Part 2: Post-Genomics

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. With a different genetic background, another drug-response pattern of a diseased individual may appear (i.e., an example of a gene-environment interaction; pharmacogenetics). Although a set of genetic markers have been identified to (directly) modify gene expression (called: eQTLs) in specific tissues, their effect may be disturbed when epigenetic mechanisms are operating.

In this project, you will consider the same complex trait as selected in Part 1 and will investigate whether there has been evidence for gene-gene interactions and gene-environment interactions.

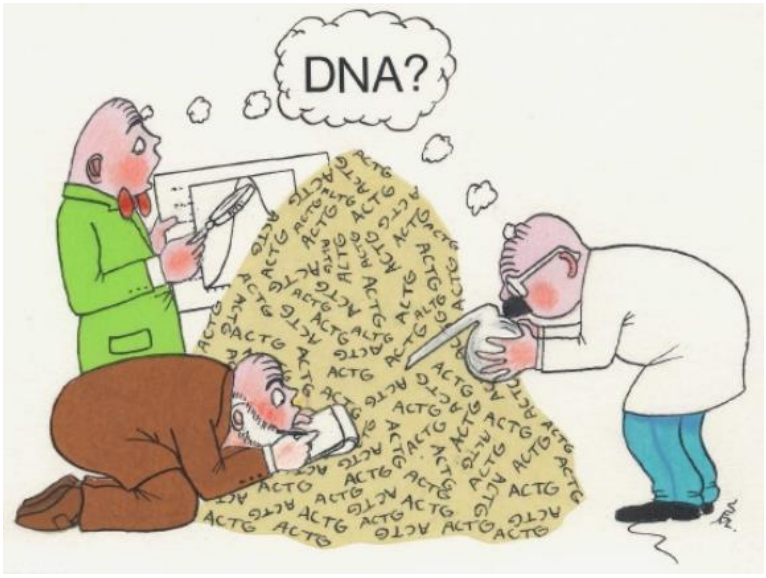
Information about gene-gene interaction studies (methodological papers as well as applied papers) can be retrieved from the "Epistasis Blog": http://compgen.blogspot.be/2006/05/mdr-applications.html. This blog is updated on an almost daily basis by Jason Moore and is an excellent resource to stay on top of achievements in the context of gene-gene (and thus also often gene-environment) interactions.

Questions

- Give some definitions of "interaction" in epidemiology. Is it different from effect modification?
- What does epistasis mean? Is there a difference between statistical and genetic epistasis? Is it easy to translate statistical epistasis into biological epistasis? How can this translation be facilitated?
- In what ways will a gene-environment interaction study be different (more complex? less complex?) than a gene-gene interaction study?
- What is meant by an exhaustive search? Is this feasible in the context of a genome-wide setting? Hence, are GWAI studies (genome-wide association interaction studies) at all possible?
- Does it make sense to investigate higher-order interactions?
- What are the criticisms to traditional regression-based approaches in the context of GWAIs and can you give alternative methods to deal with the abundance of complex data patterns?
- What is multifactor dimensionality reduction? What are its advantages and limitations?
- What are random forests? What are its advantages and limitations?
- Replication and validation are important components of any genetic association study. What would replication of a GWAI involve?
- Can you highlight the differences between "genomics for personalized medicine" and "public health genomics"?

For the selected study:

- Nowadays, editors often ask to carry out a (at least basic) interaction study. Hence, since you have selected a recent publication on a genome-wide association analysis, was an epistasis analysis carried out? Give more details about how the interaction analysis was performed.
- Does the literature in general provide any support for the existence of gene-gene or gene-environment interactions for the trait of interest? Give examples.
- For the identified interaction studies (gene-gene / gene-environment) were there different quality control measures taken compared to a classic GWA study? Why or why not?
- Is the study a case-only study? What are the advantages / disadvantages of such a design in the context of interaction analyses?
- How do the authors "validate" their interaction findings? Comment on the adopted strategies to replicate or validate the findings.
- How do the authors derive a biological interpretation for their results? For instance, in GWA studies one often complements the analysis by investigating whether an association exists between the identified genetic markers and a gene's expression, since this may give a clue about "functionality". What is typically done in GWAI settings?



Useful references

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