Cys-loop and a nonsense mutation in the AChR α subunit. Note eyelid ptosis, facial diplegia, open mouth, gastrostomy and lack of head control. (Upper panel reproduced from Ref. 47, by permission).

**Figure 8- 20.** A 4-year-old girl with severe EP AChR deficiency due to low-expressor mutations in the β subunit of AChR. Patient is using her fingers to elevate her eyelids. Also note open mouth and tracheostomy.

**Figure 8- 21.** Patient with EP AChR deficiency caused by recessive mutations in the AChR ε subunit gene. Note asymmetric ptosis, facial paresis, and mild esotropia. This patient is homozygous for ε553del7 that truncates the ε subunit in its extracellular domain. Single channel recordings revealed only γ-AChR at the patient's EPs.

**Figure 8- 22.** AChR deficiency caused by low-expressor or null mutations in the AChR ε subunit gene. **A** and **B**. Cholinesterase reactive EP regions in a patient with ε127ins5 and εP245L mutations (**A**) and in a control subject (**B**). Note dispersion of patient's EP regions over an extended length of the muscle fiber. **C** and **D**. Ultrastructural localization of AChR with peroxidase-labeled α-bgt at an EP from a patient harboring ε553del7 and εR311W mutations (**C**) and at a control EP (**D**). The control EP shows heavy reaction for AChR on the terminal expansions of the junctional folds. At the patient EP, the junctional folds are simplified, the reaction for AChR is attenuated (arrows), and the length of the postsynaptic membrane reacting for AChR is reduced. **A** and **B**, x310; **C**, x21,900; **D**, x6,500. (Reproduced from Ohno K et al, Hum Mol Genet 6:753-766, 1997, with permission.)

**Figure 8- 23.** Single channel currents recorded from a control EP and from EP of patient harboring two null mutations in the AChR ε subunit. Currents at patient EP have a lower amplitude and longer duration than currents at the control EP, signaling the presence of fetal AChR harboring the γ instead of the ε subunit. The dominant component of the burst duration histogram is shifted to the right for the patient. (Reproduced from Engel AG et al. Congenital myasthenic syndromes. In: Engel AG, Franzini-Armstrong C, editors. Myology, 3rd ed. New York: McGraw-Hill, 2004:1755-90, by permission.)

**Figure 8- 24.** Schematic diagram of low-expressor and null mutations reported in the α, β, δ, and ε subunits of AChR. Note that most mutations appear in the ε subunit and especially in the long cytoplasmic loop between M3 and M4. Square indicates a chromosomal microdeletion; hexagons are promoter mutations; open circles are missense mutations; closed circles are nonsense mutations; shaded circles are frameshifting mutations; dotted circles are splice-site mutations. The most likely consequence of a splice-site mutation is skipping of a flanking exon; therefore the splice-site mutations point to N-terminal codons of the predicted skipped exons. (Reproduced from Engel AG, et al, Muscle Nerve 2003; 27:4-25, by permission).

**Figure 8- 25.** Schematic diagram showing structure of the *RAPSN* gene (A), rapsyn domains (B), and identified mutations. Seven tetratricopetide repeats (TPRs) are required for rapsyn self-association; the coiled-coil domain binds to the long cytoplasmic loop of AChR subunits; the RING-H2 domain links rapsyn to β-dystroglycan. Shaded areas in (A) indicate untranslated regions in *RAPSN*. E, E-box.

**Figure 8- 26.** A six-year-old boy and a 27-year-old woman are homozygous for the N88K rapsyn mutation. The six-year-old boy can only stand with support; he has small stature, short neck, low set ears, and elbow, knee and ankle contractures. The 27-year-old woman shows only mild eyelid ptosis and mild fatigable weakness on exertion. (Left panel reprinted from Ref. 23 and right reprinted from Ref. 182 by permission.)

**Figure 8- 27.** Structural features of rapsyn deficient EPs. (A) Small cholinesterase reactive EP regions are dispersed over an extended length of the muscle fiber. (B) and (C) Multiple small nerve terminals are apposed against a highly simplified postsynaptic regions with no (B) or few (C) junctional folds. In (B), the distribution of AChR on the postsynaptic membrane, visualized with peroxidase-labeled α-bungarotoxin, is patchy. Bars 50 μm in (A) and 1 μm in (B) and (C). (Reproduced from Ref. 181 by permission).

**Figure 8- 28. A.** Genomic structure of *DOK7*. **B.** Identified rearrangements in 16 patients. Inset: Intron 1 retention, indicated by thick horizontal line.

**Figure 8- 29.** Phenotypic variability of Dok-7 myasthenia. Left panel: This patient has mild weakness and atrophy of limb girdle muscles, and mild eyelid ptosis. Right panels: This patient has severe diffuse weakness and atrophy of limb and axial muscles.

**Figure 8- 30.** Synaptic contact areas visualized with the cholinesterase reaction. Single small (B), multiple small (D-F), and perforated (A and C) contact areas are present. Nerve sprouts are recognizable (asterisk in D) as faint brown lines connecting contact areas. Bar = 50 μm.

**Figure 8- 31.** Electron micrographs of normal (A) and degenerating (B) EP in same patient. In (B) most junctional folds are replaced by globular debris (asterisk) causing widening of the synaptic space. This predicts a decreased synaptic response to ACh due to loss of AChR from tips of the destroyed folds, loss of ACh by diffusion from the widened synaptic space, and decreased input resistance of the remaining simple folds.

**Figure 8- 32.** EPs with pre- and postsynaptic abnormalities. **A.** EP region in shows marked degeneration of its junctional folds (asterisks). Schwann cell process (SC) is present amidst relics of the folds. A nerve sprout appears near the top. **B.** A highly abnormal EP region devoid of nerve terminal. Some junctional folds are degenerating (asterisk). The subsynaptic sarcoplasm harbors large myeloid structures. A nerve sprouts surrounded by Schwann cell (SC) appears above the junction.

**Figure 8- 33.** Patient with myasthenic syndrome caused by mutation of the $Na_v1.4$ sodium channel. Note asymmetric ptosis, strabismus, lumbar lordosis, and adduction deformities of knees and ankles. (Reproduced from Engel AG et al. Congenital myasthenic syndromes. In: Engel AG, Franzini-Armstrong C, editors. Myology, 3rd ed. New York: McGraw-Hill, 2004:1755-90, by permission.)

**Figure 8- 34. A.** Scheme of skeletal muscle sodium channel $Na_v1.4$ encoded by *SCN4A* and the identified mutations. **B.** Gating behavior of mutant and wild-type sodium channels expressed in HEK cells. Channel availability (*left*) after a 300 ms prepulse is left-shifted –33 mV for the

V1442E channel, and –7 mV for the S246L channel, whereas activation *(right)* is unchanged. **C.** Relative Na current during a 50-Hz train of 3 ms depolarizations to -10 mV from a holding potential of -100 mV. Every 200$^{th}$ response is shown after the break at the 10$^{th}$ pulse.

**Figure 8- 35.** Myopathy and CMS caused by plectin deficiency. **A** and **B**. Note marked variation in fiber size, regenerating fiber elements (asterisks), endomysial fibrosis in (B), and clusters of large nuclei at periphery of several fibers. (C) Alizarin red stain reveals focal calcium deposits in two fibers. (D) Multiple small cholinesterase reactive EP regions arrayed over an extended length of the fiber.

**Figure 8- 36.** Ultrastructural findings in abnormal muscle fibers (A) Note subsarcolemmal rows of large nuclei harboring multiple prominent chromatin bodies. (B) and (C) Subsarcolemmal and intrafiber clusters of mitochondria surrounded by fiber regions devoid of mitochondria. (D) Aberrant and disrupted myofibrils surrounded by clusters of mitochondria intermingled with glycogen, ribosomes, and dilated vesicles (x). Note pre-apoptotic nucleus at upper right. (E) Focal sarcolemma defects due to gaps in the plasma membrane. Where the plasma membrane is absent, the overlying basal lamina is thickened (x). Small vesicles underlie the thickened basal lamina. Asterisks indicate segments of the preserved plasma membrane. Bars = 4 μm in (A), 3 μm (B), (C), 1.4 μm in (D), 1 μm in (E). (Reprinted by permission from Ref. 219).

**Figure 8- 37.** Abnormal EP regions in plectinopathy. On the right, the junctional folds have disappeared and the nerve terminal is absent (asterisks). Grey streaks indicate basal lamina remnants that had invested preexisting folds. At the center a nerve sprout (ns) and a nerve terminal are separated by a Schwann cell process from the underlying degenerate folds On the left, the postsynaptic region is only partially occupied by the nerve terminal (nt). Bar= 1 μm.

**Figure 8- 38.** CMS associated with centronuclear myopathy. **A.** Patient at age 39 years. In upper panels, note decreased bulk of pectoralis major, proximal arm and thigh muscles, asymmetric enlargement of calf muscles, and increased lumbar lordosis. In lower panel shows patient rising from the floor with Gowers maneuver. **B.** Serratus anterior muscle, H&E stain. Most fibers contain internal nuclei. Bar = 50 μm. **C-E.** Paired fluorescence localization of AChE (green signal) and AChR (red signal) at control (**C** and **D**) and patient (**E** and **F**) EPs. AChR expression is mildly attenuated at patient EPs. **G** and **H.** Synaptic contacts visualized with reaction for AChE on teased patient fibers. Note double EP in (E) and multiple small EP regions (F). Bar = 20 μm. (Reprinted from Ref. 231, by permission.)

**Figure 8- 39.** Endplate ultrastructure. **A.** EP region shows poorly developed junctional folds with only a single secondary cleft opening into the primary synaptic cleft. **B.** At this EP region the postsynaptic membrane the highly simplified postsynaptic region lacks junctional folds. Empty mitochondrion represents fixation artifact. **C.** Unstained section showing localization of AChR with peroxidase labeled α-bungarotoxin. The EP region has only few folds and clefts and AChR appears mostly on tops of the folds. Bars = 0.5 μm.

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