Gene Variants Force Mental Trade-offs: Efficiency vs. Resiliency

Mouse Genetic Models Hint at Why We Can’t Always Have It All

Mice genetically engineered to have an over active version of a human gene, like their human counterparts, gain in emotional mettle under stress, but at a cost of less efficient thinking, NIMH scientists have discovered. Such talents seesawed in mice engineered to have either too much or not enough the \textit{val} version of the COMT gene, the most common of two that humans inherit. The new study in mice confirms and helps to explain the trade-offs seen in earlier studies in humans, which have suggested that the \textit{val} version slightly biases the brain's workings toward increased risk for schizophrenia.


Mice with too much of the COMT \textit{val} gene version faltered at attention and working memory tasks but seemed relatively unfazed by stress and pain. By contrast, mice lacking the gene showed better working memory but buckled under stress or pain. The stimulant amphetamine improved memory in mice with too much COMT \textit{val}, whereas the drug impaired memory in normal mice. The researchers traced these effects to COMT action on a pivotal pathway in the brain's frontal lobe that has been linked to learning and memory.

"It makes sense that a gene version that has been conserved throughout the evolution of the human brain would confer some advantages and disadvantages," explained Weinberger. "We have now created strains of genetically engineered mice that reproduce virtually every feature associated with this variation in the COMT gene in humans, and pinpointed the brain pathway through which it exerts these effects."
Like a seesaw, each of two common versions of the COMT gene was associated with tradeoffs in the way the brain works. Mice in which the val version was knocked out (KO) showed traits associated with the met version — excelling at memory and attention tasks, but at a cost of being more susceptible to stress and pain. Transgenic (tg) mice in which the val version was over-expressed showed an opposite set of attributes.

Source: NIMH Genes, Cognition and Psychosis Program

References


Genes May Make Some People More Prone To Anxiety

ScienceDaily (Aug. 11, 2008) — Inborn differences may help explain why trauma gives some people bad memories and others the nightmare of post-traumatic stress. Scientists in Germany and the United States have reported evidence linking genes to anxious behavior. The findings appear in the August issue of Behavioral Neuroscience, published by the American Psychological Association.

By showing that people who carry a common variation of a gene that regulates the neurotransmitter dopamine have an exaggerated "startle" reflex when viewing unpleasant pictures, the researchers offer a biochemical explanation for why some people find it harder to regulate emotional arousal. Their sensitivity may, in combination with other hereditary and environmental factors, make them more prone to anxiety disorders.

Researchers including Martin Reuter, PhD, of the University of Bonn, Germany, recruited 96 women averaging 22 years old from the Giessen Gene Brain Behavior Project, which investigates biomolecular causes of individual differences in behavior.

The researchers first determined which participants carried which variations (alleles) of the COMT
gene, which encodes an enzyme that breaks down dopamine, weakening its signal. (COMT stands for a catabolic enzyme named catechol-O-methyltransferase.) Scientists call its two alleles Val158 and Met158. Depending on ethnicity, more or less half the population carries one copy of each. The rest of the population is roughly divided between carrying two copies of Val158 and two copies of Met158.

Using a well-validated psychophysiological measure, the researchers next measured the intensity of each participant's startle response by attaching electrodes to the eye muscles that, upon emotional arousal, contract and cause a blink. Participants then viewed pictures that were emotionally pleasant (such as animals or babies), neutral (such as a power outlet or hairdryer), or aversive (such as weapons or injured victims at a crime scene) -- 12 pictures of each type for six seconds each. A loud, 35-millisecond white noise, called a startle probe, sounded at random while they watched. When participants blinked, showing the startle response, a bioamplifier took readings from the electrodes and sent the information to a computer for analysis.

People carrying two copies of the Met158 allele of the COMT gene showed a significantly stronger startle reflex in the unpleasant-picture condition than did carriers of either two copies of Val158 allele or one copy of each. The two-Met carriers also disclosed greater anxiety on a standard personality test. This finding confirms that specific variations in the gene that regulates dopamine signaling may play a role in negative emotionality. The authors speculated that the Met158 allele may raise levels of circulating dopamine in the brain's limbic system, a set of structures that support (among other things) memory, emotional arousal and attention. The researchers said that more dopamine in the prefrontal cortex could result in an "inflexible attentional focus" on unpleasant stimuli, meaning that Met158 carriers can't tear themselves away from something that's arousing -- even if it's bad.

The Met158 allele was created by a relatively recent mutation and only in the evolution of human beings. Other primate species such as chimpanzees carry only the Val/Val genotype. Co-author Christian Montag, Dipl. Psych., observes that for humans, wariness may have been adaptive. He points out, "It was an advantage to be more anxious in a dangerous environment."

A single gene variation, says Montag, can explain only a small portion of variation in anxious behavior -- otherwise, in theory, up to half the population could be anxious.

"This single gene variation is potentially only one of many factors influencing such a complex trait as anxiety," he says. "Still, to identify the first candidates for genes associated with an anxiety-prone personality is a step in the right direction."

Although a great deal more research is needed, Montag says that if this line of research bears fruit, one day "it might be possible to prescribe the right dose of the right drug, relative to genetic makeup, to treat anxiety disorders."

Journal reference:


http://www.sciencedaily.com/releases/2008/08/080810214000.htm
Estrogens Metabolism Associated with Polymorphisms: Influence of COMT G482a Genotype on Age at Onset of Canine Mammary Tumors

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Abstract

Catechol-O-methyltransferase (COMT) is an important enzyme participating in inactivation of carcinogenic oestrogen metabolites. In humans there is a single nucleotide polymorphism in COMT gene (COMT val158met) that has been associated with an increased risk for developing breast cancer. In dogs, there is a single nucleotide polymorphism in COMT gene (G482A), but its relation with mammary carcinogenesis has never been investigated. The aim of this study was to focus on the evaluation of such polymorphism as a risk factor for the development of mammary tumors in bitches and on the analysis of its relationship with some clinicopathologic features (dog's age and weight, number and histologic type of the lesions, lymph node metastasis) of canine mammary neoplasms. A case-control study was conducted analyzing 90 bitches with mammary tumors and 84 bitches without evidence of neoplastic disease. The COMT G482A polymorphism was analyzed by PCR-RFLP. We found a protective effect of the polymorphism in age of onset of mammary tumors, although we could not establish a significant association between COMT genotype and other clinicopathologic parameters nor with mammary tumor risk overall. Animals carrying the variant allele have a threefold likelihood of developing mammary tumors after 9 years of age in comparison with noncarriers. The Kaplan-Meier method revealed significant differences in the waiting time for onset of malignant disease for A allele carrier (12.46 years) and noncarrier (11.13 years) animals. This investigation constitutes the first case-control study designed to assess the relationship between polymorphic genes and mammary tumor risk in dogs. Our results point to the combined effect of COMT genotype with other genetic and/or environmental risk factors as important key factors for mammary tumor etiopathogenesis.

http://www.vetpathology.org/cgi/content/abstract/45/2/124

Breed differences in genotype and allele frequency of catechol O-methyltransferase gene polymorphic regions in dogs

Catechol O-methyltransferase (COMT) inactivates catecholamines and catechol-containing drugs such as L-DOPA. The common genetic polymorphism Val158Met in the human COMT gene is suspected to be associated with "persistence" or risk for schizophrenia. In this study, we attempted to identify the canine COMT gene fragment and to find a similar polymorphism and to reveal its genetic distribution among five representative canine breeds. We found that the amplified gene consisted of 663 bp nucleotides and was 84% homologous with the human COMT gene. The single nucleotide polymorphisms, guanine adenine substitution, were observed at the 39th, 216th and 482nd nucleotides. From the genotyping of the 216th polymorphism among 266 dogs by the polymerase chain reaction-restriction fragment length polymorphism method with restriction enzyme EagI, and that of the 482nd polymorphism with restriction enzyme Sfcl, we found inter-breed variations of genotypes as well as of allelic frequencies for both of these polymorphic regions. These results suggest that the identified polymorphisms will be useful tools in elucidating the genetic background of canine behavioral traits.

http://cat.inist.fr/?aModele=afficheN&cpsidt=15721970
Gene May Spur ADHD Antisocial Behaviors

November 9, 2005 08:41:10 PM PST

Antisocial behavior in children with attention deficit hyperactivity disorder (ADHD) may be associated with a variant gene involved in brain signaling, British researchers report. This variant of the "catechol O-methyltransferase" (COMT) gene may also increase a child's susceptibility to the effects of lower birth weight, the study said.

Researchers at Cardiff University in Wales looked for the COMT variant in 240 children, ages 5 to 14, with ADHD who were at high risk for early onset antisocial behavior.

The study found a significant association between the COMT variant and antisocial behavior and between birth weight and antisocial behavior.

The researchers also concluded that interaction between this COMT variant and low birth weight could be associated with antisocial behavior.

"Early onset antisocial behavior in a high-risk clinical group was predicted by a specific COMT gene variant previously linked with prefrontal cortical [brain] function and birth weight," the study authors concluded.

The findings appear in the November issue of the journal Archives of General Psychiatry.

http://www.iconocast.com/News_Files/HNews11_9_05/Health2.htm