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Jon Randolph Haber
VA Health Care System

Theodore Jacob
VA Health Care System

Andrew C. Heath
Washington University School of Medicine in St. Louis

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PATERNAL ALCOHOLISM AND OFFSPRING CONDUCT DISORDER: EVIDENCE FOR THE “COMMON GENES” HYPOTHESIS

Offspring of Alcoholism Discordant Twins Study





Investigators

- **Jon Randolph Haber, Ph.D.** VA Health Care System
- **Theodore Jacob, Ph.D.,** VA Health Care System
- **Andrew C. Heath, D. Phil.,** Washington University School of Medicine

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Introduction

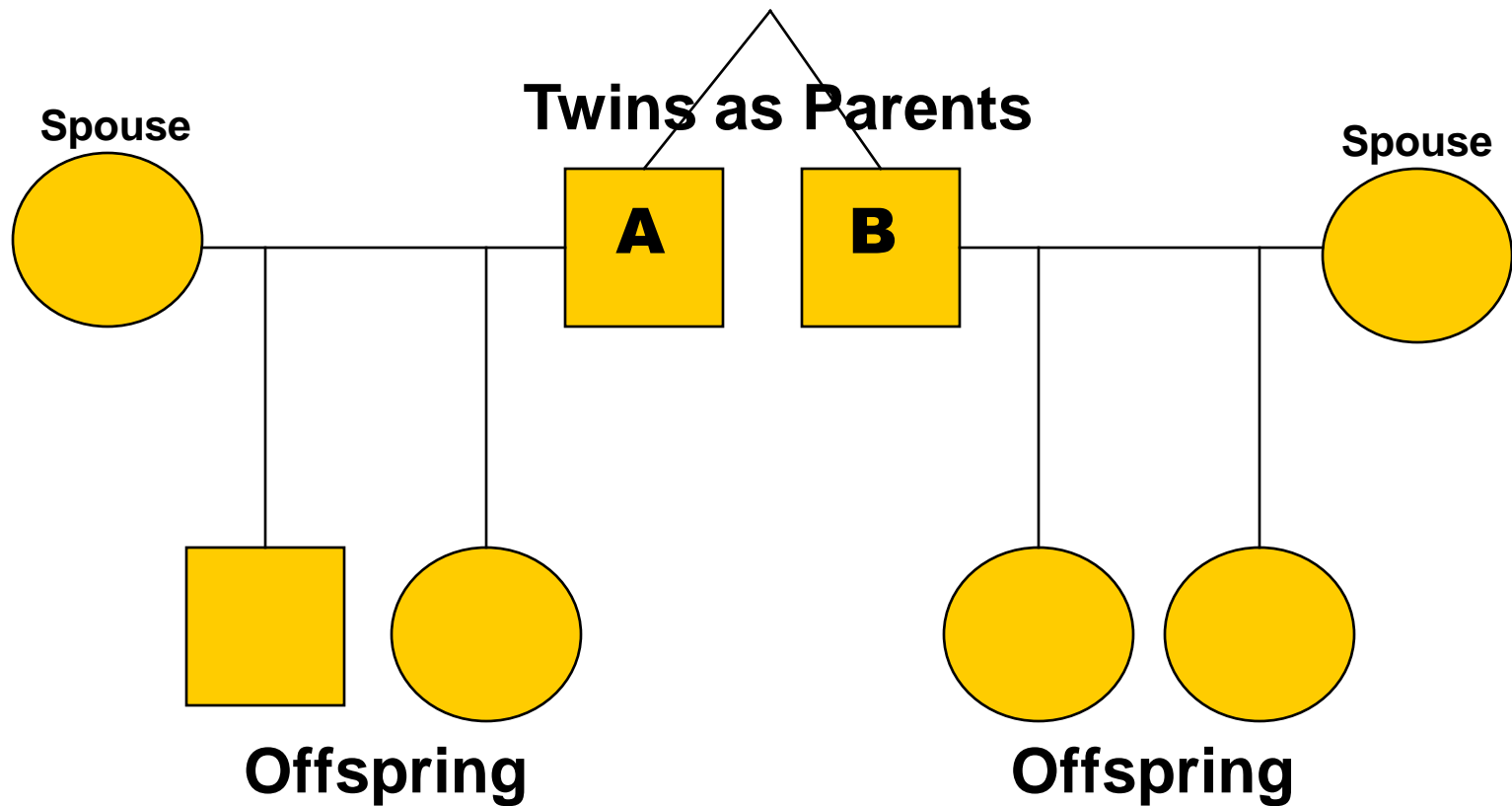
Not only are alcoholism and conduct disorder frequently comorbid, they often co-occur in families across generations. For example, paternal alcoholism predicts offspring conduct disorder just as it does offspring alcoholism. To clarify this relationship, the current study examined the “common genes” hypothesis utilizing a “children of twins” research design. The identification of genetic origins for conduct disorder and alcoholism is supported by behavior genetic studies which demonstrate that both alcoholism (Heath et al., 1997) and conduct disorder (Krueger et al., 2002; Slutske et al., 1998) are significantly heritable.

Most relevant to the association between paternal alcoholism and offspring conduct disorder is Slutske's (1998) finding that genetic influences account for over 70% of the observed (phenotypic) association between conduct disorder and alcohol dependence, and that 90% of this common genetic risk is associated with behavioral undercontrol personality traits (Slutske et al., 2002). Consistent with earlier psychosocial research, these findings provide strong evidence that genetically transmitted personality factors associated with behavioral undercontrol are causally implicated in the co-occurrence of conduct disorder and alcohol use disorders. This is the “common genes” hypothesis.

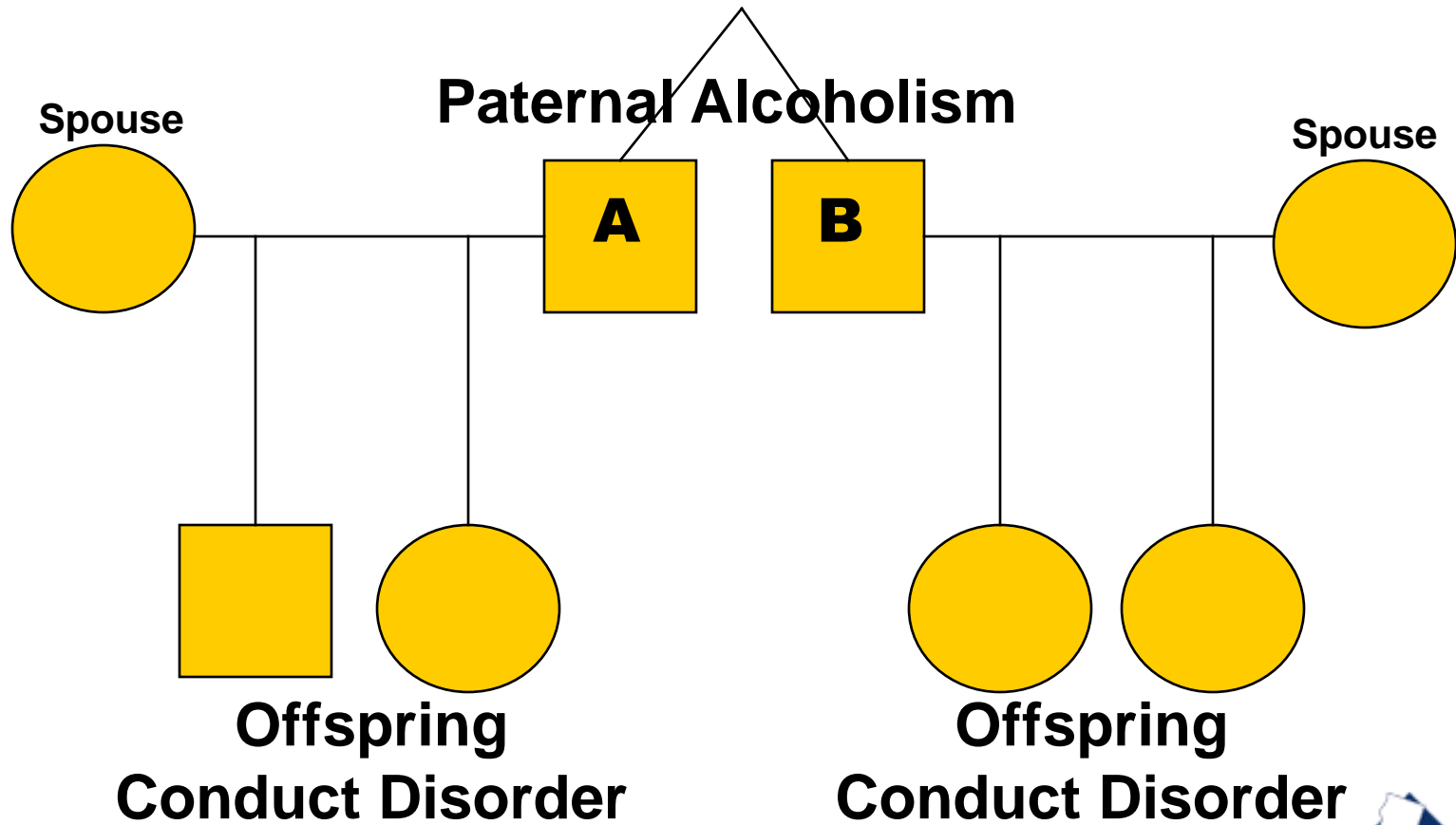
Krueger et al.'s (2002) recent work expands on these findings by placing this effect within a larger model of externalizing behaviors, demonstrating that a latent externalizing factor underlies conduct disorder, adolescent antisocial personality traits, alcohol dependence, and illicit substance dependence. His findings indicated an 81% heritability for this common latent externalizing factor, and Kendler, et al.'s (2003) recent replication is supportive of these conclusions. The congruence of psychosocial and behavior genetic research on the importance of genes at the foundation of these effects is noteworthy.



The current study utilized a “children of twins” (COT) research design (Nance & Corey, 1976) as an alternative methodology to the classic twin design in examining genetic structure.



Specifically, this study sought to demonstrate that common genes transmitted from parents to children influenced the incidence of offspring conduct disorder as was previously shown to be true of offspring alcoholism (Jacob et al., 2003).





HHypothesis 1:

Families with paternal alcoholism will be associated with increased rates of offspring conduct disorder symptoms.

HHypothesis 2:

Families with paternal alcoholism will be associated with increased rates of offspring conduct disorder symptoms in the absence of environmental influences compared to normal control families, thus supporting the hypothesis that “common genes” account for this association.



Method

The sample of twins was drawn from the Vietnam Era Twin Registry (VETR).

In the current study, the families of 730 twin fathers were assessed including 1270 offspring.

- Twin's alcohol lifetime Dx and Zygosity obtained from '92 Harvard Drug Study data (Tsuang and Lyons).**
- Twins, Mothers, and Offspring are interviewed by telephone using an adaptation of the Semi-Structured Assessment of the Genetics of Alcoholism interview (Bucholz et al., 1994).**
- Interviews assessed alcohol abuse and dependence, psychopathology (including offspring conduct disorder) and psychosocial variables.**

Data Analysis:

Groups of twins were examined according to environmental risk groups.

genetic and

	Concordant Alc	Discordant Alc	Controls
MZ	A A	A N	N N
DZ	A A	A N	N N
	+ G risk + E risk	+ G risk - E risk	- G risk - E risk
	(All Alcoholic Fathers)	(Fathers with Alcoholic Cotwins)	Low risk



**Genetic and Environmental risk can be differentiated in
Groups 2 and 3
when compared to Groups 1 and 4.**

	Parental Status	Cotwin Status	Genetic Risk	Environmental Risk
G1.	Alcoholic	Any	High	High
G2.	Unaffected	Alcoholic, <u>MZ</u>	High	Low
G3.	Unaffected	Alcoholic, <u>DZ</u>	Moderate	Low
G4.	Unaffected	Unaffected	Low	Low



Analytic Plan: Group Comparisons Hypothesis 1

For H1, a significant Gp 1 elevation in offspring conduct disorder symptoms compared to Gp 4 normal controls would confirm the phenotypic association between paternal alcoholism and offspring conduct disorder (provided mother's influence is controlled), thus confirming the cross-generational, cross-diagnosis transmission of these two disorders (as reported in the literature). While this contrast is equivalent to any “family study” (without twins) and does not differentiate between genetic risk or environmental risk, it does establish the significance of father-to-child transmission within this sample which provides the basis for genetically-informed discrimination of transmitted influence.



Analytic Plan: Group Comparisons Hypothesis 2

Analyses of group effects to test H2, the common genes hypothesis, are based on the following logic: If common genes are the primary determinant of the phenotypic association between alcoholism and conduct disorder, there should be a similar outcome risk for the child with an alcoholic father and for the child of a non-alcoholic father whose MZ co-twin is alcoholic (see Gps 1 and 2). Because MZ twins share 100% of their genes in common, genetic risk should be the same regardless of differences in environment, that is, whether the family environment involves being reared by an alcoholic father or by a non-alcoholic (MZ cotwin) father. Thus, the common genes hypothesis would be supported if offspring rates of CD were similar in Gps 1 and 2, and would be refuted if offspring rates of CD for Gp 2 were instead similar to normal controls in Gp 4. It can be seen that Gp 2 is of particular interest to hypothesis 2 because these offspring share high genetic risk with offspring in Gp 1, and share low environmental risk with Gps 3 and 4. Therefore, the dominant influence, genes or environment, will be reflected by the relative position of Gp 2 prevalence between Gps 1 and 4, and the two contrasts, Gps 1-2 and 2-4, will test the significance of the respective contributions of these competing influences.





Dependent Variable

To maximize statistical power in examining a low-prevalence disorder, an ordinal logistic model was constructed using a 4-level dependent variable based on offspring conduct disorder symptoms.

The levels were constructed to meet the parallel regression assumption and were tested with the Brant Test (Brant, 1990) with respect to our primary predictor groups.

The levels were:

- (a) 0 and 1 symptom;**
- (b) 2 symptoms;**
- (c) 3 symptoms; and**
- (d) 4 or more symptoms.**



Covariates

A rigorous definition of alcoholism was utilized in that the current study which controlled for many potentially confounding variables, most importantly, paternal and maternal antisocial personality and conduct disorder (ASP/CD). It should be noted that to partial out variance associated with parental ASP/CD, one also partials out a component of alcoholism variance that is common to both disorders. The result is a relatively “pure” alcoholism predictor. However, due to the loss of variance that may be appropriately considered a part of alcoholism variance, this approach reduced statistical power in order to increase clarity of interpretation in the examination of these closely associated variables.

Covariates included:

- paternal antisocial personality and conduct disorder**
- paternal drug abuse, depression, dysthymia, generalized anxiety, panic, post-traumatic stress disorder**
and...
- maternal antisocial personality and conduct disorder**
- maternal alcohol abuse, alcohol dependence, and depression.**



Results: Sample Characteristics

	<u>GROUP 1</u>	<u>GROUP 2</u>	<u>GROUP 3</u>	<u>GROUP 4</u>
	MZ and DZ AD twins	MZ twin unaffected; cotwin with AD	DZ twin unaffected; cotwin with AD	MZ and DZ unaffected control twins
Family Characteristics (as of date of interview)	(n=809)	(n=114)	(n=124)	(n=223)
% male offspring	49.3%	54.4%	44.4%	44.4%
Child age (yrs)	19.4 (4.1)	19.8 (4.2)	19.0 (3.9)	19.4 (4.0)
Paternal age (yrs)	50.5 (2.7)	50.8 (2.7)	50.7 (2.4)	51.1 (2.8)
Maternal age (yrs)	48.0 (5.2)	47.5 (5.1)	48.5 (6.6)	48.5 (3.8)
% Father works fulltime	92.7%	91.2%	94.4%	96.0%
Father educ.> high school	59.2%	65.8%	71.0%	63.2%
Mother educ.> high school	67.0%	54.1%	59.6%	70.0%
Marital status: divorced**	20.4%	12.3%	21.0%	13.2%
Caucasian Race	96.4%	99.1%	91.1%	94.2%

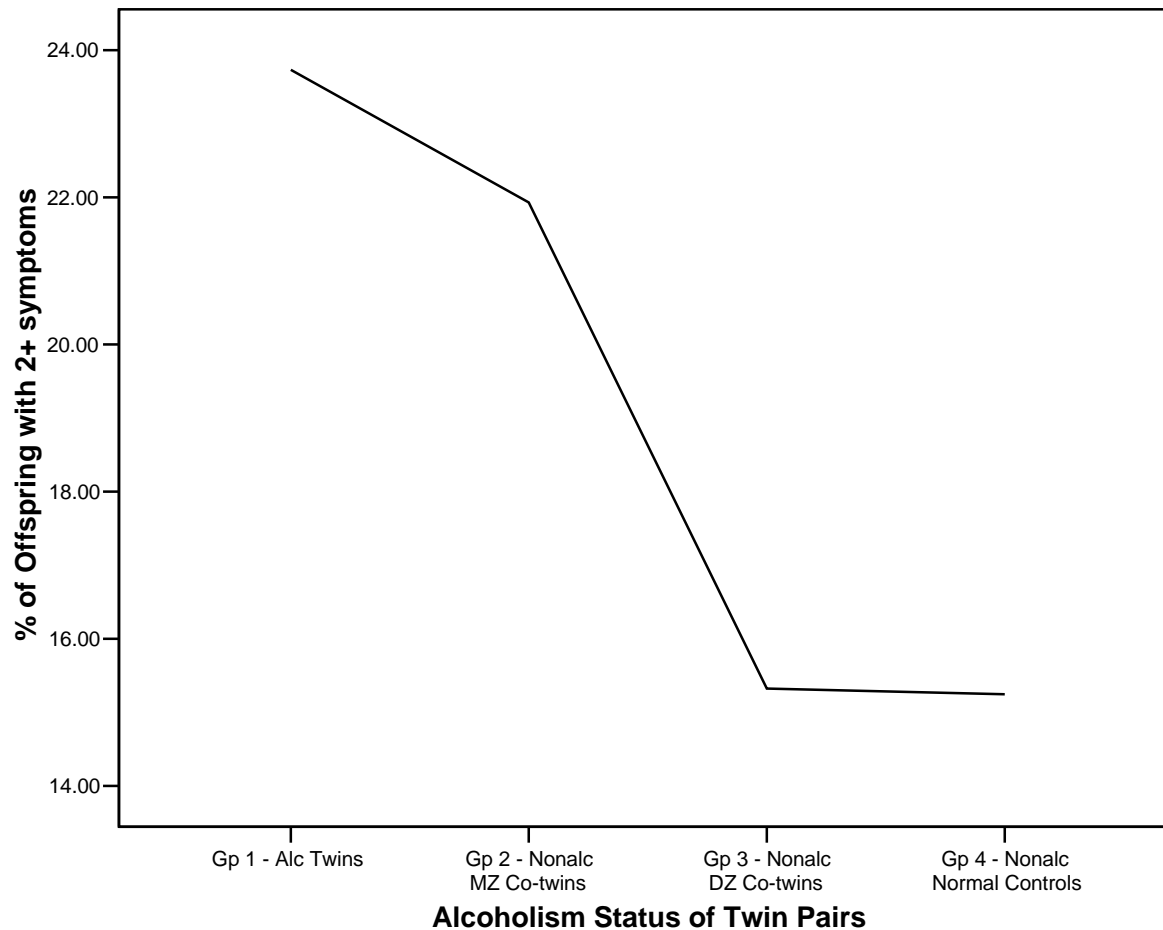


Offspring Report of Conduct Disorder Symptoms Across Paternal Alcoholism Status Groups

		Twin Pair Alcoholism Status				
Number of Sx		Group 1 Paternal Alcoholic	Group 2 MZ Cotwin of Alc	Group 3 DZ Cotwin of Alc	Group 4 Non-Alc Twin Pair	
Conduct Disorder Symptom Count	0, 1	“n” 617 %	617 76.3%	89 78.1%	105 84.7%	189 84.8%
	2	“n” 64 %	64 7.9%	11 9.6%	8 6.5%	16 7.2%
	3	“n” 53 %	53 6.6%	5 4.4%	3 2.4%	6 2.7%
	4+	“n” 75 %	75 9.3%	9 7.9%	8 6.5%	12 5.4%
	Totals:	“n” %	809 100.0%	114 100.0%	124 100.0%	223 100.0%

Offspring CD Symptoms by Paternal Twin-Pair Alcoholism Risk Group

(Note the similarity of Gps 1 & 2 compared to Gps 3 & 4)





Odds Ratios (95% confidence intervals) for DSM-IV Conduct Disorder Diagnosis in Offspring as a Function of Family Risk Status and Pertinent Covariates From an Ordinal Logistic Regression.

	<u>Offspring CD</u>	
Gp 1: MZ and DZ alcohol abuse/dependent twins	1.81	(1.11-2.96)*
Gp 2: MZ unaffected with alcohol dependent co-twin	1.60	(0.84-3.04)
Gp 3: DZ unaffected with alcohol dependent co-twin	1.04	(0.47-2.32)
paternal illicit drug abuse/dependence	1.29	(0.74-2.24)
paternal psychiatric disorder ¹	0.82	(0.55-1.24)
paternal post-high school education	0.78	(0.55-1.11)
paternal employment	0.50	(0.32-0.80)**
maternal antisocial personality diagnosis	1.42	(0.56-3.60)
maternal alcohol dependence	1.16	(0.64-2.09)
maternal major depression	1.40	(0.90-2.17)
maternal alcohol abuse	0.72	(0.40-1.30)
marital divorce	0.44	(0.29-0.68)***
offspring age 18 and over	1.76	(1.25-2.49)***
male offspring	3.50	(2.48-4.94)***





Discussion

Concerning Hypothesis 1, results clearly indicated that the offspring of alcohol dependent fathers (Gp 1) were significantly more likely to have elevated rates of CD symptoms than were offspring of normal control fathers (Gp 4). Thus, when considering these two phenotypes, the non-independence of alcoholism and conduct disorder was evident. One implication is that parent-to-child transmission of liability may be less specific than diagnostic categories imply given that the transmission of a common liability can impact different classes of disorder, that is, substance use disorders and child psychiatric disorders.

Concerning Hypothesis 2, analyses examined whether genes alone could account for this effect, thus supporting the common genes hypothesis, or whether some combination of genetic and environmental factors were involved. Results were considered in the context of competing influences. Prevalence rates for offspring CD symptoms indicated a close similarity between Gp 2 and the elevated rate of offspring CD symptoms in Gp 1 (as well as the consequent absence of similarity between Gp 2 and the offspring CD base rate in Gp 4, normal controls). The implication is that genetic factors were much more important to the determination of offspring CD symptom outcomes than environmental factors. While prevalence rates suggested genetic influences, and little evidence supported environmental influences, statistical significance was not definitive. Specifically, in support of Gp 1-2 similarity was a non-significant Gp 1-2 contrast ($p = .63$). However, the dissimilarity between Gp 2 and Gp 4 only approached significance ($p = .15$), and thus was less than conclusive in differentiating Gp 2 elevations from normal control base rates (Gp 4). Hence, a certain ambiguity remained in interpretation of these results.





Discussion

The most parsimonious interpretation of these findings is that genetic factors and, to a much lesser degree, environmental factors both are at play in these effects. That is, although there is no evidence for a substantial environmental influence in these results, the above findings could be explained as the consequence of a small environmental effect interacting with a prominent genetic effect. Specifically, the environmental effect would result in a reduction of the size of Gp 2-4 contrast and its significance estimate, and would produce the above pattern of results.

In considering these results, it should be remembered that we used an intentionally conservative design by treating parental ASP/CD, other psychopathology, and other demographics as covariates in order to reduce ambiguity in interpretation of these results. These design judgments lowered power. Thus, the significance test of the Gp 2-4 contrast may realistically be considered a “lower-bound” estimate of the true effect.

As seen, the prevalence rates were elevated in the current sample of offspring of non-alcoholics (Gp 2) and approximated the elevations of the offspring of alcoholics group. This elevation appeared to occur in the absence of environmental risk, that is, among offspring who were not raised by an alcoholic father. Therefore, current findings lead to the conclusion that environmental influences were a minimal effect in Gp 2, even though they may have resulted in a minor decrease in the effect size of an otherwise unambiguous genetic effect. Therefore, it seems reasonable to conclude that genes associated with parental alcoholism were responsible for the observed elevation in offspring CD symptom rates. To the extent this is true, the “common genes” hypothesis was supported.





Limitations

- Limitations in statistical power contributed to inconclusiveness in certain effects.
- CD is a low prevalence disorder which contributes to low statistical power.
- The COT design is more powerful in testing environmental than genetic hypotheses.
- The current model relied on twin pairs discordant for alcoholism which occur less frequently than pairs concordant for alcoholism.
- The sample was largely intact marriages that typically are of lower severity.
- The current study did not account for assortative mating.
- Assumptions as the Equal Environments Assumption and comparable treatment of twins vs. individual children were not tested within this sample.