Progressive Myoclonus Epilepsies – State of the Art

Foreword

In his 2015 State of the Union address, US President Barack Hussein Obama launched a National Precision Medicine Initiative and allocated US$215 million to revitalize research into precision medicine across the USA. That announcement makes this volume entitled **'Progressive Myoclonus Epilepsy – State of the Art'** all the more timely and necessary if the 'epilepsy community' is to apply 'high-speed' whole-genome sequencing (WGS) and whole-exome sequencing (WES) to the progressive myoclonic epilepsies (PMEs), to further understand genomic contributions to disease mechanisms and tailor and optimize genome-based diagnosis and treatments.

In line with the work in precision medicine, this volume and its 17 chapters aim to provide a comprehensive account of the genetic/genomic aspects of PMEs, as well as the associated fundamental disease pathways. Chapters 1 and 2 narrate the history of PMEs and their neurophysiological mechanisms. These two chapters provide a platform and framework on which the genotype of PMEs can be expanded and the forms of autosomal recessive inheritance (with the exception of heterozygous *de novo* mutations in *KCNC1*) and disease pathways explored (chapters 3 to 15), leading to translational research into clinical genetic testing and potential treatments (chapters 16 and 17).

Chapter 1 elegantly tracks the origin of the term 'myoclonia' and the notion of seizure, which began some 134 years ago with Prichard and spread through the treatises of Delasiauve (1854), Rabot (1899), and Friedreich (1881). The progressive, severe and distressing course for a subset of families with myoclonias led Lundborg (1903) and Unverricht (1891), and then Lafora (1911), to the concept of separate recognizable PMEs.

Having been abandoned for more than a century, the concept of PMEs would have fossilized with traditional descriptive neuropathology and electrophysiology were it not for the application of biochemical genetics in Batten CLN3 and the use of 'high-tech reverse genetics' and positional cloning in the discovery of cystatin B for Unverricht-Lundborg type PME and laforin/dual specificity phosphatase and malin/ubiquitin ligase 3 for Lafora type PME (chapter 4). There was no need for researchers in molecular biology to wait for high-speed whole-genome or whole-exome sequencing, since causative associations between mutated genes and PMEs were identified by linkage mapping and positional cloning (except for the case of *KCNC1* for which WES was performed).

The discoveries of the various mutations presumed to cause Unverricht-Lundborg type PME, with or without severe cognitive problems, are reconstructed in chapter 3 (cystatin B mutations), chapter 5 (*SCARB2/LIMP2* mutations), chapter 10 (*GOSR2* mutations in North Sea PME), chapter 11 (*KCTD7* mutations), chapter 12 (ceramide synthase 1 and 2 gene mutations), chapter 13 (acid ceramidase or *ASAH1* mutations), and chapter 14 (*KCNC1* mutations). The same approach to biochemical genetics and positional cloning was used to identify protein abnormalities in neuronal ceroid lipofuscinosis (chapter 6), sialidosis (chapter 7), mitochondrial disorders (chapter 8), and neuroserpinoses (chapter 9). Chapter 15 focuses on the as yet unsolved syndrome of autosomal dominant cortical tremor, myoclonus and epilepsy (ADCTME), also referred to as FAME, for familial adult myoclonic epilepsy. Three separate chromosomal loci have been linked to ADCME, namely, chromosome 2p11.1-q12.2, chromosome 5p15.3-p15, and chromosome 3q26.3.

For molecular biologists, 'high-speed' WGS and WES are brought to the laboratory for the primary purpose of identifying disease-associated variants that, in turn, lead to the elucidation of molecular disease mechanisms and cures. For clinicians, the primary purpose is to search for disease-causing genetic variants that can be used to support medical decision-making. Both are necessary if the precision medicine initiative is to show concrete results.

Presently, one year after US President Obama announced his initiative, the main result has been to raise the profile and 'hype' around precision medicine and advertise transformational medical diagnosis and treatment. The true practical use of precision medicine will not be in the recognition of the very rare Mendelian disorders to identify break-through treatment, but rather in the 'grunt work' of understanding molecular disease mechanisms using cell lines and tissue cultures, as well as *Drosophila Melanogaster* fly models and transgenic mice. These are exemplified in the studies on cystatin B and laforin and malin in chapters 3 and 4. The subsequent crucial experiments to rescue/suppress the phenotypes of diseases in transgenic mice are exemplified in Lafora type PME and set out by the editors and authors of this volume of PMEs. The true practical use of precision medicine will also involve the enormous task of vetting putative pathogenic variants of candidate genes for PMEs. This will be achieved through the guidelines established by the US National Human Genome Research Institute (NHGRI) and the American College of Medical Genetics and Genomics/Association for Molecular Pathology (ACMG) for assigning disease causality to sequence variants and distinguishing disease-causing genetic variants from false positive reports of causality. Finally, the editors' aspirations of future treatments are outlined in chapter 17, with the application of small molecules, antisense oligonucleotides, CRISPR/Cas, gene therapy, and protein replacement which can be performed with precision in order to rescue pathogenic variants, their disease mechanisms, and the clinical phenotypes of PME. Results from research laboratories and clinical genome diagnostic centres will justify and heighten the use of WGS and WES in clinical precision medicine, as applied to the PMEs.

In summary, this book highlights the PME syndromes according to the descriptions by clinicians, the studies on pathogenic gene variants/mutations by molecular biologists and biochemical geneticists, as well as the day-to-day work of many scientists along the way in pursuit of cures. This work is, however, more than justified and is inspired by the personal grit and courage of those affected by PME and the gravity of the situation faced by their families and other loved ones. Let us not forget that it is indeed the families affected by PMEs that fuel and inspire our research.

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