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Hereditary neuropathies: An update

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ABSTRACT

Hereditary neuropathies are the most common inherited neuromuscular diseases. Charcot-Marie-Tooth (CMT) disease represents the most common form with an average prevalence ranging from 1/2500 to 1/1200, depending on the studies. To date and with the advances of the latest generation sequencing, more than 80 genes have been identified. Although the common clinical phenotype comprises a progressive distal muscle weakness and sensory loss, foot deformities and decreased or absent tendon reflexes, clinical and electrophysiological phenotypes exhibit great variability. Moreover, atypical phenotypes are arising, overlapping with spastic paraplegia, hereditary sensory neuropathies or amyotrophic lateral sclerosis. The causative genes are involved in various biological processes such as myelin development and maintenance, biosynthesis and degradation of proteins, neuronal structural maintenance, axonal transport, endocytosis, membrane dynamics, ion-channel function and the mitochondrial network. An accurate genetic diagnosis is important for appropriate genetic counselling and treatment options. Therapeutic advances, particularly small interfering RNA therapy, are encouraging in hereditary transthyretin amyloid neuropathy.

Hereditary neuropathies encompass a large number of diseases that present with a unique or predominant neuropathy. This term is used in opposition to multisystem diseases such as mitochondrial or metabolic diseases, or spastic paraparesia and spinocerebellar ataxias. The latest generation sequencing methods have linked individual genes to very different phenotypes, both clinically and electrophysiologically. Thus, the genes generally linked with central nervous system diseases are now also recognized as the cause of hereditary neuropathies. Similarly, one same gene can give rise to different forms of Charcot-Marie-Tooth (CMT) disease such as the demyelinating form (CMT1), the axonal form (CMT2), or the intermediary form (CMTI) defined respectively by their different median motor nerve conduction velocity (MCV): < 35 m/s; > 45 m/s; between 35 and 45 m/s.

In this context, we describe the clinical, electrophysiological characteristics of the genes identified over the last two years in hereditary sensorimotor neuropathies or CMT diseases and sensory and dysautonomic neuropathies, and also detail advances made in the domain of transthyretin amyloid neuropathies.

1. New advances in CMT diseases

1.1. *Aminoacyl-tRNA transferases*

Aminoacyl-tRNA transferases – at least 20 types are described – are enzymes implicated in the first steps of translation. To date, four of these aminoacyl-tRNA

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synthetases were implicated in the dominant autosomal forms of CMT: glycyl-tRNA synthetase (GARS) responsible for CMT2 and a distal hereditary motor neuropathy (dHMN) form affecting the upper limbs [1]; tyrosyl-tRNA synthetase (YARS) responsible for one form of CMTI [2]; alanyl-tRNA synthetase (AARS) responsible for a CMT2 and dHMN [3]; and methionyl-tRNA synthetase (MARS) responsible for a CMT2 identified in a single family [4].

1.1.1. *HARS (histidyl-tRNA synthetase)*

HARS (histidyl-tRNA synthetase) is a new gene implicated in different forms of CMT. Four families (23 members) exhibiting dominant autosomal transmission of CMT disease have been identified with high throughput exome sequencing and by linkage studies. Age at symptom onset (motor deficit in the lower limbs) ranges from 7 to 56 years. Asymptomatic or quasi-asymptomatic forms have been observed in patients over 60 years. The predominant motor deficit affects the anterior compartment of the lower limbs, leading to stepping. Most patients can walk. Mutations of the *HARS* gene give rise to a wide electrophysiological spectrum including CMT1, CMT2, CMTI and even one type of dHMN with brisk tendon reflexes [5].

1.1.2. *AARS (alanyl-tRNA synthetase)*

AARS (alanyl-tRNA synthetase) has also been associated with a wider spectrum of phenotypes. A sequencing study conducted in the United Kingdom and Ireland identified six families with *AARS* gene mutations who had axonal, intermediary, and sometimes asymmetrical forms of CMT with symptom onset ranging from 18 to 50 years in most cases. These authors also observed that acute flare-ups can occur in the intermediary forms of CMT, sometimes resembling chronic inflammatory polyradiculoneuropathies. This study also described severe infantile forms of neuropathy beginning before the age of one year, affecting predominantly the lower limbs [6].

The families with *AARS* mutations reported earlier in France also have different phenotypes: CMT2, CMTI, and even dHMN (3). For the clinician, it is thus very difficult to target this gene in a family with CMT or dHMN since the phenotype is undistinguishable from other types of CMT2 or dHMN. Routine identification of this type of gene would require use of a large panel of genes specifically dedicated to the search for hereditary neuropathy.

1.2. *Molecules implicated in axonal transport*

Molecules implicated in axonal transport: variable expression affecting the central nervous system and the peripheral nervous system.

1.2.1. *DYNC1H1 (dynein, cytoplasmic 1, heavy chain 1)*

DYNC1H1 (dynein, cytoplasmic 1, heavy chain 1) codes for a cytoplasmic subunit of the dyenin/dynactin motor complex enabling retrograde transport of vesicles along the microtubules. Mutations of this gene are responsible for an autosomal dominant dHMN predominating in the lower limbs with malformations of the cerebral cortex and also a form of CMT2. An international study conducted on 1024 exomes grouping together the motoneuron diseases identified three families with *DYNC1H1* mutations expressing different phenotypes: two with DHMN predominating in the lower limbs and one presenting hereditary spastic paraparesis associated with complex partial epilepsy subsequent to polymicrogyria [7]. Another study conducted with a cohort of 30 cases of *DYNC1H1*-linked dHMN noted the variability of the severity of these neuropathies that ranged from arthrogryposis and absence of achieving motor milestones to moderate motor forms affecting the distal muscles of the lower limbs with preserved walking capacity. These authors observed that nine of the 30 cases had cognitive impairment associated with polymicrogyria [8]. Similarly, the *BICD2* gene, coding for an adapting protein of the dynein/dynactin motor complex, is responsible for either arthrogryposis, minimally or non-evolutive motor neuropathies of the lower limbs, or autosomal dominantly transmitted spastic paraparesis [9]. Muscle imaging is usually not very useful for the study of hereditary neuropathies but is highly contributive for the diagnosis of motor neuropathies linked to genes *BICD2* and *DYNC1H1*. Indeed, imaging of the thigh muscles reveals fatty atrophy of the quadriceps and hamstrings that contrasts with the preservation of the semitendinosus and the adductor muscles (Fig. 1).

Spatacsin was recently identified in an autosomal recessive form of CMT2 [10]. This gene had been identified earlier in an

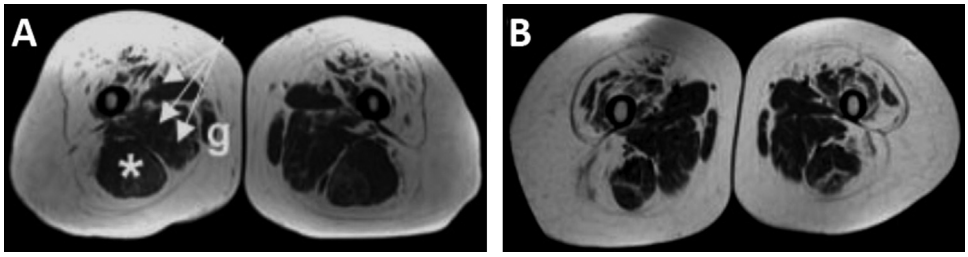

Fig. 1 – T1-weighted axial muscle magnetic resonance images of the lower limb in individuals with spinal muscular atrophy due to mutations in *BICD2*. Note the variable fatty replacement of the muscles of the anterolateral thigh but relative sparing with or without relative hypertrophy of the semitendinous muscle (white asterisk, A), the medially placed adductor muscles (adductor longus, brevis and magnus; white arrows in A), and gracilis ('g' in A).
Figure extracted from the article: "Phenotypic and molecular insights into spinal muscular atrophy due to mutations in *BICD2*. Brain 2015;138:293–310." published with permission for reproduction.