

Genetic Factors of Osteoporosis (GEFOS) Consortium

Work group collaboration agreement

Version: 2010

Workgroup: 2nd Femoral Neck and Lumbar Spine BMD meta-analysis

1. Overview

Large collaborative efforts are needed to integrate individual research studies into one large study population capable of demonstrating/identifying the real, yet very subtle genetic effects underlying complex traits and diseases. This way, the participating cohorts plan to perform a meta-analysis of genome-wide data, in which summary statistics based on a mutually-agreed-upon analysis plan will be shared across all participating cohorts to allow meta-analysis and identification of variants for replication testing (when applicable).

2. Participating Cohorts

Within each category, the cohorts are listed in no particular order.

1) Discovery cohorts

- Rotterdam Study
- Erasmus Rucphen Family (ERF) study
- Twins UK Study
- deCODE Genetics
- Framingham Osteoporosis Study
- GOOD study
- EPIC Norfolk
- Cardiovascular health Study (CHS)
- Amish Family Osteoporosis Study
- Indiana Health Study
- Health ABC
- Orkney Complex Disease Study (ORCADES)
- Australian Osteoporosis Genetics Consortium (AOGC)
- Hong Kong Osteoporosis Study (HKOS)

2) Replication cohorts

- GWAS (in-silico) IF APPLIES

- Study of Osteoporosis Fractures (SOF)
- Mr OS (US and Sweden)

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- DNA Studies (de-novo) IF APPLIES

- GENOMOS cohorts to be defined

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3. Additional Cohorts

External cohorts with genome-wide association results not yet available and not part of this group will be considered as additional potential partners once their data become available. Inclusion of these additional groups in the consortium will be subject to agreement from all current participants.

4. Key Principles of Agreement

Management of combined analysis and replication

1. The groups agree to share initially association statistics for femoral neck and lumbar spine BMD traits measured by DXA. Additional traits may be analyzed by future agreement, including phenotypes related to the main trait of interest, such as BMD measured at other sites and technologies and fracture. All cohorts have the option to opt in or out of any future proposed traits to be analyzed.
2. Analyses will be conducted according to the analysis plan agreed upon by the participating cohorts.
3. To harmonize the data or to answer specific research questions (e.g. secondary analyzes), further cohort-specific analyses may be required. These will be kept to a minimum, recognizing the difficulty of redoing analyses in multiple cohorts and as already traced in the initial analysis plan.
4. A password-protected ftp site will be used for simultaneous exchange of combined imputed meta-analysis data from each cohort. Only cohorts providing GWA data will have access to the shared-file folder.
5. All groups contributing genome-wide association results for meta-analysis will have access to the meta-analysis results through the ftp site. Every cohort will have an analyst with access to this site who can upload and download files. All (raw, QCed and meta-analyzed) data are confidential and NOT for distribution. Any other (mis)uses of the data not specified in the analysis plan are NOT permitted without prior explicit approval from the participating group contributing the data. It is expected that each group may choose to do further experimental work on genes or associations uncovered by the consortium activities, and communications would be designed to minimize or at least communicate about any overlapping or potentially competing efforts. If there are resulting papers from this separate work, there is agreement NOT to submit the findings for publication BEFORE the main paper of the work group has been approved and/or submitted.
6. Genotype-phenotype association analyses will be conducted by individual replication cohorts using the specified plan given by the consortium (or they can be performed centrally), and then summary data and statistics will be submitted with summary demography to the replication file on the ftp site. Researchers of the replication studies will only have access to replication datasets.

7. The current plan is to have GWAS results from discovery cohorts uploaded in the FTP sites by **December 4th 2009**.
8. Meta-analysis of cohort-specific GWAS will be undertaken separately by predefined analytic groups to ensure concordance of results and maximum prospect of early remedy or detection of issues. The GEFOS analytical center in Ioannina together with the following groups will run the meta-analysis in parallel, this include: Erasmus MC, and deCODE Genetics.
9. After dataset cleaning one (1) set of results will be defined to avoid minor inconsistencies on publication.
10. In case of pursuing a replication phase, replication genotyping will be carried out by the Genetic Laboratory of the Dept. Internal Medicine, Erasmus MC and additional genotyping centres (yet to be defined). Results of individual level genotyping will be posted to the FTP repository after QC status is standardised across cohorts. Phenotype information will be provided to the analytical centers.
11. The lay-out of the replication framework will be determined within the analysis plan and subject to revision depending on the shape of the meta-analysis results.
12. Centralized genotyping will be pursued for most cohorts, in which case specimens should be shipped to the selected genotyping center and in accordance with QC standards. If cohorts in the replication phase are able to do their own genotyping, then these cohorts agree there must be a fast turnaround of genotyping and analysis (no longer than 4 weeks after selecting replication signals). Cohorts are free to use the genotype information for their own investigations committing not to submit for publication before the manuscript of the GEFOS collaboration has been accepted for publication.

Publication and Authorships

13. There will be an equal number of starred first and last authors from the groups contributing GWA data. Order will be agreed upon by the members of the working group.
14. The "first-first" and "last-last" author positions will be agreed upon by the members of the working group.
15. The corresponding author(s) will be agreed upon by the members of the working group.
16. Replication cohorts will nominate authors and PI's to be included on the paper.
17. The exact ordering of the remaining authors will need to be determined by the members of the working group. Discovery cohorts will be given some priority in the ordering.

- 18. No restriction to the number of contributing authors is set at this point (but it is expected that balanced across different sets of contributing studies is procured).

Confidentiality

- 19. The groups agree to not use the information obtained from the others to gain unfair advantage over them. In this context, the groups agree to communicate with each other regularly, and agree that there should be no surprises.
- 20. By this agreement participants agree not to share until publication of this project their genotype or phenotype data with other, non-participating cohorts investigating the trait in question (stated in point 1).
- 21. Each participating cohort agrees to maintain confidentiality throughout the analysis and publication phase of this study, with regard to the status and findings of this combined study.

Intellectual property

- 22. Intellectual property may be claimed using the data of GEFOS-EU-FP7 (HEALTH-F2-2008-201865) contractual partners, conforming to the requirement of the EU funding policy. No intellectual property will be claimed by the combined consortium using shared data of all cohorts. This accord with NIH GWAS policy whereby these data will be unencumbered by patent claims.
- 23. Individual participants may subsequently take forward distinct and additional research arising from these findings that generates a drug target or biomarker. The intent to embark on such a program should be declared in general terms to the consortium at the earliest possible point for transparency. In such an instance, they would retain freedom to protect this intellectual property (IP) and commercialize this as there would be a research program underpinning the discovery that is separate from the genotype-phenotype association results, which is of necessity pre-competitive. No downstream research activities will be pursued prior to publication without the disclosure of this activity and agreement by the other consortium members. Otherwise, downstream IP generating research can only be pursued based on published results.

Name/Signature/date (cohort representative)

Cohort

The following GEFOS consortium members have signed up to this working group agreement:

Signature/date (1 representative per cohort)		Cohort
André G. Uitterlinden	October 8th 2009	Rotterdam Study
Cornelia M. van Duijn	October 12th 2009	ERFStudy
Timothy Spector	October 12th 2009	Twins UK
Douglas P. Kiel	October 12th 2009	Framingham Osteoporosis Study
Unnur Thorsteindottir	October 12th 2009	deCODE Genetics
Claes Ohlssen	December 1, 2009	GOOD Study
