

Toward precision medicine in neurological diseases

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Abstract: Technological development has paved the way for accelerated genomic discovery and is bringing precision medicine into view. The goal of precision medicine is to deliver optimally targeted and timed interventions tailored to an individual's molecular drivers of disease. Neurological diseases are promisingly suited models for precision medicine because of the rapidly expanding genetic knowledge base, phenotypic classification, the development of biomarkers and the potential modifying treatments. Moving forward, it is crucial that through these integrated research platforms to provide analysis both for accurate personal genome analysis and gene and drug discovery. Here we describe our vision of how precision medicine can bring greater clarity to the clinical and biological complexity of neurological diseases.

Keywords: Precision medicine; neurology; disease; genetics

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Introduction

With the Human Genome Project going successfully, the concept that treatments of individuals could be defined individually has often been espoused but rarely realized. The initiation of next-generation sequencing (NGS) has paved a new way of this concept, and a new name to go with it—precision medicine. Precision medicine refers to the scientific basis that underpins the personalization of medical care, particularly in the context of treatments targeted towards the precise molecular causes of disease (1). Its core, in which prevention and treatment strategies are based on taking individual variability into account, has been applied in clinical practice for centuries. Unlike personalized medicine, precision medicine emphasizes an innovative approach based on specific characteristics including genetic, biomarker and psychosocial of each patient. The realization of precision medicine is perhaps

best illustrated in cancer which is multigenetic, and its mechanism-based treatments have successfully moved from bench to bedside (2). Likewise, in most therapeutic areas, particularly the clinically multigenic neurodegenerative disease with a strong genetic component in neurological diseases, precision medicine remains aspirational.

Here we propose that, after cancer, neurological diseases also offer the most compelling opportunities to achieve precision medicine for the following reasons: the rapid progress in the gene discovery; the ability to assess targeted diagnostic biomarkers in large-scale biologic databases or clinical trials and the initiation of NGS allowing the development of targeted pathways tailored to genetically defined treatment of the neurological diseases. To realize the potential of precision medicine in neurological diseases, however, many distinct areas of basic and translational research must collaborate and cooperate together. Here, we outline a strategy for the progress of an integrated

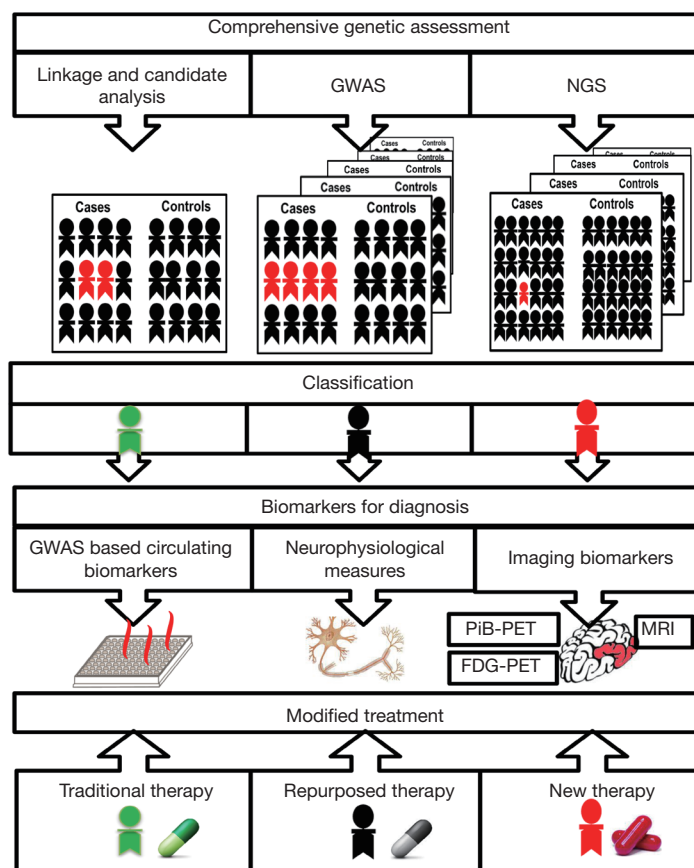


Figure 1 Four crucial elements of precision medicine for neurological diseases. We propose three crucial elements of precision medicine for neurological diseases: comprehensive genetic assessment, classification, biomarkers for diagnosis, and modified treatments specified to a person's molecular drivers. GWAS, genome-wide associated studies; NGS, next generation sequencing; MRI, magnetic resonance imaging; PET, positron emission tomography; A β , amyloid β .

program for precision medicine in neurological diseases, including the genome-wide association studies (GWAS), the development of diagnostic biomarkers in large-scale biologic databases or clinical trials, and potential treatment of neurological diseases. We conclude that fostering integrated research teams to advance precision medicine in neurological diseases will improve health care and that neurological diseases could serve as models for other therapeutic areas (*Figure 1*).

Precision genetics for precision medicine

Neurological diseases are ideal choices for enhancing the impact of precision medicine. Precision medicine has recently become popular especially among those scientists and clinicians who are applying genomics and data mining to classify individuals into subgroups with different susceptibility

to neurological diseases. Many neurodegenerative diseases, such as Alzheimer's disease (AD), Parkinson's disease (PD), Amyotrophic lateral sclerosis (ALS), are clinically heterogeneous neurodegenerative disease with a strong genetic component (3-7). Besides, gene polymorphism also plays an irreplaceable role in stroke and epilepsy (8). These are the end results of the complex effects of several genes interacting with the environment (9). In view of their high population prevalence, to identify its genetic background is as important as finding the environmental factors. Living in the era of genomics and big data, varied genetic research of neurological diseases will propel our understanding—their origins and mechanisms, and opportunities for prevention and treatment—laying a firm, broad foundation for precision medicine. Although the investigation of clinically relevant genetic variation remains a challenge, established examples are being used to stratify subgroups of patients to identify

optimal treatments (10).

Emerging new tools, such as microarray and NGS, make it possible to collect large amounts of digital genetic data. These new sources of data, together with increasingly available molecular information from the genome, transcriptome, epigenome and proteome, have created much value and interest in treatments of neurological diseases. Before the development of NGS, both linkage analyses and targeted candidate gene studies identified a number of neurological diseases candidate genes. One of the earliest ways into understanding the genetic basis of neurological diseases was through investigating the association between neurological diseases and a specific allele of a single nucleotide polymorphism within the functional candidate genes between patients and controls. For example, much of the initial work on candidate genes of AD has come from studies of rare families where early-onset AD is transmitted autosomal-dominantly, resulting from three genes: *APP*, *PSEN1* and *PSEN2*. These mutations alter production of the amyloid- β ($A\beta$) peptide which is the principal component of senile plaques (11). However, genetic variation in the *APP*, *PSEN1* and *PSEN2* genes has little or no effect on late-onset AD (12). In the search for new genes in AD, classic linkage-based and candidate-gene-based association studies have been supplanted by exome sequencing studies and GWAS. The hypothesis-free approach by GWAS contains nearly all common variants in the entire genome which can be tested for association with AD (13). GWAS allows interrogation of millions of polymorphisms simultaneously across the genome, leading to renewed hope, especially the era of large-scale GWAS. Recent large-scale GWAS have identified millions of genetic variations simultaneously across the genome and have been the driving force in the identification of more than ten main risk genes (*CLU*, *TREM2*, *CRI*, *PICALM*, *BIN1*, *MS4A*, *CD2AP*, *CD33*, *EPHA1* and *ABCA7*) for late-onset AD (9,12-17). Tremendous progress has been made in understanding genomics of PD since the identification of the mutation in the gene encoding α -synuclein as well. Like AD, large consortia have pursued genetic variants associated with PD using genomic approaches and have identified a similar number of risk loci (18,19).

Encouragingly, rapid improvements in sequencing have driven genetic discovery in neurological diseases. The genome, transcriptome and the epigenome are three major categories of information that can be acquired through various GWAS and NGS-based assays. Although the number of neurological diseases genes is too large

for sequencing for diagnostic purposes, NGS techniques enable simultaneous screening of a whole battery of genes implicated in neurological diseases. In addition to detecting novel risk factors in large samples, NGS approaches can deliver novel insights with even small numbers of patients. Furthermore, understanding the mechanisms how neurons alter and maintain their molecular signatures during disease processing is a fundamental goal of neurological diseases. Several genes, including *ABCA7* (20), *BIN1* (21), *CRI* (22), *PLD3* (23) and *PICALM* (24), were revealed as the excess burden of deleterious coding mutations in AD. In the epileptic encephalopathies alone, trio sequencing has led to the identification of *ALG*, *GABRB3*, *DNM1*, *HCN1*, *GRIN2A*, *GABRA1*, *GNAO1*, *KCNT1*, *SCN2A*, *SCN8A*, and *SLC35A2* as genes associated with epilepsy while many of the proteins encoded by these genes are involved in synaptic transmission (8). The identification of these rare genes has opened new avenues for exploration of the underlying disease mechanisms. Besides, NGS technology is rapidly transforming the ability to probe the molecular basis of neuronal function. RNA-sequencing (RNA-seq) can supply information regarding transcript structure, including single base-pair resolution of transcript boundaries and boundaries between exons. Differential transcription is examined using RNA-seq in AD brain tissue, which allows for the examination of protein coding genes, non-coding RNAs, and splicing. Networks will be discovered and this may contribute to neurological diseases mechanisms. Likewise, in animal models or blood samples, noncoding RNAs were also observed participating in AD progression (25). NGS can define not only the complete molecular signatures of cells by transcriptome analyses, but also the cascade of events that induce or maintain such signatures by epigenetic analyses. Epigenetics refers to changes in gene regulation brought about through modifications to the DNA's packaging proteins or the DNA molecules themselves without changing the underlying sequence (26). Such changes are thought to be a way in which the environment can influence genetics, bringing about potentially pathogenic alterations in the way genes are expressed. These studies provide compelling evidence for genuine, genome-wide significant associations between differentially methylated regions and neurological diseases, and suggest that the correlation relationship could reflect a causative one. Collectively, these findings could lead researchers to focus on rare variants in neurological diseases precisely when developments in NGS facilitated the comprehensive interrogation of genomes. In a word, GWAS and NGS will greatly help with personalization of treatment

for neurological diseases, particularly when treatments that target the underlying molecular causes rather than the clinical symptoms become available.

Classification, biomarkers and modified treatment modalities

Ideally, precision medicine contrasts with the traditional medicine in phenotypic classification based on genetic risk, and intervention to suppress pathophysiologic processes while still latent (27). To date, all medical disciplines are seeking to develop biomarkers to detect latent pathophysiologic processes in the expectation that the earliest detection provides the greatest opportunity for effective intervention. Due to the sources of big data analyzed by computational tools and newly available genetic technologies, targeted treatments are available for genetically defined subgroups of patients, enabling the provision of the right medication at the right dose for the right patient (28). In such a circumstance, patients are not only categorized by traditional subgroups, but also treated as individual cases based on the multi-scale data. The data will be analyzed according to genomics, transcriptome, as well as other molecular and biochemical system. The computational approaches incorporate a wide range of these personalized data sources to establish the patient's data at the molecular levels, covering traditional medical information (the history, physical examination, and laboratory tests), imaging, genomic and other analyses, to individualized objective phenotypic data on function and overall health status by mobile health technology (29). It will expand the scope of precision medicine and deepen our insight into it by redefining the classification of neurological diseases, interpreting these big data with important prognostic and treatment implications, and facilitating their application in the clinical setting.

Biomarkers that have prognostic value for survival would be of value for decision-making and planning of care. Technological developments have led to the discovery of many agents in biofluids neurophysiological measures and neuroimaging biomarkers for neurological diseases. There is an urgent need to find and validate biomarkers to predict future clinical decline. Investigators from academia and the pharmaceutical industry became interested in how "disease modification" of neurological diseases could be detected using a variety of biomarkers, including volumetric magnetic resonance imaging (MRI), fluorodeoxyglucose positron emission tomography (PET), blood and

cerebrospinal fluid analyses (25,30-34). Besides, motor unit number index, which enables quantification and tracing of motor unit numbers, might differentiate ALS from other diseases and enable disease progression to be monitored (35). What's more, a combination of viscoelastic methodologies including thomboelastography and scanning electron microscopy approach was validated useful to stroke patients in a personalized patient-centered regime (34).

Neuroimaging offers a noninvasive approach to biomarker discovery and disease monitoring not only in stroke (36-38) but also in other neurodegenerative disorders. The dopamine terminal dysfunction can be demonstrated by PET or single photoemission computed tomography with different tracers, which contribute to early and accurate diagnosis leading to appropriate medications in PD. Voxel and surface-based MRI quantification demonstrated thinning of the primary motor cortex as well. However, the correlation of imaging metrics with the absolute level of disability of MRI, using estimated rate of disease progression, was inconsistent in ALS (39). Intriguingly, these neuroimaging methods are likely to be shaped by genetic influences with heritability (32). Improved neuroimaging of AD have aided diagnosis of AD in the very early stages, and have facilitated differential diagnosis between AD and other neurodegenerative disorders with dementia (32). Evaluation of specific molecules by biochemical assay has been comparably successful in the research area (25), and both are being considered for more widespread application (40). Quantification of molecules singly or in large groups in other biofluids, such as serum, plasma, has been investigated many times, although none has yet revealed an appropriate biomarker.

After comprehensive genetic classification and accurate biomarker for latent pathophysiologic processes, the promise of precision medicine culminates in treatments that prevent, stop, or slow progression based on an individual's specialty. However, there are no widely-accepted cured therapies for most neurological diseases. New candidate treatments for genetic subtypes of neurological diseases are in urgent need. Thus re-tasking the technical capacity and expertise from the neurological diseases genome atlas to expand neurological diseases genomic sequencing efforts yet further to allow a big-data-based approach that links knowledge of variation and acquired somatic mutations with clinical phenotype is intellectually appealing. Furthermore, in terms of drug application, patients with the same or similar symptoms may use the same treatment. In fact, different patients have different sensitivity to the

same drug. The differences between individuals are closely related to their different genetic background. Precise medical treatment can be based on molecular characteristics of patients with a detailed classification and provide a reference for effective treatment. As neurological diseases require multiple targets for drug therapy, integrated analysis of studies and clinical data to identify targets is needed. To facilitate the development of new treatments for genetic neurological diseases, a clear functional understanding of the mutation that is both related to how the mutation causes disorders and whether it is amenable to screen is essential. AD is mainly characterized by amyloid deposition and tau phosphorylation, so the development of anti-AD drugs should mainly be used to reduce amyloid deposition. Many disease-modifying strategies targeting A β peptide and abnormal tau protein, as well as providing neuroprotective effects are currently under active evaluation (41). Examples of effective precision therapy in genetic epilepsy are already emerging including the mutations in *SLC2A1* and *ALDH7A1* (42). Subsequent multiple clinical trials to test the proposed disease-altering interventions have been attempted but ultimately failed, as they neglected to consider the underlying clinical and biological complexity of the disease. With precision medicine has been overlooked recently, clinical trials are emerging as disease related genes are discovered continuously, such as *SOD1*, *C9orf72*, *TDP-43* and *ATXN2* targeted therapeutic strategies in ALS (5). In addition, adaptive deep brain stimulation can provide a precision and individualized treatment for PD patient through automatically adjusting parameters according to the real-time brain/body response.

Conclusions

Precision medicine is emerging as a natural product that integrates basic research and clinical practice to build a platform that can better guide individualized patient care. The advantage for the concept of “precision medicine” is the emerging approaches and technologies which enabled tailored treatments targeted to the needs of individuals according to the precise genetic, biomarker characteristics and bioinformatics that underpin the personalization of medical care. The considerations and examples outlined above make it clear that precision medicine could transform clinical care in neurological diseases, and could lead to a new treatment framework for the neurological diseases. We propose four crucial elements of precision medicine for neurological diseases: comprehensive genetic assessment,

classification, biomarkers, and treatments specified to a person’s molecular drivers. From wearable activity trackers to meta-genomic sequencing, we are able to monitor our personal environment and health more than before. Potential toxicities of the treatment and the severity and prevalence of the disorder must be considered in the search for candidate treatments for genetic subtypes of neurological diseases. The prospect of applying this concept broadly has been dramatically improved by the recent development of large-scale biologic databases (such as the human genome sequence), powerful methods for characterizing patients (such as proteomics, metabolomics, genomics, diverse cellular assays, and even mobile health technology), and computational tools for analyzing large sets of data. However, encouragement of creative approaches to precision medicine and the ultimate usage still needs to guide clinical practice.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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