6 Summary

Spinal muscular atrophy with respiratory distress type 1 (SMARD1) is a hereditary neuromuscular disease in infants which is characterized by the degeneration of anterior horn cells. SMARD1 patients present with a distally marked muscular atrophy and respiratory distress due to the paralysis of the diaphragm. These clinical key features distinguish SMARD1 from the “classical” spinal muscular atrophy type I (SMA1). Previous studies have shown that SMARD1 results from mutations in the gene coding for *Immunoglobulin μ-binding protein 2* (*IGHMBP2*). In this work, I investigated the clinical and genetic heterogeneity of SMARD and SMARD1 as well as the genotype-phenotype relationships in SMARD1 patients and the enzymatic activities of Wt-IGHMBP2 and various SMARD1-related mutants.

15 new SMARD1 cases (21%) with 10 novel IGHMBP2 mutations were identified in a cohort of infants affected by spinal muscular atrophy with respiratory distress (SMARD). The relatively small part of SMARD1 patients within the analyzed patient group suggests that SMARD is genetically heterogeneous. Thus, I could determine two distinct groups of non-SMARD1 patients with different symptom patterns by means of hierarchical cluster analysis. I assume that mutations in different genes may be responsible for the clinical picture of both patient groups.

In two further patients I could identify two genomic rearrangements at the *IGHMBP2* gene locus which have arisen from different pathogenic processes and may be missed by the mere and standardized sequencing of exons and exon-flanking regions.

Furthermore, two SMARD1 patients with *IGHMBP2* gene mutations who presented with a highly uncharacteristic juvenile onset of respiratory distress could be described for the first time. This finding demonstrates clinical variability in SMARD1. The subsequent investigation of genotype-phenotype relationships provided evidence that residual IGHMBP2 activity might exert a protective effect if present in sufficient amounts.

Based on the observation that *IGHMBP2* missense mutations were only affecting the helicase domain of the IGHMBP2 protein I characterized the enzymatic activity of Wt-IGHMBP2 and various mutants *in vitro*. Indeed, Wt-IGHMBP2 exhibited a strictly ATP-dependent 5’-3’ RNA/DNA helicase activity while most of the SMARD1-related

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IGHMBP2 mutant proteins displayed no unwinding activity. This finding suggests that SMARD1 results from a dysregulation of the cellular RNA/DNA metabolism in motor neurons. Hypotheses about the affected cellular functions of IGHMBP2 and possible pathomechanisms leading to the specific degeneration of motor neurons are discussed.