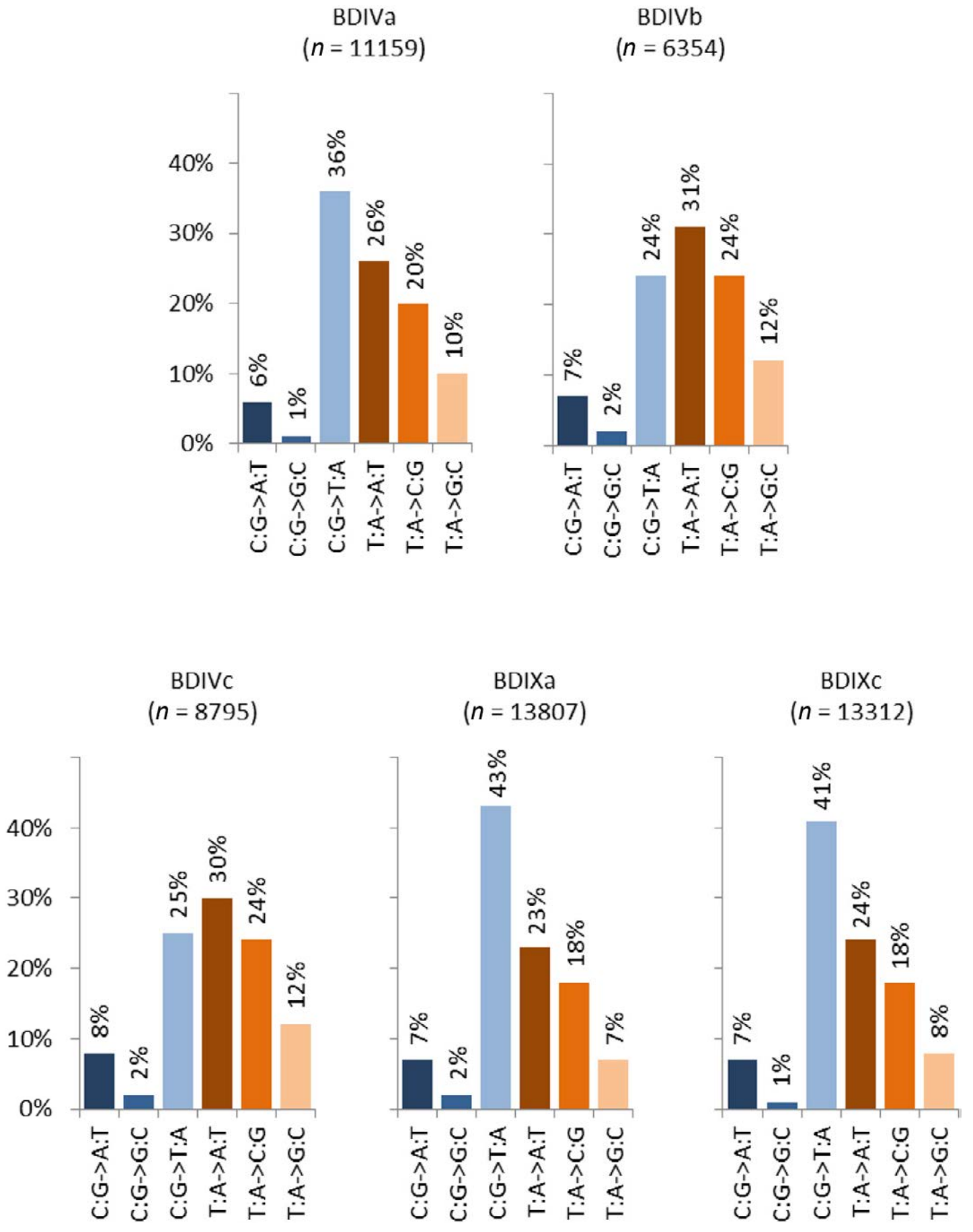

BDIVa
(n = 11159)
BDIVb
(n = 6354)
BDIVc
(n = 8795)
BDIXa
(n = 13807)
BDIXc
(n = 13312)
40%
30%
20%
10%
0%
6%
1%
36%
26%
20%
10%
7%
2%
24%
31%
24%
12%
8%
2%
25%
30%
24%
12%
7%
2%
43%
23%
18%
7%
7%
1%
41%
24%
18%
8%
C:G->A:T
C:G->G:C
C:G->T:A
T:A->A:T
T:A->C:G
T:A->G:C

Section of Molecular Pathology (MPA)

until July 2017

Section head
Dr Hiroko Ohgaki

Secretariat
Ms Anne-Sophie Hameau

Project assistant
Ms Asiedua Asante

IT assistants
Mr Alberto Machado
Ms Delphine Nicolas

Research assistants
Ms Christine Carreira
Ms Aurélie Salle

Visiting scientists and fellows
Dr Ji-Eun Oh
Dr Kaishi Satomi
(until September 2016)
Dr Koichiro Sumi

The Section of Molecular Pathology (MPA) conducts original research to elucidate the molecular basis and genetic pathways of human neoplasms. The specific aims of MPA are to provide genetic information that will be used as the basis for future molecular diagnosis and classification of brain tumours, to identify genetic markers for prognosis and novel treatment strategies, and to use genetic data to identify new clues to understand the etiology of human tumours. Genetic studies are carried out, using tumour samples from patients with excellent clinical data which have been collected at a population level or internationally, to provide unique data combining the pathology, genetics, clinical features, and epidemiology of tumours. The research programme of MPA is part of IARC's goals of elucidating the mechanisms of carcinogenesis and understanding the etiology of cancer.

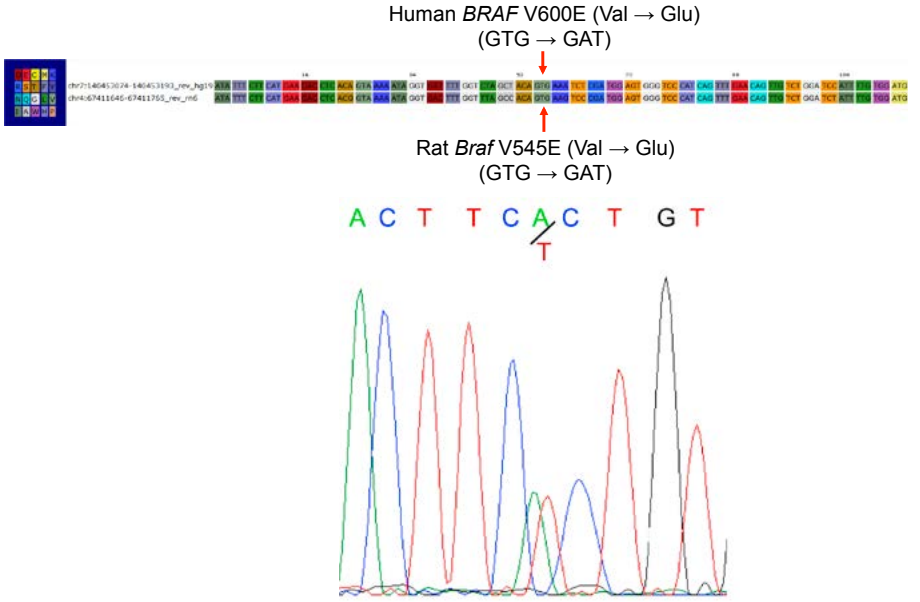
In addition, MPA is responsible for the publication of the World Health Organization (WHO) Classification of Tumours series (WHO Blue Books). MPA works with internationally recognized pathologists from around the world to reach consensus regarding tumour classification. Most human tumours have been diagnosed and classified based on histological features; more recently, molecular markers are increasingly being used to define disease entities, taking advantage of rapid progress in understanding of the genetics of human neoplasms.

Several of the main projects of MPA over the 2016–2017 biennium are detailed here.

Braf mutations initiate the development of rat gliomas induced by postnatal exposure to *N*-ethyl-*N*-nitrosourea

A single dose of *N*-ethyl-*N*-nitrosourea (ENU) during late prenatal or early postnatal development induces a high incidence of malignant schwannomas and gliomas in rats. Although T → A mutations in the transmembrane domain of the *Neu* (*c-ErbB-2*) gene are the driver mutations in ENU-induced malignant schwannomas, the molecular basis of ENU-induced gliomas remained enigmatic. Whole-genome sequencing was performed of gliomas that developed in three BDIV and two BDIX rats exposed to a single dose of 80 mg ENU per kilogram of body weight on postnatal day one. T:A → A:T and T:A → C:G mutations, which are typical for ENU-induced mutagenesis, were predominant (41–55% of all somatic single nucleotide mutations). T → A mutations were identified in all five rat gliomas at *Braf* codon 545 (V545E), which corresponds to the human *BRAF* V600E (Figure 1). Additional screening revealed that 33 gliomas in BDIV rats and 12 gliomas in BDIX rats all carried a *Braf* V545E mutation, whereas peritumoural brain tissue of either strain had the wild-type sequence. The gliomas were immunoreactive to BRAF V600E antibody. These results indicate that *Braf* mutation is a frequent early event in the development of rat gliomas caused by a single dose of ENU (Wang et al., 2016a).

Figure 1. *Braf* mutations initiate the development of rat gliomas induced by postnatal exposure to *N*-ethyl-*N*-nitrosourea (ENU). Whole-genome sequencing revealed that all rat gliomas induced by ENU contain *Braf* V545E mutation, which corresponds to human *BRAF* V600E mutation. Reprinted from Wang et al. (2016a), copyright 2016, with permission from Elsevier.



Population-based study on glioblastoma in the Canton of Zurich, 2005–2009

MPA researchers previously carried out a population-based analysis of patients with glioma diagnosed in 1980–1994 in the Canton of Zurich, Switzerland. To explore changes in outcome, registry data were re-evaluated for patients diagnosed in 2005–2009. Patients with glioblastoma who were diagnosed in 2005–2009 were identified by the Zurich and Zug Cancer Registry. A total of 264 patients with glioblastoma were identified, for an annual incidence of 3.9 per 100 000 people per year, compared with the incidence of 3.7 per 100 000 people per year in the previous study (1980–1994). The mean age of the patients at the time of diagnosis was 59.5 years in the current cohort, compared with 61.3 years previously. The overall survival rate was 46.4% at 1 year, 22.5% at 2 years, and 14.4% at 3 years in the current study, compared with 17.7% at 1 year, 3.3% at 2 years, and 1.2% at 3 years as reported previously. The median overall survival for all patients with glioblastoma was 11.5 months, compared with 4.9 months in the former patient population. The median overall survival was 1.9 months for best supportive care, 6.2 months for treatment with radiotherapy alone, 6.7 months for treatment with temozolomide alone, and 17.0 months for treatment with radiotherapy plus temozolomide. Multivariate analysis revealed that age, Karnofsky performance score, extent of tumour resection, first-line treatment, year of diagnosis, and *MGMT* promoter methylation status were associated with survival in patients with *IDH1* wild-type glioblastoma. The overall survival of patients newly diagnosed with glioblastoma in the Canton of Zurich in Switzerland markedly improved from 1980–1994 to 2005–2009 (Gramatzki et al., 2016).

Genetic alterations in gliosarcoma and giant cell glioblastoma

The majority of glioblastomas develop rapidly with a short clinical history (primary glioblastoma *IDH* wild-type), whereas secondary glioblastomas (*IDH* mutant) progress from diffuse astrocytoma or anaplastic astrocytoma. Gliosarcomas and giant cell glioblastomas are rare histological glioblastoma variants, which usually develop rapidly. The genetic patterns of 36 gliosarcomas and 19 giant cell glioblastomas were determined. *IDH1* and *IDH2* mutations were absent in all 36 gliosarcomas and in 18 of 19 giant cell glioblastomas analysed, indicating that they are histological variants of primary glioblastoma. Furthermore, loss of heterozygosity (LOH) on chromosome 10q (88%) and *TERT* promoter mutations (83%) were frequent in gliosarcomas. Giant cell glioblastomas had LOH 10q in 50% and LOH 19q in 42% of cases. Loss of ATRX expression was detected immunohistochemically in 19% of giant cell glioblastomas, but was absent in gliosarcomas. These and previous results suggest that gliosarcomas are a variant of, and genetically similar to, primary glioblastomas, except for a lack of *EGFR* amplification, and that giant cell glioblastoma occupies a hybrid position between primary and secondary glioblastomas (Oh et al., 2016).

CASP9 germline mutation in a family with multiple brain tumours

A novel *CASP9* germline mutation was identified in a family in which three brain tumours had developed within three generations, including two anaplastic astrocytomas occurring in cousins. The cousins were diagnosed at similar ages (29 and 31 years), and their tumours showed similar histological features. Genetic analysis revealed somatic *IDH1* and *TP53* mutations in both tumours. However, no germline *TP53* mutations were detected, despite the fact that this family fulfils the criteria of Li–Fraumeni-like syndrome. Whole-exome sequencing revealed a germline stop-gain mutation (R65X) in the *CASP9* gene, which encodes caspase-9, a key molecule for the p53-dependent mitochondrial death pathway. This mutation was also detected in DNA extracted from blood samples from the two siblings who were each a parent of one of the affected cousins. Caspase-9 immunohistochemistry showed the absence of caspase-9 immunoreactivity in the anaplastic astrocytomas and normal brain tissues of the cousins. These observations suggest that *CASP9* germline mutations may have played a role, at least in part, in the susceptibility to development of gliomas in this Li–Fraumeni-like family lacking a *TP53* germline mutation.

Figure 2. Working Group members at consensus and editorial meetings for two volumes of the *WHO Classification of Tumours* series: (top) *WHO Classification of Head and Neck Tumours*; meeting held at IARC on 14–16 January 2016; (bottom) *WHO Classification of Tumours of Endocrine Organs*; meeting held at IARC on 26–28 April 2016. © IARC/Roland Dray.

WHO Classification of Tumours series (WHO Blue Books)

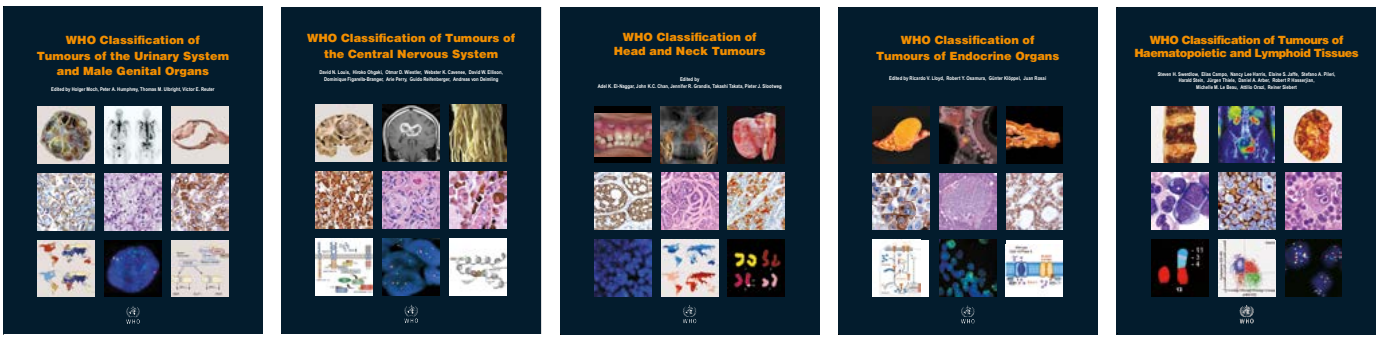
The objective of this project is to establish a histopathological and molecular classification and grading of human tumours that is accepted and used worldwide. Without clearly defined clinical and histopathological diagnostic criteria and, more recently, genetic and expression profiles, epidemiological studies and clinical trials are difficult to conduct. Therefore, this project is of great importance not only for pathology communities but also for cancer registration, epidemiological studies, clinical trials, and cancer research in general.

IARC has been responsible for this project since the third edition (2000–2005; 10 volumes). The current (fourth) edition of the *WHO Classification of Tumours* series was initiated in 2006 with four series editors (Dr Fred Bosman, Dr Elaine Jaffe, Dr Sunil Lakhani, and Dr Hiroko Ohgaki). So far, 10 volumes and 2 revisions have been published, and for each volume, 15 000–50 000 copies were printed and distributed worldwide. In 2016–2017, the following five volumes were published (Figures 2 and 3).

WHO Classification of Tumours of the Urinary System and Male Genital Organs. This volume was prepared by four volume editors (Dr Holger Moch, Dr Peter A. Humphrey, Dr Thomas M. Ulbright, and Dr Victor E. Reuter) and 110 contributors from 21 countries. The consensus and editorial meeting was held on 11–13 March 2015 in Zurich, Switzerland, in collaboration with the University of Zurich. The volume was published in January 2016.

WHO Classification of Tumours of the Central Nervous System. This volume was the revision of the fourth edition (published in 2007) and was prepared by four volume editors (Dr David N. Louis, Dr Hiroko Ohgaki, Dr Otmar D. Wiestler, and Dr Webster K. Cavenee), five senior advisors (Dr David W. Ellison, Dr Dominique Figarella-Branger, Dr Arie Perry, Dr Guido Reifenberger, and Dr Andreas von Deimling), and 122 contributors from 19 countries. The consensus and editorial meeting was held on 21–24 June 2015 in Heidelberg, Germany, in collaboration with the

Figure 3. Covers of the five volumes of the *WHO Classification of Tumours* series published in 2016–2017: *WHO Classification of Tumours of the Urinary System and Male Genital Organs*, fourth edition (January 2016); *WHO Classification of Tumours of the Central Nervous System*, revised fourth edition (May 2016); *WHO Classification of Head and Neck Tumours*, fourth edition (January 2017); *WHO Classification of Tumours of Endocrine Organs*, fourth edition (June 2017); and *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*, revised fourth edition (September 2017).



German Cancer Research Center (DKFZ). The volume was published in May 2016.

WHO Classification of Head and Neck Tumours. This volume was prepared by five volume editors (Dr Adel K. El-Naggar, Dr John K.C. Chan, Dr Jennifer R. Grandis, Dr Takashi Takata, and Dr Pieter J. Slootweg) and 135 contributors from 35 countries. The consensus and editorial meeting was held at IARC on 14–16 January 2016, and the volume was published in January 2017.

WHO Classification of Tumours of Endocrine Organs. This volume was prepared by four volume editors (Dr Ricardo V. Lloyd, Dr Robert Y. Osamura, Dr Günther Klöppel, and Dr Juan Rosai) and 166 contributors from 25 countries. The consensus and editorial meeting was held at IARC on 26–28 April 2016, and the volume was published in June 2017.

WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. This volume was the revision of the fourth edition (published in 2008) and was prepared by seven volume editors (Dr Steven H. Swerdlow, Dr Elias Campo, Dr Nancy Lee Harris, Dr Elaine S. Jaffe, Dr Stefano A. Pileri, Dr Harald Stein, and Dr Jürgen Thiele), five senior advisors (Dr Daniel A. Arber, Dr Robert P. Hasserjian, Dr Michelle M. Le Beau, Dr Attilio Orazi, and Dr Reiner Siebert), and 132 contributors from 23 countries. The volume was published in September 2017.