RESEARCH UPDATE

"Researchers should consider *MOZ* activity as a factor causing variability in DiGeorge syndrome and 22q11 deletion syndrome," Dr. Voss says.

Research Implications

Voss's findings are important because they point to a mechanism at play in more severe disease, says Paula Goldenberg, MD, Assistant Professor in the University of Cincinnati School of Medicine's Department of Pediatrics in Ohio. "Histone acetylates like *MOZ* may have something to do with it," Dr. Goldenberg says. "If we know the mechanism for more severe disease, we may determine for parents whether or not their children might be at risk for the more severe phenotype."

Previous research has found that common mutations in *Tbx1* do not explain variable cardiovascular expression in more than 1,000 patients with 22q11 deletion. Instead, studies have implicated the existence of modifiers in other genes on 22q11, and elsewhere in the genome (Guo et al., 2011). In contrast, Dr. Voss's paper suggests new pathways to examine, says Bernice Morrow, PhD, Director of the Division of Translational Genetics at Yeshiva University's Albert Einstein College of Medicine in New York.

"The connection between *MOZ* and retinoic acid—that a *MOZ* mutation sensitizes an embryo to retinoic acid—is as interesting as the interaction between *MOZ* and Tbx1 because it's an environmental factor," adds Dr. Morrow. "People want to know: Could alterations in genes or their expression increase sensitivity to environmental exposure? That's what this paper implies. We all know environment can play a role in congenital heart disease. This paper connects *MOZ* activity to the environment."

However, any future research that better explains the link would need to be proven in humans to have any clinical relevance, Dr. Morrow points out. "This paper won't help a child with DiGeorge syndrome right now, but it's a tool for understanding how environmental signals can regulate genes," she adds.

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TESTING UPDATE

NEWBORN SCREENING FOR DUCHENNE MUSCULAR DYSTROPHY GAINS SUPPORT

Researchers to push for federal recommendation to have states add DMD test to newborn panel

Spurred by recent research showing successful newborn screening of Ohio newborns for Duchenne muscular dystrophy (DMD), some researchers and advocates plan to ask the federal Department of Health and Human Services (HHS) to recommend that states add the disorder to newborn screening panels.

Researcher Jerry Mendell, MD, is considering nominating DMD for a Secretary's Advisory Committee on Heritable Disorders in Newborns and Children (SACHDNC) newborn screening recommendation. SACHDNC's recommendation must precede any from HHS. States make their own decisions regarding what to include on newborn screening panels, but are usually influenced by HHS's recommendation.

"Widespread newborn screening will allow early intervention and give us a better chance of helping kids with Duchenne muscular dystrophy, the most common and severe form of MD," says Dr. Mendell, a Pediatric Research Professor of Pediatrics and Neurology at Ohio State University in Columbus, Ohio, Director of the Paul D. Wellstone Muscular Dystrophy Cooperative Research Center, and Director of the Center for Gene Therapy at Nationwide Children's Hospital, both in Columbus.

DMD, a form of muscular dystrophy occurring in about 1 in 3,500 boys, causes progressive loss of muscle function and weakness beginning in the lower limbs. Patients can't make the protein dystrophin because of a mutation in the gene that expresses it. Boys with this X-linked recessive disorder suffer a steady decline in muscle strength until about age 11, usually resulting in the need for leg braces and ultimately, wheelchairs, and generally live only until age 30.

Most boys with DMD don't get a definitive diagnosis until shortly before their fifth birthday, says Christopher Cunniff, MD, Professor of Pediatrics at University of Arizona College of Medicine in Tucson, and an investigator with the Muscular Dystrophy Tracking and Research Network. Parents first notice DMD symptoms at a mean age of 2.5 years, but boys don't have related primary care examinations until a mean age of 3.6 years and don't get initial tests of creatine kinase (CK), a muscle damage marker, until age 4.7. (Ciafaloni et al., 2009)

A symposium held last September

on newborn screening for DMD was sponsored by the Muscular Dystrophy Association (MDA), and co-chaired by Dr. Mendell and Michele A. Lloyd-Puryear, M.D., Ph.D., Senior Medical and Scientific Advisor at the National Institutes of Health (NIH). Researchers at the symposium examined successes and challenges faced by the Ohio pilot screening program, how other disorders got screening recommendations from HHS, and current evidence about specific therapies for DMD.

Newborn Screening Requirements and Related Evidence

Part of the symposium discussion focused on SACHDNC and HHS criteria for recommending that states screen newborns for particular conditions, which generally follow Wilson-Jungner guidelines. The guidelines specify that the disease must be detectable and treatable in early stages, its progression well understood, and the screening test both effective and economical.

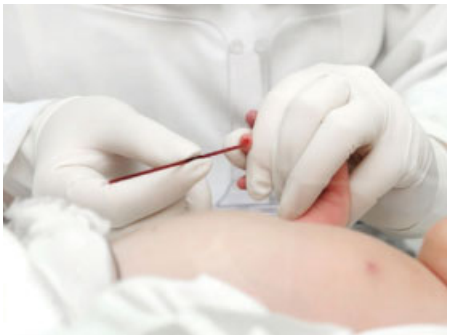
An Ohio DMD pilot newborn screening program detailed at the MDA symposium demonstrated that such testing is efficacious and cost-effective, Dr. Mendell says. His research from that pilot, published in the March 2012 *Annals of Neurology*, details the use of two blood spots which allowed initial CK testing, with follow-up on DNA.

Using a CK threshold of 2,000 U/I, the scenario had only a 0.3% false positive rate and added about $1 to the per-infant cost of newborn screening. In a population of 37,649 newborn boys, researchers found six with DMD gene mutations. In boys with CK levels above 2,000 U/I without mutations, the researchers identified limb-girdle muscular dystrophy gene mutations affecting the genes *DYSF*, *SGCB*, and *FKRP* (Mendell et al., 2012).

Regarding the progression of DMD and its early detection, Mendell points to research showing that it begins early in embryonic development due to stem cell loss and disrupted skeletal muscle formation (Merrick et al., 2009). Other research by Dr. Mendell—under review for publication in *Neuromuscular Disease*—demonstrates that apart from increases in CK, detectable motor delay also occurs in infants and toddlers with DMD.

Steroids are a widely accepted and effective DMD treatment. Guidelines from the American Academy of Neurology (AAN) and the Child Neurology Society, issued in 2005 and reaffirmed by AAN in 2008, recommend prednisone to slow muscle deterioration, prolong walking, and stabilize lung function. Deflazacort, a drug similar to prednisone, is also recommended as a treatment option, but is not available in the United States. Prednisone can also reduce risk of scoliosis (Bushby et al., 2009).

Experimental therapies may someday provide other treatment strategies. Unpublished data presented



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A push to test newborns for Duchenne Muscular Dystrophy has backing from some researchers.

by Dr. Mendell at the International World Muscle Congress show that Eteplirsen, an exon-skipping therapy using antisense oligonucleotides, increases expression of dystrophin and significantly improves walking function. This treatment is complementary to corticosteroids, and both treatments are more effective in earlier stages of the disease, he says. The drug targets "out-of-frame" deletions in the dystrophin gene in exons 45-50; 47-50; 48-50; 49-50; 50; 52; and 52-63. The negative effects of these mutations—estimated to affect about 13% of the DMD population—can potentially be lessened by skipping exon 51, according to the MDA.

Not Ready for Newborn Screening, Some Say

DMD isn't a disease that fulfills all the traditional criteria for newborn screening right now, maintains R. Rodney Howell, MD, former chair of SACHDNC, Professor and Chair Emeritus of Pediatrics at University of Miami Miller School of Medicine in Florida, and MDA's Chairman of the Board.

While Mendell's Ohio-based study produced exciting results, it isn't large enough to convince SACHDNC, Dr. Howell notes. "In newborn screening, 37,000 is small. The U.S. screens 4.2 million babies a year, so a recommendation from the advisory committee requires even more extensive validation," he adds. Dr. Mendell is aware the committee will likely want more evidence. "SCID was originally rebuffed," he said, but after advocates resubmitted their nomination with more comprehensive data, SCID earned an HHS recommendation last year.

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