**SIGNIFICANT B-DNA CONFORMATIONAL AND PHYSICO-CHEMICAL PROPERTIES OF THE DNA TOPOISOMERASE I SITES.**

PONOMARENKO M.P.+, VOROBIEV D.G., PONOMARENKO J.V., KUZIN F.E., GRUZDEV A.D., KOLCHANOV N.A.

Institute of Cytology and Genetics, Siberian Branch of the Russian Academy of Sciences, 10 Lavrentiev Ave., Novosibirsk, 630090, Russia;

+Corresponding author

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The experimental data of Perez-Stable et al. (NAR, 1988, **16,** 7975-7993) have been analyzed. Two sets of the 40 bp sequences of the topoisomerase I cleavage sites are considered in this paper. The first set comprises 82 normal sites classified by their DNA cleavage efficiency into the three subsets: 23 strong, 24 medium, and 35 weak sites. The second set contains 23 additional sites that can be induced by camptothecin, a cytotoxic alkaloid drug. In the paper cited, the 1 bp consensus of the DNA topoisomerase I cleavage site was identified, that is, the occurrence of nucleotide T at position -1 relative to the DNA cleavage point. For this reason, it was assumed that sequence-dependent B-DNA properties were responsible for topoisomerase I recognition of these DNA cleavage sites.

In this work, we have investigated the above hypothesis. For this purpose, both normal and induced topoisomerase I sites were analyzed using the computer system B-DNA-Video, developed earlier (Ponomarenko et al., Pass. Symp. Biocom., 1997, **2,** 340-351). The differences in significant conformational and physico-chemical properties between these 82 normal topoisomerase I sites and 500 random DNA sequences of the same length were tested. The results obtained are shown in the upper part of the Table. Four B-DNA properties were found to be capable of statistically significant discriminating between the normal topoisomerase sites and random DNA sequences, namely (1) Probability to be binding nucleosome core; (2) Roll; (3) Tilt; and (4) Twist, each property being averaged in the vicinity of the DNA cleavage point.

Classification of the 82 normal topoisomerase I sites according to their efficiency was used to test the significant properties found in the independent experimental data. Each property found was tested for the capability of discriminating between each subset of the actual topoisomerase I sites and random sequences (Table). It is evident from the Table that all the four properties found are typical of the strong sites; three, of medium sites; and only one, of weak sites. The dependence between the total number of the significant B-DNA properties and the site efficiency classes ranked is summarized and shown in Figure. Note that this dependence is characterized by the linear correlation coefficient **r=0.990,** which is statistically significant, alpha.gif (67 bytes)**<0.025**. This means that the four B-DNA properties (high Probability to be binding nucleosome core; high Roll; high Tilt; and high Twist), averaged in the vicinity of the 82 normal topoisomerase I sites, correlate with the independent experimental data on the site efficiency.

For the additional independent test; we have analyzed the 23 camptothecin-induced topoisomerase I cleavage sites as described above. The results obtained are shown in the bottom part of the Table. One can see that the same four B-DNA properties (high Probability to be binding nucleosome core; high Roll; high Tilt; and high Twist) were identified by this additional test. Essentially, the DNA regions in the vicinity of the DNA cleavage points selected to be significant for averaging these properties were dramatically different form those for the 82 normal sites. These results confirm the statistical significance of these four B-DNA properties for the topoisomerase I recognition of its DNA-cleavage sites.

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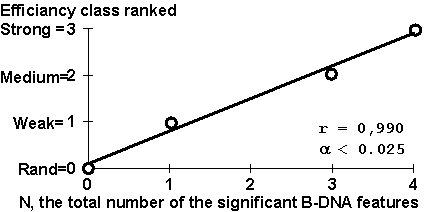


Figure. The dependence between the total number of the significant B-DNA properties and the efficiency ranked. The linear correlation coefficient r is 0.990 (significance, ?<0.025). Thus, the significances of the high Probability to bind nucleosome core; high Roll; high Tilt; and high Twist), averaged for the 82 normal topoisomerase I sites, have been confirmed by independent experimental data on efficiency of these sites.

Table. The significant difference in averaged conformational and physico-chemical B-DNA properties between all topoisomerase I DNA cleavage sites and 500 random sequences.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Significant B-DNA property averaged over a given region | | | | Range | | Mean http://www.bionet.nsc.ru/meeting/bgrs/thesis/127/plus_minus.gifs.d. values | | |
|  | Region | Name of B-DNA property | Unit | Min | Max | Topo I site | Random | Utility |
| *ANALYSIS*  All the 82 HeLa topoisomerase DNA cleavage sites | | | | | | | | |
| 1 | -19; 12 | Probability to bind nucleosome | % | 1.1 | 18.4 | *11.99http://www.bionet.nsc.ru/meeting/bgrs/thesis/127/plus_minus.gif1.34* | 11.25http://www.bionet.nsc.ru/meeting/bgrs/thesis/127/plus_minus.gif0.87 | 0.57 |
| 2 | -11; 19 | Twist | Degrees | 31.12 | 41.41 | *36.47http://www.bionet.nsc.ru/meeting/bgrs/thesis/127/plus_minus.gif0.53* | 36.14http://www.bionet.nsc.ru/meeting/bgrs/thesis/127/plus_minus.gif0.52 | 0.61 |
| 3 | -11; 19 | Roll | Degrees | -6.20 | 6.00 | *1.01http://www.bionet.nsc.ru/meeting/bgrs/thesis/127/plus_minus.gif0.78* | 0.64http://www.bionet.nsc.ru/meeting/bgrs/thesis/127/plus_minus.gif0.63 | 0.55 |
| 4 | -18; 15 | Tilt | Degrees | 0.00 | 1.90 | *0.88http://www.bionet.nsc.ru/meeting/bgrs/thesis/127/plus_minus.gif0.18* | 0.79http://www.bionet.nsc.ru/meeting/bgrs/thesis/127/plus_minus.gif0.13 | 0.53 |
| **Control test**  The 23 **strong** sites from the 82 analyzed | | | | | | | | |
| 1 | -8; 7 | Probability to bind nucleosome | % | 1.1 | 18.4 | **12.67http://www.bionet.nsc.ru/meeting/bgrs/thesis/127/plus_minus.gif1.22** | 11.34http://www.bionet.nsc.ru/meeting/bgrs/thesis/127/plus_minus.gif1.29 | 0.59 |
| 2 | -17; 17 | Twist | Degrees | 31.12 | 41.41 | **36.48http://www.bionet.nsc.ru/meeting/bgrs/thesis/127/plus_minus.gif0.35** | 36.13http://www.bionet.nsc.ru/meeting/bgrs/thesis/127/plus_minus.gif0.53 | 0.65 |
| 3 | -18; 16 | Roll | Degrees | -6.20 | 6.00 | **1.23http://www.bionet.nsc.ru/meeting/bgrs/thesis/127/plus_minus.gif0.59** | 0.63http://www.bionet.nsc.ru/meeting/bgrs/thesis/127/plus_minus.gif0.58 | 0.53 |
| 4 | -12; 15 | Tilt | Degrees | 0.00 | 1.90 | **0.92http://www.bionet.nsc.ru/meeting/bgrs/thesis/127/plus_minus.gif0.18** | 0.79http://www.bionet.nsc.ru/meeting/bgrs/thesis/127/plus_minus.gif0.15 | 0.60 |
| The 24 **medium** sites from the 82 analyzed | | | | | | | | |
| 1 | -17; 15 | Probability to bind nucleosome | % | 1.1 | 18.4 | **11.89http://www.bionet.nsc.ru/meeting/bgrs/thesis/127/plus_minus.gif1.33** | 11.25http://www.bionet.nsc.ru/meeting/bgrs/thesis/127/plus_minus.gif0.85 | 0.58 |
| 2 | -20; 17 | Twist | Degrees | 31.12 | 41.41 | **36.47http://www.bionet.nsc.ru/meeting/bgrs/thesis/127/plus_minus.gif0.53** | 36.14http://www.bionet.nsc.ru/meeting/bgrs/thesis/127/plus_minus.gif0.51 | 0.59 |
| 3 | -12; 14 | Roll | Degrees | -6.20 | 6.00 | **1.02http://www.bionet.nsc.ru/meeting/bgrs/thesis/127/plus_minus.gif0.89** | 0.65http://www.bionet.nsc.ru/meeting/bgrs/thesis/127/plus_minus.gif0.68 | 0.56 |
| *4* | *-12; 15* | *Tilt* | *Degrees* | *DID NOT FOUND TO BE SIGNIFICANT* | | | | |
| The 35 **weak** sites from the 82 analyzed | | | | | | | | |
| 1 | -8; 15 | Probability to bind nucleosome | % | 1.1 | 18.4 | **11.90http://www.bionet.nsc.ru/meeting/bgrs/thesis/127/plus_minus.gif1.74** | 11.27http://www.bionet.nsc.ru/meeting/bgrs/thesis/127/plus_minus.gif1.09 | 0.55 |
| *2* | *-20; 17* | *Twist* | *Degrees* | **DID NOT FOUND TO BE SIGNIFICANT** | | | | |
| *3* | *-12; 14* | *Roll* | *Degrees* | *DID NOT FOUND TO BE SIGNIFICANT* | | | | |
| *4* | *-12; 15* | *Tilt* | *Degrees* | *DID NOT FOUND TO BE SIGNIFICANT* | | | | |
| **ADDITIONAL test**  The 23 **additional** sites induced by camptothecin | | | | | | | | |
| 1 | -18; 16 | Probability to bind nucleosome | % | 1.1 | 18.4 | **12.14http://www.bionet.nsc.ru/meeting/bgrs/thesis/127/plus_minus.gif0.89** | 11.25http://www.bionet.nsc.ru/meeting/bgrs/thesis/127/plus_minus.gif0.83 | 0.56 |
| 2 | -7; 5 | Twist | Degrees | 31.12 | 41.41 | **36.63http://www.bionet.nsc.ru/meeting/bgrs/thesis/127/plus_minus.gif0.94** | 36.18http://www.bionet.nsc.ru/meeting/bgrs/thesis/127/plus_minus.gif0.94 | 0.55 |
| 3 | -16; 11 | Roll | Degrees | -6.20 | 6.00 | **1.27http://www.bionet.nsc.ru/meeting/bgrs/thesis/127/plus_minus.gif0.54** | 0.63http://www.bionet.nsc.ru/meeting/bgrs/thesis/127/plus_minus.gif0.65 | 0.57 |
| 4 | -12; 10 | Tilt | Degrees | 0.00 | 1.90 | **0.92http://www.bionet.nsc.ru/meeting/bgrs/thesis/127/plus_minus.gif0.15** | 0.79http://www.bionet.nsc.ru/meeting/bgrs/thesis/127/plus_minus.gif0.16 | 0.58 |