Recessive Form of OI Discovered by Foundation-funded Researcher

Medical Advisory Council Members Collaborate to Speed Results

An important article on the genetics of OI was published in the October 19, 2006 issue of *Cell*, a prestigious medical journal. The research by OI Foundation Michael Geisman Research Fellow Roy Morello, Ph.D., identifies a recessive form of OI. This will greatly improve OI diagnosis and family counseling for people with a family history of lethal or severe OI (similar to Types II and III), or Type VII OI who do not have a collagen mutation.

The research studied a protein called CRTAP (Cartilage Associated Protein) that is important for bone formation. Dr. Morello's mouse studies first showed the importance of this protein for bone, leading the way for human genetic studies. When the researchers found that CRTAP was in the same chromosomal location as Type VII OI, the genetic connection was made. When CRTAP is in low supply it causes the mild bone fragility of Type VII OI. When it is absent it causes more severe symptoms that are similar to Types II and III OI.

Important discoveries often are the result of teamwork. OI Foundation Medical Advisory Council members Francis Glorieux, MD, PhD, Shriners Hospital for Children, Montreal; Peter Byers, MD, University of Washington; and Joan Marini, MD, PhD, National Institutes of Health; contributed to this research. Dr. Glorieux discovered the Type VII form of OI. Dr. Byers provided severe OI tissue samples. Independent research from Dr. Marini identified mutations in the identical gene in several cases of recessive lethal OI.

This research provides new information about how OI is inherited for families of children with lethal or severe OI similar to Types II, III, and VII OI. Up to now, research indicated that almost all cases of OI were caused by a dominant genetic mutation in the Type I collagen genes, meaning that only one copy of the OI gene would be necessary for a person to have OI. The gene is either inherited directly from a parent who has OI or results from a new genetic change at the time of conception. This new research found that lethal or severe OI can also be associated with a recessive form of inheritance caused by changes in the CRTAP gene. In this situation, the parents do not have OI, but unlike in the dominant cases, they carry a mutation for it in their genes. For a child to have OI, he or she must inherit the OI-causing CRTAP mutation from both parents.

This study also provides an explanation for families in which the parents do not have OI, but one or more of their children does. Up until now, this occurrence had been explained as "mosaicism." Mosaicism means that one parent carries the dominant OI mutation in a percentage of the cells that give rise to the sperm or eggs. Parents who have had a child with Type II or III OI have a 2-4% risk of having another child with OI because of this mosaicism. This new research shows that if parents have a mutation in one of their CRTAP genes, they are not "mosaics". Rather, they are carriers for the newly-identified recessive form of OI. If a child with OI has this new recessive form, then his/her parents have a 25% risk with each pregnancy, of having another child with OI. There is also a 50% chance that each sibling will be a carrier of the recessive gene.

A third area addressed by this research involves the proportion of OI cases caused by collagen mutations. While most cases of OI involve a mutation in the important type I collagen proteins, approximately 10-15% of people who are clinically diagnosed with OI do not have a collagen mutation. This research shows that many (but not all) cases of severe or lethal OI which have a positive biochemical test but do not have a collagen mutation are caused by lack of CRTAP.

This research will lead to several changes in how OI is diagnosed and in the counseling families receive. It is also possible that additional research will find differences in response to treatments between the dominant and recessive forms of OI.

New diagnostic tests based on this research have been developed at Baylor College of Medicine in Houston, TX, and at the National Institutes of Health (NIH) in Bethesda, MD. This will be useful to parents who do not have a family history of OI, and who want to have a better understanding of the likelihood of having more than one child with OI. It will be helpful for parents and people with clinically-diagnosed severe or lethal OI similar to Types II, III, or VII OI who do not test positive for a collagen mutation but have a positive collagen biochemical test. It will also be helpful for their brothers and sisters who are seeking advice about their likelihood of having a child with OI. The new diagnostic test at Baylor will use a DNA (blood) sample. The new diagnostic test at the NIH will use either a blood sample or skin biopsy. Eventually it should be possible to test for CRTAP and a collagen mutation using the same sample. There is

Who will benefit from this Research?

Parents with no history of OI in their family, who want to have a better understanding of the likelihood of having more than one child with OI.

Parents whose children have clinically-diagnosed Type II, III, or VII OI but do not test positive for a collagen mutation, who want to have a better understanding of the likelihood of having more than one child with OI.

People with clinically-diagnosed Type II, III, or VII OI who do not test positive for a collagen mutation, and their brothers and sisters, who want advice about the likelihood of having a child with OI.

no data at this time showing that CRTAP can be used to diagnose Type I OI.

Information about the new test is available from:

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

OI Research Program at NIH
301-496-0741
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http://www.oiprogram.nichd.nih.gov/

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CRTAP is Required for Prolyl 3-Hydroxylation and Mutations Cause Recessive Osteogenesis Imperfecta, Roy Morello et al. Cell 127, 291-304, October 20, 2006.

Recessive lethal form of osteogenesis imperfecta caused by null mutations in CRTAP, American Society of Human Genetics annual meeting, New Orleans, 2006, Abstract 280.

News Article in The Scientist:
http://www.the-scientist.com/news/display/25107