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INSIDE THIS ISSUE

Science News

Compiled By Ali Mowjoodi

Accurate analysis of copy number variation at 16p11.2 in autism spectrum disorder and control cohorts Using TaqMan® Copy Number Assays and the ViiA™ 7 Real-Time PCR System

Christian Marshall, Guillermo Casallo and Ali Mowjoodi

In 2010 the Genetic Analysis facility at TCAG had the opportunity to test the new ViiA™ 7 Real-Time PCR System from Applied Biosystems and Life Technologies. TaqMan® Copy Number Assays were used to test for deletions and duplications at 16p11.2 that have been associated with Autism and/or Developmental Delay. The main objective of the experiment was to find new CNVs in cases that were missed by microarray screens and to determine the accurate frequency of these changes in a control population cohort. We used probes in the genes SEZ6L2 and SH2B1 that would interrogate two related but distinct genomic loci. Led by Dr. Christian Marshall, Guillermo Casallo and Ali Mowjoodi, we screened 455 ASD cases and 455 controls. In the ASD cases, all detected CNVs were previously found in the microarray experiments indicating that high resolution array technology has the sensitivity and specificity to detect the larger deletions and duplications at 16p11.2. In controls, as expected, no deletions were detected in 455 individuals. However, we detected two duplications at SH2B1 in the control cohort indicating that, although rare, copy number gains in 16p11.2 exist in the general population. TaqMan® Copy Number Assays, in conjunction with the ViiA™ 7 Real-Time PCR System, provided the necessary throughput and sensitivity to obtain accurate CNV frequencies at the loci tested.

http://www3.appliedbiosystems.com/cms/groups/mcb_marketing/documents/generaldocuments/cms_093666.pdf

Identification of the Imprinted KLF14 Transcription Factor Undergoing Human-Specific Accelerated Evolution

Layla Parker-Katiraee, Andrew R. Carson, Takahiro Yamada, Philippe Arnaud, Robert Feil, Sayeda N. Abu-Amero, Gudrun E. Moore, Masahiro Kaneda, George H. Perry, Anne C. Stone, Charles Lee, Makiko Meguro-Horike, Hiroyuki Sasaki, Keiko Kobayashi, Kazuhiko Nakabayashi, Stephen W. Scherer.

Imprinted genes are expressed in a parent-of-origin manner and are located in clusters throughout the genome. Aberrations in the expression of imprinted genes on human Chromosome 7 have been suggested to play a role in the etiologies of Russell-Silver Syndrome and autism. We describe the imprinting of KLF14, an intronless member of the Krüppel-like family of transcription factors located at Chromosome 7q32. We show that it has monoallelic maternal expression in all embryonic and extra-embryonic tissues studied, in both human and mouse. We examine epigenetic modifications in the KLF14 CpG island in both species and find this region to be hypomethylated. In addition, we perform chromatin immunoprecipitation and find that the murine Klf14 CpG island lacks allele-specific histone modifications. Despite the absence of these defining features, our analysis of Klf14 in offspring from DNA methyltransferase 3a conditional knockout mice reveals that the gene's expression is dependent upon a maternally methylated region. Due to the intronless nature of Klf14 and its homology to Klf16, we suggest that the gene is an ancient retrotransposed copy of Klf16. By sequence analysis of numerous species, we place the timing of this event after the divergence of Marsupialia, yet prior to the divergence of the Xenarthra superclade. We identify a large number of sequence variants in KLF14 and, using several measures of diversity, we determine that there is greater variability in the human lineage with a significantly increased number of nonsynonymous changes, suggesting human-specific accelerated evolution. Thus, KLF14 may be the first example of an imprinted transcript undergoing accelerated evolution in the human lineage.

PLoS Genetics, May2007; 3 (5).

'Master Switch' Gene for Obesity and Diabetes Discovered

Kerrin S Small, Åsa K Hedman, Elin Grundberg, Alexandra C Nica, Gudmar Thorleifsson, Augustine Kong, Unnur Thorsteindottir, So-Youn Shin, Hannah B Richards, Nicole Soranzo, Kourosh R Ahmadi, Cecilia M Lindgren, Kari Stefansson, Emmanouil T Dermitzakis, Panos Deloukas, Timothy D Spector, Mark I McCarthy

A team of researchers, led by King's College London and the University of Oxford, have found that a gene linked to type 2 diabetes and cholesterol levels is in fact a 'master regulator' gene, which controls the behaviour of other genes found within fat in the body.

"Scientists have found that a gene linked to type 2 diabetes and cholesterol levels is in fact a "master regulator" gene, which controls the behaviour of other genes found within fat in the body".

As fat plays a key role in susceptibility to metabolic diseases such as obesity, heart disease and diabetes, this study highlights the regulatory gene as a possible target for future treatments to fight these diseases.

It was already known that the KLF14 gene is linked to type 2 diabetes and cholesterol levels but, until now, how it did this and the role it played in controlling other genes located further away on the genome was unknown. The researchers examined over 20,000 genes in subcutaneous fat biopsies from 800 UK female twin volunteers. They found an association between the KLF14 gene and the expression levels of multiple distant genes found in fat tissue, which means it acts as a master switch to control these genes. This was then confirmed

in a further independent sample of 600 subcutaneous fat biopsies from Icelandic subjects.

These other genes found to be controlled by KLF14 are in fact linked to a range of metabolic traits, including body-mass index (obesity), cholesterol, insulin and glucose levels, highlighting the interconnectedness of metabolic traits.

The KLF14 gene is special in that its activity is inherited from the mother. Each person inherits a set of all genes from both parents. But in this case, the copy of KLF14 from the father is switched off, meaning that the copy from the mother is the active gene -- a process called imprinting. Moreover, the ability of KLF14 to control other genes was entirely dependent on the copy of KLF14 inherited from the mother -- the copy inherited from the father had no effect.

Professor Tim Spector said: 'This is the first major study that shows how small changes in one master regulator gene can cause a cascade of other metabolic effects in other genes. This has great therapeutic potential particularly as by studying large detailed populations such as the twins we hope to find more of these regulators.'

Professor Mark McCarthy said: 'KLF14 seems to act as a master switch controlling processes that connect changes in the behaviour of subcutaneous fat to disturbances in muscle and liver that contribute to diabetes and other conditions. We are working hard right now to understand these processes and how we can use this information to improve treatment of these conditions.'

Nature Genetics, May 15, 2011.

Health News

By Barbara Kellam

The Physical Activity That Curbs Hunger

Sure, strength training and aerobic exercise can help you work off those extra calories. But it might also help you say no to them in the first place.

That's just what a small study showed. People who lifted weights for 90 minutes -- or ran on a treadmill for 60 -- felt less hungry than those who didn't work out.

In fact, a good workout could suppress your appetite for as long as 2 hours afterward. Researchers speculate that the effect could have something to do with ghrelin -- an appetite-stimulating hormone. Exercise seems to suppress it but you have to do both strength training and cardio. Researchers suspect that the combination of cardio and strength exercises had the most favorable effect on blood levels of fats, glucose, amino acids, and satiety hormones -- producing a powerful combination of hunger-controlling physiological changes.

References:
Influence of resistance and aerobic exercise on hunger, circulating levels of acylated ghrelin, and peptide YY in healthy males. Broom, D. R. et al., American Journal of Physiology -- Regulatory, Integrative and Comparative Physiology 2009 Jan;296(1):R29-35.

WELCOME!

Sequencing
Nan Chen

Summer Student
Michael Gritti

Clinical Fellow
Raymond Kim

Summer Student
Alison Lai

Research Fellow
Daniele Merico

Summer Student
Anna Merkoulovitch

Summer Student
Jessica Rickaby

Upcoming Events

June 26, 2011 ***Walk Now for Autism Speaks***
7th Annual Toronto Walk
Nathan Phillips Square
Event Goal: $850,000
www.walknowforautismspeaks.ca

Celebrations

April Anniversaries!

Aparna	2 yrs.
Barbara	18 yrs.
Daisuke	2 yrs.

May Anniversaries!

Anath	4 yrs.
Jennifer	13 yrs.
Jin	4 yrs.
Jo-Anne	15 yrs.
Julie	7 yrs.
Kozue	4 yrs.
Nigel	1 yr.

June Anniversaries!

Karen	1 yr.
Lynda	3 yrs.
Mark	1 yr.
Ohsuke	2 yrs.
Patricia	11 yrs.
Thomas	1 yr.
Vanessa	1 yr.

Interesting Links

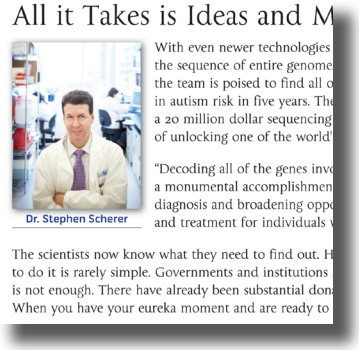
TCAG Statistical Analysis Facility supports Genome-wide association study of type 2 diabetes.

Researchers advance microarray technology to improve discovery of copy number variation.

TCAG study one of the Hottest of 2010

TCAG in the Globe and Mail

Win 1 of 4 Autographed NHL jerseys and other great stuff for Autism Speaks


All it Takes is Ideas and M

Dr. Stephen Scherer

With even newer technologies
the sequence of entire genome
the team is poised to find all o
in autism risk in five years. The
a 20 million dollar sequencing
of unlocking one of the world'

"Decoding all of the genes invo
a monumental accomplishmen
diagnosis and broadening oppo
and treatment for individuals

The scientists now know what they need to find out. H
to do it is rarely simple. Governments and institutions
is not enough. There have already been substantial don
When you have your eureka moment and are ready to

Contact Information:
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