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EXPERT OPINION

What the future holds for the genetic diagnosis for neurodegeneration with brain iron accumulation syndromes?

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We have recently seen a tremendous revolutionary development in molecular sciences with emerging genetic and genomic technologies. This has shed light on rare inherited disorders including Neurodegeneration with Brain Iron Accumulation (NBIA), a heterogeneous group of neurological disorders caused by excessive iron deposition in the brain. Despite this, a large proportion of cases cannot yet be explained by mutations in any of the known genes. However, new NBIA genes will continue to be described and strategic work-up in large patient cohorts may also unravel potential genetic and epigenetic factors influencing or determining the clinical and radiological presentation of individuals with NBIA. It is tantalizing to imagine how far platforms for transcriptome analysis and genomic profiling, such as genome-wide microRNA assays and methylation studies, and metabolomics, will also shed further light on NBIA syndromes. In turn, improved understanding may lead to novel approaches to modify the course of illness by identifying therapeutic targets that have already been validated in other relevant human disease models as well as aiding the development of potential new neuroprotective compounds. These and other timely issues of NBIA disorders are discussed in this editorial.

Keywords: genetic diagnosis, neurodegeneration with brain iron accumulation, neurological disorders

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In the last decade, we have seen a tremendous revolutionary development in molecular sciences with emerging genetic and genomic technologies for inherited disorders. Novel tools including, most recently, next-generation sequencing (NGS), whole exome and genome studies provide an innovative method to detect genetic conditions, with sequencing costs considerably plummeting over time. At the same time, advances in bioinformatics have made the concept of personalized genomic medicine a conceivable clinical reality in a matter of years [1]. Indeed, we are seeing more and more of this implemented in primary clinical care. Traditional genetic linkage analysis and candidate gene approach in the diagnostic work-up are increasingly being replaced by elegant methods of simultaneous gene testing using next generation multiple gene panels or the whole exome/genome sequencing approach. Whilst 80% of rare disorders are thought to be genetic in origin [2], many clinical syndromes display considerable genetic heterogeneity [2], and therefore such commercially available approaches are a pragmatic answer for targeted diagnostic testing. Despite these advances, several challenges remain. Capture methods remain imperfect and can result in unequal depth of coverage at different exonic regions [2]. Thus, established and well-validated molecular technologies (such as

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single gene testing and microarray studies) continue to have an important role, especially in regions of the world that have more limited access to NGS capabilities [3].

One example of a rare syndrome is Neurodegeneration with Brain Iron Accumulation (NBIA), a heterogeneous group of neurological disorders caused by excessive iron deposition in the brain [4]. Patients typically manifest with cognitive and motor regression associated with childhood-onset movement disorders, spasticity and neuropsychiatric symptoms. A handful of genetically distinct disorders have already been delineated. The first gene was identified in 2003, *PANK2*, underlying the most common type of NBIA called Pantothenate Kinase Associated Neurodegeneration (PKAN). In the past few years, further (mostly recessive) genes have been described, including *PLA2G6* and C19orf12. *De novo* mutations may also occur as seen in the *WDR45*-associated form [5,6]. Yet, a large proportion of cases (about 35% of all NBIA cases) cannot yet be explained by mutations in any of the known genes. Without doubt, new NBIA genes will continue to be described. Time will tell how many of these will turn out to be 'private syndromes' that account only for small numbers of individuals or even just single families. The challenge for the scientific community will be to provide adequate proof of pathogenicity for these rare NBIA genes.

It can be challenging for both clinicians and scientists to keep track, as one may be overwhelmed by the number of new genes and associated phenotypes reported in the literature; and there is the need for continuous education of professionals. In NBIA, the phenotypic spectrum and overlap with other neurological disorders is fascinating and it is often difficult to make a correct diagnosis based alone on the clinical findings. For example, for *FA2H*-related diseases, the phenotypic spectrum ranges from a syndrome of brain iron accumulation to hereditary spastic paraplegia and leukoencephalopathy. Another example, the age at onset may be early or late, and such clinical variability is seen in several of the NBIA disorders, including PKAN and PLAN; but this is not only unique to NBIAs but is also found in many other neurogenetic disorders. Puzzling is also the degree of radiological variability seen in patients with mutations in the NBIA genes. Although the hallmark feature and defining criterion is iron accumulation, patients with absent iron have been described [7]. The reason for such clinical variability remains unclear, but it is likely due to currently undetermined environmental or other genetic factors. Indeed, the wide spectrum of clinical phenotypes may be a clue to modifier or suppressor variations, which hopefully will be elucidated over time. A strategic work-up using latest technologies in large patient cohorts may unravel potential genetic and epigenetic factors influencing or determining the clinical and radiological presentation of an individual with NBIA. This, in turn, may lead to novel approaches to modify the course of illness by identifying therapeutic targets thathave already been validated in other relevant human disease models [2]. It is tantalizing to imagine how far platforms for transcriptome analysis and genomic profiling, such as genome-wide microRNA assays and methylation studies, and metabolomics will shed further light on NBIA syndromes.

Because of the overlap in clinical phenotypes, current classification systems are not ideal. Re-organization of classification schemes has been proposed for related diseases and other movement disorders [8]. However, it remains a matter of debate whether clinical, genetic or pathological features should ideally define new ordering systems. Currently, genes are often listed according to the time of their identification or first description.

Despite these genetic advances, treatment of NBIA syndromes remains symptomatic and palliative. There is current lack of controlled clinical trials in NBIA due to the rarity of the disease, heterogeneity of the NBIA subtypes and previous fragmentation of research efforts [9]. However, with improved molecular diagnoses this should hopefully change. Pathophysiologically, many of the NBIA syndromes map into related biochemical pathways and gene networks (as recently illustrated by gene expression studies [10]), including those of iron and lipid metabolism and involving mitochondrial function. Therapeutic efforts thus include removal of iron by chelating agents in selected cases [4] and, most recently, in a Phase II pilot open trial involving nine patients with PKAN [11]. However, although levels of brain iron reduced as assessed by quantitative MRI, there was usually no or limited clinical benefit. A large European Commission-funded randomized double-blinded placebo-controlled trial is currently underway to elucidate the true efficacy of deferiprone for PKAN [12]. Certainly, if deferiprone is found to be beneficial in PKAN, its use may be extended to other NBIA subtypes.

Animal models of different NBIA subtypes have been developed, facilitating the evaluation of potential new orphan drugs. Indeed, encouraged by findings in the Drosophila PKAN model, a different therapeutic approach would be to utilize pantethine for CoA synthesis, thereby bypassing PANK2, the defective enzyme in PKAN. In Drosophila, such treatment leads to rescue of neurodegeneration and increase in lifespan [13]. In humans, benefit is limited presumably due to instability in serum and difficulties in permeating the blood–brain barrier [14]. To overcome the current pharmacological boundaries of pantethine, alteration of its properties (e.g., by derivatization) is an interesting approach to future replacement therapy. Recent studies explore the synthesis and testing of novel derivatives in mammalian models [9,14]. Other approaches, such as gene therapy [15], may also be explored in the future for a number of NBIA subtypes. Furthermore, stem cell research has only just begun in the field of NBIA [16,17]. In addition to further insights into disease pathophysiology, pharmacogenetic testing may in the future aid the development of potential neuroprotective compounds.

Finally, although we grapple with how to interpret and handle the onslaught and ambiguity of genome-wide data, as well as tackling the urgent need to develop efficient therapies, we must not neglect the challenges regarding policy development, ethical considerations and legal regulations [3,18]. Indeed, precise guidelines on practice-based applications are missing for many scenarios or subject to interpretation. For PKAN, Best Practices in the care and management have recently been proposed [19]. Again, continuous education of professionals with training in the correct interpretation of genetic findings and communication of genetic risks is crucial, as more and more physicians in primary care are involving in diagnostic genetic testing. We also encourage the set-up of interdisciplinary clinics where consultant neurologists and geneticists work hand in hand with psychotherapists (as well as physiotherapists, social workers etc.) to provide the best clinical care for our patients. We should keep in mind that receiving a genetic result can be a life-changing situation when it comes to disease prognosis and family planning. Furthermore, the genetic result may impact on employment or insurance policies. In short, genetic testing of any form should not be taken lightly, and only embarked upon after thorough genetic counseling.

In summary, NBIA syndromes continue to profit from rapid developments and intensive research in molecular neuroscience facilitating better diagnosis. Patients and families rely on molecular diagnoses for health-care management. Earlier diagnosis and treatment will hopefully soon lead to a better prognosis for this devastating group of disorders [20].

Declaration of interest

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