

## Blue Baby Blues

A CONGENITAL HEART DEFECT IS EXPLAINED  
BY NEW GENETIC CLUES

A deep blue tint in a newborn's skin is the first sign that something's wrong. Blood cells that should be bright red and full of oxygen, creating a baby's typically rosy hue, instead lack oxygen due to a congenital heart defect. Known colloquially as blue baby syndrome, tetralogy of Fallot (TOF) occurs in one in 3,000 live births and accounts for nearly 10 percent of all serious congenital heart defects. Its cause has largely been a mystery, as the parents of babies born with TOF usually show no signs of heart defect. Now, HHMI investigator Christine Seidman of Brigham and Women's Hospital and Harvard Medical School has found a genetic cause for some cases of TOF.



The x-ray of the chest of an infant with Fallot's tetralogy, a congenital heart defect.

After hitting dead ends when trying to pinpoint specific mutations

linked to TOF, Seidman's lab group hypothesized that TOF might have its root in the number of copies of particular genes. This kind of genetic change can lead to incorrect amounts of protein being made by a cell. Down syndrome, one extreme example of a copy number variation, is caused by an entire duplicated chromosome.

Seidman's team searched the genomes of 114 TOF patients and found 11 segments of DNA that were present in too many or too few copies. They then looked at these regions in the DNA of another 398 TOF patients and confirmed that seven of the copy number variations were linked to TOF. The regions did not show incorrect copy number in the unaffected parents of the babies born with TOF, the scientists report in the August issue of *Nature Genetics*.

The team is now studying those seven regions to explore what particular genes may be implicated in TOF. Seidman also thinks that variation in copy number could be at play in other congenital heart defects, where researchers have been unable to pinpoint specific mutations.

"Our work really reiterates the theme that the dosage of certain genes is vital," says Seidman. ■ -SARAH C.P. WILLIAMS

### IN BRIEF

studies the tangled network of relationships between species in a food web. To determine how a species' extinction would affect the rest of the web, scientists like Pascual must first rank all species based on how codependent they are. A postdoctoral fellow working in Pascual's lab realized that this was how Google's "PageRank" system worked: it rates a page as more important if it is linked to other pages ranked important.

Pascual's lab group and their collaborators tweaked PageRank to apply to their ecosystem modeling. The new system performed better, they found, than traditional algorithms. They then applied it to some real ecosystems, including the Chesapeake Bay and oceanic coral reefs. The researchers compared these results from the new method with those calculated by a more computationally intensive method and found that it stands up well.

The researchers say that this system, published online on September 4, 2009, in *PLoS Computational Biology*, could also be made to analyze other biological networks, such as metabolic networks within cells or interactions of cells within organisms.

**A NEW FUNCTION OF KILLER T CELLS**  
Researchers led by Ralph Isberg, an HHMI

investigator at Tufts University School of Medicine, have discovered a previously unknown function of killer T cells in the immune system. Scientists knew that killer T cells can attack cells that have been invaded by bacteria to thwart an infection. The new research shows that killer T cells can also attack cells with bacteria attached to their outer surfaces.

Isberg's team inoculated mice with a strain of *Yersinia pseudotuberculosis*, a bacterium that attaches itself to the outside of cells in the gut. The inoculated mice had high levels of anti-*Yersinia* antibodies and increased numbers of killer T cells—unexpected findings since the bacteria generally live outside of host cells.

To investigate this finding, the scientists injected weak forms of the bacteria into mice lacking killer T cells. The mice died from this infection, whereas normal mice survived, suggesting that killer T cells are vital to fighting off the infection. The results were published September 4, 2009, in *PLoS Pathogens*.

Further experiments showed that after the killer T cells attack a cell carrying *Y. pseudotuberculosis*, other immune system cells can engulf the dead cell and bacteria. The new mechanism sheds light on how the immune system functions and suggests

new strategies for targeting extracellular pathogens.

**SPOTTING OVARIAN CANCERS EARLY**  
A new study by HHMI scientists reveals details on just how long early-stage ovarian tumors exist before they are detectable by current tests. The researchers, led by HHMI investigator Patrick O. Brown at the Stanford University School of Medicine, scoured existing data on ovarian tumors to uncover the new statistics.

They relied on details about ovarian tumors discovered by chance in healthy women who had their ovaries and fallopian tubes removed because they were at high risk for cancer. Most of the tumors were microscopic and undetectable by the naked eye. None of the women showed symptoms of cancer.

The study concluded that most ovarian tumors exist for at least 4 years before they spread, and the typical cancer is less than three millimeters across for most of this time. In addition, the researchers determined that these early tumors are more likely to be in the fallopian tubes than in the ovaries. The findings were published July 28, 2009, in *PLoS Medicine*.

Brown's lab is now looking for ways to detect such tumors earlier and intervene before the cancer spreads.