

Wednesday November, 15
10.30am – 12.30pm
Poster Session 4
Modeling Disease by Natural Variation/Complex Traits
Posters P100 – P124

- S14/ P100 USE OF CHROMOSOME 17 POLYMORPHISMS AND RECOMBINANTS TO MAP THE LIVER TUMOR SUSCEPTIBILITY LOCUS HCF1 IN C57BR/CDJ MICE**
SEM Peychal, N Drinkwater
McArdle Laboratory for Cancer Research, University of Wisconsin School of Medicine and Public Health, Madison, WI, United States
- S15/ P101 CANDIDATE TESTICULAR GERM CELL TUMOR GENES FROM THE CONSOMIC, 129.MOLF-CHR 19, MOUSE STRAIN**
R Zhu, A Matin
University of Texas M.D. Anderson Cancer Center, Houston, TX, United States
- P102 GENETIC DISSECTION OF MODIFIERS OF APCMIN DURING THE DEVELOPMENT OF MAMMARY TUMORS**
H Wang, D Teske, A Moser
University of Wisconsin-Madison, Madison, WI, United States
- S16/ P103 IDENTIFICATION OF EGFR-INDEPENDENT SIGNATURES IN INTESTINAL NEOPLASIA IN APC^{MIN} MICE: CORRELATION TO HUMAN COLORECTAL CANCER**
M Yu, TC Lee, D Threadgill
University of North Carolina, Chapel Hill, NC, United States
- P104 GENETIC ANALYSIS OF CRANIOFACIAL ARCHITECTURE OF THE MOUSE USING INTERSPECIFIC RECOMBINANT CONGENIC STRAINS (IRCS)**
G Burgio¹, M Baylac², E Heyer³, JJ Panthier¹, X Montagutelli¹
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- P105 GENE EXPRESSION IN MELIM METASTATIC MELANOCYTES**
G Egidy¹, J Julé¹, P Bossé¹, F Bernex¹, C Geffroin², V Horak³, X Sastre⁴, JJ Panthier⁵
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- P106 LOCI FOR OBESITY IDENTIFIED BY A GENOME SCAN OF AN F₂ INTERCROSS BETWEEN THE C57BL/6J AND PWK/PHJ MOUSE STRAINS**
H Shao, D Reed, M Tordoff
Monell Chemical Senses Center, Philadelphia, PA, United States
- P107 ANALYSIS OF GENE EXPRESSION AND NEURAL CREST MIGRATION IN CONGENIC LINES OF SOX10^{DOM} MICE REVEALS EFFECTS OF GENETIC BACKGROUND ON NEURAL CREST STEM CELLS IN THE SOX10^{DOM} MODEL OF HIRSCHSPRUNG DISEASE**
LC Walters¹, VA Cantrell¹, JT Mosher², EM Southard-Smith¹
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- P108 GENETIC CONTROL OF RECOMBINATION LEVELS DURING MEIOSIS**
E Gibb¹, F Pardo-Manuel de Villena², C Sapienza³, E dela Casa-Esperon¹
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- P109 BALANCING PROGENITOR ALLELES IN THE COLLABORATIVE CROSS**
 KF Manly¹, KW Broman², DR Miller³, DK Johnson³, RW Williams¹, GA Churchill⁴
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- P110 MICROARRAY AND QRT-PCR EXPRESSION PROFILING OF MULTIPLE DIFFERENTIALLY EXPRESSED GENES MAPPING TO A MURINE DIETARY OBESITY QTL**
 Y Wang, B Krishnan, AR Zuberi
 Pennington Biomedical Research Center, Baton Rouge, LA, United States
- S17/ P111 CHARACTERIZATION OF THE MECHANISM OF THE MODIFIER OF MIN 2 (MOM2) LOCUS ON INTESTINAL POLYPOSIS**
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- P112 A LOCUS FOR RECOVERY FROM HIND-LIMB ISCHEMIA IN MICE MAPS TO CHROMOSOME 7**
 D Marchuk, G LaMonte, Y Li, S Keum, A Dokun, K Shianna, F Wheeler, B Annex
 Duke University, Durham, NC, United States
- P113 THE REGULATORY MUTATION, MVWF1, CHANGES GLYCOSYLATION PATTERNS IN INTESTINE, BLOOD VESSELS, AND KIDNEY IN WILD MICE**
 J Johnsen¹, J Baines³, D Tautz⁴, D Ginsburg²
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- P114 DETERMINING THE THERMOREGULATION PHENOTYPE OF THE 8-WAY-CROSS PARENTAL LINES**
 SC Kenney¹, TE Kaminsky¹, LS Webb¹, DK Johnson², BH Voy²
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- P115 IDENTIFYING RESISTANCE MODIFIERS OF AZOXYMETHANE INDUCED COLON CANCER**
 C Eversley, A Bissahoyo, D Threadgill
 University of North Carolina Chapel Hill, Chapel Hill, NC, United States
- P116 BEHAVIOURAL WILDNESS IN EARLY GENERATIONS OF THE COLLABORATIVE CROSS**
 JS Spence¹, EK Russell¹, DR Miller¹, LD Galloway¹, R Kirova¹, KF Manly², DK Johnson¹, EJ Chesler¹
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- P117 BODY MASS INDEX DOES NOT ACCURATELY DESCRIBE OBESITY IN MICE**
 KL Svenson
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- P118 MICROARRAY ANALYSIS OF COCHLEAR GENE EXPRESSION IN HYPOTHYROID MICE AND GENETIC MAPPING OF AN AUTOSOMAL RECESSIVE MODIFIER GENE THAT PROTECTS AGAINST DEAFNESS CAUSED BY HYPOTHYROIDISM**
 SA Camper¹, M Mustapha-Chaib¹, Q Fang¹, DF Dolan¹, L Beyer¹, IJ Karolyi¹, TW Gong¹, MI Lomax¹, RK Duncan¹, Y Raphael¹, KR Johnson²
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P119 THE LIVER CANCER MODIFIER HCS7 LIES IN A 1 MB REGION RICH IN INFLAMMATORY GENES

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P120 HYPOMORPHIC MUTATIONS OF THE CLATHRIN-ASSEMBLY GENE PICALM CONFER BRAIN IRON DEFICIENCY AND BEHAVIORAL ABNORMALITIES CONSISTENT WITH DOPAMINERGIC SYSTEM DEFECTS

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P121 BACKGROUND STRAIN PHENOTYPES: WHAT YOU KNOW COULD HELP YOU

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P122 PHENOTYPIC ANALYSIS OF TWENTY-FOUR RI STRAINS OF MALE BXD (C57BL/6JXDBA/2J) MICE

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P123 ASSOCIATION ANALYSIS OF OBESITY-RELATED TRAITS AND LIVER GENE EXPRESSION PROFILES USING INTER-SUBSPECIFIC CONSUMIC STRAINS

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P124 MAPPING THE PHENOME SPACE USING COMBINATORIAL ANALYSIS OF THE EMPIRICAL ASSOCIATIONS OF GENES AND PHENOTYPES

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GENETIC DISSECTION OF MODIFIERS OF APCMIN DURING THE DEVELOPMENT OF MAMMARY TUMORS

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Breast cancer develops through multiple steps which are rigorously controlled by genetic regulators. With a well characterized mouse model the *ApcMin*⁺ mouse, we aimed to identify loci affecting tumor progression and tumor growth. More than 90% of C57BL/6J (B6) *ApcMin*⁺ female mice develop an average of four mammary squamous cell carcinomas by 75 days after ENU treatment while ENU-treated FVB6 F1 *ApcMin*⁺ female mice develop an average of four alveolar hyperplasias but squamous cell carcinomas (SCC) or adenocarcinomas only rarely and with increased latency. We used standard backcross analysis to search for loci that affect tumor progression and growth in the *ApcMin*⁺ mice. Four novel mammary modifier loci were identified. The QTL on chromosome 9 significantly affects tumor number. The QTL on chromosome 4 suggestively affects tumor number but significantly affect tumor latency. The QTL on chromosome 6 interacts with QTL on chromosome 4 and 9 to affect tumor number. Interestingly, the QTL on chromosome 18 specifically affects tumor latency and shows at least additive interaction with QTL on chromosome 4. To better understand the effect of FVB background on tumor development, we produced FVB- *ApcMin*⁺ congenic mice. A striking phenotype is most tumors are adenocarcinoma in contrast with SCC in B6-*ApcMin*⁺ mice. The molecular mechanisms underlying the different tumor phenotypes are being investigated.

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GENETIC ANALYSIS OF CRANIOFACIAL ARCHITECTURE OF THE MOUSE USING INTERSPECIFIC RECOMBINANT CONGENIC STRAINS (IRCS)

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Genetic determinism of cranial morphology is complex and largely unknown in the human. An animal model such as the mouse may be very useful in identifying genes which play a key-role in skull morphogenesis. Interspecific recombinant congenic strains (IRCS) are inbred strains produced from crosses between the laboratory inbred strain C57BL/6 and mice of the distant species *Mus spretus* (inbred strain SEG/Pas). Each of the 55 IRCS carries a small number of chromosomal segments of *Mus spretus* origin (with an average size of less than 20 Mb) in an otherwise C57BL/6 background. On average 1.5% of the genome of these strains come from SEG/Pas. Fifteen IRCS have been phenotyped for morphological and biometrical parameters and compared to C57BL/6. Statistically significant differences in the frequency of morphological features and in bone conformation have been found, using either procuste analysis or outline analysis (elliptic Fourier descriptor). Our data revealed that these strains show specific cranio-facial conformations. For example, SEG/Pas and C57BL/6 mice show significant differences in the shape of nasal bone, and IRCS strain 66H has an intermediate phenotype, as revealed by outline combined with factorial discriminant analysis. To identify which of the three genomic regions that 66H has inherited from SEG/Pas is responsible for this phenotype, an F2 cross between 66H and C57BL/6 was produced. ANOVA revealed the presence of two QTLs on Chr 1 (between *D1Mit305* and *D1Mit137*, 8 cM) and on Chr 18 (between *D18Mit23* and *D18Mit123*, 10 cM), which showed additive effects. Each combination of the three chromosomal regions was then isolated in sub congenic strains to study single gene effects and genetic interactions. Data indicate predominant effect for chr 1 QTL on shape, asymmetric effect for the Chr18 QTL and significant epistatic interaction between Chr 1 QTL and a region on Chr 13. The use of wild mouse into congenic strain allow us to identify nodular organisation of the skull and identification of causative genes of these shape.

P105**GENE EXPRESSION IN MELIM METASTATIC MELANOCYTES**G Egidy¹, J Julé¹, P Bossé¹, F Bernex¹, C Geffrotin², V Horak³, X Sastre⁴, JJ Panthier⁵¹UMR955 Institut National de la Recherche Agronomique-Ecole Nationale Vétérinaire d'Alfort, Maisons-Alfort, France,²LREG Commissariat à l'Energie Atomique Institut National de la Recherche Agronomique, Jouy-en-Josas, France,³Institute of Animal Physiology and Genetics, Academy of Sciences of Czech Republic, Libechev, Czech Republic,⁴Service d'Anatomopathologie, Institut Curie, Paris 5, France, ⁵Mouse functional Genetics, Institut Pasteur, Paris, France

Development of melanoma is still difficult to predict and even harder to check once it becomes metastatic. Melanoblastoma-bearing Libechev minipigs (MeLiM) provide an animal model for the study of spontaneous cutaneous melanoma. We compared the serial analysis of gene expression (SAGE) profile between normal skin melanocytes and tumoral melanocytes isolated from a pulmonary metastasis of MeLiM minipig. Among 5,500 putative transcripts, 72 displayed a statistically significant different abundance. Tag identification revealed several genes not yet involved in melanoma progression, including *RACK1*, *RBAP48*, *RHEB* and *ATF4*. These genes were overexpressed in metastatic melanocytes. We describe the expression and localization of *RACK1* mRNA and protein in the skin and metastases of MeLiM minipigs that developed malignant melanomas, hence confirming SAGE data. By confocal microscopy, *RACK1* was hardly detectable on normal epidermal melanocytes. However, *RACK1* was abundant in the cytoplasmic compartment of tumoral melanocytes. Furthermore, a nuclear localization of *RACK1* was observed in a subset of metastatic melanocytes. *ATF4*, β -catenin, PKC α , *RHEB*, and *RBAP48* were also nuclear on metastatic melanocytes but did not colocalize with *RACK1*. Abundant signal for *RACK1* was detected in human melanoma samples, but not in normal skin melanocytes. These data suggest a role for *RACK1* in melanoma malignancy. Targeted expression of *RACK1*, either including or not a nuclear localization signal, in melanocytes of transgenic mice is carried out to assess the functional importance of *RACK1* overexpression during tumor development.

P106**LOCI FOR OBESITY IDENTIFIED BY A GENOME SCAN OF AN F₂ INTERCROSS BETWEEN THE C57BL/6J AND PWK/PHJ MOUSE STRAINS**

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Obesity is a highly heritable complex trait. One approach to identify the genes underlying obesity is through the analysis of intercrossed mice strains that differ in fatness. In this study, we selected the C57BL/6J (B6) and the PWK/PhJ (PWK) as inbred parent strains because they differ in body weight and adiposity, and are genetically diverse. A total of 244 male and 237 female F₂ mice aged 16-18 wk were phenotyped for body weight and carcass composition using a PixiMus II DEXA. The mice were genotyped for 121 polymorphic markers from all 19 autosomes and the X chromosome. Linkage analysis was conducted with all mice, and then with each sex separately. The analysis involving both sexes combined revealed significant linkages for body weight on chromosomes 4 (LOD = 5.20, at 45 cM) and X (LOD = 6.81, at 17 cM), for carcass lean weight on chromosomes 3, 5, 7, 16, and X (all LODs > 3.22), and for carcass fat weight on chromosomes 2, 3, and X (all LODs > 3.33). In each case, the alleles associated with the increased body weight and carcass fat weight were contributed by the heavier and fatter C57BL/6J strain. In addition, there were suggestive linkages to carcass percent fat on chromosome 9 (LOD = 2.83, at 42 cM) and to fat weight carcass fat weight on chromosome 7 (LOD = 2.57, at 72 cM). We also found several sex-dependent linkages. For instance, a QTLs for carcass fat weight and percent fat were present on chromosome 11 in males (LOD = 5.3) but not females (LOD = 0.9). Conversely, a QTL for carcass fat weight on chromosome 6 was present in females (LOD = 4.11, at ~20 cM) but not males (LOD = 0.19). The identification of sex-dependent QTLs refines and expands our understanding of the underlying pathways that contribute to obesity-related traits, and will assist us in gene-identification.

P107**ANALYSIS OF GENE EXPRESSION AND NEURAL CREST MIGRATION IN CONGENIC LINES OF SOX10^{DOM} MICE REVEALS EFFECTS OF GENETIC BACKGROUND ON NEURAL CREST STEM CELLS IN THE SOX10^{DOM} MODEL OF HIRSCHSPRUNG DISEASE**

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Abnormalities in proliferation, migration, or survival of enteric neural crest (NC) can lead to aganglionosis in a variable portion of the distal intestine, causing Hirschsprung disease (HSCR) in humans. Cumulative evidence suggests HSCR is the consequence of multiple gene interactions that modulate the ability of enteric NC cells to populate the developing gut.

One of the essential genes for enteric ganglia development is the neural crest transcription factor *Sox10*. *Sox10^{Dom}* mice on a mixed genetic background exhibit variable penetrance and expressivity of aganglionic megacolon, reminiscent of human HSCR families. We have established congenic lines of *Sox10^{Dom}* mice that fix this allele on distinct C57BL/6J and C3HeB/FeJ genetic backgrounds. These lines differ in survival and extent of aganglionosis in the distal intestine.

There are multiple points in development at which total numbers of NC cells or differentials in gene expression within the NC population could give rise to the observed differences in aganglionosis. We have undertaken studies of enteric NC in *Sox10^{Dom}* congenic lines to discriminate between these potential mechanisms and define the impact of strain background on NC stem cells. Northern blots and real-time PCR for genes essential to enteric development in total gut RNA from *Sox10^{Dom}* embryos have demonstrated differences that correlate with genetic background. We will present analysis of enteric NC migration and total cell numbers defined by immunohistochemistry of whole mount embryonic gut samples. These studies will be complemented by analysis of cell numbers and gene expression in enteric NC isolated by flow cytometry.

P108**GENETIC CONTROL OF RECOMBINATION LEVELS DURING MEIOSIS**

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Meiotic recombination is a source of genetic diversity but, most importantly, it is required for proper chromosome segregation in most organisms. Abnormalities in the level or the location of recombination along chromosomes lead to aneuploidy, which result in unviable embryos in mouse. Recombination frequency varies depending on sex, age, chromosome length and location. Many genes are known to participate in the genetic control of recombination, but mutations of such genes often result in impaired chromosome segregation and fertility. However, very few natural variants associated with different recombination levels have been identified in mammals.

We have mapped a locus/loci on chromosome X that modifies the genome-wide levels of recombination in mouse oocytes. We identified two alleles of this locus, by inferring the allele-specific expression levels from the X-inactivation pattern of heterozygote females, and observed that changes in their relative expression resulted in differences in recombination levels (up to 20% increase in multiple crossover tetrads.) Our current studies are aimed to identify and characterize this X-linked gene/s that is involved in natural variation in recombination, in order to uncover the mechanisms that control meiotic crossover frequency and variability.

P109**BALANCING PROGENITOR ALLELES IN THE COLLABORATIVE CROSS**

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The Collaborative Cross is a cross among eight inbred strains of mice using a combinatorial design to yield many distinct eight-line hybrids that will be inbred to produce recombinant inbred (RI) strains. The goal of this cross at Oak Ridge National Laboratory is to initiate the production of 1680 (8x7x6x5) independent lines, and inbred as many as possible. To maximize the utility of these RI strains, the genetic contributions of each progenitor, and pairwise combinations of progenitors, should be equal when averaged across all hybrid lines. Although each progenitor contributes autosomal genes with equal probability, sex chromosomes and mitochondrial genomes come preferentially from certain progenitors. Four pairwise chromosome combinations may be significant (Y and mitochondria, X and Y, pairwise X combinations, and autosomal combinations in the first mating). Eight progenitor lines yield, for each chromosome combination, 56 pairwise combinations, each of which should be represented by $1680/56 = 30$ strains. The variance of the number of hybrid lines for each chromosome combination (calculated over 56 strain combinations) is a convenient measure of balance. Using this criterion, and using a greedy algorithm to add new hybrid combinations (from ~40,000 available) to lines already breeding, we can construct a set of 1680 hybrid lines in which each strain combination for each chromosome combination is represented by 30.0 ± 0.2 lines. This method also allows rebalancing to compensate for loss of lines, and it will allow selection of balanced subsets of various sizes.

P110**MICROARRAY AND QRT-PCR EXPRESSION PROFILING OF MULTIPLE DIFFERENTIALLY EXPRESSED GENES MAPPING TO A MURINE DIETARY OBESITY QTL**

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Male mice of a novel congenic B6.LP mouse strain are identical to the parental dietary obesity susceptible C57BL/6 (B6) strain, except for a small 10.2 Mb region of mouse Chromosome 2 derived from the LP/J (LP) genome. These congenic mice are significantly resistant to high fat (HF) diet induced obesity, and we hypothesize that this phenotype is attributable to one or more of the 171 genes positioned within this LP-derived genomic segment.

To identify possible candidate genes, microarray based gene expression comparison was performed between adipose tissue, liver and skeletal muscle of B6 and B6.LPa mice. Of the 171 genes mapping to the congenic region, 154 were represented in the Applied Biosystems 39K microarray platform. To profile the "missing" 17 transcripts, targeted qRT-PCR was performed. Interestingly, after initial microarray identification and subsequent qRT-PCR confirmation, 23 of 171 genes showed differential expression between B6 and B6.Lpa in at least one of the three screened tissues in Chow fed mice. The two mouse strains do NOT differ in adiposity when fed a Chow diet, but there is a difference in circulating insulin levels suggesting changes in overall insulin sensitivity. Additional microarray screening of HF-fed mice (prior to measurements of significant differences in adiposity between the mouse strains) is ongoing.

To characterize these differentially expressed genes further, we profiled mRNA abundance by qRT-PCR in the following metabolically relevant *in vivo* and *ex vivo* models; In Fed-Fasted-Refed mice, in mutant B6-*Lep^{ob}* and B6-*ins^{tm1Dac}* mice, during serum starvation and insulin stimulation of cultured cells lines, and during 3T3-L1 adipogenesis and C2C12 myogenesis. The genes demonstrated a complex overall expression profile not only between the different physiological models, but also a complex dietary regulation of tissue specific expression within mouse strains. Thus, all remain as potential candidates for the dietary obesity and/or insulin sensitivity phenotype.

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A LOCUS FOR RECOVERY FROM HIND-LIMB ISCHEMIA IN MICE MAPS TO CHROMOSOME 7

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Peripheral arterial disease (PAD) of the lower extremities in humans has two major clinical manifestations. One is intermittent claudication (pain upon walking) and the other is critical limb-threatening ischemia which often requires amputation. Animal models of hind-limb ischemia have been developed to investigate the pathogenesis of peripheral arterial disease. The most widely used model involves unilateral surgical ligation and excision of the femoral artery that acutely reduces blood flow to the limb. The spontaneous response to hind-limb ischemia is under strong genetic control, as evidenced by strain-specific differences in recovery. Certain inbred mouse strains such as BALB/c, show low levels of blood flow to the hind-limb after surgery with eventual loss of the limb, whereas others, particularly C57BL/6, restore normal blood flow and restore the limb. These different responses in mice parallel the different clinical manifestations of PAD in humans. We sought to exploit these strain-specific differences to map genetic loci involved in the differential recovery from hind-limb ischemia. We first determined that F1 animals from the outlier B6 and BALB/c strains exhibit a recovery phenotype not statistically different from B6, suggesting that B6 contains dominantly-acting loci that restore blood flow that enables limb recovery. To test this hypothesis, we performed a backcross of F1 mice with BALB/c. Surgery was performed on 105 N2 progeny and blood flow was determined at weekly intervals and the ischemic limbs were examined for necrosis. SNP genotypes were determined using the Illumina mouse SNP genotyping panel. Highly significant linkage results (highest LRS of 36.9 for necrosis score, $p < 0.001$) were obtained at a single locus mapping to distal chromosome 7 for all phenotypic measures of blood flow and necrosis. Although differences in the VEGF or angiotensin pathways had been previously hypothesized to underlie these strain-specific differential responses, none of the ligands and receptors for either of these angiogenesis factors map to this chromosome. These data suggesting that a novel limb ischemia-recovery gene maps to distal mouse chromosome 7. This gene, once identified, may play a significant role in the differential response toward PAD in humans.

P113

THE REGULATORY MUTATION, MVWF1, CHANGES GLYCOSYLATION PATTERNS IN INTESTINE, BLOOD VESSELS, AND KIDNEY IN WILD MICE

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We previously identified the cause of low levels of von Willebrand factor (VWF) in the RIIS/J mouse strain to be a regulatory mutation, *Mvwf1*, in an N-acetylgalactosaminyltransferase, *B4galnt2*. *Mvwf1* causes a tissue-specific switch in *B4galnt2* expression from intestinal epithelium to vascular endothelium, resulting in aberrant glycosylation of VWF and accelerated clearance. We surveyed additional tissues for *B4galnt2* expression using a DBA lectin protocol specific for *B4galnt2* GalNAc residues and found that the *Mvwf1* allele also does not express in kidney parenchyma, in contrast to the "wild type" C57BL/6J which expresses in distal tubule epithelial cells. We have identified thirteen *Mvwf1* mouse strains that share a 97kb haplotype block encompassing a 30kb region of 2-3% sequence divergence flanking Exon 1. A wild-derived recombinant *Mvwf1* allele containing the 3' half of the *Mvwf1* haplotype confers intestinal expression, indicating that the regulatory mutation(s) responsible for the switch likely lie well upstream of the proximal promoter region.

Genomic sequence from wild-caught individual mice confirmed the presence of a highly conserved *Mvwf1* founder allele in wild *Mus musculus domesticus* populations, with an allele frequency as high as 60% in French mice. French wild-caught mice homozygous for this allele exhibit the same low VWF levels and vessel(+), bowel(-), kidney(-) lectin staining pattern seen in *Mvwf1* laboratory animals. This wild mouse population has a significant reduction in microsatellite variability at the *B4galnt2* locus by the InRH statistic, likely due to a recent change in selective pressure. These data support a *B4Galnt2* allele-specific survival advantage in wild mice.

P114**DETERMINING THE THERMOREGULATION PHENOTYPE OF THE 8-WAY-CROSS PARENTAL LINES**

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Eight strains of mice, chosen for their genetic and phenotypic diversity, were selected as progenitors for the 8-Way-Cross: CAST/EiJ, NZO/HILtJ, NOD/LtJ, 129S1/SvImJ, C57BL/6J, PWK/PhJ, WSB/EiJ, and A/J. Simultaneous, controlled, comparisons of these strains to provide baseline data for analysis of 8-way-cross progeny are lacking. To address this issue, using mice raised in the same environment as the 8-way-cross mice being produced at ORNL, a panel of morphometric data was collected across male and female mice from the 8-way-cross parental strains. The cold stress test assesses a mouse's ability to maintain its core body temperature in a 4°C environment. Baseline core body temperatures were taken before, and every 30 minutes during the 120 minute exposure. Afterwards, body weights and spleen, liver, kidney, thymus, and heart weights were recorded. Results indicate that strain and gender significantly impact thermogenic response to cold. For example, NOD males exhibited a net increase in body temperature (+0.6°C), while NOD females displayed a decrease of similar magnitude (-0.6°C). PWK (both male and female) and CAST/EiJ females maintained their core temperature during the test, suggesting that the leaner strains of mice (e.g. CAST/EiJ) regulate their metabolism quickly and efficiently. Organ weights also varied markedly across strains, even when scaled to body weight. Collectively these data will be integral to evaluating genetic variability among similar traits in 8-way-cross RI strains. As the RI lines become established, each strain's morphometric variables and response to cold can be compared to the parental lines to assess the polygenic nature of these traits.

P115**IDENTIFYING RESISTANCE MODIFIERS OF AZOXYMETHANE INDUCED COLON CANCER**

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Colorectal cancer is the second leading cause of cancer deaths in the US. Nearly 90% of CRC cases are considered non-familial related or sporadic. Susceptibility to colorectal cancer is thought to be due to an individual's particular genetic makeup that modulates one's sensitivity to risk factors associated with colorectal cancer. Mouse strains exposed to azoxymethane (AOM), an organospecific carcinogen, show varying susceptibility to colon tumor formation and have many characteristics of non-familial colorectal cancer. A/J (*Mus musculus*) mice are highly susceptible to AOM-induced colon tumors while SPRET/Ei (*Mus spretus*) mice are highly resistant. ASF1 hybrid mice fail to develop colon tumors showing that SPRET/Ei mice carry strong, dominant resistance alleles. To determine the genomic location of the resistance alleles, ASF1 mice were backcrossed to the susceptible A/J strain. The resulting N2 mice range from resistant to highly susceptible to AOM-induced colon tumors. Approximately 300 N2 generation mice are being genome-typed for 312 SNPs or MIT markers to genetically map loci modulating AOM-induced colon tumor development.

P116**BEHAVIOURAL WILDNESS IN EARLY GENERATIONS OF THE COLLABORATIVE CROSS**

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The 8-way collaborative cross progenitors C57BL/6J, A/J, 129S1/SvImJ, NOD/LtJ, NZO/HILtJ, CAST/EiJ, PWK/PhJ, WSB/EiJ, consist of both wild-derived and common laboratory inbred lines. Behavioural wildness was evaluated in the collaborative cross population to determine whether the inclusion of wild-derived strains would render mice unsuitable for conventional behavioural assays, and to prospectively test hypotheses regarding the population dynamics of this trait. It is widely speculated that many of the laboratory strains became docile in part because of selection pressure against alleles that increase wildness in handling. This is because mates were historically not randomly selected. However, the breeding of the collaborative cross at ORNL is highly randomised using mating pairs determined by the husbandry management tool CCDB. Progenitors and mating pairs from each of approximately 500 breeding 'funnels' or lines were screened using the wildness scale described by Wahlsten and colleagues. Currently, mice from the first five generations have been tested, including three inbreeding generations that contain all eight backgrounds. This trait has been previously shown to be nearly bimodal among inbred strains, with a heritability of approximately 50%. Using haplotype association analysis, such a trait cannot be mapped with precision due to the wide range of loci that differentiate wild-derived from laboratory strains. Results in the collaborative cross show a population increase in wildness over the out-crossing generations, and a stabilization with early inbreeding, $p_{\text{FET}} < 0.01$. This suggests that wildness is a highly polygenic trait that may have undergone independent selections for different decreaseor alleles in each line to reach the selected state. Out-crossing results in transgressive segregation of these alleles, thereby increasing the range of phenotypic variation among lines. Heritability in the inbreeding generations is currently estimated at 26% and is expected to increase as lines become more inbred, making the trait suitable for mapping. These results suggest a retrieval of the continuous genetic diversity in this trait in the collaborative cross. Support: Ellison Medical Found.; ORNL, managed by UT-Battelle, under DOE contract.

P117**BODY MASS INDEX DOES NOT ACCURATELY DESCRIBE OBESITY IN MICE**

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Calculated body mass index (BMI; weight divided by length squared) is commonly used to predict obesity in humans (kg/m^2). In mice, however, owing to the difference in overall body shape between mice and humans, BMI (g/cm^2) can be misleading in evaluating degree of fatness, or obesity. Ideally, whole body imaging using dual-energy x-ray absorptiometry (DEXA) or computed tomography (CT) to assess body fat percent will more accurately define degree of obesity in mice, and can be performed on live animals. Dissection of regional fat depots is another way to obtain accurate measurements of obesity in mice and does not require specialized equipment, although it is a terminal procedure. A comparison is presented of body fat percent measured by DEXA analysis to calculated BMI in females and males of 30 inbred mouse strains, showing that there is no correlation between the two measurements. Hence, the use of more accurate methods to describe obesity in mice is encouraged.

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MICROARRAY ANALYSIS OF COCHLEAR GENE EXPRESSION IN HYPOTHYROID MICE AND GENETIC MAPPING OF AN AUTOSOMAL RECESSIVE MODIFIER GENE THAT PROTECTS AGAINST DEAFNESS CAUSED BY HYPOTHYROIDISM

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Hereditary inner ear disease is prevalent, has significant implications for quality of life, and is usually not curable. The mouse is an ideal model that has facilitated the discovery of genes that underlie deafness in humans and identification of their roles in inner ear development and function. We report that congenital thyroid hormone deficiency increases the risk of permanent hearing loss in three different strains of mice, the degree of hearing loss is a polygenic trait, and thyroid supplementation during pregnancy and early neonatal life is sufficient to protect against hearing loss. Because the physiological and morphological development of the cochlea appears to normalize over time in these mutants, there is no obvious basis for requiring rescue of hearing loss by thyroid supplementation during a narrow developmental time. We used microarray analysis to identify cochlear gene expression changes caused by hypothyroidism in one of these congenitally hypothyroid strains and note several classes in genes that are compelling candidates for further study. A genome scan of hearing, mutant progeny from an intercross between a hypothyroid strain and *Mus castaneus* reveals that a single, novel, autosomal recessive locus offers substantial protection against hearing loss. Together the microarray and modifier gene analyses are likely to uncover genes that protect against permanent hearing loss due to hypothyroidism and uncover the molecular basis for the basic process of thyroid hormone induced maturation of hearing in mammals.

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THE LIVER CANCER MODIFIER HCS7 LIES IN A 1 MB REGION RICH IN INFLAMMATORY GENES

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The *Hcs7* liver cancer modifier, which accounts for the majority of the high susceptibility of C3H mice relative to B6, maps to distal Chromosome 1. This region affects both spontaneous and chemically induced tumorigenesis and is orthologous to regions of human chromosome 1q that are amplified in approximately half of liver and breast cancers.

Congenic mice carrying about 10 Mb of distal Chromosome 1 from the C3H strain on a B6 background develop nine times more tumors than do inbred B6 mice. This difference in tumor multiplicity is due at least in part to a difference in the rate of neoplastic lesion growth. Tumors that develop in mice heterozygous for Chromosome 1 do not undergo loss of heterozygosity for genes in that interval.

Beginning with a 6.4 Mb region defined by congenic recombinants, we have analyzed SSLP and SNP haplotypes, gene expression in normal and neoplastic tissue, and fine-structure recombinants to identify candidates for *Hcs7*. We have combined these SNP and SSLP data with the publicly available SNP data for an additional seven strains for which we have phenotypic and mapping data. By comparing haplotypes for these strains at 38 loci throughout the 6.4 Mb region, we have identified two smaller regions (1.3 and 1.6 Mb) that display the expected haplotype patterns. Fine-structure congenic recombinant data, combined with this haplotype analysis, limit the susceptibility region to approximately 1 Mb. Gene expression pathway analysis suggests that the *Hcs7* locus is an inflammatory gene. Approximately half of the genes in the minimal 1 Mb region regulate inflammation. The expression of two of these genes differs qualitatively between B6 and C3H.

P120**HYPOMORPHIC MUTATIONS OF THE CLATHRIN-ASSEMBLY GENE PICALM CONFER BRAIN IRON DEFICIENCY AND BEHAVIORAL ABNORMALITIES CONSISTENT WITH DOPAMINERGIC SYSTEM DEFECTS**

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Misregulation of iron metabolism can have profound effects on the nervous system of mammals, from the neurological and developmental abnormalities of iron deficiency to the neuro-toxic and -degenerative impact of iron overload. Several relationships between brain iron concentration and the integrity of the nigro-striatal dopaminergic system have been hypothesized, including the co-transport of dopamine (DA) and iron into cells, the importance of iron for the synthesis and activity of tyrosine hydroxylase *in vivo* (a crucial enzyme in the conversion of L-tyrosine into the DA-precursor DOPA) and for proper densities of the dopamine transporter (DAT) and D₁ and D₂ auto-receptors on the pre-synaptic membranes of dopaminergic neurons in the mammalian midbrain. Previous studies revealed that mice homozygous for recessive ENU-induced *Picalm*^{fit1} mutations exhibit peripheral and systemic iron deficiency, but did not evaluate neurological or behavioral parameters. We will present our preliminary analyses of the neurological/behavioral effects of two of the mild effect *Picalm*^{fit1} mutations, which suggest that homozygous mutants have behavioral abnormalities indicative of poor dopaminergic neurotransmission, as well as reduced levels of iron in the dopaminergic perikarya (i.e., the ventral mid-brain, containing the substantia nigra). This model may be further studied for mechanistic understanding of the relationship between dopaminergic dysfunction and iron load, which is the basis of many neurobehavioral syndromes. The model can also be applied, to probe the activity and specificity of certain neuro-protective and/or neuro-toxic drugs. Supported in part by USPHS grants NS35088 & AG021190 & USDOE OBER under contract DE-AC05-00OR22725 with UT-Battelle, LLC.

P121**BACKGROUND STRAIN PHENOTYPES: WHAT YOU KNOW COULD HELP YOU**

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Genetically Engineered Mice (GEM) are created from a variety of inbred strains and non-inbred stocks. The most commonly used inbred mice are FVB, C57Bl/6 and various 129 substrains, but other strains or stocks are used intentionally and inadvertently. Genetically homogeneous inbred mice are valuable genetic tools in dissecting and understanding gene function. Wild derived mice and non inbred mice also can be used to advantage. Sophisticated and expensive phenotyping efforts on genetically mixed GEM can yield interesting and important results, but knowledge of the background strains and of expected phenotypes in those strains can be critical to interpretation of the results. In addition, background phenotypes that are a liability in one study may confer great advantage to another area of research and may justify back crossing a genetic manipulation into another strain. Inbred strains, and even substrains, can vary substantially with regard to immune function, metabolism, physiology, behaviour, anatomic variation (including CNS, cardiovascular, pulmonary, musculoskeletal characteristics), susceptibilities to infectious diseases, incidences of spontaneous neoplasms (with hematopoietic, mammary, lung and liver tumours being most common in most strains) and other phenotypes. Some important phenotypes of 129, A, AKR, BALB, C3H, C57, DBA, FVB and SJL mice will be summarized and demonstrated. Such phenotypes may frustrate or obfuscate, but also can be used to advantage when we are aware of them.

P122**PHENOTYPIC ANALYSIS OF TWENTY-FOUR RI STRAINS OF MALE BXD (C57BL/6JXDBA/2J) MICE**T Kaminsky¹, LS Webb¹, DK Johnson², BH Voy²¹Christopher Newport University, Virginia, United States, ²Oak Ridge National Laboratory, Tennessee, United States

Mammals normally respond to cold exposure by increasing thermogenesis, but this response can be altered by genetic factors affecting metabolic capacity and the hypothalamic-pituitary-thyroid axis. A cold stress test was used to screen a panel of recombinant inbred C57BL/6 X DBA (BXD) mice for genetic variation in metabolism. Body temperature, tail length, body and organ weights were also measured to determine if metabolic and morphometric traits were genetically correlated. To study thermoregulation, male, age-matched mice representing twenty-four BXD strains were placed in containers in a 4c environment. Core body temperatures were measured at thirty-minute intervals for two hours. Following the cold stress test, mice were euthanized and the body weights were recorded. Tail length was measured and various organs and fat pads were dissected and weighed. Baseline core body temperature was similar across all BXD strains analysed (average = 38.0° ± 0.3°). On average, body temperature dropped 1.5° after the cold exposure. However significant genetic variability in the response was apparent. For example, two strains deviated considerably from the average response. These results indicate a considerable amount of genetic variation in the ability to thermoregulate, likely reflective of core variation in metabolism and/or endocrine regulation. Organ weights also varied across strains, with spleen exhibiting the most variation. Our findings confirm that core physiological processes are impacted by naturally occurring genetic polymorphisms found in BXD strains of mice. Future efforts will determine the genetic relationships among metabolic and morphometric parameters and the genetic intervals linked to thermoregulation and other complex biochemical processes.

P123**ASSOCIATION ANALYSIS OF OBESITY-RELATED TRAITS AND LIVER GENE EXPRESSION PROFILES USING INTER-SUBSPECIFIC CONSONOMIC STRAINS**T Takada¹, A Mita¹, A Maeno¹, K Moriwaki², H Yonekawa³, T Shiroishi⁴¹ROIS TRIC, Tokyo, Japan, ²RIKEN BRC, Ibaraki-Ken, Japan, ³Tokyo Metropolitan Institute of Medical Science, Tokyo, Japan, ⁴National Institute of Genetics, Shizuoka-Ken, Japan

An inbred strain MSM/Ms is derived from Japanese wild mice, *Mus musuculs molossinus*. MSM/Ms shows extremely large extent of phenotypic differences in many complex traits including obesity, as well as vast amount (~1%SNPs) of genome difference, for a standard laboratory strain C57BL/6J that is predominantly derived from West European wild mice, *M. m. domesticus*. We are taking approach to dissect genetic determinants that control obesity, based upon inter-subspecific difference between the above two strains. Recently, we have established a series of inter-subspecific consomic strains, C57BL/6J-Chr^{MSM}, in which C57BL/6J chromosomes are substituted by corresponding MSM/Ms chromosomes. These consomic strains serve a very unique and powerful experimental system to connect the phenotype variations with the genome differences.

We have analyzed phenotypes of the consomic strains focussing on obesity-related traits, and found that these strains show very wide-range of obesity and energy metabolism-related measurements. Based upon the strain difference, we started comprehensive exploration of gene expression profiles underlying the obesity traits, to elucidate association of expression patterns of specific genes and the obesity phenotype. Currently, we are analyzing gene expression profiles in hepatic cells by use of Affymetrix GeneChips. Preliminary result shows a large difference in the gene expression patterns between the consomic strains.

P124**MAPPING THE PHENOME SPACE USING COMBINATORIAL ANALYSIS OF THE EMPIRICAL ASSOCIATIONS OF GENES AND PHENOTYPES**Z. Li, R Kirova, A Perkins, E Baker, M Langston, E Chesler¹University of Tennessee, Knoxville, TN, United States, ²Baylor University, Waco, TX, United States, ³Oak Ridge National Laboratory, Oak Ridge, TN, United States

Determining an organization of the phenome and its relation to biological networks systems and pathways is a challenging task because of the subjective nature of phenotype definition. It is unclear to what extent phenomenologically defined categories of traits map on to the actual biological systems that subserve them. The wealth of genomic data sets which can be used for determining gene-phenotype associations can be used to construct essential phenotypic categories from the biological pathways that are jointly associated to them. We have undertaken a combinatorial analysis of the bi-partite graph of phenotype to gene expression. The scope of genome data, and the potentially limitless size of the phenotype space demands scalable methods for the integration of genome and phenome. Our present approach makes use of super computing applications of fixed-parameter tractability theory to address problems which are thought to be NP-hard or NP-complete, such as the enumeration of all cliques or bi-cliques from a dense subgraph. A graph is constructed from genome-wide associations of genes and phenotypes, including genetic correlation analysis of microarray measures in reference populations, existing functional gene ontologies, and other empirically defined gene sets. Several metrics for the construction of weighted association graphs were evaluated. These associations are subject to a low-pass filtering threshold. From this unweighted graph, vertex maximal subgraphs (those which have the largest possible set of completely connected gene and phenotype nodes) are enumerated. The neighbourhood around these subgraphs is analysed to construct and analyze a regional map of the phenome.

