Induced-fit recognition of CCG trinucleotide repeats by a nickel chromomycin complex results in large-scale DNA deformation

Wen-Hsuan Tseng, Chung-ke Chang, Pei-Ching Wu, Nien-Jen Hu, Gene-Hsiang Lee, Ching-Cherng Tzeng, Stephen Neidle, Ming-Hon Hou*

Abstract: *Small-molecule compounds targeting trinucleotide repeats in DNA have considerable potential as therapeutic or diagnostic agents against many neurological diseases. $Ni^{II}(Chro)_2$ (Chro = chromomycin A3) was found to bind specifically to the minor groove of $(CCG)_n$ repeats in duplex DNA, with unique fluorescence features that may serve as a probe for disease detection. Crystallographic studies have revealed that the specificity originates from the large-scale spatial rearrangement of the DNA structure, including extrusion of consecutive bases and backbone distortions, with a sharp bending of the duplex accompanied by conformational changes in the Ni(II) chelate itself. The DNA deformation of CCG repeats upon binding forms a GGCC tetranucleotide tract, which is recognized by $Ni^{II}(Chro)_2$. The extruded cytosine and last guanine nucleotides form water-mediated hydrogen bonds which aid in ligand recognition. The recognition can be accounted for by the classic induced-fit paradigm.*

Expansion of $(CXG)_n$ (where X denotes any nucleotide) trinucleotide repeats (TNRs) is associated with many types of neurological disease.[1] $(CXG)_n$ TNRs often form transient non-canonical hairpin structures where the duplex region contains X:X mismatches sandwiched between two Watson-Crick G:C base pairs.[2] Interestingly, many small-molecule ligands bind to these unconventional duplex structures, usually through intercalation between spatially adjacent bases in a nonspecific fashion, or through interaction with specific sequences in the minor groove.[3] This binding action has served as the basis for the recent development of novel compounds that may either block TNR expansion [4] or provide a read-out for detection of TNR-related diseases.[5] Fluorescence-based small molecules that target specific TNR sequences promise to combine direct detection of TNR diseases with the convenience, speed and sensitivity of fluorescence-based techniques.

Chromomycin A3 (Chro) is an aureolic acid-type metal binding ligand containing di- and trisaccharide moieties connected to a β-ketophenol chromophore via *O*-glycosidic bonds arranged in a 2,6 relationship around the anthracene ring **(Figure S1)**. Discovered in the 1960s, Chro was originally developed as an anticancer agent and later on found use as a staining agent for DNA.[6] Studies have found that divalent metal chelates of dimeric Chro ($(Chro)_2$) have intrinsic fluorescence emission properties that are highly sensitive to the environment.[7] These complexes interact with the minor groove of G/C-rich sequences that are at least three base pairs long, with a particular preference for GGCC tetranucleotides. The sequence preference and intrinsic fluorescence properties have raised the possibility of repurposing $(Chro)_2$ metal chelates as TNR-specific reporter agents.

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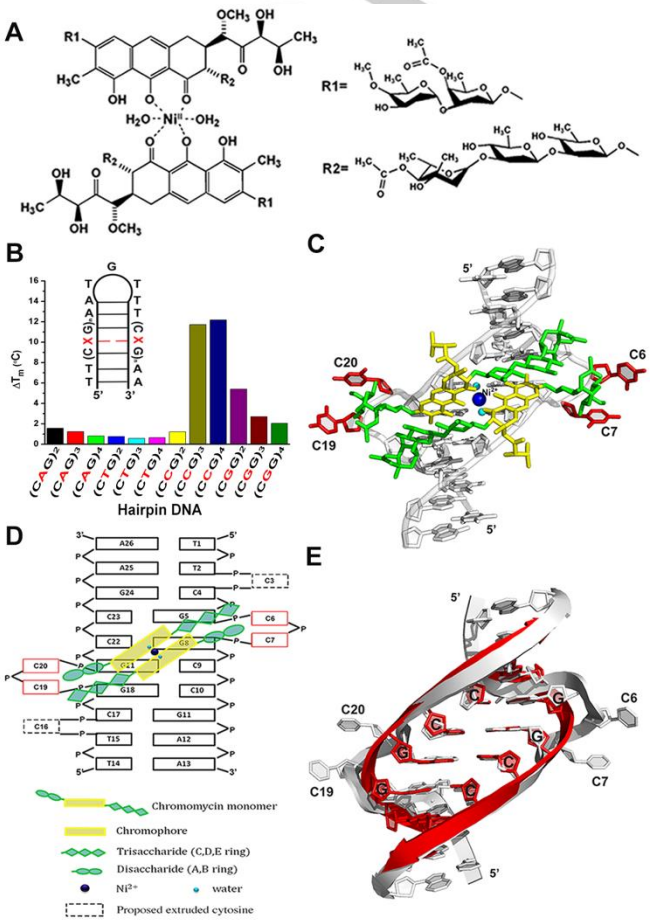

Figure 1 A) Chemical structure of $Ni^{II}(Chro)_2$ complex. B) The effects of $Ni^{II}(Chro)_2$, complexes at 12μM on the melting temperature of various DNA duplexes at 3 μM in a 50 mM sodium cacodylate buffer (pH 7.3) containing 50 mM NaCl. C) The crystal structure of $Ni^{II}(Chro)_2$-$d[TT(CCG)_3AA]_2$ complex viewed from the minor groove. D) Schematic diagram of $Ni^{II}(Chro)_2$-$d[TT(CCG)_3AA]_2$ complex at central GGCC steps of the refined structure. E) Superposition of the overall structure between $Mg^{II}(Chro)_2$-d(TTGGCCAA) (PDB: 1VAQ, red) and $Ni^{II}(Chro)_2$-$d[TT(CCG)_3AA]_2$ (gray) viewed from the minor groove.

Among the divalent metal chelates of $(Chro)_2$, the octahedral Ni(II) complex has been reported to have the highest affinity with *Ka* value of $1.266x10^7$ M^{-1} towards GGCC sequence than those of the other dimeric Chro complexes.[7a] Here we report our studies on the binding between $Ni^{II}(Chro)_2$ **(Figure 1A)** and $(CCG)_n$ TNRs involved in fragile X syndrome. The stabilization effects of $Ni^{II}(Chro)_2$ on $(CXG)_n$ TNRs located at the stem regions of hairpin DNA were determined by measuring the melting temperature differences (ΔT_m) of a duplex DNA in the presence and absence of $Ni^{II}(Chro)_2$ at a fixed compound: DNA stoichiometry of 4:1. We find that binding of $Ni^{II}(Chro)_2$ **(Figure 1B)** increases the stability of $(CCG)_n$ and $(CGG)_n$ duplexes to various extents compared to $(CTG)_n$ and $(CAG)_n$ duplexes. Remarkably, $Ni^{II}(Chro)_2$ induces a particularly large stabilization effect on $(CCG)_3$ and $(CCG)_4$ duplexes, whilst the stabilization on the shorter $(CCG)_2$ duplex is indiscernible from those on the other $(CXG)_n$ duplexes. We find that the selectivity of the Ni(II) chelate identified by ΔT_m analysis is dependent on both the presence of at least three repeat units and on the concentrations of the DNA and small-molecule

ligand. Our results suggest that $Ni^{II}(Chro)_2$ has a pronounced preference for binding to long $(CCG)_n$ duplexes rather than to other $(CXG)_n$ duplexes. The association and dissociation kinetics of $Ni^{II}(Chro)_2$ to $(CCG)_n$ repeats were determined by surface plasmon resonance (SPR) and are listed in **Table S1**. $Ni^{II}(Chro)_2$ showed no detectable binding to $(CCG)_2$ at the concentrations tested (**Figure S2**). Increasing the number of repeat units enhanced the binding of $Ni^{II}(Chro)_2$ to the DNA.

To understand the structural basis of $(CCG)_n$ recognition by $Ni^{II}(Chro)_2$, we have solved the crystal structures of $Ni^{II}(Chro)_2$ complexed to the pseudo-palindromic duplex DNA sequence d[TT$(CCG)_3$AA]$_2$, at 1.75 Å resolution. The key features of the complex are well-resolved, however due to the flexibility of the terminal residues, it was challenging to locate their precise positions, particularly C3 and C16, which have the bases extruded from the duplex structure. A single 1:1 Chro-DNA pair comprises the asymmetric unit of the complex structure. $Ni^{II}(Chro)_2$ is bound to a palindromic GGCC tetranucleotide core in the minor groove of the DNA duplex (**Figure 1C and 1D)**, in a similar way to other $(Chro)_2$ compounds.[7b] Interestingly, this tetranucleotide core was formed by extruding four cytosines in the central region of $(CCG)_3$ sequence, which then allowed the formation of G5:C23, G8:C22, C9:G21 and C10:G18 Watson-Crick base pairs while retaining the right-handed helical structure of the duplex **(Figure S3)**. The extruded cytosines from adjacent asymmetric units form i-motifs through hydrogen bonding, and are part of the crystal packing **(Figure S4)**, with these C:C contacts helping to stabilize the packing of the complex within the crystal lattice. The minor groove is also significantly widened (to ~20 Å) by the binding of $Ni^{II}(Chro)_2$ **(Figure S5)** which introduces a 40° kink in the DNA duplex with large positive roll angles (~10°) for the CpC and GpG steps of the central d(CGGCCG) motif, with the cytosines extruded out **(Figure S6A)**.

The structural deformation of the DNA duplex upon $Ni^{II}(Chro)_2$ binding is reflected in the torsion and base-pair helical parameters. The methyl groups of the E ring side chain from the Chro moiety and the ribose ring of the G5 (G18) residue from the DNA are tightly spaced, thus resulting in van der Waals contacts, and contribute to the unusually low average helical twist angle of 18° for the paired bases in the GGCC tetranucleotide region **(Figure S6B)**. This is markedly different from the average twist angle of 31.1 for A-DNA and 35.9° for B-DNA respectively. There is no significant variation in the width of the major (16.0 or 16.9 Å) and minor grooves (15.1 Å) at the GG/CC or CC/GG step. The central GpC step of the duplex has a unique δ angle of ~85° and the sugar puckers are all in the C3´-*endo* conformation. These values indicate that the duplex region maintains an overall A-DNA-type conformation, even though the distinct rise distances (~3.5 Å) at the CpG and GpC steps in the minor groove are similar to those observed for B-form DNA **(Figure S6C)**.[8] However, the G8 and G21 residues around the chromophore of Chro adopt unusual α backbone torsion angles (~60°) caused by the extrusion of adjacent C7 and C20 bases, that differ by some 120° from the α angles for both A- and B-form DNA (ideally -sc, -50°). Although the local structural deformations are significant, the overall structure of the GGCC binding core in the $Ni^{II}(Chro)_2$-d[TT$(CCG)_3$AA]$_2$ complex exhibits global similarity to that of the GGCC tetranucleotide region in the previously reported $Mg^{II}(Chro)_2$-d[TTGGCCAA]$_2$ complex (r.m.s.d. ~ 1.3 Å, **Figure 1E**).[7b]

The structural changes of the DNA duplex and $Ni^{II}(Chro)_2$ contribute towards the formation of specific intermolecular hydrogen bonds. The two O8 oxygen atoms of chromophore (CPH) moiety are perfectly positioned to form hydrogen bonds with the N2 atoms of G8 and G21 **(Figure 2A)**. Likewise, the two O1 oxygen atoms of the trisaccharide E ring can now form hydrogen bonds with the N2 atoms of G5 and G18. In addition, the two water oxygen atoms involved in octahedral coordination to the Ni(II) ion of $Ni^{II}(Chro)_2$ mediate specific hydrogen bonds between DNA and ligand **(Figure 2B)**. The extruded cytosines also play a role in $(CCG)_n$ recognition by forming hydrogen bonds between O2P[C6]/O2P[C19] and O3[Chro, B ring] **(Figure 2C)**. LIGPLOT analysis showed that the methyl group attached to the disaccharide B ring of $(Chro)_2$ is in close van der Waals contact with the two extruded cytosines **(Figure S7)**. We identified a total of 6 water molecules that were directly involved in the recognition of $Ni^{II}(Chro)_2$ to the DNA **(Figure 3A)**. The N4 amine on the extruded cytosines form water-mediated hydrogen bonds with the O3 oxygen atoms of the disaccharide B ring, whilst the N2 atoms of the last guanines form water-mediated hydrogen bonds with the O3 oxygen atoms of the trisaccharide E ring **(Figure 3B)**. Two bridging water molecules mediate the interactions between the O1 oxygen atoms of the trisaccharide C ring and the interactions all contribute towards the specific recognition of $(CCG)_n$ repeats by $Ni^{II}(Chro)_2$. We also observed two Ni^{II} ions associated with guanines G8 and G21 **(Figure 3C)**, where the electron density (σ level =1) clearly shows that each Ni^{II} ion is octahedrally coordinated by one guanine nitrogen and five water molecules.

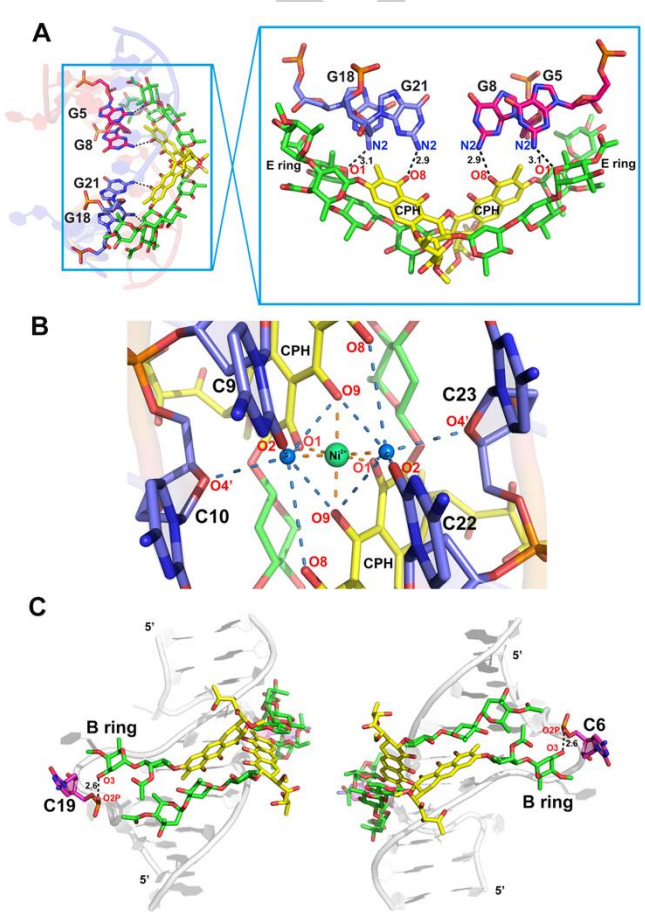

Figure 2 A) Close-up view of the specific interactions between $Ni^{II}(Chro)_2$ and GpGpCpCp sequence. The specific intermolecular Chro-DNA hydrogen bonds between the O8 of chromophore and the N2 atom of G8 (G21) base (2.9 Å), and the O1 oxygen of E ring and the N2 atom of G5 (G18) base (3.1 Å). The two last extruded cytosines were modeled by DS software. B) Close-up view of $Ni^{II}(Chro)_2$–DNA complex at Ni^{II} octahedral coordination site. C) The phosphate group of loop-out C19 or C6 form hydrogen bonds with O3 oxygen of B ring, respectively.

We also determined the structure of the free $Ni^{II}(Chro)_2$ ligand, to a resolution of 0.89 Å, using direct methods. In this structure, the Ni^{II} ion is coordinated to the oxygen atoms O1 and O9 of each CPH moiety and forms an Δ-octahedral arrangement with right-handed propeller **(Figure S8A)**. Two water oxygen atoms act as the fifth and sixth ligands of the octahedral coordination and are located at the apexes of the bipyramid. The dimer structure is stabilized by mutual stacking and hydrogen bonds between the Chro monomers **(Figure S8B)**. Superposition of the free and DNA-bound $Ni^{II}(Chro)_2$ structures gives an r.m.s.d. of 1.87 Å, showing that binding to the DNA causes structural changes in $Ni^{II}(Chro)_2$. In the structure of the ligand–DNA complex, the hydrogen bond distances between O1[A ring] and O4[D ring] of the two individual Chro monomers are shortened compared to those of free $Ni^{II}(Chro)_2$ **(Table S2)**, which allows the Chro monomers to squeeze between the two DNA backbones into the minor groove **(Figure S9)**. The saccharide moieties attached to the Chro backbone can thus penetrate deeper into the groove and form large number of van der Waals contacts. The interaction between the saccharides and the DNA results in the slight bending of the two arms of the Chro dimer toward each

other. The Ni^{II} coordination structure is also slightly twisted upon DNA binding **(Table S3)**, with the two water oxygen atoms originally involved in the coordination now also part of the hydrogen bond network between CPH of Chro and C9/C22 of the DNA duplex **(Figure 2B)**.

Although originally conceived to explain the interactions between enzymes and their substrates,[9] the induced-fit theory has been widely applied to other chemical systems and is now a key concept in supramolecular chemistry.[10] Interestingly, there are few examples which use the induced fit concept to explain the binding between DNA and small compounds.[11] This is probably due to the characteristic lack of large conformational changes observed for DNA upon minor groove binding by small molecules.[12] In contrast, the structures of $Ni^{II}(Chro)_2$ in complex with $d[TT(CCG)_3AA]_2$ results in large conformational changes in the DNA when compared to the previously reported structures for the same ligand-free DNA.[2d] A key characteristic of the complex structure is the formation of a GGCC tetranucleotide tract, which is the preferred recognition site for $Ni^{II}(Chro)_2$.[7a] Interestingly, this GGCC tract is also preferred by other dimeric chromomycin-based complexes.[7b, 7c] However, by contrast with these other ligands, the extruded cytosine and last guanine nucleotides in the DNA- $Ni^{II}(Chro)_2$ structure are stabilized by specific water-mediated interactions with the $(Chro)_2$ ligand, which may provide additional specificity. These water molecules may also play a crucial role in the groove-binding mechanism as suggested by Bailly et al.[13] Our data is best explained by invoking the induced fit paradigm, where binding of $Ni^{II}(Chro)_2$ triggers large conformational changes in the duplex region of the DNA in order to form the GGCC tract.

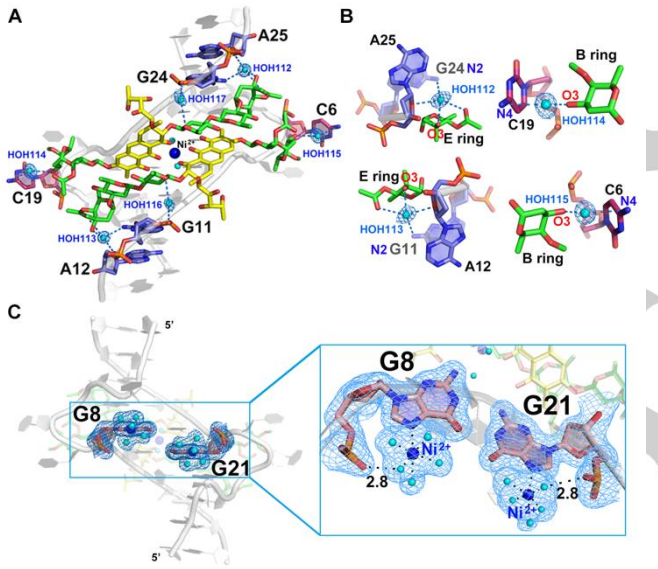

Figure 3 A) The bridging water molecules that mediate the interaction between the $Ni^{II}(Chro)_2$ and DNA, and its density is contoured at the 1.0 σ level. B) The bridging water molecules that mediate the interaction between N4 amine of C19 (or C6) and the O3 oxygen atoms of the disaccharide B ring, whilst N2 of G11 (or G24) form water-mediated hydrogen bonds with the O3 oxygen atoms of the trisaccharide E ring. C) Electron density maps show the octahedral coordination of Ni^{II} ions interacting with the unpaired N7 of G8 and N7 of G21 bases and five water molecules that mediated Ni^{II} ions and DNA interaction. Hydrogen bonds are shown as black dotted lines between two water molecules and G8/G21 bases, and the distance is 2.8 Å. The Ni^{II} ions are shown as blue spheres, and the coordinated water molecules are colored cyan.

The specificity of $Ni^{II}(Chro)_2$ towards $(CCG)_n$ may be partly due to the intrinsic instability of C-C mismatches, which are the least stable among all nucleotide mismatches.[14] This local instability is flexible enough to be able to adopt the geometrically optimal conformation that allows cytosines to extrude out to form the GGCC tetranucleotide patch compatible with specific binding mode of $Ni^{II}(Chro)_2$. Binding-induced nucleotide extrusion has also been observed in structures of complexes between DNA repair proteins and DNA complexes.[15] Other small molecules that target $(CXG)_n$ TNRs also induce nucleotide extrusion. For example, binding of actinomycin D to $(CGG)_n$ results in the extrusion of guanines,[3a] whilst binding of naphthyridine analogues to $(CAG)_n$ or $(CCG)_n$ result in the extrusion of cytosines.[3b, 5a] Barton's group has also discovered various types of Rh**(III)** compounds targeting A:A mismatches which eject mismatched adenosines into the major groove.[16] On the other hand, the octahedral Ru-dppz complexes have been found to intercalate into the DNA stack, accompanied with the extrusion of the terminal thymine and adenine residues.[17] Interestingly, all of the above compounds are intercalators and not groove binders. In these intercalator complexes, each single extruded nucleotide is flanked by nucleotides that form part of the duplex, which is distinct from the extrusion of two consecutive nucleotides observed for $Ni^{II}(Chro)_2$-$d[TT(CCG)_3AA]_2$ in this work. $(CCG)_n$ repeats tend to form extended "e-motifs" (antiparallel duplexes that are stabilized by extrahelical bases) under physiological conditions,[18] which already contains single-nucleotide cytosine extrusions. Binding of the $Ni^{II}(Chro)_2$ compound with conformational change forces an additional cytosine to flip out, accompanied by the flip-in of an extruded cytosine on the opposite strand. We suggest that the DNA regions between the flip-out events slide against each other and, together with the flipped-in cytosines, allow the re-formation of G:C base pairs originally destroyed by the flip-out events.

Inspired by the unexpected features of the crystal structures we have also investigated the potential of $Ni^{II}(Chro)_2$ for detection of fragile X syndrome sequences. Current detection methods for fragile X syndrome include Southern blot and polymerase chain reaction (PCR) on genomic DNA samples.[19] Southern blots are considered the gold standard but take days to obtain usable results.[20] In contrast, PCR tests are relatively fast (1-2 hrs including the electrophoresis step) but are unable to detect full mutations (>200 CCG repeats), which are important for confirming diagnosis, because the efficiency of the PCR reaction decreases with the number of CCG/CGG TNRs. We have investigated the possibility of applying the fluorescence and binding properties of $Ni^{II}(Chro)_2$ towards fragile X syndrome testing. We amplified genomic DNA obtained from both normal control (6-54 CCG repeats) and clinically confirmed fragile X syndrome patients (>200 CCG repeats) using PCR and measured the fluorescence emission spectra of these samples in the presence of $Ni^{II}(Chro)_2$. We observed an increase in fluorescence emission for the fragile X group and decreased fluorescence for the control group when compared to the $Ni^{II}(Chro)_2$ control **(Figure S10)**. The enhanced fluorescence emission when the ligand is bound to genomic DNA would suggest a binding mode different from the one bound to pure $(CCG)_n$ repeat sequences. Although serendipitous, this characteristic enhanced the discrimination power of the $Ni^{II}(Chro)_2$ assay. Sato et al. previously suggested 2-amino-5,6,7-trimethyl-1,8-naphthyridine (ATMND) as a potential $(CCG)_n$ fluorescence detection tool,[21] but only tested the compound on synthetic sequences up to n = 15. This is well within the repeat number of normal fragile X syndrome patients, where n may range from 6 to 54. In contrast, $Ni^{II}(Chro)_2$ allowed for distinguishing between the control and patient groups. Since single-wavelength emission measurements can be executed relatively quickly and carried out in a high-throughput fashion, our results suggest that $Ni^{II}(Chro)_2$ may have potential as a rapid diagnostic tool for fragile X syndrome.

In summary, recognition of $Ni^{II}(Chro)_2$ to CCG trinucleotide repeats (TNRs) employs the classic induced-fit paradigm by triggering large-scale DNA deformations that ultimately lead to the formation of a cognate motif. Extending the concept further, TNR-binding compounds may bind to a variety of sequences as long as the DNA sequence can be coerced to form a specific cognate structural motif without incurring a large energy penalty. A large number of structural studies of TNR-binding compounds complexed with different TNR sequences will be required to test this concept and could be a substantial step toward the development of new therapeutic or diagnostic agents for neurological diseases.

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Notes

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Keywords:
Trinucleotide repeats • neurological disease • X-ray crystallography • induced fit recognition • metal binding ligand •consecutive bases flip-out • DNA deformation • molecular diagnostics

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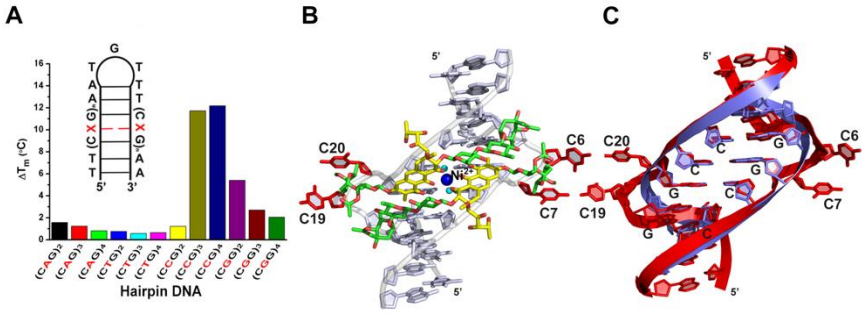

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