Absence of linkage between $\dot{V}O_{2max}$ and its response to training with markers spanning chromosome 22

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ABSTRACT

GAGNON, J., M.-A. HO-KIM, Y. C. CHAGNON, L. PÉRUSSE, F. T. DIONNE, A. S. LEON, D. C. RAO, J. S. SKINNER, J. H. WILMORE, and C. BOUCHARD. Absence of linkage between $\dot{V}O_{2max}$ and its response to training with markers spanning chromosome 22. *Med. Sci. Sports Exerc.*, Vol. 29, No. 11, pp. 1448–1453, 1997. An extensive search for linkage between DNA markers and the response of $\dot{V}O_{2max}$ to training has recently been launched in the HERITAGE Family Study. This is the first report on a genome-wide search strategy to locate chromosomal regions and positional candidate genes for cardiorespiratory endurance phenotypes. Linkage between seven markers spanning chromosome 22 spaced approximately 10 cM apart (D22S264, D22S274, D22S301, D22S304, D22S421, IL2RB, and PDGFB) and $\dot{V}O_{2max}$ at baseline, as well as its response to endurance exercise training, was examined using the sib-pair linkage method. Markers were genotyped in at least 210 sib-pairs derived from 128 adult brothers (25 ± 6 yr; mean ± SD) and 138 sisters (24 ± 6 yr) from 86 Caucasian families. $\dot{V}O_{2max}$, maximal heart rate, and maximal oxygen pulse were measured during stationary cycle tests before and after a standardized 20-wk endurance training program. On average, the initial $\dot{V}O_{2max}$ was 2654 ± 767 mL·min^{-1} while training increased $\dot{V}O_{2max}$ significantly by 430 ± 239 mL·min^{-1} or 16% ($P < 0.0001$). The $\dot{V}O_{2max}$ response was adjusted for age and initial $\dot{V}O_{2max}$. No evidence of linkage was found between any of these markers on chromosome 22 and $\dot{V}O_{2max}$ or its trainability.

HERITAGE FAMILY STUDY, ENDURANCE TRAINING, GENETICS, HUMAN, MICROSATELLITE MARKERS

Based on genetic epidemiology studies, the heritability of cardiorespiratory endurance phenotypes is thought to be about 25 to 40% for phenotypes adjusted for age, gender, and other relevant concomitants (3). These studies were based on direct measurements of $\dot{V}O_{2max}$ in parents and their children (17) and on pairs of brothers, pairs of dizygotic (DZ), and monozygotic twins (MZ) (2). Using a smaller series of twin subjects, Fagard et al. (10) reported a heritability of 66% when the data were adjusted for body weight, skinfold thickness, and sports participation. It remains to be seen if the genetic effect is oligogenic or polygenic, with several genes each contributing in a minor way to the human variation observed.

It is well documented that $\dot{V}O_{2max}$ can be increased by aerobic exercise training (24,26). However, there are large individual differences in the response to regular exercise. For example, following a 20-wk endurance training program, the range of training improvement in $\dot{V}O_{2max}$ was 5% to 88% (18). A series of endurance training experiments realized with sedentary subjects and a total of 50 MZ twin pairs indicated that there were large interindividual differences in the response to endurance training but that variation in response to training was familial and largely determined by genetic factors (1,13,23). In other words, some genotypes are more sensitive to aerobic training than others (3).

It is hypothesized that there are genes affecting cardiorespiratory endurance and its response to regular exercise, although we are unable to define precisely the genes in terms of candidate genes or candidate genomic regions at this time. The HERITAGE Family Study is a study designed to provide significant new information on the genetic basis of adaptation to exercise training (4). As only a fraction of the human genes are presently identified, one can easily miss true unknown candidate genes. For these reasons, a genome-wide search was initiated since it is an important tool to cover a larger range of chromosomal regions encoding potential candidate genes. This paper reports our first results using such an approach. We started with chromosome 22 as it is the

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TABLE 1. Characteristics of the subjects for parent and offspring generations.

	Parent				Offspring			
	Men (N = 86)		Women (N = 86)		Men (N = 128)		Women (N = 138)	
Trait	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age (yr)	52.8	5.2	51.6	5.2	24.7	5.9	24.3	6.0
Weight (kg)	87.8	14.6	72.8	13.8	81.9	16.5	63.1	12.4
Height (cm)	176.0	6.1	162.3	6.3	179.3	6.0	164.7	6.3
BMI (kg/m^2)	28.3	4.3	27.6	4.9	25.4	4.8	23.2	4.1
$\dot{V}O_{2max}$ (mL)	2603	433	1626	278	3318	506	2026	301
$\dot{V}O_{2max}$/kg	29.9	5.1	22.9	4.9	41.8	8.4	32.6	5.3
Max O_2 pulse	15.0	2.4	9.4	1.6	17.2	2.6	10.6	1.6
$\Delta\dot{V}O_{2max}$ (mL)	370[a]	223	285[a]	176	495[a]	260	369[a]	199
ΔMax O_2 pulse	2.3[a]	1.4	1.6[a]	1.0	2.9[a]	1.5	1.9[a]	1.1

[a] Changes between pre and post training are significantly different at $P < 0.0001$.

shorter chromosome and few marker were necessary to cover it. We have screened the long arm of chromosome 22 using seven markers to identify areas showing linkage with $\dot{V}O_{2max}$ and maximal oxygen pulse as phenotypes of interest in a sedentary state and in response to a 20-wk endurance training program.

METHODS

Subjects. The HERITAGE Family Study cohort has been previously described (4). The subjects came from families that included the natural mother and father (aged 65 or less) and at adult offspring, 16 yr of age or older. This paper describes the results from the first 86 Caucasian families studied at the four Clinical Centers (Arizona State University (Indiana University since January, 1996), Laval University, University of Minnesota, and the University of Texas at Austin). To be enrolled in the study, subjects had to be healthy and sedentary, meet a set of criteria (4), and pass a physician-administered physical examination, including a 12-lead electrocardiogram (ECG) during a maximal exercise test (4). Subject characteristics are presented in Table 1. The study protocol had been previously approved by the Human Subjects Committee at each of the four Clinical Centers. Informed consent was obtained from each subject.

Exercise tests. Two maximal exercise tests were administered both before and at the conclusion of the training period. All tests were conducted on a SensorMedics Ergometrics 800S cycle ergometer (Yorba Linda, CA) which was connected to a SensorMedics 2900 metabolic measurement cart. During each exercise stage, gas exchange variables ($\dot{V}O_2$, $\dot{V}O_2$,$\dot{V}E$, and RER) were recorded as a rolling average of three 20-s intervals. The maximal exercise tests were conducted with at least 48 h between tests. Subjects exercised at a power output (PO) of 50 W for 3 min, followed by increases of 25 W each 2 min until volitional exhaustion. For older, smaller, or less fit individuals, the test was started at lower PO (40 W), with increases of 10 to 20 W each 2 min thereafter. In the second test, subjects exercised for 8–12 min at an absolute PO of 50 W and at a relative PO requiring 60% of their $\dot{V}O_{2max}$ determined in the first test. They then exercised for 3 min at a relative PO that was 80% of their $\dot{V}O_{2max}$, after which resistance was increased to the highest PO attained in the first maximal test. If subjects were still able to pedal after 2 min, PO was increased each 2 min thereafter until they reached volitional fatigue. Heart rate was determined using the electrocardiogram and values were recorded during the last 15 s of each stage.

After the maximal and submaximal-maximal tests were completed, both tests were averaged if $\dot{V}E$, HR, $\dot{V}O_2$, and $\dot{V}O_2$ were within 5% of each other. If the values between both tests were not within 5%, then the test with the higher $\dot{V}O_2$ was chosen. The criteria for $\dot{V}O_{2max}$ were: RER $>$ 1.1, plateau in $\dot{V}O_2$, and HR within 10 beats·min^{-1} of the maximal level predicted for age. Maximal oxygen pulse (max O_2 pulse) was calculated using $\dot{V}O_{2max}$ divided by the heart rate obtained during the last 5 s of the maximal tests. Determinations of the maximal heart rate and $\dot{V}O_2$ were highly reproducible with intraclass correlation Coefficient reaching 0.88 and 0.97, respectively (J. S. Skinner et al., submitted to *Med. Sci. Sports Exerc.*). The technical error was 5 beats·min^{-1} and 120 mL·min^{-1} corresponding to coefficients of variation of 3% and 5%, respectively.

Training program. Following the pretraining testing periods, subjects participated in a 20-wk exercise training program using standardized cycle ergometers. Details of the training program have been reported elsewhere (4). Briefly, participants trained an average of three times per week, starting at a HR representing an intensity of 55% of their initial $\dot{V}O_{2max}$ for 30 min during the first 2 wk of training, and progressed to 75% of their initial $\dot{V}O_{2max}$ for 50 min during the last 6 wk. At mid-training ($\sim$ 10 wk), a blood sample was obtained from each subject and permanent lymphoblastoid cell lines were established for the extraction of DNA.

Microsatellite markers. Seven microsatellite markers (D22S264, D22S274, D22S301, D22S304, D22S421, IL2RB, and PDGFB) were selected from different sources (5,6,9,12,22) to span the long arm of chromosome 22 according to the maps from NIH/CEPH Collaborative Mapping Group (21) and the Genome Data Base (11). PCR (polymerase chain reaction) and gel electrophoresis were carried out according to the Généthon

TABLE 2. Description of the markers spanning the long arm of chromosome 22.

Locus	Map Distance[a] (Mb)	PIC[b]	Number of Alleles[c]	Size Range (bp)
D22S264	17.32	0.86	12	186–208
D22S421	21.75	0.82	14	200–218
D22S301	24.26	0.76	10	149–177
D22S304	30.71	0.79	11	107–129
IL2RB	39.43	0.83	12	139–163
PDGFB	42.18	0.57	15	82–98[d]
D22S274	46.50	0.80	11	196–216

[a] The markers are ordered by their distance from the *p*-telomere of the chromosome in megabases (Mb). These locations are constructed by the LDB program from all the genetic and physical data that are available from each locus (7).
[b] The polymorphic information content for each marker was computed using 172 unrelated individuals for the parental generation.
[c] Number of observed alleles in the parental generation.
[d] Imperfect dinucleotide repeat has been observed for this marker (see Table 3).

procedures (12). Briefly, amplification was done in 96 wells microtiter plaques using 250 ng genomic DNA, 20 pmol of each primer, 125 uM dNTPs, and 0.4 U Taq polymerase (Perkin Elmer, Roche Molecular Systems, Branchburg, NJ) in PCR buffer (100 mM Tris-HCl pH 8.3, 15 mM $MgCl_2$, 0.5 M KCl, 0.01% gelatin) for a final volume of 15 μL. PCR cycles consisted of 1 cycle at 95°C for 2 min, 55°C for 1 min, 39 cycles at 95°C for 30 s, 55°C for 30 s, and 1 cycle at 72°C for 2 min (EasyCycler, Ericomp, San Diego, CA). For each individual, 10 μL of the PCR products from each marker were pooled, precipitated with ethanol, and resuspended in 5 μL of TE (10 mM Tris, 1 mM EDTA, pH 8.0) to which 5 μL of loading buffer (95% formamide, 0.01% bromophenol blue, 0.01% cyanol blue) were added. Five μl of this suspension were applied to a sequencing gel and following electrophoresis, PCR products were transferred by capillarity onto a nylon membrane (Hybond N+, Amersham, Arlington Heights, IL) and probed with specific oligonucleotides labeled using a chemiluminescent Kit (ECL, Amersham, or DIG, Boehringer-Manheim, Indianapolis, IN). Genotyping was done assisted by computer (ONE-Dscan, Scanalytics, Billirica, MA) after the autoradiograms have been scanned (Scanmaker II, Microtek, Redondo Beach, CA). Mendelian inheritance was confirmed for all markers on all subjects involved in this study.

Statistical and linkage analyses. The effects of training on $\dot{V}O_{2max}$ and O_2 pulse were tested using a repeated measures ANOVA. Before linkage analysis, baseline $\dot{V}O_{2max}$ and O_2 pulse were adjusted for age and body weight using regression procedures applied in each of the sex-by-generation groups. For the response to training, the phenotypes were further adjusted for the baseline values. The residual scores from these regressions were used as phenotypes for linkage analyses. Linkage analysis was performed using the single locus sib-pair linkage method (15). The sib-pair method is a nonparametric method of linkage analysis that requires no *a priori* knowledge of the mode of inheritance of the phenotype under investigation; this represents an advantage for screening linkages for complex quantitative phenotypes such as those related to cardiorespiratory performance. The rationale underlying this method is that, in the presence of linkage between a marker locus and a putative locus influencing the quantitative trait, sib-pairs sharing a greater proportion of genes (alleles) identical by descent (i.b.d.) at the marker locus will tend to have more similar phenotypes than sib-pairs sharing fewer alleles. Thus, under the hypothesis of linkage, the regression of

TABLE 3. Fragment size (bp) pairs and allelic frequencies for seven markers spanning chromosome 22.

	D22S264		D22S301		D22S421		D22S304		IL2RB		PDGFB		D22S274	
No.	bp[a]	AF[b]	bp	AF	bp	AF	bp	AF	bp	AF	bp	AF	bp	AF
1	186	0.188	200	0.013	149	0.020	107	0.264	139	0.007	82	0.026	196	0.003
2	188	0.026	202	0.043	151	0.003	109	0.101	141	0.177	83	0.625	198	0.003
3	190	0.013	204	0.173	155	0.010	111	0.024	143	0.078	84	0.003	200	0.024
4	192	0.010	206	0.363	157	0.010	113	0.003	145	0.048	85	0.036	202	0.068
5	194	0.063	208	0.197	159	0.027	117	0.010	147	0.017	86	0.010	204	0.233
6	196	0.161	210	0.047	161	0.043	119	0.017	149	0.207	87	0.033	206	0.274
7	198	0.069	212	0.047	163	0.203	121	0.068	151	0.170	88	0.003	208	0.159
8	200	0.154	214	0.077	165	0.254	123	0.253	153	0.143	91	0.003	210	0.094
9	202	0.135	216	0.037	167	0.173	125	0.159	155	0.095	92	0.007	212	0.101
10	204	0.112	218	0.003	169	0.090	127	0.084	157	0.041	93	0.033	214	0.034
11	206	0.056			171	0.117	129	0.017	159	0.014	94	0.059	216	0.007
12	208	0.013			173	0.030			163	0.003	95	0.056		
13					175	0.013					96	0.096		
14					177	0.007					97	0.007		
15											98	0.003		

[a] Fragment size in base pair for each dinucleotide repeat.
[b] Allelic frequency.

TABLE 4. Sib-pair linkage analysis results with markers spanning chromosome 22 in the HERITAGE Family Study for $\dot{V}O_{2max}$ and max O_2 pulse at baseline.

		Sedentary State					
		$\dot{V}O_{2max}$[a]		$\dot{V}O_{2max}$[b]		O_2 pulse[c]	
Locus	N pairs	t value	P value	t value	P value	t value	P value
D22S264	238	0.11	0.54	0.02	0.51	−0.32	0.38
D22S301	236	−0.31	0.38	−0.03	0.49	−0.14	0.44
D22S421	224	−1.21	0.11	−0.33	0.37	0.05	0.52
D22S304	232	0.05	0.52	−0.34	0.37	0.23	0.59
IL2RB	210	−0.14	0.44	0.07	0.53	−0.02	0.49
PDGFB	219	−0.33	0.37	−0.29	0.38	−0.36	0.36
D22S274	237	0.05	0.52	0.23	0.59	0.66	0.74

[a] $\dot{V}O_{2max}$ was adjusted for age and sex.
[b] $\dot{V}O_{2max}$ was adjusted for age, sex, and body weight.
[c] Max O_2 pulse ($\dot{V}O_{2max}$ divided by the heart rate at maximum) was adjusted for age, sex, and body weight.

squared sib-pair phenotypic difference on the estimated proportion of genes i.b.d. (π) is expected to be negative, while in the absence of linkage the slope of the regression is expected to be zero. Marker information on both parents and entire sibships was used to estimate π. A one-sided *t*-test was used to test whether the regression coefficient was significantly different from zero. The number of degrees of freedom was based on the number of sib-pairs in each sibship. Sib-pair analysis was performed using the program SIBPAL (version 2.7.2) implemented in the S.A.G.E. statistical genetic software package (25).

RESULTS

The mean and SD of the different phenotypic variables by gender and generation groups are shown in Table 1. A total of 438 Caucasians from 86 families were used for the analysis. Changes in $\dot{V}O_{2max}$ following the 20-wk exercise training program were highly significant ($P < 0.0001$). On average, initial $\dot{V}O_{2max}$ was 2654 ± 767 mL·min^{-1} or 37 ± 8 mL·kg^{-1}·min^{-1} while training increased $\dot{V}O_{2max}$ significantly by 430 ± 239 mL·min^{-1} ($P < 0.0001$) corresponding to a 16% increase. The increases in max O_2 pulse for fathers, mothers, sons, and daughters following exercise training were also highly significant ($P < 0.0001$).

Table 2 identifies the seven microsatellite markers used to cover chromosome 22. The cytogenetic location, i.e., the map distance according to the genome location database (LDB) (7) is presented for each marker. The polymorphic information content (PIC) have been computed using 172 unrelated adults from the parental generation (86 males, 86 females). Except for PDGFB which has a PIC of 0.57, the markers are highly polymorphic. The number of alleles and their respective size range are presented (Table 2). The markers have more than 10 alleles and for each allele, individual fragment size and the allelic frequency obtained for all seven markers are summarized in Table 3.

Tables 4 and 5 show the results of the single locus sib-pair linkage analysis between $\dot{V}O_{2max}$ and max O_2 pulse and the seven microsatellite markers in the sedentary state and in response to training, respectively. For each locus, a minimum of 210 sib-pairs from the offspring generation was available. No linkages were observed with: $\dot{V}O_{2max}$ adjusted for age, and sex; $\dot{V}O_{2max}$ adjusted for age, sex, and body weight; and max O_2 pulse adjusted for age, sex, and body weight in the sedentary state (Table 4).

$\dot{V}O_{2max}$ and max O_2 pulse were also further adjusted for their baseline values for linkage studies of the response to training phenotypes. No linkages were found between these responses to training phenotypes and the seven markers on chromosome 22 (Table 5).

TABLE 5. Sib-pair linkage analysis results with markers spanning chromosome 22 in the HERITAGE Family Study for changes of $\dot{V}O_{2max}$ and max O_2 pulse in response to exercise training.

		Response to Training					
		$\Delta\dot{V}O_{2max}$[a]		$\Delta\dot{V}O_{2max}$[b]		ΔO_2 pulse[c]	
Locus	N Pairs	t value	P value	t value	P value	t value	P value
D22S264	238	0.86	0.80	0.80	0.79	0.85	0.80
D22S301	236	1.04	0.85	0.91	0.82	1.20	0.88
D22S421	224	0.71	0.76	0.66	0.74	1.68	0.95
D22S304	232	1.97	0.97	2.00	0.98	1.43	0.92
IL2RB	210	1.13	0.87	1.40	0.92	0.86	0.80
PDGFB	219	−0.29	0.38	−0.18	0.43	−1.08	0.14
D22S274	237	2.00	0.98	2.19	0.98	1.58	0.94

[a] $\Delta\dot{V}O_{2max}$ was adjusted for age, sex, and initial value.
[b] $\Delta\dot{V}O_{2max}$ was adjusted for age, sex, initial value, and body weight.
[c] Δmax O_2 pulse was adjusted for age, sex, initial $\dot{V}O_2$ value, and body weight.

Putative candidate genes and markers used on chromosome 22

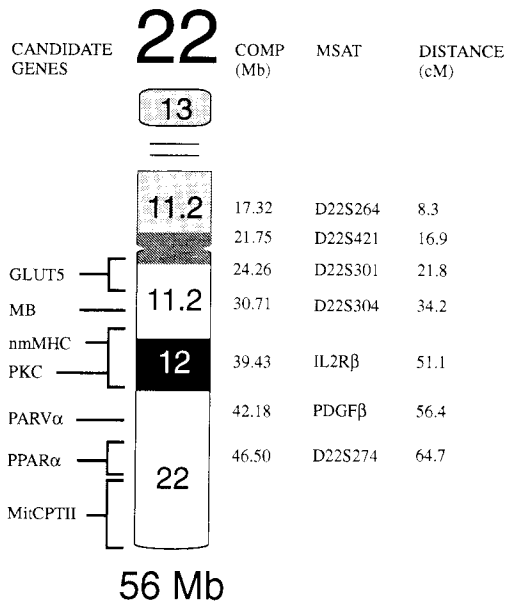

Figure 1—Schematic representation of the putative candidate genes and microsatellite (MSAT) markers used on chromosome 22. The loci are ordered by their distance from the p-telomere of the chromosome in megabases (COMP). These locations are constructed by the LDB program from all the genetic and physical data that is available for each individual locus. GLUT5, glucose transporter 5; MB, myoglobin; nmMHC, transcript highly similar to nonmuscle cellular myosin heavy chain; PARVα, parvalbumin alpha; PKC, transcript highly similar to protein kinase C substrate, heavy chain; PPARα, peroxisome proliferase activated factor alpha; CPTII, transcript highly similar to mitochondrial carnitine palmitoyltransferase II precursor.

DISCUSSION

No linkages have been demonstrated between markers on human chromosome 22 and $\dot{V}O_{2max}$, either in the sedentary state or in the response to endurance exercise training. We have chosen to begin with the last human chromosome 22 because it is the shortest one (54 cM or 56 Mb from NCBI database and 73.8 cM from CHLC database). Seven microsatellites markers were analyzed on chromosome 22 from which two (IL2RB and PDGFB) are microsatellites within interleukin-2 receptor beta chain precursor gene and platelet-derived growth factor, B chain precursor gene, respectively. These two markers can be considered as potential candidate genes affecting the response to exercise.

From the human transcript gene map (HGM) (27), more than 400 cDNA markers have been mapped to chromosome 22. Most of these markers are unidentified transcripts. Among the known genes encoded on chromosome 22, some could be conceived as candidate genes because they relate to muscle metabolism and transport mechanisms. As shown in Fig. 1, the following genes are of interest: solute carrier family 5, member 1, sodium-glucose cotransporter 1 also known as glucose transporter (GLUT5) (25–31 cM); myoglobin located at about 33 cM (MB); transcript highly similar to nonmuscle cellular myosin heavy chain (nmMHC) (31–40 cM); transcript highly similar to protein kinase c substrate, heavy chain (PKC) (31–40 cM); parvalbumin alpha (PARVα) (36 cM); peroxisome proliferase activated receptor alpha (PPARα) (40–45 cM); and transcript highly similar to mitochondrial carnitine palmitoyltransferase II precursor (MitCPTII) (>56 cM). All these candidate genes have been theoretically covered by the seven markers selected to span chromosome 22.

In the HERITAGE Family Study, we propose to investigate a large number of candidate genes. Among those, some will show linkage or association with cardiorespiratory endurance phenotypes but most will not. It should be recognized that the panel of candidate genes will not cover all the genes potentially affecting cardiorespiratory endurance and its response to regular exercise. In fact, we can expect that some unsuspected but known genes will be related to these phenotypes, as well as other genes unknown at this time.

This study constitutes the first attempt to identify linkage relationships between genetic markers and cardiorespiratory endurance phenotypes. Although the results were negative for chromosome 22, whole genome scans have proven to be useful to identify chromosomal regions encoding genes related to oligogenic and multifactorial diseases. Examples of its use come from insulin-dependent diabetes mellitus in which some chromosomal regions have shown positive evidence of linkage to the disease, including the previously known linkage region of the major histocompatibility complex (8,16,19), from noninsulin-dependent diabetes mellitus (NIDDM) in which two significant genomic regions have been evidenced in humans (14,20) and from prostate cancer in which a quantitative trait locus on chromosome 1 has been identified (28). The response to regular exercise may be regarded as a multifactorial oligogenic trait similar to NIDDM. It is not an easy task to target all possible candidate genes for a multigenic trait without deriving *a priori* a genetic hypothesis, e.g., from animal models or Mendelian disorders. Presently, no animal model is available to target by synteny relevant human chromosomal regions for cardiorespiratory endurance, either in the sedentary state or its response to exercise training. Additional markers on other chromosomes will be typed in an attempt to screen the whole genome to identify DNA markers linked to the response to training in cardiorespiratory endurance and risk factor phenotypes. We hope that the genome-wide search on the HERITAGE Family Study subjects will yield several useful linkages with cardiorespiratory endurance and risk factors for cardiovascular disease and diabetes, as well as their responses to exercise training.

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