A Practical Guide to Human Cancer Genetics

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Fourth Edition

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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

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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.

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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.

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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* (Bahuau 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/CDKIN2B*, 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)