PROJECT

Supervisor:	Prof. Stefano Carlo Previtali
Title:	**An Integrated Genomic, Phenotypic, and Functional Pipeline for the Molecular Diagnosis of Unresolved Inherited Neuromuscular Disorders**
Curriculum:	Molecular Medicine: Neurosciences and Experimental Neurology
Link to the personal page of the University or relevant hospital site website:	https://research.hsr.it/en/institutes/institute-of-experimental-neurology/neuromuscular-repair/previtali-stefano-carlo.html

Description of the Project (max 3,000 characters including spaces)

Background/gap of knowledge

Inherited neuromuscular disorders (iNMDs), including hereditary neuropathies and myopathies, are clinically and genetically heterogeneous and remain a diagnostic challenge.[1] Despite advances in NGS, targeted panels, and clinical exome sequencing, many patients with inherited neuromuscular phenotype remain genetically unresolved.[2,3]

This "missing heritability" likely reflects multiple mechanisms: undiscovered genes; variants poorly captured by short-read NGS (e.g., structural variants, repeat expansions, deep intronic/splicing variants, rearrangements);[4] variants in genes not traditionally linked to neuromuscular disease, especially in multisystem syndromes;[5] and digenic/oligogenic or polygenic contributions.[6,7] Interpretation is further limited by incomplete integration of genomics with deep phenotyping.[8] In unresolved cases, variant prioritization requires correlation with clinical course, neurophysiology, pathology, and muscle imaging. Nerve/muscle biopsy and whole-body muscle MRI, and when possible functional in vitro studies can provide patterns that support gene prioritization and interpretation.[9]

Rationale and hypothesis

We propose that unresolved hereditary neuropathies and myopathies can be reduced through an integrated strategy combining stepwise genomics (virtual panels on clinical exome data, trio exome in selected cases, and long-read sequencing in prioritized cases), deep phenotyping (clinical, histological, radiological), and targeted functional studies (on patient's fibroblasts, IPS-derived cell subtypes, or ad hoc mutagenized cell lines). We hypothesize that many unresolved cases are due to missing-heritability mechanisms (non-canonical genes, complex variants, syndromic disorders with underrecognized neuromuscular involvement, and digenic/oligogenic or modifier effects), and that phenotype-driven variant prioritization with functional validation will improve diagnosis.

Objectives and specific aims

We will establish and phenotype a cohort of unresolved patients (either retrospectively in selected cases from our database or prospectively in new recruited cases); apply a hierarchical genomic workflow in collaboration with Clinical Genetics teams (virtual panel analysis on clinical exome data, trio exome in selected cases, and long-read sequencing in prioritized unresolved cases); integrate genomic results with biopsy and whole-body muscle MRI to prioritize variants and refine genotype–phenotype correlations; and perform targeted functional studies in selected cases (e.g., reporter/overexpression assays, patient-derived fibroblasts, and induced motor neuron models when appropriate).

Expected outcomes

This project is expected to increase diagnostic yield in unresolved iNMDs, identify mechanisms missed by standard workflows (including complex variants, non-canonical genes, and digenic/oligogenic contributions), strengthen variant interpretation through functional evidence, refine genotype–phenotype correlations, and establish a reproducible translational diagnostic framework for a tertiary neuromuscular referral center.

Skills that the student should acquire (max. 600 characters including spaces):

The student will acquire advanced skills in neuromuscular clinical phenotyping (including interpretation of neurophysiology, muscle/nerve pathology and muscle MRI), genomic data review and variant prioritization in collaboration with clinical genetics, and experimental design and direct hands-on execution of functional validation in vitro (or in vivo)s studies. The candidate will also develop core wet-lab skills (cell culture, DNA/RNA/protein methods, cloning, basic imaging/assays), together with scientific writing, manuscript preparation, and publication-oriented communication.

References (max. 15)

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