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Research article

TET3 gene rs828867 G>A polymorphism reduces neuroblastoma risk in Chinese children

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ABSTRACT

Objective: Neuroblastoma (NB) is a prevalent pediatric tumor originating from primordial neural crest cells. As one of the latest epigenetics investigations focuses, RNA 5-methylcytosine (m5C) is closely related to cancer risk. TET methylcytosine dioxygenase 3 (TET3) is a demethylase for m5C modification. Whether there is an association between *TET3* gene polymorphisms and neuroblastoma risk remains unclear.

Methods: We conducted an epidemiological study in 402 patients and 473 controls to evaluate the relationship between *TET3* gene SNPs (rs7560668 T > C, rs828867 G > A, and rs6546891 A > G) and NB susceptibility.

Results: Our results showed that rs828867 G > A significantly reduced NB risk in Chinese children [GA vs. GG, adjusted odds ratio (OR) = 0.72, 95% confidence interval (CI) = 0.52–0.98, *P*=0.040; GA/AA vs. GG, adjusted OR = 0.74, 95% CI = 0.55–0.998, *P*=0.048]. Individuals with 2–3 risk genotypes had a significantly higher NB risk than those with 0–1 risk genotypes (adjusted OR = 1.40, 95% CI = 1.04–1.88, *P*=0.027). The stratified analysis showed that the rs828867 G > A associated with decreased NB risk is remarkable among children aged >18 months (adjusted OR = 0.67, 95% CI = 0.46–0.96, *P*=0.029) and patients at clinical III + IV stages (adjusted OR = 0.67, 95% CI = 0.45–0.98, *P*=0.040). Compared with the 0–1 risk genotype, the concurrence of 2–3 risk genotypes significantly increased NB risk in the following subgroups: children aged >18 months and patients at clinical III + IV stages. GTEx analysis suggested that rs828867 G > A was significantly associated with *RP11-287D1.4* and *POLE4* mRNA expression.

Conclusions: Overall, our results revealed that rs828867 G > A in the *TET3* gene is significantly associated with predisposition to NB.

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1. Introduction

Neuroblastoma (NB) is one of the most common developmental neoplasms of the nervous system in pediatrics [1–3]. It accounts for approximately 10% of pediatric tumors, affecting nearly 7.7 cases per million in Chinese children [4,5]. According to tumor resectability, NB can be classified into clinical I, II, III, and IV malignancies using the International Staging System for Neuroblastoma (INSS) and 4S stages [6]. NB is reported to spontaneously regress in low-risk patients [7–9]. However, nearly half of all newly diagnosed NBs are high-risk patients with a survival rate <50% [10], which has detrimental effects on the quality of life for patients and their families.

Genetic alteration plays a decisive role in NB susceptibility, tumorigenesis, prognosis, and survival [11]. Genome-wide association studies (GWASs) provide a powerful method to explore the causal genetic variants of NB and have achieved prominent advancements [12]. Studies have revealed that three single nucleotide polymorphisms (SNPs) in the neurofilament gene *NEFL* are associated with NB risk, among which rs1059111 is significantly correlated with increased expression of NEFL [13]. Lagmay et al. found that the *IL-6* gene rs1800795 polymorphism is a novel prognostic marker in high-risk neuroblastoma and can also predict prognosis [14]. Although many key SNPs have been identified in decades, further exploration is still needed to draw the genetic landscape in NB.

5-Methylcytosine (m5C) in DNA is one of the most studied epigenetic modifications and has been identified as a hallmark of cancer [15,16]. Recently, m5C modifications have also been observed in RNA (mRNA, tRNA, and tRNA) and are involved in cancer progression [17–19]. As a reversible RNA modification, m5C is mainly catalyzed by NOP2/Sun-domain family members 1–7 (NSUN1-7) [20,21]. We previously found that the *NSUN2* gene SNP rs13181449 C > T is significantly associated with reduced NB susceptibility [22]. Recent investigations have revealed the m5C demethylases, including TET methylcytosine dioxygenase (TET1, TET2, and TET3) [23–25]. TET3 is closely related to tumorigenesis and cancer prognosis. It is highly expressed in esophageal squamous cell carcinoma, papillary thyroid carcinoma, and ovarian cancer [26–28]. A recent study indicated that TET3 promotes acute myeloid leukemia (AML) growth by regulating glucose metabolism in AML cells [29]. Studies of TET3 regulatory mechanisms found that it could control gene expression by modulating m5C levels and recruiting proteins. In postmitotic neurons, TET3 activates mRNA expression of the neurotransmitter-releasing relative gene Rab3a by accumulating its DNA hydroxymethylation [30]. Xue et al. reported that TET3 suppressed IFN-β transcription by interacting with the gene repressor HDAC1 [31]. Recent study revealed that TET3 expression positively correlated with NB patient prognosis [32]. Therefore, we speculated that *TET3* genetic variations might correlate with NB risk. In this report, we conducted a study to elucidate the association between three *TET3* SNPs and neuroblastoma risk in Chinese children.

2. Materials and methods

2.1. Study subjects

This work was approved by the Institutional Review Board of Children's Hospital of Nanjing Medical University (Approval No.: 202112141-1). In total, 402 neuroblastoma patients and 473 control volunteers were registered in the Children's Hospital of Nanjing Medical University in Jiangsu Province, China [33]. All patients consented to participate in this research and signed informed consent.

2.2. SNP selection and genotyping

In this study, three *TET3* SNPs (rs7560668 T > C, rs828867 G > A, rs6546891 A > G) were selected and genotyped according to our published method [34–36]. These SNPs may impact RNA splicing and miRNA binding, as predicted with SNPinfo (https://snpinfo.niehs.nih.gov/snpinfo/snpfunc.html). Peripheral blood samples from controls and children diagnosed with neuroblastoma were used to extract genomic DNA with a TIANamp Genomic DNA Kit (TianGen Biotech Co., Ltd., Beijing, China). Then, we genotyped *TET3* gene SNPs by the TaqMan method using TaqMan Genotyping PCR PreMix (TianGen Biotech Co. Ltd., Beijing, China). To guarantee genotyping accuracy, 10% of the samples were randomly selected to repeat the assay, and 100% consistency was obtained.

2.3. Statistical analysis

In this study, the chi-squared test and *t*-test were used to detect significant differences between patients and controls based on the variable type. The Hardy-Weinberg equilibrium (HWE) of each SNP in control samples was evaluated using a goodness-of-fit chi-squared test. Unconditional logistic regression was conducted to analyze the odds ratios (ORs, adjusted by age and sex) and 95% confidence intervals (CIs) for the association of *TET3* gene SNPs with neuroblastoma risk, which is adjusted for age and gender. The correlation between SNPs and gene expression was assessed from the Genotype-Tissue Expression (GTEx) data (https://www.gtexportal.org/home) [37].

3. Results

3.1. TET3 polymorphisms are associated with neuroblastoma risk

Genotyping of the *TET3* gene was successfully conducted in 401 neuroblastoma patients and 473 control samples out of the 402 cases and 473 controls, whose clinical characteristics were described in a published study (table S1) [22]. The genotype distribution of

all three *TET3* SNPs complied with HWE (*P*=0.974 for rs7560668 T > C, *P*=0.817 for rs828867 G > A, and *P*=0.805 for rs6546891 A > G). As shown in Table 1, rs828867 G > A was significantly associated with reduced neuroblastoma risk (GA vs. GG, adjusted OR = 0.72, 95% CI = 0.52–0.98, *P*=0.040; GA/AA vs. GG, adjusted OR = 0.74, 95% CI = 0.55–0.998, P=0.048). No significant associations were found for rs7560668 T > C and rs6546891 A > G. Variants with OR>1 were identified as risk genotypes, including rs7560668 CC, rs828867 GG, and rs6546891 AG/GG. The presence of 2–3 risk genotypes in participants significantly increased neuroblastoma risk compared with those with 0–1 risk genotypes (adjusted OR = 1.40, 95% CI = 1.04–1.88, *P*=0.027).

3.2. Stratification analysis

We next analyzed the relationship between rs828867, rs6546891, and risk genotypes and neuroblastoma risk in subgroups separated by age, sex, site of origin, and clinical stage (Table 2). The stratification result presented a significant correlation between rs828867 GA/AA and reduced neuroblastoma risk in subgroups: children aged >18 months (adjusted OR = 0.67, 95% CI = 0.46–0.96, *P*=0.029) and patients at clinical III + IV stages (adjusted OR = 0.67, 95% CI = 0.45–0.98, *P*=0.040). The rs6546891 GG was significantly associated with improved neuroblastoma risk among patients with tumors of retroperitoneal origin (adjusted OR = 1.66, 95% CI = 1.12–2.46, *P*=0.011). Moreover, the combination of 2–3 risk genotypes presents a higher neuroblastoma risk than 0–1 risk genotypes among children aged >18 months (adjusted OR = 1.61, 95% CI = 1.12–2.32, *P*=0.011) and patients at clinical III + IV stages (adjusted OR = 1.53, 95% CI = 1.04–2.25, *P*=0.032).

3.3. TET3 rs828867 G > A correlated with gene expression

To reveal the role of rs828867 G > A in gene expression, cis-expression quantitative trait loci (eQTL) analysis was performed using GTEx (Version: V8) in Single-Tissue eQTLs analysis (Fig. 1). The results showed that rs828867 GA/AA is significantly related to reduced *RP11-287D1*.4 mRNA expression in cultured fibroblast cells (*P*=1.4e-10, Fig. 1A), whole blood (*P*=1.4e-10, Fig. 1B), adrenal gland (*P*=7.4e-6, Fig. 1C), and EBV-transformed lymphocyte cells (*P*=3.0e-5, Fig. 1D). Furthermore, cultured fibroblasts with rs828867 GA/AA had higher *POLE4* mRNA expression (*P*=1.9e-4, Fig. 1E).

4. Discussion

RNA m5C is a new focus of investigation in human malignancies. The understanding of the m5C regulatory mechanism in tumors is in its infancy [38]. To date, the association between m5C-related gene SNPs and cancer susceptibility is limited, especially the risk of

Table 1
Association between *TET3* gene polymorphisms and neuroblastoma susceptibility in children from Jiangsu province.

Genotype	Cases (N = 401)	Controls (N = 473)	*P*[a]	Crude OR (95% CI)	*P*	Adjusted OR (95% CI)[b]	*P*[b]
rs7560668 T > C (HWE = 0.976)							
TT	301 (75.06)	346 (73.15)		1.00		1.00	
TC	88 (21.95)	117 (24.74)		0.87 (0.63–1.19)	0.368	0.86 (0.63–1.19)	0.367
CC	12 (2.99)	10 (2.11)		1.38 (0.59–3.24)	0.460	1.38 (0.59–3.24)	0.458
Additive			0.763	0.96 (0.74–1.25)	0.763	0.96 (0.74–1.25)	0.763
Dominant	100 (24.94)	127 (26.85)	0.521	0.91 (0.67–1.23)	0.522	0.91 (0.67–1.23)	0.521
TT/TC	389 (97.01)	463 (97.89)		1.00		1.00	
CC	12 (2.99)	10 (2.11)	0.409	1.43 (0.61–3.34)	0.411	1.43 (0.61–3.35)	0.410
rs828867 G > A (HWE = 0.817)							
GG	125 (31.17)	119 (25.16)		1.00		1.00	
GA	180 (44.89)	239 (50.53)		**0.72 (0.52–0.98)**	**0.040**	**0.72 (0.52–0.98)**	**0.040**
AA	96 (23.94)	115 (24.31)		0.80 (0.55–1.15)	0.223	0.79 (0.55–1.15)	0.222
Additive			0.192	0.88 (0.74–1.06)	0.192	0.88 (0.73–1.06)	0.191
Dominant	276 (68.83)	354 (74.84)	0.048	**0.74 (0.55–0.998)**	**0.049**	**0.74 (0.55–0.998)**	**0.048**
GG/GA	305 (76.06)	358 (75.69)		1.00		1.00	
AA	96 (23.94)	115 (24.31)	0.898	0.98 (0.72–1.34)	0.898	0.98 (0.72–1.34)	0.896
rs6546891 A > G (HWE = 0.805)							
AA	97 (24.19)	134 (28.33)		1.00		1.00	
AG	194 (48.38)	233 (49.26)		1.15 (0.83–1.59)	0.396	1.15 (0.83–1.59)	0.396
GG	110 (27.43)	106 (22.41)		1.43 (0.99–2.08)	0.059	1.44 (0.99–2.09)	0.058
Additive			0.059	1.20 (0.99–1.44)	0.059	1.20 (0.99–1.45)	0.059
Dominant	304 (75.81)	339 (71.67)	0.167	1.24 (0.91–1.68)	0.167	1.24 (0.92–1.68)	0.166
AA/AG	291 (72.57)	367 (77.59)		1.00		1.00	
GG	110 (27.43)	106 (22.41)	0.086	1.31 (0.96–1.78)	0.087	1.31 (0.96–1.79)	0.086
Combine risk genotypes[c]							
0-1	274 (68.33)	355 (75.05)		1.00		1.00	
2-3	127 (31.67)	118 (24.95)	0.027	**1.39 (1.04–1.88)**	**0.028**	**1.40 (1.04–1.88)**	**0.027**

P, probability value; OR, odds ratio; CI, confidence interval; HWE, Hardy-Weinberg equilibrium.
[a] χ^2 test for genotype distributions between neuroblastoma patients and cancer-free controls.
[b] Adjusted for age and sex.
[c] Risk genotypes were carriers with rs7560668 CC, rs828867 GG and rs6546891 AG/GG genotypes.

Table 2
Stratification analysis for the association between *TET3* genotypes with neuroblastoma susceptibility in Jiangsu children.

Variables	rs828867 (cases/controls)		Adjusted OR[a]	*P*[a]	rs6546891 (cases/controls)		Adjusted OR[a]	*P*[a]	Risk genotypes (cases/controls)		Adjusted OR[a]	*P*[a]
	GG	GA/AA	(95% CI)		AA/AG	GG	(95% CI)		0–1	2–3	(95% CI)	
Age, month												
≤18	43/41	96/98	0.93 (0.56–1.56)	0.791	94/104	45/35	1.42 (0.84–2.40)	0.186	96/97	43/42	1.04 (0.62–1.72)	0.896
>18	82/78	180/256	**0.67 (0.46–0.96)**	**0.029**	197/263	65/71	1.23 (0.84–1.80)	0.298	178/258	84/76	**1.61 (1.12–2.32)**	**0.011**
Gender												
Females	57/52	134/173	0.71 (0.46–1.10)	0.121	146/177	45/48	1.14 (0.72–1.81)	0.589	136/172	55/53	1.31 (0.85–2.04)	0.226
Males	68/67	142/181	0.77 (0.52–1.16)	0.211	145/190	65/58	1.47 (0.97–2.22)	0.070	138/183	72/65	1.47 (0.98–2.20)	0.060
Sites of origin												
Adrenal gland	26/119	67/354	0.87 (0.53–1.44)	0.591	73/367	20/106	0.95 (0.55–1.63)	0.847	65/355	28/118	1.29 (0.79–2.11)	0.305
Retroperitoneal	53/119	114/354	0.72 (0.49–1.06)	0.099	113/367	54/106	**1.66 (1.12–2.46)**	**0.011**	115/355	52/118	1.36 (0.92–2.01)	0.120
Mediastinum	38/119	81/354	0.72 (0.46–1.11)	0.137	90/367	29/106	1.11 (0.70–1.79)	0.653	81/355	38/118	1.41 (0.91–2.19)	0.124
Others	7/119	11/354	0.53 (0.20–1.39)	0.196	11/367	7/106	2.22 (0.84–5.86)	0.109	10/355	8/118	2.40 (0.92–6.22)	0.073
Clinical stages												
I + II+4s	49/119	123/354	0.85 (0.57–1.25)	0.401	134/367	38/106	0.98 (0.64–1.50)	0.932	120/355	52/118	1.31 (0.89–1.93)	0.171
III + IV	55/119	108/354	**0.67 (0.45–0.98)**	**0.040**	114/367	49/106	1.47 (0.99–2.20)	0.058	108/355	55/118	**1.53 (1.04–2.25)**	**0.032**

P, probability value; OR, odds ratio; CI, confidence interval.
[a] Adjusted for age and gender, omitting the correspondence factor.

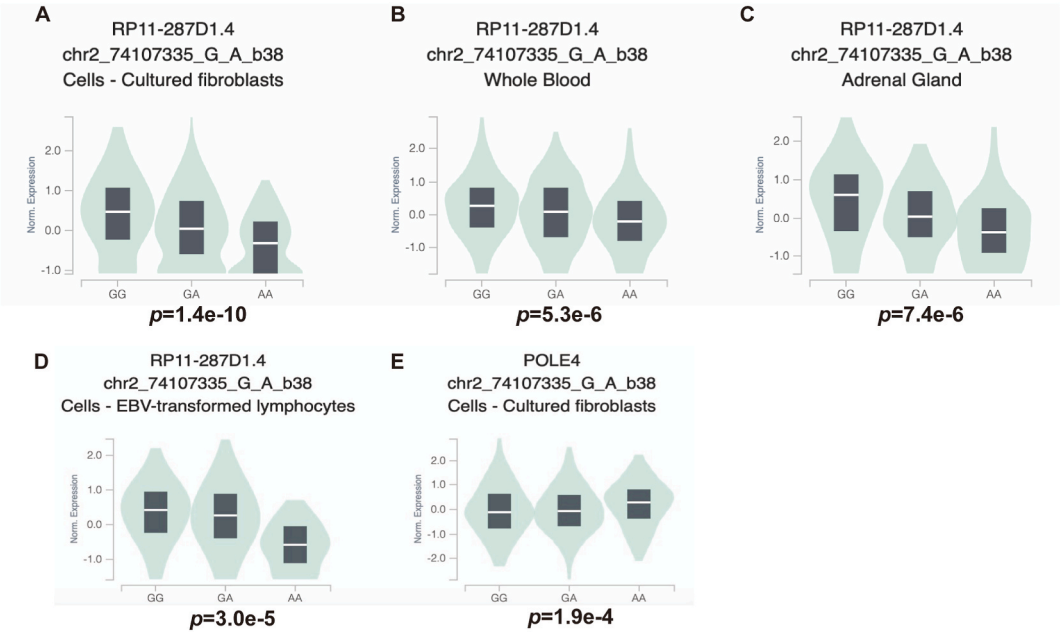

Fig. 1. Expression quantitative trait loci (eQTL) analyses for the *TET3* gene rs828867 G > A polymorphism using the GTEx portal database. The results showed that rs828867 GA/AA is significantly related to reduced *RP11-287D1*.4 mRNA expression in (A) cultured fibroblast cells (*P*=1.4e-10), (B) whole blood (*P*=1.4e-10), (C) adrenal gland (*P*=7.4e-6), and (D) EBV-transformed lymphocyte cells (*P*=3.0e-5); thus, there was higher *POLE4* mRNA expression (*P*=1.9e-4) in cultured fibroblast cells (E). The violin shows the distribution of data; the box is decided by the interquartile range; the above line: the 75th percentile of the data (Q75), the under line: the 25th percentile of the data (Q25); the white line: the 50th percentile of the data (Q50).

NB. Our previous study showed that rs13181449 C > T in the m5C methyltransferase gene *NSUN2* might reduce NB risk [22]. Liao et al. reported that *TET1* gene rs150689919 was not associated with Parkinson's disease [39]. Abdel-Wahab et al. revealed that *TET2* SNPs were significantly correlated with primary myelofibrosis susceptibility and acute myeloid leukemia survival [40]. No studies investigating the role of *TET3* gene SNPs in disease predispositions have been available until now. In this study, we conducted the first epidemiological study on the association of *TET3* gene SNPs and NB risk. The workflow and main result are shown in Fig. 2. Among three SNPs (rs7560668 T > C, rs828867 G > A, and rs6546891 A > G) in the *TET3* gene, rs828867 G > A is associated with reduced neuroblastoma susceptibility in Chinese children. This result provides new evidence to substantiate the association between m5C "eraser" polymorphisms and cancer risk.

Individuals with 2–3 risk genotypes have significantly higher NB risk than those with 0–1 risk genotypes. Moreover, we conducted a stratification analysis based on clinical information, which suggested that the protective effects of rs828867 G > A were significantly improved in children aged >18 months and patients at clinical stages III + IV. SNP data, in combination with DNA-based molecular computation, could facilitate clinical diagnosis [41]. Identification of multiple disease-disposing SNPs enables the construction of

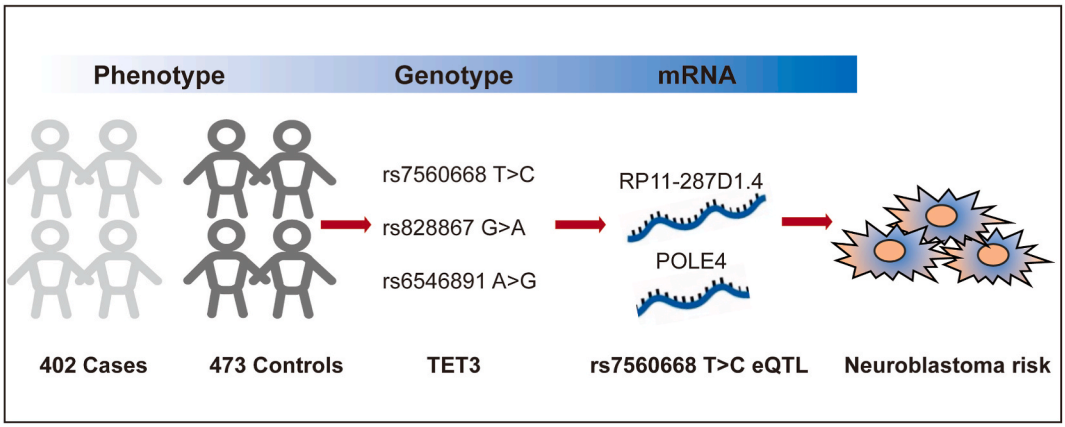

Fig. 2. The workflow and main result of this study.

logistic models for disease risk prediction [42]. We have reported the association of SNPs in genes encoding multiple epigenetic regulators with NB risk in previously published studies [43–45]. These identified susceptibility loci improve the understanding of NB risk. However, how to combine these susceptibility loci to develop NB risk prediction models is still a great challenge.

Neuroblastoma arises in the sympathetic nervous system, including the adrenal gland and sympathetic ganglia [46]. Cancer-associated fibroblast contributes to angiogenesis, immunosuppression, and tumor progression in neuroblastoma [47]. Lymphocytes and whole blood could represent the human immune system state and the overall indicator of tumor growth, respectively. In this study, we found that the *TET3* gene rs828867 affects the mRNA expression of its surrounding genes *RP11-287D1.4* and *POLE4* in cultured fibroblast cells, and *RP11-287D1.4* in the adrenal gland, EBV-transformed lymphocytes cells, and whose blood (Fig. 1). However, it is not clear whether the altered expression levels of surrounding genes contribute to reduced NB risk. Further investigation is needed to confirm and elucidate the regulatory mechanism.

5. Conclusion

In summary, we found that rs828867 G > A is significantly associated with reduced NB risk and correlated with the mRNA expression of *RP11-287D1.4* and *POLE4*. Further investigation is warranted to clarify the regulatory mechanism of rs828867 G > A in NB.

Ethical approval

This work was approved by the Institutional Review Board of Children's Hospital of Nanjing Medical University (Approval No.: 202112141-1). All patients consented to participate in this research and signed informed consent.

Conflict of interest Disclosures

The authors have no competing interests.

Data Availability Statement

All the data are available upon request from the correspondence authors.

CRediT authorship contribution statement

Xinxin Zhang: Writing – original draft, Investigation. **Bo Wang:** Writing – review & editing, Writing – original draft, Investigation, Formal analysis. **Lei Lin:** Writing – review & editing, Investigation, Formal analysis. **Chunlei Zhou:** Writing – review & editing, Resources, Investigation. **Jinhong Zhu:** Writing – review & editing, Investigation. **Haiyan Wu:** Writing – review & editing, Supervision, Resources, Conceptualization. **Jing He:** Writing – review & editing, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e27988.

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