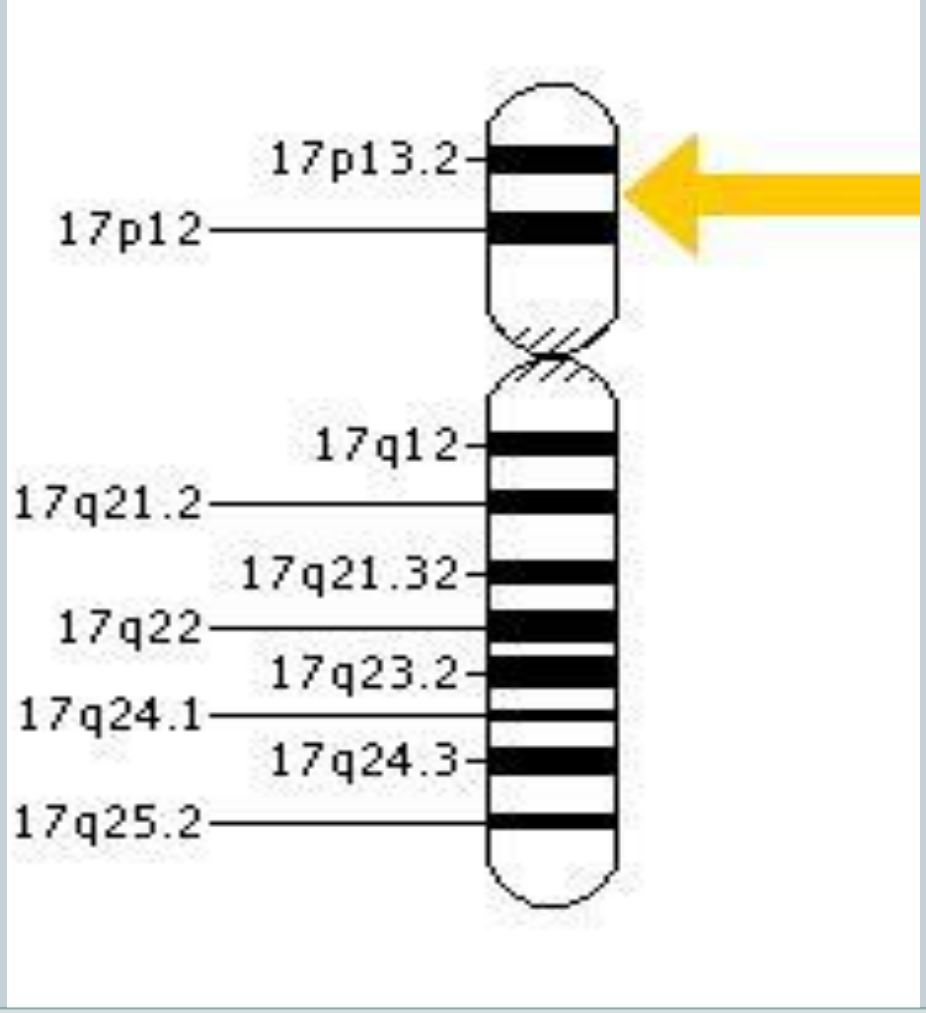
P53 Tumor Supressor Protein

ITS ROLE IN PROTECTING CELLS FROM CANCER

TP53 Tumor Suppressor Gene

- While commonly known as p53, the official name of this gene is Tumor Protein p53 and its official symbol is TP53.
- *The TP53* gene codes for the TP53 (p53) protein which acts as a tumor suppressor and works in response to DNA damage to orchestrate the repair of damaged DNA.
- If the DNA cannot be repaired, the p53 protein prevents the cell from dividing and signals it to undergo apoptosis (programmed cell death).
- The name p53 is due to the protein's 53 kilo-Dalton molecular mass.

TP53 Gene Location in the Genome

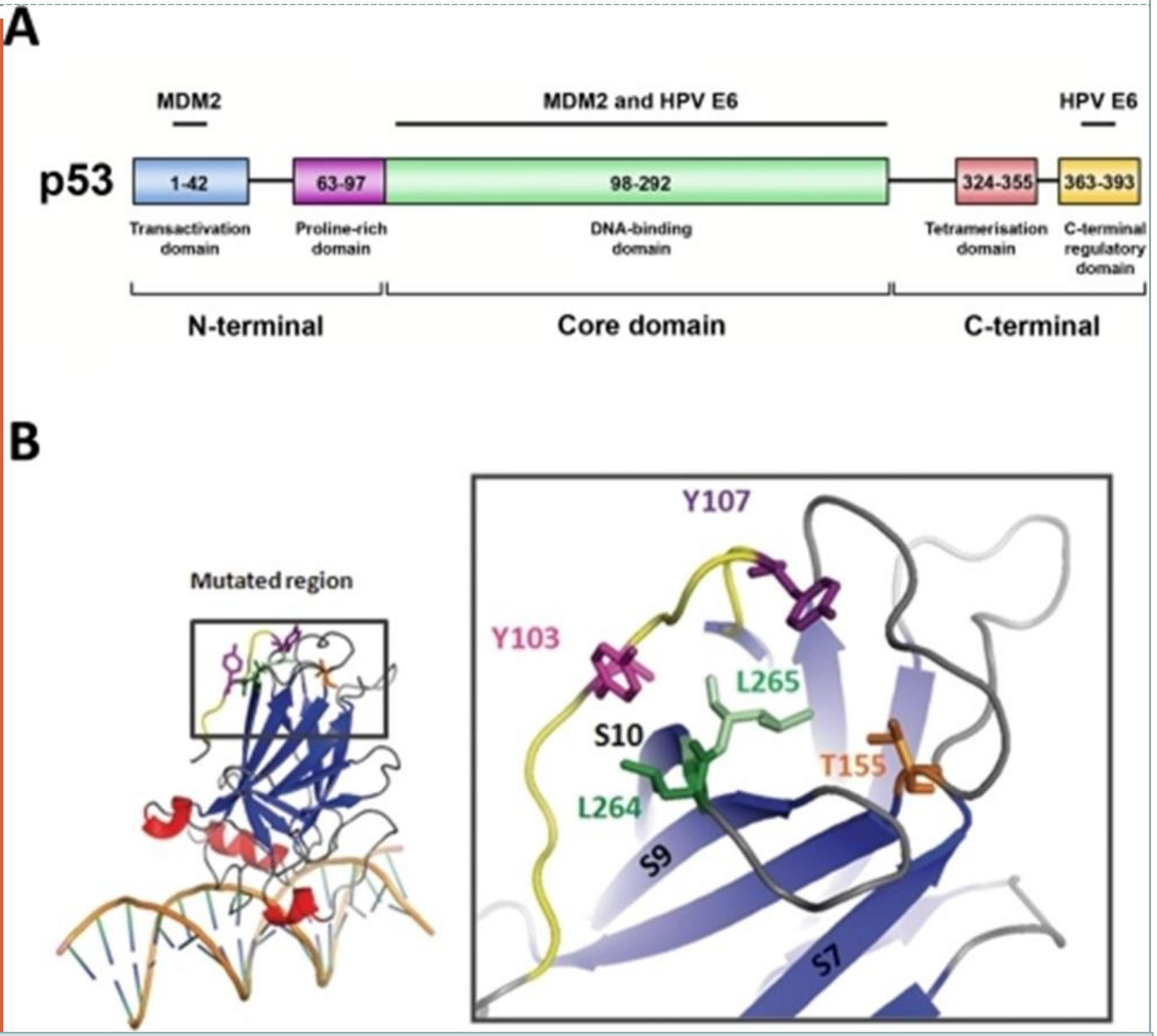


http://www.ghr.nlm.nih.gov/gene/TP53

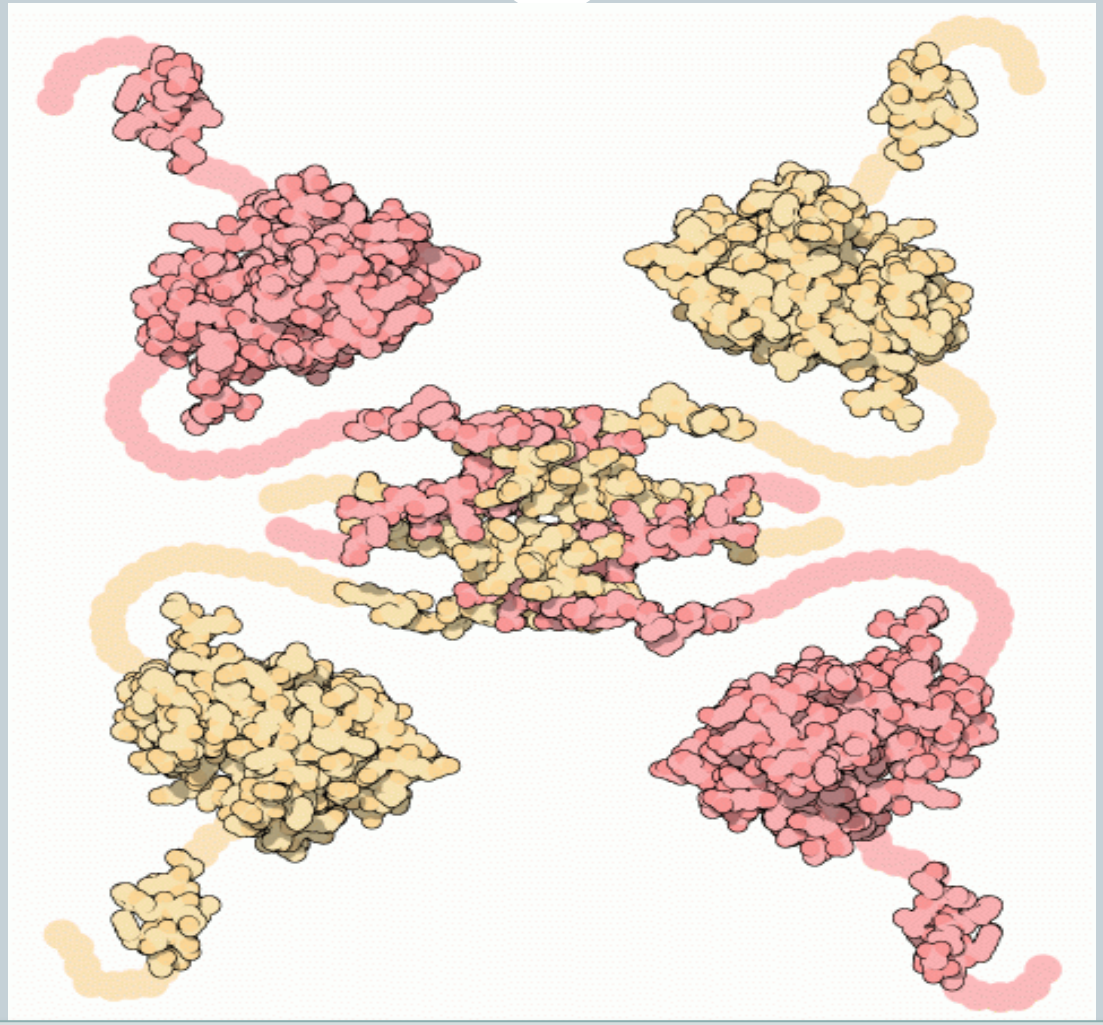
P53 Protein Domain Structure

A. The 393-amino acid residue p53 protein comprises an amino-terminus transactivation domain (blue), followed by a proline-rich region (purple), a central DNA-binding core domain (green), a tetramerization domain (pink) and a regulatory domain (yellow) at the carboxyl-terminus.

B. For more about p53 mutations, see slide 9.

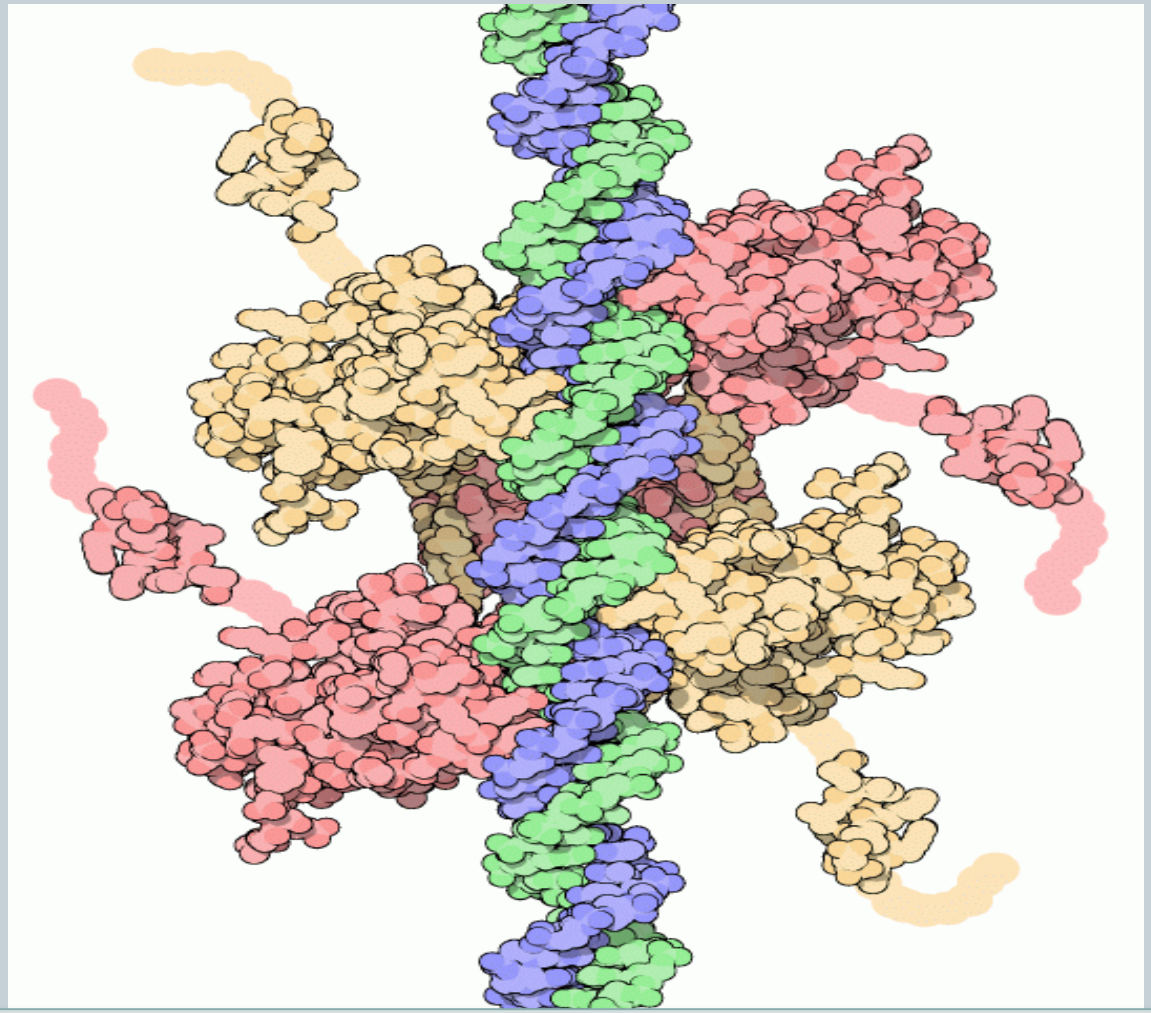


Tumor Protein p53 in Tetramer Form



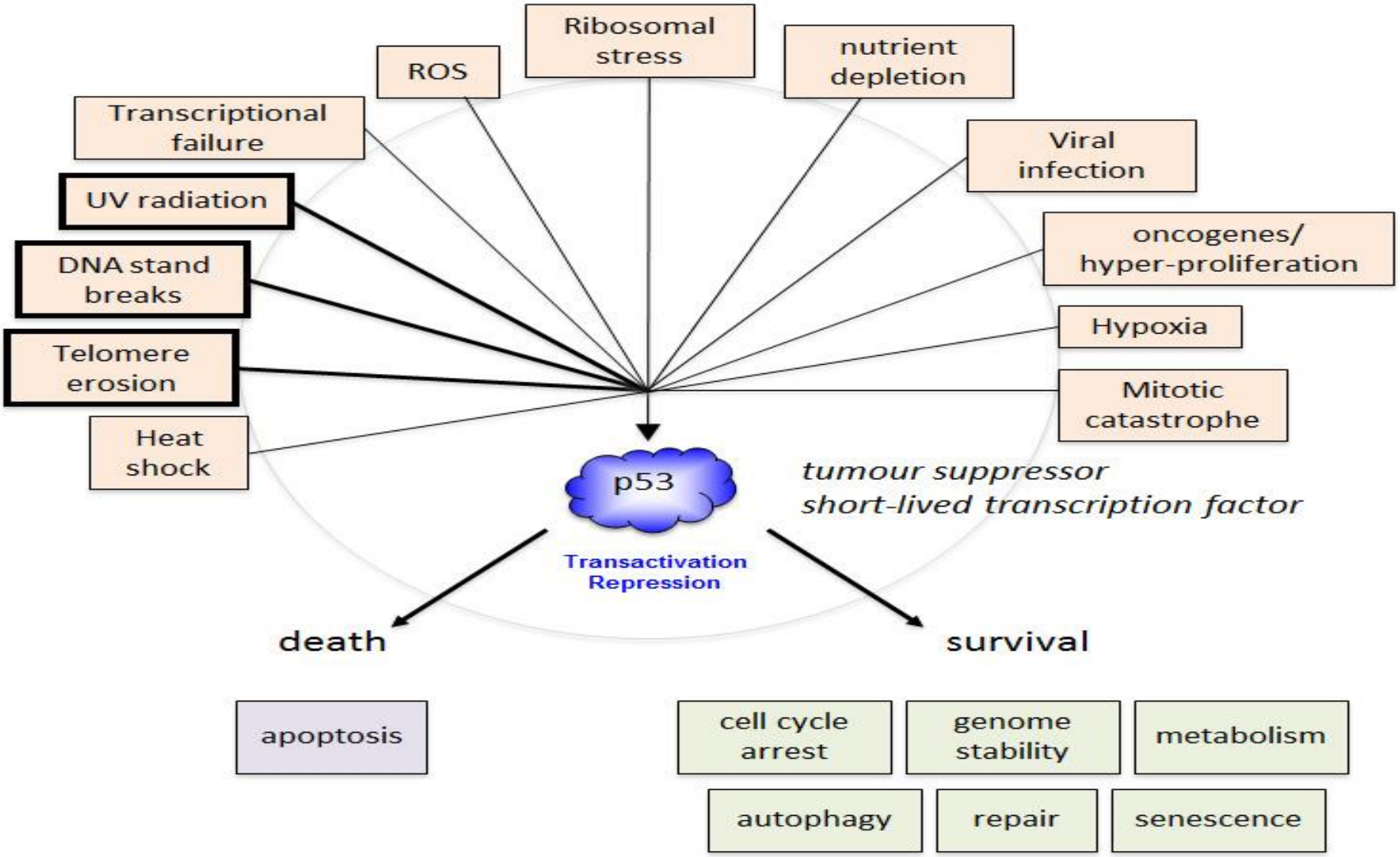
www.rscb.org by David Goodsell

Tumor Protein p53 Bound to DNA



www.rscb.org by David Goodsell

Overview of Central Role of p53



How P53 Protein Works

Go to http://www.hhmi.org/biointeractive/ and then at the top of the screen under the **Topic** tab, choose ***cancer*** with the drop down menu at the top, and in the **Search** area just below type in **p53** and click search.

Click on **p53** and then play. This animation shows p53 molecule binding to DNA to make RNA. (26 seconds)

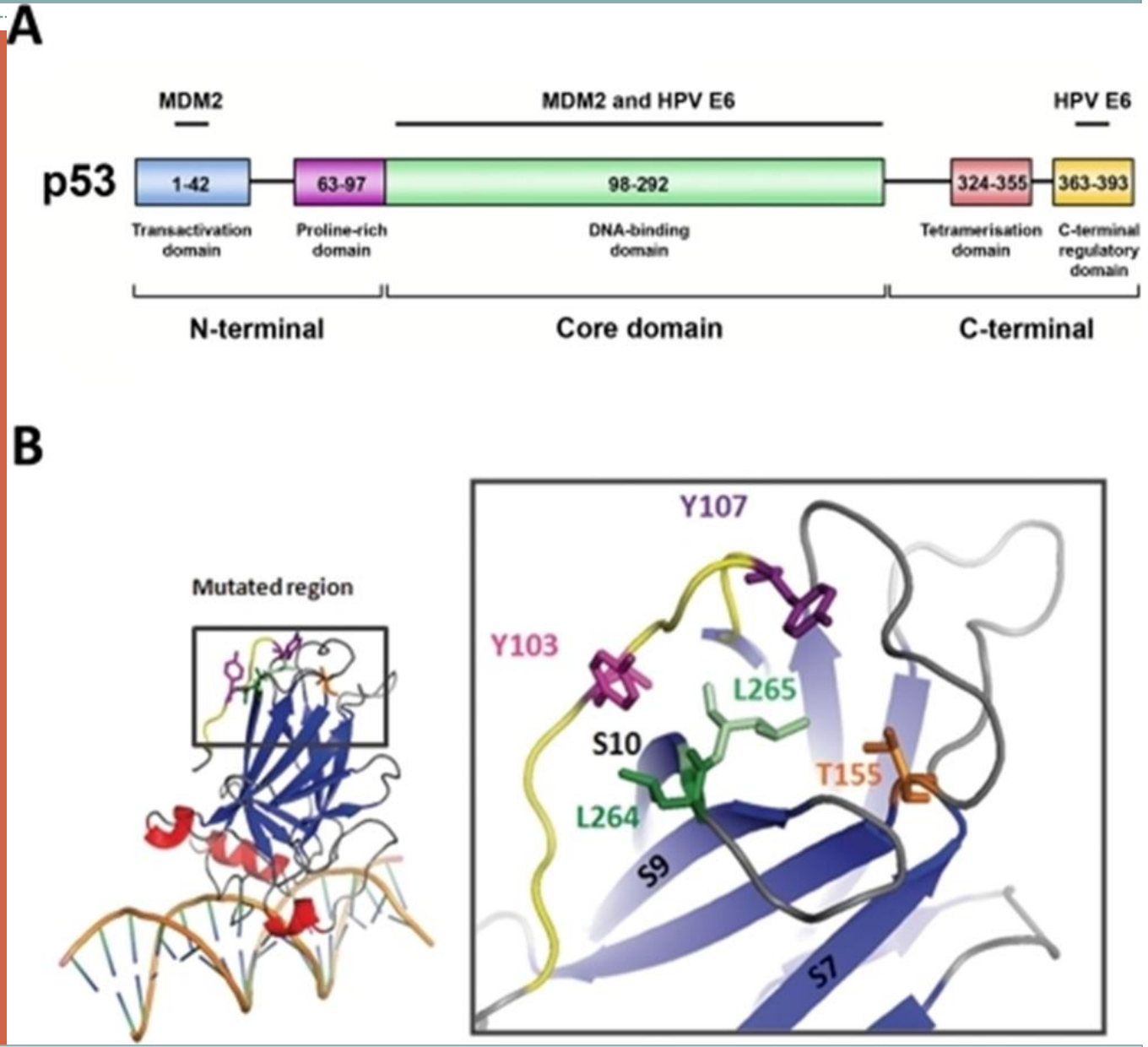
Click on **The *p53* Gene and Cancer** and then play. Eight slides explain the structure and function of p53.

Click on **Using *p53* to Fight Cancer** and then play. This animation shows how viruses infecting normal and cancer cells interact with p53 and mutant p53, respectively. Thus mutant p53 could be used to fight cancer without damaging normal cells. (1 minute, 2 seconds)

P53 Protein Mutations

B. Shown is the 3-dimensional p53 DNA-binding domain attached to DNA with mutations shown at amino acids tyrosine (Y) 103 and 107, serine (S) 10, threonine (T) 155, and leucine (L) 264 and 265, all in the DNA-finding domain (amino acid residues 98-292) but distal from the DNA binding site.

About 20% of human cancer-associated mutations are concentrated in 'hot-spot' codons, such as glycine (G) 245 and arginine (A) 175, 248, 249, 273, and 282, mostly in the DNA-binding domain proximal to the DNA binding site.

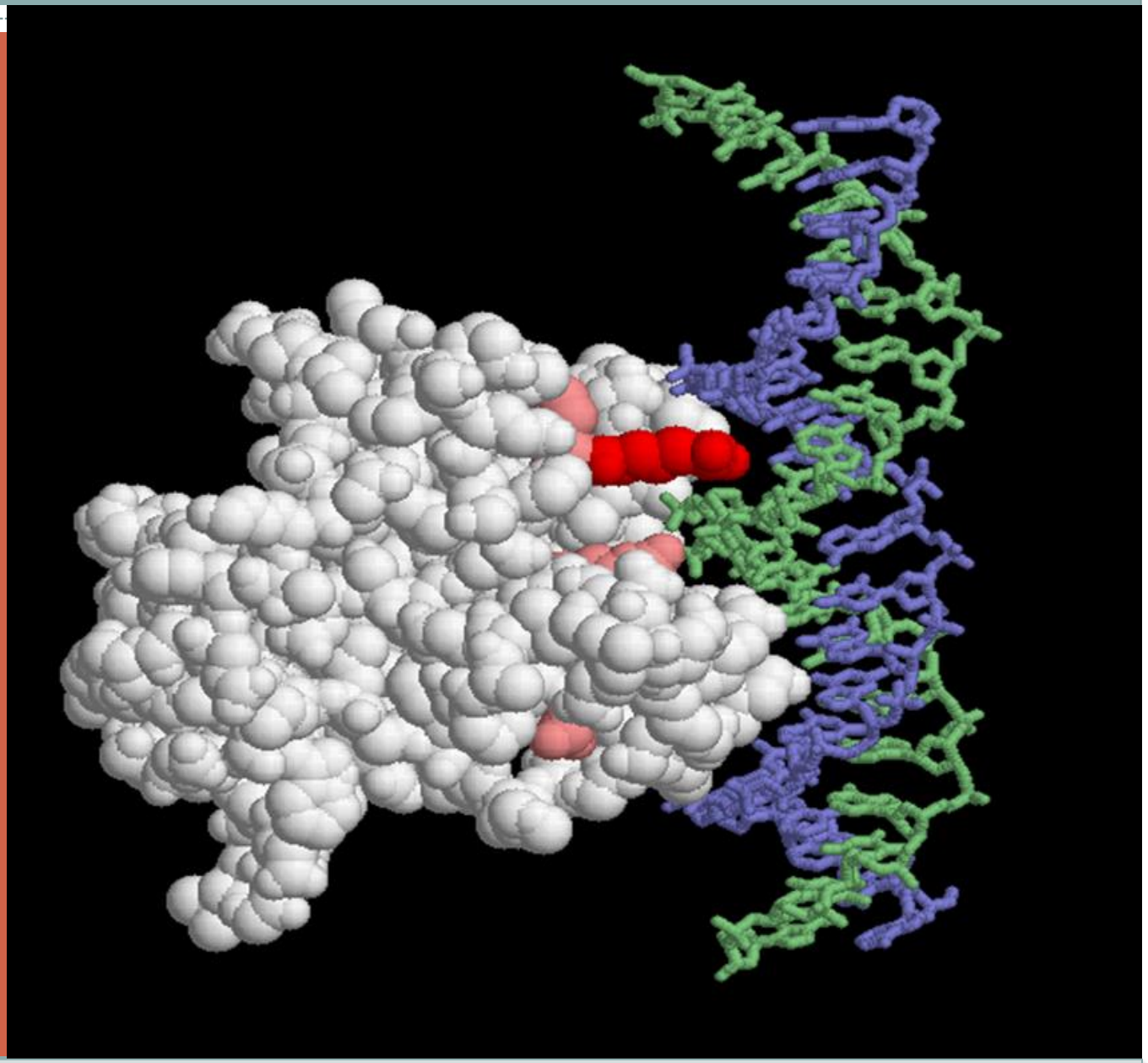


DNA-Binding Domain Mutations

Most of the p53 mutations that cause cancer are found in the DNA-binding domain in and around the DNA-binding face of the protein.

The most common mutation change occurs at arginine 248 (shown in red) which normally fits into the minor groove of the DNA as shown forming a strong stabilizing interaction. When mutated into another amino acid, this interaction is lost.

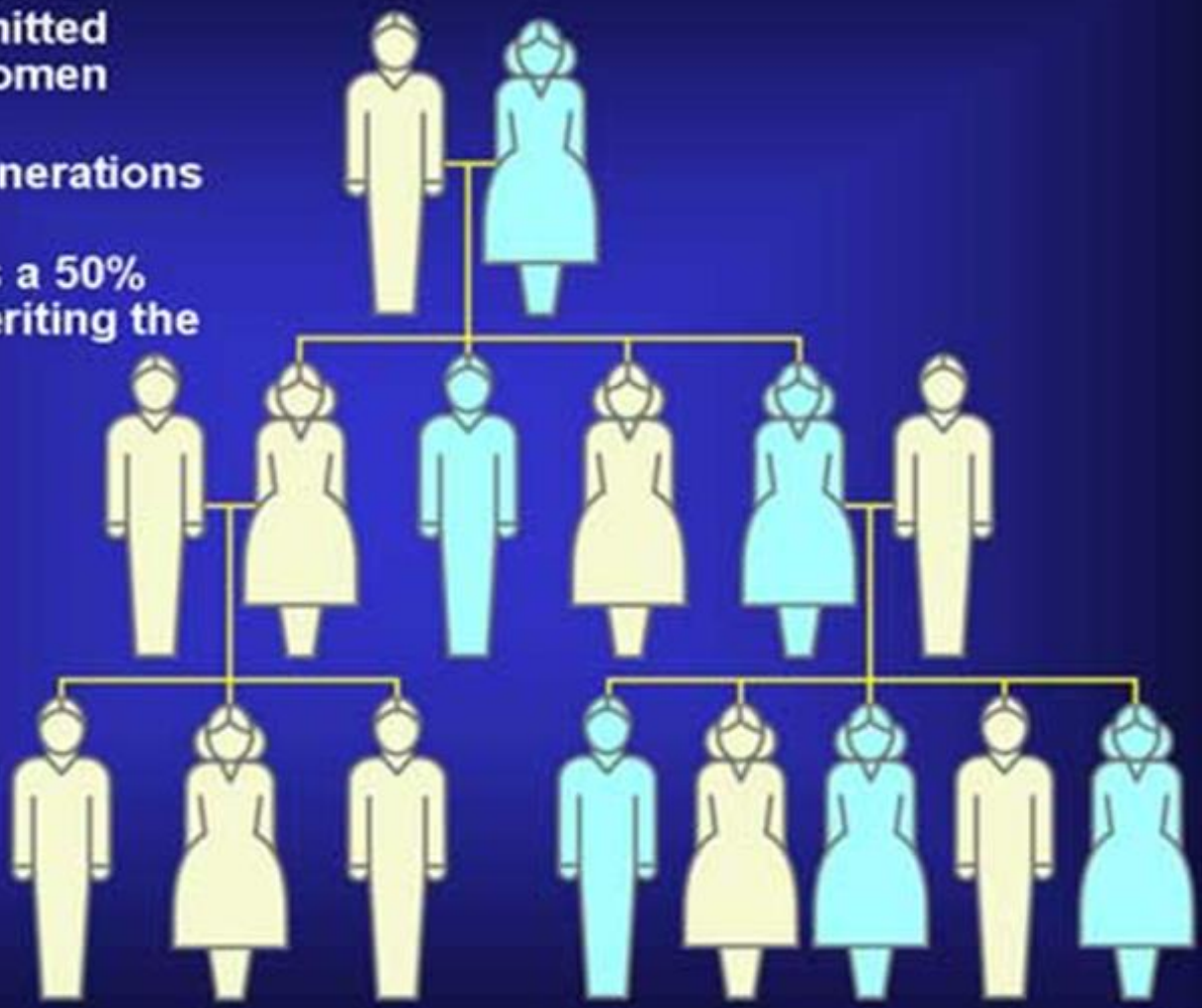
Other mutations (shown in pink) at arginine residues 175, 249, 273, and 282 and at glycine 245 occur in which some have direct contact with DNA and others are involved in positioning other DNA-binding amino acids.



www.rcsb.org/pdb/101/motm.do?momID-31

Autosomal Dominant Inheritance

- Equally transmitted by men and women
- No skipped generations
- Each child has a 50% chance of inheriting the mutation



- Normal
- Affected

NATIONAL CANCER INSTITUTE

http://www.cancer.gov/cancertopics/understandingcancer/cancergenomics/AllPages

Li-Fraumeni Syndrome

- Li-Fraumeni syndrome appears to be the only inherited syndrome associated with mutations in the *TP53* gene.
- There are more than 60 different mutations that have been identified in individuals with this syndrome.
- Since the mutation(s) is inherited from a parent, it appears in all of the body's cells, unlike in someone who has developed a somatic mutation in the *TP53* gene in a specific organ of the body.

Examples of Dominantly Inherited Cancer Syndromes

Syndrome	Associated Gene
Familial retinoblastoma	*RB1*
Li-Fraumeni	*TP53* (p53 protein)
Familial adenomatous polyposis	*APC*
Hereditary nonpolyposis colorectal cancer	*MLH1, MSH2, MSH6 PMS1, PMS2*
Wilms' tumor	*WT1*
Breast and ovarian cancer	*BRCA1, BRCA2*
von Hippel-Lindau	*VHL*
Cowden	*PTEN*

http://www.cancer.gov/cancertopics/understandingcancer/cancergenomics/AllPages