The American Society of Human Genetics
59th Annual Meeting
Honolulu, Hawaii
October 20-24, 2009

Participation from the National Human Genome Research Institute (NHGRI)
(NHGRI participation in poster sessions is not listed here.)

Wednesday, October 21

7:00 AM–9:00 AM

INVITED SESSION 1 – Informing Personalized Genomics Through Science: The Multiplex Initiative (Social Issues)

Hall I, Convention Center

Moderator: Andy Baxevanis, NIH, Bethesda, MD
Future public health applications of personalized genomics will involve providing individualized "multiplex" genetic disease risk information to healthy individuals; the first generation of such testing is already being offered directly to consumers. Considerable concern has been voiced by the scientific and medical communities about the impact of this "premature translation." However, these suppositions have not been informed by requisite social and behavioral research. In 2006, an interdisciplinary preclinical phase research project, the Multiplex Initiative, was launched to address these concerns. The primary aims were to evaluate whether healthy adults would elect genetic testing, whether those who opted in could make use of the risk information, and how such testing influences future patterns of healthcare use. This session will focus on data generated by the Multiplex Initiative to date and on how these data can be used to inform public debate and the development of the research agenda regarding such testing.

7:00 AM **Introduction.** A. Baxevanis. NIH, Bethesda, MD.

7:05 AM **Building a Research Infrastructure for Multiplex Genetic Testing.** A. Baxevanis. NIH, Bethesda, MD.

7:25 AM **Characteristics of users of online personalized genomic risk assessments: Implications for patient-physician interactions.** C. M. McBride. NIH, Bethesda, MD.

7:45 AM **Conveying genetic risk for common health conditions: Can individuals understand multiplex feedback?** K. A. Kaphingst. NIH, Bethesda, MD.

8:05 AM **Informing patients of their genetic risks: Effects on health care seeking.** R. J. Reid. Group Health Cooperative, Seattle, WA.

8:25 AM **Do perceptions of disease severity and attitudes toward testing predict decisions to undergo multiplex testing?** B. B. Biesecker. NIH, Bethesda, MD.

8:45 AM **Questions and answers.** A. Baxevanis. NIH, Bethesda, MD.

INVITED SESSION 4 – Future Vision: The Search for Genes that Cause Eye Disease (Invited Scientific)

Ballroom C, Convention Center

Co-Moderators: Joan E. Bailey-Wilson, NIH/NHGRI, Baltimore, MD; and Alison P. Klein, Johns Hopkins Medical School, Baltimore, MD
The spectrum of eye disorders is extensive and includes diseases leading to structural differences to those resulting in blindness. For more than 100 years, family studies of ocular diseases with Mendelian transmissions have been the focus of ocular genetics. As a result, numerous genes have been identified for highly penetrant ocular traits. More recently, complex ocular diseases like age-related macular degeneration and cataracts are being pursued in large scale studies to identify the genes that underlie these complex diseases. As the field of genetics advances, ocular genetics has kept pace and is a quiet reflection of the different approaches to identifying genes, from single family studies to genome wide

associations. This session will provide an overview of the current genetic knowledge for a variety of ocular diseases both Mendelian and complex and will discuss the future direction and advances in this field, with the goal of screening and early intervention.

7:00 AM **Introduction.** J. E. Bailey-Wilson. NIH/NHGRI, Baltimore, MD.

7:10 AM **The genetic architecture of age related macular degeneration.** J. L. Haines. Vanderbilt University Medical Center, Nashville, TN.

7:32 AM **Identification of genes for age-related cataract.** S. K. Iyengar. Case Western Reserve University, Cleveland, OH.

7:54 AM **Localizing genes for intraocular pressure and glaucoma: The search is on.** P. Duggal. Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD.

8:16 AM **Nature and nurture: the complex genetics of myopia.** R. Wojciechowski. NIH/NHGRI, Baltimore, MD.

8:38 AM **Molecular genetic causes of congenital complex strabismus.** E. C. Engle. Children's Hospital Boston, MA.

9:00 AM **Questions and answers.** A. P. Klein. Johns Hopkins Medical School, Baltimore, MD.

INVITED SESSION 7 – Informed Consent for Today's and Tomorrow's Genomics Research
(Social Issues)
Room 323, Convention Center

Moderator: Laura Lyman Rodriguez, National Human Genome Research Institute, Bethesda, MD

Evolving genomic technologies and the "burden" of complex consent documents weighted toward detailed discussions of technical information and uncertain risk calculations are challenging traditional models and expectations for informed consent processes. Growing emphasis on participant choice and efforts to more accurately calibrate research oversight and participant protections to the particular risks presented in specific studies have resulted in a range of distinct models for facilitating informed consent. This panel will highlight four basic approaches along the continuum of these models: specific consent, general consent, individual opt-out, and community opt-out. In this session, we will explore each of the models in general terms, examine available data to support their utility and efficacy, and discuss how current experimental designs in genomics may be altering the paradigm and traditions through which informed consent processes have been structured.

7:00 AM **Introduction.** L. L. Rodriguez. National Human Genome Research Institute, Bethesda, MD.

7:10 AM **Data release decision-making: Participant attitudes regarding specificity of choice within consent cocuments.** A. L. McGuire. Baylor College of Medicine, Houston, TX.

7:30 AM **Simplifying informed consent: stakeholder perspectives.** L. M. Beskow. Duke Institute for Genome Sciences & Policy, Durham, NC.

7:50 AM **Individual Opt-Out: Efficacy,Challenges, and Concerns.** M.D. Ritchie. Vanderbilt University. Nashville,TN.

8:10 AM **The need for new concepts and expectations for consent in translational genomics research.** P. L. Taylor. Children's Hospital Boston, MA.

8:30 AM **Questions and answers.** L. L. Rodriguez. National Human Genome Research Institute, Bethesda, MD.

9:30 AM–11:30 AM
INVITED SESSION 12 – Genetic Disorders of the Endosomal System (Invited Scientific)
Ballroom C, Convention Center

Co-Moderators: Marjan Huizing, National Institutes of Health, Bethesda, MD; and Wendy Westbroek, National Institutes of Health, Bethesda, MD

In this session, the cell biology of the endosomal system (biogenesis, cargo-selection, trafficking and docking of endosomes) will be addressed. Cells of patients with genetic disorders of this pathway provide new understanding of the novel

mechanisms involved in endosomal cell biology. Each speaker in this session will present groups of human genetic disorders associated with a specific aspect of the endosomal pathway and the insights that these disorders provide into underlying cellular mechanisms. These cellular insights, in turn, inform rational approaches to therapy.

9:30 AM **Introduction.** W. Westbroek. NIH, Bethesda, MD.

9:35 AM **Disorders of lysosome-related organelle biogenesis.** W. Westbroek. NIH, Bethesda, MD.

9:54 AM **Rab GTPases as regulators of endocytosis, targets of disease and therapeutic opportunities.** A. Wandinger-Ness. University of New Mexico Health Sciences Center, Albuquerque.

10:18 AM **The evolving role of lipid rafts and caveolae in signal transduction.** P. A. Insel. University of California-San Diego, La Jolla.

10:42 AM **Perturbations of the endosomal system in disorders of cholesterol homeostasis.** F. D. Porter. NIH, Bethesda, MD.

11:06 AM **Autophagosomes in neurodegeneration and development.** V. I. Korolchuk. Cambridge Institute for Medical Research, Addenbrooke's Hospital,, Cambridge, United Kingdom.

4:00 PM–6:00 PM

SESSION 18 - PLENARY

Hall I, Convention Center

Co-Moderators: Leslie G. Biesecker, GDRB/NHGRI/NIH, Bethesda, MD; and Edward R. B. McCabe, Mattel Children's Hospital, University of California, Los Angeles

Thursday, October 22

7:00 AM–9:30 AM

SESSION 20 – Brain Structure, Function and Degeneration

Ballroom A, Convention Center

Co-Moderators: Robert Nussbaum, University of California, San Francisco; and Maximilian Muenke, NHGRI/NIH, Bethesda, MD

SESSION 21 – Genomics Meets GWAS

Ballroom B, Convention Center

34/8:45 **Importance of sequencing rare variants after a genome-wide association study (GWAS): the *MC1R* gene, 16q24 region and melanoma story.** *F. Demenais[1,2], E. Corda[1,2], J. Barrett[3], M. Iles[3], E. M. Gillanders[4], A. M. Goldstein[5], P. A. Kanetsky[6], E. Bakker[7], D. T. Bishop[3], J. A. Newton-Bishop[3], N. A. Gruis[8], Melanoma Genetics Consortium (GenoMEL)* 1) INSERM Unité 946, Paris, France; 2) Fondation Jean-Dausset-CEPH, Paris, France; 3) Section of Epidemiology and Biostatistics, Leeds Institute of Molecular Medicine, Leeds, UK; 4) Inherited Disease Research Br., National Human Genome Research Institute, NIH, Baltimore, MD, USA; 5) Genetic Epidemiology Br., DCEG, National Cancer Institute, NIH, Bethesda, MD, USA; 6) Dept of Biostatistics and Epidemiology, University of Pennsylvania, USA; 7) Dept. of Clinical Genetics, Leiden University Medical Centre, Leiden, The Netherlands; 8) Dept. of Dermatology, Leiden University Medical Centre, Leiden, The Netherlands.

A GWAS of melanoma, performed by the GenoMEL consortium, identified the strongest association with the 16q24 region. This region includes candidate genes: *CDK10* (involved in cell-cycle regulation), *FANCA* (regulating genomic stability) and *MC1R* (previously associated with pigmentation phenotypes and melanoma). Three 16q24 SNPs had significant independent effects, rs258322 (*CDK10*), rs4785763 (*AFG3L1*) and rs8059973 (*DBNDD1*). However, none of the non-synonymous (NS) *MC1R* variants was present on the GWAS chips. To investigate whether the association signals in the 16q24 region might be accounted for by *MC1R* variants, this gene was sequenced in 1,805 GenoMEL GWAS subjects (918

cases, 887 controls). We first conducted univariate population-adjusted logistic regression with each NS *MC1R* variant. We then compared the strength of association when examining each SNP with and without each *MC1R* variant in the model and, conversely, when examining each *MC1R* variant with and without each SNP. This was followed by stepwise multiple regression and haplotype analysis (THESIAS program) with all significant SNPs and *MC1R* variants. A total of 75 *MC1R* variants were characterized, of which 9 NS variants had allele frequency between 1% and 13%. Univariate analysis showed significant effects of 3 *MC1R* variants, R151C, R160W and D294H (P ranging from $1.5x10^{-3}$ to $1.8x10^{-11}$). There was no longer evidence for association of melanoma with rs258322 after entering R151C in the model and decreased evidence for association with rs4785763 after entering either R151C or R160W (P decreased by a factor of 10^2 to 10^4) while the association with rs8059973 was barely modified. Conversely, the association with R151C was decreased in the presence of either rs258322 or rs4785763 and with R160W in the presence of rs4785763 while the association with D294H was unchanged. Stepwise regression showed independent effects of R151C, R160W and D294H (P ranging from $4.6x10^{-5}$ to $3.1x10^{-13}$) with a marginal effect of rs8059973 (P=0.06). Haplotype analysis confirmed these findings and demonstrated that the rs258322 signal was accounted for by R151C and the rs4785763 signal by both R151C and R160W. Any haplotype carrying rs8059973, which was never on the same haplotype as a significant *MC1R* variant, did not show a significant effect (P>0.20). This study clearly shows that ignoring rare variants can lead to incorrect inferences on the potential role of candidate genes carrying common SNPs identified by GWAS.

SESSION 22 – Genomics I

Ballroom C, Convention Center

41/8:00 **"Simple" Disorders, Complex Traits: A Search for Genetic Modifiers in Neurofibromatosis Type 1.** *A. Pemov[1], J. L. Sloan[2], D. R. Stewart[1]* 1) Dept GDRB, NHGRI/NIH, Bethesda, MD; 2) Dept GMBB, NHGRI/NIH, Bethesda, MD.

Background. The cause of the variation in phenotypic severity in neurofibromatosis type 1 (NF1) is unknown and may be due to genetic modifiers. A differentially expressed transcript that correlates in a statistically significant way with a measurable phenotype is referred to as a "quantitative trait transcript" (QTT). Identification of QTTs (and any corresponding expression quantitative trait loci (eQTL)) is a novel and emerging technique to identify modifier genes in animal models and humans (Passador-Gurgel et al., *Nat Genet* 2007; 39: 264-268; Morley et al., *Nature* 2004; 430: 743-747). We hypothesized that variation in *germline* gene expression of certain genes correlates with variation in the severity of quantifiable phenotypic features ("sub-phenotypes") of NF1. **Methods.** We performed whole-genome transcriptional profiling (Illumina HumanRef-8 arrays) in lymphoblastoid cell lines from 79 individuals affected with NF1 and 23 controls. A single observer quantified severity in multiple NF1 sub-phenotypes, including height, head circumference (OFC), burden of cutaneous neurofibromas (CNF), café-au-lait macules (CALM), Lisch nodules (LN), and cherry hemangiomas (CH). We examined the correlation of the 6 NF1 sub-phenotypes with the level of each of the 22,177 transcripts. To control for multiple testing, we calculated a False Discovery Rate (FDR), in addition to a nominal *P*-value of the significance of the regression. We filtered for FDR (< 0.3), expression range (~2X) and expression level (mean $\log_2 > 6.0$). **Results.** From the statistical analysis, we identified 32 unique transcript-phenotype pairs (QTTs). These included 6 genes whose expression level significantly correlated with CALM burden, 2 with CH burden, 8 with LN burden, 1 with CNF burden, 8 with height and 7 with OFC. We then validated 22 QTTs by quantitative PCR on low-density microfluidic arrays (ABI). By qPCR, 9 QTTs remained statistically significant (nominal *P*-value < 0.05). Many QTTs were gender-specific, even for traits not known for sexual dimorphism (e.g. café-au-lait macule burden). **Conclusions.** We identified 9 putative genetic modifiers (QTTs) of severity in NF1. On-going investigation of these 9 QTTs includes genotyping known eQTLs and gene-specific functional validation.

SESSION 23 – Statistical Genomics
Room 313, Convention Center

Co-Moderators: Nianjun Liu, University of Alabama at Birmingham; and Robert Wojciechowski, NHGRI/NIH, Bethesda, MD

SESSION 24 – Metabolic Diseases
Room 316, Convention Center

64/8:45 **Mutation analysis of homogentisic acid oxidase (*HGD*) in alkaptonuria: Exploring excessive homozygosity.** *T. Vilboux[1], M. Kayser[1,2], C. Ciccone-Stevens[1], T. Markello[1], W. Introne[3], P. Suwannarat[1,4], I. Bernardini[1], R. Fischer[1], K. O'Brien[3], R. Kleta[1,5], M. Huizing[1], W. Gahl[1,3]* 1) MGB, NHGRI, NIH, Bethesda, MD; 2) Warren Clinic Center for Genetics, Saint Francis Health System, Tulsa, OK; 3) Office of Rare Diseases, Intramural Program, Office of the Director NIH, Bethesda, MD; 4) Department of Pediatrics, Children's Hospital of Pittsburgh and University of Pittsburgh School of Medicine, Pittsburgh, PA; 5) UCL, Centre for Nephrology, London, UK.

Alkaptonuria (AKU) is a rare autosomal recessive metabolic disorder characterized by accumulation of homogentisic acid leading to darkened urine, pigmentation of cartilage and other connective tissues (ochronosis), joint and spine arthritis and destruction of cardiac valves. AKU is due to mutations in the homogentisate dioxygenase gene, *HGD*, which converts homogentisic acid to maleylacetoacetic acid in the tyrosine catabolic pathway. We sequenced *HGD* in 79 unrelated affected individuals and 14 affected siblings. We identified 52 *HGD* variants (22 represented novel variants), including 36 missense, 7 splice site, 6 frameshift, 2 nonsense and a no-stop mutation. Most variants reside in exons 3, 6, 8 and 13. Adding the variants found in our study to all previously reported variants results in a total of 89 potential disease-causing sequence variations in AKU patients. Of these variants, 61 are missense variations, for which we assessed the potential effect on the protein using 5 different bioinformatic tools designed for interpretation of missense variants (SIFT, POLYPHEN, PANTHER, PMUT and SNAP). We also analyzed the potential effect of splice site variants using two additional tools (BDGP and NetGene2). Interestingly, 30 patients (24 probands) appeared homozygous for 16 different variants; this high level of homozygosity cannot be explained by consanguinity levels of the probands. In some patients we suspect hemizygosity, which we are confirming using different approaches, including SNP-array analysis and allele quantification by real-time PCR. A potential HGD deletion may be common due to a founder effect or a because of susceptibility for deletion in this area. Such deletion(s) would explain the high level of homozygous AKU patients found in our study and in previously reported works.

SESSION 25 – Genetic Counseling and Testing
Room 323, Convention Center

70/7:45 **A comparison of electronic, self-directed family history collection to counselor-supplemented family history collection.** *F. M. Facio[1], W. G. Feero[1,2], A. Linn[1,3], L. G. Biesecker[1]* 1) Natl Human Genome Res Inst, NIH, Bethesda, MD; 2) Maine-Dartmouth Family Medicine Residency Program, Augusta, ME; 3) Case Western Reserve University, Cleveland, OH.

Introduction: ClinSeq is a study designed to investigate medical sequencing as a clinical research tool for evaluating risk for common conditions. Participants complete the U.S. Surgeon General's My Family Health Portrait (MFHP), a web-based tool for self-directed collection of family history information for six common disorders (heart disease [HD], stroke [ST], diabetes [DM], and colorectal [CRC], breast [BR], and ovarian [OV] cancers). Family Healthware (FHW) is a research tool created by the CDC for the electronic collection of family history that also provides familial risk categorization (weak, moderate, strong). The purpose of this study was to determine the analytic and clinical validity of patient-entered data into MFHP using the genetic counseling interview as a reference. Methods: ClinSeq participants completed MFHP and were subsequently interviewed by a genetic counselor, who supplemented the MFHP family history. The specificities and sensitivities for 1st and 2nd degree relative family histories were calculated. To measure the clinical validity of MFHP, patient entered data from MFHP and data from the genetic counseling interview were then entered separately into FHW to calculate risk scores for the 6 common conditions. Risk scores were compared using kappa statistics as a measure of

correlation. The data was analyzed for sources of inaccuracy of family history data. Results: 150 probands (avg. age 58, F:M 1.3, 96% white) with 888 1st and 2,282 2nd degree relatives were studied. Specificities and sensitivities for 1st degree relatives were for HD (92.0%, 95.7%), ST (99.7%, 98.3%), DM (100%, 97.7%), CRC (99.9%, 90.0%), BR (100%, 96.1%), and OV (99.8%, 100%). Specificities and sensitivities for 2nd degree relatives were for HD (93.9%, 66.7%), ST (99.4%, 82.1%), DM (99.9%, 69.5%), CRC (99.8%, 78.1%), BR (99.9%, 73.5%), and OV (99.7%, 85.7%). Comparison of FHW risk scores derived using MFHP data versus those derived using data from the genetic counseling interview yielded kappa statistics showing substantial agreement, with the exception of HD where agreement was moderate. Sources of error included user mis-categorization of HD cases and omitted relatives. Conclusions: MFHP has a high analytic and clinical validity for collecting family history for five common conditions when compared to MFHP supplemented with a genetic counseling interview. Improving the specificity of diagnostic choices for HD may improve tool performance.

10:00 AM–12:00 NOON

SESSION 33 – Implications in Working with Underserved Communities in the Context of Genetics and Family Health History (Social Issues)

Room 311, Convention Center

Co-Moderators: Wylie Burke, University of Washington School of Medicine, Seattle; and Vence L. Bonham, National Human Genome Research Institute, NIH, Bethesda, MD

Genetic and genomic research bring a great deal of promise to medicine and improvements in public health. As the field moves forward, it is necessary that population groups across diverse communities, cultures, geography, socio-economic status, and ethnicities, consider how genomics is ultimately translated to their communities. There is a particularly rich and, at times, troubling history of genomic research among underserved and underrepresented communities in the U.S. This session presents social implications and lessons learned from community based projects conducted in various communities, including Native Hawaiian and Native Alaskan communities. These projects seek to engage audiences around topics related to genetics and family health history information. This is important for a variety of reasons, including the development of models for the genomic research community to translate genetics education messages and technologies to diverse communities.

7:00 PM–9:00 PM

SESSION 35 – Presidential Symposium: Implementing Personalized Medicine
Coral Ballroom 1 (Mid-Pacific Conference Center), Hilton Hawaiian Village

Moderator: Edward R. B. McCabe, Mattel Children's Hospital, University of California, Los Angeles

Personalized medicine has been one of the long anticipated promises of the Human Genome Project. Now that we have high density single nucleotide polymorphism (SNP) genomic information available at affordable prices for clinical applications, and with the $1000 genome not far away, we are encountering challenges to the implementation of personalized medicine. For example, we recognize that the sequence of the genome is only a part of the information required, and additional "omic dimensions" such as transcriptomics and epigenomics must be integrated. In addition, association data on large and diverse populations across these dimensions will be critical to attain highly predictive and personalized diagnostic information. Personalized medicine should not be limited to diagnostic and prognostic approaches, and must include personalized therapeutic strategies. In this symposium we will explore the challenges as well as the progress in the implementation of personalized medicine.

7:00 PM **Introduction.** E. R. B. McCabe. Mattel Children's Hospital, University of California, Los Angeles.
7:00 PM **Systems medicine, transformational technologies and emergence of P4 medicine (predictive, personalized, preventive and participatory).** L. Hood. Institute for Systems Biology, Seattle, WA.
7:30 PM **Personalized genomes and medicine.** E. Eichler. University of Washington, Seattle.

8:00 PM **Future directions in regenerative medicine.** K. Anseth. University of Colorado, Boulder.
8:30 PM **Implementing personalized medicine.** A.E. Guttmacher. Acting Director, NHGRI/NIH, Bethesda, MD.

Friday, October 23

7:00 AM–9:30 AM

SESSION 38 – Genomics II
Ballroom C, Convention Center

Co-Moderators: Douglas Stewart, NHGRI/NIH, Bethesda, MD; and Max Baur, University of Bonn, Germany

99/7:30 **Genome sequencing coupled with cascade testing as a tool to identify rare disorders masquerading as common disease.** *C. Turner[1], F. M. Facio[1], P. Cherukuri[1,2], P. Cruz[1,2], N. F. Hansen[1,2], J. J. Johnston[1], R. Shamburek[3], J. C. Mullikin[1,2], E. D. Green[1,2], L. G. Biesecker[1], NISC Comparative Sequencing Program* 1) National Human Genome Research Institute, Bethesda, MD; 2) NIH Intramural Sequencing Center, Bethesda, MD; 3) National Heart Lung and Blood Institute, Bethesda, MD.

Clinical research studies that utilize the power of large-scale medical sequencing (LSMS), allow the development of associated infrastructure to enable personalized medicine. As such, the ClinSeq project aims to diagnose and screen patients for disease with the initial focus on atherosclerosis and risk for myocardial infarction. A well-known disease, familial hypercholesterolemia (FH) is a disorder of LDL cholesterol metabolism caused by mutations in LDLR, APOB, or PCSK9. Identified FH-causing mutations in individuals have clinical implications for other family members. Untreated individuals with heterozygous FH have an increased risk of early myocardial infarction and death before the age of 60. This risk is substantially mitigated by aggressive treatment. The World Health Organization estimates the incidence of FH to be 0.2% (1 in 500) in the United States. However, it is estimated that only ~5% of affected individuals have been diagnosed and <10% of diagnosed FH patients are adequately treated. Genetic testing could help address this unmet need. Cascade testing, defined as the identification of an index case followed by subsequent identification of affected family members, has been proposed as the most effective means to identify individuals with FH. Here, we report the identification of eight individuals with mutations causing FH out of an initial cohort of 360 individuals screened by LSMS. In our cohort, the frequency of FH is 2%, which is over ten times the expected population frequency of the disorder and suggests that participants in our study and referring physicians recognize an unmet need for FH testing. Seven previously reported mutations were identified in LDLR (p.N687QfsX29, p.P685L, c.313+1G>A, p.G218VfsX47, p.Y188X, p.W87G, and a deletion of exons 17 and 18), and one in APOB (p.R3527Q). Review of the family history of these eight probands identified 112 relatives for cascade testing with cholesterol screening and possibly mutation analysis. We will present results of the cascade testing of these 112 individuals and treatment uptake. This approach to case finding would be equivalent to screening approximately 50,000 unrelated persons in a direct case finding strategy. Significant potential exists for LSMS to identify families affected with genetic disease, as well as improve disease prevention and treatment efficacy.

104/8:45 **Complete Genome Sequencing of the hunter-gatherers of the Kalahari Desert.** *S. C. Schuster[1], W. Miller[1], E. E. Eichler[2], E. R. Mardis[3], A. Siepel[4], R. Hardison[1], J. C. Mullikin[5], F. Chiaromonte[1], A. Ratan[1], B. Harris[1], B. Giardine[1], D. I. Drautz[1], L. P. Tomsho[1], L. McClellan[1], B. M. Giardine[1], C. Riemer[1], V. Taliwal[4], D. C. Peterson[7], T. T. Harkins[6], V. M. Hayes[7]* 1) Biochemistry and Molecular Bio, Penn State University, University Park, PA; 2) Department of Genome Sciences, University of Washington; 3) Genome Sequencing Center, Washington University in St. Louis; 4) Biological Statistics & Computational Biology, Cornell University; 5) National Human genome research Institute; 6) Roche Applied Sciences; 7) Children's Cancer Institute of Australia, Sydney, Australia.

The Kalahari Bushmen may be the last hunter-gathers of our times. Their evolutionary and cultural histories distinguish them from all other ethnic groups inside and outside of Africa. They are believed to be the oldest human population, and therefore represent a unique and ancient genetic heritage. In this study we investigate the

extent of genetic variation of the Bushman genome in comparison to other publically available human genomes. For this undertaking we have performed whole-genome shotgun sequencing using Roche/454 Titanium chemistry of two complete genomes, together with exome sequencing of two matched and two additional samples. Our study investigates the SNP diversity, indel and repeat content, as well as copy number variation of this ethnic group against the human reference sequence. The genetic variations detected by sequencing are being validated in parallel using DNA SNP arrays. The study therefore aims at generating a high-quality version of a human genome that defines the outer boundaries of human diversity. The new data will aid the interpretation of other human genome sequences. As a large number of the discovered genetic variants are novel and currently not contained in dbSNP, this project will aid future studies on rare human alleles. Also, with current genome-wide association studies being largely limited to modern populations, disease associations have generally been mapped to broad genomic regions. Human diversity studies of the Bushmen will facilitate the narrowing of these regions. More important, we believe, will be the advantage to the Bushmen. It is hoped that availability of the first Southern African human genome sequences will help the development of drugs that benefit this ethnic group. Moreover, the data highlight the genetic richness of these largely forgotten people of Africa, emphasizing the importance of preserving this unparalleled archive of human cultural and genetic history, and spot-lighting the need to assist indigenous groups in Africa and elsewhere in their fight against home-land loss, disease and famine.

105/9:00 **Diversity survey of the chronic diabetic wound microbiome.** *E. A. Grice[1], L. J. Yockey[1], S. Conlan[1], N. I. S. C. Comparative Sequencing Program[2], K. W. Liechty[3], J. A. Segre[1]* 1) Genetics and Molecular Biology Branch, NHGRI, NIH, Bethesda, MD; 2) NIH Intramural Sequencing Center, NHGRI, NIH, Bethesda, MD; 3) Department of Surgery, Children's Hospital of Philadelphia, Philadelphia, PA.

As the rate of obesity increases worldwide, so does the incidence of type 2 diabetes and associated complications. One of the most common and costly complications of diabetes is chronic, non-healing wounds. Increased bacterial colonization and/or infection of diabetic wounds has a deleterious effect on healing and is a significant source of clinical complication. The precise relationship between microbes and impaired wound healing remains unclear despite general acknowledgement that the resident microflora is a source of complications. The main limitation to examining the role of bacteria in the pathogenesis of the diabetic wound healing impairment is the reliance on culture-based assays. Some bacterial species colonizing the diabetic wound have been identified in this manner, but these results are biased because it is estimated that only ~1% of bacteria are cultivable. We recently demonstrated the utility of sequencing the prokaryote-specific 16S small-subunit ribosomal RNA genes in order to profile the topographical and temporal bacterial diversity of normal human skin.

We hypothesize that unique microbial populations and/or shifts in microbial community structure contribute to impaired wound healing in diabetics and can be detected using less-biased genomic methods. Using an excisional wound model in genetically diabetic mice homozygous for the *Lepr^{db}* mutation (db/db) and non-diabetic heterozygous controls (db/+), we collected wound swabs over a time course of 28 days. 384 near full-length 16S genes were sequenced from each wound at each time point. Sequences were assigned to the prokaryotic taxonomy and community membership, structure, and phylogenetic lineages were compared. Using this method, we have identified a unique shift in the bacterial communities populating diabetic skin and wounds in the db/db mouse model. We are confirming that this selective shift also occurs in the human condition. These studies are a foundation for our long-term goal to elucidate the contribution of the diabetic wound microbiome to impaired wound healing and translate this into novel therapeutic approaches.

1:00 PM-3:30 PM

SESSION 45 - Genomics III
Ballroom C, Convention Center

176/3:15 **Mapping of the pseudoautosomal boundary in the domestic dog and comparison with mouse and human sex chromosomes.** *J. D. Degenhardt[1], A. Auton[2], A. R. Boyko[1], T. Spady[3], P. Quignon[3], B. von Holdt[4], A. G. Clark[5], R.*

Wayne[4], *E. A. Ostrander*[3], *C. D. Bustamante*[1] 1) Department of Biological Statistics and Computational Biology, Cornell University, Ithaca, NY; 2) Wellcome Trust Centre for Human Genetics, Oxford University, Oxford UK; 3) National Human Genome Research Institute, National Institute of Health, Bethesda, MD. 20892; 4) Department of Ecology and Evolutionary Biology, University of California Los Angeles, CA, 90095; 5) Department of Molecular Biology and Genetics, Cornell University, Ithaca, NY, 14853.

The mammalian pseudoautosomal region (PAR) is a short segment of homology on the X and Y-chromosomes. This shared region allows for pairing, and therefore proper segregation, of the sex chomosomes during male meiosis, and represents the sole region of X/Y recombination. To date this region has been mapped in only a small number of taxonomically divergent mammalian groups (including human/chimp, mouse, horse and cat). Comparative analysis of these groups has shown that there has been an independent reduction in the size of the PAR compared to the ancestral eutherian PAR in each of these groups. Here we present a novel method for the mapping of the PAR boundary using a comparison of male and female intensity data and heterozygosity from Affymetrix SNP chips and map the location of this boundary in the domestic dog and wolf. We show that the position of the PAR boundary is consistent between domestic dog and wolves and also between the domestic dog and the domestic cat suggesting that the position of the PAR boundary has been relatively stable over the last ~42 million years of carnivore evolution. However, we also find evidence of lower recombination near the PAR boundary in the domestic dog suggesting that the exact location of the boundary may show some instability. We examine the gene content of canine PAR and compare this to the human and mouse sex chromosomes. We find a high degree of similarity in the genic content of the canine PAR and human PAR and adjacent X and Y chromosomal regions but no similarity with the mouse PAR. Based on this finding we suggest a more extensive restructuring of the mouse sex chromosomes has occurred compared to other mammals. With the addition of the canine PAR we able to use a comparative genomics approach to reconstruct the evolutionary history of structural changes in the human PAR. We find two regions representing likely translocations to the human Y-chromosome, which may have disrupted the X/Y homology and lead to the shortening of the human PAR.

SESSION 48 – Clinical Genetics: Heads Up
Room 323, Convention Center

200/1:45 **Comprehensive Analysis of Human Holoprosencephaly Reveals Distinct Genotype-Phenotype Correlations.** *M. Muenke, B. Solomon, D. Pineda, J. Velez, A. Keaton, F. Lacbawan, E. Roessler* Medical Genetics Branch, NHGRI/NIH, Bethesda, MD.

Holoprosencephaly (HPE), the most common malformation of the human forebrain, may be due to cytogenetic anomalies, teratogenic influences, or mutations in one of at least 12 identified HPE-associated genes. Here we report the results of testing of mutations in the 4 most common HPE-associated genes (SHH, ZIC2, SIX3, and TGIF) as well as additional rare HPE-associated genes and correlate these findings with detailed clinical data as well as with functional analyses. In a comprehensive analysis of approximately 1000 individuals with HPE-spectrum anomalies we find mutations in HPE-associated genes in 25-30% of probands with normal karyotypes. To date, these include 128 families with mutations in SHH, 93 with mutations in ZIC2, 64 with mutations in SIX3, and 19 with mutations in TGIF. While there is a clear overall HPE-specific phenotype, our large cohort allows us to differentiate between the clinical characteristics of patients with mutations in the various genes, and to use functional analyses to make predictions of HPE severity among patients with mutations in the same gene. We find mutations in SHH and SIX3 in multiple multigenerational kindreds, and mutations in SHH can be correlated with specific end-organ anomalies including the liver (i.e. fatty infiltration) and adrenal glands (i.e. hypoplasia). Mutations in ZIC2 are more often de novo than with any other HPE-associated genes, result in typical HPE facies in only 35% of patients, and may also result in dorsal brain and neural tube defects. Additionally, we describe a previously unrecognized facial phenotype in some patients with ZIC2 mutations consisting of bitemporal narrowing, upslanting palpebral fissures, a short anteverted nasal tip, broad and well-demarcated philtrums, and disproportionately large ears. Patients with mutations in SIX3 over-represent the more severe forms of HPE and we can predict

HPE severity using a functional analysis in zebrafish. While mutations in TGIF are less common, chromosomal aberrations affecting the region occur relatively frequently and may result in sequelae due to deletions of TGIF and nearby genes. Finally, we are further able to explore alternate models of the genetic pathogenesis of HPE and because of these clinical findings we present new recommendations for the genetic testing of probands with HPE.

SESSION 49 – Skeletal Disorders
Room 311, Convention Center

214/2:45 **Mutations in *IFT139* contribute both causal and modifying alleles across the ciliopathy spectrum.** *E. E. Davis[1,2], Q. Zhang[3], Q. Liu[3], J. Hartley[4], D. M. Muzny[5], A. C. Young[6], P. Cruz[6], J. C. Mullikin[6], P. J. Scambler[7], P. L. Beales[7], J. G. Gleeson[8], F. Hildebrandt[9], E. R. Maher[4], T. Attie-Bitach[10], H. Dollfus[11], C. A. Johnson[12], E. D. Green[6], R. A. Gibbs[5], E. A. Pierce[3], N. Katsanis[1,2,13]* 1) McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland 21205, USA; 2) Center for Human Disease Modeling, Department of Cell Biology, Duke University Medical Center, Durham, North Carolina, 27710 USA; 3) F.M. Kirby Center for Molecular Ophthalmology, University of Pennsylvania School of Medicine, Philadelphia, PA, 19104; 4) Department of Medical and Molecular Genetics, Institute of Biomedical Research, University of Birmingham, Birmingham, United Kingdom; 5) Human Genome Sequencing Center, Baylor College of Medicine, Houston, Texas 77030, USA; 6) Genome Technology Branch, National Human Genome Research Institute, National Institutes of Health, Bethesda, Maryland 20892, USA; 7) Molecular Medicine Unit, Institute of Child Health, University College London, London WC1N 1EH, UK; 8) Department of Neurosciences, Howard Hughes Medical Institute, University of California, San Diego, La Jolla, CA 92093, USA; 9) Departments of Human Genetics and Pediatrics, Howard Hughes Medical Institute, University of Michigan, Ann Arbor, Michigan 48105, USA; 10) Département de Génétique et INSERM U-781, Hôpital Necker-Enfants Malades, Paris Cedex 15, France; 11) Laboratoire de Génétique Médicale EA 3949, Faculté de Médecine de Strasbourg, Université Louis Pasteur, 67085 Strasbourg, France; 12) Section of Ophthalmology and Neurosciences, Leeds Institute of Molecular Medicine, St. James's University Hospital, Leeds, United Kingdom; 13) Wilmer Eye Institute and Department of Molecular Biology and Genetics, Johns Hopkins University School of Medicine, Baltimore Maryland 21205, USA.

Perturbation of cilia leads to a broad range of overlapping phenotypes in humans, termed collectively as ciliopathies. This grouping is also underscored by genetic overlap, since some ciliopathy genes can also contribute modifying alleles to related, but clinically distinct disorders. Here we show that mutations in *IFT139*, a component of the retrograde intraflagellar transport (IFT) complex, and the causal locus of the *alien* mouse mutant, cause ciliopathies that range from isolated nephronophthisis (NPHP), to neonatal lethal Jeune Asphyxiating Thoracic Dystrophy (JATD), and Meckel-Gruber Syndrome (MKS). Moreover, systematic medical resequencing of a large, clinically diverse ciliopathy cohort and matched controls showed a significant enrichment of rare nonsynonymous alleles in patients. In vitro and in vivo evaluations showed most variants to be pathogenic and suggested that *IFT139* contributes null and hypomorphic alleles to as much as 5% of ciliopathy patients, with a marked excess of pathogenic alleles in severe phenotypes. Our data illustrate how genetic lesions in a ciliary transcript can be causally associated with the breadth of ciliopathies in humans and highlight how saturated resequencing and functional analysis of all variants can inform the genetic architecture of related clinical phenotypes.

Saturday, October 24

7:00 AM–9:30 AM

Concurrent Platform Sessions IV (53-59)
SESSION 53 – Cancer Genome-wide Association Studies
Ballroom A, Convention Center

222/8:15 **Nevus and pigmentation loci are associated with melanoma in genome-wide association study of European and Australian populations.** *D. Bishop[1], F. Demenais[2], M. M. Iles[1], M. Harland[1], J. C. Taylor[1], E. Corda[2], B. Bakker[3], P. A. Kanetsky[4], K. M. Brown[5], A. M. Goldstein[6], E. M. Gillanders[7], D. E. Elder[8], N. A.*

Gruis[9], N. K. Hayward[10], J. H. Barrett[1], J. A. Newton Bishop[1], The GenoMEL Consortium 1) Gen Epidemology Lab, St James Univ Hosp, Leeds, United Kingdom; 2) Fondation Jean Dausset-CEPH, 75010, Paris, France; 3) Department of Clinical Genetics, Center of Human and Clinical Genetics, Leiden University Medical Center, Leiden, The Netherlands; 4) Centre for Clinical Epidemiology & Biostatistics and Department of Biostatistics & Epidemiology, 219 Blockley Hall, University of Pennsylvania, USA; 5) Melanoma Genomics Laboratory, The Translational Genomics Research Institute (TGen), 445 N. Fifth Street, Phoenix, AZ 85004, USA; 6) Genetic Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute. NIH, Bethesda, MD 20892-7236, USA; 7) Inherited Disease Research Branch, National Human Genome Research Institute, National Institutes of Health, Baltimore, Maryland 21224, USA; 8) Department of Pathology and Laboratory Medicine, University of Pennsylvania School of Medicine, Philadelphia, PA 19104, USA; 9) Department of Dermatology, Leiden University Medical Centre, Leiden, The Netherlands; 10) Queensland Institute of Medical Research. 300 Herston Rd, Herston, QLD 4029, Australia.

On behalf of the GenoMEL melanoma genetics consortium we conducted a genome-wide association study of melanoma based on 317k SNPs in 1650 genetically-enriched cases and 4336 controls from centres across Europe and Australia. Three loci were identified and replicated using two further data sets (one of 1149 genetically-enriched cases and 964 controls and one of 1163 population-based cases and 903 controls): 16q24 encompassing *MC1R* (lead SNP rs258322, $p=2.5x10^{-27}$), the *TYR* pigmentation gene on 11q14-q21 ($p=2.4x10^{-14}$ for rs1393350), and 9p21 adjacent to *MTAP* and the familial melanoma gene *CDKN2A* ($p=4.0x10^{-7}$ for rs7023329), a locus also identified in an independent genome-wide association study of nevus count in UK twins. Multiple logistic regression analysis showed an independent effect of 6 SNPs at these loci on melanoma risk and no evidence of departure from a joint multiplicative effect. Despite variation in allele frequencies, and large differences in sun exposure, effect sizes were homogeneous across centres. We also replicated two further melanoma loci, not reaching genome-wide significance here, but identified in independent studies: a region on chromosome 20 close to *ASIP* ($p=1.3x10^{-8}$ for rs1885120) and one on chromosome 22 previously associated with nevus count ($p=2.4x10^{-9}$ for rs2284063). We investigated these three pigmentation loci (*MC1R*, *TYR* and *ASIP*) and two nevus-related loci (*MTAP*/*CDKN2A* and chromosome 22) in a UK population-based extensively-phenotyped melanoma case-control study and observed that the effect of the SNPs on melanoma risk is partially, but not entirely, attenuated by the related phenotype. Further work is underway to impute genotypes genome-wide to help identify further signals for follow-up, to fine-map these loci and to further characterise their effect on melanoma risk taking into account phenotype and environmental exposures.

7:00 AM–9:30 AM

Concurrent Platform Sessions IV (53-59)
SESSION 54 – Clinical Genetics: Syndromes
Ballroom B, Convention Center

230/7:45 **Expression as a cellular phenotype for Proteus syndrome.** *M. J. Lindhurst[1], T. C. Huber[1], A. Elkahloun[2], L. G. Biesecker[1]* 1) GDRB, NHGRI/NIH, Bethesda, MD; 2) CGB, NHGRI/NIH, Bethesda, MD.

Proteus syndrome (PS) is rare, sporadic disorder that is characterized by progressive, disproportionate, asymmetric postnatal overgrowth that is mosaic in nature. Characteristic manifestations include cerebriform connective tissue nevi (CCTN), linear epidermal nevi, disproportionate overgrowth of the limbs, and vascular malformations. Happle hypothesized that a genetic alteration occurs post-zygotically, which causes growth dysregulation in tissues with mutant cells. Because PS is not inherited, traditional methods to identify the molecular etiology have not been successful. Complicating efforts to study this disorder is the fact that while lesions can be identified at the level of the tissue, a cellular phenotype has yet to be discovered. We have compared the transcriptomes of cells cultured from affected and unaffected tissues of Proteus patients and also compared them to the transcritomes of non-Proteus cells. RNA from 29 cell lines derived from five Proteus patients and seven non-Proteus individuals was hybridized to Affymetrix GeneChip Human Gene 1.0 ST arrays. Twenty cell lines were from dermal fibroblasts and were analyzed using GeneSifter Analysis Edition

software. A comparison of fibroblast transcriptomes from affected Proteus cells and non-Proteus cells showed over 500 genes with altered expression. We found up regulation of six genes that made biological sense given the nature of the lesions commonly found in PS. They are: *COL14A1*, *COL15A1*, *COL6A3*, *COL21A1*, *FBN2*, and *CD9* and their up-regulation has been confirmed by quantitative PCR. In addition to the qPCR validation of the array results, preliminary data show that circulating leukocytes have increased levels of CD9 protein by FACS (fluorescence activated cell sorting). CCTNs found in PS contain massive amounts of collagen. FBN2 is a component of connective tissue microfibrils and may be involved in elastic fiber assembly. CD9 is a cell surface molecule with many functions including modulation of cell adhesion and motility. These gene products are all components of the extracellular matrix or are involved cell growth and migration both of which are abnormal in PS. Identification of these and other transcripts that are mis-regulated in affected PS cells is an important step in developing tools for the isolation of pure populations of cells that can be used to identify the molecular lesion responsible for PS and to develop more rigorous diagnostic criteria for the disorder.

231/8:00 **Quantitative assessment of endocrinologic and cognitive abnormalities in a cohort of 53 patients with Bardet-Biedl syndrome.** *D. Ng[1], P. P. Feuillan[1], J. C. Sapp[1], A. Bottar[1], L. Guevara[1], E. Wiggs[2], B. Brooks[3], L. G. Biesecker[1]* 1) Genet Disease Research Branch, NHGRI, NIH, Bethesda, MD; 2) Office of the Clinical Director, NINDS, NIH, Bethesda, MD; 3) Ophthalmic Clinical Genetics Section, NEI, NIH, Bethesda, MD.

Bardet-Biedl syndrome (BBS, OMIM #209900) is a disorder of primary cilium. BBS is a rare pleiotropic genetic disorder affecting the development of multiple organ systems and is characterized by cone-rod dystrophy, postaxial polydactyly, truncal obesity, cognitive impairment, male hypogonadism, abnormal genital tract in females, and renal malformations. Past studies have found a high frequency of endocrine related disorders among BBS patients and include obesity (72%), irregular menses, male hypogenitalism (89%), and pubertal delay (31%). We report a detailed cross-sectional assessment of the cognitive, endocrine and metabolic perturbations in BBS to include BMI, fat distribution, glucose metabolism (assessed with oral glucose tolerance testing [OGTT]), characterization of hypogenitalism, ultrasound measurements of ovaries, uterus, testes and formal neuropsychological evaluations. In the first 36 months of this study, 40 families containing 53 affected individuals have been enrolled. Twelve of these families had two or more affected siblings. The age range of the BBS subjects was 1.5-31 yr (mean 10.4 ± 6.8 yr). Physical findings include retinal rod/cone dystrophy (100%), polydactyly (78%), renal anomalies (60%), and microphallus (30%). The majority of affected subjects were obese (mean total body fat 41 ± 8%; normal, 22 ± 9%). The exceptions were two children with BBS6/MKKS mutations who had normal BMI. Most of the 53 patients had elevated serum glucose and insulin at baseline and between 30-120 min during the OGTT. Many of these subjects had evidence of dyslipidemia; serum cholesterol > 200 mg/dL (19%), HDL < 40 mg/dL (44%), and triglycerides > 150 mg/dL (40%). Among the fifty-three patients who underwent neuropsychological evaluations, thirty-eight full-scale IQ (FSIQ) scores were obtained. The mean FSIQ was 75.87 (range 41 to 112). These scores were matched with the patients' visual acuities and there was no correlation between poor visual acuity and IQ. Patients affected with BBS have an increased risk for developing elements of the "metabolic syndrome". By characterizing the metabolic phenotype of BBS patients, we hope to gain a better understanding of the relationship between ciliopathies and hyperhagia; determine if there are any differences among the 12 BBS genotypes, and develop effective treatment for this hyperphagia-induced obesity/metabolic syndrome.

10:00 AM–12:00 NOON
Concurrent Platform Sessions V (60-66)
SESSION 60 – Molecular Basis of Mendelian Disorders
Ballroom A, Convention Center

293/11:30 **Founder Mutation Causing Recessive Type VIII Osteogenesis Imperfecta in West Africans and African-Americans is Contemporaneous with Atlantic Slave Trade.** *W. A. Cabral[1], A. M. Barnes[1], A. Adeyemo[2], K. Cushing[3], D. Chitayat[4], F. D. Porter[5], S. R. Panny[6], F. Majid[6], J. Bailey-Wilson[7], L. Brody[3], C. N. Rotimi[2], J. C. Marini[1]* 1) BEMB, NICHD, NIH,

Bethesda, MD; 2) CGHD, NHGRI, NIH, Bethesda, MD; 3) GTB, NHGRI, NIH, Bethesda, MD; 4) Hospital for Sick Children, Mount Sinai Hospital, Toronto, Canada; 5) HDB, NICHD, NIH, Bethesda, MD; 6) MD Dept of Health, Baltimore, MD; 7) SGS, NHGRI, NIH, Baltimore, MD.

Recessive osteogenesis imperfecta (OI) is caused by defects in the genes encoding cartilage-associated protein (*CRTAP*) or prolyl 3-hydroxylase 1 (P3H1/*LEPRE1*), which form the ER-resident collagen prolyl 3-hydroxylation complex together with cyclophilin B (*PPIB*). Deficiency of P3H1 causes the severe to lethal bone dysplasia type VIII OI (OMIM #610915). We have previously identified a *LEPRE1* mutation, IVS5+1G>T, in unrelated African Americans (AA) and contemporary West African (WA) immigrants (Nat Genet 39:359-365, 2007). Our screening of gDNA from 3 groups of Mid-Atlantic AAs (Pennsylvania, Maryland, and Washington, DC) determined a carrier incidence of 1/200-300 for this mutation, predicting occurrence of homozygous lethal type VIII OI in about 1/250,000 births in this population. To trace the origin of this mutation, we screened gDNA from more than 1200 contemporary WAs. Nineteen of 1284 unrelated individuals (1.48%) from Nigeria and Ghana were heterozygous carriers, half of whom were from the Yoruba or Ibo ethnic groups of Nigeria. The high carrier frequency for this founder mutation among WAs predicts that this mutation alone would cause recessive OI in 1/18,250 births in WAs, which is equal to the incidence of *de novo* dominant OI in North America. To estimate the age of the mutation, we examined microsatellites and short tandem repeats spanning a 4.2 MB region surrounding the *LEPRE1* gene on chromosome 1p. Disease allele haplotypes were determined for probands and carriers from 10 contemporary WA and 3 AA families. All carriers shared a haplotype of 175-425Kb. Using the linkage disequilibrium analysis method of Rannala & Slatkin (2000), the mutation was estimated to have originated between 385 and 630 years before present (1379-1624 C.E.). This timing is consistent with the model that this West African allele was transported to the Americas during the peak of the Atlantic slave trade (1450-1860 C.E.). Furthermore, expansion of this allele in the West African population was approximately concurrent with transport to the New World, making it difficult to estimate the number of potential carriers transported to the Americas. We are currently exploring several hypotheses to explain the existence of the high carrier frequency for the *LEPRE1* IVS5+1G>T mutation in WAs, including genetic drift, positive selection for heterozygotes and as a "hitchhiker" linked to a selected allele of a neighboring gene on chromosome 1.

10:00 AM–12:00 NOON
Concurrent Platform Sessions V (60-66)
SESSION 63 – Human Mapping: Methods and Applications
Room 313, Convention Center

317/11:30 **Using High density 1meg SNP genotyping arrays to determine the lower size for anomalous contiguous homozygosity as a methodology for generating candidate genes in the NIH Undiagnosed Disease Program.** *T. Markello[1], D. Adams[1], W. A. Gahl[1,2,3]* 1) Med Gen Branch, NIH/NHGRI, Bethesda, MD; 2) Head, Intramural Program Office of Rare Diseases, NIH, Bethesda MD; 3) Clinical Director, NIH/NHGRI, Bethesda MD.

Recent recognition of regions of contiguous homozygosity seen by SNP array genotyping has given rise to a potential way to uncover identity by descent and segmental uniparental disomy. This allows determination of submicroscopic variations in the individual human genome undetectable by Giemsa staining, FISH studies or comparative genomic hybridization. To define the lower size limit when using high density SNP arrays for single proband homozygosity analysis, we measured the correlation lengths of homozygosity runs of consecutive snps within every one megabase interval over all chromosomes in 54 samples . We used the Illumina 1MDUO array as the single platform for genotyping. Critical to this determination is the truncating effect on the correlation lengths caused by spurious heterozygosity from low signal quality SNPs. Using group scores and individual scores as filter parameters, we found that removing less than 10% of the total snps removed 95% of the spurious heterozygous samples and made quantitative homozygosity length correlation analysis feasible for 81% of the genome. We analyzed 27 controls and 27probands in the Undiagnosed Disease Program(UDP)recently initiated at the NIH. We found each chromosome interval has a different normal homozygosity length depending on snp density and recombination frequency that roughly follows the HapMap frequencies. The occurrence of contiguous snps declines rapidly for most

intervals at 50 to 300 contiguous snps, and at 200kb to 750kb for the total homozygous length. Regions that exceed these sizes are seen in 67% (18/27) of individuals in the Undiagnosed Disease Cohort versus only 18% (5/27) for parents and unaffected sibling controls. The sum of these regions, normalized to the total genomic length visible in the snp array, gives good correlation (r^2=0.91) in 26 known consanguinity controls from 13 different pedigrees. Defining the minimum limits for declaring excess homozygosity, on a region by region basis, will facilitate the ability to call very small regions anomalous, and improve the ability to generate candidate loci for genetic recessive disorders. Combined with available haplotyping tools, this approach allows computationally simplified linkage in favorable cases. We describe one case of linkage found using this method and a second case of cryptic homozygosity not known from the medical history.

10:00 AM–12:00 NOON

Concurrent Platform Sessions V (60-66)
SESSION 64 – Genome-wide Association Studies of Diverse Complex Traits
Room 316, Convention Center

Co-Moderators: Alexander Wilson, NIH/NHGRI, Baltimore, MD; and Sudha Iyengar, Case Western Reserve University, Cleveland, OH

2:00 PM–4:00 PM

SESSION 72 – Special Symposium on the 200th Anniversary of the Birth of Charles Darwin and the 150th Anniversary of the Publication of *On the Origin of Species by Means of Natural Selection, or the Preservation of Favoured Races in the Struggle for Life*
Ballroom B, Convention Center

Moderator: Leslie G. Biesecker, GDRB/NHGRI/NIH, Bethesda, MD

It has not been more clearly or succinctly stated than by Theodosius Dobzhansky in his 1973 essay, "Nothing in Biology Makes Sense Except in the Light of Evolution": Evolution is the central organizing principle of biology. But evolutionary biology is not historical, static, or sacred. It is a major area of current investigation vitalized by modern molecular and computational biology, and a major education and public policy challenge for geneticists. This symposium highlights dynamic and exciting speakers who will present current topics in evolutionary biology research, and the controversies and challenges surrounding the ongoing battles of biologic versus creationist teaching in the U. S. education system.

2:00 PM **Introduction.** L. G. Biesecker. GDRB/NHGRI/NIH, Bethesda, MD.
2:10 PM **Pursuing signals of selection in the Human Genome.** P. Sabeti. Harvard University, Boston, MA.
2:35 PM **Population genetic inference in the personal genome era.** C. Bustamante. Cornell University, Ithaca, NY.
3:00 PM **Human Evolution and Adaption in Africa.** S. Tishkoff. University of Pennsylvania, Philadelphia, PA.
3:25 PM **Evolution, education and creationism: 150 years after** *The Origin***.** B. Alters. McGill University, Montreal, Quebec, Canada.