Genetic Association Studies

Matthew C. Cowperthwaite, PhD
NeuroTexas Institute at St. David's HealthCare
Texas Advanced Computing Center, The University of Texas at Austin

Disclosures

Nothing to declare.

Goals

- Understand the basic history of quantitative genetics
- Attain a basic understanding of the genetic terminology
- Understand the basic statistical framework of genetic association studies
- Gain insight into how genetic information can provide additional power to imaging research

The Dawn of Genetics

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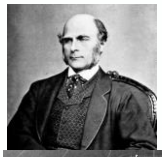
Traits

Discrete traits



Quantitative traits

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A Great Debate

Are the mechanisms of inheritance the same?

Mendelians
Traits evolve by few large mutations

Biometricians
Traits evolve by many small mutations

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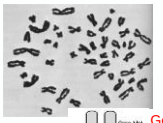
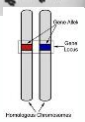
Genetic Terminology

Human Karyotype





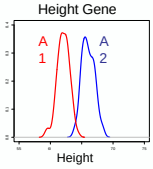
Gene := heritable "unit", corresponding to region of DNA (the *locus*)

Allele := specific form of a gene, i.e. variant

Flower Color Gene

Purple Allele White Allele

Height Gene



Height

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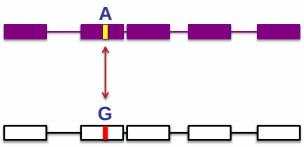
Single Nucleotide Polymorphisms



Single-base mutation at a locus

Polymorphic – variant is segregating in the human population

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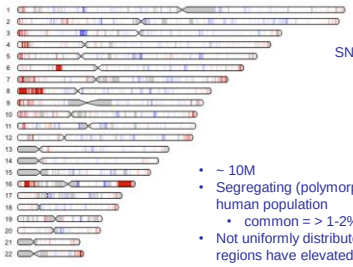
Many SNPs in the Human Genome



SNP Density

- ~ 10M
- Segregating (polymorphic) in the human population
  - common = > 1-2%
- Not uniformly distributed (red regions have elevated SNP density)

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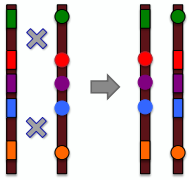
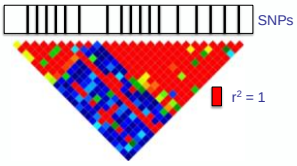
Surveying the Genome with Tag SNPs

Recombination



Linkage Dysequilibrium
- Non-independent inheritance

Tag SNPs
- SNPs that represent regions of high LD



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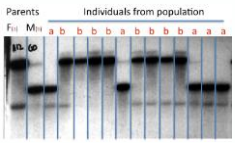
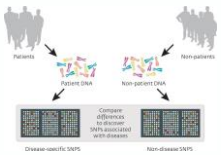
GWA Studies

Classic genetic linkage analysis



- Low throughput
- Bias – geneticist often looking at one (or a few) genes with some prior knowledge

Genome-Wide Analysis



- High throughput
- Less bias – survey SNPs that represent most of the genome

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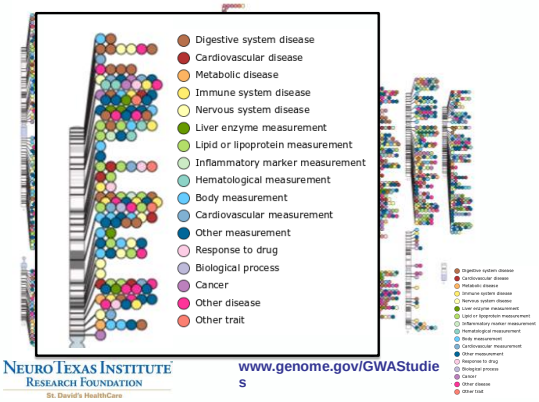
SNP:Disease Associations



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www.genome.gov/GWAStudies

SNP Genotyping

Microarray-based Assays ("chips")

Affymetrix GenomeWide 6.0
~ 1 M tag SNPs

Illumina HumanHap 550
~ 1 M tag SNPs

DNA Sequencing-based Assays

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Sequencing Based SNP Discovery

In a sequencing based method, we sequence genomes or genes of interest and compare our sequence data to known databases of variation

Next-Gen Sequencing (NGS)
- Costs are plummeting
- Exome (all protein coding genes) ~ $2K
- Whole Genome ~ $6-8K

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Arrays versus Sequencing

- "Chips"
  - Cheaper (for now…)
  - Survey common variants (> 2% within population)
  - Not identifying the causal variant(s); most introns and intergenic
- Sequencing
  - Identify common and rare variants
  - May identify new mutations and causal variant(s)
  - Can also get coding sequence of many genes

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GWA Study Design

- Trait or phenotype of interest
  - Discrete – categorical or case-control study
  - Continuous – quantitative study
- Power to detect significant associations
- Chip-based assay or NGS genotyping

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GWAS Power

Image of typical Affymetrix GW6.0 hybridization
~ 1M SNPS, 11X redundancy

Large multiple-testing load:

- Bonferroni:
  $q_{(i)} = \alpha/N = 0.05/10^6 \approx 10^{-8}$
- FDR and derivatives:

$$q_{(i)} = \frac{Np_{(}i)}{i}c(N)$$

Overcoming the load:
- Large N, but expensive and time-consuming
- Test fewer SNPs, for example two-stage GWAS

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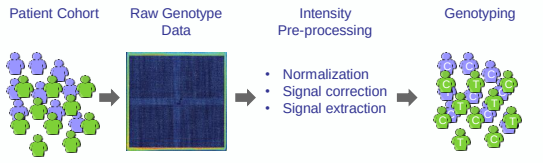
Array Data Processing



Affy: Birdsuite
Illimuna: BeadStudio

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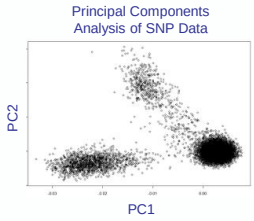
Additional Data Considerations

- Genotype curation
  - Missingness
  - Hardy-Weinberg Equilibrium
  - Odd Mendelian Inheritance Patterns
- Population Stratification



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GWAS Study Design: Case-Control

Cases
(affected with some disease)

Controls
(not affected)

	Case	Control
C	8	5
T	2	5

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Case-Control Statistics

- Count frequency of each *allele* in case and control population
- Only identify significant differences in frequency
- No models of dominance, recessiveness, etc.

	Case	Control
C	16	10
T	4	10

Chi-Square Test

$$\chi^2 = \sum_i \frac{(O_i - E_i)^2}{E_i}$$

Fisher's Exact Test

$$p = \frac{\binom{N_{cases}}{N_{cases_C}}\binom{N_{ctl}}{N_{ctl_C}}}{\binom{N}{N_C}}$$

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Case-Control Statistics

- Model frequencies of *genotypes*
- Can model interactions between alleles (e.g. dominance)

	Case	Control
C/C	6	3
C/T	3	4
T/T	1	3

Cochran-Armitage Trend Test

$$T \equiv \sum_{i}^{(CC,CT,TT)} w_i(N_{case_i}R_{ctl} - N_{ctl_i}R_{case})$$

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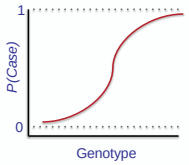
Case-Control Statistics

- Modeling probability of case
- Potential for prediction and/or classification
- Covariates can be included

Logistic Regression

$$log(\frac{P}{1-P}) = \beta_1 x + \beta_0$$



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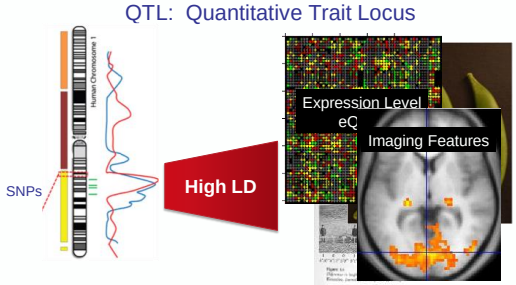
Quantitative Association Studies

QTL: Quantitative Trait Locus



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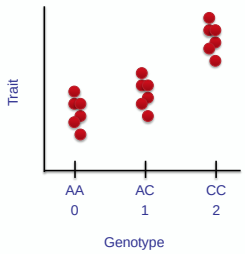
Quantitative GWAS Statistics

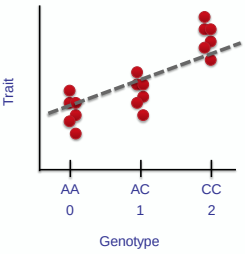


Spearman's correlation Coefficient (*rho*)

$$\rho = 1 - \frac{6\sum d_i^2}{n(n^2-1)}$$

d_i = difference in ranks between genotype and trait values

Quantitative GWAS Statistics



Linear Regression

$$Y = \beta_i X + \beta_0$$

- Models
- Covariates
- Perhaps less robust

GWAS Software

- Pre-processing:
  - Affy PowerTools/Birdsuite @ Affymetrix
  - Illumina BeadStudio for Illumina data
  - RMA adjustment – many implementations in MATLAB, R/Bioconductor, and more
  - Eigenstrat - http://genetics.med.harvard.edu/reich/Reich_Lab/Software.html
- Associations
  - PLINK: http://pngu.mgh.harvard.edu/~purcell/plink/
  - GWASTools: http://www.bioconductor.org/packages/devel/bioc/html/GWASTools.html
  - Merlin: http://www.sph.umich.edu/csg/abecasis/merlin/index.html

GWAS Data

- Raw data:
  - dbGAP: http://www.ncbi.nlm.nih.gov/gap
  - dbSNP: http://www.ncbi.nlm.nih.gov/SNP/
  - Other repositories:
    - NIH validated: http://gds.nih.gov/02dr2.html
    - ADNI: http://www.adni-info.org/
    - TCGA: http://cancergenome.nih.gov/
    - Ask researchers for source data…
- Meta-data
  - GWAS Catalog: http://www.genome.gov/gwastudies/

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Alzheimer's Disease

- Most common form of dementia
  - Familial – defects in APP processing
  - Sporadic – mutations in APOE-4, CLU, CR1, …
- Loss of memory and other cognitive functions

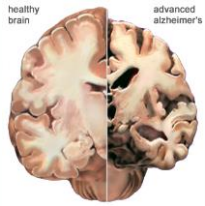

Image: www.alz.org

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Identifying Risk Factors for Alzheimer's Disease

- Diagnostic image-based biomarkers for development of AD
- Identifying genes and pathways that can improve power of imaging biomarkers
- Improve CAD systems for early detection and tracking progression of Alzheimer's disease

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AD Imaging Genomics

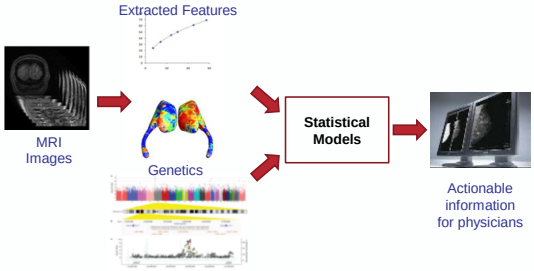

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Image-Genomics Study

- Meta-analysis of AD GWAS studies identified10 candidate genes
  - Replicated in multiple studies
  - APOE/TOMM40, ABCA7, BIN1, CD2AP, CD33, CLU, CR1, EPHA1, MS4A4/MS4A6A, PICALM
  - 66 candidate SNPs
- Quantitative phenotypes
  - Imaging features (e.g. hippocampus volume)
  - CSF biomarkers

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Example Associations

Gene	SNPs	Imaging Feature
ESR1 (Estrogen receptor 1)	rs9341052, rs9341052	Ventricular enlargement
BIN1 (Bridging integrator 1)	rs17014923, rs749008	Third-ventricle enlargement
SORCS1 (Sortilin-related VPS10 domain receptor 1)	rs6584777	Left-inferior lateral ventricle enlargement
EPHA1 (EPH receptor A1)	rs4726618	Left-inferior lateral ventricle enlargement

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Acknowledgements

TACC


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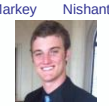
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Matthew C. Cowperthwaite, PhD

matthew.cowperthwaite@stdavids.com

(512) 544-8059

For more information:
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