Opportunities and Challenges for Health Disparities Research in the Personal Genome Era

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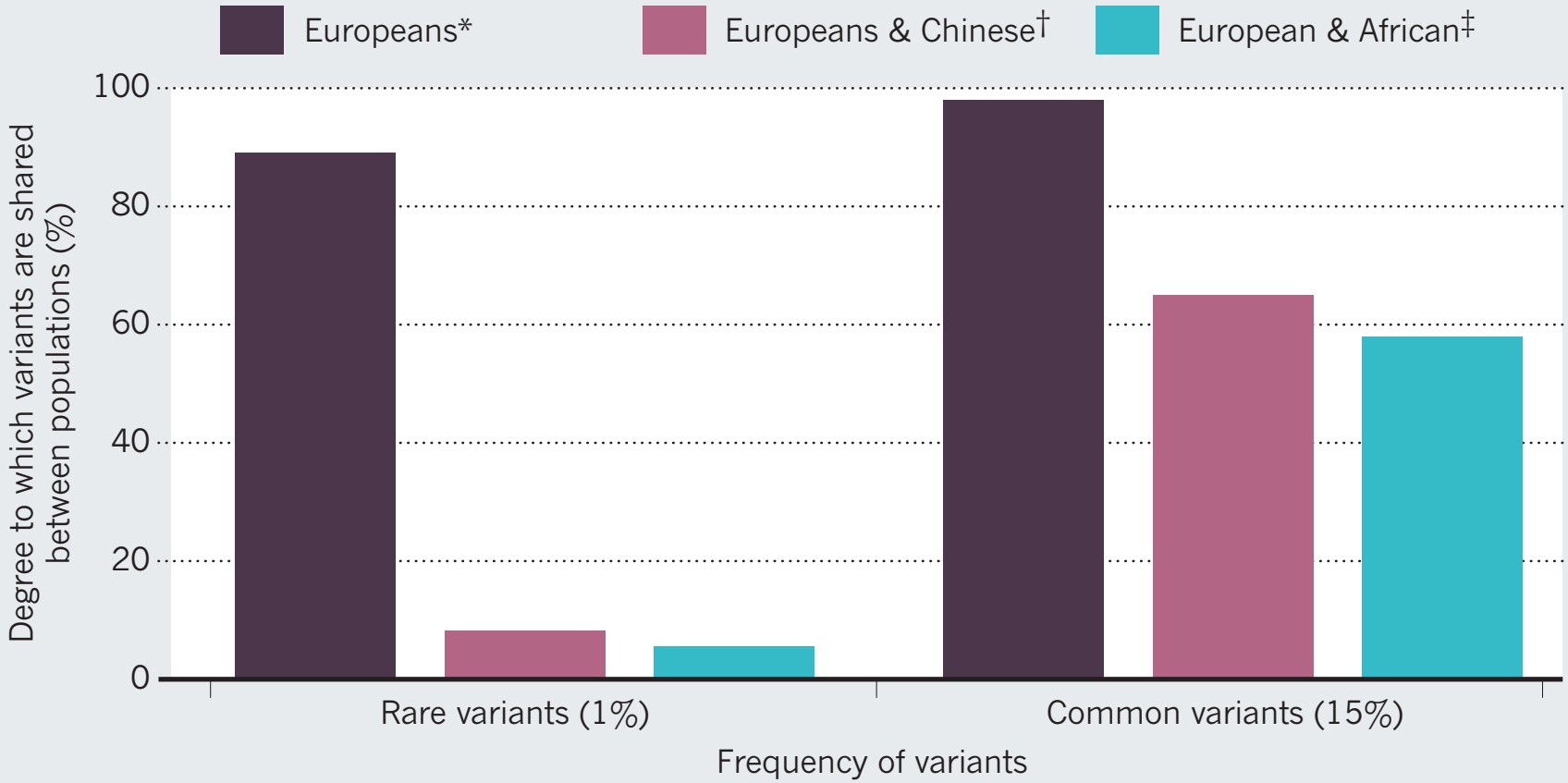
Key Driving Questions

* Why study diverse populations in clinical genomics research? What is the potential scientific gain?
* What have we learned from broadening representation thus far in GWAS/Mendelian?
* How do we properly design multi-ethnic studies so we maximize the power of discovery and interpretation?
* How do we modify protocols for recruitment, consent/enrollment process, and RoR in a multi- /trans- ethnic clinical genomic research setting?

COMPARING THE UNCOMPARABLE

The rarer a genetic variant is within a population, the less likely it is to be found in all ethnic groups. One hundred people were sampled from each population.



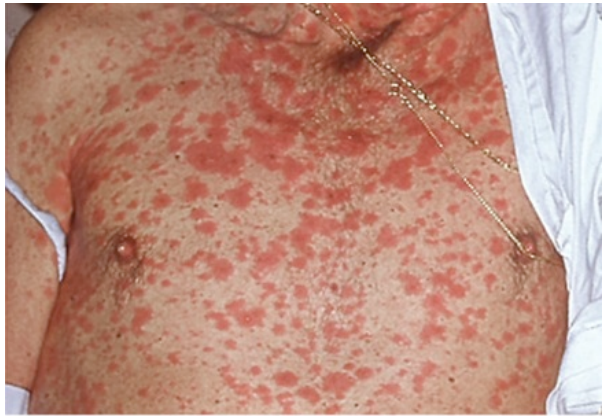
*Comparison of individuals of European descent in Utah and in Tuscany, Italy. † Han Chinese individuals from Beijing compared with Utah sample ‡ Yoruba individuals from Ibadan, Nigeria, compared with Utah sample.

Gravel, S. *et al. Proc. Natl Acad. USA* doi: 10.1073/pnas.1019276108 (2011).

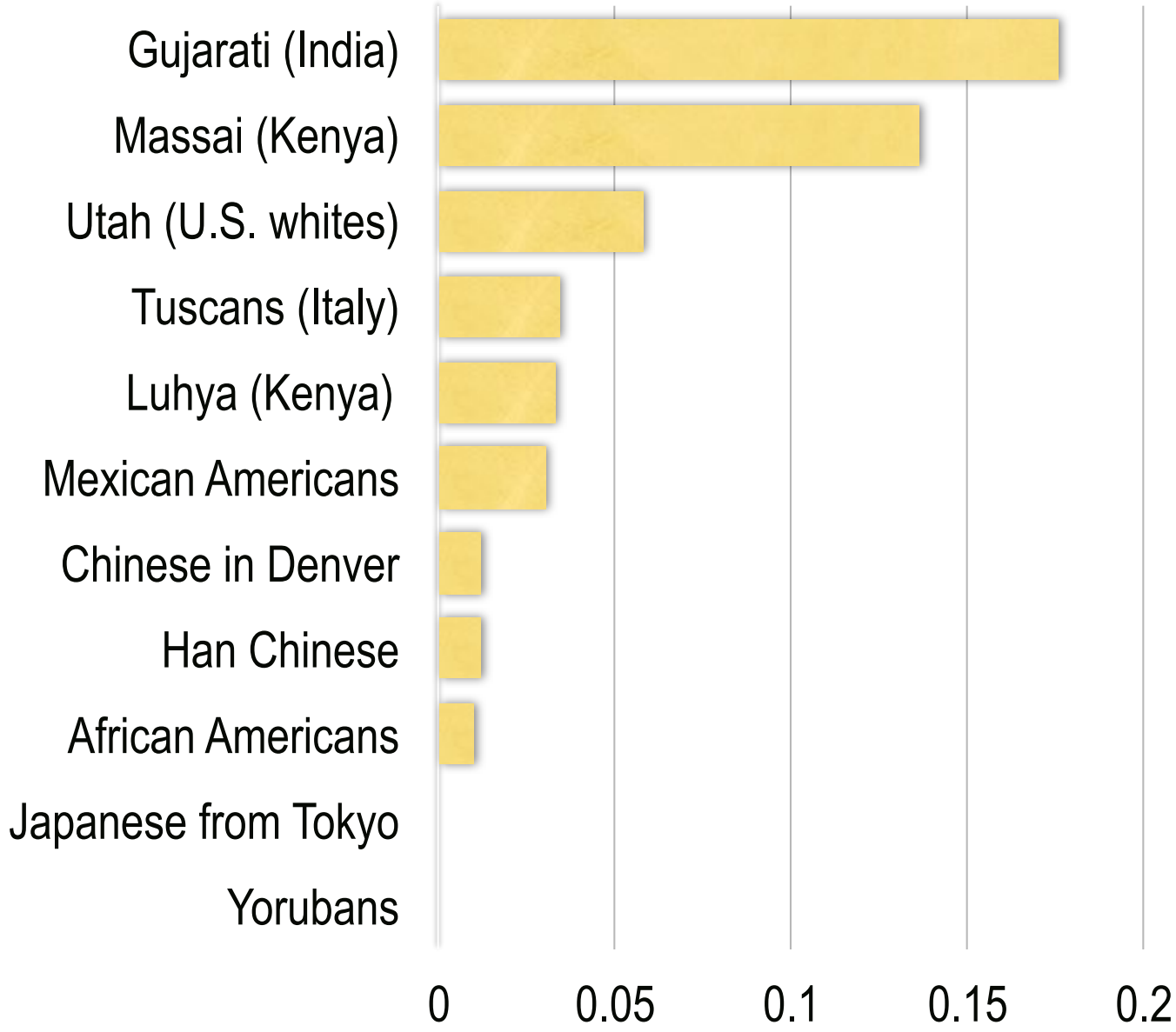
Bustamante, Burchard, and De La Vega

Broadening representation in genomics...

HLA B*5701 causes Abacavir hypersensitivity in HIV anti-retroviral therapy



Incidence: 3-5%
Onset: 4-6 wks after initiation of abacavir therapy
Symptoms:
Fever, skin rash, fatigue, GI symptoms (nausea, vomiting, diarrhea, abdominal pain), and respiratory tract symptoms (pharyngitis, dyspnea, or cough)
Management:
Discontinue abacavir
Do not re-start abacavir; severe symptoms will recur within hours, including life-threatening hypotension and death



Early results suggest broadening ethnicity for GWAS works

- Medical genetics continues to suffer from a European bias (Bustamante et al. Nature 2011), although that is slowly changing:

Asthma and lower airway disease

Genome-wide ancestry association testing identifies a common European variant on 6q14.1 as a risk factor for asthma in African American subjects

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ORIGINAL ARTICLE

HLA Class II Locus and Susceptibility to Podoconiosis

Fasil Tekola Ayele, Ph.D., M.P.H., Adebowale Adeyemo, M.D., Chris Finan, Ph.D., Elena Hailu, M.Sc., Paul Sinnott, Ph.D., Natalia Diaz Burlinson, M.Sc., Abraham Aseffa, M.D., Ph.D., Charles N. Rotimi, Ph.D., M.P.H., Melanie J. Newport, M.D., Ph.D., and Gail Davey, M.D.

N Engl J Med 2012; 366:1200-1208 | March 29, 2012 | DOI: 10.1056/NEJMoa1108448

LETTER

doi:10.1038/nature12828

Sequence variants in *SLC16A11* are a common risk factor for type 2 diabetes in Mexico

The SIGMA Type 2 Diabetes Consortium*

The genetics of Mexico recapitulates Native American substructure and affects biomedical traits

Andrés Moreno-Estrada,[1*†] Christopher R. Gignoux,[2†‡] Juan Carlos Fernández-López,[3†] Fouad Zakharia,[1] Martin Sikora,[1] Alejandra V. Contreras,[3] Victor Acuña-Alonzo,[4,5] Karla Sandoval,[1] Celeste Eng,[6] Sandra Romero-Hidalgo,[3] Patricia Ortiz-Tello,[1] Victoria Robles,[1] Eimear E. Kenny,[1§] Ismael Nuño-Arana,[7] Rodrigo Barquera-Lozano,[4] Gastón Macín-Pérez,[4] Julio Granados-Arriola,[8] Scott Huntsman,[6] Joshua M. Galanter,[6,9] Marc Via,[6||] Jean G. Ford,[10] Rocío Chapela,[11] William Rodriguez-Cintron,[12] Jose R. Rodríguez-Santana,[1,3] Isabelle Romieu,[14] Juan José Sienra-Monge,[15] Blanca del Rio Navarro,[15] Stephanie J. London,[16] Andrés Ruiz-Linares,[5] Rodrigo Garcia-Herrera,[3] Karol Estrada,[3¶] Alfredo Hidalgo-Miranda,[3] Gerardo Jimenez-Sanchez,[3#] Alessandra Carnevale,[3] Xavier Soberón,[3] Samuel Canizales-Quinteros,[3,17] Héctor Rangel-Villalobos,[7] Irma Silva-Zolezzi,[3**] Esteban Gonzalez Burchard,[6,9*] Carlos D. Bustamante[1*]

NATURE COMMUNICATIONS | ARTICLE OPEN

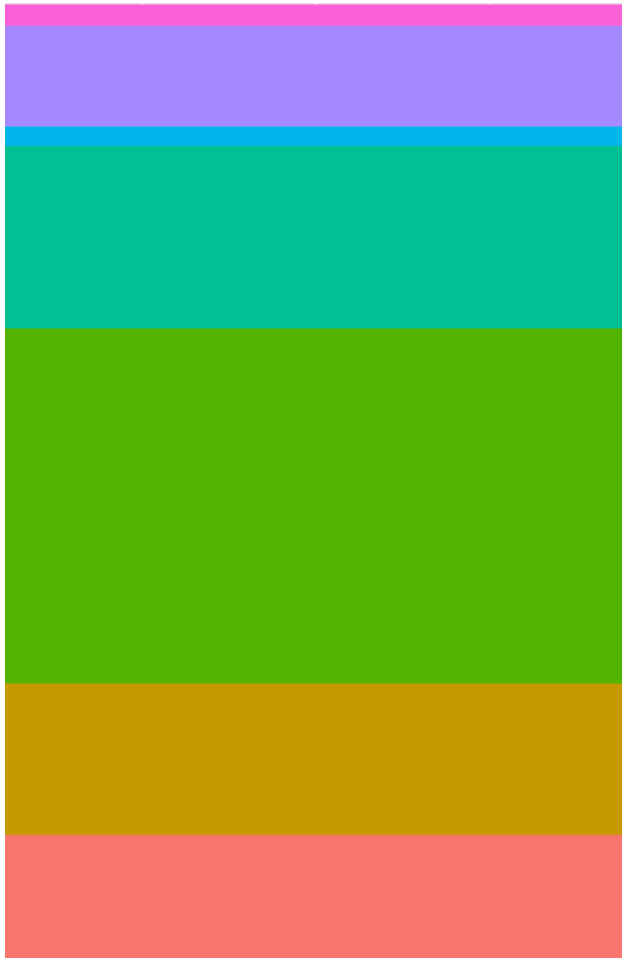
Genome-wide association study of breast cancer in Latinas identifies novel protective variants on 6q25

Laura Fejerman, Nasim Ahmadiyeh, Donglei Hu, Scott Huntsman, Kenneth B. Beckman, Jennifer L. Caswell, Karen Tsung, Esther M. John, Gabriela Torres-Mejia, Luis Carvajal-Carmona, María Magdalena Echeverry, Anna Marie D. Tuazon, Carolina Ramirez, COLUMBUS Consortium, Christopher R. Gignoux, Celeste Eng, Esteban Gonzalez-Burchard, Brian Henderson, Loic Le Marchand, Charles Kooperberg + *et al.*

Melanesian Blond Hair Is Caused by an Amino Acid Change in TYRP1

Eimear E. Kenny,[1*] Nicholas J. Timpson,[2*] Martin Sikora,[1] Muh-Ching Yee,[1] Andrés Moreno-Estrada,[1] Celeste Eng,[3] Scott Huntsman,[3] Esteban González Burchard,[3] Mark Stoneking,[4] Carlos D. Bustamante,[1,5†] Sean Myles[1,5,6†]

Multiethnic Genomewide Association (MEGA) Array



PAGE-II Custom Content, 42K

Exonic Variants, 200K

Functional Variants, 40K

GWAS Scaffold, 360K

African Power Diaspora Scaffold, 700K

Human Core Scaffold, 300K

Human Exome Array, 250K

(1.7M SNPs)

Lessons Learned thus far…

* 1000 Genomes and other population scale studies have demonstrated "Common variants are rare and shared; Rare variants are common and largely population private"

* Properly powered GWAS studies in understudied populations yield novel variants at previously associated genes (e.g., LDLR/PCSK9) and new genes underlying previously studied phenotypes (e.g., SLC16A11 in T2D for H/L).

* NHGRI efforts in diversifying medical and population genomics have led to important reagents for multi-ethnic GWAS (e.g., MEGA) and now sequencing (e.g., Centers for Common and Mendelian Diseases)

* Sequencing based population screening (e.g., CFTR sequencing in CA) yields a broad spectrum of alleles that are rare, many VUSs, and require additional clinical data for interpretation.

* Building diversity into CSER will likely yield new opportunities for biology and improve patient care/health outcomes for minority populations.

Key challenges ahead:

* Should representation in sequencing studies be proportional (65%, 15%, 10%, 5%, etc.) or stratified (25%, 25%, 25%, etc.)

* VUS rates are higher in non-white populations. Does this pose a challenge to genomic medicine and how do we address it?

* Inclusion doesn't mean just ethnic diversity. How does SES, education, etc. impact enrollment, genome interpretation, and ROR?

* New technologies pose a risk to broadening health disparities. While overall improvement in health outcomes across populations is expected, rates of improvement could vary by race, ethnicity, SES, etc. Can we study this directly and develop countermeasures?