Novel genetic determinants of the neuromuscular SMA phenotype

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Principal Investigators

MONANI, UMRAO

Institution

COLUMBIA UNIVERSITY HEALTH SCIENCES

Contact information of lead PI
Country

USA

Title of project or programme

Novel genetic determinants of the neuromuscular SMA phenotype

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1

The project/programme is most relevant to:

Spinal muscular atrophy (SMA)

Keywords

Spinal Muscular Atrophy, neuromuscular, Genetic Determinism, SMN2 gene, snRNP Biogenesis

Research Abstract

DESCRIPTION (provided by applicant): Spinal muscular atrophy (SMA) is a common, frequently fatal, autosomal recessive disorder caused by homozygous mutations in the Survival of Motor Neuron 1 (SMN1) gene that lead to a deficiency of the SMN protein. Residual protein is

expressed from SMN2, a partially functional homologue of the SMN1 gene. There is presently no cure for SMA. Currently available treatments are palliative at best. Although much has been learned about the pathology and natural history of the human disease and notwithstanding proof-of-concept studies demonstrating rescue of an SMA phenotype by restoring SMN to mouse models of the disease, the biochemical pathway(s) linking low levels of the protein to neurodegeneration remain(s) obscure. The single established function of SMN in orchestrating snRNP biogenesis has failed to shed adequate light on the motor neuron phenotype observed in SMA, prompting the search for additional functions of the protein and/or genes linking SMN paucity and disrupted snRNP biogenesis to neuromuscular disease. Increasing SMN2 copy number leads to higher levels of the SMN protein in patients and mutant mice and results in milder phenotypes. However, in rare instances the correlation between SMN2 copies and disease severity no longer holds, implying the existence of additional genetic modifiers of the SMA phenotype. Identifying such modifiers is one way to uncover new, disease-relevant functions of the SMN protein or reveal effector genes through which a disruption in snRNP biogenesis causes the SMA phenotype. In this application for funding to the NIH, we have outlined experiments in two related aims to exploit a modification of the disease phenotype in mouse models of SMA to map and identify modifying loci. In aim 1 congenic strains of SMA mice will be created to precisely define how different genetic backgrounds affect the mutant phenotype. Additionally, mutants from defined inter-strain crosses between the congenic SMA carriers will be generated and characterized by molecular, cellular and phenotypic means. In aim 2, mutants with the most distinct disease phenotypes will be used in linkage studies to map and eventually identify modifier loci. To confirm the disease modifying effects of the identified loci we will re-introduce them into SMA mice exhibiting a “”typical”” disease phenotype. Our studies will have two important outcomes. First, they will uncover novel, disease-relevant biochemical pathways and thus inform the underlying biology of spinal muscular atrophy. Second, they will identify genes that could serve as new molecular targets for future SMA therapies. The results of our experiments will constitute an important step toward the design of safe and effective treatments for SMA patients.

Lay Summary

SMA is a debilitating, frequently fatal, incurable human neuromuscular disorder caused by reduced SMN protein. We wish to define pathways that lead from reduced SMN to dysfunction and disease. To do so we have made mouse models that allows us to identify such pathways and novel associated genes. Defining the pathways and genes will not only lead to a better understanding of SMA but also serve to identify potential targets for safe and effective treatments for the disease.

Further information available at:

Types:
Investments > €500k

Member States:
United States of America

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Spinal muscular atrophy (SMA)

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2016

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