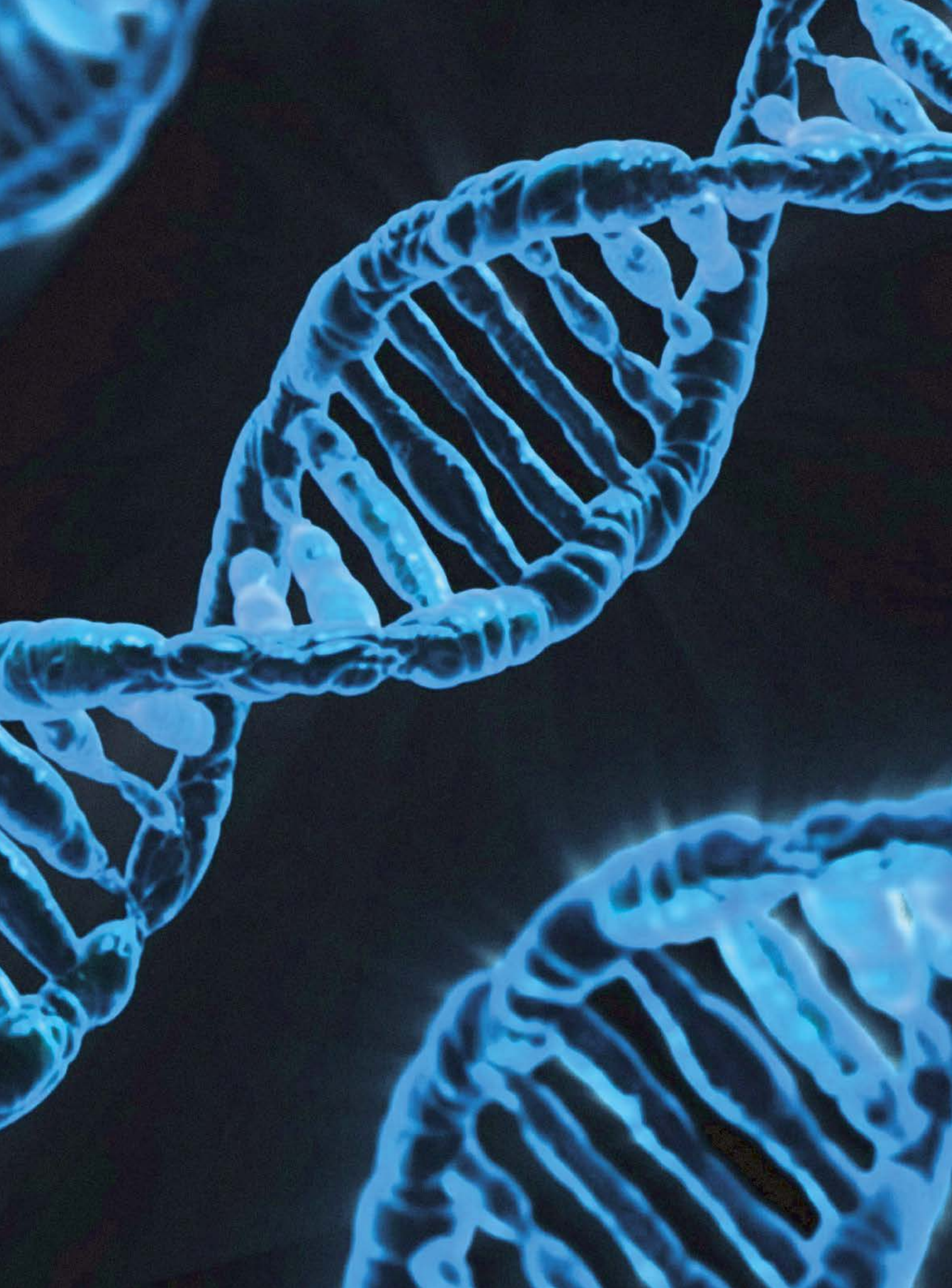

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Section of Genetics (GEN)

Section head
Dr Paul Brennan

The Section of Genetics (GEN) comprises the Genetic Epidemiology Group (GEP), the Genetic Cancer Susceptibility Group (GCS), and the Biostatistics Group (BST). The work of the Section combines large population-based studies with laboratory and bioinformatics expertise to identify specific genes and genetic profiles that contribute to the development of cancer and elucidate how they exert their effect along with environmental factors. The Section also tries to identify individuals who are at high enough risk that they are likely to benefit from existing risk reduction strategies.

GEN's projects usually involve extensive fieldwork in collaboration with external investigators in order to develop large-scale epidemiological studies with appropriate clinical and exposure data, as well as biosample collection. This typically occurs within GEP, which has a primary interest in the analysis and identification of common genetic susceptibility variants and their interaction with non-genetic risk factors. Genetic analysis comprises either candidate gene or genome-wide genotyping studies, as well as sequencing work. GEP studies also assess non-genetic exposures, partly in recognition of the importance of non-genetic factors in driving cancer incidence, and also to facilitate accurate assessment of gene–environment interactions. In contrast, GCS places more focus on identification of uncommon or rare genetic variants that may have a larger effect than common single-nucleotide polymorphisms but that are not sufficiently frequent to be captured by current genome-wide association genotyping arrays. GCS's approach has been to use genomic and bioinformatic techniques to complement more traditional approaches for the study of rare genetic variants. GCS also uses genomics to explore how the variants may be conferring genetic susceptibility to cancer. Thus, the research programme of GCS complements that of GEP, and also provides a facility for high-throughput genomic techniques and the related bioinformatics to support GEN's large-scale molecular epidemiology projects and other IARC genomics projects. BST interacts at all stages to provide overall statistical support within GEN and more widely across research Sections of the Agency.

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The Biostatistics Group (BST) continued to collaborate with several Sections at IARC. In some cases this involved the development of novel techniques, in others the identification of appropriate standard approaches, and in all cases with the goal of ensuring the reliability of scientific findings at the Agency.

Methodological highlights included the modelling contribution to the estimation of global cancer burden due to overweight and obesity (Arnold et al., 2015a), the identification of somatic mutation patterns suggesting that aristolochic acid may be an important factor in hepatocellular carcinoma in Romania (Scelo et al., 2014), the development of an approach to epigenetic analysis of childhood cancer risk (Ghantous et al., 2015), and the exploration of the "meeting-in-the-middle" approach to multi-omics analysis (Assi et al., 2015).

Other contributions included refining the use of multiple data types to identify germline genetic factors associated with risk of aerodigestive tract cancers (Delahaye-Sourdeix et al., 2015a, 2015b).

Routine statistical oversight also contributed to some articles on risk factors for thyroid cancer (e.g. Zamora-Ros et al., 2015a).

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The Genetic Cancer Susceptibility Group (GCS) has two equally weighted roles within IARC. First, GCS acts as a laboratory, bioinformatics, and pathology resource for genomic research at the Agency. Second, in close collaboration with its Section partners the Genetic Epidemiology Group (GEP) and the Biostatistics Group (BST), GCS undertakes genetic and genomics research to identify cancer-related genes and explore their mechanisms of action. Through this knowledge, GCS aims to provide insights into cancer etiology, early detection, and prevention.

During the 2014–2015 biennium, GCS has welcomed three scientists into the Group: Dr Matthieu Foll, Dr Lynnette Fernandez-Cuesta, and Dr Behnoush Abedi-Ardekani. Their joining the Group has strongly reinforced its scientific profile in bioinformatics, somatic mutations, and genomic-related pathology, respectively.

Genome-wide association studies

One of GCS's key scientific findings during the biennium was through a very large imputation-based genome-wide association study (GWAS) of lung cancer. This was undertaken through a collaboration between IARC, the Institute of Cancer Research (United Kingdom), Dartmouth College (USA), and the United States National Cancer Institute (US NCI) (Wang et al., 2014a). It included 21 594 cancer cases and 54 156 controls, making it one of the largest genetic studies of lung cancer carried out to date. This analysis identified three novel variants: one small-effect, common allele (rs13314271, located near *TP63*) and two large-effect, rare alleles (rs17879961, a missense variant [I157T] in *CHEK2*, and rs11571833, a truncating variant that results in the loss of the final 93 amino acids of *BRCA2*). Also, rs11571833 was observed to be similarly strongly associated with upper aerodigestive tract cancer (Delahaye-Sourdeix et al., 2015a). The association noted with the *CHEK2* variant validated GCS's previous observation of an inverse association with lung cancer and contrasts with the well-described increase in risk described for this variant in other cancers. In the case of *BRCA2*, susceptibility to lung and upper aerodigestive tract cancer had not been previously linked to genetic variation in this well-studied gene. Both findings suggest that alternative susceptibility mechanisms are at work and highlight how unexpected findings from agnostic genetic studies inform cancer etiology.

GCS also coordinated a meta-analysis-based GWAS of Hodgkin lymphoma that identified a susceptibility locus near *TCF3*, a gene critical to B-cell development (Cozen et al., 2014), and GCS was involved in the validation of rare variants linked with breast cancer in *RINT1* (Park et al., 2014a) and the MRE11A-RAD50-nibrin (MRN) complex (Damiola et al., 2014a). GEN has completed recruitment of a multicentre case–control study of 2535 nasopharyngeal cancer (NPC) cases and 2652 controls from centres in Malaysia (Sarawak), Thailand, Singapore, and Indonesia. Linkage analysis of 17 NPC cases from an extended pedigree recruited from Malaysia identified 6p22.1 as an area of interest. This region contains the *HLA-A* gene, previously implicated in NPC. In collaboration with the US NCI, GCS identified that allele HLA-A*24:07 segregates with NPC in this pedigree. The HLA-A*24:07 allele is relatively common to Sarawak and very rare elsewhere. Work is in progress to determine whether this allele is associated with NPC in the case–control study.

Genetic Services Platform

The Genetic Services Platform has overseen the installation of an additional liquid-handling robot to assist in GCS's laboratory protocols and the management of the almost 100 000 DNA samples, originating from about 75 studies, that are housed within GCS. In addition, an Ion Torrent Proton next-generation sequencer has been installed, and collaborative links have been maintained with local service providers to access additional genomic techniques, such as Illumina (HiSeq/HiScan technology). In bioinformatics, GCS has overseen two technical updates of IARC's high-performance computer cluster and data management systems, and has placed particular emphasis on the development of algorithms able to detect low-allele-frequency variants in the context of targeted next-generation sequencing-based resequencing. GCS has played a key role in the development of the Bioinformatics Steering Committee, a group that monitors bioinformatics across the Agency.

GCS is grateful to the following for their collaboration:

Professor Gilles Thomas and his team at Synergy Lyon Cancer (Lyon, France) for high-performance computing support. Professor Thomas was an inspiration to GCS and is deeply missed. Other collaborators include: Melissa C. Southey, Melbourne, Australia; Henrik Hjalgrim, Copenhagen, Denmark; Francesca Damiola, Charles Dumontet, Uzma Hasan, Joel Lachuer, Lyon, France; Fabienne Lesueur, Paris, France; Jajah Fachiroh, Dewajani Purnomosari, Yogyakarta, Indonesia; Beena Devi, Kuching, Malaysia; Anke van den Berg, Groningen, The Netherlands; Tam Ha, Singapore; Suleeporn Sangrajrang, Bangkok, Thailand; Ruth Jarrett, Glasgow, United Kingdom; Chris Amos, Hanover, USA; Wendy Cozen, Los Angeles, USA; David E. Goldgar, Sean V. Tavtigian, Salt Lake City, USA; Allan Hildesheim, Bethesda, USA.

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National Cancer Institute, National Institutes of Health, USA

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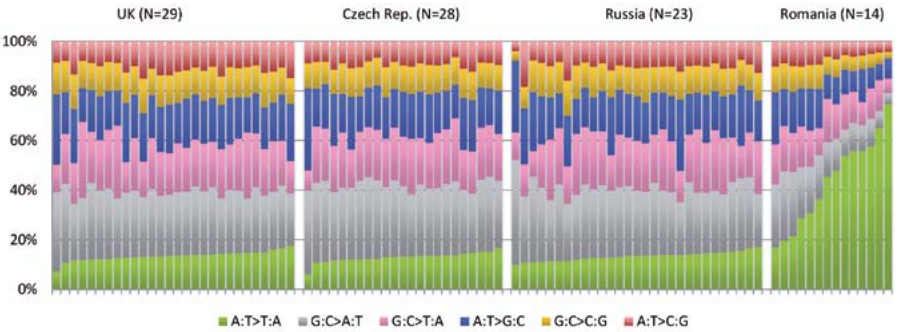
The overall goal for the Genetic Epidemiology Group (GEP) is to identify genetic susceptibility variants of various cancer sites and study their interaction with environmental factors. An additional goal is to develop accurate risk prediction models that take both demographic information (e.g. age and sex) and biomarkers (genetic and non-genetic) into account. GEP focuses specifically on cancers related to tobacco use and alcohol consumption (lung and aerodigestive tract cancers) and cancers with moderate incidence rates (such as kidney and pancreatic cancers). GEP devotes substantial resources to extensive fieldwork, with the goal of recruiting large series of cases and controls, comprising extensive questionnaire information and biological samples. Genetic analyses usually comprise a genome-wide approach initially, with subsequent large-scale coordinated replication studies in diverse populations. This latter aspect is aided by the development of international consortia in which GEP takes a leading role. Confirmed susceptibility loci are investigated in more detail with a variety of techniques, including in silico, expression, and sequencing studies, which are often conducted in collaboration with other IARC Groups. In addition to studies of genetic factors, GEP is conducting a wide range of studies involving non-genetic factors, including evaluations of circulating biomarkers such as human papillomavirus (HPV) antibodies for head and neck cancers, cotinine for lung cancer, and dietary biomarkers for multiple cancers. GEP also performs extensive evaluations of questionnaire data, particularly of data that have been collected during fieldwork. Some prominent examples of the Section's work over the 2014–2015 biennium are described here.

Genetics of kidney cancer

The first phase of the CAGEKID study (part of the International Cancer Genome Consortium) has been completed, with complete whole-genome sequencing of 100 tumour–germline DNA pairs collected through the IARC central European study and in the United Kingdom. Initial important findings included the observation of a large majority of patients from Romania who had an unexpectedly high frequency of A:T > T:A transversions, consistent with exposure to aristolochic acid (Scelo et al., 2014). These results show that the processes underlying clear-cell renal cell carcinoma (ccRCC) tumorigenesis may vary in different populations and suggest that aristolochic acid may be an important ccRCC carcinogen in Romania, a finding with major public health implications (Figure 1). In parallel, the genome-wide analysis of renal cancer susceptibility has been completed, in a large study comprising germline genetic data on more than 10 000 renal cancer cases and 20 000 controls. This work is being undertaken in collaboration with the United States National Cancer Institute, and initial analyses point to several new genetic loci for this cancer.

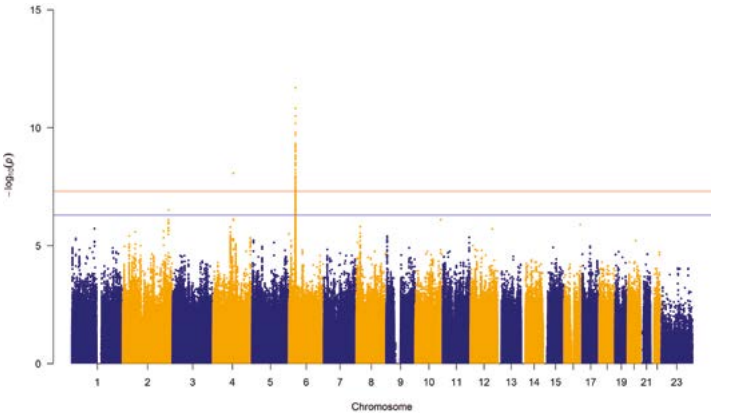
Figure 1. Mutation patterns from whole-genome sequencing of 94 conventional renal cell carcinomas from four different countries, showing a notable excess in the proportion of A:T > T:A mutations in cases from Romania. Reprinted with permission from Brennan P, Wild C (2015). Genomics of cancer and a new era for cancer prevention. PLoS Genet. http://dx.doi.org/10.1371/journal.pgen.1005522.



Genome-wide analysis of tobacco-related cancers

GEP has coordinated a large OncoArray analysis of more than 7000 cancers of the oral cavity or oropharynx, along with a similar number of controls. A prominent finding from this study is the important role of the HLA region for oropharyngeal cancer, suggesting an important interaction with HPV (Figure 2). GEP has identified specific HLA loci that are associated with multiple forms of HPV antibody expression (Chen et al., 2015). In addition, GEP is contributing a large series of cases to the genome-wide study of lung cancer that is due to report its findings at the end of 2015.

Figure 2. Manhattan plot of oropharyngeal OncoArray genome-wide association studies (GWASs). The vertical axis shows $-\log_{10}$(*P*-values) for 7.5 million single-nucleotide polymorphisms (SNPs), 432 220 genotyped sites (OncoArray platform), and 7 099 472 imputed sites. The red horizontal line represents $P = 5 \times 10^{-8}$, and the blue horizontal line represents $P = 5 \times 10^{-7}$. Noticeably, there is a strong genome-wide significant signal at 6p21.32 in the MHC region (leading SNP, rs3828805; $P = 2.03 \times 10^{-12}$). Also noticeable is rs1229984 at 4q23 ($P = 8.53 \times 10^{-9}$), a previously known locus, and there is a suggestive signal for rs1961637 at 2q36.1 ($P = 3.03 \times 10^{-7}$). *P*-values are the result of a fixed-effect meta-analysis of three GWASs by region (Europe, North America, and South America), comprising 2666 cases and 6585 controls; all analyses are adjusted by age, sex, and eigenvectors. © IARC.



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