

Muscular dystrophy: a genomic diagnosis

GROWING UP on a farm in northern Minnesota, Shirley Ross experienced pain while performing her daily chores. Her earliest memories started at the age of five. "I would go to wring out a rag and my hands would be stuck. I couldn't open them." Ross did not think anything of this, since the same thing was happening to her siblings and father. Forty years later, after struggling with progressive weakness, fatigue, body soreness and muscle cramps, Ross was diagnosed with myotonic muscular dystrophy type 2 (DM2).

Myotonic dystrophy is the most common form of muscular dystrophy in adults. It is characterized by stiff muscles, general fatigue and weakness, early onset cataracts, heart arrhythmias, diabetes and, in men, testicular failure and balding. The disease is genetically caused by either of two recognized mutations, though in both recognized types it can escape detection in a family for several generations before significant symptoms appear. In Ross' family, six of her seven siblings also tested positive for the disease. It is suspected that her father had the disease as well, although he died before the diagnostic test for it was available.

Researchers John Day, M.D., Ph.D., and Laura Ranum, Ph.D. are co-directors of the Paul and Sheila Wellstone Muscular Dystrophy Center at University of Minnesota, where they have been working to understand and treat all forms of muscular dystrophy. Part of that work involves studying families like Ross' to find the faulty gene that causes this debilitating disease.

A Minnesota Discovery

Although the genetic abnormality responsible for the first type of myotonic dystrophy (myotonic dystrophy type 1, or DM1) was discovered in 1992, Ranum and Day showed in 1998 that many Minnesota families had a different form of myotonic dystrophy. In 2001, they discovered the genetic change on chromosome 3 that causes DM2. "Normally, DNA contains a message that is rewritten in RNA before being used to make

a protein," Ranum explained. "The dogma had always been that genetic diseases were caused by a change in DNA that resulted in the loss of a protein product or in the production of an abnormal disease-causing protein. RNA was

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Muscular Dystrophy Center

considered merely the messenger in charge of a relatively neutral intermediary step in this process." Ranum and Day's research found this classic disease model to be incomplete. They discovered that in DM2, the genetic change formed a disease-causing strand of RNA but did not affect a protein at all — the DM2 mutation was in a portion of a gene that doesn't code directly for a protein and thus previously would not have been predicted to cause disease. Their discovery led to the realization that genetic changes that are expressed in abnormal RNA cause both types of myotonic dystrophy.

A New Genomics Test

As a result of the genetic discovery, Day and Ranum developed a reliable test for DM2 in 2003 — a challenging task because specific features of the genetic mutation in DM2 vary dramatically from person to person. Initial results of this test indicate that DM2 is much more common than previously thought. "Until now, myotonic dystrophy type 2 has been very difficult to diagnose," says Day. "People with the disorder have seen different clinical specialists about seemingly unrelated symptoms, without either patient or physician recognizing the underlying cause."

This discovery has led to a better understanding of how the genetic changes cause myotonic dystrophy. "Being able to diagnose these patients means we can stay a step ahead with their

treatment," says Day. Researchers now realize that altered RNA processing can cause disease, which has opened up several new therapeutic options for this common form of muscular dystrophy. Ranum and Day are currently developing a mouse model to see how RNA acts at the cellular level. They hope this model will help them find ways to repair the damage for muscle in all muscular dystrophy patients.

For Shirley Ross, these discoveries give her hope. Now a grandmother, Ross has children and grandchildren who show signs of DM2. "Right now there is no treatment for us, but I have hope that they will come up with a cure for my children." ■

The Minnesota Partnership for Biotechnology and Medical Genomics is a Minnesota initiative leveraging the scientific leadership of the University of Minnesota and Mayo Clinic into a powerful research collaboration.

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