# Ends of chromosomes protected by stacked, coiled DNA caps, study finds

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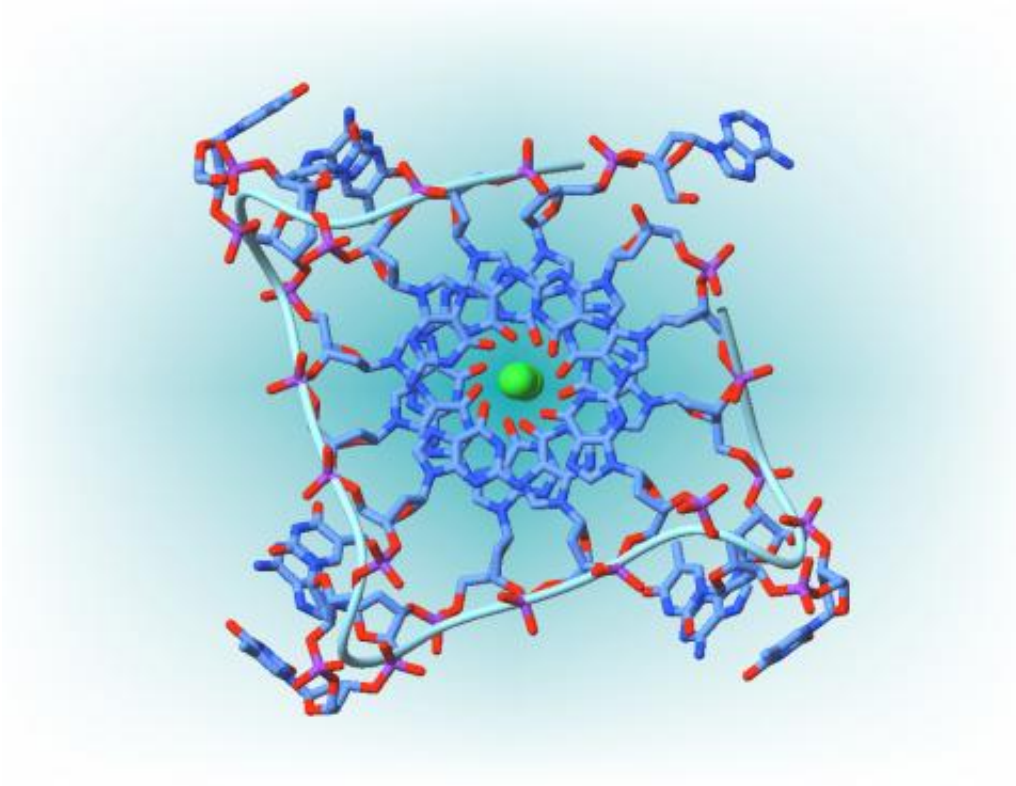

An end-on view of a G-quadruplex. Image by Julian Huppert.

(PhysOrg.com) -- Researchers at the University of Pennsylvania School of Medicine are delving into the details of the complex structure at the ends of chromosomes. Recent work, e-published in *Nature Structural & Molecular Biology* last month, describes how these structures, called telomeres, can be protected by caps made up of specialized proteins and

stacks of DNA called G-quadruplexes, or "G4 DNA." Telomere caps are like a knot at the end of each chromosome “string,” with the knot's role preventing the string from unraveling.

"Although G4 DNA has been studied in test tubes for years, we did not know whether it could contribute to telomere protection in actual cells until we performed our studies in yeast cells," stated F. Brad Johnson, MD, PhD, associate professor of Pathology and Laboratory Medicine.

The composition of the particular G4-molecular "knot" studied is complex and unusual, involving a DNA sequence with guanine building blocks that loop back and forth on top of each other to form a four-stranded stack, which is different from the two-stranded arrangement of typical DNA molecules. The stack protects the chromosome from unraveling by specialized enzymes.

The length of telomeres is associated with age. Shortened telomeres are observed in aging cells and in some rare syndromes. There is mounting evidence that loss of telomere capping may contribute to some diseases that become more common with natural aging. An example of extreme aging associated with telomere defects is Werner syndrome, a rare genetic disease in which individuals develop normally until puberty. After this they age rapidly, so that by age 40 or so they often appear several decades older.

The protein missing in people with Werner syndrome but present in healthy people, is a helicase, an enzyme that unzips DNA. A slightly different G4-unwinding helicase is missing in people with a related disease, called Bloom syndrome, which is characterized by chromosome instability and high rates of cancer. It's possible that changes in G4 DNA contribute to the symptoms of these two syndromes.

The normal unwinding of DNA is critical under many particular

circumstances, for example during replication. There are hundreds of different types DNA helicases in human cells, and each unwinds DNA under different circumstances. Although it is important to keep the strands of DNA together most of the time, if they can't be unwound when needed, serious problems could occur.

The Penn researchers hope to eventually explore the role of G4 capping in human aging after they know more about the G4 cap in yeast cells, which are easy to study because they can be engineered to make very specific changes in their DNA and proteins.

Recently, Johnson's group found that DNA sequences with the potential to form G4 DNA, which exist not only at telomeres but also at many locations throughout the entire human genome, are closely connected to changes in gene expression in cells from people with Werner or Bloom syndrome. They predict that G4 DNA abnormalities also exist at the telomeres in these human diseases and perhaps those of aging cells.

In their experiments in which telomeres were specifically examined in yeast, both elevated levels of G4 binding protein and inactivation of the yeast helicase that is similar to the one missing in human Werner and Bloom syndrome patients led to increased protection of the telomeres. This suggested that the G4 caps were present on the telomeres and that they protected the telomere from breaking down.

The overall role of G4 DNA is not simple and might seem to be contradictory. For example, work from several other research groups has suggested that G4 DNA can interfere with the replication and capping of telomeres, in contrast to the protective role observed by Johnson's group.

"This points out the complexity of G4 DNA," said Johnson. "On one hand, some G4 DNA may help cap telomeres, but too much G4 DNA or formation of G4 DNA at the wrong times or places may be detrimental.

G4 DNA is not a single thing, but is rather a family of related structures, and so it might be possible to target particular types of G4 DNA to, for example, improve telomere capping in normal cells or disrupt the growth of cancer cells. This is a very new field, and it will be fun to see how far it might go."

**More information:** www.nature.com/nsmb/journal/v1 … 4/abs/nsmb.2033.html

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