Duchenne Muscular Dystrophy

BIOC 118: Genomics and Medicine

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The Basics

- Characterized by:
  - enlargement of muscles
  - rapid progression of muscle degeneration

- X-linked recessive

- One in 3,500 boys worldwide

- Onset of symptoms: infancy to age 5

- Average Life Expectancy: late teens to mid-twenties (max mid 40s) due to cardiac or respiratory failure
Classical Diagnostics

- Gait difficulty beginning at age three
- Progressive muscle weakness and enlargement of the calves
- Cardiomyopathy and predisposition to respiratory illness
- Massive elevations of serum levels of creatine kinase
- Electromyography and muscle biopsy
- Biopsies taken early in the course of the disorder are prone to lead to misdiagnosis
Classical Treatment

- Physical therapy
  - As muscular dystrophy progresses and muscles weaken, fixations (contractures) can develop in joints.
  - Physical therapy provides regular range-of-motion exercises to keep joints as flexible as possible, delaying the progression of contractures, and reducing or delaying curvature of your spine.
- Hydrotherapy
- Braces (and canes, walkers, and wheelchairs)
- If respiratory muscles become weakened, using a ventilator may become necessary.
Classical Treatment

- **Medications**
  - Manage myotonia: mexiletine, phenytoin, baclofen (Lioresal), dantrolene and carbamazepine.
  - Muscle deterioration: prednisone may help improve muscle strength and delay progression.
  - The immunosuppressive drugs cyclosporin and azathioprine sometimes delay damage to dying muscle cells.

- **Surgery** can be used to release contractures and correct curvature of the spine.

- **Influenza shots**
The Guilty Gene

- The DMD gene is the largest known human gene.
- Codes for a protein complex called dystrophin.
- Located in skeletal muscles and cardiac muscles.
- Small amounts are present in nerve cells in the brain.
- Strengthens muscle fibers and protects them from injury as muscles contract and relax.
- Acts as an anchor, connecting each muscle cell's cytoskeleton with the lattice of proteins and other molecules outside the cell.
- May play a role in cell signaling.
- Research suggests that the protein is important for the normal structure and function of synapses in the brain.
- Hundreds of mutations in the DMD gene can lead to DMD.
- Most are deletions that cause frame-shift mutations that prevent any dystrophin from being produced.
- Muscle cells that lack enough functional dystrophin become damaged as muscles repeatedly contract and relax.
- The damaged cells weaken and die over time, causing the characteristic muscle weakness and heart problems seen in Duchenne muscular dystrophy.

The DMD gene is located on the short arm of the X chromosome at position 21.2. More precisely, the DMD gene is located from base pair 31,137,344 to base pair 33,357,725 on the X chromosome.
Genetic Diagnostics

- Composed of 79 exons
- DNA testing and analysis usually identifies the specific type of mutation or the exon or exons that are affected.
- Prenatal tests
Mechanism of PRO051 in the restoration of Dystrophin Expression through Exon Skipping

- Antisense oglioligonucleotide binds to the dystrophin mRNA.
- The modified DNA molecule allows the mRNA to skip over the affected exons, and restores the reading frame of the mRNA, for new production of dystrophin.
- Correct the reading frame in 16% of patients
Other Prospects...

- Adeno-associated viruses carrying micro-dystrophins into dystrophic muscles
- Resulted in a striking reversal of histopathologic features of the disease
- Difficult to produce
<table>
<thead>
<tr>
<th>Strategy</th>
<th>Action/effect</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Prospects</th>
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</thead>
<tbody>
<tr>
<td>Adenoviral vectors</td>
<td>Full-length dystrophin cDNA transfer</td>
<td>High transduction levels in regenerating muscle, expression of fully functional dystrophin</td>
<td>Viral immune response, limited persistence of transgene expression, maturation dependent</td>
<td>++</td>
</tr>
<tr>
<td>Herpes simplex viral vectors</td>
<td>Full-length dystrophin cDNA transfer</td>
<td>High transduction levels in regenerating muscle, expression of fully functional dystrophin</td>
<td>Viral toxicity and immune response, limited persistence of transgene expression, maturation dependent</td>
<td>+</td>
</tr>
<tr>
<td>Plasmid vectors</td>
<td>Full-length dystrophin cDNA transfer</td>
<td>Synthetic, non-infectious, relatively safe, flexible, simple engineering</td>
<td>Large molecule, delivery requires efficient transfection method</td>
<td>++</td>
</tr>
<tr>
<td>Myoblast transplantation</td>
<td>Introduce dystrophin-producing cells</td>
<td>Non-infectious, relatively safe</td>
<td>Low efficiencies, immune suppression required</td>
<td>+</td>
</tr>
<tr>
<td>Stem-cell therapy</td>
<td>Introduce dystrophin-producing cells</td>
<td>Conventional treatment, relatively safe</td>
<td>Low efficiencies, immune suppression required</td>
<td>++</td>
</tr>
<tr>
<td>Chimeric oligonucleotides</td>
<td>Correction of mutation at the DNA level</td>
<td>Cumulative, permanent effect</td>
<td>Low in vivo efficiencies</td>
<td>+</td>
</tr>
<tr>
<td>Gentamicin therapy</td>
<td>Ribosomally read-through of stop codons in mRNA</td>
<td>Conventional drug</td>
<td>Low reproducibility, risk of nonspecific adverse effects</td>
<td>+</td>
</tr>
<tr>
<td>rAAV vectors*</td>
<td>Mini- or micro-dystrophin cDNA transfer</td>
<td>High transduction efficiencies in muscle, non-pathogenic minimal immune responses</td>
<td>Unable to deliver full-length dystrophin, laborious production systems</td>
<td>+++</td>
</tr>
<tr>
<td>Antisense oligonucleotides*</td>
<td>Splicing modification of pre-mRNA</td>
<td>Synthetic, small-molecule drug, relatively safe, restores all isoforms</td>
<td>Repeated administrations and (targeting) delivery reagent needed, mutation specific</td>
<td>+++</td>
</tr>
<tr>
<td>Utrophin upregulation*</td>
<td>Replacement of dystrophin</td>
<td>Small-molecule drug, no immune response, relatively safe</td>
<td>No effective specific compound identified as yet</td>
<td>++</td>
</tr>
</tbody>
</table>

*These three relatively new strategies are most likely to lead to an effective treatment for Duchenne muscular dystrophy. The symbols in the prospects column indicate a subjective assessment of the probability of a particular strategy leading to an effective treatment, ranging from low (+) to high (+++). rAAV, recombinant adeno-associated virus.