New Methods and Ideas

Jurg Ott

Main Problem

- Common heritable traits show a complex mode of inheritance. Selection against them not efficient.
- Multiple disease genes – marker-by-marker analysis not powerful.
- Statistics: Need to develop analysis methods specifically for complex traits.
- Biology: Animal models. Conserved sequences. Expression experiments.

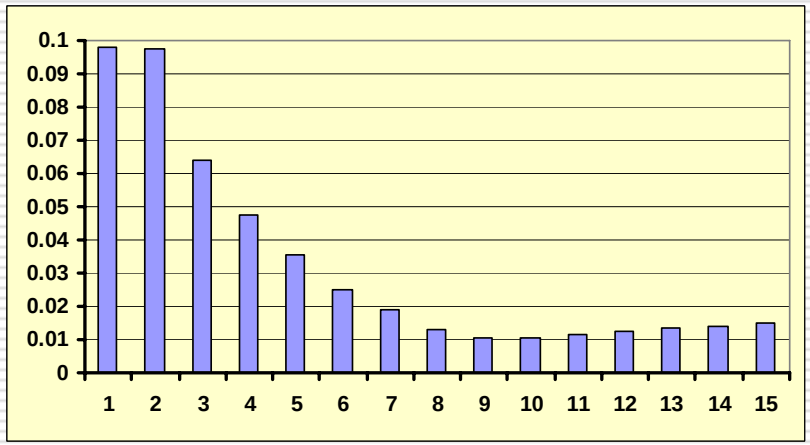
Multi-Locus Analysis Methods

- Aim: Analyze multiple SNPs/genes jointly. *Two classes*:
- (1) Combine single-locus statistics over multiple SNPs (wherever they are in genome)
- (2) Look for patterns of genotypes (or alleles) at SNPs in different genomic locations

Set Association method

Hoh *et al*. (2001) *Genome Res* **11**, 2115

- Let t_i = association statistic for i-th marker, ordered by size.
- Build sums, e.g. $s_2 = t_1 + t_2$, $s_3 = t_1 + t_2 + t_3$.
- Sums larger than expected? Permutation tests, *p*-values
- Smallest *p*-value = single experiment-wise statistic → overall significance level



Pure Epistatic Interaction

Frankel & Schork (1996) *Nat Genet* **14**, 371

P(A) = P(B) = 0.50	0.25 AA	0.50 Aa	0.25 aa	Marginal penetrance
BB 0.25	0	0	1	0.25
Bb 0.50	0	0.5	0	0.25
bb 0.25	1	0	0	0.25
Marg.pen.	0.25	0.25	0.25	

Equal penetrances:
P(AA|aff) =
P(Aa|aff) =
P(aa|aff)

But
P(AA,bb|aff)=0.25
P(Aa,Bb|aff)=0.50

Interestingly, there is linkage information (but no association information): Allele sharing for affected sibpairs exceeds 0.50 at single locus

	no sh.	share	
no sh.	0.20	0.23	0.43
share	0.23	0.34	0.57
	0.43	0.57	1

Extensions of *Set Association* Method

- Limitation of basic approach: Rests on single-locus significance
- Allow for all pairs of interactions: Create $n \times (n - 1)/2$ new variables as products of SNP codes

SNP genotype	Code
AA	-1
AG	0
GG	+1

SNP1 / SNP2	-1	0	+1
-1	+1	0	-1
0	0	0	0
+1	-1	0	+1

CPM = Combinatorial Partitioning Method

- Nelson *et al* (2001) *Genome Res* **11**, 458-470
- Extension of ANOVA to multiple loci for QTLs
- Method very time-consuming on computer. Application to plasma triglyceride levels in 188 males: Many loci involved.
- Not significant: $p = 0.14$

The *Interheart* Study

Risk factors for myocardial infarction (coronary heart disease) in 52 countries (Yusuf *et al* [2004] *Lancet* 364, 937-952)

12,461 cases
14,637 controls

	Prevalence		Odds ratio (99% CI) adjusted for age, sex, and smoking (OR 1)	PAR (99% CI)
	Controls (%)	Cases (%)		
Risk factor				
Current smoking*	26·76	45·17	2·95 (2·72–3·20)	–
Current and former smoking*	48·12	65·19	2·27 (2·11–2·44)	36·4% (33·9–39·0)
Diabetes	7·52	18·45	3·08 (2·77–3·42)	12·3% (11·2–13·5)
Hypertension	21·91	39·02	2·48 (2·30–2·68)	23·4% (21·7–25·1)
Abdominal obesity (2 *vs* 1)†	33·40	30·21	1·36 (1·24–1·48)	–
Abdominal obesity (3 *vs* 1)†	33·32	46·31	2·24 (2·06–2·45)	33·7% (30·2–37·4)
All psychosocial‡	–	–	2·51 (2·15–2·93)	28·8% (22·6–35·8)
Vegetables and fruit daily*	42·36	35·79	0·70 (0·64–0·77)	12·9% (10·0–16·6)
Exercise*	19·28	14·27	0·72 (0·65–0·79)	25·5% (20·1–31·8)
Alcohol intake*	24·45	24·01	0·79 (0·73–0·86)	13·9% (9·3–20·2)
ApoB/ApoA1 ratio (2 *vs* 1)§	19·99	14·26	1·47 (1·28–1·68)	–
ApoB/ApoA1 ratio (3 *vs* 1)§	20·02	18·05	2·00 (1·74–2·29)	–
ApoB/ApoA1 ratio (4 *vs* 1)§	19·99	24·22	2·72 (2·38–3·10)	–
ApoB/ApoA1 ratio (5 *vs* 1)§	20·00	33·49	3·87 (3·39–4·42)	54·1% (49·6–58·6)
All above risk factors combined¶	–	–	129·20 (90·24–184·99)	90·4% (88·1–92·4)

Genomic Priorities and Public Health

Merikangas & Risch (2003) *Science* 302, 599-601

- The translation of genomics to human disease will most likely involve genetic counseling, drug therapy, and gene therapy … most effective for rare diseases at the level of the individual (e.g., PKU).
- In contrast, public health prevention is most effective when applied to common diseases at the population level.

Current State of the Art

- Databases: Human DNA sequence, several millions of SNP markers
- Pharmacogenetics: Individual genetic differences in drug metabolism
- Paternity testing, personal identification
- Cloning of vertebrates, human embryos to regenerate new organs

OMIM, **O**nline **M**endelian **I**nheritance of **M**an

- Book originated by Prof. Victor McKusick
- Now database of disease genes

Status 14 Sep 2005	Autosomal	X-Linked	Y-Linked	Mitochondrial	**Total**
* Gene with known sequence	9781	449	48	37	10315
+ Gene with known sequence and phenotype	362	32	0	0	394
# Phenotype description, molecular basis known	1614	143	2	25	1784
% Mendelian phenotype or locus, molecular basis unknown	1350	134	4	0	1488
Other, mainly phenotypes with suspected mendelian basis	2106	148	2	0	2256
Total	15213	906	56	62	**16236**

Risk Prediction

- Susceptibility to Alzheimer disease
- Personal genetic profile
- Insurance companies: Recognize genetically vulnerable individuals?
- Personal set of genetic markers on “credit card”-sized computer chip
- Computer break-ins

Genetics/Medicine/Business

- Patenting of genes (BRCA1; AMD)
- Services for DNA testing

DNA Forensics

Genealogy Testing

Paternity Testing

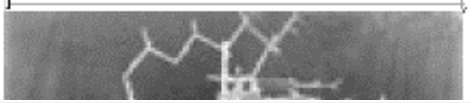
DNA Sequencing

DNA Equipment

Population Genetics

Phylogenetics

DNA History



Ads by Goooooogle

Paternity Test Kits $150
Greater than 99.9999% accuracy! Free Shipping. Results in 3-5 days.
www.internationalpaternity.com

Dna Sequencing
Gene Sequencing Analysis System. Achieve Fast & Accurate Results.
www.appliedbiosystems.com

Get a DNA Test
Testing above 99.9999% accuracy DNA paternity testing since 1997
www.dnanow.com

Gene Therapy

- Severe combined immunodeficiency (SCID), rare, most often X-linked ("bubble boy disease")
- One of the few successful gene therapies
- Cloning?

BBC NEWS WORLD EDITION

Last Updated: Friday, 17 December, 2004, 00:20 GMT

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Boys 'cured' with gene therapy

Four UK children born with a condition robbing them of their natural defences against infection have had successful gene therapy treatment, doctors say.

Gene therapy adds to the body, via a leukaemia virus, a fully functioning version of the mutated gene that causes severe combined immunodeficiency.

Rhys Evans was the first child to receive the treatment in the UK

“Will Genetics Revolutionize Medicine?”

NA Holtzman, TM Marteau (2000) *NEJM* 343, 141-144

- “The complexity of the genetics of common diseases casts doubt on whether accurate prediction will ever be possible”
- “Differences in social structure, lifestyle, and environment account for much larger proportions of disease than genetic differences”

Obesity – Genetics vs. Environment

Public Health Policies versus Genetic Intervention

Pop losing its fizz in school vending machines

Soft drink makers to stop selling sugary soda, offer alternatives to kids. NBC News correspondent Martin Savidge reports

Today show
Updated: 11:14 a.m. ET Aug. 18, 2005

According to a study, ice cold soda pop contributes the most calories to the American diet. In response to consumer pressure, the American Beverage Association is limiting the amount of sugary drinks it sells in schools. NBC News correspondent Martin Savidge reports.

Increasingly, pop in school has been going over like a belch in English class. Parents and health advocates concerned with obesity in children see the sugar-laden soft drinks as one of the prime culprits.

Soft drink makers, including giants Coca-Cola and Pepsi, will stop selling sugary soda in elementary and middle schools. They will also cut back sales in high schools – instead offering water, 100 percent fruit juices and diet drinks.