Reviews

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A CURRENT VIEW OF THE GENETICS OF SUBSTANCE USE DISORDERS AND DEVELOPMENT OF METABOLIC COMORBIDITIES

The review focuses on the main challenges and achievements of genomic research on substance use disorders (SUDs), which include drug dependence, alcohol abuse, and smoking, as well as the state-of-the-art of the comorbidity of this spectrum with metabolic disorders, on the example of metabolic syndrome. A particular emphasis is placed on genomic studies of SUDs and related health conditions in Eastern European countries, which are traditionally not or poorly included in large genome-wide association studies (GWASs). SUDs have a high degree of comorbidity and significantly increase the risk of many diseases, including other psychiatric and metabolic disorders. The question of pathophysiological and genetic causes of comorbidity attracts attention in current research and some results are already shown (genetic correlation and pleiotropic effects). At the same time, genomic studies of SUDs, even in well-studied populations, are still not sufficiently informative, and polygenic risk scores only slightly improves performance of the existing SUDs risk prognostic models. This might be partly due to the fact that SUDs represent a complex set of interrelated phenotypes rather than a set of distinct nosologic forms, which is usually not taken into account in the design of the majority of GWASs. The high level of polygenicity of these phenotypes also increases the sample number expectations to ensure sufficient statistical power. A multi-phenotype approach to genomic studies of such complex, highly correlated phenotypes can increase their efficiency.

Keywords: *substance use disorder, polygenic disorder, genome-wide association study, comorbidity, metabolic syndrome.*

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Substance use disorders (SUDs): A summary of genomic research

Substance use disorders (SUDs), including drug addiction, alcohol abuse, and smoking, are a global threat to public physical and mental health. Prevalence of alcohol use disorder in 2021 in Ukraine was 3.6%, and moreover, the country ranked 6th among countries with the highest alcohol-related mortality (alcohol-attributable fractions, all-cause deaths) [1]. According to the Ministry of Health and the Global Adult Tobacco Survey (GATS), in 2017, 20.1% of the adult population in Ukraine smoked daily [2]. According to WHO, 245,000 deaths worldwide per year occur due to drug use. The estimated global number of drug users has increased from 240 million in 2011 to 296 million in 2021 [3]. At the same time, the prevalence of amphetamine use in Ukraine according to UN data for 2016 was 0.3%, opiates — 1.05% [4], and these statistics may be underestimated [5].

SUDs are complex polygenic disorders, the development and severity of which depend on the interaction of genetic, epigenetic, family (i,e, individual environment), and environmental factors. Twin studies have shown that the contribution of genetic factors to the variability of SUDs varies largely from medium to high values. Heritability ranges from 0.39 for hallucinogens to 0.72 for cocaine use [8].

There is a large number of genetic loci involved in the genetic predisposition to the development of SUDs. The majority of the known loci identified in SUDs GWASs are mapped in/near genes of enzymes that metabolize these substances (including genes of the alcohol dehydrogenase cluster *ADH*) [9, 10, 12], their receptors or neurotransmitters (including *DRD2, HTR2A, OPRM1*) [9—15], involved in reward systems, memory, cortical connectome, as well as genes encoding various regulators of metabolism, development, signaling, *etc.* (*FTO, SOX6, BANK1*) [9, 11, 12, 15]. However, despite a large number of genome-wide association studies (GWASs) and candidate gene studies, the genetic risk factors common and specific to different substances have still not been fully identified, even among the European population of Western Europe and the USA, which comprised the majority of the datasets included in these studies [9—15]. The studies show significant polygenicity of SUDs [9—15].

The table represents a very brief comparison of the output of GWASs for different disease domains reported at EBI-NHGRI GWAS Catalog [16]. We demonstrate the number of studies, the number of reported associations (at $p < 10^{-5}$) and their ratios (i.e. mean number of associated loci per study) as a first, a very approximate measure of the studies output. We suggest the latter solely to make some comparable measure of amount of the identified loci per study that would reduce the bias of the very varying number of studies for different disease domains. It can be seen that the number of the reported loci varies from tens to thousands, and the number of GWASs varies from 3 for Alcohol + Nicotine co-dependence to 358 for Major Depressive Disorder, if we focus on the phenotypes selected in this table. It can be clearly seen even at this stage, that SUDs GWASs give relatively less output even in comparison with other psychiatric and neurological diseases and much less than metabolic and autoimmune diseases.

A more robust measure of the GWAS output for a given trait is the performance of the polygenic risk scores (PRSs) [17]. PRSs obtained for some substance use disorders, in particular alcohol (AUD), explain only a small percentage of phenotypic variation [18]. A comparison of the predictive power (area under the curve — AUC) for models of alcohol dependence development with the inclusion of genomic data by the PRS method and without this genomic data (baseline model = only other, "classic" risk factors) showed only a slight increase in AUC when genomic data were added [19]. PRSs created for some phenotypes (e.g. alcohol dependence) have limited correlation with other phenotypes in biobanks (e.g. frequency of drinking or AUDIT scores), which also indicates a lack of informativeness of the studies [20]. This might be partly due to the fact that SUDs are a complex set of phenotypes, and, e.g., alcohol dependence, the amount of alco-

hol consumed, binge drinking and problematic alcohol use (i.e., drinking too often and too much) may be associated with partially different risk factors, including genetic ones [7, 10, 12].

Furthermore, SUDs, being a part of Behavioural and mental disorders, also represent a set of epidemiologically correlated phenotypes between each other [6, 22] and with other psychiatric phenotypes, such as schizophrenia [6], major depressive disorder [6, 21, 24], bipolar disorder [6, 21] and post-traumatic stress disorder [6]. At the same time, comparatively little is known regarding genetic correlation between main addictions, and between SUDs and psychiatric traits [6, 18, 25, 26], though some evidence accumulates, e.g. in favour of the genetic relationship between cannabis use disorder and schizophrenia [14]. The direction of causality is also unclear. Furthermore, psychiatric traits, including SUDs are comorbid with metabolic traits, such as type 2 diabetes and related traits[22, 23, 27]. The possible genetic correlations and their nature are also being investigated.

Some studies were aimed to estimate genetic correlations between tobacco dependence and susceptibility to dependence on other substances, as well as other psychiatric traits with which there are shown epidemiological correlations [15, 29, 30]. LD-score regression (LDSC) of tobacco use disorder and related cigarette consumption traits have shown significant genetic correlations with cannabis use disorder, drinks per week, opioid use disorder, ADHD, *etc* [15].

It has been shown that genetic associations with complex polygenic traits can differ in populations with different evolutionary histories [31, 32]. Therefore the genetic associations and polygenic risk scales need to be validated in different populations before their further application. Moreover, the recent population-genetic studies have revealed significant differences between a pilot dataset of Ukrainians and Russians and Central European populations [33]: these populations diverge (do not cluster together) when analyzing the genome-wide data using the principal component analysis me-

Number of associated loci at p-value <10^{-5} reported in GWAS Catalog

Phenotype	Overall number of reported loci	Number of studies	Average number of associations per study
Substance use disorders domain			
Alcohol dependence	281	49	5.73
Alcohol + Nicotine co-dependence	10	3	3.33
Nicotine Dependence	146	35	4.17
Drug dependence	962	144	6.68
Other psychiatric and neurological domains			
Parkinson disease	753	100	7.53
Major Depressive Disorder	3909	358	10.92
Schizophrenia	5424	193	28.10
Autoimmune domain			
Rheumatoid arthritis	3692	195	18.93
Multiple Sclerosis	869	80	10.86
Metabolic and cardiovascular domains			
Coronary Artery Disease	4229	216	19.57
Type 1 Diabetes Mellitus	1058	86	12.30
Type 2 Diabetes Mellitus	7631	252	30.28
Metabolic Syndrome	2462	30	82.07

thod. Moreover, the sequencing of Ukrainian genomes has allowed to identify 478,000 novel genomic SNPs that have never been previously registered in the Genome Aggregation Database (gnomAD) [34]. This highlights the need to improve our knowledge of the genetic architecture of SUDs in Ukraine.

SUDs research in Eastern Europe: state-of-the-art

In Eastern Europe, a few studies of different SUDs have been published; these studies tend to investigate one substance per study [35, 36], or focus on secondary signs/manifestations, complications, or psychiatric comorbidities/personality traits outside the SUD spectrum [37]. Some loci that have been consistently associated with SUDs in Western populations, have been replicated in Eastern European populations (more precisely, in Slavic populations [35, 37, 38, 40] and in neighboring Moldova/Romania [39]), while some have not [36, 42]. SNP in *CCDC88A* was associated with alcohol use disorder and variation in *BDNF*, *DRD2*, and *SLC6A3* were associated with smoking status or severity [35, 38, 39]. *OPRM1* 118A > G polymorphism consistently associated with opiate abuse in Western populations has not been replicated with heroin dependence in Bulgarians [42]. In general the Eastern European genetic association studies quite often include investigation of genetic correlation with other comorbid diseases (outside of SUDs group), like fetal alcohol spectrum disorder [37], as well as with other psychiatric traits [38, 39] and personality traits [41] . The differences in replication success of GWAS- or candidate gene-identified associations in the US and Western European populations with Eastern European populations enforces the aforementioned need to include additional groups in genetic studies of European ancestry, especially since social norms of substance use and patterns of drug use vary greatly between countries [1—3, 5, 7].

Until recent years, there have been no genetic association studies of SUDs in Ukraine. We have previously compared the allele and genotype frequencies for genomic loci that have been associated with nicotine dependence in European and American populations, in a group of healthy Ukrainians with data from the 1000 Genomes Project [43]. Also, we have replicated some of the associations with SUDs in a small dataset including association of *ADH1B-ADH1C* rs1789891 with alcohol dependence and of *HTR2A* rs6313 with smoking [44, 45], however these earlier studies were characterized by low power and required an increase in the sample size.

In addition to the abovementioned, the studies of other risk factors for SUDs, including psychosocial ones, have been/are being conducted . They have pinpointed incline to depression and risky behaviour among the people with drug and alcohol dependence [46] as well as contribution of education background, sleep problems to drinking and male gender, family divorce, unhealthy diet and lack of awareness about harmful consequences to smoking [47]. Apart from that, the molecular genetic studies of other behavioral traits [48, 49], the effects on physical health of the use of certain substances or drugs (pharmacogenomics) [50, 51], and population genetic studies in a broader psychiatric field [52, 53] have also been published. Thus, the question of genetics of SUDs in Ukrainians is quite underrepresented comparing to other European populations.

Metabolic syndrome: epidemiological correlations with SUDs and possible links in pathogenesis

Metabolic syndrome (MetS) is one of the most common non-communicable diseases, which can affect 20—30% of the young, middle-aged, and elderly population in both developing and highly industrialized countries. MetS encompasses a whole cluster of diseases, the most well-known of which are: obesity or insulin resistance, arterial hypertension, glucose intolerance or diabetes mellitus, and dyslipidemia. In a screening study conducted in Germany among 10,000 military flight personnel, a relationship was found between the future development of MetS and alcohol and nicotine addiction [54].

It has been shown that alcohol dependence or excessive alcohol consumption increases the level of cholesterol and its fractions, especially triglycerides, which characterise lipid metabolism [55]. An increase in triglyceride levels, i.e. hypertriglyceridemia, suggests an increased risk of acute pancreatitis, fatty liver disease, and coronary heart disease. Its phenotypic expression is highly heterogenic and is strongly influenced by concurrent conditions such as obesity, alcohol consumption or metabolic syndrome. Genetic variants in the triglyceride-regulating genes *LPL*, *APOA5*, *APOC2*, *GPIHBP1*, and *LMF1* are implicated in hypertriglyceridemia, presumably via regulation of transcription and translation of proteins involved in triglyceride-rich lipoprotein metabolism [56, 57].

Three metabolic pathways of ethanol have been described in humans. They are: the microsomal ethanol oxidation system (MEOS, CYP2E1), alcohol dehydrogenase (ADH), and catalase pathways [58]. Ethanol and its metabolites have a toxic effect on biological structures. One of them, acetaldehyde, is a carcinogen that has a mutagenic effect on DNA. Ethanol oxidation contributes to acute alcoholic liver damage, causing stress, adipocyte death, and lipolysis. Data across Europe shows that 10% of all cancer cases in men and 3% in women can be attributed to alcohol consumption. Australian data suggests that 5% of the total cancer burden can be attributed to alcohol consumption. Alcohol consumption is a major cause of mortality and morbidity in many developed countries [58].

On another hand, smoking has been shown to be associated with an increased risk of metabolic syndrome in a large meta-analysis of 13 studies (56,691 participants, of whom 8,688 developed metabolic syndrome) [59], and in a recent study in the UK Biobank (data from 352,911 individuals) — with metabolic dysfunction-associated fatty liver disease (MAFLD) [60]. Smoking can increase blood pressure, waist circumference, triglycerides, and lower high-density lipoprotein cholesterol [59]. Moreover, smoking has for long been shown to be associated with insulin resistance, which may increase the risk of type 2 diabetes [61].

Search for causal genetic links between SUDs and MetS development

Whilst growing evidence pinpoints the epidemiological and pathophysiological links between MetS and SUDs [62], genetic studies with the use of Mendelian randomization have shown moderate shared genetic factors between SUDs (the most frequently studied alcohol dependence) and MetS [63, 64]. At the same time, there is emerging evidence that some of the genomic loci associated with alcohol dependence may exhibit pleiotropic effects, particularly with cardiometabolic groups of phenotypes [45, 65]. The most replicable are phenome-wide association studies (PheWAS) results for variation in the *ADH1B-ADH1C* region, particularly rs1229984 and rs1789891 which exhibit associations with alcohol-related behaviours, mental and sleep conditions, and cardio-metabolic health.

There is another clinically meaningful dimension of the issue of epidemiologic correlations between substance abuse and metabolic and developmental disorders. Numerous clinical studies have established that the use of smoking, alcohol, and psychotropic substances by parents before pregnancy, and the use of drugs by mother during pregnancy, carries a severe genetic risk for future generations. The harmful impact on health leads to the development of various diseases, including MetS [66]. In a longitudinal study of prenatal alcohol exposure (fetal alcohol spectrum disorder (FASD), it was shown that FASD is associated with 428 comorbidities covering 18 of the 22 ICD-10 categories. The most common (50 to 91%) were peripheral nervous system disorders; behavioral and speech disorders; chronic serous otitis media and other abnormalities of special sense function, as well as various metabolic disorders [67]. In mouse models of FASD, multiple changes in alternative splicing have been associated with characteristic CNS pathologies [68], suggesting an additional molecular mechanism of substance abuse influence on physical health.

Conclusions

Despite the large number of individuals included in genetic studies of SUDs, the output from these studies is quite low in comparison to more classic binary phenotypes. One reason may be a relatively high correlation between SUDs and other psychiatric phenotypes, which significantly complicates their genetic association studies. The inclusion of understudied populations, including Ukrainians, may increase the informativeness of genetic research. Taking into account the epidemiological, pathogenetic, and genetic correlations of SUDs with other socially significant diseases may lead in the future to significant improvements in risk prediction tools and approaches to the treatment of SUDs and comorbid pathologies.

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СУЧАСНИЙ ПОГЛЯД НА ГЕНЕТИКУ РОЗЛАДІВ ВЖИВАННЯ ПСИХОАКТИВНИХ РЕЧОВИН І РОЗВИТОК КОМОРБІДНИХ МЕТАБОЛІЧНИХ ПОРУШЕНЬ

Огляд сфокусований на основних викликах і досягненях геномних досліджень розладів вживання психоактивних речовин (РВПАР), які включають в себе наркоманію, зловживання алкоголем та куріння, а також стан досліджень проблеми коморбідностей цих захворювань з метаболічними порушеннями на прикладі метаболічного синдрому. Окремий акцент зроблено на геномних дослідженнях РВПАР і суміжних проблем в країнах Східної Європи, які є традиційно недооціненими в великих повногеномних дослідженнях асоціації (GWAS). РВПАР мають високий ступінь коморбідності та значно підвищують ризик багатьох захворювань, включаючі інші психіатричні і метаболічні. Питання патофізіологичних і генетичних причин коморбідності привертають на себе увагу в сучасних дослідженнях і вже показують деякі результати (генетична корреляція і плейотропні ефекти). В той же час, геномні дослідження РВПАР навіть в більш досліджених популяціях досі не є достатньо інформативними, а полігенні оцінки ризику незначно підвищують прогностичну здатність їснуючих моделей прогнозування ризику РВПАР. Це може бути частково пов'язано з тим, що РВПАР є складним для дослідження і визначення набором фенотипів, що зазвичай не враховується при дизайні більшості GWAS. Високий рівень полігенності цих фенотипів також підвищує необхідну кількість зразків для забезпечення достатньої статистичної потужності досліджень. Мульти-фенотипний підхід до геномних досліджень може підвищити їх ефективність для таких складних висококорельованих фенотипів.

***Ключові слова*:** розлади вживання психоактивних речовин, полігенне захворювання, повногеномне дослідження асоціації, коморбідність, метаболічний синдром.