Rethinking monogenic neurological diseases

Studies on monogenic diseases can provide valuable insights into the mechanisms of other neurological disorders, say **Wan-Jin Chen and colleagues**

Monogenic diseases result from modifications to a single gene. Over 10 000 monogenic diseases have been identified, around 17% of which are neurological disorders, covering a broad spectrum of brain syndromes. They affect hundreds of millions of people globally and present a substantial health threat and care burden in ageing societies.[1] Notably, monogenic neurological disorders have been estimated to account for up to 40% of the workload in hospital paediatric practice, with over 1% of children affected at birth.[2]

Many different forms of brain impairment are associated with monogenic neurological disorders. These include effects on brain development from birth (eg, fragile X syndrome, Huntington's disease, or monogenic autism), progressive degenerative neuronal deficiency that manifests in later life (eg, some forms of Parkinson's disease or amyotrophic lateral sclerosis), and young or late onset of abnormal functioning in people with brains that appear structurally normal (eg, dystonia). On a structural level, the manifestations of monogenic neurological disorders range from microcircuit impairment to nuclei degeneration or even vast brain atrophy and result in problems including cognitive decline, motor deficits, and psychiatric dysfunction.[1]

Importantly, monogenic neurological disorders share a wide spectrum of symptoms with common neurological diseases, including cerebrovascular disease and Alzheimer's disease. The pathological mechanisms of some monogenic neurological disorders are known to have a role in more common idiopathic forms of disease (eg, neuronal injury in familial and sporadic Alzheimer's or Parkinson's disease).[3 4] However, the aetiopathologies of common neurological diseases typically involve complex spatial-temporal interactions of internal genetic factors and external environmental stimuli, making it extremely difficult to understand their fundamental pathogenic mechanism(s) and develop treatments.[5] Investigation of monogenic neurological disorders is more straightforward as a single genetic factor drives disease progression. This provides several unique prospects for neurologists and neuroscientists for diagnosis, innovations in treatment technologies, and development of relatively simple experimental models for hypothesis driven mechanistic research.

We believe that medical thinking about monogenic neurological disorders urgently needs a major update. Historically, given their often overwhelming disease burdens and limited treatment options, attitudes to them in the research and clinical communities have been largely pessimistic. This reflects the long standing dogma that heritable monogenic neurological disorders are incurable, although a few, such as Wilson's disease, can be treated.[6] However, attitudes are beginning to shift as the potential of monogenic neurological disorders as a tool for investigating the mechanisms of more common neurological disorders is increasingly recognised.

The widespread deployment of DNA sequencing methods in hospitals has greatly increased our ability to identify and accurately diagnose monogenic neurological disorders. For example, targeted genetic testing followed by next generation sequencing has been shown to be a cost effective approach to molecular diagnosis in patients with genetically heterogeneous ataxia, resulting in detection rates of up to 75% in familial cases with adolescent onset.[7] Once monogenic neurological disorders cases are identified, the long duration of the pathogenic processes enables focused, long term studies across generations of families with relevant mutations and development of research models to support mechanistic insights. Since monogenic neurological disorders have a single causal factor, they are also excellent targets for innovative, specific, biotechnology enabled therapies.

Advances in diagnosis

Developed in 1977, Sanger sequencing was one of the first methods for determining nucleotide sequences in DNA.[8] It quickly became the standard in both research and commercial applications because of its technical ease and reliability of results. Low throughput and labour intensive procedures make Sanger sequencing less useful for large scale applications such as screening of whole human genomes or exomes, and it has been replaced by next generation sequencing that allows whole genome sequencing in short times and at low cost.[7]

The introduction of these modern DNA sequencing practices into hospitals has initiated a new era for genetic diagnostics and discovery of causes of monogenic neurological disorders. There are ample data to support the use of next generation sequencing to reduce diagnosis time. For example, clinical exome sequencing in patients with adult onset and sporadic presentations of ataxia is a high yield test, providing a definitive diagnosis in more than 7% patients and suggesting a potential diagnosis in more than 30% to guide additional phenotyping and diagnostic evaluation.[9] Indeed, it seems likely that patients with hereditary monogenic neurological disorders will soon be able to get an accurate diagnosis when they first seek medical attention.[10]

KEY MESSAGES

- DNA sequencing methods are increasing our capacity to identify and accurately diagnose monogenic neurological diseases
- The genetic factors underlying monogenic neurological diseases can be used to characterise molecular level mechanisms that may be applicable to more common neurological diseases
- Monogenic neurological diseases can be easily followed in families, allowing monitoring from the presymptomatic phase through to clinically manifested disease
- Experimental models for monogenic neurological diseases can be used to develop and test innovative therapeutic approaches
- Recent clinical successes show that monogenic neurological diseases are well suited to gene therapy and gene editing treatments and are a powerful testbed for innovative neurology treatments.

Linking pathological mechanisms to common neurological disorders

Each newly identified genetic variation associated with a monogenic neurological disorder is a chance both to improve medical care and to discover more about the mechanisms neurological disorders more generally. When genetic testing on a patient identifies a previously unknown mutation in a locus associated with a monogenic neurological disorder, this candidate causal genetic variant can be investigated in the proband's family and in patient derived biological materials (eg, cultured fibroblasts or induced pluripotent cell (iPSC) derived neurons). Genetically modified animal models can then be used to investigate the molecular, cellular, and circuit level mechanisms underlying the disorder. This research path is now common and has increased our mechanistic insights into monogenic forms of cerebrovascular disease, Alzheimer's disease, and Parkinson's disease.[3 4]

Importantly for brain health generally, research into the mechanisms of monogenic neurological disorders is already reshaping our understanding of neurodegenerative disease. For example, insights into causes of the monogenic disease CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) may contribute to our understanding of the mechanisms underlying other forms of cerebral small vessel disease. In particular, the monogenic forms of cerebral small vessel disease share overlapping clinical phenotypes (eg, cognitive dysfunction) and thus may help understand how dysfunction in the small arteries in the brain can cause neural injury.[11]

Developing research models and early intervention strategies

Many brain diseases progress relatively slowly, arising from a long term process that starts with subtle molecular dysregulation and proceeds to the cellular and tissue levels before manifesting as clinical symptoms.[12] Given the single genetic causal factors underlying monogenic neurological disorders, it is possible to conduct longitudinal observation of patients as well as use experimental models, including cell models, rodent models, and even non-human primate models. Imagine, for example, a family with a monogenic neurological disorder in which the first case is a father, who develops symptoms needing medical attention at the age of 60. His 30 year old son, a carrier without symptoms, may then be available for long term follow-up observations combining, for instance, imaging and electrophysiology data acquisition over several decades.

A major barrier to the development of effective therapies for patients with amyotrophic lateral sclerosis is that treatment is typically only initiated at a relatively late stage of the disease course. However, presymptomatic amyotrophic lateral sclerosis could be explored in a family with a monogenic form of the disease. This would allow researchers to study the disease process before it manifests clinically, including identification of biomarkers to predict when symptoms are likely to emerge.[13]

Disease models for translating gene therapies to preserve brain health

Broadly speaking, gene therapy involves the use of nucleic acids to alter the course of a disease. This can be achieved either by delivery of a functional, therapeutic gene as a substitute for the defective or missing endogenous counterpart or by reducing the levels of a harmful defective gene product by, for example, using sophisticated biotechnological tools such as antisense oligonucleotides (ASOs). An ASO is a small piece of synthetic DNA that is complementary to a segment of the target mRNA and may be used to stop translation, trigger mRNA degradation, or alter splicing.[14] Several targeted, genotype specific gene therapies are on the horizon[15] and offer hope for improved treatment or cure of monogenic neurological disorders.

Most gene therapies have focused on overcoming detrimental monogenetic defects. As an example, spinal muscular atrophy—a neuromuscular disease caused by an abnormality in the survival motor neuron (SMN) gene—was previously incurable and fatal but can now be treated with ASOs. The treatment was approved by the US Food and Drug Administration in 2016 and enhances the abundance of the full length SMN2 mRNA, substantially reducing the motor deficits of affected infants.[16]

More recently, the FDA approved a therapy that uses an adeno-associated virus to deliver complementary DNA encoding a functional SMN gene, which effectively restores motor function.[17] Genome editing techniques have also been used to disrupt SMN2 intronic splicing silencers to successfully restore SMN function in mice models of spinal muscular atrophy and patient derived induced pluripotent stem cells.[18] Additionally, there are exciting recent examples of using of a patient derived oligonucleotide treatment for neuronal ceroid lipofuscinosis 7, suggesting that personalised treatment of monogenic neurological disorders is possible.[19] Use of these techniques could facilitate treatment of many monogenic neurological disorders in future and end the traditional view that they are incurable.

New potential

The growing number of successful demonstrations of gene therapy approaches to treat monogenic neurological disorders suggests a promising future for the clinical practice of neurology. The clinical understanding and experience with regulatory hurdles gained from innovative treatments of monogenic neurological disorders are paving the way for the wider application of gene therapies to treat common neurological disorders. Furthermore, basic models of common neurological disorders may be advanced by future treatments for monogenic neurological disorders. An advanced CRISPR gene editing system targeting RNA (CasRx) has been used to convert glial cells into functional neurons to alleviate motor symptoms in a mouse model of Parkinson's disease.[20] It is becoming increasingly clear that the rational use of gene editing strategies can modify pathological processes shared by monogenic and common neurological disorders to improve brain health generally.

We believe that the ongoing development, regulatory approval, and clinical deployment of new therapies to treat monogenic neurological disorders represents the vanguard of neurological therapeutics. It is time to stop thinking of these disorders as uncurable and exploit the opportunities they provide to understand the nervous system more deeply and to facilitate the development of new methods of treatment.

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Wan-Jin Chen, professor[1,3]

Xuewen Cheng, associate investigator[2,4]

Ying Fu, professor[1,3]

Miao Zhao, postdoctoral fellow[1,3]

Jennifer McGinley, associate professor[5]

Ana Westenberger, privatdozentin[6]

Zhi-Qi Xiong, senior investigator[2,4]

[1]Department of Neurology and Institute of Neurology, First Affiliated Hospital, Institute of Neuroscience, Fujian Medical University, Fuzhou, China

[2]Institute of Neuroscience and State Key Laboratory of Neuroscience, CAS Center for Excellence in Brain Science and Intelligence Technology, Chinese Academy of Sciences, Shanghai, China

[3]Fujian Key Laboratory of Molecular Neurology, Fujian Medical University, Fuzhou, China

[4]School of Future Technology, University of Chinese Academy of Sciences, Beijing, China

[5]Physiotherapy Department, University of Melbourne, Melbourne, Australia

[6]Institute of Neurogenetics, University of Lübeck, Lübeck, Germany

Correspondence to: Z-Q Xiong
xiongzhiqi@ion.ac.cn

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