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MEETING REPORT

SYSGENET: a meeting report from a new European network for systems genetics

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Abstract The first scientific meeting of the newly established European SYSGENET network took place at the Helmholtz Centre for Infection Research (HZI) in Braunschweig, April 7-9, 2010. About 50 researchers working in the field of systems genetics using mouse genetic reference populations (GRP) participated in the meeting and exchanged their results, phenotyping approaches, and data analysis tools for studying systems genetics. In addition, the future of GRP resources and phenotyping in Europe was discussed.

The SYSGENET network

SYSGENET represents a network of scientists in Europe who use mouse genetic reference populations (GRP) to identify complex genetic factors that influence phenotypic traits. Studies with GRPs are expected to contribute to the discovery of principal biological processes and gene networks that are involved in disease phenotypes. The findings will be translated to human diseases and represent the basis for understanding disease etiology and developing new treatment strategies. These gene networks can be extended to other species as well.

The researchers in SYSGENET are using various GRPs as model systems to investigate the biological mechanisms and gene regulatory networks involved in disease phenotypes. This approach has been described in many reviews and reports (Bao et al. 2006; Boon et al. 2009; Bystrykh et al. 2005; Chesler et al. 2005; Churchill et al. 2004; de Haan and Williams 2005; Dejager et al. 2009; Flint and Mott 2008; Gatti et al. 2007; Hovatta and Barlow 2008; Jansen and Nap 2001; Johannes et al. 2008; Li et al. 2005; Michaelson et al. 2009; Morahan et al. 2008b; Peirce et al. 2004; Peters et al. 2007; Roberts et al. 2007). The SYSGENET network partners are studying phenotypes relevant to infectious diseases, inflammatory disorders, metabolic diseases, cancer, neurological and psychiatric disorders, and infertility. The GRPs presently exploited by the network laboratories include inbred strains, consomic strains, recombinant inbred strains, congenic strains, interspecific recombinant congenic strains, outbred populations, and the upcoming large recombinant inbred strain collection known as the Collaborative Cross.

SYSGENET integrates the different national, European, and worldwide research programs in the field of complex genetics, systems biology, and the development of sophisticated experimental model systems. SYSGENET also reaches out to systems genetics programs in the United States and Australia.

The specific objectives of SYSGENET are

- to create a European network for systems genetics for complex genetic trait studies in mouse models by combining expertise and methods, exchanging results, and connecting the different ongoing national programs
- to link to research groups studying human complex genetic diseases
- to prepare concepts for a EU mouse resource infrastructure for GRPs
- to interact with worldwide systems genetics programs
- to prepare calls for research programs in the field of systems genetics in Europe

Participants of the SYSGENET meeting are given in the appendix.

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Infectious diseases

Infectious diseases continue to represent a threat to human health. Due to global warming and travel, newly emerging diseases are spreading at an unprecedented rate around the world. Examples are the dissemination of antibiotics-resistant mycobacteria, the new swine influenza virus variant, SARS, and West Nile virus (WNV). Several research groups are using mouse GRPs to identify complex genetic influences on the host susceptibility to infections. GRPs have been and will continue to be an important basis for understanding infectious diseases in humans. A very good example for translational research was presented by Pascal Rihet, who identified genomic susceptibility regions to malaria in human populations in Africa (Delahaye et al. 2007) and then continued to compare these results with studies in mouse GRPs. In this way, a region on human chromosome 5 and its homologous regions on mouse chromosomes 11 and 18 were identified. Subsequent expression studies in mice will now help to determine the molecular networks and genes involved. Paul Denny described the mapping of genetic susceptibility to *Streptococcus pneumonia* infections in mouse inbred strains to chromosomes 7 (Denny et al. 2003) and 4 (unpublished). Infection susceptibility to influenza was described by Klaus Schughart, who also pointed out that high susceptibility includes a hyperreactive immune response in the host (Srivastava et al. 2009). Xavier Montagutelli generated a unique resource of *Mus spretus* × C57BL/6 J interspecific recombinant congenic strains that carry different genomic fragments of *Mus spretus* on a C57BL/6 J background (Burgio et al. 2007). This GRP was used to identify resistance and susceptibility regions to various pathogens, including Rift Valley fever, West Nile virus, *Yersinia pestis*, and influenza. The first lines of the Collaborative Cross strains have been screened by Fuad Iraqi for a number of susceptibility loci to various pathogens (unpublished). It was remarkable to see that several quantitative trait loci (QTL) showed high significance and that the genomic intervals for several loci were very narrow, which should make it possible to identify quickly the underlying quantitative trait genes.

Metabolic diseases

Metabolic diseases in humans are dramatically on the rise; obesity and related diseases in particular represent a serious challenge to future health systems. Several groups addressed the complex genetics of metabolic functions and disorders using different mouse GRPs. Gudrun Brockmann reported on the mapping of QTLs for obesity in a specific mouse strain isolated in Berlin and the BXD congenic strain set (Neuschl et al. 2010). The future goal is to relate these QTLs to genetic polymorphisms that influence the immune system. Joan Campbell-Tofte presented the use of herbal extracts for the treatment of type 2 diabetes in humans. She nicely illustrated the use of mouse models: from human to mouse to humans and back to the mouse. Pénélope Andreux reported on the setting up of a mouse clinic in Lausanne for a systematic analysis of mouse GRPs for a large number of metabolic phenotypes, including mitochondrial functions (Koutnikova et al. 2009). Juan M. Falcon-Perez described the genomic, proteomic, and metabolic phenotyping capabilities of their technological platform and introduced extracellular microvesicles and metabolomic profiles as two new biological sources for identifying biomarkers for the detection and monitoring of hepatic diseases (Hackenberg et al. 2009). Abnormalities and diseases of the liver are also the subject of studies presented by Karl Kashofer (Kashofer et al. 2009). Several loci for (nonalcoholic) steatohepatitis have been mapped in chromosome substitution strains, and a more detailed mapping in subcongenic strains is ongoing.

Behavior

Although rats in general were the species of choice for use by experimental psychologists to study behavior, mice have been the preferred animal for behavior geneticists since at least the 1940 s. In addition, the adaptation of behavioral assays and the development of new methods have confirmed the mouse as one of the most preferred experimental systems to learn more about the genetic underpinnings of behavior and associated phenotypes. Martien Kas described the currently underlying scientific rationale. Precise measurement of a well-described behavioral trait across a GRP will lead to the identification of associated genes and genomic regions. In the next step these genes can be used to find homologous genes and pathways that contribute to the development of neuropsychiatric disorders in humans. The translational value of this interspecies genetic approach was nicely

exemplified in a study in which a QTL for avoidance behavior in mice was related to bipolar disorders in humans (de Mooij-van Malsen et al. 2009). In a similar approach, Iris Hovatta used a cross-species neurogenomics comparison to correlate brain region-specific gene expression patterns and anxiety-like behavior in mouse GRPs to polymorphisms in the Finnish population for anxiety disorders (Hovatta et al. 2005). The mouse genes allowed identification of potential candidate genes in humans who predispose to anxiety disorders. Paul Franken presented studies on the identification of genetic traits that influence homeostatic and circadian aspects of sleep, and the electroencephalogram in the BXD GRP and in inter- and backcross panels of mice (Shaw and Franken 2003). Several genes that play a decisive role were identified, and further phenotyping of the extended BXD GRP is planned. Eero Vasar and Sulev Kõks described the role of the *Wfs1* gene in knockout mice for anxiety behavior, an altered response to morphine and the release of striatal dopamine (Koks et al. 2009; Luuk et al. 2009). Ewelina Knapska reported the use of a highly sophisticated cage system, IntelliCage, to automatically record a number of different complex behavioral traits in mice (Jaholkowski et al. 2009). Mice can be housed in social groups but nevertheless tested individually. Ryszard Przewlocki reported on a systematic study on various inbred mouse strains to identify genetic determinants of alcohol and drug addiction (Piechota et al. 2010). Combining these studies with comprehensive gene expression analyses revealed that glucocorticoid receptor-activated gene expression pathways play an important role. Wim Crusio studied behavioral traits in learning and related them to brain anatomy (Crusio and Schwegler 2005). Thereby, the extent of neuron projections in the hippocampus could be correlated to more efficient learning capabilities and these two phenotypes are very strongly correlated genetically. Guus Smit gave an overview on a collaborative effort in the Netherlands in which several research groups have determined various behavioral phenotypic traits and QTLs in a commonly used BXD population (Loos et al. 2009). Also, they established a mouse facility in which they are using automated screening cages with sophisticated video recording and analysis.

Cancer and liver cirrhosis

Cancer is still one of the most frequent causes of death in Western countries, and understanding its molecular causes as well as establishing appropriate animal model systems for the development of new treatment strategies is very important. Fragiskos Kolisis reported on the setting up of an infrastructure for a systems biology approach to carcinogenesis and aging (Chatziioannou et al. 2009). Understanding proteasome function and dysfunction as well as studying the alterations of the genome and proteome that account for different cancer phenotypes in a mouse skin carcinogenesis model are among the research goals. Javier Santos used GRPs to identify genetic traits for the susceptibility to radiation-induced thymic lymphomas in interspecific recombinant congenic and consomic mouse strains (Santos et al. 2009). Frank Lammert developed assay systems to determine genetic causes of liver fibrosis and inflammatory liver carcinogens in the BXD mouse recombinant congenic GRP (Weber et al. 2008).

Other

Leonard Schalkwyk studied allele-specific methylation in humans (Schalkwyk et al. 2010). He estimated that potentially more than 35,000 sites in the genome exhibit allele-specific modifications, and of these 10% are not in *cis*, a number that largely exceeds the number of known imprinted loci. These findings suggest that individual genetic heterogeneity may be much larger than estimated thus far and may contribute to individual phenotypic differences. Jiri Forejt used inter-subspecific consomic strains (Gregorova et al. 2008) to investigate male sterility and its consequences for interspecies hybrid sterility (Mihola et al. 2009). Furthermore, in the livers of inter-subspecific hybrid strains he discovered new patterns of gene expression that were absent from both parental strains.

Bioinformatic aspects of systems genetics

The capture, storage, handling, and analysis of large data sets will present a specific challenge for future systems genetics projects. Ritsert Jansen and Pjotr Prins presented their approaches to integrate data from various phenotypic studies, encompassing gene expression, metabolome, and classical traits, and to develop new tools for advanced and improved mapping of QTLs (Jansen et al. 2009; Li et al. 2008; Swertz and Jansen 2007). These tools will be provided to the scientific community. Andreas Beyer gave a report on how to integrate data obtained at the post-transcriptional level with RNA expression data. Several loci that influence the post-transcriptional regulation of gene products could be identified in yeast. Steffen Möller presented his suite for the analysis of expression QTL (http://eqtl.berlios.de), which is being applied to the analysis of experimental autoimmune encephalomyelitis in mouse and rat. Anastasios Bezerianos presented a platform and developments for the identification of gene regulatory networks integrating protein-protein interactions and microarray data (Bezerianos and Maraziotis 2008). They started with yeast data and will soon expand to mouse,

concentrating on time-varying gene regulatory networks. Morris Swertz presented XGAP, a software platform developed for data management and integration of large data sets from phenotyping and genotyping studies (Swertz et al. 2010). Grant Morahan described the development of an extended tool for WebQTL that allows a genome-centric analysis of QTL interactions (unpublished).

Current status of the Collaborative Cross

The Collaborative Cross (CC) is currently being generated as a community resource for more sensitive and refined mapping of QTLs. The goal is to breed a large population of recombinant inbred strains starting from eight founder strains. The eight founder strains were selected to capture a large portion of the genetic variation in the mouse genome. In fact, the genetic variation represented in the CC will be twice the genetic variation present in the human population (reviewed in Valdar et al. 2006). The three sites where the resource is being generated reported the present status of their breeding colonies; the final goal is to generate a total of 700 lines (Chesler et al. 2008; Iraqi et al. 2008; Morahan et al. 2008a). Grant Morahan gave an update on the "Southern Cross" being established in Perth, Australia. An inbreeding depression was observed at generations 7-9. At present, about 200 strains have been bred beyond generation 10. The first 40 strains are expected to be inbred by the end of the year. David Threadgill reported the status of the breeding colony at the University of North Carolina, Chapel Hill, NC, USA. About 300 lines are currently breeding at UNC. The first 50 recombinant inbred lines will be available by the end of this year and 200 lines by the end of 2011. To speed up the inbreeding process, marker-assisted breeding will be used to create homozygous lines beyond generation 12. Genome analysis demonstrated that all parental genomes are well represented in the advanced generations. The first phenotyping analysis showed a large variation in body weight, exercise propensity, and susceptibility to pathogens. Richard Mott described the genome structure of a smaller CC colony, funded by the Wellcome Trust, which was developed by Fuad Iraqi and is presently housed in Tel Aviv, Israel. A first phenotyping analysis for the QTLs that affect recombination frequencies was performed. A full-genome sequencing project to complete the parental strains with high coverage is underway at the Sanger Institute.

Conclusion

The two-day meeting in Braunschweig has clearly demonstrated the great value of mouse GRPs in identifying genetic determinants of complex genetic traits for various phenotypic traits related to diseases in humans. The partners of the network collectively have great expertise in disease phenotyping and analysis of genetic reference populations. Several examples that illustrated the translation of the knowledge gained in the mouse experimental systems to humans were presented. Links to clinical researchers already exist at several places but will have to be further expanded in the future. Furthermore, mouse GRPs can be ideally combined with mouse mutant lines carrying a gene-knockout mutation to determine the effect of a strong genetic defect in combination with modifier genes. It also became clear that a strong and sustained financial investment in mouse breeding and phenotyping facilities as well as in bioinformatic infrastructure is urgently needed to further advance a systems genetics approach in Europe.

Appendix

www.helmholtz-hzi.de/sysgenet and participants of the meeting: Klaus Schughart, Helmholtz Center for Infection Research, Germany; Danny Arends, University of Groningen, Netherlands; Pénélope Andreux, Ecole Polytechnique Fédérale de Lausanne, Switzerland; Rudi Balling, University of Luxembourg, Luxembourg; Andreas Beyer, TU Dresden, Germany; Anastasios Bezerianos, Biosignal Processing Lab, Department of Medical Physics, Greece; Gudrun A. Brockmann, Humboldt University Berlin, Germany; Wim E. Crusio, University of Bordeaux and CNRS, France; Joan Campbell-Tofte, University of Copenhagen, Denmark; Paul Denny, MRC Mammalian Genetics Unit, UK; Juan M Falcon-Perez, CIC bioGUNE, CIBERehd, Spain; Jiri Forejt, Institute of Molecular Genetics, Academy of Sciences, Czech Republic; Paul Franken, Center for Integrative Genomics, University of Lausanne, Switzerland; Iiris Hovatta, University of Helsinki, Finland; Fuad Iraqi, Sackler Faculty of Medicine Tel-Aviv University, Israel; Ritsert C Jansen, University of Groningen, Netherlands; Leszek Kaczmarek, Polish Academy of Sciences, Nencki Institute of Experimental Biology, Poland; Martien J. Kas, Department of Neuroscience and Pharmacology, University Medical Centre Utrecht, Netherlands; Karl Kashofer, Medical University of Graz, Austria; Ewelina Knapska, Nencki Institute, Poland; Fragiskos Kolisis, Institute of Biological Research and Biotechnology, National Hellenic Research Foundation,

Greece; Sulev Kõks, University of Tartu, Estonia; Frank Lammert, Saarland University, Germany; Steffen Möller, University of Lübeck, Germany; Xavier Montagutelli, Institut Pasteur, France; Grant Morahan, The Western Australian Institute for Medical Research, Australia; Richard Mott, Wellcome Trust Centre for Human Genetics, Oxford, UK; Susanne Pfoertner, Helmholtz Center for Infection Research, Germany; Pjotr Prins, Wageningen University, Netherlands; Ryszard Przewlocki, Institute of Pharmacology, Poland; Annamari Ranki, University of Helsinki, Finland; Javier Santos, Centro de Biología Molecular Severo Ochoa-Universidad Autónoma de Madrid, Spain; Pascal Rihet, Aix-Marseille University, France; Leonard Schalkwyk, King's College London, UK; August B Smit, Center for Neurogenomics and Cognitive Research, Netherlands; Morris Swertz, EBI, UK; David Threadgill, North Carolina State University, USA; Eero Vasar, University of Tartu, Estonia; Kurt Zatloukal, Institute of Pathology, Medical University Graz, Austria.

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