MSc in Bioinformatics for Health Sciences

AAD. Advanced Analysis of Disease and other complex Traits

Syllabus Information

Academic Course: 2019/20

Academic Center: 804 - Official Postgraduate Programme in Biomedicine

Study: 8045 – Bioinformatics for Health Sciences - MSc

Subject: 32545– AAD. Advanced Analysis of Disease and other Complex Traits

Credits: 5.0

Course: 1st

Teaching languages: English

Teachers: Gerard Muntané-Medina, Abel González-Pérez, Alejandro Valenzuela, Hafid Laayouni, Xavier Farré and Arcadi Navarro

Teaching Period: 3rd term

Presentation

This advanced subject aims to provide researchers & practitioners involved in genetic disease studies, particularly Genome-Wide Association Studies with (1) a comprehensive overview of concepts and experimental design in the study of human traits, with particular emphasis on quantitative traits and disease; and (2) up-to-date training in the use of the latest statistical methods and software for analysis of both, rare & complex diseases. The course will provide a comprehensive overview of the statistical methods currently in use to map disease susceptibility variants and genes in humans. Data collected from families will be considered, but the emphasis will be on data collected from populations. This includes both small-scale disease-specific studies and large-scale collaborative projects including those that can be used for analysis of multiple complex traits such as UK Biobank. The course will include an overview of the tools, standards and large-scale initiatives such as Europe's ELIXIR or the Global Alliance for Genomics and Health

Students will be able to appreciate the influx of quantitative genetics concepts into the study of disease and how the understanding of disease as a complex trait has been re-shaped in recent years. Students will become familiar with advanced concepts such as Polygenic Risk Scores, array heritability or Bayesian GWAS and will have working knowledge about how to compute them from GWAS data.

Associated skills

General:

Instrumental:

1. Proficient reading/writing/listening scientific English related to the subject.
2. Knowledge of software to do quality scientific presentations and reports related to the subject.
3. Elements of Statistics: concepts of association, correlation, and interaction.

4. Elements of Genomics: genes, alleles, genetic variants, markers, phenotypes, expression, complex traits, genomes, exomes, causal variants,
5. Elements of Quantitative Genetics: heritability, phenotypic variance, allelic effects, additivity, epistasis.
6. Concepts of association studies: association, GWAS, stratification, multiple testing.

Interpersonal:

1. Group work.
2. Ability to solve by yourself a given problem.

Systemic:

1. Analysis and synthesis abilities.
2. Ability to search and manage information from different sources

Specific competences:

1. To master the nature of the factors generating complex phenotypes.
2. To master concepts of decomposition of phenotypic variance and heritability.
3. To become familiar with the concepts underlying classical twin studies and other phenotypic correlations between relatives.
4. To master the concepts of allelic effects, dominance, additivity and interaction.
5. To understand the liability-threshold model of disease.
6. To master the essentials of Genome Wide Association studies, including array-based and sequencing-based GWAS.
7. To become familiar with meta-analysis concepts and procedures.
8. To understand the concept and history of missing heritability.
9. To understand the concept of array heritability and the role of rare variants in the configuration of complex traits.
10. To become familiar with techniques other than SNP-by-SNP association.
11. To understand gene- or set-based association analysis.
12. To master the concept of Polygenic Risk Scores and overview of other Genic Scores (such as Transcriptional Risk Scores and so on).
13. To master the concepts of pleiotropy and of genetic correlation between traits.
14. To understand the concept of conditional QQ-Plots and conditional FDR.
15. To understand the concept of Bayesian GWAS.
16. To understand the concept of PheWAS.
17. To master information retrieval from disease-related public databases.
18. To understand the different strategies to determine functional/causal variants.
19. To understand the differences between prediction and diagnosis.
20. To become familiar with data-sharing issues and the work of initiatives such as ELIXIR or the Global Alliance for Genomics and Health.

Prerequisites

Basic knowledge on genetics and molecular biology

Basic knowledge of statistics (the BDA subject in this MSc is a good starting point)

Basic knowledge on GWAS (the GPA subject in the MSc is a good starting point)

Contents

Contents Section1: Overview of Quantitative Genetics.

Concepts:

Heritability, and the decomposition of phenotypic variance.

Allelic effects, Dominance and interaction

Twin studies and regression between relatives.

Procedures:

To be able to use the basic concepts of heritability to get a basic estimation of the contributions of genetic and environmental factors to a given trait.

To be able to compute heritability estimates from different correlations between relatives,

To understand the diversity of possible genetic architectures of human traits.

Contents Section 2: Challenges of GWAS.

Concepts:

Genome-Wide Association Studies (GWAS)

The missing heritability

Array heritability and rare variants

Gene- or set-based association analysis

Simultaneous analysis of many SNPs

Sequencing and GWAS

Procedures:

To be able to interpret GWAS results from a statistical genomics perspective.

To be able estimate the genetic relationships among individuals in GWAS data.

To compute array heritability.

To partition array heritability across chromosomes or regions.

To perform set-based association analysis.

Contents Section 3: Beyond GWAS.

Concepts:

Phenome-Wide Association Studies

Meta-analysis

Pleiotropy and the genetic correlation between traits

LDScore regression

Conditional QQ-Plots and conditional FDR

Polygenic Risk Scores (PRSs) and other Scores

Bayesian GWAS

Procedures:

To understand the basic performance and interpretation of PheWAS

To understand the basic performance and interpretation of meta-analysis results.

To be able to compute and interpret PRS from GWAS data.

To be able to estimate the genetic correlation between two traits (diseases) using GWAS data.

To be able to compute and interpret LDScores from GWAS data.

To be able to perform an interpret conditional QQ-plots and condition FDR analysis.

To be able to perform and interpret Bayesian GWAS.

To get a synthesis of the different methodologies for genotype-phenotype studies in a critical way.

To be able to critically assess extant research on the genetic architecture of complex diseases.

To be able to pinpoint specific drawbacks related to different computational methodologies.

Contents Section 4: Functional variants: detection annotation and interpretation.

Concepts:

Strategies to pinpoint causal/functional variants.

Differences between cancer and complex diseases.

Functional annotation of genetic variants.

Functional interpretation of GWAS results.

Procedures:

To be able to call variants from exome or full-genome data.

To be able to understand different strategies to detect functional/causal variants and to pinpoint specific drawbacks in different approaches.

To be able to perform basic functional annotation and interpretation of GWAS results, including the effect of individual variants.

To be able to understand the experimental setups suggested by the functional interpretation of GWAS results.

Teaching methods

Approach and general organization of the subject

The course has 5 ECTS credits, comprising 15/20 hours of plenary lectures, 4/6 hours of exercises and hands-on computer classes, 6/10 hours of students' presentations in seminars, 60/70 hours of reading and personal study, and 2 hours performing tests

The subject is based on the understanding of novel conceptual and methodological developments and on the application of software useful for state-of-the-art genetic epidemiological research. As this is a very active field, lectures will be different every year so the student is advised of the need being up-to-date with the course's material. Intense interaction with the lecturers is recommended.

The course includes classical lectures and hands-on exercises. Please, bring your own laptop for the hands-on sessions

Training activities

The subject focuses on practical implementation of different types of tools for simple genotype-phenotype studies. Exercises and tutorials are distributed previous to the corresponding sessions.

Hands-on exercises are based on the use of publicly available resources and software packages, so individual development beyond what is covered in the course can be easily achieved by the students.

Each student will present a short seminar of 20-40 mins on a scientific article of relevance for the field.

Evaluation

Assessment system

The competences that need to be achieved in the course will be evaluated by means of written and oral presentations during the course, and an exam at the end of term.

Grading system

Grades are between 0 and 10 and an overall 5 is needed to pass. The weight that is given to the presentations and the exam depends on the performance of the whole group.

A minimum of 4.0/10 in the final exam is needed to pass.

Bibliography and Information Resources

There is no text-book bibliography as such, but a wide selection of papers will be distributed during the course.

Also, these books are available in the library:

- Evolution in health and disease / edited by Stephen C. Stearns and Jacob C. Koella
- The Genetic basis of common diseases / edited by Richard A. King, Jerome I. Rotter, Arno G. Motulsky
- Genetics and analysis of quantitative traits / Michael Lynch, Bruce Walsh
- Handbook of medical informatics / J.H. van Bemmel, M.A. Musen, editors; J.C. Helder, managing editor

- Handbook of statistical genetics / editors, D.J. Balding, M. Bishop, C. Cannings
- Human genome epidemiology: a scientific foundation for using genetic information to improve health and prevent disease / edited by Muin J. Khoury, Julian Little, Wylie Burke
- Statistical methods in genetic epidemiology / Duncan C. Thomas
- Genome-Wide Association Studies: From Polymorphism to Personalized Medicine / edited by Krishnarao Appasani
- GWAS: The Rise of Hypothesis-Free Biomedical Science: Could Genome-Wide Association Studies (GWAS) Transform Modern Medicine? / Igor Rudan, Harry Campbell, Ozren Polasek, Inga Prokopenko
- Design, Analysis, and Interpretation of Genome-Wide Association Scans (Statistics for Biology and Health) / Daniel O. Stram.