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Neurofibromatose

Volume Editor

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The present volume of *Monographs in Human Genetics* focuses on ‘Neurofibromatoses’, important autosomal dominant genetic disorders of the nervous system that primarily affect the development and growth of neural cell tissues. They encompass a set of distinct disorders that cause tumors to grow on nerves and, in addition, can affect the development of non-nervous tissues such as bones and skin. The first precise clinical and pathological characterization of neurofibromatosis (type I) was published in 1882 by Friedrich Daniel von Recklinghausen, a German pathologist who then practiced and taught medicine at the University of Strasbourg.

The genes and mutations causing neurofibromatoses have been identified in recent years. Moreover, very much has been elucidated about the complex molecular mechanisms leading to these diseases. By no means is it easy for the non-specialist to get an overview of the many aspects and the current knowledge of neurofibromatoses. Therefore, this volume of *Monographs in Human Genetics* aims to contribute a timely update and compilation of the manifold data obtained for these disorders by clinical studies, genetics and molecular biology.

I thank all the authors for their interesting contributions, the editor Dieter Kaufmann for his invaluable and constant efforts in organizing this book and processing the manuscripts, and the publisher Thomas Karger for his engagement in this book series.

*Michael Schmid*

Würzburg, December 2007
Preface

‘When a disease-causing gene is identified, a causal therapy is only a few steps away’. The neurofibromatoses, covered in this volume of the series ‘Monographs in Human Genetics’, illustrate that this is not so easy. A chapter called ‘Causal Therapy of the Neurofibromatoses’ is as yet missing. Still, the understanding of the molecular mechanisms underlying these diseases has increased enormously after the identification of the respective genes, which raises the patient’s hopes for successful therapies. Patients with Neurofibromatosis type 1 (NF1), formerly known as Morbus Recklinghausen, have led a shadowy existence for centuries as demonstrated by the literary character of the ‘Hunchback of Notre Dame’. This changed after foundation of patient support groups and raising large-scale funds for research. These funds were essential for advancing investigation of the neurofibromatoses and thereby caused great progress in their understanding. The data on these diseases have become very complex. In many places the present book can be seen only as an introduction to the neurofibromatoses.

The neurofibromatoses, predisposing to multiple tumours of the peripheral nervous system, are often considered classical tumour suppressor diseases. In NF1 multiple dermal neurofibromas dominate, in the much rarer Neurofibromatosis type 2 (NF2) and schwannomatosis schwannomas are the most frequent tumour type. This book centers on the genetic mechanisms underlying these three diseases. As NF1 is the most frequent of the three, the majority of chapters deal with this disease.

While the symptoms of NF2 and schwannomatosis are largely restricted to the various tumour types, NF1 presents with a distinctive pleiotropy for non
tumor-associated symptoms. These symptoms, e.g. learning disabilities or bone abnormalities, can have the same significance for the clinic as the multiple tumours. Since the symptoms do not adhere to academic boundaries interdisciplinary medical care is required. This topic and the necessary diagnostic and therapeutic measures are covered at the beginning of this book.

The NF1 gene is very large. One report concerns its structure and a second its evolution in mammals. Identifying specific NF1 mutations is laborious. The mutational spectrum and some genotype/phenotype correlations are addressed with special focus on NF1 microdeletions and associated phenotypes. NF1 shows intrafamilial variability of symptoms which is very meaningful for genetic counselling. The causes for this variability are still not known, except for the stochastic of second hit mutations in tumour progenitor cells and the higher noise in neurofibromin-associated signal transduction pathways in NF1 haploinsufficient cells.

Most tumours of NF1 and NF2 are slow growing, primarily benign and very rarely undergo malignant transformation. One chapter deals with somatic (second hit) mutations of the NF1 gene in these tumours and also in other tissues and tumour types. Furthermore there is a description of how essential the interaction of NF1 deficient cells with NF1 haploinsufficient cells is. It turns out that the NF1 gene product neurofibromin has various functions and is involved in the regulation of numerous signalling pathways. This may explain the observed pleiotropy. Some domains of neurofibromin could be characterised on a molecular level. This is shown in detail together with knowledge of the resulting neurofibromin functions.

The pathways regulated by neurofibromin overlap in part with those influenced by merlin, the protein product of the NF2 gene. One chapter covers the function of merlin in tumours, the mutations found in NF2 and the necessary clinical management of disease. In the meantime, schwannomatosis can be reliably distinguished from NF2 and NF1 in the clinic. The concluding chapter reports on the status of the molecular investigations of this disease.

I wish to thank Karger publishers and Michael Schmid (series editor of Monographs in Human Genetics) for the opportunity to make study of neurofibromatoses more popular. Furthermore, I want to thank all authors for their contributions. I hope that this book will arouse greater interest in these very common inherited tumour diseases and thereby help to step forward to causal therapies.

Dieter Kaufmann
Ulm, December 2007

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