The American Society of Human Genetics
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Participation from the National Human Genome Research Institute (NHGRI)

DAY II WEDNESDAY, NOVEMBER 12

Plenary and Platform Presentations

08:00AM-09:30AM Room 204
Education and Social Issues Session 2: Confound It!: Analysis and Interpretation Issues in Population-based Genetics Research

This session follows last year's session on design issues in population-based genetics and genomics research. Study design is a critical aspect of research. Data analysis provides the basis for interpreting study results. Analytic approaches need to be appropriate to the study design, and should consider potential confounding of results by other factors. To understand factors underlying reduced or variable penetrance in inherited disease susceptibility, or underlying more complex models of risk, interaction needs to be considered. These issues are particularly important in understanding the potential application of newly discovered gene-disease associations in clinical care to predict risk, prevent or delay disease onset, or guide treatment. In this session, we will discuss the concepts of confounding and interaction, how they can affect interpretation of study results, methods of controlling for confounding by design and analysis, incorporating interaction when designing studies, and how to look for interaction and incorporate it into analyses.

Presentation Time: 09:05AM-09:25AM
Identifying interaction in complex disease etiology. *T. A. Manolio*

08:00AM-09:30AM Room 201
Education and Social Issues Session 3: Benefits and Risks: Assessing the Experience with Open Data Access Models for Genome-Wide Association

Moderator: *F. S. Collins*
The emergence of cost-effective technologies enabling the study of the genetics of common disease is producing a deluge of exciting data. In addition, it has presented a compelling opportunity to create community resource databases to maximize public benefit from genome-wide association studies (GWAS). Designing and overseeing these resources responsibly requires sound policies to facilitate data sharing and assure participant protection in a period of evolving technologies and ethics debates. Recent publications begin to define the principles and issues to consider in the conduct and oversight of whole genome analysis, including consent, participant withdrawal, return of results, and data release. We

will explore initial experiences with GWAS resources from the standpoint of investigators, research organizations overseeing GWAS, the public, and the databases. The session will also identify the future questions and challenges to ensuring that the richness of GWAS data is translated into knowledge and tools to improve public health.

08:00AM-09:30AM Room 113
Education and Social Issues Session 4: Shaping the Future of Personalized Genetic Information--Today

Co-Moderator: *L. Brody.*
Leaders in genome science and medicine have claimed that development of genetic tests for susceptibility to common diseases will revolutionize preventive medicine, even though the clinical validity and clinical utility of these tests have not been determined. The purpose of this session will be to discuss current understanding of how this information is and can be used, and to discuss the pressing research needs and how to address them.

Presentation 08:05AM-08:20AM
Multiplex initiative; understanding the utility of genetic testing for common health conditions. *C. McBride*

08:00AM-10:00AM Ballroom A
Using DNA Sequence to Detect Variation Related to Human Disease: The Promises and Challenges of Medical Sequencing

Co-Moderator: *Adam L. Felsenfeld.*
The new sequencing platforms promise to dramatically increase the amount of data available for human genetics studies. Sequence data from many individuals has the potential to provide information at the highest resolution for identifying variants that underlie Mendelian or complex disorders, for understanding their frequency distribution, and eventually for personal diagnostics and prognostics. The presentations in this session will examine the potential of the new platforms in detail in the context of specific applications.

10:00AM-11:30AM Room 113
Education and Social Issues Session 9: From Family History to Medical Records: Electronic Integration of Health Information

Information, from family history to specific medical records, must be accessible and coordinated to be most useful. Various tools have been in use and are emerging to allow consumers and healthcare providers store medical and health information. With potential and actual genomic information available, correlations and associations are possible. Therefore interoperability, ease of use, and accessibility are critical

components in the modern healthcare system. We will explore the Surgeon General's Family History Tool and its implications for consumer capture of family health history, issues critical to electronic medical records and regional health information organizations. We will examine opportunities and challenges related to the implications of the management of these health information technologies for society, and articulate some of the available solutions.

Presentation 10:20AM-10:35AM
Family History: The Foundation for Genomic Medicine.
A. E. Guttmacher

Poster Presentations

Topic: Clinical Genetics and Dysmorphology
Exhibit Hall C   4:30PM-6:30PM

Poster 432/W
Analyses of gene and protein variations of Retinoic Acid Induced 1 (*RAI1*) in Smith-Magenis Syndrome. *T. Vilboux[1], A. C. M. Smith[3], A. Garcia[1], C. Ciccone[1], J. Blancato[2], W. Introne[3], W. A. Gahl[1,3], M. Huizing[1]* 1) NHGRI/MGB, NIH, Bethesda, MD; 2) Georgetown Univ, Washington, DC; 3) Office of Rare Diseases, OD, NIH, Bethesda, MD.

Smith-Magenis syndrome (SMS) is a complex developmental disorder involving variable symptoms such as mental retardation, craniofacial dysmorphia, height-growth delay, infantile hypotonia, brachydactyly, attention deficit, decreased sensitivity to pain, self-injury, maladaptive behaviors and sleep disturbance. Disrupted sleep patterns and behavioral problems characteristic of SMS could be related to an inverted diurnal rhythm of melatonin release. The prevalence of SMS is estimated to be 1/25000 but it is likely underdiagnosed. The syndrome is ascribed to a 2-9Mb interstitial deletion on chromosome 17p11.2. A small number of SMS patients lack any deletion, but carry dominant mutations in *RAI1* (*Retinoic Acid Induced 1*), which resides in the common deletion area. Individuals with mutated *RAI1* have many of the major features of SMS. *RAI1* function is unknown. It is highly conserved through mammalian evolution and appears to be a transcriptional regulator, likely involved in neuronal development. We analyzed *RAI1* and its involvement with the clinical features of SMS. We studied 10 patients with the SMS phenotype but without a common deletion, confirmed by FISH and copy number qPCR. We confirmed presence of two copies of *RAI1* in these patients and sequenced RAI1 exons and intronic boundaries for mutations. Multiple variants were found, including known SNPs, but also 3 unreported variants, 2 are amino-acid changing. We are analyzing the patients' RNA, isolated from skin fibroblasts and/or lymphoblast cell lines, for variations in *RAI1* transcription or splicing. Next, we will determine RAI1 protein expression through Western blotting to detect variations in translation. Identifying new mutations and understanding how they affect *RAI1* can help to define the precise cellular function of this protein. Determining how a single mutation in *RAI1* can result in the varied clinical features of this disorder may also assist in understanding the pathways involved in craniofacial development, sleep and behavior.

Poster 443/W
Establishment of the Undiagnosed Diseases Program at the National Institutes of Health. *C. E. Wahl, M. E. Nehrebecky, W. Gahl* Office of Rare Diseases, NHGRI/NIH, Bethesda, MD.

The National Institutes of Health, through the National Human Genome Research Institute and the NIH Office of Rare Diseases announces the establishment of the Undiagnosed Diseases Program (UDP). Referrals are accepted from medical providers with patients deemed undiagnosed after an adequate workup. The NIH UDP screens arriving referrals to generate a subset of patients to be invited to the NIH for further workup and evaluation. The stated goals of the UDP include providing answers to patients with mysterious conditions that have long eluded diagnosis and advancing medical knowledge about rare and common diseases. Each patient visiting the NIH is evaluated by a custom-designed multidisciplinary team based on their presenting illness and the results of prior medical evaluation. Participating specialists span the expertise of the NIH community including rheumatology,oncology, mental health, nephrology, hematology, ophthalmology, neurology, laboratory medicine, pain and palliative care, bone disorders, endocrinology, oncology, immunology, dermatology, primary immunodeficiency, dentistry, genetics, pathology, pulmonology, cardiology, primary immunodeficiency, internal medicine, pediatrics and hepatology. Medical data collected during the evaluation is returned to the referring provider regardless of whether a definitive diagnosis was achieved during the visit. In addition to the potential for diagnosis, participating patients may benefit from additional ideas for treatment of ongoing medical problems. Data from the patient evaluations is be used to generate ideas and hypothesis for continuing medical research. Since the announcement of the program on May 19, 2008, approximately 400 inquires have been received regarding potential participation. Interested medical providers and their patients may obtain more information from the program by visiting http://rarediseases.info.nih.gov/UndiagnosedDiseases/FAQ.aspx.

Topic: Metabolic Disorders
Exhibit Hall C   4:30PM-6:30PM

Poster 591/W
Subcellular localization of UDP-GlcNAc 2-epimerase/ManNAc kinase in cells of HIBM and sialuria patients. *K. Patzel, C. Ciccone, I. Manoli, D. Adams, D. Krasnewich, WA. Gahl, M. Huizing* MGB, NHGRI, NIH, Bethesda, MD.

UDP-GlcNAc 2-epimerase/ManNAc kinase (GNE/MNK) is a rate limiting, bifunctional enzyme in sialic acid (SA) synthesis, which is feedback inhibited by CMP-SA in its allosteric site. Mutations in GNE/MNK cause two human disorders, Hereditary Inclusion Body Myopathy (HIBM) and sialuria. Sialuria, clinically characterized by variable symptoms, including hepatomegaly and mental retardation, is caused by dominant mutations in the allosteric site of GNE/MNK, leading to a loss of feedback-inhibition and increased excretion of SA. HIBM is characterized by adult onset progressive muscle wasting and results from recessive, mostly missense, mutations in GNE/MNK outside the allosteric site, leading to decreased GNE/MNK enzyme activities, and decreased SA production. Recent immunofluorescence studies showed that GNE/MNK not only resides in the cytoplasm and Golgi, as expected, but also in the nucleus. This nuclear localization is remarkable, since GNE/MNK performs its enzymatic role within the cytoplasm. However, GNE/MNK contains a putative nuclear export signal and the nucleus contains CMP-SA synthase, which converts all cellular SA to CMP-SA. We propose that GNE/MNK is 'stored' in the nucleus, in its inactive, CMP-SA bound, feedback-inhibited form. If the cell needs SA, there is less SA to enter the nucleus and form CMP-SA, so there is more 'free' GNE/MNK to

translocate to the cytoplasm (through its nuclear export signal) and produce more SA. To study this proposed mechanism, we obtained preliminary data using normal, HIBM and sialuria patients' fibroblasts. Pilot immunofluorescence studies revealed a higher nuclear GNE/MNK content in sialuria cells and a lower content in HIBM cells compared to normal. Subcellular fractionation followed by Western blotting revealed similar results; higher nuclear amounts of GNE/MNK in sialuria and lower amounts in HIBM. In addition, Western blots of nuclear fractions of both sialuria and HIBM cells showed unexplained GNE/MNK bands compared to normal. These bands, as well as the function of the nuclear export signal, are being analyzed and may provide intriguing insights into the regulation of cellular SA synthesis.

Poster 602/W
Clinical and cellular correlations in Chediak Higashi Syndrome. *W. Westbroek, W. Introne, I. Manoli, G. Golas, D. Adams, D. Maynard, M. Huizing, W. A. Gahl* Medical Genetics Branch, NHGRI, NIH, Bethesda, MD.

Chediak Higashi syndrome (CHS) is a rare autosomal recessive disorder caused by mutations in the CHS1 gene, encoding the 430-kDa CHS1 protein with unknown biological function. Many cell types in CHS manifest giant lysosomes and lysosome-related organelles (LRO). Clinical characteristics can include skin, hair and eye hypomelanosis, recurrent infections, a mild bleeding diathesis and late-onset progressive neurological impairment. The clinical spectrum of CHS varies widely; most patients manifest the severe childhood form, with fatal infections and the accelerated phase while only a few suffer milder infections or progressive neurological impairment. We have shown that the clinical phenotype of CHS varies in relation to the molecular genotype. To study the cellular phenotypes in CHS, we cultured fibroblasts and melanocytes from 5 unrelated patients with vastly different clinical presentations and genotypes. Laser scanning confocal microscopy of cultured primary epidermal fibroblasts stained with the lysosomal marker, LAMP2, showed a perinuclear distribution of a few large lysosomes in severely affected patients; fibroblasts from mildly affected patients contained only slightly enlarged lysosomes. Bright field light microscopy and laser scanning confocal microscopy were used to study the localization, morphology and pigmentation of melanosomes. In control melanocytes, melanosomes exhibited a peripheral distribution with accumulation in the dendritic tips while severely affected patients' CHS melanocytes had enlarged melanosomes restricted to the perinuclear area; mild CHS melanosomes were much smaller, with a nearly normal dendritic distribution. Western blot analysis with an anti-CHS1 antibody revealed residual CHS1 protein expression in mild CHS cell lines and absent CHS1 expression in severe CHS-1 cell lines. We show for the first time that the cellular phenotype and CHS1 expression level in CHS patients correlate with the molecular genotype and the clinical phenotype.

Poster 604/W
Proteomic Analysis of Platelet α-Granules Using Mass Spectrometry: An Application to Gray Platelet Syndrome. *D. M. Maynard[1], M. Gunay-Aygun[1, 2], H. F. G. Heijnen[3], H. Edwards[1], J. G. White[4], W. A. Gahl[1]* 1) MGB, NHGRI, NIH, Bethesda, MD, USA; 2) ORD, NIH, Bethesda, MD, USA; 3) Laboratory of Clinical Chemistry and Haematology and Cell Microscopy Centre, Univ Medical Centre, Utrecht, The Netherlands; 4) Depts of Laboratory Medicine and Pathology and Pediatrics, Univ of MN, Minneapolis, MN, USA.

A deficiency in granule-bound substances in platelets causes a group of congenital bleeding disorders known as storage pool deficiencies (SPDs). For disorders such as Gray Platelet

syndrome (GPS), only the clinical and histological states have been defined. In order to understand the basic defect in this disorder, we are using proteomics and mass spectrometry (MS). Platelet α-granules contain several adhesive proteins involved in hemostasis, and glycoproteins involved in inflammation, wound healing, and cell-matrix interactions. Our research represents the first effort to define the normal platelet α-granule proteome using MS. We prepared a subcellular fraction (fr. 6) enriched in intact α-granules from human platelet lysates using sucrose gradient ultracentrifugation. Fraction 6 proteins were separated and identified using SDS-PAGE and LC-MS/MS. We identified 219 non-redundant proteins, 44 of which appear to be newly described α-granule proteins. Immuno-electron microscopy confirmed the presence of Scamp2, APLP2, ESAM and LAMA5 in platelet α-granules for the first time. Recently, we analyzed fraction 6 proteins from two GPS patients and two controls. The number of peptides from soluble proteins synthesized in the megakaryocyte was markedly decreased or undetected in GPS fraction 6 compared to normal. The number of peptides from soluble proteins endocytosed into alpha granules was slightly decreased in GPS platelets compared to normal. The number of peptides from some membrane proteins was decreased in GPS while the number was approximately the same for others compared to normal. These results support the existence of "ghost" granules in GPS. This proteomic technology can be employed to characterize the intracellular vesicles of patients with other SPD's and other genetic disorders of organelle formation and trafficking.

Poster 625/W
Idiopathic Nephrocalcinosis: Possible Genetic Causes. *G. Nesterova, W. J. Introne, G. A. Golas, C. Ciccone, M. Huizing, W. A. Gahl* Medical Genetics Branch, NHGRI, NIH, Bethesda, MD.

Nephrocalcinosis (NC) consists of calcium deposition mainly within the medullary portion of the kidneys. Many known etiologies of secondary NC exist, including Dent's disease, exogenous and endogenous forms of hypervitaminosis D, distal renal acidosis, hyperparathyroidism and others. In addition, many patients with renal calcifications have isolated, idiopathic NC, sometimes causing significant renal impairment. Some of these patients could have disorders of vitamin D metabolism not yet discovered. We evaluated two unrelated patients (ages 5 years and 12 years) at the National Institutes of Health with hypercalciuria and isolated nephrocalcinosis. Both children have high normal serum calcium, mildly elevated serum vitamin D_3 levels, and undetectable parathyroid hormone. Neither child has evidence of rickets or a history of excessive vitamin D_3 consumption. Given the high vitamin D levels despite high normal serum calcium, we hypothesize that the underlying mechanism involves dysregulation of vitamin D_3 metabolism. The enzyme 1-alpha-hydroxylase (CYP27B1) converts the inactive form, 25-dihydroxyvitamin D_3 to the active form,1- α,25 dihydroxyvitamin D_3(1- α 25(OH)$_2$D$_3$). This biologically active form plays a critical role in intestinal and renal calcium absorption, as well as in binding to the vitamin D receptor (VDR) within distal tubules of the kidney, further regulating CYP27B1 gene expression. 1- α,25(OH)$_2$D$_3$ is inactivated by the enzyme 24-hydroxylase (CYP24). A loss of function mutation within this gene could theoretically lead to increased 1- α,25(OH)$_2$D$_3$. Two additional molecules critical for calcium transport along the cells of the distal tubule are VDR and the active calcium transporter, TRPV5. Our initial investigation has targeted the enzymes responsible for regulating the active vitamin D_3, CYP24 and CYP27B1. Sequencing of both these genes is currently underway. Sequence analysis of the VDR and TRPV5 genes could be the next step.

Topic: Therapy for Genetic Disorders
Exhibit Hall C   4:30PM-6:30PM

Poster 764/W
Small-molecule screening as a novel strategy for developing therapeutics for Gaucher disease. *O. Motabar[1], D. Urban[1], O. Goker-Alpan[1], W. Zheng[2], J. Inglese[2], C. Austin[2], E. Sidransky[1], E. Goldin[1]* 1) Section on Molecular Neurogenetics, Medical Genetics Branch, NHGRI, NIH, Bethesda, MD; 2) Chemical Genomics Center, NHGRI, NIH, Bethesda, MD.

Gaucher disease is caused by mutations in the gene encoding the lysosomal enzyme glucocerebrosidase (GBA). Most GBA mutations result in a defective protein, impaired in stability, intracellular transport efficiency or activity. The identification of small molecules with therapeutic potential that are amenable to chemical optimization may provide simple, more effective and less expensive therapy for patients with Gaucher disease Small molecules may act either by activating the enzyme or by serving as pharmacological chaperones. We initially identified new leads for treatment of Gaucher disease by screening chemical libraries assembled by the NIH Chemical Genomics Center using wildtype glucocerebrosidase (GC). A quantitative high-throughput screening assay was used to screen a collection of 62,000 compounds, identifying three different structural classes that inhibited GC at nanomolar concentrations. Representatives of these compounds were found to be effective in cell culture models. It was decided to also screen mutant GC, using preparations from patient tissue samples. In these tissue samples, the pH optimum was approximately 5.0 for both wild-type and mutant tissue samples, while the Vmax was lower for the mutant enzyme than for the wild-type. An N370S homozygote with sufficient activity was selected for the compound screen. This study will enable us to pinpoint the functional units in the protein and to design potent drugs for patients with Gaucher disease.

Topic: Genomics
Exhibit Hall C   4:30PM-6:30PM

Poster 869/W
Targeted genomic sequencing at an "association" locus. *A. Kapoor[1], D. Arking[1], A. O'Connor[1], M. Sosa[1], N. Hansen[2], M. Ross[3], D. Bentley[3], J. Mullikin[2], A. Pfeufer[4], N. I. S. C. Comparative Sequencing Program[2], A. Chakravarti[1]* 1) IGM, JHU, Baltimore, MD; 2) NHGRI, NIH, Bethesda, MD; 3) Illumina, Little Chesterford, UK; 4) TU Munich, Germany.

Genome-wide association studies typically reveal a 15-150 kb locus with common variants that confer disease-susceptibility. There are yet no validated methods for identifying susceptibility variants directly, however, DNA sequencing to reveal all extant variation of target locus is a necessary first step. We describe a method to recover and sequence the entirety of 141 kb of NOS1AP locus associated with QT-interval. The target locus comprises of 5' region, exon 1 and 2, intron 1 and most of intron 2 of NOS1AP, and has 554 dbSNP/273 HapMap SNPs. DNA from target interval was recovered by long-range PCR and pooling of 16 overlapping amplicons. One amplicon showed differential allele-specific amplification that we mapped to a 1051 bp segment arising from sequence variation at a repeat motif on a haplotype marked by the A allele at rs4656349: we amplified this separately. We pooled all amplicons per sample from 8 CEU and 8 YRI HapMap samples and 48 samples from individuals with extreme QT-intervals.

Direct sequencing of amplicon pool was performed using Solexa SBS Technology and paired-end reads of 25 nt were aligned to a reference sequence (NCBI36). Data were analyzed using ELAND and MPG software and we present the findings from CEU samples. The mean coverage depth in reads ranged between 269-555 (ELAND) and 304-792 (MPG) with variation largely from amplicon-to-amplicon differences and at an ELAND threshold of 6 (2 PhredQ30 bases or 3 Q20 bases) missed coverage of only 69-593 bp of the locus. MPG detected 535 known and 127 novel SNPs. There was 98.9% concordance of genotypes with HapMap, with all discrepancies at 11 positions due to genotyping errors from calls on complementary strands or call reversals and at 2 positions from deeper Solexa coverage. These results demonstrate the high specificity and sensitivity of this approach for obtaining full-coverage and a complete inventory of all genetic variation in a genomic region. Analyses of structural variation and additional samples is under completion.

Topic: Cancer Genetics
Exhibit Hall C   4:30PM-6:30PM

Poster 1212/W
Association analysis of 42 hereditary prostate cancer (HPC) families using segregating risk haplotypes identifies a 20Kb region on chromosome 22q12.3. *B. Johanneson[1], SK. McDonnell[2], JL. Stanford[3], DM. Karyadi[1], DJ. Schaid[2], L. Wang[2], K. Deutsch[4], L. McIntosh[3], JR. Cerhan[2], JL. St. Sauver[2], SN. Thibodeau[2], EA. Ostrander[1]* 1) NHGRI, National Institutes of Health, Bethesda, MD; 2) Department of Health Sciences, Mayo Clinic, Rochester, MN; 3) Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, WA; 4) Institute for Systems Biology, Seattle, WA.

Multiple studies of HPC families identify a susceptibility locus at chromosome 22q12. In this study, a set of 24 families from the Mayo Clinic and 18 from the Seattle-based PROGRESS study, each with family-based LOD scores ≥ 0.58 at 22q12 were initially used for fine mapping and mutation scanning. Fourteen families with ≥ 5 affected men highlight a 2.53 Mb minimal recombination interval. A set of 202 SNPs were genotyped in the 18 PROGRESS families. Markers were selected from among 670 SNPs previously genotyped in 498 Mayo family-based cases and 533 population-based controls which yielded a p-value ≤ 0.05 in a family-based association study. Fifty-two of these SNPs are located inside the 2.53 Mb recombination interval described above. We then used the pedGenie software to test all 202 SNPs in the 18 PROGRESS families and the 24 Mayo families as well as the 533 population-based controls. Monte Carlo simulation compensated for related individuals. By assessing haplotype sharing between affected family members, unassigned individuals were defined as likely carriers of the "at risk" haplotype or not. This allowed us to exclude potential phenocopies and healthy carriers, increasing the power and accuracy of the overall data set. Preliminary results highlight a 20 Kb region within the 2.53 Kb minimal recombinant interval indicated by 3 SNPs that includes 1 or 2 candidate genes. The association is observed independently in both the Mayo and PROGRESS data sets, as well as the combined set of 42 families. We are currently sequencing within and surrounding the candidate gene/s to identify putative causative SNPs which will be assessed in a larger population-based, case control study of 2800 individuals.

Topic: Molecular Basis of Mendelian Disorders
Exhibit Hall C   4:30PM-6:30PM

Poster 1422/W
**Kidney and muscle phenotypes due to hyposialylation in a
mouse model of Hereditary Inclusion Body Myopathy.** *M.
Ziats[1], D. Kurland[1], D. Hickey[1], R. Klootwijk[1], I. Manoli[1,2], K.
Patzel[1], C. Ciccone[1], P. Zerfas[3], M. Starost[3], D. Darvish[4], WA.
Gahl[1,2], M. Huizing[1]* 1) MGB, NHGRI, NIH; 2) Office of Rare
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HIBM Research Group, Encino, CA.

Hereditary Inclusion Body Myopathy (HIBM) is a recessive
adult-onset neuromuscular disorder, characterized by
progressive muscle weakness due to mutations in UDP-
GlcNAc 2-epimerase/ManNAc kinase (GNE), the key enzyme
in sialic acid (SA) synthesis. We created a *Gne* knock-in mouse
model harboring the human M712T mutation. We previously
showed that these mice died before postnatal day 3 (P3) of
glomerular disease, involving effacement of podocytes due to
hyposialylation. Administration of the SA precursor ManNAc
partially rescued the kidney phenotype and allowed survival of
mutant mice. Here we evaluate SA itself as a therapeutic
agent, by oral administration to pregnant and nursing mice. SA
feeding did not significantly increase the number of surviving
mice beyond P3, likely due to the negative charge of SA
(impairing transmembrane transport) compared to the neutral
charge of ManNAc. We also evaluated the evidence of a
muscle phenotype in older surviving mutant mice. Electron
microscopy studies of the gastrocnemius, gluteus, and
quadriceps muscles of 6 and 11 month old mutant mice
showed tubular aggregates (TAs). TAs presumably originate
from the sarcoplasmic reticulum, and may be precursors of the
rimmed vacuoles (RVs) seen in the muscles of HIBM patients,
who are diagnosed late, after RVs have already formed.
Further analysis of TA formation and sialylation status of
affected muscles is being pursued, as well as evaluation of the
effect of ManNAc on their formation. Other human disorders
characterized by TAs, including sporadic limb girdle weakness,
familial myasthenia gravis, and unexplained exercise-induced
muscle cramps, may be caused by local sialic acid deficiency.
Our *Gne* M712T mouse is a model for further evaluation of
these hypotheses. In sum, our *Gne* M712T mouse
unexpectedly serves as the first genetic model of podocyte
injury due to hyposialylation, and may also prove to be a model
of the myopathy of HIBM.

Poster 1437/W
**Genotyping Oculocutaneous Albinism -- a Case Report
from an Ongoing Project.** *D. Adams, M. Huizing, W. Gahl*
NHGRI, NIH, Bethesda, MD.

Objective: We are evaluating a cohort of patients with clinical
evidence of oculocutaneous albinism (OCA), but no definitive
molecular diagnosis. The cohort includes individuals who have
unusual presentations, and who have been evaluated for other
albinism-related disorders. We describe a pair of siblings for
whom our ongoing project has yielded a new, definitive
diagnosis. **Methods:** DNA sequence was obtained from PCR
amplicons using custom primers. A known pseudogene
complicates the sequencing of the TYR gene. TYR encodes
the melanogenic enzyme tyrosinase. Allele-specific primers
were used to differentiate TYR from the TYR pseudogene.
Results: The two sisters were ages 2 y/o and 9 m/o at the time
of presentation. The initial evaluation was conducted under a
protocol for Hermansky-Pudlak Syndrome (HPS). HPS
combines OCA with platelet dysfunction and the potential for
pulmonary fibrosis and chronic colitis. In addition to OCA, both
children had intermittent abdominal pain and easy bruising.
Gastroenterological, pulmonary, hematological and

ophthalmological evaluations were performed, greatly reducing
the suspicion for HPS. Molecular analysis of the OCA2 ("P")
gene, associated with OCA, type 2 (OCA-2), revealed
heterozygosity for p.S736L, a mutation previously described in
OCA-2 patients. A tentative diagnosis of OCA-2 was assigned.
Given the lack of a second OCA2 mutation, we added the
siblings to our re-analysis project, revealing a homozygous
p.G190fs mutation in the tyrosinase gene, associated with
OCA, type 1. **Conclusion:** Technical progress has dramatically
reduced the cost of DNA sequencing, allowing for more liberal
use of sequencing in the search for definitive diagnoses. By
sequencing all known OCA genes in our undiagnosed cohort,
we hope to both assign additional diagnoses and discover
candidates for new OCA-related genes. Clinical sequencing will
allow rapid screening for common causes of OCA to confirm
clinical diagnoses and to exclude more severe conditions.
Future areas of research include characterization of
pathogenicity for known variants and discovery of variants
outside the coding sequence of OCA-related genes.

Poster 1451/W
**Mutational screening of regulatory regions flanking GBA in
patients with Gaucher disease.** *Y. Blech-Hermoni, E. Barnoy,
S. Ziegler, B. Stubblefield, K. Hruska, M. LaMarca, N. Tayebi,
E. Sidransky* Medical Genetics Br, NHGRI/NIH, Bethesda, MD
20814.

BACKGROUND: Gaucher disease (GD) is the most common
lysosomal storage disorder. Almost 300 mutations have been
identified in the gene encoding glucocerebrosidase (GBA), the
enzyme deficient in GD, resulting in the accumulation of
uncleaved substrate in cells of the reticuloendothelial system.
Genotype-phenotype correlation in GD remains limited,
encouraging the identification of other modifiers that could
underlie the high variability in residual enzyme activity and
disease severity in patients with the same genotype. The
regulatory architecture of GBA has been investigated
previously, identifying functional cis-acting regulatory elements
within the proximal promoter region of the human gene locus
(Doll et al., 1995; Moran et al., 1997), and c-Myc binding sites
within 5kb of the translation initiation site. METHODS: We used
computational multispecies comparative approaches to identify
evolutionarily conserved sequences in the GBA gene locus.
Site-directed mutatgenesis was performed to generate
constructs with alterations at these specific sites. We used the
dual-luciferase expression assay to validate the functional role
of these binding sites in COS-7 cells. Finally, we sequenced
predicted and previously reported regulatory sites in patients
sharing the same genotypes. RESULTS: Our computational
analysis of the locus identified two clusters of predicted
transcription factor binding sites. Expression assays revealed
that changes in six predicted sequences resulted in dramatic
downregulation, whereas changes in two sites resulted in
statistically significant increases in reporter gene expression.
Each sequence is being examined in patient samples to
determine whether alterations at these sites impact phenotype.
CONCLUSIONS: Computational multispecies comparative
approaches identified potential GBA regulatory regions that
appear to impact gene expression, providing sites for further
evaluation in phenotypically diverse patients with GD.

Poster 1453/W
**Analysis of atypical patients with features overlapping
Pallister-Hall and Greig cephalopolysyndactyly syndrome.**
*J. J. Johnston, J. Sapp, J. Turner, L. G. Biesecker, Clinical
Collaborators* NHGRI, NIH, Bethesda, MD.

Pallister-Hall and Greig cephalopolysyndactyly syndromes are
caused by mutations in the *GLI3* transcription factor on
chromosome 7p14.1. Although variant phenotypes, including

isolated polydactyly, acrocallosal syndrome, and severe mental retardation, have been attributed to mutations in *GLI3*, atypical phenotypes attributable to such mutations are not adequately delineated. To better understand the clinical variability resulting from mutations in *GLI3* we have studied a cohort of patients who have features of PHS and/or GCPS but do not fulfill the clinical criteria for either disorder. The group consisted of 55 probands and 6 family members. Twenty-two probands had features of GCPS including polydactyly, syndactyly, hypertelorism, macrocephaly, and/or agenesis of the corpus callosum. Twenty-three probands had features of PHS including polydactyly, hypothalamic hamartoma, panhypopituitarism, imperforate anus, and/or hypoplastic nails. Ten probands had either hamartoma or polydactyly without additional overlapping features of either disease. We identified a total of 17 mutations including one missense variant. *GLI3* has a well-established genotype/phenotype correlation with truncating mutations in the middle third of the gene, between nt 1198-3481, causing PHS and mutations outside this region causing GCPS. Of the 6 probands with features of GCPS, 3 had truncating mutations in *GLI3* that fell outside the middle third of the gene, one had a splice site mutation upstream of the middle third of the gene, one had a missense alteration, p.S903L, and one had a mutation at nt 3474 at the PHS/GCPS boundary. Nine probands with features overlapping PHS had truncating mutations in *GLI3*, all fell in the middle third of the gene. No individuals with polydactyly or hamartoma in the absence of other overlapping features had mutations in *GLI3*. In summary, individuals with multiple features of PHS and GCPS should be considered for *GLI3* mutation screening.

Topic: Complex Traits and Polygenic Disorders
Exhibit Hall C   4:30PM-6:30PM

Poster 2059/W
Fine Mapping of a Myopia Susceptibility Locus on Chromosome 22q12. *D. Stambolian[1], R. Spielman[2], G. Ibay[3], K. Gogolin Ewens[2], R. Wojciechowski[3], J. Bailey-Wilson[3]* 1) Dept Ophthamology, Univ Pennsylvania, Philadelphia, PA; 2) Dept. Genetics, Univ Pennsylvania, Philadelphia, Pa; 3) NHGRI, NIH, Baltimore, MD.

Myopia is an increasingly common disease caused by an inability to focus images on the retina. Currently, there are 14 known loci but no genes are known to cause myopia. In an effort to delineate the genetic susceptibility to myopia, we have previously performed a genome-wide screen in a Jewish population of 56 families ascertained by a proband with myopia. The genomic region with the strongest evidence for linkage with myopia was located on chromosome 22q12 (HLOD=4.73). We have recently constructed a high-density SNP map of this 35 Mb region in the Jewish population, utilizing LD data available from the International HapMap Project. A total of 1386 SNPs were genotyped with minor allele frequencies of >0.10 in this Jewish population. Eleven SNPs were not informative in the analysis. Association analyses were performed with common myopia (-1D or worse) in extended pedigrees using FBAT. Nine SNPs clustered around 30 Mb had p-values <0.001. Most of these SNPS were positioned in the intergenic regions of PISD, SFI1 and EIFENIF1. One SNP remained statistically significant after adjustment for multiple testing using the Bonferroni correction and is located in the 3' UTR of PISD. Additional work is in progress to replicate and confirm these findings in independent multi-ethnic populations and to determine the overall relevance of these SNPs in myopia susceptibility.

Poster 2077/W
Searching for independent association signals in genome-wide association studies: evidence for a second signal with HDL cholesterol level at the *LIPC* locus. *T. M. Teslovich[1], C. J. Willer[1], L. J. Scott[1], A. U. Jackson[1], L. L. Bonnycastle[2], H. M. Stringham[1], P. S. Chines[2], M. G. Rees[2], T. T. Valle[3], R. N. Bergman[4], J. Tuomilehto[3], F. S. Collins[2], K. L. Mohlke[5], M. Boehnke[1]* 1) U Mich, Ann Arbor, MI; 2) NHGRI, Bethesda, MD; 3) National Public Health Institute, Helsinki, Finland; 4) USC, Los Angeles, CA; 5) UNC, Chapel Hill, NC.

To understand better the allelic architecture of complex traits, we are seeking to identify trait loci at which multiple independent causal variants may be present. For each locus, this will further our understanding of the genetic basis of the trait and may allow better prediction of personalized risk and drug therapies. This knowledge may inform future studies that seek to identify alleles involved in common diseases as the identification of multiple independent signals may provide stronger evidence of true association.

We are examining loci that showed association with lipid levels in a meta-analysis of genome-wide scans performed by the FUSION Study, the SardiNIA Study of Aging, and the Diabetes Genetics Initiative. After follow-up in additional samples, the analysis identified genome-wide significant associations with 18 loci, including one between serum HDL cholesterol levels and SNPs rs261332 (p=2.3x10^{-15}) and rs4775041 (p=3.2x10^{-20}) near LIPC on chr 15. rs261332 is in high LD with promoter polymorphisms that have been associated with HDL. rs4775041 is located ~50kb upstream of LIPC and is not in LD with previously associated variants.

To determine whether rs261332 and rs4775041 represent independent signals, we simultaneously tested both SNPs for association with HDL in 3,738 FUSION samples using linear regression. Neither signal is attenuated in the joint analysis (FUSION p-values: rs261332 unadj 1.2x10^{-7}, adj 3.0x10^{-8}; rs4775041 unadj 1.4x10^{-8}, adj 3.6x10^{-9}). These results suggest that rs4775041 represents an independent association signal at the LIPC locus.

We are currently investigating the remaining loci with preliminary evidence for multiple association signals that may act independently to increase disease risk.

Poster 2106/W
Ongoing Genomewide Association in Familial Intracranial Aneurysm. *T. Foroud[1], D. L. Koller[1], R. Deka[2], D. Lai[1], D. Woo[2], L. Sauerbeck[2], R. Hornung[2], E. S. Connolly[3], C. Anderson[3], G. Rouleau[3], I. Meissner[3], C. Langefeld[3], J. E. Bailey-Wilson[3], J. Huston[3], R. Brown[3], J. P. Broderick[2]* 1) Indiana Univ Sch Medicine, Indianapolis, IN; 2) Univ Cincinnati, Cincinnati, OH; 3) FIA Study Group.

Subarachnoid hemorrhage due to the rupture of an intracranial aneurysm (IA) occurs in 16,000 to 17,000 persons in the U.S. annually and nearly half of affected persons are dead within the first 30 days. Individuals with 1st degree relatives harboring an intracranial aneurysm (IA) are at an increased risk (GRR=2-4) of IA. Families with multiple members having ruptured or unruptured IA were recruited and all available medical records and imaging data were reviewed to classify possible IA subjects. One definite or probable IA subject from each of 270 Caucasian families were selected for genotyping as cases. Genotyping was performed using the Affymetrix 6.0 in a sample of 270 cases and 281 controls. Quality assessment removed SNPs and samples with call rates below 95%, SNPs with deviation in controls of Hardy-Weinberg equilibrium (p<.0001), and minor allele frequency below 0.01; the data set retained 742,338 SNPs. The MDS algorithm implemented in PLINK was performed using HapMap samples to identify and exclude individuals with substantial non-Caucasian admixture. The final

analytical sample consisted of 250 FIA cases and 278 controls. The test of allelic association in the FIA case-control cohort for the SNP panel resulted in the detection of several SNPs providing strong evidence of association with FIA, which were supported by additional SNPs in the same gene or chromosomal region. These included the *DHCR24* gene region on chromosome 1p32.3 ($p<2x10^{-6}$), the *HNT* gene region at chromosome 11q25 ($p<3x10^{-6}$), and the *ZEB2* gene region at chromosome 2q22.3 ($p<5x10^{-6}$). We also detected multiple SNPs with evidence of association with FIA in intergenic regions at 4q28.3 and 2q35 (both $p<3x10^{-6}$). Additional case and control samples are currently being genotyped, which will enable us to confirm the evidence of association with FIA in these chromosomal regions and pursue additional genotyping and functional studies of these loci.

Poster 2107/W
Characteristics of SNPs Associated with Complex Traits in Genome-Wide Association (GWA) Studies: The NHGRI GWA Catalog. *L. A. Hindorff, J. P. Struewing, E. M. Ramos, H. A. Junkins, T. A. Manolio* Office of Population Genomics, NHGRI, NIH, Bethesda MD.

Over 150 GWA studies have implicated SNPs influencing a wide array of common diseases and traits, but characteristics of these SNPs have not been systematically examined. For GWA studies published through May 8, 2008 and attempting to assay at least 100,000 SNPs, we identified up to five replicated but previously unreported SNP-trait associations at $p < 9.5 \times 10^{-6}$. Estimates of risk allele frequencies, sample sizes, and odds ratios (OR) were extracted from the published reports; attributable risk percents (AR%) were calculated from published OR's. Genomic characteristics of these SNPs were retrieved from dbSNP, the HapMap website, and the UCSC Genome Browser. Genetic distances were estimated for each SNP for the three main HapMap populations. Of 284 unique SNPs identified, 139 (49%) were in genic regions. Fourteen SNPs (5%) were missense variants, 3 (1%) were synonymous coding variants, 2 were in a 5' UTR, 2 in a 3' UTR, and 118 (42%) were intronic. Median genetic distances between the HapMap YRI and CEU populations, and between YRI and JPT+CHB, were 0.023 and 0.028, respectively; 95th percentile values were 0.16 and 0.192, respectively. Reported risk allele frequencies ranged from 5%-97% (median 41%); only 3.5% of risk alleles were present at frequencies of 10% or lower. For SNPs associated with binary outcomes, reported OR's ranged from 0.43 to 20.1 (median 1.27), which translated into AR% of 3%-95% (median 22%). Several complex traits of public health interest were represented among those with AR% > 50%, including diabetes and stroke. Though SNPs assayed on genotyping platforms are likely to be overrepresented here, these results suggest that a systematic review of SNPs implicated in GWA studies may yield useful insights into the nature of genetic variation influencing complex traits. Additionally, the modest to strong increase in disease risk attributable to several genetic variants may guide future studies that assess whether these variants, or variants in linkage disequilibrium, are of clinical or public health significance.

Poster 2123/W
Genome-wide association study of blood pressure in African Americans and Nigerians. *B. Tayo[1], G. Lettre[2,3], S. Kang[4], H. Lyon[2], A. Luke[1], A. Adeyemo[5], C. Rotimi[5], J. Hirschhorn[2,3], X. Zhu[4], R. Cooper[1]* 1) Prev Medicine & Epidemiology, Loyola Univ, Chicago, Maywood, IL; 2) Children's Hospital Boston, Boston, MA; 3) Broad Institute of Harvard and MIT, Cambridge, MA; 4) Case Western Reserve University, Cleveland, OH; 5) NIH Intramural Center for Genomics and Health Disparities, Bethesda, MD.

Hypertension shares similar heritability with many other traits related to cardiovascular risk, however identifying the genetic variants involved in the etiology of high blood pressure has been difficult. To identify genetic variants influencing high blood pressure among individuals of African origin, we conducted genome-wide association study of systolic and diastolic blood pressure in two separate samples of 735 African Americans and 900 Nigerians without history of use of high blood pressure medication at the time of study recruitment. Association analyses were performed without and with adjustment for sex, age and BMI in both samples, and included 857,989 and 792,581 SNPs genotyped on Affymetrix Genome-Wide SNP array 6.0 in the African-American and Nigerian samples, respectively. Some of the significant (P<1.0E-5) BP-associated variants in these Afro-origin populations are located on known genes such as SLC12A8 and TRERF1 while others are found in regions not yet annotated. Our results present evidence of significant association of BP with a number of genetic variants in regions across the human genome.

Poster 2128/W
Combined genomewide linkage and association study of ocular refraction in the Framingham Eye Study. *R. Wojciechowski[1], D. Stambolian[2], L. D. Atwood[3], J. E. Bailey-Wilson[1]* 1) IDRB, NHGRI, Baltimore, MD; 2) Ophthalmology & Genetics, Un of Pennsylvania, Philadelphia, PA; 3) Dept of Biostatistics, Boston University, Boston, MA.

Purpose: Refractive disorders are the most common causes of visual impairment worldwide. Previous studies have reported linkage of myopia or ocular refraction to a number of loci, but no genomewide association results have been published. We report results of genomewide linkage and association scans in Framingham Eye Study (FES) families. Methods: Eye exams were conducted on 2,540 FES participants in 293 families. We performed quantitative trait linkage and association analyses on ocular refraction, defined as the spherical equivalent refractive error. Genotypes were available for 1,240 individuals at ~113,000 SNP markers. Variance-components (VC) linkage analysis was performed with the Merlin package using a subset of ~18,000 SNPs. Family-based association statistics were estimated using FBAT and Merlin-assoc. FBAT was performed under additive genetic models for single SNPs and haplotypes using a 3-SNP sliding window. Results: VC linkage analyses yielded a peak LOD score of 4.16 (p=0.00001) at 124 cM on chr. 2q14.3. The strongest association in the FBAT haplotype analysis was found in the chr. 2 linkage region (p=0.0009 at ~80.96 Mb or 103 cM) . Merlin-assoc statistics yielded the strongest evidence of association with rs1049467 (p=8.2 x 10e-7; chr1q31.2, ~190Mb or 210 cM). There was suggestive evidence of linkage to that region (LOD=1.42, p=0.005 at 232cM). Conclusions: We found significant linkage of ocular refraction to a region on chr.2q. Though not genomewide significant after Bonferroni correction, association results are consistent with the presence of loci influencing ocular refraction on chromosomes 1 and 2. Nearby genes have not previously been reported as functional candidates for ocular phenotypes. Further investigation of these regions with a denser SNP map is warranted.

Poster 2130/W
Genome-wide association for insulin resistance and secretion in 542 genotyped and imputed individuals. *F. Xiang[1], L. J. Scott[1], Y. Li[1], A. U. Jackson[1], C. J. Willer[1], H. M. Stringham[1], M. R. Erdos[2], L. L. Bonnycastle[2], K. Kubalanza[2], A. J. Swift[2], G. R. Abecasis[1], K. L. Mohlke[3], J. Tuomilehto[4], R. N. Bergman[5], F. S. Collins[2], R. M. Watanabe[5], M. Boehnke[1]* 1) Biostatistics, U Michigan, Ann Arbor, MI; 2) NHGRI, Bethesda, MD; 3) Genetics, U North Carolina, Chapel Hill, NC; 4) Nat'l Public Health Inst., Helsinki, Finland; 5) Physiology and

Biophysics, Keck School of Medicine, U Southern Cal, Los Angeles, CA.

Understanding the genetic variation that underlies regulation of insulin secretion and resistance and glucose levels will enhance our understanding of glucose homeostasis and type II diabetes. Here, we seek to test for association of genetic variants with parameters from the frequently sampled intravenous glucose tolerance test (FSIGT): acute insulin response (AIR), disposition index (DI), insulin sensitivity (S_i), and glucose effectiveness (S_g). We analyzed FSIGT data on 542 normal glucose tolerant (NGT) individuals in 185 nuclear families from the FUSION study. Using genotypes for (a) >300,000 SNPs from the Illumina HumanHap300 BeadChip available on 240 of these individuals, and (b) genome scan/microsatellite data on all 542 of these individuals and additional family members, we imputed genotypes on ~2.1 million common autosomal SNPs in the 542 individuals. Imputation was in two stages. First, we imputed genotypes from SNPs from the HapMap CEU sample in the 240 FUSION GWA individuals. Second, we used the microsatellite genotypes to identify regions of IBD sharing between family members to support imputation of SNPs in the non-GWA individuals. We tested for trait-SNP association between normalized residuals of S_i, DI, AIR, and S_g after adjustment for sex, age, age^2, and birthplace under an additive model. Imputation more than doubled our available sample for association testing, resulting in substantially increased power compared to analysis of the GWA sample alone. Initial analysis revealed substantially strengthened evidence for association of AIR with variants upstream from a known T2D-predisposing locus. We currently are completing the analysis of all four traits genome-wide.

Topic: Statistical Genetics and Genetic Epidemiology
Exhibit Hall C   4:30PM-6:30PM

Poster 2303/W
Detection and Control of Bias in Genome-wide Association Studies: A Systematic Review. *T. Pearson[1, 2], T. Manolio[2]* 1) Community and Preventive Medicine, University of Rochester Medical Center, Rochester, NY; 2) Office of Population Genomics, NHGRI, NIH, Bethesda, MD.

The heterogeneity of results from gene association studies has several possible explanations, one of which is bias in subject selection and in collection of data on genotype and phenotype. To study the potential for bias and its control in genome-wide association studies (GWAS), we performed a systematic review of the first 109 GWAS entered into the NHGRI Online Catalog of GWAS (http://www.genome.gov/gwastudies). These studies examined 91 discrete disease traits and 40 quantitative traits; 71% had a case-control design. Assessment and control of potential genotyping errors included genotyping completion rates in 75% of studies; 80% performed tests to estimate genotyping error; 56% assayed multiple samples for quality control; and 76% used methods to control for population stratification. Information on phenotype definition and the selection of study subjects was less frequent, however. The method of definition of phenotype was provided in 67% by primary reports, 28% by online supplements, and not at all in 5%. Only 36% of discovery studies used population-based cases or controls. A minority of reports (33%) presented tables comparing cases and controls for potential confounding, and 3.7% tested differences for statistical significance. Only 21% of results were adjusted for baseline differences between cases and controls; analyses stratified by potential confounders in 24% of studies. Nonresponse rates could be assessed only in the 9.2% of reports which published participation rates; only

one report compared characteristics of study participants and nonparticipants. In conclusion, the literature pertaining to GWAS has emphasized quality control of genomic analysis and genotyping. The design, conduct, and presentation of GWAS has been less consistent in quality control of phenotype description and in the avoidance and control of potential biases of selection and description of study subjects.

Poster 2312/W
PhenX: Demographic Measures for Cross-study Analyses. *M. Cockburn[1], V. Bonham[2], O. Carter-Pokras[3], G. Gee[4], R. Kington[5], N. Lange[6], D. Makuc[7], P. Kraft[8], M. Phillips[9], R. Kwok[9], D. Maiese[9], D. Wagener[9], E. Ramos[2], C. M. Hamilton[9]* 1) Department of Preventive Medicine, USC, Los Angeles, CA; 2) NHGRI, Bethesda, MD; 3) University of Maryland, College Park, MD; 4) UCLA School of Public Health, Los Angeles, CA; 5) NIH, Bethesda, MD; 6) Schools of Medicine and Public Health, Harvard University, Belmont, MA; 7) National Center for Health Statistics, CDC, Hyattsville, MD; 8) Harvard School of Public Health, Boston, MA; 9) RTI International, RTP, NC.

The potential for cross-study comparisons in genome-wide association studies (GWAS) is severely restricted by the lack of standardized or comparable phenotypic and environmental measures. PhenX (consensus measures for Phenotypes and eXposures) is a consensus-building effort to choose high-priority phenotypic and environmental exposure measures which are of public health significance and suitable for GWAS. The goal of PhenX is to improve the ability of research groups to combine their data, thus increasing statistical power and the ability to detect genes associated with common complex diseases. The selected high-priority measures will be made available to the scientific community via the PhenX Toolkit. The PhenX Steering Committee selected Demographics as the first domain to be addressed by a Working Group (WG). The PhenX Demographics WG is composed of researchers whose expertise represents the wide breadth of the field. The selected demographics domain measures assess fifteen elements including: age; race; ethnicity; gender and ancestry. The Demographics WG recommended a set of measures and associated measurement protocols. Opinions on the proposed measures were sought from the research community through a web-based survey, the results of which were then used to define a small set of high priority measures. Measures were chosen on the basis of several criteria including: clearly defined; well established; broadly applicable; and a low burden to participants and investigators. The PhenX Steering Committee has identified 19 additional research domains to be addressed by PhenX Working Groups over the course of the three-year project. Supported by: NHGRI, Award No. 1U01 HG004597-01.

Poster 2314/W
PhenX: Consensus Measures to Facilitate Cross-Study Analysis for Genome-wide Association Studies. *C. M. Hamilton[1], E. Ramos[2], R. Kwok[1], D. Maiese[1], D. Wagener[1], W. R. Harlan[3], J. Haines[4]* 1) RTI International, Research Triangle Park, NC; 2) National Human Genome Research Institute, Bethesda, MD; 3) National Library of Medicine, Chevy Chase, MD; 4) Center for Human Genetics Research, Vanderbilt University, Nashville, TN.

   Genome-wide association studies (GWAS) measure hundreds of thousands of single nucleotide polymorphisms (SNPs) across the genome and relate them to common diseases and traits. Once an individual's genome has been comprehensively characterized, it can potentially be related to any trait, not just the trait that was initially investigated. Despite the vast potential of GWAS, opportunities for cross-study

comparisons have been severely restricted by the lack of standardized phenotypic and environmental measures, even though many risk factors (e.g., obesity, smoking, low socioeconomic status) are common to multiple diseases. PhenX (consensus measures for Phenotypes and eXposures) was initiated to enhance cross-study analyses of GWAS and other large-scale genomic research efforts. The PhenX Steering Committee has identified 20 high priority research domains. Over the course of the three year project, experts from across the scientific community will participate as members of Working Groups (WGs) to address these research domains. Each WG will propose a set of high-priority measures that will be vetted with the larger research community through web-based surveys. Ultimately, the PhenX Toolkit will make the selected measures available to the scientific community. The PhenX Toolkit will make it easy for researchers to incorporate the recommended measures in proposed or ongoing genome-wide studies. To date, five PhenX WGs are in progress: Demographics, Anthropometrics, Alcohol, Tobacco and Other Substances, Cardiovascular, and Diet and Nutrition. The input of the scientific community is needed to ensure that the measures included in the PhenX Toolkit will be widely accepted and readily incorporated into ongoing and future research efforts. Investigators are encouraged to find out more details about PhenX and to participate in the web-based surveys at www.PhenX.org. Supported by: NHGRI, Award No. 1U01 HG004597-01.

DAY III THURSDAY, NOVEMBER 13

Plenary and Platform Presentations

Concurrent Platform Session 15: Genomics I   Hall A
08:00AM-10:30AM

Platform Presentation 10
09:00AM-09:15AM
Sign, Sign, Everywhere a Sign: High Density Haplotype Maps of the Dog, Human, and Cow Genomes Reveal Extensive Human Reorganization of Domesticated Genomes. *C. D. Bustamante[1], R. K. Wayne[2], M. Nordborg[3], M. R. Nelson[4], M. Cargill[5], R. A. Gibbs[6], E. A. Ostrander[7]* 1) Cornell University, Ithaca, NY; 2) UCLA, Los Angeles, CA; 3) U. Southern California, Los Angeles, CA; 4) GlaxoSmithKline, Raleigh, NC; 5) Navigenics, Redwood, CA; 6) Baylor College of Medicine, Houston, TX; 7) NHGRI, NIH, Bethesda, MD.

We have developed multi-population high-density SNP and Haplotype maps of the bovine, human, and domestic dog genomes. These maps came about through three separate efforts: (1) the CanMap Project (1,000 dogs and wolves from 85 breeds genotyped across 127K SNPs), (2) the Bovine HapMap project (500 bulls on 25K SNPs from 25 breeds), and (3) the GSK-POPRES project (3,835 humans of diverse ethnic and geographic origin genotyped on Affy 500K human arrays). Using phased-resolved haplotype maps, we estimate local population recombination rate along each chromosome, identify key determinant of population substructure, and develop maps of recent directional selection for each species. By comparing the recombination maps of the three species, we find that humans show a very high correlation at the megabase scale in estimated population recombination rates across subpopulations; however, cows and domestic dogs show a striking lack of correlation across breeds. We also find that dogs and cattle show pervasive signatures of recent selection using SNP and haplotype-based statistics. Simulations suggest that, surprisingly, domestication bottlenecks do not explain these patterns. Strong bottlenecks at the time of breed formation coupled with popular sire effects, on the other hand, are necessary. We also find that all breeds examined demonstrate high degrees of cryptic relatedness, even when close relatives are avoided at the time of sampling. This implies that great care must be taken in interpreting nominal and genome-wide corrected p-values in whole genome association mapping within domesticated species. Comparison of various algorithms for WGAM in structured populations suggests mixed-model approaches as well as weighted permutation tests may effectively control for the induced background relatedness.

Platform Presentation 12
09:15AM-09:30AM
ClinSeq: A pilot for the development of high-throughput genomic sequencing as a tool for translational genomics. *L. Biesecker[1,2], F. Facio[1], J. Teer[1], R. Cannon[3], T. Finkel[3], A. Remaley[4], G. Bouffard[2], J. Mullikin[1,2], J. Shendure[5], E. Green[1,2], NISC Comparative Sequencing Group* 1) NHGRI, NIH, Bethesda, MD; 2) NISC, Rockville, MD; 3) NHLBI, NIH, Bethesda, MD; 4) NIH Clinical Center, Bethesda, MD; 5) Univ Washington, Seattle.

ClinSeq is a pilot to develop methods and approaches for whole-genome sequencing to be used in clinical research. We will study data generation, archiving, access and sharing, sequence variant detection, determination of pathogenicity, returning results to the subjects, and informed consent. The study will initially sequence about 400 genes relevant to atherosclerotic heart disease in 1,000 patients. When advances permit, the study will be expanded to the entire exome or genome. At submission, we have recruited more than 400 subjects and have generated more than 930,000 capillary sequencing reads of ~3,500 genomic target sequences, ~275 Mbp of bidirectional genomic sequence. The accuracy of the sequencing was measured using 9 HapMap DNA samples, showing a 4% discordance rate and 90% sensitivity over a sample set of 1,256 HapMap SNPs that overlap the ClinSeq gene list. An additional 1,138 novel variants, relative to dbSNP, were detected across 201 subjects. We detected pathogenic variants in known disease genes, including LDLR, APOB1, and others. Several of these were validated in a CLIA lab and returned to the subjects, with genetic and medical counseling. We are also developing molecular inversion probe capture target selection with solid phase sequencing. When compared to the PCR/capillary sequence data, for a variant called in any patient (~3,100-3,700 positions) genotypes were called at 42% of these positions, and 98% of the time, the calls agreed. These preliminary results demonstrate that high throughput sequencing can be applied to clinical research, that scientifically and clinically useful data can be derived from such a study, that the return of appropriate results is practical and ethically appropriate, and that it is feasible to consent clinical research subjects to a whole-genome sequencing study. The clinical research opportunities made possible by high-throughput clinical genomics will be discussed.

Platform Presentation 15
10:00AM-10:15AM
Diversity profile of the human skin microbiome in health and disease. *E. A. Grice[1], H. H. Kong[2], S. P. Conlan[1], A. C. Young[3], N. I. S. C. Comparative Sequencing Program[3], G. G. Bouffard[3,4], R. W. Blakesley[3,4], M. L. Turner[2], J. A. Segre[1]* 1) Genetics and Molecular Biology Branch, NHGRI, NIH, Bethesda, MD; 2) Dermatology Branch, Center for Cancer Research, NCI, NIH, Bethesda, MD; 3) NIH Intramural Sequencing Center, NHGRI, NIH, Bethesda, MD; 4) Genome Technology Branch, NHGRI, NIH, Bethesda, MD.

The concept that the human body is host to trillions of microbes is revolutionizing our view of the human genome while underscoring the role of the gene-environment interface in complex disorders. One such disorder, with a known genetic component, is the very common inflammatory skin disorder atopic dermatitis (AD; eczema) whose incidence has tripled in the past 30 years. The skin is not only the first line of defense against invasion, but also host to a diversity of microbes associated with human health and disease. To assess cutaneous bacterial diversity and abundance, we employ 16S rRNA gene phylotyping. Our previous analysis of the most commonly affected human site in AD, the antecubital fossae (inner elbow), demonstrated a unique skin core microbiome dominated by *Janthinobacteria* and *Pseudomonas* (both phylum *Proteobacteria*) with less representation from five other bacterial phyla. Skin provides an unprecedented opportunity to sample multiple sites from the same individual, many with underlying left-right symmetry. Skin sub-sites have unique environmental niches: moist/dry, haired/non-haired, acid/basic, sebaceous (oily)/non-sebaceous. Associated with these specific areas are stereotyped human disorders; e.g. psoriasis affects outer elbow and eczema affects the inner elbow. We are currently ascertaining a wide physiological range of skin

sub-sites from healthy humans to comprehensively survey the resident microbiota and address the fundamental question of whether there is a baseline cutaneous microbiome. This data is a foundation for our studies investigating alterations of skin microbiota in a disease state, specifically AD. Our long term goal is to elucidate the contribution of the cutaneous microbiome to complex skin disorders and translate this into novel pharmacological treatments.

Concurrent Platform Session 17: Ciliopathies Ballroom B
08:00AM-10:30AM

Platform Presentation 35
10:00AM-10:15AM
Congenital Hepatic Fibrosis: A common feature in various ciliopathies. *L. Lukose[1], T. Heller[3], M. Parisi[4], P. Choyke[5], K. Daryanani[6], B. Turkbey[7], J. Bryant[1], G. Golas[1], K. O'Brien[1], A. Garcia[1], D. Adams[1], L. Guay-Woodford[7], P. Mohan[8], W. A. Gahl[1,2], M. Gunay-Aygun[1,2]* 1) Medical Genetics Branch, NHGRI, NIH, Bethesda, MD; 2) Intramural Program of the Office of Rare Diseases, DHHS; 3) NIDDK, Bethesda, MD; 4) University of Washington, Seattle, WA; 5) Molecular Imaging Program, NCI, Bethesda, MD; 6) NIH Clinical Center, Bethesda, MD; 7) University of Alabama, Birmingham, Al; 8) CNMC, Washington, DC.

Congenital Hepatic Fibrosis (CHF) is a unique, genetically-determined liver pathology, caused by defective remodeling and branching of the developing biliary and portal system referred to as ductal plate malformation (DPM). Although CHF is commonly associated with autosomal recessive polycystic kidney disease (ARPKD), it can be part of many other ciliopathies including Joubert syndrome and related disorders (JSRD), Bardet-Biedl (BBS), Meckel-Gruber (MKS), oral-facial-digital (OFD) syndromes, and skeletal dysplasias caused by ciliary defects. Through our ongoing NIH trial on ciliopathies (ClinicalTrials.gov, number, NCT00068224), we evaluated 110 CHF patients (85 ARPKD/CHF, 5 ADPKD/CHF, 10 JSRD/CHF, 10 unknown type PKD/CHF) some followed prospectively for up to 5 years. In contrast to the findings in cirrhosis, liver synthetic function in CHF was intact and liver enzymes were largely normal. Portal hypertension (PH) resulting in splenomegaly and esophageal varices was the most common clinical problem. Decreased platelet count due to hypersplenism, correlated inversely with spleen volume, making this parameter a reliable indicator of the severity of PH. The severity of kidney and liver disease were independent of each other, since creatinine clearance did not correlate with spleen volume. A subset of JSRD patients had a variant form of CHF with elevated hepatocellular and biliary enzymes. Most CHF patients, especially those with ARPKD had intra- and extrahepatic gross biliary dilatations. Longer follow up and accurate molecular diagnostic classification of this cohort of CHF patients will allow us to better define the liver phenotype of ciliopathies.

Concurrent Platform Session 32: Cancer Genetics Room 103
02:00PM-04:30PM

Platform Presentation 113
03:30PM-03:45PM
Use of multiple ethnic groups to identify causal breast cancer risk variants in the *FGFR2* and *TNRC9* loci. *M. Udler[1,3], S. Ahmed[2], M. Maranian[2], K. Gregory[2], K. A. Pooley[2], J. Tyrer[2], P. D. Pharoah[2], J. P. Struewing[3], R. Luben[1], C. A. Haiman[4], A. Wu[4], H. Anton-Culver[5], C. Y. Shen[6], D. Kang[7], A. Lindblom[8], B. A. J. Ponder[9], K. Malone[10], E. A. Ostrander[3], A. M. Dunning[2], D. F. Easton[1]* 1) Dept of Public Health & Primary Care, Univ. of Cambridge, UK; 2) Dept of Oncology, Univ. of Cambridge, UK; 3) NHGRI/NIH, MD; 4) Dept of Preventive Medicine, Keck School of Medicine, USC, CA; 5) Dept of Epidemiology, Univ of California Irvine, CA; 6) Inst of Biomedical Sciences, Academia Sinica, Taiwan; 7) Seoul National Univ College of Medicine, Korea; 8) Karolinska Inst, Sweden; 9) CR-UK Cambridge Research Inst, UK; 10) Fred Hutchinson Cancer Research Ctr, WA.

Genome-wide association studies (GWAS) have identified new breast cancer (BC) loci. We utilized data from European, Asian and African American (AA) BC case-control studies to facilitate fine-mapping of the *FGFR2* and *TNRC9* gene regions. Associated LD blocks were resequenced in 45 European individuals, creating a catalogue of genetic variation (*FGFR2*: 25kb, 117 variants; *TNRC9*: 133kb, 175 variants). For each locus, SNPs highly correlated with the best tagSNP (rs2981582 in *FGFR2*, rs3803662 in *TNRC9*) were genotyped in BC cases and controls of European (n=14,000), Asian (n=7,000) and AA (n=2,500) ethnicity. Likelihood ratio tests (LRTs) were used to exclude SNPs with likelihoods > 100 times worse than the best candidate. For *FGFR2*, we identified 28 candidate SNPs. Based on the European data alone, 3 SNPs could be eliminated by LRT. Using the Asian and AA data allowed exclusion of a further 17. SNPs showed effects in the same direction in all 3 populations (P-heterogeneity >0.05). For *TNRC9*, we identified 24 candidate SNPs. Two were excluded using European data alone and 9 more using the Asian data. Candidate SNPs had effects in the opposite direction in AAs compared to Europeans and Asians. Haplotype analysis suggested there were 2 risk haplotypes in AAs, only 1 of which also conferred risk in Europeans and Asians. These results illustrate the importance of using diverse ethnic groups in fine-mapping studies to 1) eliminate candidate SNPs and 2) replicate GWAS hits as SNP alleles may affect risk differently in distinct populations.

Concurrent Platform Session 35: Neuropsychiatric and Neurodegenerative Disorders   Ballroom A
02:00PM-04:30PM

Platform Presentation 89
02:30PM-02:45PM
Mutations in the glucocerebrosidase gene confer a five fold increased risk of developing Parkinson disease: Results of an international multi-center collaborative study. *E. Sidransky, Multi-Center Collaborative Group Studying GBA Mutations in PD* MGB, NHGRI, NIH, Bethesda, MD.

Recent studies have demonstrated an increased frequency of mutations in the gene encoding glucocerebrosidase (GBA), the enzyme deficient in Gaucher disease, among different cohorts with parkinsonism. To better establish the frequency of GBA mutations in ethnically diverse subjects with Parkinson disease (PD), and to ascertain the relative risk of developing PD in GBA mutation carriers, we assembled an international multicenter collaborative group of investigators screening for mutations in this gene. As a first step, each group was provided with a uniform panel of DNA samples to determine which mutations could be detected by their center. Next, genotypes and phenotypic data on patients and matched controls were collected and assembled. The study included four centers from North America, two from South America, six from Europe, two from Israel and three from Asia, and included a total of 5749 patients (780 Ashkenazi Jews) and 4840 controls (399 Ashkenazi Jews). All participating centers demonstrated the

ability to detect GBA mutations L444P and N370S. These two mutations were found in a total of 287 patients (5.0%), including 119 Ashkenazi Jews (15.3%) and 168 non Ashkenazim (3.4%), and 42 controls (0.87%), including 15 Ashkenazi Jews (3.8%) and 27 non Ashkenazim (0.61%). Screening for a total of 7 mutations in the Ashkenazi Jewish group increased the mutation frequency to 19.7% in patients versus 4.5% in controls. Among the non-Ashkenazi Jewish subjects, sequencing of all GBA exons was performed in a total of 1794 patients and 1446 controls, yielding a mutation frequency of 7.1% and 1.6% respectively, indicating that screens for only the L444P and N370S mutations in non-Ashkenazi cohorts may miss as many as 50% of mutant GBA alleles. Phenotypic data is being compared between heterozygous GBA mutation carriers and patients with wildtype GBA alleles. Our data demonstrate that the relative risk of developing PD in GBA mutation carriers from diverse ethnicities is increased approximately five-fold, rendering it one of the most significant PD risk factors indentified to date.

Concurrent Platform Session 35: Evolutionary and Population Genomics   Room 204
02:00PM-04:30PM

Platform Presentation 142
03:15PM-03:30PM
Accelerated genetic drift on chromosome X during the human dispersal out of Africa. *A. Keinan[1,2], J. Mullikin[3], N. Patterson[2], D. Reich[1,2]* 1) Department of Genetics, Harvard Medical School, Boston, MA; 2) Broad Institute, Cambridge, MA; 3) National Human Genome Research Institute, NIH, Bethesda, MD.

Comparing genetic variation on chromosome X and the autosomes enables a multi-locus study of differences in the demographic histories of men and women. We have recently identified subsets of 150,000 SNPs from phase 2 of HapMap that are free of ascertainment bias and usable for learning about history (Keinan et al. Nature Genetics 2007). We have now extended these data to chromosome X, offering the first large-scale data set that allows accurate comparison of chromosome X and the autosomes. We also generated a complementary data set by aligning more than a billion bases of sequence from individuals of known ancestry and estimating the average time since genetic divergence. Three independent lines of evidence suggest that during the dispersal of modern humans out of Africa, chromosome X experienced much more genetic drift than is expected from the pattern on the autosomes: (1) Chromosome X exhibits unexpectedly high allele frequency differentiation between Africans and non-Africans, but not amongst non-Africans. (2) We observed many more SNPs of high derived allele frequency on chromosome X in non-Africans, but not in Africans, compared with what is expected from the autosomes. (3) We showed a reduction amongst non-Africans in the time since the most recent common ancestor for chromosome X loci compared with what is expected from the autosomes. All lines of evidence account for differences in effective population size and mutation rate between the two parts of the genome. The results cannot be explained by known episodes of human history or natural selection, and suggest that men participated more than women in the dispersal out of Africa. A parsimonious explanation is that after an initial founder population was formed by migration of both men and women, much of its gene pool was replaced by subsequent male migrants, from whom non-African populations inherit most of their diversity. These results have methodological implications for human population and medical genetic studies, where it is currently commonly assumed that chromosome X and the autosomes reflect the same history.

Poster Presentations

Topic: Clinical Genetics and Dysmorphology
Exhibit Hall C   4:30PM-6:30PM

Poster 467/T
Cystinosis: Novel Dental Findings Involving Enamel and Root Anomalies. *C. W. Bassim[1], D. L. Domingo[1], J. Z. Balog[2], JP. Guadagnini[1], W. A. Gahl[2], T. C. Hart[1]* 1) NIDCR, NIH, Bethesda, MD; 2) NHGRI, NIH, Bethesda, MD.

OBJECTIVE: Cystinosis is an autosomal recessive lysosomal storage disorder caused by loss-of-function mutations of the cystinosin gene (CTNS), leading to cellular damage from cystine accumulation. Clinical features include growth retardation, renal failure, and hypophosphatemic rickets. Oral manifestations remain poorly defined. This study characterized dental anomalies of enamel and root morphology, both derived from enamel epithelium, in cystinosis patients and unaffected controls. **METHODS:** Oral clinical and radiographic evaluations were performed on 44 nephropathic cystinosis patients (22 males, 22 females; mean age=17.2 ±1.0, range 10-41 years) and 93 healthy controls (36 males, 57 females, mean age=18.0 ±0.4, range=10-25 years). The Taurodontism Index (TI), measuring the size of the pulp chamber in multi-rooted teeth, was used to evaluate mature first and second molar pulp chamber size from radiographs. The Developmental Defects of Enamel (DDE) Index was used to determine the prevalence of enamel defects from clinical photographs of teeth, i.e., 104 maxillary incisors each from cystinosis patients and age- and gender- matched controls. **RESULTS:** All three classifications of taurodontism were significantly more prevalent in cystinosis patients than in controls, indicating increasing severities of pulpal enlargement. Hypotaurodontism was present in 71/252 molars (28%) vs. 114/652 molars (17%; p<0.0001); mesotaurodontism in 11/252 molars (4%) vs. 4/652 molars (1%; p<0.0001); and hypertaurodontism in 5/252 molars (2%) vs. 2/652 molars (0%; p=0.020). For every unit increase in TI Index, the odds of increasing pulpal enlargement being associated with cystinosis status increased by 8%, even when adjusted for age (OR=1.08, p<0.0001). Enamel defects (diffuse opacities or hypoplasia) were found in 42% (44/104 incisors) of the cystinosis group, significantly more than for controls (1/104 incisors, p<0.0001). **CONCLUSIONS:** Our findings indicate novel dental features in cystinosis. Cystinosis associated variations in tooth morphology may be part of the disease spectrum affecting mineralized tissues and may shed additional insight on this complex disease.

Poster 493/T
The mutational spectrum of BCOR: Candidate gene analysis of patients with oculofaciocardiodental and Lenz microphthalmia syndromes, mental retardation and ocular anomalies, and cardiac laterality defects. *S. Whalen[1], E. Hilton[2], J. Johnston[3], N. Okamoto[4], Y. Hatsukawa[4], L. Biesecker[3], I. Giurgea[1], G. Black[2]* 1) INSERM 654, Department of Genetics & APHP, Hospital Henri Mondor, Creteil, France; 2) Academic Unit of Medical Genetics, St Mary's Hospital, Manchester, UK; 3) Genetic Disease Research Branch, National Human Genome Research Institute, NIH, Bethesda, MD, USA; 4) Maternal and Child Health, Osaka Medical Centre and Research Institute, Osaka, Japan.

OFCD and Lenz microphthalmia syndromes form part of a spectrum of X-linked microphthalmia disorders characterised by ocular defects, dental anomalies, cardiac defects, digital and skeletal anomalies and mental retardation. The two syndromes are allelic and caused by mutations in the BCL-6 corepressor (BCOR). To extend the series of phenotypes associated with pathogenic mutations in BCOR, we have sequenced the BCOR gene in patients with 1) OFCD syndrome 2) putative X-linked ("Lenz") microphthalmia syndrome 3) isolated ocular defects and 4) laterality phenotypes. We present a new cohort of females with OFCD syndrome and null mutations in BCOR, supporting the hypothesis that BCOR is the sole molecular cause of this syndrome. The identification of a BCOR mutation in a female with ocular defects in the absence of a classic OFCD syndrome phenotype demonstrates the phenotypic variation observed in this syndrome and suggests that OFCD syndrome may be underdiagnosed. We have sequenced a cohort of males diagnosed with putative X-linked ("Lenz") microphthalmia and found a mutation in a single case, suggesting that BCOR mutations are not a major cause of X-linked microphthalmia in males. The absence of BCOR mutations in a panel of patients with non-specific laterality defects suggests that mutations in this gene are not a major cause of isolated heart and laterality defects. Analysis of the phenotypes associated with OFCD and Lenz microphthalmia syndromes shows that in addition to the standard diagnostic criteria of congenital cataract, microphthalmia and radiculomegaly, patients should be examined for skeletal defects, particularly radioulnar synostosis and cardiac/laterality defects.

Topic: Therapy for Genetic Disorders
Exhibit Hall C   4:30PM-6:30PM

Poster 780/T
N-Acetylmannosamine for the Treatment of Muscle and Kidney Disease: From Mouse to Bedside. *I. Manoli[1,2], E. Klootwijk[1], S. Sparks[1], M. Ziats[1], D. Hickey[1], C. Ciccone[1], P. Zerfas[3], M. Starost[3], D. Darvish[4], D. Krasnewich[1], W. Gahl[1], M. Huizing[1]* 1) Section on Human Biochemical Genetics, MGB, NHGRI, NIH; 2) Intramural Program of the Office of Rare Diseases, NIH; 3) Division of Veterinary Resources, NIH, Bethesda, MD; 4) HIBM Research Group, Encino, Ca.

Hereditary Inclusion Body Myopathy (HIBM) is an adult onset, autosomal recessive neuromuscular disorder characterized by progressive muscle weakness resulting in severe incapacitation within 10 to 20 years. The causative gene, GNE, codes for the enzyme UDP N-acetylglucosamine 2-epimerase/N-acetylmannosamine kinase (GNE/MNK), which catalyzes the first 2 steps in sialic acid (SA) synthesis. Paucity of SA presumably causes decreased sialylation of muscle glycoproteins, resulting in muscle degeneration. N-Acetyl-mannosamine (ManNAc), an uncharged sugar, can readily enter cells and serve as a precursor for SA synthesis, not subject to feedback inhibition. We previously administered sialic acid to 4 HIBM patients via intravenous immune globulin (which contains 8 µmol of sialic acid/g), achieving improved muscle strength and function. We also created knock-in mice harboring the M712T Gne/Mnk founder mutation. Homozygous mutant mice did not survive beyond postnatal day 3 (P3) due to glomerular hematuria, proteinuria, and podocytopathy. Administration of ManNAc yielded survival beyond P3 in 43% of the homozygous pups. Survivors exhibited improved renal histology, increased sialylation of podocalyxin, and increased Gne-epimerase activities. Based on these findings, we now describe a phase I/II, randomized, placebo-controlled, two period cross-over study to determine the safety and efficacy of ManNAc therapy in HIBM. The primary outcome parameter will

be change in quadriceps muscle strength. This protocol has assumed increased relevance because our mouse model survivors have developed muscular tubular aggregates and vacuoles at 8-11 months. Our ManNAc trial is also pertinent to renal disorders such as minimal change nephrosis. We will discuss the Rapid Access to Interventional Development Program and the difficulty of performing pre-clinical studies for drugs not approved by the FDA.

Poster 781/T
Hermansky-Pudlak Syndrome (HPS) as a genetic model for Idiopathic Pulmonary Fibrosis (IPF): The role of MUC1 in pulmonary fibrosis. *T. Markello[1], B. Pederson[1], M. Anahtar[1], G. Srivastava[1], K. O'Brien[2], B. Gocchicco[1], W. Gahl[1]* 1) Section on Human Biochemical Genetics, Medical Genetics Branch NHGRI, Bethesda, MD; 2) Intramural Program of the Office of Rare Diseases, OD, NIH, Bethesda MD.

The 8 subtypes of HPS include occulocutaneous albinism and a platelet bleeding disorder. Genetic subtypes 1 and 4 also exhibit fatal pulmonary fibrosis (PF), making them models for the interstitial lung disease, IPF. MUC1, a membrane glycoprotein associated with invasive epithelial cancers and interstitial lung diseases, is a component of regenerating type II pneumocytes. These cells have lamellar bodies which are lysosome-like organelles resembling those affected in HPS. We propose that MUC1 is mislocalized in HPS type II pneumocytes. Indeed, using blood from HPS patients archived over the past 15 years, we see a strong correlation between MUC1 serum levels (up to 20 times the upper limit of normal) and degree of fibrosis (decline in pulmonary function) among 100 HPS individuals. No overlap is seen between normal and HPS (with fibrosis). Normal blood level of MUC1(mean)= 120U/ml (range 109-150,n=8). HPS patients without PF = 250U/ml(60-572,n=46). HPS patients with moderate PF = 590U/ml(299-2079,n=33). HPS patients with severe PF = 2141U/ml(743-10165,n=21). We demonstrated that sustained elevation of serum MUC1 in 21 HPS patients predicted present or future pulmonary fibrosis and was correlated with disease progression. A previous and current therapeutic trial of HPS fibrosis investigated pirfenidone, a TGF-beta inhibitor that functions through the SMAD signaling pathway. One HPS patient receiving pirfenidone had 3 episodes of MUC1 elevation over 10 years of treatment, but always returned to normal, presumably because of pirfenidone's inhibition of SMAD signaling. This patient exhibited no lung disease progression over those 10 years, a remarkable finding. We conclude that: 1) MUC1 serves as a biomarker for disease prediction and as an outcome parameter for therapy. 2) Pirfenidone dampens the fibrotic effects of TGF-beta stimulation and reduces the amount of MUC1 produced in the interstitium. 3) HPS serves as a genetically homogeneous model in which to study the therapy of pulmonary fibrosis.

Topic: Genomics
Exhibit Hall C   4:30PM-6:30PM

Poster 908/T
Cis-regulatory elements in the Epidermal Differentiation Complex (EDC): Towards understanding atopic dermatitis and psoriasis. *C. de Guzman Strong[1], K. Sears[2], J. Segre[1]* 1) National Human Genome Research Institute, Bethesda, MD; 2) University of Illinois at Urbana-Champaign, Urbana, IL.

The Epidermal Differentiation Complex (EDC) locus (1q21) harbors a set of genes that are specifically expressed upon epidermal differentiation and barrier formation. Atopic dermatitis (AD) and psoriasis are common skin inflammatory disorders that both share independent linkage to the EDC

suggesting a role for these genes in disease etiology. Recently, mutations in filaggrin (FLG) in the EDC are strongly linked to familial ichthyosis vulgaris and are highly associated with cases of AD that often advance to asthma (atopic march). AD familial studies excluding FLG continue to demonstrate EDC linkage suggesting additional genetic variants within the EDC in AD pathogenesis. The proximity and density of genes in the EDC suggest coordinate regulation via cis-regulatory elements for temporal and spatial epidermal expression. We hypothesize that evolutionarily conserved noncoding sequences (CNS) function as cis-regulatory elements to coordinate transcriptional regulation of the EDC genes. A genomics approach using comparative multi-species sequence analysis (MultiPip) of the EDC loci from human, chimpanzee, rhesus, mouse, rat, dog, and opossum genomes has identified 43 CNS as potential regulatory elements. The use of the opossum genome as a stringent criterion in annotating CNS in the EDC has been confirmed based on the evolutionary conservation of dorsal to ventral patterning of epidermal barrier acquisition in the opossum. Our functional analysis of the CNS using dual luciferase reporter assays in differentiating keratinocytes has identified either enhancer or repressor activity in roughly 50% of the CNS. We are currently correlating our findings with Genetic Association Information Network (GAIN) psoriasis studies. Taken together, our results suggest a high proportion of regulatory activity in the CNS that may coordinate expression of the genes in the EDC and could pose as genetic variants contributing to either AD or psoriasis.

Poster 930/T
Development and evaluation of new mask protocols for gene expression profiling in humans and chimpanzees. *D. Toleno[1], G. Renaud[2], T. Wolfsberg[2], K. Siegmund[3], J. Hacia[1]* 1) Department of Biochemistry and Molecular Biology, University of Southern California, Los Angeles, CA, USA; 2) National Human Genome Research Institute, National Institutes of Health, Bethesda, Maryland, USA; 3) Department of Preventive Medicine, University of Southern California, Los Angeles, CA, USA.

wGene expression oligonucleotide microarrays are typically designed to detect the abundance of specific transcripts based on a reference genome sequence. Consequently, sequence differences between the arrayed oligonucleotide probes and transcriptome under consideration can lead to spurious estimates of transcript abundance. Here, we developed new methods for probe masking based on the most recent releases of human and chimpanzee genome sequences. Using publicly available tools from Bioconductor, data from probes predicted to have poor hybridization sensitivity and specificity to human and/or chimpanzee transcriptomes are discarded, followed by the removal of data from probe tilings with limited numbers of remaining probes. We investigated the effects of varying probe number on estimation of gene expression scores from five tissues derived from six humans and five chimpanzees. We consistently found that probe sampling has a significant effect on the variation of gene expression scores across samples, with fewer sampled probes resulting in more apparent expression variation for a probe tiling. The effect of probe number is greater when probe tilings have less than six probes remaining relative to the effect observed for gene expression estimated from between six probes and the full complement of eleven probes. Based on replicate probe sampling analyses, we found that the false positive and false negative rates for identifying cross-species gene expression difference increase with decreasing probe number. Overall, we provide a new resource for the analysis of human and chimpanzee transcriptomes and novel guidelines for probe masking.

Poster 1288/T
Isolating genetic causes of familial lung cancer. *C. I. Amos[1], J. E. Bailey-Wilson[2], S. M. Pinney[3], A. G. Schwartz[4], M. You[5], P. Yang[6], G. Gaba[7], D. Mandal[8], P. Fain[9], Y. Li[1], J. Minna[10], E. Kupert[3], M. deAndrade[6], M. W. Anderson[3]* 1) Dept Epidemiology, MD Anderson Cancer Ctr, Houston, TX; 2) National Human Genome Research Institute; 3) University of Cincinnati, Cincinnati; 4) Karmanos Cancer Institute, Detroit; 5) Washington University, St. Louis; 6) Mayo Clinic College of Medicine, Rochester, MN; 7) Medical College of Ohio, Toledo; 8) Louisiana State University Health Sciences Center, New Orleans; 9) University of Colorado, Denver; 10) U.T. Southwestern Medical Center, Dallas.

Individuals with a first degree relative with lung cancer are at approximately a 2.5 fold higher risk for lung cancer compared with population rates that allow for smoking behaviors. We previously identified in 2004 by linkage analysis a region of chromosome 6q that harbors a susceptibility locus for lung cancer using data from 52 families with at least three relatives who had lung cancer. Previously we found that families with 5 or more affected relatives showed the strongest evidence for linkage, yielding a heterogeneity LOD (HLOD) score of 4.26. Our current studies expand to 92 the number of families that we have studied to identify a strongly familial cause for lung cancer, and increase the time of observation and number of cases with lung cancer. Evidence for a lung cancer susceptibility locus on chromosome 6q is strongly supported in families that include 5 or more affected relatives in 2 or more generations, yielding an HLOD score of 4.57 at 158 cM. Genetic linkage analysis of other chromosomes provided weaker evidence for linkage. Evidence for linkage is also provided in these families to chromosomes 6p (HLOD score of 1.72 at 63 cM), 4p (HLOD score of 1.3at 4cM) and chromosome 12 (HLOD score of 0.97 at 146 cM). Further analyses of the risk for lung cancer from the chromosome 6q locus show a dramatic increase in risk among carriers who smoke any amount, compared with nonsmokers. These results strongly support evidence for at least one locus on chromosome 6q that greatly increases risk for lung cancer particulary in response to smoking, and suggest that additional loci contribute to lung cancer risk.

Poster 1398/T
Mouse Mutants as Models for Human Developmental Malformations: The *Extra-Toes Spotting (Xs)* Mouse. *D. Gildea[1,2], S. Loftus[1], Y. Yang[1], W. Pavan[1], L. Biesecker[1]* 1) GDRB, NIH/NHGRI, Bethesda, MD; 2) Genetics, GWU, Washington, DC.

Greig cephalopolysyndactyly syndrome (GCPS) is a malformation syndrome that includes limb anomalies, specifically polydactyly and syndactyly. GCPS is caused by mutations in *Glioma-associated oncogene-3 (GLI3)*, which is part of Sonic hedgehog (SHH) signaling. The GLI3/SHH pathway regulates many developmental processes, including limb patterning. Dysregulation of this pathway due to mutations in *GLI3* can result in limb malformation. The Extra-toes (*Gli3[Xt]*) mouse is an animal model for GCPS. Like the human

phenotype, $Gli3^{Xt}$ mice exhibit preaxial polydactyly. Another mouse, Extra-toes spotting (Xs), shares a similar phenotype with $Gli3^{Xt}$. Xs mice exhibit preaxial polydactyly, coat hypopigmentation, limb length asymmetry, and microphthalmia. Previous mapping excluded mouse $Gli3$ as the gene mutated in Xs^J (Jackson allele) mice, and the gene and Xs^J mutation remain unknown. To identify the gene, we are performing recombination mapping in Xs^J mice. We maintain our Xs^J mice on a B6C3FeF1/J background, where penetrance of the phenotype is 82%. For mapping, it was necessary to outbreed Xs^J mice to castaneus mice to introduce a distinct chromosomal background, as we encountered substantial homozygosity in the candidate interval. Offspring from this outcross do not exhibit the Xs^J phenotype. When breeding offspring from the castaneus outcross to B6C3FeF1/J mice, we experienced a penetrance of 39%. These data show variable penetrance of the Xs^J phenotype that is dependent upon mouse genetic background. Here we present our genetic analysis, phenotypic characterization, mapping data, and developmental analysis of the Xs^J animal. We mapped the Xs^J locus to a 322 kb region on mouse chromosome 7 and are evaluating candidate genes. Since the $Gli3^{Xt}$ and Xs phenotypes overlap, we hypothesize that the gene mutated in Xs^J mice is a gene in the Gli3/Shh pathway. To test this hypothesis, we used *in situ* hybridization to evaluate in Xs^J embryos the expression of genes in the Shh/Gli3 pathway. Data show misexpression of Shh members in Xs^J embryos, suggesting that the gene mutated in Xs^J mice is in the Shh pathway.

Topic: Molecular Basis of Mendelian Disorders
Exhibit Hall C   4:30PM-6:30PM

Poster 1509/T
Clinical and functional studies in subjects carrying glucocerebrosidase (GBA) mutations. *J. Davis[1], K. Berman[2], G. Lopez[3], TL. Urban[1,4], E. Sidransky[1], O. Goker-Alpan[1]* 1) MGB/NHGRI/NIH, Bethesda, MD; 2) NIMH/NIH, Bethesda, MD; 3) NINDS/NIH, Bethesda, MD; 4) UPENN School of Nursing, PA.

Multiple studies indicate that GBA mutations are a risk factor for parkinsonism. A prospective study was designed and initiated to identify and objectively characterize the early parkinsonian manifestations and the rate of progression of symptoms in affected and "at risk" individuals carrying GBA mutations. All subjects undergo neurological, neurocognitive evaluations and olfactory testing. Presynaptic dopaminergic function and cerebral blood flow are assessed with F-18-L-DOPA and 15 O-H2O PET scans. Transcranial ultrasonography is explored as a noninvasive tool to evaluate hyperechogenicity of the substantia nigra. The subjects include patients with Gaucher disease and Gaucher carriers with parkinsonism, and/or with a family history of a first degree relative with parkinsonism. The genotypes identified are N370S, L444P, c.84dupG and recombinant alleles. Among 21 subjects recruited to the study, there are 10 patients with parkinsonism and two discordant sib-pairs with Gaucher disease where only one has parkinsonism. In subjects with parkinsonism(7M: 3F), the mean age of onset was 49 years, disease duration was 8 years, and UPDRS III score was 26. Six subjects were given the diagnosis of classic Parkinson disease (PD). Half of the patients reported cognitive changes later in their disease course. Three subjects were considered to have Lewy body dementia (LBD), and one "parkinson plus" syndrome. The most frequent non-motor finding was olfactory dysfunction. Thus, GBA mutations, in both homozygotes and heterozygotes, are associated with a spectrum of parkinsonian phenotypes ranging from classic PD, to a less common

phenotype characteristic of LBD. The results of the clinical and functional imaging studies will enable us to estimate the frequency and earliest onset symptoms in at-risk subjects, better define the associated parkinsonian phenotype, follow the progression of manifestations and identify "at-risk" individuals. This study will also help us to identify whether specific abnormalities in L-Dopa metabolism occur in subjects with GBA mutations.

Topic: Mapping, Linkage and Linkage Disequilibrium
Exhibit Hall C   4:30PM-6:30PM

Poster 1637/T
Model-independent linkage analysis and tests of association for familial idiopathic scoliosis and a candidate region on chromosome 6. *C. Justice[1], N. H. Miller[2], B. Marosy[3], D. Behneman[1], A. F. Wilson[1]* 1) Genometrics Section, IDRB, National Human Genome Research Institute, NIH, Baltimore, MD; 2) University of Colorado, The Children's Hospital, Denver; 3) Institute of Genetic Medicine, Johns Hopkins University School of Medicine, Baltimore, MD.

Familial idiopathic scoliosis (FIS) is a lateral curvature of the spine present in the late juvenile or adolescent period in otherwise normal individuals. It affects 2-3% of the pediatric population, and 0.2-0.5% of the population require active treatment. Idiopathic scoliosis is believed to be a complex genetic disorder in which expression of the disease state may depend on several genetic and possibly environmental factors. Previous studies have suggested autosomal dominant, X-linked and multifactorial modes of inheritance. As part of a large collaborative study of FIS, 202 families with at least two individuals with a lateral curvature greater than or equal to 10 degrees were ascertained and clinically characterized. A genomic-wide screen identified candidate regions on chromosomes 6, 9, 16 and 17 [Miller et al. 2005]. The candidate region on chromosome 6 was genotyped with SNPs using the Illumina platform. SNP marker density was ~ 58 Kb, with 537 SNPs genotyped on 6q13-q21. FIS was analyzed both as a quantitative and a qualitative trait, in which the curvature determining the threshold for affectation status was set at values of 10 and 30 degrees. Model independent sib-pair linkage analysis was performed with SIBPAL [S.A.G.E., v5.0, Case Western Reserve University, Cleveland, OH]. Tests of association were performed with FBAT [Rabinowitz and Laird 2000; Laird, Horvath, and Xu 2000; Horvath et al. 2004] for FIS as a qualitative trait and with ASSOC [S.A.G.E., v5.0] for FIS as a quantitative trait. Haplotypes of two, three and four SNPs were also tested for association with FBAT. The most significant results for the linkage analysis were obtained when the affectation status was set at 10 degrees or greater, with p-values < 0.05 in a region spanning from 74 to 80 Mb. Association analyses for the whole sample resulted in several significant p-values.

Poster 1657/T
Mapping genetic susceptibility loci of hypocholesterolemic autism using nonparametric multipoint linkage analyses. *E. Tierney[1], Y. Kim[2], K. Weissbecker-Remer[3], F. D. Porter[4], J. E. Bailey-Wilson[2]* 1) Kennedy Krieger Institute, Baltimore, MD; 2) National Human Genome Research Institute, NIH, Baltimore, MD; 3) Tulane University, New Orleans, LA; 4) National Institute of Child Health and Human Development, NIH, Bethesda, MD.

Different loci have been identified as potential susceptibility genes for autism spectrum disorder (ASD) in previous genome-

wide screens of multiplex families. To search for genes related to ASD, linkage analyses and association studies have been performed. Based on the previous finding that some individuals who had 1 or more family members with ASD were found to have low cholesterol levels, we hypothesized that either autism or other ASD subjects with hypocholesterolemia may have different genetic susceptibility loci. We obtained microsatellite genotype data for 390 loci on families with at least 2 children with ASD and hypocholesterolemia who donated blood to the Autism Genetic Resource Exchange. To analyze hypocholesterolemic probands, we defined 2 family groups: 1) cholesterol levels greater than 2 SD (standard deviation) below the mean (47 families; below-2SD), and 2) less than 100 mg/dl (28 families; below-100). In each group we analyzed different subsets depending on disease diagnosis: 1) both sibs had autism or 2) one or more sib had "Not Quite Autism" or "Broad Spectrum" using nonparametric multipoint linkage method. Additional analyses were performed on groups of male-only sibs and female-containing sibships in each subset. In the below-2SD autism families, D10S1412 at 10p14 shows nominal significance (P value of NPL score 0.005, Kong & Cox LOD=2.02); this is near a site for DiGeorge syndrome/velocardiofacial syndrome, a disorder associated with ASD, and a site of terminal deletion associated with ASD. Female containing sib pairs in below-100 autism families had nominally significant linkage at markers D5S822 (p value= 0.005, Kong & Cox LOD=1.37) and D5S1969 (p value= 0.002, Kong & Cox LOD=1.5) at 5q11.1-11.2. We cannot conclude that these loci have suggestive linkage evidence for sib pair analysis. However, they suggest that further analyses with more samples of hypocholesterolemic ASD families are needed.

Topic: Psychiatric Genetics, Neurogenetics and Neurodegeneration
Exhibit Hall C   4:30PM-6:30PM

Poster 1793/T
Effects of glucocerebrosidase (GBA) mutations on proteolytic pathways: The role of autophagy-lysosome and ubiquitin-proteosome systems in GBA-associated parkinsonism. *O. Goker-Alpan, T. Samaddar, BK. Stubblefield, E. Sidransky* MGB/NHGRI, NIH, Bethesda, MD.

Parkinson disease (PD) and other related disorders are caused by deposition of aggregated proteins and/or the failure to clear aggregates leading to neuronal degeneration. The ubiquitin-proteosome system (UPS) and autophagy-lysosome pathway (ALP) are two pathways that remove abnormal proteins. Mutations in genes causing rare familial PD cases implicate UPS dysfunction. Autophagy is the major pathway for the degradation of aggregated proteins, and α-synuclein was shown to be cleared by ALP. However, there is not yet a specific gene linking PD to ALP. Recent studies indicate an association between glucocerebrosidase (GC), the lysosomal enzyme deficient in Gaucher disease, and PD and dementia with LBs (DLB). To examine in vivo effects of mutant GC on the pathways implicated in α-synuclein clearance, brain samples from subjects with PD or DLB were examined. In samples from subjects with GBA mutations, immunofluorescence studies demonstrated that GC was present in most α-synuclein-positive inclusions. In some LBs, GC was present at the core, where aggregates destined for UPS removal often localize. Only 40-60 % of GC-positive LBs were ubiquinated, although all displayed antigenicity against lysosome markers. The effect of glucocerebrosidase on two preoteolytic pathways was examined in a cell-model system over-expressing hA53T-synuclein and wild-type or mutant GBA. UPS function was explored using the small degron CL-1, which demonstrated no

influence of either wild-type or mutant GBA on proteosome. The evaluation of ALP function by different methods including following the levels and distribution of the autophagic marker LC3, suggested defective autophagy in cell lines transfected with mutant GBA. GBA mutations may contribute to neurodegeneration by interfering with lysosomal clearance of α-synuclein, and lead to PD/DLB pathology.

Topic: Cardiovascular Genetics
Exhibit Hall C   4:30PM-6:30PM

Poster 1979/T
Clinical Assessment of Sequence Variants in the ClinSeq Large Scale Medical Sequencing Project. *C. Turner[1], P. Cherukuri[1], F. Facio[1], J. Teer[1], R. Cannon[2], R. Shamburek[2], J. Mullikin[1], E. Green[1], L. Biesecker[1], NISC Comparative Sequencing Program* 1) National Human Genome Research Institute, Bethesda, MD; 2) National Heart Lung and Blood Institute, Bethesda, MD.

Individualized genomic medicine promises to revolutionize the practice of medicine, though the interpretation of the vast amounts of data will be challenging. As part of the ClinSeq large scale medical sequencing project, we have sequenced 142 genes in 201 participants. A subset of three genes (LDLR, APOB and PCSK9) associated with Familial Hypercholesterolemia (FH) was used as a model for assessing pathogenicity of variants. There were 72 amplicons sequenced across these genes for the 201 participants that provided 18.1 Mbps of sequence. Comparison of these data to reference sequence identified 17 unique variants in LDLR, 62 in APOB and ten in PCSK9. To identify variants causing high-penetrance phenotypes we stratified variants as likely to be pathogenic, unlikely to be pathogenic, or uncertain. Likely pathogenic variants were nonsense, frameshift, splice (GT/AG), and those reported as causative. Unlikely pathogenic variants were common (MAF >2%) and synonymous. Uncertain variants were rare missense variants. One LDLR variant, p.Y188X, has been reported as causative for FH. Nine LDLR variants were synonymous, as were 20 in APOB and three in PCSK9. For the remaining nonsynonymous variants, we developed a position-specific amino acid substitution score reflecting the change and the conservation. Of the missense variants, six in LDLR, 19 in APOB and four in PCSK9 were not found in dbSNP. The literature suggests the p.P685L LDLR variant and the p.R3527Q APOB variant are causative. No causative variants were found in PCSK9. Analysis of the clinical data for the patients with mutations causing FH revealed markedly elevated LDL and severe atherosclerosis. These FH-causing variants were confirmed in a CLIA laboratory, and the results were returned to the participants and diagnosis and treatment for their families was instituted. These bioinformatic methods are being automated to analyze the variants in the other genes that will be sequenced in this project.

Topic: Complex Traits and Polygenic Disorders
Exhibit Hall C   4:30PM-6:30PM

Poster 2169/T
Assessing regulatory potential and functional consequences of Type 2 diabetes-associated variants on 9p21. *M. L. Stitzel[1], P. Deodhar[1], L. J. Scott[2], A. U. Jackson[2], N. Narisu[1], A. Swift[1], M. Boehnke[2], F. S. Collins[1]* 1) Genome Technology Branch, NHGRI/NIH, Bethesda, MD; 2) Dept. Biostatistics and Center for Statistical Genetics, University of Michigan, Ann Arbor, MI.

Variants within a 9.5 kb linkage disequilibrium block on chromosome 9p21, ~125 kb upstream of the heavily studied genes *CDKN2A/2B*, have been associated with type 2 diabetes (T2D) and decreased beta cell function in multiple studies and populations. Another gene on the opposite strand, *ANRIL*, is also a potential candidate for driving the T2D association, but its noncoding RNA is much less well characterized. Independent studies in mouse indicate that overexpression of *CDKN2A* (p16) inhibits beta cell proliferation. Taken together, these observations suggest the following hypothesis: (1) the associated region in humans harbors regulatory elements, (2) these elements regulate *CDKN2A*, and (3) the causal variant(s) increase expression in islets. We have cloned the entire T2D-associated LD block, as well as two smaller evolutionarily constrained sequences residing within this block, from risk and non-risk haplotypes present at $\geq$ 5% frequency in FUSION samples and tested them for enhancer activity in a minimal promoter luciferase assay in both beta cell-like (INS-1E) and non-beta cell (HeLa) lines. In preliminary experiments, we have observed a decrease in luciferase activity with these sequences. We are testing these elements for silencer activity and for specific enhancer/silencer activity of the *CDKN2A* promoter and cloning additional haplotypes present at a frequency of $\geq$ ~1% for testing. In addition, we are analyzing effects of the risk-associated variants on allele-specific and overall expression levels of *CDKN2A/B* and the putative noncoding transcript *ANRIL* in fibroblasts, peripheral blood lymphocytes, monocytes, adipose, and pancreatic islets. Though challenging, we expect these studies of allele-specific gene regulation in 9p21 will reveal possible mechanisms for T2D susceptibility.

Topic: Statistical Genetics and Genetic Epidemiology
Exhibit Hall C   4:30PM-6:30PM

Poster 2365/T
Multiple source genetic heterogeneity and population- and intra-familial tests of association for quantitative traits. *Y. Kim, A. J. M. Sorant, A. F. Wilson* Genometrics Section, IDRB, NHGRI, NIH, Baltimore, MD.

The presence of undetected genetic heterogeneity produces a loss of power in association studies. In this study, computer simulation was used to determine the effect of genetic heterogeneity due to multiple sources on tests of association between a quantitative trait and a causal SNP in both population and intra-familial study designs (unrelated individuals, and nuclear and extended families). G.A.S.P. [v3.3] was used to simulate a single quantitative trait in 3 sub-populations. In the "association" subpopulations (populations 1 and 2), the trait was based on a different SNP marker in each subpopulation; in the "non-association" subpopulation (population 3), the trait was due to a random effect. The heritability of the trait in the combined sample was fixed to be 0.05, and the subpopulation with the causal SNP (population 1) had a constant heritability of 0.025. In each simulation experiment, different proportions (100%, 50%, 30%, and 10%) from the "association" subpopulations (half from population 1 and half from population 2) were combined with the "non-association" subpopulation to produce samples with various degrees of genetic heterogeneity. ANOVA [SAS] was used to test for association in population-based tests of unrelated individuals. ASSOC [S.A.G.E.], FBAT and ROMP were used to perform intra-familial tests. The proportion of samples with a significant result was used to estimate the power at the causal SNP. Of the models considered, the power of the test of association, regardless of the method used, decreased dramatically as the proportion of the "non-association" subpopulation increased. The intra-familial ASSOC analysis

had the greatest power in each scenario, followed by the population-based test, and then the intra-familial based ROMP and FBAT tests. In general, it appears that the presence of even a modest amount of genetic heterogeneity within a sample, regardless of the source, can cause a substantial loss of power to detect an association. Of the methods considered, the likelihood based intra-familial ASSOC test was the most robust to the presence of genetic heterogeneity.

Poster 2412/T
Rank correlations among results of intra-familial tests of association for quantitative traits with low heritabilities. *H. Sung[1], J. E. Herrera-Galeano[1,2], A. J. M. Sorant[1], R. A. Mathias[1], A. F. Wilson[1]* 1) Genometric section, IDRB, NHGRI, NIH, Baltimore, MD; 2) Dept. of Medicine, Johns Hopkins Medical Institution, Baltimore, MD.

Several different methods are now available for testing for associations between quantitative traits and SNPs in family data. These methods use different kinds of information and have different strengths and weaknesses with respect to their statistical properties. In a study of platelet aggregation, Herrera-Galeano et al. [ASHG, 2007] used several different association methods and found little correlation between results. Computer simulation was used to investigate the lack of agreement among methods. Genetic Analysis Simulation Program (G.A.S.P. v3.3) was used to generate 10,000 samples, each with 200 nuclear families with sibship size three. A quantitative trait was simulated based on a single biallelic locus with equally frequent alleles. The underlying genetic model was additive and heritabilities considered included 0, 0.001, 0.005, 0.01, 0.05 and 0.1. The data availability was modeled as complete or 50% missing. Five tests of association were performed: ASSOC (SAGE), FBAT, GEE (SAS GENMOD), ROMP (Regression on Mid-Parent) and ROOP (Regression on One Parent). Pair-wise Pearson correlations of resulting p-values and pair-wise Spearman correlation using ranks of p-values were calculated. In general, pair-wise Spearman rank correlations have higher correlation than Pearson correlation. For example, with complete data and heritability equal to 0.01, Pearson correlation was as low as 0.03 (FBAT and GEE) but Spearman rank correlations were generally over 0.5. However, in general, different association tests did not agree well even in rank, except for ASSOC and GEE.

Topic: Evolutionary and Population Genetics
Exhibit Hall C   4:30PM-6:30PM

Poster 2569/T
High Carrier Frequency of Founder Mutation Causing Severe/Lethal Recessive Type VIII Osteogenesis Imperfecta in West Africans and African-Americans. *W. A. Cabral[1], A. M. Barnes[1], C. N. Rotimi[2], L. Brody[3], J. Bailey-Wilson[3], S. R. Panny[4], D. Chitayat[5], F. D. Porter[6], J. C. Marini[1]* 1) Bone and Extracellular Matrix Branch, NICHD, NIH, Bethesda, MD; 2) ICGHD, NHGRI, NIH, Bethesda, MD; 3) NHGRI, NIH, Bethesda, MD; 4) Maryland DHMH, Baltimore, MD; 5) Dept OB/Gyn, Mt Sinai Hosp, Toronto, Ontario; 6) HDB, NICHD, NIH, Bethesda, MD.

Type VIII OI (OMIM #610915) is a lethal or severe recessive form of OI caused by mutations in *LEPRE1*, the gene encoding prolyl 3-hydroxylase 1. We identified a recurring mutation, IVS5+1G>T, in 6 probands born to carrier parents of West African or African-American descent, suggesting an African founder mutation which had been transported to the Americas. We investigated the carrier frequency for this mutation in African-American and contemporary West African populations

and the molecular anthropology of the mutation. We screened gDNA using PCR and RE digestion, or a custom SNP assay, followed by PCR confirmation of positive samples. The recurring mutation was identified in 5/995 Washington DC, 5/1429 Pennsylvania and 2/631 Maryland samples. Thus, Mid-Atlantic African-Americans have a carrier rate of 1/200-300 and a predicted incidence of homozygosity for this mutation of 1/160,000-380,000 births. Fifteen of 1097 unrelated individuals (1.37%) from Nigeria and Ghana were heterozygous for *LEPRE1* IVS5+1G>T, all but one from Kwa-speaking tribes. The high (>1%) carrier frequency for this founder mutation among West Africans predicts an incidence of recessive OI in West Africa of ≥1/21,000 births, which is equal to the incidence of *de novo* dominant OI, and an order of magnitude greater than the 5-7% proportion of all recessive OI in North America. To estimate mutation age, we used microsatellites and short tandem repeats covering 4.2 MB surrounding *LEPRE1* on chromosome 1p to characterize the conserved haplotype. Haplotype analysis of the founder mutation pedigrees has revealed a conserved region of <450Kb, consistent with a single mutation that arose over 300 years ago and was transported by the Atlantic slave trade. We estimate that >350 carriers were transported to the American colonies, preventing the occurrence of a secondary founder effect.

Plenary and Platform Presentations

Concurrent Platform Session 41: Genetic Counseling, Testing, ELSI Issues   Room 103
08:00AM-10:30AM

Platform Presentation 177
08:00AM-08:15AM
Motivators for participation in a whole genome sequencing study: The ClinSeq experience. *F. M. Facio, B. B. Biesecker, S. Brooks, J. Loewenstein, L. G. Biesecker* Natl Human Genome Res Inst, NIH, Bethesda, MD.

Introduction: ClinSeq is a pilot study to investigate and develop large-scale medical sequencing (LSMS) and whole genome sequencing (WGS) for clinical research. A distinctive aspect of ClinSeq is that subjects can choose to receive individual genotype results. Existing literature shows that altruism, benefits to self, and benefits to family are major motivators for research participation. ClinSeq provides a novel setting to examine motivators for participation in the context of LSMS/WGS. The purpose of this qualitative study was to explore the reasons individuals participate in a LSMS/WGS study. Methods: 337 individuals (age 45 to 65), who enrolled in ClinSeq between January 2007 and May 2008, were asked an open-ended question about their reasons for participating in the study and their demographics. Responses were imported into NVIVO 7 for coding and analysis. The sample size provided data saturation. The primary coder coded all 313 responses. The secondary coder coded 25% of the responses. Inter-coder reliability was 95.4%. Results: Of 337 enrollees, 313 (93%) provided responses. The majority were White (89%), highly educated (85%), and of high socio-economic status (66%). Two main themes were identified: "altruism" and "seeking health information for oneself," with each theme arising from distinct groups. Conclusion: Our results show that ClinSeq subjects share motivations with both general research participants, as well as with those who come forth for genetic studies. Although "personal health benefits" is a more salient theme among disease cohorts than among healthy volunteers, many of our volunteers cited this as a motivator. Investigation of our subjects' health related attributes will reveal how their background parallels this finding. To our knowledge this is the first cohort to undergo LSMS/WGS with the option of receiving individual genotype results, which provides a unique opportunity to study the theme of "benefits to self" in the context of personalized genomics research. We will discuss the implications of our results for future translational genomics research and describe follow-up studies to explore preferences towards LSMS/WGS.

Concurrent Platform Session 42 Clinical Genetics II
Room 113
08:00AM-10:30AM

Platform Presentation 187
08:00AM-08:15AM
Linear clinical progression independent of age of onset in Niemann-Pick Disease, type C. *N. M. Yanjanin[1], J. I. Vélez[1], A. Gropman[2], K. King[1], C. C. Brewer[1], B. Solomon[1], W. Pavan[1], M. Arcos-Burgos[1], M. C. Patterson[3], F. D. Porter[1]* 1) NICHD, NHGRI, NIDCD or CC of NIH, DHHS, Bethesda, MD; 2) CNMC, Washington, DC; 3) Mayo Clinic, Rochester, MN.

Niemann-Pick Disease, type C (NPC) is a neurodegenerative storage disorder characterized by ataxia, dystonia, dementia, and vertical ophthalmoplegia. The heterogeneous clinical nature and variable age of onset confounds the characterization of potential biomarkers, and the absence of an accepted biomarker is an impediment to the development of therapeutic trials. Thus, we developed a clinical severity scale to correlate with potential biomarkers, and monitor disease progression. Clinical data were collected from 18 current patients and retrospective data were extracted from the records of 19 patients. Symptoms in 9 major (scored 0-5: ambulation, cognition, eye movement, fine motor, hearing, memory, speech, seizures, swallowing) and 8 minor domains (scored 0-3: ABR, behavior, gelastic cataplexy, hyperreflexia, incontinence, narcolepsy, psychiatric, respiratory) typically noted in a medical history were scored. Interestingly, both cohorts showed a linear increase in severity. Cross-sectional analysis of 18 current patients showed a linear increase (r^2=0.64, p<0.0001) with a mean progression of 1.4 ±0.3 points per year. Longitudinal chart review of 19 patients showed that although age of onset varied significantly, the rate of progression (mean=1.9 ±0.2 points per year) was independent of age of onset and similar in 18/19 patients. Combining the data from both cohorts, progression could be mathematically modeled: $Åœt_0+x=Åœt_0+1.87x$; where $Åœt_0$ is the initial score and $Åœt_0+x$ is the predicted score after x years. The standard error and the 95% CI for the slope were ±0.18 and 1.6-2.3 respectively, allowing for power estimates to be obtained. Our observation that disease progression is similar in patients and independent of age of onset is consistent with a biphasic pathological model for NPC and does not support a model of slower progression in later onset cases. In addition, this scale may prove useful in the characterization of potential biomarkers, and as an outcome measure to monitor disease progression.

Topic: Clinical Genetics and Dysmorphology
Exhibit Hall C   10:30AM-12:30PM

Poster 505/F
Molecular Characterization and Postmortem Review of Holoprosencephaly (HPE) Cases. *F. Lacbawan[1,2], A. Igbokwe[2], D. Pineda[1], M. Muenke[1]* 1) Med Gen Branch, NHGRI/NIH, Bethesda, MD; 2) SUNY Downstate Medical Center, Brooklyn NY.

HPE is the most common structural forebrain malformation in humans with genetic and environmental causes. Besides chromosomal abnormalities & submicroscopic *dels*, recurring mutations were found in *ZIC2, SHH, SIX3, TGIF1, GLI2*, & *FOXH1*. In our studies, there is variable expressivity and reduced penetrance in SIX3 mutation(+) cases and gonodal mosaicism in ZIC2 mutation(+) cases. A "multiple hit" hypothesis that predicts that several genetic &/or environmental insults are required to produce HPE in humans was proposed. In our continued efforts to characterize the clinical spectrum, we reviewed 48 cases with postmortem reports. DNA samples were screened for mutations in *ZIC2, SHH, SIX3* and *TGIF* by PCR of exons followed by sequencing. The age ranged from GA 15 wks to 8 yrs & F:M ratio was 2:1. 21 were diagnosed on prenatal USS. Maternal history was significant in only 3 (alcohol, smoking, diabetes & cocaine). 17(35%) had more than 1 clinically affected family member with known karyotype (KT) abnormalities in 4. There were also 4 of 31 sporadic cases with abnormal KT. In 1/2 of the cases with normal KT, we found 2 SHH mut(+) and 1 ZIC2 mut(+). Most cases reviewed were severe forms with 44% alobar, 25% semilobar and 13% lobar. Common craniofacial features were microcephaly, proboscis, olfactory bulb/tract agenesis, hypotelorism, CL/P, ear anomalies and cyclopia/anophthalmia. Other brain findings include corpus callosum a/dysgenesis(23%), cortical/cerebellar malformations(17%), hydrocephalus(15%) and migration defects(6%). 27% also had significant cardiac defects including ASD, VSD, PFO, and hypoplastic left heart. Associated findings included limb anomalies(27%) and GU anomalies like renal, uterine, anterior perineal anomalies and hypospadias(27%). Our review highlights the need for clinicians and pathologists to know the broad spectrum of anatomic features of HPE so that appropriate clinical diagnostic work-up like radiology and use of the algorithm of molecular and chromosomal studies are optimized. A better understanding of HPE pathogenesis will translate to a more comprehensive clinical management of patients and proper counseling of families.

Poster 507/F
SIX3 Mutation Studies Broaden Understanding of the Holoprosencephaly Clinical Spectrum. *B. D. Solomon, F. Lacbawan, B. Feldman, S. Domené, E. Roessler, M. Muenke* Medical Genetics Branch, National Human Genome Research Institute, National Institutes of Health, Bethesda, MD.

Holoprosencephaly (HPE) is the most common structural malformation of the human forebrain. SIX3, which encodes a transcription factor expressed in the developing forebrain and eyes, is one of the most the common HPE-causing genes. In this largest cohort of patients (n=800), mutation screening of ZIC2, SHH, SIX3, and TGIF was done by PCR amplification of all exons, dHPLC screening, and was then followed by bidirectional sequencing. Among these genes, mutations in

SIX3 (4.7%) were the third most common. Here we report 56 HPE cases with 38 different mutations in SIX3 and correlate their clinical manifestations. An additional 72 cases ascertained elsewhere with SIX3 mutations, submicroscopic deletions, or chromosome 2p21 abnormalities, are also included. The F:M ratio in this combined set of patients is 1.5:1. There is intrafamilial clinical heterogeneity in the 23 families, with penetrance of 68%. There are 27 patients with alobar HPE, 22 with semilobar, 7 with lobar, and 5 with MIHF. The most common associated clinical findings, in decreasing frequency, are hypotelorism, microcephaly, cleft lip/palate, seizures, premaxillary agenesis, diabetes insipidus, single central incisor, and coloboma. The majority of the mutations confer functional loss of SIX3, as clearly demonstrated by our group using an in vivo zebrafish assay (Domené et al., 2008), but the degree of severity of brain anomalies does not appear to be solely dependent on the genotype. However, there is regional clustering of the mutations within the SIX domain (43%) and homeodomain (26%) affecting the repressor function of SIX3. The related x-ray diffraction data on aa133-aa263 of SIX3 may be used in our attempts of molecular modeling to further refine genotype-phenotype correlations. As the understanding of the range of factors that could be functionally important is still incomplete, we cannot exclude important interactions between SIX3 and other genetic or environmental factors.

Poster 515/F
Extending the spectrum of Ellis van Creveld syndrome: a large family with a mild mutation in the EVC gene. *H. Ulucan[1,2], D. Gül[3], J. C. Sapp[1], J. Cockerham[4], J. J. Johnston[1], L. G. Biesecker[1]* 1) Natl Human Genome Res Inst, NIH, Bethesda, MD, USA; 2) Adnan Menderes University Medical Faculty, Department of Medical Genetics, Aydin, Turkey; 3) Gulhane Military Medical Academy, Department of Medical Genetics, Ankara, Turkey; 4) Children's National Medical Center, Department of Cardiology, Washington, DC, USA.

Ellis-van Creveld (EvC) syndrome is characterized by short limbs, short ribs, postaxial polydactyly, dysplastic nails and teeth and is inherited in an autosomal recessive pattern. We report a family with complex septal cardiac defects, rhizomelic limb shortening, and polydactyly, without the typical lip, dental, and nail abnormalities of EvC. The phenotype was inherited in an autosomal recessive pattern, with one instance of pseudodominant inheritance. Because of the phenotypic overlap with EvC, microsatellite markers were used to test for linkage to the EVC/EVC2 locus. The results did not exclude linkage, so samples were sequenced for mutations. We identified a c.1868T—C mutation in EVC, which predicts p.L623P, and was homozygous in affected individuals. We conclude that this EVC mutation is hypomorphic and that such mutations can cause a phenotype of cardiac and limb defects that is less severe than typical EvC. EVC mutation analysis should be considered in patients with cardiac and limb malformations, even if they do not manifest typical EvC syndrome.

Poster 525/F
Obstetric and Gynecologic Issues in Patients with Hermansky-Pudlak Syndrome. *M. A. Merideth[1,2], A. M. Garcia[1], J. Salas[1], K. O'Brien[1,2], T. C. Markello[1], W. A. Gahl[1,2]* 1) NHGRI, NIH, Bethesda, MD; 2) Intramural Office of Rare Diseases, NIH, Bethesda, MD.

Hermansky-Pudlak syndrome (HPS) is a panethnic autosomal recessive disorder characterized by oculocutaneous albinism, a bleeding disorder, and, in some patients, granulomatous colitis and/or a fatal pulmonary fibrosis. There are 8 known subtypes of HPS caused by mutations in 8 separate genes involved with intracellular vesicle formation and trafficking. The bleeding

disorder in HPS is due to platelet storage pool deficiency. Women with HPS often have problems with heavy menstrual periods and excess bleeding during deliveries, yet very little information has been published on the obstetric and gynecologic issues in HPS. To pursue this, we surveyed 45 patients under an NIH IRB-approved protocol. The patients ranged in age from 13-65 y with a median of 33 y, and were diagnosed with HPS at a median age of 22 y. Forty-one of the 45 patients (91%) report a history of heavy menstrual periods. Thirty-one patients were treated with oral contraceptive pills to manage heavy menses, and 21 of 31 reported improvement. Three of 4 patients had improvement of heavy menses after insertion of a Mirena progesterone IUD. Four patients underwent hysterectomy for heavy menses at a median age of 33.5 y. Twenty-one patients have been pregnant with a median of 2 pregnancies (range 1-5). Only four of 21 patients had problems with bleeding during pregnancy. Bleeding problems were reported in 9 deliveries, requiring platelets, blood transfusion or ddAVP in 4. Prophylactic platelet transfusion or ddAVP was given prior to 12 deliveries, with no subsequent bleeding problems reported. Postpartum hemorrhage occurred in 13 deliveries: treatment by surgery, transfusion of platelets or medication was required in 10. Obstetrician/Gynecologists have an opportunity to assist in the diagnosis of HPS patients, particularly since a majority of patients surveyed were diagnosed many years after the onset of menses. The history of a menstrual bleeding disorder, combined with some degree of hypopigmentation, should prompt investigation into the diagnosis of HPS.

Poster 573/F
Prospective evaluation of kidney function in Autosomal Recessive Polycystic Kidney Disease/Congenital Hepatic Fibrosis (ARPKD/CHF). *M. Gunay-Aygun[1,2], L. Lukose[1], K. Drayanani[3], J. Graf[3], J. Bryant[1], A. Garcia[1], D. Adams[1], E. Johnson[1], L. Guay-Woodford[4], P. Choyke[5], W. A. Gahl[1,2]* 1) Section on Human Biochemical Genetics, Medical Genetics Branch, National Human Genome Research Institute, National Institutes of Health, Bethesda, MD; 2) Intramural Program of the Office of Rare Diseases, DHHS, Washington, DC; 3) NIH Clinical Center, Bethesda, MD; 4) University of Alabama, Birmingham, Al; 5) Molecular Imaging Program, NCI, Bethesda, MD.

The effectiveness of targeted therapies (vasopressin 2 receptor inhibitors, somatostatin analogs, mTOR (mammalian Target Of Rapamycin) inhibitors, src-inhibitors) in preventing progression of kidney and/or liver disease in animal models of PKD/CHF highlights the importance of identifying disease-specific outcome parameters. In ADPKD, kidney volume is useful as an outcome parameter as it correlates negatively with glomerular function. Such data are not available for ARPKD/CHF, which differs from ADPKD with regard to its age of onset, and the nature of the kidney and liver disease. Between November 2003 and August 2008, we prospectively evaluated 85 probable ARPKD/CHF patients at the NIH Clinical Center (ClinicalTrials.gov, number, NCT00068224). We analyzed the cross sectional and longitudinal data of the 65 patients with at least one mutation in PKHD1, some followed for up to 5 years. Kidney volume in ARPKD/CHF was increased at birth; however, the rate of increase was much slower than for ADPKD. The weighted mean rate of decline in creatinine clearance was 4.0 ml/min/1.73m2 per year; in contrast to ADPKD, this decline rate did not increase with age or kidney volume. Glomerular dysfunction and the urinary concentration defect were significantly worse in patients with both medullary and cortical involvement compared to those with cystic changes limited to the renal medulla. Serum vasopressin was elevated despite dilute urine suggesting resistance to vasopressin. Longer follow up of more ARPKD/CHF patients,

along with safety and efficacy data from the ongoing treatment trials on adults with PKD, should enable us to design future therapeutic trials for ARPKD.

Poster 574/F
Cognitive Function in Autosomal Recessive Polycystic Kidney Disease. *E. J. Johnson[1], E. Wiggs[2], J. Bryant[1], A. Garcia[1], D. Adams[1], M. Tuchman[1], L. Guay-Woodford[3], W. A. Gahl[1,4], M. Gunay-Aygun[1,4]* 1) Medical Genetics Branch, National Human Genome Research Institute , Bethesda, MD; 2) National Institutes of Health, Clinical Center, Bethesda, MD; 3) University of Alabama, Birmingham, Al; 4) Office of Rare Disorders, DHHS, Washington, DC.

Autosomal Recessive Polycystic Kidney Disease/Congenital Hepatic Fibrosis (ARPKD/ CHF), the most common form of PKD in children, is characterized by progressive cystic degeneration of the kidneys resulting in chronic renal insufficiency and congenital hepatic fibrosis complicated by portal hypertension (PH). Although the central nervous system is not primarily involved, certain characteristics of ARPKD/CHF, might predispose affected children to developmental delay in early childhood and/or affect their cognitive function later in life. These complications include oligohydramnios, hypoplastic lungs requiring mechanical ventilation, severe systemic hypertension from birth, chronic renal insufficiency and portosystemic shunting. In our ongoing NIH study on ciliopathies (ClinicalTrials.gov, number, NCT00068224), we evaluated 60 ARPKD/CHF patients (age 12.3 + 11.9 years) with at least 1 pathogenic PKHD1 mutation. Developmental history was normal in 44 of 60 patients while 15 had mild to moderate delays in the areas of gross and/or fine motor and/or expressive speech. One patient, who required 17 amniotic fluid infusions, had severe global delays. Twenty-one of the 60 ARPKD/CHF patients (11 females, 10 males, mean age 10.1 + 5.7 years) underwent either the Wechsler Intelligence Scale for Children ®- Fourth Edition (WISC-IV) or the Wechsler Adult Intelligence Scale ®- Third Edition (WAIS-III) administered by a psychologist with extensive experience. Scores in the areas of verbal comprehension, perceptual reasoning/organization, working memory, and processing speed, were at the 65th + 15, 55th + 30, 51st + 30, and 43rd + 17 centiles, respectively. Mean full scale intelligence quotient (FSIQ) was 102 + 15 (at 58th + 28 centile). There was no correlation between FSIQ and creatinine clearance or platelet count as a measure of PH. Our results suggest that most ARPKD/CHF patients have normal cognitive development.

Poster 582/F
New Mutations Identified in Hermansky Pudlak Syndrome, Subtype 3 and Case Reports of Two Children With This Subtype. *G. A. Golas, R. Hess, A. Helip-Wooley, M. Huizing, R. Fischer, K. O'Brien, T. Markello, W. Westbroek, W. A. Gahl* Medical Genetics Branch NHGRI/NIH 10 Center Drive Bethesda, Md 20892.

Hermansky Pudlak Syndrome (HPS) is an autosomal recessive disdorder exhibiting both genetic and clinical heterogeneity with 8 distinct subtypes identified at specific loci, and characterized by oculocutaneous albinism, a bleeding diathesis, and variably, in some subtypes, pulmonary fibrosis and granulomatous colitis. We have diagnosed and described the clinical and molecular findings of 29 patients with HPS 3 in a cohort of 232 individuals with HPS studied in the NIH protocol 95-HG-0093. Analysis of gene map locus 3q24 is reported here and revealed 19 different mutations: 5 with an Ashkenazi Jewish mutation in the homozygous state; 9 with the central Puerto Rican HPS mutation in a homozygous state; and 15 others carrying 17 varied mutations, 12 of which are novel and unpublished. Two unrelated children, ages 7 and 10, diagnosed with HPS 3,

confirm the previously-documented milder clinical phenotype of HPS 3, reflecting near normal skin/hair hypopigmentation, typical ocular findings, and only a very mild bleeding tendency. Neither had any significant gastrointestinal involvement and both are too young to exhibit the pulmonary fibrosis which characterizes subtypes 1 and 4, not HPS 3. Patient 1, of consanguineous French Canadian parents, has blonde hair, blue eyes, pale skin, visual acuity 20/160-250, nystagmus, photophobia, easy bruisability and a history of one minor nosebleed. A chin laceration requiring sutures had no prolonged bleeding. Patient 2, of nonconsanguineous Jewish and Irish/French/German parents, has brown eyes, brown hair, olive skin, nystagmus, visual acuity of 20/60-80, easy bruisability, and a history of two episodes of epistaxis controlled with intranasal DDAVP. Identification of a milder subtype of HPS without the prognosis of fatal pulmonary fibrosis in early adulthood can give enormous relief to parents of these children and guide management of their milder bleeding manifestations.

Poster 669/F
Severe glutathione synthetase deficiency: Long-term manifestations in two adult brothers. *K. O'Brien[1], J. Sloan[2], A. Gropman[1], E. Baker[3], T. Pierson[4], K. Fischbeck[4], I. Macdonald[5], W. Gahl[1], C. Venditti[1]* 1) MGB/NHGRI/NIH; 2) GDRB/NHGRI/NIH; 3) DRD/CC/NIH; 4) NINDS/NIH; 5) NEI/NIH.

Glutathione synthetase deficiency (GSSD) is a rare disease due to deficiency of glutathione synthetase (GSS), resulting in glutathione depletion, 5-oxoprolinuria, hemolytic anemia, and metabolic acidosis. Clinical manifestations in two adult brothers are described and compared to other patients reported with severe GSSD in order to better understand the natural history of this disorder. Two Caucasian siblings with GSSD have been followed at the NIH for more than 30 years. The older sibling was identified at 22 months of age based on typical laboratory findings; his younger brother was diagnosed as a neonate and has been treated with vitamins C and E, and alkali replacement since 2 days of life. The brothers have missense and frameshift mutations in the GSS gene. Patient 1, age 33 y, has experienced significant deterioration over the past 6 years. Previously, he was ambulating independently and working full time. Now, he is wheelchair bound, with worsening spasticity, imbalance, and dysarthria, and cannot function independently. Patient 2, age 30 y, also experienced a decline. He has developed psychosis, including paranoia, hallucinations, delusions, and motor symptoms. He ambulates with a walker and resides in an assisted living facility. A 3.0 T brain MRI/MRS revealed diffuse white and gray matter atrophy in both the cerebrum and cerebellum, ventricular enlargement, gray matter heterotopia, and a malformed cerebellum. NAA was low in 3 locations studied by MRS. These men are among the oldest known patients with severe GSSD. Over the past 6 years, both have experienced neurological decline with differing manifestations despite stable biochemical parameters. The malformed cerebellum and heterotopia seen in patient #2 are similar to findings reported in others, albeit rarely, and suggest that CNS malformations can be a feature of the disorder. The differing neurological manifestations of these two siblings also indicate that modifier genes may influence the phenotype of GSSD and highlight the importance of oxidant homeostasis in the CNS.

Poster 1341/F
Identification of multiple novel prostate cancer predisposition loci. *R. Eeles[1], Z. Kote-Jarai[1], D. Easton[2], J. Stanford[3], E. Ostrander[4], J. Schleutker[5], S. Ingles[6], D. Schaid[7], S. Thibodeau[7], T. Dork[8], D. Neal[9], W. Vogel[10], M. A. Kedda[11], E. John[12], G. Giles[13], W. Foulkes[14], P. Chappuis[15], K. Muir[16, 17], M. Guy[1], A. Amin Al Olama[2], The PRACTICAL Group & ProtecT Group & UKGPCS Study* 1) Cancer Genetics Unit, Inst Cancer Research, Sutton, United Kingdom; 2) Cancer Research UK Genetic Epidemiology Group, Strangeways Laboratory, Cambridge, United Kingdom; 3) Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, USA; 4) National Human Genome Research Institute, National Institutes of Health, Bethesda MD, USA; 5) Institute of Medical Technology, University of Tampere and Tampere University Hospital, Tampere, Finland; 6) Department of Preventive Medicine, University of Southern California Keck School of Medicine, Los Angeles CA, USA; 7) Mayo Clinic, Rochester, Minnesota, USA; 8) Hannover Medical School, Germany; 9) Surgical Oncology, Cambridge Research Institute, Cambridge, UK; 10) Institut für Humangenetik, Ulm, Germany; 11) School of Public Health and Institute of Health and Biomedical Innovation, Queensland, Australia; 12) Northern California Cancer Center, Fremont, California, USA; 13) Cancer Epidemiology Centre, The Cancer Council Victoria, Australia; 14) McGill University, Montreal, Canada; 15) Division of Genetic Medicine and Division of Oncology, University Hospitals of Geneva, Switzerland; 16) University of Nottingham UK; 17) Chulabhorn Cancer Research Centre, Thailand.

A genome wide association study in prostate cancer (PC)involving analysis of over 500 000 SNPs in 3748 blood samples from men with prostate cancer has found genetic variants on chromosomes 3, 6, 7, 10, 11, 19 and X are associated with PC risk. Blood DNA from 7370 PC cases and 5742 control men was analysed in a follow up study in 13 groups worldwide (The PRACTICAL Group). The per allele OR was 1.12 to 1.29 and combined risks were consistent with a multiplicative risk model. These and previous loci explain 16 per cent of familial risk of PC, and men in the top 10 per cent of the risk distribution have a 2.1 fold risk relative to general population rates. Genetic profiling of such variants will enable research studies in targeted PC screening.

Poster 1343/F
Identification of a Single Gene Locus for Canine Squamous Cell Carcinoma of the Digit. *E. A. Ostrander[1], B. vonHoldt[2], E. Karlins[1], D. Mosher[1], J. Mulliken[1,3], H. Parker[1], R. K. Wayne[2], D. M. Karyadi[1]* 1) NHGRI, NIH, Bethesda, MD; 2) Dept of Biology, UCLA, Los Angeles, CA; 3) NISC, NIH, Bethesda, MD.

Squamous cell carcinoma (SCC) of the digit is a highly breed-specific skin cancer with increased risk found in large black dogs, including the standard poodle, giant schnauzer, briard and Gordon setter. This cancer is more aggressive than most SCCs with 80% of cases involving bone lysis and 5-13% recurring in multiple toes. When invasive, metastasis to the lung or lymph nodes ultimately leads to death. Using the canine-specific Affymetrix chip, containing 127,000 single nucleotide polymorphisms (SNPs), we conducted a whole genome association study for SCC of the digit using 31 standard poodle cases and 34 controls. SNPs were removed from the analysis if greater than 10% of the data was missing, there were more then 60% heterozygous calls, or minor allele

frequency was less than 1%. The final SNP set consisted of 45,078 SNPs. Using the single-locus chi-squared test of significance, we calculated the allelic association of each SNP with the disease phenotype. The top 6 most significant SNPs were all at the same genomic locus (P_{raw}=5.62x10^{-5}-1.20x10^{-7}). Chromosome-wide permutations (n=100,000) were performed to test for significance yielding a chromosome-wide empirical value of P=7.00x10^{-5} for the most significant SNP. Five other SNPs in this region were also significant (P_{emp}=0.0299-0.0010). No other genomic regions yielded peaks significant at the chromosome-wide level. Initially, the distance spanned by the significant peak was 999.4 kb, and included four known and four predicted genes. After additional SNP genotyping and sequencing haplotype analysis, utilizing over 325 markers, resolved the region to 812.2 kb with 3 crossovers on each side. A reduced region, defined by 1 crossover, spans 515.7 kb, and contains only 1 complete gene plus 2 exons of a second gene. The complete gene is an excellent candidate and is a potential oncogene. The entire region is being scanned using a capture technology combined with Solexa sequencing to identify the causal variant. Identification of the mutation underlying this canine cancer is likely to inform human forms of SCC.

Topic: Molecular Basis of Mendelian Disorders
Exhibit Hall C   10:30AM-12:30PM

Poster 1581/F
LIMP-2 expression in fibroblast cell lines from subjects with Gaucher disease. *T. Samaddar, J. Vithayathil, N. Tayebi, E. Goldin, E. Sidransky, O. Goker-Alpan* MGB/NHGRI, NIH, Bethesda, MD.

Lysosomal integral membrane protein 2 (LIMP-2) is a specific chaperone responsible for trafficking glucocerebrosidase, the enzyme implicated in Gaucher disease, to the lysosome. In this study, LIMP-2 gene and protein expression were explored in 9 fibroblast cell lines from subjects with Gaucher disease using quantitative (real-time) PCR and Western blots. The mutations included N370S, L444P, D409H+, G325R, P415R and a recombinant allele The gene and protein expression varied between cell lines, even in the ones from subjects with the same genotype. In immunofluorescence studies, GC co-localized with the early endosomal marker EEA1, instead of the lysosomal markers. In these cell lines with trafficking defects, LIMP-2 distribution was altered and steady state protein levels were relatively decreased with respect to gene expression, suggesting over-utilization of LIMP-2 protein in an attempt to rescue mistrafficked GC. Incidentally, large endosomes were observed in the cell lines where GC was mistargeted to the endosome instead of lysosomes. In addition to its function as a membrane receptor for GC, LIMP-2 is also believed to regulate the post-endosomal compartment, and LIMP-2 overexpression in these fibroblast cell lines can lead to the formation of large endosomes. These results indicate that intracellular LIMP-2 regulation may differ depending on GC mutations and folding, and LIMP-2 could be a modifier molecule affecting the cellular and hence clinical phenotype in subjects with Gaucher disease.
Topic: Complex Traits and Polygenic Disorders
Exhibit Hall C   10:30AM-12:30PM

Poster 2274/F
Association of sequence variant rs10757278 on 9p21 with intracranial aneurysm. *R. Deka[1], D. Koller[2], D. Lai[2], S. R. Indugula[1], G. Sun[1], D. Woo[1], L. Sauerbeck[1], R. Hornung[3], E. Sander Connolly[4], C. Anderson[5], G. Rouleau[6], I. Meissner[7], J. Bailey-Wilson[8], J. Huston[7], R. Brown[7], C. Langefeld[9], T. Foroud[2], J. Broderick[1], FIA Investigators* 1) University of Cincinnati School of Medicine, Cincinnati, OH; 2) Indiana University School of Medicine, Indianapolis, IN; 3) Cincinnati Children's Hospital Medical Center, Cincinnati, OH; 4) Columbia University, New York, NY; 5) University of Sydney, Sydney, Australia; 6) Notre Dame Hospital, Montreal, Canada; 7) Mayo Clinic, Rochester, MN; 8) Natioanl Human Research Institute, Baltimore, MD; 9) Wake Forest University, Winston-Salem, NC.

Several studies have recently reported association of two common variants on 9p21, rs10757278 and rs10811661, with coronary artery disease (CAD) and type 2 diabetes (T2D). A subsequent study in multiple populations reported that the G allele in rs10757278 was associated with abdominal aortic aneurysm (AAA) and intracranial aneurysm (IA) in addition to CAD (Helgadottir et al. Nat Genet 2008). We typed this variant to test for association with IA in a sample of 270 cases and 281 controls from the Familial Intracranial Aneurysm (FIA; www.FIAStudy.com) study. We found significant association of the G-allele with FIA cases (p=0.0123). We also found significant genotypic association (p=0.0367), with an excess of GG homozygotes and AG heterozygotes as observed previously (Helgadottir et al.). Our results provide nominal replication that a risk factor in the 9p21 region influences the risk of IA. Funded by R01NS039512.

Topic: Statistical Genetics and Genetic Epidemiology
Exhibit Hall C   10:30AM-12:30PM

Poster 2453/F
Scanning for gene-gene interactions involving known type 2 diabetes genes and the genome in 2335 Finnish cases and controls. *T. Hu[1], L. J. Scott[1], L. Bonnycastle[2], N. Narisu[2], M. A. Morken[2], P. A. Deodhar[2], T. T. Valle[3], J. Tuomilehto[3], R. N. Bergman[4], K. L. Mohlke[5], F. S. Collins[2], M. Boehnke[1]* 1) Department of Biostatistics, University of Michigan, Ann Arbor, MI; 2) National Human Genome Research Institute, Bethesda, MD; 3) National Public Health Institute, Helsinki, Finland; 4) University of Southern California, Los Angeles, CA; 5) University of North Carolina, Chapel Hill, NC.

~20 loci have been identified as convincingly associated with the risk of type 2 diabetes (T2D). However, little is known about the interactions among these loci or with other variants across the genome. Since gene-gene interaction may play an important role in determining disease risk, we set out to test the interactions of T2D associated variants in and around identified regions in genome-wide association (GWA) data from the Finland-United States Investigation of NIDDM Genetics (FUSION) study. Based on a sample of 1161 T2D cases and 1174 normal glucose tolerant controls genotyped for >300,000 SNPs, we tested for two-way interactions among the following loci: *IGF2BP2* (rs4402960), *CDKAL1* (rs7754840), *CDKN2A/B* (rs10811661), rs9300039, *FTO* (rs8050136), *PPARG* (rs1801282), *SLC30A8* (rs13266634), *HHEX* (rs1111875),*TCF7L2* (rs7903146), *KCNJ11* (rs5219), *JAZF1* (rs864745), *CDC123* (rs12779790), *TSPAN8* (rs7961581), *THADA* (rs7578597), *ADAMTS9* (rs4607103), and *NOTCH2* (rs10923931), using logistic regression and controlling for age, sex, and birthplace. None of these two-way interactions gave results sufficiently significant to survive correction for the 120 correlated tests. We currently are using this same strategy to

test for interaction between the T2D-associated loci and the >300,000 SNPs genotyped in our FUSION GWA.

Poster 2501/F
Genome-Wide Linkage Analysis of Platelet Phenotypes in White and African American Families with Coronary Artery Disease. *R. A. Mathias[1], Y. Kim[1], L. Yanek[2], J. E. Herrera-Galeano[2], L. C. Becker[2], D. M. Becker[2], A. F. Wilson[1]* 1) IDRB/NHGRI/NIH, Genometrics Section, Baltimore, MD; 2) Johns Hopkins Medical Institutions, Baltimore, MD.

Background: The inability of aspirin (ASA) to adequately suppress platelet aggregation is associated with future risk of myocardial infarction, stroke, and cardiovascular death; and genetic variation may be responsible for ASA responsiveness. In this study, we performed a genome-wide linkage scan for platelet phenotypes before and after ASA treatment (i.e. pre-ASA, post-ASA or change-after-ASA). Methods: Clinical data on 37 agonist-induced platelet function phenotypes were evaluated in 1231 white and 846 black healthy subjects with a family history of premature CAD before and after a 2-week trial of ASA (81 mg/day). There were 243 black and 398 white pedigrees, respectively. Principal components analyses were run separately for whites and blacks on the phenotypes adjusted for age, sex, diabetes, hypertension, smoking, LDL cholesterol, fibrinogen, and body mass index. Nine factors were identified for the pre-ASA variables, and 8 factors each were identified for the post-ASA and change-after-ASA variables. Genotyping was performed at deCODE Genetics with the standard deCODE 550 STR marker set (average spacing= 8cM). Linkage analysis was performed with the Hasemen-Elston regression approach in SAGE (v 5.1.0) for each factor and each STR within race. Results: Three loci in blacks and one in whites were significant at the 0.0001 level. A 5cM region in blacks on 1q41-42 had a pleiotropic effect (i.e. linkage to 5 platelet-rich plasma [PRP] or whole blood aggregation factors to different doses of collagen, all either post-ASA or change-after-ASA); and a 5cM region in whites on 4p12 had significant linkage to PRP aggregation to high doses of collagen post-ASA. Conclusion: Several genomic regions show significant evidence for linkage to agonist-induced platelet function phenotypes in the context of aspirin response. The strongest evidence appears to be for post-ASA or change-after-ASA aggregation to collagen as an agonist in both blacks and whites, although in different regions for the two races.

DAY V SATURDAY, NOVEMBER 15

Plenary and Platform Presentations

Concurrent Platform Session 52: Therapy for Genetic Disorders   Room 113
08:00AM-10:30AM

Platform Presentation 258
08:00AM-08:15AM
Prognosis and treatment based upon genetic subtypes of Hermansky-Pudlak syndrome. *M. Huizing[1], R. Hess[1], A. Helip-Wooley[1], R. Fischer[1], K. O'Brien[2], G. Golas[2], WA. Gahl[1,2]* 1) MGB, NHGRI, NIH; 2) Office of Rare Diseases, OD, NIH, Bethesda, MD.

Hermansky-Pudlak syndrome (HPS) comprises a group of autosomal recessive disorders of lysosome-related organelle (LRO) biogenesis. Eight human genes (*HPS1-HPS8*) are associated with eight clinical subtypes. Oculocutaneous albinism, due to abnormal melanosome formation, and prolonged bleeding, due to absent platelet dense bodies, occur in all HPS subtypes. Sporadic features include a fatal pulmonary fibrosis, granulomatous colitis and neutropenia. Over the past 10 years we extensively studied and subtyped 232 HPS patients. HPS-1 (166 patients, 23 mutations) constitutes the largest group due to a founder mutation in NW Puerto Rico. HPS-2 (3 patients, 4 mutations) results from mutations in *AP3B1*, coding for a subunit of adaptor complex-3, a coat protein that mediates vesicle formation. Our study of HPS-3 yielded 29 patients (19 mutations), with *HPS3* founder mutations in central Puerto Rico and in Ashkenazi Jews. We also identified 12 HPS-4 patients (10 mutations), 6 HPS-5 patients (8 mutations) and 4 HPS-6 patients (7 mutations). Our nearly 100 non-Puerto Rican patients are more than the total number reported elsewhere in the world. Our clinical characterization of these patients allowed us to draw several critical conclusions. First, only HPS-1 and HPS-4 patients develop pulmonary fibrosis. This knowledge allows us to enter appropriate patients into our clinical trial of pirfenidone, an antifibrotic agent previously shown to slow the decline in pulmonary function in HPS-1 patients. Second, compared with HPS-1 and HPS-4 patients, HPS-3, HPS-5 and HPS-6 patients are clinically milder and have no pulmonary involvement. Third, HPS-2 patients are the only subtype prone to infections, and their neutropenia is G-CSF responsive. Fourth, our 12 unclassified HPS patients provide opportunities to identify new HPS-causing genes. These studies provided important insights into genotype-phenotype correlations. An accurate subtype diagnosis now carries important prognostic and therapeutic implications, and future studies can provide insights into the cell biology of LROs.

Platform Presentation 257*(sic)*
08:15AM-08:30AM
Using Exon Skipping to Rescue Common Mutations in Hermansky-Pudlak Syndrome Type 1. *L. M. Vincent, R. Hess, W. Westbroek, W. A. Gahl, M. Huizing* MGB, NHGRI/NIH, Bethesda, MD.

Hermansky-Pudlak syndrome (HPS) is characterized by oculocutaneous albinism, a bleeding diathesis, and other systemic complications, including granulomatous colitis and fatal pulmonary fibrosis, due to defects in intracellular vesicle trafficking. The most common subtype, HPS-1, occurs primarily among Puerto-Ricans and results from a 16-bp duplication in exon 15 of the *HPS1* gene. Little is known about the function and structure of *HPS1*, making directed therapy difficult. In view of successful advances in therapeutic exon skipping (e.g., Duchenne Muscular Dystrophy), we utilized anti-sense morpholino oligonucleotides (MOs) to induce in-frame exon skipping of exons carrying deleterious *HPS1* mutations, specifically those in exons 12, 13, 15, and 16. Normal melanocytes positively transfected with MOs were selected using FACS analysis and observed over time. We utilized RT-PCR analysis to validate the effect of each MO on the *HPS1* transcript and immunofluoescence (IF) staining against the melanosome-specific protein TYRP1 to detect abnormal melanosomal trafficking patterns (i.e. lack of accumulation in dendritic tips). Exon 12 MO, ille12, effectively removed exon 12 in ~75% of *HPS1* transcripts. IF analysis revealed a decrease in the accumulation of melanosomes at the dendritic tips; however, it is unknown if this was due to partial activity of the mutant HPS1 protein or residual normal HPS1. Exon 13 MO, e13i13, removed exon 13 in ~95% of *HPS1* transcripts and likewise showed reduced, but not abolished, trafficking of melanosomes to the dendritic tips. We are currently administering these corresponding mutation-specific MOs to patient melanocytes in order to determine if we can rescue the HPS-1 phenotype. Interestingly, co-transfection of i11e12 and e13i13 removed both exon 12 and exon 13 in 100% of HPS1 transcripts and trafficking of melanosomes to the dendritic tips was abolished suggesting the resultant mutant product lacks HPS1 function. Further investigation into targeted exon skipping could result in clinical applications for the treatment of the fatal pulmonary fibrosis associated with HPS-1.

Platform Presentation 261
09:00AM-09:15AM
Long-term Rescue of a Lethal Murine Model of Methylmalonic Acidemia using AAV 8 Mediated Gene Therapy. *R. J. Chandler, C. P. Venditti* Genetic Disease Research Branch, NHGRI/NIH, Bethesda, MD.

Methymalonic acidemia (MMA), a severe organic acidemia, is caused by deficient activity of the ubiquitous mitochondrial enzyme methylmalonyl-CoA mutase (MUT). MMA patients exhibit increased methylmalonic acid levels in the plasma, urine and CSF and display a clinical phenotype of lethal metabolic decompensation, growth retardation, renal failure and metabolic strokes. To assess the potential of genetic therapy for MUT MMA, we employed a mouse model of MMA that produces no detectable Mut transcript or protein. AAV 8 CBA-Mut was injected directly into the liver of newborn Mut-/- pups. Currently, 28 out of the 29 Mut-/- mice injected with 1 or 2x1011GC of AAV 8 CBA-Mut are alive beyond DOL 90 with some treated Mut-/- mice older than 200 days. All the untreated mutants (n=21) perished before DOL 72. The treated Mut-/- mice are thriving and indistinguishable from their wild-type (WT) littermates. AAV 8 CBA-Mut treated Mut-/- mice achieved body weights comparable to controls while untreated mutants experienced post-natal growth retardation and reached only 40% of the weight of the WT. Plasma methylmalonic acid levels in the treated mutant mice on an unrestricted diet were significantly reduced compared to uncorrected animals, indicating that substantial Mut enzymatic activity was restored after AAV therapy. At DOL 90 the liver from a treated Mut-/- mouse had WT levels of Mut protein by Western blot analysis. These experiments provide the first evidence that gene therapy has clinical utility in treatment of MMA and support the development of gene therapy for other organic acidemias.

Concurrent Platform Session 54: Musculoskeletal Disorders   Room 204
08:00AM-10:30AM

Platform Presentation 279
08:30AM-08:45AM
Chondrodysplasia: An example of fixed trait mapping in the domestic dog. *H. G. Parker[1], P. Quignon[1], B. VonHoldt[2], T. Spady[1], D. S. Mosher[1], E. Margulies[3], C. D. Bustamante[4], R. K. Wayne[2], E. A. Ostrander[1]* 1) Cancer Genetics Branch, NHGRI, NIH, Bethesda, MD; 2) Dept of Ecology and Environmental Biology, UCLA, Los Angeles, CA; 3) Genome Technology Branch, NHGRI, NIH, Rockville, MD; 4) Dept of Biological Statistics and Computational Biology, Cornell University, Ithaca, NY.

Dog breeds are isolated populations created through application of strict breeding practices aimed at maintaining a set of characteristics deemed ideal for the breed. While the combination of traits is unique in each breed, the individual traits are not. This population architecture can be used to find the genes responsible for traits that have been bred to fixation in multiple breeds. As a first example of fixed-trait mapping we examined the phenotype of asymmetrical dwarfism or chondrodysplasia. Archetypal chondrodyplastic breeds such as Basset hounds and Dachshunds are characterized by very short legs with normal sized heads and bodies. Many of these breeds share little in common outside of the short-legged phenotype: they fall into different breed clusters in phylogenetic studies, display a variety of coat types, cranial morphologies, and behaviors, and originate from different geographic regions. A search for selected regions in all of these breeds that are not found in proportionate breeds should produce a genetic mutation responsible for chondrodysplasia. To investigate this hypothesis we have run 835 dogs from 75 different breeds including seven chondrodysplastic breeds on the Affymetrix 127K canine SNP chip. After removing SNPs with greater than 10% missing data, 60% heterozygous calls and minor allele frequency of less than 1%, a set of 41635 informative SNPs remained. Analyses from these data identified a single locus spanning 500 Kb associated with chondrodysplasia (p=10-104). Fine mapping using 70 documented SNPs, 170 newly discovered SNPs and indels, and genotypes from additional chondrodysplastic breeds revealed a region of 35 Kb that is homozygous in all chondrodysplastic breeds. Here we discuss the results from this study including the content and significance of a 10 Kb insert in a highly conserved regulatory region.

Concurrent Invited Scientific and Education Session 56: Models of Success: In Search of a Better Understanding and Improved Treatments in Genetic Disease   Hall A
11:00AM-01:00PM

Presentation
11:57AM-12:23PM
Pharmacological treatment of Hutchinson-Gilford Progeria Syndrome in mice and humans. *F. S. Collins.*

Session Descriptions:
The archetype of the application of human genetics is the ability to move rapidly from the clinic to the bench and return to the clinic with improved therapeutic strategies in rapid progression. Sadly this challenge often seems insurmountable. However, there are increasing numbers of examples where evidence from human genetic analysis, combined with precise clinical phenotyping has lead to efforts in model organisms that shed light on the mechanism and in some instances are leading to improved therapeutic endeavors. These are frequently complemented by examples of observations initially made in model organisms then leading to identification of human variation underlying disease and ultimately illuminating disease mechanisms. The main objective of the session will be to highlight success stories made possible by the astute integration of clinical phenotyping, human genetics, functional analyses in model systems and clinical chemistry.

Session 67: Special Plenary Symposium: Genome-Wide Association Studies and Their Follow-up   Ballroom A
03:30PM-05:30PM

Co-moderator: *F. Collins.*
The first generation of genome-wide association studies (GWAS) has found well over 100 loci associated with common human diseases, and many more GWAS are ongoing or in the design phase. The session will discuss the challenges and recent highlights, and consider approaches for following up association results: meta analyses for combining different GWAS of the same disease, incorporating other information such as gene expression, fine mapping and functional studies.