



EmArray *Dystrophin* Resequencing Array ©2007

Emory Genetics Laboratory now offers EmArray *Dystrophin*, a new line of tests consisting of a high resolution array CGH and a resequencing array to detect mutations in the *dystrophin* gene. The use of array permits detection of **deletions, duplications and point mutations as well as previously unidentified deep intronic mutations and can be used for testing in females and prenatal analysis.**

Emory Genetics Laboratory, Parent Project Muscular Dystrophy, leading researchers, and DMD clinicians are working together to offer improved testing and develop a mutation and clinical data collection system based on the CETT Program model of collaboration.

Current *dystrophin* diagnostic testing typically screens for the most common deletions and duplications. **Methods currently used have inherent drawbacks:** Multiplex PCR, southern blot analysis and point mutation detection is very laborious and costly. Southern blot analysis is difficult to interpret and is prone to errors. Moreover, traditional detection of deletions and duplications does not provide precise identification of the underlying mutation and the size and breakpoints remain unknown. Use of these combined methodologies will fail to identify a mutation in ~10-12% of individuals tested. In addition, female carrier testing with these approaches is *limited when a related affected male is not available.*

What is EmArray *Dystrophin* Resequencing Array?

EmArray *Dystrophin* Resequencing Array is a chip based sequencing method comprised of probes overlapping to give 8x coverage at every base position of the *dystrophin* gene. The resequencing array interrogates the 14kb coding region, 1.4 kb of intronic sequence flanking exon/intron boundaries, 8 *dystrophin* promoters, and 5 cryptic deep intronic mutations. This test is indicated for individuals suspected to carry a *dystrophin* mutation for whom a deletion or duplication is not identified.

Why use EmArray *dystrophin*?

Diagnostic testing using EmArray *Dystrophin* provides confirmation of clinical diagnosis, characterization of the *dystrophin* gene mutation, and enables carrier testing for female family members and prenatal testing. Additional advantages include:

- **Equal sensitivity and detection for males and females**
- **Deletions and duplication mapped to the exact nucleotide breakpoint**
- **Enhanced detection of duplications that may be missed by other methods**
- **Rapid turn-around time**
- **Improved access to carrier and prenatal testing**

The combined detection of both methods is estimated to be 99%, thereby providing the most comprehensive and robust analysis of the *dystrophin* gene.

Duchenne and Becker Muscular Dystrophy

Duchenne and Becker muscular dystrophies (DMD/BMD) are a spectrum of neuromuscular diseases caused by gene mutations in the *Dystrophin* gene, located on the X chromosome. Becker and Duchenne are both characterized by progressive muscle wasting and proximal muscle weakness but differ in severity and age of onset. Individuals with Duchenne muscular dystrophy often have muscle weakness that is progressive from early childhood. Calf pseudohypertrophy is common. Dilated cardiomyopathy may develop in adolescence and may become life threatening. Some individuals with Duchenne have mild mental retardation. Becker muscular dystrophy generally presents at a later age and progresses at a slower rate. Individuals with Becker muscular dystrophy may develop dilated cardiomyopathy that may be life-threatening. Women who are carriers of a *dystrophin* mutation may show observable symptoms including: histological abnormalities in skeletal muscle (70%), elevated serum creatine kinase activity (45-70%), clinical symptoms such as muscle weakness (5-10%), and are at risk for dilated cardiomyopathy.

The incidence of DMD is approximately 1 in 3500 newborn males and the incidence of BMD is approximately 1 in 18,000 newborn males. Two thirds of these cases are inherited, while one third of DMD/BMD cases result from new mutations, where the mother is not a carrier for the gene. Large rearrangements in the *dystrophin* gene are found in about two thirds of DMD patients, with approximately 60% carrying deletions of one or more exon, 5-10% carrying duplications or one or more exon. The remaining cases are caused by point mutations or smaller deletions/duplications in the *dystrophin* gene.

Indications:

This test is indicated for:

- Males with a clinical diagnosis or symptoms of Duchenne or Becker muscular dystrophy
- Females who are at risk to be a carrier or have a family history of Duchenne or Becker muscular dystrophy
- Individuals with previous deletion/duplication test results that do not clearly identify the breakpoints and size of the deletion or duplication.
- Prenatal testing is available to females who carry an identified *dystrophin* mutation

Related tests:

The *Dystrophin* Array CGH is available to test for deletions and duplications. A cDNA sequencing assay is also available for functional characterization of novel variants in the *dystrophin* gene (Please call Emory Genetics Laboratories for more information)

Methodology:

The resequencing array consists of probes overlapping to give 8x coverage at every base position of the *dystrophin* gene, and interrogates 14kb coding region, 1.4 kb of intronic sequence flanking exon/intron boundaries, 8 *dystrophin* promoters, and 5 cryptic deep intronic mutations. Mutations are confirmed by targeted Sanger sequencing of the fragment containing the mutation.

Clinical Sensitivity:

In approximately 35% of Duchenne muscular dystrophy and approximately 15% of Becker muscular dystrophy, point mutations and mutations in the promoter or intronic regions are identified in the *dystrophin* gene, which are detectable by the resequencing array. The resequencing array will not detect larger deletions and duplications (refer to the *Dystrophin* Array CGH).

Reference Range:

Qualitative assay.

Turnaround Time

2 weeks

Specimen Requirements

Collect whole blood

- Children under 2 years: Collect 3-5 ml blood in a purple top (EDTA) or yellow top (ACD) tube.
- Older children and adults: Collect 5-10 ml blood in a purple top (EDTA) or yellow top (ACD) tube.

Refrigerate sample until shipment. Send the sample at room temperature using overnight delivery within 7 days of collection.

CPT codes:

83890, 83892 (x2), 83894, 83896 (x10), 83897, 88384, 88385, 88386, 83898 (x85), 83904(x85)

Contact Emory Genetics Laboratory with your questions by calling (404)778-8500.