National Human Genome Research Institute (NHGRI)

Patented & Patent-pending Technologies Available for Licensing

Latrophilin 3, a Gene Involved in ADHD

NHGRI invention number:
E-312-2006/0
E-187-2011/0

Patent Status

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issued August 23, 2011
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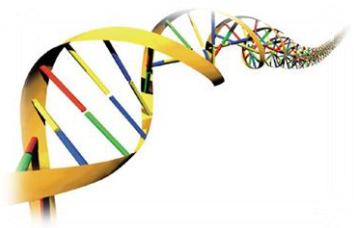

Summary

Attention Deficit Hyperactivity Disorder (ADHD) is the most commonly diagnosed childhood behavioral disorder, affecting about ten percent of children and adolescents in the U.S. At this time there is no accurate way for doctors to determine in advance which ADHD therapeutic drug is likely to be of most benefit to a particular individual.

Scientists from the National Human Genome Research Institute (NHGRI) at the National Institutes of Health (NIH) have identified specific latrophilin 3 (LPHN3) mutations and/or groups of LPHN3 variants (e.g., LPHN3 alleles) that are associated with an increased susceptibility for and severity of ADHD. LPHN3 is a G-protein coupled receptor specifically expressed in the brain's mesolimbic system, which is part of a dopaminergic pathway. This LPHN3 protein expression pattern fits with the dopamine theory of ADHD, according to which patients affected with the disorder have lower levels of dopamine receptors and transporters.

Potential Commercial Applications

Identification of mutations in this ADHD susceptibility gene could be used as the basis for both a DNA-based ADHD diagnostic test as well as used to aid in the development and clinical validation of more efficient and individualized therapies. Thus, personalized treatment options could be tailored to the genetic makeup of a person thereby potentially minimizing the amount of medication taken by those who are at less risk and/or who have a less severe form of ADHD.

Related Article

Muenke, M. et al., *A Common Variant of the Latrophilin 3 Gene, LPHN3, Confers Susceptibility to ADHD and Predicts Effectiveness of Stimulant Medication*, 15 MOLECULAR PSYCHIATRY 1053 (2010).
http://www.nature.com/mp/journal/v15/n11/full/mp20106a.html

Key Words

Attention Deficit Hyperactivity Disorder, Latrophilin 3, Pharmacogenetics

Use of Adenosine Agonists to Prevent Vascular Calcification Disorders

NHGRI invention number:
E-094-2010/0

Patent Status

PCT Application
PCT/US2011/030493 filed
March 30, 2011

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Summary

NHGRI scientists have discovered a genetic defect that causes vascular calcification. Specifically, mutations in the ecto-5'-nucleotidase (NT5E) gene encoding Cluster of Differentiation 73 (CD73) lead to a decrease in adenosine, and ultimately, an increase in vascular calcification. CD73 is an enzyme that coverts adenosine monophosphate (AMP) to adenosine in the extracellular region of the vascular endothelium. Dr. Gahl and his colleagues are now in the process of testing various adenosine agonists, in an attempt to restore normal intracellular adenosine levels, in preclinical studies with the goal of identifying promising candidate drugs that could be used in the future to treat or prevent various vascular calcification disorders.

Potential Commercial Applications

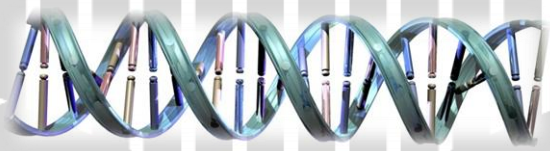
The discovery of adenosine's role in vascular calcification disorders could be used to identify and clinically test new adenosine agonist-based treatments for such conditions. Vascular or joint capsule calcification is a clinical finding of many diseases and disorders including atherosclerosis, diabetes, Monckberg medial calcification sclerosis, CD74 deficiency, Ehlers-Danlos Syndrome (EDS), Marfan/Loeys-Dietz Syndrome, fibromuscular dysplasia, Kawasaki Syndrome, pseudoxanthoma elasticum, and premature placental calcification.

Related Article

Gahl, W. et al., *NT5E Mutations and Arterial Calcifications*, 364 N ENGL J MED 432 (2011). *http://www.nejm.org/doi/full/10.1056/NEJMoa0912923*

Key Words

Vascular Calcification, Atherosclerosis, Diabetes, Adenosine



Device and Method for Direct Measurement of *In Vivo* Oxidation

NHGRI invention number:
E-099-2009/0

Patent Status

U.S. patent application
12/418,795 filed
April 6, 2009

Lead Inventor
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Summary

NHGRI inventors have developed a device and a method for measuring *in vivo* small animals' (e.g., mice) oxidation rates of amino, organic, and fatty acids via the detection and measurement of carbon dioxide production rates. Specifically, a small animal can be given a dose of an organic acid, an amino acid, a fatty acid, or a simple carbohydrate labeled with C13 – a heavy but not radioactive atom. As the labeled compounds are metabolized, the produced carbon dioxide contains a fraction of the C13 tracer. Carbon dioxide is collected using a specially-designed respiratory chamber, which is used to take measurements over time. Thus, activity of diverse metabolic pathways can be evaluated and analyzed.

Potential Commercial Applications

This technology can be used for the diagnosis and analysis of various animal models that mimic human metabolic disorders and in the development and testing of potential therapies (including enzyme replacement and gene therapies) for

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metabolic disorders. Some metabolic disorders that this technology could be used to evaluate include methylmalonic academia, phenylketonuria, maple syrup urine disease, fatty acid defects, glycolytic disorders, and organic acid metabolic disorders. Since this technique utilizes a non-radioactive tracer the method could potentially also be extended from analysis of animal oxidation to the measurement of oxidation in humans.

Related Article

Chandler, R. and Venditti, C., *Long-term Rescue of a Lethal Murine Model of Methylmalonic Acidemia Using Adeno Associated Viral Gene Therapy*, 18 MOL. THER. 11 (2009). *http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2839224/*

Key Words

Metabolic Disorders, Medical Device, Oxidation Rates, Carbon Dioxide

LMNA Gene and Its Involvement in Hutchinson-Gilford Progeria Syndrome (HPGS) and Arteriosclerosis

NHGRI invention number:
E-020-2003/0

Patent Status

U.S. patent 7,297,492
issued November 20, 2007

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Summary

Children with Hutchinson-Gilford progeria syndrome (HGPS) suffer from dramatic acceleration of certain aging symptoms, mainly cardiovascular disease that generally leads to death from myocardial infarction and/or stroke. In addition to arteriosclerosis, the children exhibit bone deformations and osteoporosis. Researchers at NHGRI have discovered the genetic basis for HGPS, namely a *de novo* point mutation in the LMNA gene, which encodes Lamin A/C. Lamin is a component of the nuclear lamina, and the discovered mutation results in a shortened form of lamin A, called progerin. Although believed to be a genetic disorder, until the present discovery the mode of inheritance, molecular basis, and pathogenic mechanism of HGPS were unknown.

Potential Commercial Applications

The identification of the mutation and the phenotype of HGPS can lead to further breakthroughs in the detection, diagnosis, prognosis, and treatment of this disease and related conditions. For example, research into arteriosclerosis (e.g., atherosclerosis and vascular calcification) and cellular aging could be further advanced.

Related Article

Eriksson, M. et al., *Recurrent De Novo Point Mutations on Lamin A Cause Hutchinson-Gilford Progeria Syndrome*, 423 NATURE 293 (2003).
http://www.nature.com/nature/journal/v423/n6937/full/nature01629.html

Key Words

Hutchinson-Gilford Progeria Syndrome, Arteriosclerosis, Aging, LMNA Gene, Lamin A

Use of Farnesyl Transferase Inhibitors (FTIs) for Treatment of Laminopathies, Cellular Aging, and Arteriosclerosis

NHGRI invention number: E-055-2005/0

Patent Status

U.S. patent 7,838,531
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Summary

Hutchinson-Gilford progeria syndrome (HGPS) is a genetic premature aging disease; affected children die of myocardial infarction or cerebrovascular accident at an average age of thirteen years. It is caused by a *de novo* single mutation in the LMNA gene, which encodes a component of nuclear lamina – lamin A/C. Thus, HGPS is a laminopathy. This mutation causes a deletion in lamin A and results in the accumulation of a truncated protein, called progerin. Progerin is improperly farnesylated and, in turn, the mutated protein contributes to abnormal nuclear scaffolding. NHGRI researchers have discovered that farnesyl transferase inhibitors (FTIs), both direct effectors and indirect inhibitors, can reduce the formation of abnormal nuclear morphology. Therefore FTIs have the potential to be used to as a therapeutic drug to treat HGPS patients as well as those diagnosed with other laminopathy disorders.

Potential Commercial Applications

Preclinical and clinical testing of farnesyl transferase inhibitors as candidate drugs to treat HGPS and other laminopathies, as well as related conditions, such as arteriosclerosis (e.g., atherosclerosis), osteoporosis, bone deformations, and cellular aging.

Related Articles

Cao, K. et al., Research Article, *Progerin and Telomere Dysfunction Collaborate to Trigger Cellular Senescence in Normal Fibroblasts*, J. CLIN. INVEST. (June 13, 2011). http://www.jci.org/articles/view/43578/pdf

Collins, F. et al., *Inhibiting Farnesylation of Progerin Prevents the Characteristic Nuclear Blebbing of Hutchinson-Gilford Progeria Syndrome*, 102 PROC. NAT'L ACAD. SCI. OF THE U.S.A. 12879 (2005). *http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1200293/pdf/pnas-0506001102.pdf*

Key Words

Farnesyl Transferase Inhibitors, Hutchinson-Gilford Progeria Syndrome, Arteriosclerosis, Aging, Lamin A, LMNA Gene, Laminopathy