<Integrated Multidisciplinary Approaches to uncover Molecular Mechanisms underlying Complex and Rare Neurological Diseases and their Phenotypes>

The possibility that different subjects may exhibit different phenotypes (clinical and/or instrumental) of the same disease, as well as they may have different response to the same treatment, has been deeply discussed and it is now recognized worldwide by the medical community. The term “Personalized Medicine” and its variations, such as precision medicine or stratified medicine, generally describe an approach to medicine that integrates the characteristics of an individual into procedures addressed towards early diagnosis of a given disease, its prognosis, the optimal choice of treatment, but also more generally to a more accurate risk estimation and targeted prevention.[1]

Overall, our research area is based on these principles. In particular, we investigated rare neurological diseases such as Multiple Sclerosis (MS), Amyotrophic Lateral Sclerosis (ALS) and Spinal Muscular Atrophy (SMA), with the main purpose to shed more lights into their molecular background, thus supporting the search for more efficient therapeutic targets. At the same time, by looking at the different phenotypes of these diseases, the immediate and translational aim of our approach was to identify reliable markers for the disease monitoring and the response to available treatments that may allow the clinicians to a more individualized medical approach for each patient.

To pursue these targets, we performed highly specialized and advanced molecular analysis of the collected samples (see below for more details). The results of this analysis, together with the clinical and instrumental data collected by our clinical Partners, were processed by a trained bioinformatics/biostatistics team. Both these steps were performed at the ITB in Bari, a CNR Unit equipped by a genomic laboratory with specialized equipment and facilities for molecular and cellular biology, and a bioinformatics laboratory in which the computational technologies required for the High-throughput Next-Generation Sequencing (HT-NGS) data analysis is available. Furthermore, this Unit is part of the PON infrastructure “National Research Center in Bioinformatics for Omics Sciences, CNRBiOomics”.

We applied these integrated multidisciplinary approaches in the following research activities:

1) **Study of molecular profiles associated with neurological multifactorial diseases and their phenotypic aspects:**
   In neurodegenerative diseases such as MS, ALS, SMA: Characterization of the transcriptomic profile and identification of complex miRNA-transcription factor (FT) co-regulation networks. In vitro functional validation of the correlations between miRNA-target gene networks, miRNA-FT feedback and feed-forward circuits and the molecular pathways involved, through the application of the main genetic engineering and molecular biology methods.[2-5]

2) **Pharmacogenomics/pharmacoepigenomics as part of the innovative strategies of Personalized Medicine for the treatment of rare neurological diseases:**
   Characterization of molecular profiles by longitudinal prospective observation in order to identify suitable biomarkers for monitoring treatment, individual response and the occurrence of side effects in patients with rare diseases like SMA and MS.
3) **Cell Vesicles (EV)s in neurodegenerative diseases:**

Study of transcriptomic and proteomic profiles in EVs (exosomes and microvesicles) isolated from serum and cerebrospinal fluid of patients with MS, through the use of advanced omics technologies. Validation and functional analysis in vitro (reporter assays, gene knock-down, RNA interference) of significant cell-free RNA and vesicular proteins.\[^{[6,7]}\]

**Conclusions:** In the last few decades the rare complex diseases became a major challenge for most of the National Health Care Systems. The cost-effectiveness of interventions in chronic progressive diseases is assessed by linking changes in disability and/or symptoms with changes in health-related quality of life and resource consumption (costs). For this reason, in our view our investigations will contribute to improve the care and treatment of neurological patients during their life-span, as well as they will lead to a significant reduction of costs related to the drugs administration. In fact, through the identification of genetic variables able to influence the responsiveness and/or the onset of side effects during a given treatment, it will be feasible to prevent its occurrence by using genetic tests carried out prior the treatment start.

**References:**


Keywords (3): Neurological Rare Diseases, Transcriptomics, Biomarkers

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