

Differentiated Thyroid Cancer International Genetics Consortium

Held on June 5, 2008 in Rockville, MD.

Attendees:

Erich Sturgis, Parveen Bhatti, Alina Brenner, Houda Boukheris, Guojun Li, Antonia Velásquez, Florent de Vathaire, Pauline Brindel, Markhaba Tukenova, Jorge Gaspar, Rebecca Leboeuf, Hank Juo, Tomo Hayashi, Roy Shore, Raffaele Ciampi, Yuri Nikiforov, Mingzhao Xing, Siegal Sadetzki, Marco Cappezzone, Marco Pierotti, Ricardo Giannini, Fulvio Basolo, Laura Ward, Ruth Pfeiffer, Jeff Yuenger, Sam Wells, Elaine Ron, Maureen Hatch, Alice Sigurdson

Working and Discussion Sessions Summary

Overview, vision, perspective

Alice Sigurdson stressed that NCI will play the role of facilitator and can offer the infrastructure to help get the consortium started. But the group must decide what “directions” the consortium will go. Yuri Nikiforov expressed the need of the group to first set goals and decide on what the group would like to achieve before getting into any discussion on data collection issues. Alice mentioned that although germline polymorphism association analyses was the initial goal, many of the investigators were also interested in clinically related research questions. Erich Sturgis reminded the group that the primary goal for putting a consortium together is for genetic association studies and potentially interaction analyses that are difficult for individual studies to conduct. Both Yuri and Erich expressed the need to keep the goals as simple as possible since the more clinically oriented research questions would be difficult to pursue.

The group did not raise any objections to making genetic association studies the primary and initial focus. Alice discussed potential phases of the study :

- First phase of the study would involve pooling existing polymorphism data
 - NCI could facilitate this initial pooling
- In the second phase the pooled studies could be used to evaluate “hot” SNPs identified in the individual studies.

- Replication of Antonia Velazquez's and Yuri Nikiforov's findings with polymorphisms on chromosome 1 were mentioned, also XRCC3, but there are several others that should be carefully weighed. Those with current genotyping potential should consider which SNPs, possibly in conjunction with a meeting of the executive committee (newly formed), might be done. Also replication of "hits" from the iSelect.
- Third phase could involve genome-wide association analyses
- Interaction or sub-group analyses could be conducted in the fourth phase

Alice Sigurdson discussed the potential role of the NCI in each phase of the analysis but expressed that the NCI did not need to be the central institution for the consortium. Erich gave an example of how having IARC as the central institution for the INHANCE consortium was very helpful.

Issues in Case-Control Association Studies to Detect Disease-Associated SNPs

Ruth Pfeiffer touched on a variety of statistical issues:

- Selection bias in genetic studies
 - Family history can influence participation of controls
- Confounding
 - Population stratification
 - Adjusting for ethnicity does not necessarily "take care" of it
- Differential genotyping error
- Cryptic relatedness
- Power
- Multi-stage designs

The bulk of the discussion focused on the pros and cons of various multi-stage designs and the need for a "proper" strategy when implementing these designs.

Control selection & co-factor collection: issues & ideas

After Houda Boukheris' presentation, Roy Shore raised the issue of disparate questionnaire data between the case-control studies of the different collaborating centers. Alice suggested that those studies that collected co-variate data should send the questionnaires to each other to determine how the data could be merged. Elaine Ron suggested that centers that have relevant expertise should take the lead on merging or consolidating specific questionnaire data.

Core Genotyping Facility, sampling handling, QC

Yuri Nikiforov asked Jeff Yeunger about the turn around time of the CGF for GWAS analyses of samples. Jeff gave an estimate of two months depending on the platform that is used. Costs are better compared to commercial genotyping companies, assuming there was an NCI requestor.

Not discussed explicitly, but needs to be addressed, is the individual study QC procedures and number of replicates etc. This might also be taken up by the executive committee (newly formed).

Candidate SNP selection

Erich suggested starting with the pooling of existing SNP data that overlaps between the studies, but mentioned the need for someone to take the lead on grant applications for additional consortia genotyping. The initial pooled analysis would help the grant application(s). Yuri supports the notion of phase one of the study, but was skeptical that we would receive funding regarding his first cost evaluation (upwards of \$5 million) for a GWAS. He suggested to consider writing a grant highlighting a radiation-induced susceptibility “angle” to get the project funded and then to write further grants according to the following objectives. Citing her experience with BTEC, Siegal Sadetzki does not

think that funding will be difficult to receive. On the other hand, it still takes a devoted person or team to write a grant.

Consortia models of operation, authorship, funding

The group discussion favored the formation of core working groups such as the working group for consolidation of questionnaire data.

Erich discussed different authorship scenarios. For example, two authors per center with additional individuals if additional people are involved. However for Yuri there is no specific rule for the number of co-authors per center and for Marco Pierotti, the number of co-authors will depend on the amount of data that each center will provide for the consortium. Also, Marco stressed we should try to promote the careers of young people. Maureen Hatch suggested the model of the writing group who write “for” the consortium with the members listed in an acknowledgement. Siegal suggested that authorship considerations cannot be properly considered until publications are prepared and journals are selected for submission. There are several models to follow and there was no true resolution to the authorship issue. Alice observed that as the prestige of the journal increases, so too does the number of authors.

Infrastructure (e.g. portal), practical issues (e.g. IRB)

The idea of a portal for the consortium was suggested, however Elaine suggested waiting to determine if a portal will be necessary after the consortium is “up and running” for a few months. Yuri thought a website would be the most important to establish early on.

What studies to do, tumor tissue ideas, etc.

Alice suggested getting genotyping “rolling” for those institutions that have the resources and capabilities. Alice will lead the initial pooled analysis. Siegal suggested that in addition to the oversight committee we need working groups for “other” aspects of the consortium/study. Siegal pointed out the importance of understanding data collection in terms of biological samples (tubes, how to ship, how to extract DNA, storage, etc). She suggested additional working groups to develop and harmonize the questionnaires, but also working groups to consult about help in collecting biological samples according to procedures that will minimize divergences between the centers.

Consortium name and acronym

Undecided (see attached email for a “vote”).

Investigator Action List

- To help the preparation phase of the consortium moving along faster, working groups among collaborators should be designed to develop specific sections of the questionnaire that will help collecting data (especially on co-factors) with homogeneity in all participating centers: (e.g. a working group for a section on ionizing radiation exposure history, a working group for the section diet, another working group for hormonal and reproductive history...etc). The working group would include the following members
 - Siegal Sadetzski
 - Eric Sturgis
 - Florent de Vathaire
 - Tomo Hayashi
 - Alice Sigurdson
 - Hank Juo
 - Antonia Velasquez
 - Laura Ward

- An executive oversight committee should be put in place and its members designated among collaborators. The following members volunteered or were urged to be on the committee:
 - Hank Juo
 - Pierotti Marco
 - Alice Sigurdson
 - Eric Sturgis
 - Florent de Vathaire
 - Siegal Sadetzski

Wrap-up

Alice asked if those present at the meeting knew of any additional groups that should be included. Roy Shore asked if more Asian populations should be considered. Also Martin Schlumberger should be asked. Please suggest others as you think of them.