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RESEARCH ARTICLE

In silico Approach for the Identification of Mirror Repeats within *ced-3* Gene of *Caenorhabditis elegans*

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Abstract

Objectives: The repetitive elements within the genome of eukaryotes form a significant portion and are associated with various molecular functions within a cell. The goal of our study is to determine a special type of repeat i.e., mirror repeat within complete *ced-3* apoptotic gene and its exons. **Methods**: A simple computational approach was used to search mirror repeats within the eight exons and complete *ced-3* gene of *Caenorhabditis elegans* (*C. elegans*). *C. elegans* is a model organism widely used to study genetics, and developmental biology and *ced-3* is the main apoptotic gene responsible for cell death. **Findings**: We identified 140 mirror repeats within the different regions of the *ced-3* gene of *C. elegans*. These identified mirror repeats are not restricted to the genome of *C. elegans* but are scattered among the genome of *C. vulgaris, Xenopus tropicalis* and *Drosophila melanogaster*. **Novelty:** This research work is the very first endeavor to characterize mirror repeats within the complete *ced-3* gene and its exons. Nobody has been studied mirror repeats within *ced-3* apoptotic gene of *C. elegans*. Mirror repeat has the potential to form triplex DNA and is also associated with several neurological disorders. Forthcoming studies will help us to explore the functions and nature of these identified mirror repeats.
Keywords: Repetitive elements, mirror repeats, *Caenorhabditis elegans* and *ced-3* gene

1 Introduction

DNA molecules act as a storehouse of genetic information in all eukaryotic organisms. It regulates the flow of genetic information and cause variations under the environmental stimulus, which are sometimes non-repairable that leads to events like slipped strand mispairing, mutation and unequal crossing over [1,2]. On the one hand, chemically and structurally, genomic DNA is very stable, while on the other hand, DNA is a dynamic molecule showing constant change in its structure [3,4]. The arrangement of bases in the genome of any organism is essential for its function, and naturally occurring DNA

molecules have a large array of repetitive elements. Repetitive DNA sequences are present in multiple copies within the eukaryotic genome and form a significant proportion of nuclear DNA[5,6]. Within the genome of various organisms, the repetitive DNA play an essential role in the regulation of the cell cycle, gene expression and stability of chromosome and chromosomal rearrangement[7–10]. Eukaryotic genomes consist of different classes of repetitive DNA, either highly repetitive DNA or moderately repetitive DNA sequences, and other repetitive DNA as shown in Figure 1[11]. Highly repetitive DNA consists of satellite DNA and moderately repetitive DNA, is further classified into tandem repeats and interspersed repeats. Tandem repeats are sequences of two or more than two nucleotides that are repeated many times in the head-to-tail fashion, consisting of mini and microsatellites (also called short tandem repeats) and multiple gene family, while interspersed repeats are randomly distributed consisting of SINEs [short, interspersed element] and LINEs [long interspersed elements][12–14].

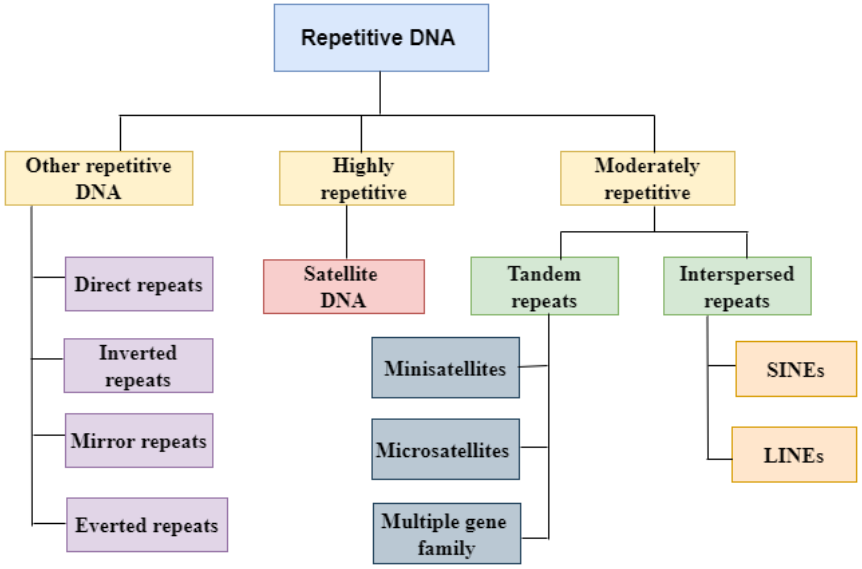

Fig 1. General classification of different types of repetitive DNA

Some other types of repeats like direct repeat, inverted repeats, everted repeats and palindromic sequences are also present within the various genome, and all these repeats have their own significant role. These various types of repeats (tandem repeats, direct repeats and inverted repeats) have potential to adopt wide range of non-canonical B-DNA structures such as cruciform, left-handed Z-DNA, slipped strand and G-quadruplexes structures and these structures have impact on many biological processes like gene regulation, DNA replication, epigenetic modification and recombination[15–17]. Among various type of repeats, a unique type of repeat sequence described as mirror repeat is also reported in various genome. Mirror repeats are DNA segments in which nucleotides are arranged symmetrically around a center. For example – AGCTGGAAGGTCGA in a given nucleotide sequence, both parts are similar and equidistance from the center[18]. Mirror repeats sequences that are rich in polypurine and polypyrimidine sequences have potentiality to make triplex DNA and H-DNA[17]. H-DNA is intrinsically mutagenic in mammalian cells and inhibit transcription initiation, elongation and replications, serve as hotspot for homologous recombination[19–21]. Mirror repeats forming H-DNA helps to point sequences that are vulnerable to big mutation, which in turn helps in understanding the molecular basis of diseases like autosomal dominant polycystic kidney disease and Friedreich's ataxia[22,23]. H-DNA associated with several disorder such as myotonic dystrophy, Friedreich's ataxia, Follicular Lymphoma, Alzheimer's Disease, Amyotrophic Lateral Sclerosis and Autosomal Dominant Polycystic Kidney Disease (ADPKD)[24–27]. One of the unique features of mirror repeat is that its parallel and antiparallel complement remain same, while in normal DNA parallel and antiparallel complement remain different which are shown in Figure 2.

Caenorhabditis elegans (*C. elegans*) is a free-living nematode widely used as model organism to study genetics, anatomy and metazoan development[28,29]. We choose *C. elegans* for our investigation due to its compact genome and has significant matches with human genome[30–33]. We have identified mirror repeats within the *ced-3* gene of *C. elegans*. Different types of repeats sequences with a range of characteristics have been identified, and these repeats are randomly distributed within the genome of *C. elegans*. Our future studies target to find out the role of mirror repeats and their applications in various genomes.

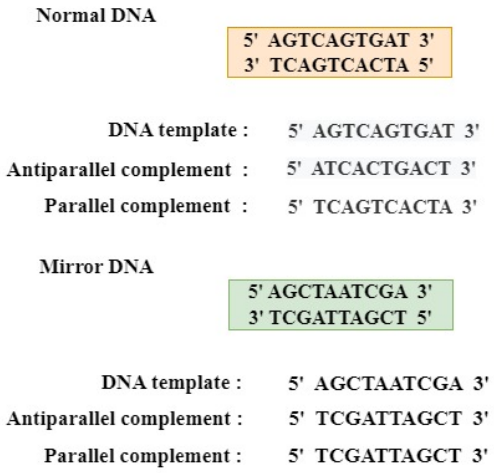

Fig 2. Parallel and antiparallel complement of normal DNA and mirror DNA

2 Methodology

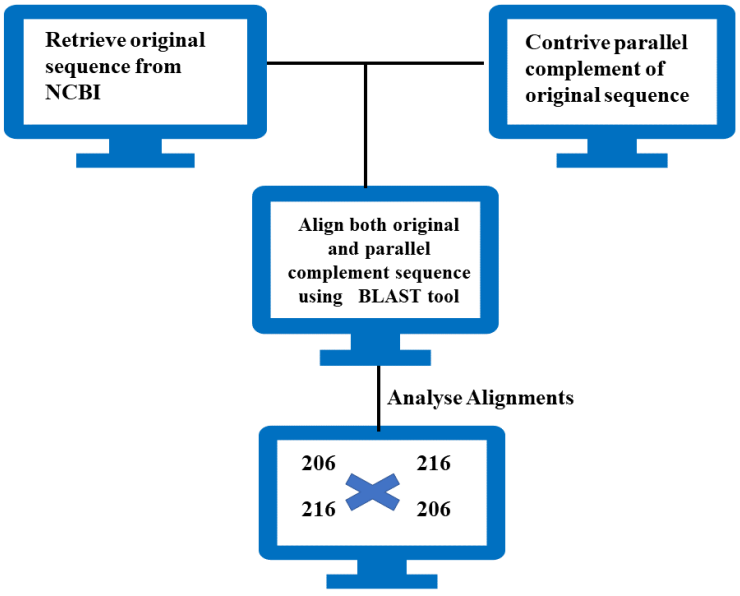

Fig 3. Diagrammatic representations of methodology used to identify mirror repeats

The complete 5877 nucleotides long CDS of the *ced-3* gene of *C. elegans* (Gene Id-178272) was retrieved from NCBI website (National Center for Biotechnology Information) in FASTA format (https://www.ncbi.nlm.nih.gov/). The nucleotides sequences of *ced-3* gene were splitted into different regions of 500 nucleotides. Using the reverse complement tool, a parallel complement of each region of *ced-3* gene was contrived. Using the BLAST tool, the original query sequence and its parallel complement were aligned for homology by selecting a word size limit of 7, and expected thresholds (E value) where maximum number of hits were observed. Mirror repeats can be identified easily as those hits where position number of the query sequence and subject sequence are exactly reversed [34]. Similarly, mirror repeats were analyzed within different exons sequences of *ced-3* gene (exon1, exon2, exon3, exon4, exon5, exon6, exon7, and exon8) as shown in Table 1. Further, mirror repeats were classified into perfect and imperfect mirror repeats. Identified mirror repeats were again searched within the genome of *C. elegans*, and various genome (*C. vulgaris, Xenopus tropicalis* and *Drosophila melanogaster*) using megablast tool.

Table 1. Total number of hits observed within the exons of *ced-3* gene at threshold value of 100

Exons	Length of exons (bps)	Expected threshold value	Number of hits	Number of mirror repeats
Exon1 (1-206 bps)	206	100	8	4
Exon2 (270-415 bps)	146	100	4	2
Exon3 (694-947 bps)	254	100	11	3
Exon4 (2136-2467bps)	332	100	26	6
Exon5 (3380-3593bps)	214	100	9	5
Exon6 (3648-3775bps)	128	100	0	0
Exon7 (4130-4369bps)	240	100	10	8
Exon8 (4846-5877bps)	1032	100	211	36

3 Result and Discussion

Programmed cell death is an important process for normal growth and development of *C. elegans*. It is genetically controlled pathways, regulated by various genes such as *egl-1, ced-4, ced-9* and *ced-3* of *C. elegans*[35,36]. The *ced-3* belongs to cysteine protease family called caspase (cysteine aspartate- specific protease) which is chief caspase responsible for cell death in *C. elegans*. The *ced-4* gene is an activator of *ced-3* gene, whereas *ced-9* inhibit the activity of *ced-3* gene[37,38].

Various past studied have revealed that presence of mirror repeats in many organisms including plants, bacteria and virus[39,40]. But no one selected the model organism *C. elegans* for their study for identification of mirror repeats. So, we have first time identified mirror repeats within the *ced-3* gene of *C. elegans*. In the present research work, a simple bioinformatic approach, was used to contrive mirror repeats present within the *ced-3* genes of *C. elegans* and its exons. This recent developed method is very efficient to characterize mirror repeats. At the E-value of 100, a maximum number of hits were observed, so we fixed this value for identification of mirror repeat. We have identified 140 mirror repeats (Figure 4) within complete *ced-3* gene and 64 mirror repeats within eight exons of the *ced-3* gene.

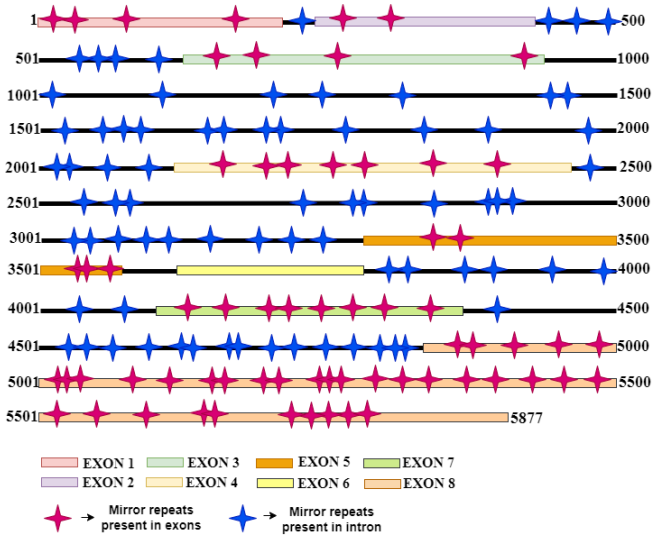

Fig 4. Diagrammatic representations of position of identified mirror repeats within *ced-3* gene of *C. elegans*

In Figure 4, exons are highlighted with different colors, the blue stars represent the position of identified mirror repeats in intron whereas pink color stars represent the position of identified mirror repeats within the exons of *ced-3* gene. We obtained 75 mirror repeats within introns and 65 mirror repeats within exons of *ced-3* gene. The exon 8th, being the largest, contain 36 mirror repeats, whereas exon 6, the smallest one does not have any mirror repeats. Mirror repeats with size varying from 7-12 base pairs are abundantly present within the *ced-3* gene while the occurrence frequency of larger mirror repeat is less as shown in Table 2. We also wish to mention here, we were not able to detect these mirror repeats using mirror repeats finding tool - non-B-DNA motif search tool (nBMST). Here, we wish to mention some mirror repeats are present more than once within the *ced-3* gene as shown in Table 3.

Table 2. Frequency of mirror repeats of different length within the *ced-3* gene

Symbol/Gene ID	Gene Regions(bps)	7-12bp	13-18bp	19-24bp	≥25bp	Total MR's
***ced- 3* /178272**	1-500	9	0	0	1	10
	501-1000	4	1	1	2	8
	1001-1500	6	1	0	0	7
	1501-2000	7	4	0	1	12
	2001-2500	11	1	0	0	12
	2501-3000	8	1	0	1	10
	3001-3500	11	0	0	0	11
	3501-4000	9	0	0	0	9
	4001-4500	10	0	0	1	11
	4501-5000	16	3	1	0	20
	5001-5500	14	5	1	0	20
	5501-5877	8	0	0	2	10

Table 3. Representation of mirror repeats that are repeated more than once within the *ced-3*gene of *C. elegans*

Sequence	Query position		Repeat Copy	Query position	
	From	To		From	To
GAGAAGAG	288	295	GAGAAGAG	3459	3466
ATACATA	2227	2233	ATACATA	5829	5835
AAGAGAA	3025	3031	AAGAGAA	3462	3468
CGACAGC	1555	1561	CGACAGC	4182	4188
GTTGTTG	4280	4286	GTTGTTG	5146	5152
TTCTCTT	4963	4969	TTCTCTT	5039	5045
AATCTAA	5078	5084	AATCTAA	5298	5304
AATTTTAA	1248	1255	AATTTTAA	5270	5277
TCTTTCT	1607	1613	TCTTTCT	5488	5494
GTAAAAAATG	1676	1685	GTAAAAAATG	4555	4564
AATTTAA	2789	2795	AATTTAA	3781	3787
				3991	3997
GTTTTTG	3151	3157	GTTTTTG	3569	3575
TTTAATTT	3368	3375	TTTAATTT	3783	3790
ATTTTTA	3828	3834	ATTTTTA	4626	4632

Identified mirror repeats have different length varying from 7 base pairs to the largest mirror repeat of 58 base pairs. Further the classification of identified mirror repeats was done on the basis of number of spacer element and the arrangement of nucleotides. Perfect mirror repeats have identical sequence around center of symmetry whereas imperfect mirror repeats have mismatch around center of axis. Perfect mirror repeats were further divided on the basis of spacer elements single spacer double spacer and multispacer. Similarly, imperfect mirror repeats may also have a spacer or no spacer elements. The frequency of occurrence of imperfect mirror repeats within *ced-3* gene was less than the frequency of perfect mirror repeats. Out of 140 mirror repeats, 7 imperfect mirror repeats, 14 imperfect mirrors with single spacer, 1 imperfect mirror with single spacer, 34 perfect mirror repeats without any spacer and 84 perfect mirror repeats with single spacer were analyzed within *ced-3* gene of *C. elegans*. The classification and location of some selected mirror repeats in different regions of *ced-3* gene is shown in Table 4. The complete detail of all mirror repeats (140) within different regions of *ced-3* gene is given in **Supplementary table 1**.

Table 4. Classification of selected Mirror Repeats distributed in the complete *ced-3* gene of *C. elegans* (complete list is available in supplementary file)

Symbol /Gene ID	Gene Regions (bps)	Location of mirror repeats	Length	Types of mirror repeats

Continued on next page

Table 4 continued

		Query Start Site		Query End Site		
***ced-3* /178272**	1-500bps	211	GTTTTTAATCGAATAAT AATTTTaaaaaaaaaTT GATAATATAAAGAATATTTTTG	266	56	Imperfect mirror
		391	AAGTTCTTGAA	401	11	Perfect mirror with single spacer
	501-1000 bps	682	CCTTTTTTCC	692	10	Perfect mirror
		761	TTGAGCCCCGCCGG CTACACTTCA-CCGACCCGAGTT	791	37	Imperfect mirror
	1001-1500 bps	1476	TTTTATATATTTT	1488	13	Perfect mirror with single spacer
	1501-2000 bps	1508	AAAAATGTAAAAA	1520	13	Perfect mirror with single spacer
		1659	aaaaaaTGTCGAATAA –TGTAAAAAA	1683	27	Imperfect mirror with single spacer
		1826	AAAACCAAAA	1835	10	Perfect mirror
	2001-2500 bps	2005	GAAAATTAAAAG	2016	12	Perfect mirror
	2501-3000 bps	2791	TTTAAAATTT	2800	10	Perfect mirror
		2809	TGGCAAACGGT	2819	11	Perfect mirror with single spacer
	3001-3500 bps	3048	AATTTGTGTTAAA	3060	13	Imperfect mirror with single spacer
	3501-4000 bps	3814	AAAATCTAAAA	3824	11	Perfect with single spacer
	4001-4500 bps	4096	ACATTTTTAAATG ATAATTAATAAATTTTTGCA	4128	33	Imperfect mirror
		4295	ACTGAAGTCA	4304	10	Perfect mirror
	4501-5000 bps	4691	AACTCATTTAAA AAATTAATTCAA	4714	24	Imperfect mirror
		4809	TTTTAGATTTT	4819	11	Perfect with single spacer
		4829	TTTAAATTAAATTT	4842	14	Perfect mirror
	5001-5500 bps	5011	TACTCATTTCACT TTA-TCAT	5030	20	Imperfect mirror
		5210	CACCCCAACCCCAC	5223	14	Perfect mirror
	5501-5877 bps	5849	AAGGTGTTAACAAA ACAAAGGTGAAA	5874	26	Imperfect mirror

Using Megablast tool, we further investigated identified mirror repeats among the genome of *C. elegans, C. vulgaris, Drosophila melanogaster* and *Xenopus tropicalis*. This result confirms the ubiquitous distribution of mirror repeats of size 11-13 base pairs (Table 5) in all the genera mentioned. These repeat sequences must have some important role in the genome; therefore, they are being maintained during course of evolution. Here we wish to mention that we were unable to look distribution of mirror repeats having a length equal to 7 bps within *C. elegans* genome as well as in other genomes. The complete Megablast tool result of all mirror repeats is shown in **Supplementary table 2**.

In this study, we observed that *ced-3* gene of *C. elegans* is enriched with mirror repeats. The gene have mirror repeats of different length and types. We have identified sequences that may have potentiality to form non-canonical B-DNA within gene. As no detailed study exists on role of various mirror repeat, we cannot tell exactly what might be function of these repeats. We wish to highlight here that other researchers have also identified mirror repeats within other genome such as *Arabidopsis thaliana* plant and gag gene of HIV-1 and HIV-2. Usha et al. studied 401 mirror repeats of different types within photosynthetic gene and 93 mirror repeats within flowering genes of *Arabidopsis*. Similarly, Yadav et al. reported 232 and 248 mirror repeats within HIV-1 and HIV-2 genome and also identified 61 mirror repeats within lacZ operon, 40 mirror repeats within trpE operon and 41 mirror repeats within *araE* gene of *Escherichia coli* strain K-12 substrain MF1655. Lang also reported imperfect mirror

Table 5. Distribution of selected mirror repeats among different genera's, here + sign depicts presence of mirror repeats and – sign depicts absence of mirror repeats

S. No.	Mirror Sequence	*C. elegans*	*C. vulgaris*	*X. tropicalis*	*D. melanogaster*
1	AATAGTGATAA	+	+	+	+
2	TGTGAAGTGT	+	+	+	-
3	CTATACTCATTTC	+	+	+	+
4	AATAATTTTAATAA	+	+	+	+
5	ACATTTTTTACA	+	+	+	+
6	CTTTCTGCGTCTCTC	+	+	-	-
7	AATTATGTATAAA	+	+	+	+
8	AAGTTCTTGAA	+	+	+	+
9	TATTTGAAGTGAAATATAT	+	-	-	-
10	TTTTATATATTTT	+	+	+	+
11	ACATTTTTTACA	+	+	+	+
12	CTTTCTGCGTCTCTC	+	+	-	-
13	CAAAATCGATCCTAAAAC	+	-	-	-
14	AACTCATTTAAAAAA TTAATTCAA	+	-	-	-
15	ACATTTTTAAATGATAA TTAATAAATTTTTGCA	+	-	-	-

repeats within *gag* gene of HIV-1 [40–43]. These identified mirror repeats have any role in within the genome of *C. elegans* is still mysterious. However, to understand the function, our future goal is to identify proteins that binds to these identified mirror repeats. We strongly believe identification of mirror repeat binding proteins will open a new chapter of molecular biology.

4 Conclusion

By using a simple computational approach, we have identified 140 mirror repeats within the *ced-3* gene of *C. elegans*. These identified mirror repeats are not restricted only in the genome of *C. elegans* but also scattered among the genome of *C. vulgaris, D. melanogaster* and *X. tropicalis*. Currently, we do not know the exact role of these mirror repeats but future investigation on these repeats and identification of mirror repeats binding protein, will definitely open a new chapter in area of biology.

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