Missing heritability at 10: reviewing the origin and impact of concepts and publications

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NHGRI missing heritability meeting
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GWAS, the early years

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ARTICLES

Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls

The Wellcome Trust Case Control Consortium*

Vol 447|7 June 2007 nature

NEWS & VIEWS

GENOMICS

Guilt by association

Anne M. Bowcock

In a tour-de-force demonstration of feasibility, a consortium of 50 research teams uses 500,000 genetic markers from each of 17,000 individuals to identify 24 genetic risk factors for 7 common human diseases.

In Retrospect: A decade of shared genomic associations

Teri A. Manolio

Nature **546**, 360–361 (15 June 2017) | doi:10.1038/546360a
Published online 14 June 2017

A paper that analysed genetic variants in 14,000 people to identify disease-associated regions set the standard for collaborative genome-wide association studies and provided methodological advances whose effects are still felt today.

Subject terms: History · Genetics · Genomics

Ten years ago this month, *Nature* published a landmark study [1] that compared the frequencies of hundreds of thousands of common genetic variants (polymorphisms) at single nucleotides in people with and without seven diseases, to look for variants associated with each disease. Such genome-wide association studies (GWAS) provide an agnostic way to identify these variants, unfettered by prevailing — and potentially incorrect — assumptions about which genomic regions are important in disease biology. The study, by the Wellcome Trust Case Control Consortium (WTCCC), set the standard for this field of research, and nearly 3,000 GWAS have since been published.

REVIEW

Five Years of GWAS Discovery

Peter M. Visscher, Matthew A. Brown, Mark I. McCarthy, Jian Yang

DOI: https://doi.org/10.1016/j.ajhg.2017

REVIEW

10 Years of GWAS Discovery: Biology, Function, and Translation

Peter M. Visscher,[1,2,*] Naomi R. Wray,[1,2] Qian Zhang,[1] Pamela Sklar,[3] Mark I. McCarthy,[4,5,6] Matthew A. Brown,[7] and Jian Yang[1,2]

Application of the experimental design of genome-wide association studies (GWASs) is now 10 years old (young), and here we review the remarkable range of discoveries it has facilitated in population and complex-trait genetics, the biology of diseases, and translation toward new therapeutics. We predict the likely discoveries in the next 10 years, when GWASs will be based on millions of samples with array data imputed to a large fully sequenced reference panel and on hundreds of thousands of samples with whole-genome sequencing data.

AJHG, Volume 101, Issue 1, p5–22, 6 July 2017.

GWAS, reviewing the early years

Review Article

Genome-wide association studies for complex traits: consensus, uncertainty and challenges

Mark I. McCarthy ✉, Gonçalo R. Abecasis, Lon R. Cardon, David B. Goldstein, Julian Little, John P. A. Ioannidis & Joel N. Hirschhorn

Nature Reviews Genetics **9**, 356–369 (2008)
doi:10.1038/nrg2344

Published: 01 May 2008

Abstract

The past year has witnessed substantial advances in understanding the genetic basis of many common phenotypes of biomedical importance. These advances have been the result of systematic, well-powered, genome-wide surveys exploring the relationships between common sequence variation and disease predisposition. This approach has revealed over 50 disease-susceptibility loci and has provided insights into the allelic architecture of multifactorial traits. At the same time, much has been learned about the successful prosecution of association studies on such a scale. This Review highlights the knowledge gained, defines areas of emerging consensus, and describes the challenges that remain as researchers seek to obtain more complete descriptions of the susceptibility architecture of biomedical traits of interest and to translate the information gathered into improvements in clinical management.

Published online 5 November 2008 | *Nature* **456**, 18-21 (2008) | doi:10.1038/456018a

News Feature

Personal genomes: The case of the missing heritability

When scientists opened up the human genome, they expected to find the genetic components of common traits and diseases. But they were nowhere to be seen. Brendan Maher shines a light on six places where the missing loot could be stashed away.

Brendan Maher

This year, three groups of researchers[2, 3, 4] scoured the genomes of huge populations (the largest study[4] looked at more than 30,000 people) for genetic variants associated with the height differences. More than 40 turned up.

Review Article

Finding the missing heritability of complex diseases

Teri A. Manolio ✉, Francis S. Collins […] Peter M. Visscher

Nature **461**, 747–753 (08 October 2009)
doi:10.1038/nature08494
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Received: 25 June 2009
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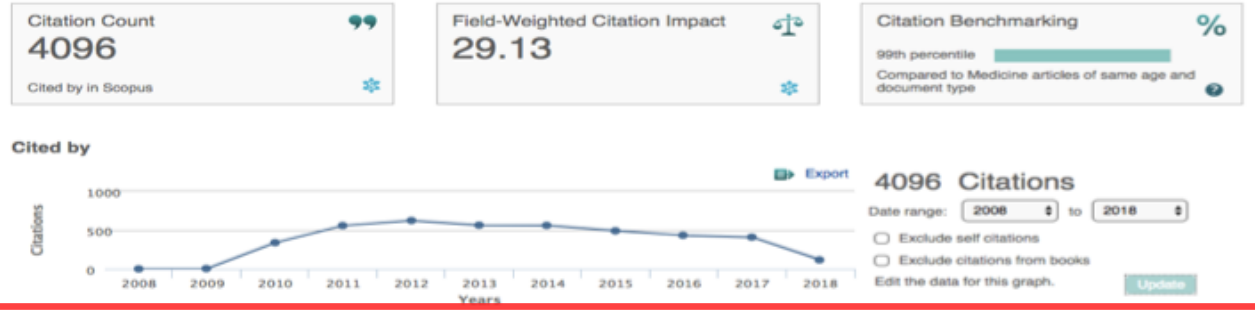
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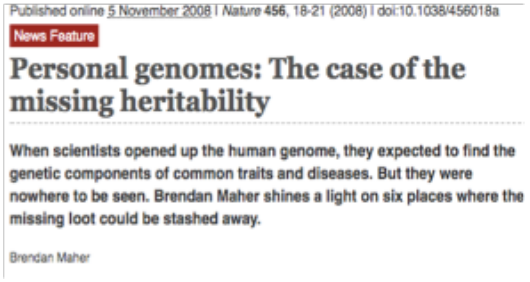
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Brendan Maher


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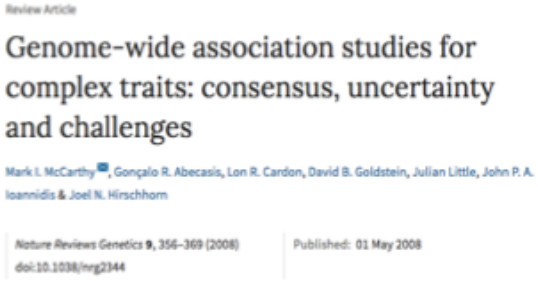
Review Article

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Our views on impact of a Review

- Resource: Comprehensive, accurate, balanced summary of the primary research in the field.
- Educational: Clear explanation of concepts to a broad scientific readership.
- Representing genetics: Central highlights for press and public readership.

Impact of the ‘so-called missing heritability problem’

- Perception and impact within the genetics community?
- Within broader scientific community?
- How has this influenced research directions?
- How has this influenced public perception of human genetics?

A few related Reviews

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Viewpoint

Missing heritability and strategies for finding the underlying causes of complex disease

Evan E. Eichler, Jonathan Flint, Greg Gibson, Augustine Kong, Suzanne M. Leal, Jason H. Moore & Joseph H. Nadeau

Nature Reviews Genetics **11**, 446–450 (2010)
doi:10.1038/nrg2809

Published: 01 June 2010

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Review Article

Rare and common variants: twenty arguments

Greg Gibson

Nature Reviews Genetics **13**, 135–145 (2012)
doi:10.1038/nrg3118

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Review Article

The heritability of human disease: estimation, uses and abuses

Albert Tenesa & Chris S. Haley

Nature Reviews Genetics **14**, 139–149 (2013)
doi:10.1038/nrg3377

Published: 18 January 2013

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Opinion

Pitfalls of predicting complex traits from SNPs

Naomi R. Wray, Jian Yang, Ben J. Hayes, Alkes L. Price, Michael E. Goddard & Peter M. Visscher

Nature Reviews Genetics **14**, 507–515 (2013)
doi:10.1038/nrg3457

Published: 18 June 2013

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Review Article

Bringing genome-wide association findings into clinical use

Teri A. Manolio

Nature Reviews Genetics **14**, 549–558 (2013)
doi:10.1038/nrg3523

Published: 09 July 2013

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Analysis

The contribution of genetic variants to disease depends on the ruler

John S. Witte, Peter M. Visscher & Naomi R. Wray

Nature Reviews Genetics **15**, 765–776 (2014)
doi:10.1038/nrg3786
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Published: 16 September 2014

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Review Article

Genetic architecture: the shape of the genetic contribution to human traits and disease

Nicholas J. Timpson, Celia M. T. Greenwood, Nicole Soranzo, Daniel J. Lawson & J. Brent Richards

Nature Reviews Genetics **19**, 110–124 (2018)
doi:10.1038/nrg.2017.101

Published: 11 December 2017

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Perspective

Concepts, estimation and interpretation of SNP-based heritability

Jian Yang, Jian Zeng, Michael E Goddard, Naomi R Wray & Peter M Visscher

Nature Genetics **49**, 1304–1310 (2017)
doi:10.1038/ng.3941
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Received: 15 December 2016
Accepted: 31 July 2017
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