#### Genome-wide Association Studies (GWAS) #6

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# LETS GET STARTED



### AGENDA

08:15 – 08:30	Recap [Complex triats and genetic parameters]
08:30 - 09:00	Group presentations from last
09:00 - 09:15	Break
09:15 – 09:45	Lecture 1 [Genetic associations + GWAS part 1]
09:45 – 10:15	Exercise 1 + 2
10:15 – 10:30	Break
10:30 - 11:00	Lecture 2 [GWAS part 2]
11:00 - 11:55	Group work
11:55 – 12:00	Evaluation at Moodle

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### MULTIFACTORIAL INHERITANCE

- Monogenic (single gene/variant)
- Polygenic (multiple gene variants at the same time)
- Multifactorial (multiple gene variants + environment variation)





#### Continous variation



#### Categorical variation



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#### Dichotomous outcome



### LIABILITY (THRESHOLD) MODEL



### **Liability model**

Only individuals with a liability over a certain threshold will become affected

The **sum** of many genetic variants with **small effect/risk**.

Each locus follow Mendelian inheritance pattern, although the trait does not

# **GENETIC VARIATION**



Multifactorial traits are caused by the sum of MANY variants exherting small effects



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Environmental variance (non-genetic factors) blurs phenotypic classes



Genotypic and environmental variance creates infinite many phenotypic classes



### **BROAD-SENSE HERITABILITY**

Broad-sense heritability ( $H^2$ ) describes the proportion of the phenotypic variance that is explained by genetic difference variation.

$$V_P = V_G + V_E$$
$$H^2 = \frac{V_G}{V_P} = \frac{V_G}{V_G + V_E}$$

TT

#### $H^2$ can take values between 0 and 1:

 $H^2 = 0$  → all variation is due to environmental variation  $H^2 = 1$  → all variation is due to genetic variation



# **USING TWINS TO ESTIMATE** $H^2$



Compare MZ  $[V_e]$  and DZ  $[V_G + V_E]$  twins – the difference is  $V_G$ 

### USING TWINS TO ESTIMATE $H^2$ QUANTITATIVE COMPLEX TRAITS



Trait value of one twin

Because DZ share 50% of the genetic material

$$H^2 = 2(r_{MZ} - r_{DZ})$$

All phenotypic variation between MZ is environment, whereas all phenotypic variation between DZ is both

Thus, the difference is genetic variation



### USING TWINS TO ESTIMATE $H^2$ DICHOTOMOUS COMPLEX TRAITS

**Concordance rate (***C***)** = the frequency with which the other twin has the trait





Discordant pair: only one in the pair has the trait

#### <u>Important</u>

$$H^2 = \frac{C_{MZ} - C_{DZ}}{1 - C_{DZ}}$$

There has to be a difference between  $C_{MZ}$  and  $C_{DZ}$  for a trait to be under genetic influence

The larger ratio  $\frac{C_{MZ}}{C_{DZ}}$  the higher  $H^2$ 

If  $C_{MZ} < 1$  environmental exposures affect the trait

# GROUP WORK

THE HERITABILITY OF HUMAN DISEASE

#### PART 1

- 1) Make 4 groups & prepare a 5-7 min presentation
  - Group 1 & 3 works with section 'Estimating heritability' p141-144
     Group 2 & 4 works with section 'Biased heritability' p144-148

#### PART 2 – *next time* (17/3)

- Group 1 present to group 2 and vise versa
- Group 3 present to group 4 and vise verse

#### What did you find difficult?



Artiklen er på et meget højt og svært niveau, som kan være ret svær at forstå - selvom man har læst den flere gange ·(



# BREA

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- **09:15 09:45** Lecture 1 [Genetic associations + GWAS part 1]
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### **GENETIC ASSOCIATION**





### **INHERITANCE PATTERN** OF MULTIFACTORIAL TRAITS

The exact inheritance pattern depends on

- The number of risk genes/alleles involved
- The effect size distribution of the genetic risk variants
- The interaction among genetic variants
- The interaction with environmental exposures



#### Monogenic disorders





Each genetic variant is both necessary and sufficient

Linkage analysis (pedigree)

#### **Common complex disorders**



Association study (unrelated population)



What does association mean

# ASSOCIATION

An association defines a relationship between two entity objects based on common attributes.



Is there an association between exposure and outcome?



### **ASSOCIATION NOT CAUSATION**

Country	Area (km <sup>2</sup> )	Storks (pairs)	Humans (10 <sup>6</sup> )	Birth rate $(10^3/yr)$
Albania	28,750	100	3.2	83
Austria	83,860	300	7.6	87
Belgium	30,520	1	9.9	118
Bulgaria	111,000	5000	9.0	117
Denmark	43,100	9	5.1	59
France	544,000	140	56	774
Germany	357,000	3300	78	901
Greece	132,000	2500	10	106
Holland	41,900	4	15	188
Hungary	93,000	5000	11	124
Italy	301,280	5	57	551
Poland	312,680	30,000	38	610
Portugal	92,390	1500	10	120
Romania	237,500	5000	23	367
Spain	504,750	8000	39	439
Switzerland	41,290	150	6.7	82
Turkey	779,450	25,000	56	1576



#### Number of stork breeding pairs

#### Coefficients: Estimate Std. Error t value Pr(>|t|) (Intercept) 2.250e+02 9.356e+01 2.405 0.0295 \* Storks 2.879e-02 9.402e-03 3.063 0.0079 \*\*

Signif. codes: 0 '\*\*\*' 0.001 '\*\*' 0.01 '\*' 0.05 '.' 0.1 '' 1

# ASSOCIATION

Is there an association between genetic variant and disease status?



Outcome

Common variants have small effect on outcome (OR=1.1-1.8)

OR>1 -allele is risk allele

-allele is seen more often among cases

#### OR<1

-allele is protective -allele is seen more often among controls

#### Odds

Odds ratio (OR) is the ratio of the odds of disease among the exposed to the odds of disease among the unexposed

$$OR = \frac{a/b}{c/d} = \frac{a \times d}{c \times b}$$

LBORG UNIVERSITY Rare variants may have a strong effect on outcome (large OR)

### ASSOCIATIONS ALLELIC VS GENOTYPIC

We can count alleles OR genotypes. Example;

Association of rs6983267 on 8q24 with colorectal cancer [C/T, allele C is the risk allele]

#### **GENOTYPIC** ASSOCIATION

$OR_{TT} =$	$\frac{odds(disease TT)}{odds(disease TT)} =$	Note (the	e, these ORs are relative to TT lowest-risk genotype)
$OR_{CT} =$	$\frac{odds(disease CT)}{odds(disease TT)} =$	$\frac{375 \times 500}{940 \times 150} =$	= 1.33
$OR_{CC} =$	$\frac{odds(disease CC)}{odds(disease TT)} =$	$\frac{250 \times 500}{460 \times 150} =$	= 1.81

	СС	СТ	П
Cases	250	375	150
Controls	460	940	500

### ASSOCIATIONS ALLELIC VS GENOTYPIC

We can count alleles OR genotypes. Example;

Association of rs6983267 on 8q24 with colorectal cancer [C/T, allele C is the risk allele]

	С	т
Cases	875	675
Controls	1860	1940

#### **ALLELIC** ASSOCIATION

Cases	C alleles = 2 * 250 CC + 375 CT = 875 T alleles = 2 * 150 TT + 375 CT = 675	
Controls	C alleles = 2 * 460 CC + 940 CT = 1860 T alleles = 2 * 500 TT + 940 CT = 1940	
	$odds(disease(C)) = 875 \times 194($	ן

$$OR_C = \frac{odds(disease|C)}{odds(disease|T)} = \frac{875 \times 1940}{1860 \times 675} = 1.35$$

### **GENETIC RISK FOR** LUNG CANCER?

#### FRS

#### A susceptibility locus for lung cancer maps to nicotinic acetylcholine receptor subunit genes on 15q25



associated with the risk of developing lung cancer.

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#### Does that then mean that CHRNA3/5 is a risk loci for LC?

#### Risk loci for nicotine addition $\rightarrow$ addicted to smoking $\rightarrow$ increase LC risk

### GENOME-WIDE ASSOCIATION ANALYSIS (GWAS) – PART 1

- What is a GWAS
- LD





# GENOME-WIDE ASSOCIATION STUDY (GWAS)

A systematic analysis of all common genetic variants without a priori hypothesis.

The aim is to identify risk variants for complex traits.

Testing one variant at a time



**ASSOCIATION TESTING** 





No association

Association



### THE BIOMETRIC MODEL WHY THIS MODEL?



Consider a single locus with two alleles;  $A_1$  and  $A_2$ , with the frequencies p and q. Under HWE, the genotype frequencies are  $p^2$ , 2pq, and  $q^2$ .

Under the biometric model, the genotypic value of  $A_1A_1$  is a, and -a for  $A_2A_2$ . The genotype calue for  $A_1A_2$  is d.

In this model, every single genetic variant with non-zero effect on a phenotype contributes to the population mean (P = G + E).



### THE BIOMETRIC MODEL WHY THIS MODEL?



The mean effect (on the phenotype) is a function of the genotype effects (-a, a, and d) weighted by allele frequencies:

$$(ap^{2}) + (d2pq) + (-aq^{2}) = a(p - q) + d2pq$$

Polygenic traits are influenced by many genetic variants; thus, assuming additive and independent effects, the population mean is:



$$u = \sum_{i=1}^{m} a_i (p_i - q_i) + \sum_{i=1}^{m} d_i 2p_i q_i$$

$$A_2 A_2 A_1 A_2 A_1 A_1$$

$$-q 0 d + q$$

### HOW MANY SITES IN THE GENOME?

Should we test ALL 3,000,000,000 nucleotides within the genome?

No necessary, because of an old fried – Linkage Disequilibrium (LD)



### WHAT IS LD?



Which gamtes can be produced?



What are the frequencies of the alleles?

P(A), P(a) P(B), P(b)

What are the frequencies of the haplotypes?

P(AB), P(Ab) P(aB), P(ab)



# WHAT IS LD?



If there is random relationship among alleles at the two loci then the frequency of the haplotypes will be the product of the

frequencies of the two alleles:

P(AB)=P(A)xP(B)P(Ab)=P(A)xP(b)P(aB)=P(a)xP(B)P(ab)=P(a)xP(b)





# WHAT IS LD?





AALBORG UNIVERSITY When the association between alleles at two loci is **nonrandom** they are said to be in **linkage disequilibrium** 

The degree of LD can be measure in several ways – the simples one is:

If D=0, no LD, if D>0 LD

 $\boldsymbol{D} = \boldsymbol{P}_{AB} - \boldsymbol{P}_{A}\boldsymbol{P}_{B}$ 


### LD AND GENE MAPPING



#### **Linkage disequilibrium** – non-random association

SNP	ð	ð	ð	ð	ð	ð	ð	ð	ð	ð	ð	ð	ð	ð
A 1 B 2 C 2 D 2 E 2 F 2 G 1	2 1 1 1 1 1 2	2 2 2 2 2 2 2 2 1	1 1 1 1 1 1 2	2 1 1 1 1 1 1 1	2 2 2 2 2 2 2 2 2	1 1 1 1 1 2	2 1 1 1 1 1 1 1	1 1 1 1 1 1	1 1 1 1 1 1 2	1 2 2 2 2 2 2 2 2 2 2	2 1 1 1 1 1 1 1	2 2 2 2 2 2 2 2 2 1	2 2 2 2 2 2 2 2 2 2 2 2 2 2 2	1 2 2 2 2 2 2 2 2 2 2
A			в		c	D			E		F			G



### LD AND GENE MAPPING



If you have allele 1 here, I know what you are at the remaing sites in this haploblok

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### HOW MANY SITES IN THE GENOME?

Should we test ALL 3,000,000,000 nucleotides within the genome?

No necessary, because of an old fried – Linkage Disequilibrium (LD)

Typically, we test 5,000,000 - 10,000,000 SNPs.



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### GENOME-WIDE ASSOCIATION ANALYSIS (GWAS) – PART 2

- What is a GWAS
- LD
- GWAS by steps





### **1. Select trait/disease**

# **SELECT PHENOTYPE**



Do we know anything about the phenotype already? Is it heritable?

Do we know whether it is monogenic or polygenic?

Is it a common or rare disorder?



**2. Extract genetic variants** 

**1. Select trait/disease** 



Because of LD you do not have to analyse all 3,000,000,000 variants in the genome.

Typically, we genotype  $\frac{1}{2}$  - 1 million variants

Because of LD we can impute ("guess" what variants are next to the genotyped variant) up til 10 million common genetic variants.



### IMPUTATION USING HAPLOTYPES

#### The true haplotypes

А	Т	С
G	С	А

This individual has inherited a chromosome with alleles A-T-C from one parent, and G-C-A from the other parent

#### We observe only the genotypes

A/G T/C C/A

Genotype data does not carry information about the haplotypes.

We do not know whether A at SNP1 is coming from the same parent as T or C at SNP2

#### **Different haplotypes**

А	С	А
А	С	С
А	Т	А
А	С	А
G	С	А
G	С	С
G	Т	А

Т

G

**Phasing** = estimate the most likely haplotypes

С

## IMPUTATION

#### Genotypes

#### **Study sample**

A A A A G C A

#### **Reference haplotypes**

CGAGATCTCCTTCTTCTGTGC CGAGATCTCCCGACCTCATGG CCAAGCTCTTTTCTTCTGTGC CGAGACTCTCCGACCTTATGC TGGGATCTCCCGACCTCATGG CGAGACTCTCCCGACCTTGTGC CGAGACTCTTCCCGACCTTGTGC CGAGACTCTCCCGACCTCGTGC CGAAGCTCTTTCTTCTGTGC

From a sequencing study

#### Study sample

A. A. A. G. C. A. A.

#### **Reference haplotypes**



#### **Study sample**

cgagAtctcccgAcctcAtgg cgaaGctcttttCtttcAtgg

#### **Reference haplotypes**

CGGCCCCCGGCAATTTTTTT CGAGATCTCCCGACCTCATGG CCAAGCTCTTTCTTCTGTGC CGAAGCTCTTTCTTCTGTGC CGAGACTCTCCCGACCTTATGC TGGGATCTCCCGACCTCATGG CGAGACTCTTCCCGACCTTGTGC CGAGACTCTTCCGACCTCGTGC CGAGACTCTCCCGACCTCGTGC



3. GWAS

2. Extract genetic variants 1. Select trait/disease

# STATISTICAL ANALYSIS

For each genetic variant [genotyping chip or after imputation] measure the degree of association between SNP and disease/trait

#### **Fischers exact test**

Outcome



#### **Linear regression**

Allow us to account for confunding effects like, sex, age and ancestry.

#### If trait follows Gaussian distribution:

- Linear regression
- Linear Mixed Model

#### If trait is dichotomous:

 Linear model with non-linear transformation [logistic regression with logit(x)]





### ANCESTRY AFFECTS ALLELE FREQUENCIES

They surveyed genetic variation in a sample of **3,192 European** individuals which were genotyped at 500,568 loci using the Affymetrix 500K single nucleotide polymorphism (SNP) chip.

"Our main result holds even when we relax nearly all of these stringency criteria, we focus our analyses on genotype data from 197,146 loci in 1,387 individuals (Supplementary Table 2), for whom we have high confidence of individual origins."







### 4. Summaries 10M linear regressions

3. GWAS 2. Extract genetic variants 1. Select trait/disease

chromosome base\_pair\_location ID REF ALT A1 TEST OBS\_CT BETA SE T\_STAT p\_value 1 752721 1:752721:A:G G A A ADD 1173 -0.0213326 0.0574282 -0.371466 0.710358 794332 1:794332:G:A G A A ADD 1173 0.0167258 0.0751683 0.222512 0.823954 1 840753 1:840753:T:C T C C ADD 1173 0.034768 0.0424801 0.818454 0.413265 845635 1:845635:C:T C T T ADD 1173 0.010575 0.0504211 0.209734 0.833912 845938 1:845938:G:A G A A ADD 1173 0.0138978 0.0501171 0.277307 0.781593 846078 1:846078:C:T C T T ADD 1173 0.0154452 0.052242 0.295648 0.767551 846398 1:846398:G:A G A A ADD 1173 0.0097726 0.0507151 0.192696 0.84723 846808 1:846808:C:T C T T ADD 1173 0.0130275 0.0521993 0.249572 0.802962 1 846864 1:846864:G:C G C C ADD 1173 0.0154452 0.052242 0.295648 0.767551 847228 1:847228:C:T C T T ADD 1173 -0.00163479 0.0514492 -0.0317749 0.974657 847491 1:847491:G:A G A A ADD 1173 0.00426234 0.0504764 0.0844423 0.932719 1 848090 1:848090:G:A G A A ADD 1173 0.00519704 0.050492 0.102928 0.918038 848445 1:848445:G:A G A A ADD 1173 -0.0174173 0.0505568 -0.34451 0.730525 848456 1:848456:A:G A G G ADD 1173 -0.0174173 0.0505568 -0.34451 0.730525 848738 1:848738:C:T C T T ADD 1173 0.00519704 0.050492 0.102928 0.918038 850062 1:850062:A:T A T T ADD 1173 0.00426234 0.0504764 0.0844423 0.932719 850123 1:850123:C:T C T T ADD 1173 0.00519704 0.050492 0.102928 0.918038 851190 1:851190:G:A G A A ADD 1173 0.00800137 0.0504533 0.15859 0.87402 851204 1:851204:G:C G C C ADD 1173 0.00799277 0.0503183 0.158844 0.873819 1 852664 1:852664:C:T C T T ADD 1173 -0.00285601 0.0508564 -0.0561584 0.955225 852758 1:852758:G:C G C C ADD 1173 -0.00285601 0.0508564 -0.0561584 0.95522 853239 1:853239:A:G A G G ADD 1173 -0.00285601 0.0508564 -0.0561584 0.955225 1 854250 1:854250:A:G A G G ADD 1173 -0.0034348 0.0508285 -0.0675762 0.946135 858040 1:858040:C:A C A A ADD 1173 0.00473544 0.0504763 0.093815 0.925272 858051 1:858051:C:T C T T ADD 1173 0.00473544 0.0504763 0.093815 0.925272 864002 1:864002:G:C G C C ADD 1173 0.0184693 0.0500163 0.369265 0.711997 865219 1:865219:G:A G A A ADD 1173 0.00750316 0.0504318 0.148778 0.881754 866893 1:866893:T:C C T T ADD 1173 0.00632305 0.0422389 0.149697 0.881029 866938 1:866938:G:A G A A ADD 1173 0.00705206 0.0485498 0.145254 0.884535 867635 1:867635:C:T C T T ADD 1173 0.00750316 0.0504318 0.148778 0.881754 1 872352 1:872352:G:C G C C ADD 1173 0.00960345 0.0468868 0.204822 0.837747 1 877147 1:877147:G:A G A A ADD 1173 -0.0115154 0.0473281 -0.243309 0.807809 881627 1:881627:G:A A G G ADD 1173 0.0502509 0.0422311 1.1899 0.234326 1 882033 1:882033:G:A G A A ADD 1173 -0.00689009 0.0470492 -0.146444 0.883596 888659 1:888659:T:C C T T ADD 1173 0.206878 0.0865338 2.39072 0.0169728 889238 1:889238:G:A G A A ADD 1173 0.21628 0.0890064 2.42994 0.0152507 890104 1:890104:G:A G A A ADD 1173 0.00331508 0.0468322 0.0707863 0.94358 894573 1:894573:G:A A G G ADD 1173 0.141979 0.0688431 2.06235 0.0393945 897564 1:897564:T:C C T T ADD 1173 0.179375 0.0798978 2.24505 0.0249507 897738 1:897738:C:T C T T ADD 1173 0.179541 0.0802621 2.23693 0.0254787 898467 1:898467:C:T C T T ADD 1173 0.21628 0.0890064 2.42994 0.0152507 900730 1:900730:G:A A G G ADD 1173 0.118829 0.073338 1.62029 0.105439 903321 1:903321:G:A A G G ADD 1173 0.00298207 0.0566348 0.0526544 0.958016 903426 1:903426:C:T C T T ADD 1173 -0.00799923 0.0476482 -0.167881 0.866706 908823 1:908823:G:A G A A ADD 1173 0.00223841 0.0556691 0.0402093 0.967933 909309 1:909309:T:C T C C ADD 1173 0.0218323 0.0549488 0.397322 0.691203 910473 1:910473:G:A G A A ADD 1173 -0.0200586 0.0576243 -0.348092 0.727834 1 911916 1:911916:C:T С Т T ADD 1173 -0.0308612 0.0547515 -0.563659 0.573094 912049 1:912049:T:C C T T ADD 1173 -0.0461071 0.0412247 -1.11843 0.263611 1 913610 1:913610:G:A G A A ADD 1173 -0.0308612 0.0547515 -0.563659 0.573094 913889 1:913889:G:A A G G ADD 1173 -0.0569182 0.0413668 -1.37594 0.169104 914333 1:914333:C:G G C C ADD 1173 -0.0631883 0.0414557 -1.52424 0.12772 1 914852 1:914852:G:C C G G ADD 1173 -0.0564599 0.0414123 -1.36336 0.173031 1 914940 1:914940:T:C C T T ADD 1173 -0.0612227 0.0411078 -1.48932 0.136672 l 916590 1:916590:G:A G A A ADD 1173 -0.0395153 0.0508336 -0.777347 0.437111 1 916662 1:916662:A:C A C C ADD 1173 -0.0288419 0.0546679 -0.527584 0.597888 1 917315 1:917315:G:A G A A ADD 1173 -0.0189492 0.0521825 -0.363134 0.71657 1 917492 1:917492:C:T C T T ADD 1173 -0.0288419 0.0546679 -0.527584 0.597888 1 917640 1:917640:G:A G A A ADD 1173 -0.0686789 0.0471771 -1.45577 0.145725 1 918238 1:918238:C:G C G G ADD 1173 -0.0686789 0.0471771 -1.45577 0.145725 1 918270 1:918270:C:T C T T ADD 1173 -0.0283636 0.0546403 -0.519097 0.603791 918384 1:918384:G:T T G G ADD 1173 -0.0612227 0.0411078 -1.48932 0.136672 I 918573 1:918573:A:G G A A ADD 1173 −0.0672691 0.0411436 −1.63499 0.102321 1 918617 1:918617:G:A G A A ADD 1173 -0.0283636 0.0546403 -0.519097 0.603791 1 919127 1:919127:T:C T C C ADD 1173 -0.0760187 0.0473807 -1.60442 0.108891 1 919419 1:919419:T:C C T T ADD 1173 -0.0131869 0.0458342 -0.287709 0.773621 1 919501 1:919501:G:T T G G ADD 1173 -0.021286 0.0410945 -0.517976 0.604573 1 919855 1:919855:G:A G A A ADD 1173 0.0272325 0.0574697 0.473859 0.635689 1 920503 1:920503:G:A G A A ADD 1173 -0.0442973 0.0559222 -0.792125 0.428448 920640 1:920640:C:T C T T ADD 1173 -0.0394462 0.0533635 -0.739197 0.459935 1 920977 1:920977:T:C T C C ADD 1173 -0.036718 0.0546361 -0.672046 0.501687 921660 1:921660:C:T C T T ADD 1173 -0.0976773 0.0474452 -2.05874 0.0397401 922009 1:922009:G:A G A A ADD 1173 -0.0976773 0.0474452 -2.05874 0.0397401 922483 1:922483:T:C T C C ADD 1173 -0.0341191 0.0546375 -0.624462 0.532446 1 924111 1:924111:T:A T A A ADD 1173 -0.0673679 0.0463855 -1.45235 0.146673 926968 1:926968:C:T C T T ADD 1173 -0.0341191 0.0546375 -0.624462 0.532446 927741 1:927741:G:A G A A ADD 1173 -0.0971668 0.0474453 -2.04798 0.0407849 1 928416 1:928416:G:A G A A ADD 1173 -0.0996545 0.0473337 -2.10536 0.0354725 1 929565 1:929565:G:T G T T ADD 1173 -0.0341191 0.0546375 -0.624462 0.532446 1 930329 1:930329:C:T C T T ADD 1173 -0.0975673 0.0473374 -2.0611 0.0395136

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1 1239935 1:1239935:A:C A C C ADD 1173 0.0517876 0.0646685 0.800818 0.4234

1 1247494 1:1247494:T:C C T T ADD 1173 0.0360545 0.0552873 0.65213 0.514445

1 1252309 1:1252309:A:T A T T ADD 1173 0.0468692 0.0642411 0.729583 0.465791

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1 1261133 1:1261133:G:T G T T ADD 1173 0.0520628 0.0645953 0.805984 0.420416

1 1279428 1:1279428:G:A G A A ADD 1173 0.0380408 0.0644592 0.590154 0.555202

1 1297065 1:1297065:C:T C T T ADD 1173 0.0316832 0.064659 0.490004 0.624223

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1 1299737 1:1299737:A:C A C C ADD 1173 0.0335727 0.0642482 0.522548 0.601388

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1 1303677 1:1303677:C:T C T T ADD 1173 0.035145 0.064318 0.546425 0.584878

1 1303894 1:1303894:C:G C G G ADD 1173 0.0335727 0.0642482 0.522548 0.601388

1 1304371 1:1304371:C:T C T T ADD 1173 0.0335727 0.0642482 0.522548 0.601388

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l 1304787 1:1304787:G:A G A A ADD 1173 0.035145 0.064318 0.546425 0.584878

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1 1305007 1:1305007:T:C T C C ADD 1173 0.035145 0.064318 0.546425 0.584878

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1305201 1:1305201:C:T C T T ADD 1173 0.035145 0.064318 0.546425 0.584878

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l 1305810 1:1305810:T:C T C C ADD 1173 0.035145 0.064318 0.546425 0.584878

1305912 1:1305912:C:T C T T ADD 1173 0.035145 0.064318 0.546425 0.584878

1 1308289 1:1308289:G:A G A A ADD 1173 0.0384997 0.0650228 0.592096 0.553901

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1 1316247 1:1316247:A:G A G G ADD 1173 0.0292424 0.0650789 0.449337 0.653272

1319123 1:1319123:T:C T C C ADD 1173 0.0292424 0.0650789 0.449337 0.653272

1 1329421 1:1329421:G:A G A A ADD 1173 0.0379752 0.0664912 0.571131 0.56802

1 1330430 1:1330430:G:A G A A ADD 1173 0.0223847 0.0890142 0.251473 0.801492

1 1330726 1:1330726:A:G A G G ADD 1173 0.0316078 0.0562552 0.561864 0.574316

1333598 1:1333598:C:A C A A ADD 1173 0.0311985 0.0660031 0.472683 0.636528

1335302 1:1335302:C:T C T T ADD 1173 0.0223847 0.0890142 0.251473 0.801492

1 1335790 1:1335790:A:G A G G ADD 1173 0.0316078 0.0562552 0.561864 0.574316

l 1337334 1:1337334:G:T G T T ADD 1173 0.0311985 0.0660031 0.472683 0.636528

1338280 1:1338280:A:G A G G ADD 1173 0.0223847 0.0890142 0.251473 0.801492

l 1338973 1:1338973:A:G A G G ADD 1173 0.0311985 0.0660031 0.472683 0.636528

1340696 1:1340696:T:C T C C ADD 1173 0.0223847 0.0890142 0.251473 0.801492

1342945 1:1342945:C:A C A A ADD 1173 0.0311985 0.0660031 0.472683 0.636528

1 1344067 1:1344067:T:C T C C ADD 1173 0.0583543 0.0834354 0.699396 0.484444

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1 1305121 1:1305121:C:T C T T ADD 1173 0.035145 0.064318 0.546425 0.584878

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1 1300074 1:1300074:T:C T C C ADD 1173 0.035145 0.064318 0.546425 0.584878

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1 2432749 1:2432749:G:A G A A ADD 1173 -0.00678173 0.0505337 -0.134202 0.893266 1 2436778 1:2436778:A:G A G G ADD 1173 -0.00810755 0.0493074 -0.164429 0.869422 1 2437305 1:2437305:G:A G A A ADD 1173 0.0123539 0.0505483 0.244399 0.806965 1 2437895 1:2437895:G:A G A A ADD 1173 0.0115262 0.052043 0.221475 0.824761 1 2438307 1:2438307:C:T C T T ADD 1173 0.0115262 0.052043 0.221475 0.824761 1 2438393 1:2438393:C:T C T T ADD 1173 0.0151133 0.0522185 0.289424 0.772308 1 2438612 1:2438612:C:T C T T ADD 1173 0.0115262 0.052043 0.221475 0.824761 1 2438828 1:2438828:C:T C T T ADD 1173 -0.0110763 0.0494521 -0.223981 0.822811 1 2438982 1:2438982:C:T C T T ADD 1173 -0.0116798 0.0503604 -0.231924 0.816638 1 2439191 1:2439191:A:G A G G ADD 1173 -0.00997032 0.0507094 -0.196617 0.844162 1 2441358 1:2441358:T:C T C C ADD 1173 -0.00985492 0.0494273 -0.199382 0.841998 1 2441392 1:2441392:T:C T C C ADD 1173 -0.0102305 0.0494438 -0.206913 0.836114 1 2442374 1:2442374:G:A G A A ADD 1173 -0.00997032 0.0507094 -0.196617 0.844162 1 2442953 1:2442953:C:A C A A ADD 1173 -0.00997032 0.0507094 -0.196617 0.844162 2443212 1:2443212:G:A G A A ADD 1173 -0.0116798 0.0503604 -0.231924 0.816638 1 2443655 1:2443655:G:A G A A ADD 1173 -0.00149073 0.0507589 -0.0293688 0.976575 2444226 1:2444226:C:T C T T ADD 1173 -0.0113433 0.0494352 -0.229459 0.818553 2445089 1:2445089:A:G A G G ADD 1173 -0.0114051 0.0497584 -0.22921 0.818745 2445406 1:2445406:A:G A G G ADD 1173 -0.0102305 0.0494438 -0.206913 0.836114 2446330 1:2446330:A:G A G G ADD 1173 -0.0102305 0.0494438 -0.206913 0.836114 L 2446960 1:2446960:T:C T C C ADD 1173 -0.0102305 0.0494438 -0.206913 0.836114 L 2447910 1:2447910:G:A G A A ADD 1173 -0.00927212 0.050568 -0.183359 0.854548 1 2448188 1:2448188:A:G A G G ADD 1173 -0.00997032 0.0507094 -0.196617 0.844162 1 2448561 1:2448561:G:A G A A ADD 1173 -0.00524131 0.0497783 -0.105293 0.916161 1 2448764 1:2448764:A:G A G G ADD 1173 -0.00695553 0.0494613 -0.140626 0.88819 1 2450394 1:2450394:A:G A G G ADD 1173 -0.00695553 0.0494613 -0.140626 0.88819 1 2452357 1:2452357:G:A G A A ADD 1173 -0.00695553 0.0494613 -0.140626 0.88819 1 2452444 1:2452444:A:G A G G ADD 1173 \_\_0.00524131 0.0497783 \_0.105293 0.916161 1 2453812 1:2453812:G:A G A A ADD 1173 -0.00563751 0.050722 -0.111145 0.91152 1 2454709 1:2454709:T:C C T T ADD 1173 -0.00377512 0.0432249 -0.0873367 0.930419 1 2454930 1:2454930:G:C G C C ADD 1173 -0.00695553 0.0494613 -0.140626 0.88819 1 2455500 1:2455500:A:C A C C ADD 1173 -0.00442178 0.046608 -0.0948716 0.924433

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	1:794332:6:4	G A			1173	0.0167258 0	0751683 0	222512 0	823954
840753	1.840753.T.C	τr			1173	0.0107250 0	0/31003 0. 0/3/801 0	818454 0	413265
046635	1.046733.1.0			ADD	1173	0.034706 0	0424001 0	200724 0	413203
045035	1:045035:0:1			ADD	11/3	0.010575 0	0504211 0	209/34 0	701502
845938	1:845938:G:A	GA	<u>^</u>	AUU	11/3	0.0138978 0	05011/1 0	2//30/ 0.	/81593
846078	1:846078:C:T			ADD	1173	0.0154452 0	.052242 0.	.295648 0.	767551
846398	1:846398:G:A	GΑ	Α	ADD	1173	0.0097726 0	.0507151 0.	.192696 0.	84723
846808	1:846808:C:T	ст		ADD	1173	0.0130275 0	.0521993 0.	.249572 0.	802962
846864	1:846864:G:C			ADD		0.0154452 0.	.052242 0.	.295648 0.	
847228	1:847228:C:T			ADD		-0.00163479	0.0514492	-0.0317749	0.974657
847491	1:847491:G:A	GΑ		ADD	1173	0.00426234	0.0504764	0.0844423	0.932719
848090	1:848090:G:A	G A	A	ADD	1173	0.00519704	0.050492	0.102928	0.918038
848445	1.848445.6.4	6 4			1173	_0 0174173	0 0505568	-0 34451	0 730525
040456	1.949456.4.6	Å G			1172	-0 017/172	0 0505560	-0 24451	0 720525
040430	1.040430.4.0	~ T		ADD	1173	-0.01/41/5	0.0503500	-0.344JI	0.730323
040/30	1:040/30:0:1			ADD	11/3	0.00319704	0.030492	0.102928	0.910030
850062	1:850062:A:T	A I		ADD	11/3	0.00426234	0.0504764	0.0844423	0.932719
850123	1:850123:C:T	СТ		ADD	1173	0.00519704	0.050492	0.102928	0.918038
851190	1:851190:G:A	GΑ		ADD	1173	0.00800137	0.0504533	0.15859 0.	87402
851204	1:851204:G:C	GΟ		ADD	1173	0.00799277	0.0503183	0.158844	0.873819
852664	1:852664:C:T			ADD		-0.00285601	0.0508564	-0.0561584	0.955225
852758	1:852758:G:C	GС		ADD	1173	-0.00285601	0.0508564	-0.0561584	0.955225
853239	1:853239:4:6	A G		ΔΠΟ	1173	-0.00285601	0.0508564	-0.0561584	1 0.955225
854250	1.854250.4.6	A G			1173	-0 0034348	0 0508285	-0 067576	0 0/6135
050040	1.959040.0.4	2.4		100	1172	0.0034540	0.0500205	0.007915	A 025272
050040	1:050040:C:A	C A		ADD	11/3	0.00473544	0.0504705	0.093015	0.925272
858051	1:858051:C:1			AUU	11/3	0.004/3544	0.0504763	0.093815	0.925272
864002	1:864002:G:C	GС		ADD	1173	0.0184693 0	.0500163 0.	.369265 0.	711997
865219	1:865219:G:A	GΑ	Α	ADD	1173	0.00750316	0.0504318	0.148778	0.881754
866893	1:866893:T:C	ст		ADD	1173	0.00632305	0.0422389	0.149697	0.881029
866938	1:866938:G:A	GΑ		ADD		0.00705206	0.0485498	0.145254	0.884535
867635	1:867635:C:T			ADD		0.00750316	0.0504318	0.148778	0.881754
872352	1:872352:G:C	GС		ADD	1173	0.00960345	0.0468868	0.204822	0.837747
877147	1:877147:G:4	G A		ADD	1173	-0.0115154	0.0473281	-0.243309	0.807809
881627	1:881627:6:4	A G			1173	0.0502509 0	.0422311_1	1899 0.2	34326
887622	1.882022.0.4	6.4		ADD	1172	_0 00620000	0 0470402	_0 1/6//4	0 883506
002033	1:002033:G:A	GA	<b>^</b>	ADD	11/3	-0.000009009	0.0470492	-0.140444	0.003590
888659	1:888659:1:0			AUU	11/3	0.2068/8 0	0865338 2	390/2 0.0	169728
889238	1:889238:G:A	GΑ	Α	ADD	11/3	0.21628 0.08	390064 2.42	2994 0.0152	2507
890104	1:890104:G:A	GΑ	А	ADD	1173	0.00331508	0.0468322	0.0707863	0.94358
894573	1:894573:G:A	ΑG		ADD	1173	0.141979 0.	.0688431 2.	.06235 0.03	393945
897564	1:897564:T:C	ст		ADD	1173	0.179375 0.	.0798978 2.	.24505 0.02	249507
897738	1:897738:C:T			ADD		0.179541 0.	.0802621 2.	23693 0.02	254787
898467	1:898467:C:T			ADD	1173	0.21628 0.08	390064 2.42	2994 0.0152	2507
900730	1:900730:G:A	AG		ADD	1173	0.118829 0.	073338 1.	62029 0.16	05439
903321	1:903321:G:A	AG		ADD	1173	0.00298207	0.0566348	0.0526544	0.958016
003426	1.003426.C.T				1173	-0 00700073	0 0476482	-0 167881	0 866706
000077	1.000072.0.4	6 1		100	1172	0.00733323	0.0470402	0.107001	0.0007000
000023	1.00020.T.C	TC		ADD	1173	0.00223041	0.0330091	207222 0	601202
909309	1:909509:1:0			ADD	11/3	0.0210323 0	0 0576040	. 39/322 0	091203
910473	1:9104/3:G:A	GA	<u>A</u>	ADD	11/3	-0.0200586	0.05/6243	-0.348092	0.727834
911916	1:911916:C:T			ADD	11/3	-0.0308612	0.054/515	-0.563659	0.5/3094
912049	1:912049:T:C			ADD	1173	-0.0461071	0.0412247	-1.11843	0.263611
913610	1:913610:G:A	GΑ		ADD	1173	-0.0308612	0.0547515	-0.563659	0.573094
913889	1:913889:G:A	ΑG		ADD	1173	-0.0569182	0.0413668	-1.37594	0.169104
914333	1:914333:C:G	GΟ		ADD		-0.0631883	0.0414557	-1.52424	0.12772
914852	1:914852:G:C			ADD		-0.0564599	0.0414123	-1.36336	0.173031
01/0/0	1:914940:T:C	ст		ADD	1173	-0.0612227	0.0411078	-1.48932	0.136672
914940					1173	-0.0395153	0.0508336	-0.777347	0.437111
916590	1:916590:G:A	G A	Α	ADD					
916590	1:916590:G:A	GA			1173	-0.0288419	0.0546679	-0.527584	0.597888
916590 916662 916824	1:916590:G:A 1:916662:A:C	GAAC		ADD	1173	-0.0288419	0.0546679	-0.527584	0.597888
916590 916662 916834	1:916590:G:A 1:916662:A:C 1:916834:G:A	G A A C A G		ADD ADD ADD	1173 1173	-0.0288419 -0.0672691	0.0546679	-0.527584	0.597888 0.102321
916590 916662 916834 917315	1:916590:G:A 1:916662:A:C 1:916834:G:A 1:917315:G:A	G A A C A G G A		ADD ADD ADD ADD	1173 1173 1173	-0.0288419 -0.0672691 -0.0189492	0.0546679 0.0411436 0.0521825	-0.527584 -1.63499 -0.363134	0.597888 0.102321 0.71657
916590 916662 916834 917315 917492	1:916590:G:A 1:916662:A:C 1:916834:G:A 1:917315:G:A 1:917492:C:T	G A A C A G G A C T		ADD ADD ADD ADD ADD	1173 1173 1173 1173	-0.0288419 -0.0672691 -0.0189492 -0.0288419	0.0546679 0.0411436 0.0521825 0.0546679	-0.527584 -1.63499 -0.363134 -0.527584	0.597888 0.102321 0.71657 0.597888
916590 916662 916834 917315 917492 917640	1:916590:G:A 1:916662:A:C 1:916834:G:A 1:917315:G:A 1:917492:C:T 1:917640:G:A	G A A C A G G A C T G A		ADD ADD ADD ADD ADD ADD ADD	1173 1173 1173 1173 1173 1173	-0.0288419 -0.0672691 -0.0189492 -0.0288419 -0.0686789	0.0546679 0.0411436 0.0521825 0.0546679 0.0471771	-0.527584 -1.63499 -0.363134 -0.527584 -1.45577	0.597888 0.102321 0.71657 0.597888 0.145725
916590 91662 916834 917315 917492 917640 918238	1:916590:G:A 1:916662:A:C 1:916834:G:A 1:917315:G:A 1:917492:C:T 1:917640:G:A 1:918238:C:G	G A A C A G G A C T G A C G		ADD ADD ADD ADD ADD ADD ADD ADD	1173 1173 1173 1173 1173 1173 1173	-0.0288419 -0.0672691 -0.0189492 -0.0288419 -0.0686789 -0.0686789	0.0546679 0.0411436 0.0521825 0.0546679 0.0471771 0.0471771	-0.527584 -1.63499 -0.363134 -0.527584 -1.45577 -1.45577	0.597888 0.102321 0.71657 0.597888 0.145725 0.145725
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### MANHATTAN PLOT

For each variant, plot the -log10(P-value) as function of chromosomal position.

 $P=0.05 \rightarrow -\log 10(0.05) = 1.3$  $P=0.001 \rightarrow -\log 10(0.001) = 3$ 

# **HYPOTHESIS TESTING**

	Null hypothesis $(H_0)$ is true	Null hypothesis $(H_0)$ is false
Reject null hypothesis (H <sub>0</sub> )	Type I error <i>α</i> False positive	Correct outcome True positive
Accecpt null hypothesis (H <sub>0</sub> )	Correct outcome True negative	Type II error <i>β</i> False negative

The probability (*P*) of making a type I error is denoted by  $\alpha$ ; we reject the null hypothesis if the inferred *P* value is less than the significance level ( $\alpha$ =0.05). I.e., the probability of rejecting the null hypothesis when should be accepted.

Why multiple testing correction? If we test 500,000 SNPs, then by chance we expect 25.000 SNPs to be significant (if  $\alpha$ =0.05)  $\rightarrow$  i.e., **25.000 false-positive associations**.

One solution is to correct for number of tests performed; Bonferroni correction; Corrected *P*-value =  $P \times n_{tests} \le 0.05$  OR  $\frac{\alpha}{n_{tests}}$  =**new significance threshold** 

### **MANHATTAN PLOT**

For each variant, plot the –log10(P-value) as function of chromosomal position.

P=0.05 →  $-\log 10(0.05) = 1.3$ P=0.001 →  $-\log 10(0.001) = 3$ P=0.000000005 →  $-\log 10(0.00000005) = 8.3$ 

Genome-wide significance level? -adjust for no. of independent statistical tests (1,000,000 independent genomic regions [LD])



а

## **POWER IS EVERYTHING IN GWAS**

the probability of detecting an effect, if there is a true effect present to detect

#### **Schizophrenia**



Has high heritabilitet ( $h^2 = 0.85$ ) The population prevalence is 1% Emerge in late teens Molecular aetiology is unknown



**5. Find the causal variant** 

Summaries 10M linear regressions 3. GWAS 2. Extract genetic variants 1. Select trait/disease

### Biological insights from 108 schizophrenia-associated genetic loci







All the "blue" variants are in LD – which gene is associated with SCZ?



Statistical "Fine mapping" fitting multiple variants at a time [adjust of LD]

### FINE MAPPING

Statistical "Fine mapping" fitting multiple variants at a time [adjust of LD]

$$y = X_i \beta_i + g + e$$

$$y = X_{i=430}\beta_{i=430} + g + e$$

**Condition on index variant** 

$$y = X_{i=430}\beta_{i=430} + X_{i=431}\beta_{i=431} + g + e$$
  
:  
:





6. Meta analysis

Find the causal variant

4. Summaries 10M linear regressions 3. GWAS 2. Extract genetic variants 1. Select trait/disease

### **META ANALYSIS**

- Meta-analysis is a set of methods that allows the quantitative combination of data from multiple studies
- Meta-analysis of GWA datasets can increase the power to detect association signals by increasing sample size and by examining more variants throughout the genome than each dataset alone
- Assume two independent estimates  $\hat{x}_1 = 1.0$  and  $\hat{x}_2 = 2.0$ , and that the precision of the first estimate is twice that of the second (precision =  $1/SE^2$ )

• 
$$\hat{x}_{meta} = \frac{(2\hat{x}_1 + \hat{x}_2)}{2+1} = \frac{2+2}{3} = 1.33$$





$$\widehat{\beta}_{l,F} = \frac{w_{1l}\widehat{\beta}_{1l} + \dots + w_{Kl}\widehat{\beta}_{Kl}}{w_{1l} + \dots + w_{Kl}} \quad \text{studies I},\dots, \mathsf{K}$$

$$\operatorname{SE}_{l,F} = (w_{1l} + \dots + w_{Kl})^{-\frac{1}{2}}, \quad \text{where the weight}$$

$$w_{kl} = \frac{1}{\operatorname{SE}_{kl}^2} \text{ is the inverse-variance of study } k.$$



#### 7. Spurious associations

, 6. Meta analysis

Find the causal variant

4. Summaries 10M linear regressions 3. GWAS 2. Extract genetic variants 1. Select trait/disease

## **SPURIOUS ASSOCIATIONS**

#### **NEWS & VIEWS**

#### Beware the chopsticks gene

Once upon a time, an ethnogeneticist decided to figure out why some people eat with chopsticks and others do not. His experiment was simple. He rounded up several hundred students from a local university, asked them how often they used chopsticks, then collected buccal DNA samples and mapped them for a series of anonymous and candidate genes.



Molecular Psychiatry (2000) 5, 11-13





Cases



Controls

## **SPURIOUS ASSOCIATIONS**

#### **NEWS & VIEWS**

#### Beware the chopsticks gene

The results were astounding. One of the markers, located right in the middle of a region previously linked to several behavioral traits, showed a huge correlation to chopstick use, enough to account for nearly half of the observed variance. When the experiment was repeated with students from a different university, precisely the same marker lit up. Eureka! The delighted scientist popped a bottle of champagne and quickly submitted an article to *Molecular Psychiatry* heralding the discovery of the 'successful-use-of-selected-hand-instruments gene' (SUSHI).



Cases p=0.50



p=0.01

SUSHI gene

#### Are there any problems?

### **SPURIOUS ASSOCIATIONS**

#### **NEWS & VIEWS**

Beware the chopstic It took another 2 years to antigen gene that has not to have different allele fr course differ in chopsticl reasons. Even though the readily replicated, they w



HLA class I diversity is illustrated by the prevalence of nine HLA-B molecules



#### 8. Post hoc analyses

**7. Spurious associations** 

, 6. Meta analysis

Find the causal variant

4. Summaries 10M linear regressions 3. GWAS 2. Extract genetic variants 1. Select trait/disease

### GWAS POST HOC ANALYSES GENE SET ENRICHMENT



Genes (+/- regulatory sequences) connected in biological pathways and networks



Looking for variants with small effects





or other newtorks such as protein interactions or metabolites

In a GWAS we go through all SNPs one by one.

Gene enrichment analyses we examine whether a group of SNPs (within a biological entity) display a more extreme association signal than by chance.

AALBORG UNIVERSITY


#### 2006 Jan







What about rare genetic variants for common diseases?

## RARE VARIANT TESTING



If variation at the locus is rare association testing is not possible (no aa or few Aa individuals exists)



Test the "burden" of all rare variants within a gene.

Often variants are group by functional consequence (missense, pLOF etc)

### GENOME-WIDE ASSOCIATION ANALYSIS (GWAS)

- What is a GWAS
- LD
- GWAS by steps





# GROUP WORK

GWAS AND FUTURE DIRECTION

Go into your 'complex traits' group [45 min]
Discuss what did you learn from the GWAS you selected
Read pages 3-10 in the ICDA white-paper

Discuss how the reccomdations could be important for your trait

2) Plenum discuss [10 min]



#### YOUR OPPINION MATTERS MOODLE EVALUATION



List the two most important things you learned today	What did you find difficult?	What did you 🏻 🖨 🕂 × find easy? +	Improvements of the set of the se
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