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Research Paper

**LIN28A polymorphisms and hepatoblastoma susceptibility in Chinese children**

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**Abstract**

Hepatoblastoma (HB) is the most prevalent primary hepatic cancer in children aged 6 months to 3 years. **LIN28A** is recurrently mutated in various diseases, and critically involved in tumorigenesis. However, a limited number of studies have examined the involvement of **LIN28A** polymorphisms in HB risk. We used the TaqMan assay to genotype four **LIN28A** polymorphisms (rs3811464 G>A, rs3811463 T>C, rs34787247 G>A, and rs11247957 G>A) in 275 Chinese children with HB and 1018 cancer-free controls from five medical centers in China. Their association with HB risk was evaluated on the basis of odds ratio (OR) and corresponding 95% confidence interval (CI). Overall, no significant associations were found in single locus and combine analysis. Interestingly, in the stratified analysis, we found that subjects with 1-3 risk genotypes were more likely to develop HB in patients ≥17 months of age (adjusted OR=1.76, 95% CI=1.04-2.98, P=0.034). The rs3811464 GA/AA genotypes were associated with decrease HB risk in patients with clinical stage II+IV disease (adjusted OR=0.50, 95% CI=0.26-0.96, P=0.038). Our results suggest that the **LIN28A** polymorphisms have a weak association with HB susceptibility in the Chinese children. **LIN28A** rs3811464 G>A may decrease HB risk in stage III+IV patients which need further validations with larger samples and different ethnicities.

Key words: Hepatoblastoma, Susceptibility, **LIN28A**, Polymorphism

**Introduction**

Hepatoblastoma (HB) is the most prevalent primary hepatic cancer of embryonic origin [1]. HB frequently exhibits a combination of histological patterns because of repeating stages in liver development [2]. The incidence of HB peaks between the ages of 6 months and 3 years, and HB is more frequently seen in males [3]. Over the last 2-3 decades, due to advances in multimodal treatments including surgical resection and adjuvant chemotherapy, 5-year overall survival rates have achieved as high as 80% [4]. Meantime, as a result of low-birth-weight infants and the enhanced survival of premature babies, the incidence of HB appears to be gradually increasing, with about 4% per year for the period of 1992 to 2004 and a current rate of 1.5 cases/million [5-7]. Furthermore, non-resectable tumors or metastases are associated with a poor prognosis [4, 8]. To improve prognosis in HB, it is essential to comprehensively
understand its pathogenesis [5, 9].

The most of HB is sporadic, but there are some familial cases associated with constitutional genetic abnormalities, such as familial adenomatous polyposis, trisomy 18 syndrome and Beckwith-Wiedemann syndrome (BWS) [10-12]. Interestingly, single nucleotide polymorphisms (SNPs) have been found to be associated with the development and poor outcome of HB. Kim et al. used SNP array for whole-exome sequencing and analyses of genome-wide loss of heterozygosity and copy number in a BWS infant with HB. They found 11p15.5 uniparental disomy and APC and PALB2 mutations at the germline level, and chromosome 1q gain and CTNNB1 hotspot mutation at the somatic level [13]. One study used high-density genome-wide SNP microarray analyses and demonstrated that 88% cases had chromosomal aberrations such as 1q,17q and 11q, among others [14]. A previous study also demonstrated that LINCO0067 rs11655237 C>T polymorphism is significantly associated with HB risk and that rs11655237 T allele carriers are more likely to develop HB [15]. These results suggested that complicated genomic abnormalities may contribute to the pathogenesis of HB.

LIN28 is an RNA-binding protein that was first shown to be a heterochronic gene controlling developmental timing. It is highly expressed during embryogenesis and plays a vital role in cell growth and embryonic development [16]. Moreover, LIN28 inhibits let-7 miRNA biogenesis and blocks pre-let-7 processing in the cytoplasm. It is known that the let-7 miRNA family targets oncogenic genes and downstream signaling pathways, thereby suppressing the progression of cell cycle and oncogenesis. Therefore, LIN28 acts as an oncogene by inhibiting the synthesis of let-7 [17]. Mammals possess two LIN28 homologs, namely LIN28A and LIN28B [18]. LIN28A resides on chromosome 1p36.11, which blocks the biogenesis of all let-7s and promotes tumor growth [19]. The temporal regulation of LIN28A expression at neurulation blocked axial elongation and embryonic growth in mice [20]. The upregulation of LIN28A by Wnt could enhance the implantation potential of human embryo surrogate spheroids [21]. Besides, Chang et al. identified the loss-of-function variant of LIN28A in patients with early-onset Parkinson’s disease. They found that correction of the LIN28A variant in the donor patient’s human induced pluripotent stem cells-improved behavioral phenotypes in the Parkinson’s disease model [22].

Moreover, LIN28A (rs6697410 in LIN28 were found to be associated with breast cancer risk [24]. However, the effect of the LIN28A polymorphisms on HB has not been studied. In the present study, we examined whether SNPs in LIN28A biogenesis genes confer HB risk in the Han Chinese population.

Material and methods

Patients and controls

In this study, we enrolled 275 cases with newly histopathologically diagnosed HB and 1018 non-cancer controls from five medical centers in Guangdong, Henan, Shaanxi, Yunnan and Liaoning provinces (Table S1). The 275 included children were examined and surgically treated in these five medical centers, diagnosed pathologically as HB, and finally staged, excluding HB cases that were examined only and did not undergo surgery, or underwent puncture biopsy only. Non-cancer controls were frequency-matched on age and sex were recruited from the same residing area as cases. Included patients provided their necessary written informed consent and trained interviewers collected their demographic information. The complete criterion for selecting participants was described previously [25, 26]. Approval for this study was obtained from the ethics committee of each participating hospital. The study protocol was complied with ethical guidelines.

SNP selection and genotyping

Four LIN28A polymorphisms (rs3811464 G>A, rs3811463 T>C, rs34787247 G>A, and rs11247957 G>A) were identified through the dbSNP database (http://www.ncbi.nlm.nih.gov/SNP) and SNPinfo online software (https://snpinfo.niehs.nih.gov/snpinfo/snpfunc.html) as we described previously [27, 28]. Then the DNA samples were further genotyped using a standard commercial TaqMan real-time PCR kit [29]. About 10% of the samples were randomly selected and re-genotyped for quality control. We obtained 100% agreement for the quality control samples.

Statistical analysis

We used χ2 test to evaluate the difference in the distribution of characteristics, risk factor, and genotypes of LIN28A SNPs between cases and controls. The goodness-of-fit χ2 test was used to check if the frequency distributions of SNP genotypes were in accordance with Hardy-Weinberg equilibrium (HWE) in controls. We performed unconditional univariate and multivariate logistic regression analyses to determine the strength of the association between the selected polymorphisms and risk of HB through the odds ratios (ORs) and 95% confidence
intervals (CIs). Adjustment for age and sex was performed in multivariate analysis. We also carried out stratification analysis based on age, sex, and clinical stages. P<0.05 was considered as statistically significant. All statistical analyses were two-sided and carried out using SAS software (version 9.1; SAS Institute, Cary, NC, USA).

Results

Relationship between LIN28A SNPs and HB susceptibility

Genotyping was successful in 275 HB cases and 1018 controls. All the four SNPs were in accordance with HWE in controls (rs3811464 G>A, P=0.165; rs3811463 T>C, P=0.823; rs34787247 G>A, P=0.193; and rs11247957 G>A, P=0.622). No significant association was found between LIN28A polymorphisms and HB susceptibility in either single locus or combined analysis (Table 1).

Stratification analysis of association between LIN28A polymorphisms and HB risk

In the stratification analysis by age, sex and clinical stages (Table 2), we found significant association with the rs3811464 polymorphism (GA/AA vs. GG: adjusted OR=1.50, 95% CI=0.26-0.96, P=0.038) in patients with clinical stages III+IV. Regarding the combined analysis, we found that the 1-3 risk genotypes carriers were at significantly higher HB risk in patients ≥17 months of age (adjusted OR=1.76, 95% CI=1.04-2.98, P=0.034).

Table 1. Association of LIN28A polymorphisms with hepatoblastoma susceptibility

| Genotype     | Cases (N=275) | Controls (N=1018) | P* | Crude OR (95% CI) | P | Adjusted OR (95% CI) b | P* |
|--------------|---------------|-------------------|----|------------------|---|------------------------|----|
| rs3811464 G>A (HWE=0.165) |               |                   |    |                  |   |                        |    |
| GG           | 208 (75.64)   | 744 (73.08)       | 1.00 |                      | 1.00 |                      |    |
| GA           | 61 (22.18)    | 246 (24.17)       | 0.89 (0.64-1.22) | 0.532 | 0.79 (0.32-1.92) | 0.573 |
| AA           | 6 (2.18)      | 28 (2.75)         | 0.77 (0.31-1.88) | 0.92 | 0.89 (0.64-1.22) | 0.727 |
| Dominant     | 67 (24.36)    | 274 (26.92)       | 0.394 |                      | 0.394 |                      |    |
| Reccessive   | 269 (97.82)   | 990 (97.25)       | 0.601 |                      | 0.602 |                      |    |
| rs3811463 T>C (HWE=0.823) |               |                   |    |                  |   |                        |    |
| TT           | 203 (73.82)   | 741 (72.79)       | 1.00 |                      | 1.00 |                      |    |
| TC           | 64 (23.27)    | 254 (24.95)       | 0.92 (0.67-1.26) | 0.603 | 0.92 (0.67-1.26) | 0.613 |
| CC           | 8 (2.91)      | 23 (2.26)         | 1.27 (0.56-2.88) | 0.913 | 0.99 (0.76-1.29) | 0.931 |
| Additive     | 0.912 | 0.99 (0.76-1.28) | 0.913 | 0.99 (0.76-1.29) | 0.931 | 0.99 (0.76-1.29) | 0.931 |
| Dominant     | 72 (26.18)    | 277 (27.21)       | 0.733 |                      | 0.733 |                      |    |
| Reccessive   | 267 (97.09)   | 995 (97.74)       | 0.532 |                      | 0.533 |                      |    |
| rs34787247 G>A (HWE=0.193) |               |                   |    |                  |   |                        |    |
| GG           | 213 (77.45)   | 793 (77.90)       | 1.00 |                      | 1.00 |                      |    |
| GA           | 55 (20.00)    | 206 (20.24)       | 0.99 (0.71-1.39) | 0.92 | 0.99 (0.71-1.38) | 0.958 |
| AA           | 7 (2.55)      | 19 (1.87)         | 1.37 (0.57-3.31) | 0.727 | 1.05 (0.79-1.39) | 0.733 |
| Additive     | 0.727 | 1.05 (0.79-1.39) | 0.727 | 1.05 (0.79-1.39) | 0.733 | 1.05 (0.79-1.39) | 0.733 |
| Dominant     | 62 (22.55)    | 225 (22.10)       | 0.875 |                      | 0.875 |                      |    |
| Reccessive   | 268 (97.45)   | 998 (98.13)       | 0.477 |                      | 0.478 |                      |    |
| rs11247957 G>A (HWE=0.622) |               |                   |    |                  |   |                        |    |
| GG           | 265 (96.36)   | 987 (96.95)       | 1.00 |                      | 1.00 |                      |    |
| GA           | 10 (3.64)     | 31 (3.05)         | 1.20 (0.58-2.48) | 0.620 | 1.22 (0.59-2.52) | 0.593 |
| AA           | 0 (0.00)      | 0 (0.00)          | /    |                      | /    |                      |    |
| Additive     | 0.620 | 1.20 (0.58-2.48) | 0.620 | 1.22 (0.59-2.52) | 0.593 | 1.22 (0.59-2.52) | 0.593 |
| Dominant     | 10 (3.64)     | 31 (3.05)         | 0.620 |                      | 0.620 |                      |    |
| Recressive   | 10 (3.64)     | 31 (3.05)         | 0.620 |                      | 0.620 |                      |    |

Risk genotypes a

| 0 | 0.175 | 1.00 | 0.10 |
| 1 | 1.23 (0.88-1.71) | 0.223 | 1.23 (0.89-1.71) | 0.216 |

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

a χ² test for genotype distributions between hepatoblastoma patients and cancer-free controls.

b Adjusted for age and gender.

c Risk genotypes were rs3811464 GG, rs3811463 CC, rs34787247 AA, and rs11247957 GA.
The findings of various studies have suggested abnormal expression of LIN28A in a broad array of tumor types, which is connected to advanced disease and poor prognosis [39]. The findings of various studies have suggested that LIN28A gene polymorphisms play a role in cancer risk. Rao et al. found that LIN28A was a good immunohistochemistry marker for the diagnosis of embryonal tumor with multilayered rosettes [40]. Li et al. showed that the downregulation of LIN28A expression suppressed differentiation and self-renewal of human breast cancer stem cells by inactivating the Wnt pathway in a let-7b-dependent manner [41]. A case-control study at four centers demonstrated that LIN28A gene polymorphisms alter susceptibility to neuroblastoma; it was found that LIN28A SNPs, particularly rs34787247 G>A, could increase neuroblastoma risk [28]. Also, LIN28A rs3811463 T>C and rs34787247 G>A have been associated with increased risk of Wilms tumor in Chinese children [27].

Our study showed that LIN28A polymorphisms affects HB susceptibility in a low-penetrating manner. We failed to find any single locos that can modify HB susceptibility. Stratified analysis indicated that rs3811464 GA/AA carriers had reduced risk to develop clinical stages III+IV tumors; the presence of rs3811464 GA/AA carriers had reduced risk to HB risk among children ≥17 months of age. To our knowledge, we are the first group to confirm the association between LIN28A polymorphisms and HB susceptibility. Interestingly, we found that the presence of rs3811464 GA/AA genotypes in LIN28A provided a protective effect for children with clinical stages III+IV HB. Liu et al. studied the association between APEX1 polymorphisms and neuroblastoma risk in Chinese children, and found that the rs1130409 GG genotype significantly reduced the tumor risk in males older than 18 months with 1-3 protective genotypes, and had a lower neuroblastoma risk [42]. The effect of gene polymorphisms on cancer risk may be affected by tumor type, sample sizes, and selection criteria. Therefore, the association between LIN28A polymorphisms and HB risk should be specified in a particular population.

Our study demonstrated that LIN28A

| Variables | rs3811464 | rs3811463 | rs34787247 | Risk genotypes |
|-----------|-----------|-----------|-----------|----------------|
|           | AOR (95% CI) * | P* | AOR (95% CI) * | P* | AOR (95% CI) * | P* |
| GG        | GA/AA     | TT       | TC/CC     | GG        | GA/AA     | 0  |
| Age (month) |           |          |           |           |          |   |
| <17       | 1.01 (0.67-1.53) | 1.08 (0.71-1.64) | 0.710 (0.59-1.47) | 0.93 (0.59-1.47) | 0.757 (0.61-1.46) | 0.804 |
| ≥17       | 0.73 (0.46-1.16) | 0.83 (0.53-1.30) | 0.420 (0.53-1.30) | 1.15 (0.73-1.80) | 0.557 (0.69-1.91) | 0.034 |
| Gender    |           |          |           |           |          |   |
| Females   | 0.97 (0.60-1.57) | 0.242 (0.83-2.09) | 2.428 (0.61-1.64) | 1.00 (0.61-1.64) | 0.991 (0.69-1.91) | 0.594 |
| Males     | 0.81 (0.54-1.21) | 0.75 (0.50-1.13) | 0.168 (0.69-1.58) | 1.04 (0.69-1.58) | 0.847 (0.84-2.00) | 0.241 |
| Clinical stages |         |          |           |           |          |   |
| I+II      | 1.00 (0.67-1.48) | 1.13 (0.77-1.67) | 0.530 (0.64-1.50) | 0.98 (0.77-1.84) | 0.938 (0.77-1.84) | 0.422 |
| III+IV    | 0.50 (0.26-0.96) | 0.60 (0.32-1.11) | 0.106 (0.69-2.09) | 1.20 (0.69-2.09) | 0.522 (0.87-3.24) | 0.126 |

Discussion

HB is the most prevalent primary hepatic cancer in children and accounts for around 1% of all childhood cancers [30, 31]. Currently, the 5-year survival rate remains only 20-30% in cases with considerable unifocal and distant metastases at diagnosis [1, 32]. A number of studies have reported that HB is related to genetic syndromes. For instance, 7.5-13.5% of children with BWS develop embryonal tumors, with the most frequent tumors being HB and nephroblastoma [31]. Studies have also demonstrated that Wnt/β-catenin signaling pathway abnormalities exist in most cases of HB [33]. Elevated expression of hTERT (human telomerase reverse transcriptase) and c-MYC appear to be predictive of a poor prognosis because both of them play crucial roles in the activation of Wnt/β-catenin signaling in aggressive phenotypes of HB [34, 35]. With further study of HB pathogenicity genes, researchers have found that methylation and polymorphism of genes, microRNAs and lncRNAs are also related to the carcinogenesis of HB [15, 36-38]. However, there has been no prior study about the association of LIN28A polymorphisms with HB susceptibility.

There have been many studies underscoring the importance of LIN28A in the regulation of stem cell pluripotency and self-renewal; however, recent investigations have shown abnormal expression of LIN28A in a broad array of tumor types, which is connected to advanced disease and poor prognosis [39]. The findings of various studies have suggested that LIN28A gene polymorphisms play a role in cancer risk. Rao et al. found that LIN28A was a good immunohistochemistry marker for the diagnosis of embryonal tumor with multilayered rosettes [40]. Li et al. showed that the downregulation of LIN28A...
polymorphisms were not significantly associated with HB susceptibility. However, LIN28A rs34787247 G>A has been reported to be connected to increased risk of neuroblastoma and LIN28A rs3811463 T>C and rs34787247 G>A to increased risk of nephroblastoma [27, 28]. Moreover, a study in East Asia showed that SNPs of LIN28A (rs11247954, rs12728900, rs3811463, rs4274112, rs4659441, rs6599845, and rs66835792) were not significantly associated with breast cancer risk [43]. According to these findings, the effects of LIN28A polymorphisms on cancer susceptibility may be tumor type-specific. Single SNPs have been shown to be insufficient to modify tumor risk, while the occurrence of several SNPs could synergistically play significant roles in carcinogenesis [44].

Although this was the first and largest case-control study to assess the association between LIN28A polymorphisms and HB risk in the Chinese population to date, it cannot represent the entire Chinese population. Moreover, this study did not involve other races of people. Selection bias is an obvious possible confounding factor. Meantime due for phased research results of this study, there was no verification. We need to expand the sample size to further confirm the above results. To better determine the association of LIN28A polymorphisms with susceptibility to HB, further investigations should be designed to consider related factors including environmental background and data on parental diet, lifestyle, and exposure to hazards.

Overall, this study demonstrates that LIN28A SNPs have a weak relationship with HB susceptibility in the Chinese population.

Supplementary Material
Supplementary table S1.
http://www.jcancer.org/v12p1373s1.pdf

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Data availability statement
All data were available upon request.

Conflict of interest statement
The authors declared that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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