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Bioinformatics up to Date

(Bioinformatics Infrastructure Facility, Biotechnology Division)
North-East Institute of Science & Technology
Jorhat - 785 006, Assam

Inside…..

Protein Data Bank

As of Tuesday Mar 25, 2014 at 5 PM PDT there are 98900 Structures

New protein markers identified that could help understand heart disease better

Researchers at the Intermountain Medical Center Heart Institute in Murray, Utah, have found that elevated levels of two recently identified proteins in the body are inflammatory markers and indicators of the presence of cardiovascular disease.

These newly identified markers of inflammation, GlycA and GlycB, have the potential to contribute to better understanding of the inflammatory origins of heart disease and may be used in the future to identify a heart patient's future risk of suffering a heart attack, stroke, or even death. Inflammation occurs in the body in response to tissue damage, irritation, or infection. Inflammation is often associated with injury (i.e., sprained ankle), infection (i.e., strep throat), and autoimmune diseases (i.e., rheumatoid arthritis). However, it has been shown that inflammation is also a risk factor for heart disease.

"There are at least two benefits evident from this study," J. Brent Muhlestein, MD, lead researcher and co-director of cardiovascular research at the Intermountain Medical Center Heart Institute said. "First, a new marker of heart attack or stroke may help us to more effectively identify which patients are at risk. Second, now that we know GlycA and GlycB are important predictors of heart disease, we'll seek to understand more about the physiology of these proteins - what causes them to increase and how we can we treat elevated levels," Muhlestein said.

Levels of GlycA and GlycB were determined from a blood test called nuclear magnetic resonance (NMR) spectroscopy, which was developed to determine the number of lipid particles contained in different cholesterol parameters. Like C-reactive protein, one of the most well-known and studied inflammatory markers shown to be associated with cardiovascular disease, GlycA and GlycB are acute phase proteins with plasma concentrations that increase or decrease in response to changes in the levels of inflammation throughout the body.

Bioinfo. Carrier

1.PhD and Postdoc Position in Computational Biology @ RWTH Aachen University, Germany.

2. Admission to the Ph.D. programme in the Department of Biophysics, Molecular Biology & Bioinformatics, University of Calcutta for the year 2014

A Crisper CRISPR: Safer Genome Modification

Researchers from the Wellcome Trust Sanger Institute and the Model Animal Research Center of Nanjing University, China, have developed a safer way of genome editing. This method can be used on any organism and dramatically minimizes the problem caused by unplanned damage to other regions of the genome. CRISPR is a molecular tool that edits the genomes of cells and organisms. The technology uses the DNA-cutting enzyme Cas9, with the help of a guide RNA sequence, to find and modify genetic targets. Previously, researchers used a Cas9 endonuclease, an enzyme that cuts through both strands of DNA. Broken DNA strands can lead to new genetic mutations at the desired site but also at other related sites. In this study, the team found that by using a Cas9 enzyme that nicks a single strand of DNA, known as nickase, they can reduce unplanned, off-target DNA cuts elsewhere in the genome. "The initial excitement around CRISPR technology has been tempered by recent studies showing significant damage at related sites of the genome," says Dr. Bill Skarnes, senior author from the Wellcome Trust Sanger Institute. "We've solved this problem by using a form of Cas9 enzyme that doesn't break DNA, except at the intended target. The improvement in specificity is remarkable."

To determine the safest and most efficient option for DNA modification in mouse models, the team compared results with the Cas9 endonuclease, inducing double strand breaks on DNA, and the Cas9 nickase, inducing single strand nicks. The team used the Cas9 nickase to make a genetic deletion on three genes in mice. Because they targeted two genes very close together - Rag1 and Rag2 - they were also able to successfully create a large deletion. The nickase successfully created cuts on both strands of DNA with no evidence of off-target damage elsewhere.

"This system greatly reduces the risk of off-target mutations in the genomes of mouse models and doesn't seem to compromise the efficiency of the previous system," says Dr. Xingxu Huang, senior author from Model Animal Research Center of Nanjing University, China.

Study Identifies Path to Safer Drugs for Heart Disease, Cancer

Massachusetts General Hospital (MGH) investigators may have found a way to solve a problem that has plagued a group of drugs called ligand-mimicking integrin inhibitors, which have the potential to treat conditions ranging from heart attacks to cancer metastasis. In a Nature Structural & Molecular Biology paper receiving advance online publication, the researchers provide a structural basis for the design of new and safer integrin inhibitors. Integrins are receptor proteins found on the surface of cells that determine whether or not cells adhere to adjacent cells and the surrounding extracellular matrix. Under normal circumstances, integrins only become activated – which allows them to bind to other cells or extracellular molecules – in response to specific signals from within the cell. If integrins become overactive, cells become too "sticky" – leading to clogged arteries, pathological inflammation, the excess tissue growth called fibrosis or the spread of cancer. Current drugs developed to inhibit integrin activation by mimicking the shape of ligands – the molecules that interact with receptors – have had unintended effects in some patients, and as a result only a handful have received FDA approval.

"Integrins have an intrinsic ability to shape-shift when they switch from an inactive to an active, adhesive state," explains Dr. M. Amin Arnaout, director of the MGH Leukocyte Biology Program and the Inflammation and Structural Biology Program, senior author of the study. "Unfortunately, under some circumstances the integrin inhibitors that have been developed to date can inadventently induce this shape shifting, and use of these drugs have produced serious, sometimes fatal side effects such as excessive bleeding."

In their search for drugs that would not induce these complications, the MGH team focused on an extracellular matrix protein called fibronectin, which binds to an integrin called αvβ3. Their detailed structural analysis of the bond between αvβ3 and various forms of FN10, the fibronectin molecule that interacts with αvβ3, identified a high-affinity version of FN10 that binds more strongly than the common form without causing unintended receptor activation. This first report of the three-dimensional atomic structure of an integrin binding with a ligand-mimicking molecule that does not cause inadvertent activation could enable the design of a new generation of integrin inhibitors without the complications that have limited their application.

New Technique for Identifying Gene-Enhancers

An international team led by researchers with the Lawrence Berkeley National Laboratory (Berkeley Lab) has developed a new technique for identifying gene enhancers - sequences of DNA that act to amplify the expression of a specific gene – in the genomes of humans and other mammals. Called SIF-seq, for site-specific integration fluorescence-activated cell sorting followed by sequencing, this new technique complements existing genomic tools, such as ChIP-seq (chromatin immunoprecipitation followed by sequencing), and offers some additional benefits.

"While ChIP-seq is very powerful in that it can query an entire genome for characteristics associated with enhancer activity in a single experiment, it can fail to identify some enhancers and identify some sites as being enhancers when they really aren't," says Diane Dickel, a geneticist with Berkeley Lab's Genomics Division and member of the SIF-seq development team. "SIF-seq is currently capable of testing only hundreds to a few thousand sites for enhancer activity in a single experiment, but can determine enhancer activity more accurately than ChIP-seq and is therefore a very good validation assay for assessing ChIP-seq results."

Dickel is the lead author of the paper in Nature Methods describing this new technique entitled "Function-based identification of mammalian enhancers using site-specific integration." With the increasing awareness of the important role that gene enhancers play in normal cell development as well as in disease, there is strong scientific interest in identifying and characterizing these enhancers. This is a challenging task because an enhancer does not have to be located directly adjacent to the gene whose expression it regulates, but can instead be located hundreds of thousands of DNA base pairs away. The challenge is made even more difficult because the activity of many enhancers is restricted to specific tissues or cell types.

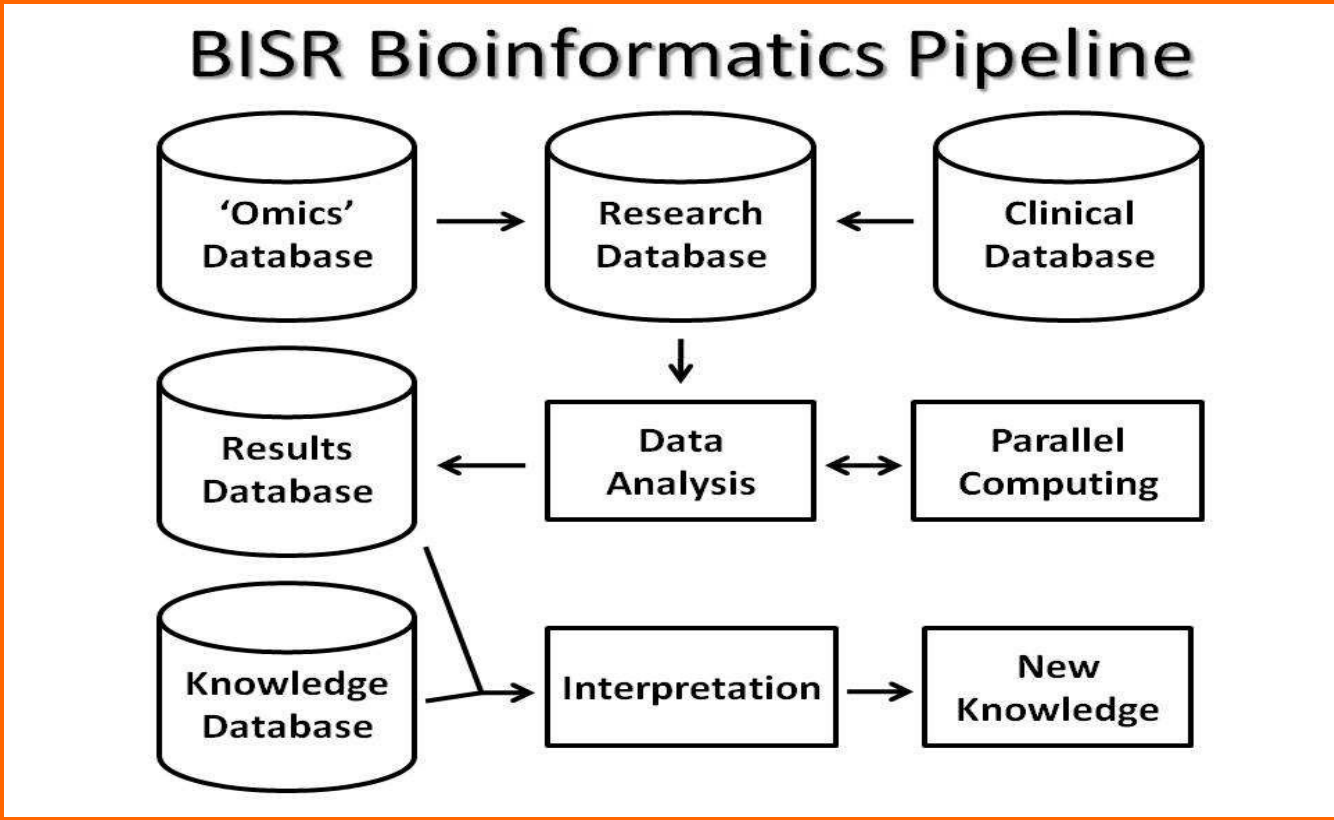
GenoCAD: Languages to Design Synthetic Living Systems

GenoCAD, an open-source software developed by researchers at the Virginia Bioinformatics Institute at Virginia Tech to help synthetic biologists capture biological rules to engineer organisms that produce useful products or health-care solutions from inexpensive, renewable materials. GenoCAD helps researchers in the design of protein expression vectors, artificial gene networks, and other genetic constructs, essentially combining engineering approaches with biology. Synthetic biologists have an increasingly large library of naturally derived and synthetic parts at their disposal to design and build living systems. These parts are the words of a DNA language and the "grammar" a set of design rules governing the language. It has to be expressive enough to allow scientists to generate a broad range of constructs, but it has to be focused enough to limit the possibilities of designing faulty constructs.

MIT's Oliver Purcell, a postdoctoral associate, and Timothy Lu, an associate professor in the Department of Electrical Engineering and Computer Science, have developed a language detailed in ACS Synthetic Biology describing how to design a broad range of synthetic transcription factors for animals, plants, and other organisms with cells that contain a nucleus. Meanwhile, Sakiko Okumoto, an assistant professor of plant pathology, physiology, and weed science at the Virginia Tech College of Agriculture and Life Sciences, and Amanda Wilson, a software engineer with the Synthetic Biology Group at the Virginia Bioinformatics Institute, developed a language describing design rules for expressing genes in the chloroplast of microalgae Their work was published in the Jan. 15 issue of Bioinformatics.

"Just like software engineers need different languages like HTML, SQL, or Java to develop different kinds of software applications, synthetic biologists need languages for different biological applications," said Jean Peccoud, an associate professor at the Virginia Bioinformatics Institute, and principal investigator of the GenoCAD project. They propose that grammars are a first step toward the standardization of a broad range of synthetic genetic parts that could be combined to develop innovative products. "Developing a grammar in GenoCAD is a little like writing a review paper," Purcell said.

Bioinfo. Animation



Patent News

Systems and methods to detect rare mutations and copy number variation

WO 2014039556 A1

Publication date Mar 13, 2014

Inventors: AmirAli TALASAZ, Helmy Eltoukhy

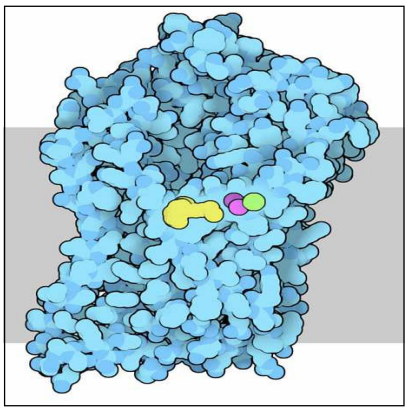
Applicant: Guardant Health, Inc.

Abstract

The present disclosure provides a system and method for the detection of rare mutations and copy number variations in cell free polynucleotides. Generally, the systems and methods comprise sample preparation, or the extraction and isolation of cell free polynucleotide sequences from a bodily fluid; subsequent sequencing of cell free polynucleotides by techniques known in the art; and application of bioinformatics tools to detect rare mutations and copy number variations as compared to a reference. The systems and methods also may contain a database or collection of different rare mutations or copy number variation profiles of different diseases, to be used as additional references in aiding detection of rare mutations, copy number variation profiling or general genetic profiling of a disease.

Neurotransmitter Transporters

(March 2014 Molecule of the Month by David Goodsell)



Nerve cells communicate with one another in two ways. Some neurons send an electrical signal directly to their neighbors, which is very fast. Most neurons, however, use chemical signals to transmit their messages, releasing small neurotransmitter molecules that are recognized by receptors on neighboring neurons. Neurotransmitters have two important advantages: since thousands of molecules are released, they amplify the signal, and since many different types of neurotransmitters are used, they can encode a variety of different types of signals. Once neurotransmitters have delivered their message, they need to be cleaned up, to get the neurons ready for the next signal. This is the job of neurotransmitter transporters. They are found in the membrane of the neuron or in associated cells. They transport the neurotransmitters out of the narrow synaptic cleft between the nerve cells, powered by the simultaneous transport of sodium and chloride ions. The transporter shown here, from PDB entry 4m48, transports the neurotransmitter dopamine.

Neurotransmitter transporters have been difficult to study by x-ray crystallography, but structures have been obtained for several bacterial transporters with very similar function. These transporters import neurotransmitter-like nutrient molecules into the bacterial cell, powered by the co-transport of sodium ions.

Upcoming Events

10th ISCB Student Council Symposium

11th of July, 2014 in Boston

http://scs2014.iscbsc.org/scs14-call

Website http://www.ncbci.servenature.in

Kindly send us your feedback to

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