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Review article

Charcot–Marie–Tooth: Are you testing for proteinuria?

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ABSTRACT

Charcot–Marie–Tooth disease (CMT) is a clinically and genetically heterogeneous group of inherited disorders affecting motor and sensory nerves of the peripheral nervous system. CMT has been reported to be associated with renal diseases, mostly focal segmental glomerulosclerosis (FSGS). However, it was unknown whether these two clinical manifestations represent one common underlying disorder or separate disease entities. Several reports have shown a high prevalence of mutations (75%) in the inverted formin gene (*INF2*) in patients with CMT-associated glomerulopathy, suggesting that these mutations are a common cause of the dual phenotype. For this reason, we strongly suggest to screen for proteinuria in CMT patients, in order to identify patients with this renal-neurologic phenotype in an early stage, and to perform genetic testing for *INF2* mutations.

Contents

Abbreviations: ACE, I angiotensin converting enzyme inhibitor; AD, autosomal dominant; ARB, angiotensin receptor blocker; CDC42, cell division cycle 42; CMT, Charcot–Marie–Tooth disease; DAD, diaphanous-autoregulatory domain; DID, diaphanous-inhibitory domain; ESRD, end stage renal disease; FSGS, focal segmental glomerulosclerosis; INF2, inverted formin 2; MAL, myelin and lymphocyte protein; MPZ, myelin protein zero; MRI, magnetic resonance imaging; NCV, nerve conduction velocity; PMP22, peripheral myelin protein 22.

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Charcot–Marie–Tooth (CMT) disease (MIM 118300) was first described in the late nineteenth century by Frenchman Jean Martin Charcot, his pupil Pierre Marie and their British colleague Howard Henry Tooth. CMT is one of the most common inherited neurologic diseases, with a prevalence of 1 in 2500 individuals.[1] It represents a heterogeneous group of hereditary peripheral motor and sensory neuropathies. The main phenotype consists of progressive distal muscle weakness and atrophy, reduced tendon reflexes and foot and hand deformities.

Until now, no curative treatment is available, only preventive and symptomatic measures can be taken. CMT is caused by inherited or *de novo* mutations in genes involved in the structure and function of the myelin sheath or the axon of peripheral nerves. Nerve conduction velocity (NCV) studies allow for classification into demyelinating (CMT1, reduced NCVs), axonal (CMT2, slightly reduced or normal NCVs) and intermediate subtypes. However, these terms should not be used based on a single NCV result, but they should be correlated with histopathological evidence of demyelinating and/or axonal lesions. These subtypes are further categorized based on inheritance pattern and gene mutations.[2] Advances in molecular biology have demonstrated that at least 50 genes or loci are associated with CMT.[2,3] Mutations in the genes peripheral myelin protein 22 (*PMP22*) and myelin protein zero (*MPZ*) underlie most cases of CMT. PMP22 and MPZ are necessary components of compact myelin in the peripheral nervous system.

In CMT patients, an increased prevalence of glomerulopathies, mostly focal and segmental glomerulosclerosis (FSGS), has been documented.[4] The estimated prevalence of FSGS in CMT is 1 in 400 CMT patients, compared to 1 in 1000 000 in the general population.[5] FSGS is a descriptive diagnosis referring to the histological pattern of glomerular scarring, rather than a single disease entity. It is classified according to the underlying pathophysiological mechanism into primary or idiopathic FSGS and secondary FSGS. The latter is caused by adaptive structural-functional responses mediated by glomerular hypertrophy or hyperfiltration, e.g. in case of reduced renal mass or obesity and hypertension; or can be due to genetic defects, infections, toxins or other underlying glomerular diseases.[6] Clinically, FSGS is associated with proteinuria, either isolated, or as part of a glucocorticoid-resistant nephrotic syndrome, loss of glomerular filtration rate (GFR) and is associated with a high rate of progression to end-stage renal disease (ESRD).[7]

Currently, mutations in several genes, highly expressed in podocytes, are known to cause familial FSGS.[8,9] *INF2* mutations account for 12–17% of autosomal dominant (AD) cases of FSGS.[8,9] The *INF2* gene encodes a member of the diaphanous formin subfamily of actin regulating proteins. The protein INF2 contains an N-terminal diaphanous-inhibitory domain (DID), the formin homology domains FH1 and FH2, and a C-terminal diaphanous-autoregulatory domain (DAD) (Fig. 1). This endoplasmic reticulum-associated protein mediates the severing of actin filaments and is the only formin that promotes not only actin polymerization, but also actin depolymerization. INF2 is regulated by auto-inhibition through DID-DAD interaction.[10] Only *INF2* DID mutations have been described in familial FSGS. DAD mutations are thought to be lethal in humans based on the observed collapse of endoplasmic reticulum in *in vitro* experiments.[9] The molecular mechanisms of *INF2* DID mutations in kidney glomerular podocytes resulting in proteinuria remain unclear, but an important role of cytoskeletal dynamics required for the maintenance of podocyte function has been suggested.[11]

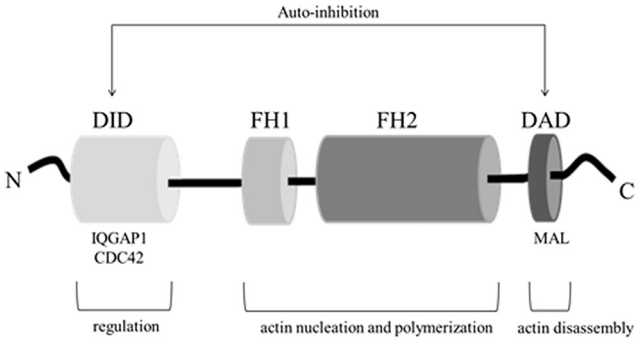

Fig. 1 – Simplified model of INF2 domain structure, relevant binding partners and function. The protein INF2 contains an N-terminal diaphanous-inhibitory domain (DID), the formin homology domains FH1 and FH2, and a C-terminal diaphanous-autoregulatory domain (DAD). INF2 mediates actin polymerization and actin disassembly through its different domains and is regulated by auto-inhibition through DID-DAD interaction. The relevant binding partners for this review are CDC42, interacting with DID; and MAL, interacting with DAD. Only INF2 DID mutations have been described in familial FSGS and CMT-FSGS.

Apart from podocytes, INF2 is strongly expressed in Schwann cell cytoplasm. INF2 has been demonstrated to co-localize and interact with the myelin and lymphocyte protein (MAL)[11–13] and with the GTP-binding protein cell division cycle 42 (CDC42).[12,13] Because MAL[14] and CDC42[15] are implicated in essential steps of myelination and myelin maintenance, *INF2* mutations are considered to be the missing link between FSGS and CMT disease.

Boyer et al. recently identified in 75% of index patients with both CMT and histologically proven FSGS heterozygous mutations in exons 2 and 3 of the gene *INF2*, encoding DID.[11] All patients presented with an intermediate type of CMT and 91% of them developed ESRD at a median age of 21 years. No *PMP22* or *MPZ* mutations were found in the studied patients, and no *INF2* mutations were found in a control population nor in patients with isolated CMT. Electron microscopic evaluation of nerve biopsies of study patients showed unusual proliferations of flattened Schwann cell cytoplasm and anomalies of non-myelinating Schwann cell cytoplasm with supernumerary extensions. These features have not been described in other intermediate CMT subtypes. Moreover, there was an abnormal beta-actin accumulation in Schwann cell cytoplasm. This has never been reported in any type of peripheral neuropathy. These neuropathological results support the concept of a global actin cytoskeleton disorder, in which the actin cytoskeleton perturbation leads to a defective Schwann