Charcot-Marie-Tooth disease type-2 associated with two missense mutations in MME gene

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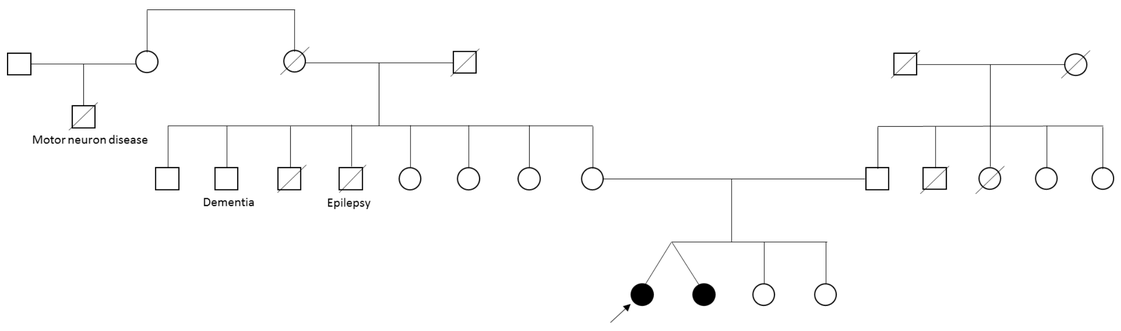
Background

The membrane metalloendopeptidase (MME) gene encodes a zinc-dependent metalloprotease, also known as neprilysin (NEP), which cleaves and inactivates a variety of neuropeptides. NEP has been found not only in the central nervous system (CNS), being one of the most prominent β-amyloid (Aβ)-degrading enzyme, but also in the peripheral nervous system (PNS) where its role is still unclear.
Mutations in MME gene have been related to autosomal-recessive late-onset Charcot-Marie-Tooth type-2 (CMT2) characterized by an axonal motor and sensory neuropathy resulting in muscle atrophy, slowly progressive weakness and sensory impairment in the distal limbs with gait disturbance. To date, all patients carried loss-of-function mutations in a homozygous or compound heterozygous state and missense mutations have been described only in trans with another different truncating mutation (e.g. nonsense, splice-site, frameshift). More recently, MME mutations segregating in an autosomal-dominant fashion with uncomplete penetrance have been described.

Case report

Gender: female
Age: 39-year-old
Ethnic group: caucasian
Physiological history: normal motor milestones, good sport practice (dance and track and field)
Past history: uneventful, in particular no ankle sprains or falls
Family history: urelated parents; one homozygous twin with similar symptoms at the same age



Clinical presentation: numbness, cold sensation and cramps in the lower limbs (LL) together with walking difficulty on toes and heels; then progressive LL distal weakness (requirement of bilateral ankle foot stabilization) and impaired hand dexterity

Neurological examination (53-year-old)
- cranial nerves: intact
- muscle tone: normal
- muscle thophism: athrophy of hand interossei, first lumbrical, anterior and posterior leg compartments bilaterally
- scheletric abnormalities: bilateral high arches; no hammer toes or scapular winging
- muscle strenght: distal upper (UL) and lower limbs (LL) weakness (hand finger extensors and first dorsal interosseus 4/5, abductor pollicis brevis 3/5, foot dorsiflexors and plantar flexors, toe extensor and flexor 0/5 bilaterally)
- deep tendon reflexes: normal in the UL, absent in the LL
- plantar response: mute
- light-touch: normal in the UL, reduced at toe
- pinprick: normal in the UL, reduced at ankle
- vibratory sense: normal in the UL, reduced at knee
- position sense: normal at four limbs
- finger-to-nose and heel-to-shin test: normal
- gait: bilateral steppage, impossible on heels and toes

Nerve conduction study (NCS): axonal sensory and motor polyneuropathy

Nerve	Latency (ms)	Amplitude (μV)	Velocity (m/s)
Sensory NCS			
L Median	3.75	6.2	41.3
L Ulnar	2.60	5.9	46.2
R Sural	4.15	1.6	36.1
Motor NCS			
R Median	4.65	1.2	36.2
L Ulnar	2.85	4.6	62.1
R/L Common peroneal	Unexcitable		

Sural nerve biopsy: reduction of myelinated nerve fibers and active axonal degeneration

Genetic analysis
- targeted Sanger sequencing of **MPZ**, **GJB1**, **GDAP1**, **NEFL**, **FKRP**, **BSCL2**, **HSPB1-8** and **MFN**: negative

SureSelect Focused Exome sequencing:
TWO MISSENSE MUTATIONS in MME
[c.263G>A,p.C88Y;c.1279T>C,p.Y427H]

Segregation analysis: in progress

Discussion and conclusions

We report two novel missense mutations in *MME* in a case of late-onset CMT2. The two mutations were absent from control databases (e.g. ExAC), affected highly conserved aminoacids and were predicted to have deleterious effects by in silico analysis. Recent data suggest that diminished neprilysin activity damages peripheral nerves probably by insufficient turnover of molecules that are crucial for their well-being.

The segregation analysis to prove that the two mutations reside on different alleles is still ongoing. We hypothesize an autosomal-recessive mode of inheritance as the most likely given the clinical phenotype and the absence of a family history although a dominant inheritance with uncomplete penetrance cannot be excluded.