Noonan Syndrome and Related Disorders
A Matter of Deregulated Ras Signaling
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Michael Schmid  Würzburg
Noonan Syndrome and Related Disorders – A Matter of Deregulated Ras Signaling

Volume Editor

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This volume 17 of *Monographs in Human Genetics* is an in-depth discourse on the disorders of the Ras-MAPK pathway (Noonan-, cardio-facio-cutaneous-, Costello-, and LEOPARD syndromes). Like the two preceding volumes of this book series, it deals with important hereditary diseases with high clinical impact, and whose molecular causes have been unravelled in recent years. Noonan syndrome belongs to one of the most frequent monogenic disorders occurring in approximately one in 1,000 to 2,500 children and therefore has significant importance in public health genomics. Molecular analyses have led to the surprising result that all four syndromes can be traced back to specific mutations in genes coding for molecules that interact in the Ras-MAPK pathway. This exciting discovery does not only permit the precise diagnosis of the diseases, but also clears promising ways for potential therapies in the future.

Martin Zenker, the Editor of the present volume, succeeded in bringing together the leading experts working on these diseases and received their contributions in a very short space of time. The articles treat both the clinical and molecular data exhaustively and give the reader a very timely update and outline of these related disorders. I thank Martin Zenker and all the authors for their time and effort to render possible the publication of this book. Furthermore, I gratefully acknowledge the constant promotion of this book series by Thomas Karger.

*Michael Schmid*

Würzburg, August 2008
Noonan syndrome (NS), which is recognized as one of the most common monogenic disorders, was defined as a separate entity by Jacqueline Noonan in 1968. Thirty-three years later, the first gene for NS was identified by Marco Tartaglia and colleagues. Their discovery represented the spark for a series of new gene discoveries eventually showing that mutations that alter the function of molecules interacting in a common signalling cascade, the Ras-MAPK pathway, are responsible for NS and the clinically related disorders cardio-facio-cutaneous syndrome (CFCS), LEOPARD syndrome (LS), and Costello syndrome (CS). Together, these findings unexpectedly related this group of disorders to a signalling pathway which was previously known for its involvement in tumorigenesis. Thereby, the association of certain types of malignancies and tumor-like lesions with NS, LS, CFCS, and particularly CS has been elucidated. Vice versa, studies on the significance of somatic mutations in the same genes in sporadic tumors have been stimulated and yielded exciting new findings. Notably, the genes mutated in Neurofibromatosis 1 and a newly defined Neurofibromatosis 1-like phenotype encode negative regulators of the same pathway. Thus, the known clinical relations between all these conditions have become intelligible through the achievements of molecular research.

The Editor of this volume of Monographs in Human Genetics greatly acknowledges the contributions of excellent experts in the field. Their comprehensive reviews provide most updated data on the various clinical and molecular aspects of known disorders of the Ras-MAPK pathway. Jacqueline Noonan herself is giving an historical overview in the first chapter. The book ends with a chapter on current and possible future treatment options for this group of disorders. Together the contributions to this volume nicely show the close relationship between clinical issues and molecular research and the mutual benefit for people working in either of these fields. It is of note that the previously established clinical entities are strongly correlated with certain mutated genes or – in the case of LS – specific functional consequences of certain mutations. The proposed term neuro-cardio-facial-cutaneous syndromes for all disorders caused by germline mutations in components of the Ras-MAPK pathway may be useful as a superordinate, but currently there is no need to replace the established nosology, which is also used in this book.

The content of this volume certainly does not represent a story that has been completed, but it is much more than a progress report. The chase for genes for NS and related disorders seems to have reached a
plateau, although it is obvious that there are still patients who do not have a mutation in the known genes. Following strict diagnostic criteria, the underlying mutation may now be found in more than 80% of patients with NS, 90% of patients with CFCS, and virtually all cases with CS. Future research will reach out for new goals by focusing on the refinement of genotype-phenotype correlations by studying larger cohorts, as well as on the development of model systems to explore the precise molecular pathogenesis of dysregulated Ras-MAPK signaling. One of the most fascinating prospects may be the possibility to invent treatment options for NS and related disorders by pharmacological modulation of Ras-MAPK signaling. Concerted international efforts will be required to reach these goals.

Martin Zenker
Erlangen, August 2008