



NATIONAL INSTITUTE OF CHEMISTRY



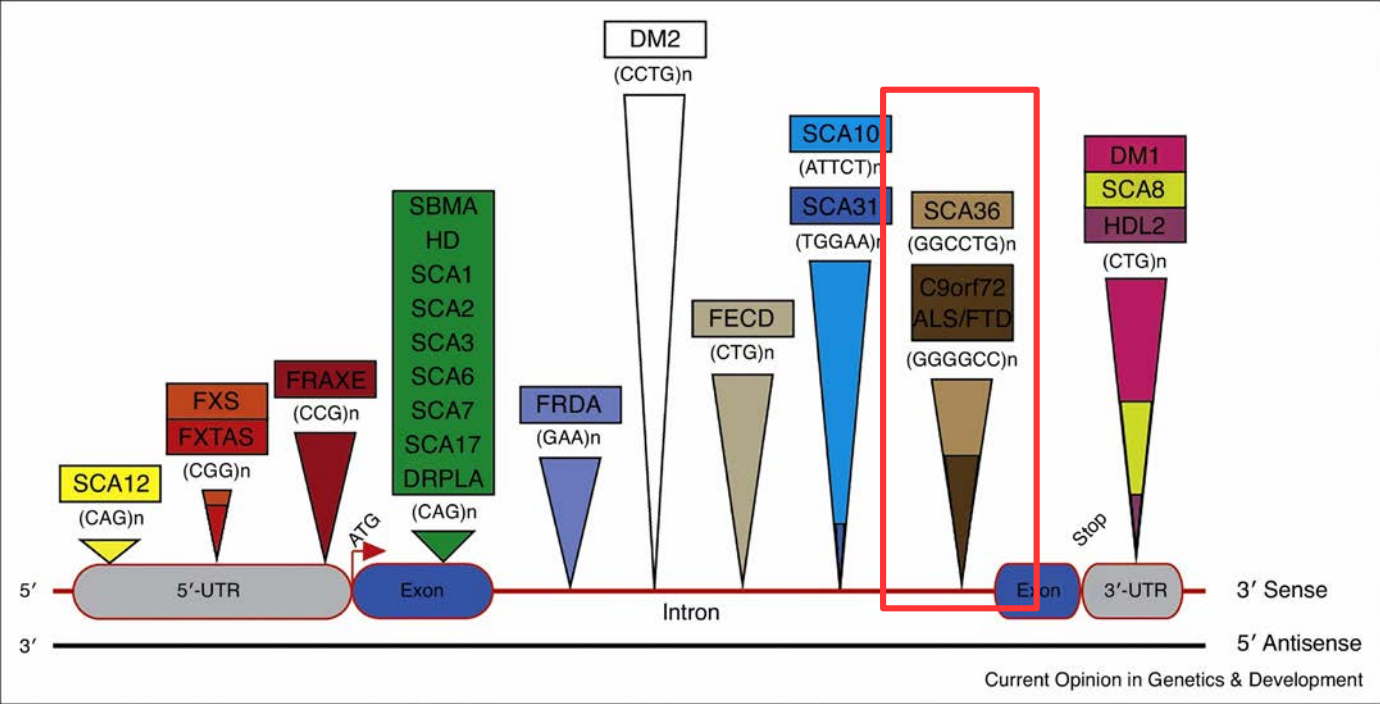
Two G-quadruplex structures adopted by oligonucleotide model of ALS and FTD linked GGGGCC repeats

Jasna Brčić

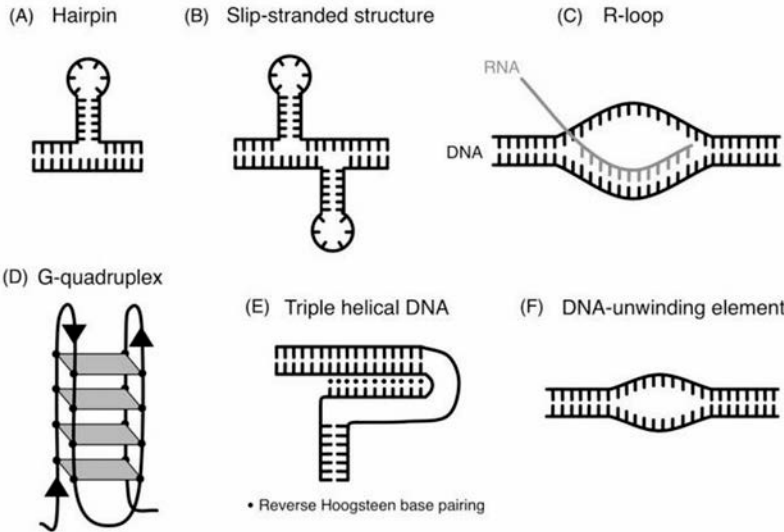
dr. Janez Plavec
Slovenian NMR centre
National Institute of Chemistry,
Ljubljana, Slovenia

ENCALS 2017, Ljubljana

Nucleotide repeat expansion in human diseases



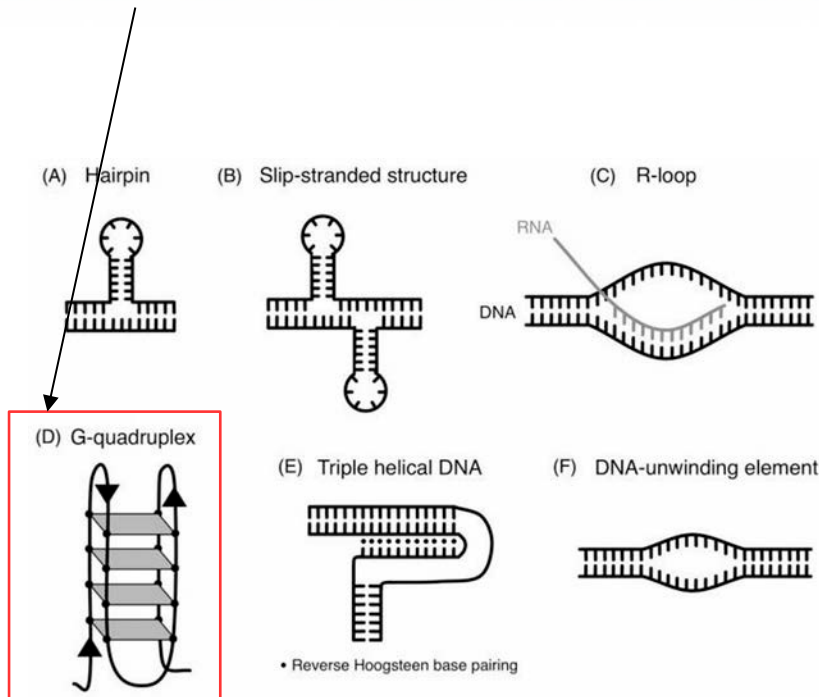
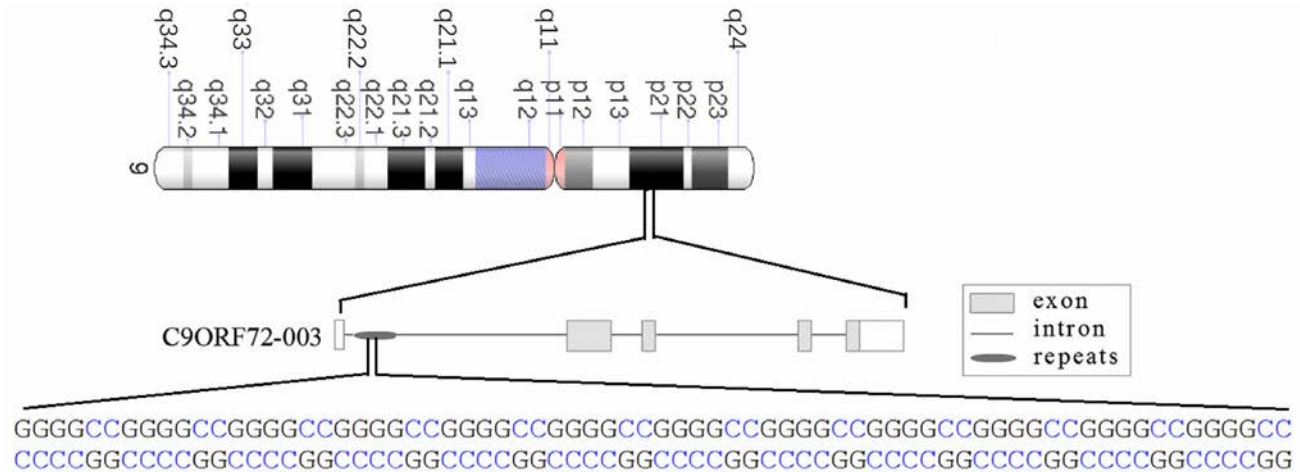
Zhang, N., Ashizawa, T.
 Current Opinion in Genetics & Development,
 2017, 44:17–29



Usdin K, House NCM, Freudenreich CH. Critical reviews in biochemistry and molecular biology. 2015; 50(2) :142-167.

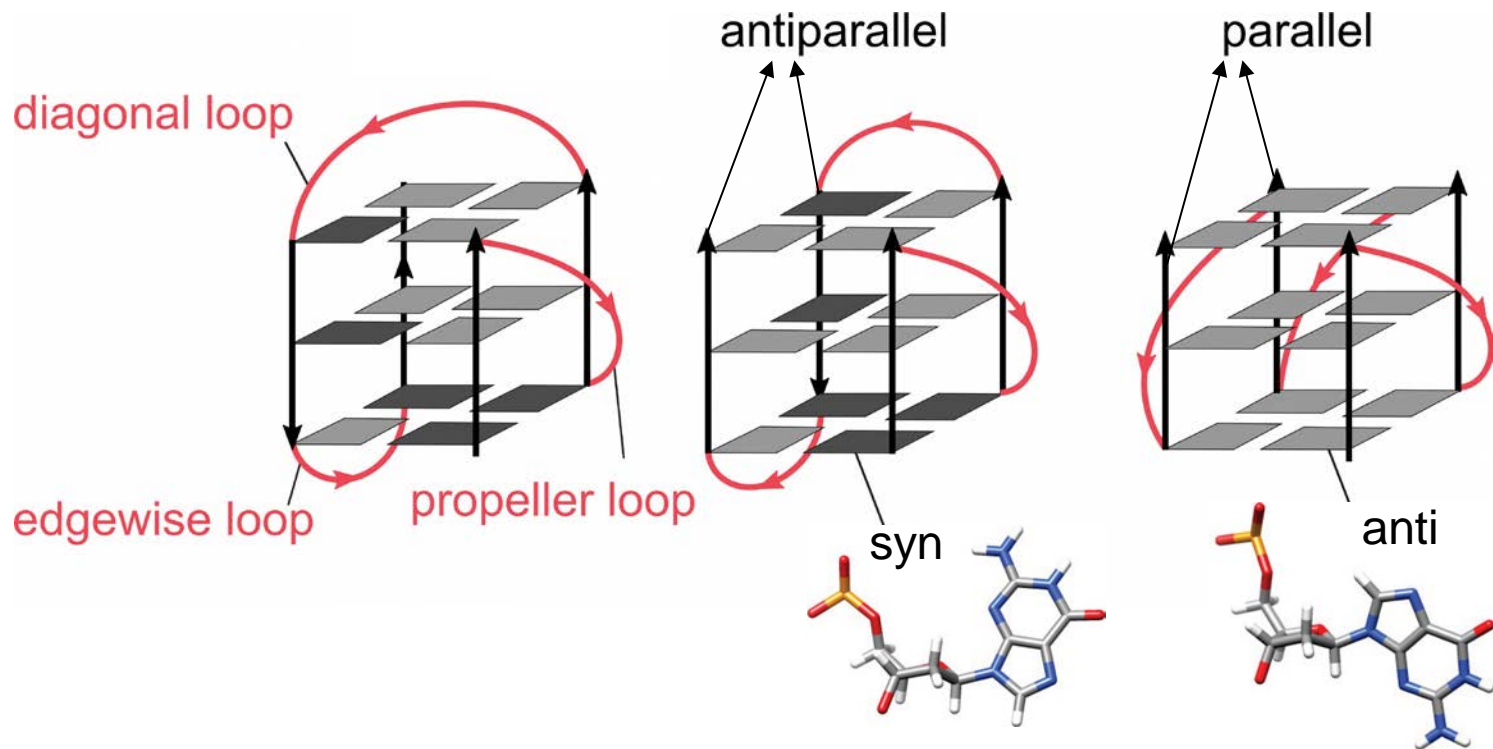
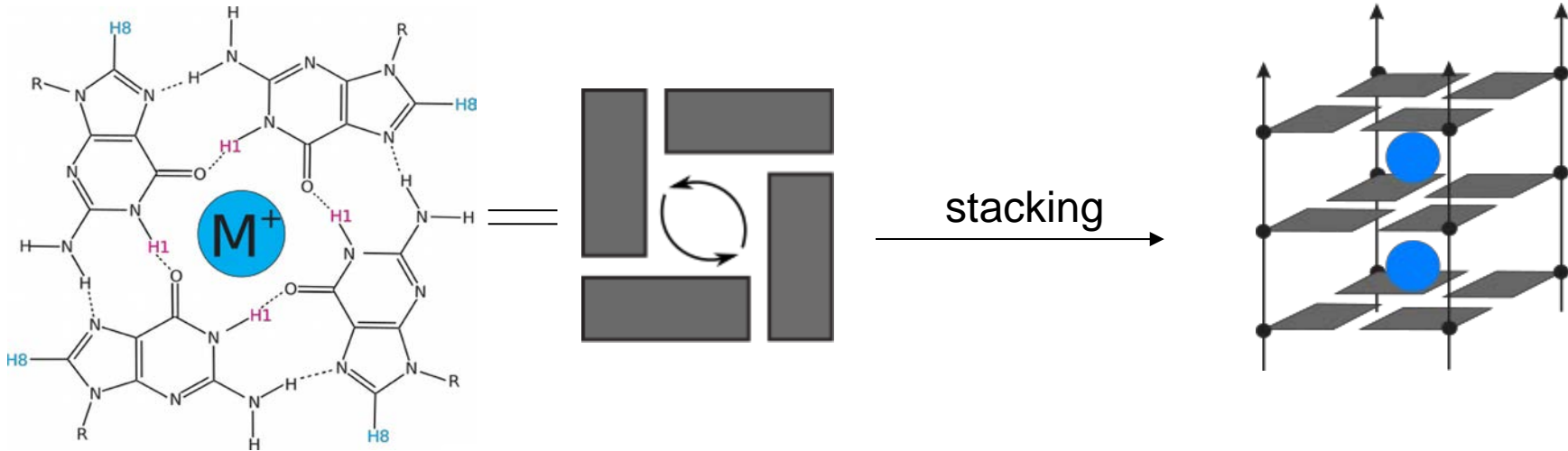
Nucleotide repeat expansion in human diseases: ALS and FTD

Expansion of **GGGGCC** repeat within *C9orf72* gene is the most common genetic cause of ALS and FTD

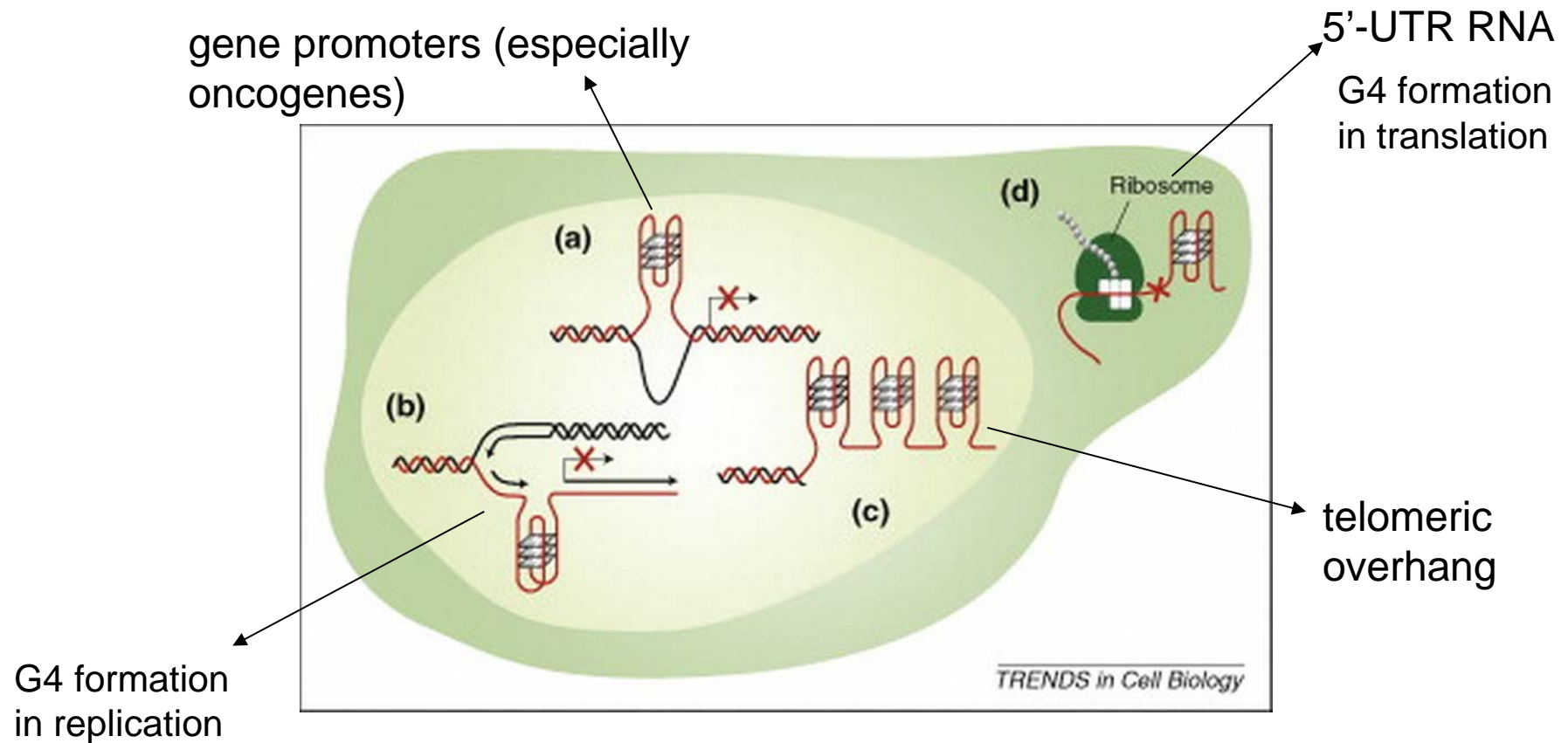


Usdin K, House NCM, Freudenreich CH. Critical reviews in biochemistry and molecular biology. 2015; 50(2) :142-167.

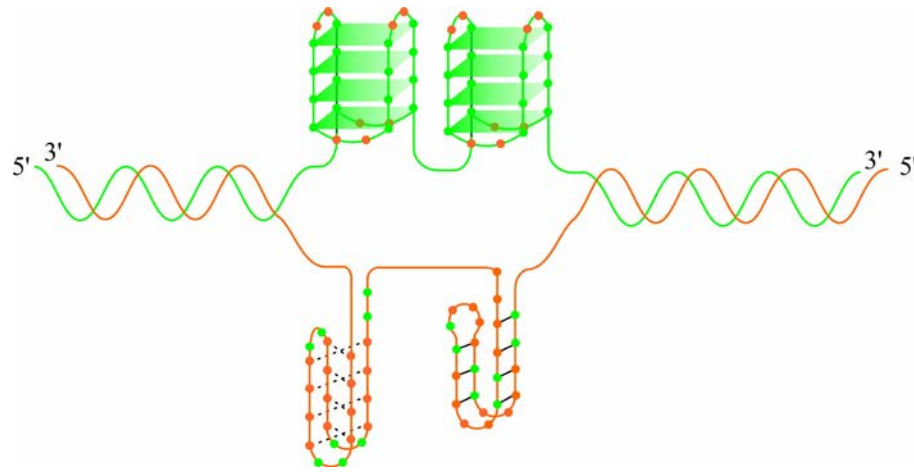
G-quadruplexes: unusual four-stranded structures formed by guanine rich nucleic acids in the presence of K^+ or Na^+ ions



Potential G-quadruplex forming sequences are enriched in some critical parts of the human genome

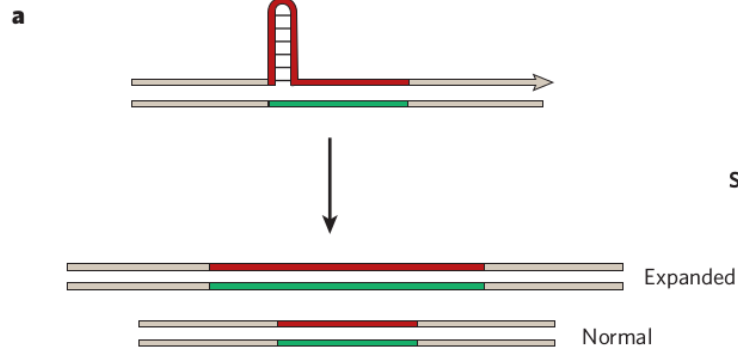
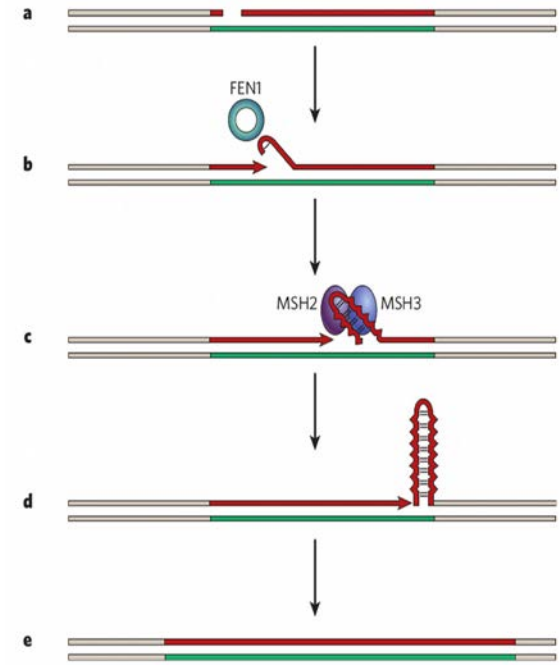


Hypothesis: unusual secondary structures adopted by GGGGCC repeat contribute to repeat instability

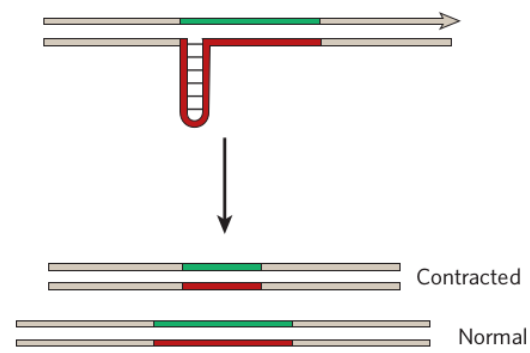


DNA replication (dividing cells)

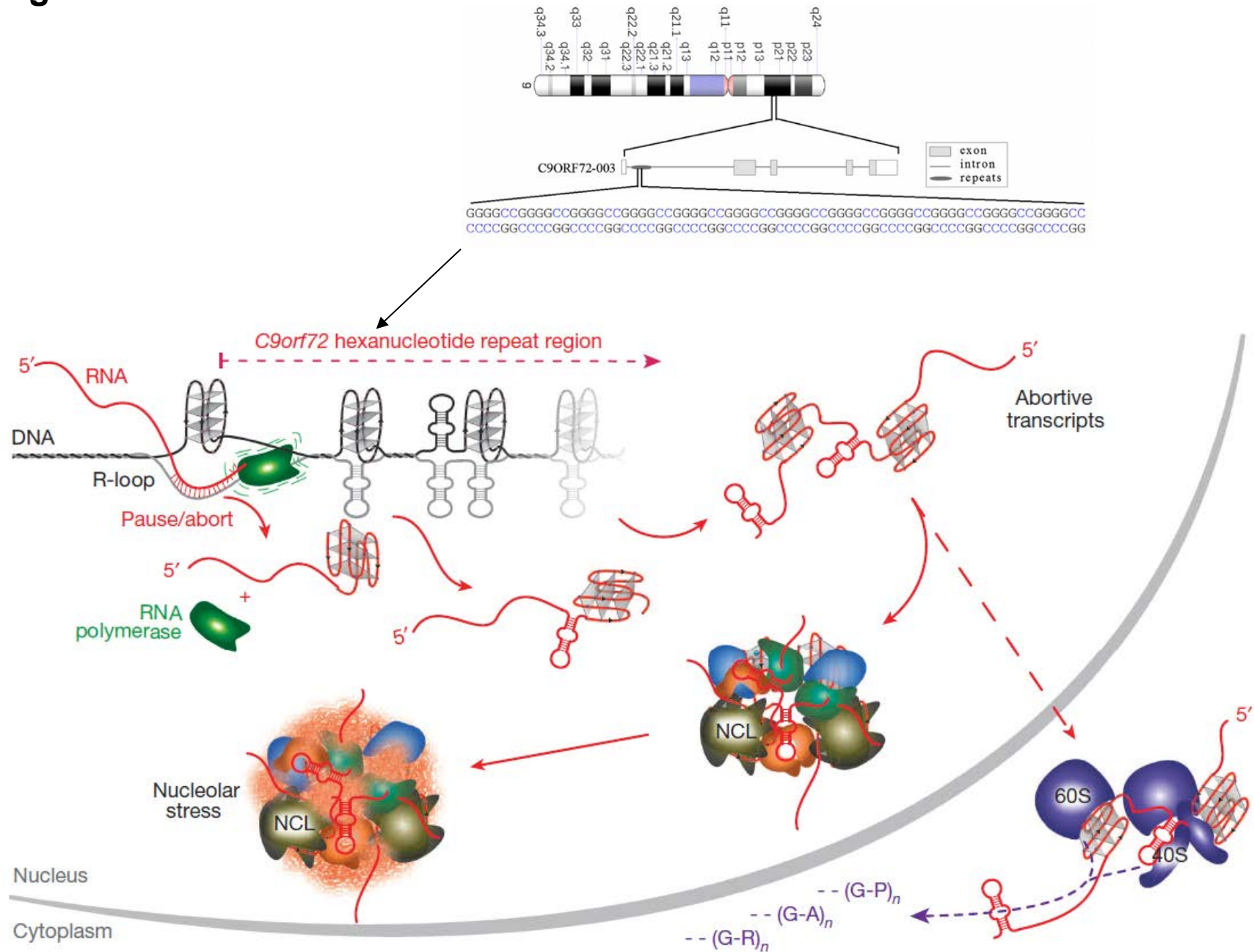
DNA repair (non-dividing cells)



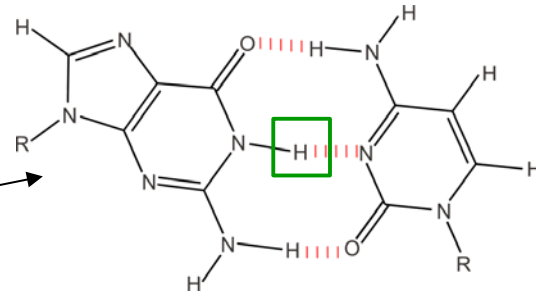
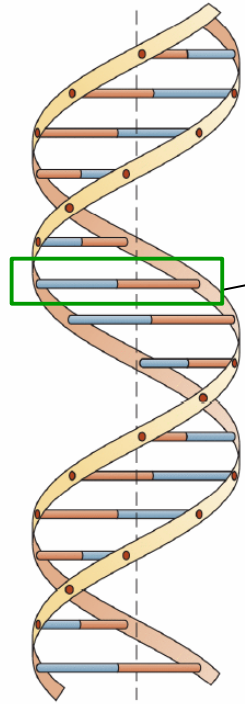
Second replication



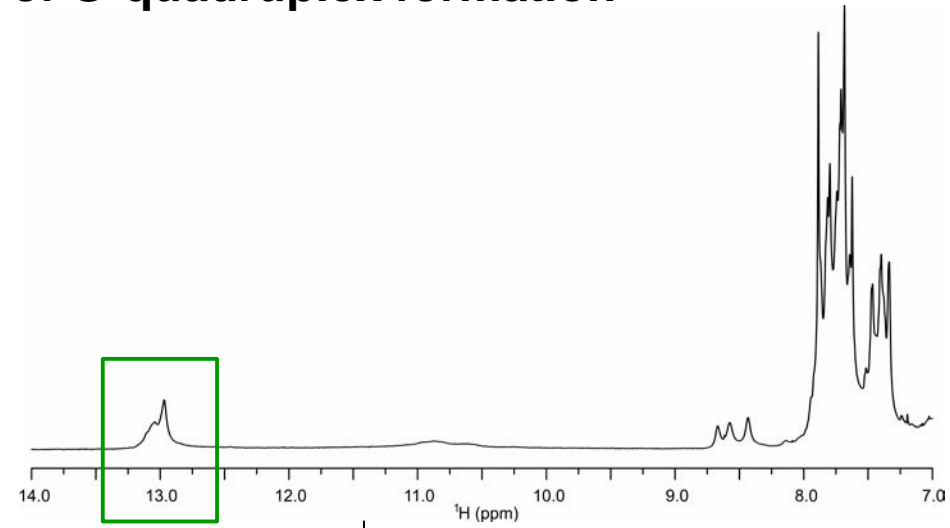
Hypothesis: unusual structures adopted by GGGGCC repeats initiate a pathogenic chain of events



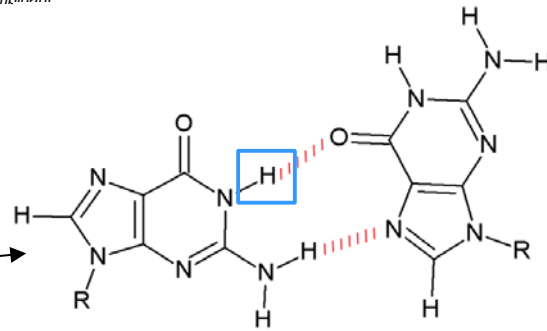
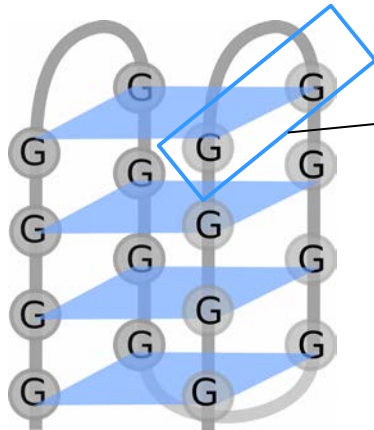
Nuclear magnetic resonance (NMR): detection of G-quadruplex formation



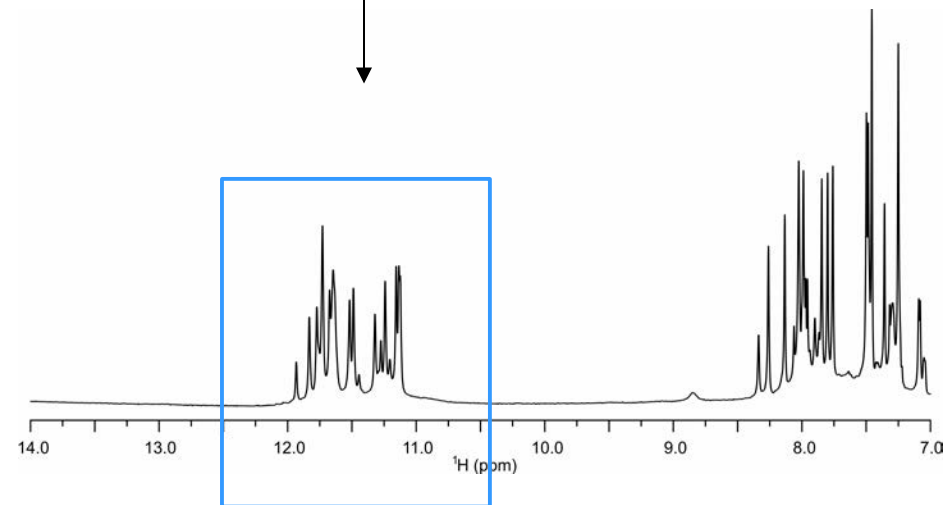
Watson-Crick base pair



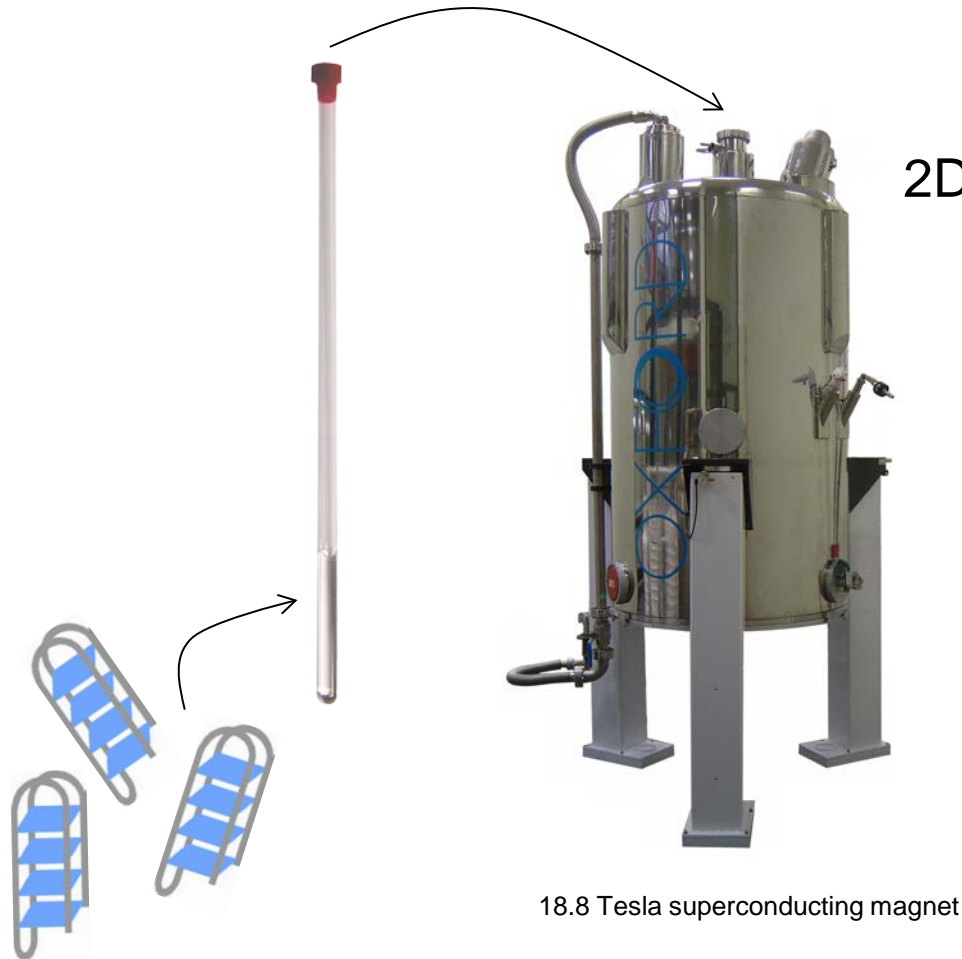
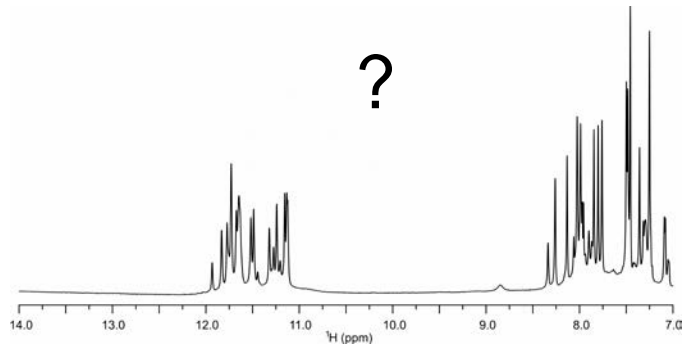
Glick, B. R., in *al. Molecular Biotechnology: principles and applications of recombinant DNA 4th ed.*, American Society for Microbiology, Washington, 2010.



Hoogsteen base pair

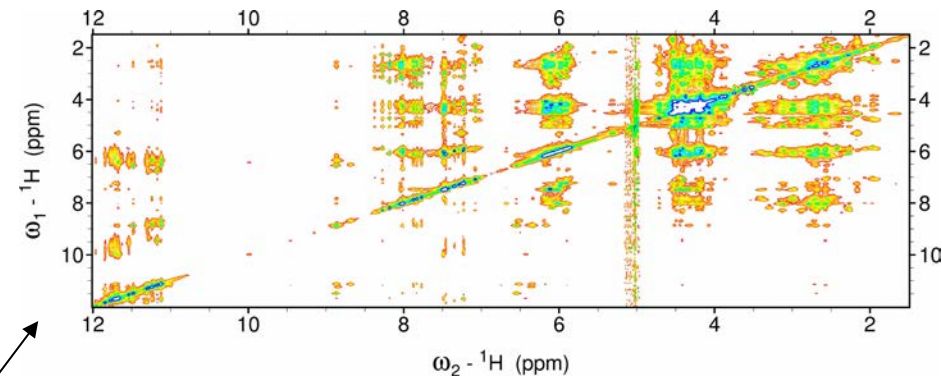


Nuclear magnetic resonance (NMR): structure determination

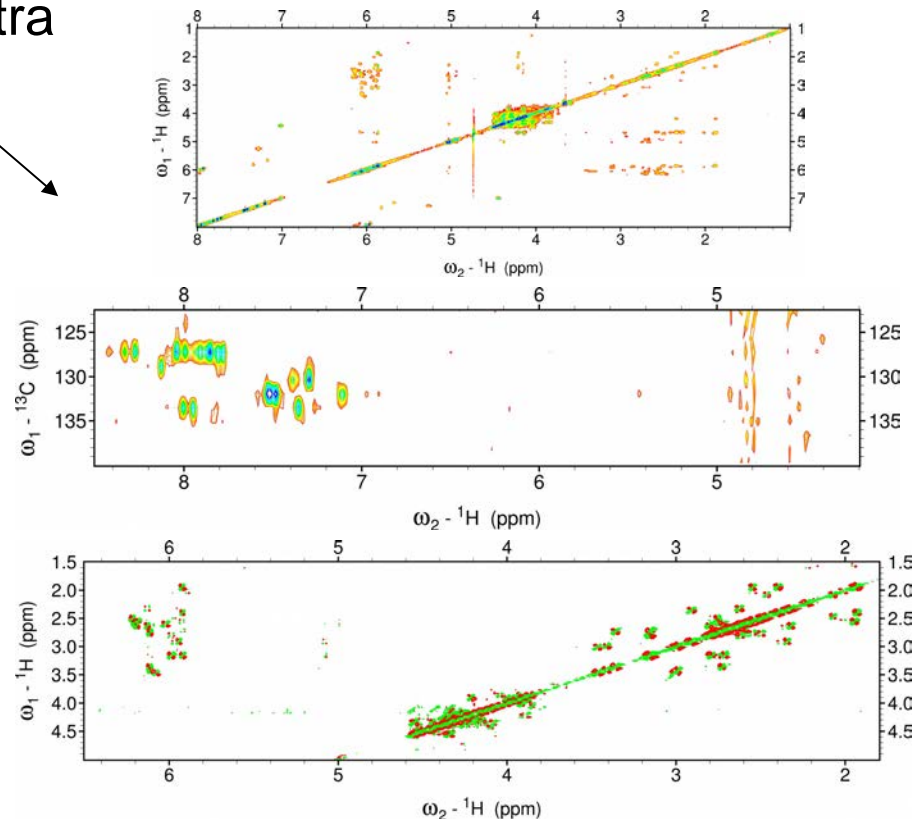


2D spectra

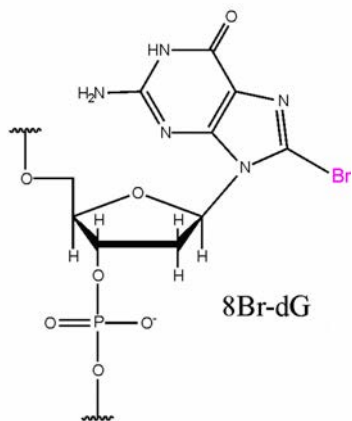
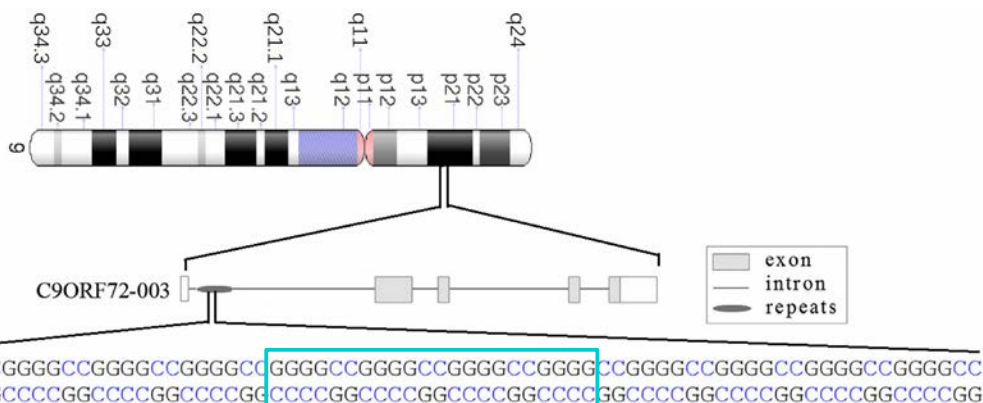
“through space” connectivity



“through bond” connectivity



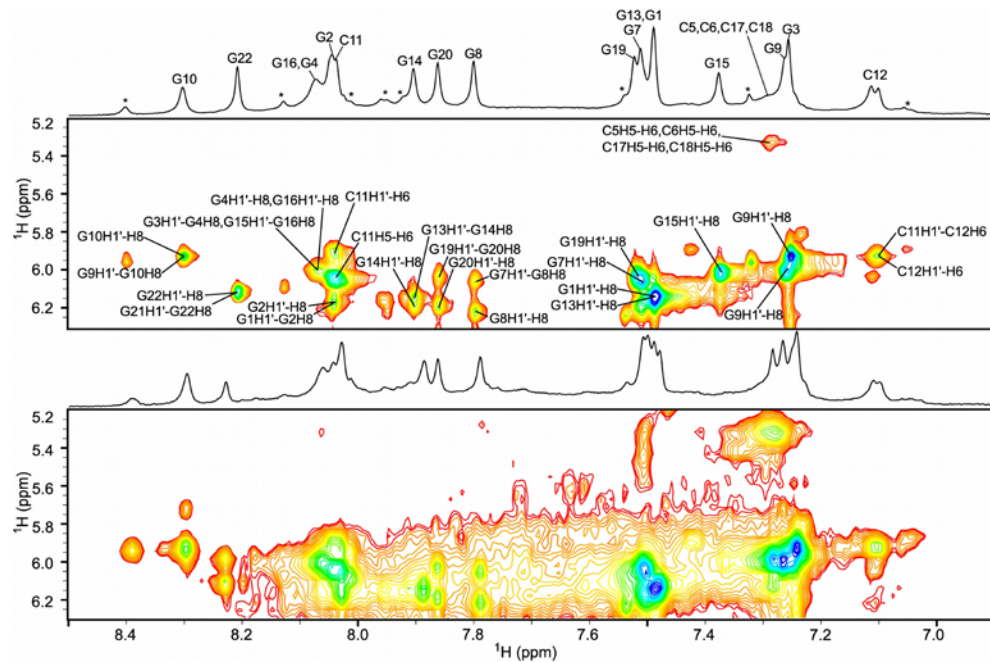
Oligonucleotide model of GGGGCC repeat folds into two major G-quadruplex structures



G21 to BrG21

d[(G₄C₂)₃GGBrGG]

d[(G₄C₂)₃GGGG]

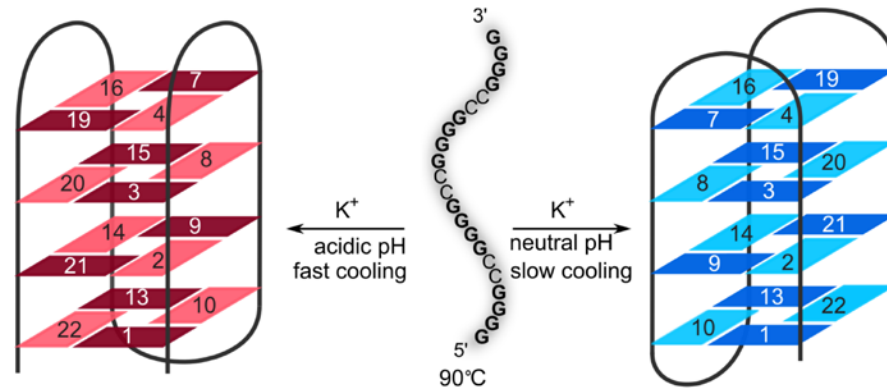


locks residue in *syn* conformation

J. Brčić, J. Plavec, Front. Chem. Sci. Eng. 10 (2016) 222–23.

J. Brčić, J. Plavec, Biochimica et Biophysica Acta, Available online 14 November 2016.

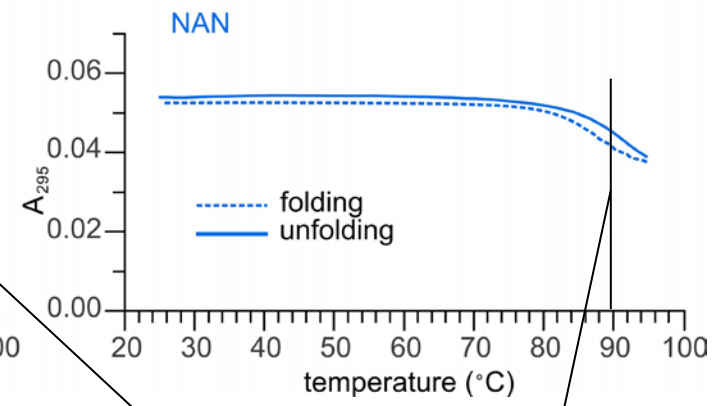
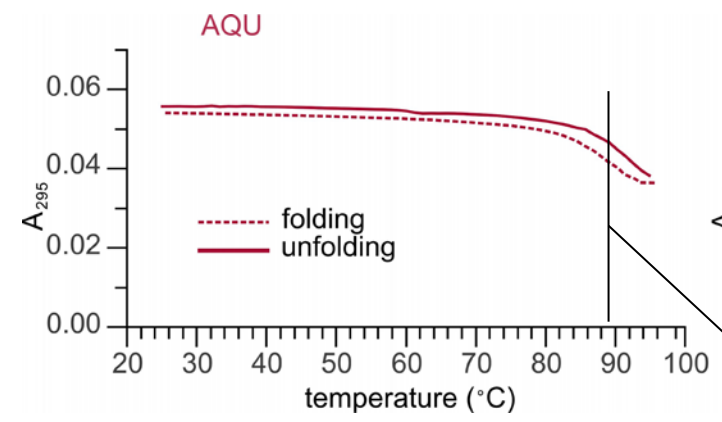
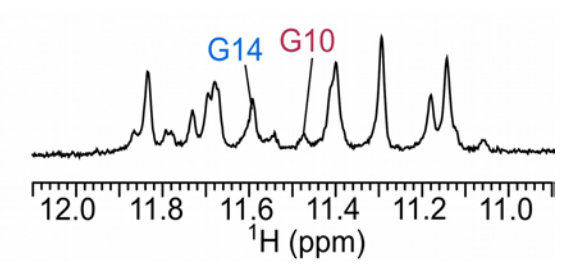
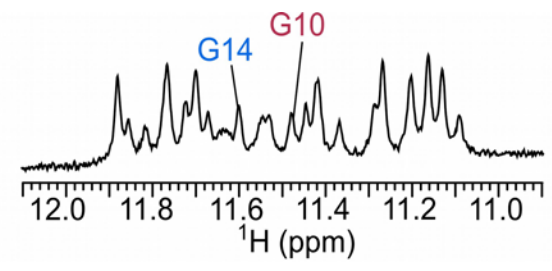
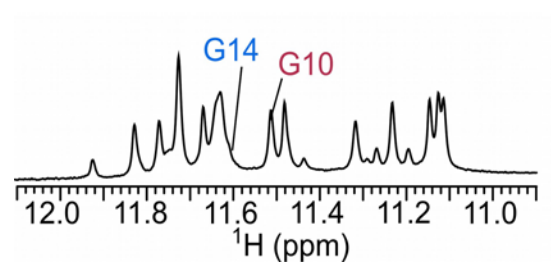
Two folding condition determine relative populations of **AQU** and **NAN**



80% : 20%

50% : 50%

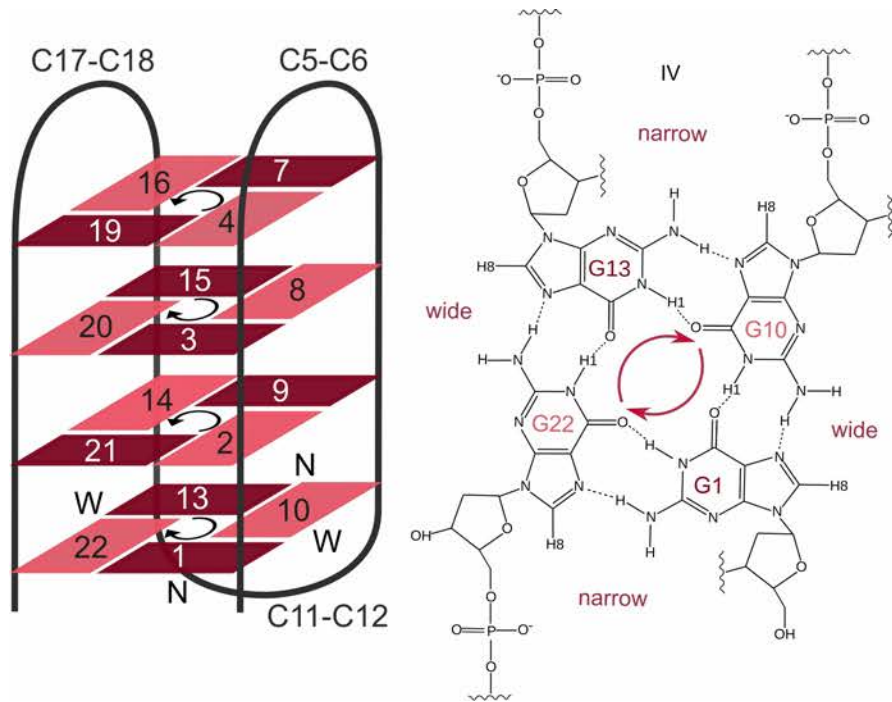
30% : 70%



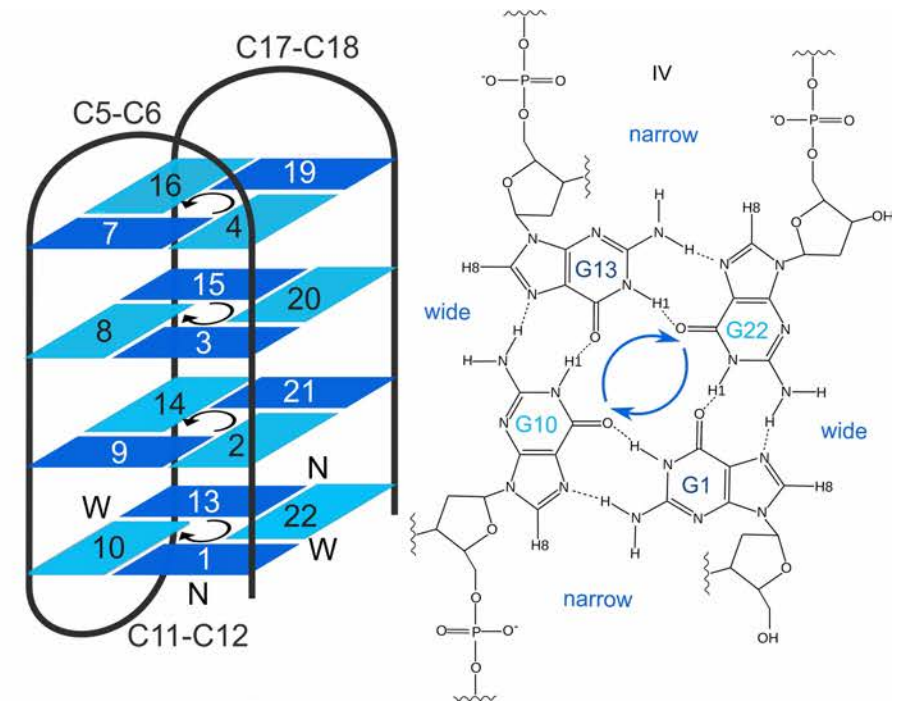
both structures are extremely stable

AQU and NAN share a similar antiparallel fold but exhibit distinct structural features

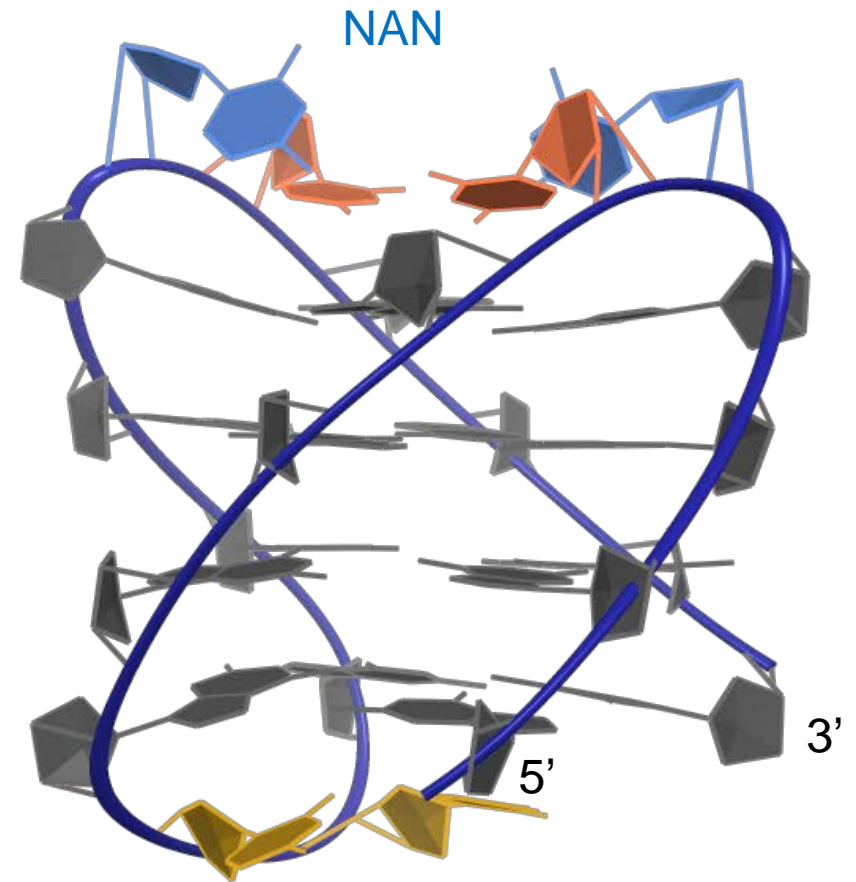
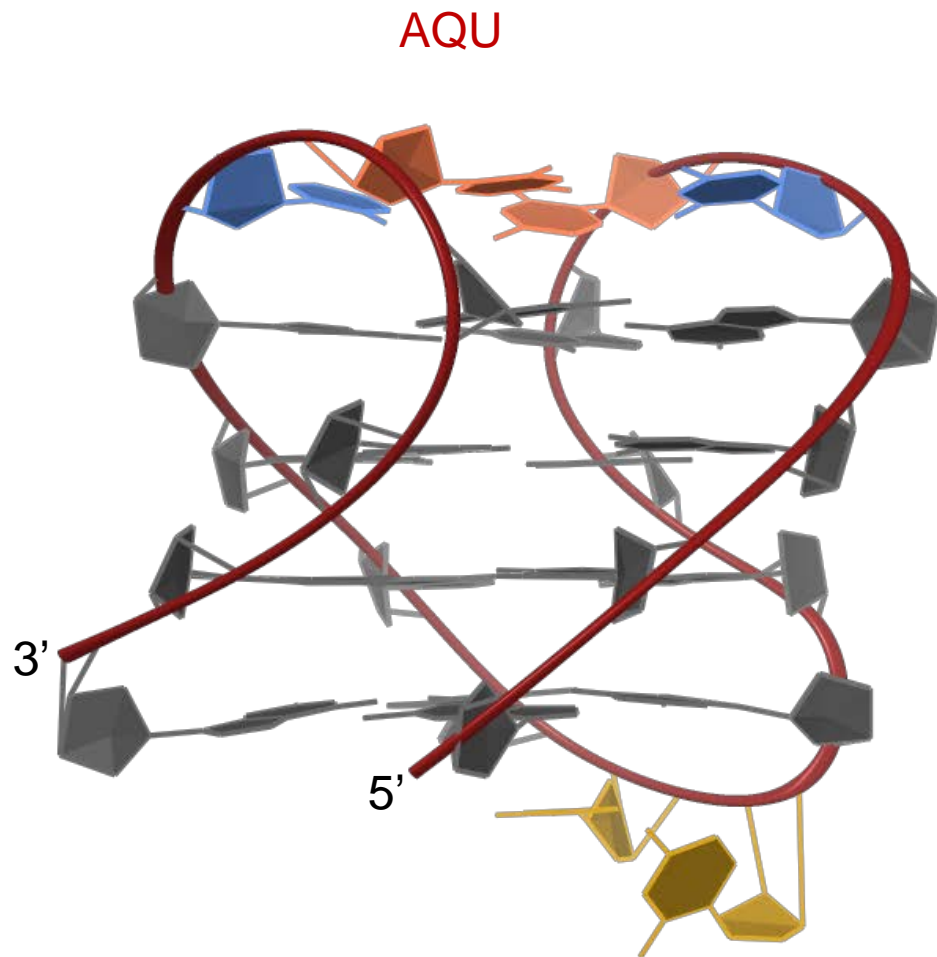
AQU



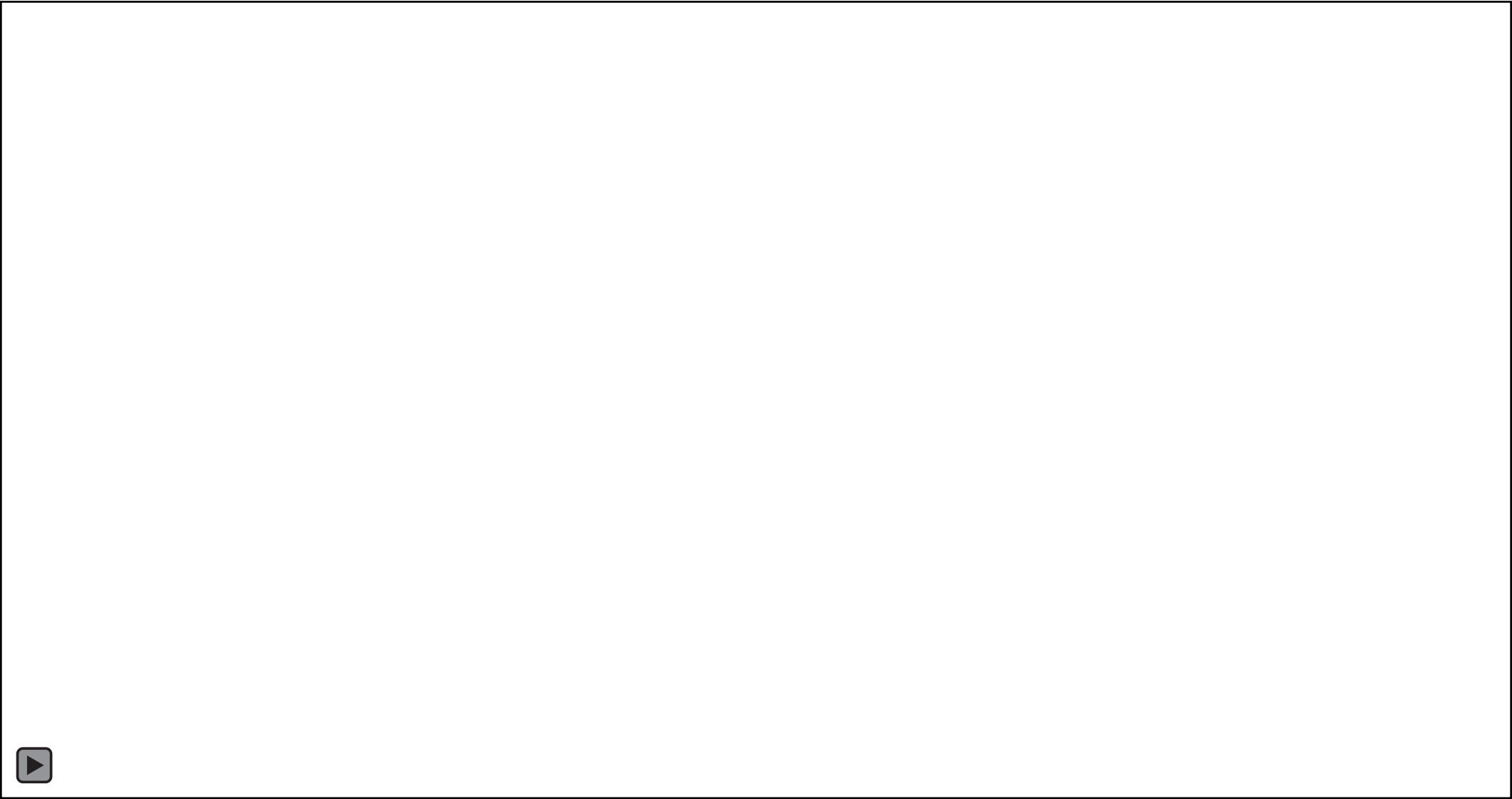
NAN



AQU and **NAN** share a similar antiparallel fold but exhibit distinct structural features



PDB 2N2D



Acknowledgement

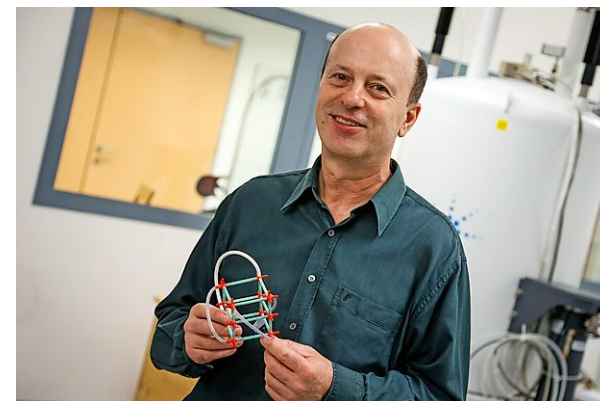


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Slovenian NMR centre




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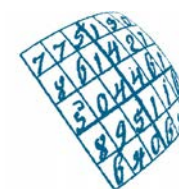


<http://www.slonmr.si/>



 **Institut
"Jožef Stefan"
Ljubljana, Slovenija**
dr. Boris Rogelj

Univerza v Ljubljani
Fakulteta za kemijo in kemijsko tehnologijo



SLOVENIAN RESEARCH AGENCY