Does psychiatric molecular genetics need to account for the birth cohort effect?

Harro J.1, Laas K.1, Vaht M.1, Eensoo D.2, Kurrikoff T.1, Sakala K.2,4, Kiive E.5, Veidebaum T.5
1 Division of Neuropsychopharmacology, Department of Psychology, University of Tartu, Tartu, Estonia
2 Department of Family Medicine and Public Health, University of Tartu, Tartu, Estonia
3 Division of Sociology, Department of Social Studies, University of Tartu, Tartu, Estonia
4 National Institute for Health Development, Tallinn, Estonia
5 Division of Special Education, Department of Education, University of Tartu, Tartu, Estonia

Summary. Major psychiatric disorders including alcohol use disorder are considered multigenic and the smallness of effects of individual genes may be attributed to either complex biological mechanisms or gene-environment interactions. The latter explanation is highlighted by the relatively fast changes in secular trends and in cohort effects on alcohol use disorder. Interactions of candidate gene variants with birth cohort have been found in the Estonian Children Personality Behaviour and Health Study, a longitudinal investigation from 1998 with a sample highly representative of birth cohorts within a region. Such interactions regarding initiation of alcohol use or alcohol use disorder have been revealed for e.g., 5-HTTLPR, VMAT1, OXR and NRG1, and suggest that rapid alterations in the socioeconomic environment promote changes in the genetic vulnerability to environmental risks factors such as alcohol.

Keywords: Alcohol use, candidate genes, gene-environment interactions, cohort effects, sex.
Grant B.F., Chou S.P., Saha T.D., Pickering R.P.,
A single nucleotide polymorphism (SNP) has higher affinity for serotonin than VMAT2 and
Storage of monoamine neurotransmitters is dependent on vesicular monoamine transporters (VMATs),
and alcohol use. Serotonin transporter is the key contributor to serotonergic neurotransmission throughout
the brain and the promoter region of its gene contains a much-studied variable number of tandem repeats polymorphism [10] that is associated with response of amygdala to fearful stimuli [3]. Studies on the association of the 5-HTTLPR genotype with alcohol consumption have been equivocal in their conclusions, but analysis of the two birth cohorts of the ECPBHS has suggested a possible reason for the inconsistency in findings. Carriers of the s-allele, with higher amygdalar response to threats, have a highly variable association with alcohol use. Specifically, we found a statistically highly significant genotype × gender × birth cohort interaction effect on the age of first consumption of half a unit of alcohol [21]: While in the older cohort of the ECPBHS the female s/s homozygotes were the group that started to drink alcohol later than any other group, the female 5-HTTLPR homozygotes of the younger cohort made the alcohol debut earlier than males and on average at almost three years younger age than their counterparts in the older cohort.

Storage of monoamine neurotransmitters is dependent on vesicular monoamine transporters (VMATs),
and the VMAT1, only recently discovered in the CNS, has higher affinity for serotonin than VMAT2 and may be important in a number of psychiatric conditions [11]. A single nucleotide polymorphism (SNP) in the human VMAT1 (rs1390938, G/A) results in substitution of isoleucine for threonine in the VMAT1 protein at position 136, and with the less common Ile variant the transport of monoamines into presynaptic vesicles is more efficient [7]. Homozygosity for the less frequent A-allele of the VMAT1 genotype was not only associated with better mental health indicators, but also with resilience toward the reduction in mean age of beginning of alcohol use: This reduction appeared on account of the G-allele carriers, in particular the G-allele homozygotes [18].

Subsequent candidate gene studies have suggested other subjects to genotype and birth cohort interaction effect on alcohol use and abuse, e.g., the neuregulin-1 gene [20] and the oxytocin receptor gene [19]. Findings of many candidate gene variants being associated with alcohol measures in one birth cohort but not in the other, or even showing opposite associations, can explain some controversies in molecular genetics of behaviour and suggest that differential response to societal changes at large are related to specific aspects of genetic background. Of course, cohort effects could be easily dismissed as rising by mere chance or biases in sample formation. If systematically appearing in samples where any selection bias is presumably low, they nevertheless may rather reflect the changes that are occurring in the environment. Birth cohort effects are likely to reflect the socioeconomic environment experienced by different generations. What is critically important is the perceived approval of drug use: Adolescents who mature in birth cohorts with low disapproval of drug use are at higher risk of using drugs during their teenage years, regardless of individual-level disapproval, perceived social norms, or perceived availability [6]. Social norms and attitudes regarding drug use are likely to cluster in birth cohorts, and this clustering has a direct effect on drug use even after controlling for individual attitudes and perceptions of norms.

Multiple mechanisms are likely to contribute to distinct environmental pressures on individual genetic vulnerabilities: In environments characterized by high levels of social control, a large proportion of individuals, irrespective of genotype, are expected to exhibit low levels of drinking. One could also speculate that in such conditions the genetic contribution to alcohol use is to a significant extent through characteristics like nonconformity. Conversely, in more permissive settings, alcohol consumption would be more dependent on reward sensitivity or, if the social norms facilitate alcohol use, rather the conformity. Alternatively the social context can act as a stressor that potentiates the behavioural expression of genetic liability on risk for alcohol consumption and alcohol use disorder.

References


Сведения об авторах

Jaanus Harro — Division of Neuropsychopharmacology, Department of Psychology, University of Tartu, Estonian Centre of Behavioural and Health Sciences. E-mail: Jaanus.Harro@ut.ee