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KNOCKDOWN AND REPLACEMENT OF MFN2 FOR TREATMENT OF DOMINANTLY INHERITED PERIPHERAL NEUROPATHY CMT2A PATIENTS

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Background/Rationale: Charcot-Marie-Tooth Disease 2A (CMT2A), the most common form of CMT2, is a severe and disabling sensory-motor axonopathy that currently lacks a cure . It is caused by autosomal dominant mutations in the MFN2 gene (Zuchner et al., 2004; Griffin et al., 2006; de Brito and Scorrano, 2008; Feely et al., 2011). Specific aims: The overall objective is to define whether silencing mutant MFN2 via RNA interference (RNAi) in combination with gene replacement therapy (GRT) with wild-type (wt)-MFN2 is an effective therapeutic strategy for CMT2A. In vitro validation and in vivo translation in reliable disease models is crucial to addressing this question. AIM1: Generate and validate a new vector carrying both the RNAi and GRT systems for MFN2. We will generate a single vector that co-expresses RNAi (short hairpin (sh)-RNA) targeting MFN2 transcripts for degradation and RNAi-resistant wt-MFN2 cDNA (AAV9-shRNA-MFN2 vector). These sequences will be tested in induced pluripotent stem cell (iPSC)-derived motor neurons (MNs; Rizzo et al., 2016), and then packaged into adeno-associated virus 9 (AAV9) for in vivo testing. AIM2: Assess the therapeutic efficacy of AAV9-shRNA-MFN2 vector in an established CMT2A mouse model (MitoCharc1). We will evaluate the efficacy of MFN2-targeting RNAi/GRT in an existing CMT2A model (MitoCharc1, Cartoni et al., 2010). Specifically, we will administer AAV9-shRNA-MFN2 vector within the central nervous system (CNS) of adult mice by intrathecal injection (Meyer et al., 2009), analyzing the effect on phenotypic and neuropathological disease features (Cartoni et al., 2010). AIM3: Test the AAV9-shRNA-MFN2 vector in newly generated preclinical mouse models. In order to study our approach in models with other CMT2A mutations or more severe phenotypes, we will generate mouse models by transferring CMT2A patient mutations to wt or MitoCharc1 mice using AAV9 and evaluate our strategy in these new models. Anticipated output: Our approach could be the first effective treatment for CMT2A and will have a broad translational impact on other genetic neuromuscular disorders.

Titolo:
Silenziamento e ri-espressione del gene MFN2 come trattamento per i pazienti affetti da CMT2A, una neuropatia periferica ereditaria

Abstract per il pubblico laico in italiano:
La malattia di Charcot-Marie-Tooth 2A (CMT2A), la forma più comune di CMT2, è una neuropatia sensitivo-motoria grave e disabilitante, attualmente priva di cura. È causata da mutazioni autosomiche dominanti nel gene MFN2. L'obiettivo di questo studio è sviluppare un approccio terapeutico per questa patologia basato sul silenziamento del gene MFN2 patologico in combinazione con la somministrazione del gene MFN2 normale. Questa strategia terapeutica sarà opportunamente validata in modelli in vitro e in vivo della malattia. Il nostro approccio potrebbe rappresentare il primo trattamento efficace per la CMT2A e avere un ampio impatto traslazionale su altri disturbi neuromuscolari a componente genetica.

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Malattia di Charcot Marie Tooth di tipo 2A

Coordinator: Stefania Corti
Duration (N. Years): 3
Starting year: 2020

Telethon Project (nr):

GGP19002

Disease Name:

Charcot Marie Tooth Disease 2A

Keywords:

Gene therapy, MFN2, CMT2A