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Meta-analysis Review

Prevalence of TECTA and GJB2 mutations in Asian children with nonsyndromic hearing loss: A meta-analysis

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ABSTRACT

Introduction: The most common sensory disorder, hearing loss, may result from genetic causes. Various inheritance patterns exist, such as X-linked, autosomal dominant, autosomal recessive, and mitochondrial. However, the genetic underpinnings of racial distinctiveness and regional variation were incompletely understood. To fully evaluate the ethnic specificity of gap junction protein beta 2 (*GJB2*) and tectorin alpha (*TECTA*) mutations in this region, data from all *GJB2* and *TECTA* gene studies on Asian children with hearing impairment were pooled and used in this research. **Methods**: All nonsyndromic hearing loss studies on the prevalence of *GJB2* or *TECTA* mutations published between 1990 and 2022 were retrieved from the PubMed database, evaluated for risk of bias, and meta-analyzed. **Results**: Twelve studies were chosen, representing twelve prevalence estimates. The prevalence of *GJB2* and *TECTA* mutations in Asian patients with nonsyndromic hearing loss was 13.36% (95% confidence interval [CI]: 7.74%–20.14%), varying significantly among trials (I^2 = 96.74%; $P < 0.001$). The pooled prevalence of *TECTA* and *GJB2* mutations was 3.6% (95% CI: 1.9%–5.7%) and 24.06% (95% CI: 11.43%–31.35%), respectively. **Conclusions**: There was an association between *TECTA/GJB2* mutations and hearing impairment, but there were also regional and ethnic differences in mutation prevalence. Studies with larger sample sizes and genetic analyses based on long-read sequencing are needed to understand the mutations resulting in hearing loss.

Key words: Asia, GJB2, Hearing impairment, meta-analysis, mutation TECTA

INTRODUCTION

The ear loses its ability to change sound's mechanical energy into electrical energy, leading to hearing loss. The cochlea's hair cells maintain this role by converting oscillation into neuronal impulses and sending messages to the brain's cortex via the VIII nerve [1]. Conductive hearing loss results from a disruption of sound transmission at the outer and/or middle ear. In contrast, sensorineural hearing loss (SNHI) occurs when the inner ear cannot communicate with the brain. Hearing loss can be genetic and/or acquired, depending on when it first appears [2,3]. One in 1000 newborns has a hearing impairment, the most frequent sensory disorder. The most prevalent sensory disorder is believed to be of genetic origin, accounting for roughly 50% of all cases [4].

Hearing loss is caused by gene mutations in 50% of cases. Environmental factors such as ototoxic medications, prematurity, and cranial trauma account for the remaining 50%. Approximately 70% of cases of inherited hearing loss are attributed to nonsyndromic hearing loss. Nonsyndromic genetic deafness has various inheritance patterns, such as autosomal recessive and dominant, X-linked, and mitochondrial [2]. Autosomal recessive inheritance, due to mutations in the gap junction protein beta 2 (*GJB2*) gene, is more common (80%) than autosomal dominant (AD) inheritance (20%) in severe and congenital pre-lingual deafness [5]. AD nonsyndromic hearing loss (ADNSHL) is a condition with diverse genetic and clinical features. Tectorin alpha (*TECTA*) mutations have been identified as contributing to ADNSHL in diverse populations, differing in their ages of onset and degrees of auditory impairment, rates of advancement, and extent of participation [6–8]. The association between deafness and *TECTA* mutations is the subject of an ongoing debate regarding the underlying mechanisms. Some studies have identified missense mutations in its zona pellucida domain as a potential biological factor contributing to ADSHNL.

These studies considered only parts of genetic figures related to ethnic particularity and regional differences. Due to the small sample sizes of case-control studies, detecting minor genetic associations in humans was difficult. To learn more about this variable, we need a meta-analysis of the association between ethnic specificity and mutations in *GJB2* and

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TECTA. In this study, all published studies on the *GJB2* and *TECTA* genes in Asian pediatric populations with hearing impairment were used in a combined meta-analysis. Based on the evaluation of the relationship between *GJB2* and *TECTA* mutations and hearing impairment and the genetic heterogeneity effect, a stratified meta-analysis was performed to determine whether *GJB2* and *TECTA* mutations causing hearing loss in Asian children are specific to that ethnic group.

METHODS

Eligibility requirements

All nonsyndromic hearing loss studies published since 1990 were considered for inclusion if the prevalence of *GJB2* or *TECTA* mutations was reported or could be calculated from the available data. Studies that presented assumptions based on specific subgroups of the overall population were excluded (*e.g.*, women or related family). Notably, certain populations, such as the Han Chinese population or those participating in the hospital-based studies, were not excluded since they were considered to reflect the broader population within a given geographic region.

Search strategy

Using a search methodology that combined appropriate key phrases and subject-specific terms within the respective databases, PubMed was searched through November 6, 2022. The search strategy incorporated *GJB2* (235delC and V37I) or *TECTA*-related terms with study design-related terms, such as epidemiology, cohort, cross-sectional, and observational study. The titles of the identified articles were examined, and those that were irrelevant to this study were eliminated. After checking the abstracts, the full texts of the remained articles were examined to identify pertinent investigations that satisfied the established inclusion criteria.

Additional pertinent articles were identified by reviewing the reference lists of full-text articles.

Risk of bias assessment

The potential bias in the included studies was assessed using the Agency for Healthcare Research and Quality (AHRQ) checklist, which is intended specifically for cross-sectional or prevalence studies[9]. This evaluation was conducted independently. The methodology checklist developed by the AHRQ comprises eleven parts. A score of "1" is assigned to each item if the response is affirmative, while a score of "0" is assigned for an unclear or negative response. Research investigations are classified into three categories of bias risk based on their quality scores: 0–3, high; 4–7, moderate; 8–11, low. The AHRQ methodology checklist findings were subjected to cross-validation, and any discrepancies were resolved through team deliberation.

Data extraction

The data extraction from each article was standardized using a data collection form. The extracted data included information on the sampled population, prevalence rate, period of the estimated prevalence (such as a point or a year), and any reported rates stratified by specific *GJB2* or *TECTA* variants, age, sex, or location. The form also contained sections to gather relevant information to assess potential bias.

Analysis

The average carrier frequency of the 235delC and p.V37I mutations of the *GJB2* and *TECTA* genes was determined in each study. According to the distribution of carriers, the included populations were divided into two categories: patients with nonsyndromic hearing loss with *TECTA* or *GJB2* gene mutations.

The investigations were subjected to preliminary descriptive statistics. The diversity among assumptions was evaluated using the I^2 statistic, which represents the proportion of variation across studies that was not due to sampling error. An I^2 >75% indicates considerable heterogeneity. A model with random effects was used to conduct a meta-analysis. A pooled prevalence with a 95% confidence interval (CI) was calculated. The statistical analyses were performed using STATA software (version 14).

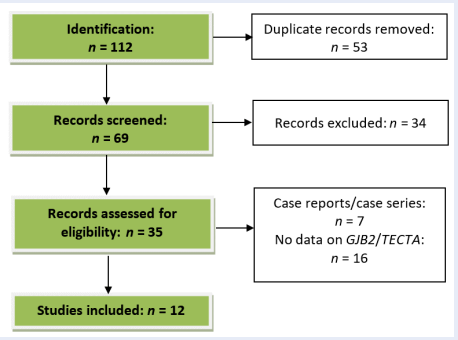


Figure 1: **A flowchart showing how articles were included and excluded from the study**.

Table 1: Characteristics of the included studies

ID	References	Survey period	Sample size (n)	Country	Sex (F/M)	Mean age (± SD/range)
1	Identification of novel variants in Iranian consanguineous pedigrees with nonsyndromic hearing loss by next-generation sequencing [10]	2020	44	Iran	NA	39.6 (7–60)
2	The prevalence and clinical characteristics of TECTA-associated autosomal dominant hearing loss [11]	2000–2017	812	Japan	NA	37.1 (0–86)
3	Mutation analysis of common GJB2, SCL26A4 and 12S rRNA genes among 380 deafness patients in northern China [12]	NA	380	China	199/181	9.9 (0.5–38)
4	Targeted next-generation sequencing successfully detects causative genes in Chinese patients with hereditary hearing loss [13]	NA	116	China	56/60	0–70
5	The prevalence of the 235delC GJB2 mutation in a Chinese deaf population [14]	NA	3004	China	1298/170(	13.8 (±4.5)
6	TECTA mutations in Japanese with mid-frequency hearing loss affected by zona pellucida domain protein secretion [15]	NA	139	Japan	NA	NA
7	Prevalence of p.V37I variant of GJB2 in mild or moderate hearing loss in a pediatric population and the interpretation of its pathogenicity [16]	2010–2012	380	Korea	NA	NA
8	High prevalence of V37I genetic variant in the connexin-26 (GJB2) gene among nonsyndromic hearing-impaired and control Thai individuals [17]	2000–2002	166	Thailand	89/77	NA
9	GJB2 (connexin 26) mutations and childhood deafness in Thailand [18]	NA	17	Thailand	10/7	NA
10	Genetic etiology study of the nonsyndromic deafness in Chinese Hans by targeted next-generation sequencing [19]	NA	190	China	53/84	14 (0–50)
11	First molecular screening of deafness in the Altai Republic population [20]	NA	76	Altai Republic	39/37	30.2 (3–80)
12	The p.V37I exclusive genotype of GJB2: A genetic risk-indicator of postnatal permanent childhood hearing impairment [21]	2009–2010	45	China	NA	7 (3.9–10.1)

Abbreviations: **SD**: standard deviation; **NA**: not applicable.

Table 2: The risk of bias in the included studies

ID	Author	Publication year	Gene	Gene sub-group	Sample (n)	No. of cases (n)	Quality rating
1	Fatemeh Bitarafan	2020	TECTA		44	26	Moderate
2	Rika Yasukawa	2019	TECTA		812	76	Moderate
3	Jing Pan	2017	GJB2	235delC	380	9	Moderate
4	Siqi Chen	2016	TECTA		116	9	Moderate
			GJB2		116	37	Moderate
5	Pu Dai	2007	GJB2	235delC	3004	488	Moderate
6	Hideaki Moteki	2012	TECTA		139	4	High
7	SoYoungKim	2013	GJB2	p.V37I	380	4	Low
8	Duangrurdee Wattanasirichaigoon	2004	GJB2	p.V37I	166	56	Moderate
9	T Kudo	2001	GJB2		17	4	High
10	Tao Yang	2013	GJB2		190	36	High
11	Olga Posukh	2005	GJB2		76	18	High
12	Lei Li	2012	GJB2	p.V37I	45	9	Moderate

RESULTS

Search results

The PubMed database search identified 112 publications, of which 69 were chosen for full-text review. Their reference lists led to the identification of 12 additional studies. The screening procedure is illustrated in **Figure 1**.

After a full-text evaluation, 23 articles were excluded. Therefore, 12 studies were selected for review (**Table 1**), representing 12 prevalence approximations. Most of the 12 studies were conducted in Asia within the past two decades. Five of the 12 studies were performed in China, two in Thailand, and two in Japan. They included sample sizes from 17 to 3004.

Risk of bias

Table 2 provides a concise overview of the bias risk associated with the articles included in this study. None of the studies met all of the checklist's quality evaluation criteria. The AHRQ scores for included articles varied from two to eight. Most studies (7/12) met at least 50% of the quality evaluation criteria. One study (8.3%; Hideaki Moteki *et al.*)[15] was deemed to have a low risk of bias for the participants and assessment of the outcomes, while four (33.3%) were deemed to have a substantial risk of bias.

Prevalence rates were often presented in an article or calculatable from the provided data. Iran had the highest prevalence of *TECTA* mutations (Fatemeh Bitarafan, 2020)[10], while Japan had the lowest prevalence (Hideaki Moteki, 2012)[15]. Thailand had the highest prevalence of *GJB2* mutations (Duangrurdee Wattanasirichaigoon, 2002)[17], while Korea had the lowest prevalence (So Young Kim, 2013)[16].

Meta-analysis

This study investigated the prevalence of *GJB2*/*TECTA* mutations in individuals with nonsyndromic hearing loss in Asia. Its findings indicate that the frequency of *GJB2*/*TECTA* mutations in Asian individuals with nonsyndromic hearing loss was 13.36% (95% CI: 7.74%–20.14%). The included studies showed significant heterogeneity, with an I^2 of 96.74% ($P < 0.001$; **Figures 2 and 3**). An asymmetric funnel plot suggested the possibility of publication bias.

A funnel plot was used to determine whether there was any publication bias in the included articles. Based on the study distribution (**Figure 3**), the funnel plot is almost the same on both sides. The meta-analysis conducted did not show any notable indication of publication bias based on the included studies.

Four studies examined the number of people with nonsyndromic hearing loss with a *TECTA* mutation. The combined occurrence rate of *TECTA* mutations was 3.6% (95% CI: 1.9%–5.8%). The studies exhibited moderate heterogeneity ($I^2 = 37.87\%$, $P = 0.18$).

Four studies reported the occurrence of *GJB2* mutations in individuals with nonsyndromic hearing loss. The combined prevalence of *GJB2* mutations was 24.06% (95% CI: 11.43–31.36). The studies exhibited moderate heterogeneity ($I^2 = 53.6\%$, $P = 0.09$).

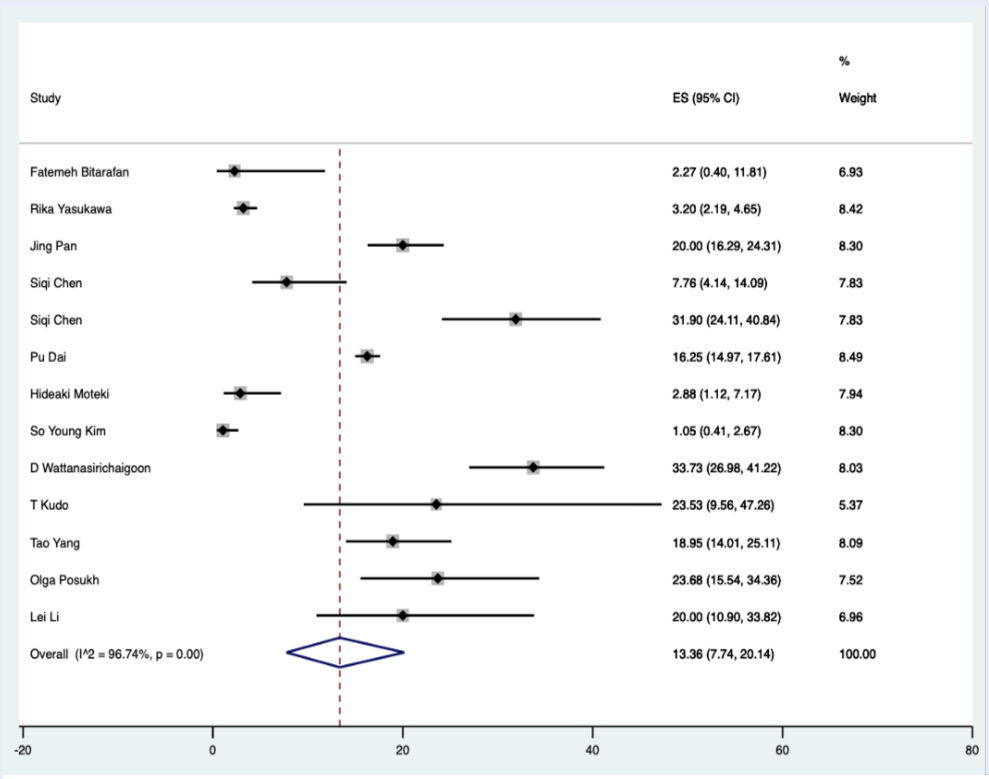
Two studies reported the prevalence of the *GJB2* gene variant 235delC in individuals with nonsyndromic hearing loss. Its pooled frequency was 16.6% (95% CI: 15.4%–17.9%).

Three studies explored the number of people with nonsyndromic hearing loss with the *GJB2* gene variant p.V37I. Its pooled frequency was 14.7% (95% CI: 0%–48.6%).

DISCUSSION

The commonly observed inherited etiology of SNHI is attributed to recessive variants in the *GJB2* gene. The prevalence of *GJB2* mutations varies significantly among different ethnic communities. For example, Europeans carry c.35delG (p.Gly12ValfsTer2) and c.101T>C (p.Met34Thr) mutations[22–24], while East Asians carry c.235delC (p.Leu79CysfsTer3) and c.109G>A (p.Val37Ile) mutations[14,25–27]. Additionally, Ghanaians carry the c.427C>T (p.Arg143Trp) mutation[28]. Three plausible mechanisms that could account for these inconclusive results exist. SNHI could also be caused by pathogenic mutations in other genes known to cause deafness. In such cases, patients who do not present with the confirmatory symptoms for SNHI may still carry mono-allelic *GJB2* variants as incidental carriers. Furthermore, mutation frequencies fluctuate widely between countries.

One study on ADNSHL communities in Japan found a prevalence of *TECTA* mutations of 2.9% (4/139), with an incidence of 7.7% (4/52) in those with moderate hearing loss[15]. These findings indicate that the frequency of *TECTA* mutations in the Japanese is relatively low compared to Iranians, whose prevalence was >50%[10]. The prevalence of *GJB2* mutations can vary widely even within the same country. In 2017, Jing Pan reported a prevalence of 2.4% for *GJB2* mutations in Northern China, while Pu Dai reported a prevalence of 16.2% in Chinese patients[29,30]. Despite having a pooled prevalence of 3.6% (95% CI: 1.9%–5.7%) for *TECTA* mutations and 24.06% (95% CI: 11.43%–31.35%) for *GJB2* mutations, this comparison indicates geographical differences in mutation frequency, emphasizing the need for further re-



Std_Eff	Coefficient	Std. err.	t	P>|t|	[95% conf.	interval]
slope	.1337983	.0375192	3.57	0.004	.0512191	.2163775
bias	.1641554	.7711297	0.21	0.835	-1.53309	1.8614

Test of H0: no small-study effects P = 0.835

Figure 2: **The prevalence of GJB2/TECTA mutations in Asian individuals with nonsyndromic hearing loss** (event: the number of cases with GJB2 or TECTA mutations; weight: the prevalence in each study).

search on regional risk factors such as lifestyles, education, and life qualities.

The prevalence of each mutation shows variation across different ethnic groups and countries. The 35delG mutation has been observed in up to 85% of Caucasians[31]. In contrast, the 235delC mutation has been identified most frequently in the Chinese[32] (20.3%), Koreans[33] (6.9%), and Japanese[34] (49.8%). The c.167delT mutation has been found in 4.03% of Ashkenazi Jews[35] and 2% of Argentinians[36]. These results indicate ethnic differences in mutation prevalence, emphasizing the need for further studies with larger sample sizes and genetic analyses based on long-read sequencing to better understand mutations associated with hearing impairment.

This study's main limitation was the heterogeneity of its included studies. The population of individuals suspected of hearing loss varied across studies, and most were not precisely defined. Several studies focused exclusively on children, while most did not provide any particular age range. The allele frequencies in various countries may be influenced by particular population samples, resulting in sampling bias. In addition, the ethnic or racial origin of part of the study population was not specified, and the scope of this analysis was limited to the geographic aspect and did not encompass ethnicity. Another limitation of this study was that its data was only extracted from the Pubmed database. Therefore, some studies indexed in Embase, Web of Science, or Scopus were not included.

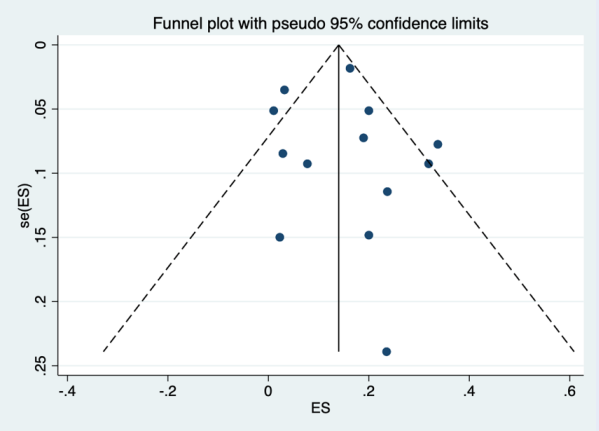


Figure 3: **The frequency of GJB2/TECTA mutations in Asian individuals with nonsyndromic hearing loss.**

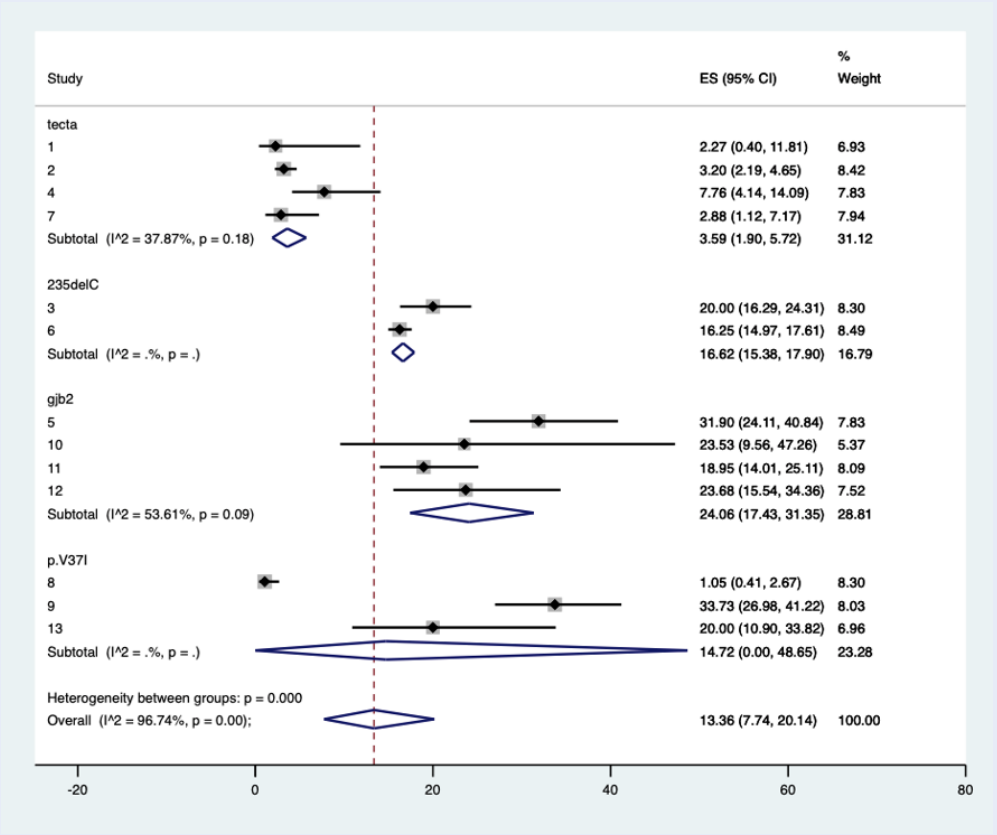


Figure 4: **The pooled frequency of specific variants carried by individuals with nonsyndromic hearing loss**.

CONCLUSIONS

Our results showed an association between *TECTA*/*GJB2* mutations and hearing impairment, but there were also regional and ethnic differences in mutation prevalence. However, studies with larger sample sizes and genetic analyses based on long-read sequencing are needed to better understand the changes resulting in hearing loss.

ABBREVIATIONS

AD: autosomal dominant; **AHRQ**: Agency for Healthcare Research and Quality; **GJB2**: gap junction protein beta 2; **SNHL**: sensorineural hearing loss; **TECTA**: tectorin alpha

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AUTHOR'S CONTRIBUTIONS

Minh Xuan Ngo and Chung Thuy Tran Phan conceived of the presented idea, developed the theory and supervised the findings of this study. Phuong Hoang Vu, Anh Thu Ha Nguyen and Thanh Vu Nguyen worked out the technical details, and performed the numerical calculations for the suggested experiment, verified the numerical results of the study. Phuong Hoang Vu and Quang An Lan interpreted the results and worked on the manuscript. All authors read and approved the final version of manuscript.

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AVAILABILITY OF DATA AND MATERIALS

Data and materials used and/or analyzed during the current study are available from the corresponding author on reasonable request.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

CONSENT FOR PUBLICATION

Not applicable.

COMPETING INTERESTS

The authors declare that they have no competing interests.

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