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Sequencing genome of entire family reveals parents give kids fewer gene mutations than was thought

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Researchers at the University of Utah and other institutions have sequenced for the first time the entire genome of a family, enabling them to accurately estimate the average rate at which parents pass genetic mutations to their offspring and also identify precise locations where parental chromosomes exchange information that creates new combinations of genetic traits in their children.

Led by scientists at the Seattle-based Institute for Systems Biology, the study, published Thursday, March 11, 2010 in *Science Express*, sequenced the entire genome of a family of four—the parents, daughter, and son. By comparing the parents' DNA sequences to those of their children, the researchers estimated with a high degree of certainty that each parent passes 30 mutations—for a total of 60—to their offspring.

Scientists long had estimated that each parent passes 75 gene mutations to their children.

"That's the kind of power you get from looking at the whole genome," said Lynn B. Jorde, Ph.D., professor and chair of the Department of Human Genetics at the University of Utah School of Medicine. "The mutation rate was less than half of what we'd thought."

Genetic Clock

Most mutations, as far as medical researchers know, have no consequence for a child's health. But knowing the rate at which parents send on mutations to their offspring is critical information, according to Jorde. "The mutation rate is our clock, and every time it ticks we have a new genetic variant," he said. "We need to know how fast the clock ticks."

Everybody has about 22,000 genes, which contain the genetic blueprint for human life. This blueprint, called DNA, comprises more than 3 billion "base pairs" that determine genetic makeup. In1990, scientists worldwide began assembling the entire sequence of base pairs in all 22,000 human genes, a process called sequencing. When they completed the project in 2003, the scientists had put together the complete picture of the proper sequence of base pairs in the human genome.

When Jorde and the Science study's senior author, David J. Galas, Ph.D., of the Institute of Systems Biology, were discussing the idea of sequencing the genome of an entire family, they decided to look for one with known genetic disorders. A family of four turned out to be right for the study. Although the parents had no genetic abnormalities, they each carried recessive genes that resulted in their son and daughter being born with two extremely rare conditions - Miller's syndrome and Primary Ciliary Dyskinesia (PCD).

Miller's syndrome, a disorder characterized by facial and limb malformations, is thought to occur in perhaps one in 1 million people and has been diagnosed in only two families in the world, along with a few sporadic other cases.

PCD is a condition in which the tiny hair-like structures that are supposed to move mucus out of airways in the lungs do not function. The chances of having PCD are estimated at one in 10,000. The odds of someone having both PCD and Miller's syndrome are less than one in 10

billion, according to Jorde.

By comparing the variants in the children's DNA sequences with the Human Genome Project and other public databases, the researchers confirmed an earlier study that identified four candidate gene mutations for causing each disorder.

Gene Mutation Rate

Genetic mutations are passed to offspring when base pairs of DNA are altered in the genome. A Mountain View, Calif., company, Complete Genomics, used new, high-powered technology to sequence the genomes of each family member. Then, using the DNA sequence established by the Human Genome Project as a reference, Chad D. Huff, Ph.D., a post-doctoral fellow in Jorde's lab and co-first author on the study, compared the family's DNA base pair sequences to those established by the Human Genome Project.

"Comparing the family's sequences to the Human Genome Project allowed us to screen out potential errors in the DNA sequencing process," Jorde said. "To estimate the mutation rate, we compared the parents' sequences with those of their children. Differences in the sequences that were not caused by sequencing errors were caused by mutations."

From this, Huff estimated the number of gene mutations each parent gives their child. This rate probably will vary, according to Jorde, depending on how old the parents are, particularly the father, when they reproduce.

To find the locations where parental chromosomes exchange genetic information, which are called crossover sites, the researchers compared variations in the parents' DNA sequences to their children's, looking for

blocks of DNA that the son and daughter inherited intact from the parents. When they found blocks that were interrupted, the researchers concluded they'd identified the crossover sites.

"We found that 60 percent of the crossovers take place in specific hotspots on the chromosomes," Jorde said. "We were able to locate these sites right down to the base pairs."

Future Studies

The study opens the door for numerous other investigations in the future. Jorde expects researchers will use family sequence analysis to begin narrowing down the genetic causes of more common diseases. And, as the cost of genome sequencing continues to drop—the Human Genome Project cost about $3 billion, and now individuals can get their genome sequenced for $5,000 to $10,000—it will be an important part of individual medical records, the researchers believe.

"We would predict that the information derived from family genomes, along with relevant environmental and medical information, will constitute the medical records of the future," the study concludes.

Provided by University of Utah