

Genome-wide Scan of Plasma Cholecystokinin in Baboons Shows Linkage to Human Chromosome 17

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Abstract

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Objective: Cholecystokinin (CCK) is known to inhibit food intake and is an important signal for controlling meal volume, indicating a possible role in weight regulation. Our objective was to investigate genetic influences on plasma CCK in baboons.

Research Methods and Procedures: Subjects were 376 baboons (males = 113, females = 263) from the Southwest National Primate Research Center, housed at the Southwest Foundation for Biomedical Research, San Antonio, Texas. Anthropometric and biochemical parameters were analyzed. Genetic effects on plasma CCK were estimated by the maximum likelihood-based variance components method implemented in the software program SOLAR (Sequential Oligogenic Linkage Analysis Routines).

Results: Male baboons (32.7 ± 6 kg) were much heavier than females (20.2 ± 4 kg). Similarly, mean (\pm standard deviation) plasma CCK values were also higher in male baboons (13.8 ± 6 pM) than female baboons (12.5 ± 4 pM). Significant heritabilities were observed for plasma CCK (0.14 ± 0.1 , $p < 0.05$), body weight ($h^2 = 0.62 \pm$

0.15 , $p < 10^{-8}$), and glucose ($h^2 = 0.68 \pm 0.17$, $p < 10^{-7}$). A genome-wide scan of plasma CCK detected a strong signal for a quantitative trait locus (QTL) on chromosome 17p12–13 [logarithm of the odds (LOD) = 3.1] near marker *D17S804*. Suggestive evidence of a second QTL was observed on chromosome 4q34–35 (LOD = 2.3) near marker *D4S2374*.

Discussion: A substantial contribution of additive genetic effects to the variation in plasma levels of CCK was demonstrated in baboons. The identification of a QTL for plasma CCK on chromosome 17p is significant, as several obesity-related traits such as BMI, leptin, adiponectin, and acylation stimulating protein have already been mapped to this region.

Key words: appetite regulation, genetics, quantitative trait loci

Introduction

Cholecystokinin (CCK)¹ is a major satiety signaling protein that is produced in the duodenum in response to the presence of food (particularly those high in fat or protein). It is secreted by the endocrine I cells in the mucosal layer of the anterior small intestine and the neurons of the central nervous system (1,2). Plasma CCK is at its highest level post-meal. As it enters circulation, it stimulates the release of pancreatic enzymes and gall bladder contraction (3). The CCK hormone interacts with its receptors CCK-1 (formerly CCK-A) present on the vagus nerve, and the resultant information is transmitted to the brainstem through the vagus nerve to inhibit food intake and control meal size (1). Although CCK is very effective as an inhibitor of meal volume, it is a short-term regulator of appetite. Its half life is only 1 to 2 mins; therefore, its action is rapid and short-lived (4).

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¹ Nonstandard abbreviations: CCK, cholecystokinin; QTL, quantitative trait locus; LOD, logarithm of the odds; ASP, acylation-stimulating protein.

The reduction in meal volume with CCK is usually compensated by an increase in meal frequency or number (3). However, the interaction of CCK with long-term signals, such as leptin, prolongs this effect and makes it a long-term energy regulator (5). It is believed that leptin and CCK act concomitantly to regulate body weight and amount of meal, as injection of leptin into the duodenum increases plasma CCK (6). In addition, administration of CCK enhances the leptin-induced reduction in body weight and meal quantity, indicating that this synergistic action has a direct influence on food intake (7).

Weight regulation is a complex process involving energy intake, body fat stores, brain and peripheral signals that regulate meal intake and termination (8), and genetics (9). In humans, heritability of obesity phenotypes has been shown to be greater than 50% (10–12). Evidence from genetic studies points to a number of chromosomal loci that affect variations in obesity-related traits (13–16) with a few of them, such as 1p31.1, 1p11.2, 2p22.3, 3q36.33, 4q31.1, 6q23.3–24.1, 11q22, 11q24, and 17p12, being replicated across family-based studies (17). Similarly to humans, obesity-related phenotypes in baboons are heritable (18,19). A study conducted by Comuzzie et al. (20) showed considerable additive genetic effects for body weight ($h^2 = 0.62$, $p < 10^{-4}$), fat mass ($h^2 = 0.41$, $p < 10^{-5}$), fat free mass ($h^2 = 0.32$, $p < 10^{-6}$), and leptin ($h^2 = 0.21$, $p < 0.05$). Previous genome scans in non-human primates, particularly baboons, have shown several chromosomal regions influencing the variation in obesity-related traits (21–23).

Baboons are an ideal model for genetic studies, especially for obesity, because the environmental variations are minimal due to consistency of diet and housing conditions. These animals have a high degree of similarity with humans with respect to genetic variation and protein and chromosomal structure (20). In our pedigreed population of baboons, 10% of the baboons become obese despite uniform environmental exposure. These primates are a valuable resource for studying the genetics of obesity-related traits; therefore, our objective was to examine the effect of genes on the variation in plasma levels of CCK and to locate the chromosomal loci that modulate these circulating levels of CCK in baboons.

Research Methods and Procedures

Subjects

The baboons for this study were obtained from a pedigreed population maintained by the Southwest National Primate Research Center, located at the Southwest Foundation for Biomedical Research in San Antonio, TX. The species of the baboons is a mixture of yellow baboons (*Papio hamadrayas cynocephalus*) and olive baboons (*Papio hamadrayas anubis*). Data on plasma CCK levels were available for 376 adults (263 females, 113 males). The

Table 1. Relative pairs in this study

Relationship	Number of pairs
Parent-offspring	50
Siblings	173
Avuncular	40
Half-siblings	2360
Half-avuncular	413
Half-first cousins	29
Half-first cousins, once removed	10
Half-siblings and first cousins	3
Half-siblings and half-first cousins	34
Half-siblings and half-avuncular	5
Total	3117

relative pairs used for this study are listed in Table 1. All of these animals shared the same living conditions, were housed in open-air group cages, and were fed ad libitum a standard low-fat diet (Harlan Teklad 15% monkey diet, 8715; Indianapolis, IN).

Sample Collection

Blood was drawn from the antecubital vein under ketamine sedation after an overnight fast (~12 hours). Total volume of blood drawn was ~11 mL; 4 mL was collected in sodium fluoride tubes for analysis of glucose and 7 mL in EDTA tubes for analyzing insulin, leptin, c-peptide, and cholecystokinin. Body weight was measured with a calibrated electronic scale (GSE, Chicago, IL). Plasma was separated by centrifugation at 2000g for 10 minutes and stored in aliquots at -80°C until analysis. All procedures were approved by the Institutional Animal Care and Use Committee of the Southwest Foundation for Biomedical Research, San Antonio, TX.

Assay for Cholecystokinin

Commercially available radioimmunoassay kits (LINCO Research, Inc., St. Charles, MO) were used to measure cholecystokinin. All samples were analyzed in duplicate.

Genotypes

A baboon genetic map has been developed using human microsatellite loci (24). Homologous microsatellite loci from baboon genomic DNA were amplified using published human polymerase chain reaction primers. Baboon genotypes were obtained by gel electrophoresis and analyzed on ABI 373 and ABI 377 automated sequencers using fluorescently labeled primers and Genescan and Genotyper software (Applied Biosystems, Foster City, CA). A total of 331

Table 2. Descriptive statistics

Phenotype	Males	Females	h^2 (SE)	p value for h^2
Age (yrs)	18.5 (0.31)	20.6 (0.29)	—	—
Body weight (kg)	32.7 (0.55)	20.2 (0.26)*	0.62 (15)	1×10^{-7}
CCK (pM)	13.8 (0.57)	12.5 (0.34)†	0.14 (0.10)	3×10^{-2}

SE, standard error; h^2 , heritability; CCK, cholecystokinin. Data are mean (SE).

* Significantly different from males ($p < 0.001$)

† Significantly different from males ($p < 0.05$).

markers per animal were typed at an average spacing of 10 cM. Baboons and humans share 96% of the DNA variation.

Linkage map of the baboon genome

The pedigreed baboons that were genotyped for the linkage map were from 10 pedigrees. These pedigrees consist of three to four generations of baboons, which are randomly mated and tested for relationships with other baboons. Comparative mapping by chromosome between humans and baboons demonstrates that eight chromosomes show one simple inversion in human relative to its equivalent in baboon, seven show different multiple rearrangements, and seven human autosomes have the same order among the loci as baboons. However, three of the baboon chromosomes are the fusion of two human chromosomes, such that baboon chromosomes 3, 7, and 10 are homologous to the fusion of human chromosomes 7 and 21, 14 and 15, and 20 and 22, respectively.

Statistical methods

To estimate the genetic component that is influencing the variation in plasma CCK, its residual heritability was estimated using age, sex, sex-specific age, and age² terms as covariates. Accordingly, the total phenotypic variance (σ^2_p) was decomposed into its additive genetic (σ^2_G) and environmental (σ^2_E) components. The heritability of a phenotype refers to the portion of phenotypic variance that can be attributed to additive genetic effects ($h^2 = \sigma^2_G/\sigma^2_p$) (25). To find a putative quantitative trait locus (QTL) or loci that might be affecting the plasma levels of CCK, a multipoint linkage analysis was conducted. This analysis is an extension of the variance components approach in which a QTL variance component is added to the basic model. The phenotypic correlations between family members can be described as the cumulative effect of a specific QTL associated with a marker and residual genetic and environmental effects. The effect of a specific QTL on the variation in phenotype can be modeled as a function of the identity-by-descent relationship at the marker locus between family members (26). A model under the null hypothesis, in which

the additive genetic variance for a specific QTL equals zero, was tested against a model under an alternate hypothesis, in which the additive variance was estimated. This is known as a likelihood ratio test, and the resultant likelihood ratio test statistic, in this particular case, was distributed asymptotically as a $1/2: 1/2$ mixture of a χ^2 variable with one df and a point mass at zero (27). Traditionally, a logarithm of the odds (LOD) score, which is computed directly from the likelihood ratio test, is reported in linkage analyses (28). Generally, a LOD score of greater than three is taken as strong evidence of a putative QTL. However, in baboons, thresholds for linkages are different, compared with humans, due to differences in pedigree configuration and marker locations. According to an approach based on the work of Feingold et al. (29), a LOD score of ≥ 2.73 is considered as evidence for significant and ≥ 1.5 as suggestive linkages in baboons.

Results

A summary of descriptive statistics and heritabilities for this sample are provided in Table 2. Females were older but had lower body weights (range 11 to 35 kg) than males (range 22 to 54 kg). Plasma levels of glucose, insulin, and leptin were higher in female baboons. In contrast, circulating levels of CCK were higher in males. Mean heritability of CCK was 0.14 ± 0.1 ($p = 0.03$), suggesting that additive genetic effects were influencing part of the variation in plasma levels.

A summary of the genome-wide univariate linkage analysis is presented in Figure 1. The strongest signal was detected on the baboon homologue of human chromosome 17 (LOD = 3.1, $p < 0.01$) near marker *D17S804* (Figure 2). To correct for deviation from normal distribution, we calculated the robust LOD score. The robust LOD score for plasma CCK was 2.8. Suggestive linkages were observed on the baboon homologue of human chromosome 4 (LOD = 2.26, $p < 0.05$) at 136 cM qter near marker *D4S2374* (Figure 3). Obesity-related phenotypes that have been previously linked to human chromosome 17 are shown in Table

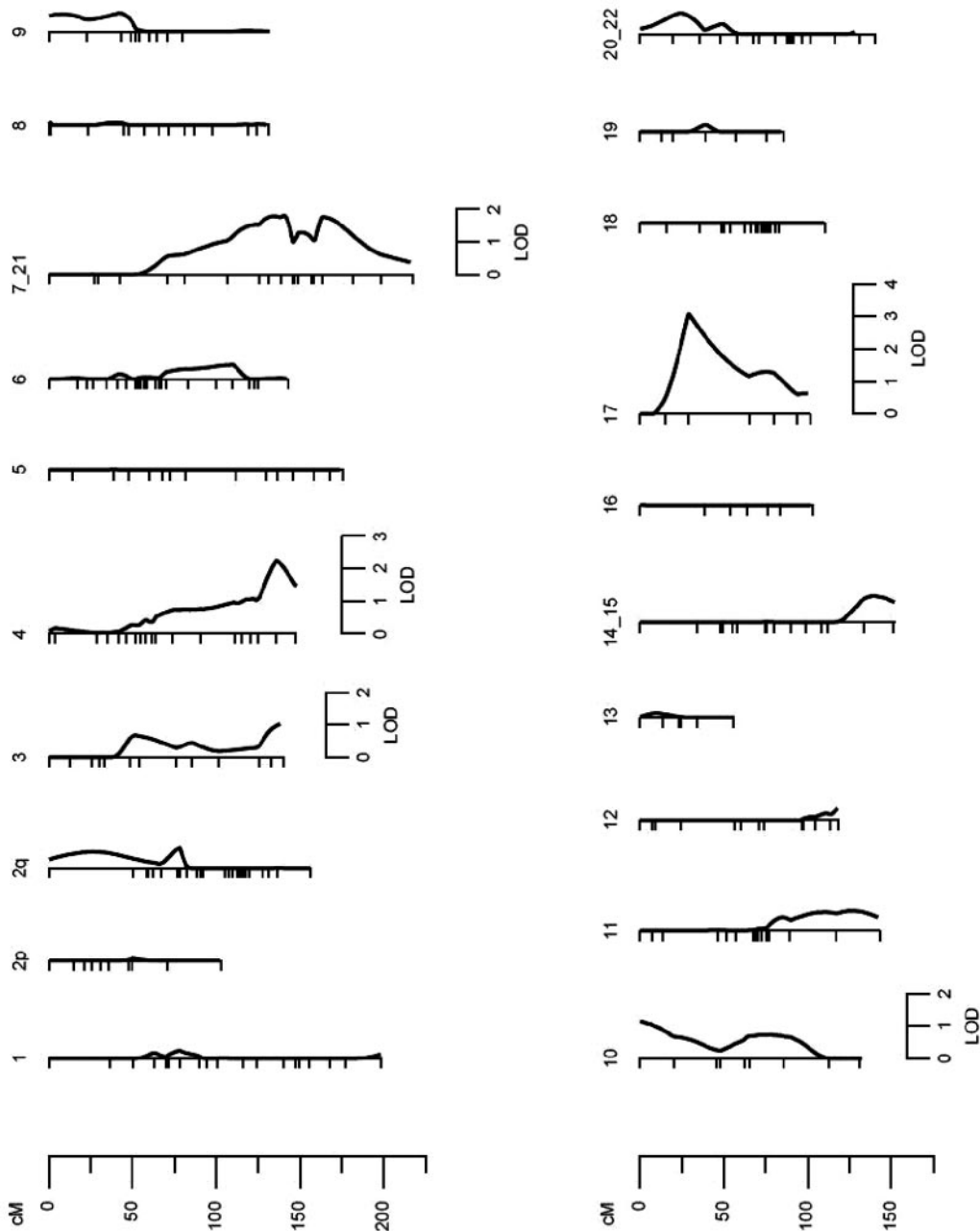


Figure 1: Summary of the univariate linkage analysis by each chromosome (*). Chromosomal location (cM) is represented on the y-axis and the LOD score shown on the x-axis. *, Chromosomes are numbered according to their human homologues.

3. The one LOD-support interval encompasses about 20 cM (range, 25 to 45 cM), cytogenetic location being 17p12–17p13.

Discussion

The most important finding of this study was the identification of a strong QTL for CCK on the baboon homolog of human chromosome 17p12–13. CCK is a major satiety hormone that regulates food intake and meal size (8). It also

controls gastric motility, pancreatic and gastric acid secretion, and gall bladder contraction (30). Circulating levels of CCK in baboons were much higher than those in humans (31,32). In baboons, males had higher levels of plasma CCK, which is in contrast to levels reported in humans (33,34).

To the best of our knowledge, no linkage analysis with plasma CCK as a phenotype has been conducted thus far. Heritability for CCK obtained in this study showed signif-

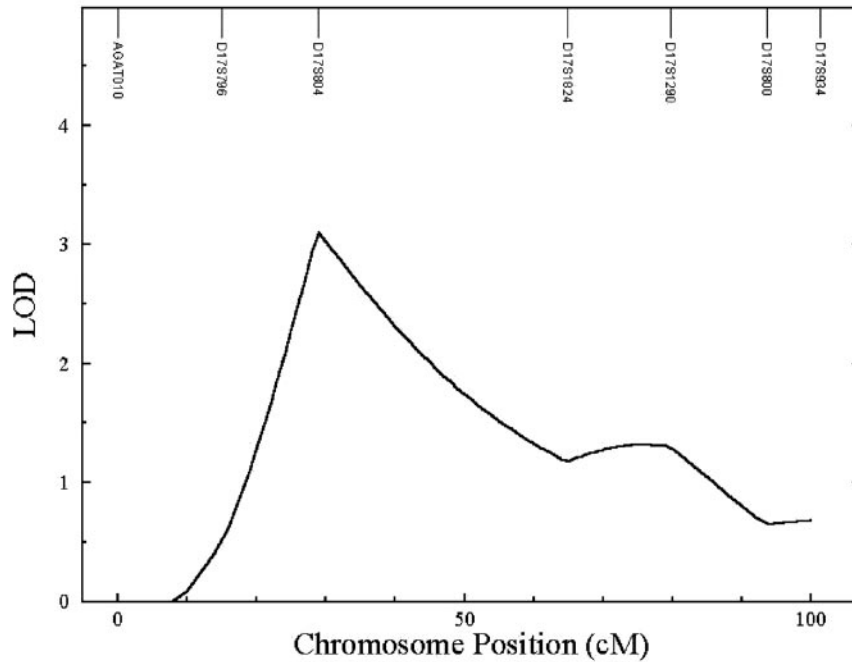


Figure 2: Map depicting LOD scores and marker distances for plasma CCK on chromosome 17.

icant genetic influence on the variation in its plasma levels. Although the heritability estimate for circulating CCK is much lower than those of other obesity-related phenotypes, lack of genetic analysis for plasma CCK in humans makes it difficult to compare the results. However, heritability

estimate for weight in this study is consistent with that reported in previous baboon and human studies (20,35).

Identifying a QTL for CCK in this chromosomal region is of considerable importance as the area has been previously linked to several phenotypes related to obesity. Kissebah et

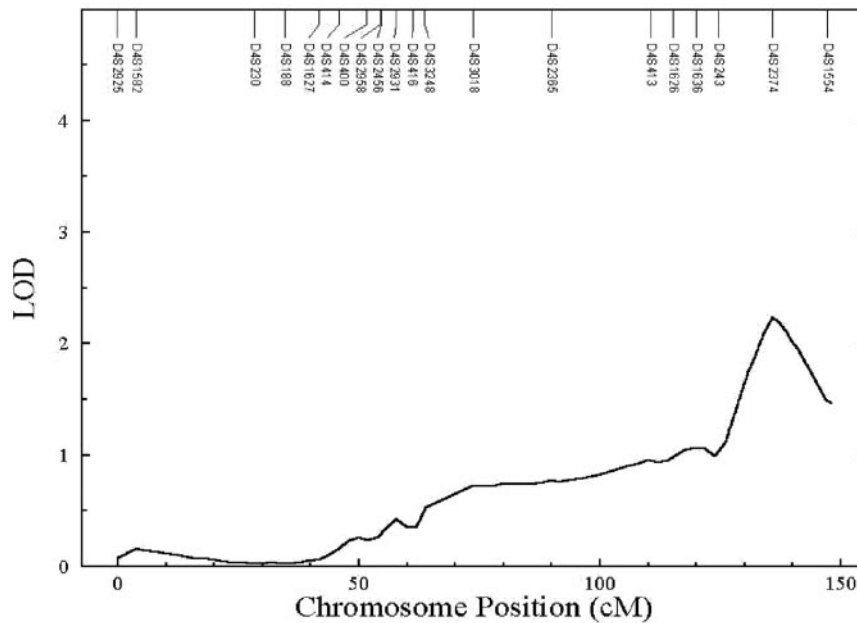


Figure 3: Map depicting LOD scores and marker distances for plasma CCK on chromosome 4.

Table 3. Obesity-related QTLs previously reported on chromosome 17 in humans

Phenotype	Location (cM)	Cytogenetic location	LOD	Reference
CCK	25–45 (1 LOD support interval)	17p12–p13	3.1	Present study
Leptin	38	17p12	5.0	Kissebah et al., 2000 (36)
ASP and BMI	28	17p11–12	4.7	Martin et al., 2004 (41)
Insulin	38–60 (1 LOD support interval)	17p11–q21	3.3	Rich et al., 2005 (38)
ASP	32	17p11.2	2.7	Martin et al., 2004 (41)
Adiponectin	38	17p12	1.7	Comuzzie et al., 2001 (42)
Glucose	38–60 (1 LOD support interval)	17p11–q21	1.44	Rich et al., 2005 (38)
BMI	21	17p13.1	1.34	Mitchell et al., 1999 (43)

QTL, quantitative trait locus; LOD, logarithm of the odds; CCK, cholecystokinin; ASP, acylation-stimulating protein.

al. (36) reported linkage with leptin near marker *D17S947* (LOD = 5.0 at 38 cM) on 17p12 in a sample of Midwestern families. Leptin is an adipocyte-derived hormone with a role in energy homeostasis (7) and is known to enhance the action of CCK in controlling the meal volume (7). Moreover, CCK is also augmented by insulin, a hormone associated with satiety (37). Two studies, one in African-Americans and Hispanics (38) and the other in whites (39), have found loci for fasting insulin in this region of chromosome 17.

QTLs for circulating levels of adipose-derived hormones, acylation-stimulating protein (ASP), and adiponectin were mapped to the same region as CCK. ASP has an important role in obesity in the regulation of fat storage and adipose tissue metabolism (40). A study conducted in Mexican-Americans revealed a QTL for ASP on chromosome 17 near marker *D17S1303* (41). In northern Europeans, Comuzzie et al. (42) found suggestive evidence for a QTL for serum adiponectin on chromosome 17 (LOD = 1.7). Also, two suggestive linkages for BMI on the same chromosome were found by Mitchell et al. (43) in the San Antonio Family Heart Study. One was near marker *D17S1293* (LOD = 2.33) and the other was close to *D17S786* (LOD = 1.34). In Pima Indians, a QTL for fat percentage was identified at adjacent marker *D17S785* (44). In a study conducted in Chinese subjects, Cheung et al. (45) found a QTL for abdominal obesity-metabolic syndrome at 17p12 that was associated with hypertension. In a subsequent study, they found ~10 single nucleotide polymorphisms in the region surrounding this QTL (~3 kb) to be associated with hypertension (46).

The region of p12–13 on chromosome 17 consists of several positional candidate genes associated with adiposity: glucose transporter 4 (47,48), hyaluronic acid-binding protein 1 (a putative adiponectin binding protein) (49), and glucagon-like peptide 2 receptor (50). Also, sterol regula-

tory element binding transcription factor 1 is located on chromosome 17p11.2, and mutations in this gene have been associated with obesity and type 2 diabetes (51). Collectively, these studies indicate the importance of a gene or genes in the region of p12–13 of chromosome 17, with reference to adiposity-related traits.

A suggestive QTL for CCK was observed at chromosome 4q34–35, with a LOD score of 2.2. Chromosome 4 has also been associated with obesity-related traits. Gorlova et al. (52) found a QTL for BMI and imprinting in children and young adults. In a study by Bell et al. (53), severe obesity (BMI > 35) was linked to chromosome 4q in French whites. In another genome-wide scan for obesity-related traits in African-American and white families, Rice et al. (54) reported linkage for subcutaneous and visceral fat in this region. Interestingly, the one LOD-support interval of this signal harbors several important obesity-related positional candidate genes such as carboxypeptidase (17), neuropeptide Y1 receptor, and neuropeptide Y5 receptor (55). In addition, genes such as neuropeptide Y2 receptor (56) and uncoupling protein 1 (57), are mapped to 4q31 that is very close to the region of our signal.

In summary, there was a significant contribution of additive genetic effects to the variation of plasma levels of CCK. The identification of a QTL for plasma CCK on chromosome 17 is important, as several obesity-related traits have already been mapped to this region.

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