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Case report

Confirmation of the *GNB4* gene as causal for Charcot–Marie–Tooth disease by a novel *de novo* mutation in a Czech patient

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Abstract

The association of *GNB4* with Charcot–Marie–Tooth (CMT) has recently been described in a publication by Soong et al. (Soong, et al., 2013). Here we present a patient with CMT in whom whole exome sequencing identified the mutation p.Lys57Glu in the *GNB4* gene (NM_021629.3:c.169A>G). The patient, now 41 years old, is a sporadic case in the family. At the age of 35 he presented with severe disability (CMT neuropathy score 29), profound muscle atrophies, pes cavus and scoliosis. Previously, the patient was tested for *PMP22* duplications/deletions and later also with 64 CMT gene panel, with no causal variant found. Subsequently, whole exome sequencing was performed. The p.Lys57Glu in the *GNB4* gene was identified as the most probable causal variant, the mutation is not present in the patient's parents, neither in his unaffected sister, therefore we assume that the mutation arose *de novo*. Taken together, these findings support the causal and pathogenic character of the variant. Our report provides important evidence that *GNB4* should become an established CMT gene and our findings confirm the original publication by Soong et al. (2013).

Keywords: Charcot–Marie–Tooth disease; *De novo*; Whole exome sequencing; *GNB4*

1. Introduction

Charcot–Marie–Tooth (CMT) disease is a heterogeneous group of disorders, with neuropathy being the sole or primary part of the disease [1]. Variants in many genes have already been associated with the phenotype (currently more than 90 causative genes).

Molecular genetic diagnosis of CMT is challenging. Variants in the four most common genes (*PMP22, MPZ, MFN2* and *GJB1*) account for almost 90% of positive cases. Achieving a genetic diagnosis for the remaining 10% of patients with clinically well stated CMT is very complicated. Targeted gene panel analysis is the method of choice, with an approximate success rate of 25%. If this approach is not able to identify the variant that could possibly explain the cause of the disease, whole exome sequencing (WES) with various evaluation models (dominant; *de novo* or recessive) is the next logical step.

The utility of WES in novel genes discoveries is well established. However, in multiple cases, finding a patient from an independent study to support the causal role of mutations in these novel genes is difficult.

Here we present a patient in whom whole exome sequencing identified a pathogenic variant in the *GNB4* gene. This is only the third patient worldwide that confirms the causality of this novel gene. The association of *GNB4* mutations with Charcot–Marie–Tooth (CMT) has only been recently described. The original publication describes two mutations in two unrelated Chinese families, one with autosomal dominant inheritance, the other a sporadic case due to a *de novo* mutation [2]. No further reports have been published so far.

Our results support the causal role of *GNB4* gene variants in Charcot–Marie–Tooth disease.

2. Case report

The patient, now 41 years old, is a sporadic case with CMT1 in the family. His parents and his sister do not show any signs of peripheral neuropathy, although they were not neurologically, nor electrophysiologically tested. He has no children.

The first signs of disease occurred during early school age. These were mainly frequent falls and difficulties while running.

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Distal muscle weakness and atrophies in the lower limbs were observed before the age of 10 years. During the growth spurt in puberty his symptoms worsened, muscle wasting became prominent (in the legs distally below the knee and also of small muscles in the hands). The patient has suffered tremors of the fingers of both hands since the age of 16 years. At the age of 31 years he underwent orthopedic surgery for foot deformities. Further progression occurred in his thirties, muscles atrophies in the upper limbs were noticed and thoracic spine scoliosis began to develop (Fig. 1). Clinical examination at the age of 30 years showed atrophy of the small hand muscles and diminished deep tendon reflexes. Muscle strength (MRC scale) was reduced both proximally and distally in the upper limbs (shoulder abduction, elbow flexion/extension 4/5, wrist extension/flexion 3/5, finger abduction 3/5). Hand grip was 50 and 52 kPa on the left and right side, respectively. Sensory testing was normal in the upper limbs. In the lower limbs, severe distal amyotrophy was present whereas more proximally atrophy was milder. There was foot deformity with calluses and Achilles tendon shortening (105°). Deep tendon reflexes were absent. Muscle weakness was observed both proximally and distally (hip flexion/extension 4/5, knee flexion/extension 4/5; foot dorsiflexion/plantar flexion 3/5). Sensory loss in a stocking distribution was noted. He was unable to distinguish sharp/blunt stimuli distally up to the knee and vibration sense was diminished at the feet. Gait without support was preserved but the patient was unable to walk on his heels. There was scoliosis. The Charcot–Marie–Tooth Neuropathy Score was 20. Clinical examination at the age of 35 years showed muscle atrophy of the forearm up to the elbow. Hypothenar muscle wasting was more prominent than thenar muscle wasting. C5-C8 deep tendon reflexes were absent. Muscle was severely diminished in the hands and finger tremor was noted. Shoulder abduction and elbow flexion/extension strength was 4/5; wrist extension/flexion was 3/5. Hand grip strength bilaterally was 25 kPa. The patient underwent orthopedic surgery twice at the age 31 (Achilles tendon shortenings). Deep tendon reflexes in the legs were absent. Sensory testing revealed tactile hypoesthesia distally up to the knee, bilaterally. Vibration sense was severely diminished at the toe tips, metatarsal phalangeal joints and tibial tuberosity and absent at the fingers. Gait was possible only with support (2 canes). The Charcot–Marie–Tooth Neuropathy Score was 29. Nerve conduction studies revealed primary demyelinatingneuropathy with secondary

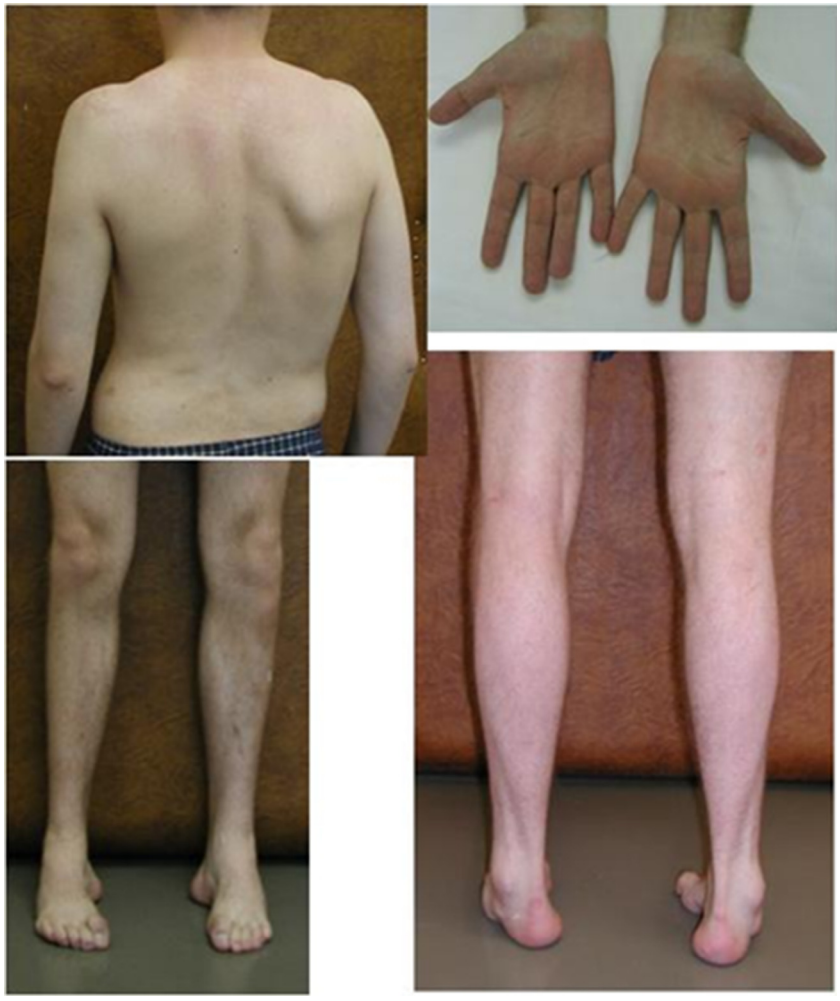

Fig. 1. Patient at the age of 35 years.