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A gene mutation for excessive alcohol drinking found

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UK researchers have discovered a gene that regulates alcohol consumption and when faulty can cause excessive drinking. They have also identified the mechanism underlying this phenomenon.

The study showed that normal mice show no interest in alcohol and drink little or no alcohol when offered a free choice between a bottle of water and a bottle of diluted alcohol.

However, mice with a genetic mutation to the gene Gabrb1 overwhelmingly preferred drinking alcohol over water, choosing to consume almost 85% of their daily fluid as drinks containing alcohol.

The consortium of researchers from five UK universities – Imperial College London, Newcastle University, Sussex University, University College London and University of Dundee – and the MRC Mammalian Genetics Unit (MGU) at Harwell, funded by the Medical Research Council (MRC), Wellcome Trust and ERAB, publish their findings today in *Nature Communications*.

Dr Quentin Anstee, Consultant Hepatologist at Newcastle University, joint lead author said: "It's amazing to think that a small change in the code for just one gene can have such profound effects on complex behaviours like alcohol consumption.

"We are continuing our work to establish whether the gene has a similar influence in humans, though we know that in people alcoholism is much

more complicated as environmental factors come into play. But there is the real potential for this to guide development of better treatments for alcoholism in the future."

Working at the MRC Mammalian Genetics Unit, a team led by Professor Howard Thomas from Imperial College London introduced subtle mutations into the genetic code at random throughout the genome and tested mice for alcohol preference. This led the researchers to identify the gene Gabrb1 which changes alcohol preference so strongly that mice carrying either of two single base-pair point mutations in this gene preferred drinking alcohol (10% ethanol v/v - about the strength of wine), over water.

The group showed that mice carrying this mutation were willing to work to obtain the alcohol-containing drink by pushing a lever and, unlike normal mice, continued to do so even over long periods. They would voluntarily consume sufficient alcohol in an hour to become intoxicated and even have difficulty in coordinating their movements.

The cause of the excessive drinking was tracked down to single base-pair point mutations in the gene Gabrb1, which codes for the beta 1 subunit, an important component of the GABAA receptor in the brain. This receptor responds to the brain's most important inhibitory chemical messenger (GABA) to regulate brain activity.

The researchers found that the gene mutation caused the receptor to activate spontaneously even when the usual GABA trigger was not present.

These changes were particularly strong in the region of the brain that controls pleasurable emotions and reward, the nucleus accumbens, as Dr Anstee explains: "The mutation of the beta1 containing receptor is altering its structure and creating spontaneous electrical activity in the

brain in this pleasure zone, the nucleus accumbens. As the electrical signal from these receptors increases, so does the desire to drink to such an extent that mice will actually work to get the alcohol, for much longer than we would have expected."

Professor Howard Thomas said: "We know from previous human studies that the GABA system is involved in controlling alcohol intake. Our studies in mice show that a particular subunit of GABAA receptor has a significant effect and most importantly the existence of these mice has allowed our collaborative group to investigate the mechanism involved. This is important when we come to try to modify this process first in mice and then in man."

Initially funded by the MRC, the 10-year project to find genes affecting alcohol consumption was led by Professor Howard Thomas from Imperial College London and initiated at the MRC Mammalian Genetics Unit. The consortium now involves researchers at five UK universities - Imperial College London, Newcastle University, Sussex University, University College London and the University of Dundee. Senior investigators are Dr Quentin Anstee at Newcastle University and Dr Susanne Knapp at Imperial College London (joint lead authors); Professor Dai Stephens at Sussex University; Professor Trevor Smart at University College London; Professor Jeremy Lambert and Dr Delia Belelli at the University of Dundee; and Professor Steve Brown at the MRC Mammalian Genetics Unit.

Professor Hugh Perry, Chair of the MRC's Neurosciences and Mental Health Board, said: "Alcohol addiction places a huge burden on the individual, their family and wider society. There's still a great deal we don't understand about how and why consumption progresses into addiction, but the results of this long-running project suggest that, in some individuals, there may be a genetic component. If further research confirms that a similar mechanism is present in humans, it could help us

to identify those most at risk of developing an addiction and ensure they receive the most effective treatment."

More information: Anstee, Q. M. et al. Mutations in the Gabrb1 gene promote alcohol consumption through increased tonic inhibition. *Nat. Commun*. 4:2816 DOI: 10.1038/ncomms3816 (2013).

Provided by Newcastle University

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