Understanding mutations and phenotypes

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Human Genome
3 billion letters (GATC)
~24,000 genes
~240,000 exons

Gene for Duchenne/Becker Muscular Dystrophy identified

~3,000 Different Genetic Diseases known
Duchenne is an ‘X linked recessive’

Carrier Mom

Affected Son
Normal Muscle

Dystrophin
Fig. 10-3. Muscle fibers contain **myofibrils**, which are bundles of **myofilaments**. Each myofibril is surrounded by the **sarcoplasmic reticulum**.
Dystrophin mutations

Gene is *DMD*

Protein is *dystrophin*

Why do some mutations cause more mild Becker muscular dystrophy or very mild disease and others cause more severe Duchenne muscular dystrophy?

**READING FRAME RULE**
Gene Expression - Central Dogma

DNA: CTGAGCCAACTATTGATGAA
RNA: CUGAGCCAACUAUUGAUGAA
CODE: CUG AGC CAA CUA UUG AUG AA

Protein: LSQLLLM
NORMAL Dystrophin
DMD causing mutant dystrophin
DMD causing mutant dystrophin

No normal protein made after ‘reading frame shift’
MILD Dystrophin gene mutation
Most mutations are deletions of exons
Magri, et al 2010 J. Neuro
DMD/BMD Diagnostics

Algorithm for DMD/BMD diagnostic testing

Step 1: Comparative genomic hybridization (CGH) array of entire dystrophin genomic sequence (2.2 MB) → CGH will identify both deletions/duplications in the dystrophin gene

Step 2: Resequencing array (RA) of dystrophin gene coding region and promoters → Sequencing will identify point mutations and sequence variations in the dystrophin gene

Step 3: If there are novel variants or no mutations detected, consider muscle biopsy for immunohistochemistry and cDNA sequencing.
Exons 45-55 are most commonly deleted region of DMD gene
DMD is observed in all populations
Dystrophin Protein domains
Deletions of higher exon number correlate with more significant brain effects.
Duchenne is variable in boys

Clinical Heterogeneity of Duchenne Muscular Dystrophy (DMD): Definition of Sub-Phenotypes and Predictive Criteria by Long-Term Follow-Up

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Are there other genetic modifiers?

- DUCHENNE CONNECT

**Age of Wheelchair Bound of DMD Patients**

**Taking Corticosteroids Verses None**

![Bar chart showing age of wheelchair bound DMD patients taking corticosteroids versus none.](chart.png)
Identification of genetic modifiers

Severe
Mild

Sequence ALL genes

Detect mutations in other genes that impact DMD
Summary

- Most Duchenne causing DMD mutations lead to complete loss of dystrophin function
- Partially functional DMD mutations lead to Becker
- All patients should receive a specific molecular diagnosis
  - Molecular diagnosis relevant to clinical trials
- A small portion of patients need muscle biopsy to establish molecular diagnosis
- Assessment of ‘outlier’ DMD patients may reveal other genetic modifiers of Duchenne and highlight new therapeutic targets.
- Register at Duchenne Connect
- Participate in clinical trials
Most patients do not need muscle biopsy.
Microarray measures locations of DNA deletions/duplications
Non-contiguous mutations