Dr. Miller: Cracking the Code for Idiopathic Scoliosis

OREF Career Development Award is the key to continuing the search for what causes spinal deformity, generation after generation

Research Summary

Nancy H. Miller, M.S., M.D.

2001 Career Development Award recipient

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Topic:

Studying which genes cause familial idiopathic scoliosis, and what specific mutations lead to the disease.

Result:

Chromosomes 1, 6, 8, 9, 16, and 17 showed the strongest linkage to idiopathic scoliosis.

Potential Patient Care Application of Results:

Potential screening for at-risk individuals, development of more specific treatments through tailored therapies and counseling, and an increased understanding of how genetics influence spinal growth and stability.

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The diagnosis of familial idiopathic scoliosis, the condition of side-to-side curves in otherwise normal spines, is heading toward a breakthrough. **Nancy H. Miller, M.S., M.D.**, associate professor, department of orthopaedics at Johns Hopkins University*, is leading the way.

In generation after generation, scoliosis brings certain families physical deformity and emotional pain, both of which can be severe. Familial idiopathic scoliosis affects 2% to 3% of the population; 90% of the patients who necessitate surgical intervention are female. There is no cure, and only bracing and surgery are available for treatment.

Dr. Miller is renowned for her work — as a researcher, teacher, and clinician — to decipher the genetics of scoliosis, a condition she first encountered as a pediatric orthopaedics resident at Boston University.

"When we got down to the scoliosis clinic in the hospital, all these kids — all these pre-adolescent females — wanted a woman resident," Dr. Miller said. "I was intrigued. But my real interest in going after scoliosis came from working with Dr. Ponseti."

Just prior to the emergence of molecular genetics, Dr. Miller began looking at the pathology of scoliosis as a research fellow under **Ignacio V. Ponseti, M.D.** at the University of Iowa. She devised a series of experiments examining the ligaments of the spine, a highly organized network of elastic fibers that connect the bones of the spinal column.

"There was a thought that perhaps the elastic fiber system had something to do with the development of scoliosis. It could be easily looked at, because one of the ligaments in the spine has a significant percentage of elastic fibers. So you could take that to the laboratory and look at it through a microscope. You could look at the cells and how they expressed different aspects of the elastic system. It turned out to be relatively fruitful."

As Dr. Miller moved into clinical practice, her focus turned to how individual proteins that make up spinal ligaments — including collagen, elastin, and fibrillin — affect spinal stability. **This work was supported in part by a 1991 OREF Research Grant.** Soon, genetic investigation became possible. Dr. Miller began gathering data and insight on families, at the point when researchers working on the human genome project had identified some genes, by making visits to families with a history of scoliosis.

> *"Patients have become much more knowledgeable regarding their conditions and current research efforts. Choices are going to be made by patients, influenced by how much their surgeons know."*

"On one of the family visits, the grandmother ran out of the room in tears. She has five beautiful granddaughters, and three of them are in braces. I think it hit her that she's the one with scoliosis; she feels responsible."

Candidate-gene and, later, sequencing studies led to Dr. Miller receiving the **2001 OREF Career Development Award.** The $225,000 OREF Award made it possible for Dr. Miller to assemble a critical mass of data,

Nancy H. Miller, M.S., M.D. (left) and Laboratory Administrator and Technician, Beth Marosy, M.S., pose near an X-ray of a scoliosis patient. Dr. Miller is holding the model she uses to explain scoliosis when she visits families.

which was the basis for securing critical support from the Center for Inherited Disease Research (CIDR) — in excess of $2 million — for a genome-wide scan of the entire population under study. It was one of the largest projects their review board had approved.

"I had identified the disease. I had my population. My population was very well described through highly detailed clinical information. I actually had the genome-wide research in hand with the statistical package behind it. That's when NIH said, 'We'll fund you,' at a time when funding for studies of complex disorders was difficult to obtain. **There would be no way I could have done this without the OREF Career Development Award. It was a big step up."**

Since then, promising pathways have surfaced. By 2005, chromosomes 1, 6, 8, 9, 16, and 17 showed the strongest linkage to idiopathic scoliosis. Now Dr. Miller is about to publish evidence that chromosomes 5, 13, and 19 also figure in.

Building blocks for a cure are yet to come. Still, Dr. Miller believes her research is a source of hope. Even for families for whom answers will come too late, knowing that the research is continuing brings some comfort.

"One woman called me and wanted to know where we were on our research. She and her husband had already decided, due to her scoliosis, not to have children. 'I couldn't have children,' she said. 'My life is just misery from day to day. I've had five back surgeries and I'm not even 40. I couldn't give this to anybody.'"

Looking forward, Dr. Miller sees the possibility of a screening test and more specific therapeutic options to help larger numbers of families. But more research — and more funding — are needed. Dr. Miller says all orthopaedic surgeons have a vested interest in supporting OREF.

"To be a better clinician your knowledge base in orthopaedic research needs to have a foundation. Patients have become much more knowledgeable regarding their conditions and current research efforts. Choices are going to be made by patients, influenced by how much their surgeons know."

*Dr. Miller will be Professor of Orthopaedics, University of Colorado, Denver in October 2006. ■

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