

PROF. MICHELANGELO MANCUSO (Orcid ID : 0000-0003-2738-8562)

PROF. CLAUDIO L BASSETTI (Orcid ID : 0000-0002-4535-0245)

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How to approach a neurogenetics diagnosis in different European countries – The EAN Neurogenetics Panel survey

M Mancuso¹, H Houlden², MJ Molnar³, A Filla⁴, M Breza², H Graessner⁵, CLA Bassetti⁶, S Boesch⁷

1. Department of Clinical and Experimental Medicine, Neurological Institute, University of Pisa, Italy
2. Department of Neuromuscular Disease, UCL Queen Square Institute of Neurology and The National Hospital for Neurology and Neurosurgery, London, UK
3. Institute of Genomic Medicine and Rare Disorders, Semmelweis University, 1082 Budapest, Hungary
4. Department of Neurosciences, Reproductive and Odontostomatological Sciences, Federico II University, 80131 Naples, Italy
5. Institute for Medical Genetics and Applied Genomics, Centre fo Rare Diseases, University of Tübingen, Tübingen, Germany
6. Department of Neurology, Inselspital, University Hospital, Bern, Switzerland
7. Department of Neurology, Center for Rare Movement Disorders Innsbruck, Medical University Innsbruck, Austria

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Corresponding:

Michelangelo Mancuso, MD, PhD

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Department of Clinical and Experimental Medicine
Neurological Institute
University of Pisa, Italy
michelangelo.mancuso@unipi.it

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Abstract

Background and purpose: 7,000 rare diseases have been identified, most of them are of genetic origin. The diagnosis of a neurogenetic disease is difficult, and management and training programs are not well defined through Europe. To capture and assess care needs, the Neurogenetics Panel of the European Academy of Neurology (EAN) has performed an explorative survey.

Methods: The survey covering multiple topics of neurogenetics was sent to all neurologists and neuropediatricians affiliated to the EAN practicing in Europe.

Results: We have collected answers from 239 members based in 40 European member states. Even though most of the responders are aware on neurogenetic diseases, when we come to amenability of carrying out a complete genetic diagnosis, almost one third of the responders declare that are not happy with the current way of ordering genetic analyses in their Countries. Furthermore, while single gene analysis is diffusely present in Europe, whole exome and genome sequencing are not easily accessible, with considerable variabilities between Countries. Almost 10% of the responders didn't know if pre-symptomatic and prenatal diagnosis is available in their Countries, and 47,3% were not aware of which newborn screening programs are available. Finally, 96,3% of responders declare that there is a need for education and training in neurogenetics.

Conclusions: We believe that this survey may be of importance for all European stakeholders in neurogenetics in identifying key priorities, targeting areas to encourage education/travel fellowships and educational seminars in the future as this area will only accelerate and diagnostic requirements expand.

Keywords: Europe; disease diagnosis; neurogenetics; rare diseases; survey.

Introduction

A rare disease (RD) is defined as one that affects fewer than 5 per 10,000 persons in the European Union (EU) or fewer than 200,000 persons in the United States. Despite their relative rarity, about 6,000 to 8,000 RDs have been identified worldwide, affecting approximately 6 to 8% of the general population (almost 30 million people in the EU) [1, 2]

Rare neurological diseases (RNDs) constitute a significant proportion of RDs. Almost 80% of the RDs are caused by genetic anomalies, and in over half cases affect the central and/or peripheral nervous system, either isolated or in combination with other systems, and may start in childhood. This is one of the main reasons why neurologists and neuropsychiatrists must be aware of and prepared to manage these diseases. Therefore, there is a growing worldwide attention in neurogenetics diseases (NGDs), with several areas of neurosciences sharing this interest.

Due to the significant clinical and genetic heterogeneity, either for the many genes involved (genetic heterogeneity) or the great variety of mutation types in a single gene (allelic heterogeneity), NGDs are often challenging to diagnose. The diagnostic process may take even years, require several specialists, and need many medical investigations, where genetic diagnosis is in our days recognized as mandatory for NGDs since it allows proper counseling, family planning, and access to therapy or novel clinical trials. This is even more relevant given the availability of personalized treatment in a growing number of diseases.

Genetic diagnostic services are already under considerable pressure to integrate the new discoveries and to ensure equal accessibility and fast responses to avoid treatment and management delays. However, does this statement apply for all European countries? Moreover, the quality of the awareness and training in neurogenetics, among medical school and residencies programs, is not completely known at European level.

The aim of this work is to gather information on different aspects of neurogenetics, as understood by the European neurologists and neuropsychiatrists affiliated to the European Academy of Neurology (EAN). Topics of interest in this survey were: (i) Provision of genetic services in Europe: current practices and issues; (ii) Genetic services in different European Countries; (iii) Genetic services throughout Europe; (iv) Pre-symptomatic and new-born screening in neurogenetics; and (v) Education on neurogenetics.

Methods

The current project is a cross-sectional survey focused on members of the EAN, who deal with both adult and pediatric patients and whose clinical practice is performed in the Europe. The Neurogenetics Panel management group of EAN designed the questionnaire (see supplementary file 1), taking into account the following elements at National level: awareness of RNDs, national policies, access to different diagnostic tests (also covering pre-symptomatic and newborn screening), education in neurogenetics. The survey was distributed by the EAN Scientific Department through the official society mailing list, which contained 1278 contacts, advertised through the official society channels, **including social media reminders**, and it was conducted online between June 15th and October 15th, 2021. We have invited, among the EAN members, only clinicians, including residents, practicing in the field of neurology and child neurology. Responses were collected through the Google forms platform and then anonymously analyzed.

Ethical statement

Ethical approval was not necessary for this study.

Results

A total of 239 neurologists (18% of the physicians listed in the EAN mailing list), of whom 6,7% Neuropediatricians, filled the survey (53% female, mean age 47,7 years), representative of 40 European member states (affiliated to the EAN, Figure 1) and of all EAN Scientific Panels. Supplementary file 2 shows the obtained results.

Of these, 77% were employed in either Academic or Public Hospitals, 7% were residents in neurology, the remaining ones were either private neurologists or specialists affiliated to research centers. The full list of queries and the results are reported in the supplementary files 1 and 2 respectively.

General aspects

Almost all participants (99,2%) were aware of neurogenetic diseases and thought that neurogenetics has an important role in clinical neurology. Most of them (91,2%) follow patients with NGDs, mainly neuromuscular (51,9%), ataxia (54%), rare dementia (31,8%), movement disorders (53,1%), monogenic cerebral small vessels diseases (27,2%), mitochondrial diseases (43,5%), hereditary spastic paraplegia (43,9%) and epilepsy (24,3%). While all the responders agreed that family history is an important finding in the diagnostic flowchart, in almost 20% of cases the same is not usually collected, which could lead to wrong or delayed diagnosis.

Regarding the prescription of genetic tests, in most symptomatic patients they are prescribed by clinicians, including residents, whereas 20% of responders declare that are prescribed only by clinical geneticists. In case of presymptomatic screening, neurologist with expertise in genetics are allowed to prescribe genetic for 60% of responders; however, the presymptomatic genetic test is preceded by a medical genetic counseling consultation in more than 90% of cases. Finally, in case of prenatal diagnosis, almost all responders who are aware of the service declare that genetic test is preceded by a medical genetic counseling.

Genetics tests availability

Even though most of the responders are aware on NGDs, however, when we come to amenability of carrying out a complete genetic diagnosis, almost one third of the responders declare that are not happy with the current way of ordering genetic diagnostic tests in their countries. As an example, PCR fragment analysis and other techniques for repeat disorders are

available in 40% of cases only for limited commoner expansions. Moreover, while single gene analysis is diffusely present in European countries, WGS is not easily accessible for more than 60% of responders. The European situation appears to vary from Country to Country with respect to access to NGS Panels, WES and WGS, where most of the differences are between western and eastern Europe (see figures 2-3-4). Both the discrepancies and completeness of the acquired data between Countries cannot be deeply evaluated in this survey due to the limited number of answers we have collected.

Another important issue is the latency between the request test and the obtained response. In more than 35% of cases, it takes more than 3 months for single gene analysis and more than 68% for NGS genes panels; in more than 40% of cases analyzed by WES it takes more than 6 months.

Information about including the new-born screening for treatable RNDs and presymptomatic diagnosis is not diffusely provided to the general neurologists, mainly to those not directly involved in the field; almost 10% of the responders don't know if presymptomatic and prenatal diagnosis are available in their countries, and 47,3% are not aware of which newborn screening programs are available in their Countries. **We should be aware about the risks neurologists run by doing presymptomatic -and more rarely- prenatal genetic testing on their own (61% and 29% of the responders respectively); however, in most cases (91 and 83 % respectively) the genetic testing is preceded by a medical genetic counseling consultation.**

Education in neurogenetics

96,3% of responders declare that there is a need for education and training of neuro-residents in neurogenetic diseases. A neurogenetic program is known to be available in 34% of the medical school curriculum, in 24,6% of the neurological residency curriculum and in 33% after the neurological residency program.

Discussion

The total number of RDs is estimated to be greater than 7000 with a global prevalence of 3.5%–5.9%, and there are an estimated 263–446 million persons affected globally at any point in time [3].

In Europe, it is estimated that more than 500 000 persons are affected by RNDs, and globally, the management presents a significant challenge [4, 5] to health policy makers, health care providers, patients, and society in general due to gaps in knowledge, lack of awareness, difficulties in gene test and treatment access due to the high costs.

With this work, we aim to provide evidence that a survey tool, used in the context of the EAN, is useful means to collect information about the state-of-the-art of health-related activities for NGDs, which may help to improve and homogenize health care service to the rare disease community.

We are aware that our survey tool has some limitations. First, the survey did not collect enough responses from neuropsychiatrists, with only 6,7% of responders being involved in the care of children. Secondly, although a large proportion of countries of the Europe were included in the study, for some of them we have obtained a very low number of responders, and this might have biased the results for some countries. Thirdly, the results were based on a single subject response per country. This might also have biased the results of care needs in some European Country. However, all respondents were affiliated to the EAN and member of different EAN Panels, and we assume they were likely to be well informed about the NGDs in their respective country. It would be important in the future to both replicate and expand our data to have more insights in the field of neurogenetics; collaboration with other entities, including additional scientific associations, could be a way to go.

Even though absolute conclusions cannot be reached, several messages arise from this survey.

1. Information about the country organization for molecular diagnosis of NGDs is not diffusely provided to the clinicians working in the neurological field, mainly to those not directly involved in the rare diseases' world.
2. The awareness of the neurologist about new-born screenings for inherited treatable diseases is relatively low.

3. This survey reveals that, in spite of the many initiatives undertaken to facilitate the diagnosis and management of RNDs in Europe, there is still much to be done in support to these patients, including easy approach to specific diagnostic gene testing, presymptomatic diagnosis, carrier and newborn screening; a deeper collaboration between all stakeholders in the arena (academia, physicians, researchers, EU politicians, patients advocacy groups and industries), is a crucial need.
4. Despite the strong epidemiological impact of neurogenetics diseases and the important costs related to them, education in clinical genetics and neurogenetics is still inadequate in most countries. Neurogenetics programs in both medical school and residency curriculum and in continuing medical education are strongly encouraged.

We believe that this work may be of importance for all European stakeholders in RNDs and NGDs in identifying key priorities that should be done to do better in the next close future:

Key Priority 1. Ensuring European patients get the right diagnosis faster wherever they live, including prenatal diagnosis and newborn screening for the treatable NGDs.

All experts in the field know that the diagnostic journey of a patient with NGD is frequently an odyssey, which is complex and burdensome [6]. It features multiple consultations and tests, and, often, conflicting diagnoses. These reflect disease variety, diagnostic uncertainty, and clinician unfamiliarity, and may lead to incorrect family planning and treatment delay.

Key Priority 2. Keep increasing awareness of rare conditions among healthcare professionals

While this survey is encouraging, we still have to work in this scenario, as different National realities revealed that neurological community is not always well aware of RNDs [7, 8].

Key Priority 3. Developing a neurogenetics curriculum during the medical school and neurological and child neurology training and continuous medical education program.

Key Priority 4. Translation about the pediatric issues getting adulthood. Given the amount of early onset genetic disorders and the possibility for early diagnosis and treatment, efforts to harmonize transition of patients with neurogenetic disorders from pediatric neurology to adult neurology is highly warranted across Europe.

Key Priority 5. Technical red flag issue / Transparency; how do you know what you get. As gene panels for each diagnostic area, such as in CMT or dystonia expand, it will be important to harmonize the genes and flanking introns being tested across European and the rest of the world

diagnostic laboratories. This is a technical issue of extracting standard data from the exome or genome that each panel is taken from such as through a collaborative PanelApp [9].

Key Priority 6. In order to speed up the diagnosis of cases not diagnosed within the own countries cross border collaboration can be offered through the European Reference Network for Rare Neurological Disorders (ERN-RND), Neuromuscular Disorders (ERN EuroNMD) and Epilepsies (ERN EpiCare) using the Clinical Patient Managements System (CPMS) developed by the EU.

Key Priority 7. Unsolved cases **and cases where the detection of VUS may seriously hamper the diagnosis of** inherited NGDs should be directed to collaborative research programs.

Key priorities 1, 2, 3, 4 and 6 are currently be taken up by the European Reference Networks ERN-RND, EuroNMD and EpiCare. Notably and in collaboration with EAN a RND postgraduate curriculum is being developed and cross-ERN working groups have been established on transition and NGS diagnostics.

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Legends:

Figure 1: European countries (in red) affiliated to the EAN where we have obtained responses of the survey. Numbers in bracket indicate the numbers of responders per Country.

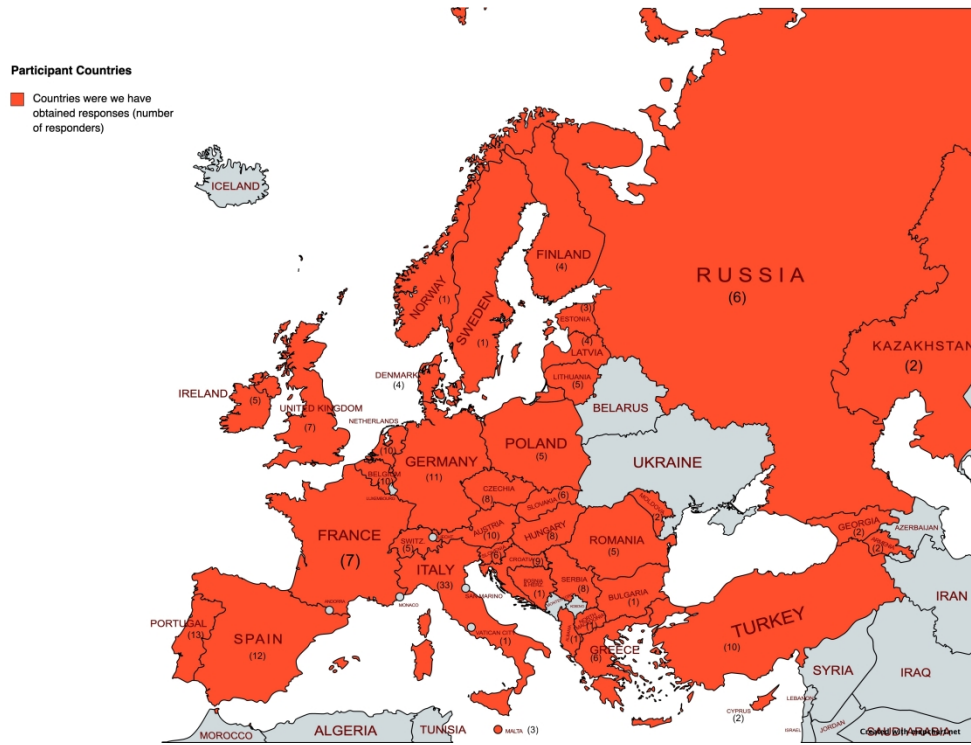
Figure 2: NGS availability based on survey responders

Figure 3: Diagnostic WES availability based on survey responders

Figure 4: Diagnostic WGS availability based on survey responders

Supplementary file 1: The EAN Neurogenetics Panel Survey

Supplementary file 2: The EAN Neurogenetics Panel Survey Results



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ene_15320_f4.png

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