

 <p>UniSR Università Vita-Salute San Raffaele</p>	<p>APPLICATION TO ACT AS SUPERVISOR AND RESEARCH PROJECT PROPOSAL</p>	<p>MO 20-5 ed. 02 of 16/01/2026 PO 20 Page 5 of 12</p>
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PROJECT

Supervisor: Prof. Massimo Filippi

Title: Genetic determinants of neuro-axonal progression in Multiple Sclerosis: a retinal endophenotype

Curriculum: Neuroscience 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/neuroimaging-research/massimo-filippi.html>

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

Background/gap of knowledge

Multiple sclerosis (MS) is characterized by marked heterogeneity in its clinical course, with patients experiencing widely different patterns of disease progression. Genetic factors are well established contributors to MS susceptibility and large genetic studies have identified more than 230 associated variants, mainly linked to peripheral immune pathways. In contrast, variants associated with disease severity appear enriched in genes expressed in the central nervous system (CNS), although this distinction is increasingly debated. Despite these advances, the genetic architecture underlying disease progression remains poorly understood.

Rationale and hypothesis

Understanding the genetic basis of variability in MS progression and neurodegenerative phenomena may provide key insights into the mechanisms driving long-term disability. However, clinical measures are influenced by multiple factors and may not accurately reflect underlying biology. Optical coherence tomography (OCT) enables high-resolution assessment of retinal neuro-axonal loss. By focusing on non-myelinated structures such as the peripapillary retinal nerve fiber layer (pRNFL) and the macular ganglion cell inner plexiform layer (mGCIPL), OCT provides a relatively pure imaging endophenotype of neurodegeneration. We hypothesize that genetic variants affecting CNS resilience and neuronal plasticity may contribute to different progression trajectories despite similar lesion burden, through effects on gene expression and epigenetic regulation.



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Objectives and specific aims

This study aims to identify genetic variants influencing disease progression and neurodegenerative processes, using OCT as endophenotype. For this purpose, a cohort of patients affected by MS, with already available OCT assessment, will be combined with a prospective cohort of newly recruited individuals; a subset of these patients has also longitudinal evaluation, providing important information on the modification of OCT measures over time, in parallel with the clinical MS course. OCT measures, including pRNFL and mGCIPL thickness and annualized thinning rates, will be analyzed cross-sectionally and longitudinally, to define endophenotypes of neurodegeneration. Polygenic risk scores (PRS) and candidate gene approaches using OCT metrics as primary outcomes will be performed, to shed light on the genetic underpinnings of neurodegeneration. The functional impact of identified variants on gene expression and epigenetic profiles, alongside environmental exposure, will also be explored to identify pathways mediating neurodegeneration.

Expected outcomes

To identify genetic variants associated with retinal neuro-axonal loss, both cross-sectionally and longitudinally. OCT-derived endophenotypes will provide a more precise characterization of progression by reducing the variability inherent to clinical measures. Uncovering the impact of these variants on gene expression and epigenetic profiles, integrated with environmental factors, will offer novel insights into mechanisms underlying CNS resilience and neuronal plasticity. These results may highlight therapeutic targets for personalized neuroprotection and support early identification of patients at risk for rapid progression.

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

During the course of the project, the student will develop the following competencies:

- Collection and management of clinical data from MS patients with different disease trajectories;
- Interpretation of clinical assessments together with OCT findings;
- Training in advanced analysis of large-scale datasets;
- Processing and analysis of genetic data, including quality control procedures, application of appropriate statistical methods and integration of genetic data with different omics;
- Preparation of scientific reports and drafting of research manuscripts.

References (max. 15)

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