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Huntington's Disease

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Preface

Huntington's disease (HD) was first described in 1872 by George Huntington, when he detailed a condition referred to as "hereditary chorea" in *The Medical and Surgical Reporter: A Weekly Journal (Philadelphia)*. Huntington was a physician in East Hampton, Long Island, and observed that this condition was confined to "certain and few families," rarely skipping a generation, with a tendency to manifest itself only in adult life, gradually developing and increasing in severity over a number of years. Choreic movements were described as "dance-like" with a "continual jigger" and had the potential to affect all voluntary muscles. Huntington also reported that those diagnosed had a tendency toward insanity and suicide. At this early date, little was known about the disease pathology, and the chorea was thought to be due to a "functional derangement" of the cerebellum.

Over 100 years later, in 1983, the gene responsible for this hereditary condition was first mapped and found to reside on the short arm of chromosome 4. After another decade, in 1993, a new gene, (interesting transcript 15), now known as "huntingtin," was isolated and cloned by the *Huntington's Disease Collaborative Research Group*, and a mutation of the huntingtin gene was found on exon 1 of the short arm of chromosome 4. This mutation was found to be an unstable expansion of the trinucleotide repeat CAG, which codes for glutamine.

This hereditary, progressive neurodegenerative disease presents with symptoms typically classified into three distinct areas: cognitive, motor, and psychiatric. Although expression of the mutation is always present, the onset of movement abnormalities tends to occur in the third and fourth decades of life, although cognitive and behavioral decline may be present much earlier than this. The characteristic neuropathology associated with HD is predominantly loss of projection neurons from the striatum, namely, medium-sized spiny neurons; however, there is concomitant loss of neurons from other regions including the cortex. The presence of aggregates formed by mutant huntingtin is also a hallmark of the disease, suggesting cellular dysfunction prior to overt atrophy and cell death. There is currently no disease-modifying treatment for this debilitating disease, and only very few symptomatic therapeutic options are available.

The field of HD research has moved on dramatically in the last few decades, with major advances in our understanding of the molecular and cellular pathology, the advent of gene and RNA manipulation technologies, and the generation of human embryonic stem cell and induced pluripotent stem cell lines. The purpose of this book is to provide a laboratory manual and guidebook for the selection, implementation, and interpretation of a wide range of techniques in contemporary use in the leading laboratories engaged in HD research worldwide. A huge range of methods are available for research aimed at understanding the genetic and molecular pathogenesis of this prototypical genetic disease, understanding how a particular gene mutation results in disturbed cellular processes and pathology, and how it leads to cellular and system dysfunction throughout the affected central nervous system. Only by understanding the pathology and pathogenic process at the fundamental molecular and cellular level can we expect to be able to slow or halt the disease process, repair the damage, and develop novel effective therapies to treat the symptoms of this condition.

As a prototype for single gene mutations and disorders, progress in understanding and treating HD will not only benefit patients and families affected by this specific rare disease, but can be expected to open new avenues for understanding and treating a broad range of single and polygenetic disorders, thus relieving the immense social, economic, and health burdens they currently cause worldwide.

The editors have been actively involved in HD research at molecular, cellular, systems, animal models, and clinical levels for over 3 decades, and we used this experience and our network of contacts to invite leading basic science and clinical experts worldwide to contribute and share their knowledge of the practical methods that work, of the technical issues to be addressed in their implementation, and of the prospects and pitfalls in their interpretation. We have asked individual authors to explain how to select and implement specific protocols with detailed instructions for their successful use, and explicit guidelines on analyzing and interpreting the results. This is targeted at both new and experienced lab researchers developing their own protocols for use in HD research programs, whether implementing a novel method or refining an existing method. The book will also be of relevance to other investigators and clinicians at many levels who need to critically evaluate project and program applications, as well as pre-publication and published research reports, in order to identify the best methods in the field to address key issues, to understand what should be considered for their selection and application, and to appreciate what cautions need to be considered when interpreting the results.

The aim for the composition of this book has been to build a volume that would prove useful to researchers by providing knowledgeable and helpful technical support. The first chapters address some of the hallmark anatomical and pathological features of HD, including cell loss and huntingtin aggregation, comprising assessment of cells of interest using immunohistochemical and stereological techniques, and detection and quantification of huntingtin aggregates. This is followed by a series of chapters considering various models of HD, including different species (nonmammalian, rodent, sheep, mini-pig and primates, as well as cellular models) in addition to different types of model (e.g., transgenic, knock-in, and excitotoxic lesion models). These chapters comprise a mix of detailed reviews and specific methods including, for example, generation of models, characterization of the models for determination of disease phenotype, and assessment of functionality and physiology. The subsequent chapters focus on imaging, with discussion of a range of imaging techniques and their useful applications in HD research. This is followed by a comprehensive review chapter on biofluid biomarkers. The authors present information on different sample materials, and methodologies utilized for analyses and outcomes for specific biomarkers. We conclude with a series of chapters addressing disease modification strategies and therapeutic targets, including gene editing, DNA repair and antisense technology, potential drug targets and delivery of trophic factors, as well as preparation of cells for cell replacement therapy.

We believe that *Huntington's Disease: Methods and Protocols* is the first time this combination of technical methods and expertise has been brought together in one place, and we hope that this new volume contributes significantly to extending the breadth and quality of research in laboratories dedicated to mastering and controlling this devastating human condition.

Cardiff, UK

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