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Review article

Molecular and clinical features of inherited neuropathies due to PMP22 duplication

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ABSTRACT

PMP22 is a transmembrane glycoprotein component of myelin, important for myelin functioning. Mutation of PMP22 gene which encodes for the production of PMP22 glycoprotein is associated with a variety of inherited neuropathies. This literature review sought to review the molecular mechanism and clinical features of inherited neuropathies caused by PMP22 duplication. PMP22 duplication causes CMT1A which accounts for more than half of all CMT cases and about 70% of CMT1 cases. It manifests with muscle weakness, depressed reflexes, impaired distal sensation, hand and foot deformities, slowing of NCV and onion bulbs. With no specific treatment available, it is managed conservatively. Future treatment may be based on the molecular genetics of the disease.

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1. Introduction

Peripheral myelin protein 22 kDa (PMP22) is a unique myelin glycoprotein component belonging to the family of cellular membrane proteins characterised by a four trans-membrane domain [66]. PMP22 is expressed in myelinating Schwann cells of the peripheral nervous system, where it plays an important role in formation and maintenance of compact myelin. It can also be detected in non-neural tissues where its function remains unknown [51]. The PMP22 gene mapped to human chromosome 17p11.2–p12 encodes for the production of PMP22 glycoprotein. Alterations in PMP22 gene expression are associated with inherited demyelinating peripheral neuropathies [31,41] These mutations appear to cause a gene–dose effect, leading to abnormal synthesis and functioning of myelin sheaths. In PMP22 duplication an increased dosage of PMP22 is the most likely pathogenic mechanism of the disease [44].

Charcot–Marie–Tooth type 1A (CMT1A) is caused by PMP22 duplication; it is the commonest of hereditary neuropathies, accounting for more than half of all CMT cases and about 70% of CMT1 cases [68]. CMT has an estimated prevalence of 1/2500 [73]. CMT1A manifests with muscle weakness and wasting, decreased reflexes, impaired distal sensation, deformities of feet and hands, slowing of nerve conduction velocity (NCV) and hypertrophic segmental demyelination and remyelination pathologically appearing as onion bulbs [14,46]. PMP22 point or frameshift mutations cause hereditary neuropathy with liability to pressure palsy (HNPP), while missense mutations cause more severe forms of CMT called Dejerine–Sottas syndrome (DSS) and congenital hypomyelinating neuropathy (CHN) [74]. Roussy–Levy syndrome (RLS) is also caused by a PMP22 duplication and generally regarded as a phenotypic variant of CMT1A [2].

Recently much interest in the molecular and genetic studies of inherited neuropathies has led to more than 60 CMT-associated genes being identified; which have been attributed to the development of next-generation sequencing [64]. These neuropathies display marked clinical and genetic heterogeneity [11]. Therefore the aim of this literature review focuses on the molecular mechanism and clinical features of inherited neuropathies caused by PMP22 duplication (CMT1A).

2. Structure and function of peripheral myelin protein 22

Myelin sheet is a specialised cover of the peripheral nerves derived from Schwann cells; made up of the compact and non-compact myelin. The compact myelin forms the bulk of the myelin sheet composed of cholesterol sphingolipids, proteins like PMP22, protein myelin zero (PMZ or P_0) and myelin basic protein (MBP). The non-compact myelin is located around paranodes and is composed of connexin 32 (Cx32) and myelin associated glycoprotein (MAG) [3,37]. PMP22 is a 22 kDa intrinsic membrane glycoprotein of the compact myelin sheet made of 160 amino acids. It forms a four transmembrane putative domain, constituting about 2 to 5% of proteins in the compact myelin [43,71] [Fig. 1].

PMP22 synthesis occurs in the endoplasmic reticulum (ER), where it is glycosylated and co-localised with binding immunoglobulin protein (BiP) — an ER resident chaperone, from where it is transported to the Golgi apparatus and finally incorporated into the cell membrane of Schwann cells [17,26]. PMP22 has an extracellular N-linked sugar moiety which serves as a homophilic adhesion molecule mediating interactions between proteins [75]. PMP22 is highly expressed in myelinating Schwann cells of peripheral nerves and dorsal root ganglia (DRG) in adults; and it is down-regulated during axonal degeneration or transection [17]. It is expressed in other tissues during embryogenesis like the neural crest, cranial nerves, heart, intestine, and cochlea, where it may be implicated in cellular processes central to tissue development and differentiation [75]. Its cochlear expression may explain why some PMP22 mutations cause deafness [59].

The function of PMP22 is not fully known, but it may serve a growth modulatory function during myelination-regulating cell proliferation, differentiation and death [44]. PMP22 is up-regulated during Schwann cell proliferation and may be involved in DNA metabolism and cell-cycle regulation [27]. Notterpek et al. [51] observed that PMP22 is associated with tight junction complex markers zonula-occludens 1 and occludin, involved in adhesion with other cells and the extracellular matrix, and noted that the interaction between the myelin proteins and with phospholipids enables the proper functioning of myelin. In non-neural tissue such as cultured fibroblasts PMP22 expression serves as growth arrest-specific (gas-3) function [75].

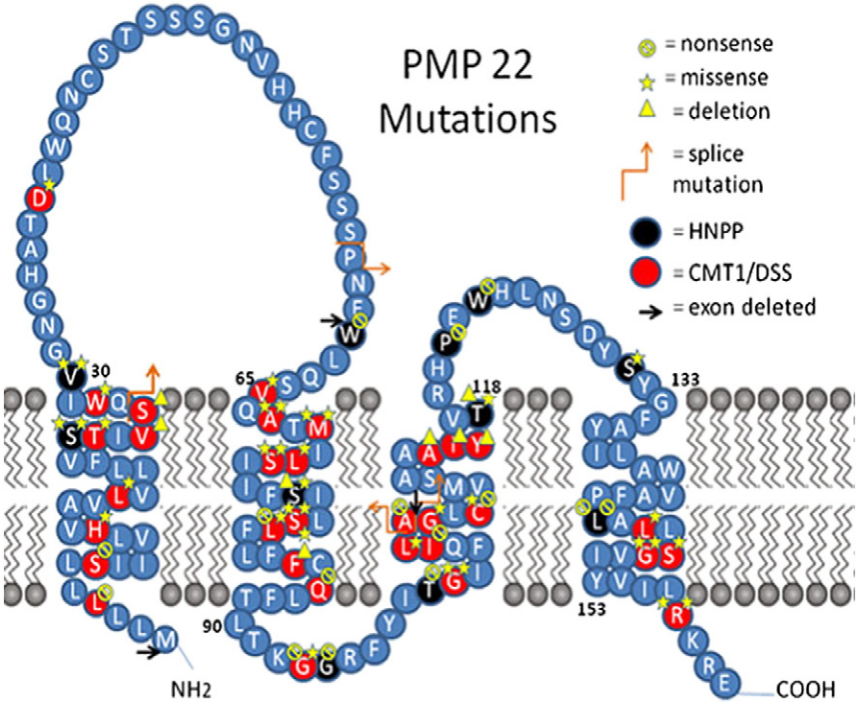

Fig. 1. The molecular structure of PMP22. Made up of 160 amino acids and showing sites for mutations. Adapted from Li et al. [41].