ciety, and Spain's National Geographical Institute, the observatory is in the process of being linked to a 30-meter telescope at Pico Veleta in southern Spain; together, they will form a so-called very large baseline millimeter array, a virtual telescope the size of the distance between the two observatories. The accident is expected to slow completion of this effort even further, Bremer says.

–ALEXANDER HELLEMANS

Alexander Hellemans writes from Naples, Italy.

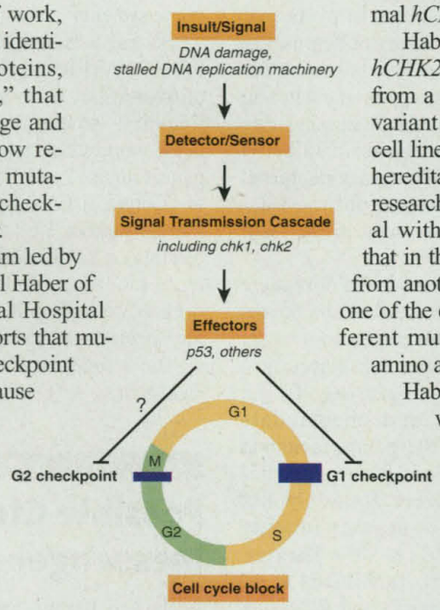
HUMAN GENETICS

## Checkpoint Gene Linked To Human Cancer

As any driver knows, reliable brakes are every bit as important to safety as the gas pedal. The same can be said about cells when it comes to dividing. They have to know when to stop, say, when their chromosomes have been damaged, because if they don't the resulting mutations may propel them down the road to cancer. Over the past several years, a great deal of work, much of it in yeast, has identified a network of proteins, called "checkpoints," that helps cells sense damage and put on the brakes. Now researchers have linked mutations in one of these checkpoint proteins to cancer.

On page 2528, a team led by cancer geneticist Daniel Haber of Massachusetts General Hospital (MGH) in Boston reports that mutations in a known checkpoint gene called *hCHK2* cause some cases of Li-Fraumeni syndrome (LFS), a hereditary cancer susceptibility that leaves its patients prone to developing any of several cancers, including breast and brain cancers and certain leukemias. This is not the first gene linked to LFS. In 1990, Stephen Friend's team, also at MGH, found that inherited mutations in the well-known tumor suppressor gene *p53* can cause the condition. Subsequent work showed that *p53* mutations account for only about 75% of the cases, however. The new work provides an explanation for some, although not all, of the remaining LFS cases. And even though the number of LFS patients may be small—only about 200 families worldwide have been reported—the discovery of *hCHK2* and additional LFS defects in the future may "help [us] to understand the molecular mechanisms of tumorigenesis" reaching far beyond LFS, says Friend, who is now at the Fred Hutchinson Cancer Research Center in Seattle, Washington.

The finger of suspicion already pointed at cell checkpoints as being important. Indeed, the p53 protein itself halts cell division in response to chromosomal damage. So Haber and his team studied several members of four LFS families that did not have *p53* mutations, looking for mutations in the human counterparts of genes previously identified in yeast as playing a major role in checkpoint control. Most such genes turned up as perfectly normal. But in one family, three LFS patients had identical mutations in one copy of the gene encoding chk2, a kinase enzyme that passes on the stop signal in damaged yeast cells by attaching phosphate tags to other proteins. The protein produced by the mutated gene would be unable to perform this function, Haber says, because part of it, including its enzymatic center, is missing. A healthy relative, in contrast, had a normal *hCHK2* gene.




**Genetic quality control.** Cells have "checkpoint" pathways that sense chromosomal damage and stop cells from dividing to allow time for repair. Mutations in checkpoint components, such as *p53* and *chk2*, can pave the way to cancer.

Haber's team next looked at *hCHK2* in 18 patients suffering from a related syndrome called variant LFS and in 49 cancer cell lines from a variety of nonhereditary human tumors. The researchers found one individual with a mutation similar to that in the first family. The gene from another individual and from one of the cancer cell lines had different mutations, changing one amino acid to another. Although Haber doesn't know for sure whether these "spelling errors" debilitate the kinase, he notes that his team failed to detect them in the gene from 50 healthy control individuals. "This suggests that these alterations are not simple sequence variants that are prevalent in the general population," says Haber.

The results are likely to receive a warm welcome in the cancer community. "This is great. People have been searching for mutations to explain LFS [in families with intact *p53*] for almost a decade and [have] found absolutely nothing," says Friend. But he adds that, because *hCHK2* mutations turned up in only one of the four families studied, "there is a good likelihood that [other LFS families] will have mutations in other interesting genes." Paul Russell, a yeast cell cycle expert

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## ScienceScope

**Star-Crossed?** The U.S. Forest Service has decided to take another look at a controversial plan to build the world's largest array of ground-based gamma ray telescopes near a Native American sweat lodge at the base of Arizona's Mount Hopkins.

In September, the agency rejected a request from astronomers at the Smithsonian Institution in Washington, D.C., for a permit to build the $16.6 million, seven-reflector array on public land (*Science*, 10 September, p. 1650). It said then that the 4-hectare site, which is less than 1000 meters from a multitribe steam hut, conflicted with "Indian religious practices." But at the Forest Service's invitation, the Smithsonian submitted a new plan last week.

The revised proposal uses the same site, says Trevor Weekes, principal investigator for the Whipple Observatory project, but moves the access road farther from the sweat lodge and sets the dishes closer to the ground. But those changes don't satisfy Native American groups, who object to the presence of any scientific facility so close to the sweat lodge. "[The Smithsonian] can't take no for an answer," says sweat lodge operator Cayce Boone, a Navajo, who feels "betrayed" by the Forest Service for keeping the issue alive.

**In the Wind** The American Meteorological Society has decided to do something about the weather—or at least what it claims is the government's relative inattention to atmospheric policy. The society has put up $400,000 to address the problem and has recruited two prominent National Science Foundation officials—former atmospheric division director Richard Greenfield and outgoing geosciences chief Robert Corell—to lead the effort from its Washington, D.C., office.

The Atmospheric Policy Program represents a "considerable investment" for the 12,000-member Boston-based organization, says executive director Ronald McPherson. The idea, he says, is to self-fund a few studies on hot topics—such as the growing commercialization of weather data—then persuade agencies and other funders to pick up the tab for future activities. Although the program won't lobby the government on legislation, Greenfield says he hopes to provide graduate students and professionals with a better understanding of atmospheric research. "I can't name anybody at the top levels of government with a strong background in atmospheric sciences," McPherson says.

at The Scripps Research Institute in La Jolla, California, notes that Haber's results point to the most obvious candidates. "One wonders whether different cancers could be explained by mutations in human versions of some of the other half-dozen or so yeast checkpoint genes around," he says.

And because LFS patients with *p53* or *hCHK2* mutations are virtually indistinguishable, Haber thinks there may be a link between the two proteins. "The most fascinating possibility is that p53 is directly phosphorylated by chk2," Haber speculates. For cell cycle expert Stephen Elledge of Baylor College of Medicine in Houston, Texas, a direct path from DNA damage via chk2 to p53 "makes perfect sense." He notes that although yeast does not have a *p53* gene, the organism makes other proteins that, when phosphorylated by chk2, induce a cell cycle stop, much as p53 does.

Still to be worked out are the details of where chk2 fits into the checkpoint control program in human cells. But, says Thanos Halazonetis of the Wistar Institute in Philadelphia, whose as yet unpublished results support a direct chk2-p53 link, "the interesting thing is that genes mutated in cancer fall in a very small number of signaling pathways, and the p53 pathway—including chk2—is likely the most important one." **–MICHAEL HAGMANN**

DEFORMED FROGS

## Link to Parasites Grows Stronger

**PHILADELPHIA**—As scientists labor to unmask the villain behind a rash of frog deformities across the United States, a suspicious character previously linked to this odd crime in California has now turned up in misshapen amphibians throughout the Northwest. The suspect—a parasitic flatworm, or trematode—has also been found in the Minnesota pond where the discovery of dozens of frogs with twisted, missing, or extra legs touched off a hunt for the perpetrator.

**Abnormal growth.** A worm caused the limb deformities in this lab-raised Western toad.

Linking trematodes to more crime scenes doesn't mean the case is closed—far from it. Abnormal frogs from some ponds still test negative for the parasite, sustaining the notion that chemicals or high doses of ultraviolet (UV) light might also be messing with frog development. "Without question there are other things that can cause [deformities]," says ecologist Pieter Johnson of Claremont McKenna College in Claremont, California, who described his team's trematode findings here last month at the annual meeting of the Society of Environmental Toxicology and Chemistry. But the circumstantial evidence suggesting that the worm is a major culprit has researchers worried that it is being nourished by a surfeit of nutrients, mainly chemicals in fertilizers, building up in U.S. watersheds.

Since students at a Minnesota middle school chanced upon misshapen northern leopard frogs on a field trip 4 years ago, deformities have been reported in more than 50 amphibian species in 44 states. Some scientists worry that the frogs are a "canary in a coal mine," the earliest victims of a developmental poison that may end up harming humans—too much UV light penetrating the thinning ozone layer, for example, or pollutants such as pesticides.

In a step toward unraveling this mystery, Johnson and his colleagues reported last spring that the trematode *Ribeiroia* burrows into tissue around the pelvic area, where a tadpole's limbs begin forming. There, the parasites encase themselves in cysts that may influence limb development by pushing cells around or by secreting hormonelike chemicals. Besides finding the parasites in Pacific tree frogs with extra or missing legs in northern California, the team infected tadpoles in the lab with the trematode, raised them to metamorphosis, and observed deformities mirroring those seen in the field (*Science*, 30 April, p. 802).

Wondering if frogs outside California are also falling victim to the dread worm, the researchers spent last summer crisscrossing six northwestern states in a van, collecting frogs, toads, and salamanders from 103 ponds, including 42 ponds where deformities were found in six species at rates ranging from 5% to 90%. The misshapen amphibians at 40 of 42 ponds had *Ribeiroia*, while those from normal ponds almost never had the parasite. A brief search in Minnesota also turned up the trematode—including at the Ney pond, where deformed frogs were first spotted, and another hot spot. Bolstering its fieldwork, the team has shown that trematodes can cause deformities in the lab in a more terrestrial amphibian: the Western toad (*Bufo boreas*), another denizen of the afflicted ponds. "The fact that they can induce [deformities in] another species gives [the theory] more breadth," says Andrew Blaustein, an ecologist at Oregon State University in Corvallis.

The findings do leave the chemical theory a leg or two to stand on. Although the northwestern waters tested free of pesticides, says Johnson, many of the ponds have a "long history of fertilizer input or cattle grazing." He speculates that such nutrients could be an accessory to the crime by spurring algal growth, which in turn would boost populations of *Ribeiroia*'s primary host, an aquatic snail. Others see a more direct role for chemicals. A group led by toxicologist Jim Burkhart of the National Institute of Environmental Health Sciences in Research Triangle Park, North Carolina, has found that the water itself from the Ney pond and other sites can cause deformities in parasite-free African clawed frogs, a widely used lab species. "It's not either-or," says Burkhart. "There are factors in the water that contribute to malformations." He believes that mixtures of unidentified hormonelike chemicals in the water, as well as the trematodes, each can trigger deformities. And they may work in concert, Burkhart says: Chemicals could be predisposing the frogs to trematode infections by weakening their immune systems.

So far, it hasn't been shown that trematodes are killing off significant numbers of frogs—they have only been blamed for deformities—so they don't appear to play a role in the worldwide decline of amphibians, notes parasitologist Peter Daszak of the University of Georgia, Athens. But Blaustein has a prime murder suspect: He's found that even low concentrations of nitrates from fertilizers can directly kill larvae of several Western species in decline, including the Cascades frog, one of the species with deformities. "The message on the effects of fertilizers is important," Blaustein says. "Fertilizers are everywhere."

**–JOCELYN KAISER**

CIRCADIAN RHYTHMS

## Possible Clock Messenger Identified

A clock is useless unless it has an output—hands, a digital display, or an alarm. The same goes for the 24-hour molecular "clock" that ticks in organisms from bacteria to humans. To impose its rhythm on behaviors such as activity, sleep, and feeding, the oscillating molecules that make up the clock must communicate, through some kind of outgoing signals, to the brain areas that drive those behaviors. Now researchers working in fruit flies have for the first time put their hands on a good candidate for such a messenger.

In this week's issue of *Cell*, a team led by Paul Taghert at Washington University in St. Louis and Jeff Hall at Brandeis University in Waltham, Massachusetts, reports evidence that a peptide called PDF is a key outgoing clock signal. The researchers have shown that

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