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The Circular DNA Size Code

Methods to detect pathological shortening or elongation of circular DNA in human cells

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Abstract

Circular DNA molecules—mitochondrial DNA (mtDNA) and extrachromosomal circular DNA (ecDNA)—are fundamental genetic elements whose structural integrity is essential for cellular homeostasis. Pathological alterations in their length, caused by deletions or duplications, are directly implicated in a broad spectrum of human diseases, from inherited mitochondrial disorders to aggressive cancers. This review provides a comprehensive methodological guide for detecting these specific structural changes. We systematically evaluate classical techniques (long-range PCR, Southern blotting, electron microscopy) that offer direct visualization and validation, and modern high-throughput approaches (short- and long-read sequencing) that enable genome-wide discovery. Special emphasis is placed on quantitative clinical tools like digital droplet PCR (ddPCR) for ultrasensitive monitoring. By presenting a comparative framework, we guide the selection of optimal methods based on resolution, throughput, and clinical applicability. We conclude that an integrated, multi-method strategy is indispensable for robust analysis, positioning the precise detection of circular DNA length alterations as a cornerstone of emerging precision diagnostics and therapeutic strategies.

Keywords: Mitochondrial DNA, Extrachromosomal Circular DNA, Structural Variation, Next-Generation Sequencing, Digital PCR, Molecular Diagnostics.

Introduction

The human genome's architecture extends beyond linear chromosomes to include dynamic circular DNA (circDNA) molecules. These circles are not mere curiosities but critical players in cellular energetics and oncogenesis. Their pathological remodeling—specifically shortening via deletions or elongation via duplications—serves as a direct biomarker and functional driver of disease. The accurate detection of these length alterations is therefore a paramount challenge in molecular biology and clinical diagnostics. This article synthesizes the current methodological landscape, providing a roadmap for researchers and clinicians to navigate from fundamental discovery to patient-specific monitoring.

The Biological Imperative: Why Circular DNA Length Matters

Circular DNA exists primarily in two forms: the multi-copy mitochondrial genome (mtDNA) and gene-amplifying extrachromosomal circular DNA (ecDNA) in cancer. MtDNA, essential for oxidative phosphorylation, is prone to large-scale deletions associated with mitochondrial myopathies, neurodegeneration, and aging (Kraytsberg et al., 2006). EcDNA, bearing oncogenes like MYCN or EGFR, lacks centromeres and segregate randomly, driving intra-tumoral heterogeneity and therapy resistance. Critically, their size is not static; ecDNA can evolve through internal duplications, increasing oncogene copy number and fostering aggressive tumor phenotypes (Wu et al., 2019; Shoshani et al., 2021). Thus, quantifying these physical changes is key to understanding disease mechanism and progression.

The Methodological Arsenal: From Visualization to Digital Counting

The detection of circDNA length changes spans several technological generations, each with distinct advantages.

Foundational Techniques: Direct Physical Analysis.

Classical methods provide tangible evidence of size alteration. Long-range PCR is a rapid screening tool for known large mtDNA deletions, producing shorter amplicons visible on gels. Southern blotting remains the gold-standard for validation, distinguishing topological forms and providing semi-quantitative heteroplasmy data for mtDNA deletions (Shadel & Clayton, 1997). Electron microscopy (EM) offers the most direct proof, allowing absolute length measurement and visualization of circular conformation, historically pivotal for identifying ecDNA (Cox et al., 1965). Fiber-FISH extends fluorescence in situ hybridization to stretched DNA fibers, enabling physical mapping of gene order and tandem duplications within large ecDNA amplicons. While

invaluable for validation, these techniques are generally low-throughput and require prior sequence knowledge.

The Sequencing Revolution: Base-Pair Resolution.

Next-generation sequencing (NGS) enables unbiased, genome-wide discovery. Short-read sequencing (e.g., Illumina) indirectly infers circular junctions and duplications through bioinformatic analysis of split-reads and read-depth coverage (Zhang et al., 2016; Beroukhim et al., 2010). However, its inability to span large repeats or reliably phase variants limits definitive structural resolution. This limitation is overcome by long-read sequencing (PacBio, Oxford Nanopore). A single long read can traverse an entire circular junction or mtDNA genome, providing unambiguous evidence of circularity, precise breakpoints, and the complete sequence of the molecule (Zhao et al., 2021). Nanopore technology adds a further dimension by enabling simultaneous detection of sequence and DNA methylation (Liu et al., 2021). Long-read sequencing is rapidly becoming the definitive tool for de novo characterization of complex circDNA.

Clinical Quantification: Digital Precision for Diagnosis.

For translational medicine, sensitive quantification is essential. Quantitative PCR (qPCR) is widely used for relative quantification of known mtDNA deletions. Its successor, digital droplet PCR (ddPCR), partitions reactions into thousands of droplets for absolute target counting. DdPCR offers superior sensitivity (detecting <0.1% heteroplasmy), precision, and resistance to PCR inhibitors, making it the emerging gold standard for diagnostic screening and monitoring of both mtDNA mutations and ecDNA in liquid biopsies (Qian et al., 2021).

A Strategic Framework for Method Selection

Choosing the right method depends on the question. For screening known mtDNA variants, ddPCR offers optimal sensitivity. For discovering novel rearrangements, short-read NGS provides cost-effective breadth, while long-read NGS delivers definitive structural resolution. For validating ecDNA structure, a combination of Fiber-FISH (visual mapping), EM (topological proof), and long-read sequencing (base-pair resolution) is powerful. In the clinic, a tiered strategy is effective: initial screening with targeted ddPCR, followed by comprehensive long-read mtDNA sequencing for unresolved cases, and subsequent monitoring with patient-specific ddPCR assays (Stenton et al., 2021).

Future Horizons: Towards Integrative and Single-Cell Analysis

The field is moving beyond detection towards functional integration. Future work requires:

- **Multi-omics Integration**: Correlating circDNA structure with transcriptional (RNA-seq) and epigenetic (e.g., nanopore methylation) data from the same sample.
- **Advanced Bioinformatics**: Developing algorithms dedicated to the de novo assembly and phasing of complex circular sequences from long-read data.
- **Single-Cell Analysis**: Applying technologies like scATAC-seq or novel multi-omic methods to understand the cell-to-cell heterogeneity of circDNA length and its functional impact in tumors and aging tissues.
- **Exploring the Dark Matter**: Systematically studying the length and function of small, non-coding eccDNAs, a vast but poorly understood component of the circular genome.

Conclusion

The pathological shortening and elongation of circular DNA are fundamental disease processes. The methodological toolkit to decode this "size code" is now rich and versatile, spanning from the visually definitive to the digitally precise. Strategic integration of these methods—combining the discovery power of long-read sequencing with the ultrasensitive quantification of ddPCR—is accelerating the transition of circDNA analysis from a research specialty to a pillar of precision oncology and genetic medicine. As we begin to integrate structural data with functional outputs at single-cell resolution, we unlock the potential for novel diagnostics and targeted interventions for some of the most challenging human diseases.

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