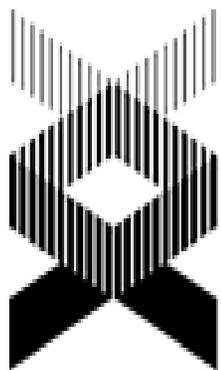


# Genetic Factors Associated with Susceptibility to Environmental Exposures

Ebony B. Bookman, Ph.D.  
Office of Population Genomics



National  
Human Genome  
Research Institute



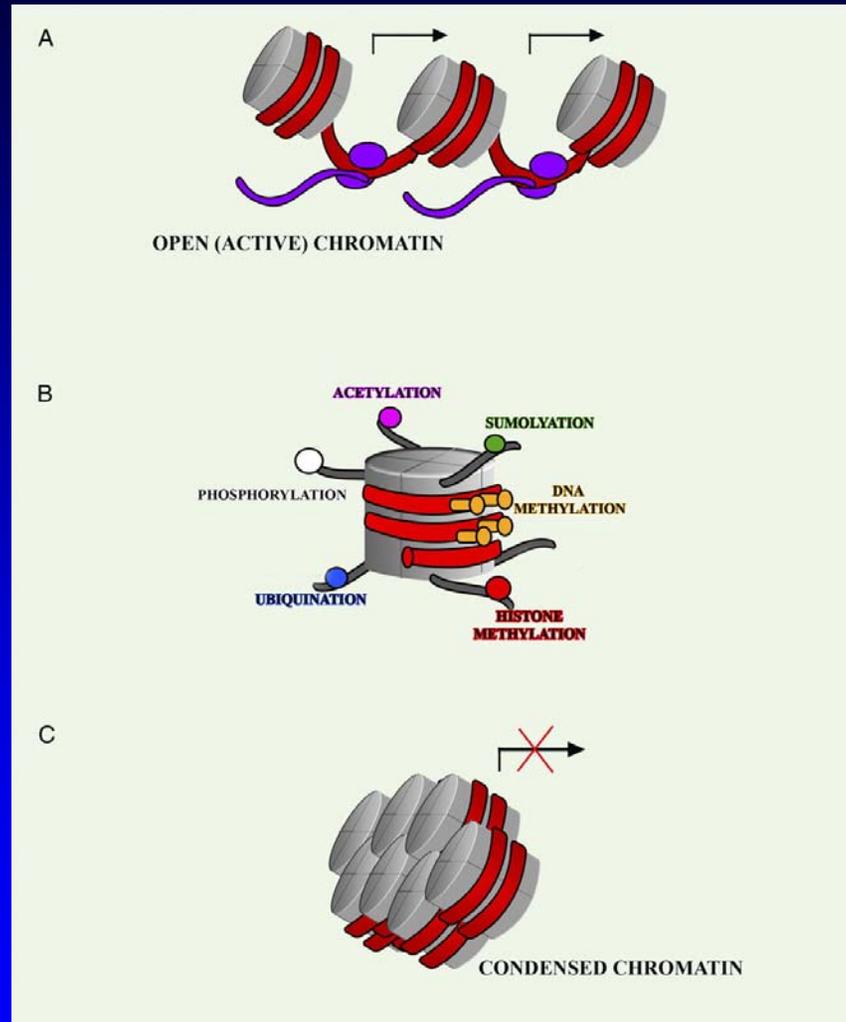
## Gene-Environment Interplay

- Allows the opportunity to discover novel genes whose effects are modified by different environments
- Provides insight into biological pathways that may not be detected outside of interaction analyses
- Provides a deeper understanding of the etiology of complex disease

## Gene-Environment Interplay, cont'd

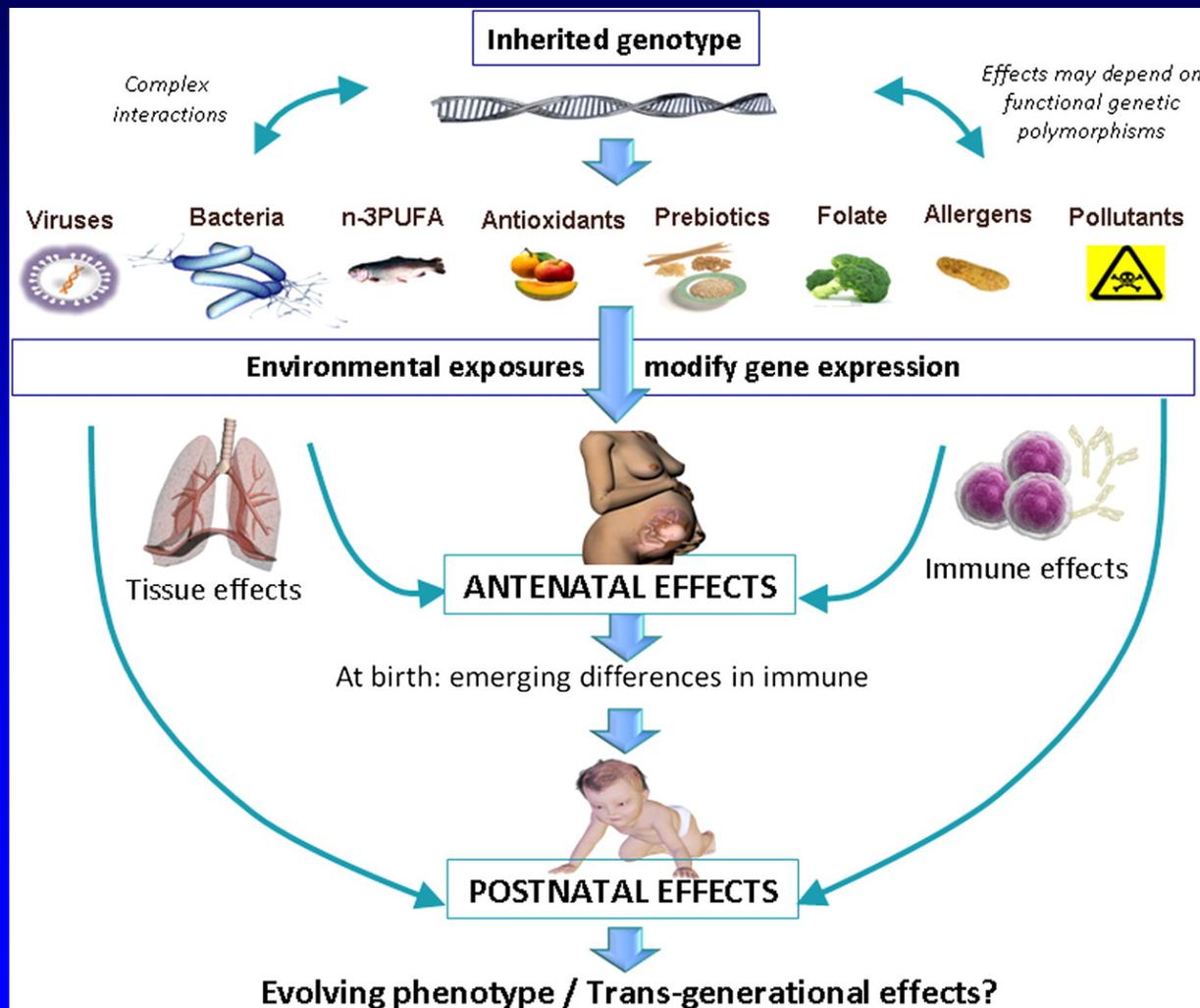
- Allows us to identify genetic vulnerabilities
- Facilitates the identification of targets for drug therapy
- Pinpoints pathways through which environmental exposures may act
- Provides opportunities for effective interventions

# Chromatin

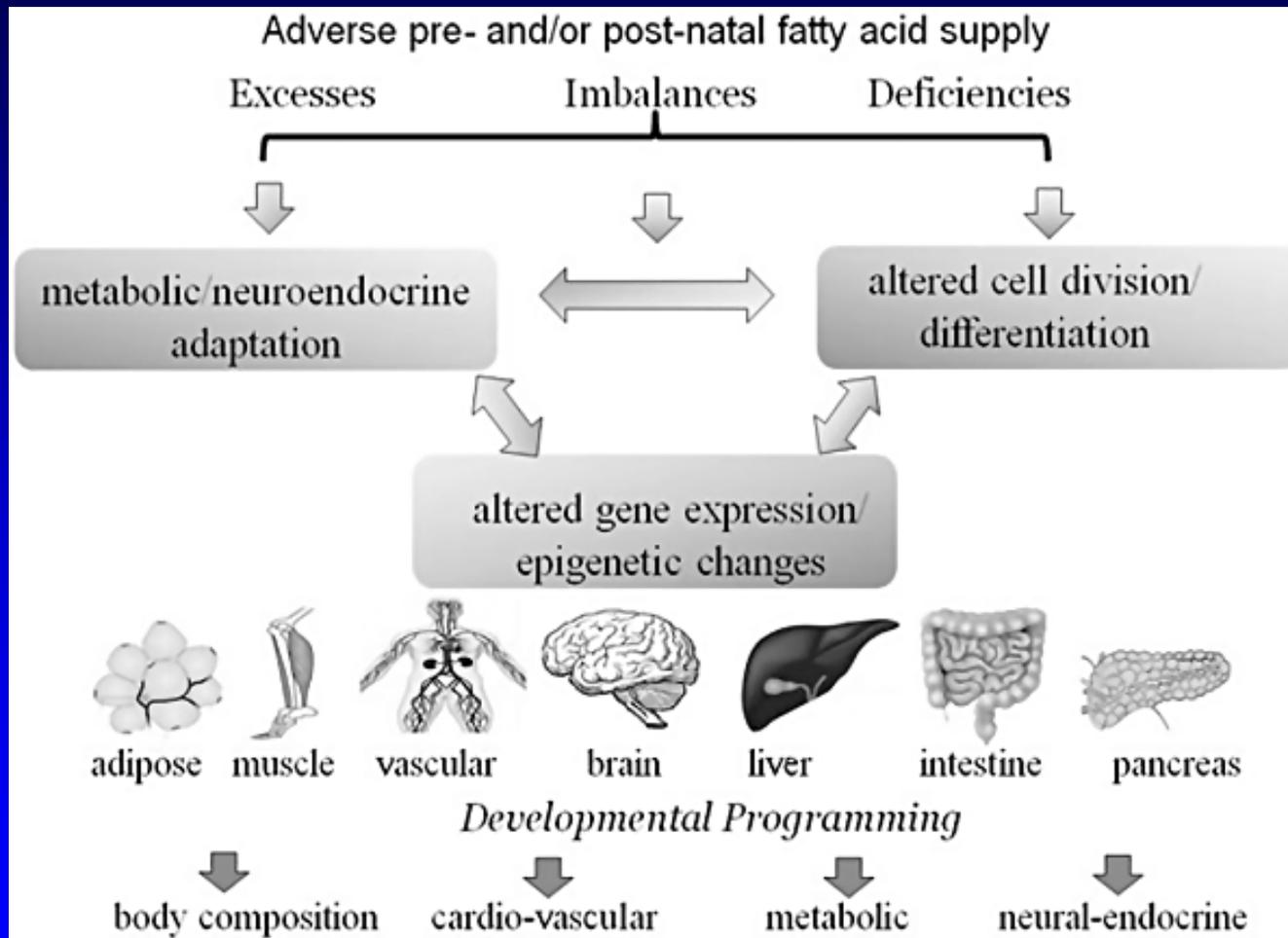


Martino D , Prescott S Chest 2011;139:640-647

# Complex gene-environmental interactions modify gene expression and phenotype during early development.

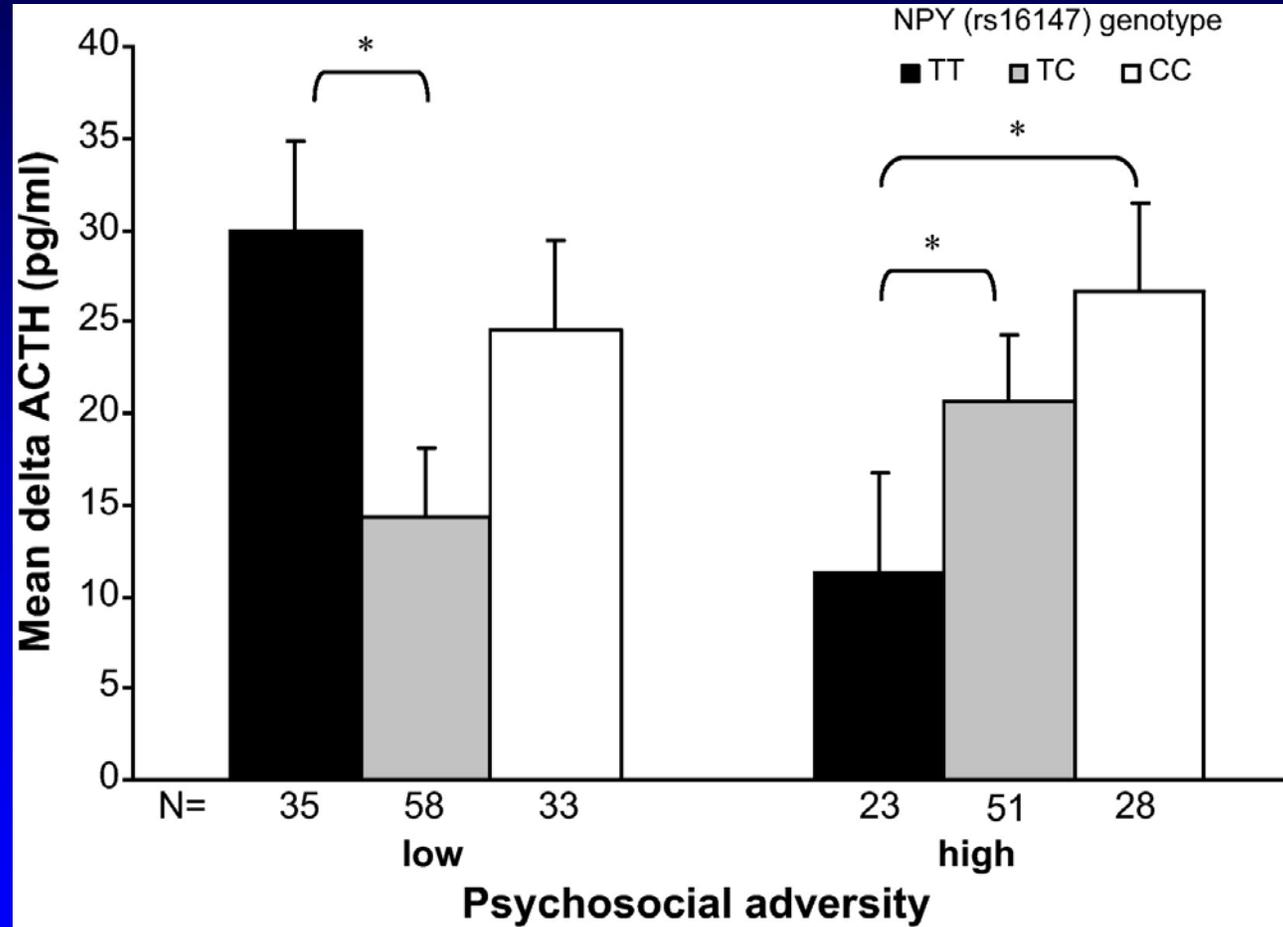


# Environmental Impact on Gene Expression



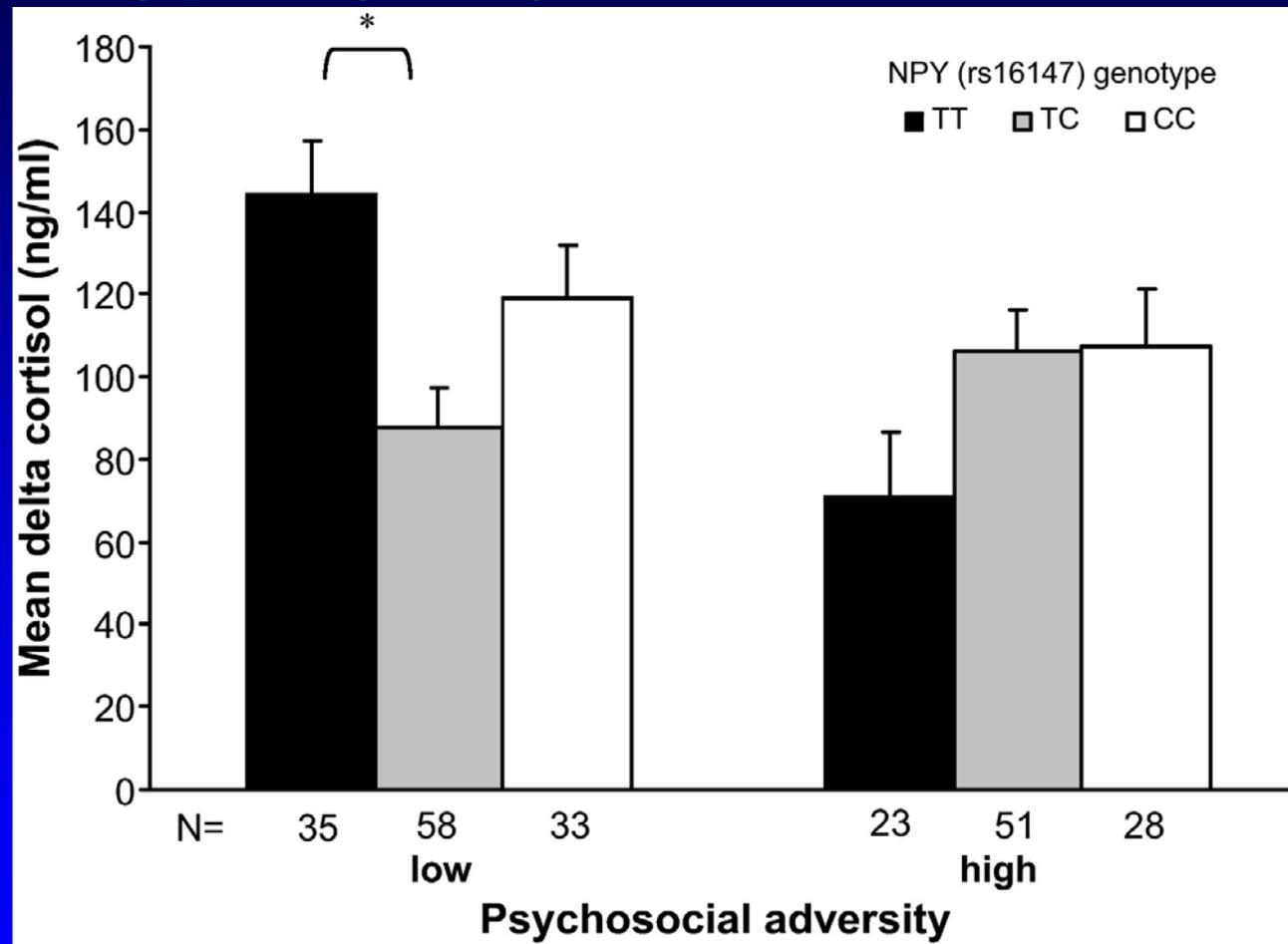
Symonds M.E., Sebert S.P., Hyatt M.A. & Budge H. (2009) Nutritional programming of the metabolic syndrome. *Nature Reviews. Endocrinology* 5, 604–610.

# Relationship of Cortisol Increase to NPY Genotype by Psychosocial Adversity



Witt SH, Buchmann AF, Blomeyer D, Nieratschker V, Treutlein J, Esser G, Schmidt MH, Bidlingmaier M, Wiedemann K, Rietschel M, Laucht M, Wüst S, Zimmermann US. An interaction between a neuropeptide Y gene polymorphism and early adversity modulates endocrine stress responses. *Psychoneuroendocrinology*. 2011 Jan 26.

# Relationship of Cortisol Increase to NPY Genotype by Psychosocial Adversity



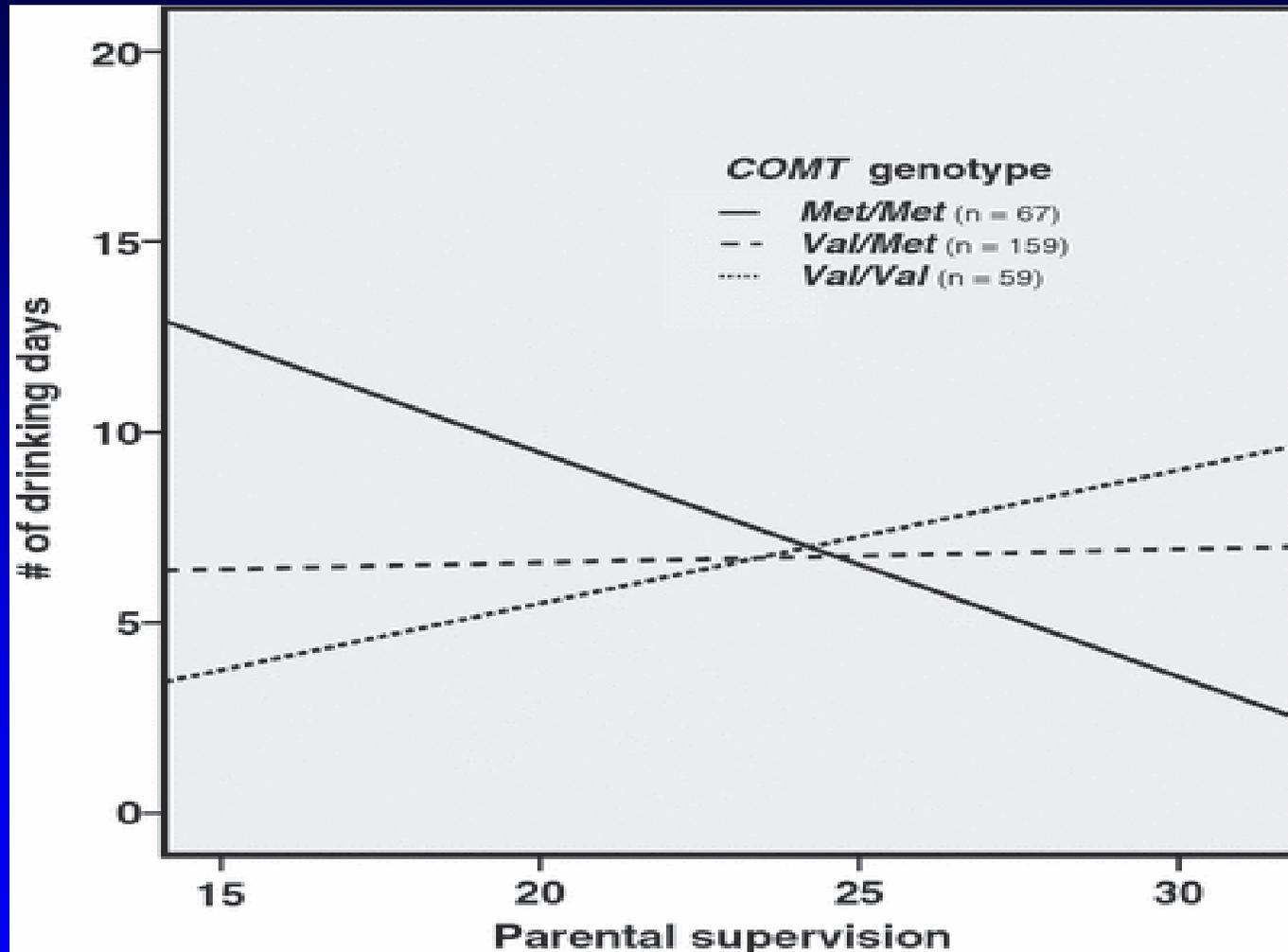
Witt SH, Buchmann AF, Blomeyer D, Nieratschker V, Treutlein J, Esser G, Schmidt MH, Bidlingmaier M, Wiedemann K, Rietschel M, Laucht M, Wüst S, Zimmermann US. An interaction between a neuropeptide Y gene polymorphism and early adversity modulates endocrine stress responses. *Psychoneuroendocrinology*. 2011 Jan 26.

# Twin Correlations and Genetic & Environmental Proportions of Variance for Sleep Measures

Sleep Measures	Correlations		Proportions of Variance (95% CI)		
	Monozygotic	Dizygotic	Addictive Genetic Influences	Shared Environmental Influences	Unshared Environmental Influences
Cosleeping	0.996	0.972	*	0.983 (0.962-0.994)	0.017 (0.006-0.038)
Sleep Duration (h)					
Night	0.946	0.808	0.308 (0.226-0.411)	0.641 (0.537-0.722)	0.051 (0.039-0.068)
Day	0.977	0.797	0.383 (0.281-0.469)	0.612 (0.506-0.696)	0.025 (0.018-0.032)
7 or more night awakenings	0.990	0.790	0.353 (0.141-0.684)	0.632 (0.303-0.836)	0.015 (0.002-0.056)
*Fixed to 0					

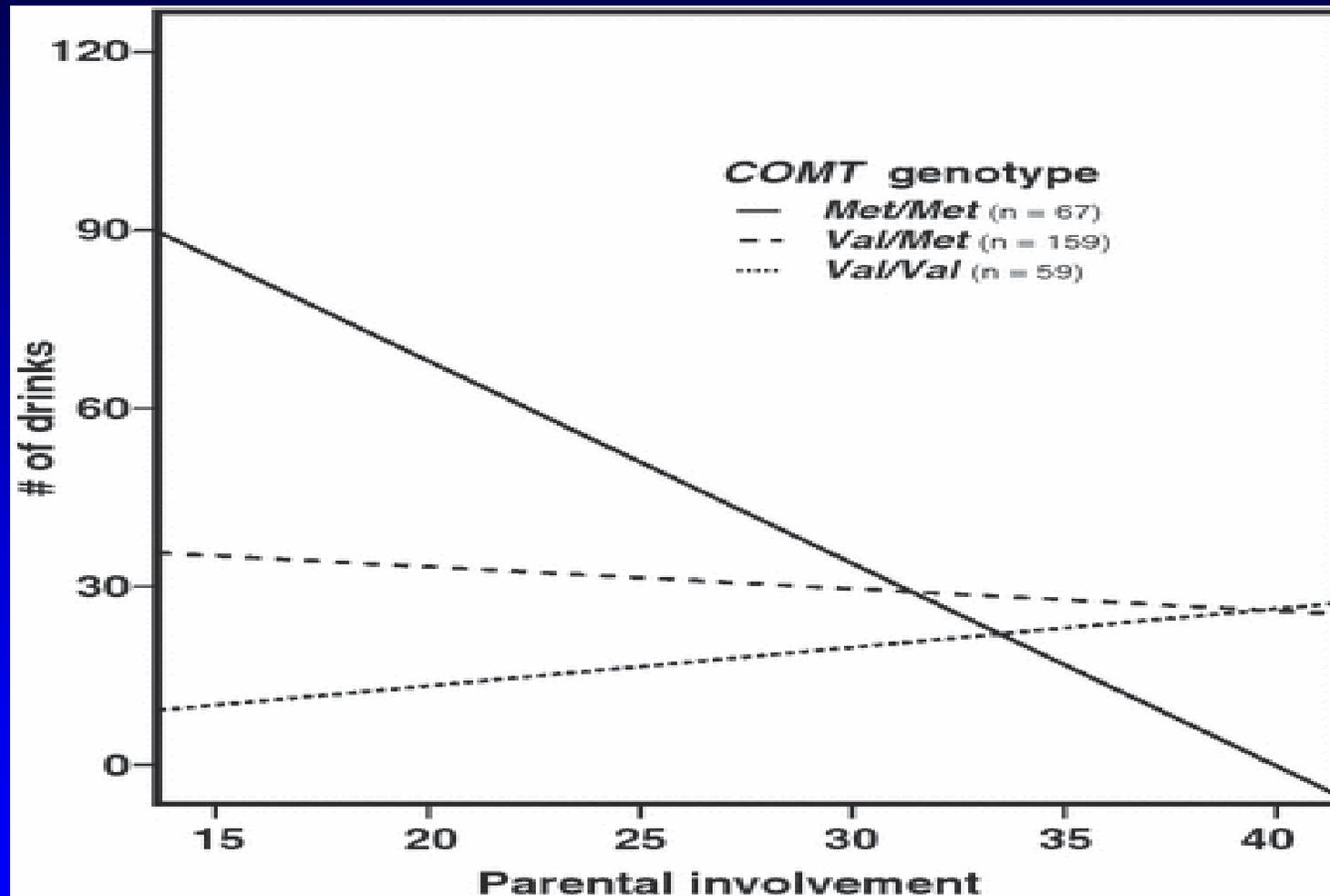
Brescianini S, Volzone A, et al. Genetic and environmental factors shape infant sleep patterns: a study of 18-month-old twins. *Pediatrics*. 2011 May;127(5):e1296-1302.

# Relationship of Drinking Behavior to COMT Genotype by Parental Supervision



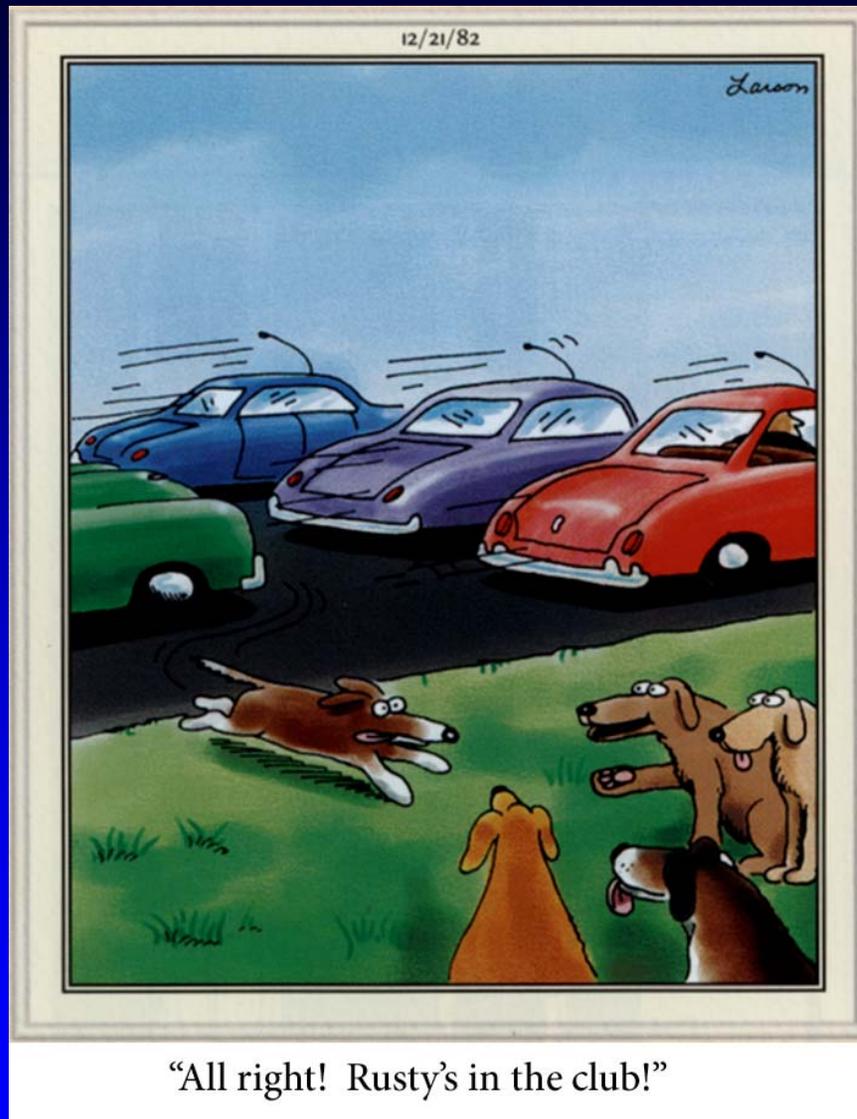
Laucht M, Blomeyer D, Buchmann AF, Treutlein J, Schmidt MH, Esser G, Jennen-Steinmetz, Rietschel M, Zimmermann US, Banaschewski T. Catechol-O-methyltransferase Val(158) Met genotype, parenting practices and adolescent alcohol use: testing the differential susceptibility hypothesis. J Child Psychol Psychiatry. 2011 Apr 19.

# Relationship of Drinking Behavior to COMT Genotype by Parental Involvement



Laucht M, Blomeyer D, Buchmann AF, Treutlein J, Schmidt MH, Esser G, Jennen-Steinmetz, Rietschel M, Zimmermann US, Banaschewski T. Catechol-O-methyltransferase Val(158) Met genotype, parenting practices and adolescent alcohol use: testing the differential susceptibility hypothesis. *J Child Psychol Psychiatry*. 2011 Apr 19.

# GxE Workshop Recommendations



Larson, G. *The Complete Far Side*. 2003.

# Study Designs

- Targeted Studies
  - Hypothesis Driven
  - Known disease associations with particular genes and/or environmental factors
  - Cost Effective
  - Miss important effects that lie outside study design
- Agnostic approach
  - Discovery-based
  - Provides a more thorough characterization of potential interrelationships of genetics and environmental exposures
- Family-Based
- Case-only

# Assessment of Environmental Factors

- Predate disease
  - Cohort studies' baseline
  - Exposures documented in databases (medical records; GPS)
  - Biomarkers
- Multiple measures over time
- Need better measurement tools

# **Ideal Cohort Study**

- **Large Sample Size**
- **Diverse demographic representation including underserved populations**
- **Broad range of genetic backgrounds and environmental exposures with early and recent exposure data**
- **Broad array of clinical and laboratory measures with regular follow-up over long periods of time**
- **High quality endpoint ascertainment and documentation**
- **Measurements appropriate for the cohort(s) being studied**
- **Appropriate policies for the collection and storage of biological specimens**
- **Open access of material and data**
- **Plan for re-contacting individuals for additional studies**
- **Precise, valid environmental/lifestyle measures**

## **Needs to improve the study of GxE Interplay**

- **Analytical methods that explore multiple levels of data**
- **Bioinformatic and biostatistical tools**
- **Interdisciplinary trained investigators in computational, statistical and molecular biology**
- **Database for standardized approaches, tools and results**

# Thank you

