

RESEARCH ARTICLE

G-QUADRUPLEXES IN THE HUMAN GENOME: ORGANIZATION, GENOMIC ROLES, ASSOCIATED DISEASES AND THERAPEUTIC POTENTIAL

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ABSTRACT

G4 are guanine-rich non-canonical nucleic acids conformations in eukaryotic genomes. The cellular, genomic and physiological significance of G4s was skeptical a decade ago. Computational and experimental methods have offered new perspectives into their roles. Biophysical research has demonstrated relationship between the G4 sequence content, topology, and thermodynamic stability. G4s are primarily located in genomic areas such as telomeres, enhancers, and gene promoters. G4s are involved in transcriptional regulation and chromatin mediated epigenetic genome changes. Abnormal formation, stabilization or resolution of G4 structures can contribute to several human diseases development. G4 sequences have been researched as target for therapy in several diseases. Several G4 targets have passed clinical approval. Thus G4 sequences have research potential both in basic biological and clinical research. The current review aims to update the current literature on the biophysical, cellular and disease roles of G4 sequences. Further, we discuss in detail its roles in cancer and therapy. This update will provide valuable insights into their structural and biology insights thus facilitating clinical applications.

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INTRODUCTION

G-quadruplexes (G4s), alternative DNA secondary structures that control transcription, telomere integrity, and genome maintenance, have been found in all kingdoms of life (Liu *et al.*, 2021). Only about 3% of the human genome is expressed in proteins, according to ENCODE project results, while RNA and DNA may create functionally significant non-canonical secondary structures (Lu *et al.*, 2019). One of the non-canonical conformations that nucleic acids can take on in guanine-rich areas of the genome or in guanine-rich RNA molecules is G4 (Yadav *et al.*, 2017). G4s are the most fascinating secondary structures of nucleic acids is G-quadruplexes. G4 are globularly folded structures that can easily form under physiologically appropriate conditions, allowing for a variety of experimental studies. In particular, Hoogsteen hydrogen-bond base pairing allows sequences with four tracks of two or more consecutive guanines to self-assemble into planar G-tetrads, which can stack on top of one another to generate G4 (Banco and Ferré-D'Amaré 2021).

Alternative G4 topologies have been identified by structural investigations, and *in vitro* research have demonstrated a relationship between G4 sequence content, topology, and thermodynamic stability (Chilton, *et al.*, 2024). Although there was continued scepticism about the physiological significance of G4s, significant developments in computational and experimental methods have offered several new perspectives. G4s are now widely acknowledged as highly dynamic structures that are functionally significant and starting to acquire widespread appreciation by research community for their diverse roles in the genome. G4s are primarily located in genomic areas that are functionally significant, such as telomeres, enhancers, and gene promoters (Nuccio *et al.*, 2026). Promoter-G4s are over-represented in genes related to cell cycle regulation, development, and stress responses and are often located upstream of transcription start sites (TSSs) (Shen *et al.*, 2021). The identification of G-quadruplex structures *in vivo* has advanced significantly. The discovery of various protein classes that identify, stabilise, or resolve G4s further emphasises their biological significance.

Replication stress, genomic instability, and aberrant gene expression have all been linked to dysregulation of G4 formation or resolution, either by depleting G4-resolving helicases or by G4-stabilizing ligands (Karatayeva *et al.*, 2023). The involvement of increased instability of G4s in a number of human disorders further emphasises the significance of G4 control in human health (Wang *et al.*, 2021).

These structures have shown significant therapeutic relevance as potential cancer biomarkers (Zhang, *et al.*, 2024). Critical insights into their coordinated roles in genome control are being provided by human control approaches. The potential application of G-4 for biomaterials, biosensors, and biocatalysts has attracted attention adding another layer of scope (Liu *et al.*, 2026). In order to have a deeper understanding of the cell and molecular activities of G4, it is necessary to explore the current literature. A step in that direction is the current review.

Biochemistry and biophysical aspects G4 quadruplexes in the human genome: G-quadruplexes are non-canonical secondary structures of nucleic acids characterized by guanines arranged in stacked tetraplex arrays. Decades of research into these peculiar assemblies of DNA and RNA, fuelled by the development and optimization of a vast array of techniques and assays, has resulted in a large amount of information regarding their structure, stability, localization, and biological significance in native system (Kharel *et al.*, 2024).G-quadruplexes (G4s) can be uni-, bi-, or tetramolecular with respect to strands, folded unimolecular conformations are most significant *in vivo*.

Unimolecular G4 can potentially form in sequences with runs of guanines interspersed with what will become loops in the folded structure: 5'G_xL_yG_xL_yG_xL_yG_x, where *x* is typically 2–4 and *y* is highly variable (Belachew 2022).. Such sequences are highly conserved and specifically located in genomes. In the folded structure, guanines from each run combine to form planar tetrads with four hydrogen-bonded guanine bases; these tetrads stack on one another to produce four strand segments aligned in specific parallel or antiparallel orientations, connected by the loop sequences (Monsen *et al.*, 2022).

Most biologically relevant G-quadruplexes are intramolecular G-quadruplexes, with three-tetrad cores being the most common. In contrast to tetramolecular structures, intramolecular G-quadruplexes form quickly and exhibit great conformational diversity, such as in folding topology, loop conformation, and capping structures. Based on G-strand directionality, a G-quadruplex can be parallel with all four G-strands in the same direction, hybrid/mixed with both parallel and antiparallel strands, and antiparallel with all adjacent G-strands antiparallel to each other. Research has identified three types of loops (lateral, diagonal, or “propeller”). Table-1 list few nucleotide sequences and their G4 configurations.

Table 1. Few nucleotide sequences and their G4 confirmation

Sequence(5'-3')	Name	G4	Refs
T ₁₈	T18	non G4	Chang et al., 2012
N ₃₀	L30	non G4	
T ₃ G ₂ T ₂ G ₂ T ₆ TG ₂ T ₂ G ₂	TBA	Antiparallel	
T ₃ G ₄ T ₄ G ₄ T ₄ G ₄ T ₄ G ₄	Oxy28	mixed parallel	
T ₃ G ₃ CGCG ₃ AG ₂ A ₂ G ₃ CG ₃	Bcl-2	Parallel	
T ₃ GAG ₃ TG ₄ AG ₃ TG ₄ A ₂	c-Myc	Parallel	
T ₂ A(G ₄ C) ₃ G ₃	RET	Parallel	
T ₃ (CG ₃) ₂ CGCG(AG ₃) ₂	c-Kit2	Parallel	

There are over 700,000 putative G4-quadruplexes (G4Qs) in the human genome, found largely in promoter regions, telomeres, and other regions of high regulation (Bourdon *et al.*, 2023) Bioinformatic searches of the human genome show that longer sequences with the potential for forming multiple G4 units are common. Numerous extended promoter sequences have similar potentials for multimeric G4 formation. X-ray crystallography and NMR methods are challenged by the longer sequences (>30 nt), hence other tools are needed to explore the possible multimeric landscape (Tevonyan *et al.*, 2025). The stacked tetrads form a central cavity that features strong coordination sites for monovalent cations that stabilize the G4 structure, with potassium (K)or sodium (Na)preferred. A single monomeric G4 typically forms from a sequence containing roughly 20–30 nucleotides (Xiao *et al.*, 2025).

Growing evidence links their presence to functionality in various cellular processes, where cellular proteins interact with them, either stabilizing and/or anchoring upon them, or unwinding them to allow a process to proceed. Interest in understanding and manipulating the plethora of processes regulated by these G4Qs has spawned a new area of small-molecule binder development, with attempts to mimic and block the associated G4-binding protein (G4BP (Meier-Stephenson, 2022). Figure 1 summarises the structural diversity, topology and recognition of the G4 sequences. These structures exhibit diverse topologies and are implicated in critical genomic regions such as telomeres and promoter regions of oncogenes, playing significant roles in gene expression regulation, genome stability, and cellular aging. I-motifs, formed by cytosine-rich sequences under acidic conditions and stabilized by hemiprotonated cytosine–cytosine (C:C+) base pairs, also contribute to gene regulation despite being less prevalent than G4s. Despite significant progress, challenges remain in observing these structures *in vivo* and fully elucidating their biological functions (Obara and *et al* 2024).

The link between the chemical stability of G-quadruplex (qDNA) structures and their roles in eukaryotic genomic maintenance processes has been an area of interest now for several decades. Single-molecule force-based techniques can provide insight into the mechanical stabilities of a variety of qDNA structures as well as their ability to interconvert between different conformations under conditions of stress. Atomic force microscopy (AFM) and magnetic and optical tweezers have been the primary tools used in these investigations and have been used to examine both free and ligand-stabilized G-quadruplex structures. These studies have shown that the degree of stabilization of G-quadruplex structures has a significant effect on the ability of nuclear machinery to bypass these roadblocks on DNA strands (Vashistha *et al.*,2023). The cellular components including replication protein A (RPA), Bloom syndrome protein (BLM), and Pif1 helicases are capable of unfolding qDNA. Techniques such as single-molecule fluorescence resonance energy transfer (smFRET), often in conjunction with the aforementioned force-based techniques, have proven extremely effective at elucidating the factors underpinning the mechanisms by which these proteins unwind qDNA structures (Kusi *et al.*, 2023). Guanine-rich DNA strands can fold into non-canonical four-stranded secondary structures named G-quadruplexes (G4s). G4s folded in proximal promoter regions (PPR) are associated either with positive or negative

Table 2. List of few drugs in cancer therapy targeting various G4

Drugs	Targets	Cancer	Ref
Tetra-Pt	Telomeric G4	Pan-cancer	Shen et al., 2020
L1 -transpt	G4-DNA	Triple-negative breast cancer	Liu et al., 2023
BMPQ-1	Telomeric multimeric G4-DNA	Lung cancer	Gao et al., 2020
BMVC-8C3O	c-FOS G4-DNA	Non-small cell lung cancer	Lu et al., 2023
13d	Telomeric G4	Gastric cancer	Ma et al., 2021
MY-8	MYCN G4-DNA	Neuroblastoma	Yang et al., 2021
Naphthalimide-benzotriazole conjugates 3c	Bcl2-G4	Lung cancer	Wang et al., 2022
Benzothiophenonaphthalimides 7c	mtDNA G4	Human renal cell carcinoma	Huang et al., 2022
Compound 15	Tel23 G4-DNA	Osteosarcoma Cervical carcinoma	Amato et al., 2022

Table 3.Virus associated G4 and binding ligands

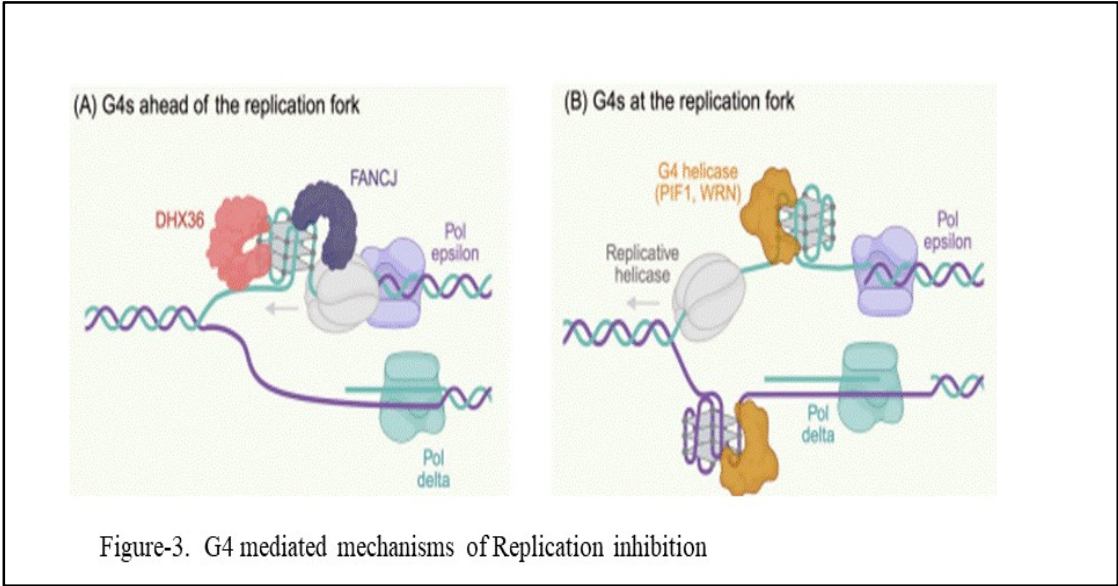
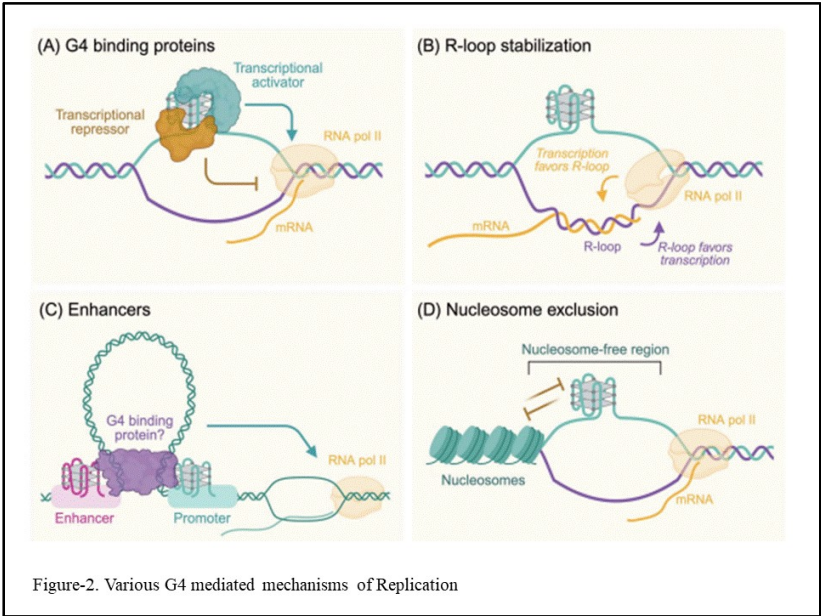
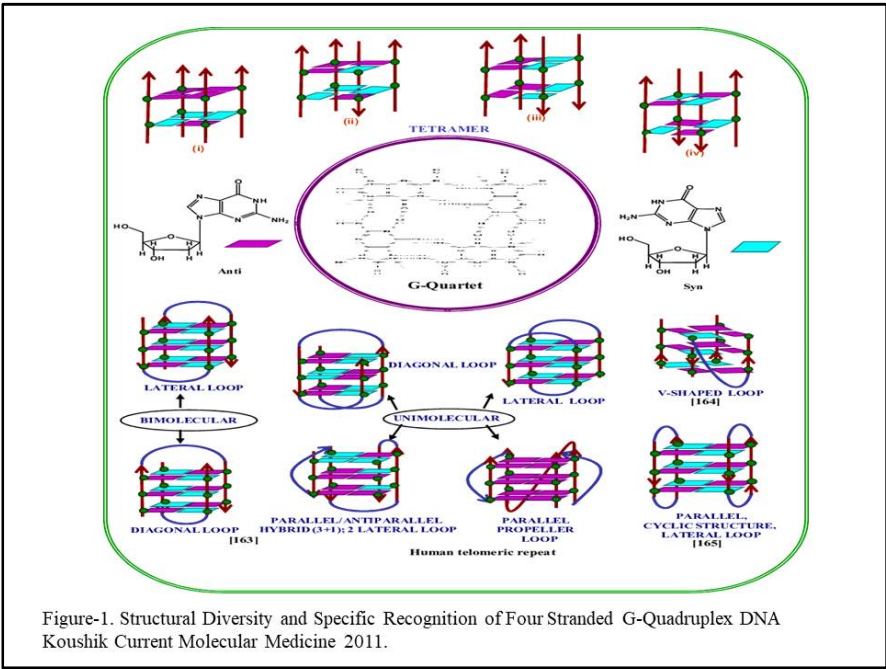
Family/Virus	Genome (kb)	Presence of pG4 Motifs	G4-Binding Ligands	Refs
Retroviridae/HIV-1	ssRNA (+) (9.75 kb)	U3 region of 5' LTR nef	BRACO-19 TMPyP4 PIPER	Pathak 2023
Coronaviridae/SARS-CoV-2	ssRNA (+) (29.7 kb)	ORF1a (position 13,385), S (position 24,268), ORF3a, Membrane (M), RG-1 of Nucleocapsid (N)	BRACO-19 TMPyP4 PDP	
Orthomyxoviridae/IAV	ssRNA (−) (13.5 kb)	PB1 (7KW), PB2 (1KW, 6KW), PA (9KW), HA (11KW)	NMM	
Papillomaviridae/HPV	dsDNA (8 kb)	E1 (HPV32), E4 (HPV9) L2 (HPVs 16, 18, and 57) LCR (HPVs 52 and 58)	PhenDC3 C8	
Polyomaviridae/ SV40	dsDNA (5 kb)	Non-coding regulatory region (NCRR)	PDI	
Herpesviridae/EBV	dsDNA (172 kb)	EBNA1 GAr mRNA	BRACO-19 PDS	

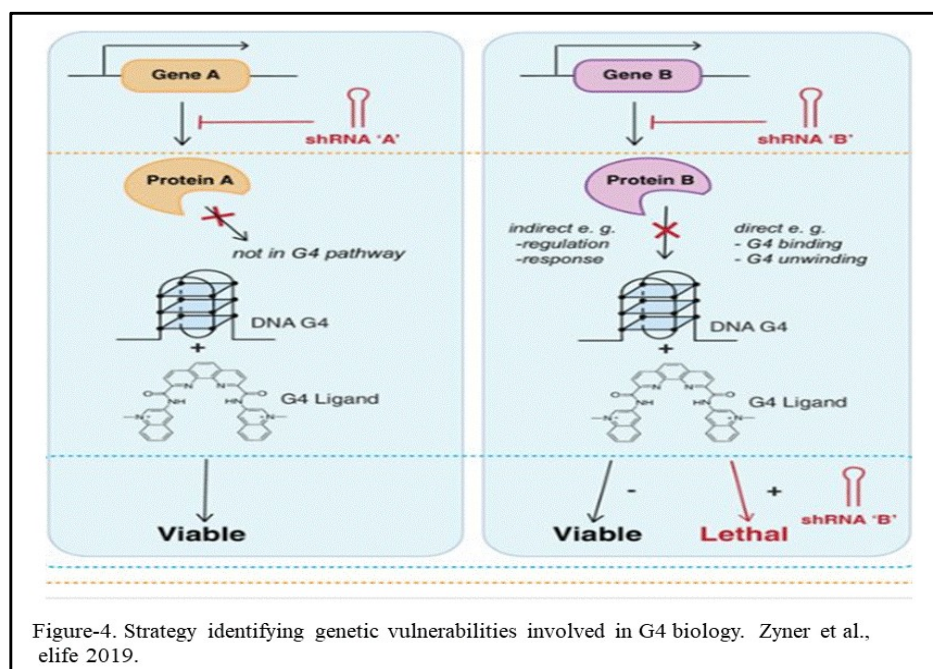
Table 4. Rare hereditary diseases associated with defects in G-quadruplex (G4) metabolism and replication stress

Disease	Causative gene/protein	Major clinical manifestations	G4-associated cellular defects / molecular consequences	Key references
Bloom syndrome (BS)	BLM	Growth deficiency, photosensitivity, immunological abnormalities, markedly increased cancer risk	Impaired G4 resolution contributes to replication-fork stress, reduced DNA synthesis, abnormal replication intermediates, elevated sister-chromatid exchange, defective synthesis of G-rich telomeric DNA, and accumulation of RNA-G4 structures	Herr, et al., 2026
Seckel syndrome type 8	DNA2	Microcephaly, growth retardation/dwarfism	DNA2 dysfunction affects replication-associated processing and G4 homeostasis, contributing to replication stress	
Fanconi anemia (FA), complementation group J	FANCF/BRI P1/BACH1	Bone-marrow failure, congenital abnormalities, abnormal digits, growth defects and cancer susceptibility	FANCF deficiency increases sensitivity to G4-stabilizing ligands, promotes G-tract instability and G4 accumulation, and impairs replication progression	
Fanconi anemia (FA), FANCD1 subtype	BRCA2/FANCD1	Bone-marrow failure, congenital abnormalities and increased cancer susceptibility	BRCA2 deficiency affects replication-associated G4 homeostasis and telomere maintenance	
Myelodysplastic syndrome (MDS)	HLTF	Cytopenia, bone-marrow dysplasia and risk of acute myeloid leukemia	HLTF deficiency promotes DNA damage and double-strand breaks and impairs PCNA polyubiquitylation, compromising replication-stress responses	

transcriptional regulation. G-quadruplexes (G4s) under physiological conditions has been recognized for its potential regulatory function of various biological processes. Among those, transcription has recently emerged as a key process that can be heavily affected by G4 formation, particularly when these structures form at gene promoters. Indeed, earlier studies linking G4-formation and transcription mainly relied on small-molecule ligands to stabilize and promote G4s, which leads to disruption of protein–DNA interactions and local environments and, therefore, does not necessarily reflect the endogenous function of G4s at gene promoters. There is now strong evidence pointing toward G4s being associated with transcriptional enhancement, rather than repression, through multifaceted mechanisms such as recruitment of key transcriptional proteins, moulding of chromatin architecture, and mode of phase separation (Antariksa *et al* 2024). G-quadruplexes have long been implicated in the regulation of chromatin packaging and gene expression. These processes require or are accelerated by the separation of related proteins into liquid condensates on DNA/RNA matrices. While cytoplasmic G4s are acknowledged scaffolds of potentially pathogenic condensates, the possible contribution of G4s to

phase transitions in the nucleus has only recently come to light (Pavlova *et al* 2023). Viral protein interact with G4 structures by which pathogens exploit these secondary structures to modulate replication, transcription, and latency, thus offering insights into novel antiviral strategies. Precise targeting of specific genomic G4 structures involves using a novel fusion protein combining catalytically inactive Cas9 (dCas9) with a G4-binding peptide enabling a dual recognition — sequence-specific and structure-specificity. This method has transformed genome targeting applications by drastically improving selectivity and reducing off-target effects (Wang 2025). G4-binding proteins are involved in vital cellular processes such as telomere maintenance, DNA replication, gene transcription, mRNA processing. G4-binding proteins are also associated with various human diseases. An intensive study of G4-protein interactions provides an attractive approach for potential therapeutics and these proteins can be considered as drug targets for novel medical treatment (Shu *et al.*, 2022). Computational approaches therefore offer efficient alternatives for G4 identification and characterization. G4ShapePredictor represents a computational tool capable of predicting G4 folding topology from sequence data alone, identifying three





sequence motifs that suggest specific topological folding. G4STAB represents the first deep learning approach for predicting thermodynamic stability with high accuracy ($R^2 = 0.8$) while incorporating salt concentration and pH. G4STAB is another tool results obtained through this tool reveal that cancer increase the number of physiologically relevant G4 structures by approximately 13.5 times (Liew 2025). Recent evidence indicates that G4 ligands may target other cellular components and compartments such as lysosomes and mitochondria (Ferret *et al.*, 2023). Crucially, a large amount of biochemical and physical evidences have enabled insights into the roles of G-quadruplexes, unique structures, assemblies hence paving path for drug targets in diseases such as cancer (Dell'Oca 2024). The structural properties of these DNA forms are explored for applications in nanotechnology and molecular devices. Cornucopia of phytocompounds are effective in binding and modulating the thermal stability of G4s and contain almost unexplored G4 motifs in their genome that could inspire new biotechnological strategies (Falanga 2022).

Genomic roles of G4 DNA: For biology, the important questions are where and when the mapped pG4s form G-quadruplex structures *in vivo*. Genomic DNA is primarily double stranded and stabilized through being packaged into chromatin. However, two exceptions are the very tips of the linear eukaryotic chromosomes that have the conserved feature of ending in a single-stranded G overhang and in mRNA (Robert, *et al.*, 2020). In double stranded DNA, the opportunity for forming G-quadruplexes arises during DNA replication, transcription and repair when DNA is rendered transiently single stranded through the breaking of Watson-Crick base pairing (Yuan *et al.*, 2020). This permits the alternative Hoogsteen base pairing present in G-quadruplexes to take place. Indeed, emerging *in vivo* observations are consistent with G-quadruplex formation and resolution providing a regulatory role. In addition, it can be envisaged that G-quadruplex formation could be favoured by superhelical stress, molecular crowding as well as specific G-quadruplex binding proteins (Dell'Oca, *et al.*, 2024). G4s are implicated in transcriptional regulation supported by substantial experimental evidences based on quantitative occupancy. In eukaryotes, G4s located at the TSS predominantly promote

transcription (Spiegel, 2021), although specific G4 conformations are recently shown to induce transcriptional repression (Yoo, *et al.*, 2025). Several models have been proposed to describe the process. The first described model considers G4s as binding sites for transcription factors. Research extensively has shown binding of transcription factors to G4-forming sequences *in vitro* and these transcription factors have been mapped at promoters in cells (Lago, *et al.*, 2021), although a comprehensive analysis of their genome-wide distribution with respect to G4s is missing. Importantly, transcriptional repressors have also been shown to bind to G4s at promoters, painting a picture in which G4s act as general hubs for the recruitment of transcriptional regulators (Huang, *et al.*, 2026). Most G4 binders show high affinity for DNA and a variable degree of selectivity for G4s over single- or double-stranded DNA *in vitro* (Wang *et al.*, 2022); however, it remains to be clarified if the transcription factor binding specificity is more sequence- or G4-dependent in physiological contexts. In the next model G4s have also been proposed to act as transcriptional amplifiers, rather than simple transcriptional activators (Robinson, *et al.*, 2025). G4s they fold as a consequence of transcription, triggered by transcription bubble formation, and supported by transcription dependent negative supercoiling. Once formed, G4s function by sustaining a stable level of gene expression through a positive feedback loop involving engagement of nascent mRNA transcripts in R-loop formation (Gallina and Richter 2026). G4s are not only enriched at promoters but are also frequently found at enhancers, intergenic regions that regulate chromatin looping and enhance the expression of multiple gene targets (Hänsel-Hertsch, *et al.*, 2016). At these sites, G4s have been proposed to promote long-range transcription by stabilizing chromatin loops, potentially through the formation of long-range intermolecular G4s or by interactions between intermolecular G4s (de Lima, *et al.*, 2026). G4-binding protein complexes enable maintain loop integrity (Migletta, *et al.*, 2020). G4s also functions as epigenetic marks, suggesting that these structures can modulate gene expression at a higher regulatory level by influencing chromatin accessibility at promoters, similar to histone modifications and DNA methylation (Feng, *et al.*, 2022). Promoters are in fact well known to carry euchromatic histone marks that confer an open

chromatin conformation, and genome-wide mapping studies reveal an extensive overlap between G4s and euchromatin regions (Galli, *et al.*, 2024). More specifically, G4s are enriched in nucleosome-depleted regions within promoters, consistent with a model in which nucleosomes and G4s are mutually exclusive (Shen, *et al.*, 2021). Promoter-associated G4 folding has been recently observed to precede transcriptional activation in cancer cell lines and to be negatively influenced by closed chromatin (Esain-Garcia *et al.*, 2024). G4-stabilizing ligands have been observed to induce specific changes in chromatin accessibility, in agreement with G4s functioning as epigenetic regulators (Lawler, *et al.*, 2023). Intriguingly, chromatin remodelers that promote open chromatin formation by actively extracting nucleosomes such as SMARCA4 can selectively bind to G4s at promoters, implying a possible causal link between G4 folding and the formation of accessible chromatin (Madden, *et al.*, 2026).

In parallel, guanine and cytosine residues have also been strongly implicated in epigenetic regulation by a different mechanism, which involves chemical modification of the DNA bases by a methyl group. This modification is actively added to cytosine residues in particular by methyltransferases such as DNMT1 (Bhattacharyya *et al.*, 2020), with DNA methylation acting as a repressive epigenetic mark that inversely correlates with euchromatin formation and selectively silences gene expression (Dhar *et al.*, 2021). Accordingly, active gene promoters are generally hypomethylated and G4-prone whereas silenced genomic loci show hypermethylation and a paucity of G4s (Mao, *et al.*, 2018). On the one hand, G4s appear to negatively impact DNA methylation by locally hindering DNMT1 activity on cytosines at the same genomic locations (Niu, *et al.*, 2023). On the other hand, cytosine methylation has been shown to locally impair G4 formation, possibly by modulating the stability of the secondary DNA structure (Medved, *et al.*, 2025). Further studies will be required to disentangle these reciprocal interactions, to establish causality and, in the end, to validate the role of G4s as primary determinants of chromatin architecture.

Figures 2 and 3 summarises the genomic roles of G4 sequences. G4s can form naturally during bulk DNA replication without an obvious function, and may even hinder replication fork progression (Herr, *et al.*, 2026). Although G4s are most frequently mapped at promoters of actively transcribed genes, they are also enriched in other regions of the human genome, namely telomeres and replication origins (Bryan 2020). Unlike in organisms such as yeast, replication origins in metazoans are not defined by a strict DNA sequence consensus (Hutchins, *et al.*, 2015). In this context, putative G4-forming sequences have been identified upstream of a subset of metazoan replication origins (Lerner, *et al.*, 2019). Origins containing these sequences share common features: they are replicated early in S phase and strongly overlap with regions of active transcription (Prorok, *et al.*, 2019). Moreover, G4-forming elements are sufficient to define replication origins when inserted ectopically into the genome, and mutation of these sequences at endogenous origins significantly reduces replication initiation efficiency. Notably, telomeric repeats (TTAGGG), located at the end of eukaryotic chromosomes are shown to fold into G4s (Fouquerel, *et al.*, 2016). Telomeric G4s fold both in the single-stranded 3' overhang at chromosome ends and within the double-stranded telomeric DNA, where they form on the strand opposite

specific R-loops generated by the telomere specific RNA TERRA (Guan, *et al.*, 2026; Paudel, *et al.*, 2024). G4s are thought to contribute to telomere homeostasis primarily by regulating telomere length (Vinayagamurthy, *et al.*, 2023). In viruses of the Herpesviridae family such as Epstein-Barr virus and human cytomegalovirus, replication origins are also defined by highly G-rich sequences with strong G4-forming potential (Park, *et al.*, 2024). These viruses maintain their double-stranded circular episomal DNA during latency by exploiting the host replication machinery. Given the extensive heterochromatinization of these viral genomes during latency, G4 formation at replication origins may be required to allow physical access of replication initiation factors, thereby ensuring viral genome maintenance (Gong, *et al.*, 2025). G4s can cause collateral damage and deeply affect genome stability if not efficiently processed. Although they are detected and processed throughout all phases of the cell cycle, G4s become particularly problematic during DNA replication (Valton and Prioleau 2016). When stably folded, G4s can act as physical obstacles to replication fork progression that, if not properly resolved to unstructured single- or double-stranded DNA, can cause DNA breaks (Varshney, *et al.*, 2021). Further it can lead to heritable epigenetic changes that can locally alter gene expression (Mukherjee, *et al.*, 2019). G4-enriched promoters have emerged as mutational hotspots in genome-wide analyses. Furthermore, stabilization of G4s using small-molecule ligands leads to increased replication stress and accumulation of DNA breaks in cells (Waisertreiger, *et al.*, 2015). The replication-associated toxicity of G4s originates from the existence of multiple helicases that are capable of unfolding these structures (Sun, *et al.*, 2026). Notably, several of these helicases, including FANCI, PIF1, WRN, and BLM, are physically associated with the replisome, underscoring the need to resolve G4s during DNA synthesis (Mendoza, *et al.*, 2016). Together, these observations support the view that at least some G4s are not inherently deleterious, as they are normally unfolded at the replication fork through multiple, partially redundant pathways. Genome instability, therefore, appears to arise primarily when G4 processing is impaired, either through stabilization by ligands or through loss of factors involved in their resolution.

G4 roles in Cancer and G4 ligands as Cancer therapeutics:

The World Health Organization reports that cancer is now one of the main causes of death worldwide (Siegel *et al.*, 2023). Therefore, it is crucial to increase research efforts to clarify the mechanisms behind the development of cancer and develop efficient treatment approaches. The promise of nucleic acids as feasible targets for the development of anticancer drugs has been increasingly confirmed by recent studies (Qiu *et al.*, 2023). G-quadruplexes (G4s), hairpins, cruciforms, and triplexes are examples of nonclassical secondary nucleic acid structures that affect important biological processes like transcription and translation (Tateishi-Karimata *et al.*, 2021). The most researched of them are G4s, which may control gene expression and preserve genomic stability in cancerous environments (Miglietta *et al.*, 2020). Furthermore, there has been a lot of research interest in small molecule medicines that target these structures (Cadoni *et al.*, 2021). G4 motifs are prevalent in the human tumour genome, especially in transcriptional regulatory elements and telomeric repeats (Che *et al.*, 2026). G4s may contribute to the development of cancer through a variety of roles in chromosome-associated genetic pathways, mainly affecting telomere maintenance, gene expression, and chromosome integrity (Richl 2024). TERRA-

mediated R-loops promote alternative lengthening of telomeres (ALT) activity and aid in the development of telomeric DNA G4 structures in human osteosarcoma cells (Xu *et al.*, 2024). BRCA2 expression is correlated with telomeric G4 stability in HeLa cells. TERRA-R-loop accumulation brought on by BRCA2 depletion stabilises telomeric G4s and attracts polycomb repressive complex 2 (PRC2), which in turn causes trimethylation of histone H3 at lysine 27 (H3K27me3) and chromatin condensation at telomeres (Lee *et al.*, 2024). When taken as a whole, our results show that G4 structures are crucial for preserving chromosomal integrity, guarding against DNA damage, and ultimately encouraging carcinogenesis. According to new research, chromosomal G4s can significantly impact the development of cancer by activating DNA damage response (DDR) pathways. Human replication protein A (RPA) binds to and resolves G4 complexes at telomeres (Lee *et al.*, 2021). In multiple myeloma (MM), TERRA G4 stabilisation encourages telomeric repeat-binding factor 2 (TRF2) dissociation, which initiates DDR activation (Scionti *et al.*, 2023).

The G4 structure of X-inactive specific transcript (Xist) RNA interacts with PRC2 to suppress H3K27me3 activity during X chromosomal inactivation (Lee *et al.*, 2024). On the other hand, in glioblastoma (GBM), the G4 in the hTERT promoter binds to TRF2, attracting the EZH2/PRC2 complex to cause H3K27 trimethylation and suppressing hTERT production (Sharma *et al.*, 2021). By preventing human DNA topoisomerase I (TOP1) activity during transcription in cancer cell lines such as HCT116, MDA-MB-231, and HeLa cells, G4s contribute to genomic instability. The findings point to a build-up of torsional stress, an increase in the development of R-loops (RNA–DNA hybrids), and ultimately transcription-replication conflicts, DNA double-strand breaks, and genomic instability (Liang *et al.*, 2024). Similar to this, deficiencies in the Fanconi anaemia complementation group J (FANCF) helicase (Lee *et al.*, 2021) or alpha thalassemia/mental retardation syndrome x-linked (ATRFX) helicase (Wang 2019) stabilise DNA G4 structures, causing replication stress, DNA damage, and ultimately apoptosis in cancer cells. In cancer treatment, ligands that target G4s have become a very promising class of structure-specific medications. Numerous metal ligands interact with DNA G4s with high affinity and selectivity, according to recent research (Zegers *et al.*, 2023). G4 ligands influence oncogenic transcription, replication stress, and RNA processing by acting at the structural level of the genome and transcriptome (Varshney *et al.*, 2020). Tetra-Pt(bpy) is one of the platinum-based ligands that concurrently targets the G4 in the PTK2 (FAK) gene and the telomeric G4, causing tumour cell senescence and preventing proliferation (Shen *et al.*, 2020). Specifically binding to the G4 in the MYC promoter, Pt-phen (Liu *et al.*, 2024) and L1-transpt (Liu *et al.*, 2023) dramatically reduce MYC expression and prevent the growth of breast cancer cells. One of the most researched families of G4 ligands are quinoline and acridine-based compounds, which show strong selectivity for G4s in oncogene promoters. Table-2 list few G4 cancer drugs.

Quinoline ligands that selectively stabilise telomeric G4, like RG260 (Song *et al.*, 2019) and BMPQ-1 (Gao C), cause DDR, cell cycle arrest, and apoptosis at telomeres. Specifically binding to the G4 in the c-MYC promoter, QN-1 (Hu *et al.*, 2019) suppresses MYC expression and prevents triple-negative breast cancer (TNBC) cells from proliferating (Hu and Lin, 2021). By stabilising telomeric G4 development,

acridine-based ligands like compound 3 and BRACO-19 (Lv *et al.*, 2022) suppress telomerase activity and cause senescence or cell death in a variety of cancer types. One of the most popular cores in G4 ligand design is naphthalene diimide (NDI), which has good planarity and modifiability. Naphthalene diimide-benzotriazole conjugates (3c) stabilise G4, downregulate BCL-2 expression, and induce apoptosis in lung cancer cells; β -Thiomaltosyl-NDI-NMe₂ can simultaneously target G4s in the KRAS and MYC promoters, downregulating the expression of both oncogenes and inhibiting colorectal cancer cell proliferation (Belmonte-Reche *et al.*, 2022). Porphyrins and G-quartets are among the most researched G4 ligands due to the strong π - π stacking interactions between their planar aromatic macrocyclic structures (Falanga *et al.*, 2024). TMPyP4 affects telomerase activity or the ALT pathway by stabilising G4 structures to interfere with telomere maintenance mechanisms (Tao *et al.*, 2024). According to Chen *et al.* (2021), the porphyrin–guanine compound mPG modulates transcription in osteosarcoma by particularly stabilising G4 in the promoter of platelet derived growth factor receptor β (PDGFR- β). A heterocyclic scaffold inspired by nature, coumarins have substituents that can be changed to improve selectivity and biocompatibility. According to Suseela *et al.* (2020), the coumarin-based substance TGP18 binds to BCL-2 G4, blocking transcription and triggering apoptosis via oxidative stress cascades and DNA damage. According to Xiao *et al.* (2024), the natural coumarin-based substance COP stabilises ATF4 G4, prevents it from interacting with TFAP2A, and lowers ATF4 levels, all of which cause cancer cells to die. Valiuska *et al.* (2022) created poly-purine reverse Hoogsteen hairpin (PPRH) oligonucleotides that target G4 structures in the MYC promoter and intronic regions based on nucleic acid and hybrid targeting techniques. By combining an HDAC inhibitory moiety with an indirubin scaffold that targets G4, Jiang *et al.* 2022 created a novel histone deacetylase (HDAC)/G4 dual-target inhibitor that demonstrated increased anticancer effectiveness against TNBC through synergistic effects. G4-targeting peptides are a new strategy that makes use of recognition patterns inspired by proteins. Transcriptional elongation or RNA translation is disrupted by the RHAU18 peptide, which binds specifically to G4 structures (De Paepe 2026). Myb A400 and Myb A412, optimised mutants of Rap1 protein Myb1 domain-derived peptides, have a substantial G4-binding affinity and cause telomeric DNA damage in tumour cells when coupled with cell-penetrating peptides (CPPs) like R²W (Merlino *et al.*, 2024). In 2023, Wang *et al.* created ApG4/LDCs, a tumor-specific theranostic platform that combines stimuli-responsive ligand–drug conjugates (LDCs) with G4-stabilizing DNA carriers. This approach co-delivers doxorubicin and sodium nitroprusside while improving G4 binding and nuclease resistance using a bifunctional fluorescent ligand (ThP-CyS). Clinical trials are being conducted on a number of these ligands. Pidnarulex (CX-5461) has anticancer properties and targets RNA polymerase I (Li *et al.*, 2025). Furthermore, G4 structures in pancreatic and breast tumours are targeted by QN-302 and CM03 (Ahmed *et al.*, 2024). A few of these ligands' limitations must be considered, such as the possible nephrotoxicity and neurotoxicity of metal ions, which restrict their dosage and practical usefulness. Off-target toxicities result from many G4 ligands' inability to distinguish between the thousands of unique G4 sites found in the human genome (Che *et al.*, 2026). Because G4 folding is dynamic and depending on the environment, it is challenging to develop predictable drug

interaction and binding affinity (Sahoo *et al.*, 2024). Due to a lack of knowledge about in vivo G4 regulatory networks, patient classification and specific treatment indications are still poorly characterised (Lin *et al.*, 2025).

G4s in human pathology and diseases: G-quadruplex (G4) structures are increasingly recognized as important regulators in neurological and neurodegenerative disorders. G4s are present in neuronal genes and can influence processes such as transcription, RNA processing, translation, RNA transport and interactions between RNA and binding proteins (Simone *et al.*, 2015). G4-associated disease mechanisms extend beyond DNA instability and may involve abnormal RNA folding, RNA-protein interactions, translational regulation and neuronal gene expression (Wang *et al.*, 2021). G4-associated mechanisms have been investigated across a broad spectrum of neurological and neurodegenerative disorders, including Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), fragile X syndrome, prion diseases and progressive myoclonus epilepsy. Several disease-relevant genes and proteins have also been linked to G4-dependent regulatory mechanisms, including *C9orf72*, *FMR1*/*FMRP*, *APP*, *BACE1*, *SNCA* and TDP-43 (Wang *et al.*, 2021). One of the best-characterized examples is the GGGGCC hexanucleotide repeat expansion in the *C9orf72* gene, which represents a major genetic cause of amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) (Mizielinska *et al.*, 2025). The expanded GGGGCC repeat within *C9orf72* produces RNA molecules that can fold into G-quadruplex (G4) structures and accumulate as nuclear RNA foci in affected tissues. These abnormal RNA structures can interact with specific RNA-binding proteins and thereby disturb normal nucleolar organization demonstrated that nucleolin, an essential nucleolar protein, preferentially recognizes the G4-containing *C9orf72* repeat RNA and becomes abnormally distributed in cells carrying the repeat expansion (Yang *et al.*, 2020). This alteration is associated with disruption of nucleolar function and evidence of nucleolar stress, providing a mechanistic connection between *C9orf72* repeat-derived RNA structures and ALS/FTD pathology (Hacusler *et al.*, 2014). In addition, the G4-binding protein fragile X mental retardation protein (FMRP) has an important role in neuronal RNA regulation, where recognition of G4-containing transcripts can influence their localization and translation. Alterations in FMRP function are closely associated with fragile X syndrome and related neurological pathology (Richter and Zhao 2021). Collectively, these findings indicate that G-quadruplex (G4) research has become an important area of investigation in neurobiology and neurodegenerative disease because these structures are widely distributed in the genome and transcriptome, while many aspects of their physiological and pathological functions remain incompletely understood. Depending on their location, sequence context and interacting proteins, G4 structures may influence neuronal processes in either protective or detrimental ways by regulating transcription, RNA metabolism, translation or genome stability (Wang *et al.*, 2021). G-quadruplex structures may contribute to the regulation of prion biology at both the DNA and RNA levels. The promoter of the human *PRNP* gene contains G4-forming sequences that have been proposed to participate in transcriptional autoregulation through interactions with PrP (Pradhan *et al.*, 2020).

Several disease-associated helicases are considered potential regulators of G4 structures, including the Werner syndrome protein (WRN), RECQ4, DNA2, and the XPD-related helicases FANCI, RTEL1 and CHL1/DDX11 (Mendoza *et al.*, 2016). Defects in these proteins are associated with distinct genomic instability and DNA-repair disorders, highlighting their potential importance in maintaining G4-containing regions. Members of this group that contain iron-sulfur (Fe-S) domains are of particular interest because their ability to participate in electron-transfer reactions has led to the proposal that they may couple G4 or DNA processing to cellular redox and signaling pathways (van der Lelij *et al.*, 2010). Further genome-wide investigations are needed to identify and characterize the full range of G4 structures recognized or processed by helicases and other regulatory proteins. Such studies will be important for establishing the functional organization of the G4 landscape and understanding how disruption of G4 metabolism contributes to human disease. Mutations in the genes encoding these auxiliary replication proteins are linked to hereditary disorders presenting with a range of clinical features, including immunodeficiency, growth restriction, congenital abnormalities, and cancer predisposition, demonstrating that these G4-metabolizing proteins also play broader roles in genome biology such as the replication stress response or DNA repair (Herr, *et al.*, 2026). Table 4 lists few diseases and associated pathology. Rothmund-Thomson syndrome (RTS) is a rare, inherited genetic disorder characterized by a distinctive skin rash, sparse hair, skeletal abnormalities, and an increased risk of childhood cancer. RTS is an autosomal recessive condition, meaning a child must inherit an altered gene from both parents. Mutations in the RECQL4 gene (and occasionally *ANAPC1*, *DNA2*, or *CRIP1*) are linked to this condition (Martins *et al.*, 2023). Warsaw Breakage syndrome (WABS) is a very rare inherited genetic disorder characterized by growth delays, small head size, and chromosome fragility. The *DDX11* gene codes a DNA helicase that repairs DNA and maintains chromosome stability (Pisani 2019).

G-Quadruplexes as Therapeutic Targets: G4-forming sequences are widely distributed throughout the human genome and transcriptome. They are particularly enriched in biologically important genomic regions, including telomeres, gene promoters, replication origins, untranslated regions (UTRs), and sites associated with transcriptional regulation. G4 structures can influence transcription, DNA replication, RNA processing, translation and genome stability. Their formation is dynamic and can be regulated by molecular factors such as helicases, G4-binding proteins, nucleic acid modifications and cellular ionic conditions. Consequently, abnormal formation, stabilization or resolution of G4 structures can disturb normal cellular functions and contribute to disease development. These characteristics have established G4s as promising molecular targets for therapeutic intervention (Balasubramanian and Neidle 2009). Figure 4 describes the strategy for drug development.

Mechanisms of G4-Targeted Therapy: G4-directed therapeutic approaches can broadly be divided into G4 stabilization, G4 destabilization or modulation of G4-associated proteins. G4 stabilization is the most extensively investigated strategy. Small molecules can bind to the external G-tetrad surfaces, grooves or loop regions and increase the thermodynamic stability of the structure (Cao *et al.*, 2026). When a G4 is stabilized at a critical genomic or transcriptomic

location, it may act as a physical barrier to DNA or RNA polymerases interfering with transcription, replication or translation depending on the location of the G4 (Gallina & Richter 2026). For example, stabilization of a promoter G4 can reduce transcription of an oncogene, whereas stabilization of a telomeric G4 can interfere with telomere maintenance (Awadasseid *et al.*, 2021; Shen *et al.*, 2022). Similarly, stabilization of RNA G4s can affect RNA folding, translation or interactions with RNA-binding proteins (Kharel, Pavel Ivanov 2024). These mechanisms demonstrate that the biological consequences of G4 stabilization depend strongly on the location, sequence and cellular context of the targeted structure. Another emerging approach involves targeting G4-associated proteins and helicases. Cellular helicases participate in the formation, resolution and regulation of G4 structures. Altering the activity of these proteins can modify G4 abundance and potentially influence disease-associated pathways (Estep *et al.*, 2019). Such strategies may be particularly relevant in cancers that have acquired defects in DNA repair or replication pathways and therefore exhibit increased dependence on mechanisms that resolve or tolerate G4-associated replication stress (Varshney *et al.*, 2020).

G-Quadruplexes and Cancer: Among human diseases, cancer is the most extensively investigated area for G4-targeted therapy. Cancer cells frequently exhibit increased proliferation, enhanced transcriptional activity, genomic instability and dependence on telomere maintenance (Anand *et al.*, 2026). Many of the genes involved in these processes contain G4-forming sequences. Promoter-associated G4 structures have also been identified in several important oncogenes, including MYC, KRAS, BCL2 and KIT. Stabilization of these structures by selective small molecules can interfere with transcription and consequently reduce the expression of genes required for cancer-cell survival and proliferation (Teng *et al.*, 2021). Telomeres represent another important therapeutic target. Human telomeres contain tandem guanine-rich DNA sequences that can fold into G4 structures. Normally, telomeres protect chromosome ends from being recognized as DNA damage. Cancer cells frequently maintain their telomeres through increased telomerase activity, enabling continuous cell division. Stabilization of telomeric G4 structures can interfere with telomerase access to chromosome ends and disrupt telomere maintenance. This may ultimately result in telomere shortening or dysfunction, DNA damage responses, cellular senescence and apoptosis. Thus, telomeric G4 stabilization provides a strategy for selectively interfering with an essential feature of many malignant cells (Balasubramanian and Neidle 2009). Several classes of G4-binding molecules have therefore been investigated as potential anticancer agents. Examples include telomestatin, BRACO-19, pyridostatin, TMPyP4, CX-5461 and QN-302. These compounds may induce cancer-cell death through mechanisms involving transcriptional repression, replication stress, DNA damage and disruption of ribosomal biogenesis (Savva & Georgiades 2021). Even though these compounds differ in chemical structure and target preference, many act by increasing the stability of G4 structures and interfering with DNA or RNA-dependent cellular processes. Some compounds can affect multiple G4-containing regions, whereas others have been designed to preferentially recognize particular G4 topologies or genomic sites.

The development of CX-5461 (pidnarulex) illustrates the translational potential of G4-targeting strategies. Initially

investigated as an inhibitor of RNA polymerase I-dependent ribosomal DNA transcription, CX-5461 was subsequently shown to have G4-stabilizing properties. It has been investigated clinically, particularly in tumours with defects in DNA-damage repair pathways such as BRCA1/2-associated cancers. Recent reviews describe its continued clinical development and its relationship with G4 stabilization and DNA damage (Li *et al.*, 2025). Another promising compound is QN-302, a tetra substituted naphthalene diimide derivative that binds G4 DNA. Preclinical studies have demonstrated potent activity against pancreatic ductal adenocarcinoma models, with suppression of cancer-associated gene transcription. QN-302 entered Phase 1a clinical evaluation, illustrating the movement of G4-targeted compounds from biochemical and cellular studies toward clinical investigation (Ahmed, *et al.*, 2024).

G-Quadruplexes in Neurological and Neurodegenerative Diseases: The significance of G4 structures extends beyond cancer. Research evidences indicates that DNA and RNA G4s participate in processes associated with several neurological and neurodegenerative disorders. G4-forming sequences occur in genes and RNA molecules involved in neuronal function, RNA metabolism, protein synthesis and cellular stress responses (Simone *et al.*, 2015). Abnormal G4 formation or altered interactions between G4s and RNA/DNA-binding proteins may contribute to disease-associated changes in gene expression and RNA processing (Wang *et al.*, 2021). One particularly important example is amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) associated with expansions in the *C9orf72* gene. The pathogenic GGGGCC repeat expansion in *C9orf72* can form G4 structures and other non-canonical nucleic acid conformations (Li *et al.*, 2025). These structures may interfere with transcription and contribute to the production of abnormal RNA species. Expanded repeat-containing RNAs can form pathological RNA foci and participate in mechanisms that disrupt cellular RNA metabolism and neuronal homeostasis (Chan *et al.*, 2014). Consequently, G4 structures associated with repeat expansion disorders have emerged as possible targets for future therapeutic approaches (Xu *et al.*, 2021). G4 structures have also been associated with Alzheimer's disease (AD), Parkinson's disease (PD), fragile X syndrome and other neurodegenerative conditions. In these disorders, G4s influences transcription, RNA stability, translation and through interactions with specific RNA-binding proteins (Kumar *et al.*, 2013). However, compared with cancer research, therapeutic development in neurodegenerative diseases is still at an earlier stage.

G-Quadruplexes as Antiviral Targets: G4 structures have also attracted attention in infectious diseases, particularly viral infections (Abiri, *et al.*, 2021). Putative G4-forming sequences have been identified in the genomes of numerous human viruses, including HIV-1, hepatitis viruses, papillomaviruses and other clinically important pathogens. Viral G4 structures may occur within genomic or regulatory regions and can influence transcription, replication, translation, genome packaging and other stages of the viral life cycle (Pathak *et al.*, 2023). This provides an alternative approach to antiviral drug development. Instead of targeting a viral enzyme or structural protein directly, a drug may recognize and stabilize a G4 structure within the viral genome or transcript (Zareie *et al.*, 2024). Stabilization of an essential viral G4 could interfere with replication or gene expression and thereby reduce viral

multiplication. An important advantage of targeting viral G4s is the possibility of exploiting structural differences between viral and host nucleic acids (Kim *et al.*, 2026). Table-4 summarises the Virus associated G4 sequences and binding ligands.

Challenges and Future Perspectives: Although G4s represent attractive therapeutic targets, several challenges must be overcome before their full clinical potential can be realized. The first major challenge is selectivity. G4 structures occur throughout the genome and transcriptome, including in healthy cells. A therapeutic ligand must therefore preferentially affect disease-associated G4s without producing unacceptable effects on essential cellular G4s (Zyner, *et al.*, 2022). The high structural polymorphism of G4s makes this problem particularly complex. A second challenge understands the precise biological role of individual G4 structures in living organisms. Much of the early G4 literature was based on biochemical experiments using isolated DNA or RNA sequences. Although cellular studies have provided increasing evidence for G4 formation *in vivo*, translating these observations into disease-specific mechanisms remains difficult. Consequently, improved imaging techniques, structural biology, genomic approaches and chemical probes are needed to identify functional G4s within disease-relevant cells and tissues (Sanchez-Martin 2024).

Despite substantial progress, G4-targeting therapy are faced with problems. Although numerous G4 ligands have been reported and several have entered clinical development, no G4-binding drug had yet received regulatory approval as a G4-directed therapeutic. Major challenges include achieving sufficient selectivity for disease-associated G4s, optimizing pharmacokinetic properties and distinguishing therapeutically relevant G4 structures from those required for normal cellular functions (Figueiredo *et al.*, 2024). A major challenge is determining whether a particular G4 structure is causative, protective or simply associated with disease progression in several degenerative disorders. Therefore, further *in vivo* studies are required to establish disease-specific G4 mechanisms and identify structures that can be safely manipulated therapeutically (Wang, *et al.*, 2021). Compounds TMPyP4, PhenDC3 and BRACO-19 remain at the preclinical stage, and issues of selectivity, cellular uptake and toxicity must be addressed before their application as antiviral agents (Ruggiero and Richter 2018).

Host cells themselves contain thousands of potential G4-forming sequences, hence a prerequisite is that the ligand that interacts with viral G4s may also affect host G4s. Therefore, designing compounds with appropriate sequence, topology or cellular selectivity is therefore a major objective of current G4-based antiviral research (Pathak 2023). Future drug-development strategies are likely to focus on highly selective G4 ligands, structure-guided molecular design, targeted delivery systems and combination therapies. Combining G4-targeting compounds with DNA-damage response inhibitors, chemotherapy or immunotherapeutic approaches may provide additional therapeutic benefits in cancer. Similarly, viral G4-targeting compounds could potentially be combined with existing antiviral drugs. Continued integration of molecular biology, structural biology, medicinal chemistry and pharmacology is expected to accelerate the development of G4-based therapeutic strategies.

DISCUSSION

Over the past ten years, G-quadruplexes have drawn a lot of attention because to their production and regulatory roles in biologically significant locations (Dobrovolě *et al.*, 2025). Numerous essential biological functions, such as gene transcription, translation, DNA replication, and genomic stability, are shown to be impacted by them. Initially noted in 1910, it was discovered in 1962 (Gellert *et al.*, 1962). G-quadruplex-specific single chain variable fragment (scFv) of an antibody was used to identify G-quadruplexes generated at telomeres in macronuclei of the ciliate *Stylonychia lemnae*, providing the first direct proof of the occurrence of G-quadruplexes *in vivo* (Schaffitzel *et al.*, 2001). Structurally, G-quadruplexes form rapidly and show a wide variety of conformations, including capping structures, loop conformation, and folding topology. Additionally, they can create numerous structures, adopt different topologies, form different sequences, and fold into different conformations given a sequence (Yang and Clement 2019). Human gene promoter sequences and telomeric DNA are two examples. The genomes of human pathogens and plants both contain G-quadruplexes. Human immunodeficiency virus (HIV) and other herpes virus species are two examples of viruses that have been found to include G-quadruplexes (Zareie *et al.*, 2024). *Neisseria gonorrhoeae* and *Escherichia coli* are two bacteria that include G-quadruplexes (Ciaco *et al.*, 2024). Additionally, ciliates, malaria parasites, and yeasts include G-quadruplexes (Yang and Clement 2019). Interestingly, both animal and human systems have helicases that resolve G-quadruplex structures, such as the RecQ and Pif1 families. Numerous biological processes, such as immunoglobulin gene rearrangements, promoter activation, and telomere preservation, have been shown to be influenced by the distinct metabolism of G-rich chromosomal regions that may form quadruplexes. Telomere deficiencies are a hallmark of several human disorders, and G-quadruplex structures at telomere ends are crucial for telomere integrity. Telomere maintenance and cellular DNA replication are expected to be disrupted in disorders with known deficiencies in G4 DNA helicases, according to evidence from cellular investigations and model organisms (Herr, *et al.*, 2026). Previous techniques for visualising G-quadruplex structures relied on subjecting living cells to G-quadruplex ligands (Biffi *et al.*, 2013).

Additionally, G4-seq or G4 algorithm predictions are also used. Furthermore, radiolabeled G-quadruplex ligands 360A, fluorescent G-quadruplex ligands BMVC, chemical footprinting, and small molecule probes were employed (Kouzine *et al.*, 2017; Granotier *et al.*, 2005). Physical property characterisation is made possible using circular dichroism (CD), NMR, X-ray, and mass spectroscopy investigation. Isothermal titration calorimetry (ITC), which can directly quantify binding enthalpies and offer thermodynamic characterisation of G-quadruplex-ligand interactions, is one of several innovations. Protein ligand-quadruplex nucleic acid interactions and small molecules can be studied in real time using biosensor-surface plasmon resonance (SPR). G-quadruplex conformations, ligand interactions, and protein interactions are studied using single-molecule techniques like optical and magnetic tweezers, atomic-force microscopy (AFM), and single-molecule fluorescence resonance energy transfer (FRET) microscopy (Paul *et al.*, 2019; Lee *et al.*, 2019).

G-quadruplex structures within living *Xenopus laevis* oocytes are studied using NMR spectroscopy, and G-quadruplex conformation in vitro and in vivo cells can be studied using ¹⁹F NMR (Krafcikova *et al.*, 2019). Given its many physiological, cellular, and genetic functions, these advancements show that researchers are realising the significance and relevance of G4 DNA. The creation of G-quadruplex-interactive small molecule ligands (G4-ligands) has been aided by the realisation of the biological significance of G-quadruplexes. The ability to specifically target these globular DNA structures for drug development has been made possible by the discovery of genomic G-quadruplex structures in areas of functional significance, such as human telomeres and oncogene promoters (Neidle 2017). Understanding G-quadruplex functions and potential as a therapeutic target has been greatly aided by G-quadruplex-interactive molecules (Das and Dutta 2021). According to Che *et al.* (2026), these structures have shown promise as biomarkers with significant clinical value. Simultaneously, research into substances that specifically identify DNA or RNA G4s as possible therapeutic agents opens up new possibilities for early diagnostic and treatment approaches. G4s show great promise as molecular sentinels in cancer early detection, especially in proto-oncogene promoters where G4-forming sequences operate as "molecular switches" for oncogenic activation (Shu *et al.*, 2025). However, the field is incomplete due to a number of gaps and restrictions. Researchers in the field have difficulties because of the evidence that G-rich sequences can generate G4 DNA in vitro and that they affect genomic stability. First and foremost, the structure–function relationship of G4 in vivo is still poorly understood, especially because of its ephemeral nature and susceptibility to cellular environments. Next, ligands with high G4-binding affinity frequently show insufficient genomic or transcriptome specificity, leading to nontarget effects. This is known as the persistent affinity-selectivity conundrum. Clinical translation is complicated by mechanistic ambiguity because treatment results are often not clearly linked to direct G4 regulation as opposed to secondary stress responses such replication stress or DNA damage. Drug transport and bioavailability issues continue to be significant barriers, especially with regard to RNA-targeting methods and massive molecular platforms. Integrating G4-targeting tactics with therapeutic modalities, including as immunotherapy and PARP inhibition, has promise for the future since well-thought-out combinations may take advantage of synthetic lethality and get past resistance mechanisms that restrict the longevity of monotherapies.

Combining G4-targeting strategies with immunotherapy, epigenetic modulators, or radiation therapy can have synergistic results. In the future, sophisticated genome-wide mapping tools allow us to improve our comprehension of context-dependent G4 landscapes, while artificial intelligence has the revolutionary potential to speed up the discovery of specific ligands. In order to evaluate the abundance of G-quadruplexes and investigate the impact of genetic changes associated with human diseases, new techniques for detecting them would be very beneficial. It is necessary to construct genetic and cell biological systems that thoroughly assess the metabolism of G-rich DNA sequences. If G-quadruplexes are successfully demonstrated in vivo, researchers will be able to concentrate on comprehending the significance of G4 nucleic acid structures in human disorders. In summary, G4 structures and its study have transitioned from fundamental biological

curiosities from the realms of biophysics, biochemistry and molecular biology to pivotal targets in precision oncology. The several advancements promise to catalyze a paradigm shift towards an integrated era of disease management that encompasses prediction, intervention, and, ultimately, curative strategies.

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