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Associations between *LMO1* gene polymorphisms and central nervous system tumor susceptibility

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ABSTRACT

Importance: LIM domain only 1 (*LMO1*) gene polymorphisms were previously found to be implicated in the risk of several cancers. No available studies were performed regarding the predisposing effect of *LMO1* gene single nucleotide polymorphisms (SNPs) on central nervous system (CNS) tumor risk.

Objective: We aimed to determine whether the *LMO1* gene SNPs were associated with the risk of CNS tumor by applying a case-control study with 191 cases and 248 controls in China.

Methods: The contributions of *LMO1* gene SNPs to the risk of CNS tumor was evaluated by multinomial logistic regression.

Results: Based on the calculations of odds ratio (*OR*) and 95% confidence interval (*CI*), we failed to detect a significant relationship between each *LMO1* gene SNP (rs110419 A>G, rs4758051 G>A, rs10840002 A>G, rs204938 A>G, and rs2168101 G>T) and CNS tumor risk, respectively. A negative association was also found in the combined effects on these five SNPs and CNS tumor risk. The stratification analysis further demonstrated the individuals with rs204938 AG/GG genotype confer to increased risk of CNS tumor compared with those with an AA genotype in males (*OR*: 1.74, 95% *CI*: 1.01–2.98, $P = 0.046$).

Interpretation: We concluded that *LMO1* gene SNPs may not strong enough to influence the risk of CNS tumor in Chinese children. More studies are required to verify this association.

KEYWORDS
LMO1, SNPs, CNS tumor, Chinese

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INTRODUCTION

Pediatric central nervous system (CNS) tumors are the most common solid tumors in children and comprise 15% to 20% of all malignancies in children.[1] Pediatric CNS tumors are clinically and biologically highly diverse, encompassing a wide spectrum from benign neoplasms that can frequently be cured by surgery alone (e.g. pilocytic astrocytoma), to highly malignant tumors responding poorly to any therapy (e.g. glioblastoma).[2] Intensive efforts have been made in understanding the etiology of CNS tumor. Many environmental factors, including excessive cell phone usage, excessive smoking and alcohol, and ionizing radiation exposure were suggested to conferring to the risk of CNS tumor.[3] However, only ionizing radiation is highly recognized as a causative factor for the risk of CNS tumor.[4] Next-generation sequencing, including whole-genome and whole-exome sequencing, has identified several high-risk rare variants/mutations associated with risk of pediatric cancer including CNS tumors.[5,6] Genetic studies, such as genome-wide association studies (GWASs), have identified a dozen of adult CNS tumor (including glioma) risk associated-SNPs, which are located in genes *CCDC26*, *PHLDB1*, *TP53*, *EGFR*, and *CDKN2A-CDKN2B*.[7-10] GWASs also implicated *PAPPA2, LRRC4*C as novel candidate susceptibility loci for CNS tumors in children[11] and 18p11.23 as novel candidate susceptibility loci for medulloblastoma in children and young adults.[12] Collectively, however, these variants only explain a small portion for the etiology of CNS tumor. Greater knowledge regarding the genetic factors is warranted to better understand the etiology of CNS tumor.

LIM domain only 1 (*LMO1*) gene is located at chromosome 11p15. It encodes a cysteine-rich transcriptional regulator composed of two zinc finger LIM domains.[13] The LIM domains of LMO1 protein can regulate several biological activities including self-renewal, proliferation, cell cycle, and metastasis.[14] LMO1 has been well documented in the initiation or the progression of various cancers.[15] A dozen of genetic studies have been performed to assess the association between *LMO1* gene polymorphisms and cancer risk, yet the data regarding CNS tumor still lacks. Four polymorphisms in *LMO1* (rs110419 A>G, rs4758051 G>A, rs10840002 A>G and rs204938 A>G) were found to be associated with the risk of several cancers in a genome-wide association study (GWAS).[16,17] SNP rs2168101 G>T is located in the *LMO1* super-enhancer, which was also reported to modify neuroblastoma susceptibility.[18] We speculated that these polymorphisms might also contribute to the risk of CNS tumor.

The objective of this study was to analyze the *LMO1* gene variants in subjects who have CNS tumor correlated, in order to confirm their clinical relevance and to evaluate their possible improvement of predicting CNS tumor when introduced in the pre-treatment screening.

METHODS

Ethics approval

The study was approval by the Ethics Committee of Guangzhou Women and Children's Medical Center (No. 2016021650) in compliance with the tenets of the Declaration of Helsinki. Written informed consent was obtained from each participant or the guardians.

Study population

The participant was enrolled from Guangzhou Women and Children's Medical Center and The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University between 2005 and 2019. Cases were defined by a confirmed diagnosis of CNS tumor by histopathology. Controls were collected in the same geographical region (Guangzhou and Wenzhou) as the cases during the same period. Eligibility criteria for controls were Chinese and no underlying medical disorder, including cancer. Finally, 191 cases and 248 controls were included. A detailed description of enrolling subjects could be obtained in our previous studies.[19,20]

Polymorphism selection and genotyping

Four *LMO1* gene SNPs (rs110419 A>G, rs4758051 G>A, rs10840002 A>G and rs204938 A>G) identified previously using a GWAS were selected for genotyping.[16] Another SNP located in the *LMO1* super-enhancer, rs2168101 G>T, reported to modify neuroblastoma susceptibility, was also included.[18] Genomic DNA was extracted from peripheral blood according to the manufacturer's instructions (QIAamp DNA Blood Mini Kit, QIAGEN Inc., Valencia, CA). DNA concentration and purity were determined using the Nanodrop 2000 spectrophotometer (Thermo Fisher Scientific, Waltham, MA, USA). We used the TaqMan SNP Genotyping Assay (Applied Biosystem, Waltham, MA, USA) for polymorphism detection. Quality control measures included the inclusion of negative control samples (water) and blinded cases and controls status by laboratory technicians. The conditions of reactions were set as follow: pre-read stage at 60℃ for 30 seconds, holding stage at 95℃ 10 minutes, repeated 45 cycles each of denaturation at 95℃ for 15 seconds, annealing and extension at 60℃ for 1 minute. In addition, 10% of the samples were randomly selected for re-genotyping, with completely concordant results.

Statistical analysis

Hardy-Weinberg equilibrium (HWE) in the controls was tested by using a goodness-of-fit χ^2 test for each SNP. Two-sided χ^2 test was adopted to determine the difference of demographic variables and SNP distribution among cases and controls. The association between the

TABLE 1 Association between *LMO1* gene polymorphisms and central nervous system tumor susceptibility in Chinese children

Genotype	Cases (*n* = 191)	Controls (*n* = 248)	*P*†	Crude *OR* (95% *CI*)	*P*	Adjusted *OR* (95% *CI*)‡	*P*‡
rs110419 A>G (HWE = 0.829)							
AA	65 (34.03)	81 (32.66)		1.00		1.00	
AG	97 (50.79)	120 (48.39)		1.01 (0.66–1.54)	0.973	1.00 (0.65–1.53)	0.989
GG	29 (15.18)	47 (18.95)		0.77 (0.44–1.36)	0.363	0.81 (0.46–1.43)	0.470
Additive			0.442	0.90 (0.68–1.18)	0.441	0.92 (0.70–1.21)	0.535
Dominant	126 (65.97)	167 (67.34)	0.763	0.94 (0.63–1.40)	0.762	0.95 (0.63–1.42)	0.787
Recessive	162 (84.82)	201 (81.05)	0.301	0.77 (0.46–1.27)	0.302	0.81 (0.49–1.35)	0.424
rs4758051 G>A (HWE = 0.693)							
GG	63 (32.98)	80 (32.26)		1.00		1.00	
GA	91 (47.64)	119 (47.98)		0.97 (0.63–1.49)	0.893	0.97 (0.63–1.49)	0.874
AA	37 (19.37)	49 (19.76)		0.96 (0.56–1.65)	0.879	0.95 (0.55–1.63)	0.837
Additive			0.871	0.98 (0.75–1.28)	0.871	0.97 (0.74–1.27)	0.830
Dominant	128 (67.02)	168 (67.74)	0.872	0.97 (0.65–1.45)	0.872	0.96 (0.64–1.44)	0.842
Recessive	154 (80.63)	199 (80.24)	0.920	0.98 (0.61–1.57)	0.920	0.96 (0.60–1.56)	0.882
rs10840002 A>G (HWE = 0.348)							
AA	59 (30.89)	75 (30.24)		1.00		1.00	
AG	89 (46.60)	116 (46.78)		0.98 (0.63–1.51)	0.911	0.97 (0.63–1.51)	0.899
GG	43 (22.51)	57 (22.98)		0.96 (0.57–1.62)	0.875	0.95 (0.56–1.61)	0.854
Additive			0.873	0.98 (0.76–1.27)	0.873	0.98 (0.75–1.27)	0.851
Dominant	132 (69.11)	173 (69.76)	0.884	0.97 (0.64–1.46)	0.884	0.97 (0.64–1.46)	0.867
Recessive	148 (77.49)	191 (77.02)	0.907	0.97 (0.62–1.53)	0.907	0.97 (0.62–1.53)	0.889
rs204938 A>G (HWE = 0.496)							
AA	117 (61.26)	173 (69.76)		1.00		1.00	
AG	64 (33.51)	70 (28.22)		1.35 (0.90–2.04)	0.152	1.39 (0.92–2.10)	0.123
GG	10 (5.23)	5 (2.02)		2.96 (0.99–8.87)	0.053	2.85 (0.94–8.63)	0.064
Additive			0.027	1.47 (1.04–2.08)	0.028	1.49 (1.05–2.10)	0.026
Dominant	74 (38.74)	75 (30.24)	0.062	1.46 (0.98–2.17)	0.063	1.49 (1.00–2.22)	0.052
Recessive	181 (94.76)	243 (97.98)	0.066	2.69 (0.90–7.99)	0.076	2.57 (0.85–7.71)	0.093
rs2168101 G>T (HWE = 0.501)							
GG	104 (54.45)	122 (49.19)		1.00		1.00	
GT	71 (37.17)	107 (43.15)		0.78 (0.52–1.16)	0.217	0.77 (0.51–1.14)	0.192
TT	16 (8.38)	19 (7.66)		0.99 (0.48–2.02)	0.973	1.01 (0.49–2.07)	0.983
Additive			0.459	0.89 (0.66–1.20)	0.459	0.89 (0.66–1.20)	0.456
Dominant	87 (45.55)	126 (50.81)	0.275	0.81 (0.56–1.18)	0.275	0.80 (0.55–1.17)	0.256
Recessive	175 (91.62)	229 (92.34)	0.784	1.10 (0.55–2.21)	0.783	1.13 (0.56–2.28)	0.728
Combined effect of protective genotypes§							
0	2 (1.05)	1 (0.40)	0.325	1.00		1.00	
1	53 (27.75)	62 (25.00)		0.43 (0.04–4.85)	0.493	0.50 (0.04–5.93)	0.584
2	12 (6.28)	16 (6.45)		0.38 (0.03–4.64)	0.445	0.46 (0.04–5.89)	0.549
3	40 (20.94)	51 (20.56)		0.39 (0.03–4.48)	0.451	0.46 (0.04–5.41)	0.533
4	60 (31.41)	80 (32.26)		0.38 (0.03–4.23)	0.428	0.44 (0.04–5.13)	0.510
5	24 (12.57)	38 (15.32)		0.32 (0.03–3.68)	0.357	0.38 (0.03–4.60)	0.446
0–3	107 (56.02)	130 (52.42)		1.00		1.00	
4–5	84 (43.98)	118 (47.58)	0.453	0.87 (0.59–1.26)	0.453	0.87 (0.59–1.27)	0.467

†χ^2 test for genotype distributions between patients with central nervous system tumor and controls. ‡Adjusted for age and gender. §Protective genotypes were carriers with rs110419 GG, rs4758051 GA/AA, rs10840002 AG/GG, rs204938 AA/AG, rs2168101 GT/TT genotypes. *OR*, odds ratio; *CI*, confidence interval; HWE, Hardy-Weinberg equilibrium.

TABLE 2 Stratification analysis of risk genotypes with central nervous system tumor susceptibility

Variables	rs204938 (case/control)		Adjusted *OR* (95% *CI*)†	*P*†	Protective genotypes (case/control)		Adjusted *OR* (95% *CI*)†	*P*†
	AA	AG/GG			0–3	4–5		
Age (months)								
<60	59/88	38/38	1.49 (0.85–2.60)	0.162	53/63	44/63	0.84 (0.49–1.42)	0.506
≥60	58/85	36/37	1.42 (0.81–2.51)	0.225	54/67	40/55	0.88 (0.51–1.53)	0.656
Sex								
Female	56/70	33/34	1.23 (0.68–2.24)	0.497	48/53	41/51	0.88 (0.50–1.55)	0.653
Male	61/103	41/41	**1.74 (1.01–2.98)**	**0.046**	59/77	43/67	0.86 (0.51–1.44)	0.562
Subtypes								
Astrocytic tumor	84/173	52/75	1.50 (0.96–2.35)	0.075	77/130	59/118	0.85 (0.55–1.30)	0.453
Ependymoma	19/173	14/75	1.69 (0.80–3.58)	0.172	17/130	16/118	1.05 (0.50–2.18)	0.904
Neuronal and mixed	9/173	5/75	1.37 (0.44–4.28)	0.587	9/130	5/118	0.62 (0.20–1.91)	0.401
Embryonal tumor	5/173	2/75	0.65 (0.10–4.22)	0.648	4/130	3/118	0.86 (0.17–4.31)	0.850
Clinical stage								
I	65173	45/75	1.59 (1.00–2.55)	0.052	63/130	47/118	0.82 (0.52–1.29)	0.386
II	26/173	12/75	1.08 (0.52–2.26)	0.843	19/130	19/118	1.11 (0.56–2.20)	0.769
III	9/173	8/75	2.14 (0.79–5.81)	0.137	9/130	8/118	0.97 (0.36–2.61)	0.951
IV	17/173	8/75	1.13 (0.44–2.90)	0.796	16/130	9/118	0.59 (0.24–1.46)	0.255
I+II	91/173	57/75	1.47 (0.96–2.26)	0.079	82/130	66/118	0.89 (0.59–1.34)	0.573
III+IV	26/173	16/75	1.43 (0.72–2.85)	0.313	25/130	17/118	0.75 (0.38–1.47)	0.400

The results were in bold if $P < 0.05$ or 95% *CI* excluded 1. †Adjusted for age and gender, omitting the corresponding stratify factor. *OR*, odds ratio; *CI*, confidence interval.

LMO1 gene SNPs and CNS tumor risk was tested using unconditional logistic regression computed odds ratios (*OR*) and 95% confidence intervals (*CI*). To evaluate potential confounders, the distributions of genotypes were examined by factors associated with CNS tumor risk (age, gender, subtypes, and clinical stages). The *P*-values were reported for two-tailed tests and the statistical significance level was set at 5%. All analyses were completed in the SAS statistical software package version 9.1 (SAS Institute Inc., Cary, NC).

RESULTS

Population characteristics

Both case and control groups had a similar distribution of age and gender ($P = 0.329$). The mean age was 62.74 ± 47.28 months for cases and 53.90 ± 33.47 months for controls ($P = 0.997$). Among these cases, the astrocytic tumors accounted for 136 (71.20%), the ependymoma for 33 (17.28%), the neuronal and mixed neuronal-glial tumors for 14 (7.33%), embryonal tumors for 7 (3.66%), not available information for 1 (0.52%). According to the WHO stages, 110 CNS tumor cases (57.59%) were classified into stage I, 38 (19.90%) into stage II, 17 (8.90%) into stage III, and 25 (13.09%) into stage IV, and 1 (0.52%) has no information (Table S1).

Effect of *LMO1* gene SNPs on CNS tumor risk

We successfully genotyped *LMO1* gene SNPs (rs110419 A>G, rs4758051 G>A, rs10840002 A>G, rs204938 A>G, and rs2168101 G>T) in 191 cases and 248 controls samples. The associations of these SNPs with CNS tumor risk were shown in (Table 1). All these SNPs were in accordance with Hardy-Weinberg equilibrium (HWE) in controls (HWE $P > 0.05$). Specifically, HWE-*P* values for rs110419 A>G, rs4758051 G>A, rs10840002 A>G, rs204938 A>G, and rs2168101 G>T is 0.829, 0.693, 0.348, 0.496, and 0.501, respectively. In single locus analysis, no associations of the five *LMO1* polymorphisms with CNS tumor risk were found in any of the models. We then allocated rs110419 GG, rs4758051 GA/AA, rs10840002 AG/GG, rs204938 AA/AG, rs2168101 GT/TT genotypes as protective genotypes. Compared to 0 protective genotypes, carriers with 1, 2, 3, 4, and 5 protective genotypes could not decrease CNS tumor risk. Carriers with 4–5 protective genotypes also failed to protect from CNS tumor in comparison to 0–3 protective genotypes.

Stratification analysis

We further explored the association between *LMO1* gene polymorphisms and susceptibility to CNS tumor in certain groups separated by age, gender, subtypes, and

clinical stages (Table 2). Individuals with rs204938 AG/GG genotype had a 1.74-fold increased risk of CNS tumor compared with those with an AA genotype in males, but such association was marginally significant (95% *CI*: 1.01–2.98, $P = 0.046$). No significant associations were detected between 4–5 protective genotypes and the risk of CNS tumor in all the subgroups.

DISCUSSION

There is growing evidence of novel genetic variants that have implications in CNS tumor susceptibility. Yet, it remains a challenge to unearth the full range of CNS tumor susceptibility variations. This hospital-based case-control study in China aimed to investigate whether genetic variations in the *LMO1* gene were associated with CNS tumor risk. The main findings of our study were: 1) individual or combined variants in the *LMO1* gene were not associated with CNS tumor risk; and 2) individuals with rs204938 AG/GG genotype significantly increased risk of CNS tumor in boys, with an *OR* of 1.74.

LMO1 was identified near the breakpoint of a chromosomal translocation t(11;14) (p15;q11) that was present in a T-acute lymphoblastic leukemia (T-ALL) cell line.[21,22] Recent research has uncovered the importance of LMO1 in cancer development. Sun et al[23] found that compared to adjacent tissues, the levels of *LMO1* expression were significantly higher in gastric cancer tissues. The overexpression of *LMO1* could be treated as a marker of poor prognosis of gastric cancer. Overexpression of *LMO1* is also found to contribute to the development and maintenance of T-ALL.[24] By now, more than five thousand SNPs in the *LMO1* gene were accessible (https://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?locusId=4004). Several shreds of evidence suggest the involvement of *LMO1* gene SNPs in the susceptibility of cancer. The first evidence of *LMO1* gene SNPs in cancer risk was provided in 2011 in a GWAS. The authors found that four variants (rs110419 A>G, rs4758051 G>A, rs10840002 A>G and rs204938 A>G) in the *LMO1* gene predispose to higher neuroblastoma risk in 2251 neuroblastoma patients and 6097 controls.[16] Their further functional experiments showed that significant SNPs may enhance the level of *LMO1* expression, and thus promote the proliferation of neuroblastoma. After that, this relationship was further validated in other ethnicities, including Italians,[17] African-Americans,[25] and Northern Chinese.[26] To be noted, in a study with 390 neuroblastoma cases and 2500 controls conducted in African-Americans, Latorre et al[25] failed to obtain a positive association between these four SNPs with neuroblastoma susceptibility. In 2015, Oldridge et al[18] further explored whether the *LMO1* gene causal DNA variants could impact the susceptibility of neuroblastoma. They comprehensively analyzed all possible polymorphisms in this locus. SNP rs2168101 G>T, located in a super-enhancer within the first intron of *LMO1*, was identified to significantly contribute to neuroblastoma risk. SNP rs2168101 G>T ablates GATA3 binding, and then leads to decreased expression of *LMO1*, which eventually causes an oncogenic dependency in tumor cells. Apart from neuroblastoma, the risk of *LMO1* gene SNPs on other types of cancers were also investigated. In 2011, Beuten et al[27] identified rs442264 A>G in the *LMO1* gene as a risk variant for ALL, in a Caucasian children population with 163 cases and 251 controls. In 2017, Al-Absi et al[28] found that *LMO1* gene SNPs (rs442264, rs3794012, and rs4237770) could not influence the risk of ALL in Yemeni children. It is no doubt that these identified roles of *LMO1* gene SNPs help to provide genetic insight into the origins of cancer risk. However, to date, no SNPs in the *LMO1* gene have been identified to influence CNS tumor risk.

In this study, no significant relationships were detected among CNS tumor risk and *LMO1* gene SNPs in single or combined locus analysis (rs110419 A>G, rs4758051 G>A, rs10840002 A>G, rs204938 A>G, and rs2168101 G>T) in 191 cases and 248 controls. Though we did detect a relationship between rs204938 AG/GG genotype and risk of CNS tumor, the relationship is only marginally significant. The relatively small sample size, as well as the too weak impact of these SNPs may account for major reasons for the negative relationship. To be noted, our group also genotyped these five SNPs in the neuroblastoma in the Eastern Chinese children. Significant associations with neuroblastoma risk were found for four (rs110419 A>G, rs4758051 G>A, rs10840002 A>G, and rs2168101 G>T) out of the five polymorphisms.[29] However, in another study, we only found that rs110419 A>G polymorphism may reduce the susceptibility to Wilms tumor in the Chinese population, out of the four polymorphisms (rs110419 A>G, rs4758051 G>A, rs10840002 A>G and rs204938 A>G).[30] Therefore, the geographic difference could not be neglected when considering the exact role of *LMO1* gene SNPs in cancer risk.

There are some limitations to this study. First, small numbers of participants in some subgroups of CNS tumors may have limited the ability to detect associations with certain *LMO1* gene SNPs. Furthermore, the risk models discussed herein require additional external validation, as all the analyzed relationships were only based on genetic factors. Selection bias also plagues the current case-control study. The hospital-based cases and controls may not well represent the same population from where they were derived from. Moreover, the conclusion obtained from the Chinese participants may not be applied to other ethnicities due to the allele frequencies variants among different populations. In addition, here we only included the five SNPs in *LMO1* gene. More potentially functional polymorphisms in *LMO1* gene awaits to be explored. Last, the relationship was only determined in the genetic model. The relationship between LMO1 and CNS tumor from the

protein level is warranted to be determined.

In summary, our findings indicate that *LMO1* gene SNPs rs110419 A>G, rs4758051 G>A, rs10840002 A>G, rs204938 A>G, and rs2168101 G>T are too weak to impact CNS tumor risk in Chinese subjects. Additional studies are required to further address this association and its underlying mechanisms.

CONFLICT OF INTEREST

There are no conflicts of interest.

REFERENCES

1. Udaka YT, Packer RJ. Pediatric brain tumors. Neurol Clin. 2018;36:533-556.
2. Kristensen BW, Priesterbach-Ackley LP, Petersen JK, Wesseling P. Molecular pathology of tumors of the central nervous system. Ann Oncol. 2019;30:1265-1278.
3. Ostrom QT, Adel Fahmideh M, Cote DJ, Muskens IS, Schraw JM, Scheurer ME, et al. Risk factors for childhood and adult primary brain tumors. Neuro Oncol. 2019;21:1357-1375.
4. Davis ME. Epidemiology and overview of gliomas. Semin Oncol Nurs. 2018;34:420-429.
5. Gröbner SN, Worst BC, Weischenfeldt J, Buchhalter I, Kleinheinz K, Rudneva VA, et al. The landscape of genomic alterations across childhood cancers. Nature. 2018;555:321-327.
6. Zhang J, Walsh MF, Wu G, Edmonson MN, Gruber TA, Easton J, et al. Germline mutations in predisposition genes in pediatric cancer. N Engl J Med. 2015;373:2336-2346.
7. Wrensch M, Jenkins RB, Chang JS, Yeh RF, Xiao Y, Decker PA, et al. Variants in the *CDKN2B* and *RTEL1* regions are associated with high-grade glioma susceptibility. Nat Genet. 2009;41:905-908.
8. Shete S, Hosking FJ, Robertson LB, Dobbins SE, Sanson M, Malmer B, et al. Genome-wide association study identifies five susceptibility loci for glioma. Nat Genet. 2009;41:899-904.
9. Melin BS, Barnholtz-Sloan JS, Wrensch MR, Johansen C, Il'yasova D, Kinnersley B, et al. Genome-wide association study of glioma subtypes identifies specific differences in genetic susceptibility to glioblastoma and non-glioblastoma tumors. Nat Genet. 2017;49:789-794.
10. Kinnersley B, Labussière M, Holroyd A, Di Stefano AL, Broderick P, Vijayakrishnan J, et al. Genome-wide association study identifies multiple susceptibility loci for glioma. Nat Commun. 2015;6:8559.
11. Foss-Skiftesvik J, Hagen CM, Mathiasen R, Adamsen D, Baekvad-Hansen M, Børglum AD, et al. Genome-wide association study across pediatric central nervous system tumors implicates shared predisposition and points to 1q25.2 (*PAPPA2*) and 11p12 (*LRRC4C*) as novel candidate susceptibility loci. Childs Nerv Syst. 2021;37:819-830.
12. Dahlin AM, Wibom C, Andersson U, Bybjerg-Grauholm J, Deltour I, Hougaard DM, et al. A genome-wide association study on medulloblastoma. J Neurooncol. 2020;147:309-315.
13. Su AI, Wiltshire T, Batalov S, Lapp H, Ching KA, Block D, et al. A gene atlas of the mouse and human protein-encoding transcriptomes. Proc Natl Acad Sci U S A. 2004;101:6062-6067.
14. Gerby B, Tremblay CS, Tremblay M, Rojas-Sutterlin S, Herblot S, Hébert J, et al. *SCL, LMO1* and *Notch1* reprogram thymocytes into self-renewing cells. PLoS Genet. 2014;10:e1004768.
15. Matthews JM, Lester K, Joseph S, Curtis DJ. LIM-domain-only proteins in cancer. Nat Rev Cancer. 2013;13:111-122.
16. Wang K, Diskin SJ, Zhang H, Attiyeh EF, Winter C, Hou C, et al. Integrative genomics identifies *LMO1* as a neuroblastoma oncogene. Nature. 2011;469:216-220.
17. Capasso M, Diskin SJ, Totaro F, Longo L, De Mariano M, Russo R, et al. Replication of GWAS-identified neuroblastoma risk loci strengthens the role of *BARD1* and affirms the cumulative effect of genetic variations on disease susceptibility. Carcinogenesis. 2013;34:605-611.
18. Oldridge DA, Wood AC, Weichert-Leahey N, Crimmins I, Sussman R, Winter C, et al. Genetic predisposition to neuroblastoma mediated by a *LMO1* super-enhancer polymorphism. Nature. 2015;528:418-421.
19. Wang J, Zhuo Z, Chen M, Zhu J, Zhao J, Zhang J, et al. *RAN/RANBP2* polymorphisms and neuroblastoma risk in Chinese children: a three-center case-control study. Aging (Albany NY) 2018;10:808-818.
20. Zhuo ZJ, Liu W, Zhang J, Zhu J, Zhang R, Tang J, et al. Functional polymorphisms at *ERCC1/XPF* genes confer neuroblastoma risk in Chinese children. EBioMedicine. 2018;30:113-119.
21. Boehm T, Baer R, Lavenir I, Forster A, Waters JJ, Nacheva E, et al. The mechanism of chromosomal translocation t(11;14) involving the T-cell receptor C delta locus on human chromosome 14q11 and a transcribed region of chromosome 11p15. EMBO J. 1988;7:385-394.
22. McGuire EA, Hockett RD, Pollock KM, Bartholdi MF, O'Brien SJ, Korsmeyer SJ. The t(11;14)(p15;q11) in a T-cell acute lymphoblastic leukemia cell line activates multiple transcripts, including Ttg-1, a gene encoding a potential zinc finger protein. Mol Cell Biol. 1989;9:2124-2132.
23. Sun Y, Ma GJ, Hu XJ, Yin XY, Peng YH. Clinical significance of LMO1 in gastric cancer tissue and its association with apoptosis of cancer cells. Oncol Lett. 2017;14:6511-6518.
24. Oram SH, Thoms J, Sive JI, Calero-Nieto FJ, Kinston SJ, Schütte J, et al. Bivalent promoter marks and a latent enhancer may prime the leukaemia oncogene *LMO1* for ectopic expression in T-cell leukaemia. Leukemia. 2013;27:1348-1357.
25. Latorre V, Diskin SJ, Diamond MA, Zhang H, Hakonarson H, Maris JM, et al. Replication of neuroblastoma SNP association at the *BARD1* locus in African-Americans. Cancer Epidemiol Biomarkers Prev. 2012;21:658-663.
26. Lu J, Chu P, Wang H, Jin Y, Han S, Han W, et al. Candidate gene association analysis of neuroblastoma in Chinese children strengthens the role of *LMO1*. PLoS One. 2015;10:e0127856.
27. Beuten J, Gelfond JA, Piwkham D, Pollock BH, Winick NJ, Collier AB, 3rd, et al. Candidate gene association analysis of acute lymphoblastic leukemia identifies new susceptibility locus at 11p15 (*LMO1*). Carcinogenesis. 2011;32:1349-1353.
28. Al-Absi B, Razif MFM, Noor SM, Saif-Ali R, Aqlan M, Salem SD, et al. Contributions of *IKZF1*, *DDC*, *CDKN2A*,

CEBPE, and *LMO1* gene polymorphisms to acute lymphoblastic leukemia in a Yemeni population. Genet Test Mol Biomarkers. 2017;21:592-599.
29. He L, Zhu J, Han F, Tang Y, Zhou C, Dai J, et al. *LMO1* gene polymorphisms reduce neuroblastoma risk in Eastern Chinese children: A three-center case-control study. Front Oncol. 2018;8:468.
30. Liu GC, Zhuo ZJ, Zhu SB, Zhu J, Jia W, Zhao Z, et al. Associations between *LMO1* gene polymorphisms and Wilms' tumor susceptibility. Oncotarget. 2017;8:50665-50672.

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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