Graduate School of Neuroscience

and

Wilhelm Johannsen Centre for Functional Genome Research,
University of Copenhagen

Ph.d.-Course "Functional Genomics in Neuroscience"

(*ECTS points = 3*)

February 23-24, 2004

Panum Institute
February 23: Lille Mødesal, 1st floor, Building 5.
February 24: Store Mødesal, 1st floor, Building 5.
http://www.wjc.ku.dk/travel/index.php?subpage=maps
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How to get to the Panum Institute: **see** http://www.wjc.ku.dk/travel/

Graduate School of Neuroscience, Faculty of Health Sciences
and
Wilhelm Johannsen Centre for Functional Genome Research,

PhD-course in: "Functional Genomics in Neuroscience"

Programme

Monday 23 February 2004

9.30-10.00	Niels Tommerup, Copenhagen	Coffee, Welcome, Introduction
10.00-11.00	Jonathan Bard, Edinburg	Gene ontologies
11.00-12.00	Manolis Dermitzakis, Geneva	Expression map of human chromosome 21
Lunch		
13.00-14.00	Manolis Dermitzakis, Geneva	Regulatory conserved non-genic sequences (CNGs)
14.00-15.00	Jonathan Bard, Edinburg	Expression databases
15.00-16.00	Dick Lindhout, Utrecht	Epilepsy Genetics

Tuesday 24 February 2004

9.00-10.00	Gitte Moos Knudsen (Lars H. Pinborg), Copenhagen	Genes and the serotonergic brain receptors in humans/ Neuroimages of MZ vs. DZ twins
10.00-11.00	Andreas Jacobs, Cologne	PET-based Molecular Imaging in Neuroscience
11.00-12.00	Bertrand Tavitian, Orsay	In vivo imaging with oligonucleotides for diagnosis and drug development
Lunch		
13.00-14.00	Morten Møller, Copenhagen	Visualization of Circadian oscillations
14.00-15.00	Nikolaj Blom, Lyngby	Gene Discovery search strategies
15.00-16.00	Niels Tommerup, Copenhagen	Chromosomal breakpoints in brain disorders. Evaluation

"Functional Genomics in Neuroscience"

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"Functional Genomics in Neuroscience"
Abstracts/Links

Jonathan Bard
http://www.bms.ed.ac.uk/research/idg/gendev/JBard/JBard.htm

Richard A. Baldock, Jonathan Bard, Roberto Brunelli, Bill Hill, Matthew Kaufman, Kristie Opstad, David Smith, Margaret Stark, Andrew Waterhouse, Yiya Yang, Duncan Davidson: The Edinburgh Mouse Atlas: Using the CD. Briefings in Bioinformatics 2(2): 159-169 (2001)

Jonathan Bard, R. Winter: Ontologies of Developmental Anatomy: Their Current and Future Roles. Briefings in Bioinformatics 2(3): 289-299 (2001)

Manolis Dermitzakis
http://www.frontiers-in-genetics.org/en/index.php

Science. 2003 Nov 7;302(5647):1033-5. Epub 2003 Oct 02. Related Articles, Links

Comment in:

- Science. 2003 Nov 7;302(5647):997-9.

Full text article at www.sciencemag.org

Evolutionary discrimination of mammalian conserved non-genic sequences (CNGs).

Dermitzakis ET, Reymond A, Scamuffa N, Ucla C, Kirkness E, Rossier C, Antonarakis SE.
Division of Medical Genetics and National Center of Competence in Research (NCCR) Frontiers in Genetics, University of Geneva Medical School and University Hospitals, 1211 Geneva, Switzerland. Emmanouil.Dermitzakis@medecine.unige.ch

Analysis of the human and mouse genomes identified an abundance of conserved non-genic sequences (CNGs). The significance and evolutionary depth of their conservation remain unanswered. We have quantified levels and patterns of conservation of 191 CNGs of human chromosome 21 in 14 mammalian species. We found that CNGs are significantly more conserved than protein-coding genes and noncoding RNAS (ncRNAs) within the mammalian class from primates to monotremes to marsupials. The pattern of substitutions in CNGs differed from that seen in protein-coding and ncRNA genes and resembled that of protein-binding regions. About 0.3% to 1% of the human genome corresponds to a previously unknown class of extremely constrained CNGs shared among mammals.

Nature. 2002 Dec 5;420(6915):582-6. Related Articles, Links

Comment in:

- Nat Biotechnol. 2003 Jan;21(1):31-2.
- Nature. 2002 Dec 5;420(6915):512-4.
- Nature. 2002 Dec 5;420(6915):518-9.

nature

Human chromosome 21 gene expression atlas in the mouse.

Reymond A, Marigo V, Yaylaoglu MB, Leoni A, Ucla C, Scamuffa N, Caccioppoli C, Dermitzakis ET, Lyle R, Banfi S, Eichele G, Antonarakis SE, Ballabio A.

Division of Medical Genetics, University of Geneva Medical School and University Hospital of Geneva, CMU, 1, rue Michel Servet, 1211 Geneva, Switzerland.

Genome-wide expression analyses have a crucial role in functional genomics. High resolution methods, such as RNA in situ hybridization provide an accurate description of the spatiotemporal distribution of transcripts as well as a three-dimensional 'in vivo' gene expression overview. We set out to analyse systematically the expression patterns of genes from an entire chromosome. We chose human chromosome 21 because of the medical relevance of trisomy 21 (Down's syndrome). Here we show the expression analysis of all identifiable murine orthologues of human chromosome 21 genes (161 out of 178 confirmed human genes) by RNA in situ hybridization on whole mounts and tissue sections, and by polymerase chain reaction with reverse transcription on adult tissues. We observed patterned expression in several tissues including those affected in trisomy 21 phenotypes (that is, central nervous system, heart, gastrointestinal tract, and limbs). Furthermore, statistical analysis suggests the presence of some regions of the chromosome with genes showing either lack of expression or, to a lesser extent, co-expression in specific tissues. This high resolution expression 'atlas' of an entire human chromosome is an important step towards the understanding of gene function and of the pathogenetic mechanisms in Down's syndrome.

Dick Lindhout

http://www.ilae-epilepsy.org/about/AnnualReport2002/genes.cfm
http://humgen.med.uu.nl/

Epilepsy is a diagnostic term for a wide variety of syndromes that are mainly characterized by recurrent seizures. Epilepsy is a common condition affecting approximately 1% of the population, and the lifetime risk of an individual developing epilepsy is 3-5%. Epilepsy therefore falls in the category of common diseases, and has a major impact on society.
There is ample evidence for a genetic contribution to epilepsy, coming from twin studies, linkage and association studies, and from chromosomal abnormalities that display epilepsy in their associated phenotype. In particular, several genes have been detected for epilepsies that show a single gene inheritance or autosomal inheritance pattern. These genes can be identified relatively simply in large families by positional cloning. It is expected that more 'single gene' epilepsies will be unraveled as new large families are identified.
The current challenge lies in the discovery of genes responsible for epilepsies showing a complex inheritance pattern, involving multiple genes and environmental factors. Idiopathic Generalized Epilepsy (IGE) is the most common form of such an epilepsy. IGE can be subdivided into several clinically distinct phenotypes such as Juvenile Myoclonic Epilepsy (JME), Juvenile Absence Epilepsy (JAE) and PhotoSensitive Epilepsy (PSE). Often, more than one phenotype occurs within a family identified through a single patient, and in some cases, more than one phenotype may occur within one patient. It is often assumed that these separate IGE sub-phenotypes are caused by a single, or limited number, of genes.
An example of independent inheritance is PSE, which is expressed by the majority of patients with JME, but has been shown to be inherited separately in an autosomal dominant fashion. PSE thus provides a prime opportunity for unraveling the complex genetic background of IGE.
We are currently performing a genome-wide linkage analysis to identify the underlying genetic factors in PSE. This work is being done with an international consortium, which gives access to a large collection of families of different origin. On a smaller scale, candidate linkage and association studies are being performed for other subtypes of IGE. Candidate genes are also screened for the presence of mutations in carefully selected subgroups of epilepsy patients. Finally, chromosomal abnormalities with epilepsy as a major phenotype are being studied for the genetic defect causing the epilepsy.

Gitte Moos Knudsen

http://www.nru.dk/people/gmk/

http://www.nru.dk/publications/annual_reports/AnnualReport2002.pdf

Andreas Jacobs

http://www.molecularimaging.org/meeting3/home04.php3

"PET-based Molecular Imaging in Neuroscience"

Positron emission tomography (PET) allows a non-invasive assessment of physiological, metabolic and molecular processes in humans and animals in vivo. With the achievements in detector technology, spatial resolution of PET has been considerably improved (1-2 mm) enabling for the first time investigations in small experimental animals such as mice. With the developments in radiochemistry and tracer technology a variety of endogenously expressed and exogenously introduced genes can be analyzed by PET. This opens up the exciting and rapidly evolving field of molecular imaging aiming towards the non-invasive localization of a biological process of interest in normal and diseased cells in animal models and humans in vivo. The main and most intriguing advantage of molecular imaging is the kinetic analysis of a given molecular event in the same experimental subject over time. This will allow a non-invasive characterization and "phenotyping" of animal models of human disease at various disease stages, under certain pathophysiological stimuli and after therapeutic intervention, respectively. The potential broad applications of imaging molecular events in vivo are in the study of cell biology, biochemistry, gene/protein function and regulation, signal transduction, transcriptional regulation, and characterization of transgenic animals. Most importantly, molecular imaging will have great implications in identifying potential molecular therapeutic targets, in the development of new treatment strategies, and in their successful implementation into clinical application. In this lecture, the potential impact of molecular imaging by PET in applications in neuroscience research will be outlined with special reference to neurodegeneration and –oncology.

Bertrand Tavitian, Orsay

Tavitian B. In vivo imaging with oligonucleotides for diagnosis and drug development. Gut 2003 Jun;52 Suppl 4:iv40-7.

Molecular imaging, the science that combines non-invasive in vivo imaging and molecular biology, has begun to use labelled oligonucleotides as radiotracers. Antisense oligonucleotides target gene expression at the RNA level, while aptamer oligonucleotides are designed to hit proteins of interest. Oligonucleotides for imaging cover a large range of applications, from the invention of new contrast agents for diagnosis to exquisite research tools for the development of new drugs.

Nikolaj Blom, Lyngby

http://www.cbs.dtu.dk/nikob/

Prediction of protein PTMs (post-translational modifications) is becoming a serious research tool, not only for studying modifications of a protein, but also for larger-scale systems biology studies, e.g. large-scale protein function prediction. Many PTMs occur at specific, yet variable motifs, in the target proteins. In contrast to simple consensus patterns, machine learning techniques, such as artificial neural networks, are often well suited to integrate the subtleties of sequence variations. The protein PTM group at CBS has a succesful historical record of developing useful tools used by large parts of the molecular biology community. In particular, the SignalP server for predicting signal peptide sequences, the NetOGlyc and NetNGlyc for predicting glycosylation sites and the NetPhos server for predicting phosphorylation sites, have been and are still widely used over the Internet.

In addition to refining existing methods, for example by developing kinase-specific phosphorylation site prediction, the protein PTM group at CBS also focuses on novel PTMs suitable for predictive bioinformatics approaches. These projects include prediction of caspase and propeptide cleavage sites as well as tyrosine sulfation sites. Also, a deeper understanding of the structural features of PTM sites has been initiated. It is clear that the modifying enzymes must recognize the native three-dimensional structure around an acceptor site and therefore structural motifs may be more conserved than sequence motifs.

There is still a lot of genes and gene products hidden in the `midnight zone' - ie. orphan proteins with no homology to any other protein of known function. Many projects are aimed at elucidating the functions of these orphan proteins, some by experimental approaches such as gene profiling/microarrays, others by predictive approaches. In the latter case, PTMs have been shown to be important features for determining protein function. This knowledge is utilized in an integrative so-called systems biology approach, termed ProtFun, which is another large project at CBS. The further development of the ProtFun project is highly dependent on feature predictors such as the ones developed by the PTM group. A close collaboration between the PTM and the systems biology group ensures that novel predictive tools may be used efficiently and also guides the planning of new PTM projects.

L.J. Jensen, R. Gupta, N. Blom, D. Devos, J. Tamames, C. Kesmir, H. Nielsen, H.H. Stærfeldt, K. Rapacki, C. Workman, C. A. F. Andersen, S. Knudsen, A. Krogh, A. Valencia, S. Brunak. Prediction of human protein function from post-translational modifications and localization features, J. Mol. Biol., 319, 1257-1265, 2002.

Rosenblad C, Gronborg M, Hansen C, Blom N, Meyer M, Johansen J, Dago L, Kirik D, Patel UA, Lundberg C, Trono D, Bjorklund A, Johansen TE. In vivo protection of nigral dopamine neurons by lentiviral gene transfer of the novel GDNF-family member neublastin/artemin. Mol Cell Neurosci. 2000 Feb;15(2):199-214.

Erratum in: Mol Cell Neurosci 2001 Sep;18(3):332-3.

The glial cell line-derived neurotrophic factor (GDNF)-family of neurotrophic factors consisted until recently of three members, GDNF, neurturin, and persephin. We describe here the cloning of a new GDNF-family member, neublastin (NBN), identical to artemin (ART), recently published (Baloh et al., 1998). Addition of NBN/ART to cultures of fetal mesencephalic dopamine (DA) neurons increased the number of surviving tyrosine hydroxylase (TH)-immunoreactive neurons by approximately 70%, similar to the maximal effect obtained with GDNF. To investigate the neuroprotective effects in vivo, lentiviral vectors carrying the cDNA for NBN/ART or GDNF were injected into the striatum and ventral midbrain. Three weeks after an intrastriatal 6-hydroxydopamine lesion only about 20% of the nigral DA neurons were left in the control group, while 80-90% of the DA neurons remained in the NBN/ART and GDNF treatment groups, and the striatal TH-immunoreactive innervation was partly spared. We conclude that NBN/ART, similarly to GDNF, is a potent neuroprotective factor for the nigrostriatal DA neurons in vivo.

Niels Tommerup

http://www.wjc.ku.dk/
http://www.mcndb.org/

Our aim is to establish a functional map of the human genome by large-scale identification of novel human disease genes, of novel genetic entities and of novel genetic mechanisms by mapping and characterization of chromosomal rearrangements associated with abnormal and normal phenotypes.