# A 71-nucleotide deletion in the periaxin gene in an Italian patient with late-onset slowly progressive demyelinating Charcot-Marie-Tooth disease

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**Background:** Charcot-Marie-Tooth disease (CMT) constitutes a group of heterogeneous hereditary motor and sensor neuropathies. Mutations in the periaxin (*PRX*) gene cause CMT4F with an autosomal recessive early-onset demyelinating neuropathy and are extremely rare in a non-Romani white population.
**Methods:** We report on a 66-year-old Italian man presenting with slowly progressive and late-onset demyelinating CMT. The molecular analysis was performed using a custom panel containing 39 genes associated with the CMT phenotype.
**Results:** The patient harbored a homozygous PRX 71-nucleotide deletion (c.3286_3356del71, I1096fsX17).
**Conclusions:** This is the first report that describes such a genetic mutation in a population of non-Romani origin.

Charcot–Marie–Tooth type 4F neuropathy (CMT4F) is caused by mutations in the periaxin (*PRX*) gene mapped on chromosome 19q13 [1–3]. The most common genetic alterations causing CMT4F are frameshift or nonsense *PRX* mutations; the corresponding clinical feature of CMT4F is an autosomal recessive early-onset demyelinating neuropathy; less common is severe Dejerine–Sottas syndrome or demyelinating Charcot–Marie–Tooth disease (CMT) with slow or no progression.

In the present paper, we report on a 66-year-old man who had a 30-year history of slowly progressive muscle-wasting in the lower limbs and mild ataxic gait. On admission, neurological examination of the patient revealed mild distal muscle hypotrophies in the four limbs, unsteady gait, absent deep tendon reflexes, and normal touch sensation with distal reduction in vibration.

Serum blood tests were normal. Electromyography showed a pattern of diffuse chronic denervation without fasciculations or fibrillation, prominently in the lower limbs and in distal muscles.

Nerve conduction velocity (NCV) studies revealed a mild reduction in motor conduction speed (mean 31 m/s in the peroneal and 34 m/s in the median nerve), with severe reduction in motor action potentials (<1 mV) in the peroneal nerves. Sensory conduction studies showed mild reduction in conduction speed (mean 38 m/s in median nerves), with severe reduction in sensory action potentials (2 mV). Sural nerve potentials were undetectable.

After informed consent had been obtained, genomic DNA was analysed using a custom panel targeting the coding sequences comprising the intron/exon boundaries of 32 genes associated with the CMT phenotype. The DNA analysis, after data filtering, showed a homozygous frameshift deletion of

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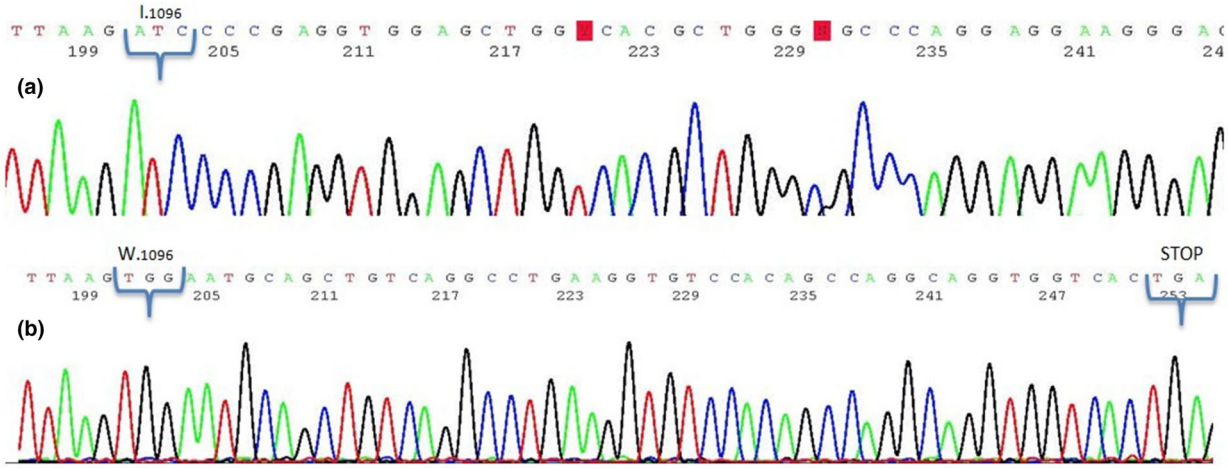


**Figure 1** (a) Sequence of the normal control with the isoleucine (ATC) at position 1096. (b) Sequence of the patient showing the deletion in homozygous state with the variation. p. I1096W and the stop after 17aa. [Colour figure can be viewed at wileyonlinelibrary.com]

71 bp on exon 7 of the *PRX* gene (NM_181882, c.3286_3356del:p.I1096Wfs*17; Fig. 1) This variation has already been described in a Romani patient with a clinical phenotype characterized by an early onset with delayed motor milestones, with severely reduced NCVs [4]. The variant c.3286_3356del71 located in the 3′ terminal of the last exon most probably escaped nonsense-mediated decay.

The most important finding in the present case was the late age at onset, with a slowly progressive mild phenotype, characterized by slight reduction in NCVs and prominent sensory involvement.

To date, most of the patients with CMT4F reported in the literature developed the CMT symptoms in the first decade of life. In only one paper, three cases with an adult onset and milder phenotype have been reported. Our findings confirm that the CMT4F caused by *PRX* mutations can also occur with a late age at onset. This information should alert physicians who may be faced with patients with late-onset sporadic or recessive neuropathies to the possible diagnosis of CMT4F.

In the Italian population, *PRX* mutations have been shown to be very rare, with only four cases with *PRX* mutations described, and gross deletions are unreported to date [5].

## Disclosure of conflicts of interest

The authors declare no financial or other conflicts of interest.

## Data availability statement

The data that support the findings of this study are available on request from corresponding author.

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