

Genetic Cause for Recessive Form of Lethal OI Discovered by Foundation's Medical Advisory Council Member

A previously unexplained form of lethal OI has been shown to result from a genetic defect in *CRTAP*, or cartilage associated protein. *CRTAP* is part of a protein complex that interacts with collagen in the cell. This discovery will greatly improve OI diagnosis and family counseling for people with a family history of lethal or severe OI (similar to Type II or II/III OI), who do not have a collagen mutation. It especially impacts siblings of infants affected with lethal OI, who may themselves carry the recessive gene.

The study was published in the December 28, 2006 *New England Journal of Medicine*. It was led by Joan C. Marini, M.D., Ph.D., at the National Institutes of Health (NIH). Dr. Marini is a past president and long-time member of the OI Foundation Medical Advisory Council. The NIH study built on the research of *Michael Geisman Research Fellow* Roy Morello which appeared in *Cell* in October 2006 and was described in the Winter 2006 issue of *Breakthrough*.

Classical OI results from dominant mutations in the genes for Type I collagen. Only one copy of the mutant gene is needed to cause dominant OI. In this new research, Dr. Marini's group discovered that mutations in the *CRTAP* gene result in a recessive form of the disorder, which requires two copies of the mutated gene to cause OI.

"This discovery provides a basis for counseling families that have lost a child to this previously unexplained form of osteogenesis imperfecta," said Duane Alexander, Director of the National Institute of Child Health and Human Development, the NIH institute that conducted the study. "It also offers insight into a crucial step needed in the formation of bone and other tissues."

Dr. Marini explained that 10 to 15 percent of people with OI do not have a mutation in Type I collagen. The first clue that *CRTAP* was involved in these unexplained cases came when Roy Morello, Ph.D., and Brendan Lee, M.D., Ph.D., both of Baylor College of Medicine in Houston, TX, developed a laboratory mouse that lacked *CRTAP*. The mouse had defective bone formation. The second clue was found through chromosomal mapping. *CRTAP* maps to the same chromosomal location as Type VII OI, a recessive form of moderately severe OI described by Francis Glorieux, M.D, Ph.D., in a Canadian family. The researchers showed that affected individuals in this family have two partially functional copies of the *CRTAP* gene.

The third clue came from the NIH OI Research Program. Dr. Marini noticed over the years that there was a group of children with severe or lethal OI, who had biochemically abnormal collagen but no collagen mutation. Dr. Marini stored the cell samples from these children, one for nearly 15 years, and her lab had been examining candidate genes for these cases for several years. They hypothesized that the culprit would be a protein that interacted with collagen.

CRTAP was a great candidate gene because its protein product is part of a complex that interacts with collagen and its absence in mice decreased bone formation. When Dr. Marini and her coworkers examined the cultured skin cells from these children, they found that three of the children had mutations in both copies of their *CRTAP* gene. These mutations totally abolished gene function, so the infants completely lack the *CRTAP* protein. These children had died during their first year of life. The three patients had symptoms that overlap, but are different from, those of infants with Type II OI. The infants all had small heads and round faces. Most infants with OI have proportionally larger heads and triangular faces. The sclerae, or "whites" of the infants' eyes were white; while in most people with OI, the sclerae are blue. Other differences can only be seen on X-rays.

In the two sets of parents who were available for genetic testing, each parent carried one mutant *CRTAP* gene and one normal *CRTAP* gene, the classical pattern of recessive inheritance. The carrier parents did not have clinical symptoms of OI. Drs. Morello and Lee collaborated on the NIH study, as did David Eyre, Ph.D., at the University of Washington.

Dr. Marini adds that, on the basis of her samples, the mutation does not appear to be connected to a particular ethnic group. Dr. Marini estimates that this recessive form of OI might occur in 2-3 percent of lethal OI cases. These cases provide more information about Type VII OI, in which *CRTAP* mutations that leave partial gene expression cause moderately severe OI, while mutations that abolish *CRTAP* expression are lethal.

This discovery will allow families who have lost a child to OI to be tested for the presence of the recessive *CRTAP* gene. Parents who have lost a child to this form of OI have a 25% risk of having another child with severe/lethal OI with each pregnancy. There is also a 50% chance that each sibling of an affected child will be a carrier of the recessive gene. If a carrier sibling marries someone who also has the recessive gene, then they too will have a 25% risk of having a child with severe or lethal OI.

According to Dr. Marini, "Scientifically, this new information is very exciting to bone researchers because it offers a new perspective on bone disease. Many new studies will focus on why this protein is so important for bone and its role in normal bone formation. For example, the NIH team is already working to understand the role of *CRTAP* in normal bone development. Since *CRTAP* protein occurs elsewhere in the body, it may play an important role in the development of multiple organs, such as heart, kidney and lung. This may explain why these children die of respiratory failure."

The discoveries on *CRTAP* mean that diagnosis and counseling for parents with a severe or lethal newborn must include both the possibility of collagen and *CRTAP* mutations. Testing is available from:

OI Research Program at NICHD
301-496-0741
Fax: 301-480-3188
oiprogram@mail.nih.gov
<http://www.oiprogram.nichd.nih.gov>

Baylor Medical Genetics Laboratories
1-800-411-GENE (4363)
Fax: 713-798-6584
geneticstest@bcm.edu
<http://www.bcm.edu/geneticlabs>

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