BRIDGING THE GAP BETWEEN GENES AND ALCOHOLISM: MECHANISMS OF ENHANCED RISK FOR ADDICTION

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Introduction
Alcoholism runs in families. Many behavioural genetic studies in different countries have now convincingly demonstrated that the risk for alcoholism is determined by genetic and environmental factors and their interactions (1). It is now widely accepted that there is not one 'alcoholism gene', but that the risk for later alcoholism is related to many genes (2). The next question is: what are the mechanisms that determine whether an individual becomes addicted or not? In this review three factors are discussed in response to alcohol and alcohol expectancies. This is not to say that other factors, such as parenting behaviours (3), are irrelevant. This review is ended with a brief discussion on multifactorial models.

Individual differences in personality
After a search for decades it had to be concluded that the 'alcoholic personality' does not exist: no consistent set of personality characteristics predicts later alcoholism (4). This conclusion does not imply that personality is not a relevant factor. The problem was that the outcome variable (alcoholism) was too heterogeneous to allow a reliable prediction. At least two types of alcoholism have to be distinguished: an early-onset type predominantly occurring in men, and a late-onset type occurring in both men and women (5). The importance of distinguishing between types of alcoholism is illustrated by the finding that the genetic component in early-onset alcoholism is much larger than in late-onset alcoholism (0.73 versus 0.30 in men (6)). Personality characteristics that precede early-onset alcoholism may be summarized under the label 'behavioural under-control' (7). Related to these characteristics is the occurrence of externalizing problem behaviours, such as conduct disorder (7). Whether there are reliable personality precursors of late-onset alcoholism is still uncertain (7). Related to the idea that behavioural under-control is predictive of (male) early-onset alcoholism is the hypothesis that sons of multi-generational male alcoholics suffer from a mild deficit in executive or 'frontal' functions (8). Although several studies have found indications in this direction, it is as yet unclear whether this relative deficit is primarily related to parental alcoholism or to problem behaviours of the child; in most studies, the experimental group differed from controls on both dimensions (3, 9). In the largest population-based study, no association was found between cognitive deficits and family history of alcoholism (10). The state of affairs may be summarized as follows: there is evidence that 'behavioural under-control' is a precursor of early-onset alcoholism. A neuropsychological deficit may underlie this factor, but a 'frontal deficit' is probably too broad given the many different functions of the frontal cortex (9).

Individual differences in response to alcohol
The response to alcohol of non-alcoholic children of alcoholics (COAs) differs from that of controls in

![Diagram](image)

**Figure 1** A hypothetical multifactorial model combining the factors presented in this review. Although hypothetical as a whole, the elements are empirically supported (see text and Wiers, 1998). The whole model should be tested with longitudinal data (see for related examples Sher et al., 1996; Schuckit, 1998).
two respects. First, they experience a stronger positive effect directly after drinking alcohol (rising limb of the BAC curve), related to an enhanced sensitivity of pituitary β-endorphin to ethanol (11). Second, COAs experience less negative effects later on, during the descending BAC. Importantly, the second factor in response was found to predict later alcoholism in all longitudinal study (12). A related protective factor is the presence of the ALDH2 enzyme in a large proportion of Asians, which is responsible for the unpleasant ‘flushing’ reaction to alcohol, due to a sub-optimal breakdown of ethanol in the liver (1). Hence, if you carry genes that make you experience the positive effects of alcohol relatively strongly or that make you feel the negative effects of alcohol relatively weakly, you are at elevated risk for alcoholism.

**Alcohol expectancies**

Alcohol expectancies are the expected positive and negative effects of alcohol. Expectancies are strong predictors of current alcohol use in both adolescents and adults (13). Expectancies longitudinally predict later drinking in adolescents and young adults even after controlling for previous alcohol use (14). Given the response to alcohol described above, the most obvious expectancies are positive expectancies for a low dose and negative ones for a high dose of alcohol (15). We demonstrated the importance of the less obvious positive expectancies for a high dose of alcohol in predicting weekend bingeing in young men (16). How do the expectancies of COAs differ from those of controls? The results of different studies are ambiguous due to several factors (7, 17). We hypothesized that these results may be understood if one takes into account personal experience with alcohol (17). According to this model, young COAs develop stronger negative expectancies more dramatically than controls, due to their relatively favourable response to alcohol. Results from our own study and those of earlier studies are generally consistent with the model (17). Hence, young children in general, and COAs in particular, primarily have negative expectancies. Once personal experience with alcohol develops, positive expectancies increase, and this is even more strongly the case in COAs. The individual differences in response to alcohol can only begin to play a role once alcohol consumption has begun (see Figure 1). The indicated reciprocal effects of expectancies on alcohol consumption, and vice versa, have been empirically supported (14).

**Multifactorial models**

As mentioned earlier, many different genes are involved in the risk for later alcoholism. It now appears that some genes are addiction-specific and others are vulnerability factors for addiction in general (2). When one considers the factors mentioned above, the 'behavioural under-control' factor most likely constitutes a risk factor for addiction in general, whereas the individual differences in negative response to a certain substance are most likely substance-specific (e.g. ALDH2). The role of alcohol expectancies in relation to other vulnerability factors is interesting. Goldman et al. (13) propose that expectancies constitute a final common pathway, mediating other risk factors. For example, negative affect will only lead to alcohol abuse if one expects alcohol to alleviate negative affect. Data available thus far better support partial mediation of different risk factors by expectancies than full mediation (7). However, this may be partly due to a lack of full coverage of the expectancy domain: most studies included only positive expectancies for a low dose of alcohol (16). We found family history-positive alcoholics to have stronger positive expectancies for a high dose of alcohol than other alcoholics (19). Another interesting relation between expectancies and other risk factors was that expected aggression is a significant positive predictor of alcohol consumption in COAs and a significant negative predictor of alcohol consumption in controls (20). These findings illustrate the importance of studying multifactorial models of the etiology of alcoholism, and the importance of alcohol expectancies in relation to actual drinking behaviour, at least partly mediating other risk factors. A simplified multifactorial model is presented in Figure 1 (see for other examples of multifactorial models: 7, 21). The mediating role of expectancies can be challenged, which leads to reduced drinking levels in contrast to 'prevention as usual' (22). Further research is needed concerning the multifactorial etiology of alcoholism. Given the reciprocal relationship between the different risk factors, this needs to be longitudinal research which is, unfortunately, hard to get funded. In addition, the promising results with the 'expectancy challenge' method should be further developed and tested for enhanced risk for later alcoholism.

**References**


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