

PERSPECTIVES IN CURRENT GENOMICS

Translational Medicine in Neurological Disorders: A Genomic PerspectiveGiulia Gentile¹ and Sebastiano Cavallaro^{1,*}¹*Institute of Neurological Sciences, Italian National Research Council, Via Paolo Gaifami 18, 95125 Catania, Italy*

According to the European Society for Translational Medicine (TM), this interdisciplinary branch of biomedical field was established on three pillars: *benchside*, *bedside* and *community*, and is devoted to promoting prevention, diagnosis and therapy of clinical disorders affecting the global population [1]. Among these, neurological ones affect up to one billion people worldwide, according to the World Health Organization, and represent one of the major social and scientific challenges. Along with an increased life expectancy and the growth of older population in all nations, the rate of some Neurological Disorders (NDs), such as Alzheimer's disease, will increase substantially over time posing a burden not only to the patient but also to the entire society [2]. A global and multidisciplinary effort is needed to conduct research on brain disorders, together with a Systems Biology (SB) strategy able to deal with complex neurological phenotypes. The complexity to be deciphered by using a SB strategy was described by the metaphor "A single protein is to a neuron as a neuron is to whole brain" by the Nobel Prize in Medicine Rita Levi-Montalcini [3].

A growing scientific community is analyzing and integrating omics data by computational and modeling approaches, comparing them with phenotypic observations and data shared on public repositories, using a SB strategy applied to neurological field [4]. The integration and comparison of this huge amount of data continuously produced and shared by the community has contributed to expanding the spectrum of pathogenic variations responsible for neurological diseases, highlighting the importance of susceptibility factors and providing insights into overlapping pathogenic mechanisms. A large part of the data produced belongs to genomic studies and represents a source of information that is able to drive the discovery of disease progression, druggable and therapeutic response biomarkers. However, additional efforts are needed to develop novel diagnostic and therapeutic approaches based on biomarkers discovery and to translate them into the clinical practice, in a society that is getting older without a cure for neurological diseases and the perspective for a long-term reliance on health care system [5]. Indeed, several therapeutic options are being explored for NDs, but very few have shown benefits in clinical trials. Treatment failure is mainly due to the lack of robust targets whose modulation results in a therapeutic benefit [6]. Instead, innovative therapeutic approaches of precision medicine for genetic neuromuscular disorders, such as RNA interference therapy, splicing modifier, exon skipping and gene therapy, seem to be very promising and their achievements could stimulate the widening of their applications [7, 8].

Here, we want to focus attention on the role of genomics in the TM process applied to NDs, the reached progress and the future challenges.

The genomic field investigates genes, their functions and expression, their different layers of regulation, their genetic variations and conservation across species. Genomics can help to elucidate common pathogenic pathways underlying complex neurological traits and, therefore, common drug targets. Moreover, it may also improve differential diagnosis of complex phenotypes. For these reasons, a number of international consortia and networks of research have been created to study complex neurological phenotypes from a genomic perspective. An example is the PsychENCODE Consortium, which developed a public resource of multi-dimensional genomic data from human postmortem brains, additional cell lines and tissues from disease and control cases. This integrated resource is able to predict models and to study shared disease mechanisms underlying psychiatric disorders including schizophrenia, bipolar and autism spectrum disorders. Using deep-learning models, it is able to predict psychiatric phenotypes from genotype and expression data, improving the detection accuracy of complex traits with a highly polygenic architecture associated with brain disorders [9]. Progressively, as previously occurred in the oncological field, a molecular taxonomy for NDs is emerging. Their genomic profiles will help neurologist to classify these disorders into subtypes with personalized diagnostic, prognostic and, hopefully, therapeutic strategies. An example is the molecular taxonomy of Amyotrophic Lateral Sclerosis that is now able to distinguish two different subtypes based on their transcriptional profiles, each associated with specific pathogenic mechanisms and potential therapeutic targets [10].

The diagnostic power of high-throughput genomic technologies is taking full advantage of technological progress. In fact, Comparative Genomic Hybridization array (aCGH) and Next-Generation Sequencing (NGS) platforms have increased the power of biomarker discovery and are moving from research to diagnostics labs. The use of aCGH, as a first-tier clinical diagnostic test, has been recommended since 2010 for developmental delay/intellectual disability and autism spectrum disorders [11]. In 2014, the American Food and Drug Administration agency cleared the first and only postnatal blood test by aCGH to aid in the

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diagnosis of developmental delay, intellectual disabilities, congenital anomalies, or dysmorphic features [12], which has further received the European Conformity marking. Several customized aCGHs have been developed and used for NDs research and diagnostic validation, among which an exon-centric able to detect new potential genetic biomarkers or shared mechanisms underlying the most common molecularly diagnosed neurological diseases [13]. Meanwhile, NGS guidelines regarding the evaluation and validation of variants for the diagnosis of genetic disorders have been published [14]. Comprehensive whole-exome or genome sequencing approaches are more often used for neurological patients without a focused genetic differential diagnosis, whereas custom-designed targeted-panels allow disease-focused evaluations [15]. However, differences in the healthcare structure of each country and within the same country, as the case of Italy, remain a major obstacle and lead to heterogeneity in service delivery and inequity in access to NGS-based diagnosis.

NDs represent a highly heterogeneous group of pathological conditions, a part of which characterized by complex traits resulting from variations within multiple genes and their interaction with nongenetic factors. A supplementary grade of complexity arises when more neurological pathological conditions affect the same patient. To deal with this complexity, a SB strategy is needed to analyze, integrate and infer models providing insights into the relationship between genotype, gene expression, and phenotype. Data provided by genomics and its technologies represent an important part of these process and are already translating their results into clinical practice. They have the power to uncover pathogenic mechanisms, stratify patients into disease subtypes, enhance the diagnostic power in order to extricate heterogeneity of complex NDs and overlapping phenotypes, identify new drug targets to be tested, and drive Neurology through therapies that are more effective. The future challenges involving genomics as a protagonist of the translational process in Neurology concern the enhancement of diagnostic power for differential diagnosis, the stratification of patients for clinical trials with respect to their gene expression, and the identification of new drug targets to be used in pathologies sharing pathogenic mechanisms.

LIST OF ABBREVIATIONS

TM	=	Translational Medicine
ND	=	Neurological Disorders
SB	=	System Biology
aCGH	=	Comparative Genomic Hybridization Array
NGS	=	Next-Generation Sequencing

CONSENT FOR PUBLICATION

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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