A minicourse on

Genomewide association analyses (GWAS)

Part III: Hot topics

Matti Pirinen

FIMM, University of Helsinki

December 5th 2012

Contents:

1.Concepts And Rationale

2.Technology and Data

3.Statistics and Analysis

4.Results and Hot topics

- Digestive system disorder
- Cardiovascular disorder
- Metabolic disorder
- Immune system disorder
- Neurological disorder
- Liver enzyme measurement
- Lipid or lipoprotein measurement
- Inflammatory marker measurement
- Hematological measurement
- Body measurement
- Cardiovascular measurement
- Other measurement
- Chemical compound
- Biological process
- Cancer
- Other disease
- Other trait
- Trait mapping in progress

EMBL-EBI

National Human Genome Research Institute

GWAS criticism

- Visscher 2012, quotes on p.1-2
  - Missing heritability
  - Missing mechanisms
  - Small effect sizes
  - Methodological flaws (e.g. population structure)

Missing heritability

- GWAS SNPs explain only at most 10-20% of the estimated genetic variance
  - We don't have power to pick out (myriad of?) still smaller effects (Yang et al. 2010)
  - We haven't covered rare variants well (Dickson et al. 2010 + replies from Wray et al. 2011 and Anderson et al. 2011)
  - Estimates of heritability may be biased (Zuk et al. 2012)

How to estimate variance explained?

- A SNP with freq f and effect b: $Var(xb)=2f(1-f)b^2$
  - Only applicable to SNPs that have been identified as relevant for the phenotype
- Variance component model
  - Don't try estimating b for each SNP
  - Estimate (joint) variance of all b over the genome
  - Only 1 parameter model
  - Yang et al. (2010) and Visscher (2010)
  - Explains ~50% of variance of height (compare to 10% explained by GWAS SNPs)

Genetics may be non-additive

- So far we have considered only additive variance
  - Alleles act independently within and across loci
- But GxG interactions may bias heritability estimates from close relatives (twins, sibs etc)
  - Zuk et al. (2012)

Causal inference

- Cholesterol levels are associated with myocardial infarction (heart attack) risk
  - Are cholesterol levels causal for MI risk? Important question for medicine.
- Causality difficult to get from observational studies
  - Observed correlation does not mean causation
  - Confounders
  - Reverse causation
- Randomized clinical trials are good
  - But Expensive, take long time

Mendelian randomisation (Lawlor et al. 2008)

- Take KNOWN genetic modifiers of cholesterol levels
  - (Assumed to be) independent of confounders
  - No reverse causation (genetics come first!)
- Causality seems likely, if these genetic variants are also associated with MI risk (in a consistent way w.r.t effect sizes)
  - (with some exceptions, see Lawlor et al. 2008)
- Voight et al. 2012