Mice help nail down gene for rare syndrome

Randy L. Johnson is interested in how limbs form, so he wondered what would happen if mice lacked a gene related to one implicated in the development of chicken limbs. Much to Johnson's surprise, his studies of such mutant mice have led to the identification of the gene responsible for a rare human disorder called nail-patella syndrome (NPS).

For more than a century, physicians have recognized this curious syndrome in which people have, to varying degrees, abnormal growth of fingernails, toenails, and knee caps, or patellae. At the extreme, people with NPS have no knee caps or nails whatsoever. Some 50 years ago, physicians linked kidney problems, often severe enough to require transplants, to the syndrome. Last year, investigators also noticed that people with the syndrome frequently have the eye disorder glaucoma.

Scientists have been puzzled by this odd collection of symptoms and have even pondered whether more than one gene must be involved. At the Society for Developmental Biology meeting last week in Palo Alto, Calif., Johnson, who works at the University of Texas M.D. Anderson Cancer Center in Houston, explained how the findings on his mutant mice strongly indicate that a single gene is behind NPS. Some of his team's results are also described in the May NATURE GENETICS.

To create the mutant animals, the scientists deactivated both copies of a mouse gene called *Lmx1b*. It encodes a transcription factor, a DNA-binding protein regulating the activity of genes. The resulting mice, which survive less than a day after birth, lack patellae and nails. Further examination revealed kidney abnormalities as well.

The gene's link to NPS grew stronger when the researchers realized that the human version of *Lmx1b* maps to the exact region of chromosome 9 where the syndrome's mutant gene is thought to reside. Finally, working with a research team led by Brendan Lee of Baylor College of Medicine in Houston, Johnson's group found that three people with NPS harbor mutations in the gene and their unaffected parents do not.

Curiously, it takes mutations in both copies of *Lmx1b* to produce symptoms in mice, although a defect in just one is sufficient to cause NPS in people. The amount of transcription factor produced may be crucial to the human disorder, which could explain why people with similar mutations are afflicted to different degrees, says Johnson.

"We want to get a handle on what causes the variation," adds Iain McIntosh of Johns Hopkins Medical Institutions in Baltimore, who is leading a study of people with NPS. "There's nothing jumping out and saying that certain types of mutations cause certain aspects of the [syndrome]."

The connection between glaucoma and NPS has been strengthened by the discovery of *Lmx1b*'s involvement. At last week's meeting, Johnson reported that the normal gene is active in the eyes of mice.

A second research group, made up of scientists from Stanford University and the University of Michigan in Ann Arbor, has independently identified the nail-patella gene by studying families with members who have both the syndrome and glaucoma. That group, led by Stanford geneticist Douglas Vollrath, is publishing its results in the July HUMAN MOLECULAR GENETICS.

Since the condition is so variable, physicians sometimes have trouble diagnosing whether a patient has NPS. Testing for mutations should resolve any confusion. "There is real potential to having this gene in hand," notes Vollrath. "Anyone with nail-patella syndrome should be tested for glaucoma." The eye disorder is still incurable, but some therapies slow its progression, he explains.

There's also a possibility, says McIntosh, that NPS's kidney problems and glaucoma would be treatable if the defects turn out to be reversible and if scientists could compensate for the dearth of the key transcription factor. —*J. Travis*

La Niña readies to steal El Niño's thunder

Water temperatures in parts of the equatorial Pacific Ocean have dropped precipitously in the last 2 months, chilling El Niño's fever and setting the stage for the arrival of another climatic hooligan: La Niña.

Meteorologists were divided earlier this year on whether an episode of La Niña cooling would follow El Niño's demise, but the recent Pacific shift has brought consensus. "All of the forecasts are consistently indicating that we will have a La Niña shortly and it will continue over the next winter," says Vernon E. Kousky of the National Oceanic and Atmospheric Administration (NOAA) in Camp Springs, Md.

La Niña and its sibling, El Niño, are opposite extremes of a Pacific pendulum that causes the equatorial waters to swing from warm to cold and back again. During El Niño, warmth normally centered over Indonesia spreads eastward across the entire Pacific, dragging with it towering thunderheads that pump heat into the atmosphere. The storms redirect jet streams and turn typical weather patterns upside down around much of the globe.

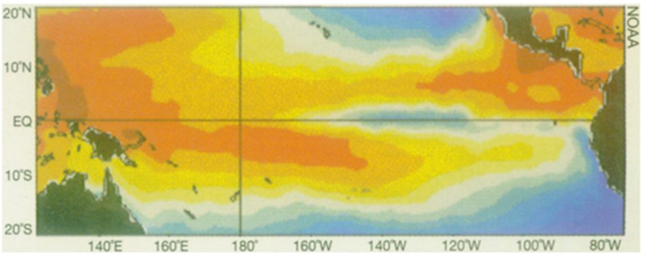
During La Niña, the equatorial Pacific waters turn cold except around Indonesia, drawing thunderstorms back to that part of the ocean basin. The Pacific jet stream weakens, and wintertime weather in the United States turns much more mercurial. "The jet stream tends to undulate more. During our winter, the jet stream may be way north in Alaska and then come diving down south in certain periods. This will be much more variable in the sense that we can go from one month to the next and have a dramatically different pattern," says Kousky.

Measurements of water temperature, taken by buoys and satellites, show that a full-fledged La Niña has not yet developed. Between early May and early June, the equatorial temperatures fell markedly from 3°C above normal to 3°C below normal around 130°W, but the cooling stayed confined and has not spread westward. Moreover, warm remnants of El Niño linger to the north and south of the equator, helping to suppress rainfall needed to quench the fires raging in Mexico.

Meteorologists will be watching in coming months to see whether water temperatures drop further to the west, near the International Date Line. That's a key spot affecting how the weather evolves downstream in North America, says Arthur J. Miller of the Scripps Institution of Oceanography in La Jolla, Calif.

The recent El Niño tamed the winter weather in the United States, bringing mild temperatures to much of the country. Researchers say it is hard to forecast what kind of weather will arrive this winter as the Pacific enters its cold phase. "La Niña conditions are much more difficult to predict. It's not as simple as the reverse of El Niño," says Miller.

La Niña tends to bring warmer-than-normal winter weather to the southeastern United States while the Northwest gets colder than normal, according to NOAA. The Pacific Northwest generally gets wet weather in late fall and early winter during La Niña, whereas the Southwest often dries out. "There is a strong potential for drought in the Southwest," says Kousky. —*R. Monastersky*



Cool water (shown in blue) has emerged in parts of the equatorial Pacific. Meteorologists predict further cooling leading to the development of La Niña.