Genetics of Mental Retardation
An Overview Encompassing Learning Disability and Intellectual Disability
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Michael Schmid  Würzburg
Genetics of Mental Retardation

An Overview Encompassing Learning Disability and Intellectual Disability

Volume Editor

Samantha J.L. Knight  Oxford

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It is my pleasure to introduce volume 18 of the book series *Monographs in Human Genetics* which is devoted to the ‘Genetics of Mental Retardation – An Overview Encompassing Learning Disability and Intellectual Disability’. Recent and astonishingly high paced progress in the detection of submicroscopic, structural genomic variations and the analysis of mutations causing mental retardation have led to remarkable discoveries with substantial clinical impact, thus making this volume an essential new edition for the series. As so often happens in human genetics, the advances have been made possible only by the development of new technologies. Although it is estimated that alterations in as many as 1,500 different genes are involved in syndromic or non-syndromic forms of mental retardation, knowledge of several of the mutations identified to date is accurate enough to recognize key elements that allow valuable general conclusions to be drawn.

It should be emphasized here that the aim of *Monographs in Human Genetics* is to deal with important genetic diseases, their molecular causes, their clinical challenge, and their eventual treatment. The present volume 18, organized by our Editor Samantha Knight, is a prime example that meets this concept perfectly. I express my gratitude to her for all the time and constant efforts in processing all 13 chapters of this exciting book. I sincerely thank all of the authors who contributed excellent manuscripts and have made the generation and publication of such a fascinating volume possible. The commitment and help of Thomas Karger with *Monographs in Human Genetics* is highly appreciated.

*Michael Schmid*

Würzburg, November 2009
Over the past 15 years, the genetics of mental retardation (also known as learning disability or intellectual disability) has been swept forward on a tide of technological revolution which has renewed and perpetuated an impetus to improve molecular diagnostic capability in this field. As a result, gene mutations and structural rearrangements of the genome are now considered to be the most important contributors to the condition.

So why is a molecular diagnosis so important? In the scientific literature, genetic studies of mental retardation are rationalized in terms of providing accurate prognostic information and genetic counseling, directing appropriate clinical care and educational needs, considering future preventative and therapeutic regimes and helping clinicians to answer the parents’ question ‘why?’ While these are true, they often fail to convey the depth of families’ feelings and needs and for this there is nothing more fitting than learning and understanding through the true life experiences of a parent bringing up a child with learning disability. To this end, I am indebted to Mrs Jane Gregory who, in the opening Chapter of this book, shares with us her experiences as a parent bringing up her daughter Chrissy and explains why understanding Chrissy’s condition is so important, thereby setting the scene for subsequent chapters that explore in detail the current state of the art approaches for clinical evaluation, research and diagnosis of mental retardation.

In Chapter 2, not only is the definition, classification and etiology of mental retardation discussed, but importantly, the general dissatisfaction and negative perceptions associated with the term ‘mental retardation’ are given due attention. Indeed, the use of the term ‘mental retardation’ is a highly sensitive, contentious topic and worldwide there are many descriptive terms that are used in place of mental retardation, including mental handicap, mental disability, intellectual disability, intellectual impairment, cognitive impairment, developmental delay and learning disability. However, the use of the same term in different countries does not always have the same meaning, thereby leaving room for misunderstanding. In view of this, the title of this volume, the ‘Genetics of Mental Retardation – An Overview Encompassing Learning Disability and Intellectual Disability’ was chosen on the premise that mental retardation is still the most universally understood term, but also respecting the fact that alternative terms may be preferred. What is clear is that the nosological debate is ongoing and that there is a need for a more appropriate terminology that is non-contentious and can be used unambiguously across all continents.
Chapter 2 also covers the more classical genetics aspects of the field paving the way for subsequent chapters that focus upon how technological advances and new discoveries in genetics have radically reshaped the clinical, research and diagnostic landscapes in mental retardation over the past 15 years. In Chapter 3, the importance of key technologies such as subtelomeric fluorescence in situ hybridization (FISH) and high resolution array comparative genome hybridization (aCGH) are explained whereas Chapter 4 details how the aCGH approach in particular has uncovered valuable information about the architecture of the human genome and allowed us to begin to understand the mechanisms of rearrangement behind newly discovered recurrent genomic disorders. As highlighted in Chapter 5, such advances have, in turn, shaped the clinical evaluation of patients, both in terms of recognizing new microdeletion syndromes through the ‘genotype first’ approach (also known as ‘reverse phenotypics’) and in presenting new genetic testing options. As well as molecular based tests, other approaches to help clinicians towards a diagnosis are also being developed. Amongst these is the study of 3D shape and molecular analyses of facial dysmorphology associated with cognitive impairment outlined in Chapter 7.

An inevitable consequence of technological progress has not only been a rapid expansion in our knowledge base regarding genetic causes of mental retardation, but also a vast expansion in the amount of genomic data being produced. Managing such information, whilst maintaining the highest quality and utility for clinicians and researchers, as well as providing information for families, is a major challenge. Chapter 6 explains how the development of databases, in particular those that bring together phenotype with genotype in the context of other genomic features, is helping in this respect, allowing improved understanding of the genetic causes of mental retardation.

To date over 80 genes on the X chromosome have been identified where a mutation results in a syndromic or non-syndromic form of mental retardation and it is thought that more than 1,400 genes on the autosomes may also give rise to the condition. These monogenic causes of mental retardation are the subject of Chapter 8 whereas Chapter 9 focuses on newly recognized mental retardation microdeletion/duplication syndromes identified through reverse phenotypics. The latter are due to regions of genome imbalance, known as copy number variants (CNVs), which are recurrent and considered pathogenic with respect to mental retardation. However, it should be noted that the majority of pathogenic CNVs discovered to date are non-recurrent. A comprehensive review of the latter is beyond scope of this volume, suffice to say that there are significant numbers noted in the literature and that they occur throughout the genome.

Importantly, the same approaches that have revealed pathogenic CNVs in mental retardation patients are also revealing numerous so-called ‘benign’ CNVs in the normal general population. These are usually considered non-pathogenic, but it is now emerging that some so-called ‘benign’ CNVs may in fact contribute to disease, either as risk factors, or directly through harboring or intersecting causative genes. Thus, the main challenge when analyzing patients’ genomes is actually determining which CNVs are associated with the phenotype. The complexities of CNV interpretation from the perspective of clinical diagnostics laboratories are discussed in detail in Chapter 10 and the concept of ‘Mendelian CNVs’ is also introduced. Furthermore, the authors explain how recent advances have blurred the traditionally implemented boundary between molecular geneticists and cytogeneticists in many genetic diagnostic laboratories and how there is a real need for reorganization of these diagnostic services.

Following this, Chapters 11 and 12 turn towards a topic currently attracting much interest: the discovery of genetic overlaps between apparently distinct neuropsychiatric disorders, in particular

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mental retardation, autism and schizophrenia. As reviewed in Chapter 11, a proportion of the disease related CNVs that have been found in these disorders are the same, leading to discussions about possible explanations such as risk factors, common disease pathways and neuronal homeostasis. This theme is continued in Chapter 12, which provides an in-depth review of rearrangements of the chromosome 22q13 region that are associated with mental retardation and autistic spectrum disorder and discusses the putative role of the SHANK3 gene. In this chapter and also in others, we learn how the search for new therapeutic avenues may at last be beginning to bear fruit.

Finally, in the closing chapter, we are brought back to the practicalities of how one actually goes about implementing new knowledge and technologies into national health services so that the advances made in research can be passed on to the families concerned. This is by no means a trivial undertaking and translational clinical practice currently trails significantly behind basic research. Chapter 13 explains the necessity of dedicated translational efforts and clarifies the stages involved, highlighting the key processes, the challenges presented and suggestions for how they may be overcome.

To conclude, I would like to express my gratitude to Karger publishers and to Michael Schmid (Series Editor) for this valuable opportunity to bring together key individuals and world class experts in the genetics of mental retardation so that they can share their specialist knowledge and expertise in a single, dedicated volume. I am grateful to all of these authors for their contributions. I am also thankful to Dr Niki Meston, Mrs Iris Knight and to Miss Natasha Németh-Knight for their enthusiastic support of the volume. It is a particularly exciting era in terms of molecular advances in mental retardation and in conveying this, I hope that this book captures the interest of a wide audience such that the high profile of mental retardation is maintained and that the tide of progress can keep moving forward for the benefit of the patients and families affected by this condition.

*Samantha J.L. Knight*

Oxford, November 2009