MINUTES

Observational Study Monitoring Board

Framingham Heart Study

12/03/2009 Meeting

PARTICIPANTS:

OSMB Members Present: Russell Luepker (Chair), Alexander Wilson, Eric Boerwinkle, James Neaton, Mary Cushman, Philip Greenland

OSMB Members Absent: Charles Rotimi

Investigators: Cashell Jaquish, Marty Larson, Chris O'Donnell, Vassan Ramachandran, Phillip Wolf

Data Coordinating Center Staff: N/A

NHLBI Staff: Richard Fabsitz, Executive Secretary; Cheryl Jennings, Mona Pandey, Austin Sachs, Phyliss Sholinsky, Paul Sorlie, Gina Wei

INTRODUCTION

The regularly scheduled meeting of the Framingham OSMB was called to order at 8:30 am. Conflict of interest issues were reviewed before the meeting through the CSOS reporting system and no conflicts were identified.

STUDY DESCRIPTION

The Framingham Heart Study is a longstanding study of the NHLBI. It was initiated by NHLBI in 1948 and currently comprises three cohorts representing three generations that have participated in multiple exams over varying lengths of time and time intervals between exams. The original cohort has been examined every two years since 1948. The Offspring cohort has been examined periodically since 1971. The third generation has been examined once since 2000. Funding for the Framingham Heart Study current exam was continued in 2008 for seven years. A reexamination of all three cohorts is part of the current contract. The next exam of the Offspring Cohort will start in 2011; the 30th exam of the Original Cohort and second exam of the Third Generation are currently in progress.

STUDY PROGRESS

Scientific progress includes 117 publications during the last 12 months with approximately 30 focused on genetics. Exam 9 for the Offspring will begin in 2011. The second exam for GEN 3 will end in about one year with an estimated 3,200 participants. The original cohort exam will continue with about 180 projected exams, mostly in nursing homes as the youngest cohort member is now at least 94 years old. Exams are behind projection for the original cohort due primarily to their age and difficulty of scheduling and examining them. The GEN3 exam is behind projection for the cardiac CT component because the imaging center had to be changed to one farther away from Framingham. The CT has also generated more alerts for planned and incidental findings due primarily to age but also perhaps to higher resolution imaging and a wider scan area. All subjects get their coronary artery calcium (CAC) score, some also get alerts for abnormally high values. Clinical lab value reporting has been expanded from serum creatinine, triglycerides, cholesterol and glucose to include many more measures. In spite of this, very few abnormal values have been reported primarily due to the age of the GEN3 participants. Cell cultures and DNA plating continue to be established. A total of 8348 unique cell lines are now available. All shared DNA is now from cell lines. The DNA Review Committee meets quarterly and has developed a more expedited review for follow-up of GWAS due to the high demand and need for a timely response. Demand for DNA seems to have declined, perhaps because of the shared genotype/phenotype data sets now available.

RESPONSES TO THE OSMB RECOMMENDATIONS

OMNI Study

The OMNI cohort was initially examined in 1990. It includes 30% African Americans and 40% Hispanics. As recommended by the OSMB, the OMNI Study will be formally folded into the Framingham Heart Study around the end of the year. Most measures from the current exam will be extended to the OMNI cohort. Other adjustments resulting from this decision include a multi-lingual recruiter and greater emphasis on use of the telephone for contact. The Board indicated it was pleased to see the OMNI cohort merged into the Framingham Heart Study.

CVD Case Control Project in SABRE

The CVD incidence case control project within SABRE has been expanded to include 214 cases and 214 controls to increase power. This number represents all the available cases after exclusion of prevalent cases and those without appropriate consent. Controls will be matched to cases on age, sex and exam year. The Board suggested that the validation cohorts for this and other components of SABRE should be identified now to be ready for the next step as results are generated.

Return of Results for Calcification Study

After reviewing the literature and recent guidelines papers, the investigators have concluded that they should maintain consistency with the previous approach of reporting high levels based on the Hoff cut-points as there "continues to be no strong evidence for clinical guidelines that base treatment algorithms on CAC cut-points". This decision can be revisited as additional information becomes available.

Plan for Large Scale Sequencing

The study pursued and was successful in participating in the NHLBI Exome Sequencing Project. This will provide sequencing for a small number of Framingham Study participants and follow-up genotyping in a much larger sample of Framingham Study participants as variants are discovered. Plans are in place for analysis of the large amount of data expected in this effort as data storage capacity has been greatly expanded.

Imaging Expert for OSMB

Dr. Fabsitz was pleased to announce that the Institute has added Dr. Pamela Douglass from Duke University to the Framingham OSMB effective immediately.

Pulmonary Expert for OSMB

Dr. Fabsitz was pleased to announce that the Institute has invited Dr. Homer Boushey from University of California, San Francisco, to serve on the Framingham OSMB and his appointment should be official in the very near future pending final submissions and approvals.

Blind Duplicates for Requested Plate Sets

The investigators noted that the high cost of genotyping, particularly as we move into sequencing, has caused several applicants to request plates without duplicates and those have been honored. However, the default response to an approved request for DNA is a plate set with duplicates included.

More Detailed Report for Opt Out Opportunities in Informed Consent

The investigators provided a detailed report of those who have opted out of allowing their samples to be used for any of the options provided in the informed consent process. The original informed consent was less specific about the uses of the genetic data but only 1.8%, 1.5% and 0.27% refused to allow their DNA to be used for genetic research in the original cohort, GEN2 and GEN3 cohorts, respectively. In the current exam, the study has provided more specific options to participants on how their DNA may be used. For those who have had the opportunity to respond, less than one percent has opted out.

GENETICS IN FRAMINGHAM

Status of Framingham SHARe activities

Framingham has provided among the largest shared genotype/phenotype data base in dbGaP with more than 21,000 phenotypes available. Imputation data will increase the genotypes available to approximately 2.5 million SNPs. The SHARe data base in dbGaP is updated quarterly to speed turnaround for genetic analyses of new phenotype data. A new social network data base has also been released on dbGaP with more limited phenotype data to minimize potential for abuse. Approximately 102 applications for data have been approved. About 80 are from academic medical institutions, 5 are from commercial organizations, 11 are from outside the United States, and 5 are from NIH units. In addition, there have been 65 approved applicants for GAW data and 2 approved users of the social network data. Framingham has experienced the second embargo breach of the dbGaP data sets by an external applicant. To date, the paper was not withdrawn. NHLBI is addressing this issue to the extent possible. CARe data will be available early next year.

Status of Framingham genetic distribution through DNA Committee

The DNA Committee evaluates requests for DNA only. Data requests are now handled through dbGaP. The committee processed 27 applications including 22 new applications and 5 addenda applications. All but three were approved. The three that were not approved were all from the same investigator and lacked sufficient detail to allow approval. Of the 22 new applications, 17 were from Boston-based investigators. The Board was concerned that the opportunity for collaboration did not appear to be very effective beyond Boston. The Board also noted the declining number of applications.

Update on Genetic Research Consortia

As described earlier, more than 30 genetics-related papers have been published by the Framingham Heart Study investigators during the last year. Participation in various consortia have accelerated the number of genetics publications and have proven the value of wide collaboration. CHARGE has been particularly productive.

Reporting of genetic results to participants

A review of the SNPs that were currently available in genotyping labs for physician use and the potential overlap with genes and SNPs genotyped in the Framingham Heart Study suggested

only 12 potentially reportable SNPs. FHS investigators narrowed the field to two genes related to HFE and Factor V Leiden as potentially reportable. The Board was impressed with the approach taken by the investigators to investigate this issue. The study is in the process of obtaining IRB approval for participant notification of significant genetic results.

ANCILLARY STUDIES

Dr. Wolf presented an ancillary study proposal that proposes an extension to a study of cognitive decline in individuals prone to dementia based on family history. Study participants are given a brain MRI and a mini-mental and neuropsych battery. Those demonstrating decline are given a second brain MRI. Investigators estimate 1700 will get one brain MRI and about 150 will get 2 brain MRIs. The Board appreciated the presentation provided by Dr. Wolf and requested a detailed written explanation before an approval could be provided.

SABRe BIOMARKER PROJECT

The Biomarker Project includes four subprojects focused on 1) Proteomics and metabolomics, 2) immunoassays of circulating proteins, 3) gene expression studies, and 4) miRNA profiling. The first project was expanded to increase power as described earlier. The second project will focus on 180 biomarkers with about half routine known measures, one quarter emerging, and one quarter newly discovered proteins. The third project is focused heavily on quality control and has determined that PaxTube samples are superior to PBMC, buffy coat and lymphoblastoid cell line samples because they are available and not subject to deterioration. miRNA is in the early stages and also subject to large QC issues. The Board expressed interest in more detail on the QC analysis as there are many issues that must be considered in the analysis. When completed, the data will be widely shared through a system comparable to dbGaP.

SCIENTIFIC PRESENTATIONS

Three presentations were planned for the meeting but only two were presented in the interest of time. One analysis dealt with arterial stiffness. There are multiple measures that could be used and the analysis compared the various measures to determine which would be preferred. Of all the measures, carotid femoral pulse wave velocity was preferred based on ease of measurement (20 minute exam) and predictive value. The Board commented that the measurement would be more appropriate for a vascular lab study than in a physician's office.

The second presentation related to intergenerational dementia. The study addressed the possibility of diagnosing a predisposition to dementia 1-3 decades earlier to clinical

manifestation. The investigators were able to determine a significant interaction of ApoE with long term memory and visual reproduction to predict dementia.

RECOMMENDATIONS

The Board commended the Framingham Heart Study investigators on their tremendous progress and leadership in GWAS data sharing, genetics results reporting, management of large data bases, and development of the SABRe Biomarker study and its quality control efforts.

The Board recommended continuation of the study overall and had the following specific recommendations:

1) The ancillary study on dementia proposed by Wolf should be submitted for Board review in written form with a more detailed description of participant burden.

2) The protocol for what genetic variants are deemed actionable and reportable and process for how this was determined should be documented and shared with the Board and the scientific community. The focus should be broad rather than specific.

3) The protocol for repeatability and other quality control efforts in SABRe should be provided to the Board before the next meeting.

4) The Oversight Committees and processes for evaluation and approval of DNA requests should be considered for modification if the number of requests continues to decline.

5) Investigators should consider sequencing DNA from whole blood or buffy coat for comparison with sequencing from cell lines to discover and document mutation rates and locations from cell lines.

6) A plan should be presented for the evaluation of non-study radiation exposure in the Framingham Heart Study cohorts to limit radiation exposure in study participants.

7) Return of research results should add the reporting of eGFR with appropriate age- and sex-specific alert values.

8) A proactive plan should be provided for reaching out to non-Boston area investigators to collaborate on ancillary studies, perhaps through K award winners or other venues to attract young investigators.

9) An overview of the fellows training component of the Framingham Heart Study should be provided at the next meeting to highlight the accomplishments and opportunities for young investigators and potential collaborators using these data.

NEXT MEETING

- The Board agreed to meet on Tuesday, November 30, 2010 in Washington DC. The meeting is expected to extend for most of the day.

SIGNATURES

_____ APPROVAL _____ DISAPPROVAL

_____ _____

Deputy Director, NHLBI Date