High-Yield Congenital Myopathy Pathology

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Case-Based Questions (please see page 3 for answers)

1.	You receive a skeletal muscle biopsy from a 2-year-old boy with proximal muscle weakness. When reviewing his clinical history, what finding is most suggestive that you will identify pathologic evidence of a congenital myopathy?	
	a.	Cardiomyopathy
	b.	Extraocular muscle involvement
	c.	Myopathic features on EMG
	d.	Normal CK level
	e.	Respiratory insufficiency

2.	While performing electron microscopic analysis of a skeletal muscle biopsy from a 1-year-old child with hypotonia, you identify aggregates of elongated electron dense material in the subsarcolemmal space of a few fibers. These structures were not apparent on frozen section histologic analysis. What feature is helpful to confirm that these electron dense structures are nemaline rods?	
	a.	Filamentous core
	b.	Finely granular internal structure
	c.	Lattice internal structure
	d.	Membrane bound
	e.	Surrounding halo of light

3.	A 21-year-old woman experienced muscle rigidity, an abnormal heart rate, and elevated body temperature while under anesthesia during a tonsillectomy procedure. Genetic testing was then performed that revealed a heterozygous variant of uncertain significance (VUS) in a single gene. A skeletal muscle biopsy was performed for further interrogation of the VUS, and it showed large central areas devoid of oxidative enzyme staining. What is the most likely altered gene that could cause this patient's presentation?	
	a.	*ACTA1*
	b.	*DNM2*
	c.	*MTM1*
	d.	*NEB*
	e.	*RYR1*

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Question 1 Correct answer and rationale: **D) Normal CK level**

The clinical presentation for congenital myopathy and congenital muscular dystrophy can show a great deal of overlap. However, in most patients with congenital myopathy, their CK level is normal or only very mildly elevated in contrast to muscular dystrophy patients who have significantly elevated CK levels. Both congenital myopathies and muscular dystrophies can have cardiomyopathy, extraocular muscle involvement, myopathic EMG findings (although not as common in congenital myopathies), and respiratory insufficiency.

Question 2 Correct answer and rationale: **C) Lattice internal structure**

Nemaline rods are thought to be derived from Z-line material and show a similar internal lattice structure to the Z-line. This can be helpful to distinguish between true nemaline rods and other structures that have a similar appearance. Cytoplasmic bodies can be confused with nemaline rods, especially since they also have an origin in the Z-line. However, cytoplasmic bodies have a dense filamentous core with a surrounding lighter halo. Giant abnormal lysosomes are fairly rare to identify, but they have a structure that can mimic nemaline rods. Giant abnormal lysosomes have a filamentous core and are membrane bound.

Question 3 Correct answer and rationale: **E) *RYR1***

The presentation describes a patient who experienced malignant hyperthermia while under general anesthesia. The muscle biopsy describes the presence of central cores. The combination of central core disease and malignant hyperthermia is seen in patients with RYR1-related disorders most often caused by autosomal dominant RYR1 variants. Alterations in the other listed genes cause various forms of congenital myopathy, but they are not known to be associated with malignant hyperthermia.