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The Section of Genetics (GEN) includes the Genetic Epidemiology Group (GEP) and the Genetic Cancer Susceptibility Group (GCS). The work of the Section combines large population-based studies as well as 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. GEN also tries to identify individuals who are at high enough risk that they are likely to benefit from potential screening strategies.

The Section's projects usually involve extensive fieldwork in collaboration with external investigators to develop large-scale epidemiological studies with appropriate clinical and exposure data, as well as biosample collection. This typically occurs within GEP. Genetic analysis comprises either candidate gene or genome-wide genotyping studies, as well as extensive 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. The approach of GCS has been to use genomics and bioinformatics techniques to complement more traditional approaches for the study of rare genetic variants. GCS also uses genomics to explore how 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 genomics techniques and the related bioinformatics to support GEN's molecular epidemiology projects and other IARC genomics projects.

Genetic Epidemiology Group (GEP)

The overall goal of the Genetic Epidemiology Group (GEP) is to contribute to understanding the causes of cancer through the study of genetic susceptibility variants of various cancer sites, and also patterns of genetic mutations that are observed in tumours. Additional goals include identifying genetic predictors of outcome, as well as developing accurate risk prediction models that take both demographic information (e.g. age and sex) and biomarkers (genetic and non-genetic) into account. The work of GEP includes studies of cancers related to tobacco use and alcohol consumption (lung and aerodigestive tract cancers) and cancers related to obesity (such as kidney, pancreatic, and colorectal 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 of inherited susceptibility 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. Analysis of these large genome-wide studies also includes a Mendelian randomization approach that aims to understand how lifestyle factors influence cancer onset.

GEP is also undertaking a large international study of the causes of cancer by analysis of mutation patterns (or mutational signatures) in cancer genomes. Most of the Group's efforts in this domain are included in the Mutographs project, which aims to understand the causes of five different cancer types across five continents.

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, and a wide range of protein and other biomarkers for lung cancer. The overall goal of these studies is to identify individuals at sufficiently high risk to justify screening and early detection.

Some prominent examples of the Group's work over the 2018–2019 biennium are described here.

Elucidating the etiological role of obesity and related risk factors in multiple cancers – a Mendelian randomization approach

Elevated body mass index (BMI) and obesity-related risk factors have been associated with multiple cancer types studied by GEP. Because these risk factors are inherently interrelated, traditional epidemiological studies have not been able to untangle which specific factors exert a causal influence and which are merely correlated with the underlying causal factor.

By leveraging data from genome-wide association studies of tens of thousands of cancer cases and controls that GEP has led or contributed to, the Group has conducted a series of studies in which the causal relevance has been interrogated for several obesity-related risk factors for various cancers. Because these analyses were based on genetic instruments, they are not influenced by reverse causation and are less sensitive to confounding than those using direct exposure measures. The results have been illuminating for a wide variety of cancer types, including colorectal, ovarian, and endometrial cancers, and extend the Group's earlier work on kidney and pancreatic cancers (Mariosa et al.,

2019). In particular, the results provide compelling evidence that earlier studies of obesity based on epidemiological data have underestimated the impact of this important risk factor. GEP's analysis also suggests a potentially important role for obesity in lung cancer, which is likely to be driven by the association between BMI and smoking status (Carreras-Torres et al., 2018).

Progress in the Mutographs study

A major initiative of the Section, Understanding of the Causes of Cancer through Studies of Mutational Signatures – Mutographs, launched in May 2017, is an effort to understand the causes of cancer by generating mutational signature profiles based on whole-genome sequence data. The study results from a major Cancer Research UK (CRUK) Grand Challenge grant – one of the world's most ambitious cancer research awards – and is co-led by Dr Paul Brennan together with overall principal investigator (PI) Professor Sir Mike Stratton from the Sanger Institute (Cambridge, United Kingdom) and four other co-PIs.

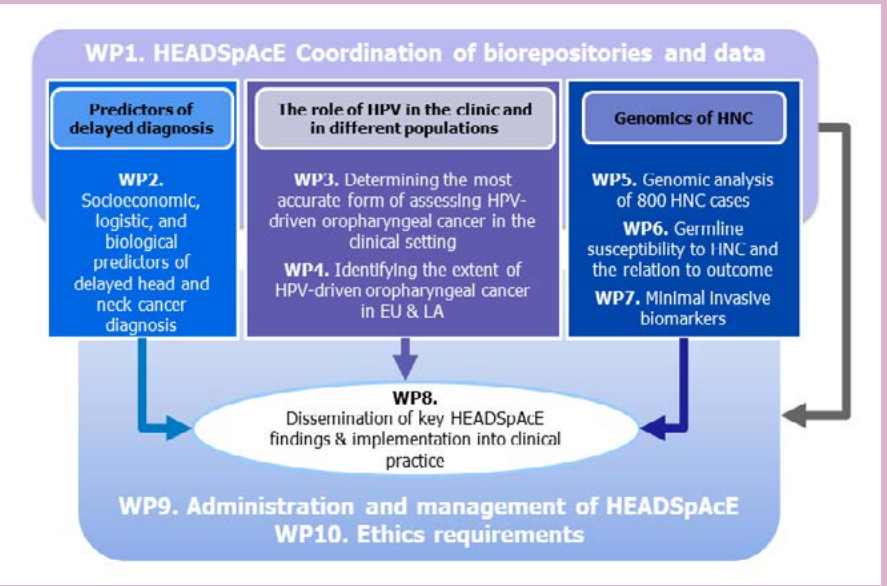
Within the Mutographs initiative, GEP is coordinating the recruitment of 5000 individuals with cancer (colorectal cancer, renal cancer, pancreatic cancer, oesophageal adenocarcinoma, or oesophageal squamous cancer) across five continents to explore whether different mutational signatures explain the marked variation in incidence. Through an international network of collaborators, biological materials are collected, along with demographic, histological, clinical, and questionnaire data. Whole-genome sequences of tumour–germline DNA pairs are generated at the Sanger Institute. Extracted somatic mutational signatures are then correlated with data on risk factors. By September 2019, 39% of the cases had been recruited and the biological samples received at IARC, with full-genome sequencing completed on 28% of those.

HEADSpAcE project

The large-scale initiative Translational Studies of Head and Neck Cancer in South America and Europe (HEADSpAcE) was recently launched to address the high mortality rate of head and neck cancer in South America and Europe. This work is funded by the European Commission as part of the Horizon 2020 European Union Research and Innovation Programme and is coordinated by GEP across 15 sites across two continents.

Head and neck cancer is the sixth most common cancer in both South America and Europe. A major reason for the high mortality rate of this cancer is the late stage of diagnosis for many patients. Accurate assessment of the prognosis of head and neck cancer cases enables appropriate treatment decisions. For this project, GEP brings together a consortium of 15 partners to understand reasons for late diagnosis and reduce the proportion of head and neck cancers that are diagnosed at a very late stage. Through the international network of collaborators, biological materials are collected, along with demographic, histological, clinical, and questionnaire data. Genomic evidence of strong predictors of prognosis that will have the potential to improve care and reduce treatment-related morbidity will be developed, along with guidelines for implementation in clinical care.

Overview of comprehensive approach (Work Packages 1–10) to assessing high mortality from head and neck cancer: the HEADSpAcE project. EU, European Union; HNC, head and neck cancer; HPV, human papillomavirus; LA, Latin America; WP, Work Package. © IARC



Genetic Cancer Susceptibility Group (GCS)

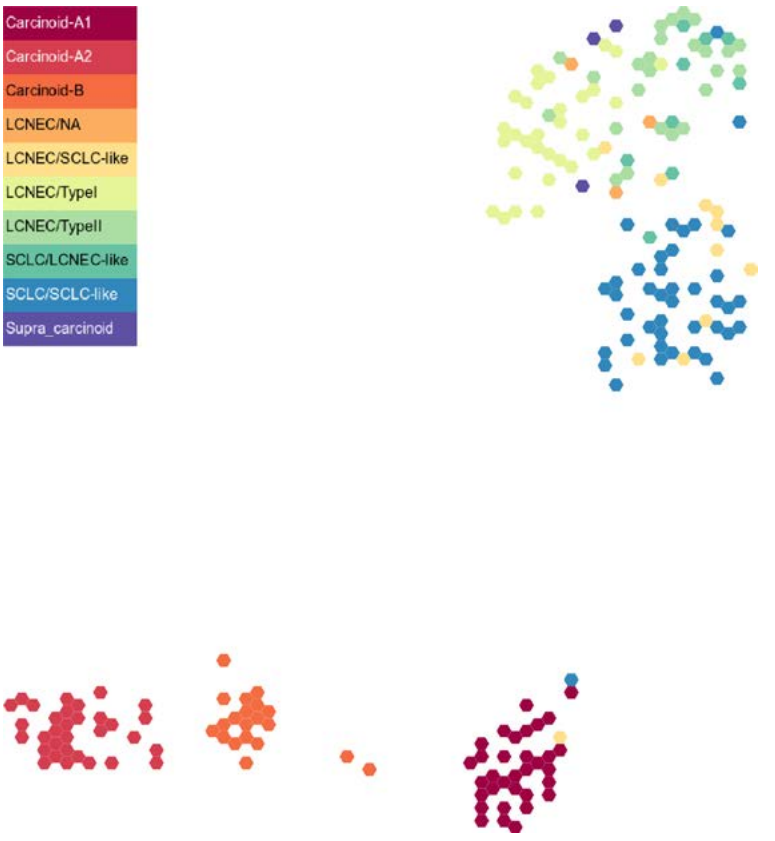
The Genetic Cancer Susceptibility Group (GCS) contains a multidisciplinary scientific team, covering genetics, genomics, bioinformatics, and pathology. These combined skills are used to undertake genetic and genomic research to identify cancer-related genes, explore their mechanisms of action, and determine how tumours are classified and detected. Working within international consortia, GCS is able to assemble the appropriate sample sizes required for informative genetic and genomic studies. GCS's multifaceted genomic analysis and multidisciplinary team provide additional depth to these consortia-based studies.

The general focus of GCS has been on four areas during the 2018–2019 biennium: the genomic characterization of lung neuroendocrine neoplasms and malignant pleural mesothelioma, the exploration of *TERT* mutations as early detection biomarkers in urothelial cancer, the Group's traditional area of understanding germline genetic susceptibility, and facilitating genetic and genomics research at IARC and within the wider community.

In the context of the Rare Cancers Genomics project (http://rarecancersgenomics.com), which is aimed at the molecular characterization of rare cancers, including lung neuroendocrine neoplasms (lungNENomics) and malignant pleural mesothelioma (MESOMICS), GCS collaborated with researchers from 20 centres in 10 countries to assemble an important collection of these rare cancers. Using this resource, GCS has (i) provided an integrative genomic profiling of large-cell neuroendocrine carcinomas, revealing distinct subtypes of high-grade neuroendocrine lung tumours (George et al., 2018), which appear to be predictive of clinical response (Derks et al., 2018a); (ii) unveiled the existence of new molecular subtypes of pulmonary carcinoids, including, of particular interest, a group named supracarcinoids (Alcala et al., 2019a); (iii) redefined malignant pleural mesothelioma types as a continuum, uncovering immune–vascular interactions, which have clinical implications (Alcala et al., 2019b); (iv) contributed to recommendations for the classification of both malignant mesothelioma and neuroendocrine neoplasms (Rindi et al., 2018); and (v) created the first molecular maps (https://tumormap.ucsc.edu) (Figure 1) for malignant mesothelioma and lung neuroendocrine neoplasms, which will assist and increase the translational impact of molecular studies in these rare cancer types.

In the context of biomarkers, GCS has explored the possibility that highly recurrent telomerase reverse transcriptase (*TERT*) gene promoter mutations (C228T and C250T) detected from tumour cells shed in the urine of patients might be potential biomarkers for urothelial cancer (Figure 2). Drawing on the Group's laboratory and bioinformatics skills, GCS developed a singleplex assay (UroMuTERT) that detects *TERT* promoter mutations, even at low abundance, and tested it using a series of cases and controls from France (blood, urine samples, and, for the cases, tumours) and Portugal (urinary exfoliated

Figure 1. Integrative molecular map of lung neuroendocrine neoplasms (LNEN) based on transcriptome data from the LungNENomics project. Uniform Manifold Approximation and Projection (UMAP) representation of 208 LNEN samples (small-cell lung cancer [SCLC]; large-cell neuroendocrine carcinomas [LCNEC]; typical and atypical carcinoids) based on the expression of the most variable genes (6398 genes explaining 50% of the total variance). The layout was created on the University of California Santa Cruz TumorMap (https://tumormap.ucsc.edu) using a hexagonal grid; point colours correspond to molecular clusters previously identified in each study individually (George et al., 2018; Alcala et al., 2019a). © IARC.



cell samples). In detecting *TERT* promoter mutations in urinary DNA, UroMuTERT showed excellent sensitivity and specificity for detection of urothelial cancer, especially for low-grade and/or early-stage cancers, and considerably outperformed urine cytology (Avogbe et al., 2019). The Group is now investigating the viability of these mutations as early detection biomarkers for bladder cancer in pre-diagnostic samples collected within a prospective population-based cohort in the Islamic Republic of Iran (the Golestan Cohort).

In the context of germline susceptibility, GCS continues to play an important role in coordinating genetic studies within the large international consortia, particularly the International Lung Cancer Case–Control Consortium (ILCCO) and the International Lymphoma Epidemiology Consortium (InterLymph). GCS aims to introduce aspects of genomics into the germline genetic studies carried out by these consortia. An example of the integrative approach of GCS in these studies is the Group's identification of *DIS3* as a multiple myeloma (MM) susceptibility gene, with important genetic effects (Pertesi et al., 2019). This study included analysis of germline material from patients with familial and sporadic MM, transcriptomics of normal blood samples, and mutation and transcriptomics of MM tumours. Although each branch of research in isolation was only suggestive, the evidence that *DIS3* is a MM susceptibility gene is more compelling when accumulated across the different areas of complementary molecular analysis.

Finally, GCS still plays an active role in the development of genomics capabilities at IARC and elsewhere. GCS has led the pathology workflow for the Mutographs project (see above), a large-scale international study that aims to unveil the carcinogenic role of environmental exposures by analysing the mutational signatures through whole-genome sequencing of 5000 cancers collected from 40 recruiting centres in five continents (https://www.mutographs.org/). Cancers of the oesophagus, pancreas, colorectum, and kidney are collected and shipped to IARC. GCS then leads the processing of samples and microscopic analysis of frozen tissues through the application of digital pathology and the contribution of a panel of expert external pathologists. With important contributions from other Groups, GCS has continued to build links within the genomics community at IARC, as well as provide access to the laboratory techniques, pathology expertise, electronic record-keeping, and computational resources for genomics-related activities at IARC. The Group is also active in ensuring the accessibility of developments and advances in knowledge within the Agency to the wider scientific community, for example, via the Group's GitHub website (https://github.com/IARCbioinfo/).

Figure 2. Overview of the detection of *TERT* promoter mutations by the UroMuTERT assay applied to body fluids and tumours, from the DIAGURO cohort, of primary and recurrent urothelial carcinoma cases and body fluids of controls. *, cancer other than urothelial; a, pTa/CIS; CIS, carcinoma in situ; MIUC, muscle-invasive urothelial carcinoma; UC, urothelial carcinoma; UP DNA, urine pellet DNA; US cfDNA, urine supernatant cell-free DNA. Reprinted from Avogbe et al. (2019), Copyright 2019, with permission from Elsevier.