Review

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The genetics of alcohol dependence and alcohol-related liver disease

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Summary

The susceptibility to developing alcohol dependence and significant alcohol-related liver injury is determined by a number of constitutional, environmental and genetic factors, although the nature and level of interplay between them remains unclear. The familiality and heritability of alcohol dependence is well-documented but, to date, no strong candidate genes conferring increased risk have emerged, although variants in alcohol dehydrogenase and acetaldehyde dehydrogenase have been shown to confer protection, predominantly in individuals of East Asian ancestry. Population contamination with confounders such as drug co-dependence and psychiatric and physical co-morbidity may explain the essentially negative genome-wide association studies in this disorder. The familiality and hereditability of alcohol-related cirrhosis is not as well-documented but three strong candidate genes *PNPLA3*, *TM6SF2* and *MBOAT7*, have been identified. The mechanisms by which variants in these genes confer risk and the nature of the functional interplay between them remains to be determined but, when elucidated, will undoubtedly increase our understanding of the pathophysiology of this disease. The way in which this genetic information could potentially inform patient management has yet to be determined and tested.

Keywords: Alcohol dependence; Alcohol metabolism; Alcohol use disorders; Liver Cirrhosis, Alcoholic; Genome-wide association study; Heritability estimates; Phenotypic variability; Substance-related disorders; Alcohol dehydrogenase; Alcoholism; Aldehyde oxidoreductases; Ethanol.

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Key point

Alcohol misuse poses major problems for health and social agencies alike; it is responsible for 5.9% of the deaths and 5.1% of the burden of disease and injury worldwide.

Introduction

Alcohol consumption is a major public health concern. In 2012 over three million deaths were attributed to alcohol consumption, corresponding to 5.9% of the global total or one in every twenty deaths worldwide [1]. In addition, 5.1% of the global burden of disease and injury, as measured in disability-adjusted life years (DALYs), were attributable to alcohol consumption [1]. There is wide geographical variation in the proportion of alcohol-attributable deaths and DALYs, with the highest alcohol-attributable fractions reported in the World Health Organization (WHO) European region [1]; estimates from this region indicate that harmful drinking, particularly when associated with alcohol dependence, is responsible for 1 in 7 deaths in men and 1 in 13 deaths in women aged 15 to 64 years [2].

Excess consumption of alcohol is associated with a wide-range of problems relating to physical health, either directly, or through contributions to other health conditions. It is the most frequent cause of cirrhosis in Europe; alcohol-related liver disease (ALD) is the most important cause of death due to alcohol in middle-aged men and women [3]. Mortality from alcoholic-related cirrhosis has declined over the past 30 years in most Western European countries, but has increased in Eastern Europe, the United Kingdom, Southern Ireland and Finland [4]. Alcohol-related cirrhosis is now the second most common indication for liver transplantation, accounting for approximately 40% of all primary liver transplants in Europe and approximately 25% in the United States of America (USA) [5].

Other conditions directly attributable to excess alcohol consumption include alcohol-related injuries [6], alcohol-related pancreatitis [7], and the fetal alcohol syndrome [8]. In addition, alcohol is an important co-factor in the development of cancers of the aerodigestive tract, liver, colorectal region, and breast [9]; a major risk factor for the development of cardiovascular diseases [10]; and a range of neuropsychiatric disorders [11].

There is considerable variability in the outcomes of excessive alcohol consumption on an individual basis. The determinants of disease susceptibility are complex and reflect the interplay of several constitutional, environmental and genetic factors. Technological advances in molecular genetics have provided a better understanding of the genetic background of alcohol-related disorders but the information is far from complete.

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Key point

Not everyone who drinks excessively will develop alcohol dependence or alcohol-related cirrhosis; constitutional, environmental and genetic factors all contribute.

A more thorough understanding of the genetic modulators of disease risk would potentially allow for better identification of risk groups, improved disease prevention and focused allocation of treatment resources. It would also help delineated the pathophysiology of alcohol-related disorders and the identification of potential drug targets for new therapies. The present review summarizes current knowledge of the genetic of alcohol use disorders and of ALD, and provides a reasoned basis for future research directions.

Alcohol use disorders

A number of terms such as 'heavy drinking', 'harmful drinking', 'alcohol misuse/abuse', 'problem drinking' and 'dependent drinking' are used to describe drinking behavior but often without clear or consistent characterization. The accurate definition of these behaviors is important if meaningful comparisons are to be made in genetic and epidemiological research. In the absence of biological phenotypes that can be used across studies, investigators tend to use criteria based on two separate but similarly structured systems: The International Classification of Diseases (ICD), published by the WHO [12] and the Diagnostic and Statistical Manual of Mental Disorders (DSM) (ICD) published by the American Psychiatric Association [13]. These criteria are subject to revisions but at present, the 4th edition of the DSM criteria (DSM-IV) and the 10th edition of the ICD criteria (ICD-10) are the ones most widely used for clinical and research purposes.

Both systems use questionnaire responses to determine the subjects' relationship with alcohol and to identify spectral differences in severity. 'Alcohol dependence' is defined, in both systems, by the presence of tolerance to the neurobiological effects of alcohol; the development of a physiological withdrawal syndrome; a preoccupation with alcohol; difficulty in controlling its use; and continued consumption despite harmful consequences (Table 1). Alcohol drinking behavior, which falls short of the definition of dependent drinking but which nevertheless can cause damage to mental and/or physical health is termed 'harmful use' in ICD-10 and 'alcohol abuse' in DSM-IV (Table 1). The ICD-10 and DSM-IV diagnostic criteria for alcohol dependence overlap to a large degree and so they can be used interchangeably for research purposes but there is considerable discordance in the classification of harmful use and alcohol abuse [14,15].

The 5th edition of the DSM manual (DSM-5), published in 2013, has integrated alcohol abuse and alcohol dependence into a single category 'alcohol use disorder', which has mild, moderate and severe sub-classifications (Supplementary Table 1). The 10th edition of the ICD is currently undergoing revision and it is likely that its criteria will mirror closely those of DSM-5 [16,17].

Risk factors for the development of alcohol use disorders

Environmental and host-mediated risk factors

A number of factors have been identified, at societal and individual levels, which affect the extent and patterns of alcohol consumption and hence the risk of developing an alcohol use disorder [18]. At a societal level, factors such as the degree of economic development, religious and cultural mores, the availability of alcohol, and the level and effectiveness of alcohol policies all play a part in determining population levels of alcohol consumption and hence of alcohol-related harm [18]. On an individual level, factors such as age, gender and socioeconomic status all play a role, in addition to behavior and alcohol exposure.

Children, adolescents and the elderly are typically more vulnerable to alcohol-related harm than other age groups [19,20]. Initiation of alcohol use before the age of 14 years is associated with an increased risk of developing alcohol abuse and dependence in later life [1,21–23]. Parental alcohol problems and high anxiety traits are significant risk factors for alcohol dependence during this period [24]. Alcohol consumption generally declines with age, but older drinkers typically consume alcohol more frequently than other age groups. As people grow older, they are typically less able to handle the same levels and patterns of alcohol consumption as in previous life years, leading to an increase in the burden of alcohol-related problems [25,26].

Gender also plays an important determinant role. In 2012, higher proportions of men died of alcohol-attributable causes than women (7.6% *cf.* 4.0%) and suffered proportionately higher rates of alcohol-related disease or injury (7.4% *cf.* 2.3%) [1]. These differences are explained mainly by the fact that men who drink alcohol do so more frequently and consume larger quantities than women. However, there is also evidence that for a given level of drinking, women may be more at risk of developing alcohol use disorders than their male counterparts [27,28]. The factors which mediate this increased vulnerability are complex but differences in body composition, which are reflected in higher tissue doses of alcohol for a given amount of alcohol consumed, play a major role [29].

People with lower socioeconomic status appear to be more vulnerable to the consequences of alcohol consumption than those with higher status [30]. Thus, manual workers are more vulnerable to severe alcohol-related outcomes, including mortality, than non-manual workers consuming alcohol at the same level [20,31]. There are several possible explanations including the fact that people with lower socioeconomic status are less likely to have a partner and tend to live less stable lives; they have

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