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Approach to the genetics of alcoholism: A review based on pathophysiology

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ABSTRACT

Alcohol dependence is a common disorder with a heterogenous etiology. The results of family, twin and adoption studies on alcoholism are reviewed. These studies have revealed a heritability of alcoholism of over 50%. After evaluating the results, it was epidemiologically stated that alcoholism is heterogenous complex disorder with a multiple genetic background. Modern molecular genetic techniques allow examining specific genes involved in the pathophysiology of complex diseases such as alcoholism. Strategies for gene identification are introduced to the reader, including family-based and association studies. The susceptibility genes that are in the focus of this article have been chosen because they are known to encode for underlying mechanisms that are linked to the pathophysiology of alcoholism or that are important for the pharmacotherapeutic approaches in the treatment of alcohol dependence. Postulated candidate genes of the metabolism of alcohol and of the involved neurotransmitter systems are introduced. Genetic studies on alcoholism examining the metabolism of alcohol and the dopaminergic, GABAergic, glutamatergic, opioid, cholinergic and serotonergic neurotransmitter systems as well as the neuropeptide Y are presented. The results are critically discussed followed by a discussion of possible consequences.

1. Introduction

1.1. *The diagnosis of alcoholism*

The alcohol dependence syndrome is defined as a cluster of physiological, behavioral and cognitive phenomena in which the use of alcohol takes on a much higher priority for a given individual than other behaviors that once had greater value. Worldwide alcohol dependence is associated with a wide range of physical, mental and social harms. Related are tremendous economic and social costs. The percentage of alcohol dependence among adult population varies between 2 and 12% in western European and North American populations [1].

Diagnostic criteria can be obtained from checklists requiring the individual to have symptoms in at least three of six (International Classification of Diseases: ICD 10) [2] or three of seven (Diagnostic and Statistical manual of Mental Disorders: DSM-IV) [3] categories. The diagnostic criteria vary between physical and psychological symptoms. As an example the diagnostic criteria of the DSM-IV include: tolerance, withdrawal symptoms or use of alcohol to avoid or relieve withdrawal, drinking more than intended, unsuccessful attempts to cut down use, excessive time related to alcohol (obtaining, hangover), impaired social or work activities due to alcohol and continued use despite physical or psychological consequences [3]. Even though these criteria are helpful for providing the diagnosis, the underlying disease of alcohol

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dependence is heterogeneous in its etiology and phenotype. For example Jellinek [4] defined in his classification five different subtypes of alcoholism based on physical or psychological aspects of addiction. Another example of different subtypes of alcoholism can be found in the Cloninger classification [5], which distinguishes a form of alcoholism with a relatively late onset and neurotic symptoms (type I alcoholism) from a form characterized by a relatively early onset and the presence of antisocial behavior, elevated novelty seeking and reduced harm avoidance (type II alcoholism).

1.2. *Pathophysiological background of alcoholism*

A better understanding of the pathophysiological background of alcoholism can be achieved by regarding the metabolism of alcohol, the involved neurotransmitter systems and the pharmacotherapeutic approaches in the treatment of alcohol dependence.

Two enzymes are of major importance for the metabolization of alcohol. Alcohol dehydrogenase (ADH) oxidizes ethanol to acetaldehyde which is converted to acetate by the enzyme aldehyde dehydrogenase (ALDH). Increased concentrations of acetaldehyde, which might be caused by an inhibition of ALDH, can result in the unpleasant acetaldehyde syndrome which can vary in intensity from facial flushing, sweating and mild headache to severe cardiovascular collapse, arrhythmias, unconsciousness and convulsions. Disulfiram, the first drug used in the field of psychopharmacological treatment of alcoholism, is a potent inhibitor of ALDH and thus creates an aversion to alcohol by accumulation of acetaldehyde. Many studies on disulfiram with inconsistent results have failed to show a therapeutic effect in enhancing abstinence [6], however an effect on fewer drinking days became evident [7].

The mesolimbic dopamine system plays a critical role in reinforcing alcoholism and in the rewarding effects of alcohol and is thus also called the dopaminergic reward system [8–11]. Consumption of alcohol activates dopamine A10 neurons in the mesolimbic system which leads to a release of neurotransmitters in the limbic system and thus mediates positive reinforcement and reward [12]. Dysfunction in dopaminergic transmission has been associated with craving for ethanol [13] and seems to influence withdrawal symptoms [14,15]. It has been postulated that dopamine neurons are sensitized to cues that provoke drinking during the development of alcohol dependence. The increase in the desirability and reward of drinking is likely to be mediated by changes in the reactivity of dopamine neurons [16].

Dopamine is metabolized by different pathways. The enzyme dopamine-beta-hydroxylase (DβH) catalyzes the conversion of dopamine to norepinephrine and thus regulates the central ratio of dopamine to norepinephrine [17,18]. Two further enzymes play a major role in the dopamine metabolism: catechol-O-methyltransferase (COMT) and monoamine oxidase A (MAO-A) [19,20]. Both enzymes are major participants in the metabolism of dopamine to its final metabolite homovanillic acid, which is considered a potential indicator of central dopaminergic neuronal activity [21]. Dopamine interacts with different cerebral dopamine receptors and is regulated in its synaptic activity by the presynaptic dopamine transporter [22].

During alcohol withdrawal dopamine receptor antagonists are successfully used to prevent agitation and reduce delirium tremens (DT) associated hallucinations [23]. Outside the context of symptom management during acute withdrawal dopaminergic drugs have not been proven to be successful [16,24,25].

Whereas dopamine mainly seems to act as a modulator in the reward system, two other neurotransmitters, γ-aminobutyric-acid (GABA) and glutamate, are directly responsible for sedative effects of alcohol. Alcohol causes an inhibition of excitatory glutamatergic neurotransmission and increases GABAergic inhibition. As a compensatory effect in chronic exposure to alcohol there is an up-regulation of the glutamatergic system and a down-regulation of the GABAergic system resulting in an increased tolerance for alcohol. Due to these adaptive changes a state of hyper-excitability with symptoms as arousal, anxiety and sleeplessness may result when alcohol is abruptly withdrawn [26].

GABAergic drugs like benzodiazepines or clomethiazol are thus useful in managing acute withdrawal [16]. Acamprosate, which influences the restoration of a normal *N*-methyl-D-aspartate (NMDA) receptor status in glutamatergic systems, is likely to be effective in maintaining abstinence [27].

Intake of alcohol also stimulates the opioid system in releasing endogenous opioid peptides (endorphins) which indirectly activate the dopaminergic reward system [28]. Interindividual differences in the sensitivity of the endogenous opioid system can be the reason for different intensities of craving and risk of becoming alcohol dependent [29]. Naltrexone, an opiate receptor antagonist, can produce a decrease in relapse rate to heavy drinking and a decrease in drinking frequency [30].

Acute intake of alcohol as well as chronic alcoholism influences the cholinergic system. For example there is a known interaction of ethanol with the nicotinic acetylcholine receptor which activates dopaminergic neurons [31,32].

Sellers et al. [33] proposed that serotonin also participates in the mediation of alcohol effects. Impulsiveness and symptoms of obsessive-compulsive disorder are effectively treated with selective serotonin reuptake inhibitors and can also be found as symptoms of alcoholism [34,35]. There are many studies on the effects of serotonergic drugs on the maintenance of abstinence with heterogeneous results [16]. This may be due to different pharmacodynamical effects of different serotonergic drugs and different co-morbidity in the involved groups of patients.

Neuropeptide Y (NPY) is a neuromodulator of the central nervous system which stimulates feeding [36,37] and is considered a potential regulator of ethanol consumption [38]. NPY deficient mice reveal an increased consumption of ethanol, whereas transgenic mice that overexpress a NPY gene have a lower preference for ethanol and are more sensitive to its sedative effects [38]. NPY is expressed in the amygdala and nucleus accumbens, two structures of the mesolimbic dopamine system [39,40].

2. Family-, twin- and adoption studies and the diagnosis of alcohol dependence

For a better understanding and an implementation of prevention and intervention programs in the treatment of

alcoholism predictors of alcoholism have been in the focus of research for many decades. Alcoholism rates are higher among persons who grew up in an environment where drinking was tolerated or encouraged, among those with certain characteristics of personality or suffering from mental illness and among those who are biologically related to an alcohol dependent person [41]. A positive family history of alcoholism thus is a strong predictor of alcoholism with the biological offspring of alcoholics being about three to five times more likely to develop alcoholism than the biological offspring of non-alcoholics [42]. As a positive family history of alcoholism might be due to either shared environmental influences or shared genes or both, researchers of behavioral genetics have used twin or adoption studies to separate genetic contributions from environmental factors. Seven out of eight major twin studies of alcoholism in men have revealed a significantly greater concordance rate for alcoholism in monozygotic twins compared to dizygotic twins [43]. For example in 9000 Swedish male twins born between 1902 and 1949 monozygotic twin concordance always significantly exceeded dizygotic twin concordance [44]. The trait heritability is defined as the proportion of trait variance that can be attributed to genetic factors. Regarding studies of male twins the heritability of alcoholism ranges between 49 and 64%, pointing out that from one half to two thirds of the variance in alcoholism liability is associated with genetic factors [41]. The most recent twin studies of alcoholism in woman have shown comparable heritability estimates [45]. The influence of shared environmental factors can be elucidated by studying adoptive families. Even though few studies have shown that individuals reared in an adoptive family containing an alcohol dependent member experienced a significant increase in alcoholism risk [46], most adoptive studies could not show an increased risk of alcoholism among the non-biologically related children of alcohol dependent adoptive parents [47]. Results of a Finnish twin study could show that the magnitude of genetic influences can vary extremely between environments with up to five-fold differences demonstrated in different environments [48], suggesting that some environments are protective whereas others may exacerbate the expression of genetic predispositions.

Alcoholism is a heterogenous disease. Phenotypic characteristics vary in the age of onset, drinking history, comorbid disorders and the onset of withdrawal symptoms. The Stockholm adoption study [5] revealed that alcoholism is a clinically heterogenous disorder giving rise to the question whether there are alternative forms of alcoholism that are differentially heritable. A form of alcoholism characterized by a late onset and neurotic features (type I alcoholism) was only moderately heritable (heritability estimate less than 40%) whereas another subtype of alcoholics with an early onset and elevated levels of antisocial behavior (type II alcoholism) was strongly heritable with an estimated heritability of 90%.

To conclude twin and adoption studies reveal that approximately 50–60% of the variability in alcoholism is associated with genetic factors. There is no classic pattern of inheritance indicating that alcoholism is a complex disorder, whose genetic effect is not caused by a single gene but rather by multiple contributing genes [41].

3. Molecular genetic techniques

In the last century it was not able to identify genes or deoxyribonucleic acid (DNA) regions that contribute to the development of alcoholism or other diseases with a genetic background until Kary Mullis introduced the polymerase chain reaction (PCR) in 1983 [49]. For the first time defined sequences of DNA were replicated and analyzed in their structure.

Interindividual variations of DNA that can be found in genes and non-coding areas of DNA are called alleles. A distinct region of DNA for which several alleles can be found is called polymorphic, the region can also be called polymorphism. Alleles of different polymorphic regions of one gene can be made visible by PCR and gel electrophoresis. Researchers thus became able to study the inheritance of the alleles and to examine whether an allele is associated with a certain disease. Polymorphism are used for genetic analysis: DNA sequences usually found in non-coding DNA regions with several repeats of two to four nucleotides which individually vary in the frequency of repetitions are called microsatellite markers. The exchange of single nucleotides in the DNA is the origin of single-nucleotide polymorphisms (SNPs) that can be found in coding and non-coding DNA regions. However, the presence of SNPs are not necessarily functional or linked to the onset of a disease.

4. Strategies for gene identification in alcohol dependence

After the introduction of modern molecular genetic technology and the epidemiological statement that alcoholism is a heterogenous complex disorder with a multiple genetic background, sufficient experimental ways to detect contributing genes had to be designed. Linkage studies and association studies are different approaches that are commonly used in the genetic research of alcoholism. Both types should be briefly introduced in the following.

4.1. *Linkage studies*

In linkage approaches families with several affected individuals are studied. The genome of all individuals is scanned with multiple microsatellite markers or SNPs that are not necessarily associated with the specific disease or any physiological trait but that are evenly spread throughout all chromosomes. It is examined whether specific alleles of the used markers are more often found in people with the disorder than in people without it. If the tested markers are in close physical proximity to a gene of physiological relevance to the examined disease, affected siblings are expected to share more identical alleles of the certain marker. Parametric and non-parametric linkage analyses are the statistical tests used to test for significant linkage. Parametric linkage analysis is applied for monogenetic diseases, whereas non-parametric linkage analysis has been designed for examination of complex diseases.

4.2. *Association studies*

In contrast to the linkage approaches association studies are designed to analyze whether a single gene and its polymorphic

structure effects the examined disease. The candidate gene analysis tests if certain alleles of the gene are associated with a disease, a special trait or a symptom. A gene is considered a candidate gene because the genes function might be related to the pathophysiology of the disease or because the gene lies in a chromosomal region that has already been linked to the disorder by linkage analysis [50]. In the pathophysiology of alcoholism multiple biochemical pathways and systems of neurotransmission are involved and thus numerous genes have been declared as candidate genes for alcoholism. For further analysis in association studies either a population based design or a family-based design is chosen.

In population based association studies the polymorphisms of two defined groups are compared with each other. In the genetic research of alcoholism these two groups could include healthy people in one group and alcoholics in the other. The two groups are required to be carefully matched regarding important factors such as ethnicity, age and sex. As multiple genes seem to be involved in the pathogenesis of alcoholism and the effects of each single gene are likely to be rather small, large sample sizes to detect such genes are necessary. Collecting a large enough sample to provide enough statistical power on the one hand and being ethnically homogenous on the other hand can be considered a major challenge. If different allele frequencies between the two groups become evident it is likely to suggest that the candidate gene participates in the pathogenesis of alcoholism. Alternatively the candidate gene itself could be in close physical proximity to a disease causing mutation.

In 1996 a family-based association test, the transmission disequilibrium test (TDT) was primarily introduced [51]. The TDT analyses the transmission of alleles from the parents to the affected offspring. By studying many families researchers can investigate whether a certain allele is associated with a disease or a trait. A matched control sample is not necessary. The alleles that are not transmitted to the affected sibling can be used as control alleles.

5. Gene identification strategies applying candidate genes for alcoholism

Alcoholism is a disease with an underlying complex biochemical pathophysiology. As a result numerous candidate genes for alcoholism have been postulated. We would like to limit this overview to the above mentioned biochemical systems with an evident functional background including the ADH and ALDH-system and well examined genes of the dopamine system, the GABAergic system, the glutamatergic system, the opioid system, the cholinergic and the serotonergic system as well as the neuromodulator NPY. We will also regard associated results of linkage studies.

5.1. *Alcohol dehydrogenase and aldehyde dehydrogenase genes*

In contrast to the complex and in some ways not completely explored effects of alcohol in the cerebral system, the hepatic metabolism of alcohol by ADH and ALDH is well understood. Functional effects of the related genes on the activity of the enzymes have been reported.

For ADH three class I isoenzymes are known with their genes closely linked to chromosome 4q22. Three different alleles, *ADH1B*2*, *ADH1B*3* and *ADH1C*1*, have been shown to alter enzymatic activity of ADH, with *ADH1B*2* and *ADH1B*3* altering the activity more than 30-fold [52]. As individuals carrying these alleles are likely to have a higher fraction of acetaldehyde a hypothetical protective effect can be proposed.

Interestingly the frequencies of the three alleles vary extremely between different ethnic populations. *ADH1B*2* is commonly found in Asian populations but rare in other ethnic groups [53], *ADH1B*3* is found with a frequency of over 15% in African populations, *ADH1C*1* is found with over 90% in Han Chinese and with 55–60% in Europeans [54,55].

In several East Asian populations lower frequencies of *ADH1B*2* and *ADH1C*2* in alcoholics compared to healthy individuals have been shown [55]. *ADH1B*2* was significantly associated to a reduced level of peak weekly alcohol intake in a Jewish population [56] and with lower levels of alcohol consumption in men in a European population [57]. A meta-analysis revealed that *ADH1B*2* has protective properties decreasing the risk of alcoholism by a factor 3 compared to the *ADH1B*1* allele [57].

The *ADH1B*2* and *ADH1B*3* allele have been shown to be protective against alcohol related birth defects in black populations and against fetal alcohol syndrome [58,59] and *ADH1B*3* was significantly associated with a negative family history of alcoholism [60].

The Collaborative Study of the Genetics of Alcoholism (COGA) has investigated genetic factors that contribute to alcohol dependence using a sample of mainly Caucasian families densely affected with alcohol dependence. It provided evidence of linkage among unaffected individuals to a region of chromosome 4 that contains the ADH gene cluster [61] suggesting the genetic background of protective factors in this region. Independent linkage studies on other populations revealed association of the same region on chromosome 4q with alcoholism and related traits [62–64]. As a consequence genotyping of 110 SNPs throughout the ADH gene cluster located on chromosome 4 was performed. Twelve SNPs in and around the *ADH4* gene were significantly associated with alcoholism [65]. It was also shown that modest evidence of association with SNPs existed in *ADH1A* and *ADH1B* suggesting that alleles of these genes contribute to alcoholism susceptibility. A protective effect of *ADH1B*3* was revealed for African American families [65]. Further it was confirmed in different populations that variations in *ADH4* contribute to the risk of alcoholism [66–68]. The results of the alcohol dehydrogenase (ADH) genes as mentioned are summarized in Table 1.

ADH metabolizes alcohol to acetaldehyde which is converted to acetate by ALDH. In 1982 Harada et al. [69] revealed that ALDH deficiency was significantly lower among Japanese alcoholics suggesting a protective effect of deficient ALDH on the diagnosis of alcoholism. Of nine gene families encoding for human ALDH [53] only *ALDH1* and *ALDH2* are centrally involved in the oxidation of acetaldehyde with *ALDH2* playing the major role in the acetaldehyde oxidation [70]. *ALDH2* is located on chromosome 12. The *ALDH2*2* allele is associated

Table 1 – Evidence from genetic studies: summary of results of alcohol dehydrogenase (ADH) genes as mentioned in the text

Examined polymorphism/ chromosomal region	Examined phenotype	Method	Positive results	Negative results
*ADH1B*2*	Protective against alcohol dependence	Case control	[55]	
*ADH1B*2*	Protective against alcohol dependence	Meta-analysis	[57]	
*ADH1B*2*	Reduced level of peak weekly alcohol intake	Case control	[56]	
*ADH1B*2*	Protection against alcohol related birth defects	Case control	[59]	
*ADH1B*3*	Protection against alcohol related birth defects	Case control	[58]	
*ADH1B*3*	Negative family history of alcoholism	Case control	[60]	
*ADH1B*3*	Protective against alcohol dependence	Linkage analysis	[65]	
*ADH1C*2*	Protective against alcohol dependence	Case control	[55]	
ADH4 AC	Alcohol dependence	Case control	[66]	
ADH4 SNP2, SNP3	Alcohol dependence	Family-based association	[68]	
SNPs: chromosomal region 4q21-23	Alcohol dependence	Linkage analysis	[61–63,65]	

with enzyme inactivity resulting in symptoms of acetaldehyde syndrome [71]. Whereas the allele is almost absent in Caucasian and African populations it is commonly found in Asian populations with a frequency of 43% for example in Japanese [72]. Thus, samples of Asian alcoholics have been examined. They reveal lowered rates of *ALDH2*2* [73–78,55,79,80]. *ALDH2*2* seem to reduce the risk of becoming alcohol dependent by the factor 10, thus providing a stronger protective effect as compared to *ADH1B* and *ADH1C* [80,73,55]. The mentioned results for ALDH are demonstrated in Table 2.

5.2. *Dopamine system*

It has already been emphasised that the mesolimbic dopamine system plays a crucial role in the pathogenesis of alcoholism. Thus, the genes of the dopamine receptors, the gene of the dopamine transporter and the genes of the dopamine metabolizing enzymes have been in the focus of researchers trying to elucidate the genetic background of alcoholism.

5.2.1. *Dopamine receptors*

The gene encoding for the dopamine D2 receptor, *DRD2*, is located on chromosome 11q22-q23 [81]. Blum et al. were the first to report an association between the TaqI-A1 polymorphism of *DRD2* and alcoholism [82]. The total number of included individuals was very low in this initial study. After a large number of international replication studies [83,84] with inconsistent results have followed, the association of the *TaqI-A1* polymorphism of *DRD2* with alcohol is discussed controversially [83]. A lower *DRD2A1* allele frequency has been found in non-alcoholics as compared to the general population, suggesting that *DRD2* does not directly influence alcohol dependence but more likely a related phenotype [85]. It has thus been suggested that DRD2 might contribute to the ''reward deficiency syndrome'' which is characterized by addictive, impulsive and compulsive behaviour, alcoholism, polysubstance abuse, smoking, obesity, attention-deficit disorder and gambling [86].

The frequency of the *DRD2 A1* allele differs between populations to a noteworthy extend [87]. To avoid difficulties with population stratification four family studies of DRD2 have been performed all revealing negative associations [84,85,87,88]. A recent TDT study could significantly associate the *DRD2 A1* allele with alcoholism [89]. Results of DRD2 are demonstrated in Table 3.

The *TaqI* polymorphism of DRD2 has been found to be located nearby a kinase gene called ankyrin repeat and kinase domain containing 1 (*ANKK1*). This gene is a member of an extensive family of proteins involved in signal transduction pathways. *DRD2 Taq1A* is a single-nucleotide polymorphism (SNP) that causes an amino acid substitution within the 11th ankyrin repeat of *ANKK1*, which may affect substrate-binding specificity. If this is the case, then changes in *ANKK1* activity may provide an alternative explanation for previously described associations between the *DRD2 Taq1A* RFLP and neuropsychiatric disorders such as addiction [90].

The dopamine D4 receptor (DRD4) is a D2-like 7-transmembrane G-protein-coupled dopamine receptor. DRD4 seems to modulate higher brain functions in the limbic system, frontal cortex and other areas of the brain [91,92]. Among other loci with relevance to the dopaminergic function, the dopamine D4 receptor gene (*DRD4*) shares molecular characteristics with *DRD2* [93]. It is located on chromosome 11p15.5 [94]. After a polymorphism with a 48 base pair variable number of tandem repeats (VNTR) had been identified in the exon 3 of *DRD4* (*DRD4 E8 48-bp VNTR*), 2–11 repeats were found with variable frequencies in several populations [95–97]. The seven repeat variant of *DRD4 E8 48-bp VNTR* reduces the potency of dopamine to inhibit cyclic AMP (cAMP) formation about two-fold [98]. Benjamin et al. [99] and Ebstein et al. [100] were the first to divide

Table 2 – Evidence from genetic studies: summary of results of aldehyde dehydrogenase (ALDH) gene as mentioned in the text

Examined polymorphism	Examined phenotype	Method	Positive results	Negative results
*ALDH2*1*	Alcohol dependence	Case control	[73,76,78]	
*ALDH2*2*	Protective against alcohol dependence	Case control	[55,74,75,79,80]	
*ALDH2*2*	Decreased daily alcohol intake	Case control	[77]	

Table 3 – Evidence from genetic studies: summary of results of the dopamine D2 receptor gene (*DRD2*) as mentioned in the text

Examined polymorphism	Examined phenotype	Method	Positive results	Negative results
DRD2 Taq1A	Alcohol dependence	Case control	[227–233]	
DRD2 Taq1A	Alcohol dependence	Case control		[88,234–236,111,237,238]
DRD2 Taq1A	Alcohol dependence	Family-based association	[89]	[84,85,87,88]

the different alleles of *DRD4 E8 48-bp VNTR* into ''short alleles'', which included the alleles with 2–5 repeats and ''long alleles'' with 6 and more repeats for further analysis. By doing so they found a significant association of ''longer alleles'' with the personality trait ''novelty seeking'' [99,100], a trait that can be found in a common type of alcoholics (''type 2 alcoholics'') according to the Cloninger classification [5]. Replication studies however have presented contradictory results [101]. Based on the hypothesis of dopaminergic dysfunction in alcoholism several association studies have focused on *DRD4 E8 48-bp VNTR* as a candidate for alcoholism however revealing inconsistent results by using different statistical approaches in samples of different nationalities [101–104]. The demonstrated results of DRD4 are summarized in Table 4.

The dopamine D3 receptor gene was also examined in several independent association and family-based studies. Significant results however were not found [105–110]. Although the dopamine D1 receptor gene was not associated with alcoholism [110,111] some studies suggest that it is related to more complex forms of addiction [112] or to the trait ''sensation seeking'' in alcohol dependent men [113].

5.2.2. *Dopamine transporter*

Dopaminergic neurotransmission is influenced by the dopamine transporter (DAT) [22]. A reduction of cerebral DAT density was found in alcoholics during drinking episodes [114]. Altered striatal DAT density was measured by single photon emission computed tomography (SPECT) in alcoholic individuals [115]. The DAT gene (*DAT1*) is located on chromosome 5q15.3 and includes variable numbers of tandem repeats (VNTR) in the 3′ untranslated region of the gene [116] which can be used as a polymorphic marker of the *DAT1* locus.

Muramatsu and Higuchi [117] could show in a Japanese sample that the frequency of the 7-repeat allele of the *DAT1* variable number of tandem repeat was significantly higher in alcoholics with a point mutation in the aldehyde dehydrogenase-2 gene (*ALDH2*2*) than in control subjects. Dobashi et al. [107] found an elevated frequency of the 7-repeat allele and a decreased frequency of the 9-repeat allele in Japanese alcoholics compared to healthy control subjects. Chen et al. [118] found that the *DAT* gene does not play a significant role in the vulnerability to alcoholism in aboriginal and Han Chinese populations.

In a German sample the allele *A9* of *DAT1* was significantly increased in 93 alcoholics with severe alcohol withdrawal symptoms compared to 93 healthy controls [119]. By analysing 48 chronically intoxicated German alcoholics Schmidt et al. [120] could show that the allele *A9* was associated with more severe effects of alcohol withdrawal. Gorwood et al. [121] found an increased number of allele *A9* carriers in 34 alcoholics with either alcohol withdrawal seizures (AWS) or delirium tremens (DT) compared to 65 healthy controls. Wernicke et al. [122] found a significantly increased number of the *A* allele of *DAT 2319A* in homozygous carriers of the allele *A10* of *DAT1* with AWS and DT. Köhnke et al. [123] tested the hypothesis that the allele *A9* carrier status of *DAT1* is associated with severe alcohol withdrawal symptoms by comparing a group of alcoholics with DT and a group of alcoholics with AWS to a group of alcoholics with a history of only mild withdrawal symptoms, however no significant association was achieved. In a family-based association study Franke et al. [124] were not able to detect a significant association of the *A9* allele with alcoholism or with severe withdrawal symptoms in a German sample. However, Samochowiec et al. [89] significantly associated the *A9* allele with alcohol dependence in a family-based study. Foley et al. [125] could not associate the allele *A9* with alcoholism in a case control study analysing 61 alcoholics and 43 controls. By analyzing 102 healthy control subjects and 216 alcoholics of German descent a significant association of the allele *A9* of *DAT1* and the diagnosis of alcoholism was found in a recent study [123].

Most studies on *DAT1* have so far presented relatively small sample numbers and additional studies on larger samples seem to be necessary to elucidate the role of *DAT1* in the pathogenesis of alcoholism. Table 5 summarizes the results for DAT1.

5.2.3. *Dopamine metabolizing enzymes: DβH, COMT, MAO-A*

DβH

As dopamine-β-hydroxylase (DβH) catalyzes the conversion of dopamine to norepinephrine, and as it is specifically

Table 4 – Evidence from genetic studies: summary of results of the dopamine D4 receptor gene (*DRD4*) as mentioned in the text

Examined polymorphism	Examined phenotype	Method	Positive results	Negative results
DRD4 E8 48bp	Increased daily alcohol intake	Case control	[102]	
DRD4 E8 48bp	Novelty seeking in alcohol dependent individuals	Case control	[99,100]	[104]
DRD4 E8 48bp	Craving for alcohol	Case control	[104]	

Table 5 – Evidence from genetic studies: summary of results of the dopamine transporter gene (*DAT1*) as mentioned in the text

Examined polymorphism	Examined phenotype	Method	Positive results	Negative results
DAT1 VNTR	Alcohol dependence	Case control	[107,117,123]	[118,125]
DAT1 VNTR	Alcohol dependence	Family-based association	[89]	[124]
DAT1 VNTR	Severe alcohol withdrawal		[119–121]	[123]
DAT1 VNTR	Severe alcohol withdrawal			[124]
DAT 2319A	Severe alcohol withdrawal	Case control	[122]	

expressed within central and peripheral cells that synthesize norepinephrine and epinephrine [17] it has been in the focus of addiction research for many years. A positive association of plasma DβH activity with alcohol consumption was found in 60 healthy female college students [126]. A non-significant trend for lower plasma DβH activity has been shown in 22 alcoholics with a positive family history for alcoholism in comparison with healthy controls [127]. Another study found no significant difference comparing 27 non-abstinent chronic male alcoholics with 24 healthy controls [128]. *DBH* knockout mice show reduced ethanol preference in a two-bottle choice paradigm and were hypersensitive to the sedative and hypothermic effects of systemic ethanol administration [129].

A milestone for the research on DβH was the discovery of the first functional polymorphisms of *DBH* in 2001 on chromosome 9q34 [130]. The polymorphism *DBH-1021C → T* accounts for 35–52% of the total phenotypic variance in plasma DβH [130]. A genotype controlled analysis of plasma DβH in German alcoholics and healthy controls revealed a significantly decreased DβH plasma activity in alcoholics which however was independent of the *DBH-1021C → T* genotype [131]. The alleles of *DBH-1021C → T* were not associated with the diagnosis of alcoholism or severe withdrawal symptoms [131]. In an independent Brazilian sample again no association of the genotype and alcoholism was found [132]. Surprisingly the *A* allele of the polymorphism *DBH*444G/A* located in exon 2 [133] was associated with alcoholism and a low plasma DβH activity [134]. Recent studies [135,136] suggest that *DBH*444A/G* is most likely not of a major functional character. The association of *DBH*444A/G* and plasma DβH activity might therefore rather results from linkage disequilibrium (LD) with a functional polymorphism in close physical proximity within *DBH*. Independent genetic examinations of *DBH* and alcoholism in the future should focus on these genotypes examining larger numbers or considering a haplotype design.

COMT

Dopamine is metabolized into its final metabolite homovanillic acid (HVA) by the action of two enzymes: catechol-*O*-methyltransferase (COMT) and monoamine oxidase (MAO) [19,20].

The polymorphic human COMT gene is located on chromosome 22q11.2. A genetic polymorphism results in three- to four-fold differences in COMT activity [137]. Studies that tried to associate the low activity (*L*) allele of *COMT* with alcoholism revealed contradictory results [89,138–142]. Men with the LL genotype have shown a significantly higher weekly alcohol consumption than individuals with other genotypes [143].

MAO-A

The MAO-A Gene is located on chromosome Xp11. A polymorphism (*MAO-A-uVNTR*) of the gene encoding for MAO A affects the transcriptional activity of the gene: alleles with 3.5 or 4 copies of the repeat are transcribed more efficiently than those with 3 or 5 copies [144].

The results of association studies examining the relation of the MAO-A gene and alcoholism remain conflicting with some significant findings [145–148] and other non-significant results [149–151]. Significant results were achieved in associations regarding the personality trait of antisocial behavior of alcoholics [152,153].

Even though a reduced HVA was found in the plasma of alcoholics compared to healthy controls [142] a genetic influence of the functional polymorphisms of *COMT* and MAO-A on plasma HVA levels were not found [142,151].

A summary of the results of the dopamine metabolizing enzymes can be found in Table 6.

5.3. GABA

GABA is the major inhibitory neurotransmitter in the central nervous system and has an influence on the behavioural effects of ethanol consumption and alcohol withdrawal symptoms [154,155]. There are two subgroups: the $GABA_A$ receptors and the $GABA_B$ receptors.

$GABA_A$ receptors are sensitive to ethanol in distinct brain regions and are clearly involved in the acute actions of ethanol, ethanol tolerance, ethanol dependence and ethanol self-administration [26].

The majority of $GABA_A$ receptor genes can be found in clusters with chromosome 4 containing the genes of *GABRA2*, *GABRA4*, *GABRB1* and *GABG2*, chromosome 5 containing *GABRA1*, *GABRA6*, *GABRB2* and *GABRG2* and chromosome 15 containing *GABRA5*, *GABRB3*, *GABRG3* [156].

A linkage study revealed evidence of linkage to a chromosomal region on chromosome 4p near the β1 GABA receptor gene (*GABRB1*) [62], a finding that was confirmed by an association study which revealed a significant association between *GABRB1* and alcoholism [157]. Association of *GABRB1* and alcoholism was also studied in a family-based design in the COGA study revealing a consistent linkage disequilibrium between *GABRB1* and alcoholism [158]. Interestingly the strongest evidence of linkage was found to an electrophysiological endophenotype: the beta frequency band of the human EEG [159]. Further associations of alcoholism and electrophysiological endophenotypes followed for SNPs across *GABRA2* [160–162]. For chromosome 15 significant associations were reported concerning *GABRB3* [158,163] and

Table 6 – Evidence from genetic studies: summary of results of the dopamine metabolizing enzymes—dopamine-β-hydroxylase (DβH), catechol-O-methyltransferase (COMT) and monoamine oxidase A (MAO-A) as mentioned in the text

Enzyme	Examined polymorphism/ localization	Examined phenotype	Method	Positive results	Negative results
DβH	*DBH-1021C → T*	Alcohol dependence	Case control		[131,132]
DβH	*DBH-1021C → T*	Severe alcohol withdrawal	Case control		[131]
DβH	*DBH Taq I*	Alcohol dependence	Case control		[132]
DβH	*DBH*444GA*	Alcohol dependence	Case control	[134]	
DβH	*DBH*444GA*	Severe alcohol withdrawal	Case control		[134]
COMT	*Val108Met*	Alcohol dependence	Case control	[139]	[138,140,142]
COMT	*Val108Met*	Alcohol dependence	Family-based association		[89,141]
COMT	*Val108Met*	Severe alcohol withdrawal	Case control		[142]
COMT	*Val108Met*	Type I alcoholics	Case control	[138]	
COMT	*Val108Met*	Increased daily alcohol intake	Case control	[143]	
MAO-A	*MAO-A-uVNTR*	Alcohol dependence	Case control	[148]	[147,149–151]
MAO-A	*MAO-A-uVNTR*	Anti-social behaviour in alcohol dependence	Case control	[152,153]	
MAO-A	*MAO-A-uVNTR*	Severe alcohol withdrawal	Case control		[151]
MAO-A	*MAO-CA-1*	Alcohol dependence	Case control	[146]	

non-significant trend for *GABRG3* [164]. Interpreting all major studies on the $GABA_A$ receptor genes [165] there is evidence for a role of $GABA_A$ receptors and their genes in alcohol dependence.

Only little genetic research has been performed on $GABA_B$ receptors. They modulate intracellular pathways via G-proteins and adenyl cyclase and thus are responsible for long-term changes of synaptic processing in the mammalian brain [166]. $GABA_B$ receptors are important mediators of excitability [167–169]. Chronic alcohol consumption seems to impair the $GABA_B$ receptor-mediated presynaptic regulation of hippocampal GABA release [170].

The gene encoding for the $GABA_B$ receptor, *$GABA_BR1$*, is located on chromosome 6p21.3 [171]. After the exonic polymorphism *$GABA_BR1$ T1974C* had been identified by single-strand confirmation analysis [171], an investigation showed a non-significant elevation of the *T*-allele in alcoholics compared to healthy controls [172]. Another German study could find no association with the diagnosis of alcoholism or the onset of withdrawal seizures [173]. All demonstrated results are summarized in Table 7.

5.4. *Glutamatergic system*

Alcohol inhibits the NMDA signalling cascade that mediates the excitatory effects of glutamate in the central nervous system [174]. Variants of the ionotropic glutamatergic *N*-methyl-D-aspartate receptor (NMDAR), the silent *G2108A* and *C2664T* polymorphisms of the *NMDAR1* and the *NMDAR2B* genes, were analysed in a case control design in a German population and in a Polish family-based association study using the TDT in polish families [175]. Genotype frequencies of the *NMDAR1* polymorphism differed significantly between control and alcoholic subjects, the *NMDAR2B* polymorphism revealed a significantly reduced *T* allele in Cloninger type 2 alcoholics and in patients reporting an early onset compared with control subjects. The family-based study revealed no significant results [175]. No association was found for the NMDA-receptor 2B gene variant and alcoholism [176]. Polymorphisms of the astroglial glutamate transporter EAAT2 were significantly associated with antisocial traits in alcoholism and the personality trait of harm avoidance [177]. An Australian study failed to associate the glutamate receptor subunit gene *NMDAR2B* (*366C/G*) with

Table 7 – Evidence from genetic studies: summary of results of the γ-aminobutyric-acid receptor (GABA) genes as mentioned in the text

GABA receptor and subunit	Examined polymorphism/ chromosomal region	Examined phenotype	Method	Positive results	Negative results
GABA-A Alpha 2 subunit	*GABRA A2 SNPs*	Alcohol dependence	Association of haplotype block	[162]	
	GABRA A2 SNPs	Alcohol dependence	Linkage analysis	[160,161]	
GABA-A Beta 1 subunit	*GABR B1 tetranucleotide repeat*	Alcohol dependence	Case control	[157]	
	GABR B1 D4S3242	Alcohol dependence	Linkage analysis	[62]	
	Chromosome 4p12	Alcohol dependence	Linkage analysis	[158]	
GABA-A Beta 3 subunit	*GABRB3 G1*	Protection against severe alcohol dependence	Case control	[163]	
	GABRB3 G1	Alcohol dependence	Family-based association	[158]	
GABA-A Gamma 3 subunit	*GABRG3*	Alcohol dependence	Family-based association		[164]
GABA-B	*GABABR1 T1974C*	Alcohol dependence	Case control	[172]	[173]

Table 8 – Evidence from genetic studies: summary of results of the glutamatergic *N*-methyl-D-aspartate receptor gene (*NMDAR*) as mentioned in the text

Examined polymorphism	Examined phenotype	Method	Positive results	Negative results
NMDAR1 G2108A	Severe alcohol withdrawal	Case control	[175]	
NMDAR1 G2108A	Alcohol dependence	Family-based association		[175]
NMDAR2B C2664T	Early onset of alcohol dependence	Case control		[175]
NMDAR2B C2664T	Alcohol dependence	Case control		[176]
NMDAR2B 366CG	Alcohol dependence	Case control		[125]

alcoholism [125]. The mentioned results for the NMDA receptor are demonstrated in Table 8.

NMDA receptors are regulated via phosphorylation by Src-family tyrosine kinases [178]. An association of alcohol dependence with the single-nucleotide polymorphism *T137346C* in the 5′ untranslated region (UTR) of the protein tyrosine kinase gene (*PTK fyn*) was performed indicating a possible association of alcohol dependence with a genotype of the SNP *T137346C* of *PTK fyn*, with *C* being the risk allele [179].

Homocystein acts as an agonist at the NMDA receptor and reveals neurotoxic effects especially on dopaminergic neurons [180–183]. The enzyme 5,10-methylenetetrahydrofolate reductase (MHTFR) plays a crucial role in homocystein metabolism. Its gene is located on chromosome 1 [184]. The SNP *MTHFR C677T* has the greatest influence on plasma homocystein levels [185–187]. The *T*-allele is coding for the thermolabile variant of the enzyme and thus leads to increased plasma homocystein concentrations, explaining about 12,3% of the variance of plasma homocystein levels [188]. Lately the *T* allele of *MTHFR C677T* was significantly associated with the diagnosis of alcohol dependence and alcohol withdrawal seizures [189]. Interestingly the *T* allele of *MTHFR C677T* was also recently associated with decreased plasma levels of the dopamine metabolite HVA in alcohol dependent patients [190].

In conclusion there are promising results for association of the NMDA system and alcoholism however more genes of functional relevance need to be investigated in a structured approach.

5.5. *Opioid system*

The opioid system seems to be linked to the pathogenesis of addiction and alcoholism. As many studies examining the association of the mu-opioid receptor gene (genetic locus *OPRM1*) with substance dependence have focused on the *Asn40Asp* (*A118G*) single-nucleotide polymorphism, a meta-analysis to examine the association of *Asn40Asp* and substance disorder was performed including 28 distinct samples and over 8000 subjects revealing that the *Asn40Asp* SNP in *OPRM1* does not appear to affect risk for substance disorder [191]. Additional research is needed to determine whether these findings reflect no role for *OPRM1* in determining risk for addiction or whether another polymorphism in the gene influences receptor function and risk for the development of addiction. The functional variant *Asn40Asp* was also not associated with naltrexone treatment response in alcohol addiction in one study [192] whereas another study could reveal a significant association [193]. Other polymorphisms of *OPRM1* revealed no significant association with alcoholism [194–196].

The COGA study has successfully examined the kappa-opioid receptor. SNPs throughout *OPRK1*, encoding the kappa-opioid receptor, and *PDYN*, which encodes its ligand prodynorphin, were genotyped in a large sample applying family-based analysis. Variations of both genes are associated strongly with the risk for alcohol dependence [197]. The mu and delta opioid receptor genes revealed no significant association with alcohol dependence in the COGA sample [65]. Table 9 gives an overview on the mentioned studies of *OPRM1*.

5.6. *Cholinergic system*

A region that was linked to alcohol dependence in the COGA study was on chromosome 7q [61,198]. *CHRM2* encoding for the muscarinic acetylcholine receptor subtype 2 is located in this region [65]. Eleven SNPs in introns 4 and 5 and downstream of *CHRM2* were examined and significantly associated with alcoholism [199]. A positive association with *CHRM2* was confirmed in an independent sample [200].

5.7. *Serotonin system*

The central serotonin system is involved in the modulation of alcohol consumption [201]. Allelic variations of the serotonin transporter polymorphism 5-*HTTLPR* are located on chromosome17q11.2 [202]. A functional polymorphism has been

Table 9 – Evidence from genetic studies: summary of results of the mu-opioid receptor gene (*OPRM1*) as mentioned in the text

Examined polymorphism	Examined phenotype	Method	Positive results	Negative results
OPMR1 A118G	Alcohol dependence	Meta-analysis		[191]
	Naltrexone treatment response in alcohol dependence	Case control	[193]	[192]

described with its shorter allele demonstrating lower transcriptional efficiency. The results of numerous genetic studies on 5-*HTTLPR* are presented in a review paper [165]. A recent meta-analysis reveals that allelic variations of the serotonin transporter polymorphism 5-*HTTLPR* contribute to the risk for alcohol dependence, especially in subgroups of patients with psychiatric co-morbidity or severe withdrawal symptoms [203]. However, in the COGA project there was no significant association or linkage between the serotonin transporter gene and alcohol dependence [204,205]. A recent case control study revealed no significant association of the *S* allele of 5-*HTTLPR* with either alcoholism or severe withdrawal symptoms [206].

Thus, the role of the serotonin transporter gene in the diagnosis of alcoholism remains controversial.

The number of studies on the serotonin receptor genes is very limited with controversial results [165].

5.8. *Neuropeptide Y*

Neuropeptide Y (NPY), a 36 amino acid polypeptide, plays an important role in behavioral and physiological processes including feeding, anxiety and seizure modulation [207–213] and there is major evidence for an inverse association of ethanol drinking and cerebral NPY levels [214–216]. There are only few studies on the genetic of NPY and alcoholism. A group of Japanese alcoholics with seizures during alcohol withdrawal had shown a significantly elevated frequency of the *T*-allele of the *C5671T* polymorphism of the NPY gene [217]. This significance however vanished after Bonferroni correction. A thymidine to cytosine (*T1128C*) polymorphism of the human NPY gene had been discovered on chromosome 7 [218] and its *C*-allele was associated with a 34% elevated alcohol consumption in male Finns [219]. In an independent case control study the same polymorphism was significantly associated with the diagnosis of alcoholism [220]. However, a third association study failed to show a significant influence on the diagnosis of alcoholism or severe forms of alcohol withdrawal [221]. To conclude there is a need for further studies to be able to elucidate the influence of the NPY gene on the diagnosis of alcoholism.

6. Discussion

A strong difference of allele frequencies between ethnic groups have been found for *ADH* and *ALDH*. Genes related to ADH have been significantly associated with alcoholism and their loci have been linked to alcoholism in family studies. Also there is major evidence for an influence of the ALDH genes on the diagnosis of alcoholism. *ADH1* and *ALDH2* are the only genes with clearly established contributions to alcoholism with ALDH2 having a stronger effect [165]. However, the examined polymorphisms can be found in higher frequencies only in certain ethnic groups, predominantly in Asian populations.

Regarding the conflicting results of many studies performed a strong role of the dopamine receptor genes in the development of addiction cannot be postulated so far. *DRD2* rather influences a more complex phenotype with addictive and compulsive characteristics. Thus, there is a necessity for additional studies with larger numbers examining these traits. Positive associations of *DRD2* might possibly be explained by a close physical proximity to *ANKK1* and its influence on addiction [90]. Also difficulties due to population stratification might have led to false negative or false positive results. The genes of the other dopamine receptors might rather be associated with personality traits that can be found in subgroups of addicted patients than with the diagnosis of addiction itself [99,100,113]. More promising are the results concerning the dopamine transporter gene. However, there is a need for more studies on larger samples to replicate recently achieved positive findings and a need for support from linkage studies.

A different approach was to associate functional genes of dopamine metabolizing enzymes with the diagnosis of alcoholism. A clear advantage is the proven functionality of the polymorphisms that influence transcription rates or enzyme activities which can be detected parallel to genotyping. Even though altered enzyme activity and altered levels of dopamine metabolites were found in alcoholics [131,142] the results of the few association studies performed on *DBH*, *COMT* and *MAO-A* are conflicting revealing the need for further approaches. Especially for *DBH* there is a need for further research: so far there are only three studies with relatively small numbers performed in a Western European and South American population [131,132,134] which have only focused on three polymorphisms. Even though the *Taq I* and the *DBH-1021C → T* polymorphism were not associated with alcohol dependence and only *DBH*444GA* was significantly associated, there are other recently discovered polymorphism of *DBH* [135] that should be examined in the future, especially in a haplotype analysis. Further support for the need of genetic studies on the influence of *DBH* on alcohol dependence comes from the results of recent research projects, including animal testing, pharmacological research and studies on alcohol dependent patients: (1) studies on *DBH* knockout mice have suggested that the genetic variation at *DBH* may modulate individual responses to alcohol [129]; (2) DBH plasma activity was found to be significantly lowered in alcoholics compared to healthy controls [131]; (3) disulfiram, one of the most commonly used medication in relapse prevention in alcohol dependence, has lately been proven also to inhibit DBH, additionally to the well known inhibition of ALDH [222,223]; (4) recently additive effects of DBH genotype and disulfiram administration on the catecholamine metabolism in the prefrontal cortex of mice have been revealed [224]. To conclude there is a definite need for further research on DBH and its influence on alcohol dependence. A better understanding of the pathophysiology and new perspectives of pharmacological interventions should be the goal.

Several polymorphisms of the $GABA_A$ receptor genes throughout different chromosomal regions have been significantly associated with alcoholism or related electrophysiological endophenotypes supporting the hypothesis of an influence on the diagnosis of alcoholism. The family-based COGA study additionally revealed association of *GABRA2* with drug dependence and antisocial behaviour pointing out the complexity of the genetic influence of the GABA system [164,225]. So far only few genetic studies have focused on the $GABA_B$ receptor genes presenting no significant association.

Promising results for association of the glutamatergic system and alcoholism have recently been published, however more data is needed especially from the examination of functional polymorphisms to further elucidate the influence of NMDA related genes.

A greater influence of the mu-opioid receptor gene and the delta-opioid receptor genes on the diagnosis of alcoholism cannot be postulated regarding the results of a meta-analysis and family studies [65,191]. The COGA study has recently presented more promising results for the kappa-opioid receptor gene (*OPRK1*) and *PDYN*, which encodes for its ligand prodynorphin [197]. Again there is a need for further replication. Future research should try to elucidate the role of *OPRM1* on naltrexone response.

CHRM2 encoding for the muscarinic acetylcholine receptor subtype 2 was shown to influence alcoholism in two large and independent family studies but also seems to have an influence on the diagnosis of depression [199,200]. After contradictory results of family and association studies the involvement of the serotonin transporter in the diagnosis of alcoholism remains controversial. Due to limited and conflicting results the role of the serotonin receptor genes in the diagnosis of alcoholism remains to be elucidated.

Additionally the influence of the NPY gene of the diagnosis of alcoholism needs to be further examined.

The research of the genetic backgrounds of alcoholism is proceeding and new interesting susceptibility genes of alcoholism have been and will be introduced. This review has covered a certain percentage of susceptibility genes of alcoholism. It has focused on important findings of genes that are related to the physiology of alcoholism or its pharmacological treatment.

To conclude for most of the discussed genes there is a need for further studies to elucidate their influence on the diagnosis of alcohol dependence. Significant results of case control association studies should be replicated in either family-based association studies or linkage studies. Two positive examples are *GABRA2* and ADH related polymorphism as they have presented significant results in independent studies with different methodological approaches.

Focussing on subgroups of alcoholics can be considered a promising approach. Such subgroups should be defined by endophenotypes such as the discussed differences in plasma HVA or DBH plasma activity or electrophysiological differences. Another possibility of defining subgroups are personality traits or the onset of severe withdrawal symptoms. However, focussing on subgroups has certain limitations: the subgroup of alcohol dependent patients with delirium tremens during alcohol withdrawal for example has been examined in 25 studies. A recent systematic review demonstrates that in 25 studies 30 different polymorphisms were examined with only 8 significant associations including polymorphisms of 4 different neurotransmitter systems [226]. Thus, a plausible genetic base for delirium tremens can be taken into consideration, however still there is no distinct marker responsible for delirium tremens. In contrast other results suggest that the onset of delirium tremens rather depends of the amount of daily alcohol consumption prior to withdrawal [221].

After the successful replication of results further research is needed to understand the influence of the genetic variant on its product and the related functional change. A better understanding of the pathophysiology of alcoholism might be achieved maybe resulting in a better pharmacological treatment of addiction. However, it remains questionable if the results of molecular genetic research on alcoholism will ever lead to better prevention programs through early intervention. It has been known for decades that a positive family history of alcoholism is a strong predictor of alcoholism and that the heritability of alcoholism ranges between 50 and 60%, leaving the remaining influence up to environmental factors. Thus, there is already enough knowledge to start with early prevention programs without further molecular genetic findings. A need for genetic testing must be controversially discussed in this matter including the possible future impact of results of genetic testing on insurance contracts and other social matters.

An optimistic perspective can be attributed to the field of pharmacogenetics in the field of addiction research. Studies that associate polymorphisms and response to pharmacological relapse prevention, such as acamprosate, naltrexone and disulfiram, can provide a key to a more detailed understanding of the complex pathophysiology of alcohol dependence to the benefit of the affected patients.

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