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New answers on multiple hereditary exostoses, rare childhood disease

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Children born with multiple hereditary exostoses (MHE) suffer from abnormal growths on their bones. These bony protrusions stunt their growth and can cause pain and disfigurement. Scientists have long known which genes are mutated in this rare disease, but not how the mutations lead to abnormal bone growth. Even attempts at replicating the symptoms in mice have been unsuccessful, hampering the search for treatments. In a study published May 31 in *Proceedings of the National Academy of Sciences*, researchers at Sanford-Burnham Medical Research Institute created a new mouse model that mimics the disease in humans, providing new opportunities to test treatments.

"MHE is not usually deadly, but it is debilitating," said Yu Yamaguchi, M.D., Ph.D., senior author of the study and professor in the Sanford Children's Health Research Center at Sanford-Burnham. "And if not removed by surgery, there is a chance these bone growths will become cancerous."

In humans, MHE is caused by a mutation in one of two genes, Ext1 or Ext2. Together, these genes encode an enzyme necessary to produce heparan sulfate—a long sugar chain that facilitates cell signals that direct bone cell growth and proliferation. But when these genes were inactivated in mice just as they are in human MHE patients, the mice failed to develop the symptoms of MHE. This had scientists scratching their heads.

Enter Dr. Yamaguchi and his colleagues, who took a different approach.

Instead of knocking out the Ext1 gene in the whole mouse, they targeted the gene only in bone cells. Moreover, they deleted the gene in only a small fraction of these cells. Surprisingly, this minimalistic approach led to a mouse with all the physical manifestations of MHE, such as bony protrusions, short stature and other skeletal deformities.

The new mouse model answered some long-standing questions about MHE. Scientists had gone back and forth on whether the abnormal growths observed in MHE are true tumors or just malformations of the bone. In this study, the protrusions were made up of two cell types. A minority were mutant cells lacking Ext1, but, amazingly, most were normal bone cells. True tumors, in the strictest sense, arise from the proliferation of mutant cells only. Hence, MHE bone protrusions must result from a different - though still very serious - type of growth.

"I have been waiting 13 years for this breakthrough," said Sarah Ziegler, vice president of The MHE Research Foundation, which has provided seed funding for Dr. Yamaguchi's research. "My son had more than a 100 of these tumors and has gone through 15 surgeries. When your child has such a debilitating condition, and you know there's nothing you can do, it's petrifying. Now we have hope."

While this study takes MHE research a giant step forward, more questions remain. For one, it is still unknown how a few mutant bone cells can convince normal cells to divide and proliferate abnormally. Researchers hope that this MHE model will help solve that mystery, as well as provide leads for new treatments.

"This new mouse system also provides a platform for screening potential drugs that inhibit bone growths in MHE," Dr. Yamaguchi explained. "We are currently developing chemical inhibitors to block their formation."

More information: Matsumoto K, Irie F, Mackem S, Yamaguchi Y. A mouse model of chondrocyte-specific somatic mutation reveals a role for Ext1 loss of heterozygosity in multiple hereditary exostoses. Proceedings of the National Academy of Sciences USA. Epub 2010 May 31.

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