Duchene Muscular Dystrophy (DMD) is an X-linked recessively inherited progressive muscle wasting disease. It has long been shown that changes in the DMD gene cause an absence of its coded protein Dystrophin. Dystrophin has an important role in maintaining the shape of muscle cells and connecting the inside of a muscle cell to the outside environment.

Becker Muscular Dystrophy (BMD), also caused by changes in the DMD gene, is a milder form of DMD. The muscle loss in BMD is slower because some Dystrophin protein is working in the muscle cells. In addition to muscle symptoms, about 1/3 of boys with DMD have problems of the central nervous system including: mental retardation, learning disability and/or language delays.

Autism or Autism Spectrum Disorder (ASD) is an inherited neuropsychiatric disorder. The genetic cause of most types of ASD is currently unknown, but many studies are ongoing. There are 3 main features of ASD: problems with social interaction, language delay, stereotypic behaviors/restricted interests. Interestingly, other genetic disorders also have autism as a feature including both Fragile X & Rett Syndromes.

Recently, reports have shown it is more likely for boys with DMD to also have autism than boys in the general population. The exact cause of this increased incidence of boys with both DMD & autism is unknown, but this link is under investigation in the Kunkel Laboratory. Studies have reported between 3-20% of boys with DMD also have autism. It is believed a key feature to explain this is the loss of Dystrophin protein from Purkinjie cells in the brain. This has been seen in both DMD and autism and has been implicated as a cause of ASD. Another idea is something called alternative splicing of the Dystrophin protein. It has been shown that Dystrophin can be found in different sizes in different body tissues. These alternative sizes are called isoforms. Each isoform is made by cutting up the DMD gene at different areas, giving not only a unique size but sometimes function too. For example, one isoform Dp140 (see figure 1) is about 1/3 the size of the full length Dystrophin protein and only found in the brain or kidney. Third, a new type of molecule that regulates gene expression was recently discovered. These molecules, called microRNA’s, are small parts of genes that do not make proteins, but are able to bind to other genes and change gene expression. The micro-RNA, miRNA486, is being studied as a possible therapy as it has been shown to down regulate gene expression in both DMD and autism.

Lastly, we have been studying animal models of both DMD and autism. Currently, we have zebrafish with DMD and are working on identifying zebrafish with autism. By using the fish as a model, we will be able to better understand how and why DMD and autism coexist and can be treated in patients. It is unlikely that the coexistence of DMD and autism is a new phenomenon, but due to the increased awareness of autism, it is just newly recognized.

Figure 1: Dystrophin Isoforms; Arrow denotes Isoform Dp 140 found in Brain and Kidney
Genetics 101—Definitions

**Chromosome:** Long coiled strands of DNA containing genes. There are 23 pairs of chromosomes in humans.

**Autosome:** Gene is located on chromosome 1-22, not X or Y 23rd pair of chromosomes otherwise known as the sex determining chromosomes.

**X or Y Chromosome:** The sex determining chromosomes; XX=female, XY=male.

**X-Linked:** A gene is located on the X chromosome.

**Dominant Inheritance:** 1 of 2 copies of a gene is changed (mutated) for trait/disorder to be seen in an individual.

**Recessive Inheritance:** 2 of 2 copies of a gene are changed (mutated) for trait/disorder to be seen in an individual.

**mRNA:** Messenger RNA is a molecule in cells that carries codes from the DNA in the nucleus to the cytoplasm of a cell for the protein it codes to be made.

**MicroRNA:** Small molecules that can change gene activity (upregulate = turn on or down regulate = turn off) by binding to mRNA.

**Isoforms:** Any of several different forms of the same protein, caused by alternative splicing of different portions of the mRNA transcript of a single gene. Isoforms are found in specific tissues of the body and can have different or similar functions.

**Purkinjie Cells:** Large neuron cells with many branches found in the cerebellum, important in controlling movement.

Meet the Kunkel Lab Members

**Included in Picture:** (L-R) Front row: Yuko Motohasi, Patricia Arashiro, Louis Kunkel, Ph.D., Jen Meyers, Elicia Estrella, Tamara Keeney, Jessica Bass, Christine Mahoney, 2nd Row: Norio Motohasi, Peter Serafini, Matt Alexander, Dick Bennett, Fedick Rahimov, Marielle Thorne, Lane Mahoney, Genri Kawahara

Missing from photo: Peter Kang, Hart Lidov, Ally Eran
The Muscular Dystrophy Association (MDA) clinic at Children’s Hospital Boston is a multi-disciplinary clinic involving neurology, orthopedics, physical therapy, genetics, and social work. The clinic has about 1000 outpatient visits each year, following children with a variety of neuromuscular diagnoses. In addition, the MDA Neuromuscular program has several ongoing clinical research projects.

**Clinical Outcomes for DMD infants and children ages 1 month to 5 years:** The purpose of this study is to identify reliable measures of gross motor development, fine motor development, speech, language, and social skills in infants and young children who have DMD. To be eligible, subjects must be one month to 3 years of age with a genetic or biopsy confirmation of DMD.

**Clinical Outcome Validation in Non-Ambulatory Boys/Men with DMD:** The purpose of this study is to find measures that are effective in evaluating non-ambulatory patients with DMD. Testing will be done on upper body strength & function and vital capacity. Quality of life of adult patients and caregivers is studied. **ENROLLMENT CLOSED**

**Natural History of Cardiomyopathy vs. DMD gene mutations & skeletal muscle function:** The purpose of this study is to better understand symptoms including cardiomyopathy in DMD/BMD patients by comparing heart function, skeletal muscle strength, and DMD gene mutations. To be eligible, a subject must have: a documented DMD gene mutation & receive an annual echo as part of their standard care.

**Spinal Muscular Atrophy (SMA) Natural History & Biorepository:** To learn more about the progression of the SMA. We will also collect tissue, blood, urine, and cheek cell samples from individuals with SMA and other neuromuscular diseases. To give researchers a bank of samples to study the pathogenesis of SMA and other related diseases.

Studies are associated with the MDA DMD clinical research network and Pediatric Neuromuscular Clinic Research Network being conducted at multiple sites across the US.

**Recent Publications from the Kunkel Lab**


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