

Half a genome better than a whole in quest to understand mutations

Israeli breakthrough in isolating male and female chromosome sets could help stem cell researchers develop cures for genetic diseases

BY DAVID SHAMAH | March 16, 2016, 8:09 pm |

Genetic research — and especially the study of how genes mutate and cause devastating diseases like cystic fibrosis, muscular dystrophy and Down syndrome — has gotten a major boost, thanks to research by scientists from Hebrew University, Columbia University Medical Center and The New York Stem Cell Foundation Research Institute.

The scientists developed a method to isolate embryonic stem cells that carry a single set of chromosomes, allowing researchers to study single sets of chromosomes in cells that generally — include the two sets of chromosomes — male and female that contribute sperm and eggs to their eventual creation.

“The upshot of this is that we can now study human genetics by focusing on mutations present in the cell” that have only one set of chromosomes, said Prof. Nissim Benvenisty, MD, director of the Azrieli Center for Stem Cells and Genetic Research at the Hebrew University and principal co-author of the study.

“By isolating the chromosomes, we can more easily determine how mutations affect cells, since we don’t have to figure out ways to differentiate between healthy and mutated gene copies.”

The scientists reported their findings Wednesday in the journal *Nature*.

Mature healthy human cells contain 46 chromosomes — 23 contributed by each parent.

“Those 46-chromosome cells are called diploid cells in the scientific literature, while the cells that have 23 chromosomes, such as sperm and eggs, are made up of 23 chromosomes, and are known as haploid cells,” said Benvenisty. “When the sperm and eggs unite they immediately become diploid cells which continue to divide into embryonic stem cells that will eventually become a baby. The genes undergo a process of ‘diploidization,’ meaning that there is a point, still unknown to us, where the conversion from two separate sets of 23 chromosome genes to a single 46 chromosome gene takes place.”

However, there is always the possibility that a couple of haploid cells will still be hanging around, missing the diploidization boat – and they may still be hanging around even as a body part forms.

“The trick is to isolate these haploid mature cells, and we have developed a method to find them,” said Benevisti. “We’ve been working on this for several years, and we now have a library of about 10,000 haploid genes with specific mutations that we can use as a library reference for genetic researchers to better understand mutations and diseases.”

In this study, the scientists triggered a process in which the unfertilized human egg cells divided, and then highlighted the DNA with a fluorescent dye, which was designed to seek out the 23-chromosome cells.

“We realized that there had to be a way to catch the cells while they were still at the haploid stage, since the conversion to diploid is not instantaneous,” said Benvenisty. “With the dye technique, we were able to track down and extract the haploid cells. In our first efforts, we examined 2,000 cells, and found only 2 haploid cells.”

That was enough to advance the research, however, and the team continued studying different lines of genes from various parts of the body, building up the current library of 10,000 haploid cells.

The mutant library is likely to be a very valuable resource for researchers, said Benvenisty. The Nature article describes a genetic testing method that uses the haploid cells to discover genes involved in a specific cellular process. “The methods we developed are ready to go right now,” Benvenisty added.

Looking to the future, the system could be used to develop cell-based therapies for diseases such as blindness, diabetes, or other conditions in which genetically identical cells offer a therapeutic advantage, said Benvenisty. “The genetic content of these cells are identical to those of the cells of the egg donor.