Genetic Studies of Comorbid Traits

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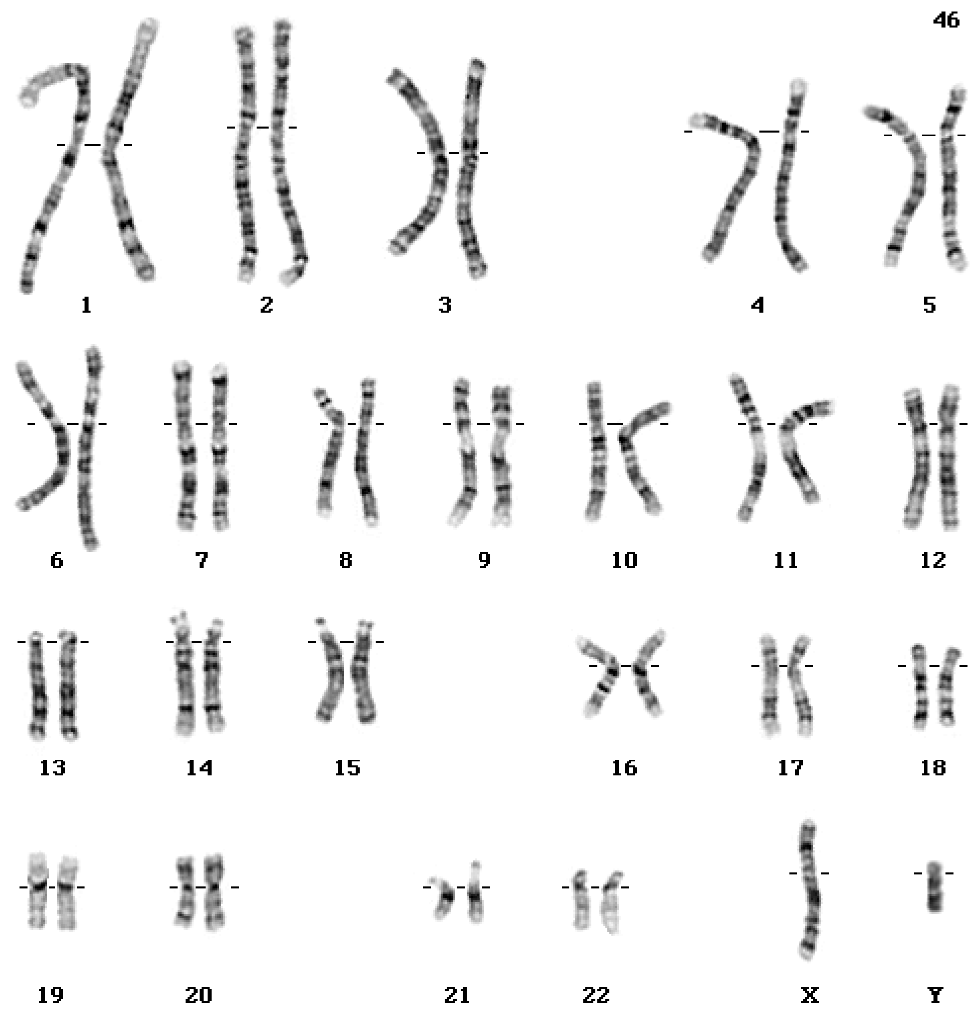
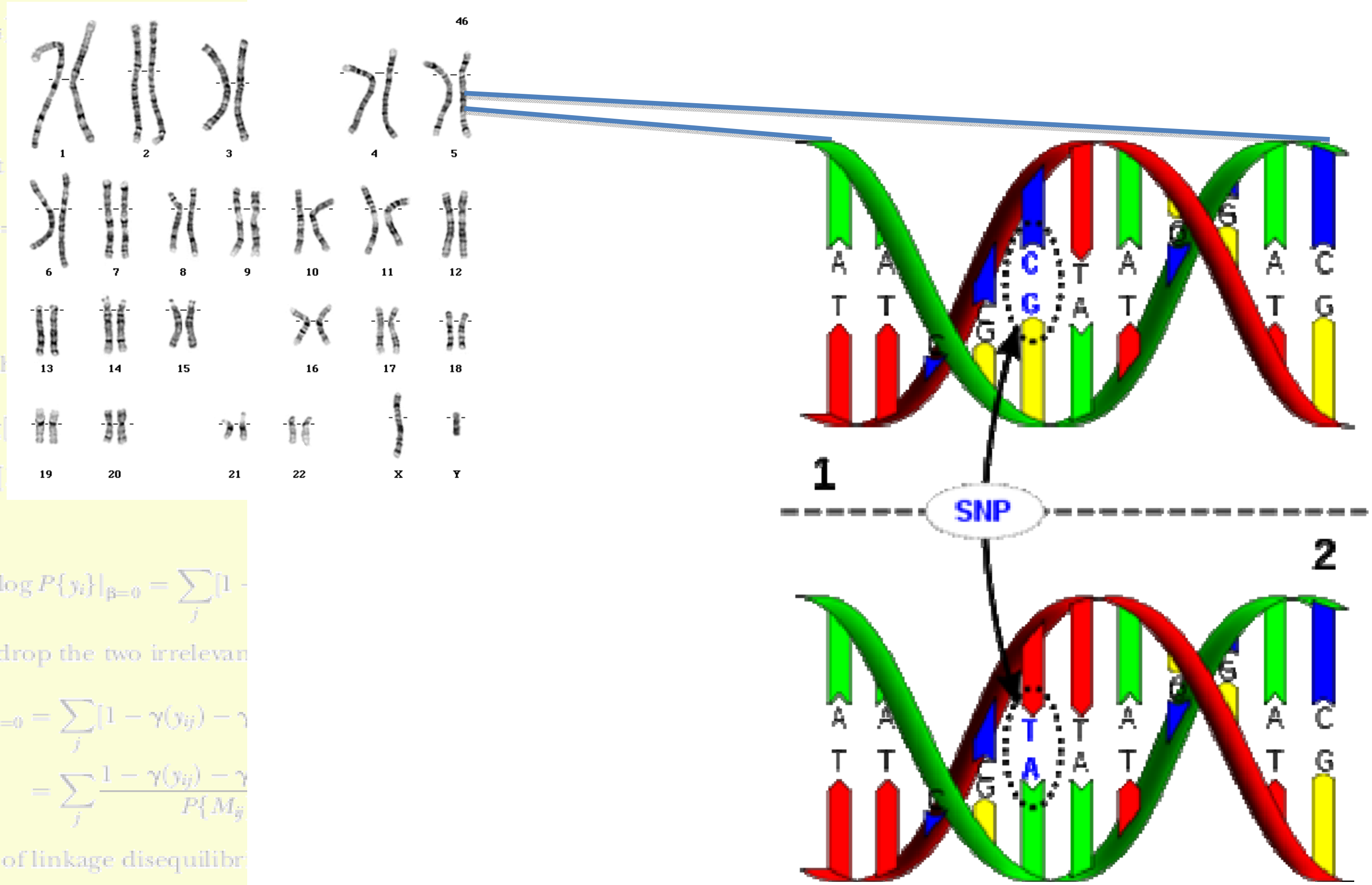
Comorbidity

The simultaneous presence of 2 or more morbid conditions or diseases in the same patient.

Genetic Studies



Genetic Studies



Outline

- Comorbidity of Psychiatric Disorders
  - A Century Ago
  - As We Are Speaking
- Association Analysis of Multivariate Traits
- Data Analysis of Alcoholism
- Closing Comments and Acknowledgements

PRELIMINARY REPORT OF A STUDY OF HEREDITY IN INSANITY IN THE LIGHT OF THE MENDELIAN LAWS

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Insane hospital statistics show plainly that heredity has much to do with the causation of certain forms of nervous and mental disease. Yet we know but little of the exact conditions under which such disease is transmitted from parent to offspring. The object of the present research has been to accumulate and examine such data as may serve to throw some light upon this obscure problem.

It has been shown that the laws governing the transmission of traits by heredity, as established by Mendel, hold good not only for plants and the lower animals, but also for man, at least as regards certain characters, such as color of hair and color of eyes. In view of this fact our problem has assumed for us a more definite form. It is simply: Are any of the forms of nervous and mental disease transmitted from generation to generation in accordance with the Mendelian laws?

§ *1. The Mendelian Laws.*—Perhaps a brief review of the essential points of the Mendelian laws will not be superfluous.

The total inheritance of an individual from his parents is divisible into unit characters, each of which is inherited independently of all the rest and may therefore be studied without reference to other characters.

The inheritance of any such character is believed to be dependent upon the presence in the germ plasm of a unit of substance called a *determiner*.

With reference to any given character the condition in an individual may be *dominant* or *recessive:* the character is dominant when, depending upon the presence of its determiner in the germ plasm, it is plainly manifest; and it is recessive when, owing to the lack of its determiner in the germ plasm, it is not present in the individual under consideration.

Correlated Phenotypes

of eleven patients at this hospital and includes thirty-five different matings, with a total of 221 offspring. This material has been arranged for convenience in the form of pedigree charts.

One of the first facts that appeared in the study of the pedigrees was that any form of insanity or even all the forms of hereditary insanity do not constitute an independent hereditary character, but that they are closely related to imbecility, epilepsy, hysteria, and various mental eccentricities that are not usually included under the designation insanity. In other words, the distinction between these conditions as clinical entities cannot, in the light of their manner of origin, be regarded as deeply essential.

We find as manifestations of the neuropathic make-up in closely related persons cases of feeble-mindedness, convulsions in childhood from trivial causes or chronic epilepsy, cases of grave hysteria, various eccentricities, cases of dementia præcox, manic-depressive insanity, paranoic conditions, involutional psychoses, and the like.

It is not to be assumed, however, that what we have called here the neuropathic make-up constitutes the basis of all the clinical forms of nervous and mental disease; for on the one hand, some of these conditions, like general paresis or alcoholic polyneuritis, are probably purely exogenous in origin, and, on the other hand, others, like Huntington's chorea, are plainly independent Mendelian characters.

The pedigree charts contain a number of instances of neuropathic children born of normal parents, but not a single instance of a normal child born of parents both of whom are neuropathic. This proves that the neuropathic make-up cannot be dominant over normal; but that if its transmission occurs at all in a manner corresponding to the Mendelian laws, it must be recessive to normal.

In preparing the pedigree charts we have made use of the following symbols and abbreviations.

□ = male individual. ○ = female individual. A square or a circle unmarked = normal individual. P = normal individual with neuropathic offspring. I = insanity. Cv. = convulsions. E = epilepsy. N = feeble-mindedness, hysteria, or other pronounced neuropathic manifestation. o within a square = normal individual without offspring. † = died in childhood. ? = data unascertained.

Number above each mating indicates type of combination.

Smoking

Fagerstrom Test for Nicotine Dependence (FTND)

1. How many cigarettes a day do you usually smoke?

1 to 10	0 point	21 to 30	2 points
11 to 20	1 point	30 or more	3 points

2. How soon after you wake up do you smoke your first cigarette?

After 60 minutes	0 point	6 - 30 minutes	2 points
31- 60 minutes	1 point	< 5 minutes	3 points

3. Do you smoke more during the first two hours of the day than during the rest of the day?

No	0 point	Yes	1 point

4. Which cigarette would you most hate to give up?

Any other cigarette than the first one	0 point	The first cigarette in the morning	1 point

5. Do you find it difficult to refrain from smoking in places where it is forbidden, such as public buildings, on airplanes or at work?

No	0 point	Yes	1 point

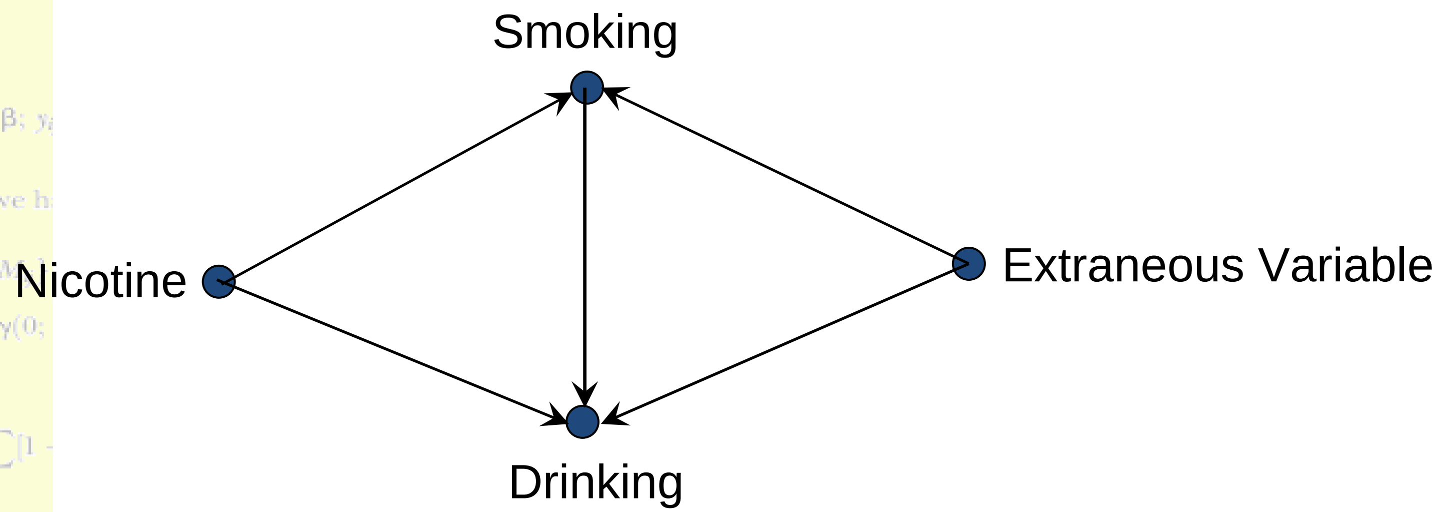
6. Do you still smoke even when you are so ill that you are in bed most of the day?

No	0 point	Yes	1 point
		Total points	

Smoking and Comorbidity

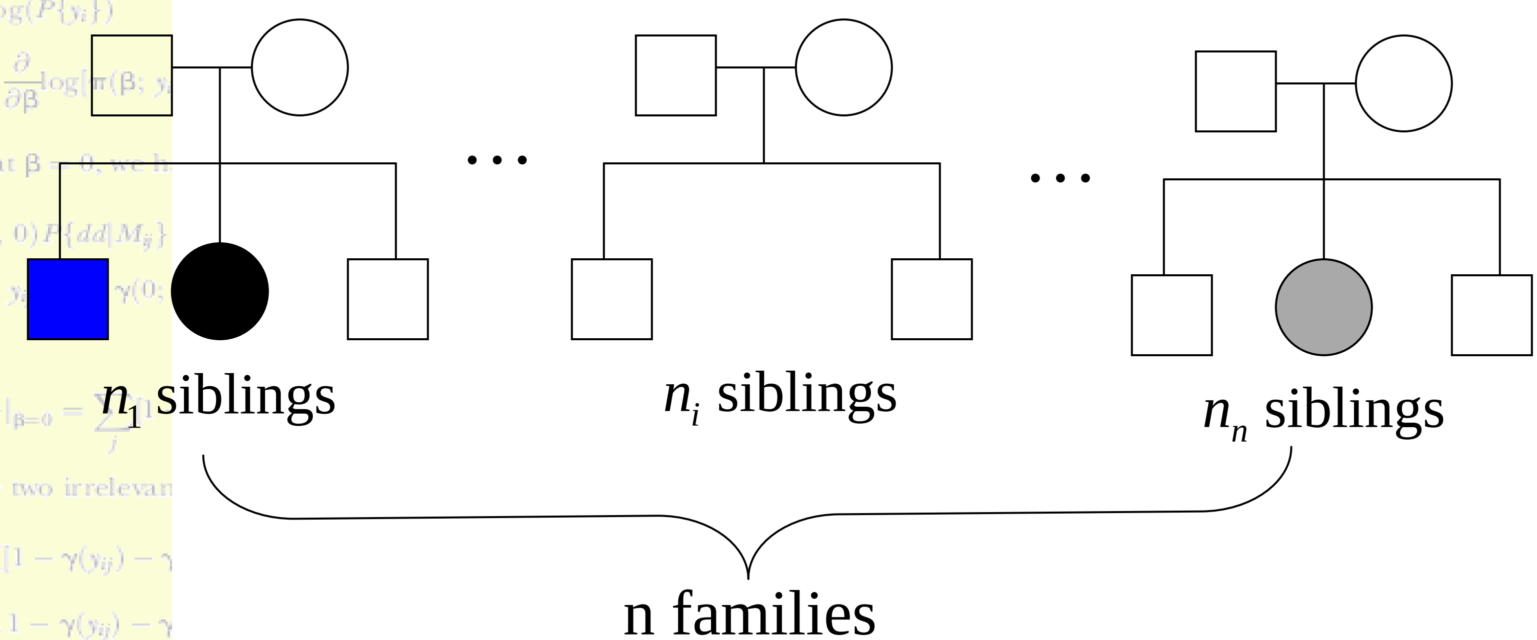
Subclinical syndromes (e.g., minor depression and heavy drinking) probably influence smoking initiation and cessation more because they are so much more prevalent. In prospective studies, comorbidity predicts smoking and smoking predicts comorbidity (**Hughes J R 1999)**

Comorbidity



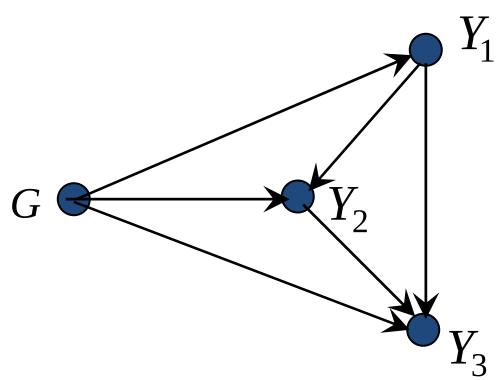
Comorbid psychiatric disorders are common and their determinants are multi-factorial.

Nuclear Families



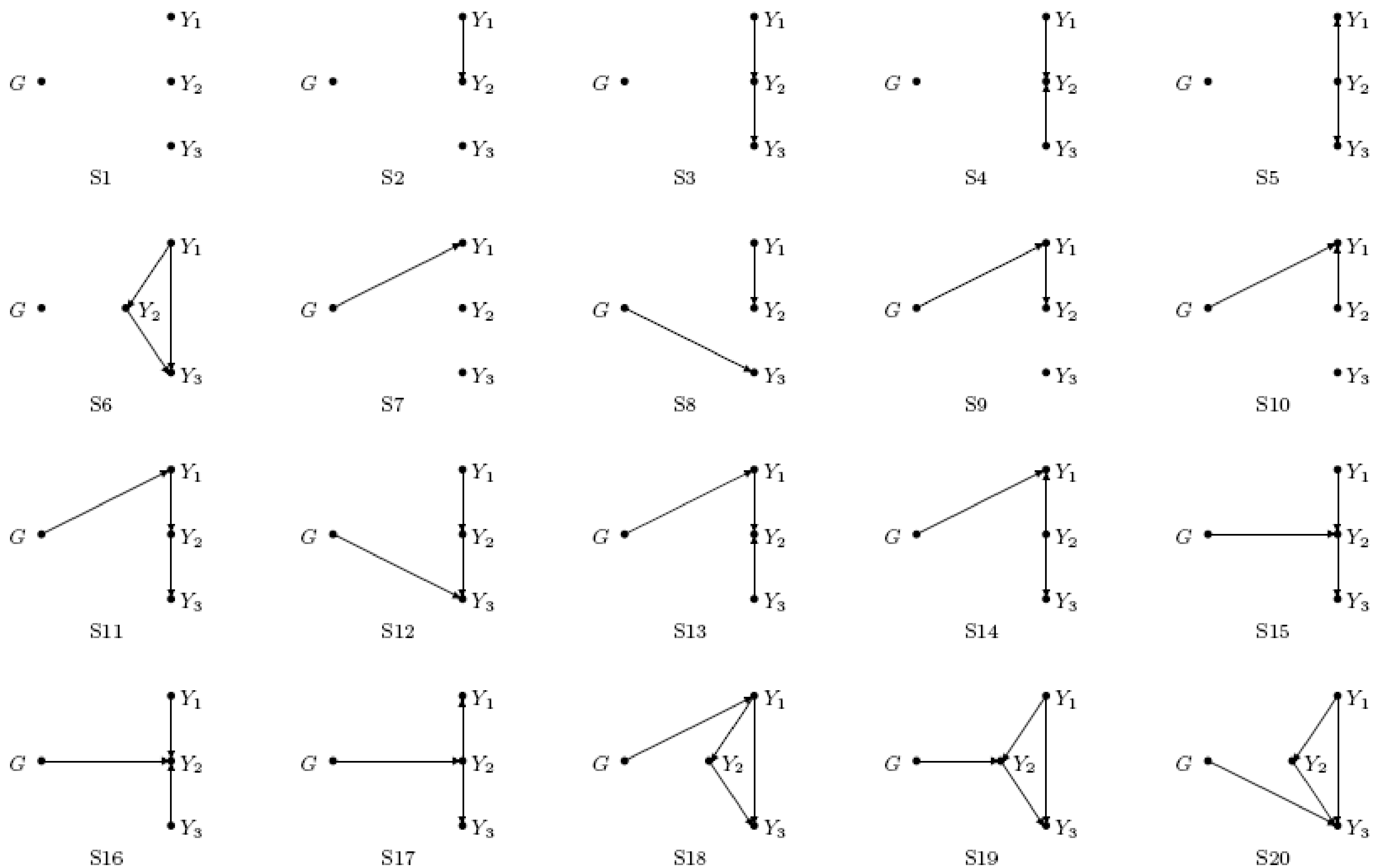
Graphical Structures for Simulation Models

Although we do not observe the causal relationship between the genotypes and traits or among the traits, we generate the data from 40 directed acyclic graphs (DAGs).



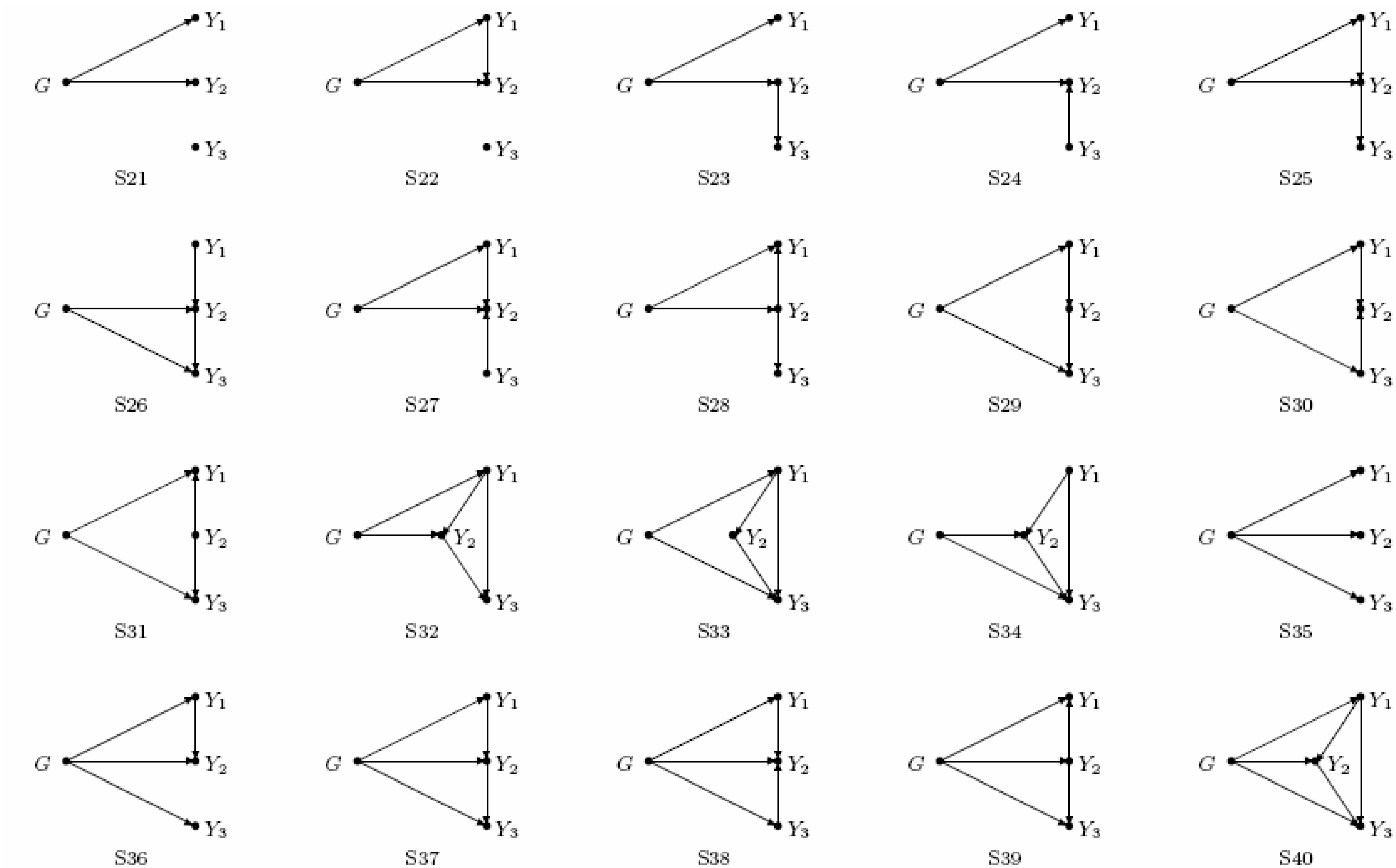
An arrow between any two elements points to a causal relationship

DAGs 1-20



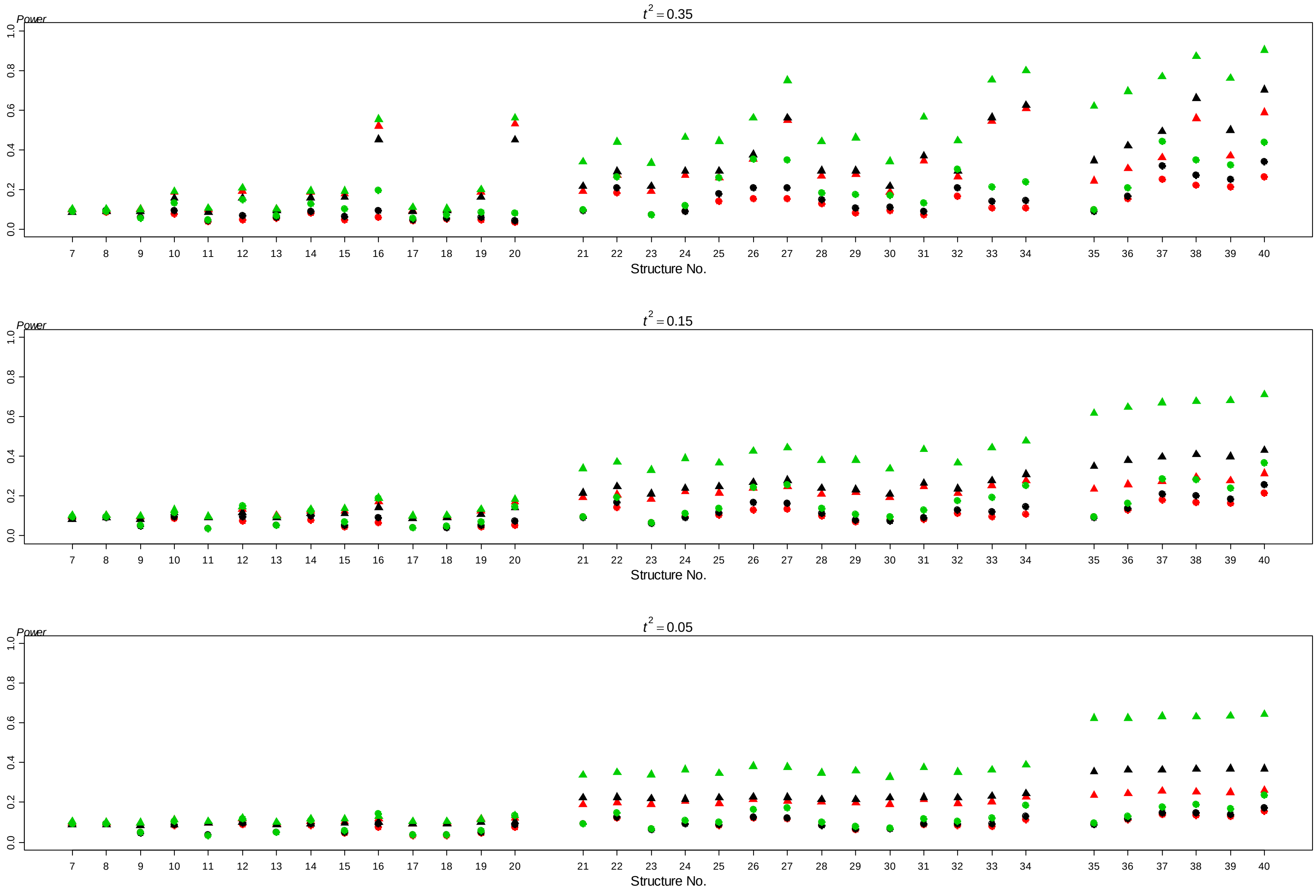
S1
S2
S3
S4
S5
S6
S7
S8
S9
S10
S11
S12
S13
S14
S15
S16
S17
S18
S19
S20
G
Y_1
Y_2
Y_3

DAGs 21-40


G
Y_1
Y_2
Y_3
S21
S22
S23
S24
S25
S26
S27
S28
S29
S30
S31
S32
S33
S34
S35
S36
S37
S38
S39
S40

Power: Quantitative Traits (Alpha=0.01)

FBAT: dots and FBAT-GEE: triangles. Black : $\rho_{kj} = -$, Red : $\rho_{kj} = 0.2$, Green : $\rho_{kj} = -0.2$.



Kendall's Tau

Kendall's Tau: a non-parametric statistic measuring the strength of the relationship between two variables

Let (X_i, Y_i) and (X_j, Y_j) be a pair of observations. If $X_j - X_i$ and $Y_j - Y_i$ have the same sign, we say that the pair is concordant. If they have different sign, we say that the pair is disconcordant.

For a sample size n. The Kendall Tau is defined as

$$\tau = 2(C - D)/n(n\text{-}1)$$

where C and D are the number of concordant and disconcordant pairs.

Association Test

A vector of traits $T = (T^{(1)},...,T^{(p)})'$ and a vector of markers $\mathrm{M} = (M^{(1)},...,M^{(G)})'$.

Association Test

Let $u_{ij} = (f_1(T_i^{(1)} - T_j^{(1)}),...,f_p(T_i^{(p)} - T_j^{(p)}))'$

where can be the identity function for a quantitative or binary trait, or the sign function for an ordinal trait (or any trait).

Let $v_{ij} = (\mathrm{C_i}(1) - \mathrm{C_j}(1),...,\mathrm{C_i}(\mathrm{G}) - \mathrm{C_j}(\mathrm{G}))'$

C is a function of marker M such as the count of any chosen allele of genotype.

Association Test

Let $U = \binom{n}{2}^{-1} \sum_{i<j} u_{ij} \otimes v_{ij}$

Kendall's tau:

$$W = U' Cov_0^{-1}(U \mid T) U \sim \chi^2_{rank(Cov_0(U|T))} - \text{distributed}$$

Association Test

For a family study

$$Cov_0(U \mid T) =$$

$$\frac{4}{(n-1)^2}\sum_{k=1}^{S}\sum_{1\le i,j\le s_k}\bar{\mathbf{u}}_{d_k(i)}\bar{\mathbf{u}}'_{d_k(j)}\mathrm{Cov}_0(C_{d_k(i)}, C_{d_k(j)}|\mathrm{T}).$$

The ith member in the kth sibship is the $d_k(i)$th subject in the entire study cohort.

$$\bar{\mathbf{u}}_i = \frac{1}{\mathrm{n}}\sum_{j=1}^{n}\mathbf{u}_{ij}$$

Simulation Study-Model Setting

Nominal type I error comparison

the coefficient of linkage disequilibrium δ takes value of 0

Power evaluation

the coefficient of linkage disequilibrium δ takes value of 0.11

Given the genotype at the trait locus, a non-proportional odds model is used to generate ordinal phenotype data and a Gaussian distributed model is used for quantitative phenotype

Type I error comparison

		alpha = 0.05		alpha = 0.01		alpha = 0.001	
#(family)	**K**	**O-FBAT**	**FBAT**	**O-FBAT**	**FBAT**	**O-FBAT**	**FBAT**
200	**3**	**0.043**	**0.044**	**0.009**	**0.009**	**0.001**	**0.001**
	4	**0.049**	**0.051**	**0.008**	**0.007**	**0.001**	**0.001**
	5	**0.059**	**0.062**	**0.013**	**0.01**	**<0.001**	**<0.001**
	6	**0.047**	**0.043**	**0.005**	**0.005**	**<0.001**	**<0.001**
400	**3**	**0.049**	**0.051**	**0.012**	**0.009**	**0.002**	**0.002**
	4	**0.055**	**0.054**	**0.009**	**0.011**	**0.001**	**0.001**
	5	**0.042**	**0.041**	**0.006**	**0.006**	**0.001**	**0.002**
	6	**0.045**	**0.045**	**0.006**	**0.008**	**0.001**	**0.001**
600	**3**	**0.036**	**0.038**	**0.006**	**0.006**	**<0.001**	**<0.001**
	4	**0.054**	**0.055**	**0.013**	**0.010**	**0.001**	**0.001**
	5	**0.061**	**0.055**	**0.005**	**0.009**	**0.001**	**<0.001**
	6	**0.038**	**0.038**	**0.006**	**0.007**	**<0.001**	**<0.001**

Power Comparison

		alpha = 0.05		alpha = 0.01		alpha = 0.001	
#(family)	K	O-FBAT	FBAT	O-FBAT	FBAT	O-FBAT	FBAT
200	3	0.783	0.778	0.553	0.541	0.261	0.249
	4	0.732	0.702	0.492	0.456	0.213	0.184
	5	0.760	0.672	0.541	0.429	0.277	0.193
	6	0.504	0.403	0.266	0.184	0.076	0.042
400	3	0.980	0.982	0.922	0.916	0.757	0.752
	4	0.961	0.946	0.882	0.857	0.664	0.627
	5	0.978	0.949	0.914	0.839	0.757	0.604
	6	0.792	0.664	0.584	0.437	0.328	0.203
600	3	0.999	0.999	0.989	0.991	0.958	0.954
	4	0.996	0.988	0.978	0.970	0.920	0.885
	5	0.999	0.990	0.987	0.957	0.935	0.837
	6	0.947	0.859	0.826	0.658	0.582	0.379

Collaborative Studies on Genetics of Alcoholism (**COGA**)

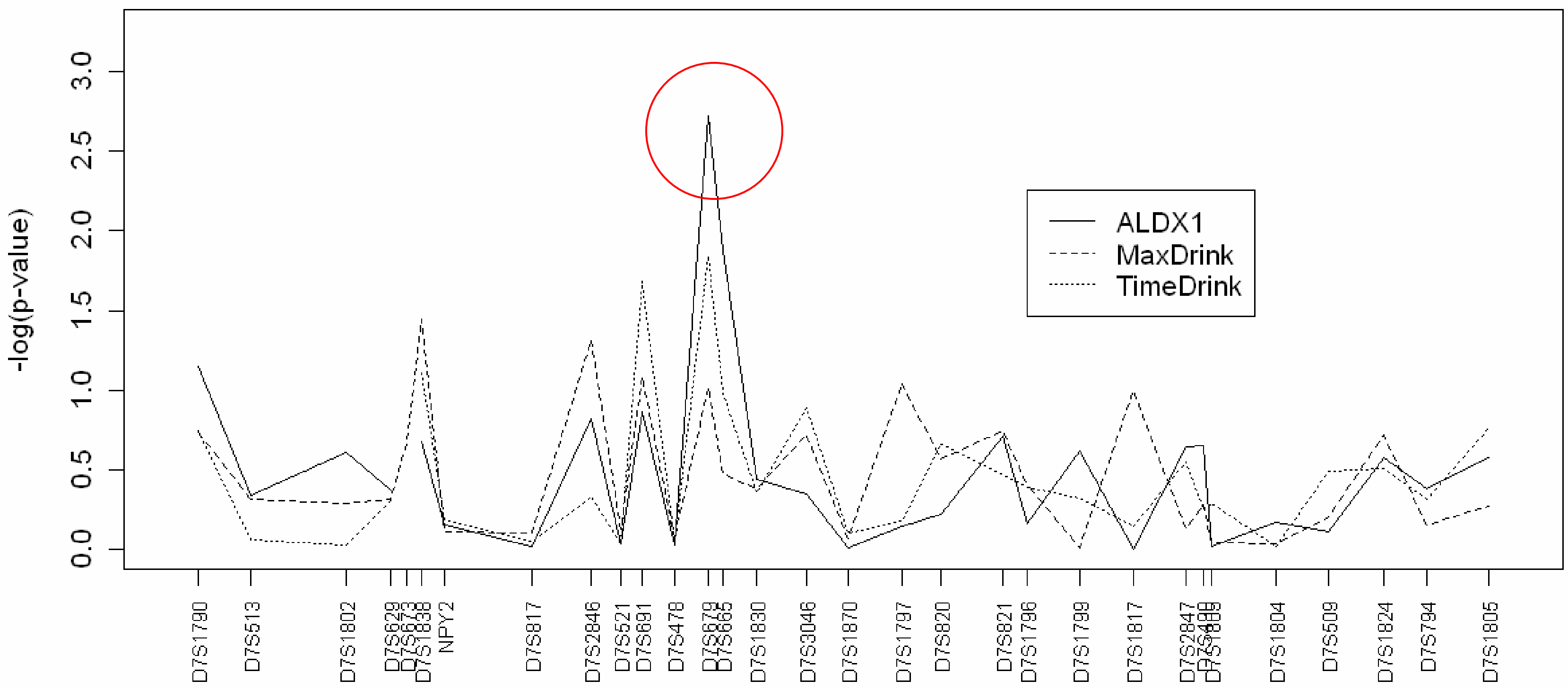
- In United States, 12.5% of Adults has ever had alcohol dependence problem in their life time (Hasin, et al, 2007)
- A large scale, multi-center study to map alcohol dependence susceptible genes.
- 143 families with 1614 individuals. 4720 SNPs from Illumina genotype data set.
- One ordinal trait with 4 levels was recorded (pure unaffected, never drank, unaffected with some symptoms, and affected).
- FBAT was also used for comparison

Application for COGA Data

- Phenotypes:
  - Alcohol DX-DSM3R+Feighner (ALDX1)
    - 4 categories
  - Maximum number of drinks in a 24 hour period (MaxDrink)
    - 4 categories
  - Spent so much time drinking, had little time for anything else (TimeDrink)
    - 3 categories

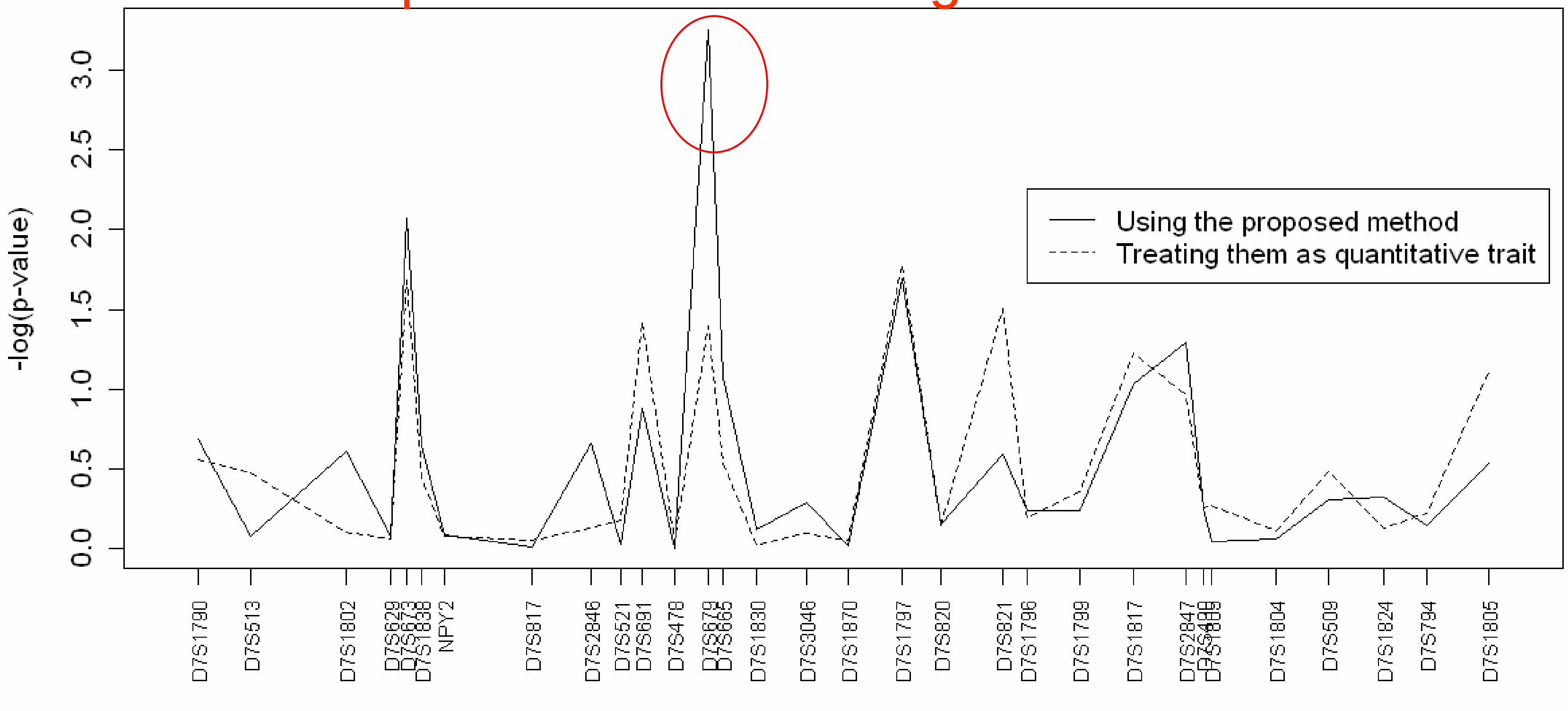
Single trait analysis

D7S679 with p-value 0.002879 for ALDX1 > 0.000538 = 0.05/(3*31)



Multiple traits analysis

P-value is 0.000553 < 0.0016129 = 0.05/31 at marker D7S679, which is around 1 cM away from D7S1793 that has been reported to have linkage evidence.

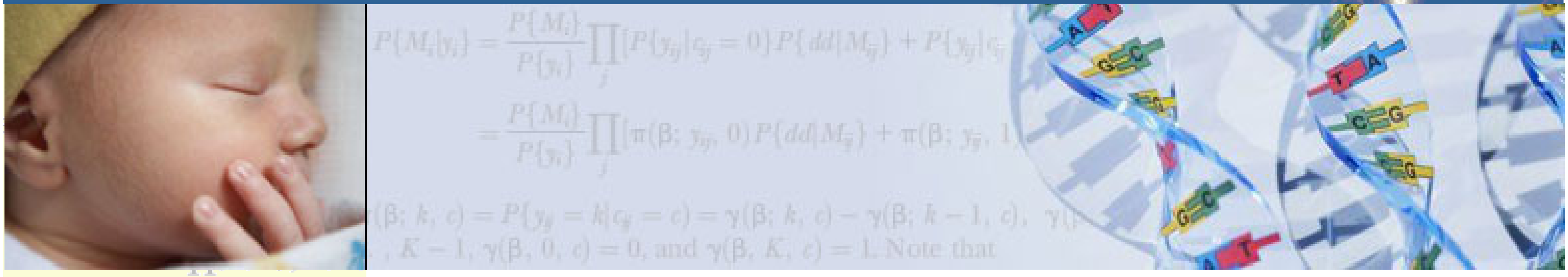


Closing Comments

- Genetic studies of mental diseases involve many challenges: some are clinical, some are statistical, and some are scientific.
- We attempt to deal with an important issue on comorbidity and demonstrate the benefit to analyze comorbidity in genetic studie.

Acknowledgements

Ching-Ti Liu Xueqin Wang Wensheng Zhu



Thank You!