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

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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.

Должна ли психиатрическая молекулярная генетика учитывать эффект когорты по рождению?

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Резюме. Основные психические расстройства, включая расстройства, связанные с злоупотреблением алкоголя, считаются мультигенными, а малый эффект отдельных генов может объясняться либо сложными биологическими механизмами или взаимодействием генов и окружающей среды. Последнее объяснение подтверждается относительно быстрыми изменениями долгосрочных тенденций и когортным эффектом на расстройства, связанные с употреблением алкоголя. Взаимодействия вариантов генов-кандидатов с возрастными когортами были обнаружены в «Эстонском исследовании личностного поведения и здоровья детей», продольном исследовании, проведенном в 1998 году, с выскопрезентативными возрастными выборками по регионам. Взаимодействия, касающиеся начала употребления алкоголя или расстройства, связанного с употреблением алкоголя, были обнаружены, например, для генов 5-HTTLPR, VMAT1, OXR и NRG1. Можно предположить, что быстрые изменения в социально-экономической среде способствуют изменениям генетической уязвимости к факторам риска окружающей среды, таким как алкоголь.

Ключевые слова: Употребление алкоголя, гены-кандидаты, взаимодействия ген-окружающая среда, когортные эффекты, пол.

Alcohol use, high-risk drinking, and alcohol use disorder are increasing and their prevalence in population can significantly change in only a few years [2]. Problematic alcohol use runs in families [15], and that higher alcohol consumption is predictable from early onset of alcohol use [9]. Genetic foundation of alcohol-related behaviours has been established in twin studies [1], but the contributing genes have remained elusive. Amongst the various reasons for this apparently "missing" heritability are the gene × environment interactions: For a given behaviour or disorder, the genetic factors should partly differ in significantly different environments [4]. Obviously the factors leading to alcohol abuse vary in their level of impact between regions and countries. In turn, in any given area these factors would be potentially changeable. Accordingly, alcohol consumption and related health problems are found to be subject to birth cohort effects [5; 8; 12; 14; 16; 17]. If societal changes are brought about rapidly, birth cohort effects on alcohol use, and consequently alcohol use disorder, could be observable within a relatively brief time span. Such rapid transitions have in recent decades taken place in countries of Central and Eastern Europe that are often referred to as transition economies or transition societies. Alcohol supply and use in these countries has responded to societal changes rapidly and in a highly dynamic manner [13].

We hypothesized that birth cohort effects on alcohol use should interact with genetic variants

known to affect the development of the CNS and social behaviour, and addressed the potential presence of interaction of genotype × cohort effect using candidate gene approach in the sample of the Estonian Children Personality Behaviour and Health Study (ECPBHS). The ECPBHS (www.ecpbhs.ee) is a longitudinal birth cohort study with the original sampling in 1998/1999 while the subjects were either in 3rd or 9th grade, corresponding to average ages of 9 and 15 years, respectively. Follow-up studies have been conducted at ages 15, 18, 25, and, for the older cohort, 33. Importantly, these two birth cohorts had been recruited in the same schools (54 out of the 56 schools in the region consented to the study, 25 of these were selected with the probability proportional to school size), all students of the 3rd and 9th grades were invited to participate, and in both cohorts nearly 80% of the invited subjects agreed. Altogether this means that the two birth cohort samples are highly representative and that there should be minimal differential bias of selection.

The first ever demonstration of genotype and birth cohort interaction in relation to alcohol involved the analysis of the association of the serotonin transporter gene promoter polymorphism (5-HTTLPR) genotype 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]. Homozygocity 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 candiate 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.

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