First gene for clubfoot identified

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Clubfoot, one of the most common birth defects, has long been thought to have a genetic component. Now, researchers at Washington University School of Medicine in St. Louis report they have found the first gene linked to clubfoot in humans. Their research will be published in the Nov. 7 issue of the *American Journal of Human Genetics*.

By studying a multi-generation family with clubfoot, the scientists traced the condition to a mutation in a gene critical for early development of lower limbs called PITX1. While other genes are also likely to be linked to clubfoot, the new finding is a first step toward improved genetic counseling and the development of novel therapies.

"To our knowledge this report is the first evidence for PITX1 mutation in human disease," said Christina Gurnett, M.D., Ph.D., assistant professor of neurology, of pediatrics and of orthopedic surgery at the School of Medicine. "Once we identified the mutation, we proved that all of the individuals in this family with lower extremity malformations also have the mutation. Having large families to work with is very helpful in genetic research."

Gurnett and her colleagues analyzed the DNA of 35 extended family members of an infant male patient of Matthew Dobbs, M.D., associate professor of orthopedic surgery at the School of Medicine and a clubfoot specialist at St. Louis Children's Hospital and St. Louis Shriners Hospital. The patient, the most severely affected in the family, had clubfoot in both feet, duplicated first toes and was missing the tibia in the right leg.

Gurnett and Dobbs visited the family members in their community to examine their lower limbs and to take DNA samples. They found that 13 family members were affected: Five additional family members had clubfoot, which was more severe in the right foot in three of them. Five others had lower limb abnormalities including flatfoot, an underdeveloped patella and hip dysplasia.

Through the genome-wide study, Gurnett and her colleagues found a region on chromosome 5 that was common to all family members affected. From there, they identified a mutation in a gene critical for early development of lower limbs called PITX1. The PITX1 mutation was found in all affected family members and in three carriers who showed no clinical symptoms.

Dobbs, senior author of the study, said the finding is an exciting step in developing a better understanding of the genetic basis of clubfoot, which affects about 1 in 1,000 new births.

"Clubfoot is a complex disorder meaning that more than one gene as well as environmental factors will be discovered to play a role in its etiology," Dobbs said. "Identifying the genes for clubfoot will allow for improved genetic counseling and may potentially lead to new and improved treatment and preventive strategies for this disorder."

Dobbs treats children with clubfoot and other orthopedic abnormalities using the Ponseti method, a treatment that involves weekly casting and the manipulation of clubfoot soon after birth. In 2007, Dobbs developed a new dynamic brace called the Dobbs brace for clubfoot that allows active movement, preservation of muscle strength in the foot and ankle and fewer restrictions on the child than the traditional brace.

About 80 percent of clubfoot cases are idiopathic, meaning the cause is unknown and the patient has no other birth defects. A familial link plays

a role in about 25 percent of cases. The condition occurs in males twice as often as in females and occurs more often in the right foot. About half of the cases affect both feet, including the bones, muscles, tendons and blood vessels. If untreated, those affected walk on the outside of their feet, which can lead to long-term pain and disability.

Gurnett said some clinical characteristics of the family members with the PITX1 mutation suggest that the genetic defect may be linked to idiopathic clubfoot. First, the majority of the affected family members had clubfoot, but no other abnormalities. Second, there were five females who carried the gene but did not have clubfoot, which supports the lower incidence of clubfoot in females. Third, clubfoot affects the right foot more frequently, a hallmark of mutations in PITX1.

Previous studies had shown a relation between PITX1 and the development of hindlimbs in other vertebrates. In mice, a loss of PITX1 leads to shorter femur length and fewer digits on the right foot than on the left. An alteration of the gene in a developing chick wing changes it so that it looks more like a leg. In vertebrates such as the manatee and stickleback fish, an alteration has resulted in evolutionary changes in the development of the pelvis.

"It's our job to prove that this is going to be important for many kids with clubfoot," Gurnett said. "Until now, we didn't know whether clubfoot was a muscle, nerve, spinal cord or brain problem. Now, we have an idea that clubfoot may result from mutations of genes that are involved in early limb development."

Gurnett said she and her colleagues will take the finding back to the lab to look for other factors involved in the pathway or how environmental effects may influence the gene. She and Dobbs, who have been studying the genetics of clubfoot for a decade, plan to investigate the frequency of PITX1 gene mutations in other families with clubfoot.

Source: Washington University School of Medicine