Familial Cancer (2010) 9:705–711
DOI 10.1007/s10689-010-9347-4

Report of the Combined Meeting of the International Society for Gastrointestinal Hereditary Tumours, the Human Variome Project and the National Cancer Institute Colon Cancer Family Registry, Duesseldorf, Germany, 24 June 2009

Maija Kohonen-Corish · Thomas K. Weber · Annika Lindblom · Finlay Macrae · the Meeting Participants

Published online: 8 June 2010

This report provides a summary of the first combined meeting of the International Society for Gastrointestinal Hereditary Tumours (InSiGHT), the NCI Colon Cancer Family Registry (C-CFR) Steering Committee and the Human Variome Project (HVP), held as a daylong pre-meeting of the 2009 Biennial Meeting of InSiGHT in Duesseldorf Germany. The meeting was attended by over 100 registrants representing over 40 countries including 26 members of the CFR Steering Committee. The meeting organizer Finlay Macrae (Melbourne, Australia), Secretary of InSiGHT, opened the meeting and explained that the purpose of the meeting was to bring together the collective expertise of the NCI CFR leadership, the HVP and InSiGHT in order to share knowledge and foster future substantive research collaboration.

InSiGHT President Gabriela Moeslein (Duesseldorf, Germany) presented a brief history of the successful merger of the Leeds Castle Polyposis Group and the International Collaborative Group on HNPCC to form InSiGHT, with its first formal meeting in Newcastle UK in 2005. Altogether 25 active countries are represented in InSiGHT from Europe, North and South America, Middle East, Africa, Asia and Oceania. Gabriela Moeslein stressed the clinical relevance of the many areas of translational research being conducted by InSiGHT members including the detailed analysis of genotype-phenotype relationships in hereditary gastrointestinal malignancy. With the advances of molecular genetics, focus is now shifting from ascertainment of hereditary cancer through the disease phenotype to the interpretation of the entire range of molecular variants of the susceptibility genes.

The chair of NCI C-CFR Steve Gallinger (Toronto, Canada) described the C-CFR as a platform for research on the genetics of colorectal cancer including gene and environment interactions. A major goal of the C-CFR is to provide resources for interdisciplinary studies designed to understand the etiology and prognosis of colon cancer. He described the Phase 1 and 2 accomplishments of the C-CFR efforts since 1998, including clinic-based and population-based studies. About 7,400 probands, 30,871 family members and 5,050 controls have been enrolled in six centres in the US, Canada and Australasia. The goals of Phase 3, initiated in 2008, were also reviewed including expansion of the number of families enrolled through clinic-based recruitment. Steve Gallinger stressed the extensive biospecimen resources, consisting of blood, paraffin-embedded and frozen tissue and transformed cell

This study is conducted for the InSiGHT, HVP and NCI-CCFR Meeting Participants: G. Moeslein, S. Gallinger, R. Cotton, M. Genuardi, S. Tavtigian, G. Byrnes, A. Spurdle, I. Bernstein, N. de Wind, M. Nystrom, R. Hofstra, M. Woods, J. den Dunnen, B. Bhapat, M. Qi, P. Propping, H. Vasen, S. Povey, R. Sijmons, H. Thomas, J. Baron, S. Thibodeau, A. Boussioutas, J. Young, M. Jenkins, M. Dunlop, R. Houlston, I. Tomlinson, U. Peters, D. Ahnen, S. Parry, B. Parry, R. Scott, G. Hannan.

M. Kohonen-Corish (✉)
Cancer Research Program, Garvan Institute of Medical Research, 384 Victoria Street, Darlinghurst, Sydney, NSW 2010, Australia
e-mail: m.corish@garvan.org.au

T. K. Weber
State University of New York at Downstate, Brooklyn, NY, USA

A. Lindblom
Karolinska Institutet, Stockholm, Sweden

F. Macrae
Department of Medicine, and Colorectal Medicine and Genetics, The Royal Melbourne Hospital, University of Melbourne, Grattan St, Parkville, VIC 3050, Australia
e-mail: finlay.macrae@mh.org.au

lines, and clinical follow-up data available from the CFR to investigators and the enthusiasm of the CFR to promote collaborative relationships with InSiGHT and the HVP.

The Convenor of the HVP and President of the Human Genome Variation Society Richard Cotton (Melbourne, Australia) provided a history of the Human Variome Project and its progress to date. The major aim of the HVP is the collection and distribution of all human genetic variation affecting health, and involves community activity to collect this information for databasing. The HVP stems from the HUGO-Mutation Database Initiative (1995) and was formally established in Melbourne, Australia in June 2006. A HVP/InSiGHT Colon Cancer Pilot project was initiated in 2007 to collect variants of the colon cancer susceptibility genes and several other similar large-scale projects are underway. Excellent progress has been made with the successful inclusion of the InSiGHT Mutation Database in the Leiden Open Variation Database (LOVD).

Plenary session A. Unclassified variants in MMR genes

Session I moderator Maurizio Genuardi (Florence, Italy) is the Chair of the InSiGHT Variation Interpretation Committee. He introduced Sean Tavtigian (Lyon, France), who presented a Report from the International Agency for Research on Cancer (IARC) Unclassified Genetic Variants Working Group. This Group met in Lyon, France in February 2009 together with members of InSiGHT to develop an algorithm for interpretation of unclassified variants (UV) in the mismatch repair (MMR) genes. Other contributors for this Report included Graham B Byrnes (Lyon, France), Maurizio Genuardi and Amanda Spurdle (Brisbane, Australia). Sean Tavtigian provided a comprehensive review of the systematic approach of IARC to the classification of BRCA1 and BRCA2 variants of uncertain pathologic significance. This includes an initial *prior probability* of pathologic significance based on multiple factors including the sequence position of the variant and *in silico* missense analysis. The prior probability value is combined with a likelihood ratio (LR) that takes into account co-segregation, co-occurrence, family history summary and tumor histopathology. This produces a classification system based on the IARC/WHO carcinogen evaluation system, including a 5-grade model with Posterior Probability (P) cutoffs (Plon et al. [1]). Class 5 includes pathogenic variants with Posterior P greater than 0.99, Class 4 includes likely pathogenic ($0.95 <$ Posterior $P \leq 0.99$), Class 3 unclassified ($0.05 <$ Posterior $P \leq 0.95$), Class 2 likely neutral ($0.001 <$ Posterior $P \leq 0.05$) and Class 1 neutral variants (Posterior $P < 0.001$). Sean Tavtigian then presented a model adapting the IARC BRCA1 system to the MMR genes and a collaborative project proposal with the members of InSiGHT, based on the outcome of the meeting at IARC in February 2009. This project aims to (1) quantitate independent characteristics of carriers of pathogenic mutations in MMR genes, such as MSI status of tumour, functional MMR protein variant assay data, clinical information including segregation where available, and computational biological predictions for the effects of amino acid substitution and nucleotide position; (2) use LR estimates for independent predictors of mutation status to evaluate MMR gene UVs by the multifactorial likelihood modeling approach. Sean Tavtigian also presented, on behalf of Amanda Spurdle and himself, a formal proposal to access MSI and other pertinent clinical information from known pathogenic carriers and also non-carrier reference patients that is submitted to the InSIGHT database, in order to develop the relevant LRs for application to UV classification.

Finlay Macrae presented the template for phenotype descriptions for annotation to the InSiGHT variant database, together with Inge Bernstein (Copenhagen, Denmark; InSiGHT Phenotype Committee). UVs continue to be a major challenge in clinical practice and phenotype data are important in assisting with interpreting the probability of pathogenicity. In 2007 Finlay Macrae and Annika Lindblom (Stockholm, Sweden) proposed a phenotype minimum dataset on the InSiGHT website. This has now been further developed at the IARC meeting in Lyon in February 2009 (Table 1), to encourage submission of data that can be used in variant classification.

This system includes five optional levels of data entry associated with the variants and can be selected by the submitter. However, InSiGHT strongly recommends that the submitter uses simple phenotype parameters to describe the *summary family history*, which could then be used to inform the Bayesian probability analysis of risk for any UVs identified. These phenotype parameters are often collected for the assessment of likelihood of a mutation being present in the family and include age at diagnosis, gender, location of the tumour, presence or absence of synchronous or metachronous tumours or endometrial

Table 1 The minimum phenotype dataset that should accompany all submissions of mutation data to the Colon Cancer Gene Variant Databases in LOVD

Five optional levels of data entry associated with variants selected by submitter[a]
1. No phenotype data
2. Family history of colorectal cancer (Yes or No)
3. Fulfils Amsterdam Criteria of HNPCC (Yes or No)
4. Summary family history
5. Pedigree (for Segregation)

[a] Developed at the IARC and InSiGHT Workshop in Lyon, France, February 2009 and endorsed by InSiGHT at this meeting

Table 2 Summary family history phenotype dataset (modified from Barnetson et al. [2]) that can be entered with mutation data to the Colon Cancer Gene Variant Databases in LOVD

Stage 1. Information on the proband and the family
Proband or relative of proband (index case)
Age is expressed in years at time of diagnosis
Gender
Location: proximal/distal
Synchronous and/or metachronous tumours
Family history
Three possible colorectal cancer family history (CRCFH) categories
CRCFH(< 50) = 1 and CRCFH(≥ 50) = 0 (youngest affected first degree relative was aged < 50 years)
CRCFH(< 50) = 0 and CRCFH(≥ 50) = 1 (youngest affected first degree relative was aged ≥ 50 years)
CRCFH(< 50) = 0 and CRCFH(≥ 50) = 0 (no affected first degree relatives)
Family history of endometrial cancer:
ECFH = 1 if there are any first degree relatives with endometrial cancer
ECFH = 0 if none.
Stage 2. Additional mutation analysis
Immunohistochemical analysis of tumour (MLH1, MSH2, MSH6 and PMS2)
MSI testing of tumour
Stage 3. Additional familial data and co-segregation
Number of HNPCC affected persons in the family
Pedigrees

cancer and the family history category according to the age of onset of the youngest affected first degree relative (Table 2; Barnetson et al. [2]). This template will be added to the InSiGHT LOVD database, with a computation that will assist submitters in gauging if a mutation is likely to be present in the family; it will also be incorporated into the Bayesian analysis of pathogenicity assignment being developed by IARC/InSiGHT.

Niels de Wind (Leiden, the Netherlands), Minna Nystrom (Helsinki, Finland) and Robert Hofstra (Groningen, the Netherlands) presented the progress made in assigning pathogenicity to UVs of the MMR genes through functional assays. Most successful assays are based on in vitro MMR assays where the sequence of the UV is generated by PCR, incorporated to the wild type sequence of the gene and expressed in insect cells or, recently, in vitro. The ability of the resulting mutant protein to correct DNA mismatches is assessed in a standard assay and the efficiency of repair is then compared to wild type MMR protein. Some mutations require further analyses (see Couch et al. [3]). Niels de Wind also described the generation of 'reverse diagnosis maps' to help identify pathological variants. These are generated by producing a large set of MMR-deficient cell lines that each carry a random missense mutation, that disrupts gene function, in a cognate MMR gene. These cell lines are then characterized for the position and nature of the mutation. Since many of these mutations are also found in undiagnosed Lynch syndrome patients the information on the position and nature of these mutations can be used to define pathogenicity of the mutation in the patient.

In summary, significant progress has been made in elaborating a classification system for MMR gene UVs, including functional assays as well as *in silico* models to evaluate the clinical significance. However, functional assays are still labor intensive although the complete in vitro variant of the assay may have improved applicability. Also, to improve success a validation set of variants is required and this can only be achieved by a world-wide collaborative effort.

Annika Lindblom presented the results of a large case–control study in Sweden, which determined the frequency of six common UVs of the APC, MLH1, MSH6 and MUTYH genes in sporadic colorectal cancer patients and healthy controls. The study determined the odds ratio (OR) of each variant in contributing to the risk of developing colon or rectal cancer. Annika Lindblom emphasized the need to collect data on UVs world-wide to get better estimates of the cancer risk associated with all variants of the colorectal cancer susceptibility genes. She proposed an InSiGHT campaign to promote the submission of UVs with phenotypic data to the LOVD.

A vigorous discussion followed with audience members presenting opposing views about the value of such studies in terms of the high workload involved and whether cancer risk can be reliably assessed with population studies as opposed to determining the family history. However, family studies can be problematic as well and many diagnostic laboratories are geared to do large-scale testing but not necessarily family studies. If a large enough amount of data is collected from the population, this is still significant. In any case, there was strong support in the meeting that InSiGHT initiates this campaign and the discussion was continued in a special session the next day.

The subsequent special meeting endorsed Finlay Macrae's and Annika Lindblom's proposal for InSiGHT to adopt the minimum phenotype dataset to accompany all submissions of mutations and variants to the LOVD (Table 1). This encourages the submission of UVs even if phenotype information is not available. It was suggested that the pedigrees are not included in the public section of the Database but access can be given on the discretion of the Curator. The database should be modified to allow the submitter to indicate if a pedigree is available from the submitter directly. It was also discussed what additional

data could be reported to increase the value of data collection. Segregation data on the mutations and UVs should be included, possibly separate from pedigrees. Sean Tavtigian explained that in breast cancer families both the pathogenic mutation and polymorphisms are reported to the central database and that this provides powerful haplotype information. He suggested that SNPs should also be reported together with the pathogenic mutations for the colorectal cancer genes. It was commented that the database should be modified so that the submitter can indicate whether other variants and SNPs were investigated or not, if none are reported. Laboratories can use their own family IDs to enter data on each mutation or variant.

It was resolved that InSiGHT initiates a "Global MMR Variant Submission Campaign", creates a list of reporting labs on their website, reports of the activity in Human Mutation and in the InSiGHT meeting in 2011 and emphasizes the rewards of this effort, which will provide easier interpretation of UVs.

Plenary session B. Databasing including uploading and responses from InSIGHT/LOVD

Session moderator Michael Woods (Newfoundland, Canada) introduced the first speaker Johan den Dunnen (Leiden, the Netherlands), the developer of the Leiden Open Variation Database (LOVD). He presented an overview of the organization of the database, and the various levels of management and curation. LOVD includes data from many different diseases and genes. Currently 6 genes are included for colorectal cancer MLH1, MLH3, MSH2, MSH6, PMS1 and PMS2. The website address is http://chromium.liacs.nl/LOVD2/colon_cancer/home.php. Each gene has its own database curated by a group of experts in the field. The colorectal cancer gene databases were merged in January 2008 from the MMR Database (created by Michael Woods), the InSiGHT Database (Hans Vasen and Paivi Peltomaki) and the MMRUV Database (Rolf Sijmons). There are currently 12,375 entries and 2,651 unique variants. Each month, the database receives 20,000 hits.

Bharati Bapat (Toronto, Canada) described the status of hereditary nonpolyposis colorectal cancer (HNPCC) gene testing in Canada and her experience on uploading data to the InSiGHT LOVD. Initial mutation analysis is carried out with MLPA followed by sequencing. LOVD is easy to use for uploading, but there are some areas for improvement, such as the Mutalyzer function causing an error message and the need to enter multiple occurrences for one variant. There should also be an option to bypass the need to enter a patient ID and allow group submission. Johan den Dunnen commented that the patient ID is mandatory but this is not shown in the public area of the Database. Ming Qi (China) reported on the establishment of the HVP-China Consortium from 11 institutions in 2008. The consortium, led by the Zhejiang University, has to date submitted 944 variants in 20 genes across three major diseases and specifically 19 MMR mutations unique to the Chinese population. Peter Propping (Bonn, Germany) reported on the German experience with LOVD, with over 1,000 MMR variant entries to InSiGHT LOVD, many of which are the same variants. He raised a question as to how often a variant should be entered. There is also reluctance to enter phenotype data, such as the pedigree, because individuals can be identified. Also, patient consent does not specifically include entry of data on a website. Johan den Dunnen commented that pedigrees could be put on the non-public part of the database and people have to register to see all data. Michael Woods commented that there is, and should be, no cap on the number of entries per variant.

Thomas Weber (New York) presented an analysis of all MMR gene sequence variants and mutations submitted to the InSiGHT Database curated by Paivi Peltomaki (Helsinki, Finland) and Hans Vasen (Leiden, The Netherlands) from investigators around the world from the time of the database's inception under the International Collaborative Group on HNPCC in 1994 to the completion of the upload of the InSiGHT database to the LOVD in November of 2008. The goal of the project was to improve understanding of the molecular genetics of MMR gene associated colorectal cancer incidence by providing a novel frequency analysis of pathologic alleles and unclassified variants organized by MMR gene, exon, codon and specific nucleotide change. The analysis included the number of independent reports for each unique alteration and also tallied the country of origin. Following a preliminary report to the HVP Planning Meeting in Barcelona in May of 2008, this effort was adopted as a component of the InSiGHT Pilot Project of the HVP. In the completed summary presented in Duesseldorf a total of 884 MMR alterations were reported including 632 unique alterations of which 531 were reported as pathogenic. Interestingly only 122 of the pathogenic mutations were reported more than once, underscoring the heterogeneity of alterations associated with the HNPCC phenotype. High frequency UVs associated with the colorectal cancer phenotype suggest alterations that warrant further study regarding pathogenicity. The analysis provides documentation of the status of the InSiGHT Database just prior to the LOVD upload and also suggests a number of analysis templates that could be applied to the LOVD MMR data as it accrues.

Richard Cotton gave a presentation on the ethical issues arising in the HVP, on behalf of Sue Povey (London, UK) the curator of the Tuberous Sclerosis Mutation Database. There are more than 750 locus-specific mutation databases mostly maintained by committed individuals and all share the

problem of too little funding and the ethical problem of collecting unpublished data mainly from diagnostic laboratories. Samples sent to genetic diagnostic labs for testing do not usually include explicit consent for sharing results in a public database, and it is often not practical to obtain consent afterwards. However, the data may be very valuable and it may be unethical to withhold the anonymised data. A HVP Working Group has developed guidelines, which address all the ethical issues, to assist database curators who provide access to the information via a web interface. A manuscript is in preparation. In future research projects, consent forms should specifically indicate what data will be included in a publicly available database and describe its intended use. Also, patients and families requesting genetic testing in the diagnostic laboratory setting should be asked to complete a consent form for sharing data for research.

Suggested wording for the consent form: "I understand that the interpretation of DNA test results, including my own is based mainly on publicly available data from other patients that were tested before me. I agree that the results of my DNA test and clinical examination may be added to these public data sets, in the accepted manner, which does not disclose my personal identity. This information will then be available to help the diagnosis of new patients, and to further understanding about the disease. Improved understanding of the molecular mechanisms of disease may be important in developing new treatments and/or prevention. Any information which could identify me or members of my family may only be stored when a high standard of privacy and confidentiality, (as defined and in accordance with national standards for health data), is maintained. I understand that I will not receive any payment for this."

Rolf Sijmons (Groningen, the Netherlands) reported on the success of a national Locus Specific Database created in the Netherlands as a response to the need to classify the MMR gene UVs, across eight academic laboratories involved in MMR gene testing. The next step is the creation of a virtual Dutch variants database within the LOVD. This will include protected comment fields for internal communication. Members of the audience indicated that similar national initiatives have been established or are being planned in Australia, UK, China, Denmark and Canada.

Richard Cotton closed the session, and highlighted the need to streamline the uploading of data to the LOVD as diagnostic laboratories have limited time.

Concurrent session C. Risk and prognosis of CRC to relatives in Type X and related familial risk pedigrees

Huw Thomas (London, UK) and John Baron (Lebanon, New Hampshire) and others presented a proposal for two collaborative studies. The first study aims to investigate the phenotype and outcome of colonoscopic surveillance in dominant colorectal cancer families without evidence of MMR deficiency (Type X families). Criteria for family selection: families with dominant history of colorectal cancer, i.e. three-first-degree relatives affected over two generations, but >50% of tumors negative for MSI and normal MMR immunohistochemistry. About 140 such families have been collected so far. Data required: family history of cancer, patient age and gender, the details of colonoscopic surveillance and pathology of any tissue removed. No specimens need to be sent. The second study aims to assess the age and gender-related adenoma incidence and prevalence in asymptomatic individuals undergoing colonoscopic surveillance. Criteria for patient selection: individuals from Lynch syndrome families who are negative for a known family mutation and have been undergoing colonoscopic surveillance. Data required: patient age and gender, the details of colonoscopic surveillance and pathology of any tissue removed. Ethics approval is not required because these are evaluation studies.

Concurrent session D. BRAF status in cancers occurring in PMS2 carriers

This session was chaired by Stephen Thibodeau (Rochester, Minnesota) and focused on the immunohistochemistry and mutation analysis of MLH1 and PMS2 genes in HNPCC patients. Alex Boussioutas (Melbourne, Australia) reported on the significance of the combined loss of MLH1 and PMS2 as determined by immunohistochemistry in cancer tissue, which is traditionally thought to be an indication of a germline mutation in MLH1. However, methylation and somatic loss of expression of MLH1 can also occur in HNPCC. He proposed a collaborative study to evaluate the significance of the combined loss of MLH1 and PMS2 in the tumor and the value of testing for PMS2 mutations in cases where no mutation is found in MLH1. Joanne Young (Brisbane, Australia) reported on similar findings in their patients and also on the low frequency of BRAF mutations in PMS2 deficient cancers.

Concurrent session F. GWAS studies

Mark Jenkins (Melbourne, Australia) chaired a session on genome wide association studies (GWAS) in sporadic and non-HNPCC familial colorectal cancer. Malcolm Dunlop (Edinburgh, UK) presented an overview of recent large collaborative studies in the UK, led by Malcolm Dunlop, Richard Houlston (Sutton, UK) and Ian

Tomlinson (Oxford, UK). This included results of a meta-analysis of two GWAS studies comprising 13,315 individuals genotyped for 38,710 common tagging SNPs (Nat Gen 2008 Dec;40(12):1426–35). Pooled data obtained by the UK team detected 10 loci that taken together account for ~6% of excess familial risk of colorectal cancer. These results included loci on 8q24 (rs7014346) and 8q23 (rs16892766) and importantly also included SNP associations that tagged multiple TGF-Beta signaling pathway genes. Ulrike Peters (Seattle, Washington) presented an overview from an international perspective of the progress and status of multiple GWAS studies on colorectal cancer. Planned studies incorporate GWAS meta-analysis, large-scale replication studies, fine mapping of susceptibility regions, functional follow-up on candidate SNPs and epidemiologic studies. The largest planned collaborative study "Transdisciplinary Study of Genetic Variation in Colorectal Cancer" (contact P.I. Steve Gruber, Ann Arbor, USA), will include over 38,000 cases world-wide and attempt to identify novel colorectal cancer predisposition loci and explore gene-environment interactions including diet, smoking, alcohol and menopausal status.

Discussion during this session was at times spirited and focused on several issues including what some audience members perceived as only modest odds ratio results supporting the colorectal cancer susceptibility loci reported to date from GWAS. Lack of reproducibility in suggesting candidate loci across methodologies such as familial linkage analysis and GWAS was noted. Members of the presenting panel vigorously defended the progress accomplished on the GWAS platform. Nevertheless audience members noted the considerable resources invested in the GWAS paradigm. Some suggested robust discussion of its current limitations and future refinements would be helpful as part of a larger discussion seeking to define future complementary collaborative approaches to identifying CRC predisposition loci. It was also noted that the InSiGHT biennial meetings provide important opportunities to solicit input on fundamental theoretical questions from a diverse range of experienced clinical and basic science hereditary colorectal cancer investigators.

Concurrent session G. Other studies

This clinical session focused on the surveillance and management of patients with colorectal cancer. Dennis Ahnen (Denver, Colorado) presented on cancer risk, screening and surveillance of family members of patients with sporadic MSI-H colorectal cancer. The consensus was that the familial risk in this group appeared to be about the same as for sporadic MSS colorectal cancer. The CFR has already examined their dataset regarding this question. There was agreement that the question of whether there is concordance of MSI-H cancers and their precursor lesions (serrated polyps) in family members of MSI-H cancers was clinically and scientifically important and worthwhile pursuing. The hypothesis would be that there is a higher prevalence of serrated polyps and MSI-H cancers in family members of patients with sporadic MSI-H cancers than in family members of patients with sporadic MSS cancers.

Susan Parry and Bryan Parry (Auckland, New Zealand) and Gabriela Moeslein suggested a project to answer the unresolved issue of surgical options in colorectal cancer patients at young age (<50) or with a familial predisposition. Bryan Parry presented a review of the literature, which shows that, to date, there is no clear evidence in favour of either mere oncological resection or extended surgery, with the aim of preventing or at the least reducing metachronous colorectal cancer. However, extended colectomy leads to complications, such as increased bowel frequency, some incontinence, restricted lifestyle and an overall deterioration in quality of life. Nevertheless, surgeons are frequently performing subtotal colectomies, especially in Anglo-American countries. The questions requiring clarification are: (1) Can metachronous cancer risk be defined more exactly for the subgroups of young patients? (2) Can existing databases be interrogated for this purpose? Gabriela Moeslein presented a collaborative proposal on behalf of the Mallorca Group, which has agreed to perform a retrospective analysis employing well-validated questionnaires from the EORTC (QLQ-C30 and QLQ-CR38) with an additional question: "To what extent are you troubled by your surveillance examinations?" Inclusion criteria are as follows: Colectomy due to colorectal cancer (age < 50); surgery at least 6 months ago; HNPCC defined as Amsterdam criteria positive and/or MMR deficient tumor. The simultaneous discussion of both presentations clearly led to unanimous support for a collaborative effort, also endorsed by present members of the CFR.

Plenary session E. Novel studies in familial CRC

Rodney Scott (Newcastle, Australia) reported on the current status of studies on modifiers of the MMR genes. Several candidate genes initially looked promising but results have not been replicated. These include ATM, TP53, NAT2, GSTM1, GSTT1, GSTP1, DNMT3B and Aurora kinase. Other genes have been confirmed as modifiers in independent studies and include Cyclin D1, IGF1, MTHFR and RNASEL. Garry Hannan (Sydney, Australia) presented the Australian proposal to identify further modifiers of MSH2 and MLH1 through GWAS and CNV analysis. Risk of colorectal cancer in MMR gene mutation

carriers decreases after the age of 55. Similar findings have been made in BRCA1 mutation carriers. Reported modifier genes of the Lynch Syndrome do not explain all of the age-related risk. The proposed study will analyse genomic DNA from >5,000 carriers of MLH1 and MSH2 mutations on SNP and CNV arrays and carry out an unbiased GWAS. Multiple funding applications are in place for the study. C-CFR and InSiGHT members are invited to collaborate and contribute material for the study. Ian Tomlinson (Oxford, UK) reported on the status of linkage studies to identify new bowel cancer genes. Several new chromosomal regions have been identified and published to date on Syndrome X Families, and efforts to identify the genes are continuing.

In closing, Richard Cotton emphasized the value of continued collaborative interaction between C-CFR, HVP and InSiGHT. C-CFR is very interested in having InSiGHT members to apply to use biospecimens. He presented a list of possible funding sources for the combined projects. These included Bill and Melinda Gates Foundation, IBM, KECK, NIH, The Wellcome Trust and the European Commission. InSiGHT-specific funding opportunities could be advertised as "Adopt a Gene for Curation" to Gastrointestinal Cancer support groups, specific drug companies and diagnostic companies. InSiGHT will need to employ a Coordinating Project Officer to promote submission of variants world-wide (pathogenic and uncertain), manage curation and also manage the international interpretation committee. He highlighted a number of relevant meetings coming up, including "The Impact of Next Generation Sequencing" organized by the Human Genome Variation Society in Hawaii, October 2009, "Spotlight on Neurogenetics", organized by the HVP in Hawaii, October 2009 and the HVP Implementation Meeting in Paris, May 2010.

References

1. Plon et al (2008) Sequence variant classification and reporting: recommendations for improving the interpretation of cancer susceptibility genetic test results. Hum Mutat 29:1282–1291
2. Barnetson et al (2006) Identification and survival of carriers of mutations in DNA mismatch-repair genes in colon cancer. New Engl J Med 354:2751–2763
3. Couch et al (2008) Assessment of functional effects of unclassified genetic variants. Hum Mutat 29:1314–1326