NEUROSCIENCE TODAY, NEUROLOGY TOMORROW

Genetic Model Proposed for Facioscapulohumeral Muscular Dystrophy

New insights into the genetic basis of facioscapulohumeral muscular dystrophy, one of the more common forms of muscular dystrophy, suggest that the disorder may arise only in people with specific chromosomal variants that permit the unusual stability of a pathogenic gene transcript.

Prior to the current discovery by Richard J.L.F. Lemmers, Ph.D., of Leiden (Netherlands) University Medical Center and his colleagues (Science 2010;329:1650-3), the complexity of the genetic setting in which facioscapulohumeral muscular dystrophy (FSHD) develops has long hampered efforts to unravel the pathogenic mechanism of the disease.

Most people have a long repeated sequence of nucleotide bases called a macrosatellite repeat array on chromosome 4q35. In healthy people, this 3.3-kilobase sequence on 4q35, called D4Z4, repeats 11-100 times. Patients with autosomal dominant FSHD have a shortened array, with only 1-10 D4Z4 units. At least one D4Z4 unit is necessary to cause FSHD. A nearly identical repeat array also occurs on chromosome 10q, but a decrease in the number of repeated units on that chromosome has not been known to cause FSHD.

Other studies have shown that translocated copies of the repeated units from either chromosome 4 or 10 are often found on the end of either chromosome. But FSHD is known to occur with only certain variants of the repeat array that is found on the end of chromosome 4q.

The major transcript from each D4Z4 unit is the DUX4 gene, which codes for a double homeobox protein. But none of these transcripts has appeared to be stable except for a transcript of DUX4 from the distal D4Z4 unit. After observing that only one D4Z4 unit is necessary to cause FSHD, Dr. Lemmers and his associates chose to examine what makes the transcriptional profile of the distal unit pathogenic.

They found that a nucleotide sequence termed pLAM that lies next to the distal D4Z4 unit gives stability to the unit's DUX4 transcript. This sequence was not found in other D4Z4 repeat-array configurations of other variants of chromosome 4q or chromosome 10q.

This finding suggested to the researchers that "FSHD may arise through a toxic gain of function attributable to the stabilized distal DUX4 transcript."

Dr. Lemmers and his colleagues then studied four families with one or more affected individuals who carried unusual hybrid D4Z4 repeat-array structures composed of units from chromosome 4q and 10q. This repeat array in one affected individual even resided on chromosome 10 rather than chromosome 4, which indicated that genes nearby the repeat array on chromosome 4q do not play a key role in the pathogenesis of FSHD. This means that when the last D4Z4 unit and its nearby pLAM sequence are found together, they cause the disease regardless of their chromosomal location.

The study "not only explains the striking chromosome specificity of the disorder, but also provides a genetic mechanism that may unify the genetic observations in patients with FSHD," the researchers concluded.

The study was supported by grants from 11 organizations, health and science agencies, and foundations. ■

Report by Jeff Evans, Managing Editor.

ADVISER'S VIEWPOINT

'Toxic Gain of Function' Not Unique

Richard J.L.F. Lemmers, Ph.D., and colleagues, part of an international consortium of scientists probing the causes of facioscapulohumeral muscular dystrophy (FSHD), have come upon a coherent genetic model of this disease that ties up many of the confusing loose ends of the FSHD puzzle, a subject which has long baffled researchers in the field and clinicians who care for FSHD patients and their families. In their report, Dr. Lemmer and coworkers found that all FSHD patients the group studied had an identical DNA sequence in the last D4Z4 unit and the immediate flanking pLAM sequence of genetic material. Quite remarkably, the specific gene sequence variants appear to convey pathogenicity to the repeat whether they occur on chromosome 4 (the traditional site of the FSHD gene) or chromosome 10. Furthermore, they propose that this faulty terminal D4Z4 unit and adjacent pLAM sequence mediate what has been termed a "toxic gain of function."

Other neurologic disorders are known to be caused by a toxic gain of function, most notably familial amyotrophic lateral sclerosis, where a superoxide dismutase 1 (SOD1) mutation is responsible for the condition, and Huntington's disease, where CAG repeats are thought to mediate the disease. Toxic gain of function has been proposed as a mechanism in other diseases as well, including idiopathic Parkinson's disease, where alpha synuclein aggregates lead to degeneration of mesencephalic neurons, and Alzheimer's disease, where tau phosphorylation in the hippocampus is thought to lead to neuronal deterioration.

The report from Dr. Lemmer's group provides convincing genetic data for a plausible model of FSHD. The hypothesis that this muscle disease occurs on the basis of a toxic gain of function brought about by stabilized DUX4 transcript may turn out to be sound. Investigation of further FSHD kindreds by Dr. Lemmer's group and others will determine whether this pathogenic model will stand the test of time.

What do these findings mean for FSHD patients and the neurology community? Establishing an incontrovertible molecular mechanism for this common inherited muscle disease is the first step to devising therapies aimed at correcting or replacing the faulty genetic machinery that underlies FSHD.

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Poor Outcomes Found for Blacks With Muscular Dystrophy

BY DENISE NAPOLI

FROM THE JOURNAL NEUROLOGY

The median age at the time of death for white patients with muscular dystrophy is 10-12 years older than it is for black patients with the disease, according an analysis of data from all death certificates in the United States.

Moreover, in the 5 most recent years of the study's 20-year time period, 24.5% of black males with muscular dystrophy (MD) had cardiomyopathy, compared with 12.8% of white males with the disease.

The findings "might have been related to different prevalences of the various types of MD, different natural histories, or differences in environmental, genetic, or behavioral risk factors," wrote Aileen Kenneson, Ph.D., and her colleagues.

With her associates, Dr. Kenneson, who is currently affiliated with consulting firm McKing Consulting Corporation in Atlanta, looked at records from the National Center for Health Statistics' Multiple Cause Mortality Files, which contain data from all death certificates in the United States, including immediate and underlying causes of death coded with the International Classification of Diseases.

The group confined their search to the period between 1986 and 2005; they excluded congenital MD from their analysis, since "the distribution of age at death [among these patients] indicated that they were clinically distinct" from other MD patient types.

VITALS

Major Finding: Among patients with MD, the median age at death was significantly higher for white males than it was for black males (33 years vs. 23 years).

Data Source: The 1986-2005 National Center for Health Statistics' Multiple Cause Mortality Files.

Disclosures: Lead investigator Dr. Kenneson reported research grants from the CDC; a coinvestigator reported receiving advisory fees and research support from several pharmaceutical companies and MD-related support from foundations.

Overall, there were 18,315 MD-associated deaths from 1986 through 2005; roughly three-quarters were male. The overwhelming majority (90.6%) were white, while 7.7% of deaths occurred among black patients. The remaining 1.7% were among patients identified as being from other races (Neurology 2010;75:982-9).

The authors found a significantly lower median age at death among black females with MD compared with white females (51 years vs. 63 years, respectively).

They also noted that among white women, the proportion who were 45 years or older at death increased, from 78.7% in the first decade of the study period to 83.8% in the second decade.

"In comparison, only about 63% of black females were 45 years or older at death, and this proportion did not change over time," the investigators wrote.

Among males, the median age at death was significantly lower among blacks than whites (23 years vs. 33 years, respectively).

The median age at death during the 20-year time span of the study increased significantly by 1.3 years annually for white males without cardiomyopathy and 0.2 years annually for those with cardiomyopathy. In contrast, the median age at death increased just 0.33 years annually for black patients without cardiomyopathy. Black patients with cardiomyopathy showed no significant gain in life expectancy at all.

The authors pointed out that although cardiomyopathy was more often reported among blacks than whites, this finding was true "even early in the study period before the widespread use of corticosteroids and [noninvasive ventilation] were likely to have had an effect."

That could mean that the increased incidence of cardiomyopathy among nonwhite patients is due to simple racial differences the course of MD, or to the higher frequency of cardiomyopathy among blacks in general, rather than a disparity in treatment.

Dr. Kenneson and her coauthors noted that "while the database contains some possible social effect modifiers, such as education and marital status, it does not include information to assess sufficiently other sociocultural variables, such as health insurance and family structure." ■