Families and Health: What Roles Might Molecular Genetics and Epigenetics play?

Guang Guo

- Department of Sociology
- Carolina Population Center
- Carolina Center for Genome Sciences

The University of North Carolina, Chapel Hill

Acknowledgement: Add Health: Dick Udry, Kathie Harris, Carolyn Halpern, Joyce Tabor… Collaborators: Jean Shih, Kirk Wilhelmsen, Mike Roettger, Tianji Cai …

Questions

- What is the nature of family effects?
- Where do we need genetics?
- What is the best evidence we have?
- What could we do at the moment and in the next 10 years?

Family influences on adolescents' well-being

- Family influences

- Binge drinking
- Smoking
- Marijuana use
- Delinquency
- Dietary patterns
- Education
- Occupation

What does a family do?

- Family is a place where social/cultural and genetic influences meet!!!
- It transmits social/cultural influences
- It transmits genetic influences
- Traditional approach: statistical models
- Traditional approach: twin studies

Example 1: Genetic variation influences family behavior (e.g., pair-bonding)

Example 2: Why genetics may be useful: Separate genetic and environmental family effects?

- The classic Wisconsin model
- Social origin (parental education, occupation, and income) -> children's education and occupation outcomes
- No doubt parents provide important social environments, but parents also provide all the genes to children: 50% from father and 50% from mother
- Traditional estimates of parental influences may be exaggerated

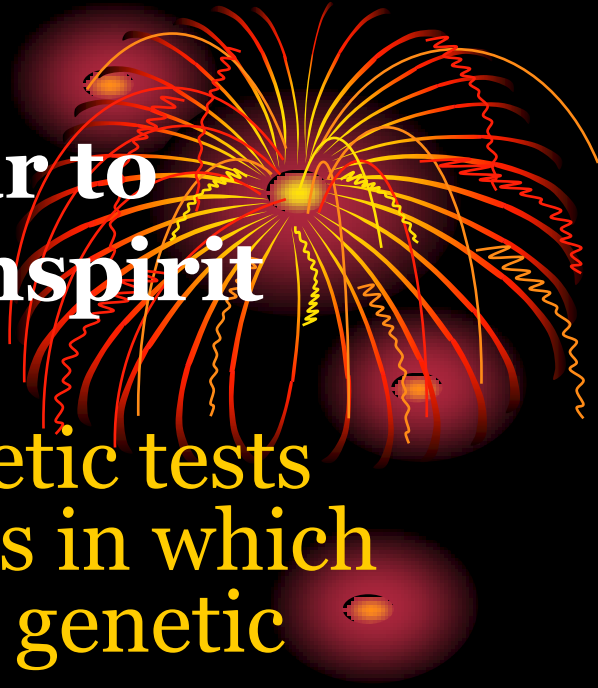
Example 3: Why genetics may be useful: G x E interaction effects?

- Genetic propensities for adolescents may depend on parental involvement
- Involved parents suppress the propensities and un-involvement parents promote the propensities.

Why are GxE interactions important?

- Ignoring genetic propensities gives an average effect across all genotypes
- Suppose: genotypes A and B
- A is sensitive to family effect; B is not
- GxE interaction will reveal family effect; family effect may be cancelled if an average is estimated

GxE interactions are similar to personalized medicine in inspirit



- Personalized medicine: Genetic tests divide individuals into groups in which the individuals are similar in genetic makeup
- For each group, personalized strategies can be developed for disease prevention and “designer” drugs to reduce adverse reactions and increase efficacy.
- Similarity: Interactions with genetic propensities

Example 1: Genetic variation influences family behavior

- Association between R53 (genetic var) in the *AVPR1A gene and* pair-bonding behavior in men
- Partner bonding, perceived marital problems, marital status, and marital quality as perceived by their spouses.

Walum et al. 2008, PNAS

Example 2: Why genetics may be useful: Separate genetic and environmental family effects?

- Can't be done easily since controlling for genetic effects requires knowledge of most of the genes involved

What is the best evidence for a main genetic effect and an GxE interaction genetic effect for any human trait?

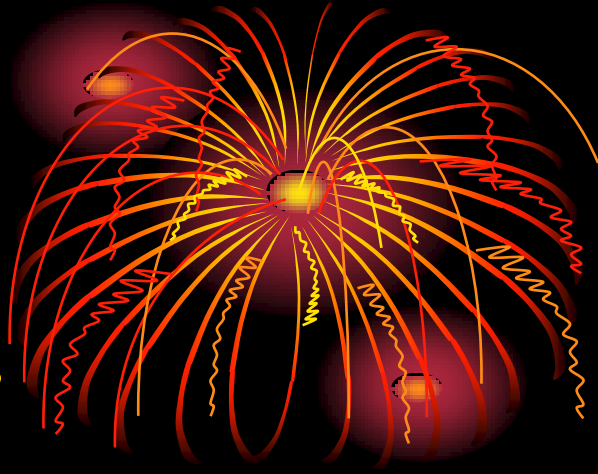
What is the best evidence for a main genetic effect for any human trait?

- 1980s: Mendelian traits – e.g., the Huntington disease (odds ratio=5000)
- Most diseases, traits, behaviors are 'complex' subject to influences of numerous genes, environmental influences, and the interactions between the two.
- Late 1990s and prior to 2006: the focus on complex traits (odds ratio<1.5), but plagued by results that can't be replicated

Best evidence for main genetic effects

- Genome-wide association studies: one million SNPs for each individual
- Articles in high-profile journals since 2007 report results from GWAS on breast cancer, prostate cancer, diabetes, leukemia…
- Two criteria: $P < 0.00000005$ (vs 0.05 we use normally); replications

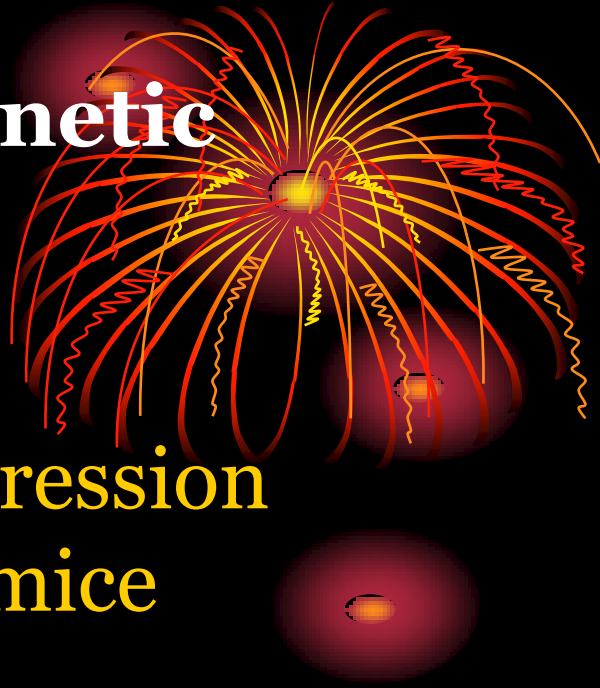
Main genetic effects



- Geneticists are thinking bigger
- International consortiums: >30,000 individuals each with >1 million SNPs
- They are going after effects averaged across all environments
- Current most expensive efforts are NOT even looking for GxE interactions.

Are there GxE interactions? What could we learn from an earlier experimental case?

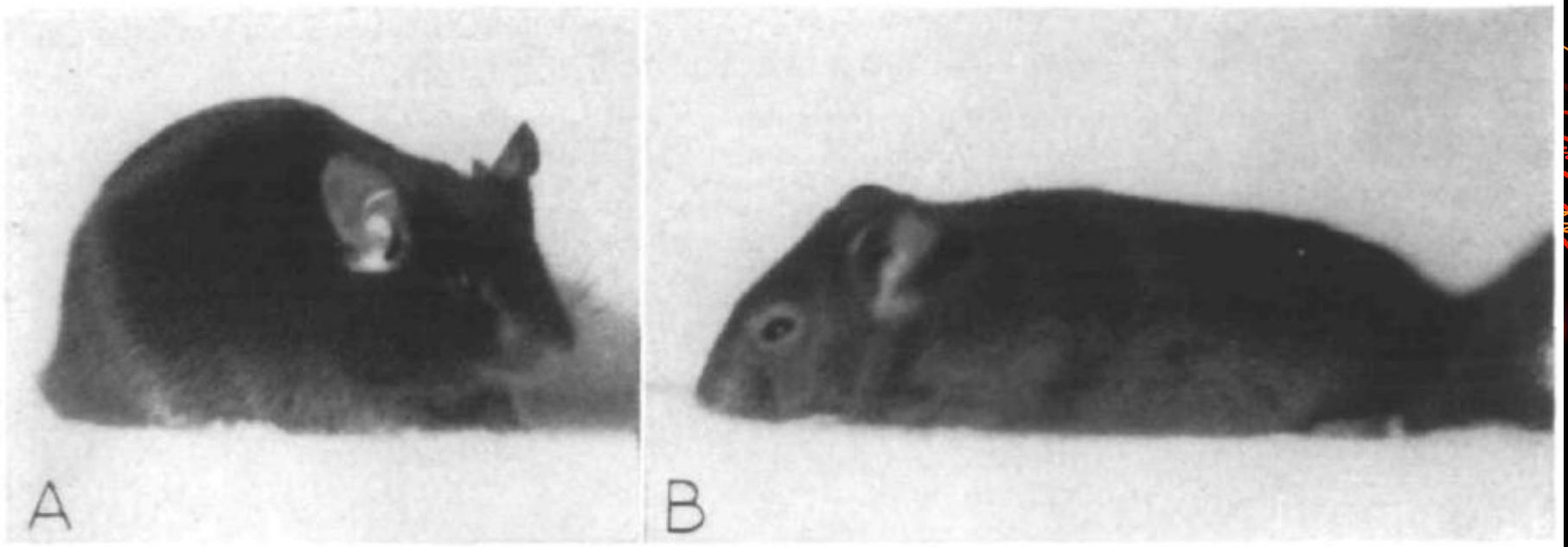
Inbred Strains of Mice: Genetic Influences on Aggression



- First genetic evidence of aggression produced in the 1940s from mice studies

Scott et al 1942

Ginsburg and Allee 1942



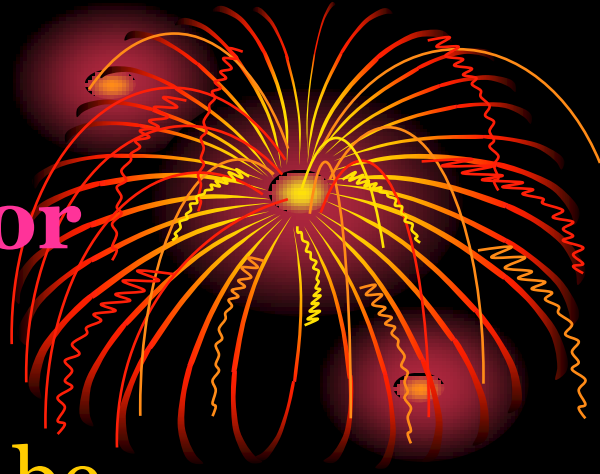
"PACIFIST" AND "AGGRESSOR" STRAINS

Figure 14

A *C57* black male (left) and a *C3H* agouti (right), both about four months of age. The more active attitude and sleeker fur of the *C57* type appears even in photographs. In several important "social" characteristics these two inbred strains differed consistently and widely.

- Inbred for >10 generations of brother-sister mating
- Each stock is nearly pure-breeding
- Small genetic differences w/n a stock and large b/w stocks
- Different aggressive behavior across stocks: Genetic

First evidence for gene-environment interaction for aggression (1940s)



- Mice of a pacific strain could be rendered aggressive through winning fights (assisted by researchers).
- Mice of an aggressive strain could be rendered pacific by experiencing defeats.

GxE Interaction Complicated (1940s)

- Social hierarchy determined by fighting
- Far easier to move a high-status mouse downward by engineered defeats than move a low-status mouse upward
- Mice lowest in social scale show extreme subordination
- Mice with middle positions more easily moved in either directions
- Clear evidence for GxE interactions
- GxE interactions abundant, but difficult to estimate

Epigenetics: Mechanisms for GxE interactions

Definition: Biochemical changes that affect gene expression, but that do not change the DNA sequence. These changes can be inherited.

- Epigenetics is a record (*readout*) for past environmental influences and provides mechanisms for gene-environment interactions
- Meaney et al.: Maternal non-licking -> methylation -> genes expression -> anxiousness among rats.

Our data source: National Longitudinal study of Adolescent Health 1994 -2010, US

- Wave I in 1994 with 20,000 aged 12-18; Wave II in 1996; Wave III in 2002; Wave IV under way
- A large-scale social science study having data measures on health behaviors
- Wave III in 2002, saliva collected from about 2,500 persons using buccal swabs
- 6 polymorphisms in 6 genes were genotyped

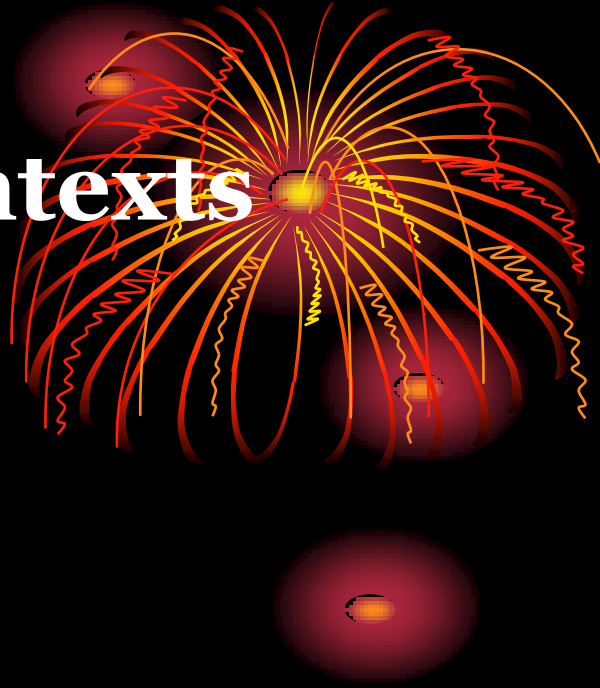
Delinquency Measures

- Serious delinquency: all items
- Violent delinquency: violent items
- Scales confirmed by factor analysis

3 genes and delinquency

- *DAT1*
- *DRD2*
- *MAOA*

Measures on Social Contexts



- Life stage
- Neighborhoods and schools
- Households
- Poverty
- Peers and Friends
- Gender
- Intelligence
- Religion

Our Data on Peers and Friends

- Study participants in ‘saturated’ schools where all students were participants
- Each dominate 10 same-sex and 10 different-sex friends starting from the best friend
- The nominated friends are study participants themselves
- Traditionally: self-reported friends’ behaviors

Add Health Males Waves I-III

	Genotype	Genotype Frequency At Wave I	Serious Delinquency			Violent Delinquency		
Age range			12-15	16-18	19-23	12-15	16-18	19-23
Gene								
DAT1	10R/10R	654	2.11	2.11	1.17	1.37	1.40	0.710
	10R/9R	378	2.28	2.23	1.23	1.63	1.51	0.73
	9R/9R	**56**	**1.17**	**1.28**	**0.62**	**0.76**	**0.92**	**0.29**
	Other/Other	42	1.97	1.59	1.65	1.46	1.04	1.03
	Sample size	1130	872	1292	1095	872	1292	1095
DRD2	178/178	619	2.03	1.84	1.20	1.33	1.21	0.68
	178/304	**425**	**2.38**	**2.56**	**1.20**	**1.68**	**1.75**	**0.67**
	304/304	89	1.52	1.69	0.95	1.09	1.13	0.62
	Sample size	1113	868	1284	1098	868	1284	1094
MAOA	**2R**	**11**	**5.78**	**3.23**	**2.20**	**4.33**	**2.53**	**1.70**
	No 2R	1115	2.07	2.10	1.17	1.40	1.40	0.70
	Sample Size	1126	865	1281	1095	865	1281	1095

Guo et al. ASR 2008

A VNTR polymorphism (variable) in *MAOA*

- Biochemical functional studies show three categories by promoter activity (gene expression): 4 repeat, 3 repeat; and 2 repeat

Guo et al. Euo J Hum Gen 2008

--*MAOA*2R*-rare allele
--Our collaborator Jean Shih of USC

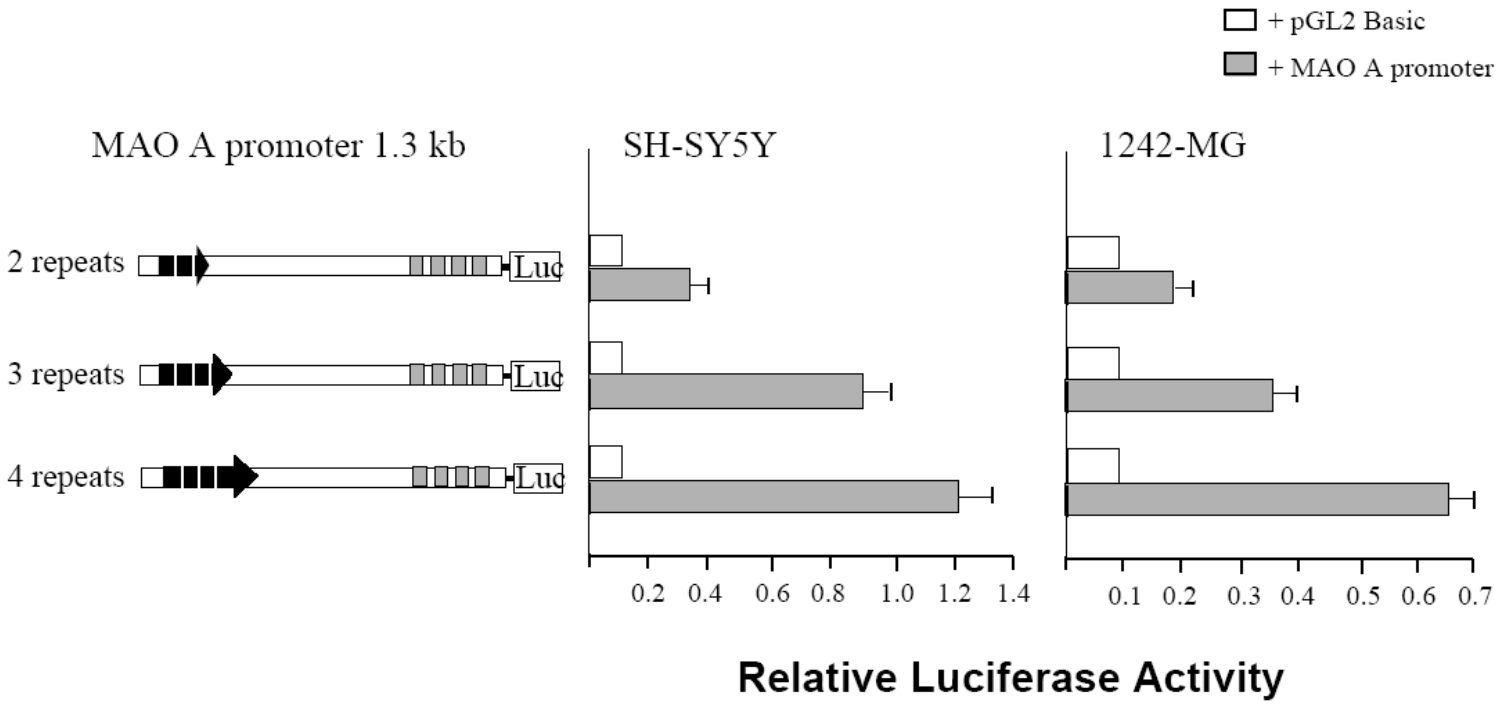


Fig. 4. The effect of 30-bp nucleotide repeats sequence on the human MAO A promoter activity in SH-SY5Y and 1242-MG cells. The MAO A promoter 1.3 kb luciferase constructs were transfected into either SH-SY5Y or 1242-MG cells for 24 h. Then cells were harvested and luciferase activity was determined. Controls were pGL2 Basic vector as indicated. Please note that 2-repeats sequence of MAO A promoter shows the lowest activity and 4-repeats sequence of MAO promoter shows the highest activity. Data were the mean ± S.D. from three independent experiments with triplicates for each experiment.

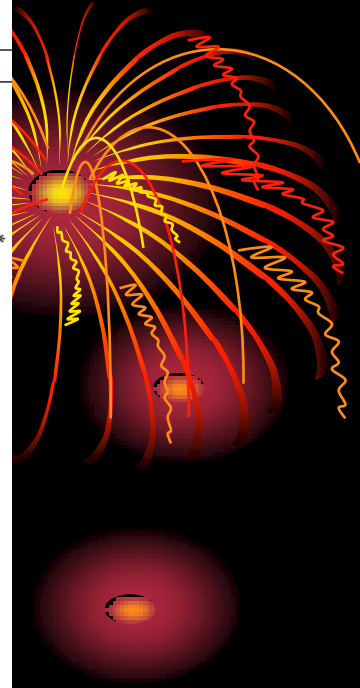
Guo et al Euro J Hum Gen 2008

Regression Analysis: Simultaneously Consider Genetic and Social Contexts

- Are genetic variants still related to delinquency after adjusted for social contexts?
- Are there interactions between genes and social contexts?

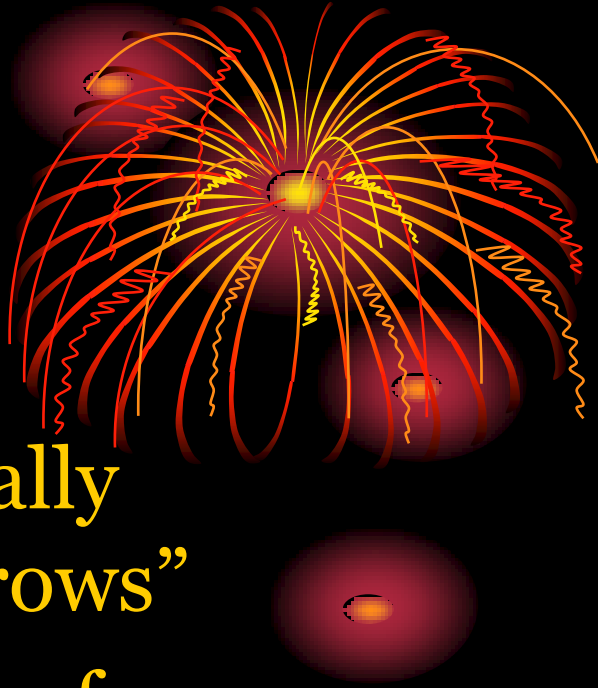
Table 3. Coefficients (standard errors) of random-effects models of **serious delinquency** among male adolescents and young adults: **Social control and genetic propensities** (Add Health Waves I-III)

Models	*Social control*	*DAT1*	*DRD2*	*MAOA*	*3 Combined*
Intercept	-2.872(2.192)	-3.614(2.211)	-2.521(2.204)	-3.012(2.195)	-3.403(2.229)
Age/ethnicity					
Age	0.685(0.242)**	0.676(0.241)**	0.668(0.242)**	0.7(0.242)**	0.678(0.243)**
Age^2	-0.023(0.007)***	0.023(0.007)***	-0.023(0.007)***	-0.024(0.007)***	-0.023(0.007)***
White					
Black	-0.078(0.326)	-0.042(0.326)	-0.041(0.327)	-0.111(0.327)	-0.038(0.328)
Hispanic	0.519(0.256)*	0.542(0.256)*	0.591(0.262)*	0.499(0.257)+	0.589(0.262)*
Asian	0.451(0.312)	0.451(0.315)	0.452(0.315)	0.44(0.313)	0.451(0.318)
School attachment					
Repeated grade	0.321(0.19)+	0.312(0.189)+	0.322(0.19)+	0.338(0.19)+	0.332(0.19)+
PVT < 90	0.034(0.254)	0.027(0.254)	0.028(0.254)	0.029(0.255)	0.023(0.256)
PVT 90-110	0.213(0.192)	0.217(0.192)	0.195(0.193)	0.215(0.193)	0.206(0.193)
PVT > 110					
PVT missing	-0.337(0.415)	-0.312(0.414)	-0.386(0.417)	-0.323(0.416)	-0.344(0.417)
Religiosity					
Weekly or more	-0.514(0.14)***	-0.516(0.139)***	-0.512(0.14)***	-0.509(0.14)***	-0.508(0.14)***
Family SES					
2 biological parents	-0.236(0.182)	-0.229(0.182)	-0.203(0.182)	-0.225(0.182)	-0.187(0.183)
Others					
Household size	0.014(0.056)	0.02(0.056)	0.016(0.056)	0.018(0.056)	0.024(0.056)
Parent jobless	0.827(0.379)*	0.828(0.379)*	0.861(0.379)*	0.821(0.38)*	0.854(0.38)*
Jobless missing	0.136(0.32)	0.157(0.32)	0.146(0.321)	0.139(0.322)	0.163(0.323)
< High school	-0.281(0.285)	-0.299(0.284)	-0.257(0.285)	-0.29(0.286)	-0.285(0.287)
High school					
> High school	0.106(0.2)	0.116(0.2)	0.105(0.2)	0.096(0.2)	0.103(0.2)
Daily family meals	-0.487(0.157)**	-0.485(0.156)**	-0.482(0.157)**	-0.48(0.157)**	-0.474(0.157)**
Contextual characteristics					
Proportion black	0.723(0.472)	0.707(0.472)	0.686(0.472)	0.681(0.475)	0.638(0.474)
Genotype					
9R/9R	-				
10R/9R	-	0.961(0.361)**			0.913(0.365)*
10R/10R	-	0.753(0.356)*			0.684(0.359)+
178/304	-	-			
178/178	-	-	-0.281(0.17)+		-0.257(0.17)
304/304	--	-	-0.868(0.312)**		-0.803(0.313)*
2R	-	-	-	1.809(0.868)*	1.731(0.866)*
No 2R	-	-	-	-	
Random effects					



Guo et al ASR 2008

Summary: main effects

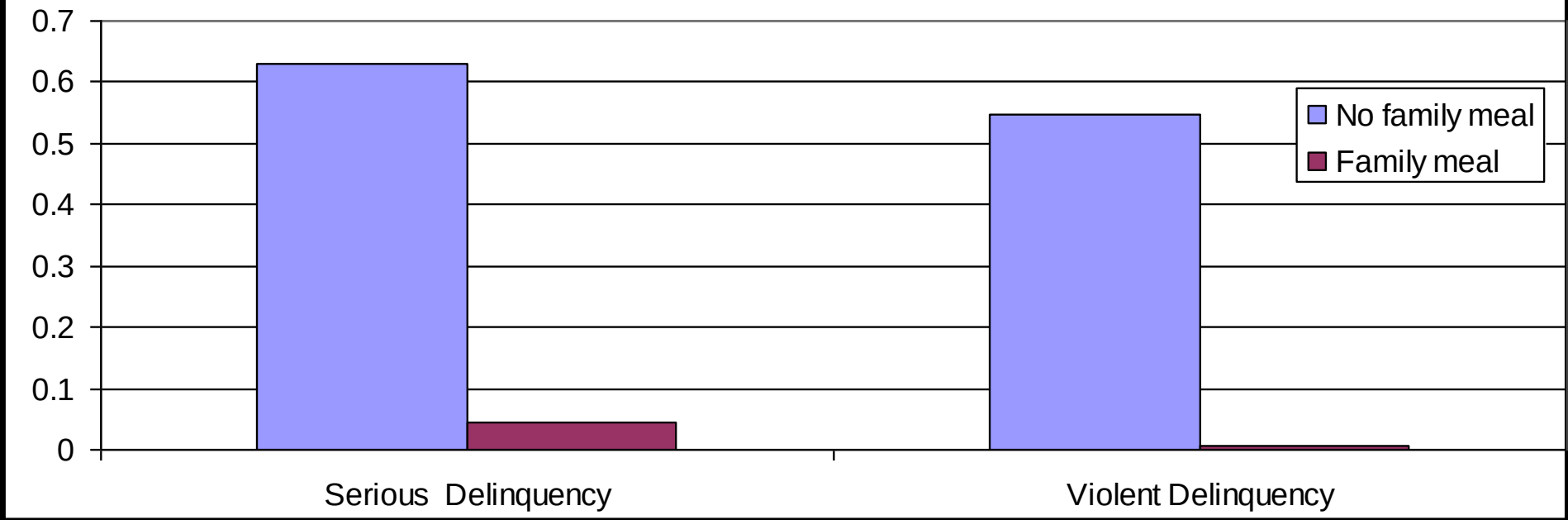


- *DAT1:* 5% (9R/9R) behaviorally "conservative"— "straight arrows"
- *DRD2: 178/304*: higher level of delinquency
- *MAOA*: 1% 2R highly delinquent;

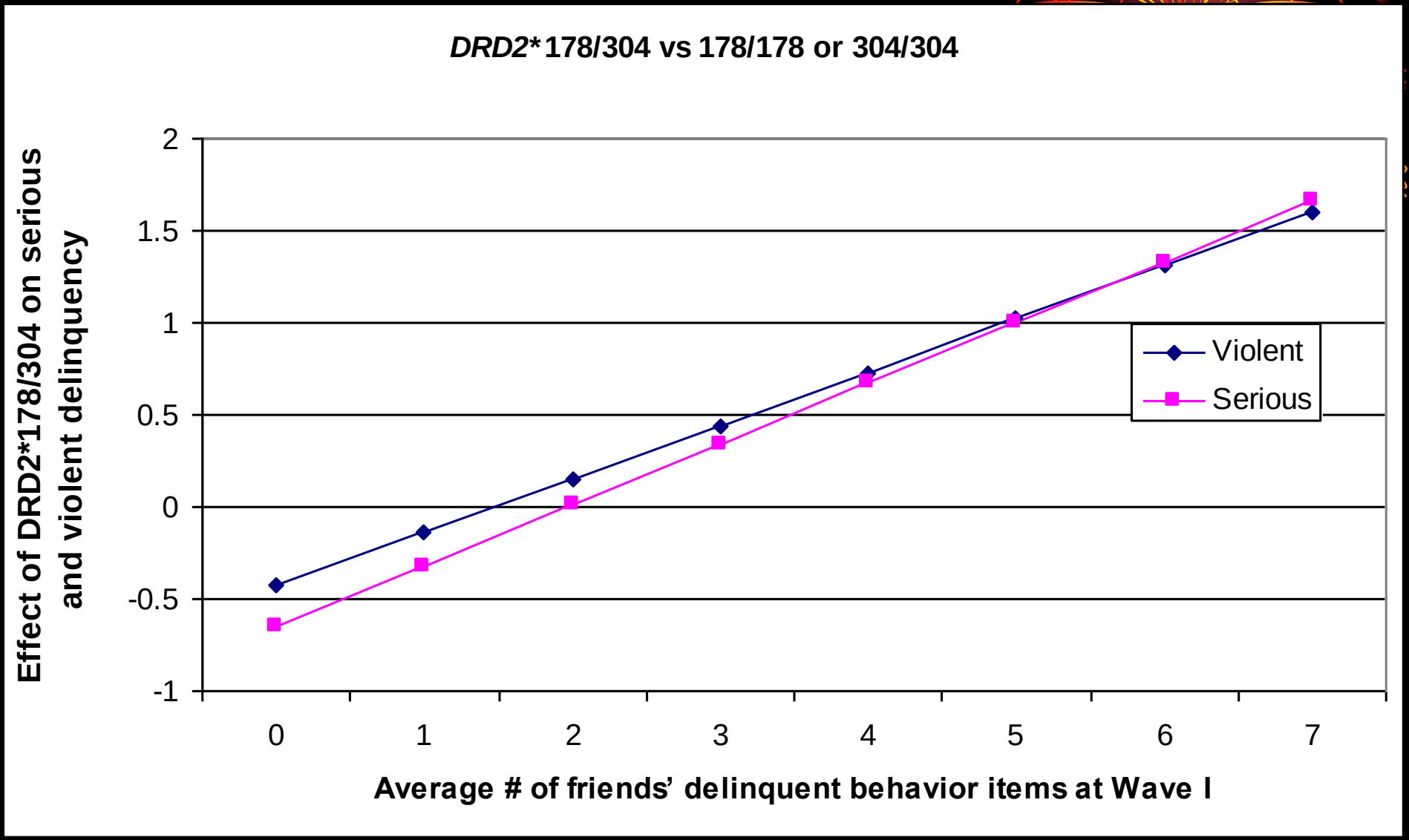
Summary: gene by social-control interaction effects

- e.g., Genotype effect depends on parental involvement. It only raises delinquency when parents are not involved

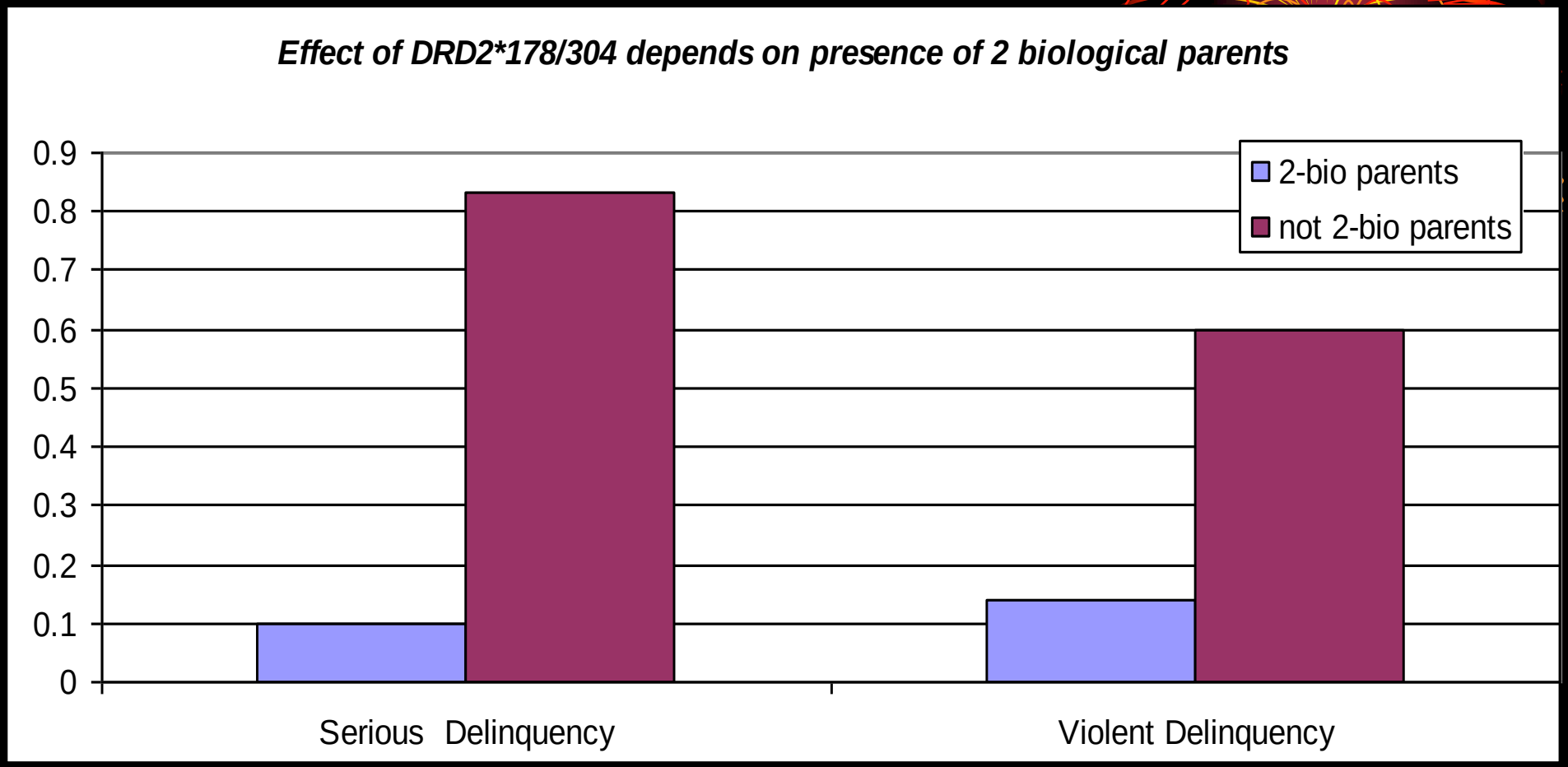
Effect of DRD2*178/304 depends on if pareants have regular meals with adolescents



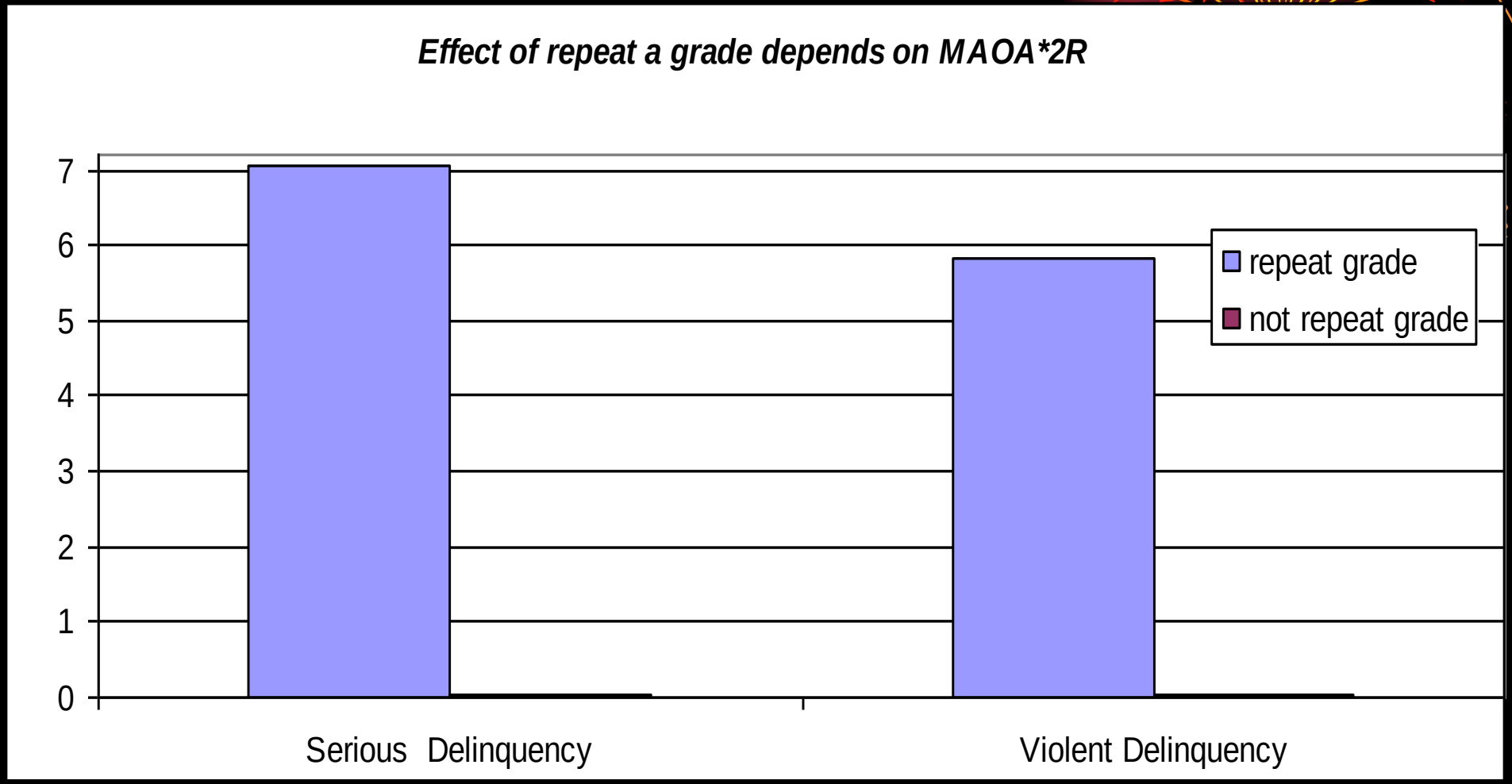
Guo et al ASR 2008



Guo et al. ASR 2008



Guo et al. ASR 2008

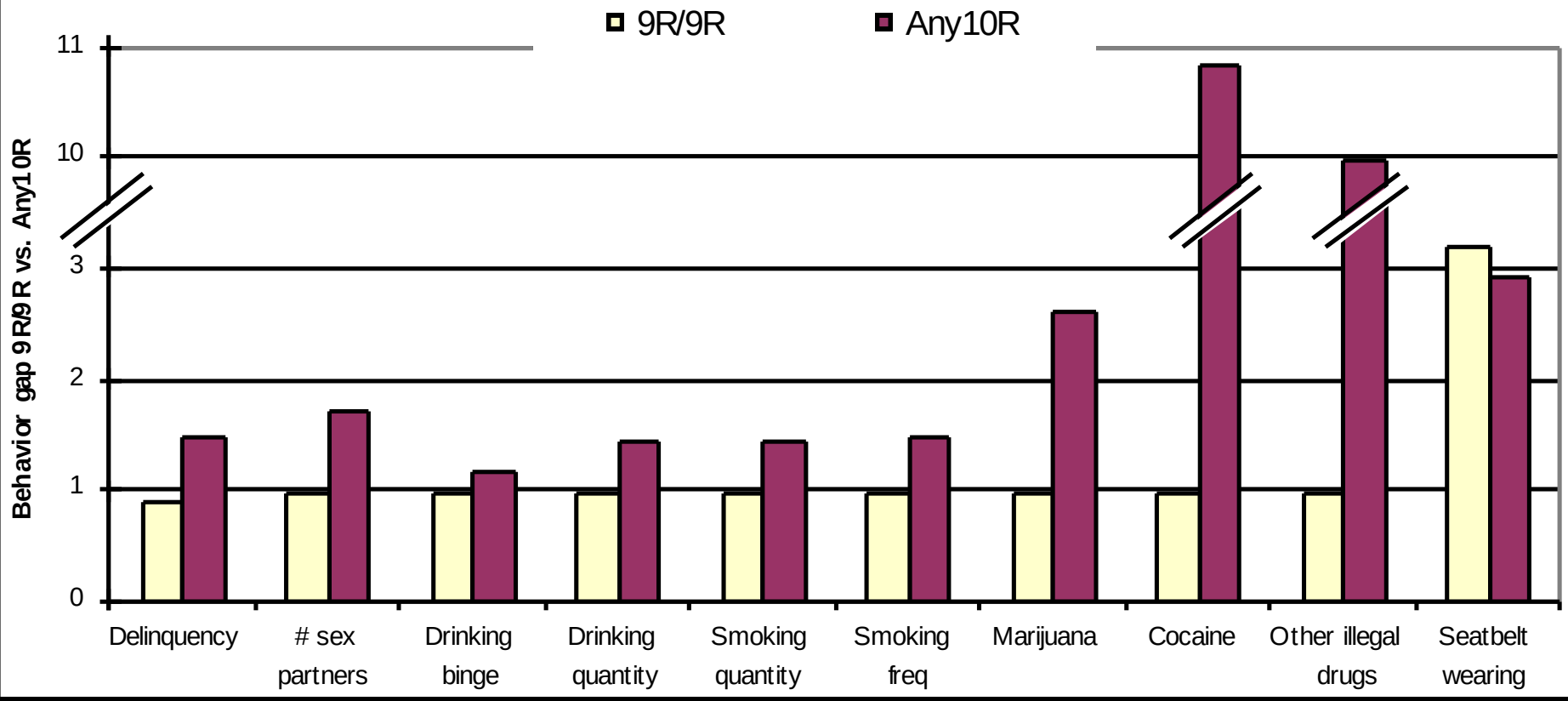


Guo et al. ASR 2008

The protective effect of DAT1 on a spectrum of risky behaviors (Main effect)

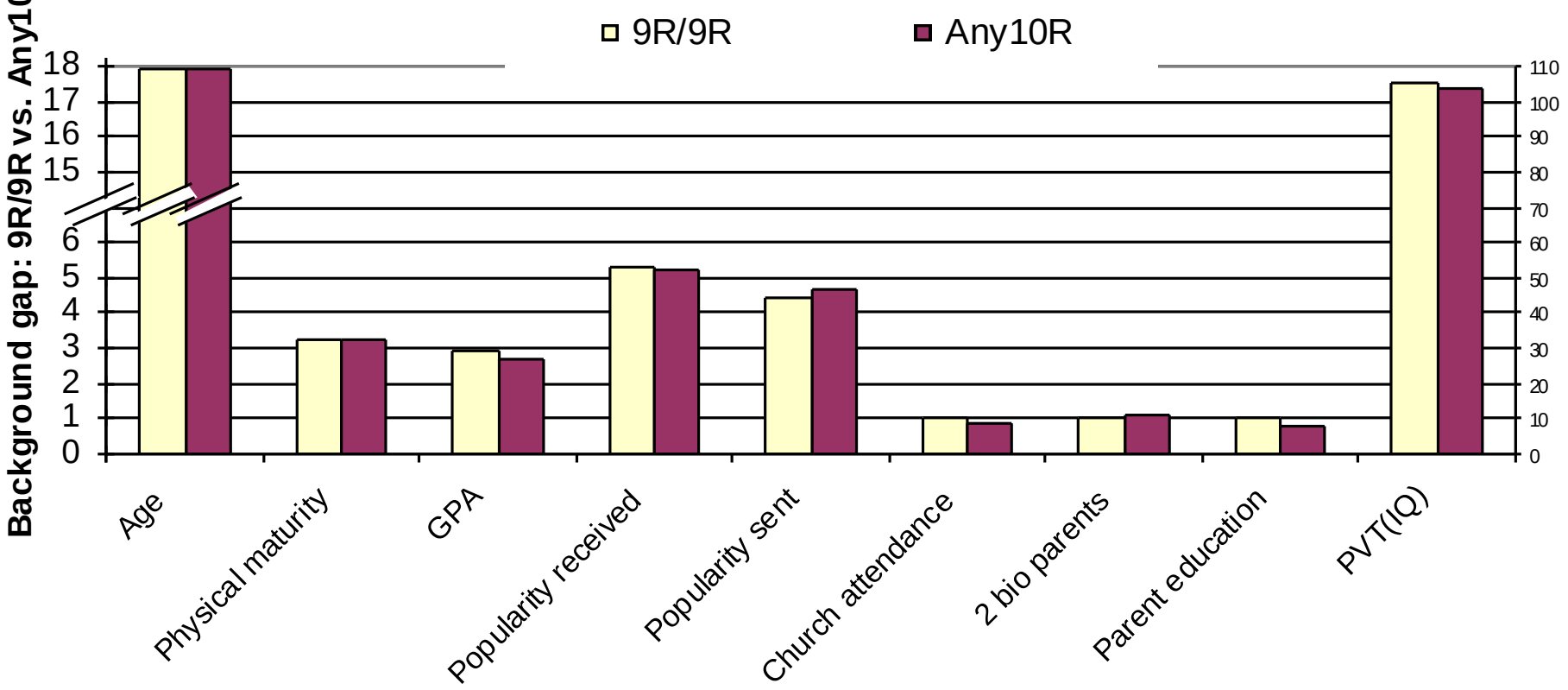
Guo et al under review

Figure 1. Behavior gap between the *DAT1 9R/9R and the *DAT1** Any10R genotypes among white males: ten risky behaviors**



Guo et al. under review

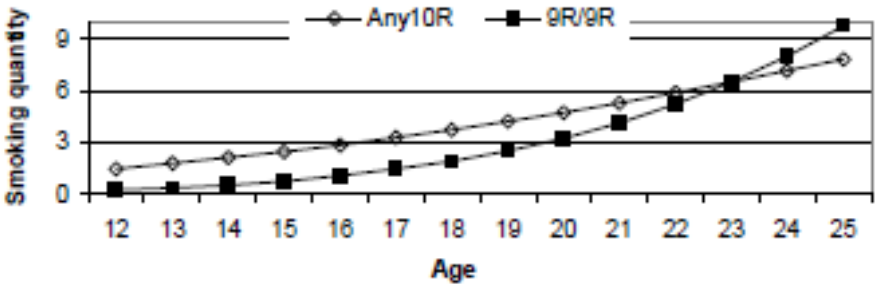
Figure 2. Background gap between the *DAT1 9R/9R and the *DAT1** Any10R genotypes among white males**



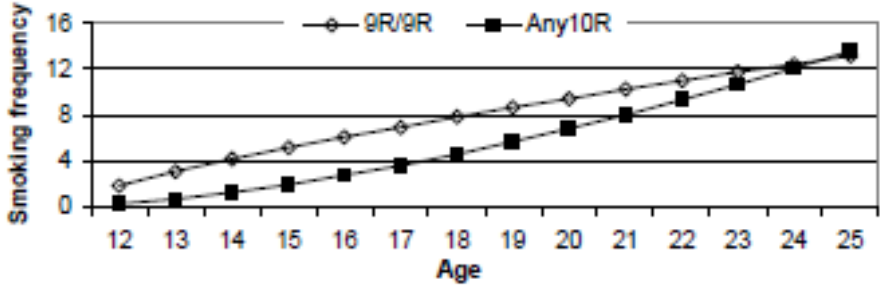
Guo et al. under review

- The protective effect depends on if the specific behavior is legal at the specific cage

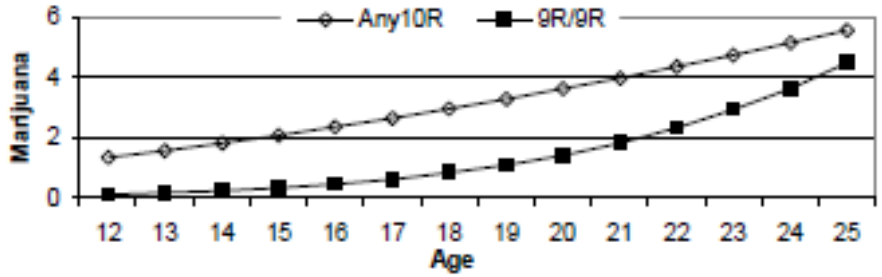
Part4: Protective effect diminished over age



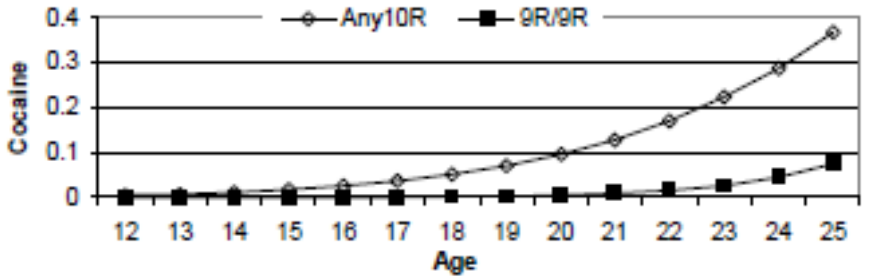
Part5: Protective effect diminishs over age



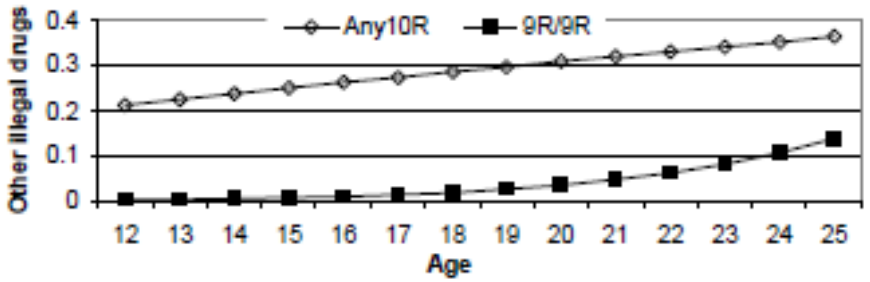
Part6: Protective effect unchanged over age



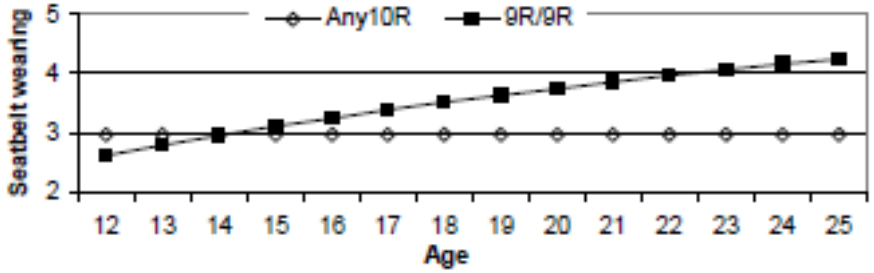
Part7: Protective effect increases sharply over age



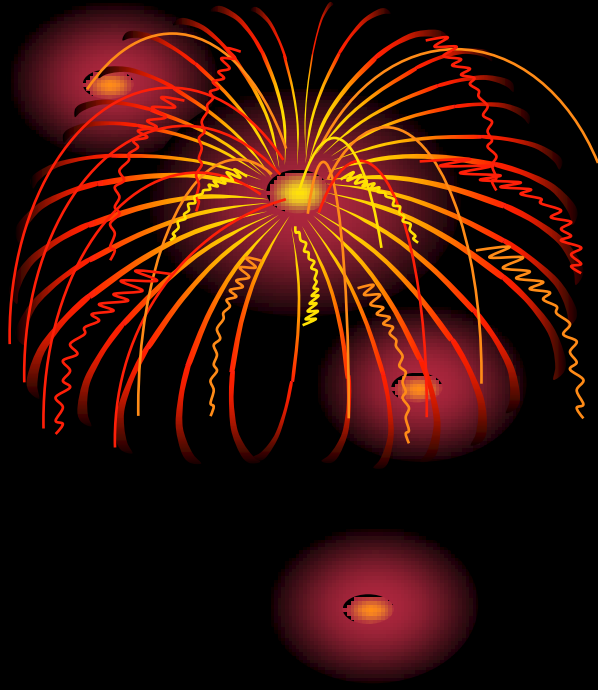
Part8: Protective effect increases sharply over age

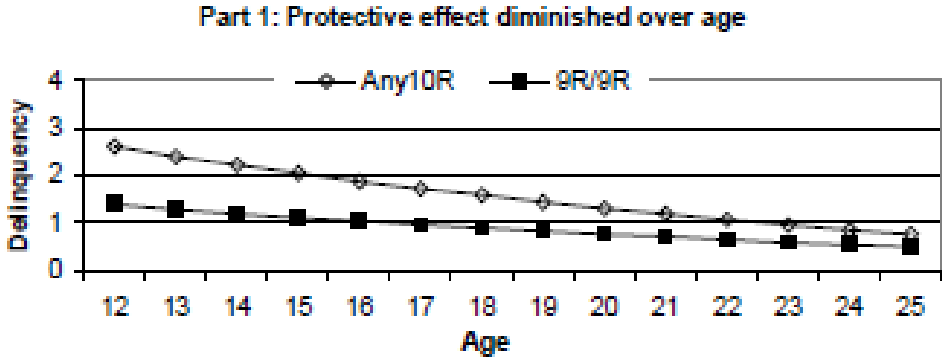


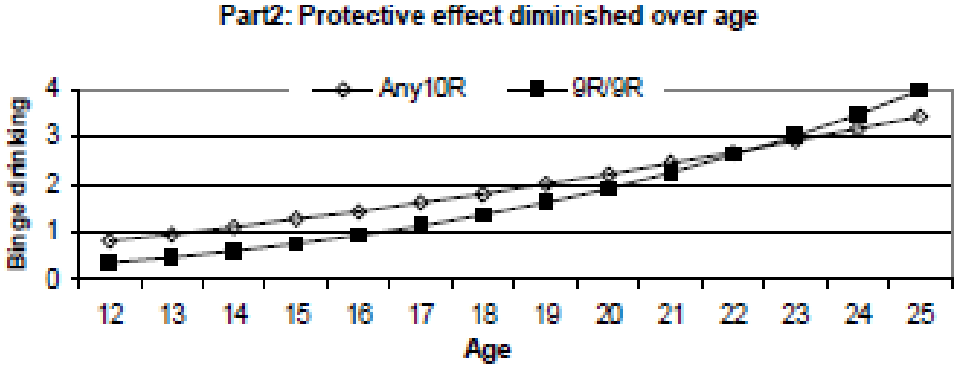
Part9: Protective effect prominent after 16

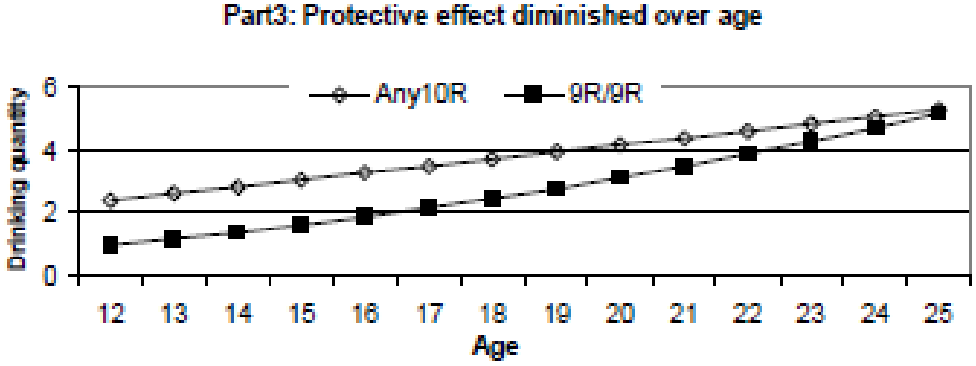


Guo et al under review









Guo et al. under review

Ongoing Project I

- Supported by the W.T. Grant Foundation, we have collected health behaviors and saliva DNA on 2,600 randomly assigned college roommates
- The study investigates if genetic propensities would moderate the roommate's influence on behaviors such as binge drinking and smoking and physical exercises
- Illumina 384 SNPs

Ongoing Project II

- Add Health Wave III: We are doing Illumina 1536 SNPs to study 80+ genes shown by rodent studies to be involved in aggression in 2,500 individuals funded by NSF (Social Dynamics Program)

What could we do now and in the next 10 years?

- Effects on family behavior (pair-bonding): possible; highly credible results difficult
- Controlling for entire genetic effect: difficult
- GxE interaction effects: Plenty of possibilities; highly credible results difficult
- Epigenetic mechanisms (methylation): possible and complicated.
- In 10 years, we may find a significant number of soc sci studies incorporating genetics and epigenetics. Soci sci have a more comprehensive view than geneticists.