Predicting genomic risk in diverse populations

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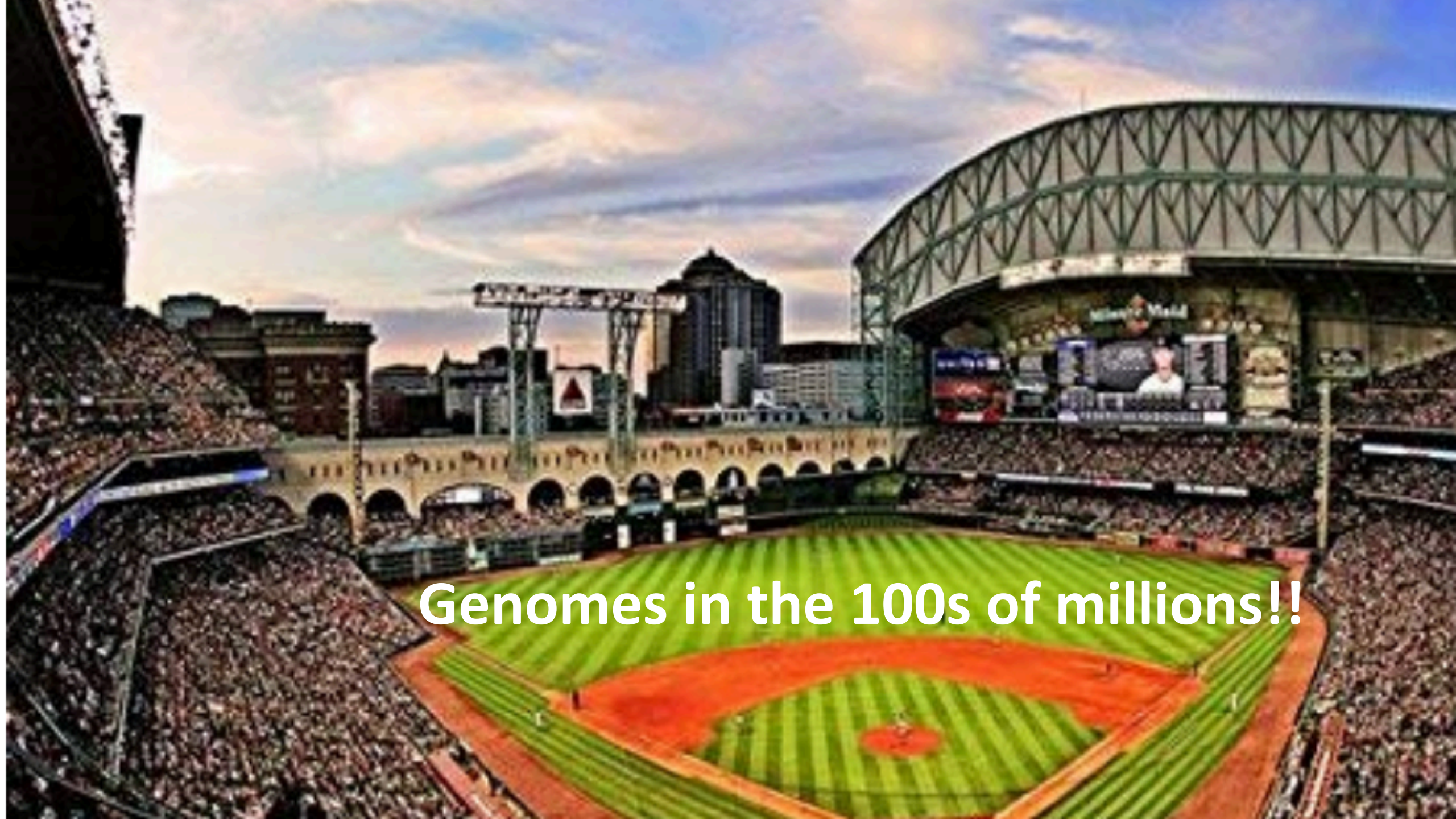
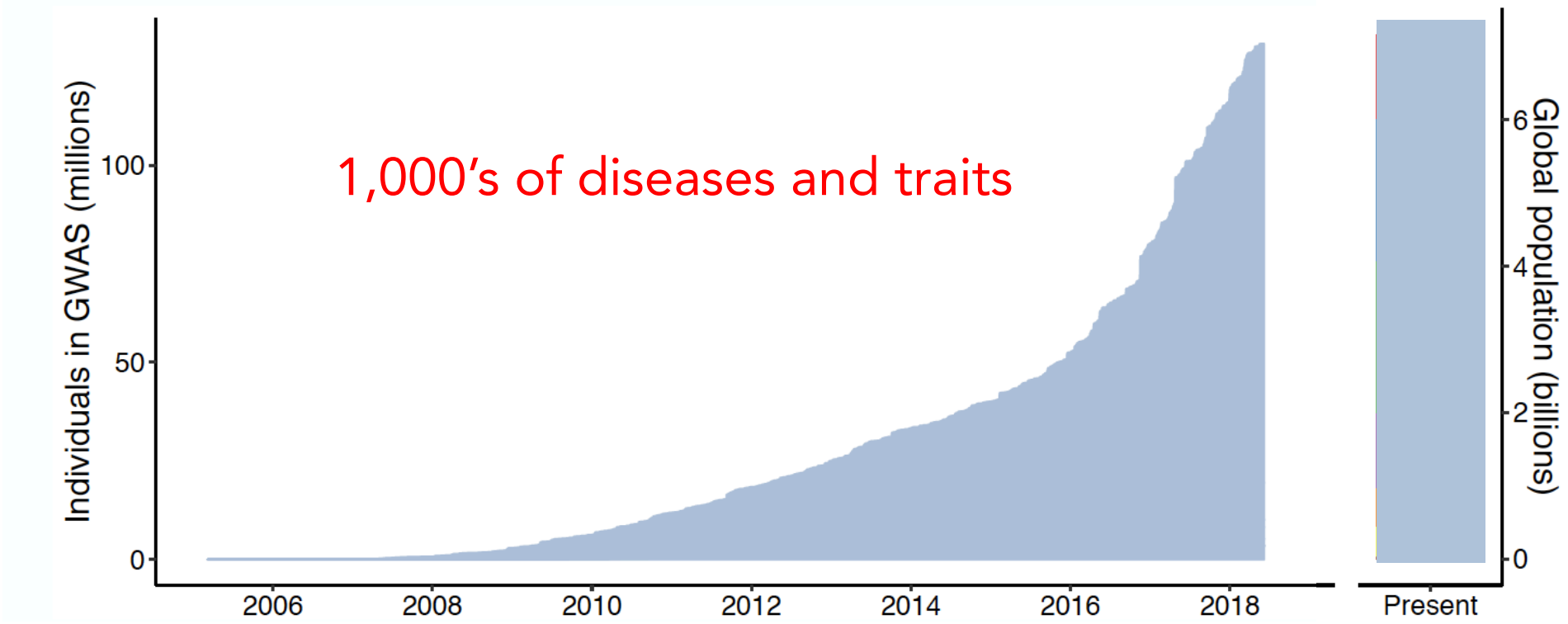
Disclosure

Eimear Kenny has received personal fees from Regeneron Pharmaceuticals and Illumina, and served on the Advisory board for Encompass Biosciences.


Genomes in the 100s of millions!!

GWAS are increasing in size and scope



Martin, et al. (2019) Clinical use of current polygenic risk scores may exacerbate health disparities. Nat Genet

How Genomics Will Change the Way We Practice Medicine

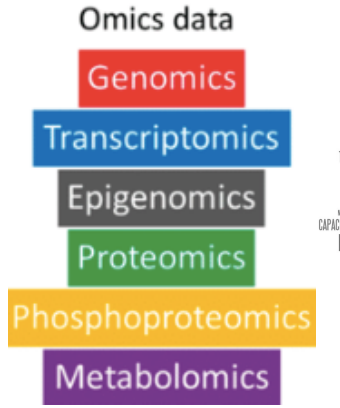
Diagnostics

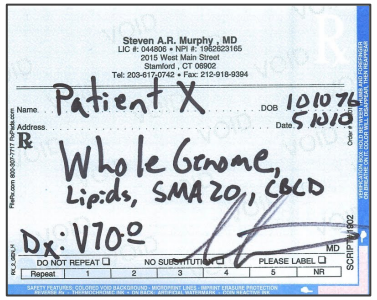
Family planning

Preventive health

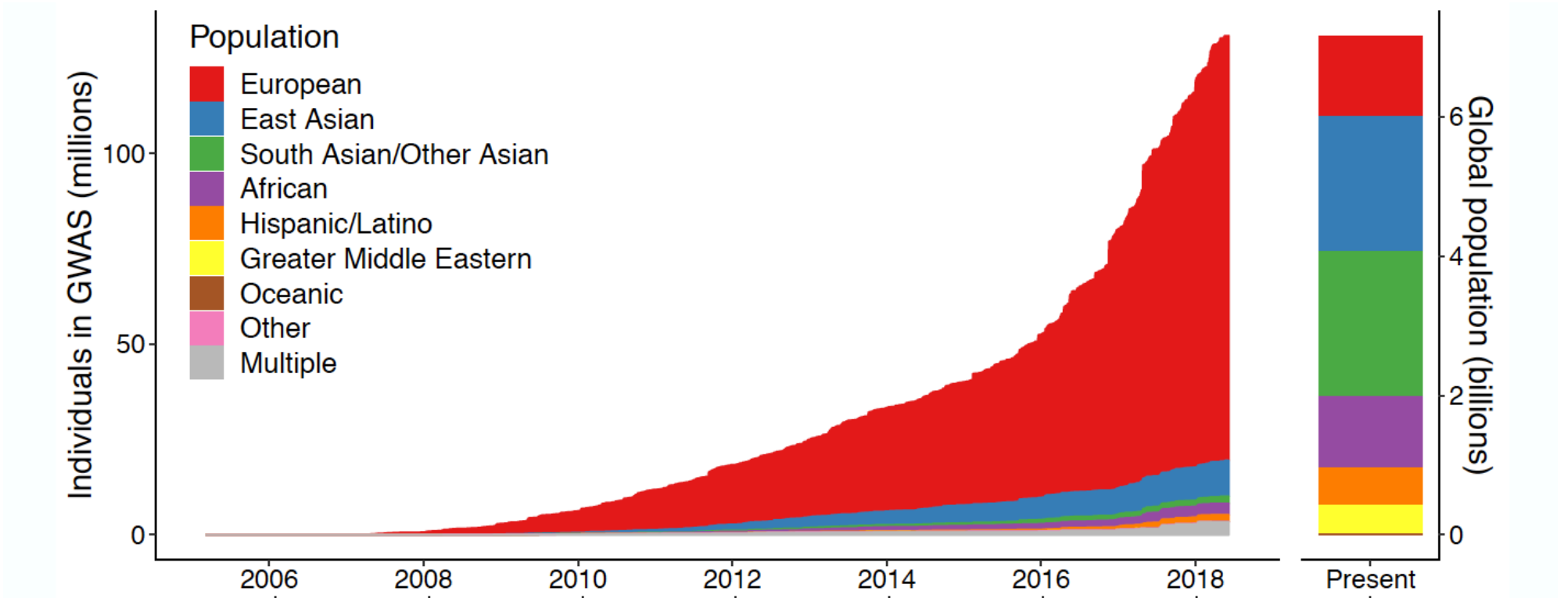
Direct-to-consumer

Pharmacogenomics





…. but genomics is failing on diversity



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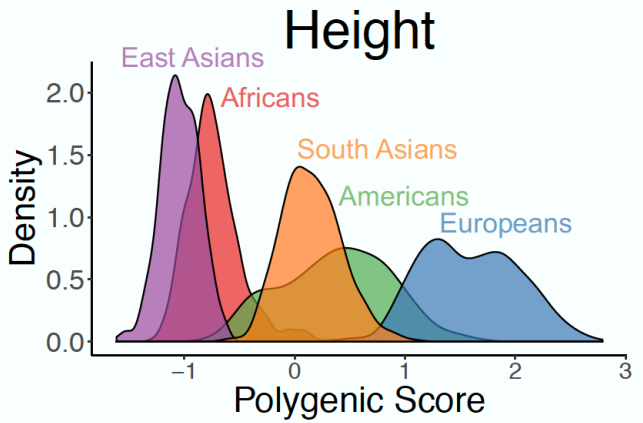
What effect does ancestry have on prediction?

ARTICLE

Human Demographic History Impacts Genetic Risk Prediction across Diverse Populations

Alicia R. Martin,[1,2,3,4] Christopher R. Gignoux,[4] Raymond K. Walters,[1,2,3] Genevieve L. Wojcik,[4] Benjamin M. Neale,[1,2,3] Simon Gravel,[5,6] Mark J. Daly,[1,2,3] Carlos D. Bustamante,[4] and Eimear E. Kenny[7,8,9,10,*]

- Genetic prediction accuracy decays with increasing genetic divergence between discovery and target data
- Polygenic scores differ across populations arbitrarily, but these biases are not meaningful
- Neutral human evolution is sufficient to explain differences



How do we integrate genomic risk to improve health and wellness?

- How to transform genetic research into medical knowledge? What are the biases in our current knowledge bases?

Mount Sinai Creates New Genomics Center as Part of $100M AI Initiative

Jun 14, 2019 | Andrew P. Han

genomeweb

Premium *Remove from my reading list*

NEW YORK (GenomeWeb) – The Icahn School of Medicine at Mount Sinai has created the Center for Genomic Health, a new clinical research entity that will be a part of a $100 million pledge to integrate artificial intelligence into healthcare.

The Center for Genomic Health will be housed in another new and larger center, the Hamilton and Amabel James Center for Artificial Intelligence and Human Health, launched earlier this week. As reported by Bloomberg, the James Center was enabled by an undisclosed philanthropic gift and other funding totaling $100 million.

- Once we have identified genes that are clinically relevant, how do we systematically identify individuals, communities and/or populations at risk? Understand other factors at play over a patients life course?

- How do we integrate genomics broadly in health systems for improved health care management?

Testing the generalizability of genomic databases in diverse populations

Chris Gignoux ***Elena Sorokin***

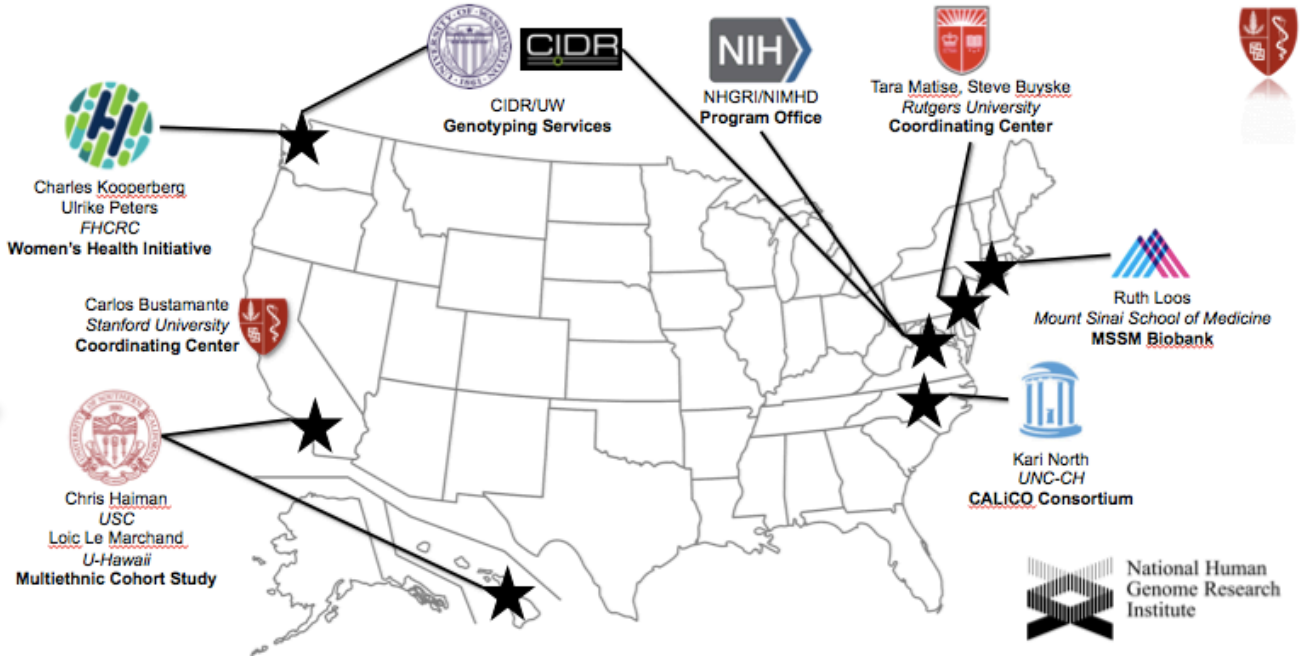
Carlos Bustamante ***Gillian Belbin***

Sinead Cullina ***Hannah Poisner***

Letter | Published: 19 June 2019

Genetic analyses of diverse populations improves discovery for complex traits

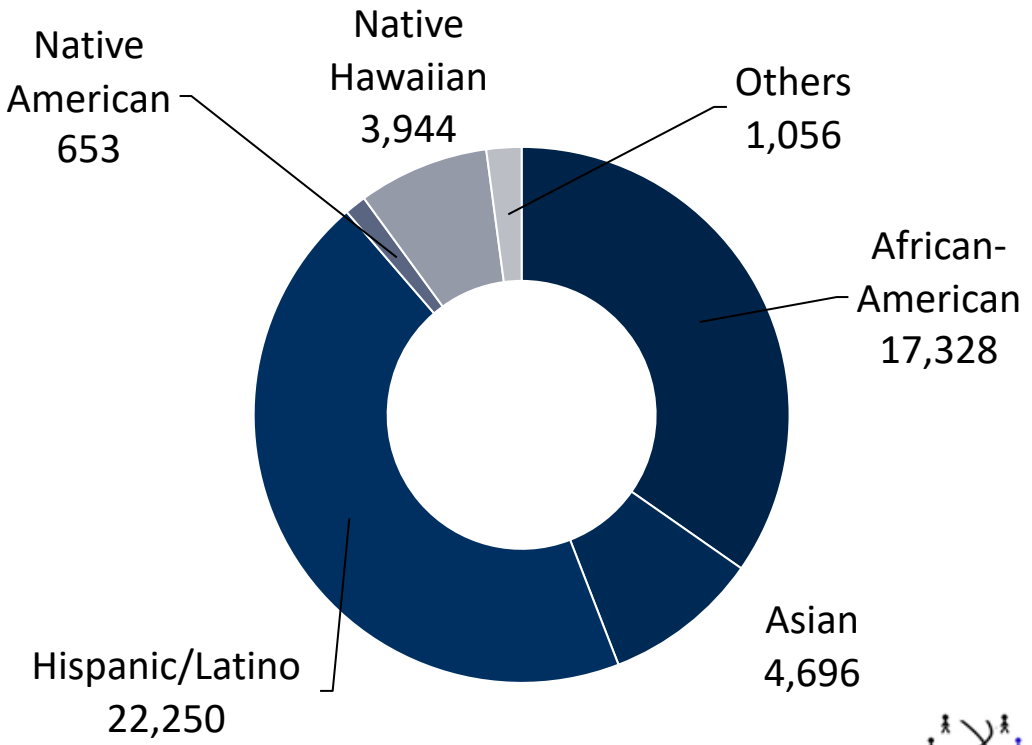
Genevieve L. Wojcik, Mariaelisa Graff, Katherine K. Nishimura, Ran Tao, Jeffrey Haessler, Christopher R. Gignoux, Heather M. Highland, Yesha M. Patel, Elena P.



Population Architecture Using Genomics and Epidemiology

Genetic diversity improves our understanding of complex traits

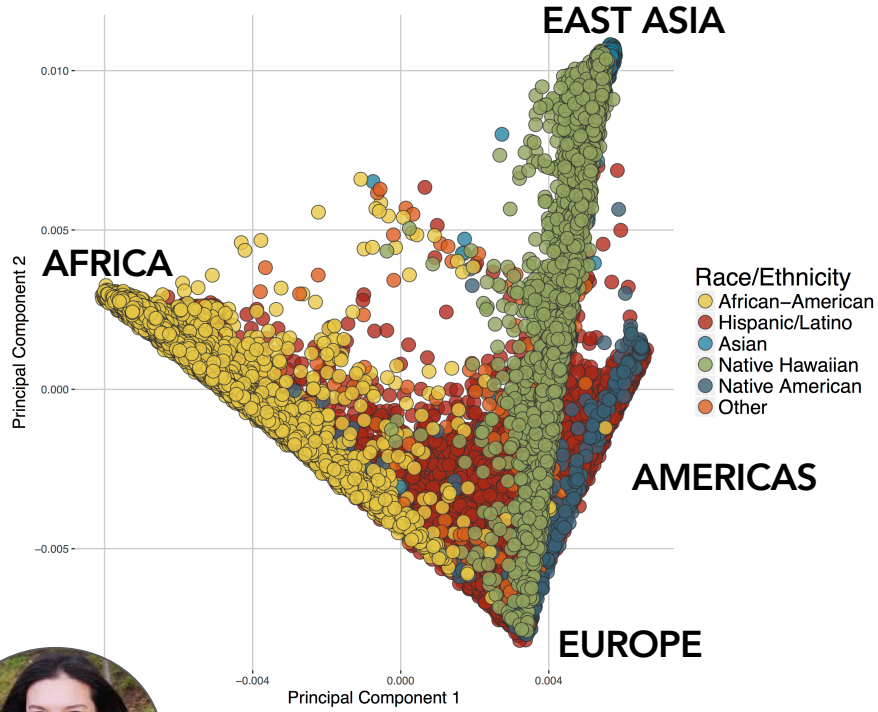
- **Goal:** Investigate ancestrally diverse populations to gain a better understanding of how genetic factors influence susceptibility to disease.
- **Focus on US minority populations.**



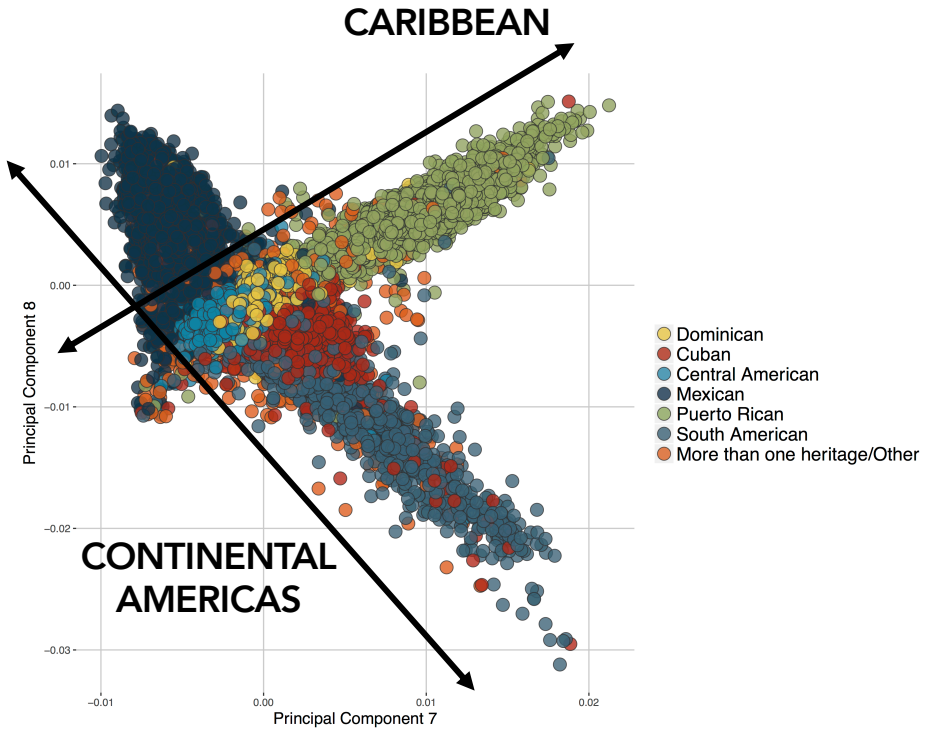
Gen Wojcik

Wojcik GL[#], Graff M[#], Nishimura KK[#], Tao R[#], Haessler J[#], Gignoux CR[#], Highland HM[#], Patel YM[#], … Kenny EE[$], Carlson CS[$]. Genetic diversity improves our discovery of complex traits. Nature (2019)

Challenge defining population groups



All PAGE Populations



PC7 vs PC8, PAGE Hispanic/Latino variation

Gen Wojcik

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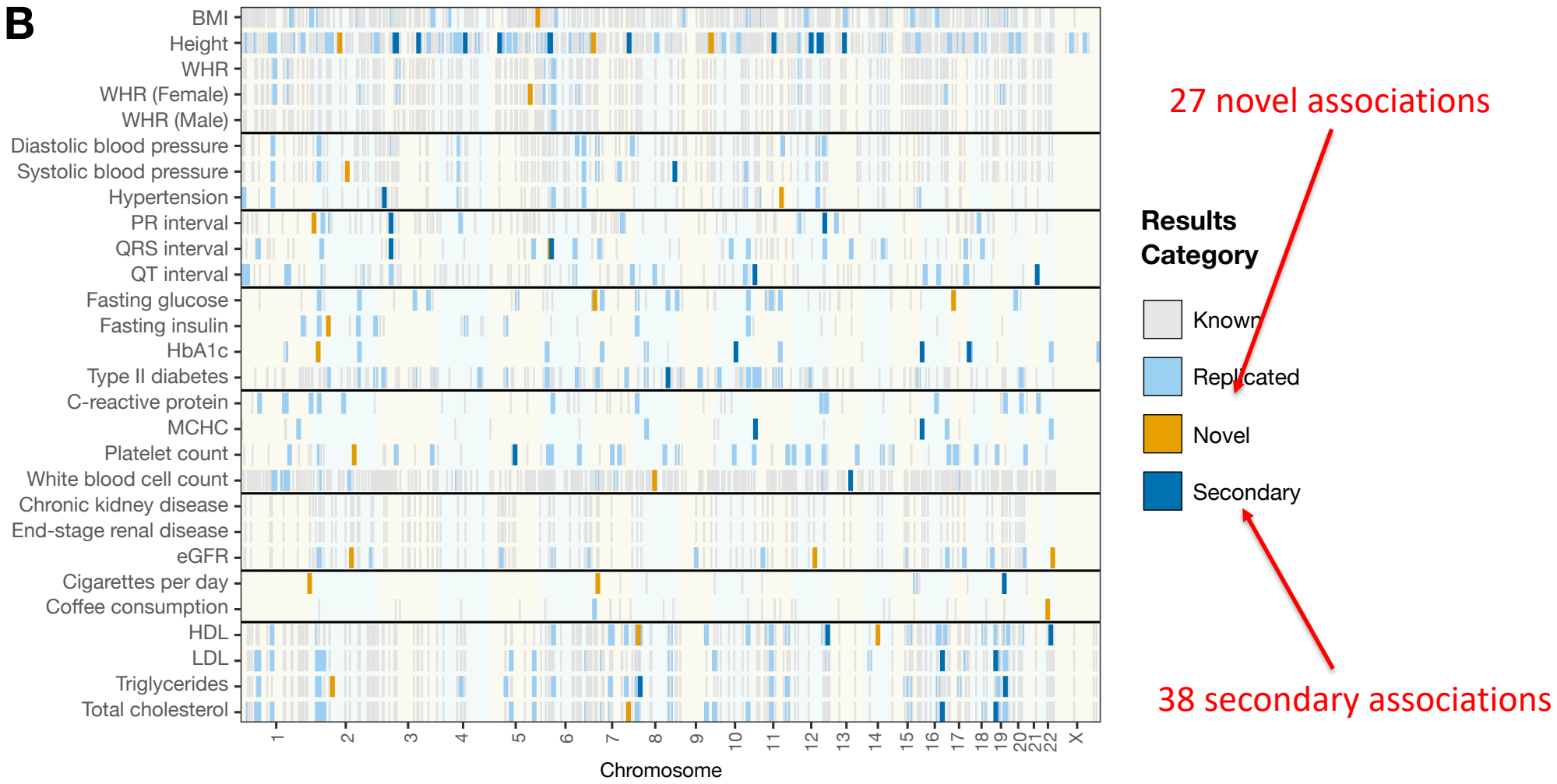
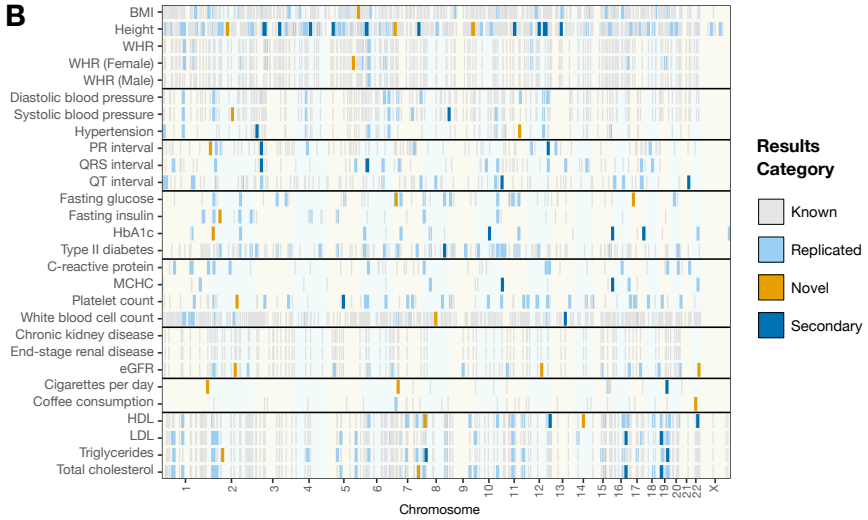
Genomic discovery and generalizability



Genomic discovery and generalizability

1,444 known trait-variant associations in PAGE



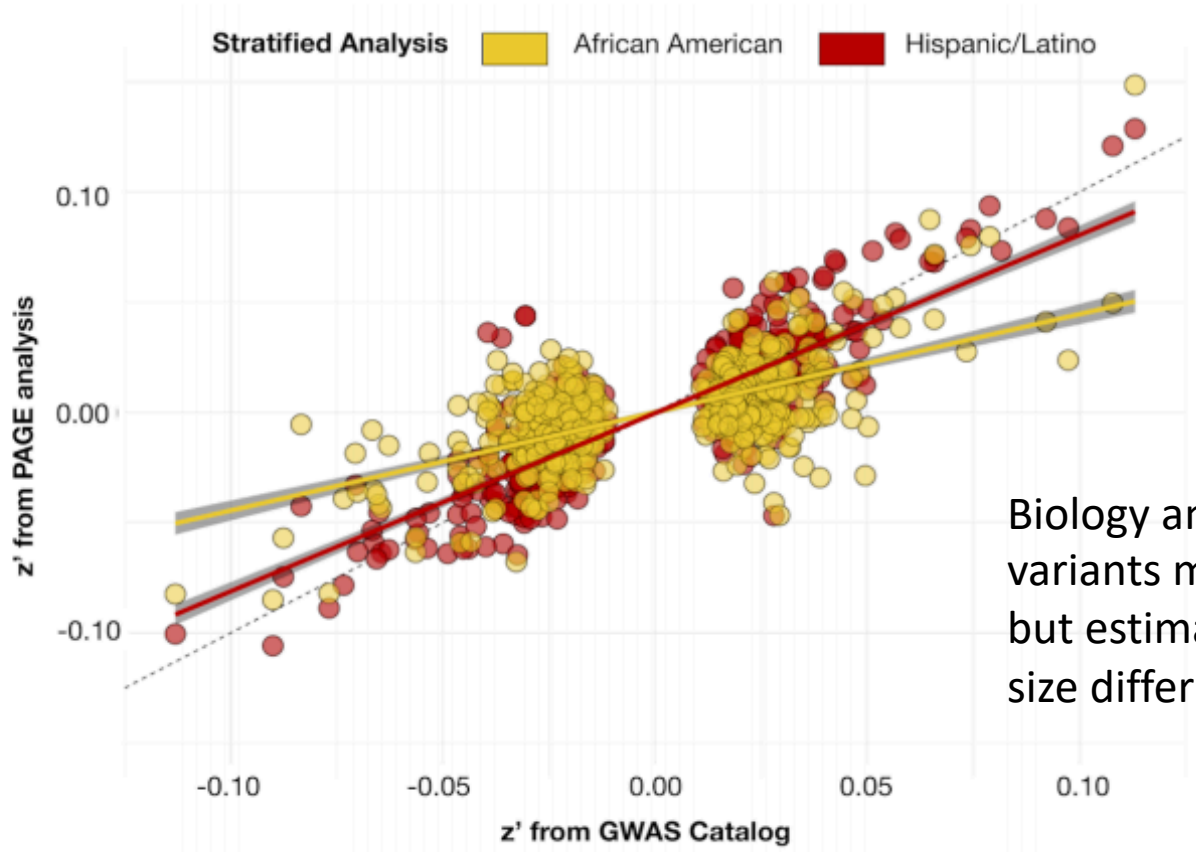
Known Signals

GWAS Catalog sites for phenotypes in PAGE

Replication

Lookup these index sites and any linked in our GWAS

Effect sizes derived in European populations are weaker in other populations

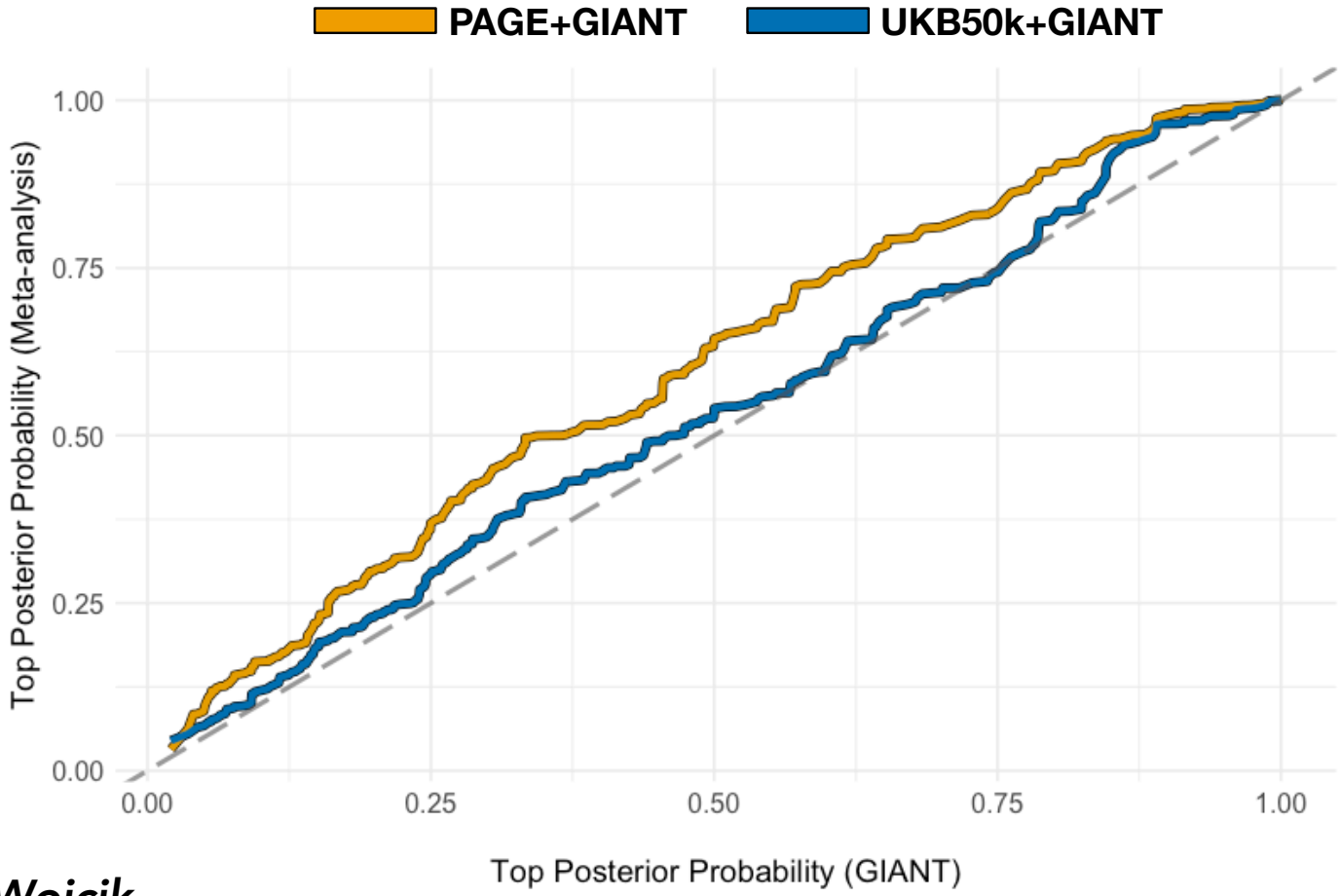


Biology and causal variants mostly shared, but estimates of effect size differ

Gen Wojcik

Wojcik GL[#], Graff M[#], Nishimura KK[#], Tao R[#], Haessler J[#], Gignoux CR[#], Highland HM[#], Patel YM[#], … Kenny EE[$], Carlson CS[$]. Genetic diversity improves our discovery of complex traits. Nature (2019)

Diversity increases confidence in potential causal variants



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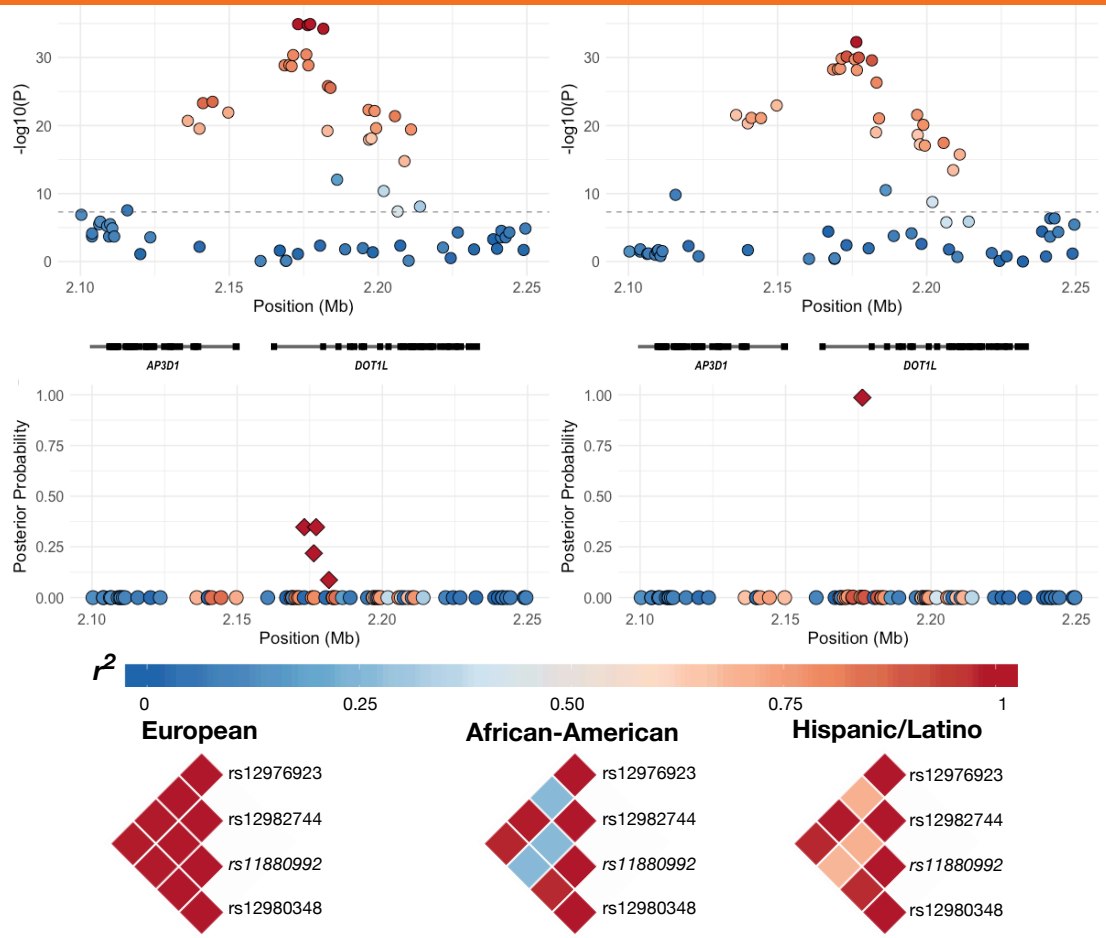

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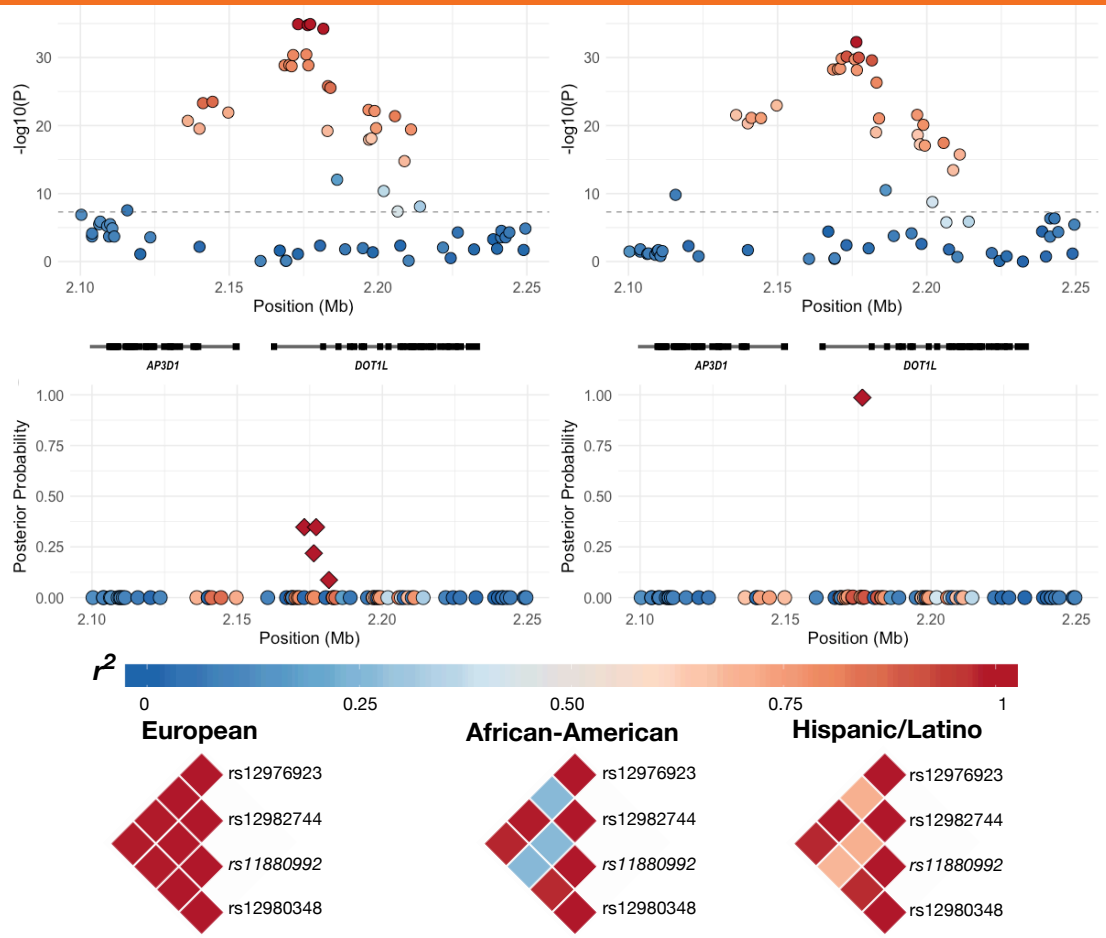

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Environmental, evolutionary and other factors impact prediction

Science

BREVIA

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 …
+ See all authors and affiliations

biobank uk
Improving the health of future generations

Liz Cirulli, Ph.D.
Nicole Washington, Ph.D.
Dr. Cirulli is Principal Scientist and Dr. Washington is the Associate Director of Research at Helix.
March 27, 2019

Researchers have access to new data on thousands of exomes. Here's what we found.

3. *TYRP1* variants and Blonde Hair

One of our novel findings is the association of *TYRP1* variants with blonde hair color in those of British ancestry. *TYRP1* made a big splash in 2012 when researchers found that a variant in this gene caused blonde hair in dark-skinned individuals of Melanesian ancestry from the Solomon Islands. This genetic variation is separate from the ones that are known to cause blonde hair in those of European ancestry and, until now, there has been no evidence that this gene also played a role in European hair coloring. The specific variant that causes blonde hair in Solomon Islanders, rs387907171, an arginine to cysteine substitution at amino acid position 93, was only found in 3 of the 40,648 individuals analyzed in our UK Biobank study. However, more than 30 other rare coding variants in this gene were found in 1% of the 4,671 British ancestry blonde individuals. Previous studies have shown that the Solomon Island variant is recessive,

Challenges and opportunities

- Genomics is yielding an enormous engine of knowledge with the potential to transform medicine and society as we know it today

- Genomics tells us about our susceptibility to disorders and diseases – but our DNA can also reveal the broader story of our evolution, ancestry and history that can be also correlated to social, environmental determinants of human phenotypes.

- Challenge and opportunity is to integrate this information in the fuller clinical and social picture of health and wellness

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