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Exome sequencing reveals homozygous *TRIM2* mutation in a patient with early onset CMT and bilateral vocal cord paralysis

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Abstract

Charcot-Marie-Tooth disease (CMT) is a heterogeneous group of inherited distal symmetric polyneuropathies associated with mutations in genes encoding components essential for normal functioning of the Schwann cell and axon. *TRIM2*, encoding a ligase that ubiquitinates the neurofilament light chain, was recently associated with early onset neuropathy in a single patient. We report a *TRIM2* homozygous missense mutation (c.2000A>C; p.D667A) in a patient with peripheral neuropathy and bilateral vocal cord paralysis, allowing for further delineation of the associated phenotypic spectrum.

Keywords

Charcot-Marie-Tooth; TRIM2; vocal cord paralysis

SHORT REPORT

Charcot-Marie-Tooth disease (CMT) is a clinically and heterogeneous group of distal symmetric polyneuropathies (DSP), with over 80 disease-causing genes identified to date (Timmerman et al. 2014). Recently, compound heterozygous mutations in the *tripartite*

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motif containing 2 (TRIM2) gene were identified in a single patient with early-onset neuropathy; the proposed pathogenesis being aberrant axonal accumulation of neurofilaments secondary to lack of their ubiquitination by TRIM2 (Ylikallio et al. 2013).

We report a Turkish male of consanguineous descent, born to a 34 yo G7P5 mother after an uncomplicated pregnancy and delivery, at 3500 grams (Fig. 1a). He was evaluated for noisy breathing and diagnosed with tracheomalacia at 15 days of life. At 6 months, he developed respiratory insufficiency and was found to have bilateral vocal cord paralysis necessitating tracheostomy. Neurological examination at 16 months revealed an alert and interactive toddler with intact cranial nerves, axial hypotonia and decreased muscle strength (2/5) throughout. Tone in the lower extremities was increased, with bilateral knee contractures, hammer toes, *pes equinus* and *pes cavus*, and absent deep tendon reflexes. Metabolic studies, thyroid functions, and muscle creatine kinase were unremarkable. Brain and spine MRI were normal. EMG revealed markedly reduced amplitudes with decreased motor nerve conduction velocities relative to laboratory normative values, consistent with severe axonal polyneuropathy. Following multiple hospitalizations for respiratory distress, he died at age 2-years-9-months.

Whole exome sequencing (methods as described in Lupski et al. 2013) identified a homozygous c.2000A>C; p.D667A (chr4:g.154,245,278 A>C [hg19]) missense variant in *TRIM2* (Fig. 1b,c), predicted to be deleterious by multiple bioinformatic algorithms (e.g., Polyphen2, MutationTaster, SIFT) and not found in publicly available or internal population-matched human genome variant databases. The affected amino acid is contained within an evolutionarily conserved residue that is present in all vertebrates and lies just before the fifth of six NHL (NCL-1, HT2A, and LIN-41) domains in the C-terminus of the TRIM2 protein (Fig. 1c). These six NHL domains form a six-bladed β-propellor structure common to only a few of the TRIM proteins, e.g. TRIM2, TRIM3, and TRIM32. Homozygosity analysis based on cSNP data revealed that the *TRIM2* variant is embedded within an ~18 Mb homozygous region (Supplementary Fig. 1). Mutations in *TRIM32* are associated with limb girdle muscular dystrophy type 2H (LGMD2H) and cluster within the NHL domains; the most common mutation affects a conserved aspartic acid residue, leading to reduced stability of the protein (Kudryashova et al. 2011).

Table 1 compares the features of the previously reported patient and our patient. Notably, our patient had a more severe course with significant hypotonia at 8 months of age and bilateral vocal cord paralysis necessitating tracheostomy. Distinctive phenotypic features have been described in association with specific subtypes of CMT, including optic atrophy in CMT2A (*MFN2*), hearing loss and pupillary abnormalities in CMT2J (*MPZ*), learning difficulties in CMT2O (*DYNC1H1*), glaucoma in CMT4B2 (*SBF2*), scoliosis in CMT4C (*SH3TC2*), neutropenia in CMTDIB/CMT2M and glomerulonephritis in CMTDIE (*INF2*) (Harel and Lupski 2014). Diaphragmatic and vocal cord paresis have classically been associated with mutations in *TRPV4* and *GDAP1*, but have also been described in association with other genes, including *MTMR2* and *MPZ*. Vocal cord paralysis arises from peripheral neuropathy affecting the vagus nerve and its laryngeal branches (Aboussouan et al. 2007).

Whole exome sequencing has enabled exponential identification of novel genes associated with CMT, as well as phenotypic expansion of known genes (e.g., *IGHMBP2*, *KIF5A*, *PLEKHG5*). We expand the *TRIM2* mutation phenotype to potentially include vocal cord paralysis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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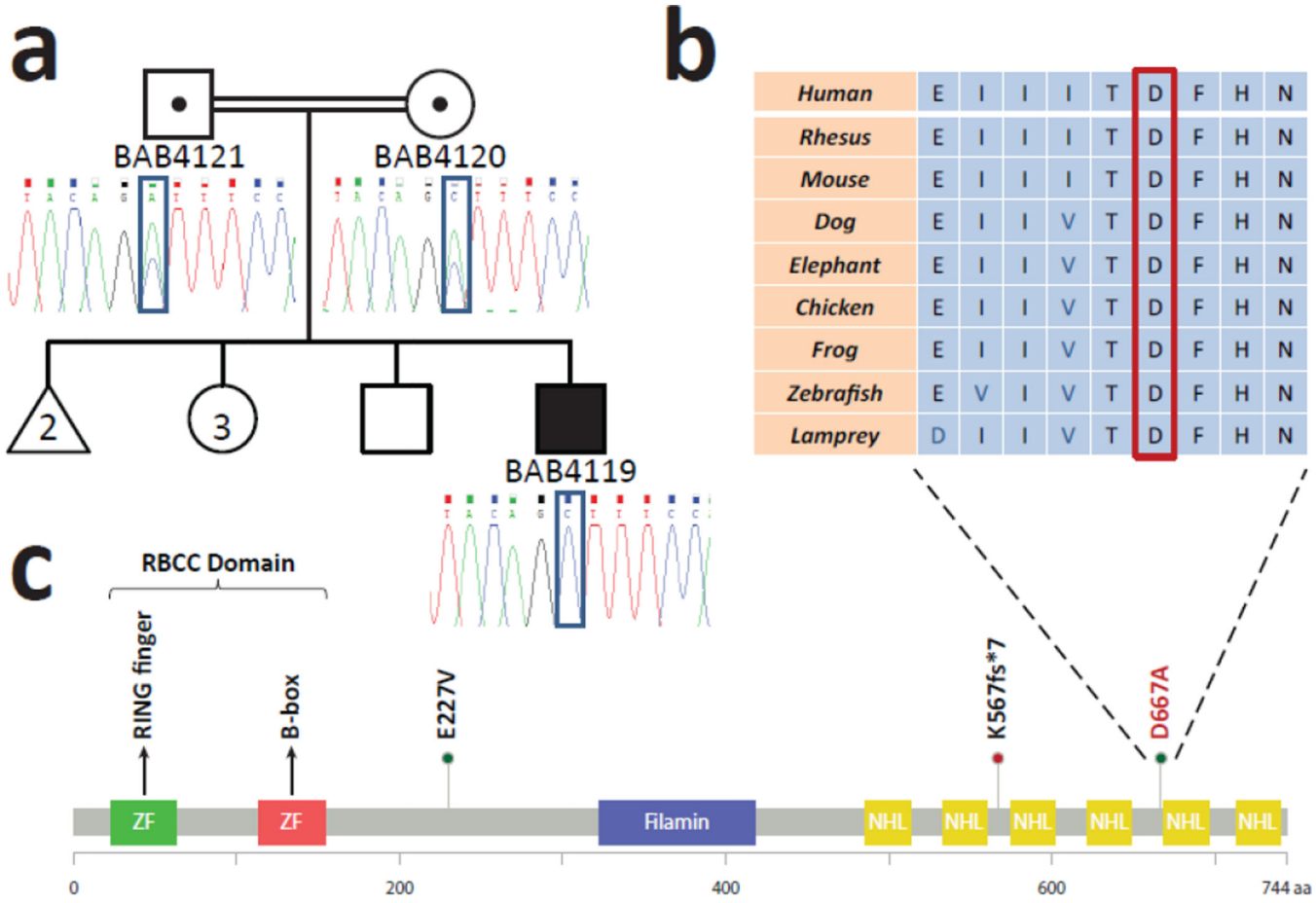

Figure 1.

Molecular and computational studies of the *TRIM2* variant. **a)** Pedigree of the family with Sanger sequencing results showing homozygosity of the c.2000A>C; p.D667A variant in the proband and heterozygosity in both parents. Unaffected siblings were not available for segregation. **b)** Conservation alignment indicating that the aspartic acid residue at position 667 is conserved across all vertebrates. **c)** Protein structure of TRIM2 and location of the mutations in our patient and the single previously reported patient (Ylikallio et al. 2013). Our mutation affects a residue just before the fifth NHL domain in the C-terminus.

Table 1

Comparison of features in patients with *TRIM2* mutations

	BAB4119	**Ylikallio et al. 2013**
Age	Deceased at 2 y 9 mo	18 yo
Onset	Infancy	Early childhood
Normal birthweight	+	+
Poor growth as infant	+	+
Delayed motor milestones	+	+
Generalized muscle hypotonia	+	+
Decreased muscle mass	+	+
Pes cavus	+	+
Absent DTRs	+	+
Vocal cord paralysis	+	-
Axonal neuropathy on NCV studies	+	+
Median motor NCV* (m/sec)	19	29
Median motor nerve amplitude** (mV)	0.1	0.7
Biopsy	NA	Axonal neuropathy
Normal brain MRI	+	+
TRIM2 variant	c.2000A>C; p.D667A (hom)	c.1699delA; p.K567fs*7 c.680A>T; p.E227V

NCV: nerve conduction velocity, NA: not available, DTR: deep tendon reflexes Laboratory age-appropriate normal ranges:

*median motor NCV (13–24 months old): 39.2–50.5 m/sec; and

**amplitude 3.7–11.6 mV.