Study on Mirror Repeats in the Vegf-aa gene of Danio rerio

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Abstract

Various types of repeated elements have been observed within the genome of different organisms. These repeated elements can be direct, inverted, tandem, or palindromic, etc. Out of all these repeats, we are interested in studying rarely explored repeats: Mirror repeats (MR's). Mirror repeats are DNA sequences that share homology with the other sequence fragments within the gene or genome. Using a simple bioinformatics strategy, we have first time identified mirror repeats within the *vegf-aa* gene, which is involved in the heart regeneration of *Danio rerio*. We have found 18 MR's in eight exons of *vegf-aa* gene and 797 MR's in the complete *vegf-aa* gene. It was observed that there are different types of mirror repeats present in the *vegf-aa* gene which can further classified as perfect repeat, perfect mirror repeats with one spacer, imperfect mirror repeats etc. These mirror repeats are not limited to the *vegf-aa* gene only but also well distributed within the genome of *Danio rerio* and in other organisms (*Mus musculus* & *Sus scrofa*). Until now, the exact role of mirror repeats has not been elucidated. Future studies may be required to determine the function of these identified mirror repeats.

Keywords: *Danio rerio*, DNA mirror repeats, *vegf-aa*, Heart regeneration, Blast tool.

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Introduction

Zebrafish is a fresh-water fish, scientifically known as *Danio rerio* is widely used as a powerful model to study developmental biology (Freeman *et al*., 2007; Kinkel and Prince, 2009; McCluskey and Postlethwaite, 2015; Lowe *et al*., 2021). The zebrafish genome sequence was started in 2001 at the Welcome Trust Sanger Institute, and the complete genome sequence of the zebrafish (*Danio rerio*) was published in 2013 (Howe *et al*., 2013). Zebrafish genome (*Danio rerio*) contains more than 26,000 protein-coding genes (Collins *et al*., 2012; Howe *et al*., 2013), and its genome size is about half of human genome (Driever *et al*., 1994; Freeman *et al*., 2007). Apart from studying various biological aspects, *Danio rerio* is also an essential model for studying regeneration abilities (Poss *et al*., 2002; Kikuchi *et al*., 2010; Gemberling *et al*., 2013; Marques *et al*., 2019). It can regenerate many organs, including the heart (Lien *et al*., 2006; Shoffner *et al*., 2020; Morejón and Mercader, 2020). Zebrafish can regenerate the heart even after amputation of up to 20% of the ventricle (Poss *et al*., 2002; Rosa *et al*., 2017, Morejón and Mercader, 2020). One of the key genes are involved in the heart regeneration of *Danio rerio* (zebrafish), like *vegf-aa*. Vascular endothelial growth factor Aa (*vegf-aa*) is a key to vasculogenesis and angiogenesis (Taimeh Z *et al*., 2013; Karra et al., 2018). It consists of 30417 nucleotide base pairs in length with eight exons and is located on chromosome 16 within *Danio rerio* genome. Various types of repetitive sequences are present in the DNA of organisms (Jurka *et al*., 2007). Repetitive DNA sequences refer to homology DNA fragments which are present in

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multiple copies in any organism (Jurka 2007; Mehrotra and Goyal, 2014; Zattera *et al*., 2020). Based on their distribution within the genome, repetitive DNA sequences are classified in two types: Interspersed repeats and Tandem repeats (Jurka, 2007; Pathak and Ali 2012; Zattera *et al*., 2020). Interspersed repeats are those repeats which are randomly arranged and dispersed throughout the various genome, while tandem repeats are the repeats which are present as clustered arrays of DNA fragments joined to each other in a head-to-tail fashion (Jurka 2007; Gurusaran *et al*., 2013). According to the length of DNA sequences, interspersed repeats are classified into two types: long interspersed elements (LINES) and short interspersed elements (SINES), while tandem repeats include microsatellite, minisatellite and satellite DNA (Pathak and Ali 2012; Mehrotra and Goyal 2014; Zattera *et al*., 2020). On the basis of the arrangement of nucleotide sequences and symmetry, DNA repeats can be classified as Inverted repeats, Direct repeats and Mirror repeats (Mirkin 2001; Gurusaran *et al*., 2013). In Inverted repeats, two or more repeating DNA fragments appear in inverted orientation and on the same strand. Direct repeats are defined as two or more repeating DNA fragments that appear in the same orientation and on the same strand. Mirror repeat can be defined as a DNA sequence that shares homology with the other sequence fragment within the gene or genome (Mirkin 2001). It indicates that one part of the sequence fragment is a mirror image of the other are shown in the figure1 below.

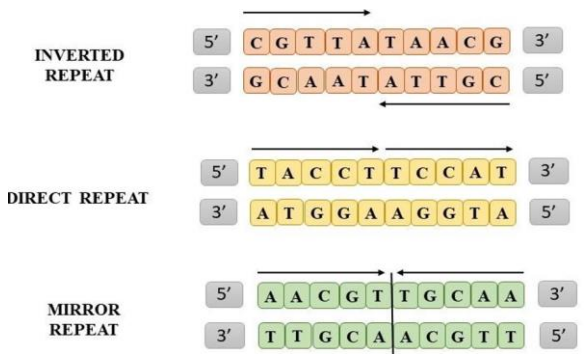

Figure 1 shows the types of DNA repeats: inverted repeat, direct repeat & mirror repeat.

In the case of mirror repeats, parallel complement and anti-parallel complement are identical but in normal DNA, both parallel complement and anti-parallel complement are non-identical.

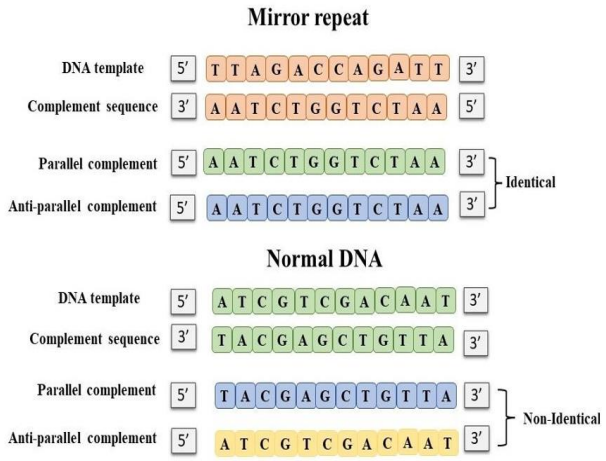

Figure 2: shows comparative analysis of mirror repeats and normal DNA. Here we wish to highlight parallel complement & anti-parallel complement of any mirror repeat sequence are same which not in case of any normal DNA sequence.

We are interested to study mirror repeats in various genes/genomes. Here our aim is to identify mirror repeats within *vegf-aa* gene of *Danio rerio* using a simple manual bioinformatics approach.

Materials and methods

The coding sequence of the *vegf-aa* gene (NC_007127.7 Chromosome 16 Reference GRCz 11 Primary Assembly) of *Danio rerio* was downloaded from the NCBI website (link: https://www.ncbi.nlm.nih.gov/). The *vegf-aa* gene (30417 bps) was divided into 500 base pairs regions. This sequence represents the query sequence. Using the Reverse complementary tool (https://www.bioinformatics.org/sms/rev_comp.html), the parallel complement of each region was retrieved. This parallel complement sequence represents the subject sequence. Using the BLAST tool, both the coding sequence (query sequence) and its parallel complement (subject sequence) were aligned for the BLAST homology search (https://blast.ncbi.nlm.nih.gov/Blast.cgi?PAGE_TYPE=BlastSearch). Here within the result of the hit, if the position number is precisely reversed in query and subject, it will be a mirror repeat. Similarly, mirror repeats were analysed within different exons of *vegf-aa* gene. As exons of *vegfaa* gene is lesser then 500bps, they were not subdivided further. The algorithm parameters were fixed for the word size 7, the threshold value at which maximum no. of hits were observed and was used to identify mirror

repeat in the *vegf-aa* gene. The identified mirror repeats were classified as perfect mirror repeats, and imperfect mirror repeats. Using the Mega Blast tool, the identified mirror repeats were searched within the genome of *Danio rerio,* as well as other organism genomes like *Mus musculus* and *Sus scrofa*.

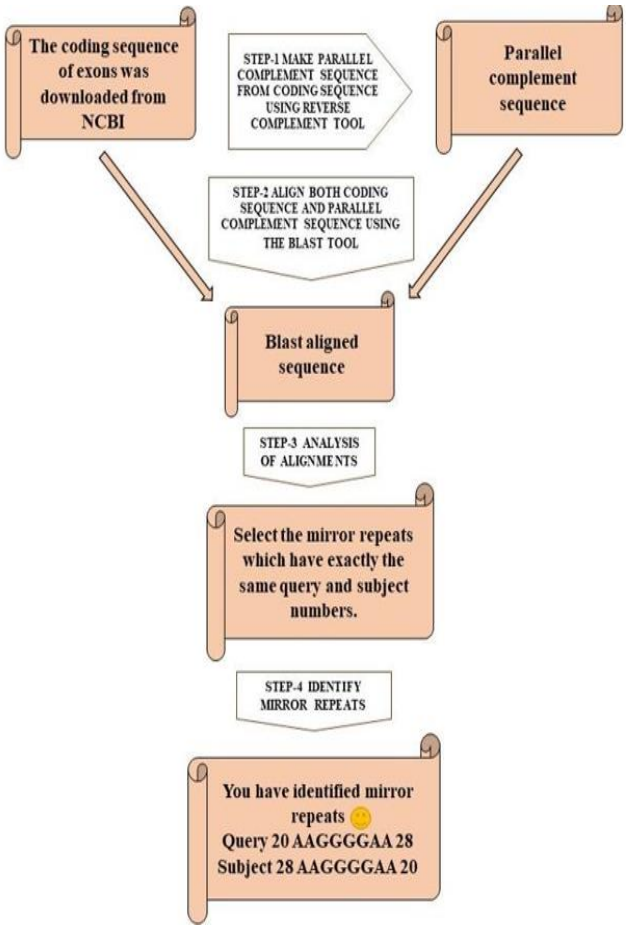

Figure 3: Schematic representation of the methodology used to identify mirror repeats

(i) The coding sequence of *vegf-aa* gene downloaded from the NCBI website (ii) Parallel complement sequence was retrieved using reverse complement tool (iii) Analysis of BLAST result for identification of mirror repeats.

Results And Discussion

In the present study, a simple bioinformatics approach was used to identify mirror repeats in the *vegf-aa* gene which is involved in the heart regeneration of *Danio rerio*. The *vegf-aa* gene consists of 30417 nucleotide base pairs in length with eight exons. Table 1 represents the position of exons and the number of mirror repeats identified within the *vegf-aa* gene of *Danio rerio*.

Table 1: showing no. of mirror repeats present in all eight exons of *vegf-aa* gene.

Name of gene	Exons	Positions of exons	No. of mirror repeats
Vascular endothelial growth factor Aa (*vegf-aa*) Gene ID: 30682	Exon-1	662-727	2
	Exon-2	3096-3138	1
	Exon-3	8628-8824	6
	Exon-4	11397-11473	1
	Exon-5	13401-13435	1
	Exon-6	21763-21854	2
	Exon-7	24506-24621	5
	Exon-8	28890-28908	0

Identification and classification of mirror repeats:

With the help of the BLAST tool and using simple manual strategy, we have identified mirror repeats within the *vegf-aa* gene of *Danio rerio*. The nucleotide sequence of the *vegf-aa* gene was divided into 500 base pair regions to identify the maximum number of mirror repeats. During the present investigation, we noticed that if we increase the threshold value(E), the number of hits changes, so firstly, we selected the threshold value at which there is no change in number of hits. The maximum number of hits were observed at threshold value 10 for exons and threshold value 100 for different regions of *vegf-aa* gene, so we identify mirror repeat at these values. A total, of 797 mirror repeats were found in different regions of the *vegf-aa* gene and 18 mirror repeats were found in all eight exons of the gene. In exons, out of 18 mirror repeats 15 are perfect mirror repeats with one spacer, 1 perfect mirror repeat without spacer, and 2 are imperfect mirror repeats. A mirror repeat with identical sequences around the centre axis of symmetry is termed as a perfect mirror repeat. A perfect mirror repeats have one spacer element is termed a perfect mirror repeat with one spacer. Mirror repeats that have mismatch sequences around the centre axis are termed imperfect mirror repeats. Table 2 represents the mirror repeats present within the different exons of *vegf-aa* gene with their length and types. The largest mirror repeat within the exons of the *vegf-aa* gene is of 17bp (an imperfect mirror repeat) while the smallest one is 7bp. We cannot detect small-size mirror repeats as a limitation of the BLAST tool to select a word size limit is 7bp.

Table 2: shows mirror repeats with length, position, and types in all eight exons of the *vegfaa* gene.

Exons	No. of hits	No. of mirror repeats	Mirror repeats	Length (bps)	Type of mirror repeats
Exon- 1 (662-727)	02	02	1. GTTTATTTG 2. TCTGTCT	9bp 7bp	1. Perfect with one spacer 2.Perfect with one spacer
Exon-2 (3096-3138)	01	01	AAGGGGGAA	9bp	Perfect with one spacer
Exon-3 (8628-8824)	06	06	1. ACAGAGACA 2. TTCCCTT 3. ATGTGTA 4. GTGCGTG 5. CGAGAGC 6. GCACACG	9bp 7bp 7bp 7bp 7bp 7bp	1.Perfect with one spacer 2.Perfect with one spacer 3.Perfect with one spacer 4.Perfect with one spacer 5.Perfect with one spacer 6.Perfect with one spacer
Exon-4 (11397-11473)	01	01	AAGTGTGAA	9bp	Perfect with one spacer
Exon-5 (13403_13435)	01	01	AAAGAAAGAAA	11bp	Perfect with one spacer
Exon-6 (21763-21854)	03	02	1. TAATAAACTCAATTAAT 2. aaaTAATAAA	17bp 10bp	1.Imperfect 2.Imperfect
Exon-7 (24506-24621)	05	05	1. GAAGGAAG 2. AGAGAGA 3. TGTATGT 4. GTAAATG 5. TTGAGTT	10bp 7bp 7bp 7bp 7bp	1.Perfect without spacer 2.Perfect with one spacer 3.Perfect with one spacer 4.Perfect with one spacer 5.Perfect with one spacer
Exon-8 (28890-28908)	00	00	Not detected		

Table 3 shows the exact positions of mirror repeats within the eight exons of the *vegf-aa* gene of *Danio rerio* by highlighting the mirror repeats so that we can see where the mirror repeats are located in all eight exons of the *vegf-aa* gene.

Table 3 shows the distribution of highlighted mirror repeats in the sequences of all eight exons of the *vegf-aa* gene.

Exons	No. of mirror repeats	Sequence with highlighted mirror repeats
Exon-1	2	ATGAACTTGGTTGTTTATTTGATACAGTTATTTCTCGCGGCTC TCCTCCATCTGTCTGCTGTAAAG
Exon-2	1	GCTGCCCACATACCCAAAGAAGGGGGAAAGAGCAAAAATG ATG
Exon-3	6	TGATTCCCTTCATGGATGTGTATAAAAAGAGTGCGTGCAAG ACCCGAGAGCTGCTGGTAGACATCATCCAGGAGTATCCCGA TGAGATCGAGCACACGTACATCCCGTCCTGTGTGGTTCTCAT GCGCTGTGCAGGATGCTGTAATGATGAGCGCTCGAATGCGT CCCGACAGAGACACGAAACGTCACTATGGAG
Exon-4	1	GTCCGTCTAGGTGCTGCGGGTCAAGCAACGCGTATCGCAGC ATAATTTTCAGCTGAGTTTCACAGAACACACCAAGTGTGAAT GCAG
Exon-5	1	GCCAAAGGCAGAAGTCAAAGCAAAGAAAGAAAA
Exon-6	2	ACTATTTAAAAAAATAATAAACTCAATTAATCGCTTTAAAA GCATCGGTTTTACTCACTTTTTTAAAGTAAAGTCAGC TTTTCAAGCATCGG
Exon-7	5	CCACTGTGAGCCTTGCTCAGAGAGAAGGAAGCGCTTGTATG TGCAGGACCCCCTCACCTGTAAATGCTCCTGCAAATTCACAC AAATGCAATGCAAGTCCAGACAACTTGAGTTAA
Exon-8	0	No mirror repeat detected

Table 4 shows the number of mirror repeats in each region of the *vegf-aa* gene.

Regions	Total no. of mirror repeats	Perfect mirror repeats	Perfect mirror repeats with one spacer	Imperfect mirror repeats
Region-1	8	1	4	3
Region-2	17	3	14	0
Region-3	13	2	11	0
Region-4	16	2	3	11
Region-5	10	5	4	1
Region-6	9	2	7	0
Region-7	14	1	7	6
Region-8	17	3	11	3
Region-9	14	2	9	3
Region-10	13	2	10	1
Region-11	17	2	9	6
Region-12	18	3	12	3
Region-13	9	2	6	1
Region-14	12	3	8	1
Region-15	17	2	12	3
Region-16	9	4	4	1
Region-17	15	0	14	1
Region-18	12	0	9	3
Region-19	4	1	1	2
Region-20	10	4	4	2
Region-21	11	2	8	1
Region-22	14	4	8	2
Region-23	5	0	5	0
Region-24	20	8	10	2
Region-25	8	0	4	4
Region-26	9	1	5	3
Region-27	13	2	9	2
Region-28	14	1	10	3
Region-29	16	4	8	5
Region-30	16	3	7	6
Region-31	12	2	7	3
Region-32	12	4	5	3
Region-33	18	4	11	3
Region-34	9	2	7	0
Region-35	13	2	9	2
Region-36	12	1	11	0
Region-37	11	0	8	3
Region-38	12	0	8	4
Region-39	10	2	2	6
Region-40	15	2	12	1
Region-41	11	2	6	3
Region-42	5	1	3	1
Region-43	19	2	14	3
Region-44	19	2	13	4
Region-45	16	6	8	2
Region-46	8	1	4	3
Region-47	13	6	6	1
Region-48	23	5	13	5
Region-49	13	3	8	2
Region-50	16	2	10	4
Region-51	10	3	4	3
Region-52	23	6	12	5
Region-53	7	2	3	2
Region-54	9	1	8	0
Region-55	10	2	5	2
Region-56	15	3	6	6
Region-57	13	2	4	7
Region-58	18	6	10	2
Region-59	8	0	8	0
Region-60	23	4	18	1
Region-61	14	0	12	2
Total =	797	147	488	162

Comparative investigation of identified mirror repeats in the genome of *Danio rerio* and other organism genomes:

Using mega blast analysis, the distribution of the above-identified 18 mirror repeats of the exons of *vegf-aa* gene (table 2) was searched among the genome of *Danio rerio*, *Mus musculus domesticus*, and *Sus scrofa domestica*. The results of exons are summarized in Table 5 below. Based on the results, we cannot detect all

small-size mirror repeats as limitations of the MegaBlast tool to search nucleotide sequences with a word size limit 16. Here, the + sign indicates the presence of mirror repeat, and the – sign indicates the absence of mirror repeat. The distribution of selected mirror repeats which are larger in size (not all) in the different regions of *vegf-aa* gene were analysed among different genomes are shown in table 6. The complete MegaBlast result for all mirror repeats in different regions of the *vegf-aa* gene is provided in the supplementary file.

Table 5 shows the comparative investigation of mirror repeats within the *Danio rerio* gene and other organism genomes (*Mus musculus and Sus scrofa*) using megaBlast.

Exons	Mirror repeats	Genome of *Danio rerio*	Genome of *Mus musculus*	Genome of *Sus scrofa*
Exon-1	GTTTATTTG	-	+	+
	TCTGTCT	-	-	+
Exon-2	AAGGGGGAA	-	+	+
Exon-3	ACAGAGACA	-	+	+
	TTCCCTT	-	-	+
	ATGTGTA	-	-	+
	GTGCGTG	-	-	+
	CGAGAGC	-	-	+
	GCACACG	-	-	+
Exon-4	AAGTGTGAA	-	+	+
Exon-5	AAAGAAAGAAA	-	+	+
Exon-6	TAATAAACTCAATTAAT	+	+	+
	aaaTAATAAA	-	+	+
Exon-7	GAAGGAAG	-	+	+
	AGAGAGA	-	+	+
	TGTATGT	-	-	+
	GTAAATG	-	-	+
	TTGAGTT	-	-	+
Exon-8	Not detected			

Table 6 shows the distribution of selected mirror repeats in the *Danio rerio* genome and other organisms (*Mus musculus and Sus scrofa*).

S.No.	Mirror sequences	*Danio rerio*	*Mus musculus*	*Sus scrofa*
1.	TTTTGTTTGTTTT	+	+	+
2.	GTATGTGTGTTTG	+	+	+
3.	AAACGGACG-CGTGTGCAGCGGTCAAA	+	+	+
4.	ACTTTGTTTCA	_	_	+
5.	ATACTGAAATTTAAGATTAA AAAGTAATACAAATATTGAGAA AATCATCTTTAAAGTCTTA	+	+	+
6.	CAACTTCCTTCAAC	+	+	+
7.	TTTCTATTAATGTAATAATATTT	+	+	+
8.	ATATTTATTATTAGATATA	+	+	+
9.	aaTCTAATTTTCTCAACATTTAATCAAA	+	+	+
10.	TTATTTGATAATTTGGTCGTTTATT	+	+	+
11.	TGTTTTGGTTAGATTTTTATAAGACTTTT AGATTAGTATTGT	+	+	+
12.	TTTTAAATTGATGTTAAATCTT	+	+	+
13.	TTTTATTCAACACATTGCTAAACATAATA GTTTTAATAACTCATTTC--TA-ATAACTTAtttt	+	+	+
14.	AATCATTGTATAACAATTGGTAACACTTC AGTATGGGGACCAGT-TCTTACTAA	+	+	+
15.	CTATTATTAAGATATTAAC---TGTCTGTATGCATTTATA-AAGTATGATC	+	+	+

Conclusion:

This study applies the bioinformatics tool to identify mirror repeats in the *vegf-aa* genes which is involved in the heart regeneration of *Danio rerio.* A gene may be found in multiple species that perform the same or different functions. The *vegf-aa* gene is analysed using a computational based tool, BLAST. This study helps us to find mirror repeats within the *vegf-aa* gene of *Danio rerio*. A total of 797 mirror repeats are identified in different regions of the *vegf-aa* gene, and 18 mirror repeats are identified in the exons of the gene. It will be highly significant to find out the role of DNA mirror repeats at the molecular level. Until now, the exact role of mirror repeats has not been elucidated. Future studies may be required to determine the exact role of mirror repeats within the genes of *Danio rerio* and other organism genomes.

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Conflicts of interest

The author don't have any conflicts of interest.

Credit author statement

Vikash Bhardwaj: Conceptualization, Methodology, Software, Supervisor, Reviewing, Editing
Namrata Dangi: Data curation, Investigation, Writing-Original draft preparation **Kavita Saini:**
Writing-Review Editing.

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