National Human Genome Research Institute (NHGRI)

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C57BL/6J Embryonic Stem Cell Lines Generated Using Serum-Free Media

NHGRI invention number:
E-038-2009/0

Key Words

Serum-Free Media, Mouse Embryonic Stem Cell Lines, Genetic Alteration

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Summary

Investigators at the National Human Genome Research Institute (NHGRI), a component of the National Institutes of Health (NIH) have generated Embryonic Stem (ES) cell clones from C57BL/6J mice in a defined serum-free medium. These cell lines enable direct genetic alteration of mice in a pure genetic background.

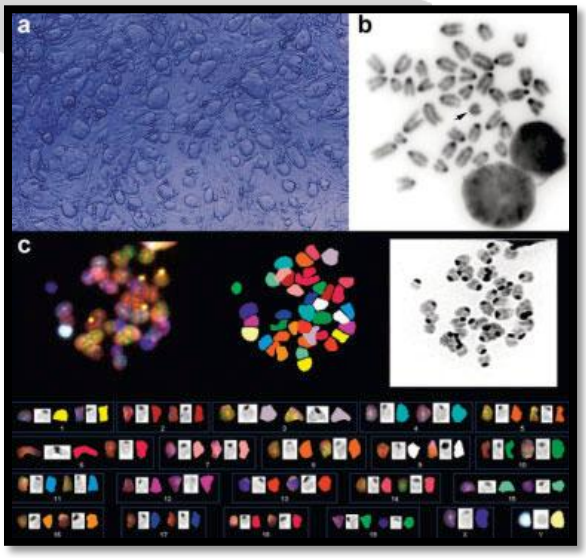
Using a defined media supplement, namely knockout serum replacement (KSR) with knockout DMEM (KSR-KDMEM), the investigators established ES cell lines from blastocysts of C57BL/6J mice. One cell line, HGTC-8, was further tested and found to be karyotypically stable and germline competent, both prior to manipulation and after gene targeting. All cell lines showed greater efficiency of transfection, as well as increased clone and chimera generation, when maintained in KSR-KDMEM.

Potential Commercial Applications

These cell lines can be used for targeted genetic alteration of mice in a pure genetic C57BL/6J background without the need for time-consuming backcrossing.

Related Article

Cheng et al., *Improved Generation of C57BL/6J Mouse Embryonic Stem Cells in a Defined Serum-Free Media*, 39 GENESIS 100 (2004).
http://onlinelibrary.wiley.com/doi/10.1002/gene.20031/pdf



*Morphology and characterization of a male C57BL/6J ES cell line, HGTC-8. **a:** Morphology of cells cultured on mouse embryonic fibroblasts (magnification x50). **b:** DAPI stained karyotype reveals 40 XY chromosomes. The arrow indicates the Y chromosome. **c:** Spectral karyotyping analysis demonstrates a normal karyotype.*

Pendrin Knockout (KO) Mouse

NHGRI invention number:
E-215-2009/0

Key Words

Pendred Syndrome, Pendrin, PDS Gene, COPD, Asthma, Knockout Mice

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Summary

Mutations in the human Pendred syndrome (PDS) gene cause the deafness and goiter disorder Pendred syndrome (PS). PDS encodes pendrin - a sodium-independent anion transporter that has been shown to play an important role in the regulation of blood pressure by the kidneys. In addition, pendrin has been implicated in the pathogenesis of asthma and chronic obstructive pulmonary disease (COPD). NHGRI investigators generated a pendrin KO mouse that is deaf and shows vestibular dysfunction. Thus, the mouse can serve as a model for auditory dysfunction and deafness in PS, as well as for asthma and COPD.

Potential Commercial Applications

This mouse could be used to screen for and/or test candidate therapeutics targeting either the PDS gene or the pendrin protein. The tested compounds could be useful for treating deafness, goiter, and hypertension, as well as lung diseases characterized by inflammation, such as asthma and COPD. Either *in vivo* experiments with the animals or *in vitro* studies with isolated cells could be carried out.

Related Article

Everett et al., *Targeted Disruption of Mouse Pds Provides Insight About the Inner-Ear Defects Encountered in Pendred Syndrome*, 10 HUMAN MOL. GENE TICS 153 (2001).
http://hmg.oxfordjournals.org/content/10/2/153.full.pdf

Novel Genotoxic Detection Assays

NHGRI invention number:
E-215-2010/0
E-108-2008/0

Key Words

Enhanced Level of Genomic Instability 1, Genotoxicity, Luciferase, High Throughput

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Summary

The Enhanced Level of Genomic Instability 1 (ELG1) protein functions in suppression of genomic instability caused by DNA damage. NHGRI researchers have demonstrated that human ELG1 (hELG1) protein is stabilized after DNA damage by various genotoxic stresses and they have developed a cell line expressing ELG1-luciferase fusion protein. This cell line can be used to detect genotoxicity of compounds in less than twenty (20) hours and it was successfully utilized to survey the National Toxicology Program (NTP) library containing known genotoxic compounds. In addition, cell lines expressing hELG1-green fluorescent protein (GFP) and hELG1-cyan fluorescent protein (CFP) were developed and are available.

Potential Commercial Applications

Use of NHGRI's cell lines expressing hELG1-luciferase, hELG1-GFP, and hELG1-CFP in testing genotoxicity of compounds could give more robust and quicker results than those obtained with current ELISA-based assays. For example, the hELG1-luciferase line was used to screen 300,000 NIH Chemical Genomics Center compounds in two weeks in a high-throughput manner.

Related Article

Sidkar et al., *DNA Damage Responses by Human ELG1 in S Phase are Important to Maintain Genomic Integrity*, 8 CELL CYCLE 3199 (2009).
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2880862/pdf/nihms201877.pdf

Antibodies Against Vangl1 and Vangl2 Proteins

NHGRI invention numbers:
E-135-2011/0
E-136-2011/0

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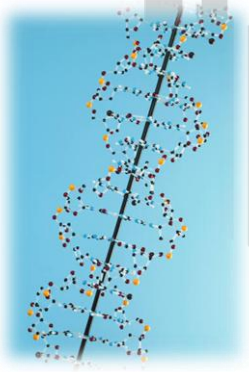

Summary

Vangl1 (Van Gogh like 1) and Vangl2 (Van Gogh like 2) are two core proteins mediating establishment of Planar Cell Polarity (PCP), which refers to the polarity of epithelial cells within a plane orthogonal to their apical-basal axis. Disruption of core PCP proteins leads to many developmental defects, including open neural tube, misorientation of sensory hair cells in the inner ear, polycystic kidney disease and skeletal deformations. In humans, mutations in Vangl1 and Vangl2 have been identified in patients with neural tube defects, such as spina bifida, the most common permanently disabling birth defect in the United States. NHGRI researchers have recently generated rabbit polyclonal antibodies against Vangl1 and phosphorylated Vangl2 proteins that are suitable for endogenous Vangl1 and Vangl2 detection.

Potential Commercial Applications

Anti-Vangl1 and Vangl2 antibodies could be used in the development of diagnostic and therapeutic treatments for PCP-related developmental defects, such as open neural tube and spina bifida, polycystic kidney disease, and skeletal abnormalities.

Related Articles

Gao et al., *Wnt Signaling Gradients Establish Planar Cell Polarity by Inducing Vangl2 Phosphorylation Through Ror2*, 20 DEVELOPMENTAL CELL 163 (2011).
http://www.sciencedirect.com/science/article/pii/S1534580711000025
Song et al., *Planar Cell Polarity Breaks Bilateral Symmetry by Controlling Ciliary Positioning*, 466 NATURE 378 (2010).
http://www.genome.gov/Pages/Research/DIR/Yang-PlanarCellPolarity.pdf

Key Words

Vangl1, Vangl2, Planar Cell Polarity, Neural Tube, Spina Bifida, Antibodies

Human Melanoma Cell Lines with ERBB4 Mutations

NHGRI invention number:
E-229-2010/0

Key Words

Melanoma, Protein Tyrosine Kinases, Small Molecule Inhibitors, Cell Lines, ERBB4

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Summary

Protein tyrosine kinases (PTKs) are frequently mutated in a variety of cancers, including melanoma. Using high throughput gene sequencing, NHGRI researchers have analyzed PTKs in melanoma and identified several novel somatic alterations, including those in PTK ERBB4 (v-erb-a erythroblastic leukemia viral oncogene homolog 4, also called HER4). These mutations were found to increase the sensitivity of cells in which they reside to small molecule inhibitors, such as lapatinib. Cell lines harboring these mutations have also been developed and can be used to identify specific inhibitors to ERBB4, as well as to improve existing melanoma treatments.

Potential Commercial Applications

The developed cell lines could be used to further understand the biology of ERBB4, such as its effects on growth, motility, invasion, and metabolite production. They could also serve as a platform for high throughput drug screening to identify and

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test ERBB4 inhibitors, which, in turn, could be used as cancer (e.g., melanoma) therapeutics. Additionally, these cell lines could assist in the development of diagnostic assays for the detection of ERBB4 mutations.

Related Article

Prickett et al., *Analysis of the Tyrosine Kinome in Melanoma Reveals Recurrent Mutations in ERBB4*, 41 NATURE GENETICS 1127 (2009).
http://www.nature.com/ng/journal/v41/n10/pdf/ng.438.pdf

Human Melanoma Metastasis Cell Line with Isocitrate Dehydrogenase 1 (IDH1) R132 Mutation

NHGRI invention number: E-232-2010/0

Key Words

Melanoma, Glioma, AML, Isocitrate Dehydrogenase 1, Cell Lines, Small Molecule Inhibitors

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Summary

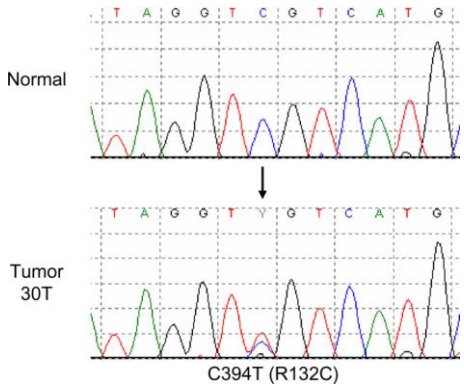
Isocitrate dehydrogenase 1 (IDH1), which during the citric acid cycle converts isocitrate to α-ketoglutarate while reducing nicotinamide adenine dinucleotide phosphate (NADP+) to NADPH, was previously identified as mutated in a large percentage of progressive gliomas and acute myeloid leukemias (AML). These mutations are found at the R132 residue. Cancers associated with the IDH1 mutation result in the accumulation of 2-hydroxyglutarate, which can serve as a diagnostic and prognostic marker. In order to further understand the biology of the IDH1 and identify specific inhibitors, a cell line harboring the mutation would be extremely beneficial. NHGRI researchers developed a human melanoma metastasis cell line harboring the R132C mutation by using low passage cell lines derived from a panel of pathology-confirmed metastatic melanoma tumor resections, paired with apheresis-collected peripheral blood mononuclear cells.

Potential Commercial Applications

This particular cell line could be used to further decipher the biology of IDH1 (using both *in vitro* and *in vivo* techniques), including its role in cell growth, motility, invasion, and metabolite production. The line could also assist with high throughput drug screening to identify inhibitors of IDH1, and thus potential therapeutics for cancers, such as glioma, AML, and melanoma.

Related Article

Lopez et al., *IDH1^{R132} Mutation Identified in One Human Melanoma Metastasis, but Not Correlated with Metastases of the Brain*, 398 BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS 585 (2010).
http://www.sciencedirect.com/science/article/pii/S0006291X10012829



Sequencing of melanoma metastases identified IDH1 R132C mutation in a melanoma cell line derived from a melanoma lung metastasis.

Mouse Model of Hutchinson-Gilford Progeria Syndrome and Vascular Abnormalities

NHGRI invention number: E-243-2011/0

Key Words

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

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Summary

Children with Hutchinson-Gilford progeria syndrome (HGPS) suffer from acceleration of certain aging symptoms, mainly cardiovascular disease that generally leads to death from myocardial infarction and/or stroke. The cause of HGPS has been discovered to be a *de novo* point mutation in lamin A (LMNA). The LMNA gene has three protein products: lamin A, lamin C, and lamin A*delta*10, which are components of the nuclear lamina. *De novo* mutation 1824 C to T (also called G608G) creates a splice donor site that results in a mutant LNMA protein called progerin. Progerin cannot be properly post-transcriptionally modified and causes alterations in nuclear structure and function.

NHGRI researchers have generated a transgenic mouse model of HGPS. This mouse carries a bacterial artificial chromosome (BAC) with the G608G mutated form of human LMNA. It also retains a normal form of mouse LMNA. A control mouse with wild-type human LMNA is also available. The mice are C57BL/6 animals that lack the external phenotype seen in human progeria, but have vascular abnormalities resembling the human syndrome. Specifically, the animals show progressive vascular smooth muscle cell loss in large arteries and replacement with proteoglycan and collagen (indicating progressive vascular calcification).

Potential Commercial Applications

This mouse model can be used to further understand the vascular pathology of progeria, and to study potential therapies. It can also be used to investigate symptoms of, and therapeutic treatments for, other cardiovascular and aging disorders, especially those that involve atherosclerotic lesions and vascular calcification.

Related Article

Varga, R. et al., *Progressive Vascular Smooth Muscle Cell Defects in a Mouse Model of Hutchinson-Gilford Progeria Syndrome*, 103 PROCEEDINGS NAT'L ACAD. SCI. 3250 (2006). *http://www.pnas.org/content/103/9/3250.full.pdf*