

Interleukin-1 receptor-associated kinase-4 gene variation may increase post-bronchiolitis asthma risk

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Abstract

Aim: Evidence based on studies of the encoding genes suggests that interleukin-1 receptor-associated kinase-4 (IRAK4) plays a role in childhood asthma and allergy. Our aim was to evaluate the associations of six *IRAK4* gene polymorphisms with presence of asthma and allergic rhinitis and use of inhaled corticosteroids (ICSs) for asthma at 5-7 and 11-13 years of ages after hospitalisation for bronchiolitis at younger than 6 months of age.

Methods: *IRAK4* rs4251513, rs4251520, rs4251522, rs4251578, rs79154645 and rs13852554 polymorphisms were determined in 141 former bronchiolitis patients prospectively followed up until 5-7 and in 125 children until 11-13 years of age.

Results: The homozygous variant *IRAK4* rs4251513 genotype was associated with the presence of asthma and allergic rhinitis and use of ICSs at 5-7 and 11-13 years of ages in univariate analyses. Statistical significance remained for the presence of asthma and use of ICSs but was lost in the case of allergic rhinitis in multivariate analyses. The adjusted odds ratios were 3.48 and 4.16 for asthma and 5.22 and 14.00 for ICS use at these two ages.

Conclusion: The homozygous variant *IRAK4* rs4251513 genotype was constantly associated with post-bronchiolitis asthma and asthma medication in school-aged children.

KEYWORDS

bronchiolitis, childhood asthma, gene variation, interleukin-1 receptor-associated kinase-4, school age

1 | INTRODUCTION

Interleukin-1 (IL-1) receptor-associated kinase-4 (IRAK4) plays a crucial role in innate immunity mediating signals initiated by toll-like receptors (TLRs). IRAK4 belongs to the IRAK family and is encoded by the *IRAK4* gene.¹ TLRs recognise the structures of various pathogens

and form with the IL-1 receptor (IL-1R), an intracellular Toll/IL1R (TIR) domain. TIR is necessary for recruiting signal-mediating molecules, such as myeloid differentiation primary response 88 (MyD88) and IRAK family members.²

The reduced IRAK4 or MyD88 functions have been associated with increased susceptibility to pneumococcus, staphylococcus

Abbreviations: CI, confidence interval; DNA, deoxyribonucleic acid; ICS, inhaled corticosteroid; IgE, immunoglobulin E; IL-1R, interleukin-1 receptor; IRAK4, interleukin-1 receptor-associated kinase-4; MAF, minor allele frequency; MyD88, myeloid differentiation primary response 88; OR, odds ratio; PCR, polymerase chain reaction; RSV, respiratory syncytial virus; SNP, single nucleotide polymorphism; TIR, Toll/IL1R domain; TLR, Toll-like receptor.

and pseudomonas, whereas their over-activation may lead to autoimmune diseases.^{1,3} IRAK4 and MyD88 deficiencies are caused by homozygous mutations in the *IRAK4* or *MyD88* genes, respectively.⁴ The patients present with severe infections caused by a narrow range of bacteria via a limited repertoire of mechanisms.^{5,6} Instead, the reports published until now have not contained patients with increased susceptibility to viral infections.

There is indirect evidence based on studies of the encoding genes that IRAK4 may play a role in allergy and asthma. The IRAK4 rs4251513, rs4251559 and rs1461567 single nucleotide polymorphisms (SNPs) were associated with serum immunoglobulin E (IgE) level, when 97 SNPs were genotyped in 206 adults with chronic sinusitis, and in a replication population of 956 subjects from families with asthma.⁷ The IRAK4 rs4251513 and rs4251520 SNPs were associated with an increased risk of early transient wheezing but not with the risk of childhood asthma, when 94 SNPs were studied in 2007 Dutch and 7242 French children prospectively followed up for 8 years from birth.⁸ In these studies, *MyD88* variations were not associated with IgE production or with childhood wheezing or asthma.

We have collected prospective follow-up data at two control visits at 5-7 years⁹ and 11-13 years¹⁰ of ages from children hospitalised for bronchiolitis under 6 months of age. As summarised previously,¹¹ *TLR5* variation was associated with virus aetiology of bronchiolitis, *TLR9* variation with post-bronchiolitis wheezing, and *TLR1* and *TLR10* variations with post-bronchiolitis asthma at school age.

The aim of the present study was to evaluate the associations of *IRAK4* rs4251513, rs4251520, rs4251522, rs4251578, rs79154645 and rs13852554 polymorphisms with presence of asthma, use of asthma medication and presence of allergic rhinitis at 5-7 and 11-13 years of ages after hospitalisation for bronchiolitis in infancy. In addition, we compared the genotypes and minor allele frequencies (MAFs) of these six SNPs between bronchiolitis cases and Finnish controls from two publicly available genome databases.

2 | MATERIAL AND METHODS

2.1 | Design

In 2001-2004, 187 previously healthy, full-term infants aged <6 months were hospitalised due to bronchiolitis in the department of Pediatrics, Tampere University Hospital, Finland.¹²

Appropriate clinical data collected during hospitalisation were available from 166 patients. Bronchiolitis was defined as a lower respiratory infection presenting with diffuse wheezes and/or fine crackles.¹² Viral aetiology of bronchiolitis, including respiratory syncytial virus (RSV) and rhinovirus, was studied with antigen detection and polymerase chain reaction (PCR) in nasopharyngeal aspirates.¹² Data on atopic dermatitis in children and asthma or allergy in parents

Key notes

- Preliminary evidence suggests that interleukin-1 receptor-associated kinase-4 (IRAK4) plays a role in early-childhood asthma.
- Six *IRAK4* gene polymorphisms were studied, and the homozygous variant *IRAK4* rs4251513 genotype was constantly associated with presence of asthma and need of inhaled corticosteroids at 5-7 and 11-13 years of ages in children prospectively followed up after bronchiolitis in infancy.
- This finding calls for studies on IRAK4 pathway in bronchiolitis and childhood asthma.

were registered during hospitalisation¹² and at the control visit at 1.5 years of age.¹³

Later follow-ups were arranged at 5-7 and 11-13 years of ages, and 166 and 138 former bronchiolitis patients, respectively, participated.^{9,10} The parents completed a structured questionnaire comprising questions on doctor-diagnosed asthma, allergic rhinitis and atopic dermatitis, on use of inhaled corticosteroids (ICSs) and bronchodilators, and on symptoms presumptive for asthma and allergic rhinitis.^{9,10} The follow-up study included an interview of the parents and children, and exercise challenge test using impulse oscillometry at 5-7 years of age⁹ and bronchodilation test using flow-volume spirometry at 11-13 years of age.¹⁰

2.2 | Definitions

As described previously,^{9,10} current asthma was defined as regular use of ICSs during the last 12 months, or alternatively, as reporting of doctor-diagnosed wheezing, prolonged cough or night cough during the last 12 months and in addition, presence of a diagnostic finding in the exercise challenge test at 5-7 years of age⁹ or presence of a diagnostic finding in the bronchodilation test at 11-13 years of age.¹⁰ Allergic rhinitis and atopic dermatitis were parent-reported but needed to be earlier diagnosed by a doctor and to be symptomatic during the last 12 months.^{9,10} Non-RSV aetiology of bronchiolitis, atopic dermatitis in infancy and asthma in mothers were significant risk factors for current asthma at 5-7 years of age.⁹ Correspondingly, allergic rhinitis in children at 5-7 years of age and asthma in mothers were significant risk factors for current asthma at 11-13 years of age.¹⁰

2.3 | Genetics

IRAK4 rs4251513, rs4251520, rs4251522, rs4251578, rs79154645 and rs13852554 SNPs (Figure 1) were studied by PCR-based sequencing, carried out at the Eurofins Genomics.

Invitrogen Platinum II Taq Hot-Star DNA polymerase (Thermo Fisher Scientific Inc Waltham) was used for PCR reaction according to the manufacturer's instructions. The primers and annealing temperatures used in the PCR are shown in Table 1. Prior to the sequencing, the PCR product was purified enzymatically with Thermo Scientific Exonuclease I and FastAP (Thermo Fisher Scientific Inc Waltham) DNA purification kits according to the manufacturers' instructions.

2.4 | Controls

The controls for the *IRAK4* rs4251513, rs4251520, rs4251522, rs4251578, rs79154645 and rs13852554 SNPs were obtained from two publicly available databases: the genotype frequencies from the Finnish data of the 1000 Genomes Project (<http://www.ensembl.org>), and the MAFs from the Finnish data of the 1000 Genomes Project (<http://www.ensembl.org>) and from the Finnish data of the Genome Aggregation Database (<https://gnomad.broadinstitute.org>).

2.5 | Characteristics of study subjects

At 5-7 years of age, current asthma was present in 19 (13.8%) of those 141 cases with data on *IRAK4* SNPs and follow-up data until 5-7 years of age available, and 18 of them used ICSs. Allergic rhinitis was present in 40 (28.4%) and atopic dermatitis in 46 (32.6%) children. During bronchiolitis in infancy, RSV was identified 96 (68.1%) cases and rhinovirus in 17 (12.1%) of 141 cases.

At 11-13 years of age, current asthma was present in 15 (12.0%) of those 125 cases with data on *IRAK4* SNPs and follow-up data until 11-13 years of age available, and 11 of them used ICSs. Allergic rhinitis was present in 19 (15.2%) and atopic dermatitis in 41 (32.8%) children. During bronchiolitis in infancy, RSV was identified 85 (68.0%) cases and rhinovirus in 15 (12.0%) of 125 cases.

The prevalence of asthma ever before or at the 5-7 years follow-up was 38 (27.0%) of 141 children. Nine (7.2%) of 125 children had persistent asthma defined as presence of current asthma at both the 5-7 years and 11-13 years follow-ups.

2.6 | Statistics

Statistical analyses were performed using the Statistics Package for Social Sciences (SPSS 26.0, IBM Corp.). Chi-square and Fisher's exact tests, when appropriate, were used in the univariate analyses. Logistic regression was used in the multivariate analyses. When the genotypes were analysed as risk factors for the outcomes at 5-7 years and 11-13 years of ages, logistic regression was adjusted for sex and RSV versus non-RSV aetiology of bronchiolitis, and for maternal asthma and atopic dermatitis in infancy. In addition, presence of allergic rhinitis at 5-7 years of age was included in the model in supplementary analyses of the 11-13 years data. The results are expressed as odds ratios (OR) and 95% confidence intervals (95%CI).

2.7 | Ethics

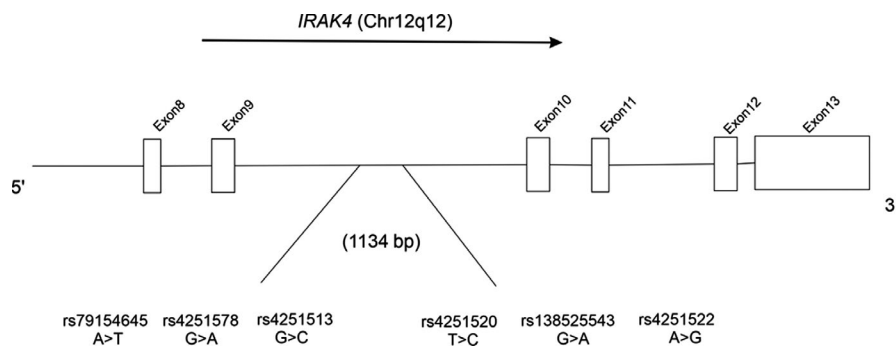
Informed parental consents, including permission for genetic studies on bronchiolitis susceptibility and on asthma and allergy risk, were obtained during hospitalisations and at all control visits. The study was approved by the Ethics Committee of the Tampere University Hospital district, Tampere, Finland. Genetic tests were done using coded data without personal information in the Research Centre of Infections and Immunity, Turku University, Turku, Finland.

3 | RESULTS

3.1 | Comparisons to controls

The *IRAK4* rs4251513 wild GG genotype was present in 22.9% of bronchiolitis cases, and the variant heterozygous GC and homozygous CC genotypes in 56.0% and 21.1%, respectively. The *IRAK4* rs4251513 genotypes and MAFs did not differ between cases and population controls (Table 2). The *IRAK4* rs4251520 wild TT genotype was present in 77.9% of bronchiolitis cases, and the variant heterozygous TC and homozygous CC genotypes in 21.5% and 0.6%, respectively. The *IRAK4* rs4251520 genotypes and MAFs did not differ between cases and population controls (Table 2). There were only occasional variant genotypes in the *IRAK4* rs4251522, rs4251578, rs79154645, and rs138525543 SNPs (Table 2).

FIGURE 1 The location of the studied intron variants of the *IRAK4* gene (NM_001114182 with 13 exons). The nucleotide change is shown below each SNP ID, and the 1134 bp indicates the distance between rs4251513 and rs4251520



Polymorphism	Primer	Product size (bp)	Annealing Ta (°C)
rs79154645 rs4251578 rs4251513	F:5'-GAACCCTAAGACTTAATGGCCAAA-3' R:5'-GGGTCAGTTCCTCTGCTTGA-3'	516	58
rs4251520 rs138525543 rs4251522	F:5'-TAGCTGGTATCCTGTTGCTCA-3' R:5'-ACTACAAAGTCTTCCAAGGCAC-3'	585	59

Note: One PCR was used for identification of three single nucleotide polymorphisms.

The *IRAK4* rs4251513, rs4251520, rs4251522, rs4251578, and rs79154645 MAFs did not differ between cases and 1731-1738 Finnish controls from the Genome Aggregation Database (Data not shown). The *IRAK4* rs138525543 MAF was 0.009 in cases versus 0.001 in controls ($P = .002$).

TABLE 2 Genotypes and minor allele frequencies of the six studied *IRAK4* gene polymorphisms in bronchiolitis cases in relation to the controls from the Finnish data of the 1000 Genome Project

<i>IRAK4</i> genotypes	Cases N = 166	Controls N = 99	P
rs4251513			.303
GG	38 (22.9%)	27 (27.3%)	
GC	93 (56.0%)	46 (46.5%)	
CC	35 (21.1%)	26 (27.3%)	
Minor allele C	163/332 (0.491)	98/198 (0.495)	.929
rs4251520*			.419
TT	127 (77.9%)	70 (70.7%)	
TC	35 (21.5%)	28 (28.3%)	
CC	1 (0.6%)	1 (1.0%)	
Minor allele C	37/326 (0.113)	30/198 (0.152)	.130
rs4251522*			.892
AA	154 (94.5%)	94 (94.9%)	
AG	8 (4.9%)	5 (5.1%)	
GG	1 (0.6%)	0	
Minor allele G	9/326 (0.009)	5/198 (0.025)	.718
rs4251578			1.000
GG	166 (100%)	99 (100%)	
Minor allele A	0	0	1.00
rs79154645			.340
AA	159 (95.8%)	97 (98.0%)	
AT	AT 7 (4.2%)	2 (2.0%)	
Minor allele T	7/332 (0.021)	2/198 (0.010)	.112
rs138525543*			.595
GG	160 (98.2%)	98 (99.0%)	
GA	3 (1.8%)	1 (1.0%)	
Minor allele A	3/326 (0.009)	1/198 (0.005)	.596

TABLE 1 Sequences of primer pairs, and annealing temperatures (Ta) and product sizes (Bp) of polymerase chain reactions (PCR)

3.2 | Univariate outcome analyses

The presence of the homozygous variant CC *IRAK4* rs4251513 genotype, compared to the GC/GG genotype, was associated with an increased risk of previous asthma, use on ICSs during last 12 months and presence of current asthma or allergic rhinitis at 5-7 years of age (Table 3), and with persistence of asthma from 5-7 to 12-13 years of age, use of ICSs during last 12 months and presence of current asthma at 11-13 years of age (Table 3). However, there were no significant differences in any outcome, when children with the wild GG genotype were compared to those with the variant GC/CC genotypes (Table 3).

There were no significant differences in any asthma or allergy outcome, when children with the *IRAK4* rs4251520 wild TT genotype were compared to those with the variant AT genotype (Data not shown). The *IRAK4* rs4251522, rs4251578, rs79154645, and rs138525543 variant genotypes were so rare that any statistical comparisons could not be performed.

3.3 | Multivariate outcome analyses

The comparisons of outcomes between children with the *IRAK4* rs4251513 variant homozygous CC genotype and those with the GC/GG genotypes were repeated as adjusted for sex, RSV versus non-RSV aetiology of bronchiolitis, maternal asthma, and atopic dermatitis in infancy. At 5-7 years of age, the adjusted OR was 3.48 for presence of current asthma and 5.22 for use of ICSs during last 12 months (Table 4). At 11-13 years of age, the adjusted OR was 4.16 for presence of current asthma and 14.0 for use of ICSs during the last 12 months (Table 4). The adjusted OR was 16.05 for persistence of asthma from 5-7 years to 11-13 years of age (Table 4).

When allergic rhinitis at 5-7 years of age was added in the model, persistent asthma from 5-7 to 11-13 years of age (adjusted OR 10.76, 95%CI 1.26-78.26) and use of ICSs during last 12 months (adjusted OR 11.66, 95%CI 2.10-64.53) remained statistically significant.

3.4 | Supplementary analyses

Children with homozygous variant CC and with wild GG genotypes of the *IRAK4* rs4251513 were compared in ad hoc subgroup

TABLE 3 Asthma, asthma medication and allergy at 5-7 and 11-13 y of ages in 141 and 125 children, respectively, who were prospectively followed up after hospitalisation for bronchiolitis under 6 mo of age, presented in relation to the *IRAK4* rs4251513 homozygous versus heterozygous genotypes

Outcomes	Wild homozygous genotype GG	Variant homozygous genotype CC	P-value	P-value
Age 5-7 y N = 141	N = 31	N = 32	GG vs GC/CC	CC vs GC/GG
Previous asthma N = 38	8 (25.8%)	14 (43.8%)	.871	.015
Inhaled steroids, the last 12 mo N = 18	2 (6.5%)	10 (31.3%)	.190	.001
Current asthma N = 19	3 (9.7%)	9 (28.1%)	.357	.006
Current allergic rhinitis N = 40	8 (25.8%)	14 (43.8%)	.455	.026
Atopic dermatitis N = 46	13 (41.9%)	11 (34.4%)	.211	.810
Age 11-13 y N = 125	N = 26	N = 26	GG vs GC/CC	CC vs GC/GG
Persistent asthma N = 9	0	6 (23.1%)	.113	.003
Inhaled steroids, the last 12 mo N = 11	0	7 (26.9%)	.068	.001
Current asthma N = 15	3 (11.5%)	7 (26.9%)	.620	.009
Current allergic rhinitis N = 19	2 (7.7%)	5 (19.2%)	.189	.355
Atopic dermatitis N = 41	7 (26.9%)	11	.473	.246

analyses. Since there were two cells without any cases, we replaced the figure 0 by 1 to enable multivariate logistic regression analyses. The added cases were supposed to be boys with RSV bronchiolitis and not to have atopic dermatitis in infancy or mothers with asthma. This ad hoc model confirmed that the *IRAK4* rs4251513 homozygous variation was associated with use of ICSs at 5-7 years (adjusted OR 5.93, 95%CI 1.06-33.16) and at 11-13 years (18.7, 1.36-239.58) and persistence of asthma from 5-7 years to 11-13 years of ages and with persistence (13.78, 1.07-176.89).

4 | DISCUSSION

There are three main results in the present study on the association *IRAK4* gene variations with bronchiolitis in infancy and with post-bronchiolitis asthma and allergy at school age. First, the frequencies of the genotypes and alleles of the six studied polymorphisms were rather similar in bronchiolitis cases and in population controls. Second, the homozygous variant *IRAK4* rs4251513 genotype was associated with asthma, ICS medication and allergic rhinitis at 5-7 and 11-13 years of ages. These are novel findings. The results on asthma and ICS medication were robust to adjustments with early-life risk factors, but those on allergic rhinitis were not. Third, the associations

of the *IRAK4* rs4251513 polymorphism with asthma and allergy were significant only, if the variation was homozygous. This is in line with infection susceptibility in *IRAK4* deficiency, which also needs that the gene defects are homozygous.^{3,4,6} Since only two cases and 0%-1.4% of controls were homozygous for the *IRAK4* rs4251520, rs4251522, rs4251578, rs79154645 or rs13852554, these variations cannot be significant risk factors for bronchiolitis or childhood asthma in the Finnish population.

There is preliminary evidence based on studies of the encoding genes that *IRAK4* may play a role in asthma and allergy. The *IRAK4* rs4251513 variation, which was included in the present study, and the rs4251559 and rs1461567 variations, which were not included, were associated with low serum IgE in 206 Canadian adults with chronic sinusitis and in 956 subjects from families with asthma.⁷ The *IRAK4* rs4251513 and rs4251520 variations, which were included in the present study, increased the risk of transient early wheezing but not the risk of other phenotypes of wheezing or childhood asthma in 2007 Dutch and 7242 French children prospectively followed up for 8 years from birth.⁸

The great majority of bronchiolitis cases, especially when caused by RSV, belong to the transient early wheezing phenotype.¹⁴ In the present cohort, two-thirds of cases were caused by RSV and their prognosis was good with an only 8.2% asthma risk at early

TABLE 4 Multivariate logistic regression: The risks of asthma and allergy outcomes at 5-7 and 11-13 y of ages related to the *IRAK4* rs4251513 homozygous CC genotype

Age 5-7 y	Adjusted OR	95% CI
Previous asthma N = 38	2.16	0.85-5.49
Inhaled steroids, the last 12 mo N = 18	5.22	1.57-17.35
Current asthma N = 19	3.48	1.15-10.48
Current allergic rhinitis N = 40	2.15	0.91-5.11
Atopic dermatitis N = 46	0.78	0.30-2.02
Age 11-13 y	Adjusted OR	95% CI
Persistent asthma N = 9	16.05	2.36-109.25
Inhaled steroids, the last 12 mo N = 11	14.00	2.71-72.21
Current asthma N = 15	4.16	1.22-14.19
Current allergic rhinitis N = 19	0.93	0.26-3.29
Atopic dermatitis N = 41	1.44	0.55-3.77

Note: The analyses were adjusted for sex, RSV vs non-RSV aetiology of bronchiolitis during hospitalisation and presence of atopic dermatitis in infancy and presence of maternal asthma. The children with the homozygous variant CC genotype of the *IRAK4* rs4251513 were compared to those with the GG/GC genotype.

school age.⁹ Despite of the low numbers of children with asthma at 5-7 years and 11-13 years of ages, we were able to show that the *IRAK4* rs4251513 variation was associated with 3.5- to 4-fold risk of asthma and 5- to 14-fold need of asthma medication in adjusted analyses. These observations mean that the association the *IRAK4* rs4251513 variation with post-bronchiolitis asthma at school age was constant and well documented.

We included the *IRAK4* rs4251513 and rs4251520 in our study based on previous findings made in two European birth cohorts.⁸ The rationale for studying *IRAK4* polymorphisms in this post-bronchiolitis cohort came from our observations on the role of *TLR* polymorphisms in bronchiolitis and post-bronchiolitis outcome.¹¹ *IRAK4* plays a crucial role in innate immunity mediating signals initiated by *TLRs* after recognising of pathogens, which are mediated to *IRAK4* and other transduction molecules via *TIR* domains which consists of *TLRs* and *IL-1* receptors.^{1,2}

Previously in this post-bronchiolitis cohort, *TLR5* gene polymorphism was associated with viral aetiology of bronchiolitis,¹⁵ *TLR9* gene polymorphism with post-bronchiolitis wheezing,¹⁶ and *TLR1* and *TLR10* gene polymorphisms with post-bronchiolitis asthma at school age.^{17,18} Polymorphism in *TLR6* was associated with increased bronchial reactivity at school age.¹⁹ In addition, *TLR3* polymorphism

was associated with an increased risk of bronchiolitis compared to 400 basically healthy non-selected infants.²⁰

The main limitation of the present study was the small number of cases, 141 former bronchiolitis patients in the 5-7 years and 125 in the 11-13 years data, which means a risk for type-2 statistical errors. Although six *IRAK4* polymorphisms were studied, only two of them, the rs4251513 and rs42511320, presented with sufficient numbers of variant genotypes allowing statistical analyses. Moreover, only the *IRAK4* rs4251513 included homozygous variant genotypes. The genome registers we used to evaluate the risk of getting bronchiolitis do not contain any clinical data, and therefore, the association between the *IRAK4* gene variations and post-bronchiolitis outcomes was evaluated only using within-cohort analyses.

5 | CONCLUSION

After surviving hospitalisation due to viral bronchiolitis in early infancy, the children with homozygous variant *IRAK4* rs4251513 genotype constantly showed an increased risk of asthma and need of asthma medication at school age.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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