FAMILIAL RESEMBLANCE OF ALCOHOL CONSUMPTION LEVELS IN JEWISH FAMILIES

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Abstract — The role of genetic and environmental factors determining the variability in alcohol consumption levels was investigated in 68 families ascertained through heroin-dependent Jewish male probands. Sibling correlations for peak weekly alcohol consumption ranged from 0.22 to 0.32, with limited changes on adjustment for sex, age and environmental variables. The parent-child correlations were relatively low. Segregation analysis indicated that a major effect of a non-transmitted environmental factor explained the mixture of distributions. There was no evidence for a polygenic effect on alcohol consumption in the families. When segregation models were fitted to sex, age and environment-adjusted alcohol levels, the mixed environment model was rejected, whereas the mixed genetic model was not. These findings are consistent with two previously published segregation analyses of alcohol dependence, and further highlight the heterogeneous aetiology and transmission of alcohol consumption and alcohol dependence.

INTRODUCTION

Quantification of the familial, and thus possibly genetic, nature of alcohol dependence began to appear at the turn of the current century (Crothers, 1909). A strong familial aggregation of alcohol dependence has since been confirmed by a multitude of family studies (see reviews by Cotton, 1979; Croughan, 1985; Merikangas, 1990). Such studies have revealed up to a sevenfold increased risk of alcohol dependence among first-degree relatives of alcohol-dependent individuals. Consistent evidence for a genetic contribution to the risk of alcohol dependence has been provided, with few exceptions, from twin studies (for review see Lumeng and Crabb, 1994) and adoption studies (Goodwin et al., 1973; Cloninger et al., 1981; Cadoret et al., 1986). Another technique to delineate the possible involvement of genetic influences on a given trait (e.g. alcohol dependence) is complex segregation analysis. This approach involves the statistical modeling of family data to determine the mode of inheritance of the trait being investigated. Results of two such complex segregation analyses of alcohol dependence suggest that the mode of transmission of the liability to alcohol dependence is heterogeneous. In a sample of 195 families ascertained through a male or female alcohol-dependent proband who had participated in the St Louis Family Interview Study of Alcoholism, a mixed genetic model representing a dominant major locus as well as additional multi-factorial effects (polygenic and/or shared environmental) best fit the data (Gilligan et al., 1987). In a separate analysis of the 140 families ascertained through male probands, a mixed model including a major gene was the preferred model, whereas among female-proband families a multi-factorial model provided the best description. Application of segregation analysis to 35 multi-generational families ascertained through pairs of male alcohol-dependent probands revealed that liability to alcohol dependence was best described by models representing a major non-Mendelian effect with or without an additional multi-factorial component (Aston and Hill, 1990; Yuan et al., 1996). No inter-generational heterogeneity in the multifactorial component was indicated.

Genetic influences on drinking patterns have also been shown in several twin studies in the US (Pickens et al., 1991; Kendler et al., 1994; Prescott et al., 1994; Reed et al., 1994), Europe (Clifford et
Table 1. Selected characteristics of the interviewed first-degree biological relatives of 68 probands from Jerusalem and Beer Sheva, Israel

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Fathers n = 16</th>
<th>Mothers n = 41</th>
<th>Brothers n = 61</th>
<th>Sisters n = 100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (SD) (years)</td>
<td>66.3 (8.6)</td>
<td>60.7 (7.8)</td>
<td>36.3 (10.9)</td>
<td>34.4 (8.2)</td>
</tr>
<tr>
<td>Mean years of education (SD)</td>
<td>3.4 (4.0)</td>
<td>3.9 (4.4)</td>
<td>9.7 (2.9)</td>
<td>10.6 (2.6)</td>
</tr>
<tr>
<td>Religious observance (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Orthodox</td>
<td>56.2</td>
<td>31.7</td>
<td>11.5</td>
<td>13.0</td>
</tr>
<tr>
<td>Secular/traditional</td>
<td>43.8</td>
<td>68.3</td>
<td>88.5</td>
<td>87.0</td>
</tr>
<tr>
<td>Alcohol abstainer (%)</td>
<td>25.0</td>
<td>65.9</td>
<td>6.6</td>
<td>63.0</td>
</tr>
<tr>
<td>Daily drinker (%)</td>
<td>43.8</td>
<td>0</td>
<td>34.4</td>
<td>4.0</td>
</tr>
<tr>
<td>Peak weekly alcohol intake (ml)</td>
<td>307.2</td>
<td>66.5</td>
<td>653.7</td>
<td>106.0</td>
</tr>
<tr>
<td>(SD)</td>
<td>(560.2)</td>
<td>(412.6)</td>
<td>(1477.8)</td>
<td>(642.9)</td>
</tr>
<tr>
<td>Illicit drug use (ever) (%)</td>
<td>12.5</td>
<td>0</td>
<td>26.2</td>
<td>9.0</td>
</tr>
</tbody>
</table>

Total n = 218.

al., 1984; Kaprio et al., 1991; Carmelli et al., 1993), and Australia (Heath et al., 1991). These investigations have revealed heritability estimates of about 30% to 60% for quantity and frequency of alcohol consumption, with shared environment accounting for 0% to 60% of the variance in these outcome measures. Estimates of parent–offspring and sibling correlation of alcohol consumption ranged from 0.18–0.35 (Clifford et al., 1984; Tambs and Vaglum, 1990; Koopmans and Boomsma, 1996).

In the present investigation, complex segregation analysis was employed in order to evaluate the role of genetic and environmental factors in the determination of variability of alcohol consumption levels in Jewish families. Evidence for the presence of a predisposing major gene, polygenes, and/or environmental factors was sought.

MATERIALS AND METHODS

Recruitment of study population

Probands. The proband group comprised 68 unrelated Jewish males, aged 25–64 years, actively enrolled at the time of interview in a heroin-dependence treatment programme in a non-private drug-treatment facility in two cities (Jerusalem and Beer Sheva) in Israel. These probands participated in a larger study on familial and genetic determinants of substance abuse, and represent those for whom at least one first-degree relative was interviewed. To be eligible for inclusion in the parent study, they must have been regularly using heroin and/or other opiates for a minimum of 3 years at the time of interview, and met DSM-III-R criteria for opiate dependence (American Psychiatric Association, 1987).

The average age of the probands was 33.0 years (±SD 5.6) at time of interview, and they had completed 8.5 years (±2.8) of schooling on average. Ninety-four per cent of the group were of non-Ashkenazic origin. Average sibship size was 6.9 (±3.0).

Many of the probands had a history of heavy alcohol consumption, with 73% classified as alcohol-dependent or formerly alcohol-dependent by the Michigan Alcohol Screening Test (MAST; Selzer, 1971). Daily drinking of alcohol during a period of at least 1 year was reported by 55% of this group. On average, members of this group consumed 1140 ± 1417 ml of ethanol each week during the period (at least 1 year) of maximum consumption. Just under half (49%) of the probands reported a past or current history of alcohol problems in at least one first-degree relative.

Family members. A summary description of the 218 parents and siblings who were successfully interviewed is presented in Table 1. There were significant differences between the two generations in terms of level of education and degree of religious observance. Members of the parental generation attained significantly fewer years of schooling overall and were more likely to classify
themselves as orthodox than their offspring. Male siblings were the heaviest drinkers overall (and were the most likely to have used illicit drugs), although fathers were somewhat more likely to have reported daily drinking. Mothers and sisters of the probands were equally likely to abstain from alcohol.

**Interview schedule**

Details of the interview schedule have been described elsewhere (Neumark et al., 1998). Briefly, all participants were interviewed using an identical structured questionnaire. Information was collected on socio-demographic characteristics including sex, age, marital status, educational experience, degree of religious observance, and parents' ethnic background. Ethnic background was defined as being of either European descent (Ashkenazic) or of non-European descent (non-Ashkenazic) (Mourant et al., 1978). Detailed information regarding present and past alcohol consumption patterns was also collected. This report addresses peak consumption levels, as many of the probands had reduced their alcohol consumption levels considerably upon initiation of regular heroin use. The MAST (Selzer, 1971) was administered to all participants who reported having ever consumed alcohol. The reliability and validity of this instrument in detecting alcohol dependence have been repeatedly demonstrated (e.g. Ross et al., 1990; Watson et al., 1995). A modified version of the Family Environment Scale (FES) was employed to assess relationship, personal growth, and system maintenance dimensions within the family, which may impact on the patterns of alcohol consumption by family members (Moos and Moos, 1981; Baider and De-Nour, 1984). Modifications to the FES were made in order to enhance its applicability to the study population. The moral-religious scale was excluded given its limited degree of relevance to the Jewish population of Israel. Each of the remaining scales was shortened, retaining those items found to be the most relevant and least ambiguous following face validity assessment and a series of pilot tests.

Pedigree information was requested from each proband (under assured conditions of anonymity regarding the source of the information) in accordance with developed techniques (Thompson et al., 1979; Weissman et al., 1986). This information, reported for all first-degree relatives, included relationship with the proband, sex, age or age at death, and current (or last known) whereabouts. Presence of a current or past alcohol and/or drug problem was also reported by the proband for each family member without the application of formal diagnostic criteria (Sher and Descutner, 1986). Age of onset of an alcohol or drug problem was not ascertained from the proband. Refusal to provide any or all of this information did not constitute disqualification from the study, although only one participant refused to provide the information. The probands were also asked which of the relatives could be contacted by the study staff for participation in the study, again upon assurance that they would not be revealed as the source of information. If permission from the proband was refused, the relative was not contacted.

Probands were interviewed at the treatment facility in which they were enrolled, and family members were interviewed at a location of their preference, usually in their homes. Interviews were conducted in the absence of any other persons after stressing to the respondent the anonymous nature of all reported information. Written informed consent was obtained from all subjects prior to the interview. Interviews were conducted between January 1992 and July 1994.

**Statistical methods**

**Adjustment.** Levels of alcohol consumption were first adjusted for the effects of sex and age through stepwise multiple regression. Phenotype levels were modelled as a function of sex, age, age$^2$, age$^3$, sex $\times$ age, sex $\times$ age$^2$, and sex $\times$ age$^3$. In addition to sex and age, we considered the effects of level of education (defined as number of years of formal schooling), degree of religious observance (orthodox vs non-orthodox), ethnic background (Ashkenazic vs non-Ashkenazic), marital status (married vs not married) and home environment variables (based on the FES). Only significant terms were retained. The appropriate estimated partial regression coefficients were used to adjust the dependent variable for each individual, and the adjusted values were further standardized to mean zero and variance of unity.

**Familial correlation.** The degree of resemblance among family members was expressed by interclass and intraclass correlation coefficients.
Because of the varying sibship size, we used an equal family weight as defined by Karlin et al. (1981), which reduces the effect of large families on the familial correlations. Interclass and intraclass correlations were estimated using the inverse of the cumulative normal function transformation of alcohol levels which reduced the skewness and kurtosis and the impact of outliers on the correlation analysis (Elston et al., 1978). Hypothesis testing of inter- and intra-class correlations was performed using the Fisher (1954) z-transformation. The 'effective sibship size' was computed in order to estimate the appropriate degrees of freedom associated with each family (Rosner and Donner, 1979; Namboodiri et al., 1983).

Segregation analysis. The mixed model of segregation analysis (Elston and Stewart, 1971; Lalouel et al., 1983) using the unified mixed model implemented in the computer program PAP (Hasstedt and Cartwright, 1981) was used to test a specific series of models which represent combinations of genetic and environmental factors which may influence the observed distribution of the quantitative trait (alcohol consumption). The basic model postulates that the observed phenotype can be expressed as the sum of the following components: a single genetic or non-transmitted environmental factor with a major effect on alcohol consumption levels, small additive allelic effects of a large number of independent polygenic loci, and a random non-transmissible effect. The polygenic effect and the random environment effect are assumed to be normally distributed. The major effect was modelled as having two alternative factors: L (low) and H (high) that may be of either genetic or non-transmitted environmental origin. These combine to define three classes (ousiotypes) of individuals denoted as LL, LH, and HH (Cannings et al., 1987). The model involves estimating the following parameters: \( p \) which represents the relative frequency of factor L, where the relative frequency of H (denoted by \( q \)) is equal to \( 1 - p \). The relative frequency of LL, LH, and HH individuals is \( p^2 \), \( 2pq \), and \( q^2 \) respectively, and these frequencies are maintained across generations in large and stable populations (Hardy, 1908). Other parameters of the model include \( \mu_{LL} \), \( \mu_{LH} \), and \( \mu_{HH} \) as the alcohol phenotypic means of each class and the phenotypic variance (\( \sigma^2 \)) among individuals within the same class. It is assumed that this variance is the same for all three classes. The fraction of variance among individuals within the same class which is attributable to polygenes is represented by the parameter \( h^2 \). In addition, the three transmission probabilities that persons of the three classes will transmit factor L to their offspring are included in the model as \( \tau_1 \), \( \tau_2 \), and \( \tau_3 \) (Lalouel et al., 1983). Under a Mendelian hypothesis in which classes are genotypes, these probabilities take on the values of 1, 0.5, and 0 respectively. The non-transmitted environmental factor, on the other hand, predicts that the probability of an individual being in one class or another is independent of both the person's generation and parental class. Under this model, each of the transmission probabilities is taken to be equal to the relative frequency of L, which is \( p \). The parameter estimation and tests of competing hypotheses are performed by maximizing the likelihood of the data under a general model and under several subhypotheses specified by imposing certain constraints on different parameters within the general model. Tests of hypotheses are carried out using the likelihood ratio test. The test criterion is expressed as minus the difference between twice the log-likelihoods under two models being compared (asymptotically distributed as \( \chi^2 \)), with degrees of freedom equal to the number of parameters restricted by the null hypothesis in the reduced model. We corrected for ascertainment by calculating the likelihood of the pedigrees conditional on the phenotypes of the probands (Cannings and Thompson, 1977; Young et al., 1988).

RESULTS

Correlation of alcohol consumption

Familial correlation of transformed peak weekly alcohol consumption levels was determined, based on unadjusted values, age- and sex-adjusted values, and upon adjustment for age, sex and those environmental factors which were found to be significantly associated with this behaviour (Table 2). From the upper half of the table (including probands), consistent statistically significant correlations of moderate strength between siblings in terms of their alcohol intake are evident across adjustment techniques, whereas no significant parent–offspring correlation was noted for
Table 2. Familial correlation of transformed peak weekly alcohol consumption in 68 families, with the proband included or excluded

<table>
<thead>
<tr>
<th>Correlation</th>
<th>Parental</th>
<th>Sibling</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r</td>
<td>95% CI</td>
</tr>
<tr>
<td>Including probands</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>0.017</td>
<td>(−0.12−0.15)</td>
</tr>
<tr>
<td>Age- and sex-adjusted</td>
<td>−0.052</td>
<td>(−0.18−0.08)</td>
</tr>
<tr>
<td>Age-, sex- and environment b-adjusted</td>
<td>−0.032</td>
<td>(−0.20−0.14)</td>
</tr>
<tr>
<td>Excluding probands</td>
<td>−0.031</td>
<td>(−0.19−0.13)</td>
</tr>
<tr>
<td>Age- and sex-adjusted</td>
<td>0.009</td>
<td>(−0.15−0.17)</td>
</tr>
<tr>
<td>Age-, sex- and environment b-adjusted</td>
<td>0.178</td>
<td>(−0.03−0.37)</td>
</tr>
</tbody>
</table>

*a95% confidence interval; benvironmental variables include marital status, and Family Environment Scale conflict and organization dimensions.

unadjusted or adjusted values.

To determine the effect of inclusion of the probands (many of whom reported extreme weekly alcohol intake values) in these pedigrees, the analyses were rerun upon omission of the probands. The results are presented in the lower half of Table 2. As expected, sibling correlations were strengthened slightly upon exclusion of the probands, whereas parent–offspring correlations, though strengthened upon adjustment for environmental factors, did not attain statistical significance.

**Segregation analysis**

Results of the complex segregation analysis of age- and sex-adjusted peak weekly alcohol consumption are presented in Table 3. Model 1 represents a general model with a weak polygenic effect ($h^2 = 0.04$) together with a major effect ($q = 0.2$). The estimated means of the three classes presented in Model 1 suggest that presence of this factor in a ‘homozygous’ form (i.e. complete exposure to this effect) increases alcohol intake ($\mu = 1.65$), while non-exposure to this effect is associated with a lower mean intake ($\mu = 0.217$). ‘Heterozygous’ exposure, however, seems to be associated with the lowest mean alcohol intake ($\mu = -0.982$). The estimated transmission probabilities ($\tau_1 = 0.731$, $\tau_2 = 0.920$, and $\tau_3 = 0.999$) do not seem to conform with a Mendelian transmission model ($\tau_1 = 1.0$, and $\tau_2 = 0.5$, and $\tau_3 = 0$), suggesting that this major effect is not genetic in nature. This is confirmed upon comparison with Model 2 (which assumes the presence of a major environmental effect by fixing the transmission probabilities to equal the frequency of the major effect) which is not rejected ($\chi^2 = 4.4$, 3 d.f., $P = 0.221$), and upon comparison with the mixed genetic model (Model 4) which is rejected. Model 5 (a dominant gene effect), and Model 6 (a recessive gene effect) are also rejected when compared to the general model. A major environmental effect with a bimodal distribution (Model 3) is similarly rejected. The polygenic component is minimal as is evidenced by the non-rejection of Model 7 (which includes a major environmental effect only), when compared to Model 1 ($\chi^2 = 5.2$, 4 d.f., $P = 0.267$) and to Model 2 ($\chi^2 = 0.8$, 1 d.f., $P = 0.371$), and rejection of the polygene only model (Model 8). Model 9, the sporadic model which assumes no familial resemblance, is found to have the poorest fit of the models tested in this hierarchical series of comparisons.

The FES portion of the interview was not completed for 25 family members. When segregation analysis of age- and sex-adjusted phenotype values was rerun only on those individuals for whom full environmental data were available (i.e. including the FES questionnaire), estimated parameters of the general, major environment, and major gene models, were very similar to those presented above for the total population of interviewed relatives. The mixed model incorporating a major gene effect was again rejected when compared to the general model, while the mixed environmental model was not rejected when compared to the less restricted general model.
Table 3. Complex segregation analysis of peak weekly alcohol intake (age- and sex-adjusted) in 68 families

<table>
<thead>
<tr>
<th>Transmission</th>
<th>1 General model</th>
<th>2 Major environment (two distributions)</th>
<th>3 Mixed co-dominant</th>
<th>4 Mixed dominant</th>
<th>5 Mixed recessive</th>
<th>6 Major environment</th>
<th>7 Polygene</th>
<th>8 Sporadic</th>
</tr>
</thead>
<tbody>
<tr>
<td>$q$</td>
<td>0.191</td>
<td>0.160</td>
<td>0.177</td>
<td>0.114</td>
<td>0.000</td>
<td>0.119</td>
<td>0.169</td>
<td>—</td>
</tr>
<tr>
<td>$\mu_{LL}$</td>
<td>0.217</td>
<td>0.254</td>
<td>0.015</td>
<td>0.147</td>
<td>0.041</td>
<td>0.027</td>
<td>0.245</td>
<td>0.067</td>
</tr>
<tr>
<td>$\mu_{LH}$</td>
<td>-0.982</td>
<td>-0.948</td>
<td>0.015</td>
<td>-0.376</td>
<td>2.502</td>
<td>0.027</td>
<td>-0.967</td>
<td>—</td>
</tr>
<tr>
<td>$\mu_{HH}$</td>
<td>1.655</td>
<td>1.939</td>
<td>2.036</td>
<td>2.560</td>
<td>2.502</td>
<td>2.598</td>
<td>1.855</td>
<td>—</td>
</tr>
<tr>
<td>$\sigma^2$</td>
<td>0.380</td>
<td>0.434</td>
<td>0.696</td>
<td>0.687</td>
<td>0.754</td>
<td>0.725</td>
<td>0.414</td>
<td>0.780</td>
</tr>
<tr>
<td>$\tau_1$</td>
<td>0.731</td>
<td>(q)</td>
<td>(q)</td>
<td>(1.0)</td>
<td>(1.0)</td>
<td>(1.0)</td>
<td>(q)</td>
<td>—</td>
</tr>
<tr>
<td>$\tau_2$</td>
<td>0.920</td>
<td>(q)</td>
<td>(q)</td>
<td>(0.5)</td>
<td>(0.5)</td>
<td>(0.5)</td>
<td>(q)</td>
<td>—</td>
</tr>
<tr>
<td>$\tau_3$</td>
<td>0.999</td>
<td>(q)</td>
<td>(q)</td>
<td>(0.0)</td>
<td>(0.0)</td>
<td>(0.0)</td>
<td>(q)</td>
<td>—</td>
</tr>
<tr>
<td>$-2 \log L$</td>
<td>508.10</td>
<td>512.47</td>
<td>523.69</td>
<td>523.79</td>
<td>535.99</td>
<td>524.34</td>
<td>513.28</td>
<td>533.49</td>
</tr>
</tbody>
</table>

Note: parameters in parentheses are fixed in the model. *$P < 0.01$; **$P < 0.001$. 
Table 4. Complex segregation analysis of age-, sex- and environment-adjusted peak weekly alcohol intake in 68 families of opiate-addicted probands

<table>
<thead>
<tr>
<th>Transmission</th>
<th>1 General model</th>
<th>2 Major environment</th>
<th>3 Mixed co-dominant</th>
<th>4 Mixed dominant</th>
<th>5 Mixed recessive</th>
<th>6 Polygene</th>
<th>7 Sporadic</th>
</tr>
</thead>
<tbody>
<tr>
<td>q</td>
<td>0.046</td>
<td>0.164</td>
<td>0.065</td>
<td>0.001</td>
<td>0.119</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>μHL</td>
<td>0.141</td>
<td>0.249</td>
<td>0.154</td>
<td>-0.016</td>
<td>-0.018</td>
<td>0.022</td>
<td>0.010</td>
</tr>
<tr>
<td>μHH</td>
<td>-0.941</td>
<td>-0.828</td>
<td>-1.045</td>
<td>1.896</td>
<td>-0.018</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>σ2</td>
<td>2.657</td>
<td>2.165</td>
<td>2.550</td>
<td>1.896</td>
<td>2.485</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>t1</td>
<td>0.761</td>
<td>0.649</td>
<td>0.731</td>
<td>0.846</td>
<td>0.835</td>
<td>0.881</td>
<td>0.883</td>
</tr>
<tr>
<td>h2</td>
<td>0.000</td>
<td>0.040</td>
<td>0.000</td>
<td>0.203</td>
<td>0.199</td>
<td>0.229</td>
<td>—</td>
</tr>
<tr>
<td>t2</td>
<td>0.099</td>
<td>(q)</td>
<td>(1.0)</td>
<td>(1.0)</td>
<td>(1.0)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>t3</td>
<td>0.169</td>
<td>(q)</td>
<td>(0.5)</td>
<td>(0.5)</td>
<td>(0.5)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>-2 log L</td>
<td>515.85</td>
<td>525.55</td>
<td>519.25</td>
<td>530.63</td>
<td>526.39</td>
<td>529.78</td>
<td>536.10</td>
</tr>
<tr>
<td>χ² from Model 1</td>
<td>9 **</td>
<td>3.4</td>
<td>14.8**</td>
<td>10.5*</td>
<td>13.9*</td>
<td>20.3**</td>
<td>—</td>
</tr>
<tr>
<td>d.f. from Model 1</td>
<td>3</td>
<td>3</td>
<td>4</td>
<td>4</td>
<td>6</td>
<td>7</td>
<td>—</td>
</tr>
</tbody>
</table>

Note: parameters in parentheses are fixed in the model; *P < 0.05; **P < 0.01

\( χ^2 = 7.3, 3 \text{ d.f., } P = 0.063 \).

The similarity of findings between the models run on the population of relatives including and excluding the 25 family members for whom FES data were missing allows for the parameter estimation for environment- (and age- and sex-) adjusted peak weekly intake. As seen in Table 4, upon controlling for associated environmental factors, the transmission probabilities of the major effect (Model 1) now more closely resembled a Mendelian transmission of a major effect. The \( h^2 \) parameter converged to zero, suggesting complete absence of a polygenic effect. The hypothesis of no transmission of the major effect (major environmental model — Model 2) was rejected, whereas Model 3 (representing a co-dominant major genetic effect) was not \( (χ^2 = 3.4, 3 \text{ d.f., } P = 0.334) \). As in Model 1, the polygenic effect in Model 3 was estimated to be zero. While Model 4, representing a dominant genetic effect, was clearly rejected when compared to Model 1, the mixed recessive model (Model 5) was less clearly rejected \( (χ^2 = 10.5, 4 \text{ d.f., } P = 0.032) \). Once again, the polygenic effect only model (Model 6) and the sporadic model (Model 7) were rejected.

**DISCUSSION**

The present study set out to assess the relative contribution of environmental and genetic factors on peak lifetime alcohol consumption levels in families ascertained through a group of opiate-dependent Jewish males, nearly 75% of whom had a history of alcohol dependence.

The presence of sibling correlation and absence of any significant parent–offspring correlation suggests a limited role for genetic influences on alcohol consumption levels within these families, and provides support for environmental factors which are not shared across generations. In the present study, pedigrees were ascertained through probands with extreme outcome (alcohol consumption) values. Since the outcome variable is associated with the pedigree selection variable (drug dependence), inclusion of the probands would tend to reduce the strength of familial correlations (Bucher and Schrott, 1982). Exclusion of the probands from this analysis indeed reveals stronger coefficients for sibling correlations of alcohol consumption levels.

The results of the segregation analysis of the age- and sex-adjusted values of peak lifetime alcohol consumption levels confirm the existence of a major environmental influence and the absence of a major gene effect. Upon adjustment for environmental factors, however, the presence of a major gene was not rejected, whereas the environmental effect model was. Rejection of the model which suggests that this genetic effect is a recessive one was not clear-cut and may be a function of the limited sample size. These results
suggest the possible presence of genetic underpinnings in alcohol consumption patterns which are masked by more dominant environmental influences.

Regarding the nature of the study population, the high proportion of opiate-dependent probands, who, earlier in their drug-taking careers, had been heavy consumers of alcohol, is not uncommon. Abuse of alcohol among individuals who abuse opiates and other drugs is indeed a widely recognized phenomenon, with between 35% and 77% of treatment-enrolled drug abusers also meeting criteria for a lifetime diagnosis of alcoholism or alcohol dependence (Rounsaville et al., 1982, 1991; Miller et al., 1989; Mirin et al., 1991). This sample of probands is representative, with regards to socio-demographic characteristics and drug-taking behaviours, of treatment-attending heroin-dependent males in Israel (Shufman et al., 1990; Maayan et al., 1994).

Treatment-ascertained populations may, however, constitute the more severely affected, and if severity of substance abuse is associated with the familial prevalence of the disorder, the selected families may not be representative of all affected families. The proband’s decision to seek treatment may itself be determined in part by the number or proportion of family members who are similarly affected. No systematic information exists on the number or nature of the population in the country not being treated.

The 218 first-degree relatives interviewed comprised some 40% of living first-degree relatives. Incomplete ascertainment of relatives was due in part to their geographical inaccessibility (e.g. living abroad), refusal to be interviewed, or our abiding by the proband’s request not to approach certain relatives. The response issue that we observe differs from the ascertainment bias that arises from sampling of affected probands. Even when families are ascertained through randomly identified probands, it is often difficult to ensure that recruitment of other family members into the study will be random. Affected relatives may be more (or less) likely to participate in our study than unaffected relatives, either by their own choice or because they were more forcefully recruited. Yet, a recent simulation study has shown that the ability to detect major genes is not markedly affected by even a fairly drastic response bias (Mitchell et al., 1995).

Notwithstanding these limitations, results of the present study reflect the likely heterogeneous aetiology and transmission of the trait being investigated, and are consistent with results of segregation analyses which addressed familial alcohol dependence (Gilligan et al., 1987; Aston and Hill, 1990). In the face of such heterogeneity, considerably larger samples of pedigrees would be needed in order to elucidate more definitively the different modes of transmission (Reich et al., 1981).

Predisposition to alcohol drinking and vulnerability to established and maintained drinking patterns are likely to be a function of the interaction of multiple familial, social, psychological as well as inherited biogenetic factors (Rutter, 1994; Schuckit, 1994). One such inherited factor may be genotypic differences at the alcohol dehydrogenase locus (ADH2), which has recently been reported to be associated with alcohol consumption patterns among our group of probands (Neumark et al., 1998). Specifically, the presence of the ADH2*2 allele seems to inhibit alcohol drinking and thus serve to lower the risk of alcohol dependence. Clearly, additional studies involving family and molecular genetic analyses are needed for further elucidation of processes that regulate alcohol consumption levels in Jewish and other families.

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