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# The association between the *CCDC88A* gene polymorphism at rs1437396 and alcohol use disorder, with or without major depression disorder

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Girdin is a protein involved in neuronal migration and hippocampal development. It is encoded by the coiled-coil domain-containing 88A (*CCDC88A*) gene, located on the short arm of chromosome 2 (2p). The *CCDC88A* gene is modulated by the intergenic single-nucleotide polymorphism (SNP) of the rs1437396, situated 9.5 kb downstream from its transcription stop site. As recent genome-wide research has associated the T allele of the SNP with increased risk of alcohol use disorder (AUD), we wanted to validate this finding in an independent cohort and to test further for an association with comorbid major depressive disorder (MDD). The study included 226 AUD patients (AUD group), 53 patients with comorbid MDD, and 391 controls selected randomly. The participants were genotyped for the rs1437396 polymorphism using the real-time polymerase chain reaction. The association between the rs1437396 polymorphism and increased risk of AUD and AUD+MDD was tested with logistic regression. Our results show significantly higher frequency of the T risk allele in the AUD group (p=0.027) and even higher in the AUD+MDD group (p=0.016). In conclusion, this is the first study that has validated the association between the rs1437396 polymorphism of the *CCDC88A* gene and AUD with or without MDD. Studies on larger samples of patients are needed to further investigate the mechanism of this association.

KEY WORDS: girdin; major depressive disorder; rs1437396 T allele

Alcohol use disorder (AUD) is one of the major causes of morbidity and mortality, affecting more than 95 million individuals globally (1, 2). Apart from psychological and environmental factors, around 45–65 % of AUD cases is owed to genetic factors (3). So far, AUD has been associated with numerous single nucleotide polymorphisms (SNPs) in genes encoding alcohol-metabolising enzymes [alcohol dehydrogenase (ADH) and acetaldehyde dehydrogenase (ALDH)] and most neurotransmitters (such as serotonin, dopamine, and glutamate), each with an effect size of less than 1 % ($R^2$<0.005) (4, 5). The most studied are the associations between AUD and the *ADH1B* gene on chromosome 4 or the *ALDH2* gene on chromosome 12, more common in Asians (6). Some functional *ADH1B* variants have been associated with excessive drinking among US veterans of European and African ancestry (7). One genome-wide meta-analysis of problematic alcohol use in 435,563 individuals (8) has identified 29 gene variants independently associated with problematic alcohol use, Other studies have also identified neurotransmitter-encoding gene variants associated with increased risk of AUD or other dependence, including the serotonin and gamma-aminobutyric acid (GABA) genes (9), μ opioid receptor gene (*OPRM1*) (10), the glucokinase receptor gene (*GCKR)* (11, 12), dopamine receptor gene (13, 14), fatty acid amide hydrolase (*FAAH*) gene (involved in cannabis use disorder) (12), prodynorphin (*PDYN*) gene (12, 15), *SLC39A8* gene (associated with both AUD and nicotine dependence) (16), and many more (17–20).

One genome-wide association study with 16,087 participants (21) described a new significant association between AUD and the rs1437396 polymorphism ($p=1.17 \times 10^{-10}$), located on the short arm of chromosome 2 (2p) in an intergenic region, 9.5 kb downstream from the transcription stop site of the coiled-coil domain-containing 88A (*CCDC88A*) and 9 kb upstream from the transcription site of the mitochondrial translational initiation factor 2 (*MTIF2*).

*CCDC88A* encodes girdin (acronym for GIRDers of actIN filaments), a large 250 kDa actin-binding protein. Since it is essential for the cytoskeleton structure, girdin regulates the migration of fibroblasts and endothelial, and tumour cells as well as neurone migration during early brain development (22). Girdin also regulates axonal development during neurogenesis through its interaction with the Disrupted-In-Schizophrenia 1 (*DISC1*) gene associated with schizophrenia, bipolar disorder (23), opioid dependence (24), cognitive impairment, recurrent major depressive disorder (25), and

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compulsive behaviours (26). Furthermore, girdin enhances the effects of the vascular endothelial growth factor (*VEGF)* (27), which mediates antidepressant-induced neuronal proliferation in the hippocampus (28).

The aim of this study was to find the association between the *CCDC88A* rs1437396 polymorphism and AUD. Since girdin mediates other known factors for depressive symptoms, we decided to further investigate its role in the pathogenesis of the major depressive disorder in AUD patients.

## MATERIALS AND METHODS

### Participants

Participants were recruited consecutively at the Psychiatry Department of the County Clinical Emergency Hospital in Cluj-Napoca, Romania between May 2017 and June 2020. In total, the study included 617 participants (417 men and 200 women), of whom 226 were AUD (53 AUD+MDD) patients (excluded were those who did not want to participate or were diagnosed psychiatric disorders other than AUD and/or MDD) and 391 healthy controls with no history of AUD or other psychiatric disorders. AUD and MDD were diagnosed in a structured clinical interview using the DSM-5 classification (29). The severity of depressive symptoms was scored on the 17-item Hamilton Depression Rating Scale (HAM-D) (30) as mild (10–13 points), mild to moderate (14–17 points), or moderate to severe (>17 points).

All participants filled out a questionnaire with their demographic data, including age, residence (urban/rural), education, employment (employed/unemployed/disability pension/retired), marital status (single/with a partner), and family history of AUD and signed informed consent before the study began. The study was approved by the Ethics Committee of the Iuliu Hatieganu University of Medicine and Pharmacy (approval No. 167/07.04.2017) and complied with the principles of the Helsinki Declaration.

### Genotyping

Blood (2 mL) was taken from all patients by venipuncture into vacutainers coated with ethylene-diamine-tetra-acetic acid (EDTA) to prevent coagulation. The samples were stored at +4 °C for a maximum of two days until processing. DNA was extracted according to the protocol of the commercial kit producer Wizzard® Genomic DNA Purification Kit (Promega, Madison, WA, USA). The genotypes of the rs1437396 polymorphism were determined using the TaqMan SNP Genotyping assay run on a QuantStudio 3 real-time polymerase chain reaction (PCR) machine (both from Applied Biosystems, Thermo Fisher, Waltham, MA, USA). The PCR primers were as follows: rs1437396 forward, 5'-AAA AGA ATG ACA TTT AGT TAT GTA-3' and rs1437396 reverse, 3'-AAT GAA TTA TAT GAG CTT TTT TTG-5'.

The studied alleles were T (the risk allele) and C, forming the TT, TC, and CC genotypes.

### Statistical analysis

Data were processed using the IBM SPSS Statistics 25.0 (IBM, Armonk, NY, USA), and we relied on the chi-squared test for the Hardy-Weinberg equilibrium (HWE). The difference in allelic and genotype distributions between patients and controls was assessed with Fisher's exact test, assuming three genetic models (co-dominant, dominant, and recessive). Binary univariate logistic regression analysis was used to estimate the additional risk of comorbid depression. The statistical power was assessed with CaTS Power Calculator for Genetic Studies (31, 32) and significance set to $p<0.05$.

## RESULTS

The median age of the AUD group was 51 (IQR 47) and of controls 45 (IQR 39). Table 1 shows the demographic and clinical information about the AUD+MDD and AUD-only patients. The allele distribution was normal and in line with the Hardy-Weinberg equilibrium for both the AUD group ($\chi^2=0.1$, $p=0.75$) and controls ($\chi^2=1.57$, $p=0.78$), indicating that the sample is representative of the population ($p>0.05$).

Table 2 shows the distribution of the SNP rs1437396 genotypes in the AUD group and controls. The T allele of polymorphism rs1437396 turned out to be significantly associated with a higher risk of AUD in dominant or codominant models of transmission. After applying binary logistic regression, the dominant model explains 1.1 % of the risk of developing AUD (Nagelkerke $R^2=0.011$) and can correctly predict 63.4 % of cases. Assuming the prevalence of AUD in Romania of 1.3 %, the relative genetic risk of 1.47 in the multiplicative model, minor allele frequency (MAF) of 24 %, and type I error of 0.05, the statistical power of the study to detect an association between the rs1437396 polymorphism and AUD is 91.8 %.

Table 3 shows the significantly higher frequency of the T allele for AUD+MDD patients than for those without MDD. This association is confirmed by log regression analysis, used also to evaluate other variables potentially contributing to MDD (Table 4). Of them, only high (college) education showed significant association with AUD. The regression pattern explains 1.14 % of cases of the dual diagnosis (Nagelkerke $R^2=0.114$) and can predict the correct categorization in 77.9 % of cases. The Hosmer-Lemeshow test confirms that the regression model is adequate for predicting depression comorbid with AUD ($p=0.819$).

## DISCUSSION

To our knowledge, this study is the first to confirm the association between the rs1437396 polymorphism and AUD

**Table 1** Demographic and clinical characteristics of alcohol use disorder (AUD) patients with or without major depressive disorder (AUD+MDD)

| Demographic data | | AUD+MDD N=53 (%) | AUD only N=173 (%) | p-value |
|---|---|---|---|---|
| Age | | 49 (35) | 52 (48) | 0.178[a] |
| Gender | Female | 7 (13.2) | 27 (13.3) | 1[c] |
| | Male | 46 (86.8) | 150 (86.7) | |
| Living environment | Urban | 35 (66) | 99 (57.2) | 0.261[c] |
| | Rural | 18 (34) | 74 (42.8) | |
| Education | College | 8 (15) | 5 (2.9) | **0.003*[b]** |
| | High school | 20 (37.4) | 53 (30.6) | |
| | Vocational school | 15 (28.3) | 78 (45.1) | |
| | Elementary school | 10 (18.3) | 37 (21.4) | |
| Marital status | With a partner | 26 (49) | 101 (58.4) | 0.261[c] |
| | Single | 27 (51) | 72 (41.6) | |
| Family history of AUD | Yes | 34 (64.1) | 114 (65.9) | 0.867[c] |
| | No | 19 (35.9) | 59 (34.1) | |
| Occupation | Employed | 24 (45.3) | 58 (33.5) | 0.052[b] |
| | Unemployed | 9 (17) | 52 (30.1) | |
| | Disability pension | 14 (26.4) | 29 (16.8) | |
| | Retirement due to age | 6 (11.3) | 34 (19.6) | |

Age (continuous variable) is presented as median with interquartile range in parentheses. Categorical variables are reported as number of participants with percentage in parenthesis. [a] Mann-Whitney *U* Test, [b] chi-squared test, [c] Fisher's exact test. Statistically significant p-values are bolded and marked with asterisk. AUD – alcohol use disorder; MDD – major depressive disorder

**Table 2** Distribution of genotype and allele frequency of the rs1437396 polymorphism in patients with alcohol use disorder (AUD) and healthy controls

| Model | | AUD N=226 (%) | Controls N=391 (%) | OR (95 % CI) | p-value |
|---|---|---|---|---|---|
| Allelic | T vs C | 120 (26.5) | 167 (21.4) | 1.33 | |
| | | 332 (73.5) | 615 (78.6) | (1.01–1.14) | **0.042*** |
| Co-dominant | TT vs CC | 15 (6.6) | 22 (5.63) | 1.38 | |
| | | 121 (53.5) | 246 (62.9) | (0.7–2.7) | 0.36 |
| | CT vs CC | 90 (39.8) | 123 (31.5) | 1.48 | |
| | | 121 (53.5) | 246 (62.9) | (1.05–2.1) | **0.031*** |
| Dominant | TT+CT vs CC | 105 (46.4) | 145 (37) | 1.47 | |
| | | 121 (53.6) | 246 (63) | (1.05–2.05) | **0.026*** |
| Recessive | TT vs CC+CT | 15 (6.6) | 22 (5.6) | 1.19 | |
| | | 211 (63.4) | 369 (94.4) | (0.6–2.34) | 0.6 |

p-values were determined by Fisher's exact test. Statistically significant p-values are bolded and marked with the asterisk

**Table 3** Distribution of genotype and allele frequency of the rs1437396 polymorphism in patients with alcohol use disorder and major depressive disorder (AUD+MDD) vs the AUD-only group

| Model | | AUD+MDD N=53 (%) | AUD N=173 (%) | OR (95 % CI) | p-value |
|---|---|---|---|---|---|
| Allelic | T vs C | 38 (35.85) | 82 (23.7) | 1.8 | **0.016*** |
| | | 68 (64.15) | 264 (76.3) | (1.12–2.87) | |
| Co-dominant | TT vs CC | 6 (11.32) | 9 (5.2) | 3.17 | 0.077 |
| | | 21 (39.62) | 100 (57.8) | (1.02–9.88) | |
| | CT vs CC | 26 (49.05) | 64 (37) | 1.93 | 0.065 |
| | | 21 (39.62) | 100 (57.8) | (1–3.72) | |
| Dominant | TT+CT vs CC | 32 (60.38) | 73 (42.2) | 2.08 | **0.027*** |
| | | 21 (39.62) | 100 (57.8) | (1.11–3.91) | |
| Recessive | TT vs CC+CT | 6 (11.32) | 9 (5.2) | 2.32 | 0.124 |
| | | 47 (88.68) | 164 (94.8) | (0.78–6.67) | |

p-values were determined by Fisher's exact test. Statistically significant p-values are bolded and marked with asterisk

**Table 4** Logistic regression for the association between the rs1437396 polymorphism and alcohol use disorder and major depressive disorder (AUD+MDD) comorbidity (N=53)

| Variables | B | SE | $\chi^2$ | df | OR (CI 95 %) | p-value |
|---|---|---|---|---|---|---|
| rs1437396 (T allele) | 0.779 | 0.338 | 5.326 | 1 | 2.17 (1.12–4.22) | **0.021*** |
| Gender (male) | 0.059 | 0.509 | 0.013 | 1 | 1.06 (0.39–2.87) | 0.908 |
| Age | -0.018 | 0.018 | 0.258 | 1 | 0.98 (0.94–1.01) | 0.324 |
| Living environment (urban) | 0.18 | 0.355 | 0.258 | 1 | 1.19 (0.59–2.4) | 0.611 |
| Education (college) | 1.923 | 0.749 | 6.6 | 1 | 6.84 (1.57–29.67) | **0.010*** |
| Marital status (with a partner) | -0.320 | 0.373 | 0.736 | 1 | 0.72 (0.34–1.5) | 0.391 |
| Family history of AUD | -0.023 | 0.377 | 0.004 | 1 | 0.97 (0.46–2.04) | 0.951 |
| Occupation (employed) | 0.093 | 0.365 | 0.065 | 1 | 1.09 (0.53–2.24) | 0.799 |
| Constant | -0.947 | 1.034 | 0.838 | 1 | | 0.36 |

p-values were determined with logistic regression. Statistically significant p-values are bolded and marked with asterisk

observed by Gelernter et al. (21). In addition, it provides preliminary evidence of even higher risk of developing depression comorbid with AUD associated with the T allele.

Our study has also singled out higher education as the only variable significantly associated with AUD and depression comorbidity (more frequent in university graduates). Literature data show the contrary – higher prevalence of depressive symptoms in people with low education (35). Furthermore, our findings about other environmental factors are not in line with evidenced association between depression and the employment, economic, and marital status, consumption of other psychoactive substances, cultural environment, and lifestyle (36–41). One possible explanation for this difference might be that in Romania, depressed people with lower education tend to avoid going to the doctor, especially to a psychiatrist due to the social stigma regarding mental illness. Most of the participants included in the study did not come to the hospital voluntarily. They were brought in by the ambulance as a medical emergency (violence in the context of alcohol intoxication or severe alcohol withdrawal symptoms).

Frequent AUD and MDD comorbidity can be explained by several theories. Alcohol has neurotoxic effects and negative social consequences (35), and some individuals use it as a form of self-medication for negative emotions (36). Genome-wide association studies (GWASs) have found multiple variants associated with AUD or MDD, but only one SNP has been associated with both disorders so far – the *SEMA3A* variation which encodes semaphorin, a membrane protein involved in axon and dendrite growth (20). However, an association analysis (36) showed that shared genetic factors had only a modest impact on this comorbidity.

The main limitation of this study is the small sample size, especially for the MDD subgroup. Furthermore, it does not explain how rs1437396 mediates AUD, and the best hypothesis is by modulating the effects of *CCDC88A* on other key genes for the activity of the central nervous system.

In conclusion, this study has confirmed a significant association between AUD and the rs1437396 polymorphism and, for the first time, an even higher frequency of the T allele in the MDD subgroup of AUD patients. This result should be validated on a larger sample and perhaps shed some light on the genetic mechanisms behind this rather frequent comorbidity.

### Conflict of interests

None to declare.

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**Povezanost polimorfizma rs1437396 gena *CCDC88A* s poremećajem zloporabe alkohola**

Girdin je protein koji sudjeluje u neuronskoj migraciji i razvoju hipokampusa, a kodira ga gen *88A* koji sadržava domenu sa smotanom zavojnicom (eng. *coiled-coil domain-containing* 88A *gene*, krat. *CCDC88A*) koja se nalazi na kraćem kraku kromosoma 2 (2p). Gen *CCDC88A* mijenja se s međugenskim jednonukleotidnim polimorfizmom (eng. *single-nucleotide polymorphism*, krat. SNP) na mjestu rs1437396, 9,5 kb nizvodno od svojega transkripcijskog završetka. Budući da je u nedavnom istraživanju na razini genoma zamijećena povezanost alela T ovoga polimorfizma s povećanim rizikom od poremećaja zloporabe alkohola (eng. *alcohol use disorder*), htjeli smo provjeriti tu povezanost u neovisnoj kohorti randomiziranih ispitanika i dodatno ispitati je li polimorfizam povezan i s popratnim povratnim depresivnim poremećajem (eng. *major depressive disorder*). Ispitivanje je obuhvatilo 226 bolesnika s poremećajem zloporabe alkohola, 51 bolesnika s popratnim povratnim depresivnim poremećajem i 391 kontrolnog ispitanika. Ispitanici su genotipizirani radi utvrđivanja onih koji imaju polimorfizam rs1437396 pomoću polimerazne lančane reakcije u stvarnom vremenu (eng. *real-time polymerase chain reaction*) te je logaritamskom regresijskom analizom utvrđena povezanost polimorfizma rs1437396 s rizikom od poremećaja zloporabe alkohola s popratnim povratnim depresivnim poremećajem ili bez njega. Naši podatci upućuju na značajno veću učestalost alela T u bolesnika s poremećajem zloporabe alkohola (p=0,027) te na još značajniju učestalost u bolesnika s obama poremećajima (p=0,016). Ovo je prvo istraživanje koje je potvrdilo povezanost između polimorfizma rs1437396 gena *CCDC88A* i poremećaja zloporabe alkohola s popratnim povratnim depresivnim poremećajem ili bez njega. Daljnja istraživanja mehanizama ove povezanosti potrebno je provesti na većim uzorcima.

KLJUČNE RIJEČI: alel T polimorfizma rs1437396; girdin; povratni depresivni poremećaj