Applications of Genomic Technologies to Population-Based Studies

Prioritizing epidemiologic studies for genome-wide scans

NCI : approaches and recent experience

Cancer in Populations and WGAS

- Cancer as a clear phenotype
  - Distinct histologies: extra power needed
- Incidence of each cancer is low
  - We need to invest in big, good studies
- Lots of data on heritability, environmental and behavioral causes:
  - Familial aggregation
  - Twin studies
  - Environmental/behavioral risk factors

Cancer in Populations and WGAS

- Diversity in populations, environments -> key in replication scan as well as primary
  - Otherwise GXE obscures confirmation
- Power / replication / confirmation
  - Essential, see recent lit: Satagopan 04;Skol 05;Wang 06
- Consortia: epidemiologists have used these before to gain power
- Ongoing studies of (less dense) WGAS

NCI: Three concurrent approaches

- R-01 supported studies
  - Majority of the portfolio
  - Draft guidelines for grant applications
  - Expensive, require council approvals
- Near-term intramural projects
  - Several good candidates
  - Vetting process challenging, informative
- NCI-led project: CGEMS
  - Study of breast and prostate cancer

CGEMS

- Breast and prostate logical candidates
- Scan and replication in existing epi. studies
- Spun off Cohort Consortium
- Genotyping at NCI-CGF (Core Genotyping Facility)
- Replication planned and integrated
- Multi-study, multi-institution, intramural-extramural

CGEMS

- Develop the informatics capacity
- Apply robust statistical approaches
  - Cone of successively vetted findings
- Ensure privacy protection, but…
- Ensure rapid access to the results
  - Creates caBIG-compatible infrastructure
- Economic tradeoffs
  - Working across technologies and platforms…
  - ..with changing price structure

Evaluating WGS Proposals
DCEG

- Why do this consortial study now?
  - Why DCEG in particular?
  - How does this complement any extramural efforts in this tumor?
  - Are there related activities across NCI?
  - Why now?
  - Are there reasons to suspect finding a high penetrance allele?

Evaluating WGS Proposals
DCEG

- What studies are in the consortium?
  - Is it an ongoing collaboration, are there publications?
- Brief comments on quality of studies
- Power computations
- Replication plans
  - If you are proposing a rapid response phase involvement only, do you know who is likely to conduct the primary scan? What studies are primary?

Evaluating WGS Proposals DCEG (cont.)

NCI / DCEG

- What epidemiologic features of this tumor make it a promising candidate for study? (< 100 words) For example:
  - Environmental and behavioral risk factors
  - Likelihood of genetic effect
  - Special clinical relevance
  - Special populations
  - Public health impact
- Funding and co-funding options
- Other key considerations

R-01 supported studies

Study Section Review Experience to date

- Comparison to other work in that tumor
  - Relies on knowledge of the reviewers
- Rare diseases may fare well
- Credit for established consort
- Diversity of populations
  - More proposals are coming in w/diverse populations
  - But reviewers concerned about power loss

R-01 supported studies
Experience to date (cont.)

- Appropriate follow-up
  - Field is changing fast, no set rules yet
- Biological sample issues
  - Study section usually well qualified on that
- Pooling of data, replication plan
  - Study sections trying to keep up with the lit.
- Pooling of DNA for cost efficiency?
  - At least one proposal fared well

Workshop 2005

- Thomas DC, Haile RW, Duggan D.
- Recent Developments in Genomewide Association Scans: A Workshop Summary and Review.
- Am J Hum Genet. September 2005; 77(3): 337–345.

DRAFT WGA guidelines

- Justification of:
  - Particular cancer phenotype
  - Population selected
- Standardized:
  - study design
  - laboratory methods
  - statistical methods
- Replication strategy for
  - May be other studies, consortia

DRAFT WGA guidelines

- Platform justification
  - cost-effectiveness
  - cost-sharing where possible
- Posting on NCI public website:
  - specific information about the study design, laboratory methods and analytic approach
  - available during grant period.

DRAFT WGA guidelines

- "Common element" informed consent
  - if new data collection is planned
- Data sharing plan
  - Consistent with NIH guidelines
- Biospecimen distribution plan
  - Consistent with new guidelines

DRAFT WGA guidelines

- Participation in an annual meeting of grantees:
  - Report negative and positive results
  - Discuss updates
  - Review and recommend next steps.
- Follow NIH results-reporting guidelines
  - Cf. CGEMs, GAIN, GEI