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GEFOS meta-analyzes - Replication phase on GENOMOS studies – 2nd teleconference

Date: 22-03-2010 15:00-16:00 h (CET)

Attendees

Present	**Abscent**
ROTTERDAM: Rotterdam: Fernando Rivadeneira & Karol Estrada	DeCode: Unnur Styrkarsdottir
FOS: David Karasik, Doug Kiel	AOS: Kim Brixen
APOS: Lynne Hocking	Liz Streeten (Apologies)
Ioannina: Vangelis Evangelou	George Dedoussis (Apologies)
CABRIO: Jose A. Riancho	AROS: Bente Langdahl
GEOS: Francois Rousseau	Carrie Nielson (Apologies)
INDIANA: Dan Coller	LARISSA: Panagoula Kollia
MrOS Sweeden: Liesbeth Vandenput	Jane Cauley
BARCOS: Daniel Grinberg, Susana Balcells	SHEFFIELD:Eugene McCloskey
SLO-PREVAL: Simona Mencej	SOF: Steve Cummings
CAMOS, MANMC: Brent Richards	CARLANTINO: Paolo Gasparini
GEVUR: Elza Khusnutdinova	EPOLOS: Marcin Kruk
LASA: Paul Lips	NEMO: JM Kaufman
UFO: Ulrika Pettersson	OPERA: Kristina Åkesson

FLOS: Maria Luisa Brandi

AUSTRIOS: Barbara Obermayer-Pietsch

EPIC: Jonathan Reeve , Stephen Kaptoge

AOGC: Matthew Brown, Emma Duncan

ORCADES: Stuart Ralston

HEALTHABC: Candy Kammerer

INDIANA: Michael Econs

David Evans

AMISH: Laura Yerges

CALEX: Sulin Cheng

VIGGOS: Marie-Christine DeVernejoul

HUNT: Siri Forsmo

SOF, MrOS: Eric Orwoll

John Robbins

Richard Prince

Alireza Moayyeri

Annie Kung

ACTION POINTS:

- **Studies to update information of phenotypes on GEFOS questionnaire (http://www.gefos.org/quest/form.php**

  username: consortium/password: cooperation

- **Studies to read carefully instructions from KBiosciences on how to send DNA for genotyping (please don't send DNA yet, just prepare your plates)**

- **Austrios (Barbara Ober-Mayer) and Rotterdam to provide quotes for genotyping 50,000 samples and 100 SNPs (to support going to KBiosciences)**

- **New proposed deadline to submit DNA is May 1st, 2010.**

- **Rotterdam will send an e-mail to start sending DNA to KBiosciences, please don't send any DNAs before this.**

Participants were welcomed to the 2nd teleconference of GENOMOS genotyping. This strategy was launched by the GEFOS DXA BMD meta-analysis of genome-wide data but will serve replication purposes of other working groups.

1. Inventory of GENOMOS samples

Karol Estrada (Rotterdam) presented an updated report of GENOMOS studies which have uploaded data to the GEFOS questionnaire. All studies were invited to verify this table and update it via the website. It was also informed that some studies have sent the working group agreement but not uploaded their information on the website.

All studies were invited to:

1) Update/Insert their numbers to the GEFOS questionnaire, (see link and login information above)

2) Send signed copy of the GEFOS BMD working group agreement to the e-mail: genomos@erasmusmc.nl.

2. Replication strategy update

In respose to Richard Prince (CAIFOS) Fernando Rivadeneira (Rotterdam) explained the main goal of this effort is NOT to do novel GWAS genotyping (that's another project), but rather performing novel genotyping of ~ 100 SNPs in a large collection of samples (GENOMOS N between 30,000 and 50,000). Stuart Ralston (Edinburgh) clarifies GWAS genotyping of GENOMOS samples is targeted for vertebral fracture cases in a different effort.

It was also told that the original GEFOS proposal stated genotyping by GEFOS partners at a cost of 10 euro cents per genotype. Many centers expressed this was a low price per genotype. We have approached a company (KBiosciences) for a quote on this project, and they have sent a proposal in which they can perform genotyping within budget, but more important they can do the genotyping at different stages (the original proposal was with multiplex technology, which does not allow to do genotyping at different stages). I.e. if the BMD working group is further ahead, we can start genotyping for those BMD SNPs first, and SNPs from Ultrasound, HSA, lean mass can be added at a later stage. The GEFOS Research Steering committee has approved this strategy, but we are currently pending approval from the European Commission to outsource the genotyping.

It was asked all participants to read the document from KBiosciences about the plate layouts and DNA specifications prior shipping. It was also informed all studies to prepare their DNA collections, but NOT to send them to KBiosciences until contract has been closed. GEFOS will sponsor the genotyping, but not the DNA handling/shipping to KBiosciences.

Rotterdam will send to KBiosciences DNAs from studies which have already sent DNA to Rotterdam.

Stuart Ralston reminded that we are going to prioritize those studies with fracture information and Fernando Rivadeneira clarified we will genotype full cohorts (including both cases and controls).

3. Update of GEFOS working groups

DXA BMD working group: Karol Estrada gave an update on preliminary results on the meta-analysis in 30,000 population-based samples plus additional 1800+ 800 samples selected from the extreme distribution of FN-BMD.

Main meta-analysis identified 43 loci (including the 21 known loci) associated with either LS-BMD or FN-BMD. Adjusting the meta-analysis for the overall genomic inflation factor reduces the list to 36 loci. In this list of 36 loci, at least 2 present a significantly higher effect on WOMEN than in MEN. Forty nine additional loci have a P-value between $5x\ 10^{-6}$ and $5x10^{-8}$ in any of the LS of FN BMD meta-analysis. Therefore, ~80 markers are potential candidates for replication.

The final list of SNPs to be genotyped is still under discussion within the BMD working group and other GEFOS working groups. We have arranged that at least 60 SNPs from GEFOS DXA BMD and 10 SNPs from the other working groups (Ultrasound, Hip Structural Analysis (HSA), Lean Mass) will be pursued. Karol Estrada mentioned that we need to be careful on the final selection of SNPs to avoid repeating the genotyping of same signals in GENOMOS studies, for this we will need communication between GEFOS working groups.

Ultrasound BMD working group: Jonathan Reeve said that this effort is divided in 2 stages. Right now we are on data cleaning, and the goal is to get data for an abstract on Heel Ultrasound (N~15,000 subjects) to be submitted to the ASBMR . In the 2nd phase, we will pursue publication, including Heel DEXA GWAS . Jonathan mentioned that SOF and MrOS will have genotyping in late summer, with a considerable increase on sample size for this effort. Stephen Kaptoge mentioned that there are results from 9 studies with imputed data within 2 weeks. Fernando Rivadeneira reminded that one advantage of using KBiosciences services is that this effort will be able to pursue their top hits at a later stage and not be done simultaneously with the main BMD effort proceeding with an earlier timeline.

Hip Structural Analysis: David Karasik summarized the status of this effort, at the present we have data of 6 studies, we will perform meta-analysis this week. Forth additional cohorts are performing analysis as we speak (GOOD, HEALTHABC, INDIANA, HSK). Phenotypes: Neck Shaft Angle, Neck Length and Narrow Neck Section Modulus. Previous effort on 3 studies yielded one genome-wide significant hit.

Lean Mass: Doug Kiel, this meta-analyzes has been completed using whole-body DXA or Bioimpedance analysis. We are looking for replication on GENOMOS. Current questionnaire only has whole-body DXA. Data for Bioimpedance will be requested acrross GENOMOS cohorts separately. For this effort we are taken all studies without regard of machine used. We are expecting less than 10 hits for replication.

Regarding the selection of SNPs, there's no decision on which SNPs to select, either based on novelty, or based on possibility to evaluate the risk of fracture on known BMD-associated SNP.

4. GENOMOS has a new website with the same structure as the GEFOS website. Please go to http://www.genomos.eu and let us know what you think via email to: genomos@erasmusmc.nl

5. Other issues

There will be two GEFOS/GENOMOS meeting this year:

ECTS (Glasgow, UK) June 27th, 2010

ASBMR (Toronto, Canada) October, 2010 date to be decided.

GENOMOS collaborators are invited to bring proposal forwards to work with candidate genes/ pathways, for example to sequence gene regions, make experiments on cell cultures and or develop model organisms (mice, zebra fish,etc) using insight from the GWAS results.

6. Next call

We will circulate a doodle link with time options, next call should be within 1 month and prior to the deadline to submit DNAs.