August 7, 2015

I am excited to report that the NHGRI-Smithsonian exhibition *Genome: Unlocking Life's Code* is now in my hometown of St. Louis, Missouri – specifically, at the Saint Louis Science Center – until September 7, 2015. I will, in fact, be traveling to St. Louis at the end of August to tour the exhibition, to give a lecture to science students from my high school alma mater (Ladue Horton Watkins High School), and to participate in a public genomics program. Below is additional information about the activities that NHGRI will co-host in St. Louis associated with the exhibition.

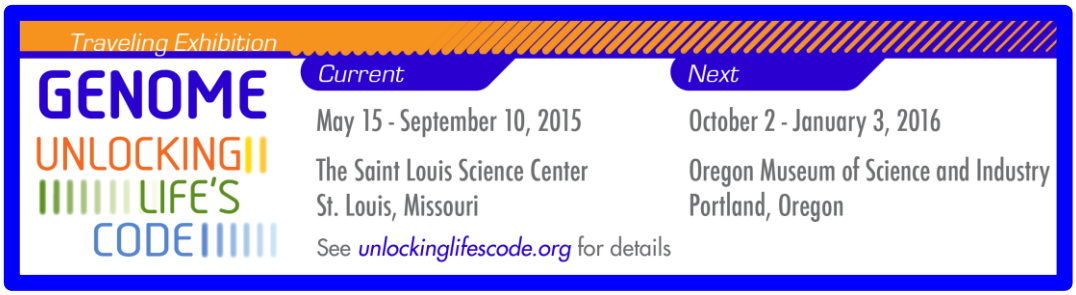
In this month's *The Genomics Landscape*, I highlight recent activities of the NHGRI- and NHLBI-funded Centers for Mendelian Genomics, in particular, a recently published review describing accomplishments of the program to date. See various details below, along with other information items that I hope will be of interest to you.

Specifically, August's *The Genomics Landscape* features stories about:

- Centers for Mendelian Genomics Program
- Report from the Genomic Medicine Meeting VIII: NHGRI's Genomic Medicine Portfolio
- NIH Strategic Planning Request for Information
- *Genome: Unlocking Life's Code* Exhibition Travels to St. Louis

All the best,

Watch here for current and upcoming locations of the Smithsonian-NHGRI exhibition "Genome: Unlocking Life's Code" as it tours North America!



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Centers for Mendelian Genomics Program

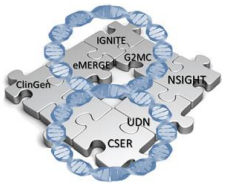
In November 2011, NHGRI and the National Heart, Lung, and Blood Institute (NHLBI) established the Centers for Mendelian Genomics (CMG) program, the goal of which is to identify genomic mutations underlying Mendelian diseases using modern genome-sequencing technologies and to develop the most effective research approaches for uncovering the genetic basis of Mendelian diseases. Mendelian diseases, named after Gregor Mendel (the founder of modern genetics), are rare diseases that are typically transmitted from parents to offspring. While 'rare' at the individual level, Mendelian diseases are thought to collectively affect 25 million people in the United States. By identifying the genomic bases of these diseases, the CMG program aims to help improve their diagnosis and to inform the development of new treatment options. Through these efforts, CMG scientists also hope to gain insights into other, more common diseases that often involve similar genes and biological pathways.

CMG researchers recently published a milestone paper in the *American Journal of Human Genetics* reviewing their progress to date relative to all efforts in studying rare diseases and describing their perspectives about what it will take to find most of the Mendelian causal genes. They report data for 'Mendelian phenotypes' – a concept that captures a number of different factors that scientists are interested in studying. A Mendelian phenotype is the collection of observable or measurable traits of an individual and results from changes in a single gene that can be handed down from parents to children. Mendelian phenotypes include both disease and non-disease traits. Studying both kinds of traits can help find genes responsible for disease and build knowledge about human genetics.

As described in the publication, the collective work of the human genetics community has now identified mutations in 2,937 genes that account for 4,193 Mendelian phenotypes. This number represents only a fraction of known Mendelian phenotypes – there are over 3,100 additional Mendelian phenotypes for which genomic mutations have yet to be identified – and the number continues to increase each year.

Using 'next-generation' DNA sequencing technologies, the CMG program has made significant contributions to understanding the genomic bases of Mendelian phenotypes that complement the historically used, more traditional approaches. The CMG program strives to cultivate efficient designs, technologies, and analysis methods for the scientific community to reveal the genetic basis of Mendelian phenotypes. Specifically, it generated whole-exome sequence, which covers only the gene-coding portion of the genome (known as exons) along with closely-related on-off switch regions, for 16,226 samples as well as whole-genome sequence for 96 samples. As reported in the paper, the CMG program was able to associate 956 genes with a portion of the Mendelian phenotypes that they studied. Of these, 375 were not previously implicated in a Mendelian phenotype. This works out to be 3 discoveries per week!

Report from the Genomic Medicine Meeting VIII: NHGRI's Genomic Medicine Portfolio



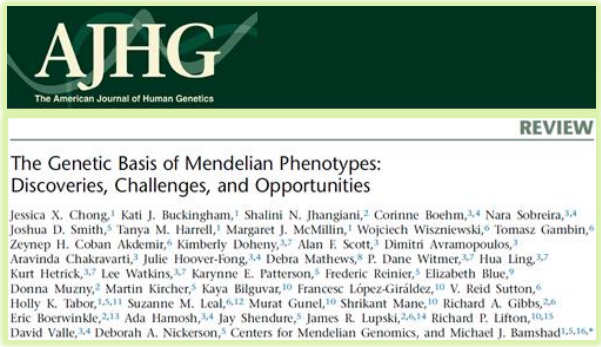
In June, NHGRI gathered experts from the U.S. and across the world to discuss progress in genomic medicine at a meeting entitled *Genomic Medicine Meeting VIII: NHGRI's Genomic Medicine Portfolio*. In particular, NHGRI programs and gaps, challenges, and opportunities for genomic medicine were discussed. Recommendations from the meeting emphasized: evidence generation; data sharing; improved phenotyping; identifying and carrying out innovative studies; facilitating genomic medicine implementation in the clinic; identifying health disparities; increasing patient engagement; and the importance of education and training. A meeting report has been released and can be found at genome.gov/Multimedia/Slides/GM8/GM8_ExecutiveSummary.pdf. Visit genome.gov/27561979 for further meeting details.

NIH Strategic Planning Request for Information

As requested by Congress, NIH is developing an NIH-wide Strategic Plan to outline a vision for biomedical research that ultimately extends healthy life and reduces illness and disability. NIH senior leadership and staff have developed a proposed framework

The CMG program has developed a 'scorecard' for Mendelian phenotypes and gene discovery that can be found at mendelian.org/about-mendelian-conditions. This accounting system provides a framework that captures important metrics such as: the number of Mendelian phenotypes for which the responsible gene is known, the number of genes that are involved in a Mendelian phenotype, and the number of genes involved in two or more Mendelian phenotypes. All of these figures reflect the progress toward understanding the genomic bases of Mendelian phenotypes and diseases. As discovery progresses, we expect to see more Mendelian phenotypes identified and described, more genes implicated in Mendelian phenotypes, and ultimately, a greater understanding of the biological mechanisms for these phenotypes.

Mendelian diseases and phenotypes are rare, enough so that for any one, there may be only a few appropriate samples to study. Therefore, it is essential that patients, families, clinicians, human geneticists, and the CMG program collaborate in order to bring together the samples, clinical data, scientific expertise, and genomic technologies. Towards that end, the CMG program has so far worked with 529 investigators at 261 institutions in 36 countries.


AJHG
The American Journal of Human Genetics
REVIEW
The Genetic Basis of Mendelian Phenotypes: Discoveries, Challenges, and Opportunities
Jessica X. Chong,[1] Kati J. Buckingham,[1] Shalini N. Jhangiani,[2] Corinne Boehm,[3,4] Nara Sobreira,[3,4] Joshua D. Smith,[5] Tanya M. Harrell,[1] Margaret J. McMillin,[1] Wojciech Wiszniewski,[6] Tomasz Gambin,[6] Zeynep H. Coban Akdemir,[6] Kimberly Doheny,[3,7] Alan F. Scott,[3] Dimitri Avramopoulos,[3] Aravinda Chakravarti,[3] Julie Hoover-Fong,[3,4] Debra Mathews,[8] P. Dane Witmer,[3,7] Hua Ling,[3,7] Kurt Hetrick,[3,7] Lee Watkins,[3,7] Karynne E. Patterson,[5] Frederic Reinier,[5] Elizabeth Blue,[9] Donna Muzny,[2] Martin Kircher,[5] Kaya Bilguvar,[10] Francesc López-Giráldez,[10] V. Reid Sutton,[6] Holly K. Tabor,[1,5,11] Suzanne M. Leal,[6,12] Murat Gunel,[10] Shrikant Mane,[10] Richard A. Gibbs,[2,6] Eric Boerwinkle,[2,13] Ada Hamosh,[3,4] Jay Shendure,[5] James R. Lupski,[2,6,14] Richard P. Lifton,[10,15] David Valle,[3,4] Deborah A. Nickerson,[5] Centers for Mendelian Genomics, and Michael J. Bamshad[1,5,16,*]

To access the recent Centers for Mendelian Genomics publication in the American Journal of Human Genetics, see cell.com/ajhg/abstract/S0002-9297(15)00245-1.

The CMGs coordinate with international efforts such as Finding of Rare Disease Genes (FORGE) in Canada and the Wellcome Trust Deciphering Developmental Disabilities (WTDDD) in the United Kingdom. The CMG program is also part of the International Rare Disease Research Consortium (IRDiRC). The CMG program has also developed web-based tools, such as GeneMatcher and Genotype to Mendelian Phenotype ($Geno_2MP$), to provide a mechanism for investigators with shared interest in particular Mendelian phenotypes and candidate genes to collaborate.

This year marks the fourth year of funding for the CMG program and the end of its first funding period. During this time, NHGRI and NHLBI awarded a total of $48 million to three centers at the University of Washington, Yale University, and Johns Hopkins University. NHGRI and NHLBI have committed to supporting a second funding period for the program through the Centers for Mendelian Genomics (UM1) Request for Applications (RFA) issued earlier this year. New grants are expected to be awarded later in 2015 and be active for another four years. For more information regarding the CMG publication, see genome.gov/27562201. Information about the CMG program and access to data can be found at mendelian.org.

for the Strategic Plan that identifies areas of opportunity across all biomedicine and unifying principles to guide NIH's support of the biomedical research enterprise. The aim is to pursue cross-cutting areas of research that span NIH's 27 Institutes/Centers. At this time, NIH seeks feedback on the draft framework through a Request for Information, due August 16. NIH will also host webinars in early August to collect community feedback. To review the framework and provide feedback on the RFI or to learn more about the webinars, visit nih.gov/about/strategic-plan.

Genome: Unlocking Life's Code Exhibition Activities in St. Louis

SAINT LOUIS science center
GENOME UNLOCKING LIFE'S CODE

NHGRI staff members are headed to St. Louis at the end of August for a series of events in partnership with the Academy of Science-St. Louis and the Saint Louis Science Center. On August 31 and September 1, staff from NHGRI's Genomic Healthcare Branch will offer two free genomic continuing education opportunities for health professionals and educators. On September 1, NHGRI leadership will moderate two conversations at a program/reception on precision medicine offered by the Academy of Science-St. Louis. For more information regarding the exhibition at the Saint Louis Science Center, see slsc.org/Genome-Unlocking-Lifes-Code.

Spotlight on the Precision Medicine Initiative (PMI)

nih.gov/precisionmedicine

- White House Blog: Six Months of Progress on the Precision Medicine Initiative
- The White House has announced the Champions of Change for Precision Medicine. Read more about them here.
- A working draft of the guiding principles to protect privacy and build public trust for the PMI has been released for comment through August 7 and can be found here.
- Dr. Jay Shendure, NHGRI Advisory Council member, is featured in the NIH "Faces of the Precision Medicine Initiative" video series here.

Genomics Research

NIH Study Identifies Gene Variant Linked to Compulsive Drinking

Studying Cancer from the Inside Out: What the Epigenetic Code Can Tell Doctors about Disease

University of Cincinnati Study: Glioma Tumor's Genetic Profile More Telling Than Physical Appearance

NIAID Researchers Identify Promising Therapy for Rare Immune Disorder

Scientists Adopt New Strategy to Find Huntington's Disease Therapies

Genome Advance of the Month

Gene-Disease Association Data Could Improve Drug Development

Funding & Resource Opportunities

Phase II SBIR Grants for Extended Development, Hardening, and Dissemination of Technologies in Biomedical Computing, Informatics, and Big Data Science

Emerging Global Leader Award

Small Business Innovation Research Grant Applications

Small Business Technology Transfer Grant Applications

Discovery of Genetic Basis of Monogenic Heart, Lung, Blood, and Sleep Disorders

Funding News

Number of Applications an Institution Can Submit to NHGRI Genome Sequencing Program Analysis Centers

Salary Level of K01 and K08 Awards Supported by NHGRI

Preliminary Guidance Related to Informed Consent for Research on Dried Blood Spots Obtained Through Newborn Screening

Guidance on Changes That Involve Human Subjects in Active Awards and That Will Require Prior NIH Approval

Prior NIH Approval of Human Subjects Research in Active Awards Initially Submitted without Definitive Plans for Human Subjects Involvement

NIH News of Interest

Vacancy Announcement, NIH Deputy Director, Extramural Research

Alzheimer's Disease Sequencing included in Professional Judgment Budget

NIH Names William T. Riley, Ph.D., Next Director of the Office of Behavioral and Social Sciences Research

NIH Clinical Center Awarded Prestigious Certification for Electronic Medical Record System

Understanding the Capacity of NIH's Peer Review System

Statement Regarding the Retirement of NICHD Director Dr. Alan Guttmacher

New Education Newsletter

Genome: Unlocking Life's Code Monthly Newsletter