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## Original Article

# TECPR2 mutations cause a new subtype of familial dysautonomia like hereditary sensory autonomic neuropathy with intellectual disability



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## ABSTRACT

**Background:** TECPR2 was first described as a disease causing gene when the c.3416delT frameshift mutation was found in five Jewish Bukharian patients with similar features. It was suggested to constitute a new subtype of complex hereditary spastic paraparesis (SPG49).

**Results:** We report here 3 additional patients from unrelated non-Bukharian families, harboring two novel mutations (c.1319delT, c.C566T) in this gene. Accumulating clinical data clarifies that in addition to intellectual disability and evolving spasticity the main disabling feature of this unique disorder is autonomic-sensory neuropathy accompanied by chronic respiratory disease and paroxysmal autonomic events.

**Conclusion:** We suggest that the disease should therefore be classified as a new subtype of hereditary sensory-autonomic neuropathy. The discovery of additional mutations in non-Bukharian patients implies that this disease might be more common than previously appreciated and should therefore be considered in undiagnosed cases of intellectual disability with autonomic features and respiratory symptoms regardless of demographic origin.

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## 1. Introduction

In 2012, Oz-Levi et al. described five children from three unrelated Jewish Bukharian families with a shared c.3416delT frameshift mutation (p.Leu1139Argfs\*75) in TECPR2.<sup>1</sup> All patients shared a phenotype of short chubby appearance, mild brachycephalic microcephaly, short broad neck, low anterior hairline and coarse faces. In addition they all suffered from infantile onset recurrent aspirations due to gastro-esophageal reflux (GERD) and exhibited moderate to severe intellectual disability (ID), hypotonia that evolved to spasticity in older age, areflexia and central apneas. The underlying gene product is involved in cellular autophagy processes and abnormal autophagy function was demonstrated with the inserted mutation.<sup>2</sup> The disease was classified as a subtype of complex hereditary spastic paraparesis (HSP) and named SPG49. We describe here three additional non-Bukharian patients with two novel mutations in TECPR2. The current report broadens the spectrum of this new disease in two important aspects. First, further analysis of clinical data from the patients highlights the prominent feature of sensory-autonomic neuropathy. This results in symptoms such as the previously described GERD, central apneas and areflexia but also blood pressure and pulse imbalance, pCO<sub>2</sub> accumulation, temperature and osmolarity instability and decreased pain sensitivity. We thus propose now, that this disease is more suitably classified as a subtype of hereditary sensory-autonomic neuropathy rather than a subtype of HSP. Second, the discovery of additional mutations in the TECPR2 in patients of non-Bukharian origin attests that this disease is not limited to a specific ethnicity nor to a single mutation in the gene and implies that its prevalence might be higher than previously presumed. We suggest that mutations in this gene should be sought for in undiagnosed patients with ID accompanied by

symptoms of autonomic neuropathy and recurrent pulmonary infections irrespective of their ethnic origin.

## 2. Methods

### 2.1. Ethical approval

For whole exome sequencing, DNA was extracted from a peripheral blood sample. The molecular studies were approved by the ethical committee of either Sheba medical center or Hadassah medical center and the Israeli Ministry of Health. Written informed consent was obtained from all participants or their respective legal guardians.

### 2.2. Exome sequencing and bioinformatics analysis

For patient 1, exonic sequences were enriched using SureSelect Human All Exon 50 Mb Kit (Agilent Technologies, Santa Clara, CA, USA). Sequences were determined by HiSeq 2000 (Illumina Inc., San Diego, CA, USA) and 100-bp were read paired-end. Reads alignment and variant calling were performed with DNAnexus software (Palo Alto, CA, USA) using the default parameters with the human genome assembly hg19 (GRCh37) as a reference.

For patient 2, exome sequencing was performed using the TruSeq Exome enrichment kit (Illumina Inc. San Diego, CA, USA). The captured regions were sequenced using the HiSeq 2000 platform (Illumina Inc, San Diego, CA, USA). The resulting reads were aligned to the reference genome (GRCh37/hg19) using the Burrows-Wheeler Alignment (BWA-0.5.10).<sup>3</sup> Polymerase chain reaction duplicates were removed using picard-tools-1.59 (<http://picard.sourceforge.net>). Genetic differences relative to the reference genome were called using

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