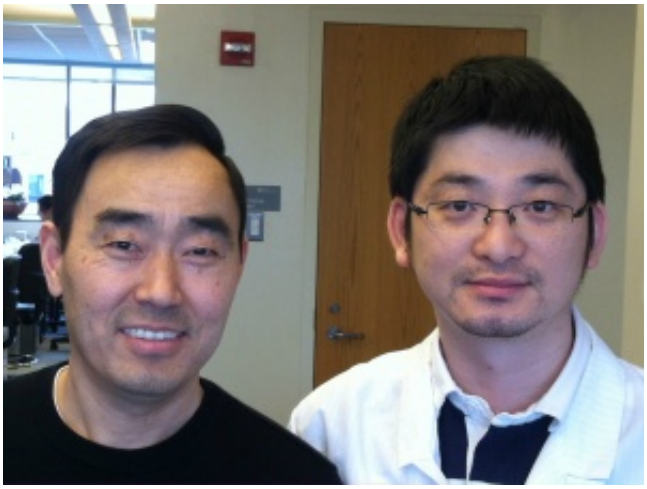
Scientists confirm link between missing DNA and birth defects

March 11 2014, by Katherine Unger Baillie



Jeremy Wang (far left) and Jian Zhou of Penn Vet led the study

In 2010, scientists in Italy reported that a woman and her daughter showed a puzzling array of disabilities, including epilepsy and cleft palate. The mother had previously lost a 15-day-old son to respiratory failure, and the research team noted that the mother and daughter were missing a large chunk of DNA on their X chromosome. But the researchers were unable to definitively show that the problems were tied to that genetic deletion.

Now a team from the University of Pennsylvania and The Children's Hospital of Philadelphia has confirmed that those patients' ailments resulted from the genetic anomaly. Creating mice that lacked the same

region of DNA, the Penn and CHOP researchers showed that these animals suffered the same problems that afflicted the mother, daughter and son—cleft palate, epilepsy and respiratory difficulties, a condition called human Xq22.1 deletion syndrome. And, by clarifying the syndrome's genetic basis, the researchers have laid the foundation for identifying the underlying molecular mechanism of these troubles and potentially treating them at their biological root.

"This study has demonstrated that deleting this region in mice causes them to respond like humans with the same deletion," said P. Jeremy Wang, senior author on the study and professor in the Penn School of Veterinary Medicine's Department of Animal Biology. "Now that we have a mouse model, we can dissect and try to genetically pinpoint which genes are responsible."

Wang co-led the study with his postdoctoral researcher Jian Zhou. Additional coauthors included Penn Vet's N. Adrian Leu and CHOP's Ethan Goldberg, Lei Zhou and Douglas Coulter.

The study appears in the journal *Human Molecular Genetics*.

To investigate the effects of missing this portion of DNA, more than 1 million base pairs long, the Penn team crossed existing mice that had particular deletions in their DNA to create a mouse that lacked the entire stretch that the human patients were missing. They quickly observed that all male mice died at birth due to respiratory failure. Females, who would have one normal X chromosome and one X chromosome with this missing stretch of genetic material, survived but had varying degrees of symptoms including epilepsy, cleft palate and other developmental problems.

"We believe this is because of skewed X chromosome inactivation," Wang said. "In females one of the X chromosomes' expression is

randomly 'silenced' so that males and females have an equal dosage of genetic material from this sex chromosome under normal circumstances. In this case, if more female cells silence the X chromosome that has the deletion, the effects of the syndrome won't be as severe."

To narrow down which part of the deleted genetic material was responsible for the observed birth defects, the researchers genetically engineered one type of mice that lacked the first two-thirds of the original genetic deletion and another type that lacked the final third.

Unexpectedly, the mice lacking the two-thirds of the region on the X chromosome, which included 17 genes, did not display any respiratory failure, cleft palate or epilepsy.

"These mice were fine," Wang said. "It was very surprising to us that deleting this many genes on the X chromosome did not cause apparent problems for the mice."

This was not the case for the mice missing the last 350 kilobase pairs of the region of interest. These mice had the same suite of problems as mice missing the entire region: males died after birth and females had cleft palates, higher rates of death soon after birth, developmental delays and had seizures.

After ruling out the genes in this smaller region that have no equivalent in humans, the researchers were left with only four genes. All four belong to the same family of genes and encode proteins that are involved in cellular signaling.

"These proteins are involved in the neuronal circuitry and activity of neurotransmitters," Wang said. "That is probably why we see that females lacking one copy of these X-linked genes have epilepsy."

Wang and colleagues plan to continue studying these four genes to determine which lead to the developmental problems such as cleft palate and epilepsy when they are missing. The information gained from this and future studies could inform prenatal testing, Wang said, giving doctors advance warning to treat possible respiratory or other problems in newborns.

Understanding how the lack of these genes leads to epilepsy could also help guide treatments for the condition.

"Epilepsy and cleft palate affect tens of thousands of children in the U.S. alone each year," Wang said, "and respiratory failure is a particular problem in premature and low birth weight babies. Finding the causative genes for these conditions could have some very clinically important implications."

More information: dx.doi.org/10.1093/hmg/ddu095

Provided by University of Pennsylvania