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## Heritability of MMPI-2 scales in the UCSF Family Alcoholism Study

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### Abstract

The present study evaluated the heritability of personality traits and psychopathology symptoms assessed by the Minnesota Multiphasic Personality Interview 2<sup>nd</sup> edition (MMPI-2) in a family-based sample selected for alcohol dependence. Participants included 950 probands and 1204 first-degree relatives recruited for the UCSF Family Alcoholism Study. Heritability estimates ( $h^2$ ) for MMPI-2 scales ranged from .25–.49. When alcohol dependence was used as a covariate, heritability estimates remained significant but generally declined. However, when the MMPI-2 scales were used as covariates to estimate the heritability of alcohol dependence, scales measuring antisocial behavior (ASP), depressive symptoms (DEP), and addictive behavior (MAC-R) led to moderate increases in the heritability of alcohol dependence. This suggests that the ASP, DEP, and MAC-R scales may explain some of the non-genetic variance in the alcohol dependence diagnosis in this population when utilized as covariates, and thus may serve to produce a more homogeneous and heritable alcohol dependence phenotype.

### Keywords

alcohol-related disorders; behavioral genetics; heredity; personality; comorbidity

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The Minnesota Multiphasic Personality Inventory-2 (MMPI-2) <sup>1</sup> is one of the most commonly used measures of psychopathology and personality. It consists of 9 basic scales that assess a broad range of behavior: Hs (Hypochondriasis - a measure of neurotic thought regarding bodily functions), D (Depression), Hy (Hysteria - a measure of somatization), Pd (Psychopathic Deviate), Pa (Paranoia), Pt (Psychasthenia - a measure of phobias and obsessive-compulsive attitudes), Sc (Schizophrenia), Ma (Hypomania), and Si (Social Introversion). In addition, a number of supplementary scales have been developed specifically to assess psychiatric symptoms of broad diagnostic categories such as mood and anxiety disorders, thought disorders, and substance abuse and dependence.

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While several studies have evaluated the heritability of personality measures such as the California Personality Inventory <sup>2;3</sup>, Eysenck Personality Questionnaire <sup>4;5</sup> and the Tridimensional Personality Questionnaire <sup>6;7</sup>, only a limited number of studies have examined the heritability of the MMPI-2 scales. Many of these studies have primarily focused on specific scales of the MMPI such as the psychopathic deviate scale <sup>8;9</sup> or examined alternative scales derived from principal components or factor analysis <sup>10;11</sup>. Thus, few studies have examined the heritability of each of the basic scales that comprise the MMPI. The earliest studies to do so used relatively small samples, and reported limited evidence of genetic influences contributing those scales examined <sup>12-16</sup>. A more recent study using a larger sample reported that genetic influences accounted for 31–57% of the variation on the MMPI-2 clinical scales with a mean value of 48% <sup>17</sup>, providing strong evidence that the MMPI-2 yields heritable measures of psychopathology and personality.

Though these results suggest scales from the MMPI-2 are heritable, these findings need to be confirmed in independent samples. Further, as molecular geneticists continue to search for genetic loci that contribute to psychiatric disorders, there is a growing consensus that understanding patterns of co-occurring personality features and/or dimensional measures of psychopathology may aid in defining more genetically homogeneous subgroups within the diagnostic category <sup>18;19</sup>. Molecular genetic studies of addiction and alcohol dependence in particular represent an important area of research <sup>20-22</sup> that has begun to utilize this approach based on a rich literature that has sought to derive alcoholic subtypes based on the clustering of personality traits <sup>reviewed in 23</sup>.

Alcohol dependence is a common, debilitating condition with lifetime prevalence rate estimates ranging from 12.5% to 13.2% <sup>24;25</sup>. It is associated with increased rates of over 60 medical conditions <sup>26</sup>, and thus, considerable resources have been dedicated to furthering our understanding of its etiology. The heritability of alcohol dependence has been suggested by numerous family, twin, and adoption studies <sup>27-29</sup> as well as by linkage analysis e.g., <sup>30;31;32</sup>. For example, a region on chromosome 4q containing the alcohol dehydrogenase (ADH) gene cluster has been linked to alcohol dependence in multiple studies <sup>31-33</sup> as has a region of chromosome 4p containing a GABAA receptor subunit gene cluster <sup>32;34;35</sup>. Notably, both gene clusters have also yielded significant evidence of association to alcohol dependence <sup>36;37</sup>. Reported associations with candidate genes such as OPRM1 <sup>38;39</sup> and CHRM2 <sup>40;41</sup> have furthered our understanding of the genetic influences contributing to alcohol dependence, and this progress has been summarized in several recent reviews <sup>42;43</sup>. Nonetheless, these reviews also note the tentative nature of these relations as there have been failures to replicate the evidence for linkage and association to each of these regions and candidate genes. In response, researchers have tried to identify phenotypes for alcohol use disorders that may represent more genetically homogeneous and heritable traits <sup>20;44;45</sup>. Thus, researchers have explored alcohol craving <sup>46</sup>, externalizing behavior <sup>47</sup>, temperament <sup>48</sup>, and electrophysiological data <sup>49</sup> as potential phenotypes for alcohol dependence.

There is a rich literature exploring the relations between aspects of personality and co-occurring psychopathology and alcohol use suggesting that these variables can be used to reduce the diagnostic heterogeneity within alcohol use disorders <sup>50;51</sup>. Building on this research, molecular geneticists have suggested that measurable aspects of personality might be used to identify refined phenotypes for understanding the genetic influences that contribute to alcohol use disorders <sup>52;53</sup>. The most prominent example of this approach has described two alcoholic subtypes with one group characterized by increased anxiety and mood symptoms and the second characterized by low-impulse control, and increased aggression and antisocial behavior <sup>20;44;54</sup>. Empirical support for these subtypes comes from studies suggesting that alcoholics with an Antisocial Personality Disorder (ASPD) diagnosis exhibit a severe form of alcoholism with higher average daily consumption of alcohol, more arrests and more personal

consequences of drinking<sup>55-61</sup> and additional studies describing high rates of co-occurrence of alcohol dependence and a range of mood and anxiety disorders<sup>62,63</sup> as well as personality disorders<sup>59,64-67</sup>.

Of direct relevance to genetic studies of alcohol use, a shared genetic etiology between aspects of personality and psychopathology and alcohol use disorders has been suggested. More specifically, quantitative genetic studies suggest that there are common genetic influences underlying both alcohol dependence and externalizing behavior, including antisocial behavior<sup>68,69</sup>, as well as common genetic influences underlying both alcoholism and mood and anxiety disorders<sup>70-72</sup>. In addition, similar genetic correlations have been reported between alcohol dependence and normal range personality traits such as neuroticism and impulsivity/lack of behavioral constraint<sup>73-75</sup>. Such findings provide support for the use of personality and psychopathology measures to help refine alcohol dependence phenotypes.

The purpose of the present study was twofold. The first aim was to estimate the heritability ( $h^2$ ) of the basic scales of the MMPI-2, and select supplemental scales, from familial correlations in a community sample of alcohol dependent subjects and their first degree relatives (The San Francisco Family Study of Alcoholism). It should be noted that this approach can lead to positively biased heritability estimates due to the potential conflation of shared environment and additive genetic influences. Nonetheless, earlier studies have reported an absence of shared environmental influences on the MMPI-2 scales<sup>17</sup>, and thus, support the use of this analytic approach to provide valid measurements of the relative contributions of genetic influences on the MMPI-2 scales. The second aim was to further characterize MMPI-2 scale scores in the UCSF sample by comparing MMPI-2 scale scores in this population to a normative sample as well as a previously published sample selected for alcohol and other substance dependence.

## Methods

### Participants

Data for this report were obtained from the UCSF Family Alcoholism Study, a nationwide study on the genetics of alcoholism and other substance dependence. The objectives and design of the UCSF Family Alcoholism Study and methods for recruiting participants have been detailed elsewhere<sup>76,77</sup>. In brief, probands were sampled from the community through semi-targeted direct mail, a web site, press releases, advertisements and from alumni of treatment centers across the nation. Probands were invited to participate if they met screening criteria for alcohol dependence at some point in their lifetime and had at least one sibling or both parents available to participate in the study. With the permission of the proband, relatives were invited by mail to participate.

Probands with serious drug addictions (defined as use of stimulants, cocaine, or opiates daily for more than 3 months or weekly for more than 6 months) and those who reported any history of intravenous substance use were excluded. Probands were excluded if, upon screening, they reported a current or past diagnosis of schizophrenia, bipolar disorder, or other psychiatric illness involving psychotic symptoms (those with depressive and anxiety disorders were accepted); a life-threatening illness; or an inability to speak and read English.

A modified version of the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA)<sup>78</sup>, an interview developed by the Collaborative Studies on Alcoholism (COGA), was administered via telephone and used to make DSM-IV alcohol and other substance misuse diagnoses and to collect demographic, medical, psychiatric, alcohol, nicotine, and other drug-use history. Telephone interviewing has been found to be an effective method, with reliability and validity equivalent to those with face-to-face interviews, and has particularly high

agreement for substance use disorders 79<sup>81</sup>. Sections of the SSAGA that assess current DSM-IV diagnoses other than alcohol and substance misuse diagnoses were not administered due to time constraints. Questionnaires selected to enrich the alcoholism phenotype and for studies related to the role of personality in familial alcoholism were administered. Self-report questionnaires, including the MMPI-2 1 and others 77, were sent to each enrolled participant to complete at home.

### Sample Demographics

2154 individuals were enrolled in the UCSF Family Alcoholism Study (see Table 1 for complete demographics). The sample had a mean age of  $48.8 \pm 13.2$  years, a mean educational level of  $14.4 \pm 2.9$  years, and a mean annual income of  $\$57,356 \pm \$54,656$  (median, \$45,000). Racial distribution was 92% Caucasian, 3% each African American and Hispanic, and 1% each Native American and other. No attempt was made to exclude or over sample minorities. Probands were 58% female. Relatives of probands were 38% alcohol dependent.

### Analysis

Prior to analyzing the data, MMPI-2 scale scores were derived and converted to T-scores using the published norms<sup>1</sup>. T-scores were calculated without K-corrections. Each subject's MMPI-2 profile was then examined to identify subjects with biased test-taking attitudes. Specifically, subjects with an F (Infrequency) score  $> 90$  were classified as over-reporting current symptoms of psychopathology. Subjects with an L (Lie) score  $\geq 80$  or a K (Correction) score  $> 70$  were classified as under-reporting current symptoms of psychopathology. Subjects' MMPI-2 profiles in both groups were designated as invalid and excluded from the present study. Ninety subjects yielded invalid profiles resulting in a sample of 2064.

Scores were generated for each participant on the following clinical scales: Hypochondriasis (Hs), Depression (D), Hysteria (Hy), Psychopathic Deviate (Pd), Paranoia (Pa), Psychasthenia (Pt), Schizophrenia (Sc), Hypomania (Ma), and Social Introversion (Si). Additional content scales were examined: Depression (DEP), Anxiety (ANX), Bizarre Mentation (BIZ), and Antisocial Practices (ASP) as well as the MacAndrew Alcoholism - Revised (MAC-R) scale.

Preliminary analyses were conducted to compare aspects of personality and psychopathology among participants with and without an alcohol dependence diagnosis in the UCSF sample. Because participants were nested within families, generalized estimating equations (GEEs) were used to correct biases in estimated means that may be introduced by correlations between family members. The adjusted means derived by the GEEs were then compared for participants with and without an alcohol dependence diagnosis using independent samples t-tests. Age and gender were used as covariates when appropriate to control for demographic differences.

Primary analyses were then conducted to estimate the heritability of the described MMPI-2 scales obtained in the UCSF Family study using SOLAR<sup>82</sup>. SOLAR estimates heritability by partitioning the trait relative pair covariance into additive genetic and environmental contributions while correcting for any covariates included in the model. Participant's age at the time of evaluation and sex were evaluated as potential covariates and retained if they accounted for at least 5% of the total variance. The total additive genetic heritability ( $h^2$ ) and its standard error were estimated, and the probability that  $h^2$  was greater than zero was determined using a Student's t-test for each scale. Rather than allowing SOLAR to estimate MMPI-2 scale means during the model-fitting procedure using the available sample data, MMPI-2 scale means were constrained to the population mean (i.e.,  $M = 50$ ) to correct for ascertainment bias when estimating  $h^2$ . Heritability estimates were then obtained separately with and without the alcohol dependence diagnosis included as a covariate. In addition, the

heritability of alcohol dependence was estimated independently and then using each of the MMPI-2 scale scores as covariates in turn.

For the heritability analyses, 713 families were considered genetically informative. Families that contained sibling, half-sibling, avuncular or cousin pairs were included as being potentially genetically informative. These families ranged in size from 3 to 20 subjects (average  $4.63 \pm 2.13$ ). The data includes: 563 parent-child, 1085 sibling, 40 half sibling, 17 grandparent-grandchild, 238 avuncular, and 32 cousin relative pairs. It should be noted that attempts to estimate the heritability of the MMPI-2 scales separately in subjects with and without alcohol dependence were made, but these analyses could not be conducted due to the small number of genetically informative families that resulted from stratifying the sample in this manner.

A secondary set of analyses were conducted to further characterize MMPI-2 scale scores in the UCSF sample. The GEE-derived mean adjusted MMPI-2 scores for the full sample, as well as those estimated separately for participants with and without an alcohol dependence diagnosis, were compared to data from the MMPI-2 normative sample<sup>1</sup> and a previously published large-scale sample of subjects undergoing inpatient treatment for a substance use disorder<sup>83</sup> using independent samples t-tests. This allowed for the comparison of MMPI-2 scale scores in the UCSF sample to a general population sample as well as a sample selected for substance abuse problems.

To further characterize the rates of co-occurring psychopathology in the UCSF sample, a cutoff score ( $T \geq 65$ ) was applied to the MMPI-2 DEP, ANX, BIZ, and ASP scales to estimate the proportion of individuals currently experiencing clinically significant symptoms of depression, anxiety, disordered thought, and antisocial personality disorder (ASPD), respectively. These proportions were then qualitatively compared to the prevalence rates of major depression, anxiety disorders, and ASPD that were assessed in a large epidemiological study [NIAAA 2001 – 2002 National Epidemiological Study of Alcohol Related Conditions (NESARC)]. NESARC diagnoses were derived from the Alcohol Use Disorder and Associated Disabilities Interview Schedule-DSM-IV Version (AUDADIS-IV)<sup>84</sup> administered during face-to-face visits by experienced lay interviewers. Because NESARC did not yield reliable estimates of thought disorder diagnoses, two alternative population-based studies were used as a comparison for this symptom domain<sup>85,86</sup>.

## Results

As shown in Table 2, mean MMPI-2 scale scores in the full sample ranged from a low of 49.89 (95% confidence interval (CI) - 49.37–50.41) for the Si scale to a high of 56.99 (95% CI - 56.47–57.50) for the Pd scale. When the sample was restricted to participants diagnosed with alcohol dependence, the values ranged from a low of 50.70 (95% CI - 50.08–51.33) for the Si scale to a high of 61.25 (95% CI - 60.62–61.88) for the Pd scale. Scores for participants without an alcohol dependence diagnosis were more closely centered on the expected value of 50 with the mean scores ranging from a low of 47.19 (95% CI - 46.50–47.88) for the ASP scale to a high of 55.08 (95% CI - 54.28–55.89) for the Hy scale. T-tests showed that the differences between groups were significant such that participants with an AD diagnosis scored higher than participants without an AD diagnosis on each of the MMPI-2 scales examined (Table 2). Nonetheless, the differences between the groups tended to be fairly small with  $R^2$  ranging from 0.00 to 0.07 for most of the scales except the Pd and MAC-R scales ( $R^2 = 0.12$  for both scales).

For the primary analyses, heritability estimates were obtained for the MMPI-2 scales using SOLAR. As shown in Table 3, each of the MMPI-2 basic scales showed evidence of heritability ( $p$ -values  $\leq 0.005$ ). When the alcohol dependence diagnosis was not included as a covariate, the highest heritability estimates among the basic scales were obtained for the Hy, Hs, Sc, and

Pt scales ( $h^2 = 0.49, 0.47, 0.47,$  and  $0.45,$  respectively) and the lowest estimates were obtained for the Pa and Ma scales ( $h^2 = 0.27$  and  $0.25,$  respectively). The remaining MMPI basic scales exhibited heritability estimates of 0.35 or higher. In addition, the supplementary scales examined showed significant evidence of heritability, which ranged from a low of 0.15 for the BIZ scale to a high of 0.50 for the DEP scale. The MAC-R scale exhibited a heritability estimate of 0.33.

When the alcohol dependence diagnosis was included as a covariate, the heritability estimates remained significant ( $p$ -values  $\leq .002$ ), but they tended to decline in magnitude. The heritability estimates for the basic scales ranged between 0.21 and 0.35 with the exception of the Sc ( $h^2 = 0.16$ ) and Pa ( $h^2 = 0.18$ ) scales. The supplementary scales remained relatively unchanged with the exception of the DEP scale, which decreased from 0.50 to 0.29, and the ASP scale which increased from 0.36 to 0.46. To supplement these analyses, the heritability of the alcohol dependence diagnosis was estimated as 0.20 ( $SE = 0.07, p = .002$ ) in the UCSF sample. When each of the MMPI-2 scales was used as a covariate in turn, the heritability of alcohol dependence remained relatively unchanged with three exceptions (Table 3). When the DEP or MAC-R scales were used as covariates, the heritability of the alcohol dependence diagnosis increased 35% from 0.20 to 0.27, and when the ASP scale was used as a covariate, the heritability of the alcohol dependence diagnosis increased 30% from 0.20 to 0.26.

In order to further characterize MMPI-2 scale scores in the UCSF sample, participants' MMPI-2 scale scores were compared to the normative population used in the development of the MMPI-2 ( $N=2600$ )<sup>1</sup>. As shown in Table 4, participants in the UCSF sample diagnosed with alcohol dependence scored significantly higher on each of the scales examined relative to the normative population ( $p$ -values  $<0.001$  for all scales except the Si scale  $p<0.05$ ). The largest elevations were observed for the Pd ( $R^2 = 0.20$ ) and Sc ( $R^2 = 0.12$ ) scales. Among UCSF participants without an alcohol dependence diagnosis the differences from the normative sample, though largely significant, were smaller in magnitude with the Hy scale showing the largest difference with an  $R^2$  of 0.04.

In order to estimate the severity of co-occurring psychopathology among participants diagnosed with alcohol dependence in the UCSF sample, MMPI-2 scales scores were compared to those obtained from a large population of individuals undergoing inpatient treatment for substance use disorders ( $N=1212$ )<sup>83</sup>. These comparisons, as shown in Table 4, suggested that participants in the UCSF sample diagnosed with alcohol dependence scored significantly lower on most of the scales examined than participants from the inpatient sample. An examination of the effect sizes associated with these comparisons suggested that the largest differences were on the D, Pt, Ma basic scales and the ANX, DEP, and MAC-R supplementary scales with  $R^2$  values ranging from 0.04–0.08 for these scales (see Table 4). The remaining scales showed smaller differences with  $R^2$  values of 0.02 and lower, suggesting little difference between samples on these scales.

A cutoff score was also applied to specific MMPI-2 scales to identify participants in the UCSF sample experiencing significant psychiatric symptoms. Using a cutoff score of  $T \geq 65$ , it was found that among UCSF participants diagnosed with alcohol dependence, 23% reported significant symptoms of depression, 23% reported significant symptoms of anxiety, 15% reported significant symptoms of antisocial personality disorder, and 9% reported significant symptoms of a thought disorder (see Table 5). Among participants without an alcohol dependence diagnosis, 10% reported depressive symptoms, 11% reported anxiety symptoms, 5% reported antisocial personality disorder symptoms, and 3% reported thought disorder symptoms. Based on these results, odds ratios (OR) were derived expressing the increased likelihood associated with experiencing symptoms in a specific domain given a diagnosis of alcohol dependence, which yielded the following results: anxiety symptoms -  $OR = 2.4,$

depressive symptoms - OR = 2.7, antisocial personality disorder symptoms - OR = 3.3, thought disorder symptoms - OR = 3.2.

## Discussion

The Minnesota Multiphasic Personality Inventory-2 (MMPI-2)<sup>1</sup> represents one of the most commonly used measures of psychopathology and personality. Despite this, only a limited number of studies have examined the heritability of the MMPI-2 scales<sup>12;15-17</sup>. Such studies are needed given that understanding patterns of co-occurring psychiatric symptomatology may aid in the creation of refined phenotypes for psychiatric disorders. For example, MMPI-2 scales have been shown to assess a portion of the genetic susceptibility to schizophrenia<sup>87</sup>. Results from the present study suggest that specific MMPI-2 scales can be used to identify genetically informative clinical and personality traits that may represent useful phenotypes for molecular genetic studies of alcohol dependence.

Primary analyses demonstrated that each of the MMPI-2 scales examined showed significant evidence of heritability. When the alcohol dependence diagnosis was not included as a covariate, the largest estimates were observed for the DEP and Hy, Hs, Sc, and Pt. In addition, the D, Pd, Pa, Ma, Si, ASP and MAC-R scales all exhibited heritability estimates above 0.25 suggesting substantial genetic influences underlie these traits. When the alcohol dependence diagnosis was included as a covariate in the model, several of the scales (Hs, D, Hy, Pd, Pa, Pt, Sc, DEP) showed decreases in their heritability estimates, though the estimates remained significant for each scale. In contrast, the heritability of the alcohol dependence diagnosis showed much smaller changes, in general, when estimated using each of the MMPI-2 scales as a covariate in turn.

The stability of the heritability of alcohol dependence when controlling for MMPI-2 scores relative to the larger declines in MMPI-2 scale heritabilities when alcohol dependence is controlled for suggests a portion of the variance in MMPI-2 scores attributed to genetic influences can in fact be explained by the presence or absence of alcohol dependence. Nonetheless, three scales, ASP, DEP and MAC-R, led to moderate increases (30–35%) in the heritability of the alcohol dependence diagnosis when used as covariates. This suggests that the ASP, DEP, and MAC-R scales may explain some of the non-genetic variance in the alcohol dependence diagnosis when utilized as covariates, and thus serve to produce a more homogeneous and more heritable alcohol dependence phenotype. Given that the ASP and DEP scales measure antisocial personality traits and depressive symptoms, respectively, this result is not unexpected due to the previous research on alcoholic subtypes<sup>20;88</sup>. Thus, these results support the use of specific MMPI-2 scales as covariates and the creation of alcohol dependence subtypes based on these scales for use in molecular genetic studies of alcohol dependence.

The findings that the MMPI-2 scales continue to show significant evidence of underlying genetic influences after controlling for the presence of alcohol dependence also add to the previous literature suggesting that the MMPI-2 yields heritable estimates of personality and psychopathology<sup>12;15-17</sup>. For example, Viken and Rose<sup>17</sup> reported significant genetic influences underlie each of the MMPI-2 basic scales with estimates of additive genetic influences that ranged from 0.31–0.57. They also reported an absence of shared genetic influences on the MMPI scales scores, which has important implications for the findings reported herein. Heritability estimates in the current study were generated using sibling pair correlations as the primary unit of measurement. Because monozygotic twin pairs were not included, the effects of genetic influences could not be distinguished from the shared environment of the sibling pairs, which could positively bias the heritability estimates. Thus, the absence of shared environmental influences on the MMPI scales suggested by Viken and Rose<sup>17</sup> indicate that the heritability estimates reported in the present study were unlikely to

be biased in this manner, and therefore, represent valid measurements of the relative contributions of genetic influences on the MMPI-2 scales.

Secondary analyses were conducted in order to further characterize MMPI-2 scale scores in the UCSF Family sample. These analyses showed that UCSF Family study participants with an alcohol dependence diagnosis scored higher than the sample used to provide the norms for the MMPI-2<sup>1</sup> on each of the scales examined, but it is noteworthy that the psychopathological symptoms reported by most participants in the UCSF sample were in the subclinical range. Thus, these participants reported only mild impairment relative to the normative sample. Further analyses suggested participants in the UCSF sample diagnosed with alcohol dependence exhibited lower scores on the D, Pt, and Ma basic scales and the ANX, DEP, and MAC-R supplementary scales relative to published data obtained from participants undergoing inpatient treatment for a substance use disorder. These results were expected given that the present study recruited participants from outpatient treatment programs and required only a positive history for alcohol dependence. Additionally, these results suggest that participants diagnosed with alcohol dependence in the present sample exhibited MMPI-2 scale scores that were intermediate to the MMPI-2 normative population and published data from inpatient participants diagnosed with a substance dependence disorder.

Further analyses demonstrated that among UCSF participants without an alcohol dependence diagnosis, the prevalence rates of individuals experiencing significant symptoms of psychopathology associated with certain disorders as indexed by cut off scores on the MMPI-2 were similar to prevalence rates for those disorders that have been reported in surveys of the general population. For example, 11% of participants reported experiencing significant symptoms of anxiety in the current sample, which is comparable to the population prevalence of anxiety disorders in the general population of 11%<sup>62</sup>. Similar results were found for other disorders examined, depression - 10% in the UCSF sample vs. 9% in epidemiological samples<sup>62</sup>, antisocial personality disorder - 5% vs. 4%<sup>59</sup>, respectively, and schizophrenia spectrum disorders - 3% vs. 4–5%, respectively<sup>85;86</sup>.

The findings reported in the present study have important implications for molecular genetic studies of alcohol dependence, but there are limitations that should be noted. First, the UCSF sample contains an over-representation of female participants given prevalence estimates suggesting males are approximately twice as likely as females to develop alcohol dependence. Attempts were made to correct for this by including gender as a covariate in all analyses when appropriate, but further studies will be needed to determine whether the reported findings will generalize to other populations. Second, it should be noted that the etiology of alcohol dependence and the development of personality traits and co-occurring psychopathology represent multi-factorial processes likely involving a range of biological as well as environmental risk factors. The influence of such environmental variables (e.g., exposure to trauma, aspects social environment) and their relation to the findings presented herein were not examined, but represent interesting lines of inquiry for future research. Third, demographic variables such as age were not available at the participant level for the MMPI-2 normative sample<sup>1</sup> and the alcohol dependence inpatient sample described by McKenna and Butcher<sup>83</sup>, and thus, could not be controlled for when comparing MMPI-2 scores. Nonetheless, comparisons of alcohol dependent and non-alcohol dependent subjects in the UCSF sample remained significant whether age was included as a covariate or not and the corresponding effect sizes showed changes that did not exceed  $\Delta R^2 = .01$  with the exception of the ANX scale ( $\Delta R^2 = .04$ ). Fourth, the present study used cutoff scores applied to specific MMPI-2 scales as proxies for DSM-IV diagnoses which were used to compare rates of psychopathology in the UCSF sample to prevalence rates in the general population. This assessment procedure could potentially produce less stringent diagnoses than might be obtained using structured interviews. Nonetheless, there is a substantial literature supporting the use of the MMPI-2 and



demonstrating its reliability and validity as a measure of psychopathology and personality <sup>89</sup>;  
90.

## Summary

In conclusion, the current study adds to the literature by estimating the heritability of MMPI-2 scales and describing levels of co-occurring psychopathology in a family-based sample of individuals diagnosed with alcohol dependence and their siblings. These results suggest that the MMPI-2 may prove useful in molecular genetic studies of alcohol dependence by identifying more homogenous subgroups of individuals diagnosed with alcohol dependence.

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**Table 1**

## Diagnostic and Demographic Characteristics of the UCSF Family Study Sample

|                       | Probands  | Relatives    | Full sample |
|-----------------------|-----------|--------------|-------------|
| Alcohol Dependence Dx |           |              |             |
| Female                | 536 (97%) | 267 (34%)    | 803 (60%)   |
| Male                  | 383 (96%) | 190 (45%)    | 573 (70%)   |
| Gender                |           |              |             |
| Female                | 552 (58%) | 785 (65%)    | 1337 (62%)  |
| Male                  | 398 (42%) | 419 (35%)    | 817 (38%)   |
| Total                 | 950       | 1204         | 2154        |
| Age (years)           |           |              |             |
| 18–25                 | 46.9      | 50.4         | 48.8        |
| 18–25                 | 34 (4%)   | 45 (4%)      | 79 (4%)     |
| 26–40                 | 260 (27%) | 244 (20%)    | 504 (23%)   |
| 41–65                 | 597 (63%) | 747 (62%)    | 1344 (62%)  |
| >65                   | 59 (6%)   | 168 (14%)    | 227 (11%)   |
| Years of education    |           |              |             |
| <12                   | 14.2      | 14.3         | 14.4        |
| <12                   | 83 (9%)   | 79 (7%)      | 162 (7%)    |
| 12–16                 | 684 (72%) | 905 (75%)    | 1589 (74%)  |
| >16                   | 183 (19%) | 220 (18%)    | 403 (19%)   |
| Income (\$)           |           |              |             |
| <20,000               | 48,622    | 64,359       | 57,356      |
| <20,000               | 278 (29%) | 197 (16.4%)  | 475 (22%)   |
| 20,000–50,000         | 355 (37%) | 423 (35.1%)  | 778 (36%)   |
| 50,000–100,000        | 252 (27%) | 434 (36.0%)  | 686 (32%)   |
| >100,000              | 65 (7%)   | 150 (12.4%)  | 215 (10%)   |
| Race                  |           |              |             |
| Caucasian             | 842 (89%) | 1133 (94.1%) | 1975 (92%)  |
| African-American      | 40 (4%)   | 15 (1.2%)    | 55 (3%)     |
| Hispanic              | 42 (4%)   | 26 (2.3%)    | 68 (3%)     |
| Native American       | 15 (2%)   | 17 (1.3%)    | 32 (1%)     |
| Other                 | 11 (1%)   | 13 (1.1%)    | 24 (1%)     |
| Marital status        |           |              |             |
| Married               | 418 (44%) | 746 (62%)    | 1164 (54%)  |
| Divorced/separated    | 313 (33%) | 253 (21%)    | 566 (26%)   |
| Never married         | 190 (20%) | 157 (13%)    | 347 (16%)   |
| Widowed               | 29 (3%)   | 48 (4%)      | 77 (4%)     |

UCSF Family Study Sample MMPI-2 Descriptive Statistics and Comparisons of 'Affected' and 'Unaffected' Subjects

**Table 2**

| Scale              | Full Sample<br>(n = 2064) |           | Alcohol Depend. Dx<br>(n = 1262) |           | No Alcohol Depend. Dx<br>(n = 751) |           | Diagnostic Group<br>Contrast | t    | R <sup>2</sup> |
|--------------------|---------------------------|-----------|----------------------------------|-----------|------------------------------------|-----------|------------------------------|------|----------------|
|                    | Mean                      | Std. Dev. | Mean                             | Std. Dev. | Mean                               | Std. Dev. |                              |      |                |
| Hs <sup>1</sup>    | 55.46                     | 11.58     | 56.95                            | 11.79     | 53.97                              | 10.63     | 5.82 <sup>a</sup>            | 0.02 |                |
| D                  | 53.87                     | 11.27     | 55.24                            | 12.75     | 52.50                              | 9.37      | 5.54 <sup>a</sup>            | 0.01 |                |
| Hy <sup>1</sup>    | 55.80                     | 11.08     | 56.34                            | 11.58     | 55.26                              | 9.98      | 2.20 <sup>b</sup>            | 0.00 |                |
| Pd <sup>1</sup>    | 56.95                     | 10.81     | 60.74                            | 11.08     | 53.16                              | 9.92      | 15.77 <sup>a</sup>           | 0.11 |                |
| Pa <sup>1,2</sup>  | 54.41                     | 10.99     | 56.49                            | 11.22     | 52.33                              | 10.22     | 8.41 <sup>a</sup>            | 0.03 |                |
| Pt <sup>1</sup>    | 53.97                     | 11.54     | 55.58                            | 11.58     | 52.36                              | 10.80     | 6.25 <sup>a</sup>            | 0.02 |                |
| Sc <sup>1</sup>    | 55.30                     | 11.27     | 57.86                            | 11.54     | 52.74                              | 10.30     | 10.24 <sup>a</sup>           | 0.05 |                |
| Ma <sup>1</sup>    | 50.93                     | 9.54      | 53.13                            | 9.91      | 48.72                              | 8.63      | 10.42 <sup>a</sup>           | 0.05 |                |
| Si                 | 49.69                     | 11.18     | 50.62                            | 11.15     | 48.76                              | 10.36     | 3.80 <sup>a</sup>            | 0.01 |                |
| ANX <sup>1</sup>   | 51.96                     | 8.72      | 54.39                            | 11.83     | 49.52                              | 4.69      | 13.34 <sup>a</sup>           | 0.08 |                |
| DEP <sup>1,2</sup> | 51.32                     | 11.77     | 54.13                            | 11.94     | 48.50                              | 11.02     | 10.65 <sup>a</sup>           | 0.05 |                |
| BIZ <sup>1</sup>   | 50.11                     | 9.58      | 51.74                            | 9.41      | 48.48                              | 9.07      | 7.63 <sup>a</sup>            | 0.03 |                |
| ASP <sup>1</sup>   | 49.93                     | 8.40      | 52.33                            | 8.63      | 47.52                              | 7.97      | 12.43 <sup>a</sup>           | 0.07 |                |
| MAC-R              | 52.54                     | 10.49     | 56.28                            | 10.48     | 48.79                              | 9.84      | 16.03 <sup>a</sup>           | 0.11 |                |

<sup>1</sup> Age was included as a covariate<sup>2</sup> Gender was included as a covariate<sup>a</sup> significant at p<.001<sup>b</sup> significant at p<.05, Alcohol Depend. Dx = Alcohol Dependence Diagnosis.

**Table 3**  
MMPI-2 Scale and Alcohol Dependence Heritabilities as Estimated by SOLAR

| Trait              | MMPI-2 Scales w/o Alcohol Dependence Dx as covariate |      | MMPI-2 Scales w/ Alcohol Dependence Dx as covariate <sup>a</sup> |                     | Alcohol Dependence Dx w/ MMPI-2 scales as covariates |         |                     |      |       |
|--------------------|--|------|--|---------------------|--|---------|---------------------|------|-------|
|                    | h <sup>2</sup>                                       | SE   | h <sup>2</sup>   | p-value             | h <sup>2</sup>                                       | p-value |                     |      |       |
| Hs                 | 0.47 <sup>/</sup>                                    | 0.06 | <.001  | 0.26 <sup>/</sup>   | 0.07   | <.001   | 0.20 <sup>/,2</sup> | 0.08 | .003  |
| D                  | 0.39   | 0.06 | <.001  | 0.28                | 0.06   | <.001   | 0.22 <sup>/,2</sup> | 0.09 | .001  |
| Hy                 | 0.49 <sup>/</sup>                                    | 0.06 | <.001  | 0.21 <sup>/</sup>   | 0.07   | <.001   | 0.20 <sup>/,2</sup> | 0.08 | .004  |
| Pd                 | 0.38 <sup>/,2</sup>                                  | 0.07 | <.001  | 0.26 <sup>/</sup>   | 0.07   | <.001   | 0.17 <sup>2</sup>   | 0.08 | .016  |
| Pa                 | 0.27 <sup>/,2</sup>                                  | 0.07 | <.001  | 0.18 <sup>/</sup>   | 0.06   | 0.001   | 0.16 <sup>2</sup>   | 0.07 | .014  |
| Pt                 | 0.45 <sup>/</sup>                                    | 0.07 | <.001  | 0.29 <sup>/</sup>   | 0.07   | <.001   | 0.20 <sup>/,2</sup> | 0.07 | .004  |
| Sc                 | 0.47 <sup>/</sup>                                    | 0.06 | <.001  | 0.16 <sup>/,2</sup> | 0.06   | 0.002   | 0.17 <sup>/,2</sup> | 0.07 | .011  |
| Ma                 | 0.25 <sup>/</sup>                                    | 0.11 | .004   | 0.30 <sup>/,2</sup> | 0.11   | 0.001   | 0.182 <sup>2</sup>  | 0.09 | .007  |
| Si                 | 0.35   | 0.06 | <.001  | 0.35                | 0.06   | <.001   | 0.20 <sup>/,2</sup> | 0.12 | .003  |
| ANX                | 0.22 <sup>/</sup>                                    | 0.06 | <.001  | 0.21 <sup>/</sup>   | 0.06   | <.001   | 0.23 <sup>2</sup>   | 0.08 | <.001 |
| DEP                | 0.50 <sup>/</sup>                                    | 0.06 | <.001  | 0.29 <sup>/</sup>   | 0.07   | <.001   | 0.27 <sup>2</sup>   | 0.08 | <.001 |
| BIZ                | 0.15 <sup>/</sup>                                    | 0.06 | .005   | 0.16 <sup>/</sup>   | 0.06   | 0.002   | 0.20 <sup>/,2</sup> | 0.09 | .003  |
| ASP                | 0.36 <sup>/,2</sup>                                  | 0.07 | <.001  | 0.46 <sup>/</sup>   | 0.07   | <.001   | 0.26 <sup>2</sup>   | 0.08 | <.001 |
| MAC-R <sup>/</sup> | 0.33   | 0.06 | <.001  | 0.35                | 0.06   | <.001   | 0.27 <sup>/,2</sup> | 0.05 | <.001 |

<sup>/</sup> Age was included as a covariate

<sup>2</sup> Gender was included as a covariate, MMPI-2 scale means were constrained to the population mean (i.e.,  $M = 50$ ) to correct for potential ascertainment bias

<sup>a</sup> Alcohol Dependence Diagnosis represented a significant covariate for all scales except Si, Dx = Diagnosis.



**Table 4**  
 Comparison of UCSF Family Sample MMPI-2 Scores to the MMPI-2 Normative and an Inpatient Substance Abuse Sample.\*

| Scale | Alc. Dep. Dx vs. Normative Sample (df = 2472) |                |                    | No Alc. Dep. Dx vs. Inpatient Sample (df = 1961) |       |                     | Alcohol Dep. Dx vs. Inpatient Sample (df = 2472) |                |        | No Alcohol Dep. Dx vs. Inpatient Sample (df = 1961) |      |                |
|-------|---|----------------|--------------------|--|-------|---------------------|--|----------------|--------|---|------|----------------|
|       | t   | R <sup>2</sup> | t                  | R <sup>2</sup>                                   | t     | Mean Diff.          | t  | R <sup>2</sup> | t      | Mean Diff.  | t    | R <sup>2</sup> |
| Hs    | 19.45 <sup>a</sup>                            | 0.09           | 10.15 <sup>a</sup> | 0.03   | 0.29  | 0.59                | 0.00   | 0.00           | -2.43  | -4.19 <sup>a</sup>                                  | 0.01 | 0.01           |
| D     | 14.49 <sup>a</sup>                            | 0.05           | 6.16 <sup>a</sup>  | 0.01   | -6.42 | -11.72 <sup>a</sup> | 0.05   | 0.05           | -9.24  | -14.74 <sup>a</sup>                                 | 0.10 | 0.10           |
| Hy    | 18.04 <sup>a</sup>                            | 0.08           | 11.91 <sup>a</sup> | 0.04   | -1.91 | -3.83 <sup>a</sup>  | 0.01   | 0.01           | -3.36  | -5.80 <sup>a</sup>                                  | 0.02 | 0.02           |
| Pd    | 31.29 <sup>a</sup>                            | 0.20           | 6.40 <sup>a</sup>  | 0.01   | -2.95 | -6.11 <sup>a</sup>  | 0.01   | 0.01           | -11.48 | -20.52 <sup>a</sup>                                 | 0.18 | 0.18           |
| Pa    | 19.37 <sup>a</sup>                            | 0.09           | 4.84 <sup>a</sup>  | 0.01   | -3.71 | -7.73 <sup>a</sup>  | 0.02   | 0.02           | -8.66  | -15.81 <sup>a</sup>                                 | 0.11 | 0.11           |
| Pt    | 16.66 <sup>a</sup>                            | 0.07           | 5.42 <sup>a</sup>  | 0.01   | -5.18 | -10.13 <sup>a</sup> | 0.04   | 0.04           | -8.97  | -15.14 <sup>a</sup>                                 | 0.10 | 0.10           |
| Sc    | 23.04 <sup>a</sup>                            | 0.12           | 6.15 <sup>a</sup>  | 0.01   | -1.14 | -2.27 <sup>b</sup>  | 0.00   | 0.00           | -6.89  | -11.88 <sup>a</sup>                                 | 0.07 | 0.07           |
| Ma    | 10.06 <sup>a</sup>                            | 0.03           | -4.06 <sup>a</sup> | 0.00   | -4.42 | -9.67 <sup>a</sup>  | 0.04   | 0.04           | -9.57  | -18.02 <sup>a</sup>                                 | 0.14 | 0.14           |
| Si    | 1.96 <sup>c</sup>                             | 0.00           | -2.18 <sup>c</sup> | 0.00   | -2.17 | -4.63 <sup>a</sup>  | 0.01   | 0.01           | -3.80  | -6.99 <sup>a</sup>                                  | 0.02 | 0.02           |
| ANX   | 13.21 <sup>a</sup>                            | 0.04           | -0.27              | 0.00   | -6.59 | -13.04 <sup>a</sup> | 0.06   | 0.06           | -11.59 | -20.08 <sup>a</sup>                                 | 0.17 | 0.17           |
| DEP   | 12.80 <sup>a</sup>                            | 0.04           | -3.41 <sup>a</sup> | 0.00   | -7.14 | -14.52 <sup>a</sup> | 0.08   | 0.08           | -13.37 | -24.27 <sup>a</sup>                                 | 0.23 | 0.23           |
| BIZ   | 5.90 <sup>a</sup>                             | 0.01           | -4.30 <sup>a</sup> | 0.01   | -3.00 | -7.07 <sup>a</sup>  | 0.02   | 0.02           | -6.76  | -13.59 <sup>a</sup>                                 | 0.09 | 0.09           |
| ASP   | 7.74 <sup>a</sup>                             | 0.02           | -6.83 <sup>a</sup> | 0.01   | -0.64 | -1.51               | 0.00   | 0.00           | -6.14  | -12.74 <sup>a</sup>                                 | 0.08 | 0.08           |
| MAC-R | 18.66 <sup>a</sup>                            | 0.08           | -3.06 <sup>b</sup> | 0.00   | -4.11 | -9.64 <sup>a</sup>  | 0.04   | 0.04           | -11.96 | -24.78 <sup>a</sup>                                 | 0.24 | 0.24           |

\* normative sample described by Butcher et al.<sup>1</sup> and inpatient sample described by McKenna & Butcher<sup>83</sup>, normative sample - mean = 50.0, SD = 10.0

<sup>a</sup> significant at p<.001

<sup>b</sup> significant at p<.01

<sup>c</sup> significant at p<.05, Alc. Dep. Dx = Alcohol Dependence Diagnosis.

**Table 5**  
Prevalence Rates and Odds Ratios for Major Categories of Psychopathological Symptoms

|                       | UCSF Family Study        |                             | NESARC                   |                             |
|-----------------------|--------------------------|-----------------------------|--------------------------|-----------------------------|
|                       | Alcohol<br>Dependence Dx | No Alcohol<br>Dependence Dx | Alcohol<br>Dependence Dx | No Alcohol<br>Dependence Dx |
| Anxiety Sxs.          | 297 (23%)                | 86 (11%)                    | 25%                      | 11%                         |
| Depressive Sxs.       | 292 (23%)                | 72 (10%)                    | 24%                      | 9%                          |
| Antisocial Behavior   | 184 (15%)                | 38 (5%)                     | 15%                      | 4%                          |
| Thought Disorder Sxs. | 112 (9%)                 | 26 (3%)                     | -                        | 4-5% <sup>a</sup>           |
|                       |                          |                             | OR                       | OR                          |
|                       |                          |                             | 2.4                      | 2.7                         |
|                       |                          |                             | 2.7                      | 3.2                         |
|                       |                          |                             | 3.3                      | 4.1                         |
|                       |                          |                             | 3.2                      | -                           |

<sup>a</sup>Data was not available from NESARC, thus data from population-based twin studies were used 85:86, Dx = Diagnosis, Sxs. = Symptoms.