

Membrane metalloendopeptidase (MME) gene mutation associated type 2T late-onset Charcot-Marie-Tooth disease: Case report

Marcos RG de Freitas, Marco Orsini, Antônio Marcos da Silva Catharino, Mauricio Sant' Anna Junior, Felipe dos Santos Souza, Acary Souza Bulle Oliveira

ABSTRACT

Introduction: Charcot-Marie-Tooth disease type 2T (CMT2T) is a slowly progressive autosomal recessive sensorimotor peripheral neuropathy with onset in middle age. Some patients may carry heterozygous MME (membrane metalloendopeptidase gene) mutations. The mutations, which were found by whole-exome sequencing, segregated with the disorder in the families in which segregation was analyzed in our patient, such as, clinical picture and prognosis.

Case Report: We report a CMT (type 2) case with symmetric foot deformities, slowly progressive weakness and wasting in the distal parts of lower limbs, and length-dependent sensory loss. Symptoms, such as paraesthesias and numbness were also present. We identified recessive mutations in MME, after thorough clinical and electrophysiological evaluation. We identified mutations in the membrane metalloendopeptidase (MME) gene in CMT disease (adult-form).

Conclusion: The MME gene encodes neprilysin (NEP), which is termed cluster of differentiation 10 (CD10), and may play a role in degrading a variety of neuropeptides. Neprilysin has been found not only in the central nervous system (CNS), but also in the peripheral nervous system (PNS). The role of NEP in PNS is unclear; however, it is well known that NEP is one of the most prominent b-amyloid (Ab)-degrading enzymes in the CNS.

Keywords: Clinical genetics, Diagnoses, Genetic screening/counseling, Neuromuscular disease, Peripheral nerve disease

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Marcos RG de Freitas¹, Marco Orsini², Antônio Marcos da Silva Catharino³, Mauricio Sant' Anna Junior⁴, Felipe dos Santos Souza⁵, Acary Souza Bulle Oliveira⁶

Affiliations: ¹Department of Neurology, The Federal University of Rio de Janeiro – UFRJ, Brazil; ²Department of Neurology – UNIG and Coordinator of the Academic Master's Degree in Neurology at the University of Vassouras, Brazil; ³Iguaçu University – UNIG – Hospital Geral de Nova Iguaçu, Brazil; ⁴Federal Institute of Education, Science and Technology of Rio de Janeiro – IFRJ, Brazil; ⁵Medical Student, Mato Grosso State University (UNEMAT), Brazil; ⁶Department of Medicine – UNIFESP – Paulista School of Medicine, Brazil.

Corresponding Author: Antônio Marcos da Silva Catharino, Iguaçu University – UNIG – Hospital Geral de Nova Iguaçu, Brazil; Email: neurocurso@globo.com

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INTRODUCTION

Mutations in the metalloendopeptidase (MME) gene were initially identified as the cause of autosomal recessive Charcot-Marie-Tooth type 2 (CMT2) disease. Later, MME variants were associated with other late-onset autosomal dominant polyneuropathies. Polyneuropathy is a simultaneous dysfunction of several peripheral nerves throughout the body. Infections, toxins, medications, cancer, nutritional deficiencies, diabetes, autoimmune diseases, and other diseases can cause many peripheral

nerves to malfunction. Thus, our objective was to define the phenotype and mode of inheritance of patients with MME alterations [1].

Charcot-Marie-Tooth disease (CMT) consists of a spectrum of disorders caused by mutations in several genes whose protein products are expressed in myelin, gap junctions, and/or axonal structures in peripheral nerves [1]. A variety of mutation types have been associated with CMT, including whole gene duplications and deletions, as well as point mutations. For example, PMP22 gene duplication causes CMT1A, the most common subtype (approximately 40% overall) [1, 2].

CMT2 is primarily characterized by axonal damage and an autosomal dominant mode of inheritance. A systematic review of epidemiological studies found that CMT2 accounts for 12–36% of all CMT cases. Classic clinical manifestations of CMT2 include distal weakness, atrophy, sensory loss, decreased deep tendon reflexes, and variable foot deformity. Onset of symptoms usually occurs in the second or third decade of life, somewhat later than in CMT1. The clinical course is similar to that of CMT1, but sensory symptoms, with loss of vibration and proprioception, may be more prominent and peripheral nerves are not palpably enlarged. Distal trophic ulcerations can occur on the feet [3].

Possible late-onset forms of CMT2, presenting between 35 and 85 years of age (mean age 57), were described in six families. Electrophysiological findings were mainly those of axonal involvement. Late-onset forms are likely to be genetically heterogeneous. Autosomal dominant inheritance was demonstrated in two of the families, while inheritance patterns were not clear in the remaining four families [4].

CMT2T is caused by mutations in the MME gene, which were identified in 10 unrelated patients from Japan with late-onset autosomal recessive CMT2. The late-onset axonal phenotype for biallelic mutations was confirmed in a cohort from Spain [3, 4].

CASE REPORT

RLF, 53 years old, male, public servant. She reports that she always walked with slight difficulty, however she never valued this issue, as she performed all of her basic and instrumental activities of daily living. There were no falls or trips during the execution of the gait patterns. In December 2014, after a strong contracture and perpetuation of the condition in the left crural proximal third, she performed some additional tests, including Magnetic Resonance of the Lumbar Spine. In the first half of 2015, he was evaluated by neurology with complaints related to weakness in the distal crural bilateral third, associated with numbness in the plants. As a past pathological history of hypothyroidism. Uncle with probable neuropathy and two brothers, as well as a son, healthy. Inspection: cavus feet, hammer toe, bilateral crural distal third atrophy. Gait: walks with

difficulty, initially touching the heel for steps. Appraiser that surface contact was not subtle. The patient sought stimuli, probably tactile and proprioceptive, as a strategy to avoid falls.

The mild muscle strength paresis was (Grade 4) in dorsiflexion, eversion, and hallux extension movements, characterizing weakness in the tibialis anterior, peroneal longus and short, extensor, and bilateral long hallux muscles. Patellar and Achilles reflexes abolished bilaterally. Thermal and painful anesthesia in the feet, in addition to tactile hypoesthesia. Electroneuromyography: axonal-predominant sensorimotor polyneuropathy. Analysis of DNA extracted from peripheral blood (Table 1): Two variants in heterozygosity in the MME gene, classified as variants of uncertain significance, were evaluated. In 2T axonal Charcot-Marie-Tooth disease, there is axonal degeneration in the absence of obvious myelin changes, weakness, and progressive distal muscle atrophy. Two variants in the MME gene were identified in the patient. The variant c.2067C>A:p.(Asn689lys), identified in heterozygosity in exon 21 of the MME gene, is of the missense type, rare. Another variant c.1479G>T:p.(=), identified in heterozygosity in exon 15 of the MME gene, is of the synonymous type, also rare and population controls. This is located in a functional domain (Peptidy M13) in which there is a high frequency of pathogenic variants, changing the splicing site. Both are related to the clinical picture under investigation by Charcot-Marie-Tooth, although they are rare.

DISCUSSION

Charcot-Marie-Tooth disease (CMT) is the most common inherited disease of the peripheral nervous system. The frequency of different CMT genotypes has been estimated in clinical populations, but prevalence data from the general population are lacking. Point mutations in the mitofusin 2 (MFN2) gene have been identified exclusively in Charcot-Marie-Tooth disease type 2 (CMT2) and in a single family with intermediate CMT. MFN2 point mutations are probably the most common cause of CMT2. The CMT phenotype caused by mutation in the myelin protein zero (MPZ) gene varies considerably, from early onset and severe forms to late onset and milder forms. The mechanism is not well understood. Myelin protein zero (P(0)) mediates adhesion in the spiral sheaths of the Schwann cell myelin sheath.

Most variants do not lead to the development of the disease, that is, that they do are uncommon in the general population. Some variants occur often enough in the population to be defined genetically [5].

The MME gene encodes neprilysin (NEP), which is called cluster 10 differentiation (CD10), and may play a role in the degradation of a variety of neuropeptides. Neprilysin has been found not only in the central nervous system (CNS) but also in the peripheral nervous system

Table 1: Variants in the MME gene identified in DNA analysis

| Chromosomes | Physical position | Gene | HGMD Clinvar | Disease | Reference sequence | Change | State | Allelic frequency | | | Classification | |
|-------------|-------------------|------|--------------|---|--------------------|--------------------------|---------------|--|----------|--------------|-------------------------|--|
| | | | | | | | | Allele fraction changed/ Position coverage | gnomAD | 1000 Genomes | ABraOM Brazilian cohort | American College of Medical Genetics and Genomics criteria |
| 3 | 154889992 | MME | ND | Spinocerebellar ataxia 43,AD (OMIM 617018) Charcot-MarieTooch disease axonal type 2T, AD, AR (OMIM 617017) | NM_007288 | c.2067C>A;p. (Asn689Lys) | Heterozygosis | 0.42/121x | 0.0001 | 0.00003 | 0.0008 | VU S |
| 3 | 154864995 | MME | ND | Spinocerebellar ataxia 43,AD (OMIM 617018) Charcot-MarieTooch disease axonal type 2T, AD, AR (OMIM 617017) | NM_007288 | c.1479G>T;p. (=) | Heterozygosis | 0.37/108x | 0.000003 | 0 | 0 | VUS |

ND - variant not detected in database so far, AD - autosomal dominant, AR - autosomal recessive

(PNS). The role of NEP in the PNS is unclear; however, it is well known that NEP is one of the most prominent b-amyloid (Ab) degrading enzymes in the CNS [6].

CONCLUSION

Metalloendopeptidase mutations that segregate in an autosomal recessive pattern are associated with a late-onset CMT2 phenotype, but heterozygous MME variants cannot be asserted to cause neuropathy. Our data highlight the importance of establishing an accurate genetic diagnosis in patients with MME mutations, especially with a view to genetic counseling. In this sense, the case presented highlights the importance that mutations involving the MME gene associated with late-onset 2T Charcot-Marie-Tooth disease is increasingly known and recorded in the scientific literature. All MME mutations can be loss-of-function mutations, and we confirm a lack/decrease of NEP protein expression in a peripheral nerve.

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Author Contributions

Marcos RG de Freitas – Acquisition of data, Analysis of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related

to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Marco Orsini – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Antônio Marcos da Silva Catharino – Analysis of data, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Mauricio Sant' Anna Junior – Acquisition of data, Analysis of data, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Felipe dos Santos Souza – Analysis of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Acary Souza Bulle Oliveira – Analysis of data, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Guarantor of Submission

The corresponding author is the guarantor of submission.

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Written informed consent was obtained from the patient for publication of this article.

Conflict of Interest

Authors declare no conflict of interest.

Data Availability

All relevant data are within the paper and its Supporting Information files.

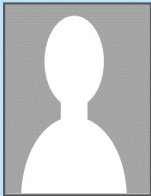
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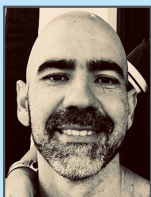
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ABOUT THE AUTHORS

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Marcos RG de Freitas, Department of Neurology the Federal University of Rio de Janeiro – UFRJ. Email: mgdefreitas@hotmail.com



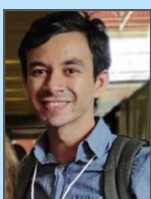
Marco Orsini, Full Professor at Universidade Iguazu and Vassoras University, Rio de Janeiro, Brazil. He earned the undergraduate degree in Medicine from Rio de Janeiro Federal University/IPUB/Rio de Janeiro/Brazil and postgraduate degree from Fluminense Federal University, Department of Medicine Niterói, RJ, Brazil. He has published 420 articles/papers in national and international academic journals and authored 2 books. His research interests include Motor Neuron Diseases, Pain, and Peripheral Neuropathies. Now he is continuing his PhD in Rio de Janeiro from Federal University and Baylor.



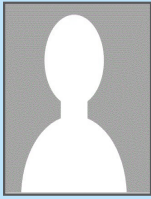
Antônio Marcos da Silva Catharino is a Physician, Neurologist, PhD student in Neurology at the Federal University of the State of Rio de Janeiro - UNIRIO, Adjunct Professor of the Medicine course at the Iguazu University, Iguazu University - UNIG/RJ, Nova Iguazu, Brazil. Orcid: <https://orcid.org/0000-0002-5736-1486>
Email: neurocurso@globo.com



Mauricio Sant' Anna Junior, Physiotherapist, Doctorate in Medical Sciences from the Fluminense Federal University - UFF. Adjunct Professor at the Federal Institute of Education, Science and Technology of Rio de Janeiro (IFRJ), Lead researcher of the Study Group on Rehabilitation in High Complexity (GERAC) working in the line of research Physical-functional aspects in In-hospital rehabilitation. Email: mauricio.junior@ifrj.edu.br



Felipe dos Santos Souza is a medical student at the State University of Mato Grosso (UNEMAT), Cáceres, Mato Grosso, Brazil. He has published in the Brazilian Journal of Emergency Medicine (ISSN-2763-776X), Brazilian Journal of Health Review (ISSN-2595-6825), Brazilian Journal of Development Magazine (ISSN-2525-8761), Journal of Biological and Health Sciences (ISSN-1518-4595), and Annals of Clinical Case Studies (ISSN-2688-1241). His research interests include neurology, internal medicine and neurological syndromes. Email: felipe.santos@unemat.br



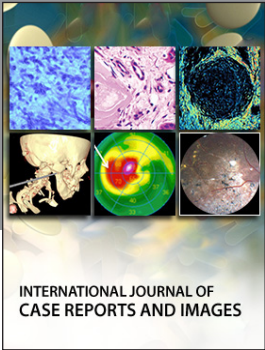
Acary Souza Bulle Oliveira, Department of Medicine – UNIFESP – Paulista School of Medicine.
Email: acarybulle@unifesp.com.br

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