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Mathematical Modeling Approaches to Understanding Severe Acute Respiratory Syndrome Coronavirus 2 (SARSCoV-2) DNA Sequences Linked Coronavirus Disease (COVID-19) for Discovery of Potential New Drugs

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ABSTRACT

The novel coronavirus called SARS coronavirus-2 is associated with severe acute respiratory syndrome. At present, intensive care unit treatment and specialized treatment have been not available [1]. Mathematical modeling approaches to understanding the evolution of the DNA sequences of SARS0CoV-2, is an efficient way to design biochemical components interacting with the virus DNA structure. This study aimed to identify specific sets of nucleotides partially "mirror repeats" sets of nucleotides in DNA sequences of SARS0CoV-2. It is suggested that understanding of the "mirror repeats" (Generalized smarandache palindrome sequence (S. Palindrome)) (Dawoudi 2018) sets of nucleotides can be informative in revealing virus gene functions. Understanding more about coronavirus genome functions and transcriptomic level might allow drug designer to design exact treatments.

KEYWORDS

COVID-19; SARS0CoV-2; S. Palindrome; Motif; Oligonucleotide; Frequency distribution; Adaptation studies

1. INTRODUCTION

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was named by the International committee on taxonomy of viruses (ICTV) [2] is causes of new pandemic dis-ease called coronavirus disease of 2019 (COVID-19) [3]. The virus is contributed to respiratory system and 'acute lung symptoms' [4]. The fatality rate of COVID-19 has been correlated with hypertension, diabetes, coronary heart disease, cerebral infarction, and chronic bron-chitis [5]. Up to now "there is no specific treatment available' [6]. Nevertheless, 'the current evidence of potential therapeutic agents, such as' [7]. Chloroquine and Hydroxychlo-roquine/Plaquenil [8], Favilavir [8], Iopinavir plus Ritonavir [9], Remdesivir, Emetine, Homoharringtonine [10], Tocilizumab [11], Peripheral lymphocyte [12], and Angiotensin receptor blockers (ARBs) [13] 'Interferon, Ribavirin, Tocilizumab and Sari-lumab' [14] are promising in blocking infection. However, according to Barlow et al. 'There is currently

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no widely accepted standard of care in the pharmacological management of patients with COVID-19' [15]. In order to obtain efficient treatment, analysis of DNA sequences of SARS0CoV-2 for development and discovery of potential new clinical treatment by mathematical modeling methods, are the essential ways for designing of new drugs. This study has been focused on 'mirror repetitive elements, in DNA se-quence of SARS0CoV-2. 'The sequence of nucleotides which are call Generalized smarandache palindrome sequence (GSPs) or mirror repeats is defined as follows: nucleotides of the form r1 r2 r3 … rn-1 rn rn-1 … r3 r2 r1 with n > 0, where r1, r2, r3, … , rn are consisting various nucleotide of A, C, G or T.' [16] According to Paulson many disease 'are caused by expansions of simple sequence repeats dis-persed throughout the human genome' [17]. This study has demonstrated the range distribution of 'mirror repetitive elements' in SARS0CoV-2 sequence and has shown the possible relevant causes of COVID-19.

2. MATERIAL AND METHODS

In order to analyses of complete genome of SARS0CoV-2, our genomic data has been provided from National Center for Biotechnology. Genomic analyses of SARS0CoV-2 were per-formed by PALINDROM_ FINDER tools (Figure 1). This program has developed for detecting and analysis of possible mirror repeti-tion in gene sequence. This gene come from FL, USA and was submitted on 16-feb-2020 in the public health and infection research group, with ID in GenBank: MT072688.1. This research study was investigated the frequency of "mirrorrepeats" of nucleotide (Generalized Smarandache Palindrome Sequence (S.palindrome)) (Dawoudi 2018) in SARS0CoV-2 sequence with regard to values of relative frequency (percentage of observation). In this research correlation between SARS0CoV-2 gene and these peptides have been considered.

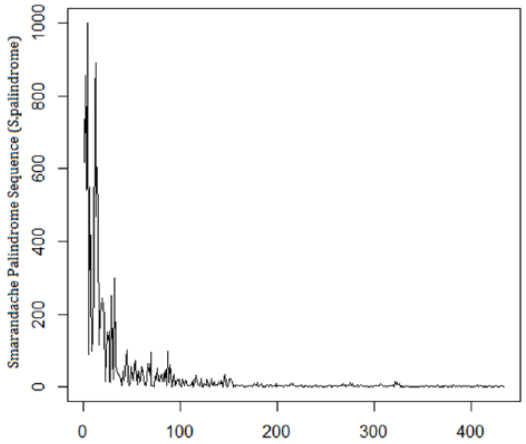

Figure 1: Observed frequencies of 3,4,5,6,7 and 8 S. palindrome in SARSOCoV-2.

Step 1: Identification of dinucleotide S.palindrome

In this step four Homozygotes ('The two alleles are in the same state') [18] including 2844 AA, 884 CC, 1091 GG and 3207 TT was recognized. (Table 1) maximum frequency is 0.399576 (TT) and minimum frequency 0.110142 (CC).

Homozygotes	Number	P. Frequency
AA	2844	0.354348
CC	884	0.110142
GG	1091	0.135933
TT	3207	0.399576

Table 1: Observed frequencies of homozygotes in SARSOCoV-2.

S. Palindrome	Number	P. Frequency	Full Name
tat	620	0.079324	Tyrosine
tgt	857	0.109647	Cysteine
tct	541	0.069217	Serine
ttt	1001	0.128071	Phenylalanine
gcg	88	0.011259	Alanine
gtg	550	0.070368	Valine
ctc	287	0.03672	Leucine
cgc	97	0.01241	Arginine
ggg	134	0.017144	Glycine
gag	296	0.037871	Glutamate
aca	807	0.10325	Threonine
aaa	891	0.113997	Lysine
ata	470	0.060133	Isoleucine
aga	604	0.077277	Arginine
cac	459	0.058726	Histidine
ccc	114	0.014585	Proline

Table 2: Observed frequencies of trinucleotide S. palindrome in SARSOCoV-2.

Step 2: Identification of trinucleotide S.palindrome

The total numbers of trinucleotide S.palindrome are 7816, including: Tyrosine, Cysteine, Serine, Phenylalanine, Alanine, Valine, Leucine, Arginine, Glycine, Glutamate, Threonine, Lysine, Isoleucine, Arginine, Histidine and Proline. The maximum sampling frequency belong to Phenylalanine (TTT) rate 0.128071 and minimum sampling frequency rate is 0.01241 belong to Arginine (Table 2).

Step 3: Identification of tetranucleotide S.palindrome

A fragment of gene with 4 base pairs mirror repetition (e.g. TAAT). The total number of tetranucleotide S.palindrome in SARS0CoV-2 were 2292. The maximum observed frequency was 298 TTTT and minimum observed frequencies is 13 CCCC (Table 3).

S. Palindrome	Number	P. Frequency
gttg	203	0.088569
taat	217	0.094677
tggt	245	0.106894
atta	218	0.095113
caac	193	0.084206
gggg	15	0.006545
agga	89	0.038831
acca	151	0.065881
cttc	130	0.056719
gaag	152	0.066318
gccg	17	0.007417
cccc	13	0.005672
aaaa	251	0.109511
tcct	79	0.034468
cggc	21	0.009162
tttt	298	0.130017

Table 3: Observed frequencies of tetranucleotide S. palindrome in SARSOCoV-2.

Step 4: Identification of Pentanucleotide S.palindrome

A fragment of gene with 5 base pairs mirror repetition (e.g. AGGGA). The total number of Pentanucleotide S.palindrome in SARS0CoV-2 was 1973. The maximum observed frequency was 102 TTGTT and minimum observed frequencies are 1 CGAGC and 1 GGGGG (Figure 2).

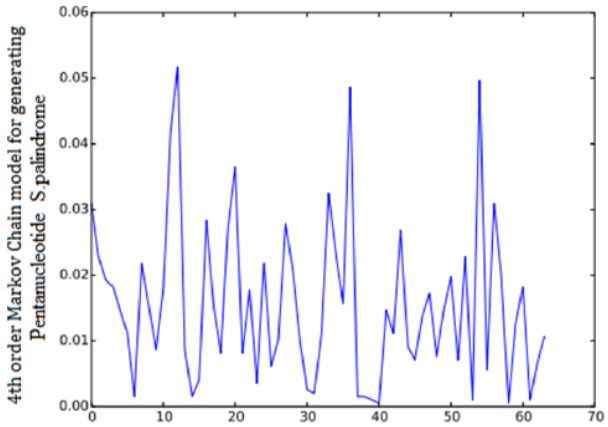

Figure 2: Observed frequencies of pentanucleotide S. palindrome in SARSOCoV-2.

Step 5: Identification of hexanucleotide S.palindrome

A fragment of gene with 6 base pairs mirror repetition (e.g. TGTTGT). The total number of Hexnucleotide S.palindrome in SARS0CoV-2 was 590. The maximum observed frequency was 34 TGTTGT and minimum observed frequencies are 1 AGGGGA and 1 CTCCTC and 1GCCCCG and 1 TCCCCT and 1 TAGGAT and 1 AGCCGA and 1 GATTAG (figure 3).

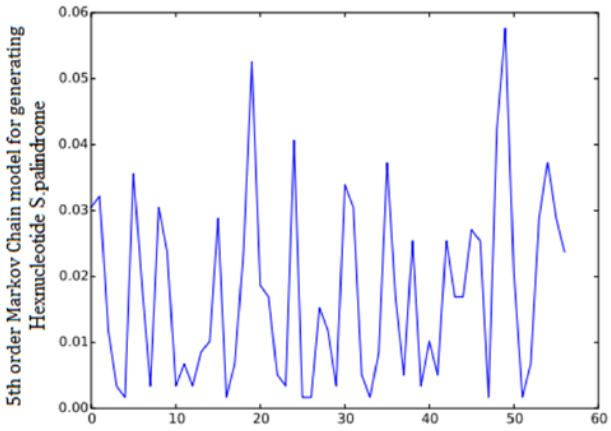

Figure 3: Observed frequencies of hexanucleotide S. palindrome in SARSOCoV-2.

Step 6: Identification of heptanucleotide S.palindrome

A fragment of gene with 7 base pairs mirror repetition (e.g. TGTTTGT). The total number of heptanucleotide S.palindrome in SARS0CoV-2 was 533 (Figure 4). Maximum observed frequencies of heptanucleotide S.palindrome in SARS0CoV-2 is 14 AGGAGGA.

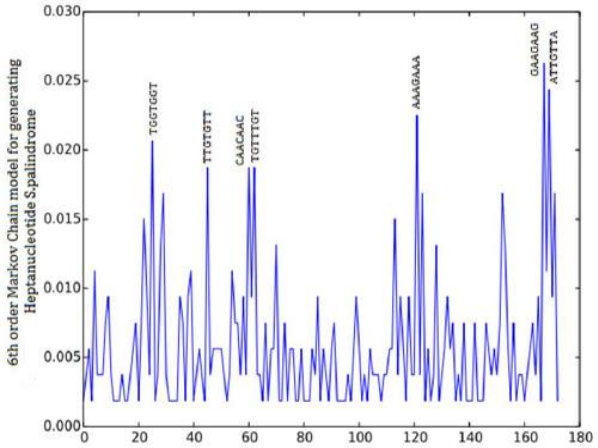

Figure 4: Observed frequencies of heptanucleotide S. palindrome in SARSOCoV-2.

Step 7: Identification of octanucleotide S. palindrome

A fragment of gene with 8 base pairs mirror repetition (e.g.). The total number of octanucleotide S. palindrome in SARS0CoV-2 was 177. Maximum observed frequencies are AAGTTGAA, ATGTTGTA and GACAACAG (Figure 5).

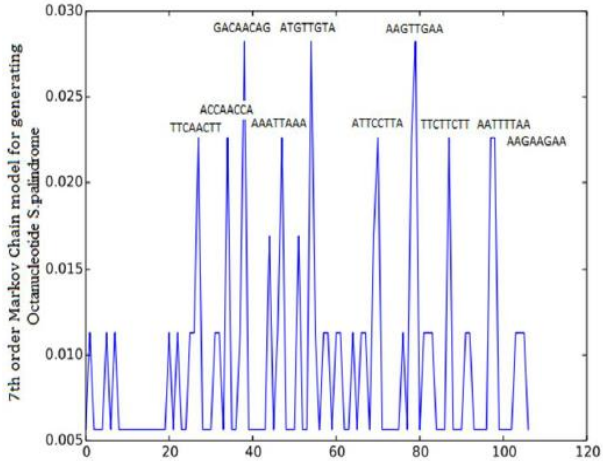

Figure 5: Observed frequencies of octanucleotide S. palindrome in SARSOCoV-2.

3. RESULTS

The study has found 4 Dinucleotide in step 1; 16 Trinucleotide in step 2; 16 Tetranucleotide in step 3; 64 Pentanucleotide in step 4; 57 Hexnucleotide in step 5; 173 Heptanucleotide in step 6; and 107 Octanucleotide S.palindrome in step 7. There are examples shows the crucial role of these peptides in human genes. Szpiech et al. suggested that runs of homozygosity (ROH) 'are associated with an infla-tion of deleterious homozygous variation' [18]. They have suggested that 'African haplotype backgrounds may play a particularly important role in the genetic architecture of complex diseases' [19]. One year later Wang et al. (2020) have shown that 'E1021K homozygous mutation in PIK3CD leads to activated PI3K-Delta Syndrome 1(immunodeficiency disease)' [20]. In other study Guo et al. claimed that 'Trinucleotide repeat containing 6c (TNRC6c) is essential for microvascular maturation during distal airspace sacculation in the developing lung' [20]. The study was conducted by Chuang et al. suggested 'that the consensus SOX2 binding sequence, (T/A)TTGTT, could regulate the expression of COL1A1' [21]. Their finding 'show evidence of BP as a potential therapeutic treatment in pulmonary fibrosis' [22]. 'Zhang et al. [23] found that the binding sites of circRNAs for some RBPs exhibit common patterns, such as the "GAAGAAG"' motif common among several RBPs in-cluding Argonaute 2(Ago2) (associated with colorectal cancer and eunuchism and α-ketoglutarate-dependent dioxy-genase alkB homologue 5 (ALKBH5) (associated to retinitis pigmentosa 71 and Smith-Magenis syndrome)' [24].

As a result there are significant evidence that the higher rate observed frequencies of S.palindromes appear in Step 6 and 7. The maximum observed frequencies of heptanucleotide S.palindrome GAAGAAG(14), ATTGTTA(13), AAAGAAA(12), TGTTTGT(11), CAACAAC(10), TGGTGGT(10). The top three significant heptanucleotide S.palindrome on SARSCoV-2 are: GAAGAAG, CAACAAC and TGGTGGT. Peptide GAAGAAG is included two consec-utive GAA. Tsuda et al. 'revealed that the hTra2-β RRM strongly binds to the [5′-(GAAGAA)-3′] sequence' [25]. Peptide CAACAAC is included two consecutive CAA. Feng et al. (2009) identified GAAGAA 'as the potential binding sites of SRSF10 within the alternatively spliced or flanking exons by using the SELEX approach' [26]. Peptide TGGTGGT is included two consecutive TGG. In other experiment Rosani et al. claimed that 'Among the 104

invertebrate dsDNA viruses present in the dataset, only a truncated chi-motif (TGGTGG) (Chuzhanova et al.) was widely enriched (in around 50% of the viruses, including OsHV-1 but not AbHV-1-AUS)'[27].

4. CONCLUSION

Those characteristics of oligonucleotide and peptides that have been mentioned in this study are mostly related to Nonviral genes. However, exploring the interface between human gene function and coronaviruses gene structure, could be the effective way to better understanding of SARS0CoV-2 functions. This 'adaptation studies' might be efficiency way for understanding aetiology of COVID-19 and 'and provides potential new targets for designing drugs against' SARS0CoV-2 functions.

5. DISCUSSION

In this study, mathematical modeling approaches to under-standing mechanism of SARSCoV-2 was introduced. This model has been bested on S. Palindrome algorithm. There are numerous mathematical models are developed as identification of genomic function. The following computational modeling of SARSCoV-2 sequence are proposed to acquiring better understanding of genomic function in COVID-19, e.g. 'nth order Markov chain (nth-OMC) mapping' and 'Biological model of distribution of prime numbers and using complex network'.

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