Brazilian Family with X-linked Charcot-Marie-Tooth disease type 6 (CMTX6) p.R158H mutation in the PDK3 gene

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INTRODUCTION

Charcot-Marie-Tooth disease (CMT) is the most common inherited peripheral neuropathy, with a prevalence of 1:2500 people. X-linked CMT corresponds to approximately 15% of the cases. Here we describe a very rare CMTX variant in the first known brazilian family.

Methods

Ten members of a kindred spanning three generations, five women and five men, with clinical history of slowly progressing distal motor and sensitive symptoms, were examined in a neurogenetics reference center.

Results

One woman had mild symptoms, complaining of distal leg pain beginning in their

twenties. The five men had distal leg pain and weakness in the first decade of life, associated with areflexia, calf atrophy, and pes cavus deformity. Electrophysiologic studies were compatible with severe axonal motor-sensitive polyneuropathy.

Whole exome sequencing was performed in the family, revealing c.485G>A p.R162H mutation in the PDK3 gene in five symptomatic men, one mild symptomatic woman and four asymptomatic women.

Conclusion

Here we describe the first brazilian family with CMTX related to PDK3 gene mutation. The R158H missense is related to a gain of function and hyperphosphorylation of the E1 alpha subunit of the Pyruvate dehydrogenase complex, leading to impaired ATP production and lactate accumulation.