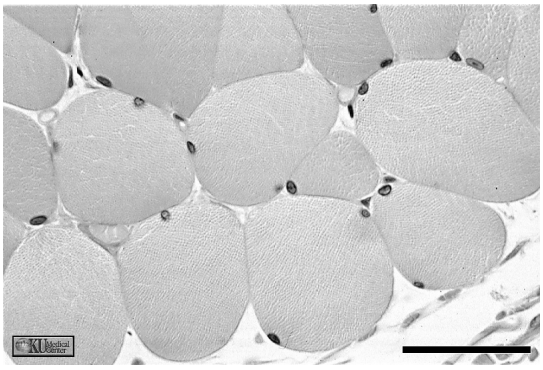
a) Control Muscle Biopsy



b) Patient's Muscle Biopsy

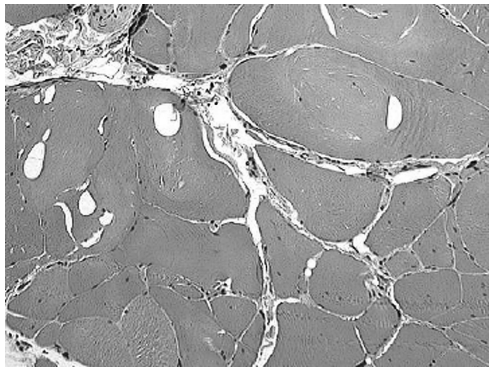


FIGURE 10.1 • Histology of *wt* and patient's skeletal muscle biopsy. a) Wild-type skeletal muscle histology. Notice that the fibers are regular in size, spacing, and "texture," with peripheral nuclei. Bar is 50 μm long. **b)** Patient's skeletal muscle biopsy. The white spaces show where fat had impregnated the muscle. Nuclei are not peripheral.

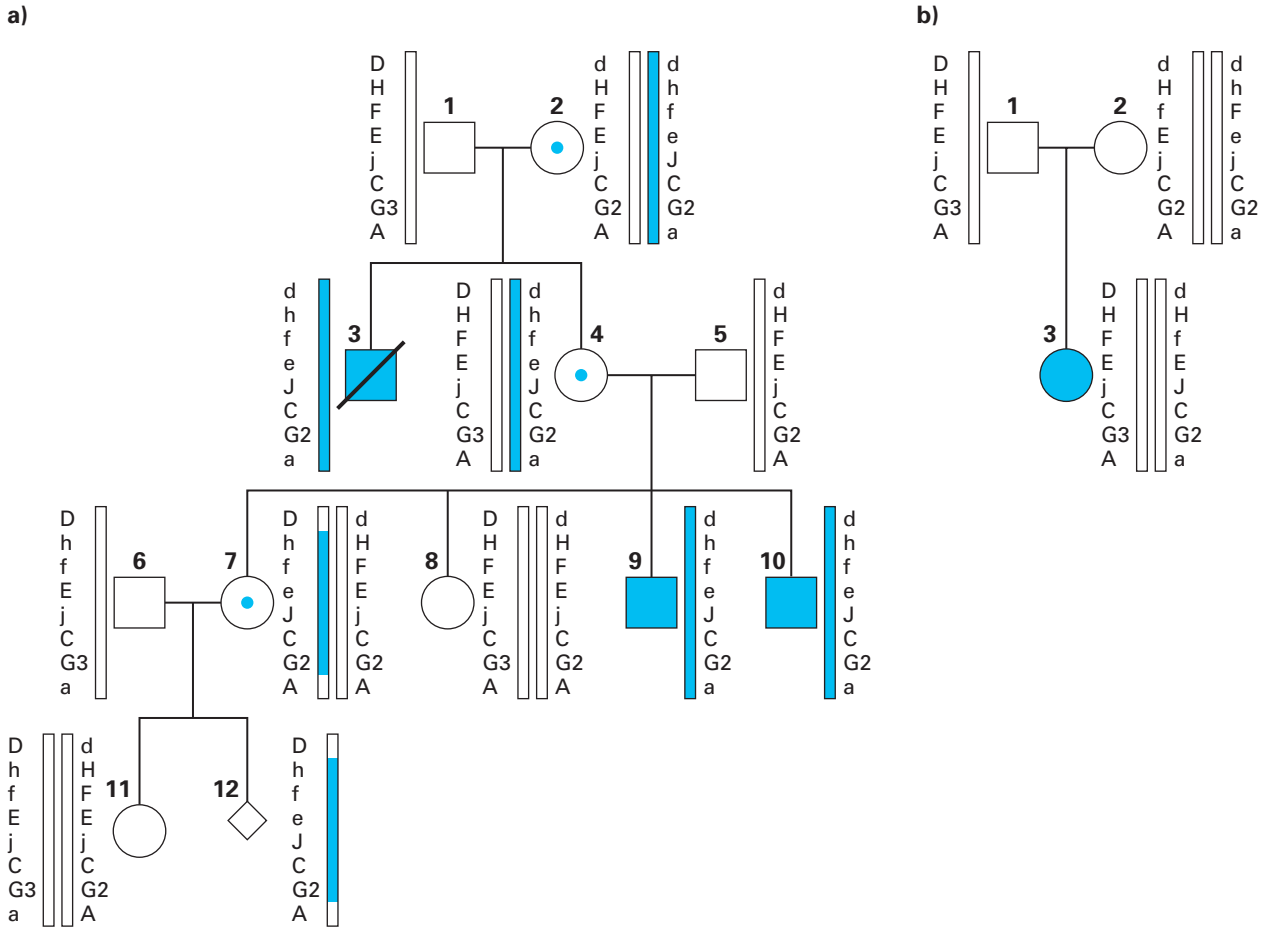


FIGURE 10.2 • Linkage analysis for the families. a) The original boy is individual number 9. Dots indicate carrier status, and the bars represent X chromosomes with the RFLP markers as indicated. Blue on the chromosomes indicates regions carrying the disease allele. The capital letters indicate the most frequent markers in the population. **b)** Pedigree and linkage analysis information for the affected girl and her parents.

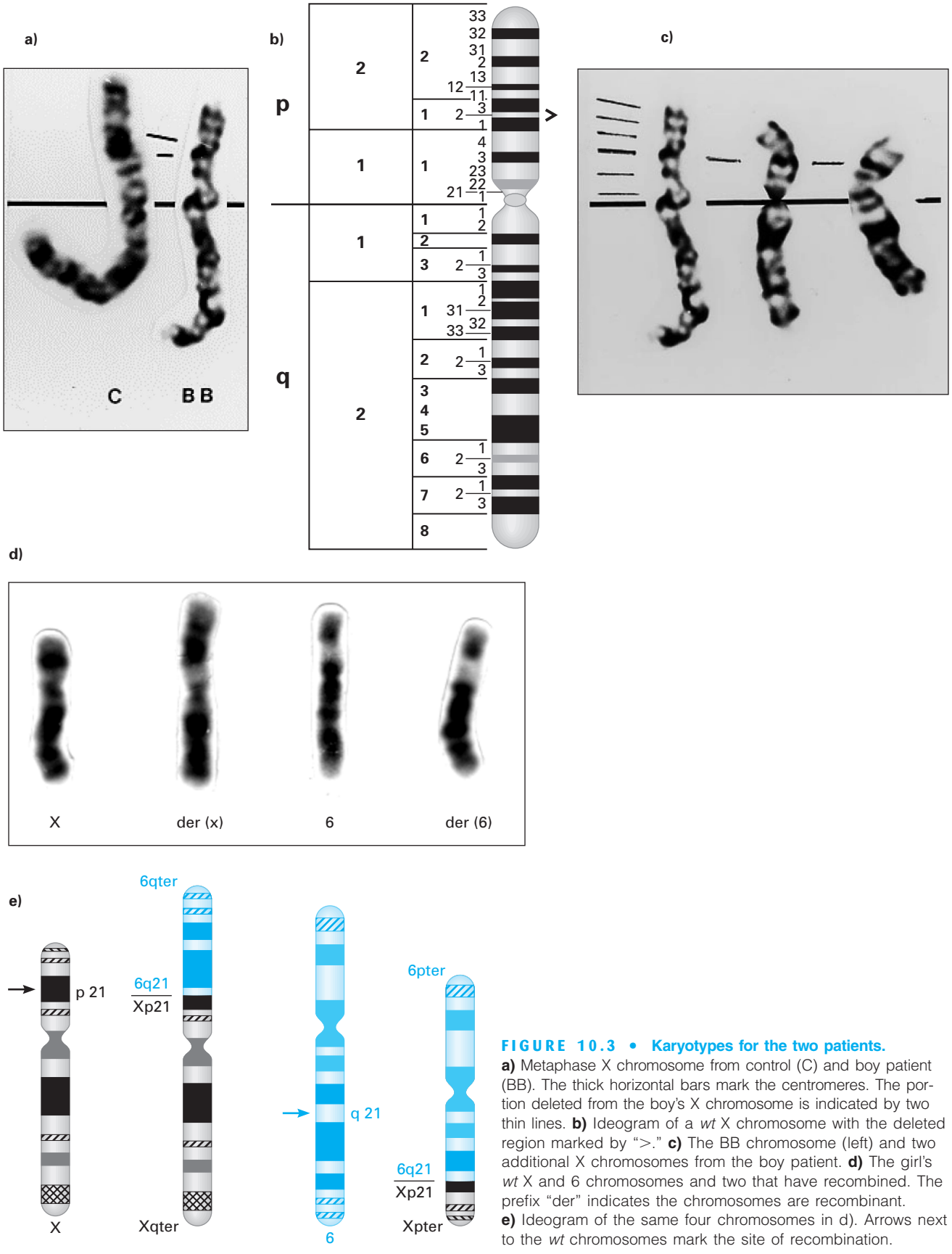


FIGURE 10.3 • Karyotypes for the two patients.
a) Metaphase X chromosome from control (C) and boy patient (BB). The thick horizontal bars mark the centromeres. The portion deleted from the boy's X chromosome is indicated by two thin lines. **b)** Ideogram of a *wt* X chromosome with the deleted region marked by ">." **c)** The BB chromosome (left) and two additional X chromosomes from the boy patient. **d)** The girl's *wt* X and 6 chromosomes and two that have recombined. The prefix "der" indicates the chromosomes are recombinant. **e)** Ideogram of the same four chromosomes in d). Arrows next to the *wt* chromosomes mark the site of recombination.

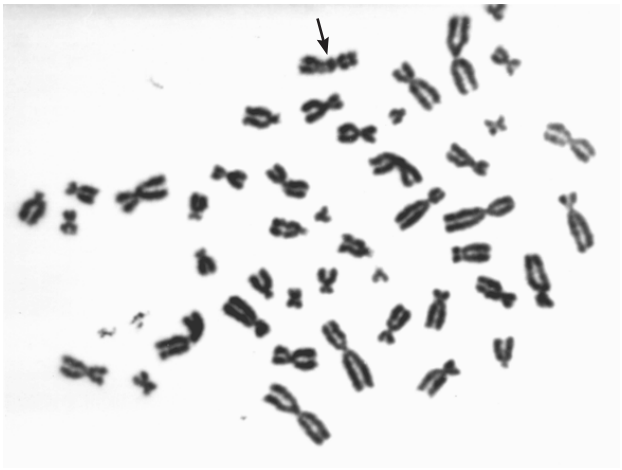


FIGURE 10.4 • Inactivated X chromosome. A full karyotype that is focused on a *wt* X chromosome of the girl patient (arrow). The X chromosome is delayed in its progression through mitosis.

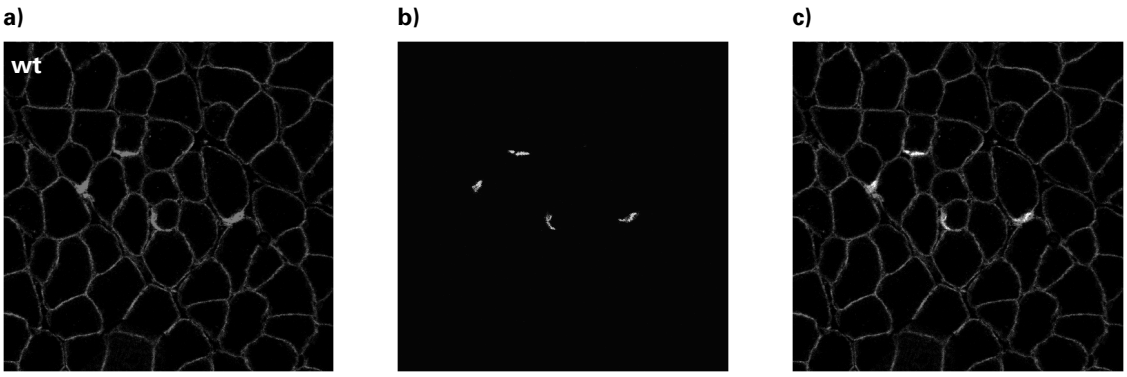


FIGURE 10.5 • Immunofluorescent labeling of dystrophin and utrophin. Wild-type adult mouse thigh muscle labeled for **a)** dystrophin, **b)** utrophin, and **c)** where they overlap is shown as bright white label.

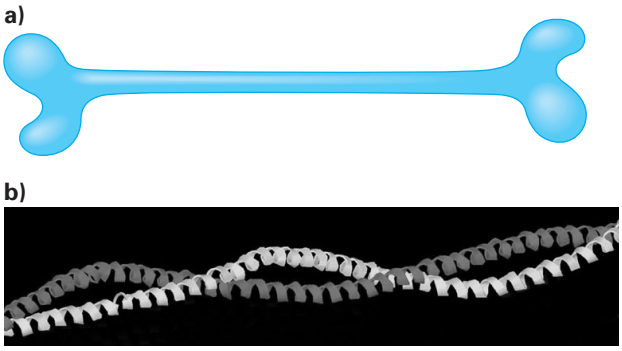


FIGURE 10.6 • Proposed structure of dystrophin.
a) Based on amino acid sequence, dystrophin was believed to be shaped like an elongated bone. **b)** The middle portion of dystrophin was predicted to form a coiled-coil as shown in this structure view of another protein with a similar motif. (PDB ID# 1C1G.)

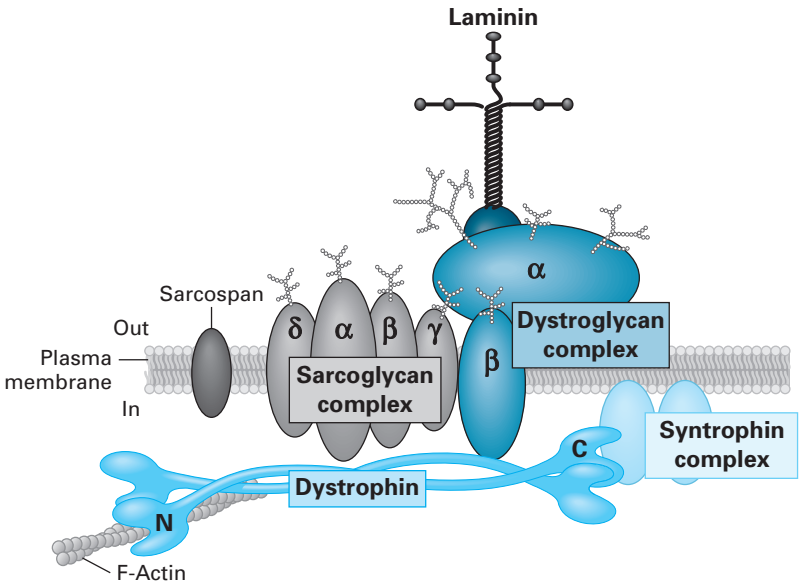


FIGURE 10.7 • Diagram summarizing dystrophin and associated protein interactions. Notice that some labels do not name each molecule individually and only the group names are provided. The carboxyl (C) and amino (N) termini of dystrophin have been labeled. The branched beads represent glycosylation of the proteins.

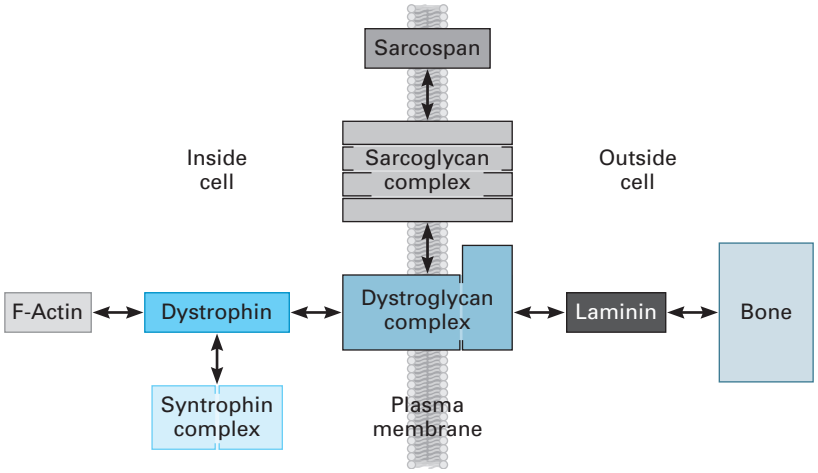


FIGURE 10.8 • Circuit diagram summarizing dystrophin and associated protein interactions. Dystrophin fits into the flow of information between the outside of the cell and the inside. The connection between laminin and bone is simplified here for clarity.

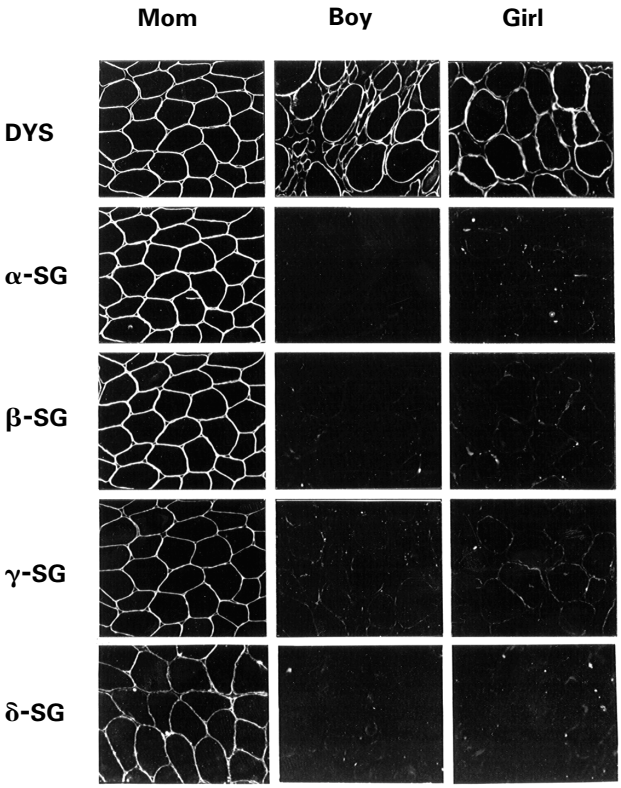


FIGURE 10.9 • Immunofluorescence labeling of biopsies from the mother and her two affected children. Each panel represents a different section of the thigh muscle labeled with a different antibody. The white label in these photos marks the presence of the indicated proteins (DYS: dystrophin; SG: sarcoglycan).

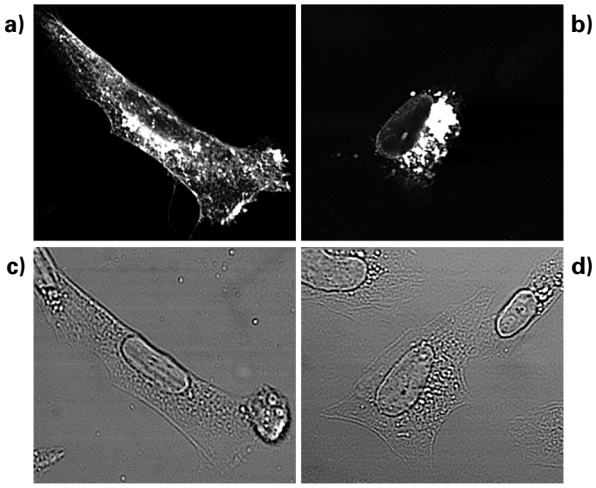


FIGURE 10.10 • Immunefluorescence localization of muted β-sarcoglycan. Immunofluorescence labeling of the sarcoglycan complex **a)** in a *wt* cell and **b)** in a cell where the β-sarcoglycan has been mutated. **c)** and **d)** Phase contrast images of the same cells let you see the full extent of the cells.

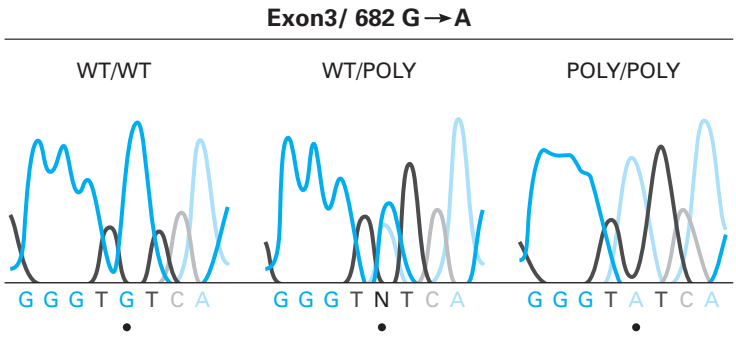


FIGURE 10.11 • Sequence chromatograms showing homozygous *wt*, heterozygous, and homozygous mutant sequences for sarcospan. The mutation is highlighted with a dot below and is called "POLY" because the different base is a polymorphic site.

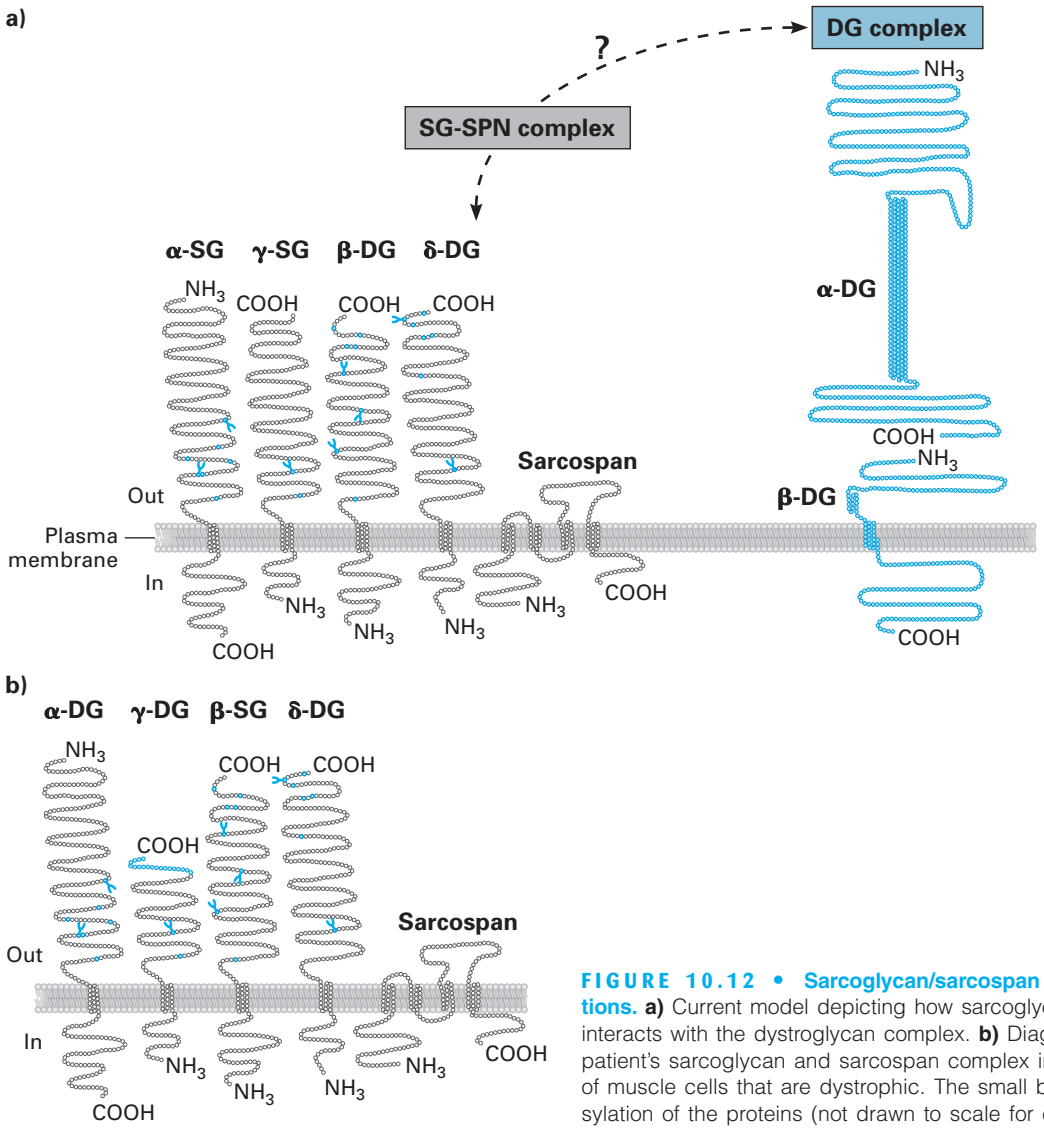


FIGURE 10.12 • Sarcoglycan/sarcospan protein-protein interactions. **a)** Current model depicting how sarcoglycan/sarcospan complex interacts with the dystroglycan complex. **b)** Diagram depicting one patient's sarcoglycan and sarcospan complex in the plasma membrane of muscle cells that are dystrophic. The small blue "Y"s represent glycosylation of the proteins (not drawn to scale for clarity).

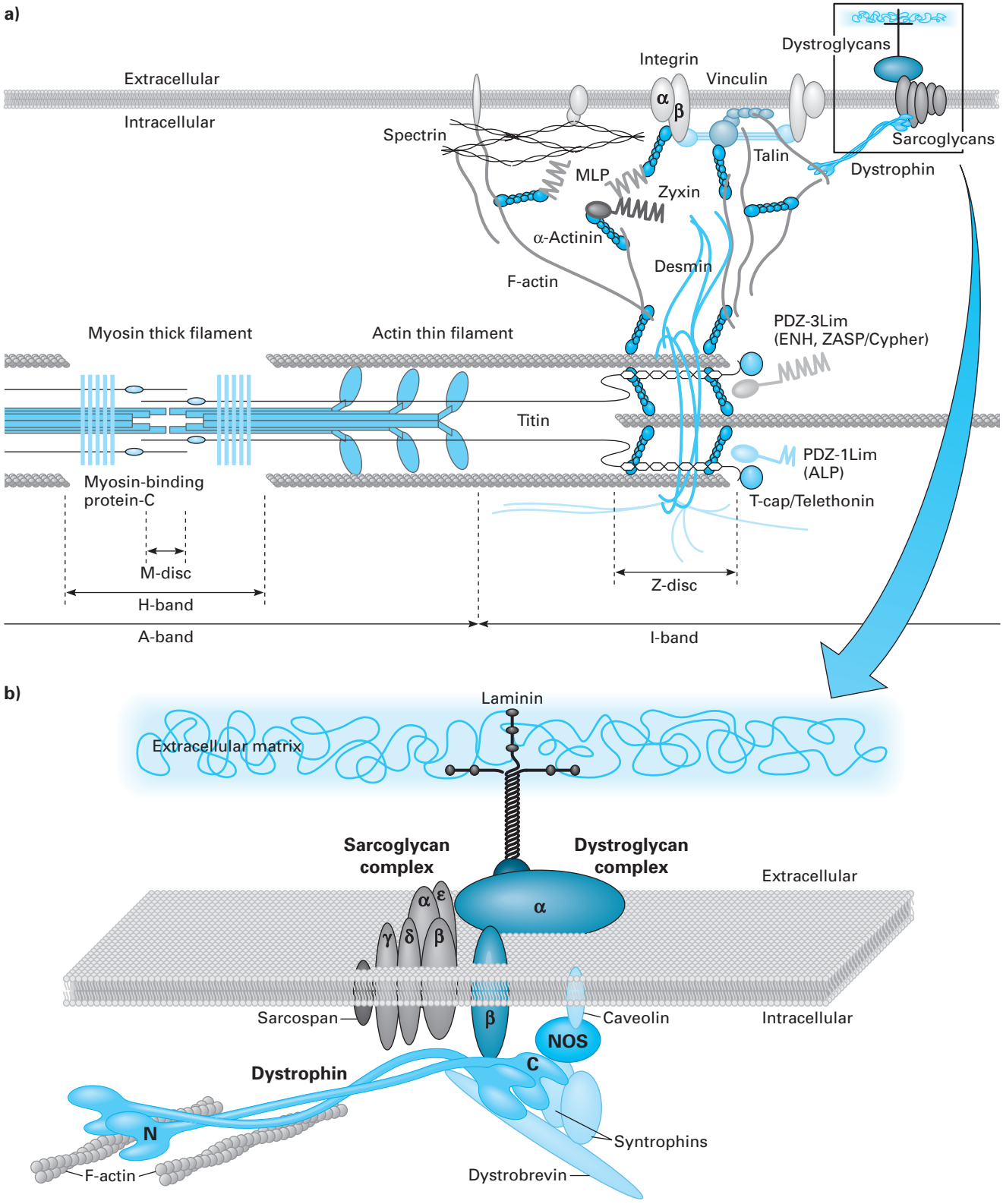
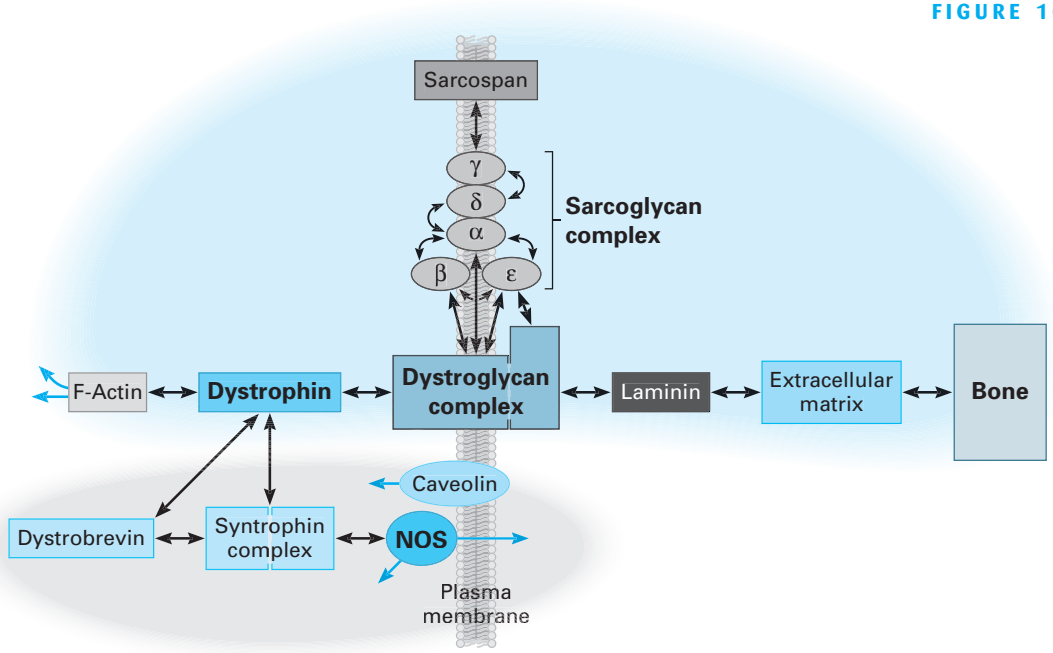


FIGURE 10.13 • Working model of muscle molecules near dystrophin. **a)** Schematic diagram of the major proteins involved in striated muscle function. **b)** Closer view of the dystrophin complex of proteins. **c)** Circuit diagram showing a different view of panel b. The blue arrows indicate additional connections to other parts of the cell web. Added to this diagram are two large circles that encompass two functional units of the circuitry—the structural unit (circled in blue) and the signaling unit (circled in gray).

FIGURE 10.13 • Continued



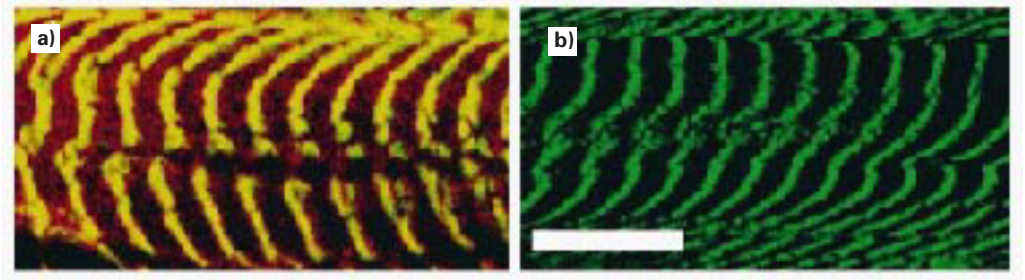


FIGURE 10.14 • Immunofluorescence detection of proteins adhering to plasma membrane. Images of plasma membranes isolated from **a)** control, or **b)** *mdx* mice, and immunofluorescently labeled with two monoclonal antibodies. One antibody labels α-actinin (green) and the other labels γ-actin (red). Areas of coincidence between the two antibodies appear yellow a). Only α-actinin is labeled in b). Bar in b). represents 10 μm.

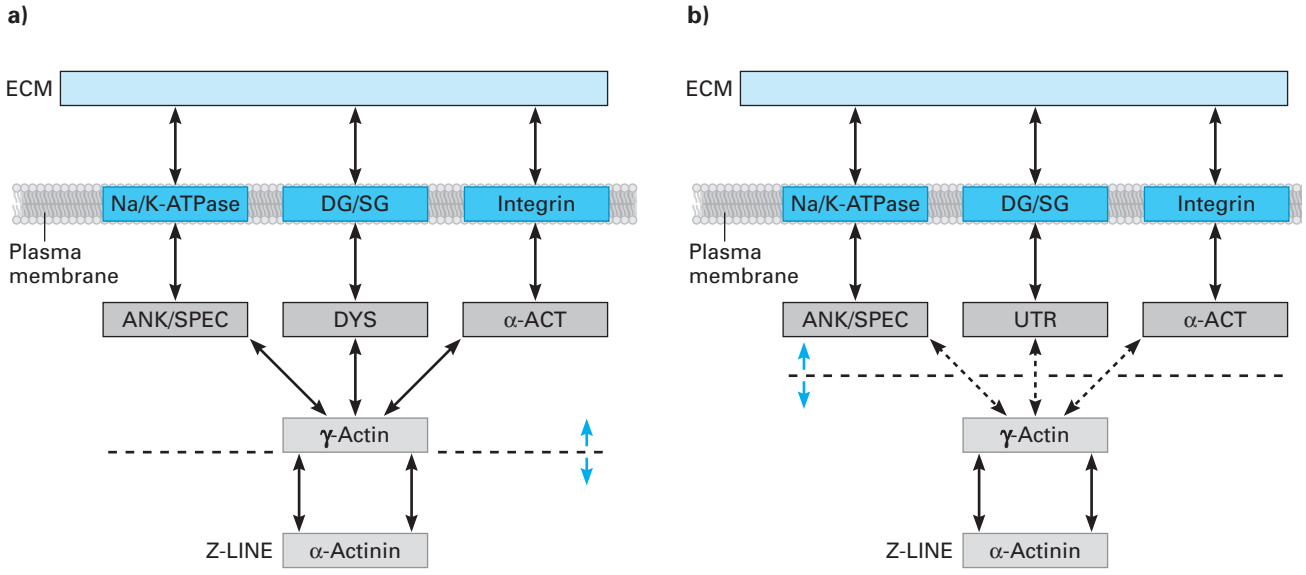


FIGURE 10.15 • Circuit diagrams of proteins adhering to *wt* and *mdx* plasma membranes. Circuit diagrams of **a)** *wt* and **b)** *mdx* linkage between the plasma membrane and cytoskeleton. The horizontal dashed line marks where the separation occurs in the experiments. Abbreviations: ANK/SPEC: ankyrin/spectrin cytoskeletal proteins; α-ACT: α-actinin cytoskeletal protein; IF: intermediate filament; DYS: dystrophin; DG/SG: dystroglycan/sarcoglycan; UTR: utrophin.

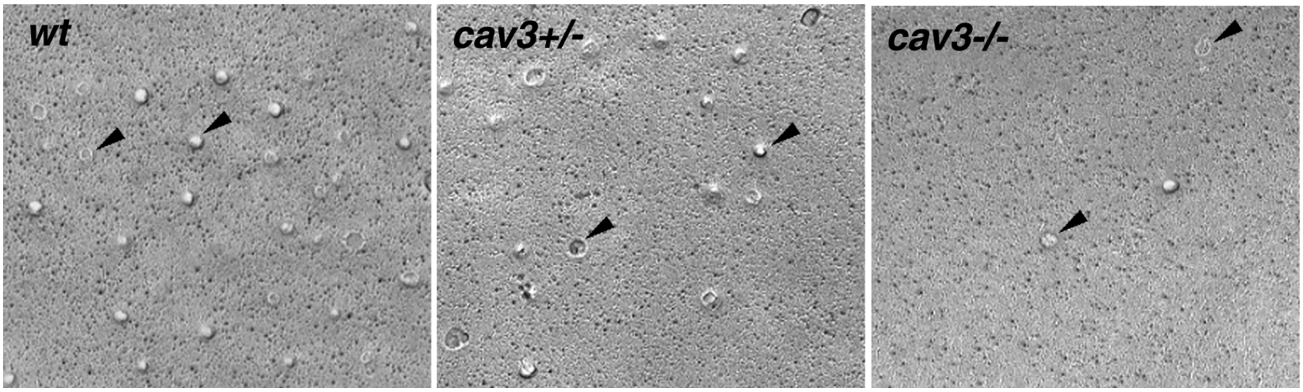


FIGURE 10.16 • Electron micrograph of the cytoplasmic side of muscle plasma membranes from the indicated mice. The bumps and craters are caveolae caught in the act of forming on the plasma membrane of muscle cells.

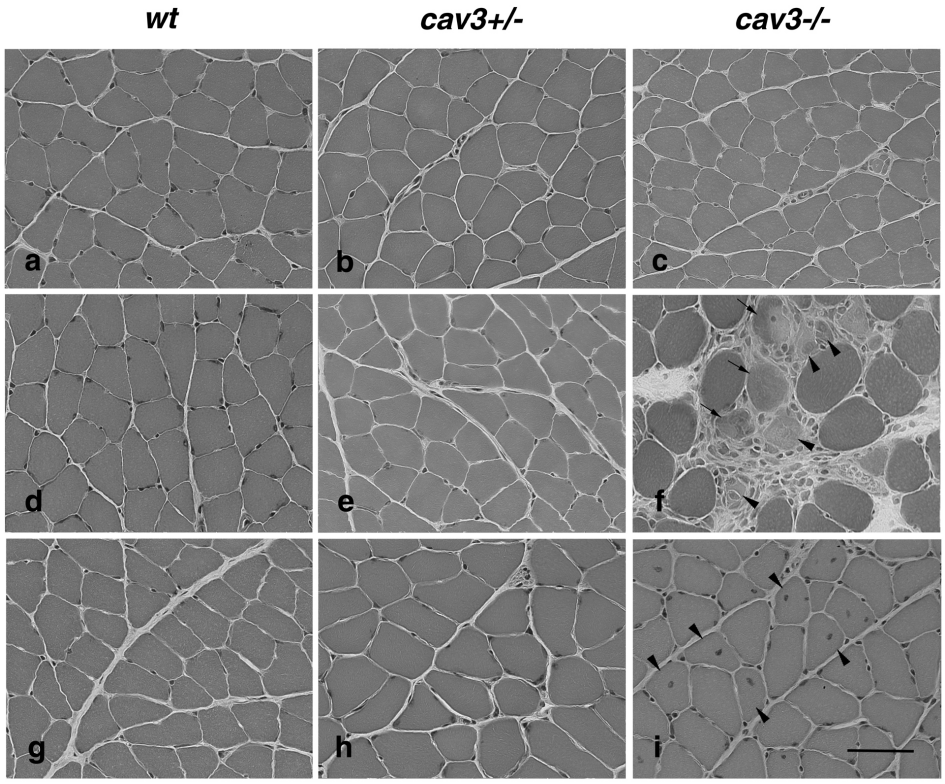
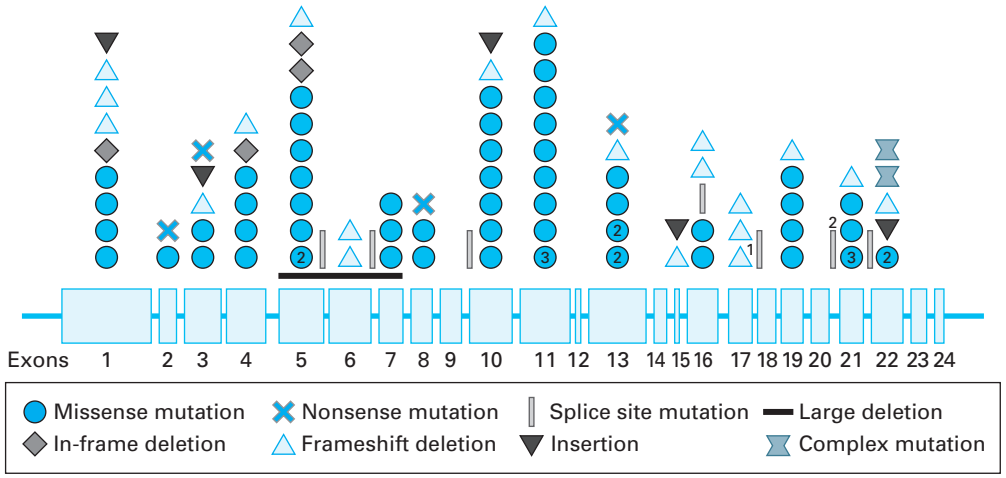


FIGURE 10.17 • Effects of caveolin mutation on muscle development. Histology of the soleus muscles from **a)** to **c)** 6-week-old mice; **d)** to **f)** 8-week-old mice, and **g)** to **i)** 12-week-old mice from three strains of mice as indicated at the top of each column. Pathology is only apparent at 8 weeks of age and macrophages have invaded the tissue (arrowheads in panel f). By 12 weeks, the muscle has regenerated but many of the nuclei are abnormally located in the middle of the cells (arrowheads in i). Black bar in the lower right corner of i) equals 50 μm.



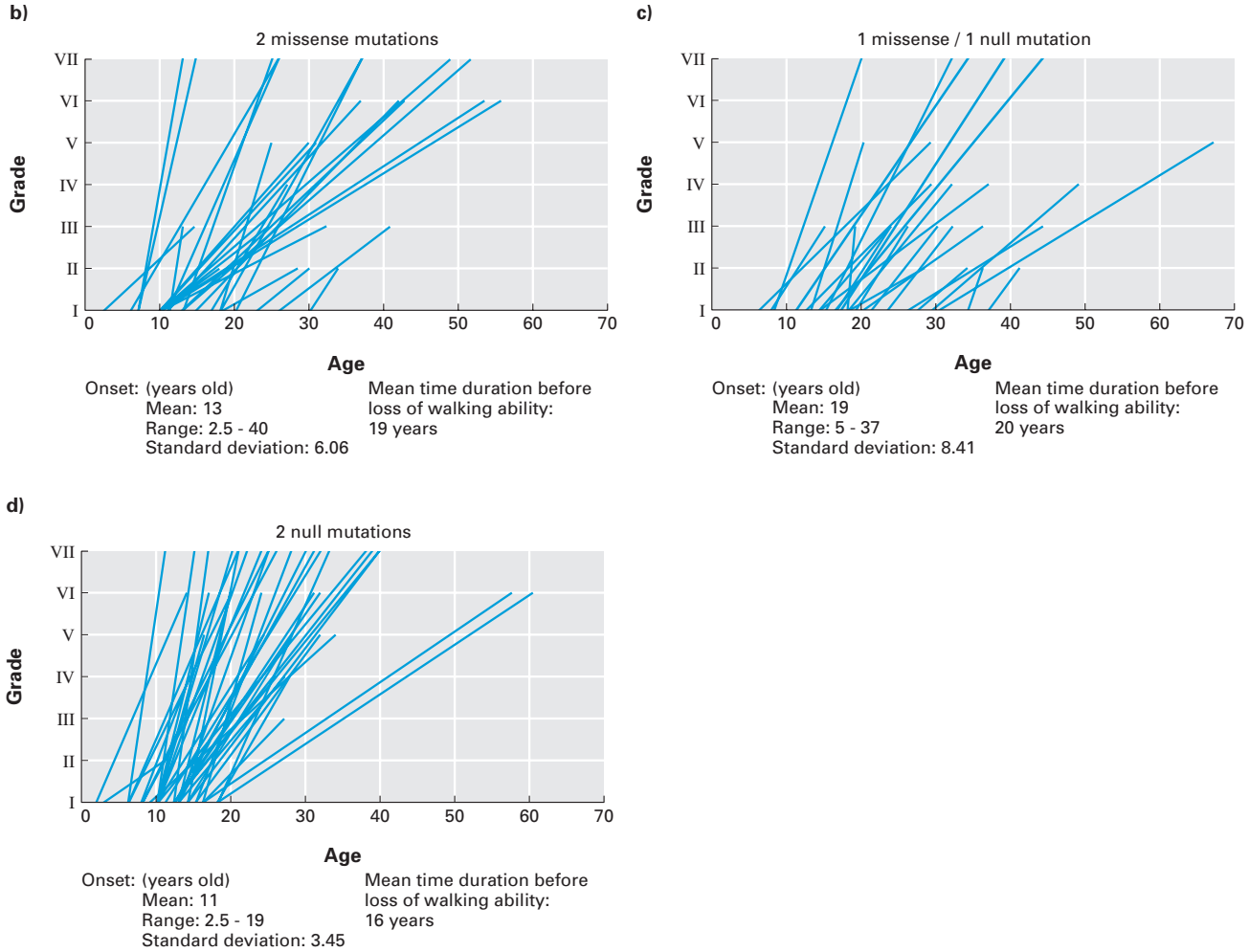


FIGURE 10.18 • Different mutations in calpain and phenotype variations. a) The 24 exons are indicated by open boxes with exon numbers below. The number of independent mutations is given either inside or above the symbol. **b)** to **d)** Progression-of-disease curves for LGMD2A patients. Functional stages are graded as I–VII. Lines are presented only for patients for whom there are at least two data points of disease progression, whereas the calculation of means and duration takes into account all available data.

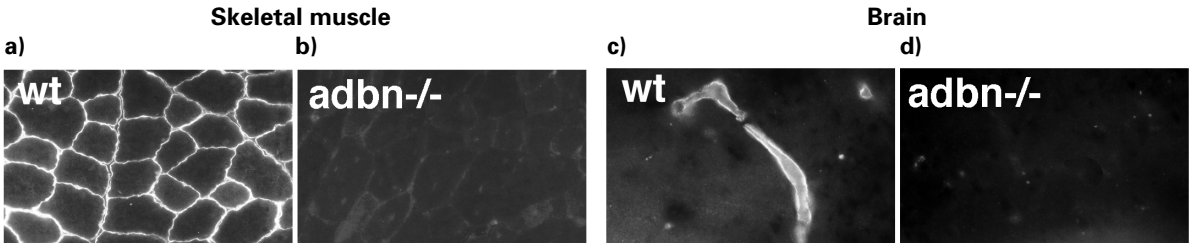


FIGURE 10.19 • Location of α-dystrobrevin in *wt* and mutant mice. Antibody labeling of *adbn* in skeletal muscle (a and b) and brain tissue (c and d) in: **a)** and **c)** *wt*, **b)** and **d)** dystrobrevin knockout mice.

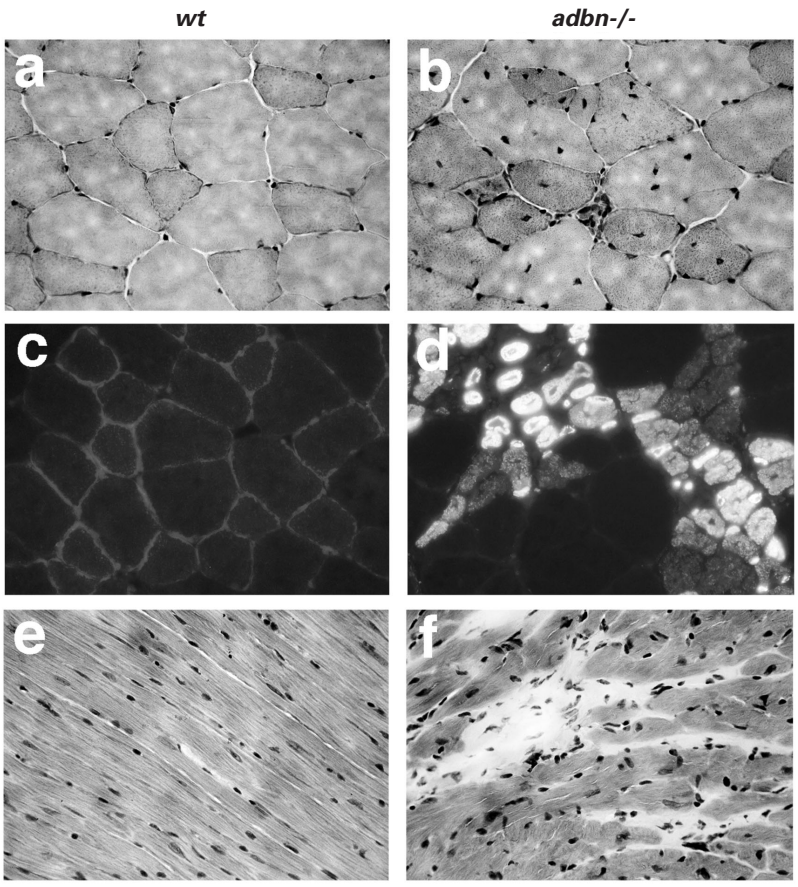


FIGURE 10.20 • Pathology of *adbn*$^{-/-}$ muscle. **a)** and **b)** Sections of skeletal muscle from *wt* and *adbn*$^{-/-}$ mice. Small areas of necrosis and centrally nucleated fibers are seen in *adbn*$^{-/-}$ muscle. **c)** and **d)** Sections of skeletal muscle labeled with an antibody to embryonic and fetal myosin heavy chains. The positive fibers in *adbn*$^{-/-}$ muscle indicate actively regenerating muscle fibers. **e)** and **f)** Sections of cardiac muscle, showing dystrophic areas in *adbn*$^{-/-}$ tissue.

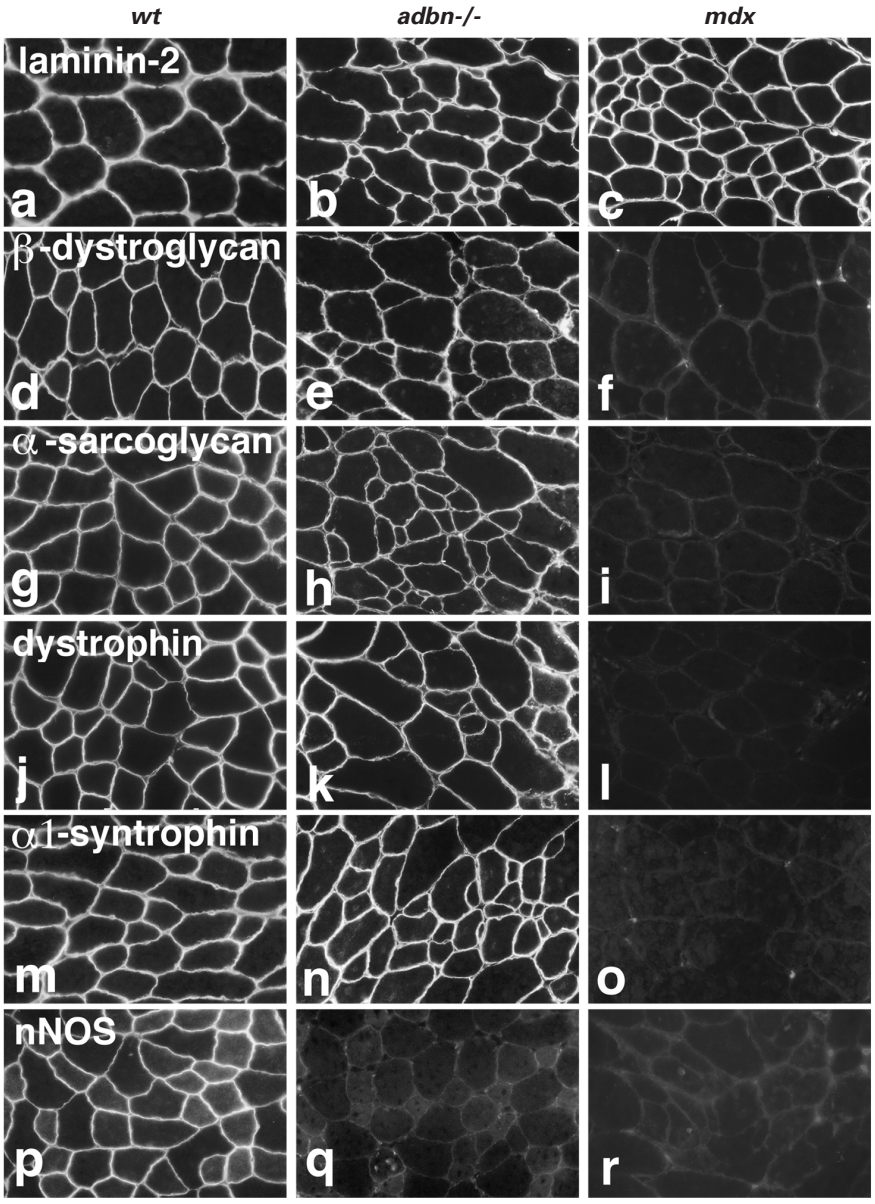


FIGURE 10.21 • Immunofluorescence labeling of skeletal muscle from *wt*, *adbn*$^{-/-}$ and *mdx* mice. **a)** to **c)** Levels of laminin-α2 were similar in all three genotypes. **d)** to **o)** Levels of the DGC proteins β-dystroglycan, α-sarcoglycan, dystrophin, and α1-syntrophin were markedly reduced in *mdx* muscle but normal in *adbn*$^{-/-}$ muscle. **p)** to **r)** In contrast, levels of nNOS were greatly reduced in both *mdx* and *adbn*$^{-/-}$ muscle.

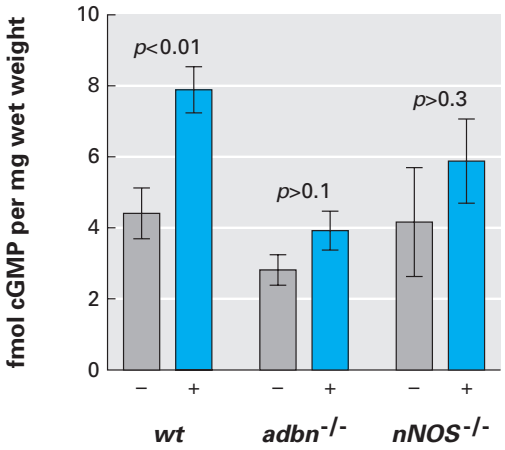


FIGURE 10.22 • cGMP levels in control and mutant muscle. Amounts of cGMP in isolated extensor digitorum muscles from unstimulated (−) or electrically stimulated (+; 30 Hz for 15 s) *wt* ($n = 4$), $adbn^{-/-}$ ($n = 6$), or $nNOS^{-/-}$ ($n = 6$) mice. Bar graphs show means ± s.e.m. The significance of differences between stimulated and unstimulated muscles was assessed by the *t*-test.