THE GLOBE AND MAIL
THURSDAY, NOVEMBER 23, 2006

Study turns human genetics on its head

Research finds abnormal is really normal, puts in question some medical tests

BY CAROLYN ABRAHAM
MEDICAL REPORTER

It was nice while it lasted. But the idea that all the world's people are 99.9 per cent genetically identical — that a mere sliver of DNA separates a Dolly Parton from a Dalai Lama — is untrue.

An international research team has overturned the harmonious message that flowed from the Human Genome Project in 2000 and discovered more DNA differences exist among people than the experts expected.

Using new technology to study the genomes of 270 volunteers from four corners of the world, researchers have found that while people do indeed inherit one chromosome from each parent, they do not necessarily inherit one gene from mom and another from dad.

One parent can pass down to a child three or more copies of a single gene. In some cases, people can inherit as many as eight or 10 copies.

In rare instances a person might be missing a gene.

Yet despite these anomalies, they still appear to be healthy — countering the notion of what doctors have deemed "normal" in genetics.

The work highlights how DNA helps to make each human unique, hinting that a towering basketball player, for example, might boast extra copies of a growth gene or that a daughter really might be more like her dad.

But the landmark report, published today by the journal Nature, also has disturbing implications.

It suggests that some medical tests —such as prenatal scans — may have incorrectly flagged these kinds of genetic quirks as signs of potential defects).

However, it also makes clear that scientists have missed clues to the kinds of genetic traits that can underpin disease.

"The genome is like an accordion that can stretch or shrink . . . so you have no idea what's normal," said Steve Scherer, a senior scientist at the Hospital for Sick Children in Toronto and study co-author.

Even the number of genes people can inherit, he said, a premise set out 150 years ago by Austrian monk Gregor Mendel, the father of modern genetics, has been upended.

FRED LUM / THE GLOBE AND MAIL

Steve Scherer, middle, a senior scientist at the Hospital for Sick Children in Toronto and co-author of a new genetic study, stands yesterday outside the hospital with some of the members of the international research team.

"We have to think of genetics in an entirely different way. We're actually more like a patchwork of genetic code than bar codes that line up evenly," Dr. Scherer said. "Everything we've been taught is different now."

The Sick Kids team worked on the project for more than two years with scientists at Harvard Medical School, the Wellcome Trust Sanger Institute in England, the University of Tokyo and the California-based Affymetrix Corp.

Their research finds that the size of at least 12 per cent of the genome — including 2,900 genes and regions between them — can differ dramatically between people, and in some cases, between certain ethnic groups.

The size differences are the result of DNA that is either duplicated or deleted or contains unexpected added bits of genetic code. Scientists call the phenomenon "copy number variation" or CNV for short. And it is already reshaping genetic research.

"When we're accounting for what the human genome means, there's not going to be a single human genome map that is going to be useful to one person," said Robert Hegele, a noted genetic scientist at the Robarts Research Institute in London, Ont., who read the study. "It's a huge surprise that there's so much variation of this type . . . that is so common in so many healthy people."

For this reason, scientists agree that doctors looking at less-detailed genetic tests — such as karyotyping — might have mistaken unusually-sized bits of DNA as signs of a medical problem.

Patients, or prospective parents receiving results of a prenatal test, for instance, might have been informed that something looked abnormal when, the new work suggests, it isn't.

Glossary of genetics

The human genome: All of the genetic information carried inside a cell.

DNA: Deoxyribonucleic acid is the chemical code that provides the genetic instructions to build and operate a human being. It is wound like a spiralling ladder into the 23 pairs of chromosomes found in the nucleus of our cells. There are about three billion rungs on the ladder.

Chromosomes: The rod-shaped structures inside our cells made up of DNA.

They house genes along their length like box cars on a train. People inherit 46 chromosomes from their parents, 23 from the mother and 23 from the father.

Genes: The essential units of heredity. Each gene encodes a recipe to make a protein and proteins make the stuff that help to make us human — lips, liver, the frontal lobes of our brains.

Humans carry about 30,000 genes. They make up only about 3 per cent of the genome. It was thought people inherit only two copies of a gene, one from each parent. But the new work shows this can vary. A person can, in some cases, inherit as many as 10 copies or none at all.

Nucleotides: These chemicals are the building blocks of DNA. They are represented by the letters A, C, G and T — A stands for adenine, C for cytosine, G for guanine and T for thymine. One letter is found at the end of each rung on the ladder that makes up DNA. This way A joins to T and C to G. The partnering is called a base pair.

The letters, or nucleotides, can combine to spell out the recipe for a gene, or a protein.

Junk DNA: This refers to the 97 per cent of genetic code in DNA that does not encode the recipe for a gene. These long stretches of code are now thought to be linked to regulating genes.

SNiPs: The mutation type best known in human DNA. It stands for "single nucleotide polymorphism" and refers to a single-letter change in the DNA code, a T where others carry a C, for example.

— Carolyn Abraham

While the report does not delve into the issue directly, Dr. Scherer acknowledged this is a possibility. He offered as an example a genetic test that relies on a "diagnostic probe" to evaluate the length of DNA code near the ends of chromosomes.

Shorter chromosomes, he said, are implicated in developmental delay or mental retardation due to DNA code that might be missing.

"But we found that in a large number of cases (shorter chromosomes) exist in the general population," said Dr. Scherer, who is also director of the Centre for Applied Genomics. "The chromosomes don't necessarily line up evenly . . . so people really need to scrutinize these results more closely before assuming it's pathogenic.

"The bottom line is that there's so much natural variation you have to go back and look closer."

Dr. Hegele agreed that such things might have been misread. "It's always been assumed those big changes would result in some type of disease, that they were rare and would lead to sort of catastrophic conditions," he said, noting that Down syndrome is the result of an extra copy of chromosome 21.

"But you're always dealing with clinical uncertainties and the best knowledge that's available at the time."

Human DNA is a chemical code of roughly three billion letters. These letters, A, C, G and T, are nucleotides that can spell out the recipe for a gene. Previously, scientists have paid almost exclusive attention to mutations that involved a single letter change in the recipe — an A, where others carry a T — a so-called SNiP. But the new report shows that a gene recipe, like any recipe, can also change if quantities of an ingredient are much larger or missing.

Dr. Hegele, an endocrinologist who has been studying the genes of patients with a family history of high cholesterol said, "We assume there are normal numbers of copies [of genes] there when we're looking at their code. But in fact, it could be that one [gene] is totally missing."

Scientists suspect that evolutionary pressures likely triggered some genes and DNA regions to increase in one part of the world, yet wither in another.

The international consortium found that a gene already known to be involved in HIV susceptibility, for example, is carried in higher numbers in the DNA samples from Africa, where HIV rates dwarf those in other parts of the world.

In total, the report found that about 15 per cent of the 2,000 disease-related genes known can be affected by such a variation.

Researchers conducted the study using the 270 DNA samples and health information that had been collected for the Haplotype Map. That map, completed last fall, was the first catalogue of common genetic differences — SNiPs — between four major ethnic groups, the Han Chinese, the Japanese, U.S. citizens of European descent and the Yoruba tribe of Nigeria.

The Haplotype Map, like the 2000 Human Genome Map, suggested there were few differences between these groups of people, with only rare examples of mutations that appeared only in one population.

The new work suggests the differences could be slightly more pronounced, largely because researchers had access to new technology that changed the vantage point of the genome.

Using a microchip developed by Affymetrix, Dr. Scherer explained that they were able to view the genome in chunks as small as 1,000 nucleotides, but still be able to pull back and see as many as five million. He compared it to a telescope that allows you to home in and see a single sun and its neighbouring planet, but that also has to the power to zoom out and reveal the wider solar system and "find out there are two suns."

Tom Hudson, who led Canada's contribution to the Haplotype Map, applauded the new work, calling it a "a tool that will be immediately useful." He said he is using it to reanalyze the genomes of 1,200 people with colon cancer and compare them to 1,200 people without it.

"In the early years it's going to be hard to interpret," said Dr. Hudson, who is also the scientific director of the Ontario Institute for Cancer Research. "We are going to see things and want to conclude that this is possibly what makes people sick, but it may not be."