Complex Traits

Oral Presentation **Tuesday November 8** **2.30pm – 2.45pm**

O-34

FOUR –AT-A-TIME APPROACH TO THE EXTENDED RIX DIALLEL CROSS AND F2 GENARATION OF THEIR PROGENITOR STRAINS: NEW TOOL FOR GENETIC DISSECTION OF QUANTITATIVE COMPLEX TRAITS

A V Osadchuk[1], YuV Baburov[1], D C Airey[2], Lu Lu[3], D W Threadgill[4], R W Williams[3]
[1] Institute of Cytology and Genetics, Novosibirsk, Russia, [2] Vanderbilt University, Nashville, TN, United States,
[3] University of Tennessee, Memphis, TN, United States, [4] University of North Carolina, Chapel Hill, United States

We have developed an effective statistical approach to study complex traits that are modulated by multilocus systems with epistatic interactions. The approach was tested in the context of a large but incomplete RIX diallel generated from the CXB strain set and a complementary BALB/cByJ x C57BL/6ByJ F2 population. The phenotype was cerebellar weight (CW). The analytical suite consists of six statistical tests. 1. Multiple regression analysis was used to evaluate segregation models characterized by minimal number of loci that can account for among-line variation relative to within–line environmental noise. A beam search procedure with a priority queue size of up to 1.5 million different 4-locus genotypes was used to extract adequate solutions. 2. We used a multilocus search procedure to evaluate linkage between these models and sets of marker loci. Based on the segregation model, genotypic CW values for all 81 RIX lines were estimated. 3. We then used a G test to compare expected and observed distributions of F2 phenotypes. 4. The similarity between observed and predicted CW values for non-recombinant intervals in the F2 were tested. 5. 4-marker multiple regression was tested for all variants of flanking markers in the F2. 6. The similarity between all 81 genotypic values produced by segregation models and 4-marker multiple regression in the F2 was tested. Twenty-six 4-locus solutions were not rejected by the above tests. The major factor preventing convergence on a single solution is the severe non-syntenic association and the partial diallel. However, a simulation study revealed that it is possible to achieve a single solution by increasing the number of RI strains used to generate the RIX and by producing a complete diallel cross.

(The work was partly supported by the grant of BRP of the PRAS)

Complex Traits

Oral Presentation **Tuesday November 8** **2.45pm – 3.00pm**

O-35

A SYSTEMATIC GENETIC DISSECTION OF DIET-INDUCED METABOLIC SYNDROME USING THE B6-CHR^{A} CHROMOSOME SUBSTITUTION STRAIN PANEL OF MICE.

D S Sinasac, M E Slaughter, S K Iyengar, J H Nadeau
Case Western Reserve University, Cleveland, Ohio, United States

The metabolic syndrome (MetS) is a cluster of obesity-associated risk factors for cardiovascular disease, diabetes and stroke. Despite the established consequences of diet and lifestyle on MetS, the underlying genetic susceptibilities in humans remain elusive. Male C57BL/6J mice fed a high fat/high sucrose (HF/HS) diet represent a diet-induced model of MetS, while other inbred stains like A/J appear resistant. To systematically dissect the genetics of diet-induced MetS, a screen examining traits related to obesity, insulin resistance, dyslipidemia and fatty liver in the B6-Chr^{A} chromosome substitution strain (CSS) panel is currently underway. When completed, the screen will consist of 30 males per strain (A/J, (B6XA/J)F1, C57BL/6J and 22 CSSs) maintained for 16 weeks on the HF/HS diet, fasted overnight, bled and sacrificed for tissue. Preliminary observations have revealed that, in addition to strain differences in weight gained on the HF/HS diet, strong correlations exist between many of the MetS traits across strains. To determine if the relationships between MetS traits within a strain might differ by strain, principal components analyses were performed on data for 13 CSSs and C57BL/6J, followed by ANOVA to compare component loadings for each principle component. The analyses indicated that 10 of the CSSs have similar relationships compared to C57BL/6J, while three of the CSSs comprise 2 groups whose MetS trait relationships are both different from C57BL/6J and each other. These results suggest that genetic susceptibility to MetS may act through either a propensity for weight gain or through modulation of the physiological relationships between MetS traits.

Complex Traits

Oral Presentation **Tuesday November 8** **3.00pm – 3.15pm**

O-36

MATERNAL GENOTYPE AFFECTS ADULT OFFSPRING LIPID, OBESITY, AND DIABETES PHENOTYPES IN LGXSM RECOMBINANT INBRED STRAINS

J P Jarvis[1], J Kenney-Hunt[1], T H Ehrich[1], L S Pletscher[1], C F Semenkovich[2], J M Cheverud[1]
[1] Washington University School of Medicine, Department of Anatomy and Neurobiology, St. Louis, MO, United States,
[2] Washington University School of Medicine, Department of Medicine, St. Louis, MO, United States

Maternal effects on offspring phenotypes occur because mothers in many species provide an environment for their developing young. While these factors are correctly “environmental” with respect to the offspring genome, their variance may have both a genetic and an environmental basis in the maternal generation. Here, reciprocal crosses between C57BL/6J and 10 LGXSM recombinant inbred (RI) strains were performed and litters divided at weaning into high and low fat dietary treatments. Differences between reciprocal litters were used to measure genetic maternal effects on offspring phenotypes. Nearly all traits, including weekly body weights and adult blood serum traits show effects indicative of genetic variation in maternal effects across RI strains allowing the quantitative trait loci (QTL) involved to be mapped. Though much of the literature on maternal effects relates to early life traits, we detect strong and significant maternal effects on traits measured at adulthood (as much as 10% of the trait variance at 17 or more weeks post-weaning). We also found an interaction affecting adult phenotype between the effects of maternal care between RI strain mothers and C57BL/6J mothers and a later environmental factor (dietary fat intake) for some age-specific weights.

Complex Traits

Oral Presentation **Tuesday November 8** **3.15pm – 3.30pm**

O-37
INSIG2 : A CANDIDATE GENE FOR CHOLESTEROL REGULATION

A Cervino[2], G Zastrow-Hayes[2], J Zhu[1], M Pletcher[2], N Tsinoremas[2], E Schadt[1]
[1] Rosetta/Merck, Seattle, WA, United States, [2] Scripps Florida, Jupiter, FL, United States

We followed up on a previously identified linkage region from a B6 and C3H-/- F2 cross by testing for in silico association using our high density SNP map. In this study we genotyped 10,657 SNPs from 62 inbred strains. By integrating quantitative trait locus (QTL) mapping methods and in silico analysis, we identified insig2 as a candidate gene for total plasma cholesterol levels.

Furthermore, using expression analysis, we reconstructed a genetic pathway that included known and novel genes involved in cholesterol synthesis. To validate the network in humans, we performed siRNA of insig2 in HepG2 cell lines. Affymetrix genechips were run on cells that showed a 61% and a 59% knockdown according to the real-time PCR data. The knock down results confirmed the functional role of insig2 in the cholesterol pathway in both human and mouse.

Complex Traits

Oral Presentation **Tuesday November 8** **4.00pm – 4.15pm**

O-38

STUDYING DOSAGE EFFECTS FOR HUMAN CHROMOSOME 21 HOMOLOGOUS GENES USING CHROMOSOMAL ENGINEERING IN THE MOUSE

V Besson[1], A Duchon[1], V Brault[1], L Magnol[1], J-C Bizot[2], L Dauphinot[3], M-C Potier[3], Y Herault[1]
[1] CNRS Institut de Transgenose, Orleans, France, [2] Key-Obs, Orleans, France, [3] CNRS-ESCPI, Paris, France

Human chromosome 21 (HSA21) is associated with two syndromes that depend upon gene-dosage balance: the Trisomy 21 (or Down syndrome) and the Monosomy 21. Both syndromes lead to different set of features affecting various organs like the skeleton, the heart, the gastrointestinal tract and the nervous system. In the mice, the homologous regions to HSA21 are found on three distinct chromosomes: 10 (MMU10), 16 (MMU16) and 17 (MMU17). The most commonly used model, Ts65Dn, corresponds to a subpart of MMU16 and displays some features of the Down syndrome, but does not resume the complete panel of alterations found in human patient. So we develop mouse models for the centromeric and telomeric HSA21 regions in order to establish a genotype-phenotype relationship. The corresponding models display a deletion (or a tandem duplication) of the homologous regions to HSA21 leading to the corresponding Monosomy (or Trisomy) in the mouse. In this meeting, we will present the preliminary analysis of mutant models carrying deletion or duplication of the regions of interest trying to show how these genetic configurations are helpful to locate genes with dosage effects homologous to the human chromosome 21 genes.

Complex Traits

Oral Presentation **Tuesday November 8** **4.15pm – 4.30pm**

O-39

GENETIC AND PHYSIOLOGICAL ANALYSIS OF INTESTINAL LENGTHENING IN MOUSE STRAINS

S Bellier[1], G Aubin-Houzelstein[1], N Da Silva[1], JM Vanderwinden[2], X Montagutelli[3], J J Panthier[3]
[1] Ecole Nationale Vétérinaire d'Alfort INRA, Maisons-Alfort, France, [2] Université Libre de Bruxelles, Bruxelles, Belgium, [3] Institut Pasteur, Paris, France

How does an organ grow to a specific size ? Is the regulation of the size specific to each organ ? George Cuvier (1835) stated, in what is commonly referred to as the *law of coexistence,* that " a living organism is a unique and self-contained whole. All of its parts are mutually related and cooperate for the same purpose. Although no part can change unless the others also change, each part considered separately suffices to indicate the others ". PRM/Alf mice stand in contradiction to this law. They exhibit an obvious and selective lengthening of the intestine ; their intestine is 74.8 ± 5.3 cm long compared with 51.0 ± 3.0 cm in other inbred mice, such as DBA2/J. This unusual phenotype is acquired postnatally, before weaning. We investigated the functional consequences of such a lengthening and found that physiological mechanisms compensate for this anatomical variation. Genetic crosses showed that intestinal length is inherited in a polygenic way. More interestingly, cross-adoption of progeny to surrogate mothers revealed that the dam's genotype acted synergistically with the offspring's genotype to confer the longest intestine. In other words, maternal effects strongly contribute to intestinal lengthening in PRM/Alf mice. Two mutually non-exclusive mechanisms could well account for the maternal effects. First, the intestine of PRM/Alf mice could contain a specific society of indigenous gut microorganisms (microbiota). Germ-free PRM/Alf mice are being produced to test this hypothesis. Second, the milk of PRM/Alf females could contain intestinotrophic factors. Characterization of PRM/Alf milk proteins is carried out using proteomic techniques.

Complex Traits

Oral Presentation **Tuesday November 8** **4.30pm – 4.45pm**

O-40

DISSECTING THE GENETIC AND EPIGENETIC EFFECTS ON TUMOR SUSCEPTIBILITY IN A MOUSE MODEL OF NEUROFIBROMATOSIS TYPE 1

K M Reilly[1], R G Tuskan[1], K W Broman[2], S Tsang[3], D J Munroe[3]
[1] NCI-Frederick, Frederick, MD, United States, [2] Johns Hopkins School of Public Health, Baltimore, MD, United States, [3] SAIC-Frederick, Frederick, MD, United States

Neurofibromatosis type 1 (NF1) is a familial disease of the nervous system with predisposition to cancer. It affects 1 in 3500 people, regardless of race or ethnicity. The clinical heterogeneity of NF1 and the potential role of modifier genes in determining the severity of the disease present serious challenges to patients and clinicians. We are using a mouse model of NF1 (NPcis mice) to understand the role of modifier genes in the malignancies associated with NF1. NPcis mice develop many of the malignancies associated with NF1, in particular glial tumors of the central and peripheral nervous system (secondary glioblastoma and peripheral nerve sheath tumors (PNST), respectively). We have found imprinting effects linked to chromosome 11 and strain-specific modifiers that affect the incidence of these tumors. The effect of imprinting on chromosome 11 has opposite parental effects on glioblastomas and peripheral nerve sheath tumors. We have analyzed the genetic interaction between an imprinted locus on mouse chromosome 11 and the modifier loci for nerve sheath tumor resistance, *nstr1* on mouse chromosome 19 and *nstr2* on mouse chromosome 15. The imprinted locus interacts epistatically with *nstr1* and *nstr2* to affect resistance to PNSTs. In the case of NPcis mice inheriting the mutant chromosome 11 from their father, loci on chromosome 19 in the A strain background act to increase resistance to PNSTs. In the case of NPcis mice inheriting the mutant chromosome 11 from their mother, a locus on chromosome 15 in the A strain background further increases the resistance to PNST. The relevance of these results to human NF1 patients is supported by the overlap of these loci with regions altered in PNSTs. Consistent with these loci being low-penetrance modifiers for PNST susceptibility, these genomic regions are altered in a relatively low number of mouse and human tumors. However, the observation that these regions are translocated in multiple human tumors suggests that these rearrangements are not random. Identification of modifiers of NF1 in mouse models will allow these modifiers to be tested directly in human association studies, specifically in cases where tumors can be tested for the change in expression of candidate imprinted genes. These data demonstrate that modifier genes affect tumorigenesis under very specific conditions. The understanding of these conditions will allow for more accurate risk assessment and genetic counseling for individuals at high-risk for cancer, and better targeting of cancer therapies based on the genetic and epigenetic alterations occurring within an individual tumor.

Complex Traits

Oral Presentation **Tuesday November 8** **4.45pm – 5.00pm**

O-41

FUNCTIONAL GENOMICS OF MOUSE ACTIVITY AND ANXIETY – A MULTI-DIMENSIONAL SURVEY

L Liu, C Fernandes, F V Rijsdijk, J L Paya-Cano, M J Parsons, L C Schalkwyk
Institute of Psychiatry, King's College London, London, United Kingdom

Behavioural traits, such as anxiety, baseline and exploratory activity, are quantitative and complex, being determined by multiple and interactive genetic and environmental components. There is also a strong interaction between the traits in that exploratory activity plays a pivotal role in anxiety tests, yet it is unclear to what extent these two traits overlap in terms of their genetic and environmental sources of variation. We applied a large behavioural test battery consisting of baseline activity, exploratory activity and anxiety paradigms, to four different populations of mice: C57BL/6J mice (n=100, in 10 groups different environmental manipulations), a panel of 8 standard inbred strains (n=10/strain), 24 BxD RI lines (n=279) and >600 Boulder HS mice consisting of full sibs and half sibs. We will report our research on the following four dimensions with emphasis on the dissection of activity and anxiety: 1) Quantitative assessment of environmental variation and heritability of the behaviour measures. In addition to the inbred mice, we also used the HS population to assess the structural relationship between activity and anxiety measures in terms of their unique and shared environmental as well as additive genetic effects; 2) We made extensive use of the WebQTL tool on data collected from the BXD panel, this includes *in silico* QTL mapping, genetic correlation analyses with published phenotypic traits and brain gene expression from WebQTL; 3) Association study on GABA A receptor genes in the HS population; 4) hippocampus expression profiling using Affymetrix gene chips on HS individual mouse selected on phenotypic variation.