740	-3.515	≤ 0.001	0.711	0.820
	AA vs. AG+GG	Random	57.04	0.001	0.644	0.457-0.908	-2.512	0.012	0.733	0.714
Ethnicity										
Asian	A vs. G	Random	77.90	≤ 0.001	0.705	0.571-0.871	-3.248	0.001	0.692	0.812
	AA vs. GG	Random	68.91	≤ 0.001	0.570	0.363-0.896	-2.437	0.015	0.912	0.715
	AC vs. GG	Random	84.83	≤ 0.001	0.524	0.372-0.738	-3.700	≤ 0.001	0.276	0.313
	AA+AG vs. GG	Random	79.93	≤ 0.001	0.590	0.444-0.785	-3.629	≤ 0.001	0.921	0.823
	AA vs. AG+GG	Random	64.77	≤ 0.001	0698	0.465-1.048	-1.732	0.083	1.000	0.626
Caucasian	A vs. G	Random	74.56	0.020	0.568	0.218-1.481	-1.257	0.247	1.000	0.356
	AC vs. GG	Random	74.84	0.019	0.564	0.214-1.488	-1.156	0.248	1.000	0.365
	AA+AG vs. GG	Random	74.84	0.019	0.564	0.214-1.488	-1.156	0.248	1.000	0.365
Mixed	A vs. G	Fixed	0.00	0.514	0.886	0.667-1.177	-0.837	0.403	1.000	0.923
	AA vs. GG	Fixed	0.00	0.654	0.687	0.127-3.720	-0.435	0.663	NA	NA
	AC vs. GG	Fixed	0.00	0.515	0.821	0.557-1.211	-0.993	0.321	0.296	0.031
	AA+AG vs. GG	Random	98.35	≤ 0.001	0.242	0.011-5.579	-0.886	0.376	1.000	0.128
	AA vs. AG+GG	Fixed	0.00	0.600	0.686	0.128-3.672	-0.440	0.660	NA	NA

No obvious visual asymmetry was observed in Begg's funnel plots, and the results of Egger's test revealed no statistical evidence for publication bias of the literature for the *IRF6* polymorphisms (Table 2).

Minor Allele Frequencies (MAFs): The minor allele frequencies (MAFs) of the *IRF6* gene polymorphisms by ethnicity are shown in Table 1. The allele and genotype distributions of *IRF6* polymorphisms exhibited ethnic variations. The rs2235371 A, rs2013162 A, rs642961 A, and rs2235375 C allele frequencies were 24.70% (1.40%-48.0%), 36.85% (27.10%-46.60%), 20.50% (13.90%-27.10%), and 39.75% (25.0%-54.50%), respectively. Therefore, the MAF of the rs642961 polymorphism was less than other SNPs.

Discussion

The rs2235371 is located in exon 7 producing a change of the amino acid valine to isoleucine at codon 274 (Val274Ilu) and rs2013162 in exon 5 is a silent variant at codon 153 (Ser153Ser). Our meta-analysis results showed that the association between rs2235371 and the risk for NSCL ± P is statistically significant in the overall population. In the subgroup analyses by ethnicity, the rs2235371 was found to be insignificantly associated with NSCL ± P risk in Asians. Similarly, the previous meta-analysis found that the rs2235371 was significantly associated with NSCL ± P risk in Asians, but not in Caucasians.[14] Moreover, we did not find a significant association between rs2013162 polymorphism and NSCL ± P risk, whereas there was a significant association between rs2013162 polymorphism and NSCL ± P risk in Caucasian and mixed populations. Recently, a meta-analysis by Xia et al has showed a significant association between rs2235371 and NSCL ± P in Chinese Han populations.[16] This was also consistent with Wattanawong et al meta-analysis that showed a significant association between rs2013162 polymorphism and increased NSCL ± P risk.[14] Recently, six studies were conducted to examine the association between p53 Arg72Pro polymorphism and lymphoma risk.

Significant association between-study heterogeneity was displayed among all genetic models. Besides, other factors such as

subtype of IS, gender distribution, past medical history, personal history diversity in design, the difference of ethnicity, sample sizes, and measurement errors and so on, might also be responsible for the heterogeneity. Considering that ethnicity may contribute to common sources of heterogeneity, we conducted the subgroup analysis by ethnicity to clarify the sources of heterogeneity. Unluckily, we did not effectively eliminate the heterogeneity, indicating that ethnicity especially should be taken into consideration. Moreover, after removing the study deviating from HWE and leaving out certain studies for sensitivity analysis, the heterogeneity did not eliminat, which suggests the study deviating from HWE, as the main source of heterogeneity in the three models for Asians).

The advantage of this meta-analysis is that the information from the eligible studies is utilized as much as possible through the genetic model and stratified analysis). However, there are several limitations to this study. First, the number of eligible studies for some ethnicities is small), which restricts the application of the conclusions drawn from ethnicities. Second, we have selected only published studies in English and Chinese languages in this meta-analysis. Unpublished data, ongoing studies and articles published in languages other than English and Chinese were not sought, especially those with negative findings, which may have biased our findings, although no obvious publication bias was apparent. Third, our results were based on single-factor estimates without adjustment for other risk factors such as age, gender, prenatal exposures, environmental factors and other variables, which might have caused serious confounding bias. Finally, lacking the original data for the included studies limited our further evaluation of potential interactions among gene-gene, gene-environment, or even different polymorphism loci of *IRF6* gene, which all may affect NSCL ± P risk.

Conclusion

This meta-analysis suggested that *IRF6* rs2235371 is associated with the risk of NSCL ± P. Due to the limitations discussed above, further studies estimating the effect of gene-gene and gene–environment interactions may eventually lead to a better and comprehensive understanding of the association between the *IRF6* polymorphism and NSCL ± P risk.

Conflict of Interests

Authors have no conflict of interests.

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