New gene discovered for recessive form of brittle bone disease

January 20 2010

Researchers at the National Institutes of Health and other institutions have discovered the third in a sequence of genes that accounts for previously unexplained forms of osteogenesis imperfecta (OI), a genetic condition that weakens bones, results in frequent fractures and is sometimes fatal.

The newly identified gene contains the information needed to make the protein Cyclophilin B. This protein is part of a complex of three proteins that modifies collagen, folding it into a precise molecular configuration, before it is secreted from cells. Collagen functions as molecular scaffolding that holds together bone, tendons, skin and other tissues.

Most types of osteogenesis imperfecta result from a dominant mutation in collagen itself, requiring only one copy of the mutated gene to bring about the disorder. Osteogenesis imperfecta involving the Cyclophilin B gene is a recessive trait, requiring two defective copies of the gene to cause the disorder.

"The discovery provides insight into a previously undescribed form of osteogenesis imperfecta," said Alan E. Guttmacher, M.D., acting director of NIH's Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD). "The advance also provides new information on how collagen folds during normal bone formation, which may also lead to greater understanding of other bone disorders."

The finding was published online Jan. 20 in the New England Journal of

Medicine. The investigation involved a collaboration between researchers at the NICHD, led by Dr. Joan Marini, and the Hospital for Special Surgery in New York City. There, Dr. Cathleen Raggio diagnosed the children in the study as having a novel form of OI. In addition, researchers at the University of Washington in Seattle and the NIH's National Institute of Human Genome Research also took part in the study.

The NIH's National Institute of Arthritis and Musculoskeletal and Skin Diseases estimates that in the United States a minimum of 20,000 and possibly as many as 50,000 people are affected by osteogenesis imperfecta. About 85 percent of all OI cases are caused by mutations in the genes that contain the information needed to make collagen.

Researchers at the NICHD and other institutions had earlier learned that osteogenesis imperfecta could also be caused by defects in the protein complex that modifies collagen into its final form. Joan Marini, M.D., Ph.D., chief of NICHD's Bone and Extracellular Matrix Branch and colleagues had discovered that recessive mutations in the genes for two proteins in the complex, cartilage associated protein, or CRTAP, and prolyl 3-hydroxylase 1 (P3H1), could result in severe forms of osteogenesis imperfecta. Individuals with mutations in CRTAP have all died in childhood. Mutations in P3H1 are sometimes fatal in early life.

In the current study, the researchers determined that a 12-year-old boy and his 4-year-old sister had mutations in the gene for Cyclophilin B. The children's parents were immigrants from Senegal, consanguineous (blood relatives) and were living in New York. Although the children's bones were brittle and highly susceptible to fracturing, they did not have shortening of the upper portion of limbs (rhizomelia) seen in the children with mutations in CRTAP and P3H1.

Proteins must be carefully folded into distinct configurations needed to

function. Dr. Marini explained that a previous study concluded that Cyclophilin B was essential for folding collagen into its final form. In the current study, however, she and her coauthors found that the collagen from the two children was folded into its usual configuration, strongly suggesting that Cyclophilin B is not uniquely involved in its role in collagen folding, and that another, currently unknown, protein must also be involved.

Dr. Marini noted that additional research is needed to determine why, despite the seemingly normal collagen folding, the children with the recessive mutation in Cyclophilin B developed osteogenesis imperfecta.

Provided by NIH/National Institute of Child Health and Human Development