Integrating functional genomics with DNA sequence variants

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Opportune time to study “function” on a large scale

• Huge number of variants available from many studies from NHGRI & beyond
  – Functional characterization = connection between genomes & biology

• Recent development of new technologies
  – CRISPR, large-scale epigenomics, single cell, etc.

We need a foundational resource to integrate functional information on many discovered variants
What should the resource be?

• Different types of function
  – At molecular/biochemical and cellular levels
    • can be studied at scale & systematized
    • Also, is closer to the variants
  – At organismal level
    • Not as easy to scale or to systematize

• NHGRI should find the “sweet spot”
  – Problems that capitalize on the new technologies
    • Lots of readout with modest investment
  – Best models – cells? mouse? model diseases?
Dichotomy of Directions

• Top-down: Develop catalogs of elements &/or all possible variants & then intersect them with variants found in disease studies
  – ex: Shendure challenge talk

• Bottom-up: Start from a list of disease variants & characterize them functionally

Both have merits
Multiple Approaches

• Approaches that look at large numbers of genes, variants, cell types, etc. in a standardized, high-throughput way

• In contrast: Deep disease/gene-specific studies
  – Require domain experts & detailed assays, many of which cannot be scaled
  – Not the province of NHGRI -- at least not on their own

• Important to have both & integrate them
  – Build special informatics infrastructure to tie them together
Other considerations

• Scaling from the genome-scale assays to population-scale
  – Success of eQTL & related projects
  – Personal functional genomics, value in longitudinal studies

• Functional genomics is valuable beyond just variant characterization
  – Use high-throughput sequencing to characterize cell types
    • e.g., to develop cellular biomarkers
    • ex: Regev challenge talk
      (Single-cell transcriptomics & Human Cell Atlas Project)
Integrating function & sequence variation: The opportune moment

• Large-scale resource projects as frameworks for functional characterization
  – Scaling of molecular & cellular assays vs organismal phenotypes
  – "Top down" & "bottom up" both good
  – Need the interaction between standardized catalogs & domain experts

• Other aspects
  – Scaling beyond the genome to the population
  – Functional genomics regardless of variants