Myelin sheaths are a fundamental adaptation of vertebrates. Our lives depend on high-velocity, high-frequency propagation of axonal “saltatory conduction” of action potentials over long distances by the myelinated fibers. Although the structural components of myelin have been well characterized, the molecular mechanisms regulating the formation and maintenance of myelin are less well understood. Recent studies have revealed that a wide variety of devastating neurological diseases result from genetic or autoimmune disruption of the intricate glial pathways that are specialized to support myelin integrity, particularly those glial mechanisms that provide for long-distance siphoning of K⁺ released from myelinated axons during each action potential and for transport and release of obligatorily associated osmotic water. In that regards, it is noteworthy that recessive mutations in the gene GJC2 encoding gap junction connexin-47 (Cx47) are one cause of Pelizaeus-Merzbacher-like disease (PMLD), which is characterized by severe vacuolization and myelination defects, and demyelination. Cx47 is expressed in oligodendrocytes, the myelin-forming cells in CNS. Gap junction channels are formed among oligodendrocytes (O/O), among astrocytes (A/A), between oligodendrocytes and astrocytes (O/A), which results in formation of an extensive panglial network interconnected via gap junction channels. We have investigated the gap junction channels formed by wild type Cx47 involved in the O/O and O/A coupling and the effects of Cx47 mutations that lead to PMLD. The results show that the O/O and O/A channels of Cx47 have specific properties of permoselectivity to ions and other molecules, and that PMLD mutants lead to a loss-of-function, suggesting that if the O/O and O/A coupling is disrupted, K⁺ siphoning is blocked, axonal saltatory conduction ceases and myelin is destroyed.

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