Please see Proc Natl Acad Sci U S A. 2003 Jul 8;(100)14:8466-71. Epub 2003. Jun 27

Coordinated reduction of genes of oxidative metabolism in humans with insulin resistance and diabetes: Potential role of PGC1 and NRF1

Patti ME, et. al.

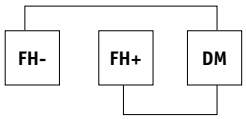
Question

- Can we define patterns of gene expression in human subjects with diabetes and those at high risk for development of diabetes?
- Mexican-American subjects
- Stratified by diabetes and family history
- Diabetics treated with lifestyle changes or sulfonylureas
- No exercise for 48 hours
- Fasting biopsy of vastus lateralis

Results

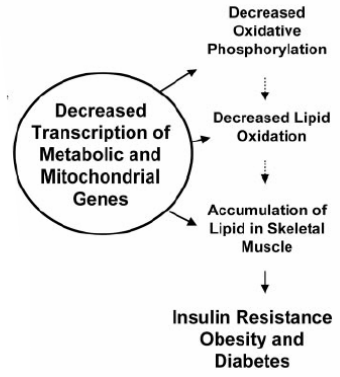
- Unequal variance, unpaired t-test, $p < 0.05$

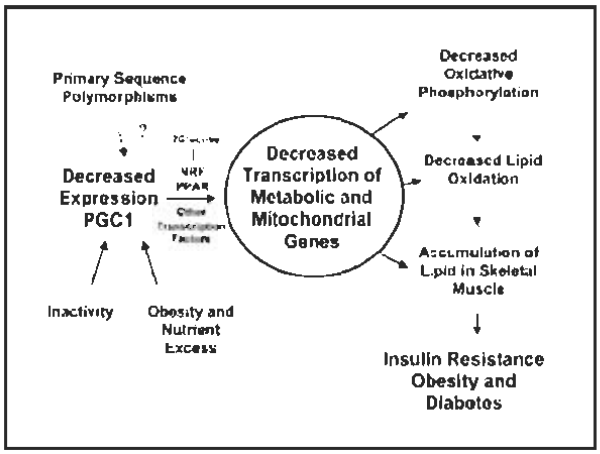
187 / 7129 different



166 / 7129 different

- None significant after Benjamini-Hochberg correction
- 55 intersecting genes
- Many coded for mitochondrial proteins involved in ATP synthesis and oxidative phosphorylation




Primary Sequence Polymorphisms
Decreased Expression PGC1
Decreased Transcription of Metabolic and Mitochondrial Genes
Decreased Oxidative Phosphorylation
Decreased Lipid Oxidation
Accumulation of Lipid in Skeletal Muscle
Insulin Resistance Obesity and Diabetes
Inactivity
Obesity and Nutrient Excess

Web-accessible data

- Great amounts of publicly available microarray data are available on the Internet
- *CardioGenomics Program in Genomic Applications*
  - http://cardiogenomics.med.harvard.edu/public-data.html
  - 142 microarrays involving mouse models of cardiac development and signal transduction, including measurements made in time-series.
- *Whitehead Institute Center for Genome Research*
  - http://www-genome.wi.mit.edu/cgi-bin/cancer/datasets.cgi
  - Microarrays from 12 publications involving many types of cancer, including some clinical measurements associated with each sample.

Web-accessible data

- *Children's National Medical Center (HopGenes Program in Genomic Applications)*
  - http://microarray.cnmcresearch.org/pgadatatable.asp
  - Over 500 microarrays from many human diseases, including muscular dystrophy, dermatomyositis, and heart failure, as well as mouse, rat and dog models of spinal cord injury, pulmonary disease, and heart failure.
- *Human Gene Expression Index*
  - http://www.hugeindex.org/databases/index.html
  - 121 microarrays from 19 normal human tissues.

Web-accessible data

- *Stanford Microarray Database*
  - http://genome-www5.stanford.edu/MicroArray/SMD/
  - 3290 microarrays measured across 11 species, from 80 publications.
- *National Center for Biotechnology Information Gene Expression Omnibus*
  - http://www.ncbi.nlm.nih.gov/geo/
  - 2354 microarrays from 105 types of microarrays, measured across 78 experiments.
- *TREX Program in Genomic Applications*
  - http://pga.tigr.org/data.shtml
  - 565 microarrays from mouse and rat models of sleep, infection, hypertension, and pulmonary disease.

Cluster

- An absolute standard tool in microarray analysis
- http://rana.lbl.gov/EisenSoftware.htm
- Performs a variety of types of cluster analysis and other types of processing on large microarray datasets
  - hierarchical clustering
  - self-organizing maps (SOMs)
  - k-means clustering
  - principal component analysis
- For Windows 95/98/NT only

GeneCluster 2.0

- Whitehead Institute
- http://www-genome.wi.mit.edu/cancer/software/genecluster2/gc2.html

- Java based
  - Nearest neighbor
  - Self-organizing maps (SOMs)
  - Marker analysis

Genesis

- Free for the moment
- http://genome.tugraz.at/Software/GenesisCenter.html
- Very polished, Java based
  - Hierarchical clustering
  - Self-organizing maps (SOMs)
  - Principal components
  - Support vector machines

TIGR MEV

- Multi-experiment viewer
- http://www.tigr.org/softlab

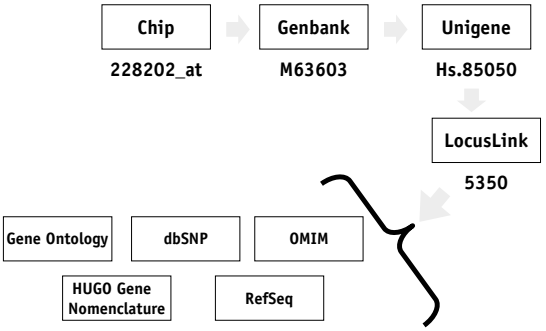
Relnet

- Java-based software to make relevance networks
- http://www.chip.org/relnet

GenMAPP

- Gene Microarray Pathway Profiler
- Paints pathway pictures in the context of microarray measurements
- http://www.genmapp.org

Accession Numbers

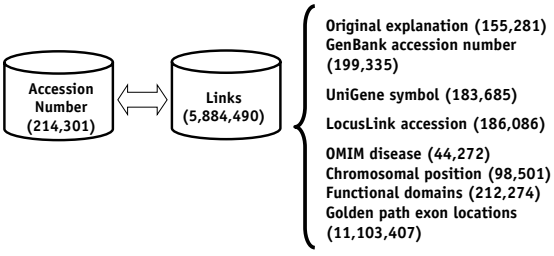


Looking up results

- Database Referencing of Array Genes Online
  - http://www.kennedykrieger.org/pevsnerlab/dragon.htm
- Unchip
  - http://www.unchip.org
- Resourcerer
  - http://pga.tigr.org/tigr-scripts/nhgi_scripts/resourcerer.pl
- Netaffx
  - http://www.netaffx.com

Unchip translation tables

- Databases linking Affymetrix microarray findings to national databases solely using the data files (public information)



www.unchip.org

- "Before and after" example
  - 33640_at: Cluster incl. Y14768: Homo sapiens DNA, cosmid clone
  - Unchip: Allograft inflammatory factor 1
- Search for "95654_at"
  - valyl-tRNA synthetase 2, heat shock protein cognate 70, etc.
- Search for "M35416_at"
  - Affymetrix: RALB V-ral simian leukemia viral oncogene homolog B
  - Edition 2: v-ral simian leukemia viral oncogene homolog B (ras related; GTP binding protein)
  - Edition 3: stathmin 1/oncoprotein 18

- Can find official names, symbols, and synonyms for accessions
- Can search for expression by functional domain or meaning
- Available as database and web-site, at www.unchip.org
- Updated periodically

Discovery portals

- Binding data and the tools that operate on them
- Physgen
  - http://pga.mcw.edu
- PGAGene
  - http://pgagene.chip.org

- NCBI Geo
  - http://www.ncbi.nlm.nih.gov/geo/

Cross-PGA results integration

- Integrated view of PGA gene-centric data
- Available today at pgagene.chip.org
- Data from over 1,200 microarrays publicly available
- Contains and references 5.9 million pieces of PGA data
- No additional work required from the external sites

Kyungjoon Lee, Atul Butte. PGAGENE: integrating quantitative gene-specific results from the NHLBI Programs for Genomic Applications. In press, Bioinformatics.

Cross-PGA results integration

- Uses LocusLink as common denominator
- Links microarrays, SNPs and mutations
- Out of 156,386 genes in LocusLink
  - 29,320 have been measured on a PGA microarray
  - 485 have been sequenced for SNPs
  - 4 have been sequenced for mutations

in vivo, in vitro, in http

- Let's try a live example

- Start with a rat model QTL / physiological finding
- Go to rat genomic map
- Move to multi-species expression data

Please refer to the Medical College of Wisconsin's Programs for http://pga.mcw.edu/

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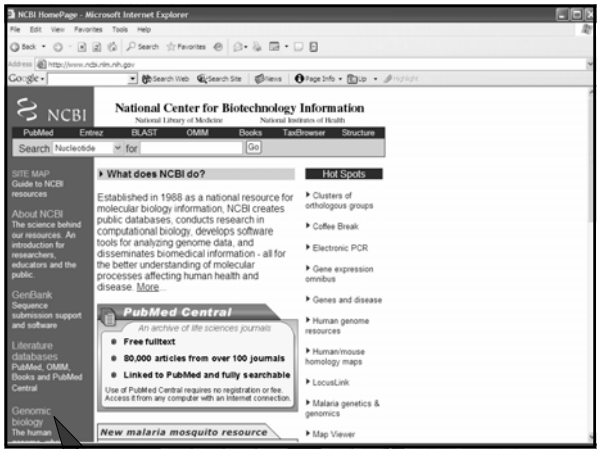
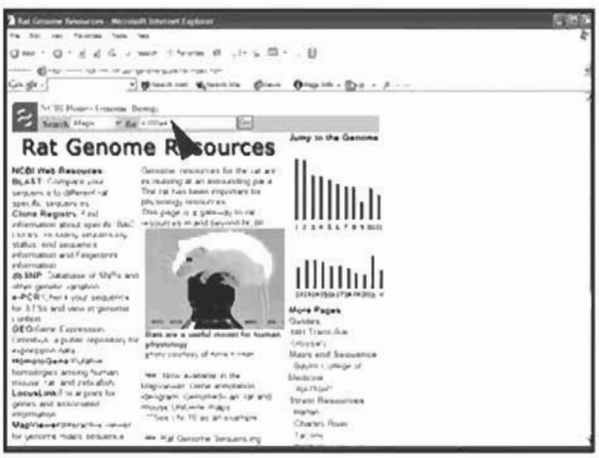
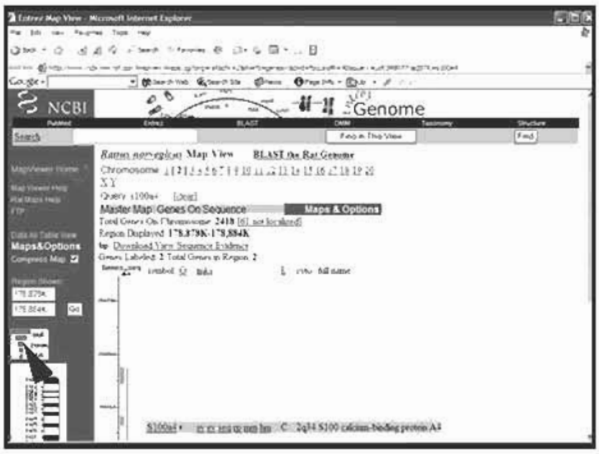
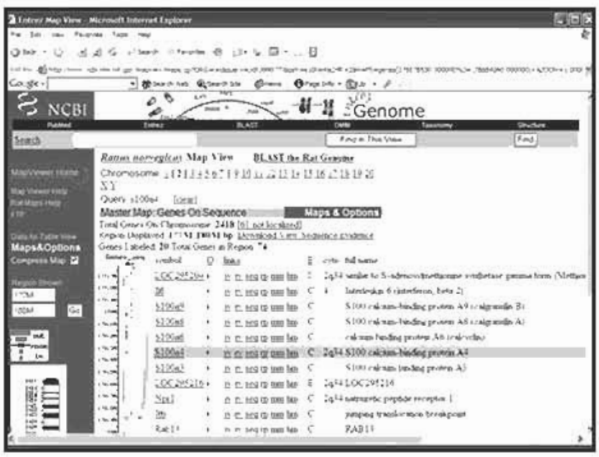


NCBI
Genomic Biology
Draft Human Genome
The SNP Database


Rat Genome Resources
Jump to the Genome
More Pages

NCBI
Genome
Rattus norvegicus genome


NCBI
Genome
Rattus norvegicus Map View
BLAST the Rat Genome
Master Map: Genes On Sequence
Maps & Options
Maps&Options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Take Home Points

- Thousands of microarray results and tools are available on the Internet; annotations are harder to find.
- Due to rapidly changing information, one is never truly finished analyzing a microarray data set.
- Web-based discovery portals are usable and empower investigators to integrate across genomic data.

Thank you. – Atul Butte