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ORIGINAL RESEARCH

HMGA2 Polymorphisms and Hepatoblastoma Susceptibility: A Five-Center Case-Control Study

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Background: Hepatoblastoma is a rare disease. Its etiology remains obscure. No epidemiological reports have assessed the relationship of *High Mobility Group A2* (*HMGA2*) single nucleotide polymorphisms (SNPs) with hepatoblastoma risk. This case-control study leads as a pioneer to explore whether *HMGA2* SNPs (rs6581658 A>G, rs8756 A>C, rs968697 T>C) could impact hepatoblastoma risk.

Methods: We acquired samples from 275 hepatoblastoma cases and 1018 controls who visited one of five independent hospitals located in the different regions of China. The genotyping of *HMGA2* SNPs was implemented using the PCR-based TaqMan method, and the risk estimates were quantified by odds ratios (ORs) and 95% confidence intervals (CIs).

Results: In the main analysis, we identified that rs968697 T>C polymorphism was significantly related to hepatoblastoma risk in the additive model (adjusted OR=0.73, 95% CI=0.54–0.98, *P*=0.035). Notably, participants carrying 2–3 favorable genotypes had reduced hepatoblastoma risk (adjusted OR=0.71, 95% CI=0.52–0.96, *P*=0.028) in contrast to those carrying 0–1 favorable genotypes. Furthermore, stratification analysis revealed a significant correlation between rs968697 TC/CC and hepatoblastoma risk for males and clinical stage I+II. The existence of 2–3 protective genotypes was correlated with decreased hepatoblastoma susceptibility in children ≥17 months old, males, and clinical stage I+II cases, when compared to 0–1 protective genotype.

Conclusion: To summarize, these results indicated that the *HMGA2* gene SNPs exert a weak influence on hepatoblastoma susceptibility. Further validation of the current conclusion with a larger sample size covering multi-ethnic groups is warranted.

Keywords: hepatoblastoma, *HMGA2*, polymorphism, susceptibility

Introduction

Hepatoblastoma is the most common form of pediatric liver malignancies. It takes up nearly 80% of all pediatric liver cancers.[1,2] However, hepatoblastoma is a rare disease overall and constitutes just over 1% of all pediatric cancers.[3] Most of the hepatoblastomas are originated from epithelium, primarily composed of immature hepatocytic elements.[3] The 5-year overall survival (OS) in hepatoblastoma children is nearly 70%.[4,5]

Unlike adult hepatocellular carcinoma, the etiology of hepatoblastoma remains obscure, due to its extreme rarity (1.1 per million for Chinese children).[6] Hepatitis B virus, chronic hepatitis, and cirrhosis are causative factors for hepatocellular carcinoma rather than the hepatoblastoma.[7,8] Accumulating data suggested several risk factors that might lead to hepatoblastoma including thrombocytosis, Beckwith-Wiedemann syndrome, fetal alcohol syndrome, hereditary adenomatous polyposis,

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and glycogen storage disease.[9–12] A few epidemiological reports have indicated that single nucleotide polymorphisms (SNPs) might also be predisposing factors for hepatoblastoma.[13–16] However, it is difficult to obtain a significant association owing to the scarcity of included patients. Therefore, unveiling the underlying etiology of hepatoblastoma using a larger sample size, especially causative genetic factors, is of great significance.

HMGA2, short for High Mobility Group A2, pertains to the high mobility group family.[17] HMGA2 is a non-histone nuclear-binding protein with three DNA binding domains, namely AT-hooks, short basic repeats, and terminal with an acidic carboxyl group. It can serve as an architectural transcription factor through interacting with the minor groove of A: T-abundant DNA fragments.[17] As an oncofetal protein, HMGA2 is omnipresently expressed during embryogenesis.[18] However, this protein rarely exists in differentiated cells and adult human tissues.[19] HMGA2 acts as a critical regulator in the development of the embryo. It is noteworthy that the evidence of oncogenic activities of *HMGA2* increasingly grows. Re-expression and amplification of *HMGA2* were detected in a variety of cancers.[20,21] Interestingly, intensive research has suggested a significant association between *HMGA2* gene variants and childhood/adult heights.[22–24] Recently, evidence has been published, supporting the impact of *HMGA2* gene SNPs on uterine leiomyomata risk.[25] However, the relevance of *HMGA2* gene SNPs to hepatoblastoma risk has not been reported so far.

To shed light on this topic, we investigated the relationship of *HMGA2* SNPs with the risk of hepatoblastoma using a set of 275 patients and 1018 controls enrolled from five unrelated medical centers. Our findings aid in understanding the etiology of hepatoblastoma.

Materials and Methods

Study Subjects

Children histologically verified with hepatoblastoma were enrolled from five independent hospitals (Guangzhou Women and Children's Medical Center, the First Affiliated Hospital of Zhengzhou University, Shengjing Hospital of China Medical University, Kunming Children's Hospital, Xijing Hospital) located at Guangdong, Henan, Liaoning, Yunnan, and Shaanxi provinces in China. Patients with multiple cancers and those who underwent chemotherapy or radiation were excluded from the study. The healthy controls without cancer hereditary history in the family were recruited from the same respective hospital as the cases. The cases and controls were comparable in age, sex, and non-relatives of each other. In total, 275 children with hepatoblastoma and 1018 matched controls were included in the current investigation. Each eligible subject's parents or guardians signed written informed consent before the collection of patient samples and associated clinical data. A detailed description of subjects could be found in the previously published studies.[15,16] The study protocol was permitted by the Ethics Committee of each participating hospital (Ethical approve number: 2017120101). This study was conducted in accordance with the Declaration of Helsinki.

Genotyping

SNPs were selected based on the published criteria.[26,27] Genomic DNA extraction from subjects' blood was performed utilizing a customized TIANamp Blood DNA Kit manufactured by TianGen Biotech Co. Ltd. (Beijing, China). SNP genotyping was conducted by PCR-based TaqMan methodology, as outlined in the manufacturer manual.[28–30] Blinded fashion without knowing the status of samples was adopted to ensure genotyping accuracy. We also re-genotyped 10% randomly selected samples. A 100% concordance rate was achieved in the re-genotyped samples.

Statistical Analysis

All SNPs were tested for the Hardy-Weinberg equilibrium (HWE) separately in the controls using a χ^2 test. In cases and controls, the differences in clinical characteristics were determined by the adoption of a two-sided χ^2 test. The association of the SNP with hepatoblastoma risk was tested using multivariable logistic regression analysis with adjustment for age and gender. Multivariate logistic regression analysis was employed to generate odds ratios (ORs) for the associations, with 95% confidence intervals (CIs). $P < 0.05$ indicates differences were statistically significant between the groups. All P values are two-sided. The SAS 9.1 (SAS Institute, Cary, NC) was chosen to perform all statistical tests.

Results

Participant Characteristics

The clinical features of the study population are listed in Supplemental Table 1. We selected a total of 275 cases with an average age of 23.81 ± 25.82 months and 1018 healthy controls with an average age of 25.10 ± 19.35

months. Similar distributions between patients and control subjects were found, concerning age (P=0.365) and gender (P=0.589).

Evaluation Association of SNPs with Hepatoblastoma Risk

The association between the selected SNPs (rs6581658 A>G, rs8756 A>C, rs968697 T>C) and risk of hepatoblastoma was presented in Table 1. The distribution frequencies of the SNP genotypes of the control group were in accordance with HWE (P>0.05). Of the three SNPs, only SNP rs968697 T>C displayed a statistically significant association with hepatoblastoma risk under the additive model (adjusted OR=0.73, 95% CI=0.54–0.98, P=0.035). The rs6581658 GG, rs8756 AC/AA, and rs968697 TC/CC were then assumed as protective genotypes. Compared to the subjects with 0–1 protective genotype, the carriers of 2–3 favorable genotypes exhibited a lower probability of developing hepatoblastoma (adjusted OR=0.71, 95% CI=0.52–0.96, P=0.028).

Stratification Analysis

We then assessed the effects of the rs968697 genotype and the joint protective genotypes in stratification analyses by age (<17 months old vs ≥17 months old), gender (male vs female), and clinical stages (stage I+II vs III+IV) (Table 2). It was observed that rs968697 TC/CC genotypes were notably correlated with a decreased risk of hepatoblastoma in males (adjusted OR=0.64, 95% CI=0.42–0.98, P=0.040) and clinical stage I+II children (adjusted OR=0.63, 95% CI=0.41–0.98, P=0.042) diseases. In

Table 1 Association Between *HMGA2* Gene Polymorphisms and Hepatoblastoma Risk

Genotype	Cases (N=275)	Controls (N=1018)	P^a	Crude OR (95% CI)	P	Adjusted OR (95% CI)[b]	P^b
rs6581658 A>G (HWE=0.507)							
AA	166 (60.36)	644 (63.26)		1.00		1.00	
AG	99 (36.00)	327 (32.12)		1.18 (0.89–1.56)	0.264	1.17 (0.88–1.56)	0.269
GG	10 (3.64)	47 (4.62)		0.83 (0.41–1.67)	0.593	0.82 (0.41–1.67)	0.591
Additive			0.624	1.06 (0.84–1.33)	0.624	1.06 (0.84–1.33)	0.632
Dominant	109 (39.64)	374 (36.74)	0.378	1.13 (0.86–1.49)	0.378	1.13 (0.86–1.48)	0.385
Recessive	265 (96.36)	971 (95.38)	0.482	0.78 (0.39–1.56)	0.483	0.78 (0.39–1.56)	0.482
rs8756 A>C (HWE=0.512)							
AA	207 (75.27)	798 (78.39)		1.00		1.00	
AC	64 (23.27)	209 (20.53)		1.18 (0.86–1.62)	0.308	1.19 (0.86–1.63)	0.297
CC	4 (1.45)	11 (1.08)		1.40 (0.44–4.45)	0.566	1.39 (0.44–4.42)	0.575
Additive			0.254	1.18 (0.89–1.57)	0.254	1.18 (0.89–1.58)	0.248
Dominant	68 (24.73)	220 (21.61)	0.270	1.19 (0.87–1.63)	0.271	1.20 (0.88–1.63)	0.262
Recessive	271 (98.55)	1007 (98.92)	0.607	1.35 (0.43–4.28)	0.608	1.34 (0.42–4.25)	0.618
rs968697 T>C (HWE=0.896)							
TT	216 (78.55)	743 (72.99)		1.00		1.00	
TC	57 (20.73)	254 (24.95)		0.77 (0.56–1.07)	0.118	0.77 (0.56–1.06)	0.112
CC	2 (0.73)	21 (2.06)		0.33 (0.08–1.41)	0.134	0.32 (0.08–1.40)	0.130
Additive			0.037	**0.73 (0.54–0.98)**	**0.037**	**0.73 (0.54–0.98)**	**0.035**
Dominant	59 (21.45)	275 (27.01)	0.062	0.74 (0.54–1.02)	0.062	0.73 (0.53–1.01)	0.058
Recessive	273 (99.27)	997 (97.94)	0.137	0.35 (0.08–1.49)	0.155	0.35 (0.08–1.48)	0.152
Combined effect of protective genotypes[c]							
0	1 (0.36)	5 (0.49)		1.00		1.00	
1	209 (76.00)	704 (69.16)		1.48 (0.17–12.78)	0.719	1.49 (0.17–12.82)	0.718
2	64 (23.27)	302 (29.67)		1.06 (0.12–9.22)	0.958	1.06 (0.12–9.22)	0.960
3	1 (0.36)	7 (0.69)		0.71 (0.04–14.35)	0.826	0.71 (0.04–14.20)	0.820
0–1	210 (76.36)	709 (69.65)		1.00		1.00	
2–3	65 (23.64)	309 (30.35)	0.029	**0.71 (0.52–0.97)**	**0.030**	**0.71 (0.52–0.96)**	**0.028**

Notes: The values were in bold, if the 95% CI excluded 1 or P-value less than 0.05. [a]χ^2 test for genotype distributions between hepatoblastoma patients and cancer-free controls. [b]Adjusted for age and gender. [c]Risk genotypes were rs6581658 GG, rs8756 AC/AA and rs968697 TC/CC.

Abbreviations: OR, odds ratio; CI, confidence interval; HWE, Hardy-Weinberg equilibrium.

Table 2 Stratification Analysis for Association Between *HMGA2* Gene Genotypes and Hepatoblastoma Susceptibility

Variables	rs968697 (case/control)		OR (95% CI)	*P*	AOR (95% CI)[a]	*P*[a]	Protective genotypes (case/control)		OR (95% CI)	*P*	AOR (95% CI)[a]	*P*[a]
	TT	TC/CC					0–1	2–3				
Age, month												
<17	112/329	36/130	0.81 (0.53–1.25)	0.343	0.82 (0.53–1.25)	0.350	108/315	40/144	0.81 (0.54–1.22)	0.318	0.81 (0.54–1.23)	0.324
≥17	104/414	23/145	0.63 (0.39–1.03)	0.066	0.63 (0.39–1.03)	0.067	102/394	25/165	**0.59 (0.36–0.94)**	**0.027**	**0.59 (0.37–0.94)**	**0.028**
Gender												
Female	85/292	28/108	0.89 (0.55–1.44)	0.637	0.88 (0.55–1.43)	0.613	83/281	30/119	0.85 (0.53–1.37)	0.508	0.85 (0.53–1.35)	0.484
Male	131/451	31/167	**0.64 (0.42–0.98)**	**0.041**	**0.64 (0.42–0.98)**	**0.040**	127/428	35/190	**0.62 (0.41–0.94)**	**0.023**	**0.62 (0.41–0.94)**	**0.023**
Clinical stages												
I+II	115/743	27/275	**0.63 (0.41–0.99)**	**0.043**	**0.63 (0.41–0.98)**	**0.042**	113/709	29/309	**0.59 (0.38–0.91)**	**0.016**	**0.59 (0.38–0.90)**	**0.016**
III+IV	54/743	17/275	0.85 (0.49–1.49)	0.573	0.85 (0.48–1.49)	0.561	51/709	20/309	0.90 (0.53–1.54)	0.698	0.90 (0.53–1.53)	0.687

Notes: The values were in bold, if the 95% CI excluded 1 or P-value less than 0.05. [a]Adjusted for age and gender, omitting the corresponding stratify factor.
Abbreviations: OR, odds ratio; AOR, adjusted odds ratio; CI, confidence interval.

subgroups of age ≥17 months (adjusted OR=0.59, 95% CI=0.37–0.94, *P*=0.028), males (adjusted OR=0.62, 95% CI=0.41–0.94, *P*=0.023), and children in clinical stage I+II (adjusted OR=0.59, 95% CI=0.38–0.90, *P*=0.016) diseases, the existence of 2–3 protective genotypes was correlated with 0.59-fold, 0.62-fold and 0.59-fold decreased risk of hepatoblastoma, respectively, when compared to 0–1 protective genotypes.

Discussion

GWAS and case-control studies have persistently linked the *HMGA2* gene SNPs to human height and cancer risk.[23, 25, 31] The genetic importance of these SNPs in hepatoblastoma risk is not clear. In this study, we explored the genetic relevance of potential functional SNPs of the *HMGA2* gene to the hepatoblastoma risk. We detected a weak association between *HMGA2* SNPs and hepatoblastoma risk.

HMGA2 gene is located in a human chromosome region 12q15. *HMGA2* gene is extensively expressed in the embryonic period, but hardly detected in normal adult cells and tissues. In 2013, Lee et al[32] verified that *HMGA2* is expressed in all hepatoblastomas and may serve as a marker for the diagnosis of hepatoblastoma. HMGA2 has been shown to promote tumor growth,[33] differentiation,[34] metastasis,[35,36] transformation,[37] and DNA damage repair.[38] Li et al[39] found that HMGA2 stimulates cell proliferation, aggression, and epithelial-to-mesenchymal transition (EMT) in colon cancer via upregulating the transcription factor Slug. HMGA2-FOXL2 axis could directly regulate malignant progression and EMT of chemo-resistant gastric cancer.[40] Hodge et al[25] revealed that TC227 allele in the 5′-UTR of the *HMGA2* gene alone was closely linked to uterine leiomyomata development in White women. Functional experiments implied that increased *HMGA2* expression caused by TC227 allele is causative of elevated risk of uterine leiomyomata development. Liu et al[41] identified *HMGA2* rs1563834 as a predictor of long-term survivors in glioblastoma. The first case-control study on the association between *HMGA2* SNPs and cancer risk was performed in 2016. The study focuses on cervical cancer in 247 patients and 285 healthy women in Xinjiang Uygur population.[42] Among three SNPs in the *HMGA2* gene (rs8756, rs11175982, rs1042725) investigated, only minor allele "C" of rs1042725 predisposes to increased risk of cervical cancer.

It is worth pointing out that the *HMGA2* gene is a critical member of the *MYCN/LIN28B/Let-7/HMGA2* axis, which is implicated in the occurrence of various cancers.[35,43–46] Accumulating evidence proves that HMGA2 is a downstream target of the miRNA let−7. Let−7 could bind to multiple target sites in the HMGA2 3′-UTR to promoting its degradation. Indeed, let−7 is often down-regulated in cancers, and line with a high level of HMGA2. Di Fazio et al[47] demonstrated that

increased transcription and maturation of the tumor suppressor miRNA *hsa-let-7b* reduced *HMGA2* expression in liver cancer cell lines. The maturation of *let-7* is negatively regulated by the *LIN28B*. Nguyen et al[48] demonstrated that *LIN28B* likely acts through both *let-7*-dependent and -independent mechanisms to drive hepatoblastoma tumorigenesis, implicating the *LIN28B*/*let-7* network as an important pathway in hepatoblastoma. Our group has provided evidence of the effects of *MYCN/LIN28B/Let-7* gene SNPs on the childhood cancer risk, including hepatoblastoma.[49–51] Considering the intimately mutual relationship inside *MYCN/LIN28B/Let-7* genes and the vital role of individual *HMGA2* gene in cancers, it is quite biologically feasible to speculate the role of *HMGA2* SNPs in hepatoblastoma risk. Moreover, it is of great significance that the current study provides the first identification of the role of *HMGA2* SNPs in hepatoblastoma risk.

Herein, we by far explored the correlation of *HMGA2* SNPs with the hepatoblastoma susceptibility with the largest study population. Of the three SNPs, we only detected a statistically significant association of SNP rs968697 T>C with hepatoblastoma risk in the additive model. Moreover, we found the children harboring 2–3 favorable genotypes had a lower probability of developing hepatoblastoma. Our data also showed that rs968697 TC/CC and the presence of 2–3 protective genotypes were associated with decreased hepatoblastoma risk, respectively, at some stratification strata. The initiative outcome obtained here implies that *HMGA2* SNPs may affect hepatoblastoma susceptibility in a weak impact pattern. The SNP rs968697 T>C is located in transcription factor binding sites (TFBS). We speculated such polymorphism may affect the expression of *HMGA2*, thus affect hepatoblastoma susceptibility.

This study was the first attempt to interrogate the correlation of *HMGA2* gene SNPs and hepatoblastoma risk. The unprecedently large-scale and multi-center based study design are the primary strengths of our study. The study also has some limitations. Firstly, the sample size was relatively moderate because of the low prevalence of hepatoblastoma. Augmentation of the number of hepatoblastoma cases will be further taken to strengthen the statistical power. Secondly, environmental factors that may impact the role of *HMGA2* gene SNPs were not investigated. Last, the selection bias cannot be excluded as all the subjects were from hospitals. Moreover, the studied population was restricted to the Han Chinese. The exclusion of other ethnicities limits the generalization of the conclusion.

Conclusions

In conclusion, we identified that rs968697 T>C polymorphism was significantly related to hepatoblastoma risk. The characterization of *HMGA2* gene SNPs sheds light on the role of *HMGA2* gene SNPs in hepatoblastoma susceptibility and helps to elucidate the etiology of hepatoblastoma. Future larger studies combining genetic and environmental risk factors should be warranted.

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Disclosure

The authors have no conflicts of interest to declare.

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