Capturing Complexity: The Scientific, Societal, and Ethical Meanings of "Environment" in Genetic Research

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History and Philosophy of Gene Environment Interaction

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Outline

- Definition and roles of environment in genetic studies (Plomin et al.)
- Classical historical controversies (SZ and IQ)
- Recent philosophical arguments: DST: Lewontin, Oyama, Griffiths, etc.
- Controversies over the " nonshared environment"
- Why is studying environment so hard?: No consensus " theory" of the environment; Feldman and Cavalli-Sforza approach
- Methodological and substantive advances: Caspi-Moffitt-Rutter group in UK; epigenetics in Canada (SZ and BPI)
- Technological advances;Microarrays to the rescue? Plomin' s speculations
- Recent federal initiatives: Cancer; NHGRI' s GEI

Several slides will use information from the new Plomin et al 2008 text

COVER PHOTOS: (*Front*) Twin boys,

FIFTH EDITION

behavioral genetics

Robert Plomin | John C. DeFries | Gerald E. McClearn | Peter McGuffin

One definition of environment

- " ... in quantitative genetic theory, the word environment includes all influences other than inheritance, <u>a much broader use of the word than is usual in the behavioral sciences</u>. By this definition, environment includes, for instance, prenatal events and biological events such as nutrition and illness, not just family socialization factors." -- Plomin et al, 2008, pp 306-307

- Is this a consensus? Are there other definitions we need to consider? How might a definition relate to the need for a theory of environment, considered later.

# Classical historical controversies (SZ and IQ)

- Interesting controversies that challenged the basic assumptions of behavioral and psychiatric genetics in the 1960s and 1970s, and also again in the mid-1990s, were primarily over the different size (better, the amount of the variation) of the influences of nature <u>OR</u> nurture

- Examples:
  - The " schizophrenogenic mother" of Fromm-Reichmann contradicted by Heston' s 1966 and Kety' s (1968) adoption studies showing sz is mainly genetic
  - The Jensen-Lewontin IQ controversy (recapitulated in *The Bell Curve* controversy in 1994-1995) on how much of IQ is genetic *rather than* environmental
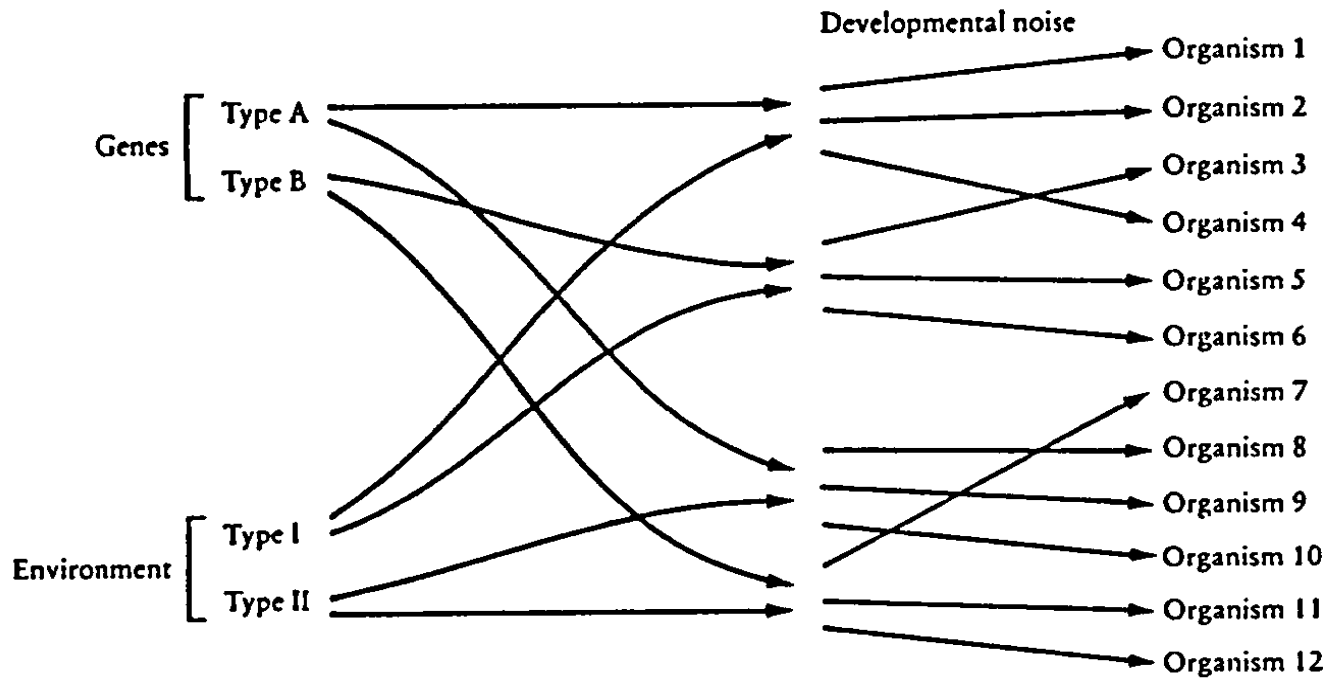
Lewontin response to IQ controversy

- Lewontin's 1970s response, continued in a number of later publications, was to attack Jensen's claim of a high IQ heritability (and the inference that IQ was largely genetic) on at least two grounds:

- 1. The failure to appreciate <u>gene-environment interaction</u>, which made pessimistic inferences about interventions by Jensen unsupported

- 2. The claim that GxE interactions supported an <u>indivisibility thesis</u>, such that one could not reason back from the phenotype to ascertain genetic and environmental

Gene-environment interactions

- Crossing curves based on norms of reaction were used as the empirical basis of point 1 (from Lewontin, 1974)
- P = phenotype; G = environment G's are two genotypes
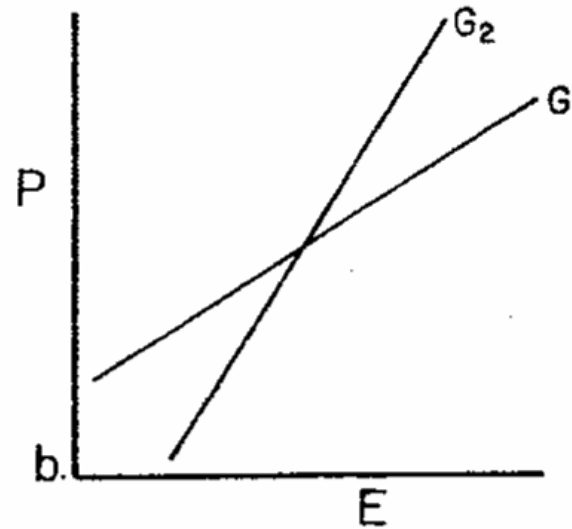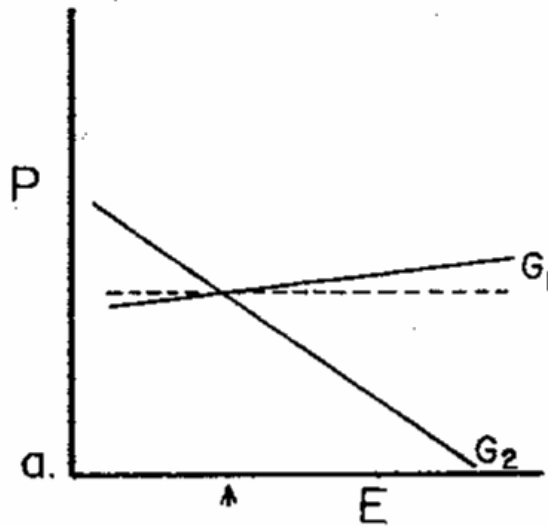
Lewontin diagram of indivisibility: from the organism's phenotype, one cannot infer the amount of the G and E causes/contributions

Developmental noise

Genes
- Type A
- Type B

Environment
- Type I
- Type II

Organism 1
Organism 2
Organism 3
Organism 4
Organism 5
Organism 6
Organism 7
Organism 8
Organism 9
Organism 10
Organism 11
Organism 12

From Lewontin 1995, depicting what he characterizes as the "correct model" of development.

DST

- A very loose confederation of BG critics, including Lewontin, Oyama, Gottleib, and Griffiths developed an approach that we can term " developmental systems theory" or DST

- DST has been influential in philosophy of science, and very productive of books and articles

- Largely criticized by some BG proponents (Gottesman and Turkheimer, Goldsmith, Scarr), or just ignored (Plomin, Rutter (?))

- I published an extended critique of DST in *Philosophy of Science*, 1998, and found it not well supported by work on simple organisms, including the worm, *C. elegans*.

KFS five core concepts of DST that are in contention-SKIP

All of the five core concepts apply to genes, and the last two of these to the relation of genes and environment, in connection with traits or phenotypes. The concepts are those of *parity, nonpreformationism, contextualism, indivisibility,* and *unpredictability.* Basically, *parity* means genes are not special—not "master molecules." *Nonpreformationism* implies that we do not find "traitunculi"—little copies of the traits the genes determine—in the genes. *Contextualism* indicates that genes have little meaning (as "informational molecules") per se, only in context with other genes, and in an environment that is cellular, extracellular, and extraorganismic. *Indivisibility* refers to the thesis that genes and environment cannot be identified by their effects on traits in any separable sense: the effects are a seamless unification, an amalgam. *Unpredictability* means that from total information about genes and environment, we cannot predict an organism's traits: they are, accordingly, emergent. These five concepts seem to capture the core of the 11 or so theses described in Section 2. What do successful research programs in the *C. elegans'* area tell us about the soundness and applicability of these concepts?

Indivisibility—and humans

- Time does not permit a review of the five core themes of DST, but the bottom line is that simple organism studies show they are unsupported in criticsl areas, though suggestive in others.

- The indivisibility thesis is wrong, distinctions are made, in the worm.

- And recent work with humans—covered later when Caspi and Moffitt's work is reviewed, indicates indivisibility fails there as well.

So, Back to human studies of the environment (From Plomin et al, 2008, p. 332)

- " Three of the <u>most important findings</u> from genetic research in the behavioral sciences involve the environment.

- First, genetic research has shown that environmental influences work in a <u>nonshared manner</u>, making children growing up in the same family no more similar than children growing up in different families. **[NSE]**

- Second, <u>genetic factors often contribute to measures of the environment</u> that are widely used in behavioral research and are responsible in part for the correlation between environmental measures and behavioral traits. **[rGE or GE]**

- Third, the effect of environments on behavior can depend on genetics, and <u>the effect of genetics on behavior can depend on the environment</u>." **[GxE]**

The Nonshared Environment

- Plomin views this as one of the most important discoveries in BG. It has stimulated extensive research looking for effects on behavior, and iis the root of contentious views about the nonrelevance of the hom environment—Harris, and also Pinker.

- Others see it differently:

  - Bernie Devlin views it mainly as an <u>error term</u> in his important study of the maternal environment and IQ published in *Nature* 1997.
  - Neil Risch also seems to view it similarly (personal conversation, 2003)
  - Eric Turkheimer in his 2000 meta-analysis with Waldron presents a gloomy view of NSE's ascertainability/ significance.
  - Michael Rutter seems to think NSE may have been overestimated in its effects (*Genes and Behavior*, 2006), p. 85.

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A root problem in studying the environment

- No theory of the environment – KFS in Parens et al. *Wrestling with Behavioral Genetics*, 2006:

- "Though environment is broadly conceived in behavioral genetics, there is no "theory of the environment." This stands in stark contrast with genetics, which can appeal to the framework of genes, chromosomes, and general knowledge about gene actions and interactions discovered by classical and molecular biology (Also compare BSCS, Ed. (2000). Genes, Environment and Human Behavior. Colorado Springs, Biological Sciences Curriculum Study.)

- The lack of such a theoretical orientation or environmental framework may prove important and also indicate the need for a major research effort

A view echoed in Plomin et al., 2008:

- " Although much remains to be learned about the specific mechanisms involved in the pathways between genes and behavior, we <u>know much more about genes than we do about the environment</u>.
- We know that genes are located on chromosomes in the nucleus of cells, how their information is stored in the four nucleotide bases of DNA, and how they are transcribed and then translated using the triplet code.
- **In contrast**, <u>where in the brain are environmental influences expressed, how do they change in development, and how do they cause individual differences in behavior</u>?
- Given these differences in levels of understanding, genetic influences on behavior may be construed as being easier to study than environmental influences." (my emphases)Plomin et al., 2008, p. 305

Environment and Culture

- Attempt to develop a broad theory of the environment, including culture

- Cavalli-Sforza and Marc Feldman in 1973, also 1981, and later publications as well

- Somewhat similar to Rice, Cloninger, and Reich work in late 1970s and 80s.

- Never seems to have caught on in BG

The molecular story since 2002

- The articles in *Science* by Caspi and Moffitt in 2002 and 2003 have transformed our understandings of behavioral genetics and the role that gene environment interaction plays in the BG area.

Caspi and Moffitt

Kendler: 4 paradigms/levels of BPG
(from the CIRGE 2006 symposium)
(modified from Kendler, January 2005, *American Journal of Psychiatry*)

Number	Title	Samples Studied	Method of Inquiry	Scientific Goals
1	Basic Genetic Epidemiology	Family, Twin and Adoption Studies Example: IQ (or SZ) heritability ≈ 0.8	Statistical: (simple twin studies; no specific genes)	To quantify the degree of familial aggregation and/or heritability.
2	Advanced Genetic Epidemiology	Family, Twin and Adoption Studies Example: genetic effects double the risk that stress produces depression	Statistical: (complex path analysis models; no specific genes)	To explore the nature and mode of action of genetic risk factors
3	Gene-Finding	High-density families, Trios, Case-Control Samples Example: MAOA gene affects aggression	Statistical: (linkage and association studies; specific genes)	Determine genomic location and identify of susceptibility genes.
4	Molecular Genetics	Individuals Example: RGS4 affects presynapse neuron function in schizophrenia	Biological (specific gene knockout and knock-in; gene chips)	Identify critical DNA changes. Trace the biological pathways from DNA to disorder.

Need to get to here

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Caspi et al. 2002 study (note crossing "norms of reaction")
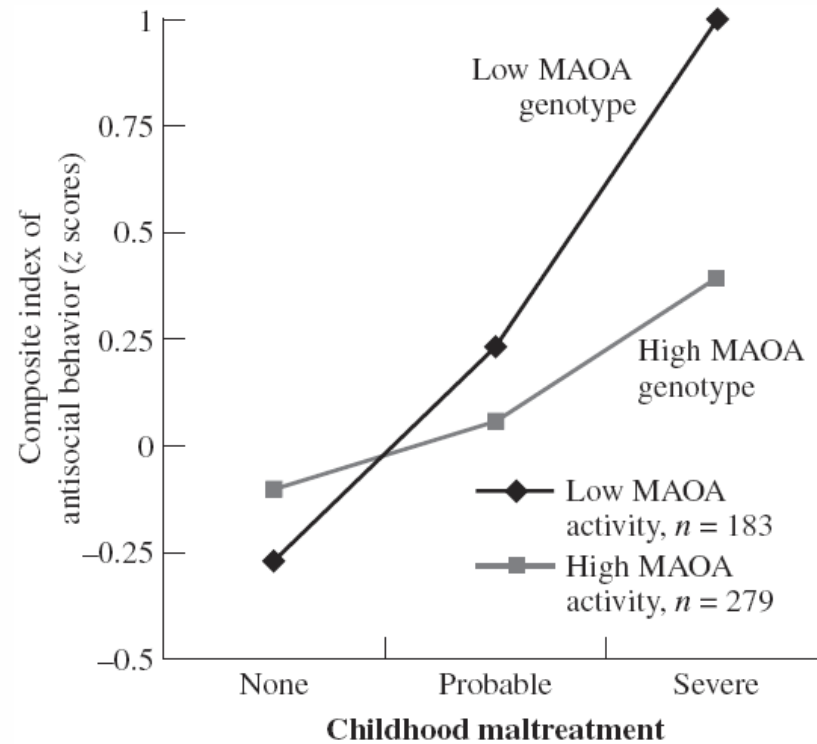
Gene-environment interaction: The effect of a polymorphism in the *MAOA* gene on antisocial behavior depends on childhood maltreatment. (From Caspi et al., 2002. Reprinted with permission from AAAS.)

The Caspi et al. method is extendable

- A methodologically similar 2003 study from the Caspi group on two serotonin transporter alleles (5-HTT) and depression showed similar gene-environment interaction (GxE) effects dependent on stressful life events

- Individuals with the *s* genotype of 5-HTT were much more susceptible to depression if they experiences many serious stressful life events; in contrast, those with the *l* allele were protected.

- Also see methodological papers by Rutter, Caspi, and Moffitt on further extensions.

The 2003 Caspi, Moffitt et al. GxE depression study (*Science*, 2003)

Fig. 3. The percentage of individuals meeting diagnostic criteria for depression at age 26, as a function of 5-HTT genotype and number of stressful life events between the ages of 21 and 26. The figure shows individuals with either one or two copies of the short allele (**left**) and individuals homozygous for the long allele (**right**). In a hierarchical logistic regression model, the main effect of genotype (coded as s group = 0 and l group = 1) was not significant, $b = -0.15$, SE = 0.21, $z = 0.72$, $P = 0.47$; the main effect of number of life events was significant, $b = 0.34$, SE = 0.06, $z = 5.70$, $P < 0.001$; and the interaction between genotype and number of life events was significant, $b = -0.30$, SE = 0.15, $z = 1.97$, $P = 0.05$.
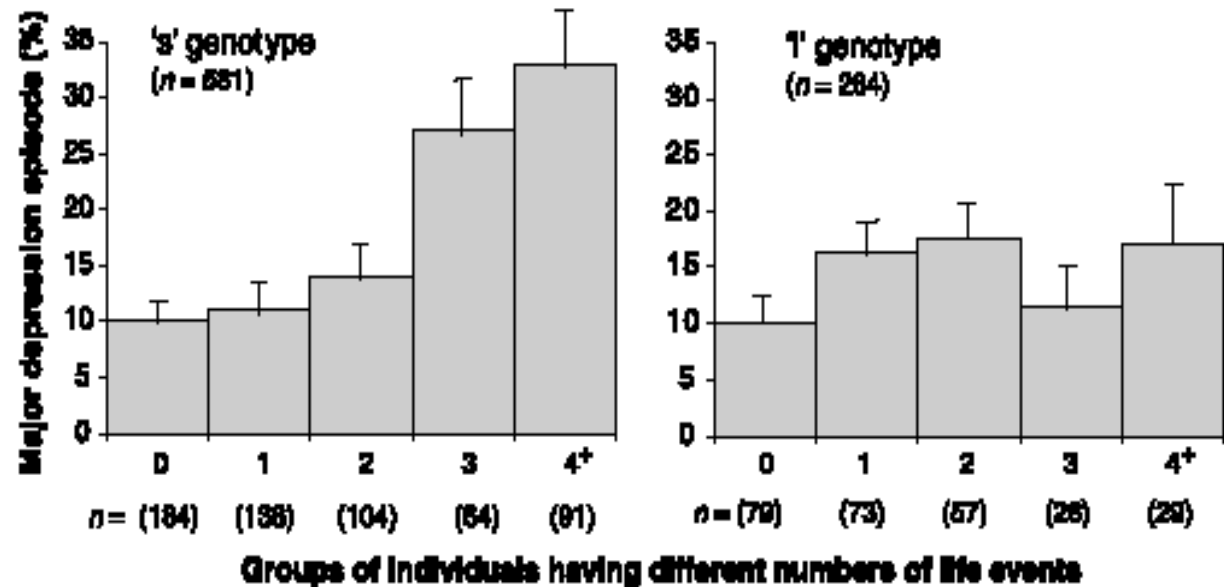
Epigenetics--SKIP

- The past five years have seen greater attention to the role of epigenetics, roughly definable as "modifications in genetic expressions that are controlled by heritable but potentially reversible changes in DNA methylation and/or chromatin structure" (Henikoff et al. 1997).

- Some recent studies have shown that there are potentially relevant differences in methylation of the DNA of identical twins discordant for schizophrenia. Whether these are induced by the " environment" or due to replication " noise" , or to both (most likely) is not yet clear.

New technologies?

- Neuroimaging – nice preliminary synergy with BG (Ahmed Hariri, the amygdala, and the 5-HTT serotonin transporter gene); but not ready for prime time in the clinic: per Hyman on *DSM V*

- Animal models – KFS and Kendler-Greenspan indicate extraordinary complexity in G-E interplay even in very simple organisms, such as the worm and the fruit fly; see KFS 1998 *PoS* and 2006 *Synthese,* and K&G, *AJP*, 2006

- Microarrays (gene chips) to the rescue?

Plomin at al 2008 on gene expression patterns analyzed by microarrays

- "...gene expression evolved to be responsive to intracellular and extracellular environments. Individual differences in gene expression appear to be only moderately heritable, which implies that most of the variance in gene expression is due to environmental factors. It was suggested that the transcriptome could lead to a paradigm shift in studying environmental influences on behavior: Gene expression can be considered as a biological index of environmental influence. In other words, <u>environmental influence could be assessed in terms of its change in gene expression profiles across the genome</u>."

More work has been needed to investigate E and G-E interplay SKIP

- In preparation for a AAAS-sponsored presentation to two U.S. Congressional members (Reps. Slaughter and Morella) and their staffs on genes and environments, related to Rep. Slaughter's bill on the Genetic Information Nondiscrimination Act (GINA), I conducted a Medline search of citations with the breast cancer gene (BRCA1) in its title or abstract, and another search with BRCA1 <u>and environment</u> in the title or abstract.

- The hits were about 2500 for the first search and 44 for the second search (repeated June 24, 2002).

- This suggested the major focus is on the genetics, not on the gene-environment interaction in breast cancer studies, even though there is strong evidence for environmental effects in breast cancer.

More IS now being done on breast cancer

And more generally, at the NHGRI

NIH Genes, Environment and Health Initiative (GEI)--2006

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- **Genes, Environment, and Health Initiative: Translating Whole Genome Association Data into Clinical Practice**
- The NIH Genes, Environment, and Health Initiative (GEI) was <u>launched in 2006</u> to support efforts to identify major genetic susceptibility factors for diseases of substantial public health impact and to develop technologies for reliable and reproducible measurement of potentially causative environmental exposures (http://www.gei.nih.gov/index.asp). GEI encompasses both basic research on genetics and exposure biology and translational research that will attempt to relate the research findings to clinical settings.
- The purpose of this meeting, "Translating Whole Genome Association Data into Clinical Research and Practice", is to explore the challenges in using GEI basic findings to have a positive impact on health. The meeting will feature presentations on important new genetic findings on certain diseases, approaches to using those findings for therapeutic or diagnostic purposes, <u>and the ethical and social issues inherent in such research.</u> There will be keynote addresses from leaders in the field and extended opportunities for discussion.
- For further details, please refer to http://www3.niddk.nih.gov/fund/other/GeiTranslation/.
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Summary and Conclusions

- We considered a definition of environment in genetic studies (Plomin et al.) and asked if this will suffice, or if there are better ones
- Pointed out that several classical historical controversies (SZ and IQ) were critically reacted to by appealing to gene-environment interaction, as elaborated in DST, but DST was found incomplete
- Asked whether the nonshared environment is a helpful concept
- Suggested that studying environment is hard because there is no consensus " theory" of the environment
- Mentioned several methodological and substantive advances: esp. from the Caspi-Moffitt-Rutter group in UK; epigenetics in Canada (SZ and BPI)
- Speculated about technological advances including microarrays
- Noted several recent federal initiatives in Cancer and the NHGRI's GEI, which point to much more work that will need to be done on the environment and its relation to genomics

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