RESEARCH PAPER

Functional Analysis of Mirror Repeats in transcripts of Human PAH Gene

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ABSTRACT

Mirror repeats are noncanonical DNA motifs capable of forming alternative DNA structures that may influence transcriptional regulation and genomic stability (Frank-Kamenetskii & Mirkin, 1995; Wells, 2007). Although their presence has been documented in various genomic contexts, their functional relevance in metabolically critical human genes remains insufficiently explored (Bacolla & Wells, 2004; Mirkin, 2008). In this study, we performed a functional analysis of mirror repeats previously identified in human PAH gene transcripts. Using exon-wise and transcript-wise distribution data, we examined patterns of mirror repeat enrichment and clustering across canonical and alternative PAH transcript variants. Our analysis revealed non-uniform and transcript-specific distribution of mirror repeats, with notable enrichment in specific exonic regions, particularly within longer exons. Such enrichment patterns are consistent with the behavior of other non-B DNA-forming motifs associated with structural DNA features (Kouzine et al., 2013; Bacolla et al., 2011). These findings suggest that mirror repeats may contribute to localized structural hotspots within the PAH gene and highlight their potential involvement in regulatory mechanisms and genomic vulnerability.

KEYWORDS: *Mirror repeat clustering, Alternative DNA structures, Exonic enrichment, Structural DNA motifs, Transcriptional regulation.*

INTRODUCTION

DNA sequence organization is not solely defined by its linear nucleotide composition but also by its capacity to adopt alternative conformations that directly influence gene function. Non-B DNA structures, arising from specific sequence motifs, are increasingly recognized for their role in modulating transcriptional activity, replication efficiency, and genome stability (Sinden, 1994; Wells, 2007). These structural transitions are particularly relevant in functionally active genomic regions, where dynamic changes in DNA topology can regulate access of transcriptional machinery and associated regulatory proteins (Mirkin, 2008; Wang & Vasquez, 2014).

Mirror repeats represent a functionally significant class of such motifs, characterized by symmetrical arrangements that enable the formation of intramolecular triplex (H-DNA) structures. These conformations are not merely structural anomalies but actively participate in gene regulation by altering the physical state of DNA. Triplex formation can create steric hindrance for RNA polymerase progression, influence transcriptional elongation rates, and contribute to transcriptional pausing or premature termination (Frank-Kamenetskii & Mirkin, 1995; Jain et al., 2008). In addition, these structures may serve as binding platforms for specific regulatory proteins, thereby integrating sequence architecture with transcriptional control mechanisms (Kouzine et al., 2013).

From a functional perspective, mirror repeats are also implicated in replication dynamics and genome maintenance. Their ability to form stable secondary structures under superhelical stress can interfere with replication fork progression, leading to replication stalling and increased susceptibility to DNA damage (Bacolla et al., 2011; Wells, 2007). Such effects are particularly critical in actively transcribed genes, where conflicts between replication and transcription machinery can exacerbate structural instability. Consequently, mirror repeats may contribute to localized mutation hotspots and influence gene integrity over time.

The phenylalanine hydroxylase (PAH) gene provides a relevant framework to investigate these functional implications. As a gene essential for phenylalanine metabolism, its expression must be tightly regulated to maintain metabolic homeostasis (Blau et al., 2010). While pathogenic mutations within coding regions are well documented in phenylketonuria, functional regulation at the level of DNA structure remains underexplored. The presence of mirror repeats within the PAH gene introduces the possibility that noncanonical DNA conformations may influence transcriptional efficiency and gene output independent of sequence variation.

Importantly, the existence of multiple PAH transcript variants suggests that functional outcomes may be influenced by transcript-specific sequence architecture (Johnson et al., 2003). Mirror repeat distribution across different transcripts and exonic regions may differentially affect transcription kinetics, co-transcriptional folding, and RNA processing. For instance, mirror repeats located near exon–intron boundaries may alter local DNA topology in a manner that impacts splice-site recognition or spliceosome assembly, thereby contributing to variability in

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transcript formation. Similarly, repeats positioned within coding regions may influence transcriptional elongation dynamics, ultimately affecting mRNA stability and translational efficiency.

Furthermore, the functional impact of mirror repeats may extend to chromatin-level regulation. By inducing localized structural alterations, these motifs can affect nucleosome positioning and DNA accessibility, thereby modulating the interaction between DNA and transcription factors. In the context of the PAH gene, such effects could contribute to differential gene expression patterns under varying physiological conditions, potentially influencing disease severity or phenotypic variability in phenylketonuria.

In this context, the present study focuses on the functional interpretation of mirror repeats within PAH transcripts. By examining their exon-wise and transcript-specific distribution, the analysis aims to identify patterns that may correlate with regulatory roles in transcription, RNA processing, and genome stability. This function-oriented approach provides a deeper understanding of how intrinsic DNA structural features contribute to gene regulation and offers a basis for future experimental investigations into their role in disease-associated gene function.

MATERIALS AND METHODS

Step 1: Data Acquisition and Transcript Selection

Nucleotide sequences of the human phenylalanine hydroxylase (PAH) gene were retrieved from the National Center for Biotechnology Information (NCBI) database. Two transcripts were selected: the canonical transcript (NM_000277.3) and an alternative variant (NM_001354304.2), based on annotation reliability and relevance to PAH gene expression. Sequences were obtained in FASTA format and used without modification for subsequent analysis (GeneReviews® Editors, 2025; MedlinePlus Genetics, 2023).

Step 2: Mirror Repeat Dataset Utilization

Mirror repeat data were obtained from a pre-existing dataset generated using a BLAST-based FPCB (Fragmentation, Complementation, Pairing, and BLAST) approach. As repeat identification had been previously validated, the present study utilized curated outputs solely for downstream functional interpretation, ensuring methodological consistency (Bhardwaj et al., 2013; Gusfield, 1997; Pevzner, 2000).

Step 3: Mapping to Transcript Architecture

Mirror repeats were aligned to transcript structures using exon annotation data from NCBI. Each repeat was mapped to its corresponding exon based on positional coordinates. Redundant and overlapping entries were removed to ensure accuracy and avoid analytical bias (Benson, 1999; Cooper et al., 2011; Treangen & Salzberg, 2012).

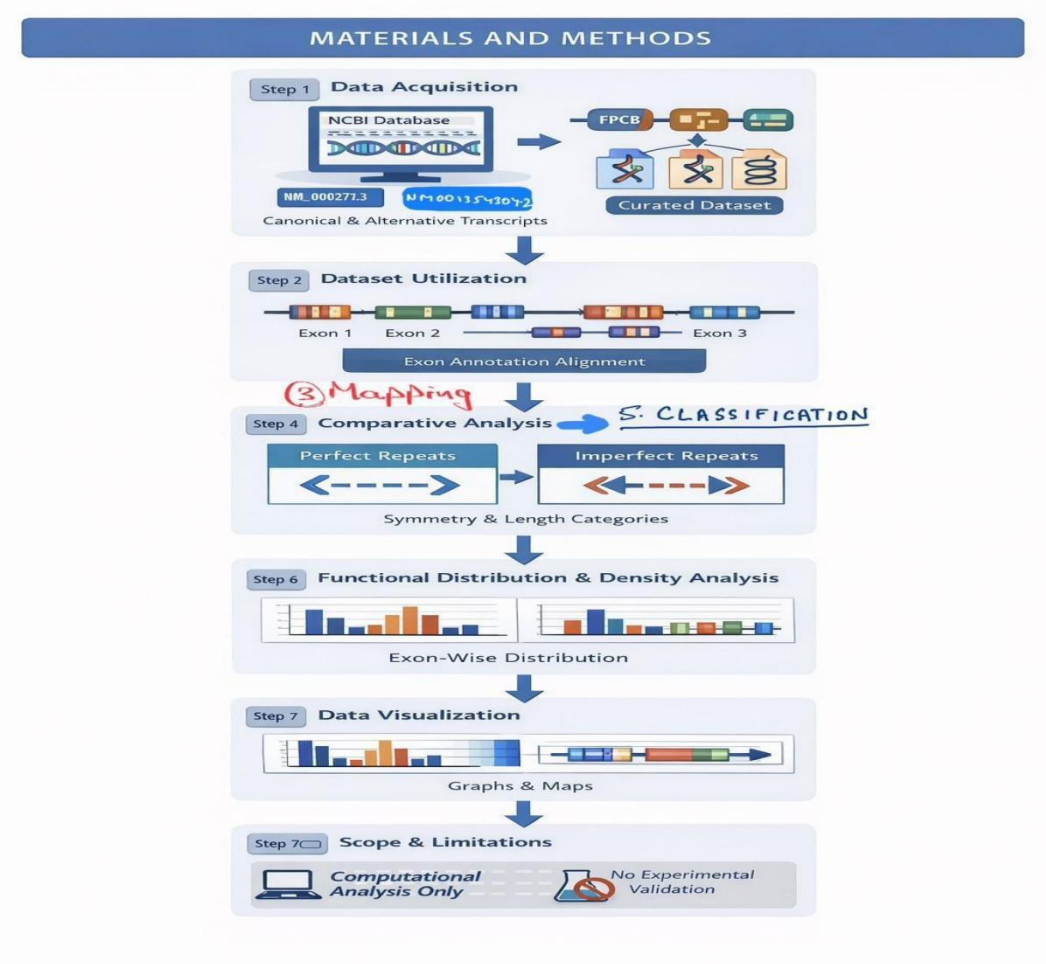


Figure 1: Representation of methodology

Step 4: Comparative Transcript Analysis
A comparative analysis was conducted between the canonical and alternative transcripts to examine differences in repeat distribution, density, and clustering. Variations in exon organization were considered to ensure accurate positional and structural interpretation (Johnson et al., 2003; Zhao et al., 2018).

Step 5: Classification of Mirror Repeats
Mirror repeats were categorized into:

- **Perfect repeats:** exhibiting uninterrupted symmetry

- **Imperfect repeats:** containing mismatches or spacers

Additionally, repeats were grouped by length to assess structural variability and their potential to form non-B DNA conformations (Frank-Kamenetskii & Mirkin, 1995; Mirkin, 2008; Pearson et al., 2005).

Step 6: Functional Distribution and Density Analysis
Exon-wise distribution of mirror repeats was analyzed to identify clustering and enrichment patterns. Repeat density was calculated as the number of repeats per kilobase (kb) of exon length, enabling normalized comparisons across exons. Observations were interpreted in the context of potential roles in transcriptional regulation, DNA structural transitions, and genomic stability (Bacolla & Wells, 2004; Benham & Mielke, 2005; Kouzine et al., 2013; Zhao et al., 2018).

Step 7: Data Visualization
Results were represented using exon-wise bar plots, density heatmaps, and schematic transcript maps to highlight biologically relevant distribution patterns and structural trends (Tufte, 2001; Wong, 2011).
This study constitutes a secondary computational analysis of a previously generated dataset. Findings are limited to inferred structural and functional associations based on repeat distribution patterns, without experimental validation. Further empirical studies are required to confirm the biological significance of mirror repeats in PAH gene regulation (Bacolla et al., 2011; Wells et al., 2007).

RESULTS:
The purpose of the results is to **compare patterns**, **identify enrichment**, and **highlight biologically meaningful trends** according to the data previously collected and discussed in paper .
Functional interpretations from the data collected are as follows:

1. Transcript-Specific Variability in Mirror Repeat Distribution
Comparative analysis of mirror repeat distribution between the canonical and alternative PAH transcript variants revealed notable transcript-specific differences. Although both transcripts contained mirror repeats across multiple exons, the number and density of repeats varied between corresponding exonic regions. Such transcript-dependent variability in repetitive DNA distribution has been reported previously and may reflect differences in transcript architecture and regulatory context (Johnson et al., 2003; Cooper et al., 2011).

Table1. Comparative summary of mirror repeat distribution in PAH transcript variants

Feature	**Canonical transcript (NM_000277.3)**	**Alternative transcript (NM_001354304.2)**
Transcript length (bp)	2,556	3,987
Number of exons	13	14
Total mirror repeat hits (full transcript)	86	401
Mirror repeats within exons	63	44
Proportion of exonic mirror repeats (%)	73.3	11.0
Dominant exon with highest enrichment	Exon 13	Long terminal exon
Predominant repeat type	Perfect with 1 spacer	Perfect with 1 spacer

Exon Length and Mirror Repeat Enrichment

Mirror repeat density did not correlate linearly with exon length. While longer exons tended to contain a greater absolute number of mirror repeats, several shorter exons lacked repeats entirely, and some moderately sized exons displayed disproportionately high repeat densities. Similar observations have been reported for other non-B DNA motifs, suggesting that sequence context rather than length alone governs repeat localization (Benham & Mielke, 2005; Zhao et al., 2018).

Table 2. Exon-wise mirror repeat density in PAH transcript variants

Transcript	Exon	Exon length (bp)	Exonic mirror repeats	Mirror repeat density (MRs/kb)
Variant 1	Exon 3	184	8	43.5
Variant 1	Exon 6	197	5	25.4
Variant 1	Exon 13	2330	36	15.5
Variant 2	Exon 4	184	8	43.5
Variant 2	Terminal exon	2330	14	6.0

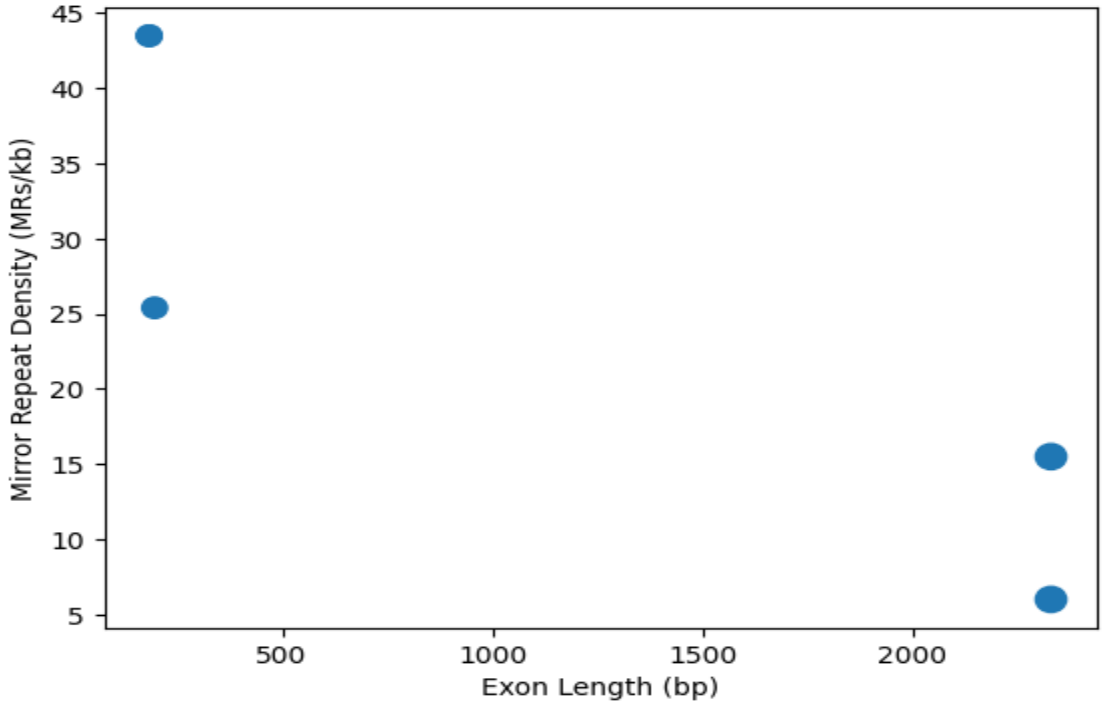


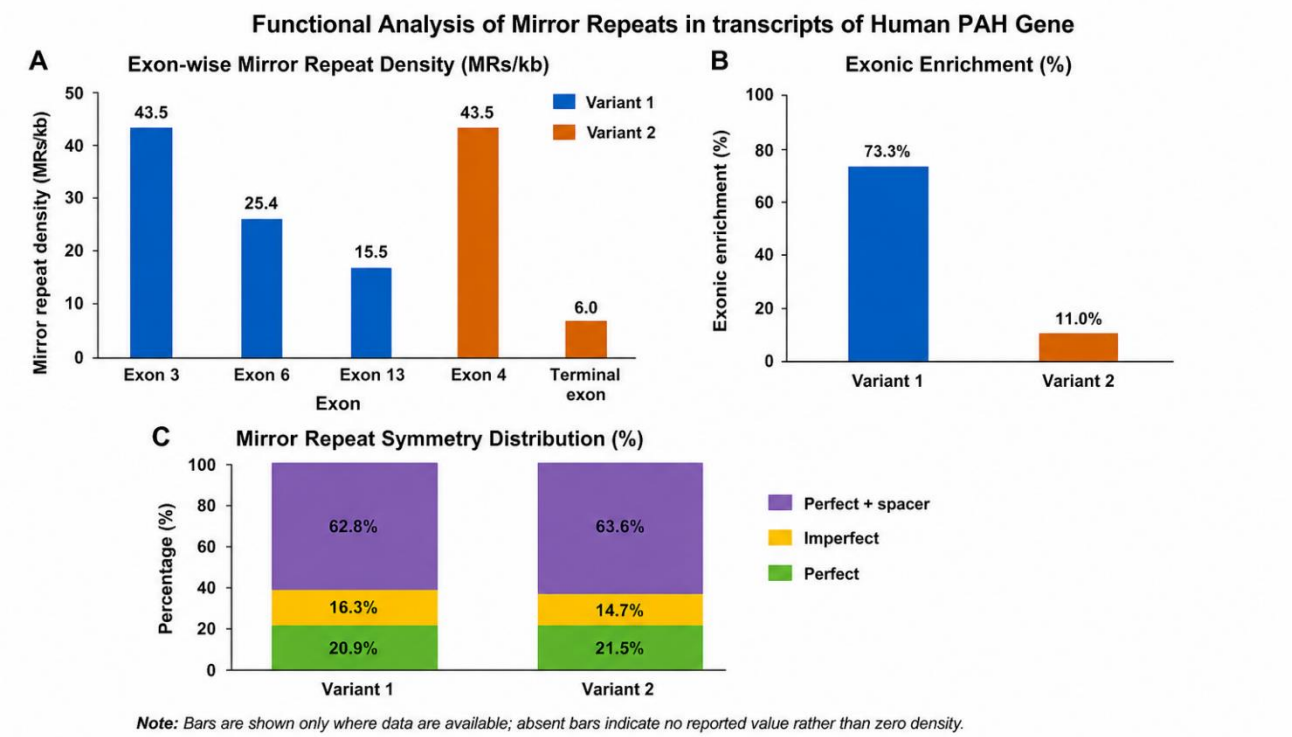
Figure 2 : Non- Linear relationship between exon length and mirror repeat density

"Density does not correlate linearly with exon length". The number of mirror repeats per kilobase (MR/kb) does NOT increase proportionally as exon length increases. In simple words : Longer exon ≠ automatically higher repeat density.

The figure 2 depicts the relationship between exon length and mirror repeat density (MR/kb) across selected exons of both PAH transcript variants. A linear relationship would imply that longer exons consistently exhibit proportionally higher density values. However, the observed data do not support such a pattern.

The longest exon examined (2330 bp) displays density values of 15.5 MR/kb in the canonical transcript and 6.0 MR/kb in the alternative transcript. In contrast, a much shorter exon of 184 bp exhibits the highest density (43.5 MR/kb), while the 197 bp exon shows an intermediate density (25.4 MR/kb).

These results indicate that mirror repeat density is not directly proportional to exon length. Rather than being determined solely by exon size, repeat enrichment appears to depend on local sequence characteristics and regional genomic context. The absence of a linear trend suggests selective localization of mirror repeats within specific exonic regions of the PAH gene.



Note: Bars are shown only where data are available; absent bars indicate no reported value rather than zero density.

Figure 3: Composite functional representation of mirror repeat distribution in PAH transcript variants. (A) Exon-wise mirror repeat density (MRs per kb) across selected exons; bars are displayed only where values are reported. (B) Proportion of mirror repeats located within exonic regions (exonic enrichment). (C) Distribution of mirror repeat symmetry types, including perfect, imperfect, and spacer-containing repeats.

Figure 3 : Composite functional representation of mirror repeat and hits distribution in PAH transcript variants.

(A) Exon-wise mirror repeat density (MRs per kb) across selected enriched exons in canonical and alternative PAH transcripts.
(B) Proportion of total mirror repeats localized within exonic regions for each transcript variant.
(C) Distribution of mirror repeat symmetry types, including perfect, imperfect and spacer containing repeats.
All values represent derived metrics based on mirror repeat mapping described previously (Paper 1).

3. Clustering of Mirror Repeats

Mirror repeats were found to cluster within specific exonic regions rather than being evenly dispersed. These clusters were particularly evident in long exons and untranslated regions, where multiple mirror repeats occurred in close proximity. Such clustering patterns are characteristic of non-B DNA-forming motifs and are often associated with localized structural DNA features (Bacolla & Wells, 2004; Kouzine et al., 2013)

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4. Distribution of Perfect and Imperfect Mirror Repeats

Functional comparison revealed that perfect mirror repeats with single spacer predominated and imperfect mirror repeats were present within exonic regions of both transcript variants. Perfect mirror repeats were comparatively fewer and often shorter in length. The presence of imperfect repeats may provide structural flexibility while preserving coding integrity, a feature previously noted for symmetry-disrupted repetitive motifs (Pearson et al., 2005; Mirkin, 2007). The perfect mirror repeats were of shorter length as compared to the longer lengths of imperfect mirror repeats. It can be concluded that longer the length of sequence higher is the probability of it being an imperfect mirror repeat or might be perfect with a spacer.Perfect + spacer repeats are included as a separate functional category derived from mirror repeat dataset of an earlier paper (Singh and Dangi, 2026).

Table 3. Symmetry-based functional classification of mirror repeats

Transcript variant	Perfect mirror repeats	Imperfect mirror repeats
Canonical	18	14
Alternative	19	13

5. Comparative Distribution in Transcript Variant 2

Analysis of the alternative transcript variant NM_001354304.2 revealed mirror repeats distributed

unevenly across exons, with certain regions exhibiting enrichment while others lacked detectable repeats. Transcript-wise variation in repeat localization supports the influence of alternative transcript architecture on repetitive DNA organization (Cooper et al., 2011; Zhao et al., 2018).

Exon-wise analysis of the alternative PAH transcript variant (NM_001354304.2) revealed mirror repeats distributed across multiple exonic regions. Of the 401 mirror repeat hits identified in the full-length transcript, 44 were localized within exonic regions. The distribution was uneven, with selective enrichment in specific exons, while several exons lacked detectable mirror repeats entirely.

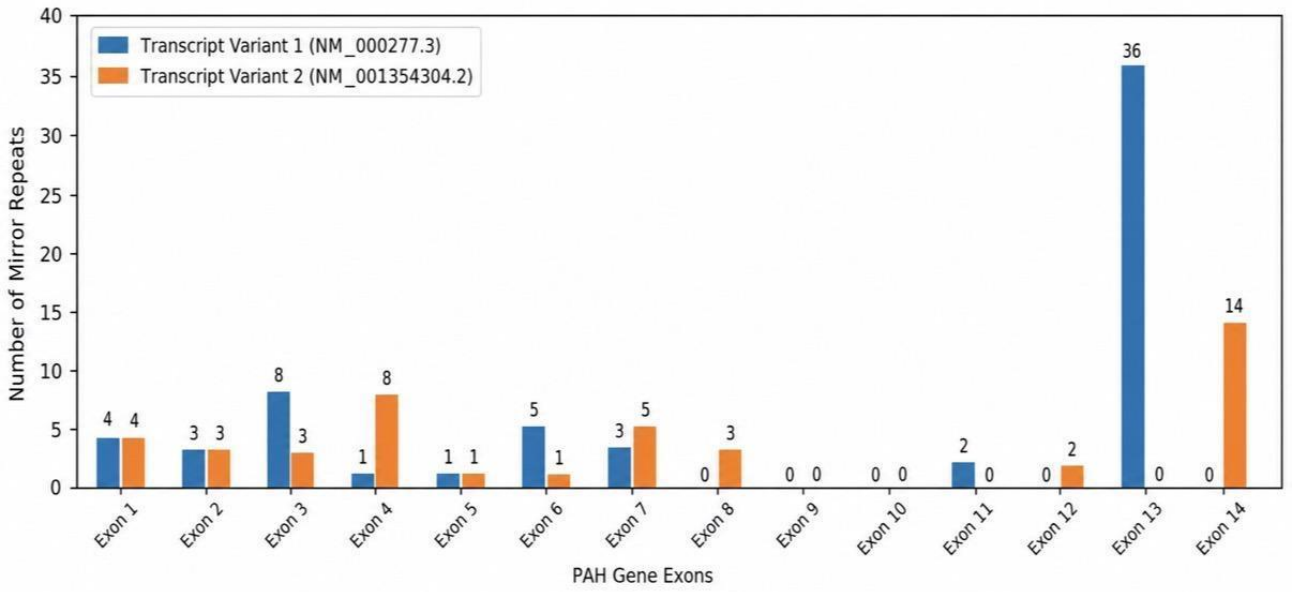

Figure 4 : Variant-wise exon distribution of mirror repeats in PAH gene

This comparative mapping in figure 4 demonstrates transcript-specific variation in mirror repeat distribution within the PAH gene.

6. Integrated Functional Patterns

Collectively, the functional analysis demonstrates that mirror repeats within PAH transcripts exhibit:

- Non-random spatial distribution
- Transcript-dependent variability
- Exon-specific enrichment and clustering
- Presence of imperfect symmetry

These features suggest that mirror repeats are structurally organized elements rather than passive sequence artifacts.

DISCUSSION

This study extends prior computational mapping of mirror repeats in human PAH gene transcripts by examining their exon-wise and transcript-specific distribution in a functional context. The observed patterns demonstrate that mirror repeats are not randomly dispersed but instead show structured localization across the PAH gene architecture. Such non-uniform distribution is consistent with previous observations that repetitive DNA motifs capable of forming non-B DNA structures often accumulate in specific genomic regions rather than being evenly distributed (Bacolla & Wells, 2004; Mirkin, 2008). Based on the distribution patterns identified in the present study, we propose a mechanistic model illustrating how mirror repeat clusters may facilitate secondary structure formation and modulate RNA polymerase progression **(Figure 5)**.

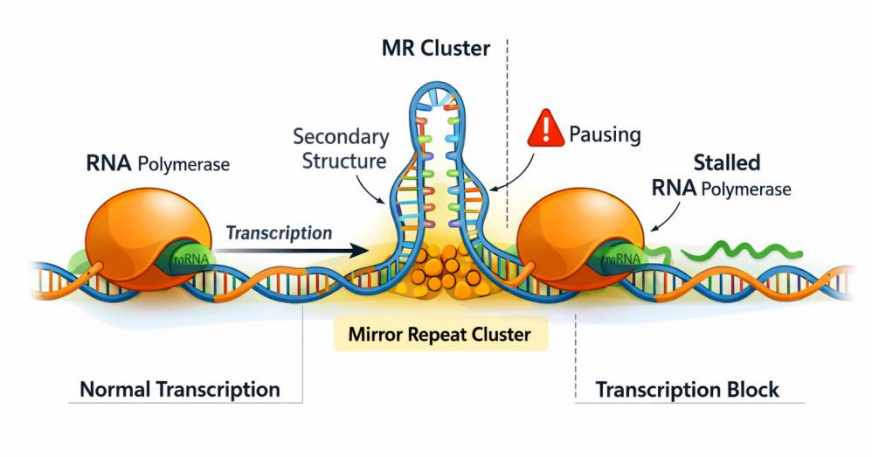

Figure 5 : Impact of Mirror Repeats on Transcription

One of the most notable findings is the enrichment and clustering of mirror repeats within particular exonic regions, especially within longer exons. Although exon length contributes to the absolute number of repeats, the lack of a strict linear relationship between exon length and mirror repeat density suggests that sequence composition and local nucleotide context play a more significant role than spatial availability alone. Similar enrichment patterns have been reported for other noncanonical DNA motifs, which frequently localize to regions involved in transcriptional regulation and genome structural dynamics (Zhao et al., 2009; Kouzine et al., 2013).

Comparative analysis of PAH transcript variants further revealed transcript-specific differences in mirror repeat distribution. Despite encoding the same protein, variations in exon organization and untranslated regions influenced mirror repeat localization and density. This observation highlights the importance of transcript architecture in shaping repetitive DNA landscapes and suggests that alternative transcript structures may differentially accommodate noncanonical DNA motifs. Such transcript-dependent variability has been proposed as a mechanism influencing RNA stability, transcriptional efficiency, and regulatory flexibility (Sharma, 2011; McGinty et al., 2025).

The presence of imperfect mirror repeats within exonic regions is particularly noteworthy. Imperfect symmetry may allow transient formation of alternative DNA conformations, such as triplex DNA, while maintaining coding sequence integrity. This balance between structural flexibility and functional constraint has been suggested as a common feature of non-B DNA motifs within coding regions, where excessive structural rigidity could be deleterious (Frank-Kamenetskii & Mirkin, 1995; Pearson et al., 2005). The enrichment of imperfect repeats may therefore represent an evolutionarily tolerated compromise that permits structural modulation without disrupting gene function.

Potential Experimental Validation Strategies

Although the present study is computational in nature, the observed mirror repeat enrichment and clustering patterns suggest several experimentally testable hypotheses. Electrophoretic mobility shift assays (EMSA) could be employed to assess the ability of mirror repeat–containing sequences to adopt alternative conformations or interact with DNA-binding proteins under physiological conditions (Carey, Peterson, & Smale, 2013). Triplex formation assays, including chemical probing and nuclease sensitivity assays, could be used to directly evaluate the propensity of identified mirror repeats to form triplex DNA structures in vitro, as previously demonstrated for polypurine–polypyrimidine mirror repeats (Frank-Kamenetskii & Mirkin, 1995; Wells, 2007). Additionally, reporter gene assays incorporating repeat-rich exonic or untranslated regions could be designed to investigate whether mirror repeats influence transcriptional activity, transcript stability, or splicing efficiency (Kouzine et al., 2013; Belotserkovskii et al., 2018). Such experimental approaches would provide valuable validation of the functional implications inferred from the computational patterns described in this study.

While experimental validation was beyond the scope of the present work, the identification of repeat-enriched exonic regions provides a rational framework for targeted functional assays. Given the clinical relevance of the PAH gene, future integration of computational and experimental approaches may offer deeper insight into how repetitive DNA motifs contribute to gene regulation and genomic vulnerability in disease-associated loci.“Mirror repeat identification and classification were performed as described previously (Singh and Dangi, 2026).

CONCLUSION

The functional analysis of mirror repeat distribution across PAH transcript variants highlights the structured and non-random organization of these motifs within a clinically important gene. Transcript-specific enrichment, exon-wise clustering, and the presence of imperfect mirror repeats and predominance of perfect mirror repeats with single spacer collectively suggest that mirror repeats may contribute to localized structural features with potential regulatory or stability-related roles. These findings provide a functional context for mirror repeat organization in PAH and establish a foundation for future experimental investigations into their biological significance.

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