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Research Article

Quadruplex Structures In Complex Eukaryotes

Dissecting G-Quadruplexes and I-Motifs in Cis-Regulatory Regions of Mammals and Plants

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Abstract: The evolutionary constraints of a gene consist of *cis*-gene regulatory regions, such as promoters and enhancers, which contribute to the regulation of gene expression. Several genomic and computational studies stated the roles of G-quadruplex and i-motif structures in vital cellular processes like transcription, translation, gene regulation, etc. The formation of these non-B DNA structures is supported by the occurrence of unique repeated sequences. However, many studies lean toward understanding the role of the G-quadruplex, and only recent studies indicated i-motif significance. In this study, we attempted to dissect the enrichment of G-quadruplex and i-motifs in promoter regions of mammals and plants. To this end, we employed the genomic sequences encompassing -500 to +500 region relative to the gene start positions in mammals and plants retrieved from the UCSC browser and Plant Genome database (PlantGDB). We computed the putative G-quadruplexes and i-motifs with well-recognized regular expression sequence patterns. We observed that G-quadruplex motifs showed preponderance in mammals, algal species, namely, green algae, and Chlamydomonas when compared to plants. Contrastingly i-motifs are enriched in both monocot and dicot plants compared to G-quadruplex motifs. The comparative examinations in this study revamp our understanding of the two quadruplex structures and their emerging functional roles in complex eukaryotes.

Keywords: Gene Regulation, Cis-Regulatory Regions, Promoters, G-Quadruplex, I-Motifs

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1. INTRODUCTION

Regulation of gene expression is the most fundamental cellular process to originate phenotypic information from the genotype. *Cis-regulatory* genetic elements of gene regulation in eukaryotes include both primary sequence canonical elements such as promoter motifs, enhancers, CpG islands, etc, and noncanonical secondary structural elements such as G-quadruplexes, low stability, unique rigid and curved DNA. Research from the past half-century now revealed that non canonical DNA structures play a key role in gene regulation in addition to the canonical B-DNA nucleic acid structures. The roles of G-quadruplexes in eukaryotic *cis*-regulation have been now widely accepted. The putative G4-rich sequences were found in both prokaryotes and eukaryotes including humans. These are profoundly present in human telomeric regions of the chromosome, protecting from nuclease degradation.[1] These motifs are widely allocated in various gene locations such as promoter regions, the origin of replication sites, and some parts of the genome like telomeric regions. Dey U et al.[1] well explained the functionality of G-quadruplexes in the cis-regulatory regions of pathogenic bacteria. The tetraplex-forming guanine-rich sequences are also found in promoter regions of the human genome explained by J.L. Huppert et al.[2] Furthermore, G-rich sequences were also found to be novel targets for breast cancer therapy by blocking telomere elongation in cancer cells.[3] G-quadruplexes are formed by four-stranded confirmation forming guanine tetrads that can be embraced by guanine-rich DNA sequences through Hoogsteen hydrogen bonding.[4]In vivo, the G4 structure formation environment is favored by transient disruption of the B-DNA base-pairing model of Watson-Crick during key cellular events like replication, transcription, DNA repair, and recombination. However, the transient disruption of double-stranded DNA during G-quadruplex formation provides the opportunity for the formation of another tetraplex structure called an intercalated motif on the other strand. Sometimes, on the complementary strand of DNA where G-quadruplexes are arranged, i-motifs can also be formed mutually under some thermodynamic conditions.[5]The i-motifs are formed by cytosine-rich sequences due to the intercalation of two parallel duplexes consisting of neutral cytosine and hemi-protonated cytosine (C+)bases held together by hydrogen bonding with an antiparallel orientation.[6]Although some i-motif structures were discovered, recent studies revealed their formation in neutral pH conditions of the cellular environment.[7]These motifs are found to be involved in biological functions like the binding of transcription factors during gene transcription and gene regulation.[8]These are also found in many different cell locations, including nucleus, cytoplasm, telomeres, and promoter regions. Recent studies disclosed that these structures are found in the G1/S phase of the cell cycle.[9]Additionally, i-motifs are responsible for genomic instability in tumor cells and may use as therapeutic targets for cancer.[10]The in vivo surveys of G-quadruplexes and i-motifs suggest that both structures may play interdependent roles during the regulation of gene expression.[11]The significant role of i-motifs in the human genome was explained by Zeraati et al.[11] G-quadruplexes and i-motifs can be characterized by numerous in vivo or in vitro methods such as X-ray crystallography, NMR techniques for structure determination, UV for thermal stability, CD Spectra, fluorescence microscopy. In addition, they are also screened by computational approaches based on regular expressions. In this paper, we carried out a deep investigation on the distribution of G-quadruplexes and i-motifs in the genome sequences of 77 species of plants including 21 algae and 56 mammals to evaluate their distribution.

2. MATERIALS AND METHODS

2.1. Datasets

The datasets of both plants and animals were collected from web-based resources. The mammalian genome cohort including 56 different species like human, dog, cat, rat, monkey, mouse, dolphin, pig, elephant, rabbit, etc., were retrieved from the UCSC genome browser (http://genome.ucsc.edu).[12] 21 plant genome datasets consisting of monocotyledons and dicotyledons were retrieved from the Plant Genome Database with an accessible URL (http://www.plantgdb.org/).[13] The genome sequences −500 to 500 nucleobases relative to gene start sites (where position 0 indicates the gene start site indicated by the database) were retrieved for investigation.

2.2. Computation of G-quadruplex and I-motif

The major aim is to decipher the occurrence of motifs across the sequence and compare between plant and mammalian species. Computation of several non-B DNA structures was reported by a recent tool.[14] However, G-quadruplex and i motifs are not considered separately. The two non-B DNA structural motifs, G-quadruplex and i-motifs, were computed in this study. A four-stranded G-quadruplex structure is formed by runs of G-tracts separated by spacer sequences. Similarly, the tetraplex i-motif structure is formed by runs of C-tracts separated by spacer sequences. Here, we used search motifs $G_{3-5}N_{1-7}G_{3-5}N_{1-7}G_{3-5}N_{1-7}G_{3-5}$ and $C_{3-5}N_{1-7}C_{3-5}N_{1-7}C_{3-5}N_{1-7}C_{3-5}$ for prediction of G-quadruplexes and I motifs. The N in the regular expression indicates N is any of the four nucleobases, A, C, G, or T. We employed in-house Linux shell scripts to compute these structural motifs in -500 to +500 regions relative to gene start sites of different mammalian and plant genomes. A two-sample Kolmogorov–Smirnov test (KS test) has been implemented to see statistically significant differences in distribution between two classes of non-B DNA motifs

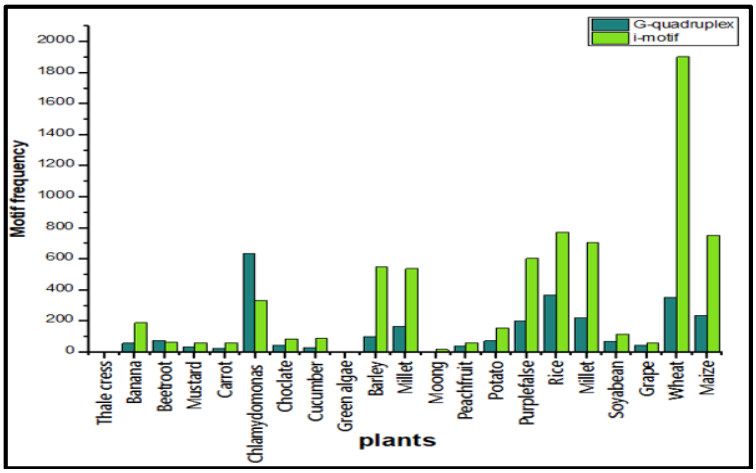
3. RESULTS

The genomic studies of G4 and i-motifs are studied so far using various experimental methods which help in identifying the prevalence of motifs in the required genomic sites. In this computational study, the distribution of G-quadruplexes and i-motifs is analyzed using sequence patterns in plants and mammals. We present our results on G-quadruplex and i-motif preponderances in plants and mammals, indicating their similarities and differences.

3.1. Frequency of G-quadruplexes and i-motifs in plants

The genome information of plants and mammals was collected from the PlantGDB, which provides well-annotated information[13]. This database is useful in collecting data on genomic markers for developing novel agronomic traits.[15] The G-quadruplex and i-motif frequencies within the -500 to +500 regions relative to gene start sites in 21 plant genomes were examined (Figure 1). It was observed that thale cress, green algae, and Moong exhibited low levels of the two non-B DNA motif occurrence when compared to other plants. Meanwhile, cereal grain genomes of wheat, maize, millet, and rice showed

a high enrichment of G-quadruplex and i-motifs. However, within the genomes, there were significant differences in the G-quadruplex and i-motif frequency distributions (KS, $p<0.001$). A greater level of G-quadruplex enrichment compared to i -motifs were observed in Chlamydomonas. Interestingly, the cereal grain crops have i-motif enrichment more than G-quadruplex motifs.

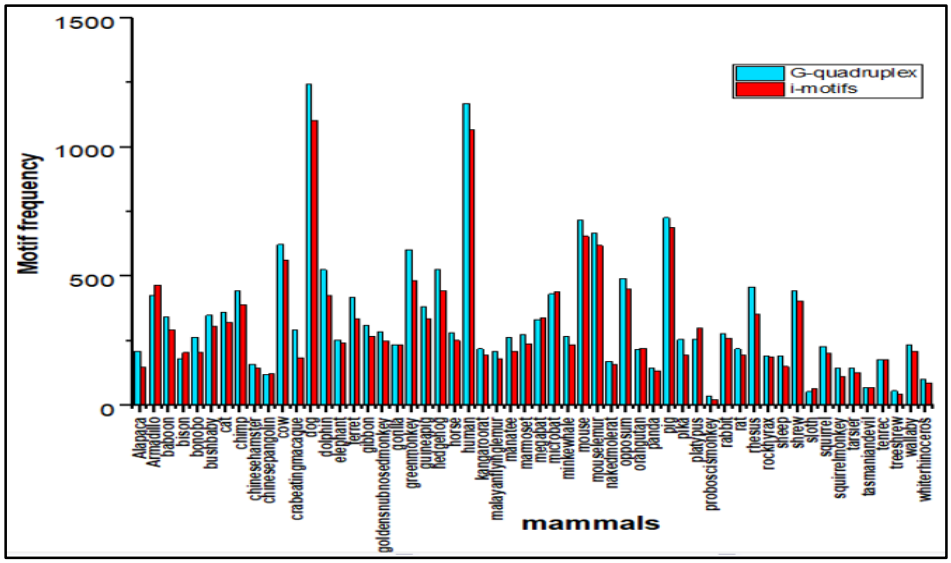


The Y-axis takes the measure of motif frequency in each plant and illustrates that Thale, cress, moong, and green algae have very few numbers of motifs than other plants. Wheat consists of a high number of i-motifs and low G-quadruplexes, whereas Chlamydomonas shows a high peak of G-quadruplex than other plants (KS , p<0.001).

Fig 1: *Comparison of the distribution of G-quadruplexes (and i-motif frequency in plants based on the number of motifs*

3.2. *Frequency of G-quadruplexes and i-motifs in mammals*

Similarly, mammal datasets were also explored using the UCSC table browser and evaluated their motif prevalence using this computational research. It is observed that the G-quadruplexes are more dominant in mammals than i-motifs. Figure 2 reports that mammals like Chinese hamsters, gorillas, humans, mice, dogs, dolphins, and bushbaby contain elevated peaks of G4-rich sequences, whereas some mammals such as microbat, tarsier, and pig showed relatively low peaks. Likewise, armadillo, manatee, naked mole rat, hedgehog, megabat, marmoset, pika, platypus, and tenrec depicted a normal range of i-motifs and very low in gorillas, tarsiers, proboscis monkeys, and white rhinoceros. Our analytical method for mammals clearly shows the motif predominance and depicts that the dog, human have a high number of G-quadruplex and i-motifs and very low in treeshrew, proboscis monkey, sloth, and tasmanian devil in Figure 2.

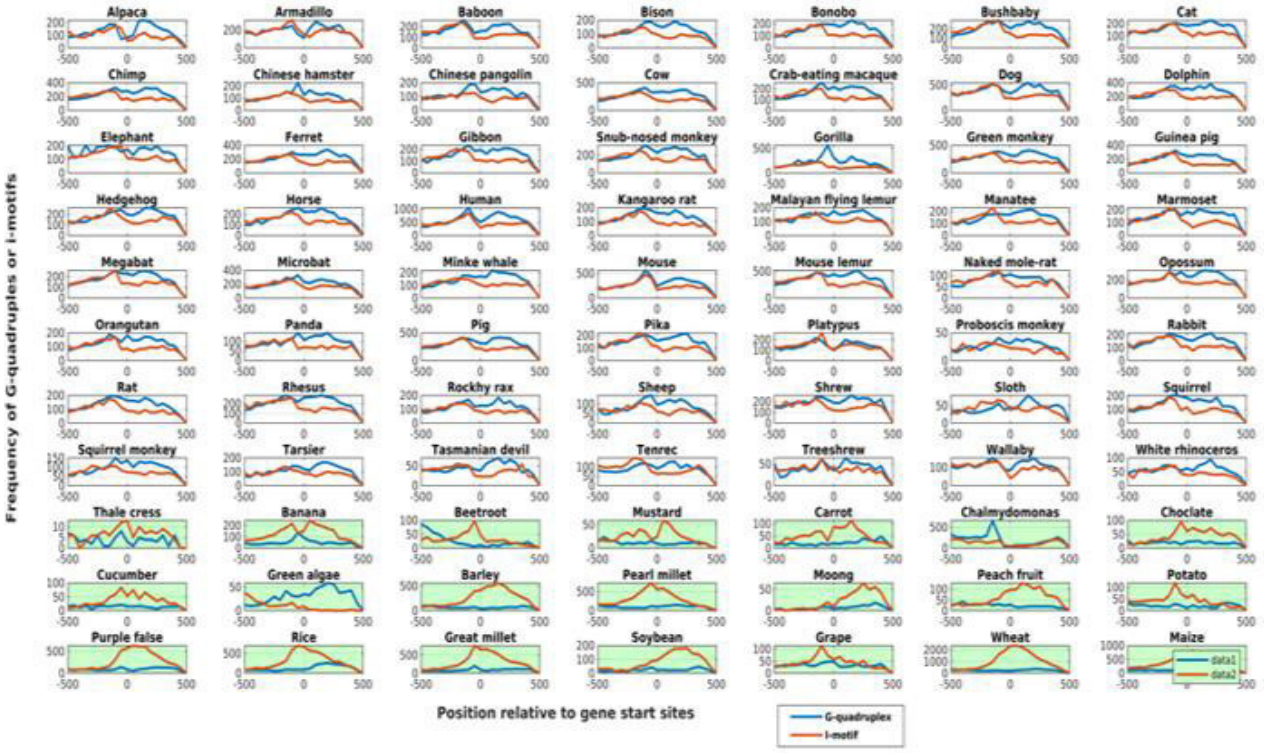


The figure depicts that mammals are enriched with guanine-rich sequences than i-motifs(KS , p<0.001).. Promoter regions in dogs and humans possess a greater number of G-quadruplexes or I motifs than other mammals.

Fig 2: *Comparison of the distribution of G-quadruplexand i-motif frequency in mammals based on the number of motifs.*

3.3. *Comparative positional distribution of G-quadruplex and I motifs in mammals and plants*

Next, we evaluated the positional distribution of the two non-B DNA sequences in 21 plant and 56 mammalian genomes. The distribution of G-quadruplex and i-motifs in plants relative to the gene start sites and their comparison with mammals were described in Figure 3. The green-colored subplots represent plants and the unmasked ones were for mammalian species. Conspicuously, in all mammalian species, high to moderate enrichment of G-quadruplex motifs has been observed. Figure 3 reports that mammals like Chinese hamster, gorillas, humans, mice, dogs, dolphins, bushbaby contain elevated peaks of G4-rich sequences, whereas some mammals such as microbat, tarsier, pig showed relatively low peaks. However, armadillo, manatee, naked mole rat, hedgehog, megabat, marmoset, pika, platypus tenrec depicted a normal range of i-motifs and very low in gorillas, tarsiers, proboscis monkeys, and white rhinoceros. A quite opposite trend has been observed for plants. Our analysis revealed that the plants such as Beta vulgaris (beetroot), Brassica rappa (mustard), Daucus carota(carrot), Theobroma cacao (chocolate), Musa paradisiaca Linn (banana), Cucumis sativus (cucumber), Hordeum vulgare(barley), Pennisetum glaucum(millet), Vigna radiate (moong), Prunus persica (peach fruit), Solanum tuberosum (potato), Brachypodium distachyon (purple false), Oryza sativa (rice), Sorghum bicolor (millet), Glycine max (soybean), Vitis vinifera (grape), Triticum (wheat), Zea mays (maize) contain a high frequency of cytosine-rich motifs than guanine sequences nearin the vicinity of gene start sites. Interestingly, green algae and chlamydomonas exhibited low levels of motif occurrence when compared to G-quadruplexes.



The graph is plotted by considering the frequency of the motif preponderance relative to the position of the start site. The green masked graphs are for plants and unmasked graphs are for mammals. This analysis helps in understanding and differentiating the high motif occurrence in plants and mammals. The differences between the distributions are statistically significant in all species through KS test (P<0.001)

Fig 3: *Comparison of the distribution of G-quadruplexes and i-motifs in mammals and plants*

4. DISCUSSION

DNA exhibits enormous polymorphism in its structure which play key roles in cellular physiology. In our previous research[16], we characterized the structural properties of motifs like DNA stability, bendability, and the distribution of A tract, G-quadruplex, and CpG islands in TATA-containing and TATA-less promoters of mammals namely mice and humans. Ofnote, the study reported the results of G-quadruplexes for 6 model organisms only[16]. In this current research, we evaluated several eukaryotes with main emphasis on similarities and differences between G-quadruplex and i-motif preferences. We observed that G-quadruplex sequences showed a high quantity among mammals and some green algae. In contrast, plants showed high-frequency levels of i-motifs than G-quadruplexes. Our results on plants indicate novel insights on differential motif preferences. In this connection earlier literature in plant genomes reported differences in these motifs. The motif-binding potential of G-quadruplexes having vital roles in gene regulation was done by using a plant model organism "Arabidopsis thaliana (Thale cress)".[17] Research studies on Hordeum vulgare (Barley) clearly state that the DNA-binding proteins in barley seedlings are rich in potential G-quadruplexes, although the genome is rich in i-motifs.[18]. Previous research on rice plants justifies that the G-motifs were higher in monocotyledon plants than dicotyledons.[19]. The characterization of i-motifs, the evolution of transposable elements, and their potential capabilities in rice were explained by Xing Ma et al.[20] Algal species like Chlorophyta and Chlamydomonas showed peak levels of G-quadruplexes around gene start positions. Recent studies of these motifs in algal species suggest that the G4s could act as sensors for UV

radiation in Chlorophyta and other green plants.[21] These motifs are highly preponderant in DNA repair promoter regions and photosynthetic genes that might be responsible for algal physiology.[22] These characteristic distribution profiles of i-motifs in plants may aid in understanding the function of the genomic context, epigenetic regulatory mechanisms, and their intrinsic relationship with the process of DNA methylation for the development of plant genomic traits . A comprehensive survey on computational prognosis of G-quadruplexes in mammals has been reported in a recent literature.[23,24] Extending the previous researches, in, our research we evaluated two motif prevalence. It is observed that the G-quadruplexes are more dominant in mammals than i-motifs. This study may help in finding new molecular targets and new therapeutic techniques by finding the specific locations where the motifs responsible for the disease are present in the genome. Numerous research studies proved that the G-quadruplexes are abundant in the promoter regions of oncogenes like c-MYC.[25,26] The regulation process of early promoters of alphaherpes viruses that affects the human nervous system by G-motifs was clearly explained by Frasson et al.[27] The conservation of G-quadruplexes and their evolution in mammals and non-mammal species were spelled out by using QGRS (Quadruplex forming G-rich sequences)-Conserve method.[28,29] The presence of putative G4 and C-rich sequences in plants and mammals may help understand the inhibitory actions of binding proteins and ligands especially at telomeric regions, which facilitate finding novel therapeutic effects.[30] The physical properties like DNA meltability, flexibility of non-B-DNA structures were discussed in eukaryotic core promoters by a recent research.[31] The pathophysiological studies of neurodegenerative diseases affecting the brain in higher primates like humans can be done by using G-quadruplex motifs and aids in designing new diagnostic ways.[32] Although previous research utilized several non-B DNA in eukaryotes, i-motif has not been considered exclusively[32-34]. We speculate that research on motifs could have several implications in future research. For instance, they might enhance to improvise novel strategies for disease-resistant crop plants like rice or provide new insights on genetic determinants that lead to cancers.[35,36] Current work provides novel updates on non-B-DNA biology and will enhance further research in i-motifs.

5. CONCLUSION

In this study, we focused on uncovering the preponderance of G4-rich and cytosine-rich DNA sequences, which are key motifs in plants and mammals. We reported that the number and distribution of guanine (G4 tetrads) and cytosine-rich sequences are exclusively increased from lower to higher organisms. Interestingly, intercalated motifs are shown more in plants compared to mammals. As these structures are enriched nonrandomly, we surmise that selectively enriched motifs in cis-regulatory regions may facilitate additional regulatory mechanisms. Our research may help in developing new gene regulation methods that can lead to finding new therapies independent of primary genomic sequences. The positional preference of these motifs near the regulatory regions is made interesting for further investigation of motif-mediated gene regulation and their evolutionary relationships within the species. Through this work, the high occurrence of i-motifs in plants compared to mammals is examined, which can help to screen the therapeutic targets that may assist in discovering new medicines.

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7. AUTHORS CONTRIBUTION STATEMENT

Dr. Venkata Rajesh Yella conceptualized the work. Dr. Venkata Rajesh Yella, and Vemparala Renuka gathered and analyzed the data and wrote the manuscript. All authors discussed the methodology and results and contributed to the final manuscript.

8. CONFLICT OF INTEREST

Conflict of interest declared none.

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