PRESS RELEASE

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Media Contact:
ASHG Press Office
240-281-2386
press@ashg.org

Understanding the Structure of the Human Genome: What is Essential, What is Expendable, and What is Important to Health?

Researchers Present Latest Findings from Genome Sequencing Studies at The American Society of Human Genetics 59th Annual Meeting in Honolulu

BETHESDA, MD – October 21, 2009 – Thousands of the world's top scientists and clinicians in the human genetics field will convene to present their latest research at the 59th Annual Meeting of The American Society of Human Genetics (ASHG) in Honolulu, Hawaii, on October 20-24, 2009.

ASHG is the primary professional membership organization for human genetics specialists worldwide, representing nearly 8,000 researchers, academicians, clinicians, genetic counselors, nurses and others with a special interest in the field. The Society's Annual Meeting is the world's largest gathering of human genetics professionals and a forum for renowned experts in the field to share their latest research results.

At the ASHG 2009 Annual Meeting, a number of scientific presentations will feature important new research findings that advance our understanding of the structure of the human genome and provide a clearer picture of the impact that certain variations in genome structure will have on human health and disease.

ASHG will be hosting a press briefing session to highlight a selection of the most interesting and insightful research results on human genome structure and variation presented at the 59th Annual Meeting. Each of the abstracts featured in this press briefing session provides more information about the structure of the human genome and offers new insights into recent advances in high-throughput sequencing technology and novel research methods that allow a more comprehensive look at the complex architecture of the human genome and the impact that variations in specific areas may have on health.

The expert panelists speaking in this session will cover different topic areas related to the study of genome architecture and mapping – from identifying the 'essential' areas of the human genome that play an important role in human health, to using high-depth sequencing methods to discover new regions of the human genome that may contribute to the development of a specific disease (such as cancer), to pinpointing the 'dispensable' (or non-essential) areas of the human genome that can withstand DNA losses without any perceptible consequences on health outcomes.

ASHG invites members of the media to attend this press briefing session titled, *"Understanding the Structure of the Human Genome: What is Essential, What is Expendable, and What is Important to*

Health?," which will be held on Wednesday, October 21, 2009, from 1:00-2:00 p.m. (HST) in the ASHG Press Briefing Room, located on the third level of the Hawaii Convention Center (Room #319A). Members of the press who cannot attend this event in person can register to view the webcast of this session that will be posted online about two to three hours after the event has ended *(*see section in red below for more information about the webcast)*.

This press briefing will be moderated by the ASHG 2009 Program Committee Director, Leslie Biesecker, MD, Senior Investigator and Chief of the Genetic Disease Research Branch at the National Human Genome Research Institute (NHGRI) of the National Institutes of Health (NIH). Dr. Biesecker will provide an overview of the session topic and the implications of the latest findings in this research area. The other three speakers will discuss key findings from their research that is being presented in plenary and platform scientific sessions at the ASHG 2009 meeting. The research presented in this session by the following three speakers focuses on investigating the specific components of DNA sequencing to obtain a more in-depth understanding of the structure of the human genome and how variations in some DNA regions can contribute to disease – and in others, make no impact on health at all:

- Michael Bamshad, MD – *"Researchers Identify New Approach to Discovering the Basis of Rare Single Gene Disorders through Exome Resequencing"*
- Gad Getz, PhD – *"The Next-Generation View of the Cancer Genome"*
- Terry Vrijenhoek – *"The First Map of Dispensable Regions in the Human Genome: Large DNA Losses in 'Non-essential' Regions of Genome Are Not a Threat to Healthy Life"*

Dr. Biesecker will also provide a brief overview of the crucial role that recent advances in technology and high-throughput sequencing have played in enabling genetic scientists to better understand the structure of the human genome and make important discoveries in this particular area of research. With the increasingly widespread use and application of these superior technological tools, scientists are now able to generate accurate, detailed results through methods that are faster, cheaper and more efficient.

Brief summaries of the major research findings reported in these three abstracts are included below:

Researchers Identify New Approach to Discovering the Basis of Rare Single Gene Disorders Through Exome Resequencing

The study of rare single gene (or monogenic) diseases that result from modifications in a single gene occurring in all cells of the body have been of incredible value to biomedical research, as the identification of the genes underlying disease yields important medical insights. Although single gene diseases affect millions of people worldwide, the genetic basis of many of them still has yet to be discovered. In most instances, this is because only a small number of affected individuals and/or families are known to exist, which limits the power of traditional gene mapping strategies.

As most genetic variants that cause monogenic diseases affect coding DNA sequences, comprehensive resequencing of all human genes has the potential to serve as a genome-wide scan to find the gene(s) underlying rare monogenic diseases. While the routine sequencing of full human genomes continues to be cost prohibitive, the cost of sequencing all protein-coding regions, called exomes[1], may soon be on par with that of common genotyping chips.

Michael Bamshad, PhD, Professor of Pediatrics and Adjunct Professor of Genome Sciences at the University of Washington in Seattle, and his research team set out to sequence the exomes of twelve humans, including eight healthy HapMap individuals representing three populations, and four unrelated individuals with a rare, dominantly inherited disorder called Freeman-Sheldon syndrome (FSS). They did this in an effort to evaluate whether rare abnormal single genes might be found by comparing massive

[1] The *exome* is the ~1% of the human genome that is most functionally relevant and most likely to cause perceptible differences in phenotype (including health and disease outcomes); it is comprised of short segments of DNA called exons that code for proteins.

genome sequencing data from affected individuals against that of known normal individuals. If successful, this new approach would allow researchers to search for potential candidate genes for single gene disorders using a much cheaper – yet still highly sensitive – type of sequencing technology.

After completing their analyses, Bamshad's research team was able to successfully assess nearly 96% of each human exome, and demonstrate the specific identification of rare and common variants of coding sequence. They were able to show that the gene for a monogenic disorder (i.e., FSS) can be identified by completing exome sequencing of a small number of unrelated, affected individuals (i.e., HapMap data). In this case, the researchers completed their analyses using data from just four individuals with FSS, thereby showing that this new approach does not require a large number of study participants in order to be successful.

"An important outcome of this work is that low-cost, high throughput technologies for exome resequencing have the potential to rapidly accelerate the discovery of candidate genes and mutations that contribute to rare monogenic diseases that have been resistant to conventional research approaches in the past," Bamshad explained. "Furthermore, this strategy may also be applicable to identifying genetic modifiers of common monogenic diseases (e.g., cystic fibrosis) and variants influencing risk for common diseases, though much larger sample sizes are likely to be needed."

The Next-Generation View of the Cancer Genome

Recent advances in genome sequencing technology have dramatically increased scientific researchers' ability to comprehensively and accurately characterize the genomic alterations in tumor genomes. During the past year, genetic scientists have witnessed the initial steps of this revolution, from sequencing of a single tumor genome to the current research, which involved sequencing and analyzing about 20 tumor/normal pairs from various tumor types, as well as sequencing of whole exomes in a large number of samples.

Gad Getz, PhD, Team Leader for Cancer Genomics Analysis in the Genome Biology Program at the Broad Institute of MIT and Harvard, and his research team set out to distill these vast amounts of data to the small number of somatic events required for the development of highly accurate analysis tools which are both sensitive and specific. These data were then combined together to form a systematic and robust analysis pipeline that spanned from raw sequencing output to significant events in cancer development.

In his press briefing presentation, Dr. Getz will describe the results of applying these methods to a wide variety of data sets, including 20 whole cancer genomes.

"The emerging picture from this research is that tumor genomes vary in terms of their rates of mutation and – even more pronounced – in terms of the number of rearrangements and copy-number alterations that they harbor," Dr. Getz explained. "Our research results indicate that some genomes have very few alterations and others are highly rearranged."

Getz further illustrated his point with the following example: "In ovarian cancers, for instance, we have detected rearrangements involving tumor-suppressor genes, which suggests that rearrangements are another mechanism of tumor-suppressor gene de-activation."

The First Map of Dispensable Regions in the Human Genome: Large DNA Losses in 'Non-essential' Regions of Genome Are Not a Threat to Healthy Life

At least 2.7 million base pairs of the human genome are dispensable, or non-essential. They reside in 58 distinct regions of DNA that can be completely lost without obvious consequences on people's health. Medical geneticist Terry Vrijenhoek from Radboud University Nijmegen (the Netherlands) and his research team led by senior investigator Dr. Joris Veltman are the first to provide a comprehensive overview of these 'lost' regions of the human genome.

Previous microarray and next-generation sequencing studies have revealed many disease-related genetic variants in the 'essential' parts of the human genome. Building on these findings, Vrijenhoek and his colleagues used Affymetrix's microarray technology to identify homozygous deletions in 600 young, healthy Dutch individuals. The researchers report that nearly all of the individuals that participated in this study carry complete DNA losses with an average size of 50,000 base pairs.

Their research results also indicate that most people can easily live with thousands of DNA base pair losses in the dispensable regions of the human genome without any discernable consequences to our health. Surprisingly, the researchers found that some of the genes we can afford to lose may play a role in disease or vital processes – such as psoriasis, male infertility and food digestion.

The researchers also found that some of the 'lost' regions contain genes, which may indicate the action of evolution on these genes. For certain people, the researchers hypothesize that these genes are dispensable, and evolution makes sure that they are not lost without compensation. On the other hand, evolution generally protects 'vital' genes by keeping them outside of the frequently lost regions of the genome.

"The results of this study have provided insight into the 'non-essential' parts of the human genome, which will aid in expanding our current understanding of genetic variation among humans," said Vrijenhoek. "Clearly, while the large majority of our genes are essential, the current research results suggest that hardly anyone of us possesses a complete genome."

PRESS BRIEFING SESSION & WEBCAST INFORMATION

ASHG invites members of the media to attend this press briefing session on *"Understanding the Structure of the Human Genome: What is Essential, What is Expendable, and What is Important to Health?,"* which will be held on Wednesday, October 21, 2009 from 1:00-2:00 p.m. (HST) in the ASHG Press Briefing Room (Room 319A), located on the third floor of the Hawaii Convention Center.

For those members of the press who wish to view the session remotely via webcast, please note that the online webcasts of all three ASHG Press Briefing Sessions held at this year's Annual Meeting, will *NOT* be webcast live, in real time. To view the *archived* webcast recording of this event, please click on the link below (no sooner than) two to three hours after the press briefing session is over *(i.e., ~5:00 p.m. HST / 11:00 p.m. EST) on Wednesday, Oct. 21, 2009:*
http://www.ashg.org/genesequencing/

Please direct all media inquiries to ASHG Press Office, ASHG Communications Manager, via e-mail at press@ashg.org, or by phone at 240-281-2386.

ABOUT THE AMERICAN SOCIETY OF HUMAN GENETICS

Founded in 1948, The American Society of Human Genetics (ASHG) is the primary professional membership organization for human genetics specialists worldwide. The nearly 8,000 members of ASHG include researchers, academicians, clinicians, laboratory practice professionals, genetic counselors, nurses and others involved in or with a special interest in human genetics.

The Society's mission is to serve research scientists, health professionals and the public by providing forums to: (1) share research results through the Annual Meeting and in *The American Journal of Human Genetics* (*AJHG*); (2) advance genetic research by advocating for research support; (3) educate future genetics professionals, health care providers, advocates, teachers, students and the general public about all aspects of human genetics; and (4) promote genetic services and support responsible social and scientific policies. For more information about ASHG, please visit http://www.ashg.org.

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