A Twin-Family Study of Alcoholism in Women


**Objective:** The authors seek to understand in general the sources of familial resemblance for alcoholism and in particular how parents transmit the vulnerability to alcoholism to their daughters. **Method:** The authors interviewed 1,030 pairs of female same-sex twins of known zygosity from the population-based Virginia Twin Registry and 1,468 of their parents. They examined a narrow definition of alcoholism, requiring tolerance or dependence, and a threshold approach that classified individuals either as unaffected or as suffering from one of three levels of severity of alcohol-related problems. Twin-family structural equation models were fitted to the observed tetrachoric or polyserial correlation matrices by using asymptotic weighted least squares. **Results:** In the best-fitting model from both diagnostic approaches, 1) the familial resemblance for alcoholism was due to genetic factors, with the heritability of liability estimated at 51% to 59%; 2) genetic vulnerability to alcoholism was equally transmitted to daughters from their fathers and from their mothers; and 3) alcoholism in parents was not environmentally transmitted to their children. Assortative mating for alcoholism was found only for the broader definitions of illness. Genetic factors that influenced the liability to alcoholism were the same in the parental and twin generation for the narrow definition of alcoholism. When broader definitions were used, these factors, while substantially correlated, were not identical. **Conclusions:** The transmission of the vulnerability to alcoholism from parents to their daughters is due largely or entirely to genetic factors.


The last decade has seen an increasing interest in the impact of parental alcoholism on children (1). While children of alcoholic parents may differ from other children in a variety of ways, the best demonstrated effect is that they themselves have an increased risk for alcoholism (1–4). How do parents with alcoholism transmit an increased vulnerability to this disorder to their children?

Two basic mechanisms must be considered: genetic and environmental. While the operation of genetic factors is well understood, rigorous models for environmental parent-offspring transmission have only recently been used in psychiatry (5–8). Environmental parent-offspring transmission has been termed direct "vertical cultural transmission" (8). In direct vertical cultural transmission, traits or disorders are passed from parents to children through social learning or modeling (9). Vertical cultural transmission for alcoholism would imply that children "learn" alcoholism (or traits that increase the vulnerability to alcoholism) from their parents in the same way that they learn language, social attitudes, or religious affiliation. Put another way, vertical cultural transmission would indicate that exposure to parental alcoholism "teaches" children attitudes or personality characteristics that increase their own vulnerability to alcoholism.

In traditional intact families, genetic and environmental causes of parent-offspring resemblance are completely confounded because parents both transmit their genes to their children and form an important part of their environment. Therefore, to date, this issue has been examined using only adoption designs. Specifically, vertical cultural transmission has been tested by examining whether adoptees raised in homes where the parents have alcohol problems are at increased risk for alcoholism.

In adoption studies in Denmark (10) and Sweden (11), alcoholism in male adoptees was related to alco-
holism in the biological parents but not in their adoptive parents. However, in the major U.S. adoption study of alcoholism, early results suggested findings similar to those of the European studies (12), but later findings suggested that alcohol problems in the adoptive family did increase the risk for alcoholism in male adoptees (13, 14).

The role of vertical cultural transmission in influencing risk for alcoholism in women has been even less well studied. Cadoret et al. found that alcohol problems in the adoptive family approximately doubled the risk for alcohol abuse in 87 female adoptees from Iowa, but this did not approach statistical significance (13). Bohman et al. found that the rate of alcohol abuse was nearly identical in 913 female adoptees from Sweden when adoptive parents did (3.7%) or did not (3.4%) themselves suffer from alcohol abuse (15).

While of great theoretical power, adoption studies do have significant limitations in their study of vertical cultural transmission. Most important, adoption agencies usually make a concerted effort to screen prospective adoptive parents for mental health, thereby considerably reducing rates of alcoholism in adoptive parents (16, 17). In particular, individuals with severe and early onset alcoholism are especially unlikely to be selected as adoptive parents. By contrast, individuals with alcoholism are probably overrepresented in biological parents of adoptees (11). Additional methodologic limitations of many adoption studies of alcoholism include small sample size (10, 12-14, 18), ascertainment through treatment facilities (10, 18), and diagnoses based on institutional records in biological parents (10, 12-14, 18) or in biological and adoptive parents and adoptees (11, 15).

We here report results from a new methodologic approach to clarifying the role of genetic and environmental factors in the familial transmission of alcoholism: the study by personal interview of a large population-based sample of female-female twins and their parents. While rarely used in psychiatric research, the twin-family design, and specifically twins and their parents, compares favorably with adoption designs in its ability to discriminate vertical cultural transmission from parent-offspring genetic transmission (19). Furthermore, for the study of alcoholism, the twin-family design may be less influenced by selection bias than adoption designs. In particular, parents of twins, especially when ascertained through a population-based register, are likely to be representative of the general population with respect to their risk for alcoholism. We have previously examined results for alcoholism in the twins from this sample (20).

METHOD

Sample and Diagnostic Methods

The Virginia Twin Registry is a population-based register formed from a systematic review of all birth certificates, from 1918 onward, in the Commonwealth of Virginia. Current addresses are obtained largely by matching birth certificates to state records. Twins were eligible to participate in this study if they were born between 1934 and 1971 and both members of the pair had previously responded to a mailed questionnaire. The individual response rate to the questionnaire was approximately 64%. The common response rate was certainly higher than this, since an unknown number of twins did not receive their questionnaire because of faulty addresses, improper forwarding of mail, and so forth. Of the total 2,352 eligible twins (from 1,176 pairs), we were able to personally interview 2,163 (92%), including both members of 1,033 twin pairs. The mean age of the participating twins was 30.1 years (SD=7.6). Eighty-nine percent of the interviews were conducted face-to-face, usually in the twin's residence, and 11% by phone. Zygosity was determined by an algorithm that was based on questionnaire responses, photographs, and, when these sources were ambiguous, DNA polymorphisms (21) and yielded 590 monozygotic pairs, 440 dizygotic pairs, and three pairs of unknown zygosity.

When interviewing the twins, we obtained names and addresses of all available biological parents, thus identifying 1,698 parents of the 1,033 twin pairs in which both members had been assessed. Attempts were then made to interview these parents, of whom 26 were found to be deceased on contact, 33 were too medically ill or demented to be interviewed, five were lost to follow-up, and two were adoptive parents. Of the remaining 1,632 parents, 1,472 (90.2%) were interviewed and 160 (9.8%) refused. Of those interviewed, 855 were mothers and 617 were fathers. Of the completed interviews, 92% were performed face-to-face, nearly always in their home, while 8% were done on the telephone (primarily for parents living outside Virginia). The mean age of the participating parents was 58.6 years (SD=9.3).

All interviews were conducted by individuals who had a master's degree in a mental health-related discipline or a bachelor's degree and at least 2 years of clinical experience and who had undergone 80 hours of clinical training in alcohol problems. The interviewers were matched with the period of field work. All interviews were conducted by individuals with no prior contact with another family member, so that in complete families (both twins and both parents), four different interviewers were required.

This report focuses on the 1,030 twin pairs of known zygosity and, when available, their interviewed parents (853 mothers and 615 fathers). The sample contains four family types: twins only (N=129), twins and their father (N=48), twins and their mother (N=226), and twins and both parents (N=567).

The personal interviews with both twins and their parents contained the section for alcohol dependence from the Structured Clinical Interview for DSM-III-R (SCID) (22). Because of previous evidence that the role of genetic factors in the etiology of alcoholism in women may differ as a function of severity (23) and because DSM-III-R criteria for alcohol dependence are less widely adopted and were used only by an individual who displays none of the symptoms of physiologic dependence, we defined three levels of severity of alcoholism. The first, termed "alcoholism with dependence/tolerance," was defined as meeting full DSM-III-R criteria for alcohol dependence and specifically endorsing SCID items that reflect DSM-III-R psychoactive substance dependence criterion A7 (marked tolerance), A8 (dependence as evidenced by withdrawal symptoms), or A9 (dependence as evidenced by drinking to avoid withdrawal symptoms). The second level of severity was termed "alcoholism without dependence/tolerance" and was defined as meeting DSM-III-R criteria for alcohol dependence but not endorsing items that reflect criterion A7, A8, or A9. The third level of severity of "alcoholism" defined in this study was termed "problem drinking" and was defined as meeting one of the two SCID "stem" questions for alcohol dependence (admitting to having had a "problem wound in your life when you drank too much" or admitting to "a period in your life when someone else objected to your drinking") but not meeting DSM-III-R criteria for alcohol dependence. For each of these questions, interviewers were instructed not to count single episodes of overindulgence. Furthermore, for the second question (someone else objecting), interviewers were instructed to rate this item only if the other individual felt that the respondent had a "drinking problem." From these three levels of severity, we created the following three definitions of alcoholism: 1) narrow—only alcoholism with dependence/tolerance, 2) intermediate—alcoholism with or without depend-
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The observed phenotypes are in boxes and the latent variables in circles. Three classes of latent variables are postulated: A—additive genetic effects, C—common or familial environmental effects (environmental factors that make twins similar for their liability to alcoholism), and E—individual-specific environmental effects (which influence one twin’s liability to alcoholism but not her co-twin’s). In addition, the model contains potentially differentiating genetic factors for alcoholism in the parental generation (A) and the twin generation (A’). Subscript F or f refers to father, M or m to mother, T1 to twin 1, T2 to twin 2, and T to both twins. Path coefficients (one-headed arrows) that equal standardized regression coefficients are pictured as lower-case letters, as follows: a—additive genetic factors, c—common environmental factors, e—individual-specific environmental factors, w—vertical cultural transmission, and r—the correlation between additive genetic effects in the parental and twin generations. The delta path μ (line with no arrows) reflects assortative mating, here modeled as the tendency for spouses to select each other on the basis of their liability to alcoholism. Genotype environment correlation is expressed by the correlation (two-headed arrow) p and is assumed to be at equilibrium. To express the proportion of variance accounted for in the dependent variable, the path coefficient must be squared.

tolerance (which corresponds to the DSM-III-R definition of alcohol dependence), and 3) (broad) alcoholism with or without dependence/tolerance or b) problem drinking.

Interrater reliability was measured in 98 randomly chosen twins and parents assessed at a single interview by two raters. For the DSM-III-R diagnosis of alcohol dependence, reliability was excellent (kappa=0.86) (24). In those interviews in which one of the stem questions for alcohol dependence was answered positively, and therefore the respondent was queried on the nine specific DSM-III-R criteria for alcohol dependence, the interrater reliability for the individual criteria was high (kappa=0.90).

The Twin Family Design

The traditional approach to the analysis of twin and family studies in psychiatric genetics has been to examine the rates of illness in relatives of ill individuals (termed ‘‘probands’’) selected (or, more technically, ascertained) at a treatment facility. However, the twins and their parents in this study were from the general population and were ascertained independent of their psychiatric status. Our design contains no identified proband. While we present our data in the more traditional form, as if individuals affected with alcoholism in our sample were ascertained because of their illness, our analysis emphasizes a more efficient and appropriate analytic approach based on a liability threshold model. We assume that underlying the observed dichotomy of affected/unaffected for alcoholism, there exists a continuous latent liability with a threshold so that individuals with a liability above the threshold become affected, while those whose liability is below the threshold remain unaffected. We examine the correlations between these liabilities in relatives; the correlations are termed “tetrachoric correlations” (sometimes termed the “correlation of liability”) (25, 26) when dichotomous affected/unaffected variables are used and “polychoric correlations” when multiple affection classes are employed. These correlations assume that liability to illness can be approximated by a normal distribution. Such a distribution would arise if the genetic and environmental risk factors acted additively, were relatively numerous, and were of small effect. However, a normal distribution can be closely approximated by a small number of risk factors of moderate size (27).

A tetrachoric correlation fit to a two-by-two table is a “perfect fit” and provides no test of the liability-threshold model. However, in the testing of whether our three definitions of alcoholism represent different levels of severity on the same liability continuum (28), a polychoric correlation is calculated from a four-by-four table, cross-classifying each member of the family as unaffected or meeting criteria for one of our three levels of severity of alcoholism. A chi-square goodness of fit test is available for testing this multiple threshold model (29).

Figure 1 depicts, in the form of a path diagram, the model used for the analysis of these data. This model assumes four major sources of familial resemblance: 1) additive genetic effects (a), 2) shared or common environmental effects (c), 3) direct vertical cultural transmission (w), and 4) assortative mating (μ). Vertical cultural transmission is modeled as a path going from the phenotype of the parent to the shared or familial environment of the twins. Thus, in this model, the familial environment influences twin’s liability to alcoholism. Likewise, it is divided into that due to direct vertical cultural transmission from mother and father that due to other risk factors shared by twins such as those related to social and ethnic class, school, peer group, neighborhood, and so forth. Because of possible differences in impact on female offspring with paternal versus maternal alcoholism (4, 30), the strength of the vertical cultural transmission path from fathers (w) and mothers (w) is allowed to differ. Furthermore, because social attitudes toward alcohol consumption have changed dramatically in this century, it is possible that the genetic factors that predispose individuals to drinking problems may differ over generations. To encompass this in our model, we include two latent variables that present the genotypes that are transmitted to the offspring (A and A’). The paths from the parents’ own genotype (A and A’) to their transmitted genotype are estimated as free parameters (r and r) that represent the genetic correlation between generations. Finally, the model assumes that spousal resemblance for the liability to alcoholism results from phenotypic assortative mating in which spouses select one another in part on the basis of their predisposition to alcoholism (31–33). The correlation in liability to alcoholism in spouses is modeled by a delta path (34, 35).

In this twin-family design, models that contain both w and w and r (r and r) are not identified, since the three paths are founded. We address this problem by initially fitting models that constrain to unity and estimate values of w. If no evidence is found for vertical cultural transmission, we then set w to zero and fit models that include variable values for r.

Because our sample currently contains no male-male or male-fe-
TABLE 2. Prevalence of Alcoholism in Twins, Co-twins of Affected Monozygotic and Dizygotic Twins, and Daughters of Affected Mothers and of Affected Fathers

<table>
<thead>
<tr>
<th>Definition of Alcoholism</th>
<th>Twins in General Population</th>
<th>Co-Twins of Affected Twins</th>
<th>Daughters of Affected Parents</th>
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<tr>
<td></td>
<td>Monzygotic</td>
<td>Dizygotic</td>
<td>Mothers</td>
</tr>
<tr>
<td></td>
<td>26.2</td>
<td>11.9</td>
<td>9.1</td>
</tr>
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<td></td>
<td>31.6</td>
<td>24.4</td>
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<tr>
<td></td>
<td>46.9</td>
<td>31.5</td>
<td>27.8</td>
</tr>
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</table>

TABLE 3. Tetrachoric and Polychoric Correlations for Three Definitions of Alcoholism and the Threshold Model in Monozygotic Twins, Dizygotic Twins, Mother-Daughter Pairs, Father-Daughter Pairs, and Mother-Father Pairs

<table>
<thead>
<tr>
<th>Definition of Alcoholism</th>
<th>Monzygotic Twins</th>
<th>Dizygotic Twins</th>
<th>Mother-Daughter Pairs</th>
<th>Father-Daughter Pairs</th>
<th>Mother-Father Pairs</th>
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</thead>
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<tr>
<td></td>
<td>Correlation</td>
<td>SE</td>
<td>Correlation</td>
<td>SE</td>
<td>Correlation</td>
</tr>
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<td>0.53</td>
<td>0.11</td>
<td>0.15</td>
<td>0.15</td>
<td>0.11</td>
</tr>
<tr>
<td>Intermediate</td>
<td>0.54</td>
<td>0.09</td>
<td>0.36</td>
<td>0.11</td>
<td>0.17</td>
</tr>
<tr>
<td>Broad</td>
<td>0.61</td>
<td>0.06</td>
<td>0.30</td>
<td>0.09</td>
<td>0.20</td>
</tr>
<tr>
<td>Threshold</td>
<td>0.58</td>
<td>0.06</td>
<td>0.29</td>
<td>0.09</td>
<td>0.18</td>
</tr>
</tbody>
</table>

male twin pairs, we have limited ability to test whether the genetic and environmental factors that influence the liability to alcoholism differ across the genders. First, after fitting the full model with $r_1$ and $r_2$ constrained to unity, we test separately for the significance of the vertical cultural transmission path from fathers ($w_4$) and from mothers ($w_5$). Second, we can separately relax the constraint that $r_1$ and $r_2$ is unity. If the environmental influences of paternal and maternal alcoholism have different effects on the risk for alcoholism in twin daughters, then we would expect different estimates of $w_4$ and $w_5$. If genetic factors that influenced the liability to alcoholism differed in males and females, we would expect this "genetic correlation" to be lower in father-daughter ($r_{11}$) than in mother-daughter ($r_{12}$) pairs.

Statistical Analysis

Eight tetrachoric or polychoric correlation matrices, along with standard errors, were calculated by the program PRELIS II (36) for the four family types (twin with both parents, twins with father only, twins with father only, and only twins) separately for monozygotic and dizygotic twins. The sample size of families with fathers only was, however, too small to provide stable estimates. Therefore, fathers in these families were eliminated and the twins included in the twin only families. For each definition of illness, models were fitted jointly to these six correlation matrices with their standard errors by the computer program Mx (37), using asymptotic weighted least squares. After fitting the full model, we then fit a series of simpler models, with the goal of explaining the observed data as well as possible with as few parameters as possible. We operationalize this goal with the use of Akaike's information criterion (AIC) (38), which, equaling the chi-square value minus twice the degrees of freedom, is a metric that reflects the balance of simplicity and explanatory power of a model. We seek to obtain the most negative possible value of the AIC, thereby obtaining the model with the optimal balance of goodness of fit and parsimony. Further details of the application of biometrical genetic models to twin and twin family data are outlined by us elsewhere (29, 39-41).

The final step of twin analysis is to estimate, on the basis of the best-fitting model, the proportion of variance in liability to alcoholism due to individual-specific environment ($e^2$), additive gene action ($a^2$), or common environment ($c^2$), as well as the best estimates for assortative mating ($\mu$) and the genetic correlation between parents and offspring ($r$). The proportion of variance in liability due to additive genetic effects is often termed "heritability."

RESULTS

Prevalence in the Population and in Relatives

Table 1 contains the lifetime prevalence rate for the three levels of severity of alcoholism in the 2,060 personally interviewed twins from complete pairs with known zygosities, their fathers, and their mothers. The pattern is consistent in showing highest rates in fathers, next highest in twins, and lowest in mothers.

The population prevalence for the three definitions of alcoholism in the female twins, in co-twins of affected monozygotic and dizygotic twins and in daughters of affected mothers and daughters of affected fathers is shown in table 2. For each definition of alcoholism, the prevalence of alcoholism is highest in monozygotic co-twins of affected twins, next highest in dizygotic co-twins of affected twins, and slightly lower and similar in the twin daughters of affected mothers and affected fathers.

Tetrachoric Correlations

The tetrachoric correlations in pairs of relatives for our three definitions of alcoholism are shown in table 3. For all definitions of illness, the correlations are substantially higher in monozygotic twins than in other pairs of relatives. The correlation in dizygotic pairs is generally greater than that seen in mother-daughter or father-daughter pairs. While the father-daughter correlation varies little across all three definitions of illness, the mother-daughter correlation increases modestly as the definition of alcoholism broadens. The tetrachoric correlation in mothers and fathers does not differ from zero for the narrow and intermediate definitions of illness. However, it is positive and moderate for the broad definition of alcoholism.
Multiple Threshold Model

The multiple threshold model tests whether our three categories of alcohol-related problems—problem drinking, alcoholism without dependence/tolerance, and alcoholism with dependence/tolerance—represent different levels of severity on a single dimension of liability to alcoholism. This model (all df=8) fit well in monozygotic twins ($\chi^2=7.36$, p=0.50), dizygotic twins ($\chi^2=7.11$, p=0.53), mother-daughter pairs ($\chi^2=7.52$, p=0.48), father-daughter pairs ($\chi^2=5.30$, p=0.73) and mother-father pairs ($\chi^2=12.79$, p=0.12).

We can then examine resemblance in relatives for this underlying liability dimension indexed by our three severity levels of alcohol-related problems by calculating polychoric correlations in relatives with this multiple threshold model (table 3). The correlation in monozygotic twins is exactly twice that found in dizygotic twins, while the mother-daughter and father-daughter correlations are similar and moderately lower than that found in dizygotic twins.

MODEL FITTING

We present in appendix 1 detailed results of model fitting for the narrow definition of alcoholism and for the multiple threshold model. Details of model fitting to other definitions of alcoholism are available from Dr. Kendler on request.

Narrowly Defined Alcoholism

For alcoholism with tolerance and dependence, the best-fitting model was a very simple one (figure 2). All familial resemblance for alcoholism was due to genetic effects. The only environmental factors of etiologic importance were those unique to the individual. No evidence was found for vertical cultural transmission for the liability to narrowly defined alcoholism from either mothers or fathers. That is, the resemblance for the liability to alcoholism between parents and their daughter could be best explained solely by genetic factors and not by any environmental effect of parental alcoholism. No evidence was found for assortative mating for narrowly defined alcoholism. The best-fitting model estimated that the genetic effect on the daughter’s liability to alcoholism was equal from mothers and fathers.

The parameter estimates of the best-fitting model, depicted in figure 2, estimated the heritability of liability to narrowly defined alcoholism at 51%, with the remaining 49% of variability in liability due to individual-specific environmental effects.

The Multiple Threshold Model

Because the multiple threshold model provided an excellent fit for the distribution in relatives of our three classes of alcohol-related problems, analyzing all three categories jointly by this model probably represents the best single approach to the analysis of the full range of manifestations of “alcoholism.” As detailed in appendix 1, the best-fitting model (figure 3) was here very similar to that found for narrowly defined alcoholism, with two notable differences. First, significant assortative mating (path coefficient=0.22) was found for the liability to this broad range of alcohol-related problems. Second, for narrowly defined alcoholism, the best-fitting model estimated that the genetic effects in the parental and offspring generation were identical. However, when the broader definitions of alcoholism were used, the best-fitting model indicated that while highly correlated (0.57), the genes influencing liability to alcoholism in the parents were not identical to those in the offspring.

The parameter estimates for the best-fitting model to the range of definitions of alcohol-related problems are shown in figure 3. The heritability of liability (59%) is slightly higher than that seen for narrowly defined alcoholism.

DISCUSSION

Our goal in this study was to use the twin-family design to clarify the causes of the familial transmission of alcoholism. We were especially interested in understanding how parents transmit the vulnerability to alcoholism to their daughters. We review our major results in turn.

Genetic Effects

Consistent with our previous results in the twins only (20), the best-fitting models for both the narrow and
multiple threshold definitions of alcoholism included additive genetic factors. Indeed, for both definitions, a model that attempted to explain familial resemblance for alcoholism as a function of only environmental factors could be strongly rejected.

Estimates of the heritability of liability to alcoholism for the two definitions ranged from 51% to 59%. Of the three adoption and two twin studies that have previously examined this issue, two suggest that genetic factors are etiologically unimportant for alcoholism in women (18, 42). One study suggests that while significant, genes are less important as risk factors for alcoholism in women than in men (15). Another study initially found a modest role for genetic factors in the etiology of alcoholism in women but only when alcoholism was narrowly defined (23). However, a further report from that study with an expanded sample reported no evidence at all for genetic heritability of alcoholism in women (43). Only one small-sample adoption study has suggested that genetic factors play a major role in the etiology of alcoholism in women, comparable to that observed in men (13). Our results provide substantial evidence that the heritability of alcoholism in women is substantial, similar for narrow and broad definitions, and comparable to what has been previously reported in other studies in men (23, 43, 44).

Parent-Offspring Transmission of the Liability to Alcoholism

We found no evidence for direct vertical cultural transmission for the liability to alcoholism. In fact, although never significant, parameter estimates for vertical cultural transmission from the full model (results not shown) were usually negative, implying that the environmental effects of alcoholism in a parent are, if anything, to reduce the risk of alcoholism in the daughters. These results are consistent with the findings in female adoptees from the Swedish adoption study of alcoholism (15), although, as noted earlier, in a small American adoption study, Cadoret et al. found nonsignificant increases in alcohol problems in adoptees reared by alcohol-abusing parents (13). There is limited evidence in intact families for negative vertical cultural transmission for alcohol consumption, since rates of abstention from alcohol intake may be increased in the offspring of alcohol-abusing parents (30, 45).

While we find little evidence for direct vertical cultural transmission in this study—that alcoholism in parents, through modeling or social learning, predisposes to alcoholism in their offspring—this should not be interpreted as evidence against any environmental effect that parents may have on their children’s risk for alcoholism. Parental behavior unrelated to their drinking habits, such as their method of discipline (46) or rearing style (47), may environmentally contribute to their offspring’s risk for alcoholism by what has been termed “indirect” vertical cultural transmission (8). That is, while parental alcoholism does not appear to environmentally influence the risk for alcoholism in daughters, that risk might be substantially affected by other aspects of parental behavior.

Assortative Mating

We found no evidence for significant spousal resemblance for our narrow definition of alcoholism in parents of twins. However, when we included problem drinking in our multiple threshold definition, spousal correlations became significant and were similar in magnitude to the correlation between parents and their children. These results are largely consistent with previous reports of substantial correlations in spouses for alcoholism (48–50), problem drinking (51), and amount of alcohol consumed (52–54).

Parent-Offspring Genetic Transmission of the Liability to Alcoholism

The parents of the twins were, on average, 28 years older than their twin daughters. The lifetime prevalence rate for alcoholism was almost twice as high in daughters as in their mothers despite their mothers’ additional years of risk. The genetically influenced temperamental variables that influence the risk for alcoholism could differ across the two generations. Therefore, our model-fitting included the possibility that the genetic factors influencing the liability to alcoholism might differ in the parental and twin generations. For our narrow definitions of alcoholism, our best-fit model suggested that the same genetic factors influence alcoholism in the two generations. However, for the multiple threshold definition, the best-fit model suggested that while substantially correlated, the genetic factors
that influenced liability to alcoholism in the parental and twin generations were not identical. These results suggest that the genetic factors influencing more severe "alcoholism" have changed little in the last two generations, but that "problem" drinking, from a genetic perspective, may not be entirely the same condition in our twins and their parents. The genetic factors that influence the risk for problem drinking in our female twins, who grew up when alcohol was relatively accessible to women and drinking less acceptable, may differ from those that influenced risk for problem drinking in their mothers, who grew up at a time when access to alcohol for women was more restricted.

Gender Effects in the Transmission of Risk for Alcoholism

As recently reviewed (44), most studies suggest that the genetic factors that influence liability to alcoholism in men and women are, if not identical, at least substantially correlated. In a meta-analysis of parent-offspring transmission from intact families, Pollock et al. found that father-daughter correlations for alcoholism tended, across studies, to be moderately higher than mother-daughter correlations (4).

While the absence of male-male and male-female twins from our sample limits our ability to address this question definitively, the available evidence in this study strongly supports the existence of genetic factors that influence the liability to alcoholism in both genders. The results of our model fitting indicated that fathers genetically transmitted the liability to alcoholism to their twin daughters. In fact, consistent with results from intact families (4), the correlation in liability to alcoholism was modestly but nonsignificantly greater in father-daughter than in mother-daughter pairs.

Limitations

The results of this study should be interpreted in the context of four methodologic limitations. First, the analytic approach taken here does not include information about the year of birth and age at evaluation of all relatives and the age at onset of alcoholism in affected individuals. This limitation was forced upon us by the great complexity of properly modeling, at the same time, age at onset, censoring, and cohort effects. While we have developed a model for examining age at onset, it can be currently implemented only in twins without censoring and cannot jointly treat cohort effects (55). We have attempted several preliminary analyses to assess the possible impact of including these variables in future analyses. Our results suggest that while these additional variables are not trivial in their impact, their inclusion is unlikely to substantially alter the basic pattern of the findings reported here.

Second, our results should be interpreted in the context of the statistical power of this sample and the twin-family method (19). For example, in the presence of the relatively high levels of heritability found for alcoholism, this sample probably has good power to detect strong vertical cultural transmission but quite limited power to detect a modest environmental effect on the liability to illness.

Third, the differences between our best-fitting and second best-fitting models were not striking either for our narrowly defined or threshold models for alcoholism. With the narrow definition of illness, we could not rule out the possibility that while the genetic correlation for alcoholism between generations was high (0.75), it was less than unity. With the threshold model, we could not rule out the possibility that instead of a cross-generational genetic correlation of less than unity, the observed pattern of resemblance in our twin families might be due to modest common environmental influences (0.20) on the liability to alcoholism. Indeed, in examining our intermediate definition of alcoholism in this sample, we found that the best-fit model contained a small common environmental component.

Fourth, these analyses examined only alcoholism, excluding consideration in both parents and twins of other comorbid psychiatric disorders. We have recently completed an analysis in the twins of only the relationship between alcoholism and major depression (56). Future analysis in twins and their parents will include the consideration of multiple psychiatric disorders.

Finally, our assessments of alcoholism in both the twins and their parents were performed at only one time. Since psychiatric diagnosis is not perfectly reliable and measurement error in our models is usually indistinguishable from individual-specific environment, it is possible that the heritability of liability to alcoholism would be higher than here reported if we had included multiple assessments or formally corrected for unreliability.

REFERENCES


TABLE 4. Model Fitting to Twin Family Data for Narrow Definition of Alcoholism and for the Multiple Threshold Model

<table>
<thead>
<tr>
<th>Model</th>
<th>Parameters*</th>
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<td>ACEμw1m</td>
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<td>-27.5</td>
</tr>
<tr>
<td>IV</td>
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<td>17</td>
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<td>-29.1</td>
</tr>
<tr>
<td>V</td>
<td>ACE</td>
<td>18</td>
<td>5.4</td>
<td>-30.6</td>
</tr>
<tr>
<td>VI</td>
<td>CE</td>
<td>19</td>
<td>29.0</td>
<td>-9.0</td>
</tr>
<tr>
<td>VII</td>
<td>AE</td>
<td>19</td>
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<td>-32.3b</td>
</tr>
<tr>
<td>VIII</td>
<td>CEμ</td>
<td>18</td>
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<td>—</td>
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<tr>
<td>IX</td>
<td>AEμ</td>
<td>18</td>
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<td>-21.4</td>
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</table>

* A=additive genetic factors; C=common environmental factors; E=individual-specific environmental factors; μ=assortative mating; w1=vertical cultural transmission from father; w1m=vertical cultural transmission from mother; r=correlation between additive genetic effects in parental and twin generations.

bBest fit by Akaike's information criterion (38).

APPENDIX 1. Model-Fitting Results

Narrow Definition of Alcoholism

The full or ACEμw1m model (model I) fit the observed twin family data very well ($\chi^2=2.69$, df=15, n.s.; AIC=-27.3) (table 4). Models II, III, and IV set the vertical cultural transmission paths (w1 and w1m) to zero from mothers only, fathers only, and both fathers and mothers, respectively. Each of these fit the data better than model I, as indexed by AIC (-27.4, -27.5, and -29.1, respectively). In model V the assortative mating parameter μ was set to zero, with a further resulting improvement in AIC (-30.6). In models VI and VII additive genetic effects and common environment were respectively set to zero. Model VI failed badly ($\chi^2=29.03$, df=19, AIC=-9.0), while model VII fit well, with the AIC improving over that obtained with model V (AIC=-32.3). Models VIII and IX are not considered here but are used for multiple threshold model, which produced substantial evidence for assortative mating. Model X is almost equivalent to model V except that we relaxed the assumption that the correlation between the genetic effects in parents and children (r) is unity. The addition of this extra parameter did not result in an improvement in the AIC (-29.5). Finally, in model XI we set C to zero from model X, and this resulted in a total fit that was still inferior to model VII (AIC=-31.5). In summary, the best-fitting model for narrowly defined alcoholism is model VII—the very simple AE model that postulates that the sources of variance in liability to alcoholism are simply additive genetic effects and individual-specific environment.

Multiple Threshold Model of Alcoholism

The full model fit the multiple threshold data well ($\chi^2=10.21$, df=15, n.s.) (table 4). There was no evidence for vertical cultural transmission, since both the w paths could be set to zero with an improvement in the AIC (models II, III, and IV). However, there was strong evidence for assortative mating, since setting the path μ to zero (model V) resulted in a substantial deterioration in fit of the model. Working from model IV (ACEμ), it was not possible to set either C or A to zero without a deterioration in the AIC (models VIII and IX, respectively). Allowing the correlation in additive genetic effects across generations to differ from zero (model XII) did not result in an improvement in the fit of model V. However, when this was added to model IX (AEμ), a large improvement was seen that produced the single best-fitting model (model XIII—AEμ; AIC=-23.2).

Further Model Fitting

We report here briefly further model fitting efforts applied to the narrow and multiple threshold definitions of alcoholism. First, models that contained dominance genetic effects were fitted, but none of these improved upon the fit of the models obtained previously. Second, we fit models that relaxed the assumption that the vertical cultural transmission parameter (w1) was equal from fathers and from mothers. The fit of these models was inferior to that of the best models previously obtained. Third, a model that relaxed the assumption that genetic factors were correlated perfectly in daughters and their father was fitted to the data. As noted earlier, such a model should detect evidence for gender-specific genetic factors influencing the liability to alcoholism. In no case did the fit of such a model improve upon those previously obtained. Finally, we obtained a more rigorous test for the presence of genetic effects on the liability to alcoholism by setting A to zero in the full model. This ACEμw1m model encapsulated the hypothesis that the familial resemblance for the liability to alcoholism could be explained by common twin environment, vertical cultural transmission, and assortative mating. This model (df=16) fit much more poorly than the full model for both the narrow ($\chi^2=9.69$, AIC=-22.31) and threshold ($\chi^2=16.22$, AIC=-15.78) definitions of alcoholism. For these definitions of alcoholism, the CEμw1m “environmental” model could also be strongly rejected against the full model by the chi-square difference test (all df=1); narrow: $\chi^2=7.01$, p=0.008 and threshold: $\chi^2=6.01$, p=0.01.