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ORIGINAL RESEARCH

LncRNA SOX2OT rs9839776 Polymorphism Reduces Sepsis Susceptibility in Southern Chinese Children

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Background: Sepsis in children is one of the main causes of death in pediatric intensive care units (PICUs); however, the pathogenesis of sepsis is not fully clear. Previous studies revealed that many genetic variations were related to sepsis susceptibility. A long non-coding RNA *SOX2 overlapping transcript* (*SOX2OT*) may play a role in mitochondrial homeostasis and antioxidative activity, but the relationship between the lncRNA *SOX2OT* polymorphism and sepsis susceptibility has not been reported.

Methods: In this study, 474 pediatric sepsis patients and 678 healthy controls were recruited from southern China. After genotyping, the strength of the associations was evaluated through odds ratios (ORs) and 95% confidence intervals (CIs).

Results: The *SOX2OT* rs9839776 T allele was associated with decreased susceptibility to sepsis in southern Chinese children (TT/CT vs CC adjusted OR = 0.778, 95% CI = 0.610–-0.992; P = 0.0431). Moreover, the difference in susceptibility was greater in children of age >60 months (adjusted OR = 0.458, 95% CI = 0.234–0.896; *P* = 0.0225), survivors (adjusted OR = 0.758, 95% CI = 0.585–0.972; P = 0.0358), males (adjusted OR = 0.655, 95% CI = 0.479–0.894; P = 0.0077) and the sepsis subgroup (adjusted OR = 0.548, 95% CI = 0.343–-0.876; P = 0.0120).

Conclusion: The rs9839776 T allele may contribute to decreased sepsis risk in Chinese children. Future studies with a larger sample size are needed to verify these results.

Keywords: sepsis, *SOX2OT*, rs9839776, susceptibility, polymorphism

Introduction

Sepsis, severe organ dysfunction due to the body's maladaptive response to infection, is one of the main causes of death in pediatric intensive care units (PICUs). According to disease severity, sepsis patients can be divided into three groups: sepsis, severe sepsis, and septic shock.[1] Although sepsis treatment in the PICU has been improved by advanced mechanical ventilation and extracorporeal membrane oxygenation (ECMO), curing pediatric sepsis patients once severe sepsis or septic shock develops remains a difficult task; the mortality rate has ranged from 10 to 20% during the past few decades in the PICU.[2,3] The World Health Organization (WHO) estimated that one million people die each year from neonatal sepsis.[4] Therefore, early diagnosis and prognosis improvements have become a challenging subject in clinical work. Multiple factors influence sepsis in children, including pathogen infection, immature inflammatory responses and immunosuppression. In recent years, some studies have focused on the relationship between genetic

variation and the incidence of sepsis in children. For example, the genetic variant rs16944 in the *IL1B* gene and the genetic variant rs1205 in the *C-reactive protein* gene have been confirmed as risk factors in infant patients.[5,6] These previous studies indicate that additional genes may influence the mechanism of sepsis development in children, but relevant studies are limited.

Long noncoding RNAs (lncRNAs) are defined as RNA molecules longer than 200 nucleotides with little or no translation capacity. Although lncRNAs do not encode proteins, they can affect a variety of biological processes, including chromatin modification, alternative splicing, and mRNA stability.[7] LncRNAs have been shown to be associated with various diseases, such as inflammatory diseases and tumors, by changing the epigenetic regulation and cellular processes.[8,9] Several studies have revealed that some lncRNAs, such as those in *MALAT1*, *NEAT1*, and *HOTAIR*, contribute to the development of sepsis in different ethnic groups.[10–12] According to these studies, some lncRNAs can play a role in modifying susceptibility to sepsis and even predict prognosis. For instance, *SOX2OT* was reported to be correlated with the expression of the *SRY-box 2* gene, and overexpression of these transcripts may promote cell proliferation.[13] In a previous study, Mengfei Chen reported that *SOX2OT* contributed to the progression of mitochondrial dysfunction by inhibiting *SOX2* expression in septic cardiomyopathy.[14] The expression of *SOX2OT* is also reportedly related to retinal degeneration, non-small cell lung cancer and central nervous system diseases.[15–17] In recent years, many studies have concentrated on the association between cytokine and protein single nucleotide polymorphisms (SNPs) and sepsis.[5,18] However, the relationship between lncRNA SNPs and sepsis has not been reported. Therefore, whether the lncRNA *SOX2OT* polymorphism can affect sepsis is unclear.

This study aimed to identify the association between the lncRNA *SOX2OT* polymorphism and sepsis. We chose the rs9839776 polymorphism of the *SOX2OT* gene in a case-control study including 474 cases and 678 controls from a population of children in southern China.

Materials and Methods

Study Population

A total of 474 sepsis patients and 678 healthy controls were recruited at the Guangzhou Women and Children's Medical Center between January 2016 and December 2018. Sepsis patients were diagnosed according to the International Sepsis Definitions Conference in 2012, and the sepsis, severe sepsis and septic shock groups were classified according to international guidelines.[1] This study was approved by the Ethics Committee of Guangzhou Women and Children's Medical Center (Permission number:2,015,042,202) and based on the guidelines of the Declaration of Helsinki. Each parent or guardian of the patients and control subjects provided informed consent for study participation. Personal information, clinical data, and demographic information were collected from the hospital inpatient record system.

Genotyping and DNA Extraction

Peripheral blood was collected in an EDTA tube from each sepsis patient and control. Following the guidance of the manufacturer's instructions, genomic DNA was extracted with a Blood DNA Isolation Kit (Tiangen, Beijing, China), and then we stored these samples in the −80°C equipment before genotyping. A 384-well plate on an ABI Q6 instrument (Thermo Fisher Scientific, United States) was used for amplifying DNA samples according to the protocol of the TaqMan real-time polymerase chain reaction protocol. Specific fluorescent probes labeled with VIC or FAM for rs9839776, which can differentiate wild-type and variant alleles, were purchased from ABI (ThermoFisher Scientific, United States). The PCR reaction system include 2 × Genotyping PreMix, PCR primer pool and template DNA. The total reaction volume of each sample was 5 mL. The qPCR reaction step were as follows: predeformation needs 95°C for 2 min, then 40 cycles of 95°C for 15 s and 60°C for 30 s were set for amplify, and 60°C for 5 min for extension sufficiently.

Statistical Analysis

The data analysis was performed using SAS software (version 9.1; SAS Institute, Cary, NC). We calculated the odds ratios (ORs) and 95% confidence intervals (CIs) to evaluate the association between the *SOX2OT* gene polymorphism (rs9839776) and sepsis susceptibility. In addition, multivariate unconditional logistic regression analysis was used to calculate the adjusted ORs after adjustment for age and sex. Furthermore, analyses stratified by age, sex, sepsis subtype, prognosis and number of organs with dysfunction were performed. All statistical analyses were performed using a two-sided chi square test, and a *P*-value less than 0.05 was regarded as statistically significant.

Table 1 Frequency Distribution of Selected Characteristics in Sepsis Cases and Healthy Controls

Variables	Cases (n = 474)		Controls (n = 678)		*P*[a]
	No.	%	No.	%	
Age range, month	1–180		1–168		
Mean ± SD	35.04 ±34.26		35.53 ±29.37		0.1811
≦60	403	85.02	595	87.76	
>60	71	14.98	83	12.24	
Gender					
Male	301	63.5	399	58.85	0.1110
Female	173	36.5	279	41.15	
Sepsis subtypes					
Sepsis	98	20.68			
Severe sepsis	291	61.39			
Septic shock	85	17.93			
Prognosis					
Survivors	394	83.12			
Non-survivors	80	16.88			
Number of organs with dysfunction, n (%)					
1–2	276	58.23			
3 or more	95	20.04			

Note: [a]Two-sided χ^2 test for distributions between sepsis patients cases and controls.

Results

Population Characteristics

As shown in Table 1, age, sex, sepsis subgroup prognosis and the number of organs with dysfunction were assessed in our total sample of 1152 children, including 474 sepsis patients and 678 healthy controls. No difference in age (35.04 ± 34.26 months vs 35.53 ± 29.37 months, P = 0.1811) or sex (P = 0.111) was found between the two groups. Among the sepsis cases, 98 children (20.68%) were diagnosed with sepsis, 291 children (61.39%) were diagnosed with severe sepsis, and 85 children (17.93%) were diagnosed with septic shock. In addition, based on the number of organs with dysfunction, 276 children (58.23%) had 1–2 organs with dysfunction, while 95 children (20.04%) had 3 or more organs with dysfunction.

Association Between SOX2OT Gene Polymorphism and Sepsis Susceptibility

As shown in Table 2, the independent correlation between the *SOX2OT* genotype frequency distribution of the SNP rs9839776 C>T and sepsis was assessed by the goodness-of-fit chi square test. The rs9839776 C>T polymorphism frequencies followed the Hardy-Weinberg equilibrium (P_{HWE} = 0.5275). The genotype analysis of the lncRNA *SOX2OT* polymorphism revealed a significant difference in the carriers of the rs9839776 genotypes exhibiting TT/CT allele (adjusted OR = 0.778, 95% CI = 0.610–0.992, and P = 0.0431), suggesting that rs9839776 TT/CT genotypes decrease sepsis susceptibility.

Stratified Analysis of the Selected Polymorphism and Sepsis

As shown in Table 3, we further explored the association between the lncRNA *SOX2OT* rs9839776 polymorphism and susceptibility to sepsis stratified by age, sex, sepsis subtype, prognosis and number of organs with dysfunction. After adjusting for age and sex, we observed that compared with the rs9839776 CC allele, the TT/CT alleles were more predominant for children > 60 month for age (adjusted OR = 0.458, 95% CI = 0.234–0.896; P = 0.0225). The TT/CT alleles also are a protective factor in males (adjusted OR = 0.655, 95% CI = 0.479–0.894; P = 0.0077). For the sepsis

Table 2 Genotype Frequency Distribution of SOX2OT in Sepsis Cases and Healthy Controls

Genotype	Cases (N = 474)	Controls (N =678)	P-value[a]	OR (95% CI)	P-value	Adjusted OR (95% CI)[b]	P-value[b]
SOX2-OT/rs9839776 C>T (HWE =0.5275)							
CC	308(64.98)	401(59.14)		1.000		1.000	
CT	146(30.80)	237(34.96)		0.802(0.622–1.034)	0.0889	0.803(0.623–1.036)	0.0911
TT	20(4.22)	40(5.90)		0.651(0.373–1.136)	0.1309	0.631(0.361–1.103)	0.1063
			0.1031	0.804(0.657–0.984)	0.0343	0.799(0.653–0.978)	0.0296
Dominant[c]	166(35.02)	277(40.85)	**0.0447**	**0.780(0.612–0.995)**	**0.0453**	**0.778(0.610–0.992)**	**0.0431**
Recessive[c]	454(95.78)	638(94.10)	0.2015	0.703(0.405–1.218)	0.2086	0.681(0.392–1.182)	0.1720

Notes: [a]χ^2 tests were used to determine differences in genotype distributions between the children with sepsis and the controls. [b]Adjusted for age and sex. [c]Dominant:CT/TT genotypes, recessive:CC/CT genotypes. The results were in bold, if p <0.05.
Abbreviations: OR, odd ratio; CI, confidence interval.

Table 3 Stratification Analysis of Susceptibility in Sepsis Patients

Variables	CC	TT/CT	P-value	OR (95% CI)	P-value	Adjusted OR (95% CI)[a]	P-value[a]
	Patients/Controls						
Age, months							
≦60	258/358	145/237	0.2187	0.849(0.654–1.103)	0.2195	0.849(0.653–1.103)	0.2191
>60	50/43	21/40	**0.0179**	**0.452(0.232–0.880)**	**0.0195**	**0.458(0.234–0.896)**	**0.0225**
Gender							
Male	201/226	100/173	**0.0063**	**0.650(0.476–0.887)**	**0.0066**	**0.655(0.479–0.894)**	**0.0077**
Female	107/175	66/104	0.8521	1.038(0.702–1.535)	0.8519	1.054(0.712–1.560)	0.7937
Sepsis subtypes							
Sepsis	71/401	27/277	**0.0101**	**0.551(0.344–0.880)**	**0.0126**	**0.548(0.343–0.876)**	**0.0120**
Severe sepsis	184/401	107/277	0.2321	0.837(0.630–1.111)	0.2335	0.834(0.628–1.108)	0.2116
Septic shock	53/401	32/277	0.5686	0.874(0.549–1.391)	0.5702	0.860(0.540–1.371)	0.5263
Prognosis							
Survivors	258/401	136/277	**0.0392**	**0.763(0.590–0.988)**	**0.0400**	**0.758(0.585–0.972)**	**0.0358**
Non-survivors	50/401	30/277	0.5616	0.869(0.539–1.401)	0.5634	0.852(0.528–1.377)	0.5140
Number of organs with dysfunction, n (%)							
1–2	173/401	103/277	0.3105	0.862(0.646–1.150)	0.3118	0.851(0.637–1.137)	0.2752
3 or more	60/401	35/277	0.4532	0.844(0.542–1.317)	0.4556	0.833(0.533–1.301)	0.4214

Notes: [a]Adjusted for age and gender. The results were in bold, if p <0.05.
Abbreviations: OR, odd ratio; CI, confidence interval.

subgroup, the TT/CT variant alleles were associated with a decreased risk of sepsis (adjusted OR = 0.548, 95% CI = 0.343–0.876; $P = 0.0120$); however, no significant association was found between severe sepsis, septic shock and the TT/CT variant genotypes. Moreover, our stratified analyses revealed that among the survivors who suffered from sepsis, the TT/CT variant had a protective effect (adjusted OR = 0.758, 95% CI = 0.585–0.972; $P = 0.0358$). Significant associations were not found for the other stratifications by age, prognosis and number of organs with dysfunction.

Discussion

Recently, some genetic factors were reported to closely affect the sepsis development; however, the association of genetic variations in *SOX2OT* with sepsis susceptibility among children is not fully known. A previous study claimed that *SOX2OT* can mediate mitochondrial dysfunction during inflammation, indicating the potential mechanism underlying the pathophysiology of sepsis.[14] Nonetheless, the relationship between sepsis and *SOX2OT* in children remains unclear. We chose rs9839776 as our study object to design a case-control study and investigated whether the rs9839776 C>T variant genotypes can reduce sepsis risk in southern Chinese children.

In this case study, we compared the blood samples between 474 sepsis patients and 678 healthy controls via qPCR analysis and chi square testing. We verified that the lncRNA *SOX2OT* rs9839776 T allele is associated with a decreased risk of sepsis in children and that the protective effect is more obvious in males and the age more than 60 months. Furthermore, the stratified analysis revealed that the rs9839776 T allele is a protective factor during early stages of sepsis in the subgroups. To the best of our knowledge, our study is the first to investigate the association between the lncRNA *SOX2OT* gene polymorphism (rs9839776) and sepsis susceptibility in southern Chinese children.

The *SOX2OT* gene is located in the 3q26.3–q27 locus of the human chromosome and harbors the *SOX2* gene, extending in a highly conserved region of over 700 kb that is one of the major regulators of pluripotency.[19,20] Marjan E indicated that *SOX2OT* plays an important role in the induction and maintenance of *SOX2* expression in breast cancer.[21] A previous study identified that lncRNA *SOX2OT* expression in non-small cell lung cancer can act as a biomarker and could be used as an independent prognostic factor.[15] The

study by Xiaomin Shi demonstrated that *SOX2OT* upregulation promotes metastasis in hepatocellular carcinoma cells and leads to worse outcomes.[22] Moreover, *SOX2OT* SNP was reported to increase the susceptibility to the development of some diseases. For example, V Boraska clarified that in a genome-wide association study, rs9839776 in *SOX2OT* is associated with anorexia nervosa susceptibility.[23] Xiuwu Tang reported that rs9839776 increases the risk of breast cancer in Chinese women.[24] A recent study conducted by our group revealed that an increased risk of recurrent miscarriage in the southern Chinese population can be attributed to the rs9839776 CT genotype, which may act as a prognostic biomarker in recurrent miscarriage patients.[25] Therefore, we speculate that the rs9839776 polymorphism has different functions in different diseases. In this study, we found that this variant can decrease the risk of sepsis in southern Chinese children.

Previous studies have analyzed lncRNA *SOX2OT* expression. For example, a higher expression level of *SOX2OT* mRNA was identified in somatic cancers such as breast cancer, lung squamous cell carcinoma and osteosarcoma.[19,26] In the Mina study, SOX2OT was overexpressed in breast cancer tissues and correlated with breast cancer susceptibility;[27] however, research on *SOX2OT* is mostly limited to the area of oncology, and the role of lncRNA in inflammatory diseases remains largely unknown. Huyu Lin reported that LncRNA SOX2O*SOX2OT* downregulation can suppress the proliferation, apoptosis, oxidative stress, and inflammatory respond of vascular smooth muscle cell through regulating miR-145.[28] Moreover, Chao-Peng Li speculated that *SOX2OT* knockdown can protect retinal ganglion cells against high glucose-induced injury in mice and has an antioxidative function by regulating NRF2/HO-1 signaling activity.[17] Mengfei Chen reported that upregulated *SOX2OT* expression in LPS-induced septic cardiomyopathy and downregulated expression in cardiomyocytes could restore mitochondrial homeostasis.[14] High glucose levels are a risk factor in sepsis and mitochondrial dysfunction is involved in organ dysfunction of sepsis.[29] These researches indicated that *SOX2OT* expression level is related to sepsis development. Based on a previous study, we hypothesized that *SOX2OT* is a detrimental factor and that the rs9839776 polymorphism alters the expression of *SOX2OT* in sepsis. We posited that among children with sepsis, those with the rs9839776 CT/TT allele may have a different survival rate than those with the CC allele. The observed improved survival rate among CT/TT allele patients confirmed our hypothesis. Prognosis prediction and reducing the fatality rate remains an important problem in the context of sepsis. Our findings can provide a new viewpoint to solve this problem, and further research in this regard is warranted.

Although this study is the first to report the relationship between lncRNA *SOX2OT* and sepsis risk in southern Chinese children, a number of limitations should be explained. First, a case-control study was performed to evaluate the association between lncRNA *SOX2OT* and sepsis risk in southern Chinese children. We did not detect *SOX2OT* expression in sepsis patients, and a definite mechanism underlying this polymorphism was not explored. Second, our study referred only to the *SOX2OT* rs9839776 polymorphism. The *SOX2OT* gene is largely polymorphic, is harbored in the *SOX2* gene, and extends in a highly conserved region of over 700 kb; thus, other SNPs potentially influence the expression of *SOX2OT*. Potential chain SNPs based on the linkage disequilibrium theory should be considered in future studies. Third, this retrospective study included only southern Chinese children. Gene polymorphisms are diverse, and therefore our results cannot be generalized to other ethnicities simply. Finally, our study sample was not sufficiently large, and a larger sample size is needed in future studies.

In conclusion, this study demonstrated that the *SOX2OT* rs9839776 T variant is a protective factor associated with sepsis in Chinese children. The protective effect was reflected more substantially in children of age > 60 months, survivors and male patients. Moreover, the protective effect was pronounced in the sepsis subgroup compared to the severe sepsis and septic shock subgroups. The association between the *SOX2OT* gene variant and sepsis should be validated in a larger sample size and in different ethnicities in future studies.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work. The authors are

accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Disclosure

The authors have no conflicts of interest to declare.

References

1. Dellinger RP, Levy MM, Rhodes A, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock, 2012. *Intensive Care Med*. 2013;39:165–228. doi:10.1007/s00134-012-2769-8.
2. Emr BM, Alcamo AM, Carcillo JA, Aneja RK, Mollen KP. Pediatric sepsis update: how are children different? *Surg Infect*. 2018;19:176–183. doi:10.1089/sur.2017.316.
3. Ruth A, McCracken CE, Fortenberry JD, Hall M, Simon HK, Hebbar KB. Pediatric severe sepsis. *Pediatr Crit Care Me*. 2014;15:828–838. doi:10.1097/PCC.0000000000000254.
4. Edmond K, Zaidi A. New approaches to preventing, diagnosing, and treating neonatal sepsis. *PLoS Med*. 2010;7:e1000213. doi:10.1371/journal.pmed.1000213.
5. Varljen T, Sekulovic G, Rakic O, et al. Genetic variant rs16944 in IL1B gene is a risk factor for early-onset sepsis susceptibility and outcome in preterm infants. *Inflamm Res*. 2020;69:155–157. doi:10.1007/s00011-019-01301-4.
6. Liu C, Jin P, Luo Y, et al. Association of single-nucleotide polymorphisms of C-reactive protein gene with susceptibility to infantile sepsis in Southern China. *Med Sci Monit*. 2018;24:590–595. doi:10.12659/MSM.908602.
7. Guttman M, Rinn JL. Modular regulatory principles of large non-coding RNAs. *Nature*. 2012;482:339–346. doi:10.1038/nature10887.
8. Boeckel J, Jaé N, Heumüller AW, et al. Identification and characterization of hypoxia-regulated endothelial circular RNA. *Circ Res*. 2015;117:884–890. doi:10.1161/CIRCRESAHA.115.306319.
9. Zacharopoulou E, Gazouli M, Tzouvala M, Vezakis A, Karamanolis G. The contribution of long non-coding RNAs in inflammatory bowel diseases. *Digest Liver Dis*. 2017;49:1067–1072. doi:10.1016/j.dld.2017.08.003.
10. Chen J, Gu X, Zhou L, et al. Long non-coding RNA-HOTAIR promotes the progression of sepsis by acting as a sponge of miR-211 to induce IL-6R expression. *Exp Ther Med*. 2019;18:3959–3967. doi:10.3892/etm.2019.8063.
11. Chen H, Wang X, Yan X, Cheng X, He X, Zheng W. LncRNA MALAT1 regulates sepsis-induced cardiac inflammation and dysfunction via interaction with miR-125b and p38 MAPK/NFκB. *Int Immunopharmacol*. 2018;55:69–76. doi:10.1016/j.intimp.2017.11.038.
12. Zhang C, Niu F. LncRNA NEAT1 promotes inflammatory response in sepsis-induced liver injury via the Let-7a/TLR4 axis. *Int Immunopharmacol*. 2019;75:105731. doi:10.1016/j.intimp.2019.105731.
13. Han L, Zhang W, Zhang B, Zhan L. Long non-coding RNA SOX2OT promotes cell proliferation and motility in human ovarian cancer. *Exp Ther Med*. 2018;15:2182–2188. doi:10.3892/etm.2017.5618.
14. Chen M, Guan Y, Li A, et al. LncRNA SOX2OT mediates mitochondrial dysfunction in septic cardiomyopathy. *DNA Cell Biol*. 2019;38:1197–1206. doi:10.1089/dna.2019.4839.
15. Xie Y, Zhang Y, Du L, et al. Circulating long noncoding RNA act as potential novel biomarkers for diagnosis and prognosis of non-small cell lung cancer. *Mol Oncol*. 2018;12:648–658. doi:10.1002/1878-0261.12188.
16. Qureshi IA, Mattick JS, Mehler MF. Long non-coding RNAs in nervous system function and disease. *Brain Res*. 2010;1338:20–35. doi:10.1016/j.brainres.2010.03.110.
17. Li C, Wang S, Wang W, Song S, Liu X. Long noncoding RNA-Sox2OT knockdown alleviates diabetes mellitus-induced Retinal Ganglion Cell (RGC) injury. *Cell Mol Neurobiol*. 2017;37:361–369. doi:10.1007/s10571-016-0380-1.
18. Shao Y, Zhao T, Zhang W, et al. Presence of the apolipoprotein E-epsilon4 allele is associated with an increased risk of sepsis progression. *Sci Rep*. 2020;10(1):15735. doi:10.1038/s41598-020-72616-0.
19. Shahryari A, Jazi MS, Samaei NM, Mowla SJ. Long non-coding RNA SOX2OT: expression signature, splicing patterns, and emerging roles in pluripotency and tumorigenesis. *Front Genet*. 2015;6. doi:10.3389/fgene.2015.00196.
20. Fantes J, Ragge NK, Lynch S, et al. Mutations in SOX2 cause anophthalmia. *Nat Genet*. 2003;33:462–463. doi:10.1038/ng1120.
21. Askarian-Amiri ME, Seyfoddin V, Smart CE, et al. Emerging role of long non-coding RNA SOX2OT in SOX2 regulation in breast cancer. *PLoS One*. 2014;9:e102140. doi:10.1371/journal.pone.0102140.
22. Shi XM, Teng F. Up-regulation of long non-coding RNA Sox2ot promotes hepatocellular carcinoma cell metastasis and correlates with poor prognosis. *Int J Clin Exp Pathol*. 2015;8:4008–4014.
23. Boraska V, Franklin CS, Floyd JAB, et al. A genome-wide association study of anorexia nervosa. *Mol Psychiatr*. 2014;19:1085–1094. doi:10.1038/mp.2013.187.
24. Tang X, Gao Y, Yu L, et al. Correlations between lncRNA-SOX2OT polymorphism and susceptibility to breast cancer in a Chinese population. *Biomark Med*. 2017;11:277–284. doi:10.2217/bmm-2016-0238.
25. Fang Z, Che D, Qing S, et al. The lncRNA SOX2OT rs9839776 C>T polymorphism indicates recurrent miscarriage susceptibility in a Southern Chinese population. *Media Inflamm*. 2019;2019:1–6. doi:10.1155/2019/9684703.
26. Wang Z, Tan M, Chen G, Li Z, Lu X. LncRNA SOX2-OT is a novel prognostic biomarker for osteosarcoma patients and regulates osteosarcoma cells proliferation and motility through modulating SOX2. *Iubmb Life*. 2017;69:867–876. doi:10.1002/iub.1681.
27. Mina D, Naiemeh H, Hamidreza K, et al. Correlations between overexpression of SOX2OT long non-coding RNA and susceptibility to breast cancer. *Accel Technol Biotechnol Bioassays Med Chem Nat Prod Res*. 2020;23:1–7. doi:10.2174/1386207323666200514075042.
28. Lin H, You B, Lin X, et al. Silencing of long non-coding RNA Sox2ot inhibits oxidative stress and inflammation of vascular smooth muscle cells in abdominal aortic aneurysm via microRNA-145-mediated Egr1 inhibition. *Aging (Albany NY)*. 2020;12(13):12684–12702. doi:10.18632/aging.103077.
29. Ameziane-El-Hassani R, Dupuy C. Detection of reactive oxygen species in cells undergoing oncogene-induced senescence. *Methods Mol Biol*. 2017;1534:139–145. doi:10.1007/978-1-4939-6670-7_13.