



# Research Connections

News and Events in Shriners Hospitals for Children's Research Department

September 2013

## **Distal Arthrogyposis: *Understanding the Gene Responsible for this Disease of Limb Contractures***

*Distal Arthrogyposis* is a disorder in which contractures of the limbs make it difficult for a child to move their hands and feet normally. The disorder affects approximately 1 in 10,000 children worldwide. Many children have clubfeet or vertical talus, contractures of the hands, and some more seriously affected individuals also have contractures of the face.



Pediatric hand contracture arthrogyposis



Image of a pediatric clubfoot associated with arthrogyposis

Treatment for both vertical talus and clubfoot associated with arthrogyposis has traditionally involved extensive surgery which is associated with many short and long-term complications. For those reasons Dr. Matthew Dobbs at the Shriners Hospital-St. Louis, has pioneered with good results minimally invasive treatment methods for both clubfoot and vertical talus in patients with arthrogyposis. Though outcomes are better, treatment is still involved and requires weeks of casting and years of bracing. Further improvements in treatment for this patient group, depends on gaining further insight into the cause of arthrogyposis.

Our understanding of the causes of distal arthrogyposis has improved tremendously over the past ten years, particularly as the genes responsible for familial cases have been identified. Many of these genes are important for normal muscle function.

However, translation of gene discoveries into new methods of treatment for distal arthrogyriposis has not yet occurred. Now, as a first step toward that goal, Dr. Dobbs and his colleagues at Washington University, have developed a model of human distal arthrogyriposis using a very small and popular aquarium fish called a zebrafish. The zebrafish has become a widely used scientific tool because fish have large numbers of offspring, and because development occurs rapidly in a transparent embryo. The arthrogyriposis zebrafish studied by Dr. Dobbs has a slightly flexed trunk and does not swim well because it makes a protein which contains the same human gene mutation that gives rise to this disease. Although this protein is a rare cause of arthrogyriposis, similar studies can now be performed with other genes that cause the disease to see if the same mechanisms apply.



Picture of the zebrafish (control) used in Dr. Dobb's research



Picture of the arthrogyriposis zebrafish in Dr. Dobb's research

By studying human mutations in zebrafish, Dr. Dobbs determined which human gene variants were disease causing and which were not, a not so trivial question when we consider the large number of gene variants that we all have in our genome. Children with arthrogyriposis may be tested clinically to determine if they have mutations in “arthrogyriposis” genes, though at least half of all children will not have a mutation in the currently known genes. Many genetic test results are returned to the patient as being inconclusive because a “gene variant of unknown significance” is found. Zebrafish studies may ultimately improve diagnostic accuracy for distal arthrogyriposis because they can help determine that the variant is actually disrupting the normal function of the gene, and is therefore a disease ‘mutation’.

This research also opens up the possibility of using zebrafish to identify drugs that can lessen the impact of these mutations on muscle function. This would be an improvement over current treatments for distal arthrogyriposis that typically consist of physical and occupational therapy, casting and surgery.

Dr. Dobb's team and Shriners Hospitals for Children, hope that their dedication in research with zebrafish will eventually lead to a new treatment for this disorder and improve patient's care.