An important genetic study conducted through Mayo Clinic has identified vital new information concerning alcoholism in subjects with European ancestry, according to a recent issue of Alcohol: Clinical and Experimental Research.

Research findings indicate that alcohol dependence is highly inheritable, although specific genes and their variations associated with this illness remain unknown. Animal model studies allow identification of potential candidate genes but their relevance to alcoholism in humans and its complications, including alcohol withdrawal and seizures, require additional research. Under the direction of Victor Karpyak, M.D., Ph.D., of the Mayo Clinic Department of Psychiatry and Psychology, a team of clinical and basic scientists investigated the sequence of the human MPDZ gene and its association with risks for alcohol dependence and alcohol withdrawal seizures.

"We have long known that the presence of severe withdrawal and seizures indicates strong physical dependence on alcohol," states Dr. Karpyak. "Focus on this group of subjects increases our chances to successfully identify the genetic variations associated with alcoholism in general and the presence of withdrawal symptoms specifically."

Sophisticated genetic research in mice isolated small regions on mouse chromosomes linked to severity of acute alcohol and barbiturate withdrawal measured by the presence and severity of seizures. Further research demonstrated that MPDZ gene is the only one in this chromosome region which has variants associated with severity of acute alcohol and barbiturate withdrawal and seizures.

The MPDZ protein is an important scaffolding brain protein, responsible for synaptic structure and plasticity. It is also known to be involved in learning and memory as well as seizures and epilepsy and, thus, is a good candidate for the human study focused on genetic predictors for alcohol withdrawal. Unfortunately, little was known about sequence variability of the MPDZ gene in humans. It is also a very long gene and its sequencing required considerable effort and costs.

To investigate the relevance of the model findings in animals for human alcoholism, Dr. Karpyak and his collaborators resequenced the human MPDZ gene in 61 subjects with a history of alcohol withdrawal seizures, 59 subjects with a history of withdrawal without seizures and 64 samples from non-alcoholic subjects -- all with European American ancestry. Sixty-seven new, mostly rare variants were discovered in the human MPDZ gene. Sequencing allowed the first opportunity of comparing the MPDZ gene in humans and mice. The new Mayo study found that the human gene does not have variations identical to those comprising the MPDZ gene associated with alcohol withdrawal seizures in mice.

Second, researchers used common variants to compare haplotype structure of the MPDZ gene in alcohol dependent subjects with and without history of withdrawal seizures and in controls who did not have alcoholism. The study revealed a significant association between MPDZ gene variant alcohol-dependency without seizures, compared to the control subjects. Contrary to initial hypothesis and animal findings, the study showed no significant association between MPDZ sequence variants and withdrawal seizures in humans. This suggests the potential role of MPDZ in alcoholism and/or related phenotypes other than alcohol withdrawal seizures.

This important new information supports further investigation of the role of MPDZ gene in alcoholism and its complications including withdrawal syndrome. It also indicates the importance of close collaboration between clinical and basic scientists that could provide critical
insights into the mechanism of the association and reveal significant genetic markers of alcoholism.

Source: Mayo Clinic (news : web)


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