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Review Article

The Genetic Predisposition of Alcohol Abuse Risk: A Review

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Abstract: Alcoholism; the an important health problems in the population particularly among Iraqi individuals, different factors contributed on the alcohol abuse incidence, both social and environmental factors weigh heavily on the outcome. The Genetic factors also impact in the alcohol consumption level and the risk of diseases associated with alcohol-. the genetic factors included Genes contributed in the Alcohol metabolism and Risk Genes of Alcoholism included such as γ-amino butyric acid receptor A2 (GABRA2), The muscarinic cholinergic receptor 2 gene (CHRM2), The peroxisomal trans-2-enoyl-coA [coenzyme A] reductase (PECR), Potassium Inwardly-Rectifying Channel, Subfamily J, Member 6 (KCNJ6), Autism susceptibility candidate 2 gene (AUTS2), Importin 11-5-Hydroxytryptamine Receptor 1A (IPO11-HTR1A), all these gene have SNPs or variation association with alcoholism, the interaction between environment factors and SNPs have an impact in the alcohol abuse. The current review concluded that there were several genes responsible on the alcoholism risk.

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INTRODUCTION

Alcoholism or Alcohol abuse is patternsof maladaptive drinking lead to repeated, consequences problems for the drinker. Investigations considered alcoholism is one of the Mental Disorders[1], according to (DSM-IV-TR, henceforth DSM-IV) criteria, which proposed that meeting three criteria in individuals for enrolled in alcoholism.

Alcoholism or Alcohol dependence mean the severe alcohol uptake disorder, is considered as amultifactorial genetic disease, Its be noted that it's found among family individuals, however it couldn't be demonstrated that the genetic variation as a risk factor. Some evidences pointed that the genetic factors contributed to its etiology, the Adoption researches suggested that alcoholism in adoptees strong associated with biological

parents than their adoptive parents[2-4]. Kendler and others studies in the US and Europe of twins proposed that about 45-65% belong to genetic factors. There were evidences proved that the genetic factors have role in alcohol dependence[5-7].

Although of the genetic factor is contributed in the alcoholism, there is no evidences about gene for alcoholism but an association of both social and environmental factors weigh heavily on the outcome. The Genetic factors also impact in the alcohol uptake level and the risk diseases of alcohol-related, including upper GI cancers and cirrhosis[8].

As in complex disease the alcoholism and alcohol use disorder belong to the diverted in hundreds of genes and interacting with different social environments. There was clinical heterogeneity in genetic variants of the AUDs risk among those meeting criteria, The clinical heterogeneity may be reflected the disease genetic heterogeneity. The genetic documents difficulties are compounded by environmental heterogeneity in access to alcohol and social norms related to drinking[9,10].

GENES CONTRIBUTED IN THE ALCOHOL METABOLISM

There are two genes direct association with alcoholism risk and consumption of alcohol, aldehyde dehydrogenase 2 or ALDH2; mitochondrial aldehyde dehydrogenase and alcohol dehydrogenase 1B (ADH1B), these genes is a central of the alcohol metabolism, The begin steps in Alcohol metabolism is oxidation to acetaldehyde mediated by ADHs, then it convert to acetate by ALDHs [11].

The genetic variation in booth showed an effects in the alcohol metabolism in different populations, investigation found that Individuals have one copy of the ALDH2×504K (ALDH2×2 allele; rs671) when consume small amount of alcohol were displayed the Asian flushing reaction, this is because that the ALDH2×504K is relatively common in East Asia, while more than (30-40%) of Japanese and Han Chinese that have one copyat least; its rare allele outside Asia, European or African didn't carry it[12-14]. The genetic polymorphism of ALDH2×504K allele is a substitution mutation lead to change glutamate to lysine at site 504 that inhibits the enzyme activity by inactivation the tetramer structure or degraded it[11,15,16]. This lead to accumulation acetaldehyde in the circulation, the multiplies of ALDH2×504K have a protective effect against AUDs[17,18]. While single copy protection is not completed, that affected by societal circumstances, As observed in Japan by Higuchi[19] during (1970-1992) that coincides with elevation social pressure for drinking as partial of the business culture. The two copies of the ALDH2×2 have completely protection in individuals didn't consume very little level of alcohol. The genetic variation of the ALDH2×504K is benefit in the risk for alcohol dependence and how can be overridden by social and environmental factors[20].

There are triple polymorphisms of the ADH1B enzyme (β-ADH), the cytosolic variant found in elevation level in the liver of adult(21) .Which found in more than 95% in European descent population, its called as ADH1B (ADH1B×1) encodes (β1–ADH) enzyme has arginine in the positions 48 and 370. The β2–ADH encoded by ADH1B×48His (ADH1B×2; rs1229984) has histidine the position 48 and β3-ADH encoded by ADH1B×370Cys (ADH1B×3; rs2066702) has cysteine in the position 370. The variation in these genes have role in the alcohol level in Japanese population that havedouble copies of ADH1B×1 had high level of alcohol than those with single copy of ADH1B×48His[21].

Studies found that the ALDH2 and ADH1B have strong association with alcoholism risk than other genes. other alcohol dehydrogenases variants have small effects as well as ADH1C and ADH4 and other aldehyde dehydrogenase genes which have modest effects. However, studies found significant linkage disequilibrium in many variants of the ADH genes. Also strongest effects have been seen in ADH1B×48His, ADH1B×370Cys and ALDH2×504K which are rare in European populations. However there was complex interaction between genetic factors and environments factors in the risk for alcoholism[22-24].

THE RISK GENES OF ALCOHOLISM

There are several other genes responsible in the risk of alcohol dependence in addition of key endophenotypes. In the early studied that deal with families have individuals with alcohol dependence, the genes were detected according to analyses based on family[25]. In several investigations, some families were recruited that having multiple members with alcohol dependence; such as families are likely to segregate variants that impact the risk of alcohol dependence. The linkage analysis is the most common initial ways utilized to determine the chromosomal regions segregation across families. That may be found different variants in genome consist of some hundreds of genes. Edenberg and Foroud[26] pointed that The linkage researches were followed with more information's genetic Studiesused Single Nucleotide Polymorphisms (SNPs) that were

genotyped at high density across the linked regions Some genes have been proved to be associated with the alcoholism risk for instance γ-amino butyric acid receptor A2, The muscarinic cholinergic receptor 2 gene, peroxisomal trans-2-enoyl-coA [coenzyme A] reductase, KCNJ6, AUTS2 and IPO11-HTR1A with brief descriptions as a following:

γ-amino butyric acid receptor A2 (GABRA2): Studies analysis genetic linkage of some family found an association between a region on chromosome 4p with alcohol dependence[27]. several SNPs genotyping were detected in candidate genes in this region, some variations in the $GABA_A$ receptor genes and GABRA2 (γ-amino butyric acid receptor A2) gene, that found to be strong association with alcohol dependence and observed at least in part to underlie the observed linkage outcomes[28]. It'sfound in the European[22-32] and African ancestrypopulation[33]. Agrawal *et al*.[34] suggested that This relation was stronger in the alcoholics with early onset or comorbid drug dependence, In addition, the GABRA2 may also have the adjacent GABRG1 gene[35,36]. haplotypes of these genes may be contributedin the alcohol dependence risk.

The muscarinic cholinergic receptor 2 gene (CHRM2): The linkage study found that the CHRM2was related to with alcohol dependence[37]. it seems to be robustwith alcoholics early onset or comorbid drug dependence[38].

The peroxisomal trans-2-enoyl-coA [coenzyme A] reductase (PECR): The Genome Wide Association (GWA) studies with German male inpatients found correlation of alcohol dependence with 2 SNPs in the 3 flanking region of PECR[39], this enzyme is one of the short-chain dehydrogenase family,found within broad linkage peaks for some trait related to alcohol, inclusive alcoholism[40], response to alcohol level[41], comorbid alcoholism and depression[42], and amplitude of the P3(00) response[43,44].

Potassium Inwardly-Rectifying Channel, Subfamily J, Member 6 (KCNJ6): In GWA studies the phenotypes of frontal theta band event associated oscillations (theta ERO) is notable success. A good endophenotype is The Event-related oscillations (EROs) are highly heritable neuroelectricassociated withcognitive mechanisim which clarified deficits in alcohol abusers and their offspring at high risk to develop alcoholism. Some studies found association between theta ERO with some SNPs in KCNJ6 using GWA of 17 families[45]. KCNJ6 gene encodes a potassium inward rectifier channel, GIRK2, responsible on the activation slow inhibitory postsynaptic potentials that alternated neuronal excitability, thus influences neuronal networks[46,47]. In humansKCNJ6 controlled on the opioid impacts on analgesia and addiction[48].

Autism susceptibility candidate 2 gene (AUTS2): In different European population A large meta-analysis of alcohol consumption found high significant association with SNPs in the AUTS2 which proved by the association of AUTS2 expression with genotype in human brain tissue[49].

Importin 11-5-Hydroxytryptamine Receptor 1A (IPO11-HTR1A): Investigation of some genes related with addiction in general Zuo *et al*.[50] analysis the comorbid alcohol and nicotine dependence and detected GWS of SNPs spanning a region on chromosome 5 included IPO11 (importin 11) and HTR1A (5-hydroxytryptamine (serotonin) receptor 1A, G protein-coupled). The Importins are used in proteins and RNA transport between cytoplasm and nucleus, a study found the RNA level in lymphoblastoid cell lines proposed that SNPs within this region had cis-acting regulatory impact on the HTR1A or IPO11generation. The samplesnumber are very important to prove robust association results, in studies of alcoholism Unfortunately, ithas not yet attained these sample sizes[26].

CONCLUSION

The alcoholism is a health problem and complex genetic disease, some variants in different genes contributing to the alcoholism risk. Genes association with alcohol metabolism have robust impact on risk; also the ADH1B and ALDH2 functional variants are protective against alcoholism. Alcoholism needs more investigations and GWS in different population with its interaction with environment and social factors to demine the specific risk.

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