

# A Practical Guide to Human Cancer Genetics

Shirley V. Hodgson  
William D. Foulkes  
Charis Eng  
Eamonn R. Maher

Fourth Edition

 Springer

# A Practical Guide to Human Cancer Genetics



Shirley V. Hodgson • William D. Foulkes  
Charis Eng • Eamonn R. Maher

# A Practical Guide to Human Cancer Genetics

Fourth Edition

 Springer

Shirley V. Hodgson  
Cancer Genetics  
St Georges Hospital  
London  
UK

Charis Eng  
Genomic Medicine Institute  
Cleveland Clinic  
Cleveland, OH  
USA

William D. Foulkes  
Program in Cancer Genetics  
Department of Human Genetics,  
Medicine and Oncology  
McGill University  
Montreal  
Québec  
Canada

Eamonn R. Maher  
Department of Medical Genetics  
University of Cambridge  
Cambridge  
UK

Previous edition published by Cambridge University Press as  
A Practical Guide to Human Cancer Genetics, 2007

ISBN 978-1-4471-2374-3 ISBN 978-1-4471-2375-0 (eBook)

DOI 10.1007/978-1-4471-2375-0

Springer London Heidelberg New York Dordrecht

Library of Congress Control Number: 2013954666

© Springer-Verlag London 2014

This work is subject to copyright. All rights are reserved by the Publisher, whether the whole or part of the material is concerned, specifically the rights of translation, reprinting, reuse of illustrations, recitation, broadcasting, reproduction on microfilms or in any other physical way, and transmission or information storage and retrieval, electronic adaptation, computer software, or by similar or dissimilar methodology now known or hereafter developed. Exempted from this legal reservation are brief excerpts in connection with reviews or scholarly analysis or material supplied specifically for the purpose of being entered and executed on a computer system, for exclusive use by the purchaser of the work. Duplication of this publication or parts thereof is permitted only under the provisions of the Copyright Law of the Publisher's location, in its current version, and permission for use must always be obtained from Springer. Permissions for use may be obtained through RightsLink at the Copyright Clearance Center. Violations are liable to prosecution under the respective Copyright Law.

The use of general descriptive names, registered names, trademarks, service marks, etc. in this publication does not imply, even in the absence of a specific statement, that such names are exempt from the relevant protective laws and regulations and therefore free for general use.

While the advice and information in this book are believed to be true and accurate at the date of publication, neither the authors nor the editors nor the publisher can accept any legal responsibility for any errors or omissions that may be made. The publisher makes no warranty, express or implied, with respect to the material contained herein.

Printed on acid-free paper

Springer is part of Springer Science+Business Media ([www.springer.com](http://www.springer.com))

# Foreword for the 4th Edition

Though cancer is essentially a genetic disease at the cellular level and mostly not clearly inherited, studies of familial cancers are not only interesting in their own right but have also made a major contribution to the identification of key genetic changes at the somatic level during cancer progression. The genetics of cancer at the germline level remains one of the most exciting and interesting developments in cancer research, if anything increasingly so with the enormous developments in the technology of DNA sequencing. This has made it possible to recognize the genetic basis of quite rare inherited conditions, sometimes based on only a few cases in only a single family. The new technologies have also made much more widespread testing of families for the presence of the commoner clearly inherited cancer susceptibilities economically feasible. Cancer genetics in this sense has thus become a major part of the workload of clinical genetics services.

Human genetics at the clinical level traditionally focused largely on congenital and pediatric problems. Cancer families, however, pose a completely different problem, since they mostly involve genetic susceptibilities with a late age of onset, offering in most cases the opportunity for effective intervention once individuals at risk have been identified. Such families can provide intriguing opportunities for testing the effectiveness of the removal of early cancers or precancerous growths.

The range of hereditary cancers is quite extraordinary, even though many are individually quite rare. They provide a unique source of material for understanding the carcinogenic process and a major challenge to the human and clinical geneticist.

This fourth edition of the book, originally published in 1992 by Shirley Hodgson and Eamonn Maher, is a substantial reworking of the first edition that takes into account the major developments over the last 20 years, with the addition of two new authors, William Foulkes and Charis Eng to the third and fourth editions. In addition to providing information on many new genes involving strong inherited susceptibility, there is increased coverage of lower-penetrance genes, possibilities for new therapies, and updated screening information. The new edition will be most

valuable as an up-to-date account of cancer genetics with a comprehensive survey of a wide range of cancer predispositions, gathered together in a form that will be of great practical value to the clinician but also of great interest for the basic laboratory scientist.

May 27, 2013

Walter Bodmer, FRCPATH, FRS  
Cancer and Immunogenetics Lab.  
Weatherall Institute of Molecular Medicine  
John Radcliffe Hospital  
Oxford, OX39DS, UK

# Preface

Since the third edition of this book, the rapid development in our understanding of inherited cancer susceptibility has continued apace. This edition is the first to be published by Springer, and the change in publisher has been accompanied by a thorough revision and updating on the whole book to reflect the numerous cancer gene discoveries since the last edition and the increasing relevance of genetic information for prognosis and management of individuals with or at risk of inherited cancers.

Although novel discoveries facilitated by technological advances (e.g., high-throughput second-generation sequencing) are often the most high-profile developments in cancer genetics, it remains true that improving the care of families affected by inherited cancers mainly uses information about highly penetrant genes and requires a well-coordinated multidisciplinary approach. Engaging families by sensitive counseling practices for predictive testing and awareness of psychosocial, insurance, and ethical issues remain fundamental to the delivery of an excellent clinical service. This edition of this book takes into account the many new developments in our understanding of cancer genetics – ranging from molecular pathways of oncogenesis to the translation of scientific knowledge into the development of novel clinical and diagnostic services. This edition reflects current clinical practice in Europe and North America and should therefore be of wide utility to those interested in clinical cancer genetics internationally.

Cancer genetics now accounts for at least half of the workload in most comprehensive genetics centers, and a knowledge of this discipline is now germane to an enormous range of specialties. Additionally, the increasing mainstreaming of cancer genetics means that clinicians from many disciplines will need to gain insight into details of cancer genetics. We therefore hope and believe that the popularity of previous editions of this book will sustain and enhance this edition and will be helpful to the many clinicians, laboratory scientists, and healthcare professionals who are faced with the ever-enlarging demand for knowledge of familial cancer risks.

London, UK  
Montreal, QC, Canada  
Cleveland, OH, USA  
Cambridge, UK

Shirley V. Hodgson  
William D. Foulkes  
Charis Eng  
Eamonn R. Maher





## Acknowledgements

The authors are grateful to Dr. Julia Newton-Bishop for her contribution to the section on skin cancers and to Dr. Marc Tischkowitz for his help with the section on Fanconi Anemia and Dr. Andrew Shuen for his help with parts of chapter 6. They would also like to thank Prof. Gareth Evans, Prof. Diana Eccles, Prof. Doug Easton, and Prof. Ros Eeles for contributing tables, Prof. C. Mathew and Prof. Gill Birch for comments, and Prof. Patrick Morrison for illustrations. They also thank Virginia Manning for her help with the preparation of the manuscript.



# Contents

|  |    |
|--|----|
| <b>1 Central Nervous System</b> . . . . .                  | 1  |
| Vestibular Schwannoma (Acoustic Neuroma) . . . . .         | 2  |
| Choroid Plexus Tumor . . . . .                             | 2  |
| Ependymoma . . . . .                                       | 3  |
| Gliomas (Including Astrocytoma and Glioblastoma) . . . . . | 3  |
| Hemangioblastoma . . . . .                                 | 4  |
| Hemangioma . . . . .                                       | 5  |
| Medulloblastoma . . . . .                                  | 5  |
| Meningioma . . . . .                                       | 6  |
| Nerve Root Tumors . . . . .                                | 6  |
| Neuroblastoma . . . . .                                    | 7  |
| Pineal Tumor . . . . .                                     | 8  |
| Primitive Neuroectodermal Tumors . . . . .                 | 8  |
| References . . . . .                                       | 9  |
| <b>2 Eye</b> . . . . .                                     | 15 |
| Retinoblastoma . . . . .                                   | 15 |
| Retinal Astrocytic Hamartoma . . . . .                     | 19 |
| Optic Glioma . . . . .                                     | 19 |
| Ocular Choristoma . . . . .                                | 20 |
| Ciliary Body Medulloepithelioma . . . . .                  | 20 |
| Cavernous Hemangioma . . . . .                             | 20 |
| Hemangioblastoma . . . . .                                 | 20 |
| Melanoma . . . . .   | 21 |
| Meningioma . . . . .                                       | 22 |
| References . . . . .                                       | 22 |
| <b>3 Cardiorespiratory System and Thorax</b> . . . . .     | 25 |
| Head and Neck Cancer . . . . .                             | 25 |
| General . . . . .  | 25 |
| Specific Sites . . . . .                                   | 26 |
| Tumors of the Lung . . . . .                               | 27 |

Mesothelioma. . . . . 28

Cardiac Tumors . . . . . 28

References . . . . . 29

**4 Endocrine System. . . . . 31**

Thyroid Tumors . . . . . 31

    Papillary Thyroid Carcinoma (PTC). . . . . 31

    Follicular Thyroid Carcinoma (FTC) . . . . . 33

    Medullary Thyroid Carcinoma (MTC) . . . . . 33

    Benign Neoplasia of the Thyroid . . . . . 34

Parathyroid Tumors . . . . . 34

Pituitary Tumors . . . . . 35

Adrenal Gland Tumors. . . . . 36

    Pheochromocytoma. . . . . 36

Adrenocortical Adenoma and Carcinoma . . . . . 39

Glomus Tumors (Non-chromaffin Paraganglioma) . . . . . 40

Pancreatic Endocrine Tumors . . . . . 41

References . . . . . 41

**5 Gastrointestinal System. . . . . 47**

Salivary Gland Tumors . . . . . 47

Gastrointestinal System . . . . . 48

Esophageal Tumors . . . . . 48

Management. . . . . 50

Gastric Tumors. . . . . 50

Gastric Carcinoma . . . . . 51

Hepatic Tumors . . . . . 53

Hepatoblastoma . . . . . 53

Hepatocellular Carcinoma . . . . . 53

Cholangiocarcinoma of the Liver . . . . . 56

Hepatic Angiosarcoma. . . . . 56

Tumors of the Gallbladder . . . . . 57

Pancreatic Cancer. . . . . 57

Tumors of the Small Intestine . . . . . 60

Gastrointestinal Polyposis . . . . . 62

Tumors of the Colon and Rectum . . . . . 63

Identification of High-Risk Families . . . . . 67

Pathological Features. . . . . 69

Surveillance Strategies. . . . . 69

Chemoprophylaxis. . . . . 71

References . . . . . 72

**6 Reproductive System . . . . . 89**

Breast Cancer. . . . . 89

    Background: Epidemiology  
    and Family History . . . . . 89

BRCA1 and BRCA2 . . . . . 91

    The Genes and the Risks for Cancer. . . . . 91

|   |            |
|---|------------|
| BRCA Protein Function . . . . .   | 93         |
| Other Genes Involved in Breast Cancer Susceptibility . . . . .  | 95         |
| Histopathology of Breast Cancer and Its Relationship to Genetics. . . . .                               | 97         |
| Genetic Counseling . . . . .  | 98         |
| Screening and Prophylaxis. . . . .  | 99         |
| Uterine Tumors . . . . .  | 101        |
| Uterine Leiomyoma . . . . .   | 101        |
| Carcinoma of the Uterus . . . . .   | 102        |
| Choriocarcinoma . . . . .   | 104        |
| Fallopian Tube Carcinoma. . . . .   | 104        |
| Ovarian Cancer . . . . .  | 105        |
| Ovarian Carcinoma . . . . .   | 105        |
| Other Ovarian Neoplasms . . . . .   | 112        |
| Cancer of the Cervix . . . . .  | 113        |
| Other Tumors of the Female Reproductive System. . . . .   | 114        |
| Cancer of the External Genitalia . . . . .  | 114        |
| Vaginal Carcinoma. . . . .  | 114        |
| Prostate Cancer . . . . .   | 115        |
| Testicular Neoplasms. . . . .   | 117        |
| Testicular Tumors in Intersex States . . . . .  | 119        |
| Epididymal Tumors . . . . .   | 121        |
| References . . . . .  | 121        |
| <b>7 Urinary System. . . . .</b>  | <b>137</b> |
| Renal Neoplasms . . . . .   | 137        |
| Wilms Tumor. . . . .  | 137        |
| WAGR Syndrome (Wilms Tumour-Aniridia-Genital Abnormality-Mental Retardation) and the WT1 Gene . . . . . | 138        |
| Renal Cell Carcinoma (Adenocarcinoma, Hypernephroma) . . . . .  | 140        |
| Cancer of the Ureter and Renal Pelvis. . . . .  | 141        |
| Bladder Cancer. . . . .   | 142        |
| References . . . . .  | 143        |
| <b>8 Blood and Lymph. . . . .</b>   | <b>145</b> |
| Leukemia . . . . .  | 145        |
| Acute Lymphoblastic Leukemia (ALL) . . . . .  | 146        |
| Acute Myeloid (Myelogenous) Leukemia . . . . .  | 147        |
| Chronic Myeloid Leukemia . . . . .  | 148        |
| Chronic Lymphocytic Leukemia. . . . .   | 149        |
| Polycythemia. . . . .   | 152        |
| Thrombocythemia. . . . .  | 153        |
| Lymphoma . . . . .  | 153        |
| Hodgkin Disease . . . . .   | 154        |
| Non-Hodgkin Lymphoma . . . . .  | 156        |
| Myeloma . . . . .   | 157        |
| Waldenstrom Macroglobulinemia . . . . .   | 158        |
| Histiocytoses . . . . .   | 158        |
| References . . . . .  | 159        |

|  |     |
|--|-----|
| <b>9 Musculoskeletal System</b> . . . . .  | 167 |
| Bone Tumors . . . . .  | 167 |
| Osteosarcoma . . . . .   | 167 |
| References . . . . .   | 173 |
| <b>10 Skin</b> . . . . .   | 177 |
| Specific Skin Cancers . . . . .  | 177 |
| Genetic Predisposition to Melanoma . . . . .   | 178 |
| Familial Melanoma . . . . .  | 180 |
| Giant Congenital Melanocytic Nevus . . . . .   | 185 |
| Basal Cell Carcinoma (BCC) . . . . .   | 185 |
| Bazex Syndrome (Bazex–Dupré–Christol Syndrome) . . . . .   | 187 |
| Rombo Syndrome . . . . .   | 189 |
| Squamous Cell Carcinoma (SCC). . . . .   | 189 |
| Epidermodysplasia Verruciformis . . . . .  | 190 |
| Ferguson-Smith-Type Self-Healing Epithelioma<br>(Multiple Self-Healing Squamous Epithelioma) . . . . .           | 190 |
| Inherited Conditions Predisposing to Dermatological Malignancy . . . . .   | 192 |
| Albinism . . . . .   | 192 |
| Birt–Hogg–Dubé Syndrome . . . . .  | 192 |
| Brooke–Spiegler Syndrome (Multiple Cylindromatosis) . . . . .  | 192 |
| Cheilitis Glandularis . . . . .  | 193 |
| Chronic Mucocutaneous Candidiasis Syndrome . . . . .   | 193 |
| Congenital Generalized Fibromatosis . . . . .  | 194 |
| Dyskeratosis Congenita . . . . .   | 194 |
| Ectodermal Dysplasias . . . . .  | 195 |
| Epidermolysis Bullosa . . . . .  | 195 |
| KID Syndrome . . . . .   | 196 |
| Multiple Cylindromatosis . . . . .   | 197 |
| Flegel Disease (Hyperkeratosis Lenticularis Perstans) . . . . .  | 197 |
| Juvenile Hyaline Fibromatosis . . . . .  | 197 |
| Klippel–Trenaunay Syndrome . . . . .   | 198 |
| Lichen Planus . . . . .  | 198 |
| Porokeratosis of Mibelli . . . . .   | 198 |
| Proteus Syndrome . . . . .   | 199 |
| Sclerolytosis (Scleroatrophic and Keratotic Dermatoses of Limbs;<br>Scleroatrophic Syndrome of Huriez) . . . . . | 199 |
| Steatocystoma Multiplex . . . . .  | 200 |
| Syringomas . . . . .   | 200 |
| Trichoepithelioma . . . . .  | 200 |
| Tylosis . . . . .  | 200 |
| Lichen Sclerosus Et Atrophicus . . . . .   | 201 |
| Mast Cell Disease . . . . .  | 201 |
| Multiple Cutaneous Leiomyomas . . . . .  | 201 |
| Multiple Lipomatosis: Familial . . . . .   | 202 |
| Multiple Lipomatosis: Symmetric . . . . .  | 202 |

|   |            |
|---|------------|
| NAME Syndrome: Carney Complex . . . . .   | 203        |
| Pachyonychia Congenita . . . . .  | 203        |
| Palmar Keratoses . . . . .  | 204        |
| Pilomatrixoma (Benign Calcifying Epithelioma of Malherbe) . . . . .   | 204        |
| References . . . . .  | 205        |
| <b>11 Inherited Cancer-Predisposing Syndromes . . . . .</b>   | <b>219</b> |
| Ataxia Telangiectasia (OMIM 208900) . . . . .   | 219        |
| Ataxia-Telangiectasia-Like Disorder (ATLD) (OMIM 604391) . . . . .  | 220        |
| Bannayan–Riley–Ruvalcaba Syndrome (Bannayan–Zonana Syndrome, Ruvalcaba–Riley–Smith Syndrome) . . . . .  | 221        |
| Beckwith–Wiedemann Syndrome (EMG Syndrome and IGF2 Overgrowth Disorder) (OMIM 130650) . . . . .   | 221        |
| Birt–Hogg–Dubé Syndrome (OMIM135150) . . . . .  | 224        |
| Blackfan–Diamond Syndrome (OMIM 105650) . . . . .   | 225        |
| Bloom Syndrome (OMIM 210900) . . . . .  | 226        |
| Blue Rubber Bleb Nevus Syndrome (OMIM112200) . . . . .  | 227        |
| Carney–Stratakis Syndrome (Carney Dyad; Dyad of Paragangliomas and Stromal Tumors) (OMIM606864) . . . . .   | 228        |
| Carney Complex (NAME Syndrome, LAMB Syndrome, Carney Syndrome) (OMIM 160980) . . . . .  | 228        |
| Cockayne Syndrome (OMIM 216400) . . . . .   | 230        |
| Celiac Disease . . . . .  | 231        |
| Common Variable Immunodeficiency (CVID) (OMIM 607594) . . . . .   | 232        |
| Constitutional Mismatch Repair Deficiency (CMMRD), also known as Autosomal Recessive Childhood Cancer Predisposition Syndrome (OMIM 276300) . . . . . | 232        |
| Costello Syndrome (OMIM 218040) . . . . .   | 232        |
| Cowden Syndrome (Multiple Hamartoma Syndrome) (OMIM 158350) . . . . .   | 233        |
| Denys–Drash Syndrome (OMIM 194080) . . . . .  | 239        |
| Down Syndrome (OMIM 190685) . . . . .   | 240        |
| Familial Adenomatous Polyposis (OMIM175100) . . . . .   | 241        |
| Management . . . . .  | 246        |
| Fanconi Anemia (OMIM 227650) . . . . .  | 249        |
| Frasier Syndrome (OMIM 136680) . . . . .  | 252        |
| Gorlin Syndrome (Nevoid Basal Cell Carcinoma Syndrome) (OMIM 109400) . . . . .  | 252        |
| Hemihypertrophy/Hemihyperplasia . . . . .   | 255        |
| Hereditary Non-polyposis Colorectal Cancer, Lynch Syndrome (OMIM 120435) . . . . .  | 256        |
| Background: History and Epidemiology . . . . .  | 256        |
| Clinical Features and Pathology . . . . .   | 257        |
| Diagnostic Features . . . . .   | 258        |
| Molecular Genetics . . . . .  | 261        |
| Extracolonic Cancer in Lynch Syndrome . . . . .   | 262        |



|   |     |
|---|-----|
| Screening . . . . .   | 263 |
| Genetic Counseling in Lynch Syndrome . . . . .  | 265 |
| Hyperparathyroidism–Jaw Tumor Syndrome<br>(CDC73-Related Disorders) (OMIM 145001) . . . . .   | 266 |
| Juvenile Polyposis Syndrome (JPS) (OMIM 174900) . . . . .   | 267 |
| Clinical Surveillance . . . . .   | 269 |
| Klinefelter Syndrome . . . . .  | 270 |
| Kostmann Syndrome (Kostmann Infantile<br>Agranulocytosis, SCN3,) (OMIM #610738) . . . . .   | 270 |
| Li–Fraumeni Syndrome (OMIM #151623) . . . . .   | 271 |
| Clinical Features . . . . .   | 271 |
| Genetics . . . . .  | 272 |
| Genetic and Medical Management . . . . .  | 274 |
| Maffucci Syndrome (OMIM 166000) . . . . .   | 274 |
| McCune–Albright Syndrome (OMIM 174800) . . . . .  | 275 |
| Mosaic Variegated Aneuploidy Syndrome 1 (OMIM #257300) . . . . .  | 277 |
| Mosaic Variegated Aneuploidy Syndrome 2 (OMIM #614114) . . . . .  | 277 |
| Multiple Endocrine Neoplasia Type 1 (OMIM 131100)<br>and the <i>CDKN</i> -opathies . . . . .  | 278 |
| Clinical Features . . . . .   | 278 |
| Genetics . . . . .  | 279 |
| Genetic and Medical Management . . . . .  | 280 |
| Multiple Endocrine Neoplasia Type 2 MEN 2 – OMIM 171400 . . . . .   | 281 |
| Multiple Endocrine Neoplasia Type 2A . . . . .  | 282 |
| Multiple Endocrine Neoplasia Type 2B . . . . .  | 282 |
| Familial Medullary Thyroid Carcinoma . . . . .  | 283 |
| Molecular Genetics of MEN 2 . . . . .   | 283 |
| Molecular-Based Medical Management in MEN 2 . . . . .   | 285 |
| Muir–Torre Syndrome (OMIM 158320) . . . . .   | 286 |
| MUTYH-Associated Polyposis (MAP) (OMIM 608456) . . . . .  | 287 |
| N Syndrome (OMIM 310465) . . . . .  | 288 |
| NAME Syndrome . . . . .   | 288 |
| Neurofibromatosis Type 1 (NF1) (Von Recklinghausen Disease,<br>Peripheral NF) (OMIM 162200) . . . . .                                     | 288 |
| Specific Tumor Types in NF1 . . . . .   | 290 |
| Neurofibromatosis Type 2 (NF2) (Central Neurofibromatosis<br>and Bilateral Acoustic Neuroma Neurofibromatosis)<br>(OMIM 607379) . . . . . | 293 |
| Neurofibromatosis: Atypical . . . . .   | 296 |
| Nijmegen Breakage Syndrome, NBS (also known as<br>Seemanova Syndrome II) (OMIM #251260) . . . . .   | 296 |
| Noonan Syndrome (OMIM 163950) and the RASopathies . . . . .   | 297 |
| Perlman Syndrome (OMIM 267000) . . . . .  | 298 |
| Peutz–Jeghers Syndrome (PJS) (OMIM 602216, OMIM 175200) . . . . .   | 299 |
| Clinical Features . . . . .   | 299 |

|  |     |
|--|-----|
| Genetics . . . . .   | 300 |
| Genetic and Medical Management . . . . .   | 301 |
| Pleuropulmonary Blastoma – Familial Tumor Dysplasia Syndrome (PPB-FTDS) (OMIM #601200, #138800) . . . . .  | 301 |
| Porphyria . . . . .  | 302 |
| Rhabdoid Tumor Predisposition Syndrome 1 (OMIM #609322) . . . . .  | 303 |
| Rhabdoid Tumor Predisposition Syndrome 2 (OMIM #613325) . . . . .  | 303 |
| Rothmund–Thomson Syndrome (OMIM 268400) . . . . .  | 304 |
| Severe Combined Immunodeficiency Disease (OMIM 102700) . . . . .   | 305 |
| Shwachman–Diamond Syndrome (OMIM 260400) . . . . .   | 305 |
| Simpson–Golabi–Behmel Syndrome (OMIM 312870) . . . . .   | 306 |
| Sotos Syndrome (OMIM 117550) . . . . .   | 307 |
| Tuberous Sclerosis (Tuberosc Sclerosis) (OMIM 191100 and 191092) . . . . .   | 307 |
| Turcot Syndrome (OMIM 276300 and 175100) . . . . .   | 311 |
| Turner Syndrome . . . . .  | 312 |
| Tylosis (Keratosi Palmaris et Plantaris) (OMIM 148500) . . . . .   | 312 |
| Von Hippel–Lindau Syndrome (OMIM 193300) . . . . .   | 313 |
| Cerebellar Hemangioblastoma . . . . .  | 314 |
| Spinal Cord Hemangioblastoma . . . . .   | 314 |
| Brain Stem Hemangioblastoma . . . . .  | 314 |
| Retinal Angiomatosis . . . . .   | 315 |
| Renal Cell Carcinoma . . . . .   | 316 |
| Pheochromocytoma . . . . .   | 316 |
| Pancreas . . . . .   | 317 |
| Endolymphatic Sac Tumors (ELSTs) . . . . .   | 317 |
| Molecular Genetics . . . . .   | 317 |
| Werner Syndrome (OMIM #277700) . . . . .   | 318 |
| Wiskott–Aldrich syndrome, OMIM #301000; X-Linked Thrombocytopenia, #313900; Intermittent X-Linked Thrombocytopenia, #313900; and X-Linked Neutropenia, #300299 . . . . . | 319 |
| X-Linked Lymphoproliferative Disorder (Duncan Disease) (OMIM 308240) . . . . .   | 320 |
| Xeroderma Pigmentosum (OMIM #278700, 610651, 278720, 278730, 278740, 278760, 278780, and variant 278750) . . . . .   | 320 |
| References . . . . .   | 322 |
| <b>Appendix</b> . . . . .  | 361 |
| Genetic Differential Diagnoses by Organ System Neoplasms . . . . .   | 361 |
| References . . . . .   | 377 |
| <b>Index</b> . . . . .   | 405 |



# Contributors

**Charis Eng** Genomic Medicine Institute, Cleveland Clinic, Cleveland, OH, USA

**William D. Foulkes** Program in Cancer Genetics, Department of Human Genetics, Medicine and Oncology, McGill University, Montreal, QC, Canada

**Shirley V. Hodgson** Cancer Genetics, St Georges Hospital, London, UK

**Eamonn R. Maher** Department of Medical Genetics, University of Cambridge, Cambridge, UK

**Julia Newton-Bishop** Department of Dermatology, University of Leeds, Leeds, UK

**Marc Tischkowitz** Department of Medical Genetics, University of Cambridge, Cambridge, UK

**Andrew Shuen** Department of Human Genetics, McGill University, Montreal, QC, Canada

# Chapter 1

## Central Nervous System

Primary central nervous system (CNS) neoplasms affect about 1 per 10,000 of the population. Although the incidence of brain tumors increases with advancing age, intracranial neoplasms are the most common cause of solid cancer in children. The distribution and histological type of brain tumor differ in children and in adults. In children, brain tumors most often arise in the posterior fossa, and the most frequent tumor types are medulloblastoma, spongioblastoma (including cerebellar astrocytoma and optic nerve glioma), and ependymomas. In adults, most tumors are supratentorial, and meningiomas and gliomas are the most frequent types. Familial brain tumors may occur as part of a rare specific inherited cancer syndrome (Table 1.1). Epidemiological studies have suggested that there is a small increased risk of cerebral neoplasms among relatives of brain tumor patients compared to controls: Choi et al. (1970) and Gold et al. (1994) found a ninefold increase in the incidence of brain tumor among relatives of patients with glioma compared to controls, whereas Burch et al. (1987) found a (statistically insignificant) sixfold increase among relatives of brain tumor patients. Nevertheless, the absolute risk to relatives is small, 0.6 % in the study by Choi et al. (1970). Miller (1971) found a ninefold increase in the expected number of sib pairs among children with brain tumors and a similar excess of families in which one child died of brain tumor and another of cancer of bone or muscle. Soft tissue sarcomas and brain tumors occur as part of the Li–Fraumeni syndrome. Mahaley et al. (1989) found a family history of cancer in 16–19 % of patients with brain tumors (similar to the expected incidence) but that the incidence was 30–33 % in patients with glioblastoma multiforme, malignant lymphoma, and neuroblastoma. A family history of neurofibromatosis was obtained in 1.6 % of cases. In a recent large joint Nordic study, 2.6 % of patients with nervous system cancer were familial. The SIR of brain tumors was 1.7 in offspring of affected parents, 2.0 in siblings, and 9.4 in families with a parent and sibling affected (Hemminki et al. 2010). As high-penetrance multiplex families with CNS tumors accounted for only a minority of cases, it has been suggested that most familial risks might be attributable to lower-penetrance genes (Hemminki et al. 2009). The familial risks for nervous system tumors do vary according to tumor histopathology (Hemminki et al. 2009), and the genetic implications of specific CNS tumors are described below.

**Table 1.1** Genetic disorders associated with tumors of the CNS

---

|  |
|--|
| Neurofibromatosis type 1                                       |
| Neurofibromatosis type 2                                       |
| von Hippel–Lindau disease                                      |
| Li–Fraumeni syndrome   |
| Familial adenomatous polyposis                                 |
| Turcot syndrome (including homozygous mismatch gene mutations) |
| Tuberose sclerosis   |
| Gorlin syndrome  |
| Ataxia telangiectasia  |
| Werner syndrome  |
| Blue rubber bleb nevus syndrome                                |

---

Details of individual conditions are given in Chap. 11

## Vestibular Schwannoma (Acoustic Neuroma)

This tumor accounts for around 8 % of all intracranial tumors and has an incidence of 13/million per year (Tos and Thomsen 1984). Although sometimes called acoustic neuromas, these are Schwann cell tumors. They usually arise from the vestibular nerve but can develop on the fifth cranial nerve and less often on the ninth and tenth nerves. Within the spinal canal, they usually arise on the dorsal spinal root. Familial and bilateral vestibular schwannomas are features of neurofibromatosis type 2 (NF2). About 4 % of vestibular schwannomas are bilateral, and all patients with bilateral tumors have NF2 (see p. 293). Sporadic vestibular schwannoma is typically seen in the fifth and sixth decades of life, which is about 20 years later than in patients with NF2. The clinical features and diagnostic criteria for NF2 are discussed on p. 293. Although vestibular schwannoma in NF2 is usually bilateral, it can be unilateral. Those mosaics for an *NF2* gene mutation may present with milder- and later-onset disease (see p. 294).

Multiple extracranial schwannomas (cutaneous and spinal) without vestibular schwannomas may be inherited as a dominant trait (Evans et al. 1997) and may be caused by germline mutations in *SMARCB1* (see *Nerve Root Tumors below*). Occasionally *SMARCB1* mutations have been described in individuals with unilateral vestibular schwannomas and multiple central and cutaneous schwannomas (Smith et al. 2011).

## Choroid Plexus Tumor

Choroid plexus neoplasms are rare (0.5 % of all brain tumors) and are most frequent in infancy. The majority of choroid plexus tumors are benign papillomas, but up to 30 % are classified as carcinomas.

Childhood choroid plexus tumors in sibling pairs have been reported and autosomal recessive inheritance suggested (Zwetsloot et al. 1991). Tumors of the choroid

plexus have been reported in the X-linked disorder Aicardi syndrome (Robinow et al. 1986). Germline *TP53* mutations are relatively frequent in children with choroid plexus tumors (Gozali et al. 2012). Though the family history may be suggestive of Li–Fraumeni syndrome in many cases, in others there may be no family history of cancer (Krutilkova et al. 2005; Tabori et al. 2010). The germline founder *TP53* mutation R337H occurs at high frequency in Brazil and can be detected in most children who develop choroid plexus carcinomas (Custodio et al. 2011).

Choroid plexus angiomas were reported in two out of four patients with Perlman syndrome (p. 298) reported by Henneveld et al. (1999).

Choroid plexus tumors should be differentiated from endolymphatic sac tumors, which are a feature of von Hippel–Lindau disease (p. 313).

## Ependymoma

These glial cell tumors of the brain and spinal cord occur both sporadically and in association with cancer susceptibility syndromes. In children, the tumor usually presents as a posterior fossa mass. Ependymoma may be a feature of neurofibromatosis type 2 (see p. 293) and has rarely been reported as part of Turcot syndrome (Torres et al. 1997), multiple endocrine neoplasia type 1, and in association with a germline *P53* mutation. Familial ependymoma consistent with autosomal dominant inheritance with incomplete penetrance has also been described (Gilchrist and Savard 1989; Nijssen et al. 1994).

## Gliomas (Including Astrocytoma and Glioblastoma)

Astrocytoma and glioblastoma account for about 4 % of brain tumors in childhood and 17 % in adults. Genetic conditions associated with a predisposition to glioma include neurofibromatosis type 1 (NF1) (p. 288), NF2, Li–Fraumeni syndrome (p. 271), tuberose sclerosis (p. 307), Gorlin syndrome (p. 252), Turcot syndrome (p. 311), and Maffucci syndrome (p. 274). The precise tumor type in some cases can be correlated with specific disorders, for example, in tuberose sclerosis a benign astrocytic tumor (subependymal nodule) is typically seen, although giant cell astrocytoma can occur. However, in NF1 and Turcot syndrome, both astrocytoma and glioblastoma multiforme may be seen. Kibirige et al. (1989) found that of 282 children with astrocytoma, 21 had neurofibromatosis and 4 had tuberose sclerosis, and there was evidence that a similar proportion might have had Li–Fraumeni syndrome.

Familial glioma not associated with the inherited syndromes described above occurs, but is uncommon. In a review by Vieregge et al. (1987), of 39 reports, most (60 %) were of affected siblings, and one-quarter was of affected twins or of individuals with affected relatives in two generations. There were three pairs of monozygotic twins with glioma. In most affected sibling cases, the onset in the

second sibling was usually within 5 years of that of the first sibling. A high incidence of cerebral glioma was found in an isolated inbred community by Armstrong and Hanson (1969) and Thuwe et al. (1979). Glioblastoma multiforme is rare in children, but Duhaime et al. (1989) reported an affected sib pair aged 2 and 5 years with simultaneous onset of symptoms.

Rare families have been reported with a combination of melanoma and gliomas. In some families submicroscopic germline deletions of 9p21 have been identified which completely or partially involve *CDKN2A*±*CDKN2B* (Bahau et al. 1998; Tachibana et al. 2000). The *CDKN2A* locus encodes two gene products, p14 and p16, and there is evidence that p14 loss is critical for this disorder (Randerson-Moor et al. 2001). Thus, in brain tumor–melanoma kindreds, deletion studies of this region may be warranted if clinical testing for *CDKN2A* mutations has been undertaken and is negative.

In general, candidate gene analysis in non-syndromic familial glioma cases has been largely unproductive. Thus, although a study from the Mayo Clinic of 15 brain cancer patients who had a family history of brain tumors found that one had a germline *TP53* mutation, and another had a germline hemizygous deletion of the *CDKN2A/CDKN2B* region (Tachibana et al. 2000), a more recent, larger analysis ( $n=101$ ) of familial glioma cases did not detect germline *CDKN2A* mutations and only one *TP53* mutation (Robertson et al. 2010).

In the light of the evidence that lower-penetrance genes might represent a major contribution to familial risks for nervous system tumors (Hemminki et al. 2009), large collaborations such as the GLIOGENE consortium have undertaken genome-wide association studies and identified a number of polymorphic variants that predispose to glioma (Scheurer et al. 2010; Shete et al. 2011). Among the genes linked with susceptibility variants are *TERT*, *EGFR*, *CDKN2A/CDKN2B*, and *PHLDB1*, but only a small part of familial risk can be explained by the linked variants (Shete et al. 2009, 2011).

## Hemangioblastoma

These vascular tumors occur most frequently in the cerebellum followed by the spinal cord, brain stem, and, least frequently, supratentorially. Approximately 30 % of all cerebellar hemangioblastomas occur as part of von Hippel–Lindau (VHL) disease (see p. 313). Patients with multiple CNS hemangioblastomas satisfy the clinical diagnostic criteria for VHL disease. Hemangioblastoma is a benign tumor but may recur if surgical removal is not complete. In such cases the possibility of a new primary (and hence a diagnosis of VHL disease) should also be considered. The risk of VHL disease is highest in younger patients: the mean ages at diagnosis of cerebellar hemangioblastoma in this disease and in nonfamilial cases are 29 and 48 years, respectively (Maher et al. 1990). All patients with apparently sporadic hemangioblastomas should be screened for subclinical evidence of VHL disease. In addition, *VHL* mutation analysis is helpful, particularly in patients aged less than 50 years. Germline *VHL* gene mutations were detected in 4 % of apparently sporadic hemangioblastoma cases without clinical or radiological evidence of VHL



disease (Hes et al. 2000). In view of the possibility of false-negative mutation analysis results (e.g., if mosaic), younger patients (less than 40 years) may be kept under review in case evidence of VHL disease develops later.

## Hemangioma

Cavernous hemangiomas may occur sporadically or as a familial trait when they are inherited as a dominant trait with incomplete penetrance (Riant et al. 2010). Familial cases, which account for about 20 % of the total, frequently develop multiple cavernous hemangiomas, but these may be asymptomatic and only detected by magnetic resonance imaging (MRI) scanning. Retinal cavernous angiomas may be found in some patients (see p. 20).

Familial cavernous hemangiomas are genetically heterogeneous. The first gene to be mapped and identified was *CCM1/KRIT1* and accounts for about 40 % of all cases (Laberge-le Couteulx et al. 1999). Subsequently two further genes were described (*CCM2/MGC4607* and *CCM3/PDCD10*) which account for about 20 and 40 % of all familial cases, respectively (Dubovsky et al. 1995; Craig et al. 1998; Riant et al. 2010). There is a significant (40–60 %) mutation detection rate in sporadic individuals with multiple lesions, and some mutation negative cases might be mosaic (Riant et al. 2010).

Meningeal hemangioma and facial nevus flammeus constitute the Sturge–Weber syndrome, and cerebral vascular lesions occur in Rendu–Osler–Weber syndrome. Although the Sturge–Weber syndrome is sometimes designated the fourth phakomatosis, there is no evidence of a genetic basis and there is no predisposition to neoplasia.

## Medulloblastoma

This tumor accounts for about 25 % of all brain tumors in children and has an incidence of approximately 1/100,000 per year. Medulloblastoma occurs predominantly in the first two decades of life, with a peak incidence between 3 and 5 years of age. Familial medulloblastoma appears to be uncommon, but has been reported in twins and siblings (Hung et al. 1990). Familial non-syndromic medulloblastoma occurs rarely (von Koch et al. 2002). Genetic disorders associated with medulloblastoma include Gorlin syndrome, familial adenomatous polyposis and Turcot syndrome, blue rubber bleb nevus syndrome, and ataxia telangiectasia (see p. 219). Gorlin syndrome is caused by germline mutations in the *PTCH* gene which encodes the sonic hedgehog receptor (see p. 252). In addition, germline and somatic mutations in another of the sonic hedgehog pathway, *SUFU* (encoding the human suppressor of fused), may be found in a subset of children with early-onset (before 3 years) medulloblastoma and can be dominantly inherited with incomplete penetrance (Taylor et al. 2002; Brugieres et al. 2010). Medulloblastoma may also occur in patients with homozygous *BRCA2* mutations (Fanconi Anaemia Type D1, see p. 249) (Offit et al. 2003; Hirsch et al. 2004).

Cancer genome analysis of medulloblastoma revealed that the most commonly altered genes were implicated in the Hedgehog, Wnt, and histone methylation pathways (Parsons et al. 2011).

## Meningioma

The most common benign brain tumor, meningioma, accounts for about 15 % of all primary brain tumors. The frequency of meningioma increases with advancing age, and it is more common in women. Multiple or familial meningioma is associated with (a) neurofibromatosis type 2 (NF2), (b) pure familial meningioma, (c) constitutional chromosome 22 rearrangements, and (d) familial schwannomatosis and *SMARCB1* mutations (see below). Meningioma also occurs with increased frequency in Werner syndrome (p. 318) and Gorlin syndrome (p. 252).

Multiple meningioma is frequent and occurs in about a third of patients with NF2 (see p. 293). Expression of NF2 is variable, so a careful search for evidence of NF2 and a detailed family history should be performed in all patients with multiple or familial meningioma, or with a young age at onset. Although many reports of familial meningioma may be variants of NF2, dominantly inherited meningioma with no evidence of NF2 does occur. However, signs of NF2 should be assiduously sought in all cases of familial meningioma as these may not be obvious. For example, Delleman et al. (1978) reported a family in which four members in two generations had meningiomas with no evidence of neurofibromatosis, but another relative had multiple meningiomas and bilateral vestibular schwannomas.

Rearrangements of chromosome 22 have been associated with meningioma: multiple tumors developed in the third decade in a mentally retarded patient with a ring chromosome 22 (breakpoints p12 and q13.3) (Arinami et al. 1986), and familial meningiomas associated with a Robertsonian chromosome 14;22 translocation have also been described. In addition, Pulst et al. (1993) reported exclusion of linkage to the NF2 kindred with familial meningioma.

Germline *SMARCB1* mutations have been identified in patients with a combination of multiple meningiomas and schwannomatosis (van den Munckhof et al. 2012). However, among a cohort of patients with multiple meningiomas and no schwannomas, germline *SMARCB1* mutations appeared to be rare (Hadfield et al. 2010) though Smith et al. (2013) described *SMARCE1* mutations in kindreds with familial spinal meningiomas with clear cell histology.

## Nerve Root Tumors

The commonest nerve root tumor is the benign schwannoma or neurolemmoma, and the most frequent site is the eighth cranial nerve (see vestibular schwannoma, p. 2). Multiple schwannomas are a feature of neurofibromatosis type 2 (NF2)