

Prof. Brunhilde Wirth
Institute of Human Genetics, Cologne
Spinal muscular atrophy: from gene to therapy

Spinal muscular atrophy (SMA) is the second most frequent autosomal recessive disorder in human and the major cause of genetically determined lethality in early childhood. SMA is characterized by progressive muscle weakness and atrophy of proximal muscles as a consequence of degenerated α -motoneurons in the spinal cord.

The genetic cause for SMA is a homozygous deletion/mutation of the *SMN1* gene, whereas the severity of the disease is mainly influenced by the *SMN2* copy number that vary in SMA patients between 1-4 rarely more copies. Each *SMN2* copy produces only about 10% correctly spliced transcripts whereas the majority is aberrantly spliced due to a silent mutation in exon 7 that disrupts an exonic splicing enhancer. In rare cases we and others identified families in which siblings present different phenotypes (affected versus fully asymptomatic) despite carrying identical *SMN1* mutations and identical number of *SMN2* genes. This strongly suggests the influence of modifying genes that protect against SMA. Recently, we have identified plastin 3 (PLS3) as the first SMA modifying gene that fully protects females from developing SMA. To learn more about the mechanism of protection, we generated a conditional transgenic mouse overexpressing PLS3 that is analyzed in the context of SMA and other motoneurone diseases. In addition, we have new SMA discordant families, in which we excluded PLS3 as the SMA modifier and we have already strong evidence for new SMA modifiers. The functional and biochemical analysis of these modifiers and the understanding of the molecular network are the main aims of the group. Finally the group has a strong interest in therapy of SMA by use of drugs that act epigenetically on transcription activation and restoration of correct splicing as well as stabilization of the protein. The group is carrying out preclinical and clinical studies using histone deacetylase inhibitors (HDACi).

Literature:

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NOTE: All these papers arose as part of the PhD or MD theses of the first authors listed above