

## Review

# Comparative review on left-handed Z-DNA

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### 1. Abstract

Being polymorphic, deoxyribonucleic acid is worthy of raise a variety of structure like right-handed B to left-handed Z conformation. In left-handed contour of DNA consecutive nucleotides substitute between syn-arrangement and anti-arrangement, through the chain. 2D gel electrophoresis comprising d(PCpG)<sub>n</sub> of topo isomers of a plasmid inserts d(pCpG)<sub>n</sub>, in this 'n' ranges among 8 to 21, indicate the change of B-Z DNA. The high denseness of salt is required for conversion of B configuration d(CG)<sub>n</sub> toward Z configuration. The rate of B to Z transition is measured by "Cytosine Analogues" and "Fluorescence Spectroscopy". h-Z $\alpha$ ADAR1 that a Z-DNA's binding domain, binds and stabilizes one part in Z configuration and therefore the remaining half in B deoxyribonucleic acid configuration. At halfway point, it creates B-Z junction. "Stacking" is the main reason for the B-Z DNA junction construction. Upregulation of ADAM-12, related with Z-DNA is said to a cause for cancer, arthritis, and hypertrophy. Z-DNA forming sequence (ZFS) conjointly generates massive - scale deletion in cells from mammals.

### 2. Introduction

In 1979, a left-handed crystal deoxyribonucleic acid structure was published, which convey a unique zigzag, sugar-phosphate backbone, it's named as Z conformation of deoxyribonucleic acid (Z-DNA) and it's all biological relevance had yet to be established [1, 2]. It was already known that normal right-handed B conformation can assume a diverse number of configurations, under certain torsional stress [3]. Z configuration exists in high energy state than the common B-DNA configuration. This conformation has negative super helicity which soothes the structure. In contrast to B form with anti-conformation, in Z-DNA convey anti-conformation and syn-conformations alternately by rotating around glycosyl bonds, along with the chain [4]. Under bound condition non-B-DNA structure like cruciform, triplex, hairpin, etc. are formed by collapsible monotonous DNA sequence. This unusual structure has effects on several biological progressions [5]. Super helicity is the most significant inducer for Z contour in usual DNA. Non-super helical, natural DNA holds practically no Z-DNA, but other hand the same DNA under extreme negative super helicity, as in "form V" may have as much as 35–40% of its sequence in Z arrangement [6]. Except for Z-DNA, X-ray fiber diffraction outlines were framed and

**Table 1. Comparable information between A-DNA, B-DNA, Z-DNA [2, 9].**

Parameter	A-DNA	B-DNA	Z-DNA
Helix sense	Right-handed	Right-handed	Left-handed
Axial raise [ in Armstrong]	2.55	3.4	3.7
Helix pitch	28°	34°	35°
Base pair tilt	20°	-6°	7°
Rotation per residues	33°	36°	-30°
Diameter of helix [in angstrom]	23	20	18
Glycosidic bond configuration	Anti	Anti	Anti
da, dT, dC, dG	Anti	Anti	Syn
Inserted phosphate phosphate distance [in Armstrong]	5.9	7.0	7.0
da, dT, dC, dG	5.9	7.0	5.9
Suger pucker	C3'-endo	C2'-endo	C2'-endo
da, dT, dC, dG	C3'-endo	C2'-endo	C3'-endo

differentiates several conformations of DNA. Most DNA enters the A-DNA conformation which's per turn contain 11 bp through right-handed helix [7]. The single-crystal method resolute the complementary structure, oligo deoxy nucleosides, d(GGTATACG) and d(IODO-CCGG) [7, 8] (Table 1).

Existence of B-Z transition and Z-DNA is further deep-rooted by the specific ZBP discovery [10]. *In vitro*, Z-DNA was postulated for identification of proteins that bind with it in a structure-precise manner, act as a cis-element and aid in biological development. RNA Double Strand adenosine deaminase 1 is a type of the ZBP [11]. This ADAR1 has a Z $\alpha$  domain capable of transform B into Z conformation and create the junction [12, 13]. Formation of Z-DNA is induced by a unique sequence motif. Sometimes, it presents frequently adjacent with the start site of transcription and induce the transcription [14–16]. The junction between B-Z is formed with the help of ZBP. Formation of this portion carries out flipping over of bases, stacking of bases, and infringement of one base pair [17]. In another study also verified that normal B form also transfers into Z form by elevation of salt of aggregation [18, 19]. In humans, Z-DNA first came into consideration through the autoimmune disease Lupus erythematosus [20]. Z-DNA formation sequence (ZFS) is found to be associated with immune retorts and infection genome uncertainty. The Z configuration is also evidenced to be linked with large scale deletion in the cells of mammals [21, 22]. It also controls the genes transcription regulation of c-myc and CRH of human [23, 24].

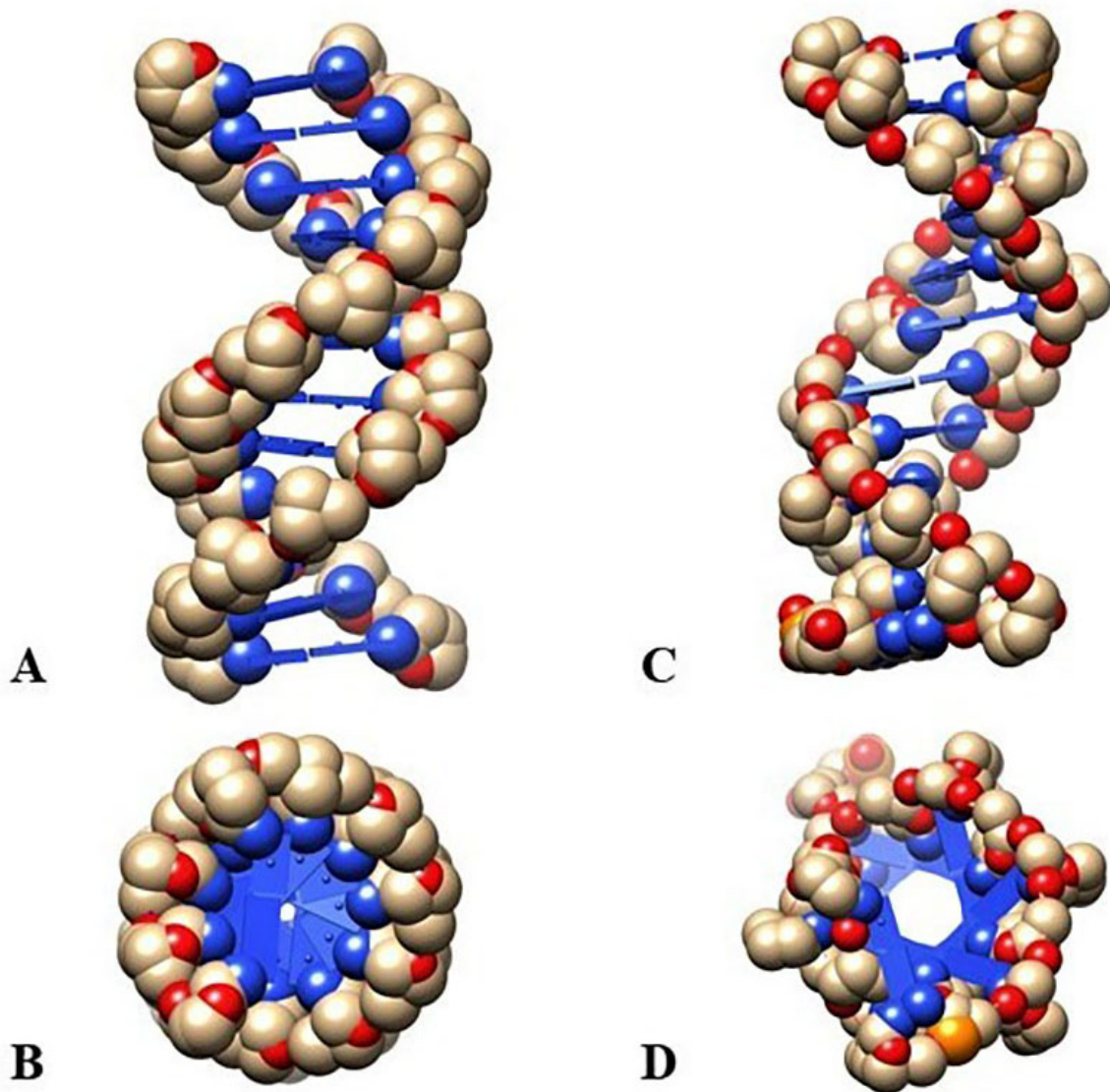
### 3. Z-DNA structure

The optical investigation originally proposed the Z-DNA. The result of the experiment exhibited that a 4 mL NaCl solution contains a polymer which consists of discontinuous cytosine and guanine residue and formed a nearly inverted circular dichroism gamut [25]. Until 1979, the invention of Z-DNA remained unknown. Orig-

inal atomic steadfastness exposed that it was not the same right-handed B-DNA which was invented by James D. Watson & H.C. Crick in 1953. Despite that, this new left-handed helical structure named as Z deoxyribonucleic acid. This Z form consists of extremely immunogenic antibodies to recognize the configuration, unlike B form of DNA [26]. There have some familiar features of B form with the d(Cg)<sub>3</sub> system. The antiparallel double-helical structure holds Watson-Crick base pairing between the base of Guanine and Cytosine. The left-handed helicity oligomers have six base pairs with significant regularity. Balance correlated hexamers stack on one other so closely in an endless polymer of alternating cytosine guanine residues sequence [2].

Various conformational topographies differ the Z-DNA from the B-DNA (Fig. 1). The double-helical Hexanucleoside Penta Phosphate molecules allied with the crystal. Crystal of Z arrangement contains discontinuous cytosine and guanine residues'-DNA is dinucleotide while B-DNA is mononucleotide with anti-configuration. All deoxycytidine has anti-configuration whereas all the deoxyguanosine has anti syn-configuration.

In Z arrangement the base pair is lifted from the center, so the guanine imidazole ring is originated at the edge, but in case of B-DNA those bases are at the center. In B configuration 34Å pitch with 10.5 bp is present where Z configuration convey 44.6Å pitch with 12 bp per turn [9]. Six levels of base pairing have been seen in the d(Cg)<sub>3</sub> structure because of C1 base pair with G12, G2, C11 and so on. Z-DNA is not slanted with each other straight, but they remain linked to a literal translation of 7Å relative to each other so that it can shear the appearance from one another with a little rotation throughout the chain. Despite being stacked on other bases the guanine is loaded upon the oxygen atoms of prior deoxyribose residues. The backbone of sugar-phosphate is constant for both the Z form and B form. In B configuration the minor-grooves are above the base pairs. But in Z form minor-grooves exist below the base pair [2].



**Fig. 1. Evaluation of the structure between Z and B-DNA configuration.** (A, B) Z-DNA configuration showing left-handed elongated spiral with a lateral view and a polar view. (C, D) B-DNA configuration showing right-handed elongated spiral with a lateral view and a polar view.

#### 4. B-DNA to Z-DNA transition

Earliest Harvey model is used for examining B-Z transition. This model defines the procedure which is engrossed by another longitudinal DNA conscious models. Base pairs opening was another early observed mechanism regarding this model before the Wang model. At the present portrait of Zipper Model demonstrated that Z-DNA contains high energy joint that grows through the DNA polymer until the full B-Z trans polymer gets transferred into Z-DNA. Though there are some problems in the model because it does not disclose many vibrant structural details, so it has limited applications in thermodynamics. There are several facts regarding the transition of B-Z such as the high concentration of salt in the solution which balance the Z-DNA due to massive reduction in electrostatic repulsion in the pillar of phosphate. Negative helicity of deoxyribonu-

cleic acid needs energy that can also uncoil B form to configure the Z form. Z-DNA can also be stabilized by transcription.

Maruyama and colleague establish the B-DNA to Z-DNA transition communed by a method called “cationic graft copolymer” where the Poly (L-lysine)-graft dextran (PLL-g-Dex), begins with two-step method including the creation of a clear intermediate [27]. Amid DNA phosphate group electrostatic repulsion reduce by the cationic backbone of the copolymer and the transition is a result of these 2 factors. The most plausible Z form created negative supercoiling, utilizing B-DNA occurs during several metabolisms like Transcription and replication processes [28]. For reducing the transition stress, unusual such DNA as Z-DNA is formed [6, 29]. Lee *et al.* (1992) used “Magnetic-tweezers” and FRET combinedly to examine at molecule level of negative supercoiling [30]. Mag-

netic tweezers are a very useful technique for investigating wind/unwinding procedure of twisted DNA through precisely controlling infinite tension [28, 31]. Therefore, B-Z change can be active by tiny negative super helicity and approximately one Pico Newton Tension. This outcome suggests that in tension Z arrangement is formed more easily *in vivo* [32]. Methanol, Ethanol, Ethylene Glycol (Dehydrating agent) balance the Z-DNA configuration. Due to adjacent clustering counteractions all over the DNA, though more strong ionic properties, thus it provides additional mutually repelling phosphate groups [6]. Antibodies and ZBP can bind the Z form of DNA selectively. This conformation has triggering capability. The Qu group had been reported that Alzheimer amyloid protein brings about the Z-B transition. Forming the Z-form is correlated with Alzheimer's disease [33, 34]. Bae *et al.* analyzed to transition from B-Z conformational change occurs by Z-DNA binding protein unravel the detailed binding machinery and whether the protein industriously initiates Z-DNA's or passively traps transitionally performed Z form. Therefore, it proved that the conformational selection mechanism stabilized the Z-DNAs by alternating the "induced fit" mechanism. A chemical modification also stabilizes Z-DNA transformation [4]. Bulky group's introduction precise in a certain base also steady the growth of Z arrangement by increasing static hindrance.

## 5. B-DNA and Z-DNA hybrid junction

Double-stranded adenosine deaminase RNA is an enzyme of the deaminase family which edited the appearance of the ds-mRNA by converting adenosine to inosine and creating diversity between RNA and Protein [11]. It is noted as a naturally stirring protein with obvious specificity for methylated and hemi-brominated DNA contains discontinuous deoxy guanosine-deoxycytidine residues [13]. ADAR1 carry two binding motifs for Z-DNA,  $Z\alpha$  and  $Z\beta$  [11].

A few numbers of investigations were completed to show the interface between the solution of DNA and  $Z\alpha$  ADAR1 domain. If the DNA solution is interacting with dodecamer ( $d(CG)_6$ ) it produces the B-DNA circular-dichroism spectrum. When  $Z\alpha$  ADAR1 is mixed into the solution the spectrum progressively altered, which mirrored Z conformation. This demonstrated that the  $Z\alpha$  domain is equipped for alleviating the dodecamer in the Z configuration. Brownian motion or Pedesis is the reason for this twist of dodecamer fragment. After this conformational change, DNA binds with the  $Z\alpha$  domain to prevent the reappearance of B-DNA conformation [12, 13].

Kim *et al.* in 2005 developed a DNA duplex with 15 bp and with two hanging nucleotides [17]. This DNA duplex is co-crystallized with the  $Z\alpha$ ADAR1 domain (amino acids 140-202). So, Z-DNA is tightly bound with the binding domain of Z DNA, h- $Z\alpha$ ADAR1. After the binding,

it stabilizes one half in the Z configuration and remaining part in B form. In the centre portion, a B-Z junction is created [17]. At this DNA duplex, eight bases stabilized with normal Z-DNA conformation [2]. The remaining six bases are maintaining the typical B conformation [35]. On the link point, A-T bases are disrupted from each other and make a sharp turn, which obliged an inversion in the way of the backbone. This creates a bent at the intersection point of B-Z DNA. The disrupted A, T bases adopted anti-conformation. Base A is extended out from the helix and T is slanted analogous to the spiral. But first base-pair from the Z-DNA after the junction creates a long rise distance which clearly showed the stacked A-T the bases within the B-DNA conformation. Stacking is the main stabilizing factor for the junction, and it is proved that one bp extruding by breaking can cause reversion of the handedness of the duplex. Other than A-T bases, it is equally possible for other G-C bases to be extruded [17]. Thermodynamic examinations of the melting of oligomers holding the junction show that the edifice of the hybrid junction from B-DNA declines the melting free energy by 0.5 kcal/mol [36]. This B-Z configurational change and syn-conformation of both bases are done by base 'flipping over'. A torsional strain breaks and causes base extrusion. This extruded base is allowed to flip over and reorganization the bp, which creates a ZIP-like movement in two direction. This movement for the limitation of the ZFS with an extruded base at the intersection. Base-pair disruption, expulsion, and reconstruction are lengthening the Z-DNA segment through an additional negative torsional strain of chromatin [17].

Another investigation also proved that B-Z DNA junction can be produced by oligomeric sequences in the aqueous solution at 3 M or high salt concentration. The 5.5 M NaCl with a 95 mM combination induces the A-T sequence into the Z-DNA conformation [18]. This study re-establishes that when  $NiCl_2$  is added in the salt solution, it creates a striking change in Raman Spectra, indicating A-T bases are adopting the Z conformation [19].

## 6. Z-DNA in human disease

In living body, Z-DNA can form and role as a dynamic component in various genome's metabolic courses under certain biological circumstances [21]. Z-DNA is used in many precise activators or repressors enrolment for directive gene countenance, genome uncertainty control [22]. Another study proved that in cells of mammal's ZFS fetch genetic uncertainty. Repair mechanism can proceed with the Z-DNA development in the mammal's body, which creates a large genomic alteration. These sorts of changes are relevant to the breakage and translocation near ZFS in human lymphoma and leukaemia [9]. In humans, Z-DNA links with the transcription of the c-myc genes, which means when the Z-DNA development is turned off the cell gives a signal as a result, c-myc transcrip-



tion also starts to down-regulate [23]. In the same way, Z-DNA development is also associated with the corticotropin-releasing hormone (CRH) gene transcription [37]. On the other hand, the human body also shows the activation of the Nrf2 gene which is relevant to the HO-1 gene's promoter, which allied with Z-DNA development [24]. A few numbers of immunoglobulin-related genes (example-ETV6) are enriched by the Z-DNA sequence. But in blood cancer, these genes are related to translocation of the chromosome [22]. Interferonopathies disease like Aicardi-Goutières Syndrome is caused by Mutation, which reduces p150 Z-binding with impaired enzymatic activity. This is induced by dsRNAs and most commonly these dsRNAs derive from Alu retroelement. The Z-DNA and Z-RNA both are essential for limiting Alu retroelement intrusion of primate genomes [38]. Z-DNA provides a base for therapeutically reducing the chances of Arthritis, Cancer, and cardiac hypertrophy. This role is believed to be arbitrated by the downregulation of ADAM-12. It was observed that ADAM-12 protein expression is raised when there are pieces evidence of arthritis, cancer, and cardiac hypertrophy. Whereas ADAM-12 expression level is exceptionally low in certain adult tissue. The regulation of ADAM-12 is related to the highly conserved region containing a stretch of dinucleotide repeat sequence and known as negative regulatory element (NRE), which serves as a repressor of ADAM-12 expression. There is a certain Z-DNA binding protein-like MeCP2. It modulates the ADAM-12 repression by recruiting NF1 transcriptional factors. Loss of ZFS leads to a low level of MeCP2 which results in metastatic breast cancer [22, 39]. Apart from this, HIF1 $\alpha$  induced Z-DNA development in the microsatellite of slc11a1 gene promoter. It was also perceived to control its definite allele expression in patients of rheumatoid arthritis, tuberculosis [40]. Z-DNA also has an immunogenic character and it can prevent systemic lupus erythematosus. But in the patient's sera of these diseases, some anti-Z-DNA antibody are found. Two kinds of antibody are found, first-one responsible for denaturation of both B and Z form and second-one is Z-DNA specific [20, 41]. Z arrangement also induce conformation instability by acting as a site for cancer-related genes like scl, bcl2, and c-myc [9]. B-Z junction is a site where CAG trinucleotide repeat instability happened. X fragile chromosome and skeletal dysplasia associated with CGG repeats and GAC trinucleotides repeat respectively [42–44]. In a study, typical left-handed Z-DNA was originated in brains of severe AD affected patients. Similarly, the moderately affected patients showed the existence of B-Z intermediate conformation in their brain DNA. Immunohistochemical data has proved that the total amount of Z form is one-seventh than B arrangements in human's genome [45, 46]. It was also observed that some genes, related to Alzheimer's like presenilin-1, presenilin-2, APOE (Apolipoprotein E), etc. are overexpressed in patients and has an important appeal in Alzheimer's pathogenesis. Z-

DNA existing in the brains of Alzheimer's patients are far more vulnerable to hydroxyl radical-induced damage of DNA, in comparison to A-DNAs or B-DNAs. This was due to the occurrence of more exposed bases and patients with severe Alzheimer's showed the existence of both Z-DNA and damaged DNA of similar types [47]. This finding has again been confirmed from another study which showed that Z-DNA became sensitive to hydrolytic enzyme DNase I, on incubation with A $\beta$  protein for a certain period [34]. This results in alteration of Z arrangement back into normal B form. These transition of Z form to normal B form is verified as quicker process when an interaction of A $\beta$  is made, in the existence of ethylene glycol also [48].

## 7. Conclusions

Z-DNA is a double-helical structure that preserves antiparallel backbone of sugar-phosphate chains with Watson Crick pairing. Despite that, it has a contour which is fundamentally dissimilar from B configuration of DNA. Two-dimensional Gel Electrophoresis offers us a powerful method to examine the super helicity-induced physical revolution in the DNA. Besides this, B-Z conversion is also designated here. One of a reasons for transition is a cause of free unfavourable energy. Affected advances are unrestricted from the uniting effect of genomics, human genetics, biophysics, and molecular studies on non-B-DNA configurations through mutation causing agents, intricate in Genetic diseases. Autoimmune processes may be suspected in all clinical conditions where specific anti-Z-DNA antibodies are found, but for further investigation, larger population is wanted to prove such an immunological hypothesis. Future prominence will challenge to tune the acceptance of the non-B-DNA configurations at a definite location of genes to correlate this behavior extra thoroughly with the generation reposition terminuses. Also, the analysis to recognize the kind of non-B-DNA structures that obtain certain sort of mutations and the fascinated enzyme on the evolution of therapeutics, to ameliorate the disturbing corollaries of these disorders.

## 8. Author contributions

PC and RR conceptualize this review article. RR analyzed and interpreted the information regarding Z-DNA structure and B-Z DNA transition. PC performed a study on B-Z DNA hybrid junction formation and effects of Z-DNA on human disease and was a major contributor in writing the manuscript. AC developed the figure based on available data. PC prepared the final draft of the manuscript under the supervision of JS. All authors read and approved the final manuscript.

## 9. Ethics approval and consent to participate

The work reported here in the manuscript is original and free from any plagiarism. All the data in the article are real and authentic. All the co-authors have read and agree to publish all the items listed above.

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Reetabrita Roy and Pallab Chakraborty contributed equally to this article.

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## 12. Conflict of interest

The authors declare no conflict of interest.

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**Abbreviations:**  $A\beta$  protein, Amyloid  $\beta$ -protein; AD, Alzheimer's disease; ADAM, a disintegrin and metalloproteinase; ADAR1, Adenosine Deaminase Acting On RNA; APOE, apolipoprotein E; CRH, corticotrophin-releasing hormone; DNA, Deoxyribonucleic acid; FRET, fluorescence resonance energy transfer; HO-1, heme oxygenase-1; IODO, 3-Iodo-L-tyrosine; MeCP2, methyl CpG binding protein 2; mRNA, messenger RNA; NF1, neurofibromatosis type 1; NRE, negative regulatory element; PLL-g-Dex, Poly (L-lysine) - graft dextran; RNA, Ribonucleic acid; ZBP, Z-DNA binding protein; ZFS, Z-DNA forming sequence.

**Keywords:** Alzheimer's disease; Wang model; Z-DNA-binding protein; Z-DNA-forming sequence; Review

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