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Insulin-Like Growth Factor 1 (IGF1) Pathway Member Polymorphisms Are Associated with Risk and Prognosis of Chondrosarcoma

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Background: The insulin-like growth factor 1 (IGF1) pathway is deeply involved in cell proliferation, including tumorigenesis. Aberrant genetic alterations of IGF1 pathway members were revealed in certain malignancies, including chondrosarcoma (CHS). We proposed that genetic polymorphisms in IGF1 pathways might be associated with susceptibility to tumorigenesis and prognosis of CHS in Chinese populations.

Material/Methods: We recruited 112 pathologically diagnosed CHS cases and 104 cancer-free controls in this study. There were 5 single-nucleotide polymorphisms of IGF1 pathway members (IGF1R rs2016347, IGF1 rs1520220, IGF1 rs2946834, IGF3BP3 rs2270628, and IGF2 rs4320932) genotyped that subsequently underwent bioinformatic analyses. DNA from validated CHS cases was extracted from frozen blood samples preserved in liquid nitrogen, while DNA from tumor-free controls was extracted from fresh blood. SNP genotyping was conducted by PCR.

Results: The variant T allele of IGF1R (rs2016347) is potentially correlated with poor outcome in patients with conventional CHS. The GT and TT genotypes of IGF1R rs2016347 predicted statistically significant higher risk of tumor metastasis and higher histological grade of CHS.

Conclusions: We hypothesized that IGF1 member polymorphisms are associated with chondrosarcoma. We found that genetic polymorphisms in IGF1 pathway members are associated with elevated risk and poor prognosis of conventional CHS patients in Chinese populations. IGF1R rs2016347 polymorphisms were associated with the risk of lung metastasis of CHS. The IGF1 pathway members do not appear to be involved in the tumorigenesis of CHS.

MeSH Keywords: Bone and Bones • Chondrosarcoma • Polymorphism, Genetic

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Background

Chondrosarcoma is the second most common primary malignancy originating from mesenchymal tissue; it is an aggressive sarcoma that requires complete surgical excision and threatens patient quality of life [1]. Lung metastasis is one of the characteristics of CHS [2]. Current therapeutic regimens, especially en bloc resection surgery, have increased the 5-year-overall survival (OVS) to 60–70%. However, in high-grade cases and unresectable tumors, the prognosis tends to be very poor [3]. In addition, in low-grade cases, whether the tumor should be resected en bloc or treated with curettage only is unclear. Also, controversies still exist regarding non-surgical therapeutics, especially radiotherapy. It is widely accepted that conventional chondrosarcoma responds poorly to conventional radiotherapy, while some studies provided evidence that high-dose radiotherapy can be effective in certain cases [4–6]. As there are controversies regarding non-surgical treatment, questions arise about when and which CHS patients should receive more aggressive treatment, including en bloc resection or radiotherapy [7,8]. Many studies have been performed to find biomarkers to predict poor prognosis in order to provide more aggressive treatment. However, there are few available methods or predictors to indicate the prognosis of certain CHS patients or to predict the effectiveness of curettage or en bloc resection. Availability of more reliable biomarkers or predictors to predict the susceptibility or the prognosis of patients with conventional CHS would allow medical oncologists and surgeons to use aggressive oncologic therapies for CHS patients who are high-risk or who are likely to have a poor outcome.

Abundant evidence has revealed that the insulin-like growth factor 1 (IGF1) system is deeply involved in the cell proliferation and tumorigenesis of bone and soft tissue sarcomas, including chondrosarcoma [9–13]. Altered expression of IGF1 pathway members was observed in multiple bone and soft tissue sarcomas, and there is increasing evidence suggesting that the IGF1 pathway has an important role in CHS [13–15]. In addition, somatic alterations of IGF1 pathway members were recently revealed in multiple malignancies, suggesting that these kinds of heritable risk alleles in IGF1 pathway members play key roles in tumor oncogenesis and progression [16,17]. Thus, it is rational to hypothesize that genetic alterations of IGF1 members are associated with CHS risk and outcome. As the morbidity of CHS is relatively lower than in other malignancies such as lung cancer or breast cancer, systematic study utilizing a relatively large number of CHS case cohorts could be challenging. Thus, in the present study, we used blood samples preserved in liquid nitrogen to extract DNA to further study the genetic SNPs in IGF1 pathway members in CHS patients.

Recent studies have provided evidence that single-nucleotide polymorphisms (SNPs) of certain genes or *loci* are associated with the risk and/or prognosis of multiple malignancies [18]. However, functional SNPs are still elusive in CHS patients because of the low morbidity. Thus, it is important and clinically significant to assess and find functional SNPs in given genes, such as members in IGF1 in CHS. In other solid malignancies, the genetic polymorphisms in IGF1 members were revealed to be potentially related with the risk of cancer and/or the treatment outcome [19,20]. Therefore, we hypothesized that functional SNPs play a role tumor progression in chondrosarcoma.

In this study, we genotyped 112 frozen blood samples from validated CHS cases by real-time polymerase chain reaction (PCR) and from 104 tumor-free healthy controls to test the hypothesis that functional SNPs in IGF1 members are correlated with the susceptibility, tumor grade, and prognosis of CHS patients. We included 5 tagging SNPs of IGF1 pathway members: IGF1R rs2016347, IGF1 rs1520220, IGF1 rs2946834, IGF3BP3 rs2270628, and IGF2 rs4320932.

Material and Methods

Ethics approval

As this study used frozen blood samples from patient, ethics approval was obtained in Aug 2008 (approval no. K20080020), before we initiated the study, from the Ethics Committee of the Fourth Affiliated Hospital of Zhejiang University School of Medicine, the Second Affiliated Hospital of Jiaxing University, and Fudan University. All of the experimental procedures were conducted according to the Declaration of Helsinki. In addition, informed consents were signed and obtained from adult CHS patients or the legal guardians of adolescent patients before the collection of peripheral blood. All participants agreed to allow analysis of their blood samples.

Patient information

Patients with special pathological types of chondrosarcoma, such as myxoid chondrosarcoma and soft tissue chondrosarcoma, were excluded. Finally, 112 patients with conventional CHS and 104 tumor-free control individuals were recruited in this case-control study. Tumor-free control individuals were selected from the Trauma or Osteoarthritis Departments, and the tumor-free status was validated by past medical history. All participants were identified as Chinese Han people, and the information was confirmed by the registered ID and signed signature of the individuals. All of the CHS cases received pathology validation from 09/07/2008 to 20/06/2014. Only conventional CHS cases were included in this study. Blood samples were collected before performing chemotherapy and were subsequently preserved in liquid nitrogen for further DNA extraction. All of the conventional CHS patients underwent surgery

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performed by qualified orthopedic surgeons and were followed up for at least 5 years. Tumor-free control individuals were matched to CHS patients by age, sex, and hometown. Clinical information was recorded by clinicians in the medical operating system of 2 participating hospitals.

SNP information

Five tagging single-nucleotide polymorphisms of IGF1 members were selected by reviewing the tagger tool in the HapMap web site in Chinese Han people. IGF1R rs2016347, IGF1 rs1520220, IGF1 rs2946834, IGF3BP3 rs2270628, and IGF2 rs4320932 were chosen for further analyses.

Sample processing and tagging SNP genotyping

Total DNA of frozen blood samples were isolated with the phenol-based protocol using the Blood DNA Extraction Kit (Qiagen, Germany) following the instructions of the manufacturer. In brief, total DNA (2 μl at the final concentration of 5 ng/μl) was added into the 384-well PCR plates and were run in triplicate. The TaqMan assay by design reagent mix (ThermoFisher, Waltham, MA) was utilized to perform the PCR following the instructions of the manufacturer. The amplification was performed following the protocol: (1) starting denaturing at 95°C for 10 min; and (2) start to run for 40 cycles at 95°C for 15 s, and then 60°C for 1 min and 72°C for 1 min. Analyses of the expression of the 5 selected tagging SNPs was performed on a 7900HT plate reader (ABI, Foster City, CA).

Haplotype analysis

To perform haplotype analysis, we used the online SHEsis system (*http://analysis.bio-x.cn/myAnalysis.php*), which was established by the Bio-X lab group. Haplotyping was conducted using computational methods, and the 5 included SNPs were analyzed to find frequent haplotypes with over 3% prevalence.

Statistical analysis

SPSS software (v22.0; IBM Corporation, Armonk, NY) was used to perform appropriate statistical analysis. SNPs were tested and validated for the Hardy-Weinberg equilibrium by Fisher's exact test. Pearson's chi-square test was used to evaluate differences in the distributions of genotypes of IGF1 pathway members, chosen variables, and subject characteristics between conventional CHS patients and tumor-free controls. Odds ratios (ORs) were calculated in combination with the evaluation of 95% confidential intervals (95% CIs). In addition, we used logistic regression analyses to evaluate crude odds ratios and then adjusted the crude OR for age and sex. All statistical analyses were two-sided. P<0.05 was regarded as statistically significant.

Results

Patient demographics

The clinical information and related characteristics of all recruited conventional CHS patients and tumor-free healthy controls were analyzed and are displayed in Table 1. The medium ages of included conventional CHS patients and tumor-free healthy controls were 45.21±4.53 years and 45.39±4.64 years, respectively. Regarding sex ratios, 64 out of 112 (57.14%) conventional CHS patients were male and the other 48 (42.86%) were female. There was no significant difference in age or sex between the CHS patient group and the control group (*P*=0.765 for age and 0.566 for sex). Pathology evidence was used to stage the histological features of CHS patients [21]. In the included 112 conventional CHS patients, 21 out of 112 (20.59%) had low-grade tumors (WHO grade I), and the other 91 (79.41%) had high-grade tumors (WHO grade II and III). Ten patients had positive tumor margins and received radiotherapy and the other 102 patients did not receive radiotherapy. Surgical excisions were performed as amputation or limb salvage. Among these series of patients, 10 (8.93%) received curettage because they had low-grade tumors, and 102 (91.07%) received tumor en bloc resection and prosthetic reconstruction. Concerning the metastasis status, 35 (31.25%) patients had an evaluable lung mass during the follow-up.

IGF1R rs2016347 is associated with the risk of conventional chondrosarcoma

Five tagging SNPs (IGF1R rs2016347, IGF1 rs1520220, IGF1 rs2946834, IGF3BP3 rs2270628, and IGF2 rs4320932) were selected and genotyped for further analyses. The pooled data on genetic polymorphisms are displayed in Table 2. In tumor-free healthy controls, we found that the genotype distributions of the evaluated SNPs were all within Hardy-Weinberg equilibrium (P=0.232, 0.251, 0.383, 0.295, and 0.351, respectively). We performed further logistic regression analyses, which suggested that IGF1R polymorphism is correlated with susceptibility of conventional CHS. In IGF1R rs2016347, 8 out of 112 CHS patients were TT homozygote genotype, while only 3 individuals in the tumor-free control group had this genotype. When we set the TT genotype as the reference group, the GT genotype showed a statistically significant elevated risk of morbidity in conventional CHS patients (crude OR=1.45, 95% CI=1.16–1.67, P=0.021). The adjusted OR was 1.46, and 95% CI=1.17–1.69, P=0.020). Furthermore, the TT homozygote genotype seemed to be correlated with higher risk of conventional CHS (crude OR=1.58, 95% CI =1.21–1.93, P=0.009). The adjusted OR was 1.60, and the 95% CI was 1.24 to 1.99, P=0.008). When we applied the T dominant model (GT and TT) in analysis series, a significant statistical difference was revealed (GT+TT *vs.* TT: crude OR=1.57, 95% CI=1.25–1.87, P=0.012). The adjusted OR

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Table 1. General characteristics.

Variables		OS Cases [n (%)]	Tumor-free Control [n (%)]	*P*
Age	Mean ± SD (year)	45.21±4.53	45.39±4.64	0.765
Sex	Male	64 (57.14)	58 (55.77)	0.566
	Female	48 (42.86)	46 (44.23)	
Location	Trunk	29 (25.89)		
	Limbs	83 (74.11)		
WHO grades	Low-grade (I)	21 (20.59)		
	High-grade (II, III)	91 (79.41)		
Radiotherapy	No	102 (91.07)		
	Yes	10 (8.93)		
Operation	Curettage	10 (8.93)		
	En bloc resection	102 (91.07)		
Metastasis	No	77 (68.75)		
	Yes	35 (31.25)		

was 1.59 and the 95% CI was 1.28–2.01, P=0.014). When the G dominant model (GG and GT) was compared with TT genotype, a significant difference was also found. The crude OR was 1.88 and the 95% CI was 1.38–2.15, P=0.009). The adjusted OR was 1.86 and the 95% CI was 1.36–2.18, P=0.010.

The other 4 included SNPs (IGF1 rs1520220, IGF1 rs2946834, IGF3BP3 rs2270628, and IGF2 rs4320932) did not show potential correlations between IGF1 pathway polymorphisms and the risk of conventional CHS in Chinese populations.

IGF1R rs2016347 was correlated with higher stage and lung metastasis of chondrosarcoma

We included several clinical characteristics (tumor location, stage, chemotherapy, operative therapeutics, and metastasis status) of conventional CHS cases to assess whether IGF1R rs2016347 was associated with the stage or the risk of forming lung metastases. The stage and metastasis status were validated to be directly correlated with the prognosis of CHS. As shown in Table 3, the frequency of genotype GT in high-grade tumors (II or III, account for 32.97%) was higher when compared with low-grade CHS cases (I, 14.29%), and a statistically significant difference was revealed (P=0.018). Furthermore, analyses of the status of metastasis also revealed a potential association between genetic polymorphisms of IGF1R and lung metastasis. The genotype GT has significantly higher frequency (40.00%) in individuals with lung metastases when compared with cases without detectable remote metastases (29.87%). In addition, in TT homozygote genotype, only 1 individual was metastasis-free, while there were 7 with lung metastasis. There was a statistically significant difference in the distribution of frequency (P=0.007).

The potential confounding variables (i.e., tumor grades and status of remote metastasis) were evaluated and are displayed in Tables 4 and 5, respectively. No significant difference was found.

Statistically significant differences were revealed in haplotype analyses

Ten frequent (frequency over 3%) haplotypes were detected by online analyses of the 5 candidate SNPs – CGTAT, CGTTT, CGATT, CGAAT, CCTAT, CGGTG, CGGCG, CCTCG, CCCCT, and CCCCG – as shown in Table 6. We performed further analyses to find potential statistical significances between CHS cases and normal controls. Among the 10 haplotypes, CGATT and CGGCG were found to show significant differences between CHS cases and matched normal tumor-free cases (P=0.035, 95% CI=0.254–0.761, and P=0.023, 95% CI=1.054–1.916, respectively).

Discussion

Conventional chondrosarcoma is genetically unstable and highly heterogenous, complicating mechanism research. Although efforts have been made to study the tumorigenesis and progression mechanism of conventional CHS, the low morbidity of the

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Table 2. Logistic regression analyses for the potential correlations between IGF1R rs2016347, IGF1 rs1520220, IGF1 rs2946834, IGF3BP3 rs2270628, and IGF2 rs4320932 polymorphisms and the risk of CHS.

IGF1 member Genotype	Cases (n=112)		Controls (n=104)		Crude OR (95%CI)	P	Adjusted OR (95%CI)	P
	n	%	n	%				
IGF1R rs2016347								
GG	67	59.82	81	77.88	1.00		1.00	
GT	37	33.03	20	19.23	1.45 (1.16–1.67)	0.021*	1.46 (1.17–1.69)	0.020*
TT	8	7.14	3	2.88	1.58 (1.21–1.93)	0.009*	1.60 (1.24–1.99)	0.008*
GT+TT	45	40.18	23	22.11	1.57 (1.25–1.87)	0.012*	1.59 (1.28–2.01)	0.014*
GG+GT	104	92.86	101	97.11	1.00		1.00	
TT	8	7.14	3	2.88	1.88 (1.38–2.15)	0.009*	1.86 (1.36–2.18)	0.010*
IGF1 rs1520220								
CC	16	14.29	15	14.42	1.00		1.00	
CA	45	40.18	42	40.38	0.92 (0.61–1.58)	0.862	0.91 (0.62–1.59)	0.866
AA	61	54.46	47	45.19	1.16 (0.72–2.20)	0.601	1.17 (0.73–2.21)	0.610
CA+AA	106	94.64	89	85.57	1.10 (0.69–1.75)	0.788	1.08 (0.65–1.78)	0.768
CC+CA	61	54.47	57	54.80	1.00		1.00	
AA	61	54.46	47	45.19	1.25 (0.79–1.62)	0.251	1.24 (0.81–1.63)	0.256
IGF1 rs2946834								
CC	50	44.89	44	42.31	1.00		1.00	
CT	37	33.04	36	34.62	0.94 (0.77–1.25)	0.522	0.88 (0.69–1.26)	0.525
TT	25	22.07	24	23.08	1.07 (0.80–1.41)	0.525	1.09 (0.79–1.42)	0.526
CT+TT	62	55.36	60	57.70	0.93 (0.64–1.21)	0.493	0.92 (0.64–1.25)	0.500
CC+CT	87	77.93	80	76.93	1.00		1.00	
TT	25	22.07	24	23.08	1.10 (0.76–1.64)	0.449	1.09 (0.80–1.63)	0.452
IGF3BP3 rs2270628								
GG	17	15.18	17	16.35	1.00		1.00	
GT	39	34.82	34	32.69	0.68 (0.43–1.11)	0.221	0.70 (0.41–1.15)	0.223
TT	56	50.00	53	50.96	0.83 (0.65–1.67)	0.771	0.82 (0.64–1.61)	0.772
GT+TT	95	84.82	87	83.65	0.88 (0.60–1.47)	0.455	0.86 (0.60–1.48)	0.456
GG+GT	56	50.00	51	49.04	1.00		1.00	
TT	56	50.00	53	50.96	1.01 (0.62–1.65)	0.345	1.03 (0.64–1.68)	0.350
IGF2 rs4320932								
CC	70	62.50	64	61.54	1.00		1.00	
CG	32	28.57	30	28.85	1.21 (0.83–1.55)	0.591	1.23 (0.85–1.57)	0.589
GG	10	8.93	10	9.61	0.92 (0.47–1.42)	0.871	0.91 (0.51–1.43)	0.861
CG+GG	42	37.50	40	38.46	1.21 (0.72–1.55)	0.496	1.24 (0.71–1.58)	0.488
CC+CG	102	91.07	94	90.39	1.00		1.00	
GG	10	8.93	10	9.61	0.84 (0.88–1.25)	0.472	0.85 (0.85–1.29)	0.498

* Statistically significant (P<0.05).

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Table 3. Associations between genotype frequencies of IGF1R rs2016347 and clinical characteristics in CHS individuals.

Variables	n	GG n (%)	GT n (%)	TT n (%)	*P*
Location					
Trunk	29	15 (51.72)	11 (37.93)	3 (10.34)	0.753
Limbs	83	49 (59.03)	28 (33.73)	6 (7.23)	
WHO grades					
Low-grade (I)	21	18 (85.71)	3 (14.29)	0 (0.00)	0.018*
High-grade (II, III)	91	46 (50.55)	30 (32.97)	5 (5.49)	
Chemotherapy					
No	102				N/A#
Yes	10				
Operation					
Curettage	10	9 (90.00)	1 (10.00)	0 (0.00)	0.182
En bloc resection	102	60 (58.82)	34 (33.33)	8 (3.23)	
Metastasis					
No	77	53 (68.83)	23 (29.87)	1 (1.14)	0.007*
Yes	35	14 (40.00)	14 (40.00)	7 (20.00)	

* Statistically significant ($P<0.05$); # the number of cases was too small to analyze.

Table 4. Confounding variables (tumor grades).

Confounding variables		Low-grade cases [n (%)]	High-grade cases [n (%)]	*P*
Age	Mean±SD (year)	44.21±3.36	44.52±4.02	0.387
Gender	Male	9 (42.86)	37 (40.66)	0.561
	Female	12 (57.14)	54 (59.34)	

Table 5. Confounding variables (remote metastasis).

Confounding variables		Metastasis cases [n (%)]	Metastasis-free cases [n (%)]	*P*
Age	Mean±SD (year)	45.29±3.91	45.33±3.42	0.411
Gender	Male	14 (40.00)	37 (48.05)	0.127
	Female	21 (60.00)	40 (51.95)	

tumor severely restricts the collection of clinical samples, and thus weakens data interpretation. Currently, predicting factors or biomarkers, especially those that can be easily detected by commonly used methods such as PCR or immunohistochemistry, requires further exploration. Thus, we performed this study by utilizing liquid nitrogen-preserved peripheral blood samples from conventional CHS patients.

Genomic factors are valuable markers to predict the susceptibility and prognosis of cancers and sarcomas. Recent reports have provided some strong evidence that SNPs are associated with the biological behavior of tumors [16,22,23]. Therefore, in the present study, we performed gene array by PCR to find possible genetic variations and thus assess their significance in a relatively large cohort.

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Table 6. Haplotype analysis.

Haplotype	CHS cases frequency	Controls frequency	p	OR (95% CI)
CGTAT	0.076	0.069	0.433	1.115 (0.652–1.635)
CGTTT	0.064	0.060	0.825	0.867 (0.402–1.971)
CGATT	0.028	0.059	0.035*	0.529 (0.254–0.761)
CGAAT	0.049	0.044	0.612	1.909 (0.606–2.019)
CCTAT	0.021	0.029	0.215	0.722 (0.492–1.307)
CGGTG	0.055	0.063	0.092	0.865 (0.777–1.121)
CGGCG	0.225	0.108	0.023*	1.215 (1.054–1.916)
CCTCG	0.058	0.052	0.744	1.117 (0.485–2.817)
CCCCT	0.042	0.046	0.595	0.914 (0.587–1.411)
CCCCG	0.071	0.076	0.416	1.710 (1.054–2.226)

* Statistically significant (P<0.05).

Several SNPs in IGF1 pathway members were found to be potentially related to tumorigenesis and/or tumor progression [15,24–28]. The expression of IGF1 protein was also found to be potentially associated with the prognosis and treatment effects of conventional CHS [29]. However, the role genetic factors of IGF1 members in conventional CHS is still unclear. In this study, we demonstrated that genetic polymorphisms in SNPs of IGF1 pathway members were potentially correlated with the susceptibility and tumor outcome of conventional CHS. Our data demonstrated that IGF1R rs2016347 polymorphisms ware associated with the risk of conventional CHS, and the GT and TT genotype potentially increase the tumor risk. In addition, IGF1R rs2016347 polymorphism GT and TT genotype were also correlated with higher tumor stage and higher risk of remote metastasis. Thus, according to our data interpretation, physicians should consider that patients carrying IGF1R rs2016347 GT and TT genotypes have significantly higher risk of lung metastasis. Therefore, more aggressive chemotherapy regimens and more frequent follow-ups are import. Of note, further research is needed to verify our findings.

As IGF1R was shown to be associated with chondrosarcoma, it is reasonable to consider IGF1R or IGF1 targeted therapy in this tumor. IGF1R antibodies and inhibitors have been evaluated in the treatment of multiple solid malignancies, including breast cancer [30], ovarian cancer [31], and sarcomas [32]. In chondrosarcoma, the IGF1R antibody Ganitumab was utilized in a Phase I trial [33]. The treatment with Ganitumab against treatment-naïve chondrosarcoma achieved stable disease for over 24 months [33]. This trial highlighted the role IGF1 members play in this tumor. Further clinical trials involving IGF1 members will help the non-surgical treatment of this refractory tumor.

Our study has some limitations. First, as all of the blood samples were collected from hospitals, selection bias could not be avoided. Second, the small number of patients carrying some homozygotic types was very small, which could weaken have weakened our data interpretation and conclusions. Further studies recruiting more conventional CHS patients will certainly help to improve the efficacy of assessing IGF1 pathway member polymorphism in evaluating the susceptibility and tumor outcome of conventional CHS.

Conclusions

In conclusion, we provide evidence that genetic SNPs in IGF1 pathway members are potentially associated with higher risk and poor prognosis of conventional CHS in Chinese Han people.

Conflicts of interest

None.

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