Li-Fraumeni

also known as P53, LFS1, and TP53

Presented by Justin Lee

BioC 118Q Winter 2011

Background

- Li-Fraumeni syndrome is a genetic disorder that increases the risk of various cancers in children and young adults.

- Typical cancers include breast cancer, bone cancer (osteosarcoma), muscle cancer (soft tissue sarcomas), brain tumors, leukemia, and adrenal cancer (adrenocortical carcinoma) among others.

- Li-Fraumeni syndrome is extremely rare; there are perhaps fewer than 400 known cases of the disease across 64 families.

Methods for Diagnosis

- More than 70% of individuals diagnosed clinically have an identifiable disease-causing mutation in TP53, the only gene known to be associated with LFS.

- Classic LFS is defined by the following criteria:
  - A proband[1] with a sarcoma[2] in the LFS tumor spectrum[3] diagnosed before age 45 years
  - A first-degree relative with any cancer before age 45 years
  - A first or second-degree relative with any cancer before age 45 years or a sarcoma

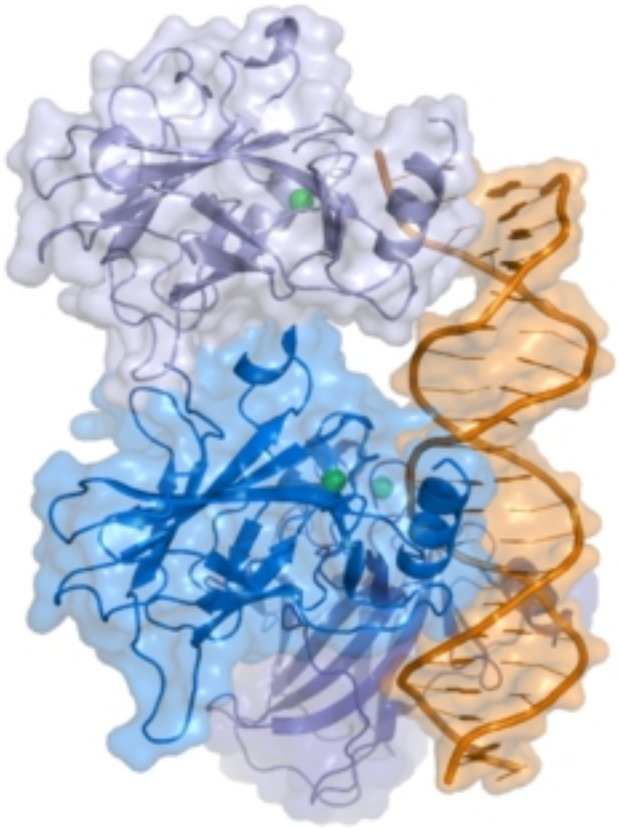
- [1] A proband is the affected individual through which a genetic disorder is linked to a pedigree
- [2] A sarcoma is a cancer of the connective tissue or soft tissues (i.e. fat, bone, and blood vessels)
- [3] The LFS tumor spectrum includes (soft tissue sarcoma, osteosarcoma, pre-menopausal breast cancer, brain tumor, adrenocortical carcinoma, leukemia, or lung cancer)

Treatment?

- No panacea for cancer (yet)

- The key is to engage in preventative medicine:
  - Children and adults undergo comprehensive annual physical examination
  - Adults undergo routine screening for colorectal cancer
  - Women undergo age-specific breast cancer monitoring (annual mammograms, breast MRI, and clinical breast examination from 25 years of age) at age 25 years
  - All individuals should undergo organ-targeted surveillance based on the pattern of cancer observed in the family
  - Genetic counseling and testing to all relatives who are at risk of a mutation in the TP53 gene.

"Understanding a problem is the first step to solving it." -Anna Liem

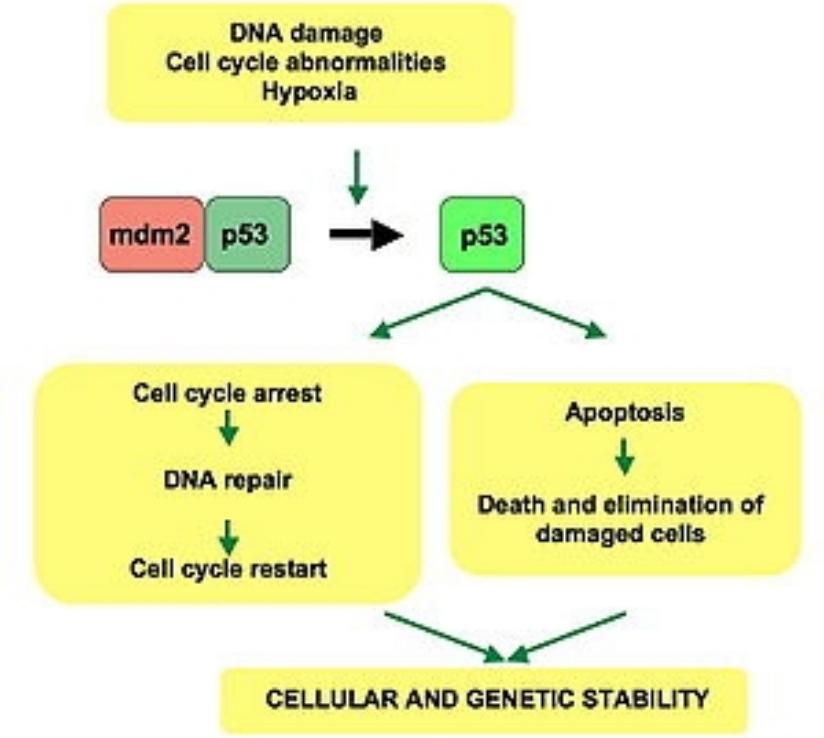


Tumor Protein p53

- Most Li-Fraumeni syndrome cases are due to mutations in the TP53 gene, a tumor suppressor known as "the genome's guardian angel."
- Mutated TP53 genes give rise to mutated protein p53, which can cause cells to divide uncontrollably into tumors.
- Mutations in CHEK2, another tumor-suppressing gene can cause "Li-Fraumeni-like" syndrome.

Tools of the Guardian Angel

- Human p53 is 393 amino acids long with seven known functional domains (N to C terminus):
  1. N-terminal transcription-activation domain (TAD) that activates factors needed for transcription
  2. Activation domain 2 (AD2) important for apoptotic activity (regulated cell death)
  3. Proline-rich domain for apoptotic activity
  4. Central DNA-binding core domain (DBD)
  5. Nuclear localization signaling domain (NLS)
  6. Homo-oligomerisation domain (OD)
  7. C-terminal involved in regulation of DNA binding

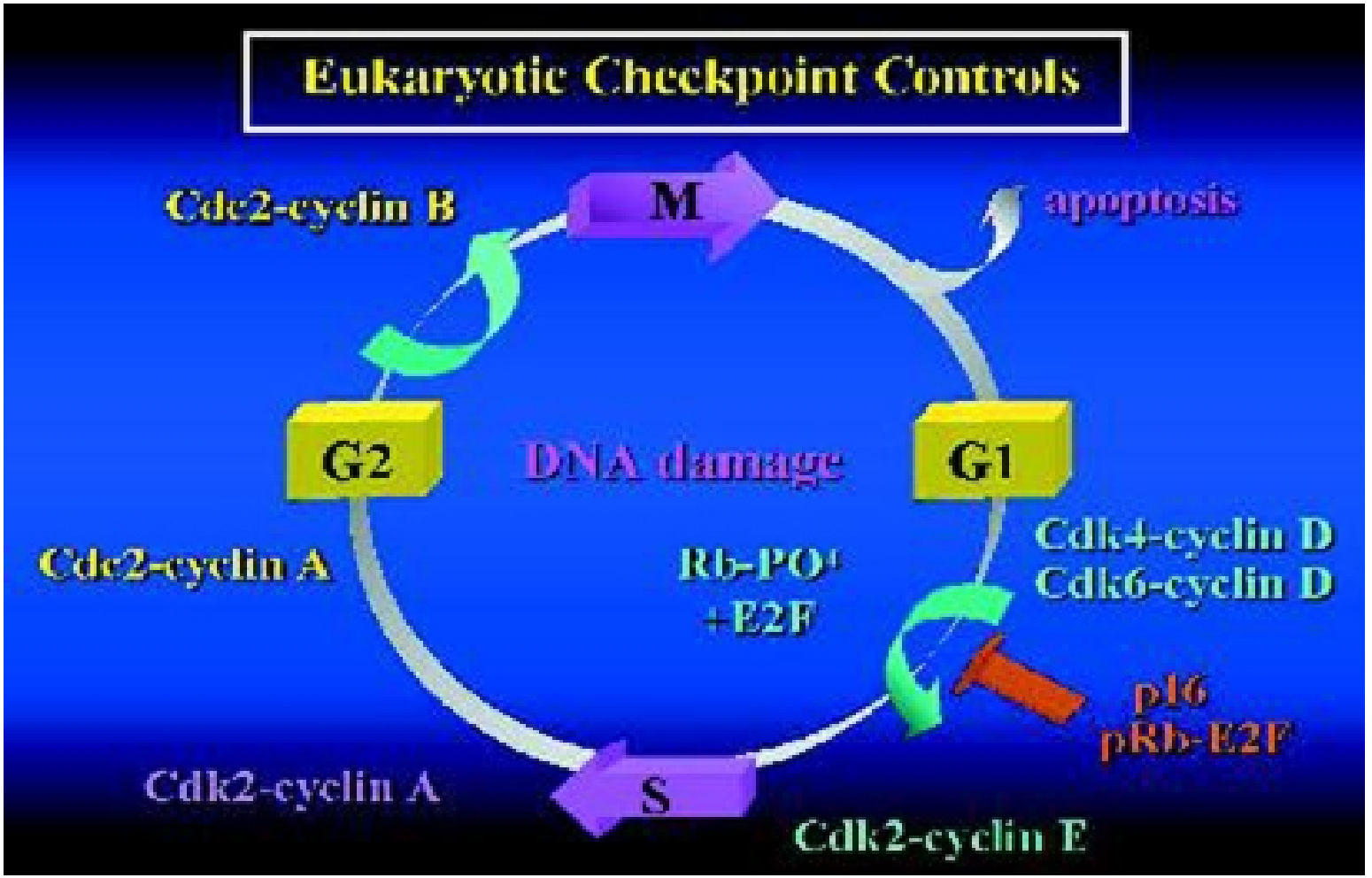


•If DNA is damaged, p53 arrests transcription by holding the cell cycle at the G1/S (growth phase of mitosis) regulation point; it halts transcription long enough so DNA repair proteins have time to fix the damage and resume the cell cycle.

•If DNA damage is beyond repair, p53 can initiate apoptosis (programmed cell death).

- Normal p53 binds DNA and activates expression of a gene called WAF1/CIP1 that encodes p21. p21 can then bind to and inhibit the G1-S/CDK and S/CDK complexes, which are important for the G1/S transition in the cell cycle.

Role of p53 in Regulating Mitosis



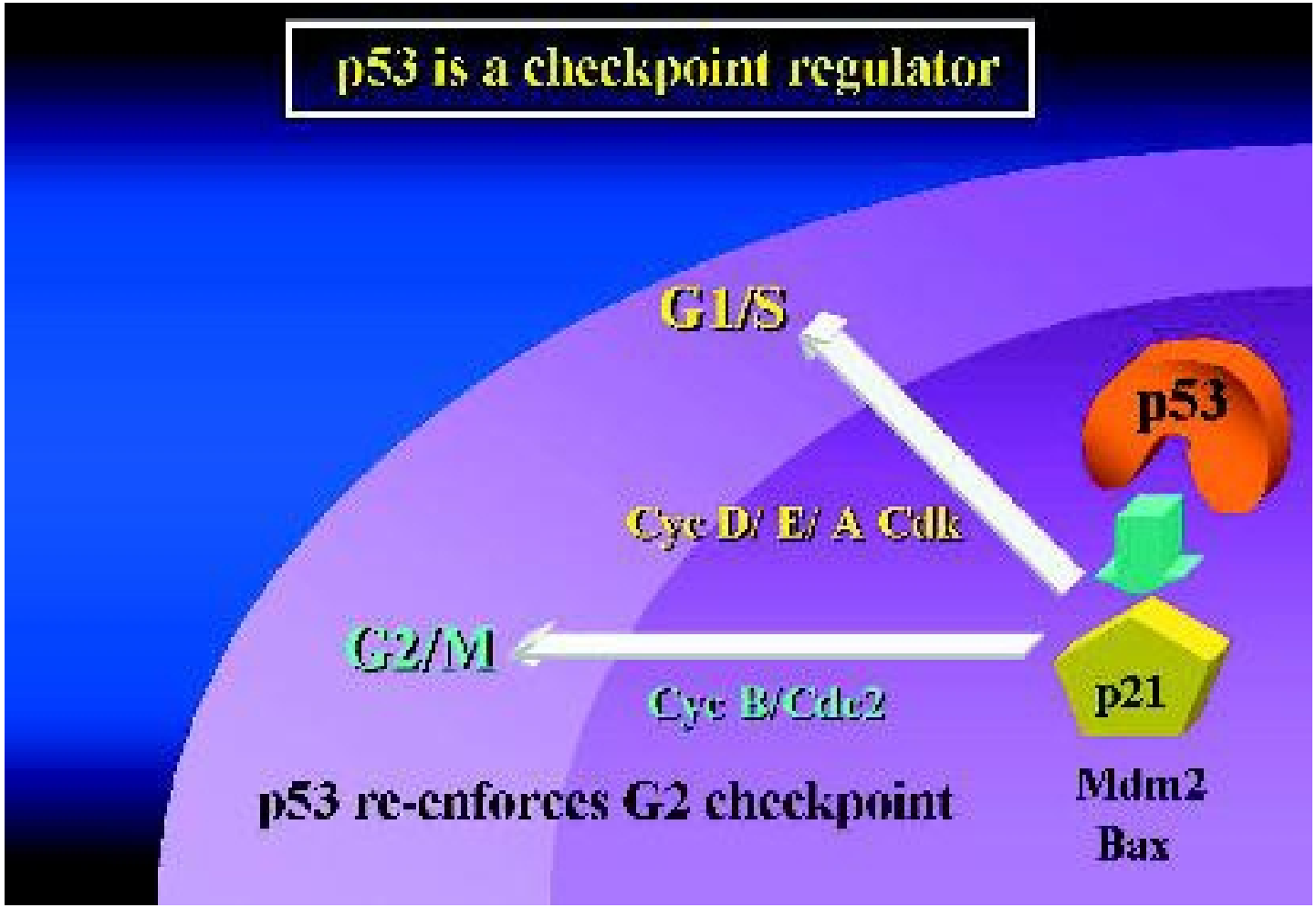
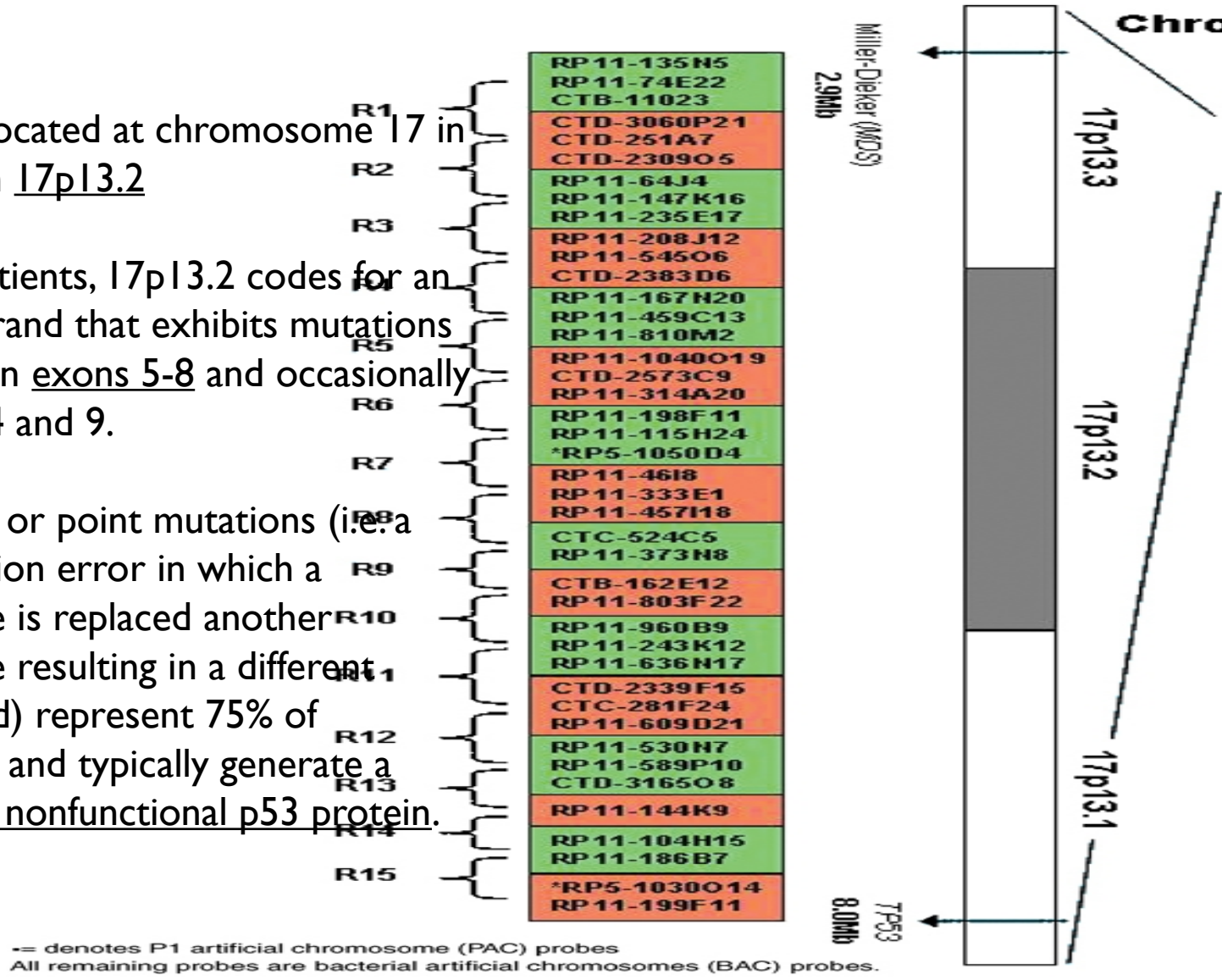


Photo courtesy of http://www.rcsed.ac.uk/journal/vol47_4/47400002.html

- TP53 is located at chromosome 17 in the region 17p13.2

- In LFS patients, 17p13.2 codes for an mRNA strand that exhibits mutations primarily in exons 5-8 and occasionally in exons 4 and 9.

- Missense or point mutations (i.e. a transcription error in which a nucleotide is replaced another nucleotide resulting in a different amino acid) represent 75% of mutations and typically generate a truncated nonfunctional p53 protein.



-= denotes P1 artificial chromosome (PAC) probes
All remaining probes are bacterial artificial chromosomes (BAC) probes.

Summary of LFS

- Li-Fraumeni syndrome is caused by a faulty p53 protein, which is responsible for regulation of cell replication.
- LFS is an autosomal dominant genetic disorder; one copy of the defective TP53 gene in each cell increases the risk of cancer.
- In most cases, an affected person has a parent and other family members with cancers characteristic of the condition (i.e. a method for diagnosis).
- Cancer rates due to LFS are estimated at 50% by the age of 30 and 90% by the age of 60.
- For now, preventative precautions like genetic testing and cancer screening are the most effective ways to combat LFS.

Citations

1. Genetics Home Reference: http://ghr.nlm.nih.gov/condition/li-fraumeni-syndrome
2. National Cancer Institute: http://lfs.cancer.gov/chapter22.html
3. NCBI Bookshelf: http://www.ncbi.nlm.nih.gov/books/NBK1311/
4. NCBI Entrez Gene: http://www.ncbi.nlm.nih.gov/gene/7157
5. NCBI OMIM: http://www.ncbi.nlm.nih.gov/omim/151623
6. Wikipedia: http://en.wikipedia.org/wiki/P53

THE END