Second Multi-IC Symposium Working Group 2:

Follow-Up Studies

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Follow-Up Studies in WGA Designs

- How to choose fine mapping or sequencing approaches?
- What is the likely impact of new sequencing technologies?
- What don't we know about the genome but could have great impact on follow up studies?
- At what point do we initiate functional studies and how do we determine function?
- What types and numbers of biospecimens are necessary for the different approaches?

How to choose fine mapping or sequencing approaches

- The utility of the HapMap for fine mapping studies.
- Can the use of custom-SNP arrays fully capture variation in a gene/region?
- Rare variants in complex disorders and strategies to include them in study design.
- What does deep sequencing mean?
- Why don't we sequence everything?
- Even if we could would we want to?
  - Analytical challenges

New sequencing technologies

	ABI	454	Solexa
Read lengths now (bases)	650	250	40
Read lengths in a year	650	400	50
Paired ends	yes	year	soon
Accuracy	high	probs homopol indels	high
Cost / Mb	$880	$160	$5

(Rough indication: costs are uncertain and will change!)

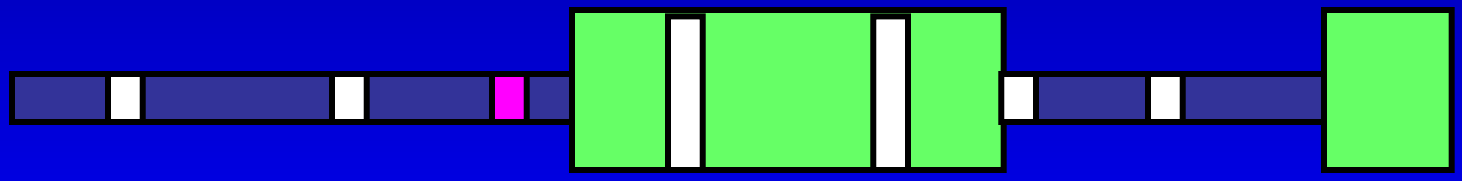
(data from Elaine Mardis, Wash. U.)

What is the likely impact of new sequencing technologies?

- What new questions can be addressed by high-capacity human resequencing?
- What is the economic and scientific impact of new sequencing technologies?
- How many samples are needed?
- Are deep sequencing technologies feasible for complex traits? At what cost?

Which is the causal variant?

An association hit shows a genome region associated with a disease, and generally many variants in LD.



What don't we know about the genome but could have great impact on follow up studies?

- What types of variation are we missing in GWAS studies?
- What is the phenotypic impact of these genomic variants? How do they contribute to genetic heterogeneity?
- How is function determined in coding regions and in non-coding regions, including gene deserts?
- Should we only focus on SNPs in Exons?
- How important are synonymous codon changes?
- What about Introns and regulatory regions?
- What have CNVs taught us about the genome?
- Most of the genome codes for nothing – what if we get a hit there?

At what point do we initiate functional studies and how do we determine function?

- What are functional studies?
- How do we understand and assay function?
- What is needed to establish causality?
  - E.g. Association between a variant(s) and phenotype (e.g. drug response) is not sufficient
- Multiple lines of evidence must agree; integrated approaches are best.
  - A multi-pronged approach is best (e.g. cells, mice, humans)
- Understanding mechanism often leads to paradigm shifts in thinking

What strategies should be considered to have sufficient sample materials available for follow-up studies?

- Make sure study subjects are consented appropriately.
- In the beginning decide to store DNA, create cell lines or both. Can be cryo-preserverd almost indefinitely.
- The quantities of DNA required are very low.
- First choice is always DNA extracted from peripheral blood
- DNA extracted from saliva or cheek swab is an option as is whole genome amplification but with caveats