The following 2 cases illustrate the clinical variability seen in patients with the same common genetic disorder.

Patient 1:

Chief complaint: A 10-year-old Caucasian female presents with the following:
- Mild proximal muscle weakness, affecting the lower extremities more than the upper.
- She was on time with all of her developmental milestones, and was walking around a year of age. According to her parents, she has always been somewhat clumsy and “does not move in normal patterns.” She has difficulty running and throws her legs out when she runs. She used to play volleyball and dance, but has stopped because they became increasingly difficult for her to do.
- Reflexes, sensation, and muscle tone are normal. She has a straight spine and walks with a good heel-toe gait pattern without difficulty.
- CPK, AST, ALT, lactic acid, carnitine profile, pyruvate, thyroid panel and LDH all within normal limits.
- Nerve conduction studies are normal. EMG is consistent with a chronic neuropathic process affecting primarily the motor fibers.
- The family history was non-contributory.

Patient 2:

Chief complaint: A 3-month old female Caucasian infant presenting with the following:
- Weakness and hypotonia.
- Irritability, decreased leg movements, difficulty supporting her head, and respiratory difficulty.
- Tongue fasciculations.
- She was otherwise alert and attentive, with good eye contact and a social smile. Her reflexes and sensation are intact.
- Her history included a one-week hospitalization shortly after birth for viral bronchiolitis and respiratory problems related to her underlying weakness.
- The family history was non-contributory.
- She subsequently died of respiratory insufficiency at 5 months of age.

What is your diagnosis?

Read the reverse side to find out if you are correct, and to find out more about this disease!
SMA (Spinal Muscular Atrophy)
Spinal Muscular Atrophy (SMA) is an autosomal recessive disorder characterized by progressive muscle weakness due to degeneration and loss of the anterior horn cells in the spinal cord and the brain stem nuclei. Approximately 1/10,000 people are affected, making it the most common fatal childhood muscular disorder after Duchenne Muscular Dystrophy. The symptoms and age of onset of SMA are extremely variable, as illustrated in the 2 case studies. SMA is classified into subtypes based on clinical presentation, including the age of onset of symptoms and maximum function achieved (see table below). However, the phenotype spans a continuum, sometimes making the delineation of subtypes unclear.

<table>
<thead>
<tr>
<th>SMA Type</th>
<th>Age of Onset</th>
<th>Life Span</th>
<th>Motor Milestones</th>
<th>Other Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>SMA I (Werdig-Hoffman)</td>
<td>Before 6 months</td>
<td>2 years or less</td>
<td>Sit with support only</td>
<td>Mild joint contractures, facial weakness, variable suck and swallow difficulties</td>
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<tr>
<td>SMA II</td>
<td>6-18 months</td>
<td>70% alive at 25 years old</td>
<td>Independent sitting when placed</td>
<td>Postural tremor of fingers</td>
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<tr>
<td>SMA III</td>
<td>After 12 months</td>
<td>Normal</td>
<td>Independent ambulation</td>
<td></td>
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<tr>
<td>SMA IV</td>
<td>Adulthood</td>
<td>Normal</td>
<td>Normal</td>
<td></td>
</tr>
</tbody>
</table>

Diagnosis:
The diagnosis of SMA, regardless of type, is easily made by DNA testing on a blood sample. 95% of SMA patients are homozygous for a common recurring deletion of exons 7 and 8 in the SMN1 gene. The two patients described on the reverse page tested positive for the same deletion mutation! 5% of SMA patients have the deletion on one allele and a point mutation on the second copy; these patients will be missed by the standard test, which does not detect carriers for the deletion. Carrier testing relies on SMN1 dosage testing and is available on a limited clinical basis.

Molecular genetics:
The SMN region on chromosome 5q12.2-q13.3 is unusually complex. Normally, the SMN1 gene and a closely-related copy gene, SMN2, are arranged in tandem on each chromosome. Except for a few nucleotides, SMN1 and SMN2 are identical; however, due to differences in splicing, the SMN2 copy expresses decreased amounts of functional protein and can not fully compensate for the loss of SMN1. However, increased expression of SMN2 can reduce the severity of SMA, as seen when multiple copies of SMN2 are present, both in patients and mouse models. This is one explanation for why two patients can have the same SMN1 deletion mutation but such disparate symptoms: patients with 3-4 copies of SMN2 tend to have the milder form of SMA.

DNA testing for SMA is available at Children’s Mercy. The specimen requirements are 1-3 cc whole blood in an EDTA (lavender top) tube. The turn-around time is 1 week.