Behavioral and Psychiatric Genetics: Learning from History

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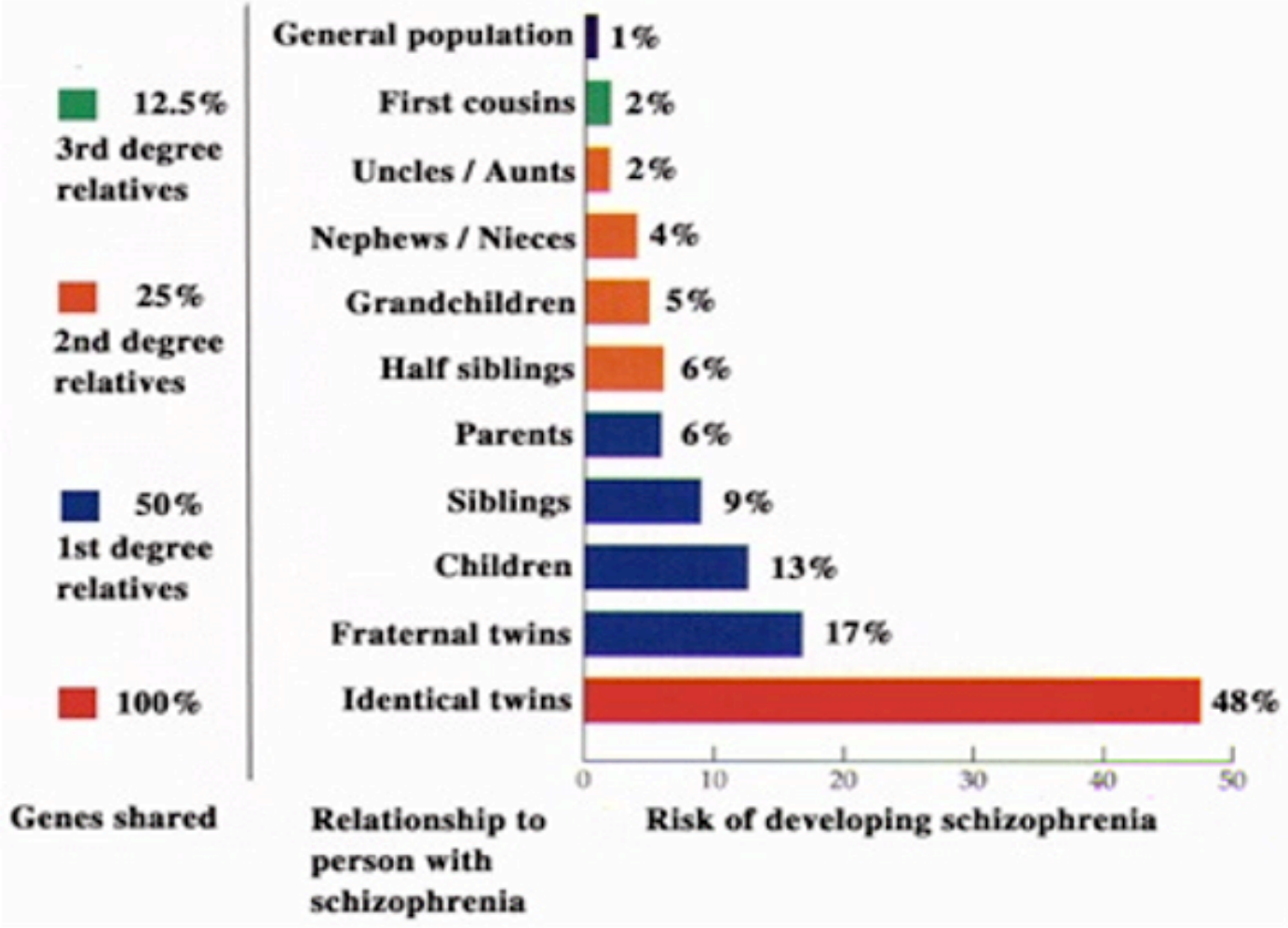
One reason why Behavioral and Psychiatric Genetics (BPG) is important:

- Severe mental illnesses devastate many millions of lives in the US and worldwide
- Major mental disorders, such as schizophrenia and bipolar illness, have very strong familial risk factors.

Classical results from Gottesman's work summarizing many studies show strong familial/genetic influence on schizophrenia



Genetics may be best first step

- The serious mental disorders are very difficult to understand, and over the long run will require complex and intertwined genetic, proteomic, neuroscientific, brain imaging, phenotype refinement via clinical dialogue, and environmental studies.
- But genetic etiology (causes) and/or genomically-related pathophysiology may give us the best purchase on these illnesses in the short run.

Why BPG is also controversial: Some social risks of behavioral genetics

- Studies in IQ can be misappropriated to further "benign neglect" social agendas (recall *The Bell Curve* debate in the mid-90s, which revisited a 1969 controversy initiated by Arthur Jensen about IQ and heritability:
- Careless use of BPG results – either of classical (quantitative) or molecular – might be used to impugn ethnic groups with socially disfavored behavioral patterns regarding aggression/ criminality, etc.

Current and Past State of BPG

- Currently BPG is in a positive and optimistic mood – maybe too optimistic
- A very short historical overview will help to evaluate better where the field has recently been, and where it may be going
- But first we need to refer to a framework to understand the fourfold structure of the field, and within which to discuss advances and forecasts
- Keep in mind all the genes or "alleles" (different forms of the gene) I discuss are "susceptibility genes" – risk factors related to disorders

Kendler: 4 paradigms/levels of BPG

(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.

A quick history:1960s and 1970s work

- There were significant early antecedents to BPG, from Galton, Fisherean statistics, and the psychology of individual differences.
- But the subject was also misused in the horrific eugenic sterilizations in the US and in Nazi death camps.
- The subject began as a separate professional discipline in 1960 with the publication of the first textbook in the field, Fuller and Thompson's *Behavior Genetics*.
- There were major substantive and methodological advances in BPG during the 1970s in BPG, including Benzer's fly work, many twin studies, as well as new multivariate methods by Jinks, Fulker, and Eaves, among others.
- These were all at Kendler levels 1 and 2.

A social flashpoint

- One major social flashpoint in behavioral genetics occurred in 1969 with the publication of Arthur Jensen's "How Much Can We Boost I.Q. and Scholastic Achievement?," *Harvard Educational Review* (1969) 39, 1-123
- Many behavioral geneticists have criticized this work as inferentially flawed, as did Lewontin, Feldman, and many others throughout the 1970s.

The 80s and 90s

- BPG had initial "breakthroughs" at the molecular level in late 1980s in schizophrenia and depression, but these subsequently turned out to be errors, and were withdrawn
- BPG began to flourish more generally in the 1990s with gene finding results (at Kendler's level 3) – but with too high expectations, which were very frequently accompanied by excessive hype

From 1993 *Science*—many just read the headline of this report based on a finding by Dean Hamer's lab

Evidence for Homosexuality Gene

A genetic analysis of 40 pairs of homosexual brothers has uncovered a region on the X chromosome that appears to contain a gene or genes for homosexuality

How much of sexual orientation is determined by a person's genes, and how much by familial and cultural influences? That has proved to be an exceptionally controversial question. Several recent studies of twins and adoptive siblings have pointed toward a large genetic component in homosexuality, implying that a gene or genes should exist that create a predisposition for homosexuality, but there was no direct proof. Now, a team of geneticists at the National Cancer Institute has come closer to that proof.

On page 321, Dean Hamer and his colleagues Stella Hu, Victoria Magnuson, Nan Hu, and Angela Pattatucci report linking some instances of male homosexuality to a small stretch of DNA on the X chromosome. If the finding can be confirmed, it might eventually lead to a better understanding of the biological basis of homosexuality and of sexual orientation in general.

No one is breaking out the champagne just yet, however. The field of behavioral genetics is littered with apparent discoveries that were later called into question or retracted. Over the past few years, several groups of researchers have reported locating genes for various mental illnesses—manic depression, schizophrenia, alcoholism—only to see their evidence evaporate after they assembled more evidence or reanalyzed the original data. "There's almost no finding that would be convincing by itself in this field," notes Elliot Gershon, chief of the clinical neurogenetics branch of the National Institute of Mental Health. "We really have to see an independent replication."

Despite the caution, researchers familiar with the work say this study appears to have a very good chance of holding up because it avoids some of the methodological problems of earlier work. One way or the other, the verdict may be in before the end of the year since a replication can probably be performed quickly.

To look for a possible homosexuality gene, Hamer and his colleagues took a two-step approach. First they recruited 76 homosexual men and traced out pedigrees for each, determining which other members of each family were themselves homosexual. They found 13.5% of the gay men's brothers to be homosexual—much higher than the rate of 2% or so that the Hamer group measured in the general population. (While this is lower than previous estimates of 4% to 10%, other recent studies have come up with similar low figures.) Earlier studies had also found that brothers of homosexual men are more likely to be homosexual than are men in the general population.

But once Hamer and colleagues ventured outside the immediate family, they found something new. "When we collected the family histories," Hamer says, "we saw more gay relatives on the maternal side than on the paternal side." In particular, they found homosexuality to be significantly more common among maternal uncles of gay men and among cousins who were sons of maternal aunts than it is among males in the general population.

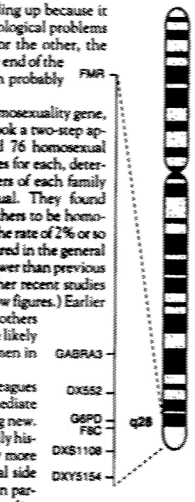
This implied that, for some male homosexuals at least, the trait is passed through female members of the family. And this in turn gave the researchers an obvious place to start looking for a homosexuality gene: the X chromosome, the only chromosome inherited exclusively from the mother.

To search for such a gene, Hamer recruited 40 pairs of homosexual brothers, took DNA samples from each, and performed a genetic linkage analysis using gene markers. The idea behind the analysis is simple: On average, each pair of brothers will have about half the DNA on their X chromosomes (and other chromosomes) in common. If both brothers are homosexual because they inherited a particular gene on the X chromosome, the gene must lie somewhere in the shared sections of the chromosome, which can be identified by the gene markers. The researcher examines many pairs of brothers, looking for a stretch of DNA that all or most of them have in common. If such a stretch exists, then it probably contains the target gene.

When Hamer and colleagues performed their analysis, they found that such a shared stretch did indeed exist. Of the 40 pairs of brothers, 33 pairs shared a set of five markers located near the end of the long arm of the X chromosome in a region designated Xq28. It's unlikely the linkage between the markers and the homosexuality trait was due to chance, Hamer says. The linkage has a LOD score of 4.0—a technical measure that translates to a 99.5% certainty that there is a gene (or genes) in this area of the X chromosome that predisposes a male to become homosexual.

Gene team. Dean Hamer, and *(from left)* Stella Hu, Nan Hu, Angela Pattatucci, and Victoria Magnuson are studying the genetics of sexual orientation.

DARROW MONTGOMERY



X marks the spot. The markers indicated pointed to Xq28 as the possible gene site.

Hamer warns, however, that this one site cannot explain all male homosexuality. Although his pedigree analysis showed that the homosexuality trait is usually maternally inherited, he did see some families where the trait seemed to be passed paternally. And, even among his 40 sets of brothers, chosen so that there was no evidence of the trait passing through male family members, seven sets of brothers did not share the stretch of Xq28 where the gene appears to lie. Instead, Hamer says, it seems likely that homosexuality arises from a variety of causes, genetic and perhaps environmental as well.

Still, researchers can hardly wait to get their hands on the gene in order to study just what it does. "It's very exciting," says Michael Bailey of Northwestern University in Chicago, co-author of a study 2 years ago that found half of the identical twins of gay men to be themselves gay. "If we can find a gene for sexual orientation, we can start to find out what the gene does."

The list of questions to be asked about

Also from *Science* in 1993

Abnormal behavior associated with a point mutation in the structural gene for monoamine oxidase A

[also known as MAOA – this is an enzyme that metabolizes or breaks down neurotransmitters]

Brunner H. G. , et al.

"Genetic and metabolic studies have been done on a large kindred in which several males are affected by a syndrome of borderline mental retardation and abnormal behavior. The types of behavior that occurred include impulsive aggression, arson, attempted rape, and exhibitionism…."

Genes and Crime at UMD in 1995

- By NATALIE ANGIER (from *NY Times, September 1995*)
- "LIKE the late Richard M. Nixon, the notorious University of Maryland conference on the genetics of criminal behavior has been deplored, defeated, kicked around, thrown to the ground, hounded offstage, and still it lurches back to the ring, fists clenched, eager to fight the fight of its own design. Three years ago, David Wasserman, a legal scholar at the University of Maryland and his colleagues caused a political Pinatubo [a catastrophic volcanic eruption] when they sought to organize a meeting to discuss, as they put it, 'the meaning and significance of research on genetics and criminal behavior.'"

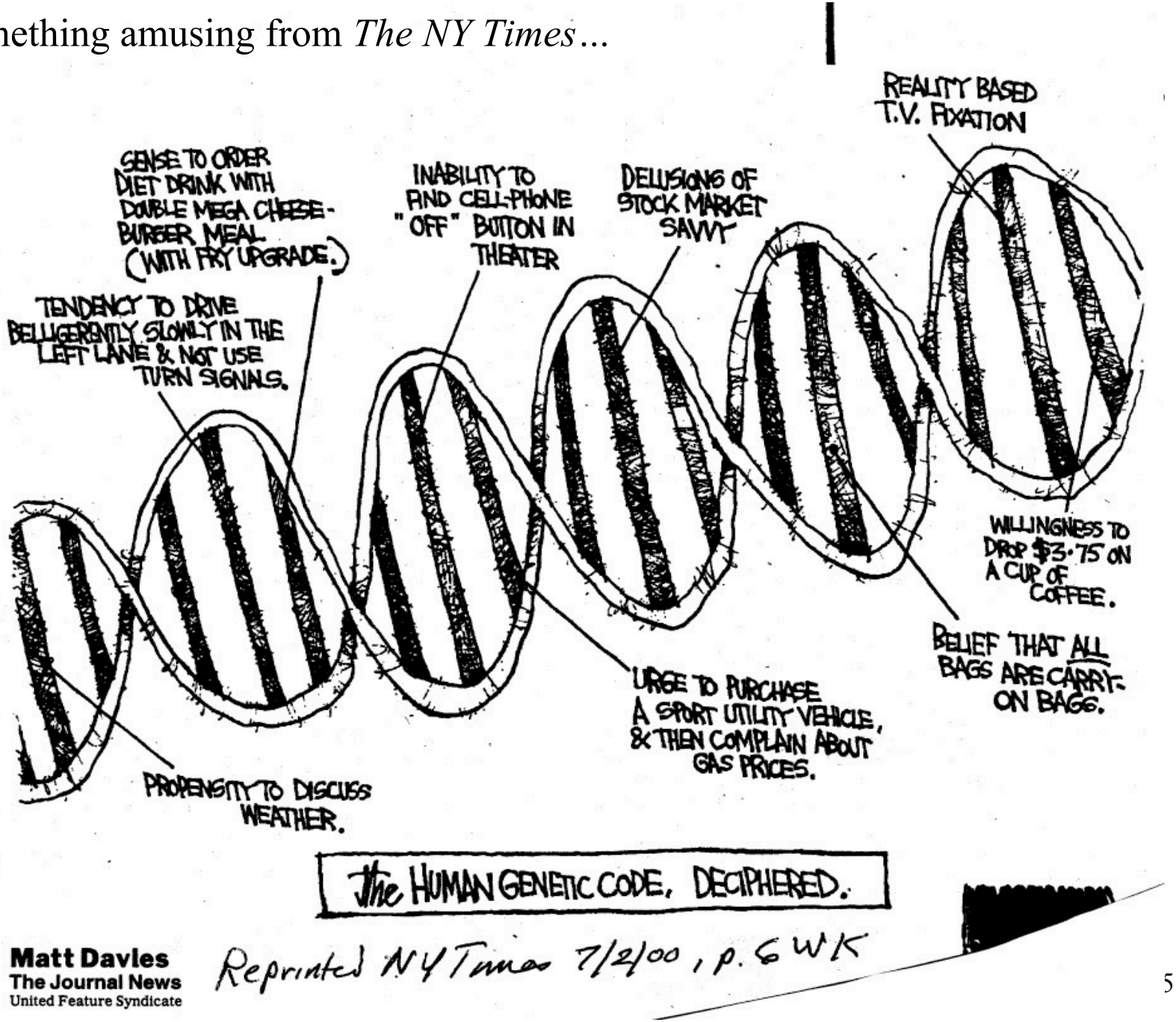
And from *Nature Genetics* in 1996

- **Population and familial association between the D4 dopamine receptor gene and measures of Novelty Seeking**

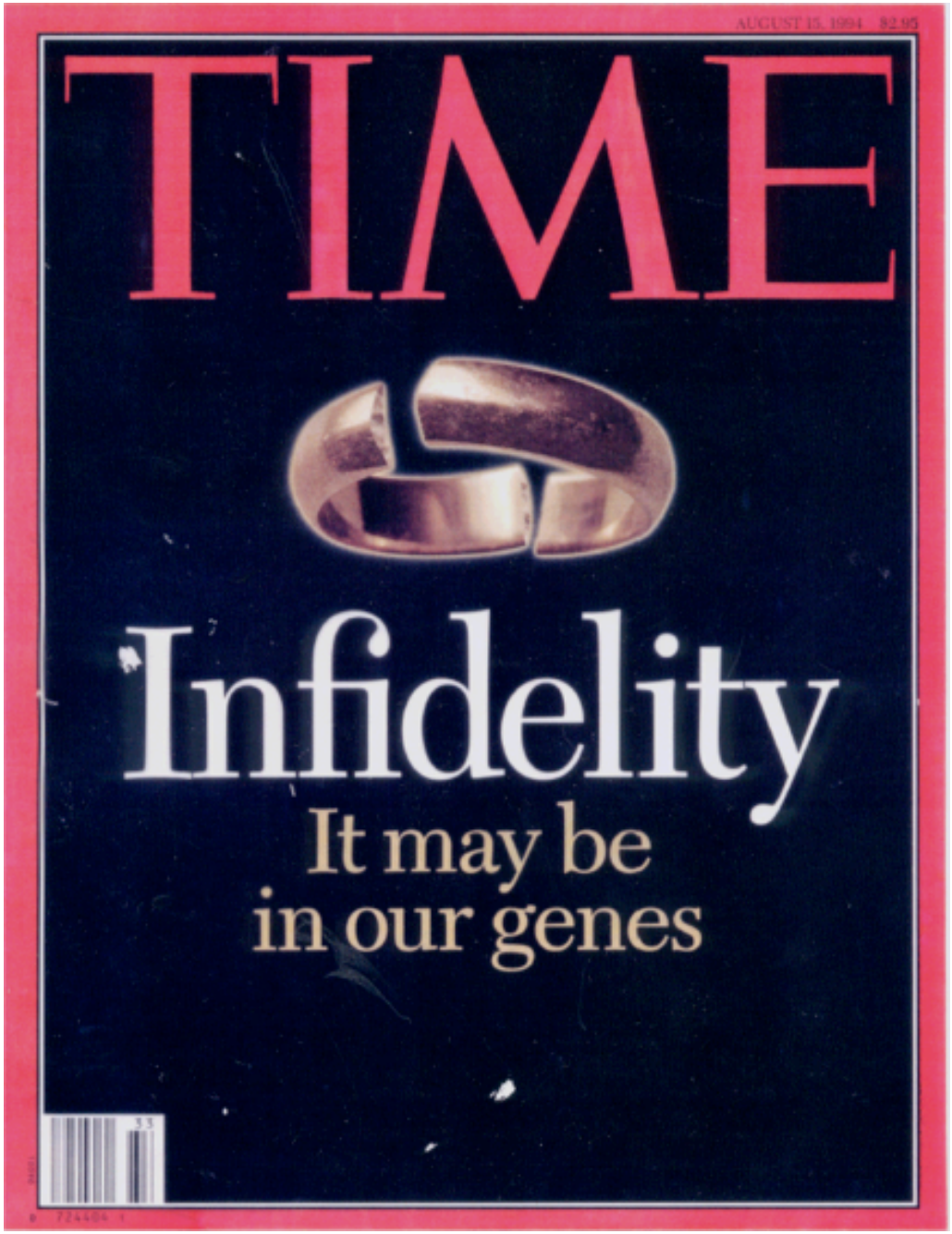
  Benjamin J, Li L, Patterson C, Greenberg BD, Murphy DL, Hamer DH.

  Laboratory of Clinical Science, National Institute of Mental Health, National Institutes of Health, Bethesda, Maryland 20892.

Something amusing from *The NY Times*...



And even everybody's favorite (?) excuse…



The crash of the late 90s and early 00s: a Y2K that did happen for BPG

- The initial BPG results did not replicate – that is additional studies did not support the first one or two reported findings for homosexuality genes, for aggression genes, for novelty seeking genes, etc.
- No new useful results in schizophrenia nor depressions (bipolar or other forms) were discovered through 2001

The hand wringing of ‘02

- Typical of the state of BPG in 2001-2002, though expressed by a most unusual spokesperson, was Dean Hamer’s comments in his watershed October 2002 essay in *Science*
- That essay spoke of the gloom in the field, but also of possibly emerging promise – IF the field were to change its paradigm

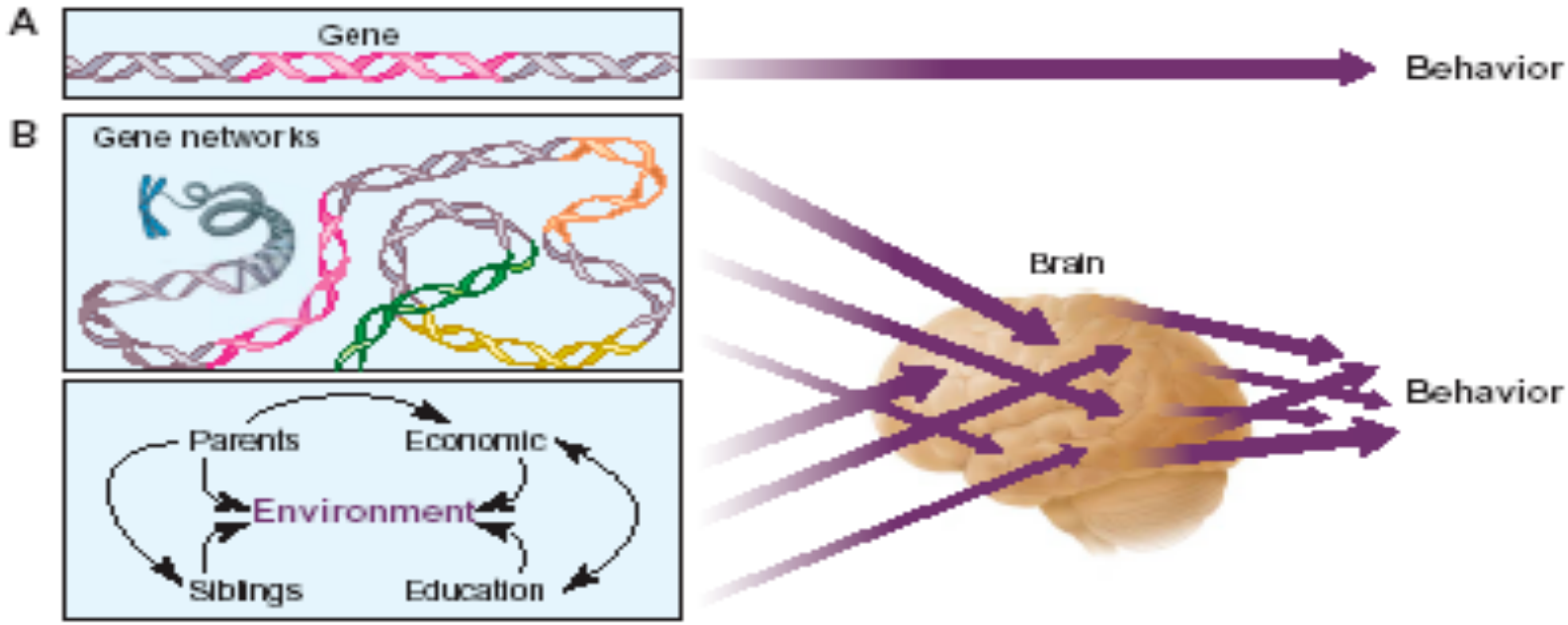
Dean Hamer's Hula-Hoops

- "The results [in human behavioral and psychiatric genetics] have been disappointing and inconsistent. Large and well-funded linkage studies of the major psychiatric disorders including schizophrenia, alcoholism, Tourette syndrome, and bipolar disorder have come up empty-handed; not a single new gene has been conclusively identified. Most candidate gene findings have failed consistent replication, and even those that have been verified account for only a small fraction of total variation. Meanwhile, the statisticians who are supposed to be guiding and evaluating the research are unable to agree on how to design experiments or to interpret the results; their advice has proven as faddish (and useful) as the Hula-Hoop. (from *Science*, October, 2002)

Dean Hamer's diagnosis…

- "What's the problem? It's not the basic premise of linkage and candidate gene analysis; these approaches have identified dozens of genes involved in inherited diseases. Nor is it the lack of DNA sequence information; virtually the entire code of the human genome is now known. The real culprit is the assumption that the rich complexity of human thought and emotion can be reduced to a simple, linear relation between individual genes and behaviors. This oversimplified model [**A** on the next slide], which underlies most current research in behavior genetics, ignores the critical importance of [1] the brain, [2] the environment, and [3] gene expression networks [**B** on the next slide]"(my emphases)

Hamer's old and new models



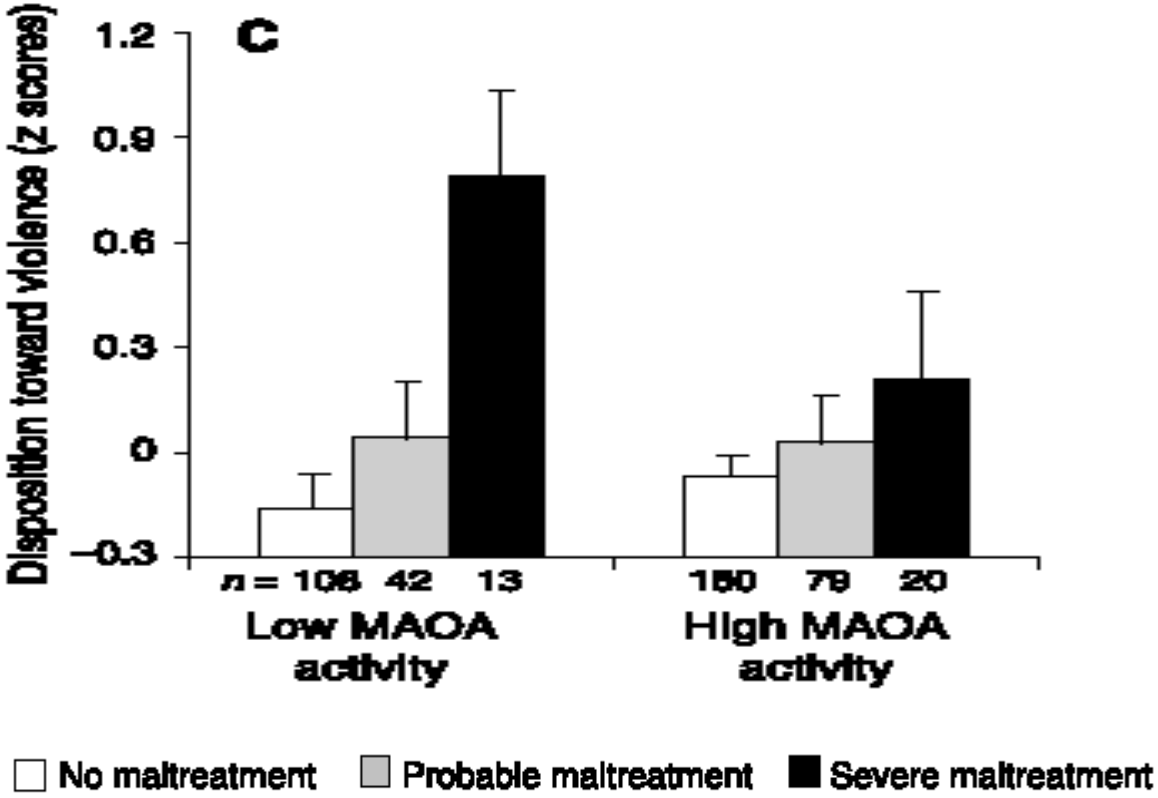
Two views of behavior genetics. (A) A simplified model underlying much behavior genetics research envisages a direct linear relationship between individual genes and behaviors. (B) The reality is likely to be far more complex with gene networks and multiple environmental factors impacting brain development and function, which in turn will influence behavior.

The 2002 Caspi et al. MAOA study

- One study Hamer referred to as beginning to meet the demands of a more complex model was related to his point [2] – the environment
- The Caspi et al. study reported in *Science* in August 2002 indicates two different MAOA alleles (one with high and the other low activity in metabolizing neurotransmitters) have large associations with conduct disorder, a conviction record, violent behavior, and antisocial personality disorder.
- But the gene difference shows itself fully **ONLY IF** the subject experienced abuse/maltreatment during childhood.
- Caspi et al. use the environment as a lens through which to look for the effects of gene (allele) differences

The *Science*, 2002 Caspi et al MAOA violence study:

Increased MAOA allele activity decreases chances that early maltreatment leads to a violent personality



The Caspi et al. method is extendable and integrates with neuroscience

- 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
- This study was motivated in part by neuroscience finding: knockout mice, stressed primates, and the Hariri et al. 2002 amygdala study (which I'll mention later), and shows how neuroscience and BPG can be integrating and mutually "bootstrapping" (Caspi and Moffitt, 2006, in press)

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

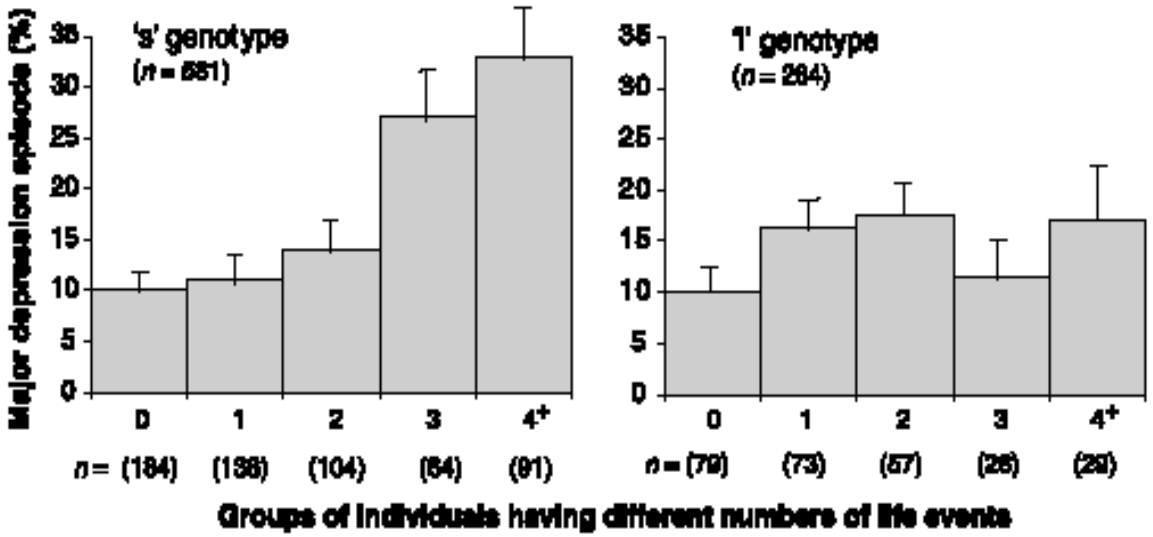


Fig. 3. The percentage of individuals meeting diagnostic criteria for depression at age 26, as a function of 5-HTT genotype and number of stressful life events between the ages of 21 and 26. The figure shows individuals with either one or two copies of the short allele (**left**) and individuals homozygous 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, $z = 1.97$, $P = 0.05$.

And has been extended again…

- Yet another methodologically similar 200 study from the Caspi group on two COMT alleles showed an increased risk for psychosis (schizophrenia) of one allele
- But **only IF** there was significant cannabis use during a vulnerable period in the teenage years

A start, but maybe not enough?

- Hamer indicated that this 2002 MAOA study is a significant advance (similar for 2003 study)
- And the Caspi 2002 study on aggression has been replicated several timesand failed once (meta-analysis is in press) so it's likely this is a real MAOA effect)
- But these studies are still wedded to a single gene approach (MAOA or 5-HTT).
- Is there a better way – to go **beyond just single genes**, and also **involve the brain,** as Hamer recommended**?**

Involving the brain -- endophenotypes

- Increasingly behavioral and psychiatric geneticists are using neuroscience and coupling it with genomics, as already mentioned
- One approach uses "endophenotypes" – gene effects that are intermediate between gene action and the final disorder such as schizophrenia. NIMH has funded a large 7 centered grant to examine endophenotypes in schizophrenia
- They are looking at memory changes and disturbances in eye tracking that seem to be associated with early schizophrenia, as well as at neuroimaging patterns – to hopefully get a clearer signal of gene action.
- Other studies, by Hariri and Weinberger, looked at neuroimaging amygdala responses related to anxiety and depression for a signal 10x stronger than subjective information for the (5-HTT) gene.

Another way of involving the brain and many genes – using microarrays

- Microarrays are gene chips – a small glass slide (less than an inch square) on which many thousands of gene detectors (small stretches of complementary DNA) are sequentially arranged
- Cells can be obtained by autopsy from disordered brains and from normal brains (used as controls)
- Many alleles can be tested for simultaneously, and also the mRNAs in the cell contents -- reflective of which genes are turned on or expressed -- can be smeared over the gene chips, and the different expression profiles compared.
- Caveat: many false positives without appropriate corrections for multiple testing and the very low prior probabilities.

Implications of the new complexity

- Gene chip results are underscoring Hamer's points noted earlier that any simple gene→disorder models are likely to fail
- Results from simpler model systems like yeast, the worm (*C. elegans*), and the fruit fly by KFS and Kendler and Greensapn show that the neuroscience of behavior involves very complicated ways that genes act to build and maintain neurocircuits; many genes act together
- And environment counts! In yeast – a one celled organism – about 4000 of its 6000 genes are turned on and off by environmental signals like temperature and acidity.

Some predictions for the near-term future of BPG

- Fairly steady progress will occur, but there will be false starts. We may need protein chips before the results we get from gene chips clarify, and protein chips are much harder to make than gene chips, and probably involve monitoring > 200,000 proteins.
- The steady progress will, however, be slow – there will be many sets of genes with small effects that will probably interact to produce disorders. Sorting out all the genetic heterogeneity will take many studies.

More predictions…

- The mental disorders will themselves turn out to be a mix of disorders that need further clarification and resorting; the disorders will be somewhat reclassified as we learn more at levels 3 and 4 of BPG (as we already have in Alzheimer's Disease(s))
- Reclassification and clarification will involve many levels of simultaneous study, not just genomics and proteomics. Neuroimaging studies as well as human subjective reports from patients or their clinical records will be needed – as this process goes on. The methods will have to be integrative and multi-level, not only simply reductionistic.

Some troubling implications on the horizon

- Further discovery of genes that make us different and can be screened for, may stigmatize some individuals behaviorally – recall the MAOA findings of Brunner (1993) and also Caspi et al. (2002)
- It is also possible we may find correlations with ethnicity of both harmful and protective genes, currently emerging in pharmacogenomics, which could lead to new forms of stereotyping and discrimination.

Troubling implications…

- Though I have not discussed it today, there is a molecular genetics IQ program run in the UK by Robert Plomin, which has published some weak results for genes of small effects on IQ. I have discussed this IQ research program elsewhere In *Wrestling with Behaioral Genetics,* Parens et al (eds.)….
- If successful and cognitive capacity genes for IQ and memory are identified, soon after we will see the pursuit of "enhancement" therapies. These will be new "smart drugs," or as *Fortune* magazine labeled them, "Viagra for the mind"

Conclusions

- Understanding and utilizing these advances will also require greater appreciation of these subtle complexities by policy makers as well as the public, as patients and consumers
- Policy makers will have to proceed both knowledgeably and cautiously to avoid enhancement stampedes, as well as to protect against individual and group discrimination.

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- Any opinions, findings, and conclusions or recommendations expressed in this material are those of the author and do not necessarily reflect the views of the National Science Foundation, or anyone else, living or dead ….