

# A new variante of INF2-gene mutation: Correlation with Charcot-Marie-Tooth type E neuropathy?

Stefan Bittmann<sup>1</sup>, Luchter E<sup>1</sup>, Weissenstein A<sup>1</sup>, Villalon G<sup>1</sup>

Bittmann S<sup>1\*</sup>, Luchter E<sup>1</sup>, Weissenstein A<sup>1</sup>, Villalon G<sup>1</sup>

<sup>1</sup> Ped Mind Institute (PMI), Medical and Finance Center Epe, Germany

\* Corresponding Author: Stefan Bittmann, PED MIND INSTITUTE Ärzte-und Finanzzentrum Epe, Department of Pediatrics, Hindenburgring 4D-48599 Gronau, Germany, stefanbittmann@gmx.de

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## ABSTRACT

Charcot-Marie-Tooth disease (CMT) affects 1 in 2500 people and more than 30 gene mutations play a causative role. It is the eponym for heritable peripheral neuropathy and is named for 3 investigators in the late 1800s. Different forms of CMT exist and the classification is still not completely ruled out. Mutations of the inverted formin-2 gene (INF-2) were identified in patients with focal segmental glomerulosclerosis<sup>[1]</sup> (FSGS) and autosomal dominant intermediate Charcot-Marie Tooth (DI-CMT) disease. A novel unclassified variante, c.2659GA; p.E887K(het.), located on chromosome 14q32.33, was identified in a 21 months old child with unknown peripheral neuropathy and muscular weakness. The mutation leads to a change of amino acid glutamate to lysine in position 887. This variante was not described yet in world literature.

**Keywords:** INF 2; mutation; child; CMT disease

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## 1. Introduction

Charcot and Marie and independently Tooth in 1886 described the first time a heritable peripheral neuropathy<sup>[5,6]</sup>. Charcot-Marie-Tooth disease (CMT) affects 1/2500 people and is caused by mutations in more than 30 genes. INF2 gene mutations can possibly play a causative role in the development of the disease. The INF2 gene represents a member of the formin family of proteins. It is considered a diaphanous formin due to the presence of a diaphanous inhibitory domain located at the N-terminus of the encoded protein. Studies of a similar mouse protein indicate that the protein encoded by this locus may function in polymerization and depolymerization of actin filaments. By searching databases for FH2 domain sequences, researchers identified mouse and human INF-2, a member of the inverted formin group. Inverted formins have an N-terminal FH2 domain rather than the C-terminal FH2 domain found in all other formins. Chhabra and Higgs (2006) cloned full-length mouse INF2. The 1,274-amino acid protein has an N-terminal diaphanous inhibitory domain (DID), followed by an FH1 domain, an FH2 domain, and a C-terminal diaphanous autoregulatory domain (DAD)/WASP homology-2 domain. Inf2 is not an inverted formin, but is most similar to diaphanous formins (DIAPH1). By immunohistochemical staining, it was demonstrated robust INF2 expression in peripheral nerve Schwann cells and light staining in some axons. INF2 colocalized with the myelin and lymphocyte protein in human peripheral nerve and mouse Schwann cells, and with MAL2 in human podocytes.

## 2. Case Report

We report about a 21 months old female child. Pregnancy was uneventful. Delivery was performed by c-section in the 39th week. Birth weight was 3450g, length 51 cm and head circumference 35 cm. APGAR was not documented, umbilical-pH was 7.22. Phototherapy was performed due to mild hyperbilirubinemia. The mother suffered from an amniotic infection syndrome and was treated with antibiotics at the ICU for 10 days.

The newborn period was complicated by muscular hypotonia and general delay in development. Neurography showed signs of sensorimotor neuropathy with low nerve conduction velocity of N. medianus and N. suralis. Myography was

inconspicuous. The MRI tomography of the head showed occipital leukencephalopathy. ECG, echocardiography, sonography of the muscles and ophthalmologist examination were negative. Organic acids and mucopolysaccharids in urine were not found. Molecular analysis of SMN1-Gen was inconspicuous (Institute of Human Genetics, Aachen, Germany). Homozygotic or heterozygotic deletions of exons 7 and 8 in SMN-1-Gen were not found. Tests for beta-Galaktosidase, beta-Hexosamidase A/B, Galactocerebrosidase Krabbe, Creatinkinase, CDG and Glucosidase were negative. Free fatty acids were mildly increased. Physiotherapy three times the week was initiated immediately. A novel unclassified variante, c.2659GA; p.E887K(het.), located on chromosome 14q32.33, was identified by gene analysis (Cegat, Center for Genomics and Transcriptomics, Tübingen, Germany). The female child is to date 21 months old.

### 3. Molecular Analysis

The genomic DNA was isolated by the polymerase chain reaction and all codons of the genes GDAP1, KIF1B, MFN2, MPZ, PMP22, RAB7A and TRPV4 were amplified (Cegat, Center for Genomics and Transcriptomics, Tübingen, Germany). All introns around these regions were analysed and sequenced with internal primers. A deletion- and duplication analysis for the genes MFN2 and MPZ with MLPA (MRC Holland, SALSA MLPA Kit P-143-B1) was performed. Analysis was based on relative quantification in correlation to reference-DNA. A novel unclassified variante, c.2659GA; p.E887K(het.), located on chromosome 14q32.33, was identified.

### 4. Discussion

The inherited Charcot-Marie-Tooth peripheral neuropathies (CMT) were first described independently by Charcot and Marie in France and by Tooth in England<sup>[5,6]</sup>. The degeneration of peripheral nerves, nerve roots, and even the spinal cord leading to progressive weakness and wasting of the distal muscles of the legs and arms was initially described by Schultze in 1884<sup>[3]</sup>. However, it was the work of Charcot that brought further elucidation of the disease by first correctly labeling it as a neuropathy rather than a myopathy<sup>[5]</sup>. This peroneal form of muscular atrophy, which was described by Howard Tooth in the same year as Charcot and his assistant Pierre Marie, has now come to be known as Charcot-Marie-Tooth Disease (CMT)<sup>[4]</sup>. The heterogeneous nature and different forms of inheritance of the condition were soon recognized. In the late 1960s, neurophysiologic testing allowed the classification of CMT into 2 groups, one with slow nerve conduction velocities and histologic features of a hypertrophic demyelinating neuropathy (hereditary motor and sensory neuropathy type 1 or CMT1) and another with relatively normal velocities and axonal and neuronal degeneration (hereditary motor and sensory neuropathy type 2 or CMT2). Since the early 1990s, patients with both CMT1 and CMT2, while often clinically similar, were found to be genetically heterogeneous. Now a large and ever increasing number of genetic subtypes has been described, and major advances in molecular and cellular biology have clarified the understanding of the role of different proteins in the physiology of peripheral nerve conduction in health and in disease. Dejerine-Sottas disease is also known as CMT3. Autosomal recessive forms can be also divided into demyelinating (CMT4 or AR-CMT1) and axonal forms (AR-CMT2). Subtypes with velocities within the intermediate range are called DI-CMT. However, there is less agreement on the nomenclature of the recessive and intermediate-conduction velocity subtypes. In this case, a new variant of gene mutation, named c.2659GA; p.E887K(het.), located on chromosome 14q32.33, was identified. To date, there are only 6 known gene mutations found in relation to dominant intermediate Charcot-Marie-tooth disease (CMT E). These are INF2, Cys104Arg; INF2, Cys104Phe; INF2, Cys104Trp; INF2,Leu128Pro; INF2, Leu132Arg and INF2,9-BP DEL,NT490. The gene c.2659GA; p.E887K(het.), located on chromosome 14q32.33, mutation c.2659GA; p.E887K(het.) on chromosome 14q32.33 was never found before and the first case in world literature. This mutation is yet not described and possibly a correlation to DI-CMT disease cases (CMT type E) can exist.

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