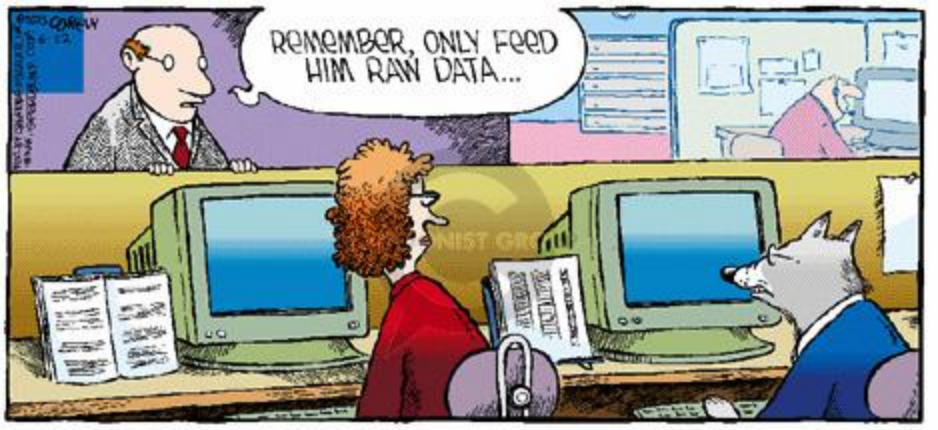
Psych 3102
Introduction to Behavior Genetics

Lecture 10

Quantitative genetic theory

Model-fitting



Basic underlying tenet behind all methods:

genetic similarity between organisms will lead to phenotypic similarity - if genes influence the trait being measured

Methods allow us to

1. get estimates for genetic and environmental components of variance
2. organize large amounts of data in meaningful way in the form of models
3. provide evidence that individual differences are an important result of evolution

In humans, methods are not as direct and powerful as animal studies

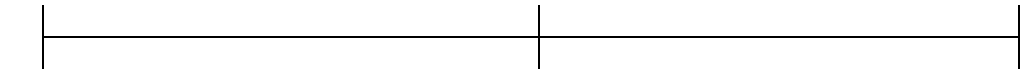
All models are still based on segregation at a single locus

SINGLE-GENE MODEL

Consider a single locus with 2 alleles A_1 and A_2

assign genotypic values to show effects of each allele on phenotype:

A_1A_1 A_2A_2 genotypes



+a 0 -a genotypic values

(average trait value of those with the genotype)

where heterozygote falls on this scale depends on nature of allelic interaction at the locus

heterozygous genotype is given value d

d = +a if allele A_1 is completely dominant

d = -a if allele A_2 is completely dominant

d = 0 if A_1 and A_2 are codominant, ie allele effects are additive

ADDITIVE GENETIC VARIATION - the additive effects of alleles

- phenotypic effect of the alleles is the mathematical sum of all alleles present for the trait since all alleles have an effect
- additive alleles produce predictable phenotypic scores in offspring - the score of the offspring is just the average of the parental scores
- this gives us a prediction about the offspring

if the offspring score is NOT the average of the parental scores, we have evidence for NON-ADDITIVE action of the alleles.

at a single locus, we have evidence of DOMINANCE DEVIATION

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Individual and Additive Effects of the *CNR1* and *FAAH* Genes on Brain Response to Marijuana Cues

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As previous work has highlighted the significance of the *cannabinoid receptor 1 (CNR1)* and *fatty acid amide hydrolase (FAAH)* genes with respect to cannabis dependence (CD), this study sought to characterize the neural mechanisms that underlie these genetic effects. To this end, we collected DNA samples and fMRI data using a cue-elicited craving paradigm in thirty-seven 3-day-abstinent regular marijuana users. The participants were grouped according to their genotype on two single-nucleotide polymorphisms (SNPs) earlier associated with CD phenotypes: rs2023239 in *CNR1* and rs324420 in *FAAH*. Between-group comparisons showed that carriers of the *CNR1* rs2023239 G allele had significantly greater activity in reward-related areas of the brain, such as the orbitofrontal cortex (OFC), inferior frontal gyrus (IFG), and anterior cingulate gyrus (ACG), during exposure to marijuana cues, as compared with those with the A/A genotype for this SNP. The *FAAH* group contrasts showed that *FAAH* rs324420 C homozygotes also had greater activation in widespread areas within the reward circuit, specifically in the OFC, ACG, and nucleus accumbens (NAc), as compared with the *FAAH* A-allele carriers. Moreover, there was a positive correlation between neural response in OFC and NAc and the total number of risk alleles (cluster-corrected $p<0.05$). These findings are in accord with earlier reported associations between *CNR1* and *FAAH* and CD intermediate phenotypes, and suggest that the underlying mechanism of these genetic effects may be enhanced neural response in reward areas of the brain in carriers of the *CNR1* G allele and *FAAH* C/C genotype in response to marijuana cues.
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Keywords: CNR1; FAAH; genes; marijuana; cannabis; fMRI

INTRODUCTION

The main psychoactive compound in marijuana, delta-9-tetrahydrocannabinol (Δ^9-THC), binds to central cannabinoid, or CB_1, receptors, in which it mimics the effects of endogenously produced cannabinoids. The administration of CB_1 antagonists in mice results in a decrease in reward behavior in response to cannabinoids and other substances of abuse (Arnone *et al*, 1997; Berrendero *et al*, 2003; Castane *et al*, 2002; Ledent *et al*, 1999), and the administration of the antagonist SR141716A (Rimonabant) extinguishes reward-related behaviors such as conditioned place preference and self-administration suggesting that CB_1 activation modulates these behaviors (Gardner *et al*, 2002). In the first study of cue- and drug-induced reinstatement of cannabinoid-seeking in non-human primates, it was found that continuous administration of rimonabant, but not naltrexone, decreased cue-induced drug seeking, THC-induced drug seeking, and the direct reinforcing effects of THC in squirrel monkeys (Justinova *et al*, 2003, 2008). Moreover, single-cell recordings in the ventral tegmental area (VTA), the origin of dopaminergic cell bodies, have shown that Δ^9-THC increases neuronal firing rates in this area (Cheer *et al*, 2000). More interestingly, increased dopamine (DA) neuronal firing rates are coupled with increased DA neuronal bursts, and these effects are blocked by SR141716A (Diana *et al*, 1998; French *et al*, 1997). These findings suggest that cannabinoids increase DA activity in the NAc and prefrontal cortex (PFC) by activating CB_1 receptors in the VTA, which increase DA neuronal firing and burst rates. In other words, CB_1 receptors increase DA activity by local disinhibitory mechanisms. The gene that encodes for CB_1, cannabinoid receptor 1 (*CNR1*), thus likely modulates endocannabinoid and DA-mediated reward signaling; consequently, it has attracted substantial attention in the search for genetic mediators of liability to substance use disorders (SUD).

Among human drug users, *CNR1* variants have been associated with both SUD phenotypes generally (eg, Ballon *et al*, 2006; Comings *et al*, 1997; Covault *et al*, 2001; Herman *et al*, 2006; Racz *et al*, 2003; Schmidt *et al*, 2002; Zhang *et al*, 2004; Zuo *et al*, 2007, 2009) and cannabis dependence (CD) specifically (Agrawal and Lynskey, 2009; Hopfer *et al*, 2006), although some groups have also reported null findings for this gene (eg, Covault *et al*, 2001; Hartman *et al*, 2009; Li *et al*, 2000). A report by Zhang *et al* (2004) suggest that one variant, a G to A single-nucleotide polymorphism (SNP) in

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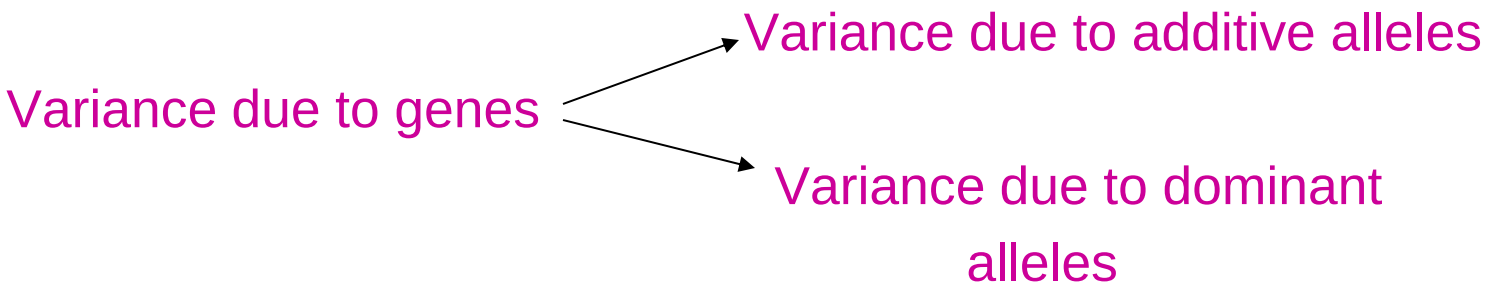
NON-ADDITIVE GENETIC VARIATION - the result of dominant alleles

- dominant alleles produce dominance deviation

  = the difference between the expected additive genotypic score and the actual phenotypic score
- dominance produces unpredictable results for the scores of offspring
- offspring score depends on combination of alleles inherited and is NOT just an average of parental scores

Variance components so far:



POLYGENIC MODEL

extending the single-gene model to accommodate traits influenced by many genes

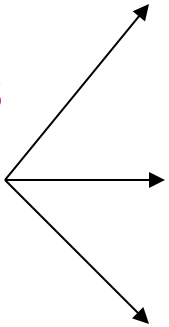
additive and dominance effects are just summed over loci

But

new source of variation : interaction between alleles of genes at different loci

epistasis

Genetic components of variance (G)



Additive variance (A)

Dominance deviation (D)

Epistatic interaction (I)

G = A + D + I

Amyloid-β and tau synergistically impair the oxidative phosphorylation system in triple transgenic Alzheimer's disease mice

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Alzheimer's disease (AD) is characterized by amyloid-beta (Aβ)-containing plaques, neurofibrillary tangles, and neuron and synapse loss. Tangle formation has been reproduced in P301L tau transgenic pR5 mice, whereas APP^{swe}PS2^{N141I} double-transgenic APP152 mice develop Aβ plaques. Cross-breeding generates triple transgenic (^{triple}AD) mice that combine both pathologies in one model. To determine functional consequences of the combined Aβ and tau pathologies, we performed a proteomic analysis followed by functional validation. Specifically, we obtained vesicular preparations from ^{triple}AD mice, the parental strains, and nontransgenic mice, followed by the quantitative mass-tag labeling proteomic technique iTRAQ and mass spectrometry. Within 1,275 quantified proteins, we found a massive deregulation of 24 proteins, of which one-third were mitochondrial proteins mainly related to complexes I and IV of the oxidative phosphorylation system (OXPHOS). Notably, deregulation of complex I was tau dependent, whereas deregulation of complex IV was Aβ dependent, both at the protein and activity levels. Synergistic effects of Aβ and tau were evident in 8-month-old ^{triple}AD mice as only they showed a reduction of the mitochondrial membrane potential at this early age. At the age of 12 months, the strongest defects on OXPHOS, synthesis of ATP, and reactive oxygen species were exhibited in the ^{triple}AD mice, again emphasizing synergistic, age-associated effects of Aβ and tau in perishing mitochondria. Our study establishes a molecular link between Aβ and tau protein in AD pathology in vivo, illustrating the potential of quantitative proteomics.

amyloid-beta peptide | electron transport chain | energy metabolism | mitochondrial complexes | tau protein

Alzheimer's disease (AD) is a devastating neurodegenerative disorder affecting >15 million people worldwide (1). The key histopathological features are amyloid-beta (Aβ)-containing plaques and microtubule-associated protein tau-containing neurofibrillary tangles (NFTs), along with neuronal and synapse loss in selected brain areas (2, 3). In determining the role of distinct proteins in these processes, traditionally, candidate-driven approaches have been pursued, linking neuronal dysfunction to the distribution of known proteins in healthy compared with degenerating neurons, or in transgenic compared with control brain. In comparison, proteomics offers a powerful nonbiased approach as shown by us previously (4, 5).

APP152 (APP/PS2) double-transgenic mice model the Aβ plaque pathology of AD (6); they coexpress the N141I mutant form of PS2 together with the APP^{swe} mutant found in familial cases of AD. The mice display age-related cognitive deficits associated with discrete brain Aβ deposition and inflammation (6). pR5 mice model the tangle pathology of AD (7–9). They express P301L mutant tau found in familial cases of frontotemporal dementia (FTD), a dementia related to AD. The pR5 mice show a hippocampus- and amygdala-dependent behavioral impairment related to AD (10). Crossing of pR5 and APP/PS2 mice revealed that total tau and APP levels, respectively, were not altered in ^{triple}AD mice, suggesting that there is no titration of transcription factors for the promoters driving either mutant APP or tau transgene expression (11). Of particular relevance in the ^{triple}AD mice is the low interanimal variability and early onset of tau pathology (11).

Here, we performed a comparative, quantitative proteomic analysis of single-transgenic pR5, double-transgenic APP/PS2, and ^{triple}AD (pR5/APP/PS2) mice, as well as wild-type controls, and found that one-third of the deregulated proteins were mitochondrial. In evaluating our findings, we could establish mitochondrial dysfunction in ^{triple}AD mice, synergistically induced by tau and Aβ pathologies.

Results

Comparative ITRAQ (Isobaric Tags for Relative and Absolute Quantitation) Mass Spectrometry. Crude vesicular fractions of forebrains obtained from 10-month-old single-transgenic pR5 mice, double-transgenic APP/PS2 mice, a cross of the 2 strains (^{triple}AD), and nontransgenic littermate controls were trypsin digested ($n = 6$ animals for each group), and peptides labeled with iTRAQ. Then, these were separated by HPLC, using both reverse-phase (RP) and strong cation exchange (SCX) columns, followed by nanoLC-ESI MS/MS mass spectrometry (3 iTRAQ runs and 4 two-dimensional LC ESI MS/MS data sets were used to obtain iTRAQ data). Data processing identified 1,598 proteins, 1,539 of which were quantified; 1,275 with more than 2 peptides. Twenty-four proteins were found to be differentially expressed in ^{triple}AD compared with the other samples (Table 1 and Table S1).

Deregulated Proteins Identified by ITRAQ. ProteinPilot requires a minimum of 40 counts of iTRAQ reporting ion intensities to

Author contributions: A.E. designed research; V.R., X.S., A.W., L.M.I., G.B., F.M., S.D., U.B., E.S., and J.G. performed research; L.O., H.B., and C.C. contributed new reagents/analytic tools; V.R. and X.S. analyzed data; and J.G. and A.E. wrote the paper.

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PHENOTYPIC VALUES

considered to be the sum of all genetic and environmental effects

individual phenotypic scores are combined and phenotypic values are measured as deviations from the population mean

for analysis, deviations from the mean are converted into variances

Phenotype = Environmental effects + Genetic effects + Genotype/Environment interaction effects

$P = E + G + GxE$

Variance components are now:

$V_{(P)} = V_{(E)} + V_{(G)} + V_{(GxE)} + 2cov(G)(E)$

$V_{(P)}$	$V_{(E)}$	$V_{(G)}$	$V_{(GxE)}$	$2cov(G)(E)$
observed variation in phenotype In population	variation due to environment	variation due to genes	variation due to interaction between genes & environment	correlation between genetic and environmental effects

Inbred strains: $V_{(G)} = 0$

so, $V_{(P)} = V_{(E)}$

Humans : only less direct estimates possible from resemblance between relatives

in the case of MZ twins, $V_{(G)} = 0$ and $V_{(P)} = V_{(E)}$

Genotype x Environment interaction (G x E)

- genotype and environment are not independent
- effect of environment can be modified by genotype
- gene effects can be modified by certain environments
- effects can be quite large

Example

Liability to become a smoker (Heath et al, 2002)

both genes and environments have main effects

but there is extra liability, more than additive effects, due to interaction

25% of total variance is from interaction between genetic risk alleles and environment that encourages smoking

Genotype x Environment correlation (rG x E)

- genotype and environment are not independent
- neither main effect is altered
- because of choice, certain genotypes are more common in certain specific environments than others
- results in a measurable genetic influence on an environmental variable's effects

- few environmental measures used in behavioral science do not show genetic influence – suggests people create their own experiences in part for genetic reasons

genetic influence found for

- life events experienced at home and school: eg. tendency to be bullied, victimized, other aspects of school environment like teachers' response
- life events experienced throughout life: eg.TV viewing, work experiences
- levels of stress experienced, exposure to trauma, accidents
- relationships: friends, peer groups, friend characteristics, divorce
- financial disruptions

likely mediated in part by personality, which shows genetic influence

genetic influence goes up childhood to adulthood, as individuals make their own choices

Examples of gene x environment correlations

1. Genotypes present in members of competitive basketball teams are NOT a random selection

- certain people have talent to play certain sports as a result of their genotype (muscle type, size, height, aerobic capacity etc)

- these genotypes (people) are found more frequently in an environment where the sport is played

2. Musical ability

- gifted children are likely to have gifted parents if ability is heritable

- parents are therefore likely to provide

1. not only genes but an environment conducive to developing ability

= PASSIVE rGxE

2.talented children may be picked out at school and given special opportunities

= EVOCATIVE rGxE

3. children themselves may seek out own musical environment by selecting musical friends, experiences etc.

= ACTIVE rGxE

3. Continued correlation for behavioral measures into old age

- shown by MZ, DZ twins, in spite of changes in level of phenotype

eg heritability of cognitive ability continues to rise into adulthood and remains very high into old age

- at least part of this high twin correlation may be due to fact that twins are able to construct similar environments that continue to reinforce their phenotypic similarity