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Triplex DNA and human disease

John J. Bissler

Clark D. West Chair of Nephrology, Department of Pediatrics, Divisions of Nephrology and Hypertension, Cincinnati Children's Hospital Medical Center and the University of Cincinnati College of Medicine, Cincinnati, OH

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1. ABSTRACT

Mutagenesis is the fulcrum for the balance between the fidelity of the genetic code and evolution. While there are an enormous number of extrinsic factors driving mutagenesis, alternative DNA secondary structure is one of the intrinsic components that impacts regional genomic stability. Some alternative DNA structures are associated with human diseases, and this review focuses on disease-associated polypurine·polypyrimidine mirror repeat sequences.

2. INTRODUCTION

The precarious balance between preservation of the genetic code and mutagenesis is at the very root of cell, organism, and species survival, while also being paramount for the generation of biologic diversity. Mutagenic potential is greatest during DNA replication, and can be facilitated by both environmental and intrinsic factors. Repeat DNA sequences reside within the conceptual domain of intrinsic factors that can interfere with the fidelity of DNA replication. DNA repeats can be direct, inverted, or mirror

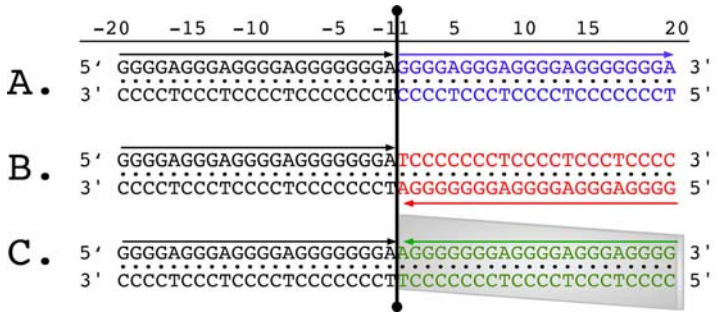

Figure 1. DNA repeat types. The numbers at the top of the figure represent the relative position, and the vertical bar indicates the center of symmetry for the three repeat types. A. Direct repeat. The basepairs in blue are a direct repeat of those in black that precede them so that the nucleotide at -20 is the same as 1. B. Inverted repeat. The black sequence is repeated in the complementary strand in the 5' to 3' direction as shown in red so that the nucleotide at -1 in the top strand is the same at 1 in the bottom. C. Polypurine·polypyrimidine mirror repeat. The green sequence is seen as if it were the reflection in a mirror (gray box) of the black sequence. The result is such that the bases are the same for -1 and 1, -2 and 2 etc. While all three types of repeats are shown without any bases between the repeats, they can also be separated by a variable number of nucleotides at the center of mirror symmetry.

in orientation (Figure 1). While all three types can facilitate mutations, the remainder of this review will focus upon mirror repeat sequences.

3. POLYPURINE·POLYPYRIMIDINE MIRROR REPEAT TRACTS AND TRIPLEX DNA

The major groove of the double helix can support the binding of a third strand, forming a triplex (1-4) (Figure 2). The third strand uses alternative hydrogen bonding called Hoogsteen base pairing (5). Such base pairing is illustrated in Figure 3. Often the pairing is written with the triplex strand first and in italics to indicate the conformation. Either the 5' or 3' end of either the purine-rich strand or pyrimidine-rich strand can fold into the major groove to form triplex DNA. Under most experimental conditions, cytosine requires protonation to bind into the major groove. However, Potaman et al. elegantly demonstrated that, even at neutral pH, short (GAA)n·(TTC)n repeats could form protonated triplex structures under appropriate superhelical tension (6). This ability to form at neutral pH did not require stabilization by magnesium or polyamine cations (7-9) and may be due to the significant proportion of the T*A·T triads which are pH-independent.

4. TYPES OF TRIPLEX DNA STRUCTURES

Triplex DNA formation depends upon the presence of a polypurine·polypyrimidine tract, and a third single-stranded DNA element. The third strand can come from the same molecule, for example from the other half of a mirror repeat sequence to form an intramolecular triplex (Figure 4A), or from a different molecule to form an intermolecular triplex structure (Figure 4B). This latter configuration has been leveraged to alter gene expression using triplex forming oligonucleotides. Lastly, triplex structures can form during the replication of mirror repeat sequences, called replicative triplex structures in this review for clarity (Figure 4C).

5. IDENTIFICATION OF TRIPLEX DNA

DNA triplex formation occurs under favorable thermodynamic conditions. For an intramolecular triplex to form, the energy driving formation is the negative superhelical tension. When such energy is applied, the $T_{1/2}$ of formation can be as little as two minutes (10), though the rate of formation would be dependant on the length and composition of the mirror repeat, pH, supercoiling, temperature, and the presence of stabilizing agents like divalent cations and polyamines. The formation of intermolecular triplex would depend also on the concentration of the duplex and single-stranded components, and the replicative structures would depend on the ability of other proteins to compete for binding to both the duplex and single-stranded components. There are a variety of methods to characterize triplex DNA.

5.1. Two-dimensional gel electrophoresis

When an intramolecular triplex forms in a plasmid, approximately one superhelical turn is absorbed for every 11 base pairs of the repeat participating in the triple-stranded structure (11). Subtle differences in energy absorption occur depending on whether the 3' or 5' pyrimidine strand fold into the major groove and whether or not the third strand is linked or unlinked at the tip (12, 13).

5.2. Chemical Modification of unpaired strand

Base pairing significantly influences the chemical reactivity of nitrogenous bases. When one strand of a mirror repeat half binds the major groove, the complementary single-strand is exposed to the solvent phase and vulnerable to chemical modification (Figure 4A) (14). Chemical agents can be used to probe for unpaired bases: chloroacetaldehyde and bromoacetaldehyde for cytosines and adenosines, diethylpyrocarbonate for unpaired purines, and osmium for thymine. These modified bases can be identified by cleavage methods such as with hydrazine followed by piperidine, or by primer extension methods.

5.3. Antibody recognition of triplex DNA conformation

The mammalian immune system can form antibodies that recognize DNA structures, for example

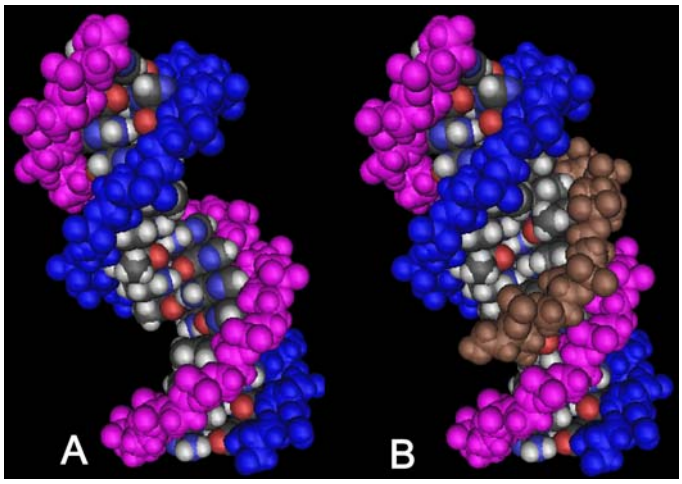

Figure 2. Crystal structure of triplex DNA dervived by Radhakrishnan *et al.* (1-4). A. Space fill model of duplex DNA. B. Model as in A with third strand (brown) in major groove forming triplex DNA.

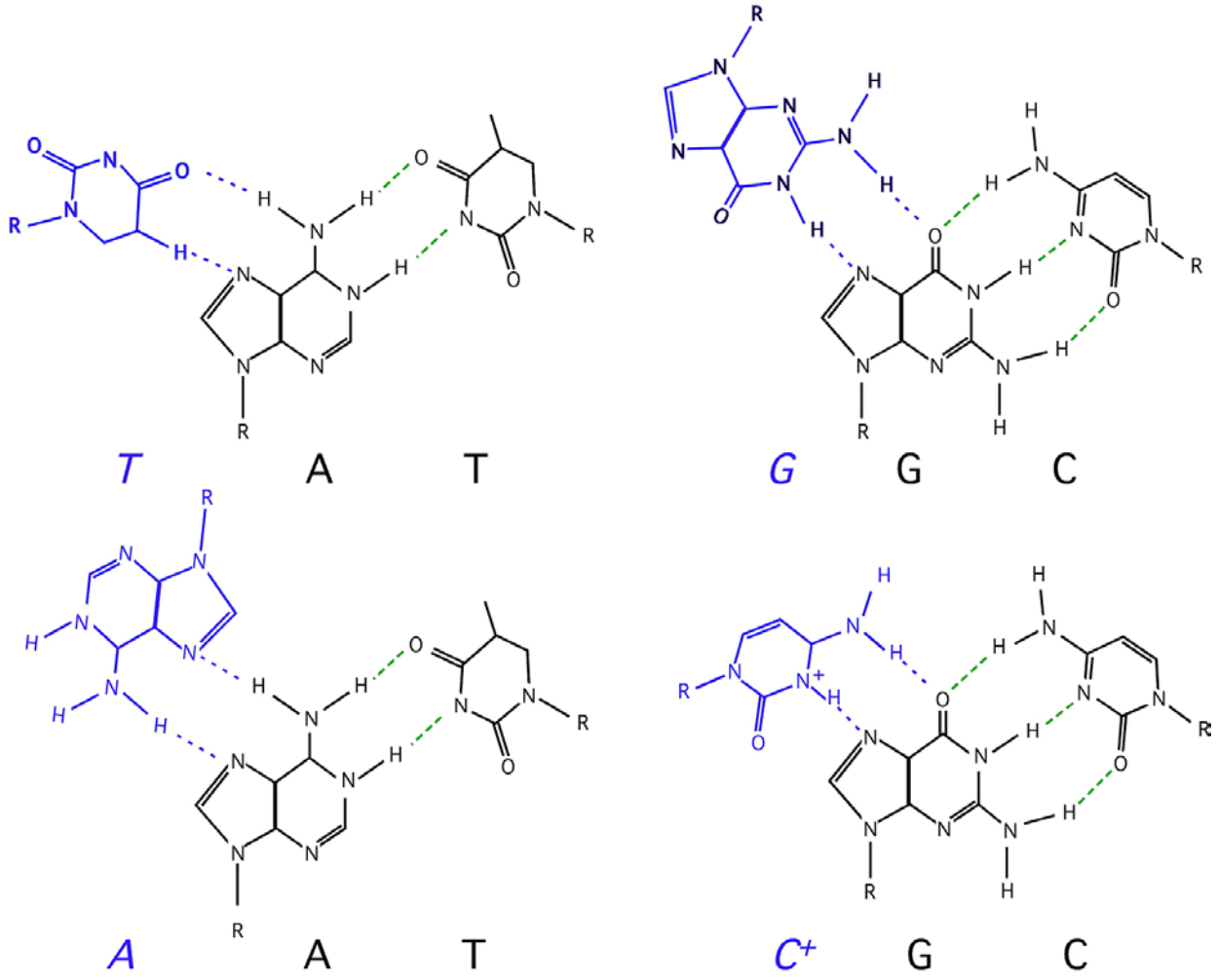

Figure 3. Hoogsteen base pairing includes two pyrimidines and a purine. The third base is flipped when the configuration is two purines and a pyrimidine, and this is called reverse Hoogsteen base pairing. Watson-Crick base pairing is illustrated in green dotted line, Hoogsteen in blue. The *T**A·T triplex base pairing can actually be Hoogsteen or reverse Hoogsteen in nature.

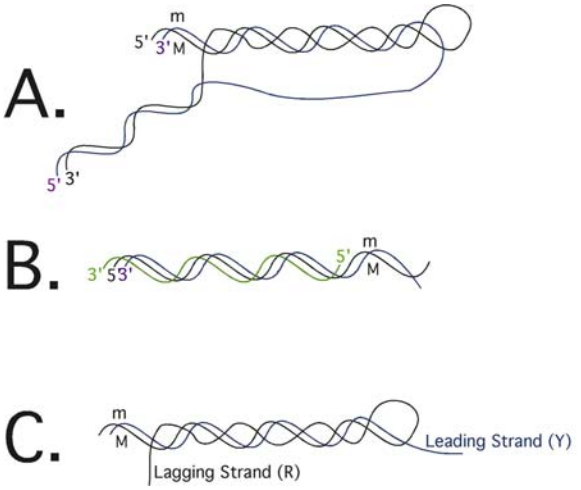

Figure 4. Types of triplex structures. A. Intramolecular triplex. B. Intermolecular triplex. C. Replicative form of triplex. 'M' denotes major groove, 'm' denotes minor groove.

patients with systemic lupus erythematosus and rheumatoid arthritis can develop antibodies to Z-DNA (15). Studies using murine monoclonal antibodies to triplex DNA suggest both A·T and C·G rich triplex structures are present in chromatin (16-18).

5.4. Nucleases

Single-strand specific nucleases, like the S1, P1, and mung bean nucleases, are efficient at cleaving single-stranded DNA at low pH. This single-strand specificity can be used to map the location of triplex structures by cleaving the associated single-strand (Figure 4C) in combination with restriction endonucleases.

5.5. Chemical Cross-linking

While single-stranded DNA can be identified by its reactivity to different chemical agents or nucleases, 4, 5', 8-trimethylpsoralen photobinding is dependent on B-form DNA. Psoralen intercalates into the B-form of DNA and can be activated to bind to 5' TA. Because intercalation fails to occur in single-stranded DNA, detection of perturbations in B-form DNA has been used to characterize triplex structures (19).

6. ROLE OF MIRROR REPEATS IN DISEASE

Polypurine·polypyrimidine tracts in the genome represent potential causes as well as therapeutic targets to ameliorate disease. Mirror repeat polypurine·polypyrimidine tracts may lead to disease because of mutagenesis or alterations in gene expression. Genome instability is associated with double-strand breaks (20). The formation of an intramolecular triplex *in vivo* may be subject to cleavage by a host of processes including a variety of repair mechanisms leading to double strand breaks and instability or by formation of the replicative triplex structure that leads to fork collapse and subsequent double-strand breaks. Alternatively mirror repeat polypurine·polypyrimidine may be mutagenic because they can be decorated by DNA repair proteins that lead to targeted genetic destabilization.

6.1. Possible role of replication blockade and mutagenesis

Triplex DNA can adversely effect DNA replication and potentially lead to replication fork collapse (22). There are two features of polypurine·polypyrimidine tracts that may further potentiate their effects on replication. The replication primers created by the polymerase α holoenzyme usually start with purines, making the purine stand a very unlikely template since pyrimidines would needed for the primer base pairing (23). In addition, the binding of replication protein A, the single-stranded binding protein in mammalian cells, to pyrimidines is 50 fold better than to purine (24). These two features mean that there is a reduced probability of the polypurine strand being bound to a primer or to replication protein A, and this 'nakedness' facilitates the probability of the purine strand binding in the major groove to form triplex DNA at neutral pH. Baran *et al* even postulated that such regions may function as replication terminators (25). If the fork collapse with a double-strand break occurs, then a recombinational repair may facilitate mutagenesis, for example by templating from a similar sequence elsewhere in the genome as suggested by evidence of gene conversion events (26, 27). Such double-strand breaks resulting from triplex structures may be repaired either by homologous recombination or non-homologous end-joining and may result in translocation events (28-30).

6.2. Possible role of intramolecular triplex DNA as scaffold for repair proteins

If an intramolecular triplex forms, driven by negative superhelical tension (31), the single-stranded polypyrimidine strand (Figure 4) may facilitate recombination without replication by acting as an annealing target leading to the development of a D-loop (32), or by acting as the invading strand to another region of homology.

Because polypyrimidine strands are the preferred substrate for replication protein A (RPA) binding and this strand will be single-stranded in intramolecular triplex structures at neutral pH, persistent RPA binding may lead to RPA hyper-phosphorylation that may trigger repair reactions (33). The intramolecular structure also may be targeted by nucleases resulting in single- or double-strand breaks and subsequent mutagenesis or recombination. The triplex structure itself may trigger repair-mediated mutagenesis. Synthetic oligonucleotides have been extensively investigated as a means of sequence-targeting mutagenesis (34-37). Nucleotide excision repair (NER) proteins appear to bind to intermolecular triplex structures (38), and are involved in the mutagenesis and recombination that occurs in cells (37, 39). In bacterial cells, NER proteins UvrB and UvrC were required for triplex-induced cell growth retardation (21).

The ability for polypurine·polypyrimidine tracts to engage in the formation of different forms of triplex structures may also effect gene expression. Such tracts are

Table 1. Human diseases associated with triplex-forming DNA

Disease	OMIN#
Autosomal Dominant Polycystic Kidney Disease (ADPKD)	#173900
Tuberous Sclerosis Complex (TSC)	#191100
Lymphangioleiomyomatosis (LAM)	#606690
Friedreich's ataxia	#229300
Follicular Lymphoma	*136440
Hereditary Persistence of Fetal Hemoglobin (HPFH)	*142470

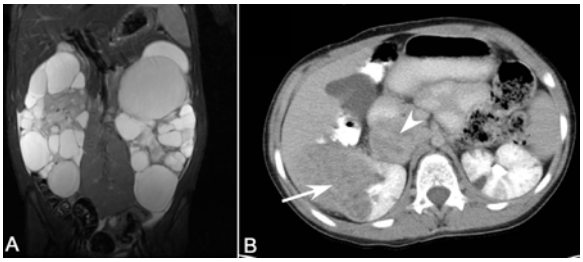

Figure 5. Manifestations of ADPKD and TSC. A. ADPKD in a child with TSC. Note numerous bilateral renal cysts (white). B. Large right angiomyolipoma (arrow) with invasion of the vena cava (arrowhead).

over represented in the 5' end of genes and have been postulated to potentiate or suppress transcription. Lee *et al.* postulated that the alternative secondary structure formation may act as a molecular switch to turn genes off (16), and such appears to be the case at the γ-globin locus (40). The ability of triplex formation to modulate gene expression or alter the genetic code has lead to the therapeutic considerations of administering oligonucleotides that, once in place, may even be cross-linked to induce effects (41, 42).

7. DISEASES ASSOCIATED WITH MIRROR REPEATS

There are a number of inherited as well as acquired human diseases that are associated with triplex-forming DNA (Table 1). Both inherited and acquired diseases may require somatic mutation for phenotypic expression.

7.1. Chromosome 16p13.3 and autosomal dominant renal disease

Both tuberous sclerosis complex (TSC) and autosomal dominant polycystic kidney disease (ADPKD) dramatically affect renal architecture and function as the patient ages (Figure 5). Renal manifestations of TSC include angiomyolipomata, cysts, and, rarely, malignant tumors. ADPKD is associated with the development of renal cysts and approximately 50% of patients will require renal replacement therapy by the age of sixty years (43), making up 10% of the end stage renal disease population (44).

Both the ADPKD-related renal cysts and TSC-related angiomyolipomata are associated with a remarkable variability of expressivity. Angiomyolipomata are hamartomas consisting of abnormal vessels, smooth muscle cells and adipose tissue (45). Typically, angiomyolipomata are present in the young (46) and continue to grow during adulthood (47-49). These lesions distort renal architecture and can compromise renal function. Because of the dysmorphic vasculature, aneurysms can develop that rupture and bleed, resulting in significant morbidity and even death. A more dramatic, though rare, renal manifestation of TSC is polycystic kidney disease. The *TSC2* and *PKD1* genes lie closely adjacent in a tail-to-tail orientation at 16p13.3 (50). Frequently, mutational analyses in such polycystic kidney variant TSC patients reveal a deletion involving both the *TSC2* and *PKD1* genes. A large number of such patients have new mutations or exhibit mosaicism (51, 52) and these children have rapid development of cysts (Figure 5A). Renal failure is a long-term complication of TSC (46, 53, 54) and end stage renal disease is the leading life threatening complication of TSC in the adult (55).

Analysis of somatic and germline mutations in the *TSC2* and *PKD1* genes, as well as the comparison of physical to recombinational distances of 16p13, identify recombination as a mechanism of mutagenesis in this region. In heteroallelic individuals the normal *TSC2* and *PKD1* genes are the targets of somatic second mutation resulting in a cell lacking the functional protein (two hit hypothesis). Evidence supporting the two hit hypothesis for both TSC and ADPKD has come from the analysis of DNA and protein from affected tissues. Henske *et al.* demonstrated an absence of tuberin, the protein product of the *TSC2* gene, in spindle and epithelioid cells from giant cell astrocytomas and in the smooth muscle, blood vessels, and adipose tissue in angiomyolipomata from patients with TSC (56). The loss of tuberin immunostaining correlated with the demonstration of loss of heterozygosity (LOH) at the *TSC2* locus in these tissues such that only the mutant allele could be identified (57). In angiomyolipomata, LOH has been found at the *TSC2* locus (56, 58) as well as at the *TSC1* locus (59, 60) suggesting that deletion or mitotic recombination as a second hit may be widely distributed. In a study of 130 sporadic TSC cases, 68% had *TSC2* mutations, 22% had no identifiable mutation, and 10% had *TSC1* mutations (61). Dabora *et al.* demonstrated that de novo mutations in *TSC2* are six times as frequent as in *TSC1* (62).

Similarly. lymphangioleiomyomatosis, a pulmonary disease of woman, can occur sporadically or in association with TSC. In the sporadic form of this disease, approximately half of the women also have renal angiomyolipomata. Microsatellite marker analysis revealed that in the sporadic form of lymphangioleiomyomatosis there is also *TSC2* LOH in the angiomyolipomata (63), while LOH at the *TSC1* locus has not been identified. In addition, Lininger *et al.* examined benign and malignant mammary papillary neoplasms and found that loss of heterozygosity was frequently found at 16p13, while other regions, such as p53, INT-2, and several other loci on chromosome 16 were preserved suggesting that 16p13 may be somehow prone to LOH (64).

Mutational analysis of both germline and somatic mutations in the *PKD1* gene support a role for recombination. Germline mutations in the *PKD1* gene are

associated with more than 85% of the cases of ADPKD. The proposed mutagenic mechanism involves recombination, such as gene conversion, to repair double-strand breaks following replication fork blockade. Rossetti *et al.* screened for mutations in 131 unrelated patients with ADPKD and found that mutations were more than twice as frequent in the 3' half of the gene compared with the 5' half. Furthermore the mutation frequency was higher on either side of the peculiar polypurine·polypyrimidine tract in intron 21 than at the 5' end of the gene. They suggested that the tract may have a long-range effect that was reflected in the higher rate of mutation overall in the 3' end of the gene (65). Besides finding more mutations in the vicinity of the *PKD1* polypurine·polypyrimidine tracts, Rossetti *et al.* also found several mutations that could be attributed to germline gene conversion.

Somatic mutations may also implicate the polypurine·polypyrimidine tract. Cystogenesis in ADPKD is thought to result from the inheritance of a dysfunctional *PKD1* allele coupled with a somatic mutation in the *PKD1* allele from the non-affected parent occurring in the renal tubular cell (66). Such somatic mutations can be multiple and reflect possible gene conversion as a mechanism of somatic mutagenesis (27, 67, 68). Gene conversion uses homologous sequences as targets to facilitate repair. Watnick *et al.* surmised from their mutational analysis of cystic tissue that gene conversions occurred and that the templating occurred at 16p13.1 [49]. This region has more than three transcriptionally active homologous (HG) genes with significant homology to *PKD1* (67, 69), and the mutations in the *PKD1* gene in the cysts identical to the sequence from one of the centromeric homologous genes. These mutations suggested that gene conversion had rendered the previously functional *PKD1* gene mutant, allowing for cysts to develop. Gene conversion notwithstanding, many lines of evidence support the two hit hypothesis for ADPKD (70). Analysis of the cells lining the cystic dilatation revealed only the mutant allele for *PKD1* (71-73), precluding the ability of such cells to correctly synthesize polycystin-1. Such somatic mutagenesis leading to polycystic disease is also seen in *PKD1* knockout mice. Two of eight mice heterozygous at the *PKD1* locus by gene knock out, developed significant renal cystic disease with cysts devoid of polycystin-1 by immunostaining, indicating that the wild-type allele had undergone a somatic mutation (74, 75).

Analysis of physical and recombinational distances of 16p13 also point to a recombination as a cause for mutation in this region. The HG genes have ~ 97% homology to the first 34 exons of *PKD1* and containing the polypurine·polypyrimidine tract. Callen *et al.* demonstrated that this region is a hot-spot for meiotic recombination by comparing the genetic distance with the physical map of 16p (76). One interpretation of the Callen *et al.* work is that the polypurine·polypyrimidine tract promotes meiotic recombination because these sequences block replication and induce recombination. Because this effect is sequence specific, it may, likewise, also promote mitotic recombination.

DNA that can form triplex structures such as the *PKD1* polypurine·polypyrimidine tract, is associated with blockade of the mammalian replication fork (77) and may lead to mutations in a mouse model (36). Such polypurine·polypyrimidine tracts block DNA replication (see for review (12) and (13)) by forming a triplex structure between the mirror repeat template strand and the nascent strand that sequesters the 3' end of the nascent DNA leading strand and prevents fork extension (22, 78-83). We demonstrated that the *PKD1* gene contains polypurine·polypyrimidine tracts that form triplex structures (84), and strongly interfere with replication in prokaryotic models and in human replication systems (85, 86). Bacolla *et al.* studied the stability of the *PKD1* polypurine·polypyrimidine tract in a bacterial model and concluded that the alternative DNA conformations could also trigger genomic rearrangements through recombination-repair activities (21).

7.2. Hereditary persistence of fetal hemoglobin

A myriad of physiological and gene expression changes occur to accommodate extrauterine survival, including down regulation of fetal genes. Patients who are homozygous or compound heterozygous for the ß-globin allelic variant (*Hb S*) exhibit sickle cell disease. Symptoms are most often identified within the first six months of life, but there is considerable variability in the disease (87). The patient's genotype is the major determinant for disease severity, and patients with Hb SS are most severely affected (87). Several therapies for sickle cell disease, for example hydroxyurea, function by increasing the levels of fetal hemoglobin (Hb F) in affected individuals (88). Increased expression of Hb F ameliorates the disease phenotype (89). Some patients have a genetic predisposition to unusually high levels of Hb F due to the failure to down-regulate the γ-globin chains. This condition, called hereditary persistence of fetal hemoglobin, occurs in 1/188,000 patients with sickle cell disease, and these patients have a less severe disease (90).

O'Neill *et al* used S1 nuclease to map a 250 base pair polypurine·polypyrimidine tract upstream from the human δ-globin gene (91). Ulrich *et al.* characterized the secondary DNA structure that lies upstream from the $^{A}\gamma$ and $^{G}\gamma$-globin genes. They identified that four out of five HPFH mutations destabilize triplex formation using S1 nuclease and oligonucleotides to map the structure (40). Structure dependence of the sequence was already well established, but this was the first example of such point mutations effecting disrupting triplex structure that also had a biologic outcome effecting human health (10). Bacolla *et al* used osmium tetroxide, chloroacetaldehyde, and diethyl pyrocarbonate to more clearly map out the triplex structures that could form and again noted the influence of negative supercoiling, low pH, and magnesium ions on structure formation (92).

7.3. Friedreich's ataxia

Friedreich's ataxia is an autosomal recessive disease that exhibits progressive degeneration of nerve tissue in the spinal cord and of nerves that control muscle movement in the arms and legs. This condition was

described in the 1860s and affects about 1 in every 50,000 people in the United States. Males and females are affected equally, and symptoms range from gait disturbance and speech problems to heart disease. Symptom onset typically is between the ages of 5 and 15 years and usually manifests as the gait disturbance known as ataxia. The ataxia is progressive and also involves the arms and trunk. The gene associated with Friedreich's ataxia is located on chromosome 9 and contains 7 to 22 GAA triplet repeats. Approximately 96% of Friedreich's ataxia carriers have an expansion of this repeat into the hundreds or thousands, which great reduces the amount of frataxin produced (93). Frataxin, a mitochondrial protein, is generally thought to participate controlling cellular iron homeostasis by directly binding iron (93). Friedreich's ataxia is the first known example of an autosomal recessive genetic disease caused by a triplet repeat expansion.

The Friedreich's ataxia $(GAA)_n$ repeats can form stable length dependent triplex structures (6), and two molecules that form triplex can interact through the triplex regions to form "sticky-DNA (94). Friedreich's ataxia $(GAA)_n$ repeats also present a formidable polar blockade to replication fork progression. This repeat-length dependant effect is pronounced only when the polypurine strand of the repeat is in the lagging strand template for replication. The $(GAA)_n$ repeats effect on replication may be mechanistically involved in their expansion. Mirkin *et al.* excluded a role for aberrant transcription (95), and protein binding to the polypurine·polypyrimidine tract is perhaps unlikely as the replication inhibition would be equally pronounced in both orientations of the repeat, although yeast have found a way around this with in the rRNA region using the polar replication terminators ter 1 and ter 2 (96). The mechanism is likely related to the ability of the sequence to form triplex DNA (97-99) and interfere with replication (97, 100) in a polar fashion (101). Regardless of the mechanism, replication blockade is recombinogenic and may play a role in the tract expansion (102).

7.4. Lymphoma

Certain sequences adversely affect DNA replication, repair, or recombination and may lead to mutations such as translocations (103-105). The most common chromosomal translocation in human cancer is the t(14;18) translocation that occurs in almost all follicular lymphomas (106-109). This translocation appears to result from recombination between the *bcl-2* gene and V(D)J subexons during V(D)J recombination and juxtaposes the *bcl-2* locus on chromosome 18 to the intron enhancer of the immunoglobulin heavy chain locus on chromosome 14. This positioning leads to over expression of the antiapoptotic protein, Bcl-2, and hence, to follicular lymphoma (106, 108-113). In most follicular lymphoma patients, the break at chromosome 18 occurs within a small 150-bp region designated as the major breakpoint region (Mbr) (108, 109). Within this 150-bp Mbr region, there are three translocation hotspots (113). The precision and distribution profile within the bcl-2 Mbr strongly suggest a DNA structural effect. Recently, the bcl-2 Mbr was identified as being polypurine·polypyrimidine in nature and possibly capable of forming triplex DNA structures (28-30). The breaks at the V(D)J sites on chromosome 14 involve cleavage at a pair of signal sequences (12- or 23-signal) by the RAG complex (RAG1, RAG2, and HMG1).

8. PERSPECTIVES

Polypurine·polypyrimidine mirror repeat tracts in the human genome have unique characteristics that confer unique regulatory ability, at least with respect to fetal hemoglobin expression, while putting the region containing them at risk for mutation. It is tempting to speculate that the persistence and enrichment of such sequences in the genome may be because they can participate in the regulation of gene expression and DNA replication. While these roles contribute to the positive selective pressure, the tracts also contribute to reduced genomic stability that is unmasked in patients who are heterozygotic at gene loci, like *TSC2* and *PKD1,* and in cells that proliferate throughout life, like lymphocytes. The risk of phenotypic expression in these latter two cases are due to mutation of the functional gene in the cell and increased risk proportional to increased replication. If these polypurine·polypyrimidine mirror repeat tracts are capable of facilitating mutation, as suggested by the human *PKD1* mutation data (114) and the mouse and chimpanzee sequence data (115), then such sequences may also drive evolution and speciation in addition to heritable disease and cancer.

9. ACKNOWLEDGMENTS

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Send correspondence to: John J. Bissler, M.D., Cincinnati Children's Hospital Medical Center, MLC #7022, 3333 Burnet Avenue, Cincinnati, OH 45229-3039, Tel: 513-636-4531, Fax: 513-636-7407, E-mail: john.bissler@cchmc.org