Genomics and Epigenomics of Substance Use Disorders: An Introduction

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Substance use disorders (SUD) are common disorders around the world, with important health and societal impacts, particularly in the burden of disease (disability-adjusted life years) (Whiteford, 2015). A previous Global Burden of Disease Study estimated the global number of cases for SUD for several substances as follows: 94.8 million for alcohol, 17.2 million for amphetamine, 15.5 million for opioids, and 13.1 million for cannabis (Whiteford, 2015). In the United States, the lifetime and 12-month prevalences of SUDs were 9.9 % and 3.9%, respectively (Grant, 2016). In addition, polysubstance use is an important challenge in the field of addiction research (Whiteford, 2015).

SUD are complex psychiatric conditions that result from the interaction of genetic, epigenetic, and environmental risk factors. Several studies have shown an important role of genetic factors in the etiology of major SUD, with estimated heritabilities of 65 % for cocaine, 59% for nicotine, 51% for cannabis and 50% for alcohol (Wang 2012). In the last decades, many candidate gene and genome-wide association studies (GWAS) have been performed to identify those genetic risk factors that underlie SUD, highlighting some relevant genes for the development of dependence to several drugs of abuse like alcohol (e.g. *ADH1B, ADH2C* and *ALDH2*), nicotine (e.g. *CHRNA*) and opioids (e.g. *OPRM1*) (recently reviewed by Lopez-Leon et al. 2021). Furthermore, some studies have started to identify genetic risk factors that are shared by several SUD and also comorbid psychiatric disorders (Cabana-Dominguez et al. 2019, Gurriarán et al. 2018). However, the genetic risk variants identified so far explain only a small fraction of the heritability of this complex disorder, so further studies and larger sample sizes are needed.

Recent research has focused also on epigenetics to understand the interplay between environmental and genetic factors and drug-induced changes involved in remodelling brain circuits and functional changes that underlie the transition from use to dependence. Repeated drug use has been shown to induce chromatin and histone modifications and alterations in DNA methylation that contribute to stable gene expression changes involved in these mechanisms, and that are also relevant for relapse in drug use (Beayno et al. 2019; Hamilton & Nestler, 2019;

Werner et al. 2021). Furthermore, studies investigating the role of miRNAs have highlighted miR-124 and miR-181, among others, in the development of the addictive process (Gowen et al. 2021).

This special issue includes a total of seven works (Maldonado et al. 2021, Vilar-Ribó et al. 2020, Lai et al. 2020, Gerring et al. 2020, Markunas et al. 2020, Soundararajan et al. 2021, Cabrera-Mendoza et al. 2021) that cover different topics on the genomics and epigenomics of substance use disorders (SUD), one of them a review and the rest original research articles.

We open our issue with a review paper, where Maldonado et al. (2021) examine how behavioral genetic research has contributed to advance our understanding of the links between genes, environment and behavior, which conform the substrate of resilience and vulnerability to drug addiction. The fact that not all individuals who consume drugs develop addiction, even if access to the substance is present, poses an interesting question on the biological basis of this phenotype. The authors start by reviewing the genetics of drug addiction, they continue with epigenetic factors that influence both resilience and vulnerability, and they conclude with focus on miRNAs as potential biomarkers due to their capacity to be secreted extracellularly and to the systemic circulation. They also report novel approaches to alter miRNA expression, like antagomiRs, sponges or Tough Decoy inhibitors (TuD), which may pave the way to new therapeutic tools.

The six research papers of the issue cover a broad range of substances, including tobacco, alcohol, cocaine and cannabis. State-of-the-art methodologies are used, including genome-wide admixture mapping, integration of genetic variation and expression data through system-based analysis, mendelian randomization to infer causality between phenotypes, genetic correlation, polygenic risk score analysis or co-expression networks. Conceptually, three of the research papers put their focus on the genetic bases of substance use disorders based on genome-wide association study (GWAS) data, two other works examine the presence of methylation changes in the blood of patients with alcohol or cannabis use disorders, and the last work aims at identifying pharmacological treatments for SUD and suicide based on gene expression data and drug repositioning.

Vilar-Ribó et al. (2020) address the important topic of genetic overlap in psychiatric disorders. They use different tools to explore the shared genetics between SUD and attention-deficit hyperactivity disorder (ADHD), two conditions that are frequently comorbid. The results point at a common genetic background between ADHD and SUD and support the causal effect of the liability to ADHD on the risk for SUD, specifically smoking and lifetime cannabis use. Interestingly, a causal effect from cannabis use to ADHD risk was also observed for the first time. Finally, investigation of subjects with ADHD and from the general population revealed a shared genetic background underlying SUD. Lai et al. (2020) put the focus on genetic risk factors for alcohol-related phenotypes in the African American (AA) population. This paper highlights the growing interest of the scientific community in the genetic analysis of populations others than those with European ancestry. The latter have concentrated greater than 80 percent of genomic analyses in psychiatry as of 2018, and the Psychiatric Genomics Consortium (PGC) recently formed the PGC Cross-Population Special Interest Group to face this problem. The authors use admixture mapping on GWAS data to identify a significant association between a region on chromosome 4 and self-rating of the effect of ethanol. This region contains a gene, *PPARGC1A*, involved in the regulation of energy metabolism, previously associated with alcohol consumption. The third paper on the genetics of SUD, by Gerring et al. (2020), addresses the functional links and biological underpinnings that lie behind association signals identified in GWAS analyses. To do so, the authors integrate GWAS data with expression data in the form of expression quantitative trait loci (eQTLs) and brain co-expression networks. Thus, they identify more than 250 genes whose expression is influenced by genetic variation underlying disease risk. Variants in one of them, *CADM2*, are associated with alcohol, smoking and cannabis phenotypes. Also, co-expression modules of functionally related genes, including ‘Nervous system development’ or ‘Trans-synaptic signaling’, are found enriched with signals of association to substance use phenotypes.

Markunas et al. (2020) and Soundararajan et al. (2021) perform methylation analyses. The first paper reports the first epigenome-wide association study (EWAS) of lifetime cannabis use (ever versus never) in blood. The authors find an association with a particular CpG site, located at the 5’ untranslated region of the *CEMIP* gene, previously implicated in bipolar disorder and

schizophrenia. Interestingly, they also develop a classifier of the disorder based on the top 50 CpGs. This points to blood methylation as a source of biomarkers for this condition. The second study focuses on the dynamics of epigenetic adaptations during the treatment of alcohol use disorder (AUD). Methylation changes have been associated with the progression and persistence of dependence states, so it might be useful to test whether these molecular adaptations reverse under alcohol abstinence. The authors study methylation at global level (*LINE-1*) and also at two specific alcohol-related genes (*ALDH2* and *MTHFR*) in the blood of subjects following an abstinence treatment. Methylation levels are compared in AUD subjects versus healthy controls, too. These two groups show epigenetic changes at *ALDH2*, *MTHFR* and at global level, but these persist in patients at least during the first three months of treatment, indicating that epigenetic adaptations are stable over time in persons with chronic and heavy alcohol use.

We close our issue with a work by Cabrera-Mendoza et al. (2021) that aims at identifying potential pharmacological targets for SUD in the context of suicide behavior, given that 40% of patients seeking treatment for SUD report at least one suicide attempt. The authors hypothesize that SUD patients with comorbid suicidal behavior may require a treatment different from those without this behavior. Thus, transcriptomic data from post-mortem brains of individuals that committed suicide (or not) and had SUD (or not) are used to construct co-expression networks and then hub genes are selected for drug-gene interaction testing. Interestingly, some drugs interact with genes identified only in the suicide individuals, others are specific to non-suicide subjects, whereas one medication emerges in both groups of patients.

The articles of our special issue provide novel and interesting results and perspectives of the molecular basis of SUD. We hope the readers enjoy and find useful this special issue and that it inspires future research projects in genomics and epigenomics of SUD around the world.

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