Sequence Data Processing

Workshop on

Central Resource of Data

From Genome Sequencing Projects

Why?

- Many analyses will benefit from combining information across sequencing projects

- Possibilities include …
  - Meta-analyses that improve on analyses of any single sample
  - Case-control studies of rare variation that use many controls
  - High-resolution of analyses of natural selection

- Differences in sequence processing between projects can affect these analyses to different degrees

Case-Study #1

Rare variant in CFH and macular degeneration

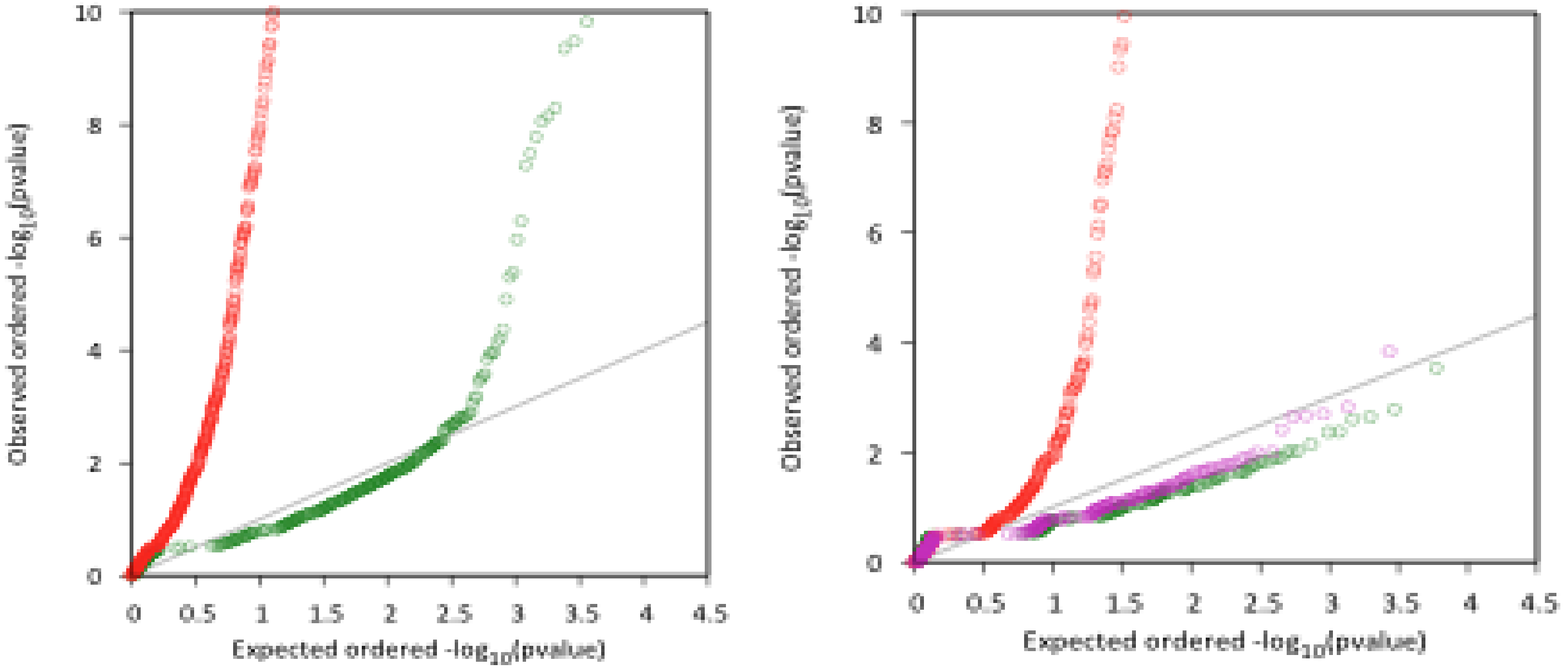
- R1210C, rare variant in *CFH* that abrogates C-terminal ligand binding, is associated with AMD
  - Initial demonstration by Raychaudhuri et al (2012)

- What would it take to rediscover the variant in an exome wide experiment?

- We sequenced 2,348 AMD cases and 789 controls in collaboration with Washington University Genome Center
  - Variant is seen in 23 cases, 0 controls (good!)
  - P-value is about .003 (middling!)
  - Variant present 2 of 12,000+ exomes used for exome chip design (impressive!)

Case-Study #2

Comparison of Exomes Sequenced at Two Centers



Comparison of Initial Calls

Comparison of Refined Joint Calls

- Initial calls show many differences between centers
- Calling and filtering with uniform process reduces differences
- Many differences are not intrinsic to sequence generation, but to calling

Filtered, **On-Target**, **Near-Target**

Options for Sequencing Processing

- Laissez-Faire:
  - Each project provides its own calls
  - Focus on standard formats, queriable structures
- Central Planning:
  - Define minimum standards for calls that are deposited
  - Define analysis tools for calls that are deposited
  - Increases similarity between datasets
- Central Analyses:
  - Calls generated centrally, using data across many projects

Option #1
Using Calls Provided by Each Project

- Some valuable analyses are relatively robust to differences between sequence analysis protocols
  - Meta-analyses of association study results for quantitative traits

- Facilitating this option still requires:
  - Harmonization of phenotypes
  - Consistent use of standard formats
  - Streamlining of data access protocols
  - Data models that facilitate combining data across studies

Option #2
Minimum Standards for Calls

- A set of minimum standards for calls generated by each project could help…
  - Analyses should include variant types beyond SNPs
  - Analyses report per base coverage in addition to discovered variants

- Standards could even require that each study is processed with the same set of tools

- This would provide incremental improvement on option #1, but probably still only allow meta-analysis
  - The power of artifact filters, for example, depends on sample size
  - Old and new projects would likely be analyzed with different tools

Option #3
Joint Processing of Many Projects

- Most compute and labor intensive

- Many analyses improve with sample size
  - Power to discover variants
  - Ability to resolve complex events
  - Ability to resolve haplotypes
  - Ability to filter sequencing artifacts

- Allows benefits of new analysis tools to percolate

- Technically feasible to call 10,000s of samples ….
- … especially if we are happy with 80% solution

Challenges for Joint Processing of Many Projects

- Uniform protocols for accessing sequence data across studies are essential
  - Much more difficult if analysis require manual intervention
- The challenges of handling corner cases can’t be underestimated
  - When are we willing to drop legacy data?
    - Shortest reads
    - Higher error rates
    - Obsolete platforms
  - A few samples with poor quality data can influence results

Sharing of “Derivates”

- Some information, like allele frequencies, could allow many benefits of joint calling without sharing raw sequence data

- Examples include:
    - Distilled summaries of haplotype structure
    - Distilled prior evidence for variant bases

- The risks of sharing these derivatives are similar to those involved in sharing allele frequencies

Final Thoughts

- All these options are likely to be pioneered by investigators with shared scientific interest
  - What happens when we combine individuals with information on a favorite trait across sequencing studies?

- Currently, not fully exploiting what can be done with calls from individuals projects (whether GWAS or sequencing)

- Many opportunities for improved sequence analysis by combining data processing across projects