International Agency for Research on Cancer

World Health Organization

Scientific Council **SC/47/WP4**
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Princess Takamatsu Hall

SCIENTIFIC REPORT OF THE SECTION OF GENETICS (GEN) REVIEW

BACKGROUND INFORMATION

Working papers

The written submissions from the Section of Genetics (GEN), presenting a comprehensive overview of the work performed during the last five years (2006–2010) and the future research directions of the Groups, form the framework for the review.

The following submissions from the GEN Section were sent to the Review Panel on 13 September 2010:

- ✓ Provisional Agenda – Rev.2 (dated 29 September 2010)
- ✓ Provisional List of Participants (dated 06 September 2010)
- ✓ Guidelines for Reviewers (dated June 2009)
- ✓ SC/47/WP1 General Introduction to the work of GEN
- ✓ SC/47/WP2 Group Review 1: Genetic Cancer Susceptibility Group (GCS) – Head, Dr James McKay
- ✓ SC/47/WP3 Group Review 2: Genetic Epidemiology Group (GEP) – Head, Dr Paul Brennan
- ✓ Key publications for GCS and GEP

Oral presentations

The presentations gave a short overview of the written material and focused on topics related to the Groups' future plans and directions.

Membership of the GEN Review Panel has been established as follows:

External Reviewers:

- Professor Fergus J. Couch (Mayo Clinic, Rochester MN, USA)
- Professor Peter Donnelly (The Wellcome Trust Centre for Human Genetics, Oxford, UK)
- Dr Paul Pharoah (Strangeways Research Laboratory, Cambridge, UK)
- Professor John S. Witte (Helen Diller Family Comprehensive Cancer Center, University of California, San Francisco, CA, USA)

Scientific Council members:

- Professor Ian Frazer **(Review Panel Chair)** (The University of Queensland Diamantina Institute, Australia)
- Professor Henrik Grönberg (Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden)
- Professor Sir Alex Markham (Institute of Molecular Medicine, University of Leeds, UK)
- Dr Marina Pollán Santamaria (Centro Nacional de Epidemiologia, Instituto de Salud Carlos III, Madrid, Spain) (unable to attend)

Their assessments and recommendations follow.

SECTION OF GENETICS

Mission:

Identify genes involved in cancer, characterize pathogenic sequence variants and study interactions between genetic and non-genetic factors contributing to cancer risk.

Composition:

Three Groups:

Genetic Epidemiology Group (GEP)

Genetic Cancer Susceptibility Group (GCS), which includes the Genetics Services Platform (GSP)

Biostatistics Group (BST).

The last mentioned Group has been recently created and was not included in this review.

GENERAL OVERVIEW OF THE SECTION OF GENETICS (GEN) – as provided to the Panel

The Genetics Section, headed by Dr Paul Brennan, comprises two Groups with the overall mission of identifying genes involved in cancer, characterizing the spectrum of pathogenic sequence variants that they harbour, and understanding how they interact with non-genetic factors. The two Groups are the Genetic Epidemiology Group (GEP) and the Genetic Cancer Susceptibility Group (GCS).

The Genetic Cancer Susceptibility Group (GCS) is mainly involved in identification of rare variants or mutations in known or strong candidate cancer loci that result in a substantial cancer risk. The main focus has been on breast cancer, although there is a growing interest in melanoma and also tobacco related cancers. Findings from the GCS Group may have direct prevention implications by resulting in more accurate analysis of clinical mutation screening data from high-risk susceptibility genes such as BRCA1, BRCA2, MLH1 and MSH2. GCS also provides a genotyping platform service for both Groups. The previous Group Head, Dr Sean Tavtigian, left IARC in October 2009, and was replaced by Dr James McKay in September 2010 (Dr Fabienne Lesueur was acting Head between November 2009 and August 2010). Dr McKay, who was previously in the GEP Group, has therefore had limited opportunity to participate in the development of GCS future plans as they are currently presented.

The Genetic Epidemiology Group (GEP), headed by Dr Paul Brennan, is mainly involved in coordinating large population-based epidemiological studies and analysis of multiple common genetic variants in order to identify new susceptibility loci. Cancers of primary interest include those of the lung and upper aerodigestive tract (including the nasopharynx) as well as kidney cancers. GEP has taken a lead in developing genome-wide association studies (GWAS) for several cancer sites, in collaboration with outside genotyping laboratories, and places an equal emphasis on the evaluation of both genetic and non-genetic risk factors. GEP scientists collaborate extensively with external partners and support the conduct of large IARC epidemiological studies with appropriate clinical and biosample collection in over 20 countries.

The Section of Genetics also includes the Biostatistics Group (BST), headed by Dr Graham Byrnes, which provides biostatistical and bioinformatics support to the range of Section projects. It also has a wider role in supporting biostatistical activities across the Agency. Because of this broader role, and also its recent inception, the Biostatistics Group is not participating in this review. Its activities are however the focus of a separate BST advisory meeting that is planned for late in 2010.

GROUP REVIEW 1: Genetic Epidemiology Group (GEP) (see document SC/47/WP3)

Head of the Group: Paul Brennan

Objectives:

- Identify new common genetic variants of susceptibility in large population-based epidemiological studies.
- Cancers of primary interest: lung, upper aerodigestive tract and kidney.
  - Selection based in their incidence in low- and middle-income countries, unknown etiology or very low incidence and therefore difficult to study
- Emphasis on both genetic and non-genetic risk factors.

Composition:

Scientists: 2 currently in GEP (P5 P. Brennan & P2 G. Scélo) + 2 vacant posts (P3 + P2) + 1 part-time vacant (pathologist to be shared with MOC) (last two recently filled).
Technical Assistants: 2
Laboratory Technician: 1
Secretary: 1
Postdoctoral fellows: 6
Students: 2

1. GEP's past work:

1.1 Overview of GEP's work in the last five years

Projects

In the last five years, GEP has led 10 research projects. Most of them (7) had external funding.

Topics include:

- Lung cancer epidemiology (Project A NCI+AICR), (Project D WCRF), (Project G NCI)
- Upper aerodigestive tract cancer (Project B NIH), (Project F AICR, ARC), (Project G NCI)
- Kidney Cancer (Project C internal funding)
- Lymphomas (Project E internal funding)
- Rare childhood cancers (Project I internal funding)
- Pancreatic cancer in Europe (Project J NIH/NCI)
- New cohorts in middle-income countries (Russia and Iran) (Project H EC).

Scientific productivity of these projects:

- Projects A, B, C and G performed well.
- Project I: recently started and nothing has been published yet.
- Project D: paper published.
- Project F: two papers published.
- Project J: a paper has been submitted.

1.2 Critical appraisal of GEP's work in the last five years

The Review Panel noted that the research output of GEP over the past five years had been outstanding:

- A project on lung cancer genetics has resulted in two high profile papers.
- Projects on renal carcinoma and lymphoma were expected to be published in the near future.
- Overall, more then 170 papers have been published in the last five years.
  - the first author is part of GEP in 31 papers (18%),
  - the senior author is part of GEP in 44 papers (25%).
- In keeping with the objectives of GEP, almost half of the senior author papers (around 20) are not related to genetic variants.

Several other collaborative studies have been initiated in the quinquennium.

The Group Head, Paul Brennan, has published more than 150 papers since 2006. He is the senior author of 39 (25%) and first author in 4. Most of these publications appeared in internationally recognized journals.

GEP has been involved in major breakthroughs in their primary areas of research. They are to be commended for their successes. GEP has developed many collaborative projects, helping IARC to maintain its leading role in cancer epidemiological research. GEP has been able to concentrate collaborations in lung cancer and upper aerodigestive cancers, taking advantage of on-going studies already available. The collaboration with the Centre National de Génotypage in France has allowed GEP to undertake extensive genetic studies, including GWAS. Finally, GEP has been involved in setting up new cohorts in countries of interest to IARC's mission in the developing world.

GEP has been able to obtain enough resources from external research funders (NCI, AICR, WCRF, NIH, EU). Most of their projects have been scientifically productive and others, as the new cohorts mentioned, should be fruitful in the near future.

Recommendations of previous Review Panel 2005

These have been delivered or are no longer relevant.

2. GEP's future plans:

2.1 Overview of GEP's future plans and strategic vision

The Group Head indicated that their efforts over the next five years would be distributed as follows:

1. Kidney cancer (30%)
2. Lung cancer (35%)
3. Head and neck cancers (15%)
4. Rare cancers (10%)
5. Cohorts (10%)

This range of planned projects was fully supported and held to provide variety without becoming unduly unfocused. Below we provide details of the plans and vision for these projects.

Projects A/B: Kidney cancer

The proposed IARC led component of this work is an expansion of the current GWAS, using a case-cohort design for evaluation of genetic associations with outcome, and correlation between germ line variants and gene expression levels. An NIH proposal for funding received a 22nd percentile score, and is being resubmitted. A strength of this study is that there is relatively extensive clinical information available.

A further component led by Mark Lathrop (CNG) will involve recruitment of 2000 cases with a comprehensive biorepository. The main role of GEP will be collecting and annotating biological samples. The initial research plan is for whole genome sequencing of 100 cases. Sequencing is being undertaken at three different laboratories. The bioinformatics infrastructure to analyse these data is not yet in place at IARC.

Projects C/D: Lung cancer

GWAS of lung cancer susceptibility. Pooled meta-analysis of GWAS on 13 000 cases and 25 000 controls (Brennan is co-PI, funded by NIH U19 grant, NCI initiative to follow-up GWAS). The goals of this project are to impute unmeasured variants, evaluate interactions and undertake pathway based analyses, perform fine mapping of confirmed loci and replication studies of suspected loci. Fine mapping genotyping is being undertaken in Toronto; analyses will be performed at IARC (and elsewhere). This is a straightforward continuation of an on-going project.

Genetics of early stage lung cancer and outcome. At present this is mainly the development of a bioresource to ultimately contain 2000 cases of stage I/II NSCLC (March 2011 submission of R01). Potential projects include exome sequencing and evaluating prognostic value of genetic variants. Vision underlying the project is clear. It will be interesting to see whether some of these cancers have a distinct molecular etiology—rather than an earlier stage of the same disease—than observed in other lung cancers.

Project E: Head and Neck cancer

This project entails a combination of GWAS, confirmatory studies, and evaluation of the role of HPV and genetic predictors of HPV antibody response. This entails a routine implementation of multi-phase GWAS.

Project F: Genetics of B-vitamins and their effects on multiple cancers

Goal here is to replicate results of protective effect for lung cancer in other cohorts (Europe, US, Australia and Asia), and explore this association in other tobacco related tumours. Moreover, evaluate how vitamin B effects are modified by genetic variants and smoking. This approach is being extended to renal cell carcinoma. GEP is spearheading this consortium project. The Panel views this as a very interesting and novel project.

Project G: Genetic epidemiology of nasopharyngeal cancers

GWAS on 2000 case / control pairs from Singapore, Thailand, and Malaysia. Also look at interaction with environmental and infectious causes, plus prognostic value of genetic variants. In addition, undertake a parallel study in North Africa. This may be primarily a project to develop a resource.

Project H: International study of rare childhood embryonal tumours

A multi-centre collaboration examined the role of suspected risk factors in embryonal origin tumours (study in 12 countries). 1000 case trios for each of the five tumours and 5000 unrelated controls. This is currently unfunded, although there are some possible sources for future funding. GEP is acting as central coordination group, and this is a good example of IARC international coordination role. If a grant is proposed, GEP will be the PI.

Project I: Prospective cohort in Russia

A retrospective analysis of a cohort of 50 000 individuals found a very large impact of alcohol intake on mortality in Russia. This has had a large public health impact. A prospective cohort of 200 000 adults replicated the results for alcohol.

Project J: Prospective cohort in Iran

Iranian cohort (Golestan) of 50 000 participants recruited. Determinants of oesophageal cancer mortality (hot tea consumption, opium, diet) are being examined.

2.2 Critical appraisal of GEP's future plans

Overall

The proposed work plan is a logical extension of the work undertaken over the last five years, building on the Group's established strengths. There was more focus of the proposed activities at the oral presentation than was evident in the written submissions.

Case ascertainment

Correct diagnostic attribution of material from the extensive bioresource available to the Group will be of increasing importance for future studies and the plan to advance this area was commended.

3. GEP's assessment (SWOT):

3.1 Assessment of GEP's Strengths

- Dr Brennan as a respected, world-class investigator is clearly a significant asset to IARC.
- The consistent ability to raise external financial support from Europe and abroad.
- Ongoing collaborations within IARC, with CNG, and with groups around the world.
- Experience in the field work involved in setting up new cohorts.
- Extensive curated biobanks.

3.2 Assessment of GEP's Weaknesses

- No evident route for following up on biological or clinical significance of genetic findings.
- Accuracy of case ascertainment within the Group and IARC appears inadequate.
  - Access to expert histopathology review is not routine.
  - Use of serology for HPV detection in head and neck cancer studies.
  - No current program for assessment of tumour gene expression profiles.
- Limited collaboration with other IARC epidemiology groups (INF, LCA).
- Access to technical infrastructure for sequencing and support in bioinformatics is suboptimal by international standards.

3.3 Assessment of GEP's Opportunities

- The combination of skilled field work, good biobank access, access to in-house and local genetics expertise and skilled epidemiology is unique in a global setting.
- Existing networks with other similar groups and with large genomics facilities (e.g. CNG).
- The non-genetic epidemiology projects are focussed on public health issues.
- Continuing intellectual yield from mining the various IARC collections, painstakingly assembled over years.
- A potential role longer term in curation of large cohorts collected around the world, as their "owners" retire/lose their funding.
- Availability of outcome data for some cohorts is an asset.

3.4 Assessment of GEP's Threats

- Staff vacancies and understaffing may reduce competitiveness.
- One large external grant terminating next year, and only one other continuing, may compromise productivity.
- The international reputation of the Group lies largely with the Group Head.
- Funding constraints may compromise international competitiveness of available infrastructure for sequencing, computing, and data analysis.
- International shortage of top quality talent in bioinformatics/ computing/ analysis.
- An expectation to deliver service for multicentre genomics studies in which they become minor players.

4. Evaluation of GEP

a. Assessment of scientific quality (using the four-point scale below)[1]

Past Performance: Outstanding
Future Plans: Outstanding

b. Assessment of the relevance of the work to the mission of IARC[2]

Past Performance: Perfect Fit
Future Plans: Perfect Fit

5. Overall recommendations for GEP

The Panel note the outstanding performance of this Group over the last five years, and recommend that GEP:

1. Maintain their research focus and distribute their research effort as recommended by the Group Head.
2. Note the risks associated with further diversification of effort, particularly for studies where they perform a largely service role.
3. Facilitate and make use of continually improving ability to categorize the tumours they study.
4. Collaborate with other groups in IARC who have common interests and complementary expertise.
5. Fill vacant posts promptly.

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[1] The following classification will be used:
1: **Outstanding**: Work of the highest international calibre, pioneering and trend-setting.
2: **Satisfactory**: Work that is internationally competitive and will make a significant contribution to science or public health.
3: **Questionable**: Work which is not of a high scientific standard, but which could be improved.
4: **Unsatisfactory**: Work which is of poor scientific standard and is unlikely to make a contribution to science or public health.

[2] The following classification will be used:
1: **Perfect fit**: This type of work is ideally suited to the mission of IARC.
2: **Good fit**: This type of work is suited to the mission of the Agency.
3: **Questionable fit**: Uncertain.
4: **Poor fit**: Work which should not continue.
Scores should be accompanied by justifications and recommendations for action, where necessary.

GROUP REVIEW 2: Genetic Cancer Susceptibility Group (GCS) (see document SC/47/WP2)

Head of the Group: James McKay

Objectives:

Understand the contributions of genetics to cancer risk. Develop and maintain genotyping / genomics techniques and apply them to large populations based genetic studies. Integration of genomics techniques into genetics studies.

Composition:

Scientists: 3
Technical Assistant: 1 (bioinformatician)
Laboratory Technicians: 4 (+1 vacant)
Secretary: 1
Postdoctoral fellows: 4
Student: 1

1. GCS's past work:

1.1 Overview of GCS's work in the last five years

The prior work of this Group was under the direction of the previous Group Head, and there has been a significant change in the scientific direction of the Group. The prior work is therefore not reviewed here.

Projects included:

- Development of informatics tools for evaluating rare variants, and applying these to breast cancer.
- Establishing DNA biorepositories for large studies.
- Developing a genetic services platform and data management system (LIMS).

The Panel noted and commended the newly appointed Group Head for his substantial contribution to the success of the research work of the GEP Group over the last five years.

2. GCS's future plans:

2.1 Overview of GCS's future plans and strategic vision

The recently appointed Group Head did not appear to have had an opportunity to contribute to the written proposal, from which his verbal presentation differed substantially. This evaluation relates largely to the verbal presentation.

A substantial part of the new Group Head's vision revolved around the role for GCS in genome wide association studies (GWAS) of genes contributing to cancer risk. This was articulated to cover two broad aspects: (i) new GWAS in diseases not yet studied by this approach; and (ii) additional work on GWAS already undertaken (typically within GEP), including quality control, SNP prioritization, SNP imputation, replication genotyping and functional analysis.

The Panel's general view is that GWAS is not an appropriate focus for GCS in the medium or long term, not least because it overlaps very considerably with the plans and stated mission of GEP. Notwithstanding this, we can see merit in pursuing at least (i) above in the short term to allow the new Group Head to establish his independent research career. We are not convinced that (ii) naturally fits within GCS. Quality control and choice of SNPs for follow-up is an essential part of primary GWAS analysis, and SNP imputation naturally follows these analyses, so that this work does not naturally separate itself from the GWAS into GCS. Replication genotyping, if undertaken locally, should be within GSP, as part of its service role. Experimental work to follow up GWAS findings functionally is a substantial undertaking which would require a major change of research direction and of expertise within GCS. It seems unlikely that an appropriately broad range of expertise in key functional tools could be combined within GEN, and that these are best pursued through collaborations.

Proposed research plans for GCS outside of GWAS related further pursuit of genes potentially associated with lung cancer risk (Project B in the submitted paperwork), and studies on the genetics of melanoma (Projects A, C, D in the submitted paperwork).

The lung cancer studies as proposed by the Group Head were held to be closely related to the lung project proposed by GEP, and could extend this work by identifying and determining the significance of rare variant mutations. The Review Panel felt that this was an appropriate short term goal for the Group.

The Group Head indicated that the melanoma studies, being led by senior scientists within the Group, would only be pursued if external funding applications were successful. The Review Panel agreed with this assessment.

3. GCS's assessment (SWOT):

3.1 Assessment of GCS's Strengths

- New principal investigator.
- Two of the senior scientists (F. Lesueur and F. Le Calvez-Kelm) have been in place for a several years.
- A number of proposed projects are heavily aligned with the interests of the GEP Group, which may help the new Group Head to maintain research productivity in the short term, while developing a longer term research strategy.
- Proposed future research projects are closely aligned with the interests of other IARC researchers.
- Access to the IARC biobank.

3.2 Assessment of GCS's Weaknesses

- A relatively junior team.
- Lack of a clearly espoused hypothesis/vision for GCS that will distinguish this Group from GEP.
- Lack of state-of-the-art equipment for high throughput SNP analysis and next generation sequencing.

- Lack of support in bioinformatics.
- The GSP service shares a budget with the research programmes within GCS which may negatively impact on the Group's research activities.
- Lack of a business plan for GSP.

3.3 Assessment of GCS's Opportunities

- The new GCS Head has the opportunity to define the scientific direction of the Group.
- Collaboration with other researchers at the Agency particularly in the GEP Group.
- Available unique study populations.
- Collaboration with the new Biostatistics Group.

3.4 Assessment of GCS's Threats

- Implementation of next generation sequencing and bioinformatics does not occur promptly enough for the Group to retain international competitiveness.
- Current absence of a clear research direction will leave the Group uncompetitive.
- The Group would not flourish if GCS were to rely on GEP for research direction.
- New projects proposed in melanoma and non-melanoma skin cancer are subject to external funding requests currently under review with potential loss of senior staff.

4. Evaluation of GCS

a. Assessment of scientific quality

Past performance: Satisfactory
Future plans: Satisfactory

b. Assessment of the relevance of the work to the mission of IARC

Past Performance: Perfect fit
Future Plans: Perfect fit

5. Overall recommendations for GCS

The Panel notes that the Head of GCS was appointed to his position during the course of the review of the GEN Section.

The Panel therefore recommends that:

1. The Head continue to develop a vision for GCS that distinguishes its goals and activities from those of GEP and takes into consideration the place of the activities of GCS within global research activity in cancer genetics.
2. A further review of this Group's research goals and activities is conducted by a subcommittee of the current Panel in January 2012.

The Panel recommend that support be given to expanding the postdoctoral research capacity within this Group.

Overall evaluation of the section of Genetics (GEN)

General Comments:

A contribution to the worldwide research effort on whether and how genetic variability contributes to the risk of cancer is an expected part of IARC's mission to assist in cancer control through research.

The Review Panel noted that the IARC Section of Genetics is relatively small, when considered in terms of the global international effort in cancer genetics. The Panel recommended that the Section should work in areas where through their international collaborative links and their unique collection of curated specimens they would have a particular ability to make an international impact.

While the Section of Genetics has a unique opportunity to collect curated samples from hard-to access places to feed into studies led elsewhere, they should not limit their activity to this, as the international impact of the Section's contribution to such studies might be relatively low.

The Review Panel were impressed by the contributions of the early career scientists to the review process and to the research efforts of GEN.

The stated strategy of the Section of Genetics is to focus on the genetic basis of certain groups of cancers:

- cancers of high prevalence in developing countries,
- rare cancers requiring multinational collaborations,
- cancers where the etiology remains obscure (and therefore requires coordinated international efforts).

The Review Panel considered this a sensible approach.

Assessment of scientific quality (see scale above)

Past Performance: Outstanding

Future Plans: Outstanding

Assessment of the relevance of the work to the mission of IARC

Past Performance: Perfect Fit

Future Plans: Perfect Fit

Overall recommendations for GEN

The Panel recommend that IARC, to retain its current international competitiveness in the field of genetics:

1. implement high throughput sequencing capacity, and commit urgently to the purchase of a next generation sequencing platform, guided by GEP/GCS. The Review Panel note that the GEN Section has recommended the HiSeq platform, which has the Panel's strong endorsement.
2. recognize an urgent need for adequate computing and data storage hardware to support the Section's and IARC's activities.
3. expand bioinformatics, informatics and statistical genetics support to a level appropriate for the proposed activities. The Panel's strong recommendation is for the appointment of a senior bioinformatician/statistical geneticist with experience of high throughput sequencing, to be placed within GSP, leading a new team of five. This team, under the supervision of GCS, would support both research activity within GEN and the sequencing service for IARC.
4. separate the budget of the GSP service platform in genetics/genomics from the GEN Section budget.
5. avoid creating an artificial division between the research focus of the activities of GEP and GCS. For example, the Panel noted the advantage of joint activity on some projects.

The Panel recommend extending the breadth of research training and formal mentoring of career development for postdoctoral staff.

The Panel recommend wider use of the option to extend the tenure of postdoctoral positions to three years.