



Ann-Kathrin Zaum<sup>1</sup>, Simone Rost<sup>1</sup>, Beat Wolf<sup>2</sup>, Clemens R. Müller<sup>1</sup>, Thomas Musacchio<sup>3</sup>, Erdmute Kunstmann<sup>1</sup>, Stephan Klebe<sup>3</sup>

<sup>1</sup>Department of Human Genetics, University of Würzburg, Germany

<sup>2</sup>Department of Bioinformatics, University of Würzburg, Germany

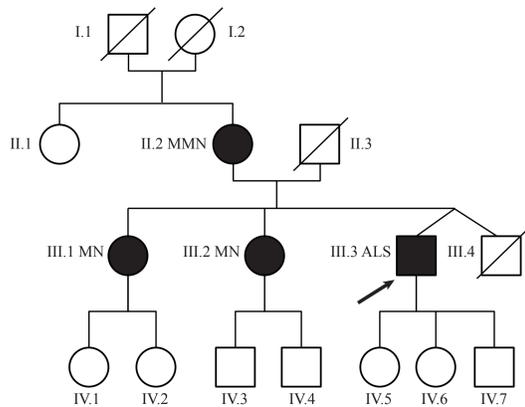
<sup>3</sup>Department of Neurology, University Hospital Würzburg, Germany

## INTRODUCTION

Distal hereditary motor neuropathy (dHMN) is a group of diverse neuromuscular disorders ranging from dHMN-I to dHMN-VIIB, which are characterized by distal muscular atrophy and progressive motor

weakness without sensory impairment. Clinically, dHMN can present with variable phenotypes even within a family and is sometimes misdiagnosed as amyotrophic lateral sclerosis (ALS).

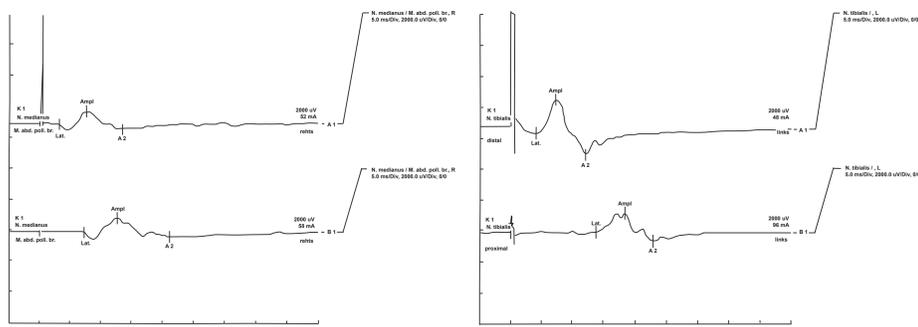
## CLINICAL FINDINGS



**Figure 1:** Pedigree of the examined motor neuropathy (MN) family. The index patient (arrow, III.3) has two sisters (III.1 and III.2) who suffer from a moderate form of MN, his twin brother (III.4) died at the age of 23. Their mother (II.2) was diagnosed with multifocal motor neuropathy (MMN) and the index patient's aunt (II.1) does not display any neurological symptoms. We sequenced the index patient, his mother (II.2) and sister (III.2). All three displayed a heterozygous BSCL2 mutation. Subsequent Sanger sequencing confirmed this mutation in the other sister (III.1) but not in the aunt (II.1).

**Figure 2:**

Left hand of a patient suffering from a BSCL2-related neuropathy. The black arrows indicate the atrophy of the first interosseus muscle (IOD I) which is typical for distal hereditary motor neuropathy type VA (dHMN-VA) patients. This form of muscle wasting was observed in the index patient, his mother and sister. All three patients have been sequenced on a MiSeq (Illumina).



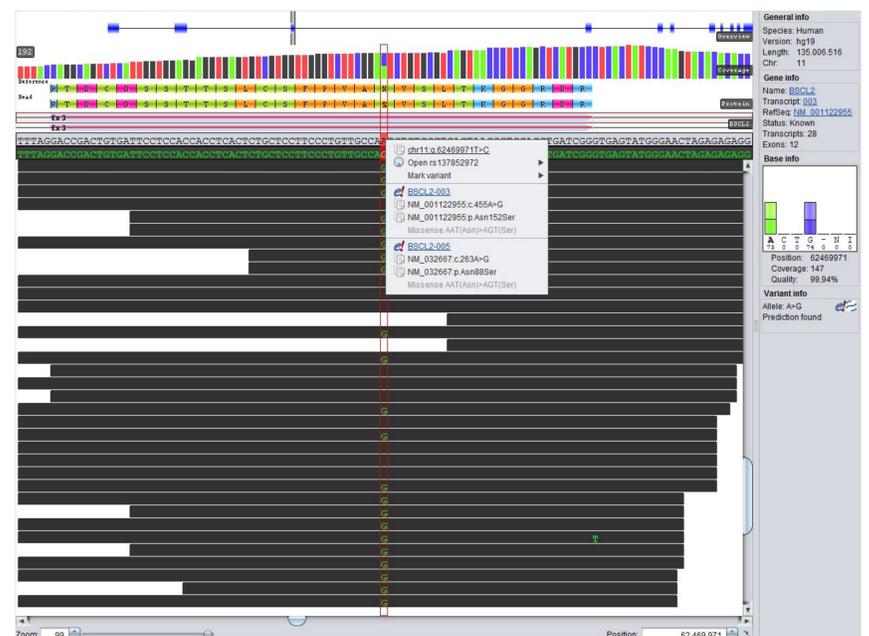
**Figure 3:**

Motor nerve conduction study (MNCS) of the index patient's mother. Figure 3A displays the median nerve and the musculus abductor pollicis brevis (M. abd. poll. br.) with a reduced amplitude (1,18 mV; normal >5 mV) and normal velocity. Figure 3B displays the tibialis nerve distal and proximal with reduced amplitude (1,01 mV; normal: >5 mV) and normal velocity.

We report on a family suffering from motor neuropathy of variable severities. The index patient was a 50-year-old man who first noticed fasciculation at age 48. First examination showed bilateral first interosseus (IOD I) atrophy and distal muscle weakness of the upper and lower extremities. After the electrophysiological work-up he fulfilled the criteria of a clinically probable ALS. Early in the disease course nerve conduction studies (NCS) also revealed an axonal neuropathy. Clinical symptoms were rapidly progressive. His sister showed at age 51 a unilateral atrophy of the IOD I and an axonal neuropathy of the peroneal motor nerve. Needle EMG only denoted denervation in the affected IOD I. Another 45-year-old sister did not notice any clinical symptoms and the examination was normal. However, the NCS and needle EMG displayed a pure motor axonal neuropathy. Their mother was diagnosed at age 62 with a multifocal motor neuropathy (MMN) due to a unilateral atrophy and weakness in the IOD I and a motor neuropathy with conduction block in the ulnar and peroneal nerve.

## METHODS & RESULTS

We analyzed 68 genes associated to dHMN, ALS and Charcot-Marie-Tooth disease (CMT) from the TruSight Exome panel (Illumina) in the index patient, his mother and one sister following sequencing on a MiSeq (Illumina). Data analysis was performed by GenSearchNGS (PhenoSystems) and pathogenicity predictions were made by Alamut (Interactive Biosoftware). We filtered for variants common to all three family members and found a heterozygous missense mutation in the BSCL2 gene (c.455A>G) creating a known amino acid change from asparagine to serine (rs137852972; p.N152S; OMIM # 600794) which was predicted to be pathogenic by Alamut. This mutation could be confirmed by Sanger sequencing in one additional affected family member and was not present in family members without neuromuscular symptoms. BSCL2 mutations comprise diverse clinical findings with overlapping phenotypes of distal hereditary motor neuropathy type VA (dHMN-VA) and hereditary spastic paraplegia (SPG17; Silver Syndrome). It is most likely that modifier mutations exist explaining the variable phenotypes and the known reduced penetrance. However, no additional mutation in BSCL2 or in any of the other genes tested could be detected which could explain the differences within the presented family.



**Figure 4:**

NGS analysis of the index patient. For examination we used the GenSearchNGS software (PhenoSystems). Black lines indicate reads which completely match to the reference sequence (grey line with black letters); the grey box displays the mutation in exon 3 of the BSCL2 gene in two different transcripts; the nucleotide exchange is shown in the red column.

## CONCLUSION

In summary, by using clinical exome sequencing we could identify a known BSCL2 mutation in a family suffering from variable symptoms of MN (dHMN-V to ALS). It was convenient to apply next generation sequencing (NGS) technologies, since the disease could not be definitively categorized clinically and the large number of genes associated with distal hereditary motor neuropathy precluded successive Sanger sequencing.