Genetics of Diabetes and Its Complications: Consortia Meeting

Holiday Inn Select
Bethesda, Maryland

July 20, 2005
Executive Summary

Introduction and Background

Dr. Josephine Briggs of the NIDDK and Ms. Margery Perry of the Juvenile Diabetes Research Foundation (JDRF) made opening comments. As outlined by Dr. Briggs, this workshop was convened in response to specific recommendations of the Expert Panel on the Special Statutory Funding Program for Type 1 Diabetes Research in their January 2005 meeting. The Panel strongly encouraged enhanced coordination between the four major genetics consortia supported by the special statutory program to facilitate exchange of data and distribution of valuable research materials. The four studies are:

a) FIND (Family Investigation of Diabetes & Nephropathy)
b) GoKIND (Genetics of Kidney Disease in type 1 diabetes)
c) EDIC (Epidemiology of Diabetes Interventions and Complications Study) Genetics
d) the Type 1 Diabetes Genetics Consortium.

The purpose of the workshop was to develop recommendations for facilitating interactions among the studies and for future analytic strategies. Ms. Margery Perry, chair of research for the Juvenile Diabetes Research Foundation, emphasized the importance of consortial interactions to enhance the value of the individual studies that aim to develop new strategies for prevention and treatment to alleviate the suffering from type 1 diabetes.

Study representatives presented a broad outline of each study. In addition, Dr. John Todd provided an overview of five major European studies with relevance to diabetic complications (Oxford Regional Prospective Study, Nephropathy Family Study, Golden Years study, EURODIAB, and EURAGEDIC). In preparation for this workshop, the study groups had participated in an exercise to identify common variables. Mr. Phil Cooley and his colleagues from the NIDDK Database Repository at RTI presented the results of that exercise. The table assembled was provided to all workshop participants.

Summary of discussion

As summarized by Dr. Michael Boehnke, the subsequent discussion focused on several areas:

1. Goals – the overall goal is to identify genetic variants that influence risk of DM and its complications. The prerequisites for accomplishing this goal are:

    a. Information on all the studies must be conveniently available.

    b. It must be easy to determine the numbers of specific types of samples available by combining across studies.

    c. A resource must exist to facilitate combining data across studies.

2. Phenotypes – the meeting participants discussed various questions related to the issue of phenotype:

a. Should all phenotypes be considered?

b. One key variable should be diabetes duration (lifetime exposure to hyperglycemia).

c. It may be difficult to combine across studies when the traits have a large variance.

d. Genetic effects may be small relative to covariates (measured or not), such as environment. This will impact design significantly, so one approach is to choose an extreme, well designed set.

e. It is very important to have some phenotypic measures that are all from a single laboratory.

f. Genotyping data can and should be used to assess and account for varying genetic backgrounds of participants.

g. An additional interesting avenue of investigation may be clustering of complications

h. One difficult question is how to approach using repeated measures (as from the EDIC study) versus point-in-time measures (from the other studies). One way is to use summary values.

3. Genotypes

a. Which data should be provided? In terms of the data that are provided in the common database, the database should publicly post the methods, markers genotyped, definitions and qualitative descriptions of the sample set. Investigators will have to apply for access to the actual raw genotyping data (to assure that human protection and privacy

regulations are followed). There was some discussion of whether to provide derived data as well.

b. Issues related to QC and updating must be addressed:
    1. It is important to track the investigations using the samples;
    2. check agreement of duplicates;
    3. standards need to be established with respect to the minimum size of data that will be accepted into the database and minimum QC requirements.
c. One key issue is whether to do genome-wide association study on all samples and how to plan this.

4. Samples – there are numerous questions related to genetic samples from the studies, in terms of what is available:

a. How will the samples be selected for whole genome association studies?
b. What will be the conditions for sharing?
c. What should be the policies with non-renewable samples, such as serum and urine?

5. Practical concerns – there are numerous practical issues in going forward, including:

a. Informed consents must be consistent with proposed studies.
b. Need for defined data release plans and procedures for phenotypes, genotypes, samples.
    1. Should summaries and fundamental ('vanilla") analysis results be posted?
    2. What should be public and should be available by application?
c. Data curation and maintenance is crucial.
d. There must be mechanisms for addressing continuing user feedback.
e. There is a continuing need for improved analytic methods.
f. How should the results be disseminated?

Conclusions and Recommendations of the Workshop

1. High throughput genotyping and "WGA (whole genome association)" analysis represents the obvious next research opportunity. The initial round of genotyping, testing several hundred thousand markers on each sample and covering every identified gene, should be carried out with

sample sets focused on individuals with an extreme, highly heritable phenotype and relatively limited size (<5000)

2. One possible less costly scheme is to do much less genotyping, but analyze every sample. For example, genotype a small set of approximately 3000 markers in every sample. This would allow candidate gene analyses, focusing only on variants in genes of interest.

3. After the candidate gene analyses, selected samples could be genotyped for markers in virtually every gene in a high-throughput "WGA" study.

4. In addition, it is worthwhile considering the possibility of specifically recruiting patients with the most severe diabetic nephropathy (those with end-stage renal disease) and matched controls.

5. Consider providing guidelines for consensus phenotype definitions across all the studies.

6. Maintain a flexible approach driven by the science in selecting samples, genotyping methods and analytic approaches.

AGENDA

8:30 a.m. **Registration/Continental Breakfast**

9:00 a.m. **Welcome and Greetings –** Josephine Briggs, Margery Perry

9:15 a.m. **Overview of Studies (5-minute talk, 15-minute discussion):**

1. Type 1 Diabetes Genetics Consortium – Steve Rich (Wake Forest University)
2. EDIC Genetics – Andrew Paterson (Hospital for Sick Children, Toronto)
3. FIND – Barry Freedman (Wake Forest University)
4. GoKinD – Paddy Cleary (George Washington University)
5. UK Studies – John Todd (Cambridge University)

10:35 a.m. **Break**

10:50 a.m. **Common Variables –** Phil Cooley, NIDDK Database Repository (RTI)

11:15 a.m. **Future Analytic Strategies**

a. Phenotype, and Combining Longitudinal (EDIC) and Single Measure Studies
Discussion leader: Mike Steffes – *"common laboratory analyses: completed and possible"*

b. Finding Type 1 and Type 2 Diabetes Genes
Discussion leader: Joel Hirschhorn

c. Finding Nephropathy Genes
Discussion leader: Richard Spielman – *"testing candidate genes for diabetic nephropathy"*

d. Finding Complications (2+ phenotypes) Genes
Discussion leader: Craig Hanis

12:30 p.m. **Working Lunch**

3:30 p.m. **Recommendations**

4:30 p.m. **Adjourn**

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