Friend, S.H. et al. (1986) A human DNA segment with properties of the gene that predisposes to retinoblastoma and osteosarcoma. Nature 323, 643-646

Background and significance: Following Knudson's seminal hypothesis on the Rb tumor suppressor gene (as it is now called), slow progress was made over many years that eventually resulted in the determination of the genetic map position for the Rb trait. By the time of this paper, it was known that cytologically visible chromosomal deletions and rearrangements occur in some retinoblastoma and osteosarcoma tumors (which are also associated with the Rb trait), and it was presumed that these resulted in inactivation of the Rb gene, leading to a tumor. It was known that some cases of familial Rb are associated with being heterozygous for visible deletions of this region and that tumor cells from such people often had become homozygous for this deletion (this is also called "loss of heterozygosity" and is thought usually to be due to a chromosome loss or mitotic recombination event in a precursor cell to the tumor). This paper is the first to locate the specific gene involved on the basis of molecular analysis of smaller deletion alleles of Rb. They are appropriately conservative about claiming that they have proved that this is the Rb gene itself, but it is now well established that it is. This paper was one of the key events in the gradual realization that tumor suppressor genes are even more commonly important in cancer than the dominant oncogenes such as *ras* and *src*.

Explanation of some terms:
osteosarcoma - a type of bone cancer that is frequently found in familial Rb patients. There are also several other rarer tumor types associated with Rb.

Suggestions for reading the paper: Most parts of the paper should be fairly straightforward for you to understand. Don't get bogged down worrying about whether the hard-to-xerox bands on your copy support their interpretation - in the original they are a lot clearer.

Questions to answer:

1. How do you suppose researchers zeroed in on this region (q14 band of chr. 13) as being responsible for Rb?
2. Why does one cDNA (p4.7R) detect scattered *Hin*DIII fragments over a 70 Kb region of the human genome? Hint: think about how the cell produces the mRNA that gave rise to the cDNA.
3. Why are deletions OS-15 and 43 critically important to their case that this is the Rb gene, rather than simply being a different nearby gene?
4. What kind of cellular functions are likely to be carried out by the normal copies of tumor suppressor genes?