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Research sheds light on cause of Down syndrome and other genetic disorders

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Scientists have a better understanding of what causes an abnormal number of chromosomes in offspring, a condition called aneuploidy that encompasses the most common genetic disorders in humans, such as Down syndrome, and is a leading cause of pregnancy loss.

To pinpoint what goes awry in these cases, researchers at the U.S. Department of Energy's Lawrence Berkeley National Laboratory and the University of Tennessee, Knoxville studied mice. They found that if a mother's egg cell has a mutation in just one copy of a gene, called Bub1, then she is more likely to have fewer offspring that survive to birth.

Usually, both copies of a gene in a chromosome must carry the same mutation in order for an organism to be adversely effected.

"But we found that a mutation in a single copy of the Bub1 gene can have an impact — and this is not the case with most genes. With Bub1, if you have one bad gene and one healthy gene, there's a problem," says Francesco Marchetti of Berkeley Lab's Life Sciences Division. He worked with Sundaresan Venkatachalam of the University of Tennessee and other scientists on the research. Their findings appear in the online early edition of the Proceedings of the National Academy of Sciences the week of July 13.

The importance of their discovery is underscored by the fact that it's rare for humans to have mutations in both copies of a gene, while it is quite common to have a mutation in only one copy. Usually, the healthy gene

overrides the mutated gene -- but not in Bub1, at least in mice.

"This means that having only one mutated Bub1 gene could be a significant predisposing factor for passing on an abnormal number of chromosomes to offspring," says Marchetti.

The scientists also found that the harmful effects of this mutation increased with a mother's age. The older the female mice got, the fewer offspring they had. The same is true in humans: the chance of having an aneuploid pregnancy increases with the age of the mother. In addition, the scientists found that the same mutation in sperm cells had no effect on the health of offspring.

The research sheds light on the genetic underpinnings of aneuploidy, a condition marked by having an abnormal number of chromosomes. It is the underlying cause of many genetic diseases - such as Down syndrome, Edwards syndrome, and Patau syndrome - as well as many cases of pregnancy loss.

For the past several years, scientists have used mice to study the genetic causes of aneuploidy. They've zeroed in on mutations in a handful of genes as the culprits, including Bub1. The gene plays a role in a cell's spindle assembly checkpoint, which is a control mechanism that ensures that chromosomes are properly divided during meiosis, the cell division process that enables a stem cell to become an egg. This checkpoint hiccups when Bub1 is mutated, sometimes producing an egg with an extra chromosome and sometimes producing an egg with a missing chromosome.

Bub1 is also a favorite target of scientists studying cancer development, which is why Venkatachalam initially developed mice that were heterozygous for the gene, meaning they had one normal and one mutated copy. As so often happens in science, however, he

serendipitously noticed that these mice had fewer babies. Intrigued, he enlisted the help of Marchetti and Berkeley Lab postdoc Aris Polyzos of the Life Sciences Division to help understand why.

The team found that when a male with one bad copy of the gene mated with a normal female, their number of offspring was normal. But when a female with a bad copy of the gene mated with a normal male, very few babies were born. Further research revealed this is because aneuploidy was generated in the egg and passed on to the single-cell zygote that forms when a sperm fertilizes an egg. And this led to the loss of the embryo.

"We found that in female mice a single copy of an abnormal Bub1 gene is sufficient to produce aneuploidy, and this risk increases with age," says Marchetti. "Our work may help explain how aneuploidy occurs in humans, and why the risk for the condition increases with a mother's age."

More information: "Heterozygosity for a Bub1 mutation causes female-specific germ cell aneuploidy in mice" is published in the July 13-17, 2009 online early edition of the *Proceedings of the National Academy of Sciences*.

Source: Lawrence Berkeley National Laboratory (news : web)