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Paternal Alcoholism and Offspring Conduct Disorder: Evidence for the ‘Common Genes’ Hypothesis

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Not only are alcoholism and externalizing disorders 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. Participants were male monozygotic (MZ) and dizygotic (DZ) twins from the Vietnam Era Twin Registry who were concordant or discordant for alcohol dependence together with their offspring and the mothers of those offspring. All participants were conducted through a structured psychiatric interview. Offspring risk of conduct disorder was examined as a function of alcoholism genetic risk (due to paternal and co-twin alcohol dependence) and alcoholism environmental risk (due to being reared by a father with an alcohol dependence diagnosis). After controlling for potentially confounding variables, the offspring of alcohol-dependent fathers were significantly more likely to exhibit conduct disorder diagnoses than were offspring of nonalcohol-dependent fathers, thus indicating diagnostic crossover in generational family transmission. Comparing offspring at high genetic and high environmental risk with offspring at high genetic and low environmental risk indicated that genetic factors were most likely responsible for the alcoholism-conduct disorder association. The observed diagnostic crossover (from paternal alcoholism to offspring conduct disorder) across generations in the context of both high and low environmental risk (while genetic risk remained high) supported the common genes hypothesis.

The overrepresentation of children with conduct disorder symptoms or diagnoses in families with an alcoholic parent has remained a consistent finding throughout the past several decades (McGue, 1997; Sher et al., 1991; West & Prinz, 1987; Windle, 1997; Windle & Searles, 1990). However, the origins of this association remain unclear in two important ways. First, although family studies of the children of alcoholics (COAs) frequently note elevated rates of child conduct disorder problems (Helzer & Pryzbeck, 1988; Lynskey et al., 1994; Stewart et al., 1980; Zucker, 1994), few studies have adequately controlled for potential confounds, and therefore are not conclusive regarding the causal relationship between paternal alcoholism and offspring conduct disorder. In examining this issue, Loukas et al. (2001) reported that the frequent comorbidity between alcoholism and externalizing disorders precluded firm conclusions regarding whether it is specifically parental alcoholism or parental antisocial personality disorder that augmented risk for conduct disorder in children. Given that an antisocial diagnosis is 21 times more likely to occur in an alcoholic versus nonalcoholic population (Zucker, 1994), the likelihood that parental antisociality may confound parental alcoholism in the prediction of offspring conduct disorder is substantial. Furthermore, of those studies that have controlled for parental antisociality, none were designed to distinguish between genetic and environmental influences in evaluation of this association. This report attempts to address these concerns within a novel, highly controlled and genetically informative design.

The many medical and psychosocial consequences of parental alcoholism on the offspring of these families have been repeatedly reported by psychosocial researchers. Family studies have emphasized the impact of family disruption that results in offspring behavior problems and subsequently a developmental trajectory that is associated with negative outcomes (Jacob et al., 2003). Parental alcoholism and parental antisociality, as two separate and additive contributions, can result in child externalizing behaviors (Loukas et al., 2001). During the past several decades, accumulating evidence has indicated that child exter-
nalizing problems are key precursors of adult externalizing disorders including alcoholism, antisociality, and drug abuse (Windle & Windle, 1993; Zucker et al., 1995). For instance, Caspi et al. (1996) reported that children with externalizing (undercontrolled: impulsive, restless and distractible) behaviors at 3 years of age were significantly more likely than control children to exhibit antisocial personality disorder, and to be involved in crime at 21 years of age. Supporting this finding is a substantial literature indicating that one major pathway to adult alcoholism is through externalizing behaviors in early childhood (Tarter & Vanyukov, 1994; Zucker et al., 1995). In a review of this literature, Zucker (2002, p. 6) concluded that ‘a robust group of studies spanning the interval from very early childhood to adulthood strongly implicate behavioral undercontrol as a factor preciputive to adult onset of alcohol abuse and dependence’. By identifying a significant, heritable personality factor, Zucker moved the origin of these psychosocial effects to the earliest point in development: genes.

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 et al.’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.

In an earlier study of the transmission of alcoholism risk from parents to children, the authors used a children-of-twins (COT) design to determine the structure of genetic and environmental influences (Jacob et al., 2003). Results indicated that (a) paternal abuse/dependence predicted offspring abuse/dependence; (b) paternal alcohol abuse and paternal alcohol dependence predicted highly similar outcomes for offspring; and (c) both genetic and environmental influences were evident in offspring alcohol abuse/dependence outcomes.

In extending this line of inquiry, the current study examined the common genes hypothesis proposed by Slutske et al. (1998, 2002) and Krueger et al. (2002) by assessing transmission of genetic and environmental influences in an alcoholic family context, here defined as a family in which the father satisfied lifetime criteria for alcohol abuse or dependence (here referred to as ‘alcoholism’). The current study utilizes a 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). The approach was to first examine the phenotypic relationship between paternal alcohol abuse/dependence and offspring conduct disorder. Second, genetic and environmental risk groups would be examined to determine the nature of the common variance between paternal alcoholism and offspring conduct disorder. It was hypothesized that first, families with paternal alcoholism will be associated with increased rates of offspring conduct disorder symptoms (H1); and, second, that 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 (H2).

**Methods**

**Subjects**

The subjects of this study were members of the Vietnam Era Twin Registry (VETR; Eisen et al., 1987), which is comprised of male–male twin pairs born between 1939 and 1957 who served in the United States military between May 1965 and August 1975 (Eisen et al., 1987; Henderson et al., 1990). In 1987, twins completed a mailed questionnaire on general health (Eisen et al., 1991) from which data on their biological offspring, including gender and age, were obtained. In 1992, registry members were administered a telephone psychiatric diagnostic interview covering a range of disorders including alcohol and drug dependence (Harvard Drug Study; Tsuang et al., 1996). For the present study, information from these two studies was used to create a subset of twins based on the following criteria: (1) both twins completed the 1987 and 1992 surveys; (2) at least one twin reported that they had children born between 1974 and 1988; and (3) at least one twin met criteria for a lifetime diagnosis of Diagnostic and statistical manual of mental disorders, (3rd ed., rev.); (DSM-III-R, American Psychiatric Association, 1987) alcohol dependence, or both twins were part of a random sample of nonalcohol-dependent control pairs. The
The current study operationalized genetic and environmental influences by categorizing participants into...
levels of genetic and environmental risk. In the current 
model, genetic risk was operationalized as an alcohol 
abuse or dependence diagnosis in the parent (indicating 
high genetic risk) or the parent’s co-twin (indicating 
high genetic risk if monozygotic [MZ]; intermediate 
genetic risk if dizygotic [DZ]). Environmental risk was 
operationalized as the alcohol abuse or dependence 
status of the twin parent in the home environment; that 
is, whether the child lived with a father who had ever 
met criteria for alcohol abuse or dependence.

**Data Analysis**

**Predictor Groups**

Twin pairs were classified according to zygosity and 
alcohol abuse/dependence diagnoses to form four risk 
groups: group 1 — all twin fathers with a lifetime diag-
nosis of alcohol dependence or abuse regardless of the 
alcoholism status of his co-twin; group 2 nonalcoholic 
fathers with a MZ co-twin having an alcohol depend-
ence diagnosis; group 3 nonalcoholic fathers with a 
DZ co-twin having an alcohol dependence diagnosis; 
and group 4 nonalcoholic twin pairs. The normal 
control reference group, group 4, excluded parents 
with a diagnosis of alcohol abuse or dependence, but 
included parents with subclinical symptomatology to 
limit unrealistic group differences and to enhance gen-
eralizability. The classification scheme was intended 
to create groups that differentiated the level of genetic risk 
and environmental risk. As can be seen in Table 1, risk 
decreases sequentially through the groups from group 1 
to group 4. Since environmental risk levels are different 
for offspring of alcoholic twins and their nonalcoholic 
co-twins, offspring of nonalcoholic discordant twins 
were categorized into separate environmental risk 
groups, groups 2 and 3. For genetic influences, risk 
levels were defined as follows: for twins discordant for 
alcoholism, the offspring of nonaffected co-twins are 
included in group 2 if from an MZ pair, and group 3 if 
from a DZ pair, and the offspring of affected (alcoholic) 
co-twins are included in group 1. As well, group 1 
included the offspring of twins concordant for alco-
holism. Thus, all offspring of alcoholic fathers were 
classified into group 1 regardless of the status of 
father’s co-twin. Confirmation of the homogeneity of 
genetic liability for alcoholism across the group 1 sub-
groups is described below. Offspring outcomes could 
then be examined across the four risk groups with their 
respective levels of genetic and environmental risk.

**Covariates**

A rigorous definition of alcoholism was utilized in 
that the current study 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 vari-
ance 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 statisti-
cal power in order to increase clarity of interpretation 
in the examination of these closely associated vari-
ables. Other covariates were paternal conduct 
disorder; drug abuse; depression; dysthymia; general-
ized anxiety, panic, and posttraumatic stress disorders; 
and, for maternal variables, alcohol abuse, alcohol 
dependence and depression. Although maternal alco-
holism may be an important determinant of offspring 
conduct disorder, this was a low prevalence occur-
rence in the current sample of high-risk military 
personnel. However, to control for variation resulting 
from differences in maternal alcoholism risk across 
groups, maternal variables (including ASP/CD) were 
handled as covariates in this design.

**Dependent Variable**

To maximize statistical power in examining a low-
prevalence disorder, an ordinal logistic model was 
constructed using a four-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.

**Analytic Plan: Group Comparisons**

The analysis plan proceeded through two hypotheses. 
For H1, a significant group 1 elevation in offspring 
conduct disorder symptoms compared to group 4 
control reference group. other covariates were 
maternal antisocial personality and conduct disorder 
(ASP/CD). It should be noted that to partial out vari-
ance 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 statisti-
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and, for maternal variables, alcohol abuse, alcohol 
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holism may be an important determinant of offspring 
conduct disorder, this was a low prevalence occur-
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levels were: (a) 0 and 1 symptom; (b) 2 symptoms; (c) 3 
symptoms; and (d) 4 or more symptoms.

**Table 1**

<table>
<thead>
<tr>
<th>Group by Offspring Genetic and Environmental Risk</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paternal alcoholic twin</td>
<td>High</td>
<td>High</td>
<td>Moderate</td>
<td>Low</td>
</tr>
<tr>
<td>Paternal nonal. with MZ alc. co-twin</td>
<td>High</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paternal nonal. with DZ alc. co-twin</td>
<td>Moderate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Both twins nonal.</td>
<td>Low</td>
<td>Low</td>
<td></td>
<td>Low</td>
</tr>
</tbody>
</table>

disorder (provided mother’s influence is controlled), thus confirming the cross-generational, cross-diagnosis transmission of these two disorders 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 that provides the basis for genetically informed discrimination of transmitted influence.

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 nonalcoholic father whose MZ co-twin is alcoholic (see groups 1 and 2 in Table 1). That is, 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 a nonalcoholic (MZ co-twin) father. Thus, the common genes hypothesis would be supported if offspring rates of conduct disorder were similar in groups 1 and 2, and would be refuted if offspring rates of conduct disorder for group 2 were instead similar to normal controls in group 4. It can be seen that group 2 is of particular interest to hypothesis 2 because these

Table 2
Sociodemographic Characteristics for All Subjects by Paternal Alcoholism Status
(Percentages given for dichotomous variables; mean (SD) given for continuous variables*)

<table>
<thead>
<tr>
<th>Family characteristics (as of date of interview)</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
<th>Entire sample</th>
</tr>
</thead>
<tbody>
<tr>
<td>MZ and DZ AD twins (n = 809)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% male offspring</td>
<td>49.3%</td>
<td>54.4%</td>
<td>44.4%</td>
<td>44.4%</td>
<td>48.4%</td>
</tr>
<tr>
<td>Child age (yrs)</td>
<td>19.4 (4.1)</td>
<td>19.8 (4.2)</td>
<td>19.0 (3.9)</td>
<td>19.4 (4.0)</td>
<td>19.4 (4.1)</td>
</tr>
<tr>
<td>Paternal age (yrs)</td>
<td>50.5 (2.7)</td>
<td>50.8 (2.7)</td>
<td>50.7 (2.4)</td>
<td>51.1 (2.8)</td>
<td>50.7 (2.7)</td>
</tr>
<tr>
<td>Maternal age (yrs)</td>
<td>48.0 (5.2)</td>
<td>47.5 (5.1)</td>
<td>48.5 (6.6)</td>
<td>48.5 (3.8)</td>
<td>48.1 (5.0)</td>
</tr>
<tr>
<td>% Father employed fulltime</td>
<td>92.7%</td>
<td>91.2%</td>
<td>94.4%</td>
<td>96.0%</td>
<td>93.3%</td>
</tr>
<tr>
<td>Father educ. &gt; high school</td>
<td>59.2%</td>
<td>65.8%</td>
<td>71.0%</td>
<td>63.2%</td>
<td>61.7%</td>
</tr>
<tr>
<td>Mother educ. &gt; high school</td>
<td>67.0%</td>
<td>54.1%</td>
<td>59.6%</td>
<td>70.0%</td>
<td>66.3%</td>
</tr>
<tr>
<td>Marital status: divorced **</td>
<td>20.4%</td>
<td>12.3%</td>
<td>21.0%</td>
<td>13.2%</td>
<td>18.4%</td>
</tr>
<tr>
<td>Caucasian race</td>
<td>96.4%</td>
<td>99.1%</td>
<td>91.1%</td>
<td>94.2%</td>
<td>95.7%</td>
</tr>
</tbody>
</table>

Note: * no between group comparisons significant at p < .10.
** biological parents of this offspring are divorced.

Table 3
Offspring Report of Conduct Disorder Symptoms Across Paternal Alcoholism Status Groups

<table>
<thead>
<tr>
<th>Number of Sx</th>
<th>Twin-pair alcoholism status</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group 1</td>
<td>Group 2</td>
</tr>
<tr>
<td></td>
<td>MZ and DZ AD twins</td>
<td>MZ twin unaffected; co-twin with AD</td>
</tr>
<tr>
<td>0,1</td>
<td>n 617</td>
<td>89</td>
</tr>
<tr>
<td>%</td>
<td>76.3%</td>
<td>78.1%</td>
</tr>
<tr>
<td>2</td>
<td>n 64</td>
<td>11</td>
</tr>
<tr>
<td>%</td>
<td>7.9%</td>
<td>9.6%</td>
</tr>
<tr>
<td>3</td>
<td>n 53</td>
<td>5</td>
</tr>
<tr>
<td>%</td>
<td>6.6%</td>
<td>4.4%</td>
</tr>
<tr>
<td>4+</td>
<td>n 75</td>
<td>9</td>
</tr>
<tr>
<td>%</td>
<td>9.3%</td>
<td>7.9%</td>
</tr>
<tr>
<td>Totals:</td>
<td>n 809</td>
<td>114</td>
</tr>
<tr>
<td>%</td>
<td>100.0%</td>
<td>100.0%</td>
</tr>
</tbody>
</table>
groups in the current study, it was necessary to examine their similarity regarding offspring conduct disorder. The results are presented in the Results section, Confirming Similarity of Alcohol Abuse and Alcohol Dependence Outcomes. Also, given that group 1 is composed of different subgroups of alcoholic fathers, it was necessary to verify the homogeneity of variance across these subgroups to ensure that emergent findings involving group 1 did not result from variation in genetic liability due to differences in the co-twin’s risk status within group 1. These results are presented in the Results section, Confirming Homogeneous Genetic Variance in Group 1.

**Nested Observations**

Family studies and twin studies involve nested subgroups in which individual characteristics may be correlated. Because clustering may violate the assumption of independence of observations required by many statistical procedures, analyses were conducted both without and with adjustments for clustering. Preliminary analyses were conducted using SAS (SAS, 1989); final analyses were conducted using STATA (StataCorp., 2001) including the Huber–White robust variance estimator to adjust for clustering of offspring within families, perhaps the most proximal covariation regarding current analyses. Results were approximately identical to unadjusted findings, and slightly strengthening of current directions of effects.

**Results**

**Sample Characteristics**

As shown in Table 2, the four groups of offspring exhibited no significant differences ($p > .10$) for family characteristics. As of the date of interview, twin fathers and mothers averaged 51 and 48 years of age, respectively; over 62% of fathers had more than a high school education; 93% were employed full-time within families, perhaps the most proximal covariation regarding current analyses. Results were approximately identical to unadjusted findings, and slightly strengthening of current directions of effects.

**Group Differences in Offspring Conduct Disorder Outcome**

As seen in Table 3, for 2, 3 and 4 conduct disorder symptoms, groups 1 and 2 offspring exhibited elevated prevalence rates compared to offspring in groups 3 and 4; in contrast, for 0 and 1 symptoms, groups 1 and 2 offspring exhibited lower prevalence rates compared to offspring in groups 3 and 4. Aggregating across symptom levels, figure 1 shows dichotomous offspring conduct disorder symptoms (2 or more conduct disorder symptoms vs. 0 to 1 symptoms) according to paternal twin-pair alcoholism group. As seen, both group 1 and 2 have elevated risk compared to group 3 and group 4. This Figure is most illustrative of the pattern emerging

**Table 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

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

* $p < .05$; ** $p < .01$; *** $p < .001$

Note: ‘paternal antisocial personality disorder; conduct disorder; drug abuse; major depression; dysthymia; generalized anxiety, panic and posttraumatic stress disorders.

offspring share high genetic risk with offspring in group 1, and share low environmental risk with groups 3 and 4. Therefore, the dominant influence, genes or environment, will be reflected by the relative position of group 2 prevalence between groups 1 and 4, and the two contrasts, groups 1 to 2 and 2 to 4, will test the significance of the respective contributions of these competing influences.

Group 3 provides a test of moderate genetic influence. That is, contrasts of groups 2 to 3 and 3 to 4 test the relative influence of high, medium and low genetic risk in the context of environmental risk that is low and (approximately) equivalent across groups. If group 3 is more similar to groups 1 and 2, moderate genetic factors would be influential; if group 3 is more similar to group 4, moderate genetic factors associated with paternal alcoholism would be shown to be of little consequence to offspring conduct disorder symptom outcomes.

**Confirming Design Attributes**

The analytic plan included examination of two features of this research design that could potentially influence its validity. In the earlier examination of offspring alcohol use outcomes (Jacob et al., 2003), paternal alcohol dependence and paternal alcohol abuse were similarly predictive of offspring alcohol behaviors. In order to confirm the validity of combining these two
from analytical findings as described below. (Note, other graphs were consistent with this pattern; for instance, the 3+ graph differed only in being slightly more linear with less ‘knee’ accent).

The results of the ordinal logistic regression analysis are presented in Table 4. All group comparisons are referenced to group 4 (normal controls). Results can be considered in view of levels of genetic and environmental risk shown in Table 1. Concerning group 1, MZ and DZ alcohol abuse/dependent twins, children of alcoholics (group 1) were significantly more likely to exhibit conduct disorder symptoms than were children of nonalcoholics (group 4) after controlling for covariates (odds ratio: 1.81; \( p = .02 \)). Thus, paternal alcoholism (inclusive of genetic and environmental components but adjusted for covariates) significantly predicted offspring conduct disorder.

Concerning group 2, unaffected twins with an alcohol-dependent MZ co-twin, two contrasts were most important, the group 1 to 2 contrast, and the group 2 to 4 contrast. The group 1–2 contrast yielded a nonsignificant group difference (odds ratio: 1.02; \( p = .63 \)), indicating that offspring with high genetic but low environmental risk (group 2) were not different from offspring with both high genetic and high environmental risk (group 1). The group 2–4 contrast, after controlling for paternal and maternal antisocial disorder and other covariates, indicated a trend toward statistical difference in contrast to normal control offspring (group 4; odds ratio: 1.60; \( p = .15 \)) due to higher rates of conduct disorder symptoms although statistical significance was not achieved. Given the context of competing influences, the evident similarity between group 2 and the elevated offspring conduct disorder rate of group 1 (instead of a similarity between group 2 and the base rate reflecting group 4 normal controls) suggested the prominence of genetic over environmental influences. Given that the group 2 to 4 contrast did not reach significant difference, this finding suggests (but does not conclude) that genetic influences are the primary determinants of offspring outcome.

Group 3 examined the results of moderate genetic risk given low environmental risk (environmental risk was equivalent and low across groups 2, 3 and 4). As illustrated in Figure 1, offspring of a nonalcoholic twin with a DZ co-twin who was alcoholic (group 3) did not exhibit elevated conduct disorder rates compared with offspring of nonalcoholic control fathers (group 4; odds ratio: 1.04; \( p = .92 \)). Thus, moderate genetic risk (group 3) did not differentiate these offspring from normal control offspring. This was in contrast to high genetic risk (group 1) which did differentiate offspring from normal controls.

**Figure 1**
Percent offspring with two or more conduct disorder symptoms by group.
Note elevation of groups 1 and 2.
In addition to outcome differences related to alcohol risk status, several covariates were significantly related to offspring outcomes even after controlling for alcohol risk and other covariates: age of offspring \( (p = .0002) \); gender of offspring \( (p = .0001) \); father's employment status \( (p = .004) \); and divorce status of the parents \( (p = .0002) \). These are known risk factors for offspring conduct disorder. In the case of divorce, however, the direction of the effect is counterintuitive, that is, divorce appears to lower the risk of conduct disorder. This could be a simple anomaly or an artifact of the removal of parental antisocial personality disorder variance (given that antisocial personality disorder notably contributes to marital dissolution). Paternal educational level, paternal psychiatric comorbidity, and maternal alcohol and psychiatric comorbidity were not significantly related to outcome.

**Confirming Design Attributes**

To strengthen interpretability of the above findings, analyses were undertaken to confirm the validity of two design features.

**Confirming Similarity of Alcohol Abuse and Alcohol Dependence Outcomes**

Our previous finding that paternal history of alcohol dependence (AD) and paternal history of alcohol abuse (AB) were similarly predictive of offspring alcohol behaviors (Jacob et al., 2003) suggested that twins with AB history could be grouped with AD twins in the current analysis. Nevertheless, it was necessary to confirm this AD-AB similarity when considering offspring conduct disorder as the outcome of interest. Therefore, AB and AD twins were reclassified to distinguish paternal alcohol abuse from paternal alcohol dependence for both MZ and DZ pairs. Six groups were formed: group 1 — all AD twin fathers regardless of co-twin status; group 2 — AB fathers with alcohol-dependent MZ co-twins; group 3 — nonalcoholic fathers with AD MZ co-twins; group 4 — AB fathers with AD DZ co-twins; group 5 — nonalcoholic fathers with AD DZ co-twins; group 6 — nonalcoholic twin pairs as a reference group (any control pair currently found to meet diagnostic criteria for AB or AD was deleted). As expected, offspring in both group 1 and group 2 exhibited elevated rates of conduct disorder symptoms compared to the offspring in group 6 (odds ratios = 6.5 and 2.8 respectively; \( p = .01 \) and \( .09 \)) whereas all other contrasts with group 6 were non-significant. These findings support the combining of group 1 and group 2 into a single category within the current four-group design.

**Confirming Homogeneous Genetic Variance in Group 1**

To ensure that emergent findings involving group 1 were not dependent on variation in genetic liability arising from differences in the co-twin's risk status within group 1, another examination of subgroup differences was undertaken. These subgroups of group 1 alcoholic fathers were based upon each co-twin's alcoholism status (AD, AB or unaffected) and zygosity (MZ and DZ pairs). Here, all twins were AD whereas co-twin status was: (1) alcohol-dependent MZ co-twins; (2) alcohol-abusing MZ co-twins; (3) nonaffected MZ co-twins; (4) alcohol-dependent DZ co-twins; (5) alcohol-abusing DZ co-twins; and (6) nonaffected DZ co-twins. Although each subgroup represented potentially different influences on child outcome arising from differential genetic loading across the subgroups, results confirmed the homogeneity of odds ratios for group 1 across co-twin zygosity (MZ, DZ) and across co-twin history of alcohol use (AD, AB, unaffected). These results suggest that offspring with an alcohol-dependent father whose co-twin is nonabusing and nondependent is at no less genetic risk than the child of a dependent father whose co-twin is abusing or dependent. The absence of heterogeneity in offspring outcome as related to the co-twin's alcohol status supported the decision to include all families with an alcoholic father as a single predictive category, group 1.

**Discussion**

Current findings provide additional evidence for the contention that alcoholism and conduct disorder both arise, to a significant degree, from common genetic factors. Specifically, findings indicated that (1) paternal alcoholism predicted subsequent offspring conduct disorder in the same way that it predicted offspring alcoholism; and (2) paternal alcoholism, to a large extent, predicted offspring conduct disorder even when family environmental risk was minimized, thus suggesting that genetic mechanisms underlie the observed effects.

Concerning hypothesis 1, results clearly indicated that the offspring of alcohol-dependent fathers (group 1) were significantly more likely to have elevated rates of conduct disorder symptoms than were offspring of normal control fathers (group 4). Thus, when considering these two phenotypes, the nonindependence 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 conduct disorder symptoms indicated a close similarity between group 2 and the elevated rate of offspring conduct disorder symptoms in group 1 (as well as the consequent absence of similarity between group 2 and the offspring conduct
disorder base rate in group 4, normal controls). The implication is that genetic factors were much more important to the determination of offspring conduct disorder 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 groups 1–2 similarity was a nonsignificant group 1 to 2 contrast ($p = .63$). However, the dissimilarity between group 2 and group 4 only approached significance ($p = .15$), and thus was less than conclusive in differentiating group 2 elevations from normal control base rates (group 4). Hence, a certain ambiguity remained in interpretation of these results. Several considerations were examined in an effort to identify the most parsimonious explanation of current findings.

First, it was clear that little or no evidence supported an environmental interpretation. That is, if environmental effects were primary, their removal should have resulted in a substantial lowering of risk for offspring conduct disorder symptoms; this did not occur. Instead, risk for group 2 offspring remained substantially elevated. Second, findings indicated an elevation of group 2 offspring conduct disorder symptom rates approximating those of group 1 levels which was, at the least, suggestive of the influence of a high level of genetic risk present in group 2 offspring. On the other hand, the lack of statistical significance of the group 2 to 4 contrast required resolution.

The most parsimonious interpretation of these findings is that genetic factors and, to a lesser degree, environmental factors both were 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 group 2 to 4 contrast and its significance estimate, and would produce the above pattern of results.1

It appears likely that greater statistical power would have produced a more conclusive genetic finding. If true, it should be remembered that, in addition to other limiting factors (see Limitations), 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 also lowered power. As such, it may be that the significance test of the group 2 to 4 contrast is a ‘lower-bound’ estimate of the true effect.

In summary, the ‘common genes’ hypothesis would be supported if the offspring of nonalcoholic twins (low environmental risk) who had an alcohol dependent MZ co-twin (high genetic risk) exhibited elevated rates of conduct disorder symptoms (see Hypothesis 2). In fact, the prevalence rates were elevated in the current sample of offspring of nonalcoholics (group 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 group 2, but that they appeared to be present sufficiently to result in a minor decrease in the effect size of an otherwise unambiguous genetic effect. Therefore, it seems reasonable to conclude that the genes associated with parental alcoholism were responsible for the observed elevation in offspring conduct disorder symptom rates. To the extent that this is true, the common genes hypothesis is supported.

In an effort to strengthen interpretation of observed effects, we examined other offspring diagnoses including depression, generalized anxiety disorder, agoraphobia, social phobia, attention-deficit/hyperactivity disorder, oppositional–defiant disorder, and marijuana and nicotine dependence. No pattern of findings across groups emerged with sufficient clarity so as to be interpretable as evidence for common genetic influences. However, these were preliminary tests and were limited by several factors: (a) some diagnoses had small $n$s; (b) this is a high-risk alcoholism sample which may not be representative of internalizing disorders; and (c) more extensive analyses would be required to provide an adequate basis for interpreting these results. Nevertheless, drawing from the current study and our previous effort, it appears clear that offspring alcohol abuse/dependence and offspring conduct disorder are clearly associated with paternal alcoholism through a genetic mechanism.

**Limitations**

Consideration of limitations is important in the interpretation of present findings. For instance, examination of the etiology of conduct disorder is limited by the low prevalence of this disorder in the general population and by the difficulty in obtaining sufficient sample size and statistical power when a sample is not selected to be high risk for conduct disorder. As well, statistical power was limited in this particular COT model due to its dependence on twins who are discordant for alcoholism, and by the desire to account for many potential confounds (D’Onofrio et al., 2003). Further, since the study sample was largely composed of intact marriages with children, more extreme forms of alcoholism, antisocial behavior, and family disruption may have been lost through divorce and/or refusal (very disturbed families participate less often in family studies) thus reducing the variability due to negative environmental influences. Finally, all designs are associated with certain assumptions and limitations. In general, the COT design is more powerful for detecting environmental rather than genetic effects (Heath & Eaves, 1985); even though it was important as an alternative methodology in the current study, this application may not have
been its strongest application. Other general limitations of the COT design include the inability to identify reciprocal environmental influences, reliance on the equal environments assumption (EEA, Xian et al., 2000), and on comparable treatment of twins and singletons (Rutter et al., 2001). Most evidence to date has supported these assumptions. (For a critical review of genetic designs and their limitations, see Rutter [2001], and for the COT design, see Heath & Eaves [1985] and Silberg & Eaves [2004]).

The current study contributes to a growing body of evidence addressing the proposition that there are two primary dimensions of psychopathology, an externalizing and an internalizing dimension, each having a sizeable genetic component. The various disorders that are subsumed under each broad band factor appear to share common genetic variance which accounts, in part, for observed patterns of comorbidity within these dimensions and for transmission characteristics across generations. As summarized by Widiger and Clark (2000), and most recently demonstrated by Kendler et al. (2003), these two genetically influenced factors may be two cornerstone dimensions central to our understanding and classification of psychiatric disorders. The current study supports the notion of common genes underlying at least two disorders in the externalizing dimension, alcoholism and conduct disorder. Use of alternative methodologies, such as the COT design, contributes a unique perspective in efforts aimed at elucidating these relationships.

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**Endnote**

1 The psychosocial literature and, to a lesser extent, the behavioral genetic literature both indicate a role for environmental influences in these effects. For instance, Krueger et al. (2002) found that after accounting for a latent broadband externalizing factor, shared environmental influences remained, accounting for 26% of the outcome variance associated specifically with conduct disorder diagnoses. In this case, shared environmental influences appeared to play a greater role in the development of conduct disorder than in alcoholism and other externalizing disorders. As well, our earlier study of offspring alcoholism (Jacob et al., 2003) reported that offspring alcohol abuse/dependence was significantly elevated in families with an alcoholic father (compared to normal controls) whereas symptoms were less elevated in the nonalcoholic, high genetic risk families, thus suggesting a gene × environment (GxE) interaction. Therefore, it seems plausible that environmental influences were present and made some contribution to the above effects in the manner described.

**References**


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