Subtyping of alcohol dependence in Indian males: A cluster analytic approach

Savita Malhotra, Debasish Basu, Abhishek Ghosh, Madhu Khullar¹, Neeraj Kakkar
Departments of Psychiatry and ¹Experimental Medicine and Biotechnology, Postgraduate Institute of Medical Education and Research, Chandigarh, India

ABSTRACT

Objectives: Two cluster solutions for the subtyping of alcohol dependence (AD) was investigated in an Indian male population. Subtypes were compared for various personality traits and childhood externalizing disorders. They were also compared with respect to single-nucleotide polymorphisms (SNP) of various candidate genes.

Materials and Methods: This was a clinic-based study conducted among 202 patients with AD. All patients were assessed with SSAGA-II for comorbid antisocial personality disorder (ASPD) and childhood conduct disorder (CD), oppositional defiant disorder (ODD), and attention deficit hyperactivity disorder (ADHD). For the assessment of personality traits, the Indian Adaptation of Sensation Seeking Scale (SSS) and Barratt’s Impulsiveness Scale were administered. SNP genotyping was done using taqmann assay by real-time polymerase chain reaction.

Results: Among those with AD, the two-cluster model which was able to produce the maximum degree of cohesion among disorders in the same cluster and separateness from the other cluster was the one with or without ASPD and CD. The quality of the cluster analysis was reduced when ODD and ADHD were included in the model along with ASPD and CD. Thus, in our index population, there are two distinct clusters of AD, one with ASPD and CD or the externalizing cluster (Cluster 2) and the other without ASPD and CD or the nonexternalizing cluster (Cluster 1). Externalizing cluster had significantly higher score in both the impulsiveness and the SSS. This cluster was also significantly associated with childhood ADHD and ODD. The genotype frequencies of all candidate genes were found to be nonsignificantly distributed among the two groups.

Conclusion: Our study has conferred a cross-cultural validation of the known alcoholism subtypes.

Key words: Alcohol dependence, cluster analysis, externalizing disorders, subtypes

INTRODUCTION

Alcohol dependence (AD), although has been defined as a single diagnostic entity, is well known for its heterogeneity in premorbid vulnerabilities, clinical expression, comorbidity pattern, and treatment outcome.[1] Hence, it is quite intuitive to explore for relative homogeneous groups or subtypes of AD. The search for subtypes dated back to early 1960s when it was entirely based on the clinical description of “cases,” without any statistical validation.[2] The first multivariate, multidimensional typology of “alcoholism” was conducted by Cloninger et al. on Swedish adoptees, which revealed two distinct subtypes of AD. One with later age of onset...
of alcoholism, more environmental influence, high in harm avoidance, reward dependence, and low in novelty seeking was labeled as Type 1 and the other with earlier age of onset, more severe alcohol problems, more genetic influence, and high in novelty seeking (and low in other two temperamental parameters) was known as Type 2. Later, these findings were nearly replicated in another study which had included both genders and childhood behavior problems to classify AD. Schuckit et al., using a clustering algorithm approximating that of Babor et al., found two similar groups like Babor’s Type A/B. These two cluster solutions of AD were replicated in a separate analyses of Hispanic, African-American, and Alaska native samples. Therefore, these two subtypes of AD appear to be valid across time, geography, and ethnicity. The two-cluster subtype of AD has become all the more appealing as it closely resembles the developmental trajectories, namely the externalizing and the internalizing pathways to alcohol use disorders. Barring substance use disorders, externalizing disorders include conduct disorder (CD) and antisocial personality disorder (ASPD). Oppositional defiant disorder (ODD) and attention deficit hyperactivity disorder (ADHD) are also included by some authors. All externalizing disorders have a common underlying theme of behavioral disinhibition, “an inability to inhibit socially undesirable or restricted actions.” This general vulnerability was found to be highly heritable and purported to be mediated by dopamine (DA). Hence, the common candidate genes studied for externalizing disorders were related to DA turnover, availability, and/or metabolism (like DA receptor D2/D4; Catechol-O-methyltransferase [COMT]; Mono-amine oxidase: MAO genes). Other candidate genes studied were related to serotonergic pathway.

In the present study, the authors aimed to investigate the two-cluster solution for AD in a clinic-based sample consisted of all male patients. To the best of our knowledge, there is no published literature regarding the subtyping of AD in Indian and even in the Asians. Further in this study, subtypes were compared with respect to single-nucleotide polymorphisms (SNP) of gamma aminobutyric acid receptor A1 and A2 (GABRA1/A2), SHT transporter long promoter region (5’HTTLPR), and COMT genes.

MATERIALS AND METHODS

This was a clinic-based study utilizing cases of AD. In this study, 202 alcohol-dependent male patients, attending the Drug De-addiction and Treatment Centre, Department of Psychiatry, PGIMER, Chandigarh, India, were enrolled by purposive sampling. This tertiary care institute caters to a population from the northern states of India (Punjab, Haryana, Himachal Pradesh, and western Uttar Pradesh) and some western states (Rajasthan). Most of the patients shared a common language and ethnicity. Patients with a history of any other substance abuse/dependence, other than nicotine, were excluded from the study. Patients with mental retardation, or having psychosis, and bipolar disorder were also excluded from the study. The study period was from September 2010 to August 2012. AD was diagnosed by administration of a semi-structured interview by a trained clinician using modified version of SSAGA II. This interview generated the lifetime diagnosis of AD according to the International Classification of Diseases-10 as well as the Diagnostic and Statistical Manual 4th Edition. This same instrument was also applied to diagnose ASPD, CD, and ODD in the study patients. Barratt’s Impulsiveness Scale (BIS) was administered for measuring impulsivity. It has a total score of 30 and contains three subscales related to impulsiveness. The first measures motor impulsiveness and lack of perseverance. The second measures cognitive impulsivity by assessing inattention. The third scale evaluates nonplanning impulsivity by scoring lack of self-control and intolerance of cognitive complexity. Finally, Zuckerman’s Sensation Seeking Scale (SSS) was developed to evaluate sensation-seeking construct. The latest version (SSS-V) contains four subscales: Thrill and Adventure Seeking (TAS), Boredom Susceptibility (BS), Experience Seeking (ES), and Disinhibition (DIS). The total SSS score is obtained by summing up the subscale scores. Indian adaptation of the SSS-V was used in the present study. Ethical committee clearance was obtained prior to recruitment of the patients. All patients gave written informed consent to participate in the study. Clinical details, including ethnicity, age at the first use of alcohol and quantity of alcohol consumed (ml/day), duration of alcohol use, duration of dependence, and presence of withdrawal seizures, were assessed and recorded.

Genomic DNA extraction and genotyping

Intravenous blood samples (about 6 ml each) were collected in sterile ethylene diaminetetraacetic acid-coated vacutainers and stored at −20°C until processing for DNA extraction was carried out. DNA was isolated from whole blood using the standard organic method (Phenol-Chloroform-Isomyl). SNP genotyping for all the polymorphisms analyzed in the present study was done using ABI Taqmann assay kits (Life Technologies) by real-time polymerase chain reaction (q-PCR) on ABI 7500 fast real-time PCR system. The oligonucleotide sequence of the probes for different candidate genes studied is described in Table 1.

Statistical analysis

Two-step cluster analysis has been used to classify the alcohol-dependent patients. Predetermined two-cluster solution has been sought. The two clusters were compared by independent sample unpaired t-test, with regard to their clinical profile, impulsiveness, and SSS. The genetic
association of two clusters with different candidate genes in relation to polymorphic prevalence was evaluated using Chi-square test. Power analysis was performed using Quanto (Version 1.0) (http://hydra.usc.edu/gxe). A two-sided \( P < 0.05 \) was considered statistically significant. Genotype distributions were tested for deviation from the Hardy-Weinberg Equilibrium proportions using the HWSIM program.

**RESULTS**

In the two-step cluster analysis, ASPD and CD were entered as classifying variables. In the two-cluster solution, two subgroups were identified, Cluster 1 with no ASPD and CD and Cluster 2 with 86.4% ASPD and 64.8% CD. The quality of clusters was found to be good (cohesion-separation coefficient = 0.8) [Figure 1]. When the same two-cluster solution was tried entering ODD and ADHD in addition to ASPD and CD, the quality of cluster worsened (cohesion-separation coefficient = 0.7).

Table 2 shows the clinical variables, namely, age at the first drink, age of onset of AD, duration of alcohol use, and dependence and compares these variables between Clusters 1 and 2. Results showed that there are significant differences among the age of the patients \( (P = 0.01) \), the age of onset of AD \( (P = 0.002) \), and age at the first drink \( (P = 0.004) \) between Cluster 1 and Cluster 2. However, no difference has been observed with regard to duration of alcohol use \( (P = 0.6) \) and dependence \( (P = 0.8) \) between the two clusters.

Comparison of the mean of total scores and scores on various subscales of SSS and BIS has been done. Barring disinhibition \( (P = 0.6) \), the mean scores of other subscales of SSS, namely, TAS \( (P = 0.02) \), ES \( (P = 0.006) \), and BS \( (P = 0.01) \) were found to be significantly higher in the Cluster 2. The total score in the SSS was also significantly more \( (P = 0.001) \) among the Cluster 2 patients. However, the differences in the mean scores of other subscales were not statistically significant. The Cluster 2 had scored significantly more in all subscales of BIS, namely, motor impulsiveness \( (P = 0.0001) \), nonplanning impulsiveness \( (P = 0.004) \), and attentional impulsiveness \( (P = 0.0001) \) of BIS. The total score on BIS was also significantly more in the Cluster 2 \( (P = 0.0001) \) [Table 3].

Comparison of the two clusters with regard to the presence of ADHD and ODD in childhood has revealed that the Cluster 2 had a significant association with both ADHD \( (P = 0.0001) \) and ODD \( (P = 0.0001) \) [Table 3].

The genotype frequencies of the studied genes (COMT, GABRA1, GABRA2, and 5’HTTLPR) in the Clusters 1 and 2 are as follows:

**Table 1: Context gene sequence of various candidate genes for subgroups of alcohol dependence**

| Genes       | Context gene sequence                                      |
|-------------|------------------------------------------------------------|
| COMT        | 3’ CCACGGGATGGTGATTTGCCTGCA[A/G] TGAAGCAAAGGTGGTGGCTTAS*   |
| GABRA1      | 3’CGAGAAGCTTAGAAAATATCAGCAGA[A/G] CTACATTATATATATAAAAAGCS*  |
| GABRA2      | 3’ATTTCTCTGACATGTGTGATATATT[A/G] TTTTTTAAAAAAAAATCATTTTTGTC5*|
| 5HTTLPR     | 3’CTCTCGGGCATCCCCCCTGCACCACCA[A/G] GCATCCCCCCTGCAGCCCCSAC5*  |

| Population characteristics | Cluster 1 (nonexternalizing subgroup), \( n=111 \) | Cluster 2 (externalizing subgroup), \( n=91 \) | Comparison between Clusters 1 and 2 |
|----------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------|
| Age (years)                | 42.4±9.1                                     | 39.4±7.6                                     | 2.4 (0.01)                        |
| Age at the first use of alcohol (years) | 23.7±6.5                                   | 21.1±5.6                                     | 2.9 (0.004)                       |
| Age of onset of alcohol dependence | 31.7±8.6                                   | 28.3±6.6                                     | 3.1 (0.002)                       |
| Duration of alcohol use     | 18.7±8.8                                    | 18.3±7.8                                     | 0.34 (0.735)                      |
| Duration of alcohol dependence (years) | 10.7±7.9                                    | 11.1±8.3                                     | 0.35 (0.726)                      |

SD – Standard deviation
2 are shown in Table 4. The genotype frequencies (of single-nucleotide polymorphisms) of all candidate genes, namely, COMT, GABRA1, GABRA2, and 5HTTLPR were found to be nonsignificantly distributed among the two groups. Comparison of allele frequencies also demonstrated the same results [Tables 5 and 6].

DISCUSSION

Among those with AD, the two-cluster model which was able to produce the maximum degree of cohesion among disorders in the same cluster and separateness from the other cluster was the one with or without ASPD and CD. The quality of the cluster analysis was reduced when ODD and ADHD were included in the model along with ASPD and CD. Thus, in our index population, there are two distinct clusters of AD, one with ASPD and CD or the externalizing cluster and the other without ASPD and CD or the nonexternalizing cluster.

There has been a significant difference in all the subscales of impulsiveness and SSS between the two clusters, with the externalizing cluster having higher scores as opposed to the nonexternalizing one. As disinhibition, impulsivity, and novelty seeking are core traits of externalizing disorders, this result is quite understandable.[20-24] However, this finding has actually validated the existence of an externalizing subgroup in AD by extending the association beyond the level of disorders to the basic, inherited, and enduring traits. Moreover, the nonexternalizing cluster indirectly points toward a different trajectory of development of substance use disorders, which mostly remains underrecognized, i.e., the internalizing subgroup.[25] As we have not assessed any internalizing disorder or trait in our study, the latter could only be a conjecture which would need further validation and confirmation. When the presence of ODD and ADHD in childhood was compared between the two subgroups, the result showed a significant association of these childhood disorders with the externalizing subgroup. This finding is also concordant with the available literature where the concurrence of ADHD and ODD with adult antisocial disorder has been observed.[25] Although another study from a similar population (as in the present study) demonstrated an association of ODD with AD, in light of the current findings, it would be safe to speculate that it is one of the subgroups (the externalizing subgroup) of AD with which the association is more significant.[26] Perhaps, this result alludes to one of the developmental trajectories of ADHD and ODD, which follows the externalizing spectrum and ends with AD. The age at the first drink and the age of onset of dependence were found to be earlier in the externalizing subgroup as opposed to the nonexternalizing cluster. This result is similar to the Conning’s or Babor’s subtype where Type 2/B AD resembling our externalizing

### Table 3: Comparison of personality characteristics between two clusters

| Personality traits                           | Mean±SD | Cluster 1 | Cluster 2 | t (P) |
|----------------------------------------------|---------|-----------|-----------|-------|
| Thrill and adventure seeking                 | 2.8±2   | 3.6±2.8   | 2.4 (0.01)|       |
| Experience seeking                          | 2.6±1.9 | 3.3±1.9   | 2.8 (0.006)|      |
| Disinhibition                                | 2.9±1.6 | 3.0±1.5   | 0.5 (0.6) |       |
| Boredom susceptibility                       | 2.4±1.7 | 3.1±1.8   | 2.5 (0.01)|       |
| Total score on sensation seeking            | 10.7±4.9| 12.9±4.7  | 3.2 (0.001)|      |
| Nonplanning impulsiveness                   | 24.3±4.9| 26.3±3.9  | 6.6 (0.0001)|     |
| Motor impulsiveness                         | 22.3±5  | 27.4±5.8  | 6.6 (0.0001)|     |
| Attentional impulsiveness                   | 15.9±3.8| 19.8±4.4  | 6.7 (0.0001)|     |
| Total score on impulsiveness scale          | 62.6±10 | 73.4±11.8 | 6.9 (0.0001)|     |

SD – Standard deviation

### Table 4: Comparison of clusters with regard to attention deficit hyperactivity disorder and oppositional defiant disorder

| Disorders                  | Cluster 1, n=111 (%) | Cluster 2, n=91 (%) | χ² (P) |
|---------------------------|----------------------|---------------------|--------|
| ADHD                      | 3 (2.7)              | 17 (18.7)           | 14.3 (0.0001)|     |
| ODD                       | 2 (1.8)              | 23 (25.3)           | 25.4 (0.0001)|     |

ADHD – Attention deficit hyperactivity disorder; ODD – Oppositional defiant disorder

### Table 5: Genotype frequency of candidate genes

| Genes                  | Genotypes                              | Cluster 1, n=111 (%) | Cluster 2, n=91 (%) | χ² (P) |
|------------------------|----------------------------------------|----------------------|---------------------|--------|
| COMT (A/G)             | Homozygous recessive (A/A)             | 28 (25.2)            | 16 (17.6)           | 1.7    | 0.4  |
| [Val158Met] rs4680     | Heterozygous (A/G)                     | 56 (50.5)            | 52 (57.1)           |       |     |
|                         | Homozygous wild (G/G)                  | 27 (24.3)            | 23 (25.3)           | Reference |
| GABRA1 (A/G)           | Homozygous dominant, wild type (A/A)   | 46 (41.4)            | 41 (45.1)           |        | Reference |
| rs980791                | Heterozygous (A/G)                     | 49 (44.1)            | 40 (44)             | 0.1    | 0.9  |
|                         | Homozygous recessive (G/G)             | 16 (14.4)            | 10 (10.9)           |        |     |
| GABRA2 (A/G)           | Homozygous dominant, wild type (A/A)   | 11 (9.9)             | 10 (11)             |        |     |
| rs279871                | Heterozygous (A/G)                     | 47 (42.3)            | 39 (42.9)           | 0.08   | 0.9  |
|                         | Homozygous recessive (G/G)             | 53 (47.8)            | 42 (46.1)           |        |     |
| 5HTTLPR (A/G)          | Homozygous dominant, wild type (A/A)   | 27 (24.5)            | 22 (24.4)           |        | Reference |
| rs25531                | Heterozygous (A/G)                     | 82 (74.5)            | 67 (74.4)           | 0.04   | 0.9  |
|                         | Homozygous recessive (G/G)             | 1 (0.9)              | 1 (0.2)             |        |     |

COMT – Catechol O-methyl transferase; GABRA1 – Gamma aminobutyric acid receptor A1; GABRA2 – Gamma aminobutyric acid receptor A2; 5HTTLPR – 5HT transporter long promoter region
subgroup had an earlier onset of alcoholism.[13,14] Another recent study from our center has also shown an association of early-onset AD (but not late-onset AD) with childhood externalizing disorders (CD, ODD, and ADHD).[27] Therefore, overall in the present study, we have identified two distinct subgroups of AD, the externalizing subgroup defined by the presence of CD/ASPD which has a significant comorbidity with ODD, ADHD, higher impulsiveness and sensation seeking, and an earlier onset of alcohol use/dependence. The nonexternalizing subgroup which does not have CD/ASPD has significantly lower comorbidity of ODD or ADHD, lower externalizing temperaments, and later age of alcohol use/dependence.

When the subgroups were compared with respect to SNP of GABRA1/A2, SHTTLPR, and COMT genes, no significant association has been demonstrated with either of the subgroups. Although another study has raised a possibility of an association between SHTTLPR polymorphism and Type-II alcoholism, after correction for multiple comparisons, the association has become nonsignificant.[14] No study so far has been conducted with regard to COMT Val/Met polymorphism and externalizing disorders. However, a recent study has found significant associations between COMT and variability in some components in continuous performance test, a measure for impulsivity and inattention. The association was stronger at higher levels of externalizing psychopathology.[28] This study reiterates the importance of studying more basic endophenotypes/traits rather than complex behavioral phenotypes for determining genetic association. No association with GABRA2 is in line with a recent large-scale study, in which GABRA2 has been found to be associated with subthreshold externalizing symptoms rather than diagnosed externalizing disorders.[29] The lack of significant association in our study could also be due to the fact that we have explored only one SNP each from a candidate gene, and we have only studied few among the multiple genes considered to be implicated in externalizing disorders.[20] Hence, in our study, although the negative associations of SNPs of various candidate genes are disappointing, they are not unexpected or un-understandable.

The current research is based on clinic-attending males with AD. Hence, the results appear to be more applicable for treatment-seeking subset of AD. As we have exclusively studied males with AD, the results may not be generalized to the female population. The diagnosis of externalizing disorders in our study is retrospective. Hence, the potential for recall bias must be taken into account. The characterization of the nonexternalizing subgroup of AD could not be done as we did not assess nonexternalizing disorders or traits in this study. Finally, although a rational assumption of population homogeneity has been made, to obviate the role of systematic difference of allele frequencies between subpopulations (ethnicity/ancestry), control for population stratification could have been done. Future study might look into this issue.

**CONCLUSION**

Our study unambiguously has found out two distinct subgroups of AD in a different population which has not been studied till date, conferring a cross-cultural validation of the known alcoholism subtypes.

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

**REFERENCES**

1. Hesselbrock MN, Hesselbrock VM. Relationship of family history, antisocial personality disorder and personality traits in young men at risk for alcoholism. J Stud Alcohol 1992;53:619-25.
2. Jellinek EM. The Disease Concept of Alcoholism. New Haven, Connecticut: Yale Centre of Alcohol Studies; 1960.
3. Cloninger CR, Bohman M, Sigvardsson S. Inheritance of alcohol abuse. Cross-fostering analysis of adopted men. Arch Gen Psychiatry 1981;38:861-8.
4. Babor TF, Hofmann M, DelBoca FK, Hesselbrock V, Meyer RE, Dolinsky ZS, et al. Types of alcoholics. I. Evidence for an empirically derived typology based on indicators of vulnerability and severity. Arch Gen Psychiatry 1992;49:599-608.
5. Schuckit MA, Tipp JE, Smith TL, Shapiro E, Hesselbrock VM, Bucholz KK, et al. An evaluation of type A and B alcoholics. Addiction 1995;90:1189-203.
6. Hesselbrock VM, Segal B, Hesselbrock MN. Alcohol dependence among Alaska Natives entering alcoholism treatment: A gender comparison. J Stud Alcohol 2000;61:150-6.
7. Hussong AM, Jones DJ, Stein GL, Baucoum DH, Boeding S. An internalizing pathway to alcohol use and disorder. Psychol Addict Behav 2011;25:390-404.
8. Iacono WG, Malone SM, McGue M. Behavioral disinhibition and the development of early-onset addiction: Common and specific influences. Ann Rev Clin Psychol 2008;4:325-48.
9. Krueger RF. The structure of common mental disorders. Arch Gen Psychiatry 1999;56:921-6.
10. Hicks BM, Markon KE, Patrick CJ, Krueger RF, Newman JP. Identifying psychopathy subtypes on the basis of personality structure. Psychol Assess 2004;16:276-88.
11. DeYoung CG. Toward a theory of the big five. Psychol Inq 2010;21:26-33.
12. Faraone SV, Mick E. Molecular genetics of attention deficit hyperactivity disorder. Psychiatr Clin North Am 2010;33:159-80.
13. Gizer IR, Ficks C, Waldman ID. Candidate gene studies of ADHD: A meta-analytic review. Hum Genet 2009;126:51-90.
14. Parsian A, Cloninger CR. Serotonergic pathway genes and subtypes of alcoholism: Association studies. Psychiatr Genet 2001;11:89-94.
15. Hesselbrock M, Easton C, Bucholz KK, Schuckit M, Hesselbrock V. A validity study of the SSAGA – A comparison with the SCAN. Addiction 1999;94:1361-70.
16. Barratt ES, Stanford MS. Barratt impulsiveness scale, version 11 (BIS 11). Handbook of Psychiatric Measures. Washington, DC: American Psychiatric Association; 2000. p. 691-3.
17. Patton JH, Stanford MS, Barratt ES. Factor structure of the Barratt impulsiveness scale. J Clin Psychol 1995;51:768-74.
18. Zuckerman M. Behavioral Expressions and Biosocial Bases of Sensation Seeking. London: Cambridge University Press; 1994.
19. Basu D, Verma VK, Malhotra S, Malhotra A. Sensation seeking scale: Indian adaptation. Indian J Psychiatry 1993;35:155-8.
20. Acton GS. Measurement of impulsivity in a hierarchical model of personality traits: Implications for substance use. Subst Use Misuse 2003;38:67-83.
21. Casillas A, Clark LA. Dependency, impulsivity, and self-harm: Traits hypothesized to underlie the association between cluster B personality and substance use disorders. J Pers Disord 2002;16:424-36.
22. Lynam DR, Leukefeld C, Clayton RR. The contribution of personality to the overlap between antisocial behavior and substance use/misuse. Aggress Behav 2003;29:316-31.
23. Sher KJ, Bartholow BD, Wood MD. Personality and substance use disorders: A prospective study. J Consult Clin Psychol 2000;68:818-29.
24. Slutske WS, Heath AC, Dinwiddie SH, Madden PA, Bucholz KK, Dunne MP, et al. Common genetic risk factors for conduct disorder and alcohol dependence. J Abnorm Psychol 1998;107:363-74.
25. Krueger RF, Markon KE. Reinterpreting comorbidity: A model-based approach to understanding and classifying psychopathology. Annu Rev Clin Psychol 2006;2:111-33.
26. Ghosh A, Malhotra S, Basu D. Oppositional defiant disorder (ODD), the forerunner of alcohol dependence: A controlled study. Asian J Psychiatr 2014;11:8-12.
27. Ghosh A, Malhotra S, Basu D. Are childhood externalizing disorders harbingers of early onset alcohol dependence? Indian J Med Res [In press].
28. Park Y, Waldman ID. Influence of the COMT val 108/158 met polymorphism on continuous performance task indices. Neuropsychologia 2014;61:45-55.
29. Dick DM, Aliev F, Latendresse S, Porjesz B, Schuckit M, Rangaswamy M, et al. How phenotype and developmental stage affect the genes we find: GABRA2 and impulsivity. Twin Res Hum Genet 2013;16:661-9.
30. Salvatore JE, Aliev F, Bucholz K, Agrawal A, Hesselbrock V, Hesselbrock M, et al. Polygenic risk for externalizing disorders: Gene-by-development and gene-by-environment effects in adolescents and young adults. Clin Psychol Sci 2015;3:189-201.