Part 1: Genetic Associations

Introduction

Genetic epidemiology accommodates different viewpoints to look at "disease". Unraveling important functional determinants to or causal factors for complex diseases requires a systems biology view, combining evidences from different data sources, involving the genome, the transcriptome, and epigenome, amongst others.

In this project, you will select a human "complex disease" or "complex trait" of interest (ideally, take one for which also evidence of disease-associated epigenetic mechanisms exist – reference Cortessis et al. 2012). Verify with the instructor whether your selected trait is ok for the purposes of this course. Then search the "Catalog of GWAS" for published genome-wide association studies for the approved disease/trait. The link to this catalog is http://www.genome.gov/gwastudies/#searchForm.

You can then use the most recently published genome-wide association studies obtained via your search, upload the associated publication, and discuss its content using the specific questions below.

Obviously, you are not restricted to publications from the aforementioned catalogue to build up your story.

Questions

- What is the relationship between genomics, statistical genetics, genetic epidemiology, and epidemiology?
- Is your DNA your destiny? Why? Why not?
- How does epigenetics fit into the "genetic epidemiology" picture? Has our understanding about epigenetics and its potential contribution to human disease management evolved over time? Do several types of epigenetic mechanisms exist?
- What is a genetic association study? How does it fit into the general work flow within "genetic epidemiology"?
- Is there a difference between association and causation?
- What is the difference between replication and validation?

For the selected study:

- Describe the biological question(s).
- What is the design of the study? (markers, subjects). Is it different from the designs seen in class? If so, what was the motivation to select a different design?
- Which quality control procedures have been put in place? Are they in line with the Travemunde criteria? If not, was there a motivation given in the paper for adopting a different criterium, or can you come up with a motivation yourself? Be critical.
- How did one make use of the concept of LD (linkage disequilibrium)? Was it used to reduce the number of tests? Was it used after the analysis to identify causal variants?

- What type of association test was carried out? Single locus at the time? Haplotype-analysis was considered as well? What is the possible advantage of performing a haplotype analysis? What are the drawbacks?
- Was there a need to correct for population stratification? What is population stratification? How did one correct for it? Are there other ways?
- Were the genetic association results supported by a replication analysis or a validation analysis? If so, what did it involve? What are the factors causing a non-replication? May it also be the existence of gene-gene interactions?
- What are the final conclusions of the study and how much trust can be given to them (when looking at the replication/validation results)?
- What type of follow-up analyses do the authors advocate? Can you place these in the context of (modern) "genetic epidemiology"?

Useful references

- Psychiatric GWAS Consortium Coordinating Committee, Cichon S, Craddock N, Daly M, Faraone SV, Gejman PV, Kelsoe J, Lehner T, Levinson DF, Moran A, Sklar P, Sullivan PF (2009). Genomewide association studies: history, rationale, and prospects for psychiatric disorders. Am J Psychiatry. 166(5):540-56.
- Klein C, Lohmann K, Ziegler A (2012). The promise and limitations of genome-wide association studies. JAMA 308(18): 1867-1868.
- Petersen A1, Spratt J, Tintle NL (2013). Incorporating prior knowledge to increase the power of genome-wide association studies. Methods Mol Biol. 1019:519-41.
- Zhu Y1, Xiong M (2012). Family-based association studies for next-generation sequencing. Am J Hum Genet. 90(6):1028-45.
- Cortessis VK, Thomas DC, Levine AJ, Breton CV, Mack TM, Siegmund KD, Haile RW, Laird PW (2012). Environmental epigenetics: prospects for studying epigenetic mediation of exposure-response relationships. Hum Genet. 131(10): 1565-89.