How can we best exploit quantitative trait analysis in large scale genetic studies?

- QTs (and endophenotypes) are supposed to be more amenable to genetic analysis than (often arbitrary) disease categories
- QTs are ideal for population-based studies
  - No need for diseased group, everyone who can be measured has an informative trait
  - Side-product of many disease-oriented studies
- Successful approach in experimental models
- Theoretical studies very promising

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- But in practice, many QTLoci but still few QTGenes
  - Is it just a matter of time (Blangero's King Harvest)?
- Recent convincing success stories:
  - eQTLs
  - GWAS of height
  - ...
- Why did they work?

It’s the phenotype, stupid…

- Definition of phenotype is crucial (as always!)
  - Evaluate application of methods to new phenotypes truly reflective of underlying biological mechanisms and genetic variation
- There can be multiple versions of the “same” quantitative trait (residuals, covariates, etc.)
  - Facilitate standardization across multiple studies targeting the “same” phenotype
- Cohort (with follow-up) studies are important
  - Most QTs change with time and genetic factors influencing variability over time should be considered
- And don’t forget family-based studies…
  - Although the population-based QTL approach is straightforward, family-based studies are ideal for QTL analysis (what type of families? Trios, sibpairs, nuclear pedigrees, extended pedigrees…)

GxG and GxE interactions: Are we there yet?

- GxG and GxE effects are often invoked to explain disappointing or contrasting results in genetic studies
  - May cause variability across populations if they differ in frequencies of genotypes or exposures
- Few biologically realistic models support significant increase in power in tests that directly address interactions in addition (or alternative) to main effects
  - More powerful and efficient methods are needed than simple evaluation of all possible combinations of risk factors

GxG and GxE interactions: Are we there yet?

- If one is genuinely interested in the interactions *per se:*
  - Then one should know the main effects first
- At least for “G” we (kind of) know what we need to look for (SNPs, CNVs,…) and how to measure it
  - What is “E” and how do we measure it?
  - Need to identify environmental risk factors and methods to measure exposure
  - Need more geneticists x epidemiologists interactions
- Catalogs of the environmental factors?
- Design of intervention studies to target individuals at genetic risk whose environment can be modified

A couple more thoughts…

- Use disease models where major gene defect is known
  - Studies of modifiers of Mendelian disease
    - Genetics of health?
  - Establish international collaborations
  - Develop analytical methods
- Family studies (again...)
  - Parental (maternal) genotype and exposure