Towards reproducible science: lessons from human genetics

Daniel MacArthur
Analytic and Translational Genetics Unit,
Massachusetts General Hospital
Harvard Medical School
Broad Institute of Harvard and MIT
www.macarthurlab.org
Twitter: @dgmacarthur

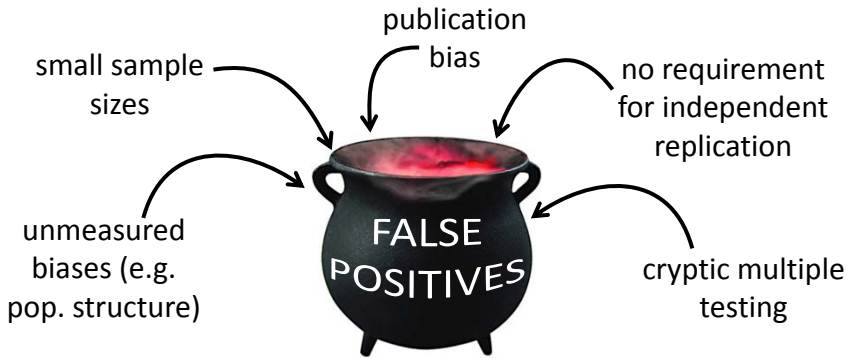
The cartoon history of human complex trait genetics

Prior to 2007: candidate gene era

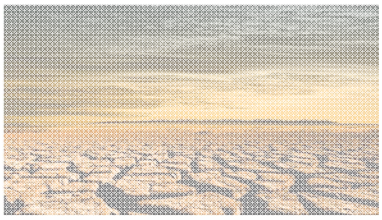
- Targeted testing of variants in "biologically plausible" genes
- Small sample sizes (hundreds)
- 1000s of reported associations, **~none consistently replicated**

What drove false positives in candidate gene studies?

- Most "biologically plausible" variants are **not** actually associated with disease!



The cartoon history of human complex trait genetics



Prior to 2007: candidate gene era

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Post-2007: genome-wide association studies

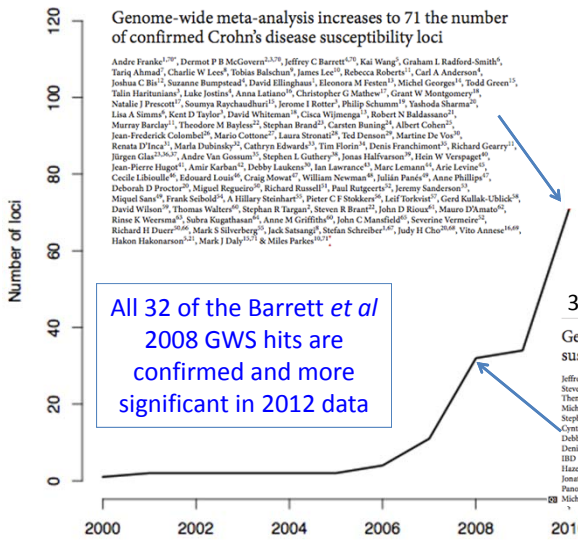
- Unbiased genome-wide scans
- Big samples (1000s-10,000s)
- 1000s of reported associations, **near-perfect replication rates**

GWAS for Crohn's Disease

6,333 cases and 15,056 controls

Genome-wide meta-analysis increases to 71 the number of confirmed Crohn's disease susceptibility loci

Andre Franke[1,70*], Dermot P B McGovern[2,3,70], Jeffrey C Barrett[4,70], Kai Wang[5], Graham L Radford-Smith[6], Tariq Ahmad[7], Charlie W Lees[8], Tobias Balschun[9], James Lee[10], Rebecca Roberts[11], Carl A Anderson[4], Joshua C Bis[12], Suzanne Bumpstead[4], David Ellinghaus[1], Eleonora M Festen[13], Michel Georges[14], Todd Green[15], Talin Haritunians[2], Luke Jostins[4], Anna Latiano[16], Christopher G Mathew[17], Grant W Montgomery[18], Natalie J Prescott[17], Soumya Raychaudhuri[19], Jerome I Rotter[5], Philip Schumm[19], Yashoda Sharma[20], Lisa A Simma[8], Kent D Taylor[5], David Whiteman[18], Cisca Wijmenga[13], Robert N Baldassano[21], Murray Barclay[11], Theodore M Bayless[22], Stephan Brand[23], Carsten Buning[24], Albert Cohen[25], Jean-Frederick Colombel[26], Mario Cottone[27], Laura Stronati[28], Ted Denson[29], Martine De Vos[30], Renata D'Inca[31], Marla Dubinsky[32], Cathryn Edwards[33], Tim Florin[34], Denis Franchimont[35], Richard Gearry[11], Jürgen Glas[23,36,37], Andre Van Gossum[35], Stephen L Guthery[38], Jonas Halfvarson[39], Hein W Verspaget[40], Jean-Pierre Hugot[41], Amir Karban[42], Debby Laukens[30], Ian Lawrance[43], Marc Lemann[44], Arie Levine[45], Cecile Libioulle[46], Edouard Louis[46], Craig Mowat[47], William Newman[48], Julián Panés[49], Anne Phillips[47], Deborah D Proctor[50], Miguel Regueiro[50], Richard Russell[51], Paul Rutgeerts[52], Jeremy Sanderson[53], Miquel Sans[49], Frank Seibold[54], A Hillary Steinhart[55], Pieter C F Stokkers[56], Leif Torkvist[57], Gerd Kullak-Ublick[58], David Wilson[59], Thomas Walters[60], Stephan R Targan[2], Steven R Brant[22], John D Rioux[61], Mauro D'Amato[62], Rinse K Weersma[63], Subra Kugathasan[64], Anne M Griffiths[60], John C Mansfield[65], Severine Vermeire[52], Richard H Duerr[20,66], Mark S Silverberg[32], Jack Satsangi[8], Stefan Schreiber[1,67], Judy H Cho[20,68], Vito Annese[16,69], Hakon Hakonarson[5,21], Mark J Daly[3,5,71] & Miles Parkes[10,71*].



All 32 of the Barrett *et al* 2008 GWS hits are confirmed and more significant in 2012 data

Jostins, Ripke et al Nature 2012
163 distinct confirmed associated loci in IBD (CD and/or UC)
N=75,000 samples

3,230 cases and 4,829 controls

Genome-wide association defines more than 30 distinct susceptibility loci for Crohn's disease

Jeffrey C Barrett[*1], Sarah Hansoul[2], Dan L Nicolae[3], Judy H Cho[4], Richard H Duerr[5,6], John D Rioux[7,8], Steven R Brant[9,10], Mark S Silverberg[11], Kent D Taylor[12], M Michael Barmada[3], Alain Bitton[13], Themistocles Dassopoulos[6], Lisa Wu Datta[6], Todd Green[6], Anne M Griffiths[14], Emily O Kistner[15], Michael T Murtha[4], Miguel D Regueiro[6], Jerome I Rotter[12], L Philip Schumm[13], A Hillary Steinhart[11], Stephan R Targan[12], Ramnik J Xavier[16], the NIDDK IBD Genetics Consortium[13], Cécile Libioulle[2], Cynthia Sandor[2], Mark Lathrop[17], Jacques Belaiche[18], Olivier Dewit[19], Ivo Gut[17], Simon Heath[17], Debby Laukens[20], Myriam Mni[2], Paul Rutgeerts[21], André Van Gossum[22], Diana Zelenika[17], Denis Franchimont[22], JP Hugot[23], Martine de Vos[24], Severine Vermeire[21], Edouard Louis[18], the Belgian-French IBD Consortium[25], the Wellcome Trust Case Control Consortium[25], Lon R Cardon[3], Carl A Anderson[3], Hazel Drummond[26], Elaine Nimmo[26], Tariq Ahmad[27], Natalie J Prescott[28], Clive M Onnie[29], Sheila A Fisher[26], Jonathan Marchini[27], Jilur Ghori[29], Suzannah Bumpstead[29], Rhian Gwilliam[29], Mark Tremelling[29], Panos Deloukas[29], John Mansfield[30], Derek Jewell[31], Jack Satsangi[26], Christopher G Mathew[26], Miles Parkes[26], Michel Georges[2] & Mark J Daly[8,32]

Mark Daly

Lessons from GWAS

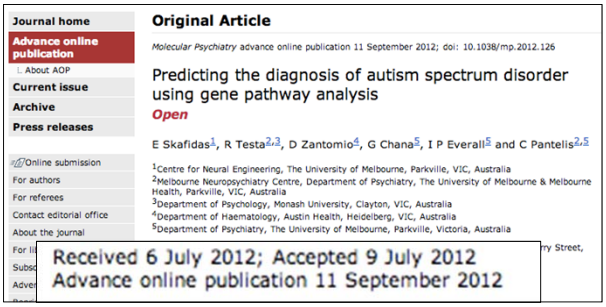
- Perform **well-powered** studies
- Where possible, perform **unbiased scans**, *then* pursue specific results
- Leave little room for *post-hoccery*
  - Establish **consensus on statistical approaches** and *P* value thresholds
  - Require **raw data and critical software** be made available to other researchers
- Work in consortia: access **more samples** and get **internal peer review**

New challenges in the genome era

- We no longer start with hypotheses: we *sift results* from large, noisy data sets
- Challenge: any process extracting "interesting" results will also enrich for biases and artifacts
- Avoiding false positives requires:
  - **deep understanding of errors** (manual spot-checking, visualization)
  - **validation** using independent technology

MacArthur 2012 *Nature* **487:**427-428

Science needs nimble discussion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Original Article

Molecular Psychiatry advance online publication 11 September 2012; doi: 10.1038/mp.2012.126

Predicting the diagnosis of autism spectrum disorder using gene pathway analysis

Open

E Skafidas[1], R Testa[2,3], D Zantomio[4], G Chana[5], I P Everall[5] and C Pantelis[2,5]

[1]Centre for Neural Engineering, The University of Melbourne, Parkville, VIC, Australia
[2]Melbourne Neuropsychiatry Centre, Department of Psychiatry, The University of Melbourne & Melbourne Health, Parkville, VIC, Australia
[3]Department of Psychology, Monash University, Clayton, VIC, Australia
[4]Department of Haematology, Austin Health, Heidelberg, VIC, Australia
[5]Department of Psychiatry, The University of Melbourne, Parkville, Victoria, Australia

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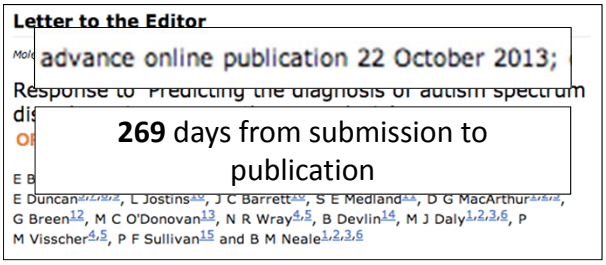
Letter to the Editor

advance online publication 22 October 2013;

Response to "Predicting the diagnosis of autism spectrum dis

269 days from submission to publication

E Duncan[2,7,8,9], L Jostins[10], J C Barrett[10], S E Medland[11], D G MacArthur[2,12], G Breen[12], M C O'Donovan[13], N R Wray[4,5], B Devlin[14], M J Daly[1,2,3,6], P M Visscher[4,5], P F Sullivan[15] and B M Neale[1,2,3,6]

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PubMed Commons
A forum for scientific discourse

Specific recommendations

- Establish **standards workshops** with domain experts and statisticians to define consensus protocols for widely used techniques
- Fund creation of software for **intuitive visualization** of complex data sets
- Mandate **availability of raw data and software** to enable replication and reuse
- Facilitate **large-scale collaborative science** across more domains of science
- Provide career incentives for **open pre- and post-publication peer review**