Evaluation of Microsatellites in Panopsin Gene in Mammals

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ABSTRACT: *Panopsin is a GPCR protein which is sensitive to blue wavelength of light. It is also known as opsin 3 or OPN3 or encephalopsin or ECPN. It is highly conserved among vertebrates. Panopsin protein is encoded by a gene, called OPN3, which is located on chromosome 1 (1q43) in humans. The gene has four exons, three introns and many alternate splice transcript variants encoding different isoforms. This study aims to analyze occurrence and density of perfect microsatellites in the panopsin gene in different organisms and compares the repeats in human panopsin gene with those present in its orthologs in chimpanzee, gorilla, orangutan, gibbon and mouse. Most of the repeats found are dinucleotide and are present in the intronic region. SSR densities show no variance among the studied organisms and most SSRs have low CG%.*

Key Words: : *Panopsin, Encephalopsin, Microsatellites, SSRs, Intron*

Abbreviations: GPCR, G-protein coupled receptor; OPN, opsin; ECPN, encephalopsin; TMT, teleost multiple tissue; RGR, retinal G-protein coupled receptor; cAMP, cyclic adenosine monophosphate; cGMP, cyclic guanosine monophosphate; LED, light emitting-diodes; HCC, hepatocellular carcinoma; SSR, simple sequence repeat; STR, short tandem repeats

Introduction

Environmental cues affect physiology, behaviour, reproductive patterns, migration etc. in most animals. Among these cues, light is an important environmental signal which regulates visual and non-visual functions (Reviewed in (Shichida & Matsuyama, 2009). In order to receive a light signal, many organisms have proteins that are sensitive to different wavelengths of light. These proteins are called photoreceptor proteins or light-sensitive proteins or opsins. Opsins bind with chromophore to form photosensitive pigment. The chromophore, retinal, is vitamin A derivative. On activation by a photon, the opsins trigger a cascade of response through the coupled G-protein. Thus, opsins are light-sensitive G-protein coupled receptor (GPCR) proteins (Reviewed in (Koyanagi & Terakita, 2014; Peirson, Halford, & Foster, 2009; Terakita, Kawano-Yamashita, & Koyanagi, 2012; Terakita & Nagata, 2014).

Based on the subfamily of G-proteins with which opsins couple, they are grouped under eight subfamilies, among which panopsin is a member of Encephalopsin (OPN3)/TMT-opsin subfamily (c-opsins or pteropsins) (Reviewed in (Terakita et al., 2012; Terakita & Nagata, 2014). Panopsins bind 11-*cis*-retinal, which is converted into all-*trans*-retinal after light absorption (Hao & Fong, 1999; Koyanagi, Terakita, Kubokawa, & Shichida, 2002) (Reviewed in (Terakita, 2005). The homologs of OPN3 bind with 11-*cis*-retinal and form blue-sensitive photopigment in vertebrates but forms green photopigment in invertebrates and activates Gi and Go protein, but OPN3 homolog in mosquito binds predominantly to 13-*cis*-retinal instead of 11-*cis*-retinal. 13-*cis*-retinal-binding pigment activates G-protein more efficiently than 11-*cis*-retinal-binding pigment but the most efficient activator is all-*trans*-retinal-binding pigment (Koyanagi, Takada, Nagata, Tsukamoto, & Terakita, 2013). In mammals, especially in humans, retinal photoreceptors express visual opsins (OPN1 and OPN2), OPN3, OPN4, OPN5, peropsin and RGR (retinal G-protein coupled receptor, a homolog of retinochrome) (Reviewed in (Terakita & Nagata, 2014).

Among the opsins, panopsin is one of the ancestral type opsins and is highly conserved among vertebrates (Fischer et al., 2013) and is also known as opsin 3 protein or OPN3 or encephalopsin or ECPN (Blackshaw & Snyder, 1999) or PPP1R116 (Accession No. AF140242). It plays a role in non-visual functions such as circadian photoentrainment and regulation of pineal melatonin secretion (Kasper et al., 2002). Like other opsins, panopsin is a GPCR protein and sensitive to the blue wavelength of the spectrum (Sugihara, Nagata, Mason, Koyanagi, & Terakita, 2016). Panopsin shows its maximum absorption at 460-470 nm. Its homolog activates G_o and G_i subtypes of G-protein, inhibits adenylate cyclase and decreases cyclic adenosine monophosphate (cAMP) concentration (Koyanagi et al., 2013) (Reviewed in (Terakita & Nagata, 2014).

Maximum expression of panopsin is found in the brain of human, mouse, pufferfish, zebrafish, honey bee and annelid besides testes but low amount is also reported in other tissues (Blackshaw & Snyder, 1999). For

example besides retina, panopsin expression is reported in liver, heart, lung, skeletal muscle, kidney, pancreas (Reviewed in (Shichida & Matsuyama, 2009), skin (Delroisse, Duchatelet, Flammang, & Mallefet, 2018), keratinocytes and melanocytes (Haltaufderhyde, Ozdeslik, Wicks, Najera, & Oancea, 2015). In the brain, it is highly expressed in the preoptic, paraventricular nuclei of the hypothalamus, cerebral cortex, some thalamic nuclei, cerebellar Purkinje cells and a subset of interneurons in the ventral horn of the spinal cord. Cerebrum and cerebellum of mouse adults have higher expression of panopsin compared with newborn in mammals (Blackshaw & Snyder, 1999). Expression of *OPN*3 mostly occurs in tissues that are not photosensitive and have less amounts of 11-*cis*-retinal to form photosynthetic pigments. It is reported that transcranial light increases lateral visual network connectivity of brain (Starck et al., 2012), suggesting that transcranial light penetrates the skull, reaches the brain and affects non-visual functions through the expression of OPN3 (Flyktman, Mänttäri, Nissilä, Timonen, & Saarela, 2015).

Panopsin protein is encoded by a gene, called *OPN3*, which is located on chromosome 1 (1q43) in humans (Accession No. AF140242) (Halford et al., 2001). *OPN3* gene has four exons, three introns and many alternate splice transcript variants encoding different isoforms (Haltaufderhyde et al., 2015). Panopsin is 402 amino acids long seven-pass transmembrane protein which is a member of GPCR superfamily. A lysine residue at site 299 (K299) in the 7th helix of panopsin protein binds with a retinaldehyde chromophore via a Schiff base linkage, which helps in phototransduction. The negatively charged glutamate residue at position 113 (E113) stabilizes the positively-charged Schiff base (GenBank: AAK37447.1) (Blackshaw & Snyder, 1999). Phototransduction via panopsin takes place in two parts - Light absorption and G-protein activation. The opsin protein absorbs visible light but the retinal chromophore absorbs UV light. When K299 of panopsin binds with the chromophore, the absorption spectrum of the retinal shifts to visible light. This shift causes photoisomerization of the retinal chromophore from 11-*cis* to all-*trans* form leading to G-protein activation cascade (Reviewed in (Peirson et al., 2009; Terakita, 2005). Activation of G-protein causes closure of cyclic guanosine monophosphate (cGMP)-gated cation channel and hyperpolarization of the photoreceptor cell (Reviewed in (Terakita, 2005) which ultimately converts photic information to physiological response (Reviewed in (Shichida & Matsuyama, 2009).

Panopsin is reported to have many applications. It induces autophagy in the presence of blue light emitting-diodes (LED) irradiation at 465 nm which results in the suppression of the colon cancer cell growth (Yoshimoto et al., 2018). It enhances apoptosis and inhibits 5-fluorouracil resistance, thus improves chemotherapy sensitivity in hepatocellular carcinoma (HCC) (Jiao et al., 2012). By absorbing blue light, panopsin triggers calcium flux leading to a cascade of transduction that stimulates melanogenesis (Regazzetti et al., 2018; Setty, 2018). Panopsin, in addition to OPN2, may be responsible for hair growth when exposed to light of wavelength 453 nm (Buscone et al., 2017). Overexpression of *OPN3* gene in skin epithelial cells of humans is associated with enhanced wound healing by blue light (Castellano-Pellicena et al., 2018). Airway smooth muscle photorelaxation (Yim et al., 2018) and pulmonary vasorelaxation (Barreto Ortiz et al., 2018) are activated by blue light via OPN3 receptors. Moreover, *OPN3* gene is regarded as asthma susceptibility gene as polymorphism in this gene is associated with asthma and atopic asthma (White et al., 2008) (Reviewed in (Agrawal & Shao, 2010).

Microsatellites are tandem repeats of nucleotides of different lengths (Powell, Machray, & Provan, 1996), generally from 1-6 bps (Reviewed in (Hoshino, Bravo, Nobile, & Morelli, 2012). The motif may be repeated up to 60 times (Reviewed in (Goldstein & Pollock, 1997). Microsatellites are also called short tandem repeats (STRs) (Edwards, Civitello, Hammond, & Caskey, 1991) or simple sequence repeats (SSRs) (Reviewed in (Gupta, Balyan, Sharma, & Ramesh, 1996; Oliveira, Pádua, Zucchi, Vencovsky, & Vieira, 2006). SSRs are found in almost all organisms studied so far (Reviewed in (Chambers & MacAvoy, 2000; Ellegren, 2004; Kashi & King, 2006). These are present throughout the genome (Reviewed in (Chistiakov, Hellemans, & Volckaert, 2006) but the distribution is not uniform (Reviewed in (Oliveira et al., 2006). These are mostly present in the non-coding segments of the genome and are very rarely present in the coding sequences. Microsatellites are the hypermutable sequences with mutation rates 10^{-6}-10^{-2} per generation (Levinson & Gutman, 1987) (Reviewed in (Schlötterer, 2000). The mutation rate in SSRs is high due to high chances of replication slippage (Messier, Li, & Stewart, 1996) and unequal crossing over during meiosis (Levinson & Gutman, 1987). Microsatellites have many applications such as in forensics, genome mapping, phylogeny and population studies, conservation biology, diagnosis and identification of human diseases and cancer detection (Dietrich et al., 1996; Hearne, Ghosh, & Todd, 1992; Koskinen et al., 2002) (Reviewed in (Chambers & MacAvoy, 2000; Chistiakov et al., 2006; Jain, Joshi, Jatwa, Sharma, & Mahajan, 2014; Li, Korol, Fahima, & Nevo, 2004; Oliveira et al., 2006).

However, perusal of literature indicates that SSRs have not been investigated in panopsin gene sequences. Since a mutation in panopsin gene may affect its function and lead to disorder in humans, analysis of

sequences that may be susceptible to mutation is important. The present study was done to find SSRs (if any) in human panopsin gene sequence and its orthologues in some mammals like chimpanzee, gorilla, orangutan, gibbon and mouse.

Materials and methods

1. Human (*Homo sapiens*) panopsin (*OPN3*) gene ID was obtained from the National Center for Biotechnology Information (NCBI) database (https://www.ncbi.nlm.nih.gov/gene/) on 08-01-2019.
2. The Entrez ID was submitted to Ensembl genome database version 95 (https://asia.ensembl.org/index.html) (Flicek et al., 2014; Kinsella et al., 2011) to obtain Ensembl gene IDs of human panopsin gene and its orthologues in chimpanzee (*Pan troglodytes*), gorilla (*Gorilla gorilla*), orangutan (*Pongo pygmaeus*), gibbon (*Nomascus leucogenys*) and mouse (*Mus musculus*). Other features such as gene start, gene end, transcript start, transcript end, strand, transcript count, GC%, 5'-UTR start, 5'-UTR end, 3'-UTR start, 3'-UTR end, CDS length, exon region start, exon region end, exon rank etc. associated with each gene, were also obtained from Ensembl genome database version 95 on 08-01-2019.
3. Unspliced panopsin gene sequences of human and its above mentioned orthologues were retrieved using the Ensembl gene IDs on 08-01-2019.
4. The software, SciRoKo (Kofler, Schlötterer, & Lelley, 2007) was used to search perfect SSR with all default parameters except for choosing minimum repeat as 3 in panopsin gene sequences on 10-01-2019.
5. Repeat density per kbp (kilo basepair) in each gene was determined by dividing total number of repeats with gene length for each panopsin gene. Further, it was determined that the repeats are present in the exonic or intronic region by analysing the SSR start and SSR end and comparing these with the gene sequence obtained from Ensembl 95.
6. SSR length was measured based on number of nucleotides between SSR start and SSR end positions in each gene as per SciRoKo output. For SSR CG percentage, total numbers of occurrences of C/G in each SSR unit were considered.
7. SSR motif densities were also calculated and heat maps were produced for representing the densities by using Matrix2png (Pavlidis & Noble, 2003).
8. Using one-way ANOVA, statistical significance was determined using the data of SSR density. A p-value less than 0.05 was considered statistically significant.
9. Correlation analysis was done between gene CG% vs. SSR CG%, gene CG% vs. SSR length, gene length vs. SSR CG% and gene length vs. SSR length.

Results

Mononucleotide repeats less than 8 bp in length were not included in this study. SSR density was found highest in the human gene sequence, followed by the mouse gene (fig. 1).

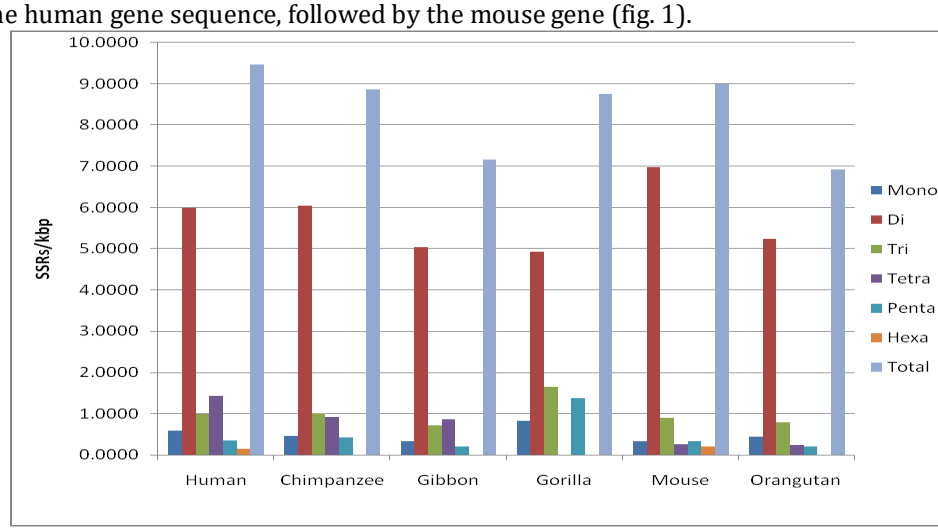

Fig. 1 - Densities of total SSRs and repeat types in panopsin gene in humans and in its orthologues

Mononucleotide repeats, C_n and G_n, are only found in mouse (fig. 2) and dinucleotide $(CG)_n$ repeats are found only in humans (fig. 3). Among trinucleotide SSRs, AAT and ATA are found in the highest amount in gorilla

(fig. 4). Among all organisms used for the study, humans contain most tetranucleotide SSRs (fig. 5). Pentanucleotides are found in very low quantity (fig. 6). Only three types of hexanucleotide SSRs are found in humans and mouse (fig. 7).

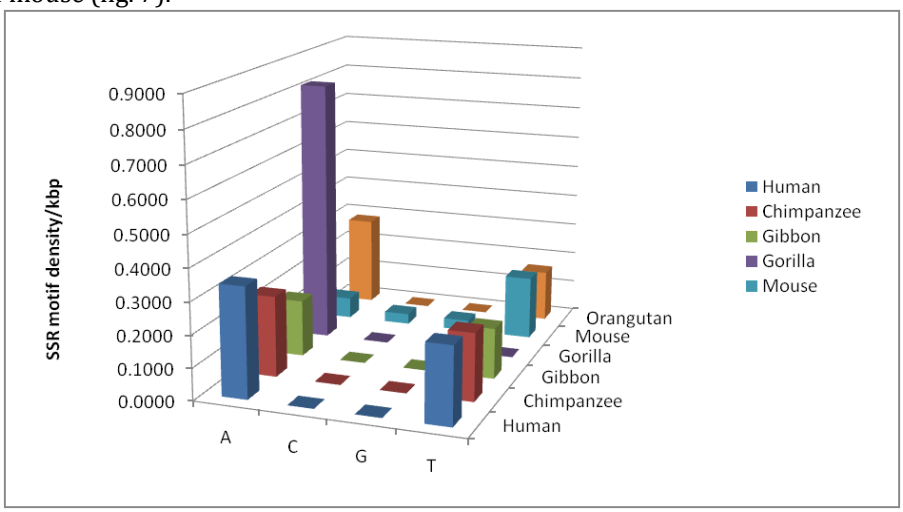

Fig. 2 - Density of each mononucleotide repeat across human and its orthologues

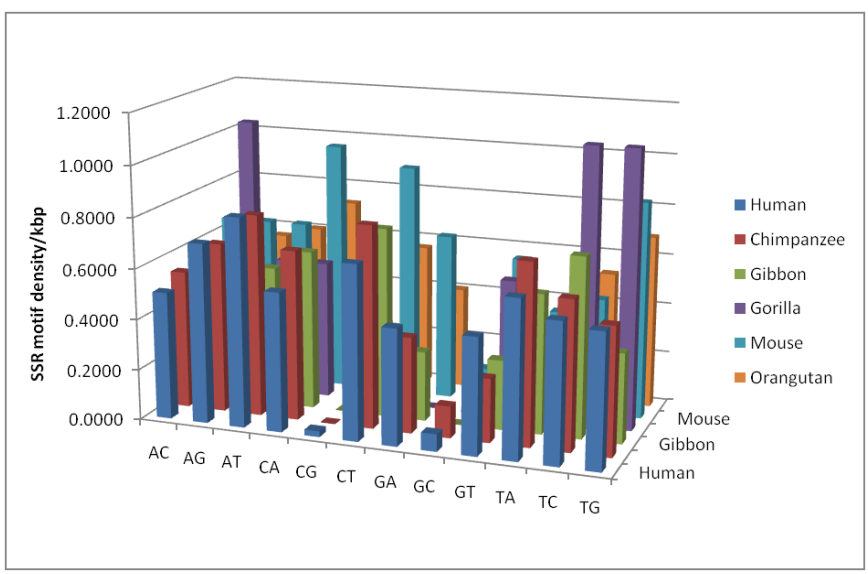

Fig. 3 - Density of each dinucleotide repeat across human and its orthologues

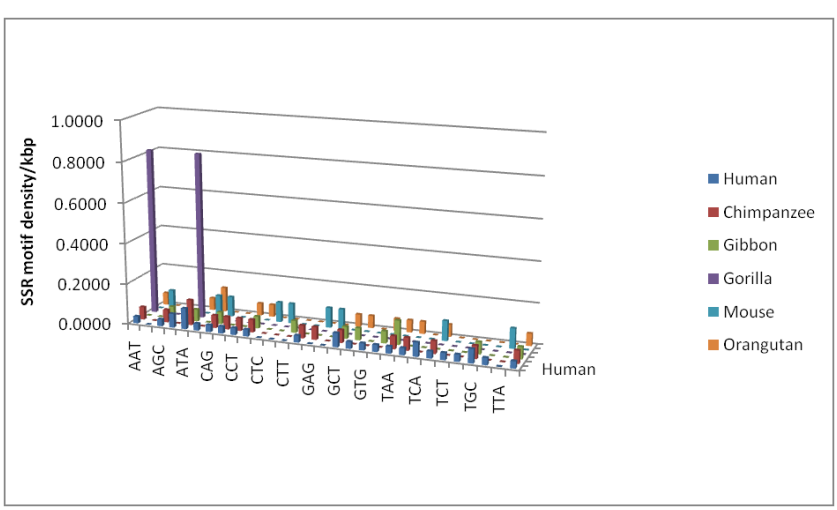

Fig. 4 - Density of each trinucleotide repeat across human and its orthologues

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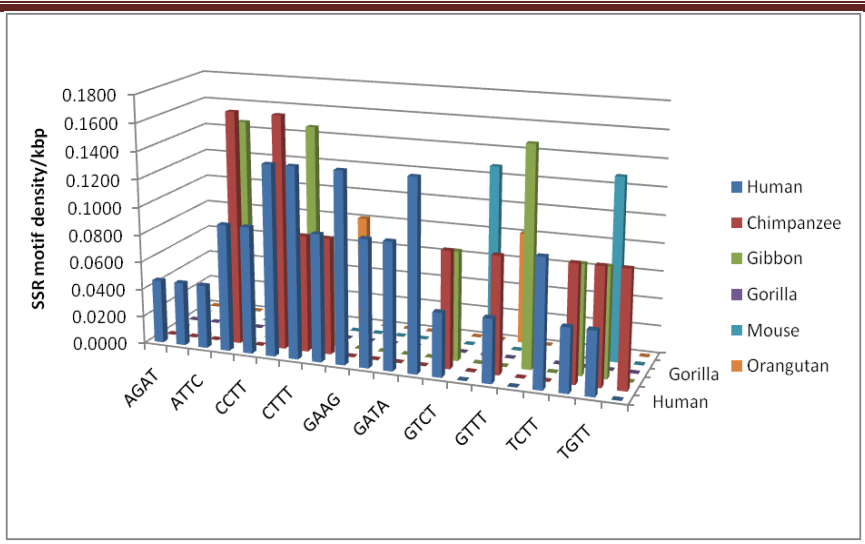

Fig. 5 - Density of each tetranucleotide repeat across human and its orthologues

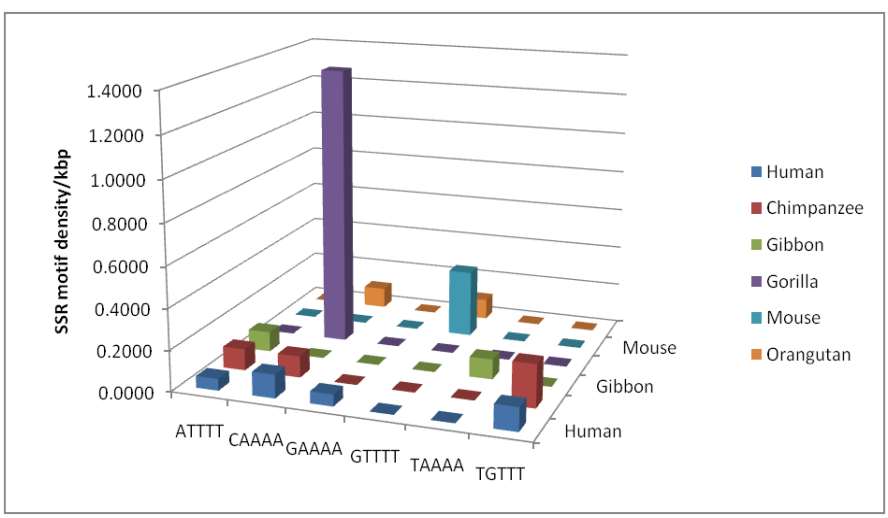

Fig. 6 - Density of each pentanucleotide repeat across human and its orthologues

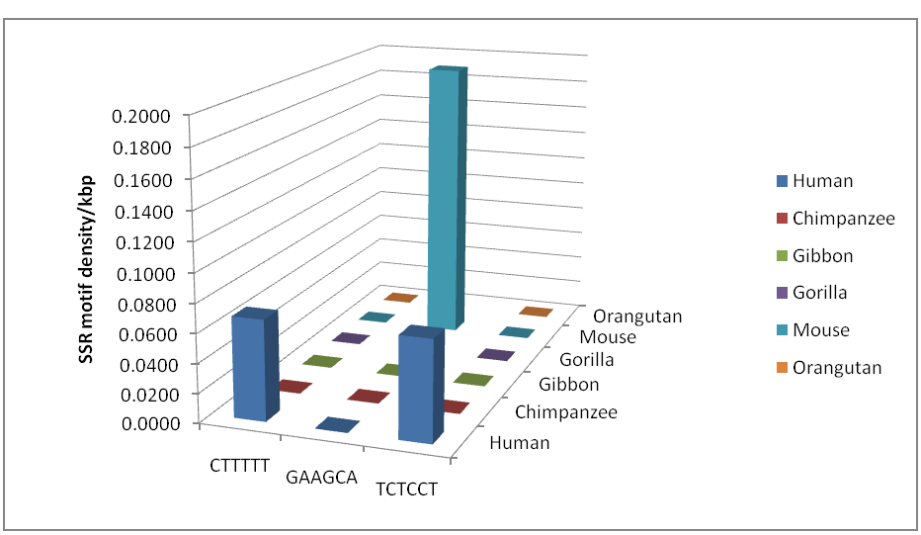

Fig. 7 - Density of each hexanucleotide repeat across human and its orthologues

Dinucleotides are the most abundant SSR present shown in the scale bar colour intensity graph (fig. 8).

Fig. 8 – Motif densities (per kbps) in human panopsin gene and its orthologues. Blank cells show an absence of motif

The longest repeat (44nt) is a tetranucleotide motif in humans and pentanucleotide motif in gibbon. SSR is present mostly in introns. Most of the SSRs have low CG richness. The results from single factor ANOVA gives a p-value more than the α-level selected and F-value is less than F-critical value. Correlation analysis shows a positive correlation between gene GC% and SSR GC%, between gene GC% and SSR length and between gene length and SSR length but a negative correlation between gene length and SSR GC%.

Discussion

SSRs are found to be present mostly in introns. Most of the study revealed that dinucleotides are the most abundant repeats among which (CG)n is the least preferred SSRs in most organisms (Cardle et al., 2000) (Reviewed in (Trivedi, 2004). The present study also shows the same result. Most of the SSRs are found to have low CG richness to avoid mutation due to strand slippage. SSRs are not found to be too long to evade higher chances of slippage. Single factor ANOVA of SSR densities give a result with p-value more than the α-level selected and F-value is less than F-critical value. So, we cannot reject the null hypothesis which means that there is no variance between the groups. It clearly shows that SSRs present in the panopsin gene in human and its orthologs have similar densities and they are related. Correlation analysis between gene GC% and SSR GC%, between gene GC% and SSR length and between gene length and SSR length gives a positive value but between gene length and SSR GC% gives a negative value which shows that SSR length is increasing but SSR CG% is decreasing with increasing gene length. It suggests low CG richness in SSRs to evade strand slippage.

Thus, to the best of my knowledge, this study is the first to analyze some of the mammalian species on the basis of microsatellites or SSRs.

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