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EDITORIAL

Unravelling the mysteries: a reflection on rare neurological diseases

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On February 28, we celebrated Worldwide Rare Diseases Day, a full day devoted to spreading knowledge, conducting research, and generating tangible changes for the 300 million people worldwide who live with a rare disease and their families.

A disease is considered rare if it affects less than 5 per 10,000 individuals in the EU or less than 200,000 individuals in the USA. In the vast landscape of neurological disorders, there exists a group of conditions that stand out not only for their complexity but also for their rarity. Rare neurological diseases (RNDs) affect a limited number of individuals, making them challenging to study and understand. Despite the hurdles, the importance of addressing RNDs cannot be undervalued, as their study may not only lead to breakthroughs in understanding these specific conditions but may also shed light on broader aspects of neurobiology and pave the way for innovative treatment approaches.

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One of the defining features of many RNDs is their genetic basis. Recent advancements in genetic research, such as next-generation sequencing and CRISPR technology, have opened new avenues for unraveling the intricate genetic landscapes underlying these disorders. The identification of causative mutations not only facilitates accurate diagnosis but also provides critical insights into the mechanisms driving disease phenotype and progression. As we delve deeper into the genetic bases of RNDs, we inch closer to personalized and targeted therapeutic interventions. As mentioned by Jensen et al. in a review on gene therapies in RNDs, "gene therapies might become a game changer" and "have the potential of a paradigm shift where we move from symptomatic alleviation to disease modification and even cure" [1]. As evidence of this, in recent years, technological advances have allowed for disease-modifying pharmacological, molecular, or gene therapies that can radically change the evolution of some serious RNDs.

Italian neurology has a very long tradition in the study of RNDs, and several neurological Italian centers actively participate in the European Reference Network (ERN) for rare and low-prevalence complex diseases (Table 1), as well as other international rare disease organizations.

The scientific production of Italian neurological community is significant, as quoted by PubMed, with a progressive increase on the number of publications in the last 10 years from 486 in 2014 to 767 in 2023 (Table 2).

In addition to the referral neurological centers, also general neurologists play a crucial role in both care and management of patients with rare diseases. They should be aware of RNDs, encouraging clinical investigations and developing a strong interaction with the specialty centers for follow-up, long-term care, and new therapies for those diseases.

The Italian Society of Neurology (SIN, www.neuro.it) promotes knowledge and awareness in RNDs. As we embark on a new era of scientific discovery, it is imperative to shine a spotlight on the key priorities in RND research. It is our collective responsibility to ensure that no one is left behind and that individuals with rare diseases receive the attention, understanding, and care they deserve. By addressing the

Table 1 Neurological Italian centers participating in the European Reference Networks (ERNs) for rare or low-prevalence complex diseases

EpiCARE: European Reference Network for Rare and Complex Epilepsies	ERN-RND: European Reference Network on Rare Neurological Diseases	EURO-NMD: European Reference Network for Rare Neuromuscular Diseases	MetabERN: European Reference Network for Rare Hereditary Metabolic Disorders
IRCCS Institute of Neurological Sciences, Bellaria Hospital, Bologna	Bambino Gesu' Children's Research Hospital IRCCS, Rome	AOU Federico II, Naples	AOU—University Hospital Siena
Meyer University Hospital, Florence	AOU—University Hospital Siena	City of Health and Science University Hospital of Turin	
IRCCS Foundation Carlo Besta Neurological Institute/Claudio Munari Epilepsy Surgery Centre, ASST Niguarda Hospital/ASST Santi Paolo e Carlo—San Paolo Hospital, Milan	AOU—University Hospital Pisa	Polyclinic University Hospital, Bari	
Mondino Foundation, IRCCS National Neurological Institute of a Scientific Character, Pavia	AOU—University Hospital Padua	Bambino Gesu' Children's Research Hospital IRCCS, Rome	
Bambino Gesu' Children's Research Hospital IRCCS, Rome	Polyclinic University Hospital, Bari	IRCCS—Foundation of the Carlo Besta Neurological Institute, Milan	
AOUI of Verona, Complex Unit (UOC) of Child Neuropsychiatry, Verona	AOU Federico II University Hospital, Naples	IRCCS Giannina Gaslini Institute, Genoa	
IRCCS Giannina Gaslini Institute, Genoa	IRCCS Institute of Neurological Sciences, Bellaria Hospital, Bologna	IRCCS Istituto Auxologico Italiano, Milan	
	IRCCS—Foundation of the Carlo Besta Neurological Institute, Milan	IRCCS Policlinico San Martino Hospital, Genoa	
	IRCCS—Humanitas Clinical Institute of Rozzano, Milan	Nemo Clinical Center, Milan	
		University of Campania "Luigi Vanvitelli" University Hospital "Luigi Vanvitelli", Naples	
		AOU—University Hospital Padua	
		University Hospital "Maggiore della Carità", Novara	
		AOU—University Hospital Pisa	
		ASST "Spedali Civili", Brescia	
		University Hospital, Messina	
		IRCCS Ca' Granda Maggiore Policlinico Hospital, Milan	
		IRCCS Institute of Neurological Sciences, Bellaria Hospital, Bologna	
		IRCCS San Raffaele Hospital, Milan	
		University Hospital St. Anna, Ferrara	
		A. Gemelli University Polyclinic Foundation, Rome	

Table 2 PubMed search results in the last 10 years using the words "rare neurological diseases and Italy"

Year	Number of papers
2023	767
2022	908
2021	989
2020	979
2019	800
2018	680
2017	657
2016	659
2015	512
2014	486

following priorities, we can unlock the mysteries surrounding these conditions and pave the way for innovative treatments and improved patient outcomes.

1. Early and accurate diagnosis. A paramount priority in rare disease research is the development of robust diagnostic tools that facilitate early and accurate identification of these conditions. Importantly, an increasing number of rare disorders have treatment implications and, therefore, should not be missed. As mentioned, many rare diseases have a genetic basis, and understanding the underlying genomic and molecular mechanisms is pivotal for developing targeted therapies. Facilitating access to technologies and bioinformatics will accelerate the identification of genetic mutations associated with the diseases. Moreover, exploration of the intricate molecular pathways involved will provide critical insights, enabling the development of precision medicine approaches tailored to individual patients.
2. The power of collaboration. The rarity of each specific disease often results in fragmented and isolated research efforts. To overcome this obstacle, fostering a culture of data sharing and collaboration is crucial. Establishing centralized repositories for rare disease data, promoting open-access platforms, and encouraging collaboration among researchers, institutions, pharmaceutical companies, and other stakeholders will accelerate new discoveries and enhance our collective understanding of these conditions.
3. Patient-centered approaches. Embracing a patient-centric approach is integral to rare disease research. Patients and their families are often the true experts on the daily challenges posed by these conditions. Engaging them as partners in research, clinical trials, and decision-making processes ensures that research priorities align with the needs and experiences of those directly affected.
4. Rare disease education and awareness. Building awareness among healthcare professionals, policymakers, and the public is essential in ensuring timely diagnosis and appropriate care for individuals with RNDs. Educational programs, public campaigns, and targeted outreach efforts can help dispel misconceptions, reduce stigma, and foster a supportive environment for those living with rare conditions.

The diagnosis, care, and treatment of individuals and families affected by RNDs present formidable healthcare challenges that remain unsolved. Effecting necessary changes in healthcare and research demands extensive multistakeholder cooperation, substantial resources, and strategic leadership. In recognition of these imperatives, SIN, in collaboration with all stakeholders, including the European Academy of Neurology, the European Reference Networks for Rare and Complex Diseases, and patients' associations, is dedicated to addressing these challenges and driving positive transformation in the realm of healthcare and research.

Declarations

Ethical approval None.

Conflict of interest The authors declare no competing interests.

Reference

1. Jensen TL, Gøtzsche CR, Woldbye DPD (2021) Current and future prospects for gene therapy for rare genetic diseases affecting the brain and spinal cord. Front Mol Neurosci 14:695937