HUMAN GENETICS

Interest Rises in DNA Copy Number Variations—Along With Questions

PHILADELPHIA, PENNSYLVANIA—Like a kaleidoscope, the human genome keeps offering up new views. The latest, causing excitement here last week at the annual meeting of the American Society of Human Genetics, concerns duplicated or missing blocks of DNA, known as copy number variations (CNVs). Large CNVs, millions of DNA bases in length, have been detected for some time, for example, in children with mental retardation. But as geneticists peer closer, they are finding CNVs everywhere, in every size, all across the genome (*Science*, 7 September 2007, p. 1315). "Many of us in the field were just blown away when we realized how often all of us have regions of the genome that are missing or present in extra copies," says Jan Friedman of the University of British Columbia in Vancouver, Canada, who attended last week's meeting. "We just had no idea [the genome] was so plastic."

The study of CNVs, like any emerging field, is plagued by uncertainty. Often the technology used was not designed to detect CNVs, making results difficult to interpret. And it's not at all clear which CNVs alter the function of genes or influence disease. Last week, scientists at the meeting described links between CNVs and various cancers, schizophrenia, autism, body mass index, and Crohn's disease. But in nearly all these cases, questions remain as to whether CNVs are coincidentally present, are linked to another genetic disease driver, or are themselves causing ill health.

Many research groups are now conducting broad sweeps of genomes in various species, and in healthy and sick people, to get a sense of CNV patterns. Alexandre Reymond of the University of Lausanne in Switzerland presented unpublished research describing a survey of CNVs in mouse genomes and six different mouse tissues, including the brain, liver, and heart. Reymond wanted to learn how often CNVs popped up in different mouse strains—including wild mice caught outdoors. He was curious as to whether CNVs affected gene expression and whether expression changed across tissues and during development. He found wide effects: Genes that fell within CNVs tended to be expressed at lower levels; CNVs influenced expression of genes nearby; and the expression of affected genes varied depending on where one looked in the body.

Other CNV maps are being assembled at the Wellcome Trust Sanger Institute in Hinxton, U.K., and the Broad Institute in Cambridge, Massachusetts. Don Conrad and his colleagues at the Sanger Institute have their eyes on smaller common CNVs, as little as 500 base pairs in length. Checking about every 50 base pairs across parts of the genomes of people of African and European ancestry, they uncovered more than 10,000 CNVs—suggesting that other efforts, which have identified about 1500 common ones, are missing most CNVs. Although "there haven't been many" CNVs linked to disease yet, Conrad said in his talk, "there might be quite a few out there." Indeed, he noted that 129 of the 419 genetic-association regions pinpointed in genome-wide association studies hunting for disease DNA contain a common CNV.

The Wellcome Trust Case Control Consortium, which has scanned the genomes of thousands of people for variations in single DNA bases that might be associated with seven chronic diseases, is now performing a similar survey of copy number variation. They want to learn whether certain patterns of CNVs stand out in particular diseases. So far, they're not finding more CNVs in individuals with disease compared with those without but are finding that the CNVs in the genomes of those with, say, diabetes are not the same CNVs that show up in healthy people. The key variable with these CNVs is "kind of where they are rather than how many there are," says Matthew Hurles of the Sanger Institute, who presented the unpublished research.

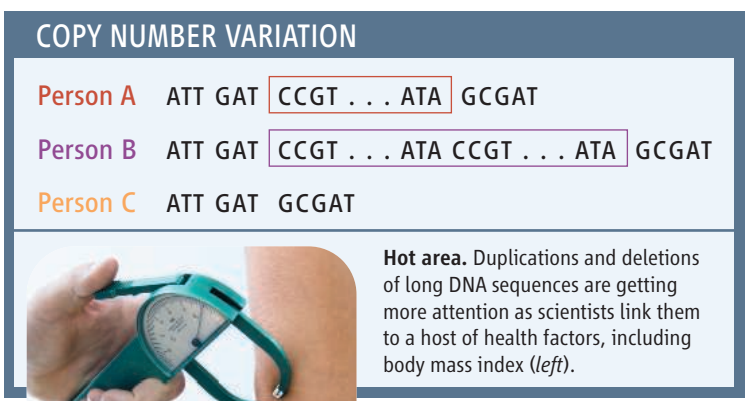
In the Wellcome Trust work, as in many other CNV studies, quality control is a major challenge. Rare CNVs can trigger false positives, says Hurles, suggesting a connection to disease that isn't really there. In addition, it's easier to detect deleted DNA than it is DNA that has been duplicated, which may bias results.

Although results are often murky, some solid work points to a role for CNVs in neuropsychiatric disease. Earlier this year, research published in *The New England Journal of Medicine* tied a deletion in chromosome 16 to cases of autism, and other work linked it to cases of developmental delay. But two recent papers on schizophrenia, published earlier this year in *Science* (25 April, p. 539) and *Nature*—some data from which were also presented last week—came up with very different results. One group reported that rare CNVs were three to four times more common across the genome in those with schizophrenia than those without; the other reported 1.15 times as many. "There must be some underlying truth that explains both," says Steven McCarroll of the Broad Institute, who described his efforts to examine CNVs that might travel with DNA previously linked to disease. Technology may play a critical part, he says: "The smallest CNVs you might see on one platform but not on the other."

Despite such limitations, CNVs have become a popular target for disease gene studies. At last week's meeting, Rehab Abdel-Rahman of the University of Edinburgh in the U.K. described a CNV culled from more than 2200 cases of colorectal cancer. The CNV, which includes a gene that helps control the immune system, appeared in 14% of cancer cases but fewer than 4% of controls, she said. Other work linked CNVs to body mass index and to retinoblastoma that may be passed to children by their fathers.

One critical question is whether these CNVs are inherited or spontaneous. The latter, many believe, are much more likely to drive disease but also much less common. Another question is whether CNVs show up in many cases of a disease or just a handful. "We're still really in a learning curve," said Stephen Scherer, who studies autism genetics at Toronto's Hospital for Sick Children. Much of the work remains imprecise and very preliminary, but, he notes, "the data are getting much better."

–JENNIFER COUZIN



Hot area. Duplications and deletions of long DNA sequences are getting more attention as scientists link them to a host of health factors, including body mass index (*left*).

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