Novel human genome variants associated with alcohol use disorders identified in a Lithuanian cohort

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Background. Alcohol use disorder (AUD) is a chronic relapsing brain disease characterized by compulsive alcohol use, loss of control over alcohol intake, and a negative emotional state when not using (1). Abusive alcohol consumption directly affects a person’s physical and psychological health and social life. The World Health Organization has shown that Lithuania is a leading country in pure alcohol consumption in the world (2). The aim of this study is to find novel genome variants that are associated with the AUD in the Lithuanian cohort.

Materials and methods. A case-control study included 294 individuals of Lithuanian ethnicity, who were divided into two groups based on their habits of alcohol use. Single nucleotide polymorphism array analysis was performed using Illumina HiScanSQ™ genome analyzer.

Results. Our study showed that rs686141T>C variant in NALCN gene is more prevalent in the non-drinker group compared to the alcohol drinker group (relative allele frequency, respectively: 0.38 and 0.27, OR = 0.60 (CI 95% 0.37–0.98), p = 0.0408). Meanwhile, rs6354C>A, in SLC6A4 gene, variant’s genotype distribution showed statistically significant difference between the non-drinker and alcohol drinker group (distribution of genotypes in the case group: 9/72/172 (CC/CA/AA) and in the control group: 5/7/29, p = 0.0264).

Conclusion. We analyzed 23 genes associated with AUD and identified two novel genome variants (rs686141T>C and rs6354C>A). The study shows that genome analysis is an important tool for AUD research. The results supplement the known information about genes associated with AUD.

Keywords: Alcohol Use Disorder, Illumina HiScanSQ, genotyping, NALCN, SLC6A4

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INTRODUCTION

Alcohol use disorder (AUD) is a chronic relapsing brain disease characterized by compulsive alcohol use, loss of control over alcohol intake, and a negative emotional state when not using (1). In 2010, alcohol-attributable cancer, liver cirrhosis, and injury caused 1,500,000 deaths or 2.8% of all deaths worldwide (3). According to the World Health Organization, Lithuania is a leading country in pure alcohol consumption in the world with 18.2 litres of pure alcohol consumption per capita within a calendar year (2).

Recent studies have shown strong evidence to support the hypothesis that AUD is a complex disease with hereditary and environmental effects, and with 50–60% heritability (4). Genes involved in vulnerability to AUD include genes that act on common metabolic pathways involved in addiction to different substances and predisposition to other psychiatric disorders. Alcohol-specific genes include genes for metabolic enzymes involved in the metabolism of ethanol, as well as genes encoding gatekeeper molecules such as receptors or neurotransmitters (5).

An understanding of the molecular mechanisms and metabolic pathways involved in excessive alcohol consumption is crucial for treatment of and screening for AUD. The aim of this study was to find novel genome variants associated with AUD in a Lithuanian cohort.

METHODS

Single nucleotide polymorphism array analysis was performed on 294 selected Lithuanians, whose family members were born in Lithuania for three generations, using Illumina HiScanSQ™ genome analyzer. The case groups (alcohol drinker group) and the control (non-drinker group) were formed based on questionnaire. Descriptive statistics of the study groups are shown in Table 1.

DNA was extracted from venous blood samples using either MagneSil® Genomic, Large Volume System (Promega Corp., USA) automated for the TECAN Freedom EVO® platform (TECAN Group Ltd., Switzerland), according to the manufacturer’s instructions, or the phenol-chloroform extraction method. We used Illumina HiScanSQ™ platform and Illumina HumanOmniExpress-12 v1.1 array, adhering to the Infinium® HD Assay Ultra Protocol Guide (Illumina Inc., USA). The genotyping data visualization, primary quality control analysis, filtering, and output file generation were accomplished using the Illumina GenomeStudio v2011.1 Genotyping Module software.

Genotyping data contained 98 genome variants from 23 genes associated with AUD. Genome variants were picked for further investigation from these genes: ADH1A, ADH1B, ADH1C, ADH4, ADH5, ADH6, ADH7, ALDH1A1, ALDH2, CYP2E1, CHRNA3, CHRNA5, GABRA2, OPRM1, HTR2A, HTR3B, NALCN, COMT, DPYSL2, GAD2, SLC6A4, ANKK1, NPY. Genome variants, whose minor allele frequency was larger than 0.01, were selected for frequency evaluation in the Lithuanian population. The Hardy-Weinberg equilibrium and allele/genotype frequencies were determined using the PLINK v1.90b3.44 64-bit (2016-11-17) software (6). Pearson’s chi-squared test and Fisher’s exact test (for genotype counts less than 5) were used to evaluate the results.

RESULTS

Minor allele frequency (MAF) evaluation was done and only 65 genome variants with MAF greater than 0.01 were selected for further analysis. Three of them did not meet conditions of the Hardy-Weinberg equilibrium. Table 2 shows descriptive statistics of single nucleotide variants (SNV) used in the study.

Allele frequency analysis showed that rs686141T>C genome variant found in NALCN gene showed statistically significant difference

Table 1. Descriptive statistics of the study groups

| Sex  | Case group (n = 253), (%) | Control group (n = 41), (%) | Total (N = 294), (%) |
|------|-------------------------|---------------------------|----------------------|
| Female | 120 (47.43)           | 25 (60.98)                | 145 (49.32)         |
| Male   | 133 (52.57)           | 16 (39.02)                | 149 (50.68)         |
Genome variants associated with alcohol use disorders

in relative alternative allele frequency between the study groups. Relative allele frequency of rs686141T>C variant was 0.27 in the alcohol drinker group and 0.38 in the non-drinker group (OR = 0.60 (CI 95% 0.37–0.98), \( p = 0.0408 \)).

After the evaluation of genotype frequencies in the study groups, only one genome variant rs6354C>A in the \( SLC6A4 \) gene showed statistically significant difference between the study groups. Variant genotype distribution (CC/CA/AA) was 9/72/172 in the case group and 5/7/29 (\( p = 0.0264 \)) in the control group.

Table 2. SNV statistics of 65 genome variants used in analysis

| SNV | Counts (%) |
|------|------------|
| Intronic variants: | 33 (53.23) |
| UTR 3' variants | 28 (84.84) |
| UTR 5' variants | 5 (15.16) |
| Exonic variants: | 29 (46.77) |
| Synonymous | 11 (37.93) |
| Nonsynonymous | 17 (58.62) |
| Stopgain | 1 (3.48) |

Table 3. Table of results of allele frequency evaluation in the study groups

| Gene | SNV | Variant | Case group MAF | Control group MAF | \( p \) value\( ^\dagger \) | OR\( ^\ddagger \) |
|------|------|---------|----------------|------------------|----------------|-----------|
| \( ADH5 \) | rs7669660 | NM_000671:c.*966T>C | 0.08 | 0.10 | 0.5257 | 0.77 |
| \( ADH5 \) | rs11547772 | NM_000671:c.*775T>G | 0.05 | 0.05 | 0.8938 | 0.93 |
| \( ADH5 \) | rs6827292 | NM_000671:c.*574T>C | 0.03 | 0.05 | 0.4919 | 0.68 |
| \( ADH5 \) | rs1803037 | NM_000671.4:c.*417G>A | 0.05 | 0.05 | 0.8938 | 0.93 |
| \( ADH4 \) | rs1042364 | NM_000670.4:c.*19A>G | 0.34 | 0.24 | 0.0982 | 1.57 |
| \( ADH4 \) | rs1126673 | NM_000670.4:c.1120G>A | 0.38 | 0.33 | 0.3833 | 1.25 |
| \( ADH4 \) | rs1126672 | NM_000670.4:c.1051C>T | 0.34 | 0.24 | 0.0982 | 1.57 |
| \( ADH7 \) | rs284787 | NM_000673:c.*749C>T | 0.38 | 0.33 | 0.3653 | 1.26 |
| \( ADH7 \) | rs3805331 | NM_000673:c.*373T>C | 0.05 | 0.06 | 0.6708 | 0.81 |
| \( ADH7 \) | rs971074 | NM_000673.4:c.690G>A | 0.13 | 0.15 | 0.7696 | 0.91 |
| \( ADH7 \) | rs1753795 | NM_000673:c.*40T>C | 0.16 | 0.15 | 0.7518 | 1.11 |
| \( OPRM1 \) | rs6912029 | NM_000914:c.-172C>A | 0.04 | 0.05 | 0.5588 | 0.72 |
| \( OPRM1 \) | rs1799971 | NM_000914.4:c.118A>G | 0.07 | 0.07 | 0.9988 | 1.00 |
| \( OPRM1 \) | rs563649 | NM_001145287:c.-3004G>A | 0.10 | 0.10 | 0.9836 | 0.99 |
| \( OPRM1 \) | rs650245 | NM_001145286:c.*4A>G | 0.08 | 0.10 | 0.6153 | 0.82 |
| \( IPCEF1 \) | rs9479767 | NM_001130699:c.*4435T>C | 0.46 | 0.54 | 0.1777 | 0.73 |
| \( IPCEF1 \) | rs17277929 | NM_001130699:c.*3050T>C | 0.09 | 0.07 | 0.5631 | 1.30 |
| \( IPCEF1 \) | rs2236256 | NM_001130699:c.*2523G>T | 0.46 | 0.54 | 0.1777 | 0.73 |
| \( IPCEF1 \) | rs2236259 | NM_001130699:c.*2070T>C | 0.46 | 0.54 | 0.1777 | 0.73 |
| \( NPY \) | rs16139 | NM_000905.3:c.20T>C | 0.06 | 0.02 | 0.1963 | 2.52 |
| \( DPYSL2 \) | rs708621 | NM_001197293.2:c.1821T>C | 0.30 | 0.26 | 0.4142 | 1.25 |
| \( DPYSL2 \) | rs1058332 | NM_001197293:c.*1071G>A | 0.10 | 0.05 | 0.1586 | 2.09 |
| \( DPYSL2 \) | rs920633 | NM_001197293:c.*1557A>G | 0.14 | 0.09 | 0.1575 | 1.79 |
| \( DPYSL2 \) | rs17666 | NM_001197293:c.*2236A>G | 0.29 | 0.29 | 0.9738 | 1.01 |
| \( ALDH1A1 \) | rs8188000 | NM_000689:c.*455T>C | 0.07 | 0.11 | 0.2225 | 0.62 |
| \( ALDH1A1 \) | rs13959 | NM_000689.4:c.225C>T | 0.42 | 0.35 | 0.2507 | 1.33 |
Table 3. (continued)

| Gene   | SNV          | Variant                  | Case group MAF | Control group MAF | \(p\) value\(^\dagger\) | OR\(^\ddagger\) |
|--------|--------------|--------------------------|----------------|-------------------|--------------------------|----------------|
|        |              |                          |                |                   |                          |                |
| GAD2   | rs2236418    | NM_000818:c.-243A>G      | 0.21           | 0.21              | 0.9968                   | 1.00           |
|        |              |                          |                |                   |                          |                |
| CYP2E1 | rs6413419    | NM_000773.3:c.553G>A     | 0.01           | 0.00              | 0.2840                   | NA             |
|        |              |                          |                |                   |                          |                |
| CYP2E1 | rs2515641    | NM_000773.3:c.1263C>G    | 0.13           | 0.09              | 0.2695                   | 1.58           |
| ANKK1  | rs17115439   | NM_178510.1:c.255T>C     | 0.32           | 0.25              | 0.2264                   | 1.39           |
| ANKK1  | rs4938013    | NM_178510.1:c.453A>C     | 0.33           | 0.26              | 0.2061                   | 1.41           |
| ANKK1  | rs7118900    | NM_178510.1:c.715G>A     | 0.16           | 0.12              | 0.3990                   | 1.35           |
| ANKK1  | rs4938016    | NM_178510.1:c.1324G>C    | 0.36           | 0.29              | 0.2126                   | 1.38           |
| ANKK1  | rs2734849    | NM_178510.1:c.1469A>G    | 0.48           | 0.59              | 0.0719                   | 0.65           |
| ANKK1  | rs2734848    | NM_178510.1:c.1683C>T    | 0.18           | 0.15              | 0.4843                   | 1.26           |
| HTR3B  | rs1176744    | NM_006028.4:c.386A>C     | 0.28           | 0.29              | 0.7644                   | 0.92           |
| HTR3B  | rs17116138   | NM_006028.4:c.547G>A     | 0.04           | 0.05              | 0.5588                   | 0.72           |
| HTR2A  | rs9595552    | NM_001169547:c.*1542T>C  | 0.07           | 0.06              | 0.8508                   | 1.10           |
| HTR2A  | rs6314       | NM_000621.4:c.1354C>T    | 0.07           | 0.06              | 0.7846                   | 1.14           |
| HTR2A  | rs6313       | NM_000621.4:c.102C>T     | 0.32           | 0.37              | 0.3725                   | 0.80           |
| NALCN  | rs8922       | NM_052867.2:c.*1454T>G   | 0.22           | 0.22              | 0.9656                   | 0.99           |
| NALCN  | rs682767     | NM_052867.2:c.*1018T>C   | 0.38           | 0.45              | 0.2296                   | 0.75           |
| NALCN  | rs682666     | NM_052867.2:c.*946C>T    | 0.39           | 0.45              | 0.2578                   | 0.76           |
| NALCN  | rs9557581    | NM_052867.2:c.*931A>G    | 0.38           | 0.45              | 0.2296                   | 0.75           |
| NALCN  | rs1289556    | NM_052867.2:c.4416A>C    | 0.38           | 0.33              | 0.4210                   | 1.23           |
| NALCN  | rs17677552   | NM_052867.2:c.3714C>T    | 0.37           | 0.30              | 0.2721                   | 1.33           |
| NALCN  | rs868141     | NM_052867.2:c.3570T>C    | 0.27           | 0.38              | 0.0409                   | 0.60           |
| CHRNA3 | rs660652     | NM_000743:c.*1114T>C     | 0.36           | 0.33              | 0.5473                   | 1.16           |
| CHRNA3 | rs472054     | NM_000743:c.*952T>C      | 0.36           | 0.33              | 0.5536                   | 1.16           |
| CHRNA3 | rs578776     | NM_000743:c.*546C>T      | 0.25           | 0.24              | 0.8608                   | 1.05           |
| CHRNA3 | rs1051730    | NM_000743:c.645C>T       | 0.38           | 0.43              | 0.3940                   | 0.81           |
| CHRNA3 | rs8040868    | NM_000743:c.159A>G       | 0.42           | 0.46              | 0.4470                   | 0.83           |
| CHRNA3 | rs8192475    | NM_000743:c.110G>A       | 0.03           | 0.04              | 0.8898                   | 0.92           |
| SLC6A4 | rs3813034    | NM_001045:c.*670T>G      | 0.43           | 0.48              | 0.4897                   | 0.85           |
| SLC6A4 | rs1042173    | NM_001045:c.*463T>G      | 0.43           | 0.48              | 0.4897                   | 0.85           |
| SLC6A4 | rs6354       | NM_001045:c.*922G>T      | 0.18           | 0.21              | 0.5214                   | 0.83           |
| COMT   | rs4633       | NM_000754.3:c.186C>T     | 0.46           | 0.51              | 0.3659                   | 0.81           |
| COMT   | rs4680       | NM_000754.3:c.472G>A     | 0.46           | 0.51              | 0.3659                   | 0.81           |
| COMT   | rs769224     | NM_000754.3:c.597G>A     | 0.04           | 0.07              | 0.1405                   | 0.50           |
| COMT   | rs165599     | NM_000754.3:c.*522G>A    | 0.35           | 0.44              | 0.1277                   | 0.69           |
| COMT   | rs165728     | NM_000754.3:c.*764C>T    | 0.11           | 0.17              | 0.1193                   | 0.60           |

* MAF – Minor Allele Frequency
† \(p\) value – Pearson's Chi squared test \(p\) value
‡ OR – Odds Ratio

Statistically significant results are bolded
DISCUSSION

In this study, we examined the association of AUD with genome variants found in genes related to various enzymes, that are responsible for the metabolism of ethanol, neurotransmitters, or function of the receptors. Our data revealed novel genome variants in the association of NALCN and SLC6A4 genes with AUD. rs686141T>C variant has never been studied before in similar AUD-related studies. Meanwhile, rs6354C>A variant was known but never studied more extensively. As a further matter, NALCN and SLC6A4 genes were considered responsible for depressive phenotype and other psychiatric diseases.

In similar studies, it was hypothesized that the aetiology of both psychiatric diseases and AUD was related to a dysfunctional serotonergic system (7, 8). Serotonin is a monoamine known to affect anxiety, cognition, reward, emotion, drug responses, and stress (9, 10). The role of serotonin in alcohol consumption has been studied in animal models. The serotonergic system has been found to have only a minor role in mediating sensitivity to high doses of alcohol, but to be crucial for the development of alcohol reinforcement (8, 11). A study by Jieken Yang and Ming D. Li showed that haplogroup formed by rs6354C>A, rs25528C>A, rs2066713C>T, rs8071667A>G, and rs16965623T>C showed a marginal association with AUD under the additive model ($P = 0.005$) (12).

Recent Genome Wide Association Study (GWAS) performed in a group of 2322 individuals demonstrated significant SNV (rs17484734G>A) located in the NALCN gene and a high risk of AUD (13). NALCN is a protein that contributes to the resting membrane potential in these neurons by eliciting a depolarizing current to counterbalance the hyperpolarizing current (14, 15). Changes in this system might be associated with substance addiction and AUD. A rodent study showed that mice that carry a hypomorphic mutation in the Unc-79 gene (one of the NALCN subunits) voluntarily consume more ethanol than wild-type mice (16).

The identification of novel genome variants and AUD is important to improve our ability to predict the risks and treatment responses, to develop new treatments and screening techniques.

CONCLUSIONS

We analysed 23 genes associated with AUD and identified two novel genome variants (rs686141T>C and rs6354C>A). The study shows that genome analysis is an important tool in AUD research. The results supplement known information about genes associated with AUD.

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DECLARATION OF INTEREST

The authors declare no conflicts of interest. The authors alone are responsible for the content and writing of this article.

ETHICAL APPROVAL

All procedures performed in this study involving human participants were conducted in accordance with the ethical standards of the Vilnius Regional Research Ethics Committee (No. 158200-05-329-79. date: 2011-05-03) and with the 1964 Declaration of Helsinki and its later amendments.

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Santrauka

Įžanga. Alkoholio vartojimo sutrikimas (AVS) – tai lėtinė atsinaujinančių nervų sistemos liga, kuri pasižymi alkoholio vartojimo priklausymu, kontrolės praradimu vartojant ir neigiama emocine būsena, kai jis nevartojamas (1). Piktnaudžiavimas alkoholiu tiesiogiai veikia žmogaus fizinę, psichologinę sveikatą ir socialinį gyvenimą. Pasaulio sveikatos organizacijos duomenimis, Lietuva yra pirmaujanti šalis pasaulyje pagal grynojo alkoholio suvartojimą, tenkantį vienam žmogui (2). Dėl šių priežasčių pasirinktas tyrimo tikslas – identifikuoti naujus genomo variantus, susijusius su AVS Lietuvos kohortoje.

Tiriamieji ir metodai. Tyrimo metu analizuoti 294 lietuvių kilmės asmenų, kurie pagal alkoholio vartojimo įpročius buvo suskirstyti į vartojančių ir nevartojančių grupes, duomenys. Genotipavimas atliktas vieno nukleotido polimorfizmo paremtu lyginamosios genomo hibridizacijos metodu, naudojant Illumina HiScanSQ™ genetinį analizatorį.

Rezultatai. Tyrimo rezultatai parodė, kad NALCN geno variantas rs686141T>C yra labiau paplitęs nevartojančių alkoholio grupėje, palyginti su alkoholį vartojančia grupė (santykinis alelio dažnis atitinkamai 0,38 ir 0,27, šansų santyksis (ŚŚ) = 0,60 (pasikliautinas intervalas (PI) 95 % 0,37–0,98), p reikšmė = 0,0408). O rs6354C>A SLC6A4 geno varianto genotipų grupėse analizė parodė statistiškai reikšmingą skirstumą tarp alkoholį vartojančių ir nevartojančių asmenų grupių (genotipų pasiskirstymas atvejo grupėje: 9/72/172 (CC/CA/AA) ir kontrolinėje grupėje: 5/7/29, p reikšmė = 0,0264).

Išvados. Atlikus 23 su AVS asocijuotų genų analizę nustatyti du genomo variantai (rs686141T>C ir rs6354C>A), kurie iki šiol nebuvo siejami su AVS. Tyrimas rodo, kad tolimesni genominiai tyrimai yra svarbi priemonė tiriant AVS. Gauti rezultatai papildo iki šiol gautą informaciją apie su AVS asocijuotus genus.

Raktažodžiai: alkoholio vartojimo sutrikimas, Illumina HiScanSQ, genotipavimas, NALCN, SLC6A4