## Modifiers of spinal muscular atrophy

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SMA is caused by loss of the *survival motor neuron gene 1* (*SMN1*) whereas the severity of the phenotype primarily depends on the *SMN2* copy number, the major SMA modifier. SMN is ubiquitously expressed and has housekeeping functions in various cell types such as small nuclear ribonucleoprotein (snRNP) assembly, translational regulation and stress response. However, the selective vulnerability of motor neurons combined with the predominant axonal localization of SMN early implicated an additional axon-specific function of the protein.
A major breakthrough towards a better understanding of which of the plethora of SMN functions underlies SMA pathology was achieved through the identification of the first fully protective SMA modifier in human, plastin 3 (PLS3) (Oprea et al., 2008). High expression of PLS3, an F-actin bundling protein, protects individuals from developing SMA despite carrying homozygous deletion of *SMN1*. PLS3 influences F-actin levels and rescues axon length and outgrowth defects associated with SMN reduction in cultured motor neurons of SMA mouse embryos and in zebrafish. Despite this knowledge we still do not understand what is the exact mechanisms underlying PLS3-mediated protection in unaffected patients of discordant families. To address this question we generated mice conditionally overexpressing human PLS3 and studied the effect in SMA mouse model on various congenic backgrounds.
Our data demonstrate a yet unidentified role of PLS3 in NMJ maturation, maintenance and function and thus highlight PLS3 as a potential therapeutic target in SMA but also other neuromuscular diseases such as myasthenia gravis and amyotrophic lateral sclerosis (ALS).

Oprea, G. E., *et al* (2008). Plastin 3 is a protective modifier of autosomal recessive spinal muscular atrophy. Science *320*, 524-527.