Word frequency analysis reveals enrichment of dinucleotide repeats on the human X chromosome and [GATA]$_n$ in the X escape region

John A. McNeil, Kelly P. Smith, Lisa L. Hall, and Jeanne B. Lawrence

Department of Cell Biology, University of Massachusetts Medical School, Worcester, Massachusetts 01655, USA

Most of the human genome encodes neither protein nor known functional RNA, yet available approaches to seek meaningful information in the “noncoding” sequence are limited. The unique biology of the X chromosome, one of which is silenced in mammalian females, can yield clues into sequence motifs involved in chromosome packaging and function. Although autosomal chromatin has some capacity for inactivation, evidence indicates that sequences enriched on the X chromosome render it fully competent for silencing, except in specific regions that escape inactivation. Here we have used a linguistic approach by analyzing the frequency and distribution of nine base-pair genomic “words” throughout the human genome. Results identify previously unknown sequence differences on the human X chromosome. Notably, the dinucleotide repeats [AT]$_n$, [AC]$_n$, and [AG]$_n$ are significantly enriched across the X chromosome compared with autosomes. Moreover, a striking enrichment (>10-fold) of [GATA]$_n$ is revealed throughout the 10-Mb segment at Xp22 that escapes inactivation, and is confirmed by fluorescence in situ hybridization. A similar enrichment is found in other eutherian genomes. Our findings clearly demonstrate sequence differences relevant to the novel biology and evolution of the X chromosome. Furthermore, they implicate simple sequence repeats, linked to gene regulation and unusual DNA structures, in the regulation and formation of facultative heterochromatin. Results suggest a new paradigm whereby a regional escape from X inactivation is due to the presence of elements that prevent heterochromatinization, rather than the lack of other elements that promote it.

[Supplemental material is available online at www.genome.org.]
only from XS, but from autosomal chromatin as well, since the latter is at least partially subject to inactivation.

Results

Overview analysis of small word frequencies in the whole genome

There are 131,072 possible nine base complementary word pairs derived from four letters (ACGT). In the masked human genome (~1500 Mb), each word would be present roughly 11,000 times in the genome, or ~7.6 times per Mb, if the frequency of words were random. Figure 1 illustrates the distribution of word frequencies observed. Each possible word is present in the human genome, but there was an extremely wide range of frequencies. While the ubiquitous \([A]\) occurs 472,658 times, words containing multiple bases occur at lower frequencies. Figure 1 shows the distribution of word frequencies (between 1 and 1.5 copies per Mb), 96% contain exactly one CpG. In contrast, of 20,765 words that occur at 10-fold frequencies (between 1 and 1.5 copies per Mb), 96% contain exactly one CpG. In contrast, of 20,765 words that occur at 10-fold frequencies, only 0.06% contain any CpG.

The other major word class present at frequencies notably deviant from normal frequency distribution consists of words derived from simple sequence repeats (SSRs) or microsatellites (repeats of 1–6-bp units). For example, ATATATATA occurs 604 times per MB, in contrast to the median 9mer word frequency of 5.76 words/MB. The abundance and wide distribution of SSRs, which comprise 3% of the genome (Lander et al. 2001) is not well understood, and while often presumed to be a neutral byproduct of mutation, these sequences have also been speculated to have some regulatory or structural role within the chromosome (e.g., Subramanian et al. 2003b; Ellegren 2004). These observations confirm our approach accurately identifies words that are statistically and functionally distinctive in the human genome.

Figure 1. Distribution of word frequencies in the genome. The x-axis represents the frequency of word pairs in the genome, and the y-axis is the number of word pairs that occur at that frequency. The highest peak is largely populated by complex words that contain no CpGs. Words containing two and one CpGs, respectively, populate the first two peaks. The rarest words in the left tail have three or four CpGs, while the shoulder on the right tail is composed of simple sequence, largely mono- and dinucleotide repeats (see arrow).

Enrichment of specific SSRs on XS vs. autosomes

Of the 131,072 possible word pairs, 7644 (6%) occurred on XS at frequencies significantly different from those in an average autosomal sequence (\(\chi^2\) analysis, \(P < 0.01\), see Methods), but the vast majority of these reflect relatively minor differences that correlate with G/C content. Of the 20 words that are at least twofold enriched on X over the autosomes, many overlap into larger sequences. Physical distribution analysis shows that most of these are derived from a tandem repeat (minisatellite) with 189 well-conserved copies of a 37-bp unit that is both A/T and CpG rich, and which has not been previously described (see Supplemental material for sequence). This sequence is at Xq21.2–21.33 and has a Y homolog at Yp11, which are the boundaries of an Xq/Yp homologous region that is a landmark for a recent evolutionary sex chromosome rearrangement (Lahn and Page 1999; Tilford et al. 2001). Other words enriched at least twofold were found to be other minisatellite sequences; thus, no well-dispersed words were found to be enriched more than twofold on X.

We adapted our search method to not only identify words with unusual frequencies on X, but to favor more common and widely distributed motifs, screening out those repeated at one or a few sites and rare words, since the lower the copy number of a sequence, the less meaningful enrichment on any individual chromosome would be. Therefore, we ranked words by the difference in word density (words/Mb) on XS and XE vs. autosomes, which takes both abundance and enrichment into account. We also imposed a coefficient of variance cut-off to verify broad physical distribution (see Methods).

Under these constraints, the most enriched words on XS relative to autosomes are three dinucleotide repeats, \([\text{AT}]_{8}, [\text{AC}]_{n},\) and \([\text{AG}]_{n}\). These are enriched between 1.2 and 1.5 times on the X chromosome. This is more striking when one considers that the copy number is very high already on the autosomes. For example, there are 590 words per MB for \([\text{AT}]_{8}\) on autosomes compared with about 900 per MB on XS, with quite uniform distribution. Since the X chromosome is rather A/T rich and \([\text{AT}]_{8}\) showed more variation among individual autosomes than did AG or AC, we compared the \([\text{AT}]_{8}\) density relative with A/T content for all chromosomes. XS and XE (as well as Y) are clearly

Is bulk X chromosome sequence more different from autosomes than individual autosomes are from each other?

Since the X chromosome is subject to different evolutionary forces, its overall sequence content could be distinct from that of the autosomes. To assess this, we quantified the extent to which each individual chromosome contained words at frequencies different from the genomic average. This involved summing the differences between the individual chromosomal densities and the mean autosomal density (words/Mb), for each possible word, treating enriched and depleted words (relative to the autosomal average) separately. The bulk deviation in word frequencies for each autosome correlates well with its deviation from average G/C content (Supplemental Fig. 1). The XS segment does not have a great bulk of word frequencies that set it apart from autosomes of similar G/C content. Thus, if certain word types are found enriched in the masked XS sequence, this would not be due to a gross overall difference in sequence content, but would suggest a more subtle, specific enrichment. As will be discussed below, the XE segment and the Y chromosome, however, do appear to have differences from the genomic average beyond what would be expected from their G/C content deviation.
outliers in terms of \([\text{AT}]_n\) enrichment, even when compared with similarly A/T-rich, gene-poor chromosomes (Fig. 2); thus, A/T content does not account for this enrichment.

We also performed comparisons of the deviance of the dinucleotide motif word densities from the autosomal mean among all individual chromosomes, (Fig. 3). The X chromosome, both XS and XE, is strikingly more enriched than any other individual autosome for these three dinucleotides. Unlike \([\text{AT}]_n\), the \([\text{AC}]_n\) and \([\text{AG}]_n\) dinucleotides do not vary with gene density or A/T content, and they are present at similar levels on each of the autosomes, with the exception of chromosome 19, which is anomalous in other ways; it is the most gene-rich chromosome (Grimwood et al. 2004) and has increased density of the various classes of SSRs (Subramanian et al. 2003b). As will be considered in the discussion, each of these dinucleotide sequences has been linked to regulation of individual genes and can form usual DNA structures.

Comparison of XE vs. XS

In considering the biological significance of any enrichment on XS compared with autosomes, it is important to also consider its distribution on XS relative to XE. Although XE and XS occupy the same physical chromosome, their transcriptional behavior under silencing conditions is quite different. The XE region as defined here is one continuous 7.5-Mb block, in which all of the genes escape inactivation, whereas throughout the \(-145\ MB\) of XS, most, but not all genes are silenced. The XE region also includes the important pseudoautosomal region (PAR), which is homologous to the PAR on the Y chromosome with which it engages in meiotic recombination in males. Given that this region undergoes recombination in both sexes, similar to an autosome, it provides clues as to whether any differences in the repeat content of the X chromosome might be explained by the more limited recombination of XS.

In this respect, it is important to note that the enrichment of dinucleotide repeats is not restricted to the XS region, but is also seen in XE (Fig. 3). This does not preclude the possibility that this motif could have some role related to X inactivation, particularly since we did not find a spatial difference between escape and silenced genes relative to the XIST RNA territory (C.M. Clemson, L.L. Hall, and J.B. Lawrence, in prep.). However, it does indicate that escape of the XE region from inactivation is not due to depletion of dinucleotide repeats. The fact that both XE and XS are enriched for dinucleotide repeats makes the important point that the enrichment is not easily explained by differences in the rate of recombination of XS and autosomes.

Only eight words that can be described with three motifs are significantly \((P < 0.01)\) enriched on XS as compared with XE: \([\text{AAGGC}]_n\), \([\text{CCCACCCC}]_n\), and \([\text{CAG}]_n\). However, \([\text{AAGGC}]_n\), and \([\text{CCCACCCC}]_n\) are excluded based on their coefficient of variance \((V > 100)\) due to the fact that they are localized large-tandem repeats on XE. The CAG repeat has approximately a twofold enrichment and more even distribution, \([\text{CAG}]_n\) but it encodes polyglutamine common in proteins and is highly correlated with gene density, so the enrichment on XS can be attributed to greater gene density than XE (data not shown). Therefore, it is notable that our search found no 9mer or larger words that met the criteria for abundance and distribution that were significantly enriched on XS over XE. This finding is further noteworthy because it contrasts with the distribution of LINE L1 elements in unmasked genomic sequence, which we confirm are enriched (in unmasked sequence) on XS vs. XE (Bailey et al. 2000). We further this result by showing the enrichment of L1 elements on XS vs. all individual autosomes (Supplemental Fig. 2). Interestingly, our analysis shows that the Y chromosome is also enriched in L1 elements.

The most striking word frequency difference turned out to be a marked enrichment of a specific motif on XE as compared not only with XS, but also to autosomes. The 9mer word frequency analysis revealed that words representing the tetramer repeat \([\text{GATA}]_n\) are overwhelmingly enriched in XE. While there is some enrichment also for the \([\text{ATCC}]_n\) repeat, this was less pronounced and also found in specific segments of other chromosomes (J.A. McNeil and J.B. Lawrence, in prep.), whereas the \([\text{GATA}]_n\) was enriched on XE over all other autosomes and XS. The \([\text{GATA}]_n\) repeats constitute a remarkable feature of the XE region, being almost 12 times more frequent on XE than the autosomal mean. Although the X chromosome in its entirety initially appears somewhat enriched with this sequence, about 1.3 times the autosomal average, when one considers our finding that \([\text{GATA}]_n\) frequency shows an inverse correlation with gene density, the XS is not enriched for \([\text{GATA}]_n\) over autosomes with similarly low-gene density, in contrast to the dramatic enrichment on XE (Fig. 4).

We scanned the RepBase libraries (which is used by Repeat-Masker) for human LINEs and SINEs and found that these interspersed repeats generally do not have GATA, although some do contain dinucleotide repeats. To ensure that the distribution differences seen for these SSR’s was not related to differences in distribution of interspersed repeats, a limited analysis on unmasked sequence involving XE, XS, and chromosome 7 was performed. The same patterns were seen and the enrichment on XS and XE were still significant.

Detailed analysis of [GATA]n distribution

We examined the genomic distribution of this motif using an alternative method, i.e., fluorescence in situ hybridization. Hybridization of a biotin-labeled 21-bp oligonucleotide probe...
well with the region we find to be enriched with [GATA]n. The entire region populated by genes escaping inactivation, which corresponds to the region identified by McNeil et al. (2005) reported a larger 10-Mb region populated on earlier studies (Carrel et al. 1999), a very recent study (Carrel et al. 2005) showing that individual escape genes on XS are separated from the adjacent silenced genes by CTCF boundary sites, unlike contiguous escape genes in the XE region.

Enrichment of GATA in chimps and dog pseudoautosomal regions

Finally, we examined whether the GATA enrichment seen in the escape region of the human X chromosome is also present in the analogous region of other mammalian species. In this case, the mouse model is less informative because mice (Mus musculus) have a much smaller PAR of different evolutionary origin (Perry et al. 2001) and most of the genes that escape inactivation in the human are silenced in the mouse (Brown and Greally 2003). Many genes found in the human PAR are autosomal in mouse, and there are only two escaping genes in the mouse PAR (plus just five others, including Xist, across the whole chromosome). We found no significant enrichment of GATA in the mouse PAR, although the entire mouse genome is more enriched for GATA.

More informative is the analysis of dogs and chimps, because they have pseudoautosomal regions similar to the human. While not fully characterized, some evidence has shown that genes in this region (in both dog andchimp) escape inactivation (Jegalian and Page 1998), as would be expected to provide equal dosage between males and females. We found that the distribution of GATA and dinucleotides on X in chimps (Pan troglodytes) is similar to humans (data not shown). Perhaps most striking is that a marked enrichment in GATA (approximately sevenfold, Supplemental Fig. 3) is present in dogs (Canis familiaris), which have an X chromosome structure and PAR gene content similar to humans (Kirkness et al. 2003). Dinucleotides in dogs are also enriched on X over autosomes (data not shown).

Discussion

Despite the enormous success in identifying conventional genes within the human genome, knowledge of how to relate “non-coding” genomic sequence to the structure and function of a

![Image 69x626 to 405x729]

Figure 3. Individual chromosomal deviation from the autosomal mean frequency of dinucleotide repeat derived 5mer words, expressed as a ratio and plotted on a log scale.

![Image 362x84 to 546x269]

Figure 4. Scatter plot of [GATA]n-derived word density vs. gene density for each chromosome.
chromosome is at a primitive stage. Using an open-ended word frequency approach, we identified distinctive sequence features on the X chromosome; these provide new clues to the unique biology of this chromosome, and to the potential role of certain “junk” DNA. Recently there has been increased interest in the abundant microsatellites throughout the human and other genomes (Subramanian et al. 2003b; Ellegren 2004). The idea that SSRs might have functional significance has been discussed (Epplen et al. 1996) and their capacity to adopt nonstandard DNA forms enhances their attraction as candidates in chromosome structure and regulation. Findings here lend credence to this notion by revealing differences in specific SSR content that correspond to functional differences on the X chromosome. The enrichment of particular SSRs, and not others, suggests specificity that is not easily reconciled with neutral mutational mechanisms involving errors in replication or recombination of highly repetitive DNA.

In our view, the complex biology of chromosome inactivation (and escape from it) is unlikely to be controlled by or dependent upon any one sequence element. For example, there may be motifs that support the propagation of XIST RNA along the chromosome, others that help retain XIST RNA, and still others required for chromatin modifications, DNA methylation, or architectural changes. Substantial attention has been paid to the proposed involvement of LINE L1 elements in these activities (Gartler and Riggs 1983; Lyon 1998; Bailey et al. 2000). We do not interpret our results to rule out a role for LINE elements, but to suggest that motifs other than these interspersed repeats may be involved in X inactivation. In fact, we did not find any widely dispersed words enriched on X over XE or autosomes at levels that have been seen for L1 (Bailey et al. 2000; Ross et al. 2005), and we have further confirmed the L1 enrichment on XS and showed that it is unique by comparing the L1 densities of all of the individual chromosomes, which had not been done previously. We have shown that transcription of widely dispersed repetitive elements appears to be silenced on Xi, as detected by hybridization to Cot-1 RNA (Hall et al. 2002a; C.M. Clemson, L.L. Hall, and J.B. Lawrence, in prep.); this silencing of repetitive elements themselves, not just protein coding genes, may be intrinsic to the mechanism of chromosome inactivation.

A critical consideration, however, is the pattern of enrichment on XS relative to XE and autosomes that should be expected for candidate sequences involved in X inactivation. While it has generally been presumed that the region at Xp22.2–22.3 would be similar to an autosome and have lower levels of putative “X inactivation motifs,” autosomes show substantially more competence for inactivation when in cis with the XIST gene than the XE region, which is markedly resistant. The most dramatic chromosomal sequence difference identified by our comprehensive search was the ∼11-fold enrichment of GATA repeats scattered widely through the 10-Mb XE chromosome segment. This unique enrichment on XE fits with the singular nature of this region and suggests a new paradigm whereby escape from inactivation may be due to the presence of elements that overcome heterochromatinization, rather than lack of those that promote it.

It is also important to consider the impact of recombination differences, since most of the X chromosome does not recombine in male meiosis, which may impact the evolution of sequence content. The enrichment of L1 LINES on XS over XE, and their enrichment on Y, could be consistent with the possibility that they accumulate due to lower recombination on XS/Y (Smit 1999). Since the PAR region of XE undergoes homologous recombination with Y much like an autosome, then neither the accumulation of GATA on XE nor the accumulation of dinucleotides across the X chromosome (including XE) are likely a consequence of the lower recombination on XS. In male meiosis there is an obligatory recombination event between the PARs of X and Y (Burgoyne 1982); thus it is possible that the GATA accumulation here could facilitate or be related to a high rate of recombination (Lien et al. 2000). Although GATA repeats have not been linked to recombination hotspots, however, the [AG]n has (Myers et al. 2005) and we find [AG]n more modestly, but significantly elevated on the XE.

Although there has been substantial interest in identifying sequences involved in mammalian chromosome inactivation, the dinucleotide repeat enrichment of the human X chromosome was not previously recognized. In fact, microsatellites were suggested to be underrepresented (Jarne et al. 1998). Interestingly, an early study pointed to enrichment of dinucleotide repeats related to sex-chromosome dosage in Drosophila (Lowne-haupt et al. 1989), providing evidence that this may occur in other species. GATA tandem repeats were previously reported as the Bkm satellites associated with sex chromosomes of some reptiles (Singh and Jones 1982). Here we have included an analysis of the GATA repeat, which shows that this striking enrichment is indeed present in other eutherians with an analogous PAR, such as dogs and primates.

Subramanian et al. (2003a) reported that [GATA]n is enriched on the human sex chromosomes, focusing on a localized [GATA]enrichment on the Y chromosome as potentially involved in the regulation of a domain of Y-linked genes expressed coordinately during gametogenesis. These authors did not, however, point out the specific enrichment in XE or the potential link to the X escape region, but rather discussed more even distribution across the entire X chromosome. We find that XE has ∼11-fold more GATA than XS, and that the enrichment on XE is substantially greater than that on Y (Fig. 5). However, it remains possible that this sequence feature serves a purpose on the Y chromosome, as genes in both the XE region and the Y chromosome must be expressed from a largely heterochromatic environment.
A remarkable feature of the sequence elements identified here is that they all have the capacity to form nonstandard DNA forms, and there is substantial literature linking them to gene regulation. The \([\text{GATA}]_n\) repeat satisfies the consensus-binding-site motif (WGATAR) for the GATA transcription factor family involved in gene regulation (Patient and McGhee 2002) and recently linked to formation of a higher-order loop in the globin gene (Vakoc et al. 2005). However, the distribution of GATA across the intergenic region of a large chromosome region may reflect a wholly different mechanism than gene-specific regulation through canonical transcription factors. \([\text{GATA}]_n\) satisfies the motif for a SATB1-binding site, an AT-rich region (with G and C on opposite strands) (Dickinson et al. 1992) that has high base-pair unwinding (Bode et al. 1992) and positions at the bases of chromatin loops (de Belle et al. 1998). More recently, SATB1 sites, which can function in either gene repression or activation, have been directly implicated as “landing platforms” or “entry sites” for chromosome remodeling complexes across broad (~50 kb) regions (Yasui et al. 2002; Wen et al. 2005).

The dinucleotide motifs also have unusual and labile physical properties, with dual effects of repression or activation. \([\text{AG}]_n\) has been strongly linked to chromatin regulation and is a polypurine/polypyrimidine motif (PP) capable of forming triplex DNA (Maueler et al. 1998; Ohno et al. 2002). Triplex DNA can link distant sequences and be either a positive or negative regulator of gene expression (Kohwi and Kohwi-Shigematsu 1991). GAGA DNA elements can impact nucleosome packaging (Lehmann 2004), and the Trl (trithorax-like) gene widely involved in developmental regulation encodes the GAGA binding factor. Other evidence shows GAGA is required for silencing by Polycomb group proteins (Strutt et al. 1997), which themselves have recently been linked to mammalian X chromosome inactivation (Silva et al. 2003). X chromosome up-regulation in the male *Drosophila* involves a smaller number of “chromatin entry sites” believed important in chromatin remodeling (Kelley et al. 1999). Interestingly, \([\text{AG}]_n\) is present at the two known such sites at the Rox1 and Rox2 RNA genes, and a recent study directly implicates GAGA factor and/or \([\text{AG}]_n\) in *Drosophila* X chromosome dosage compensation (Greenberg et al. 2004).

\([\text{AT}]_n\) and \([\text{AC}]_n\) have also been linked to specific gene regulation (for example, Rothenburg et al. 2001); these motifs are APPs, which are able to form left-handed or Z-DNA involved in gene expression (Rich and Zhang 2003). A/T rich sequences also show high base-pair unwinding (Bode et al. 1992; Yasui et al. 2002), and ATATAT was initially identified as a core SATB1 contact site within a larger ATC consensus sequence. Thus, the prevalent dinucleotide repeats and their derivatives, particularly for \([\text{AT}]_n\), may relate to binding of proteins involved in chromatin organization, such as SATB1 (Dickinson et al. 1992) and SAF-B (Nayler et al. 1998). Recently, a polymorphism in \([\text{AC}]_n\) and \([\text{AG}]_n\) repeats has been identified as a “regulatory microsatellite” in voles (Hammock and Young 2005) and, interestingly, the *Xist* itself is subject to a 450-bp APP sequence 25 kb upstream of the promoter that suppresses promoter activity (Hendrich et al. 1997).

While we focus here on the X chromosome, it is likely that the sequence elements involved in X inactivation are present at significant levels on other chromosomes where they may be involved in the widespread formation of facultative heterochromatin in different regions of the human genome that occurs throughout development. The ubiquitous nature of SSRs throughout the human and other genomes is often taken as indicative of mere “junk.” Yet, in human language, common words such as “to” or “the” are critical for syntax, modifying the meaning of more specific, but less common words (e.g., “to puzzle” vs. “the puzzle”). We suggest that common motifs such as \([\text{GATA}]_n\) and other SSRs are candidates for common words in the human genome that modify the structure and function of chromosomal
domains. Thus, the concept of a “regulatory microsatellite” may apply not only to specific instances of individual genes, but more broadly to the regulation of heterochromatin and euchromatin throughout the genome.

Methods

Genomic sequences used for word-frequency analysis were derived from NCBI release B33. Two regions of the X chromosome, designated XE and XS, were treated as separate chromosomes. The 7.5-MB XE region includes PAR-1 and most of the evolutionary stratum 4 (defined by Lahn and Page 1999) and stratum 5 (defined by Ross et al. 2005), and XS contains the remainder of the chromosome largely subject to inactivation. Interspersed repeats (e.g., SINEs and LINEs) were removed from all sequences using RepeatMasker (A.F.A. Smit and P. Green, http://ftp.genome.washington.edu/RM/RepeatMasker.html, v.2002/05/15) at normal sensitivity, excluding low-complexity sequence (RepeatMasker -nomatch -no_is -pa 2). A sliding window was used to tally word frequencies, excluding overlapping identical words and words containing “wildcard” codes (anything other than ACGT). The statistical significance of the differences among proportions for each word was evaluated based on a test of the equivalence of Poisson parameters, number of occurrences per 1,000,000 words, using the χ² distribution, and P < 0.01 significance cutoff. The P-values were corrected to compensate for the large number of tests being performed (P' = 1-(1-P)k). Distribution analysis on XS was performed by determining the individual word frequencies in 1-MB bins along the chromosome. The coefficient of variance ((stddev*100)/mean) of bin word frequencies was calculated and a cutoff value (V < 100) was used to eliminate words in highly localized satellites. Words were ranked by the difference between regional (XS, XE) word densities and autosomal word density (words/million words). These analyses were performed on a dual processor pentium III computer running GNU/Linux using custom scripts written in GAWK (release 3.1.1).

For fluorescence in situ hybridization, biotinylated oligonucleotide probes were hybridized (5 pM/ul. probe in 5% formamide, 2XSSC for 2 min. Hybridization was performed as previously described (Clemson et al. 1996; Hall et al. 2002b; Tam et al. 2002) and detected with Texas Red streptavidin and counterstained with DAPI.

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