PGC Worldwide Lab Call Details

DATE: Friday, December 13th, 2013

PRESENTER: John McGrath AM, MBBS, MD, PhD, FRANZCP
Queensland Brain Institute, The University of Queensland, Australia

TITLE: "Where GWAS and Epidemiology Meet: Opportunities for the Simultaneous Study"

START: We will begin promptly on the hour.
1000 EDT - US East Coast
0700 PDT - US West Coast
1500 BST - UK
1600 CET - Central Europe
0000 AEDT – Australia (Saturday, June 14th, 2013)

DURATION: 1 hour

TELEPHONE:
- US Toll free: 1 866 515.2912
- International direct: +1 617 399.5126
- Toll-free number? See http://www.btconferencing.com/globalaccess/?bid=75_public
- Operators will be on standby to assist with technical issues. "*0" will get you assistance.
- This conference line can handle up to 300 participants.

PASSCODE: 275 694 38

Lines are Muted **NOW**

Lines have been automatically muted by operators as it is possible for just one person to ruin the call for everyone due to background noise, electronic feedback, crying children, wind, typing, etc.

Operators announce callers one at a time during question and answer sessions.

Dial *1 if you would like to ask a question of the presenter. Presenter will respond to calls as time allows.

Dial *0 if you need operator assistance at any time during the duration of the call.

UPCOMING PGC Worldwide Lab

DATE: Friday, January 10th, 2014
PRESENTER: Ronald C. Kessler, Ph.D.
TITLE: "An overview of the cross-national descriptive epidemiology of common mental disorders in the WHO World Mental Health (WMH) Surveys"
START: We will begin promptly on the hour.

1000 EDT - US East Coast
0700 PDT - US West Coast
1500 BST - UK
1600 CEST - Central Europe
0000 AEST – Australia (Saturday, August 11th, 2013)

DURATION: 1 hour

TELEPHONE:
- US Toll free: 1 866 515.2912
- International direct: +1 617 399.5126
- Toll-free number? See http://www.btconferencing.com/globalaccess/?bid=75_public
- Operators will be on standby to assist with technical issues. "*0" will get you assistance.
- This conference line can handle up to 300 participants.

PASSCODE: 275 694 38

Where GWAS and Epidemiology Meet

John McGrath

Queensland Centre for Mental Health Research

qbi queensland brain institute

The University Of Queensland AUSTRALIA

Artwork from QCMHR Gallery
www.qcmhr.uq.edu.au

Broad aims for this talk

- to trigger a discussion about *new* ways to combine clues from genetic and epidemiology
    - *and thus to avoid old debates about the statistical nuances of GxE*

- to propose candidate exposures for PGC consideration

Outline of this talk

- Schizophrenia – *then and now*
- How to build a brain – *where are the instructions?*
- Modifiable risk factors – *what are the best clues?*
- Glance backwards – *GxE*
- Looking forwards – *new tools for exploration*
- Discussion and input from PGC investigators

McGrath JJ, Mortensen PB, Visscher PM, Wray NR. (2013) Where GWAS and epidemiology meet: opportunities for the simultaneous study of genetic and environmental risk factors in schizophrenia. *Schizophr Bull* 39(5)**:** 955-959.

The Past

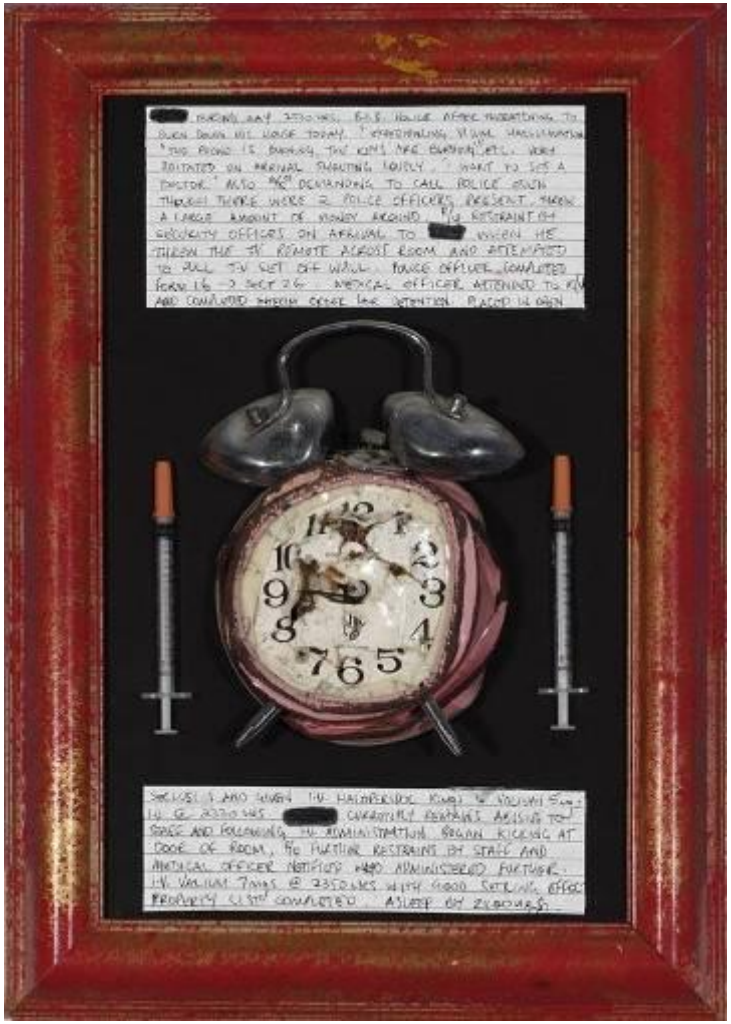
- Schizophrenia was a relatively homogenous disease construct, albeit with sub-types.
- Schizophrenia affected men and women equally, and had a flat epidemiological profile across time, place and persons.

Morgan C, O'Donovan M C, et al. How can risk and resilience factors be leveraged to optimize discovery pathways? In: Silverstein SM, Moghaddam B, Wykes T, eds. Schizophrenia: Evolution and Synthesis. Cambridge, MA: MIT Press, 2013:137-64.

The Past

- Schizophrenia would have a small, manageable set of risk factors.
- Neuroscience would reveal a readily interpretable mechanism of action that would then lead to effective treatments.

The Present



- Schizophrenia is a poorly understood group of disorders that defies ready simplification based on symptoms, putative neurobiology or aetiopathogenesis.
- Schizophrenia affects men more than women, and the incidence of the disorder varies significantly by place and subgroup.

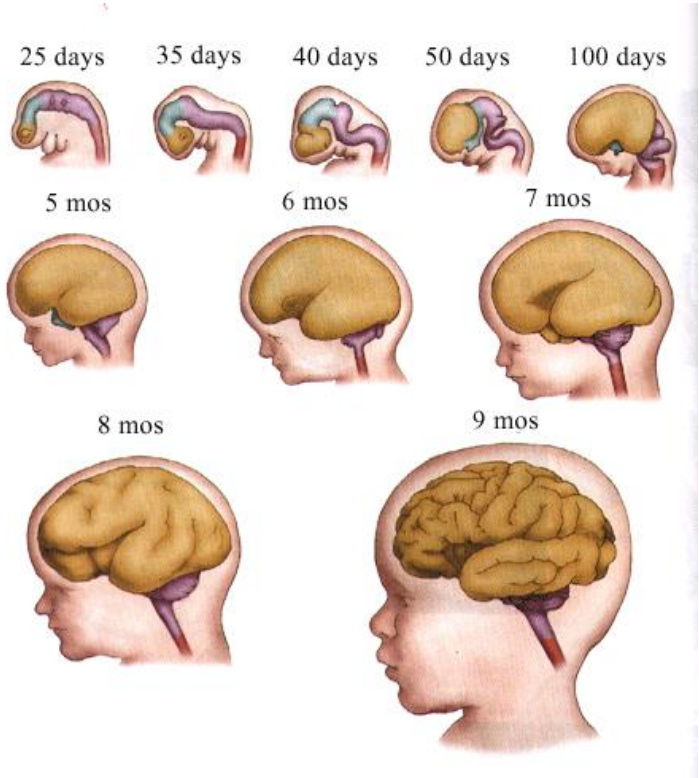
The Present

- Risk factors for schizophrenia are also associated with a wide range of other brain-related adverse health outcomes.
- The genetic architecture of schizophrenia is a mixed economy of many common risk alleles of small effect size and many different rare risk alleles with mixed effect sizes.
  - *It is feasible that a comparable pattern of nongenetic risk factors will be found.*

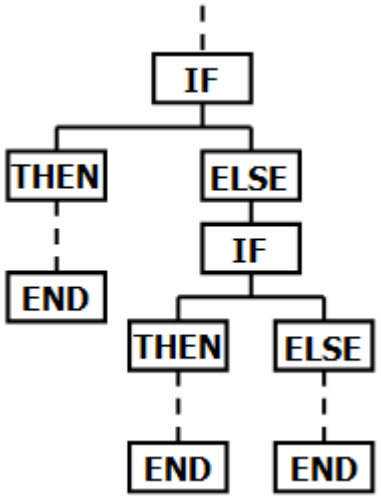
The Present

- Common mental disorders like anxiety and depression often precede and co-exist with schizophrenia.
- Isolated and transient psychotic experiences are prevalent in the community and are strongly associated with common mental disorders such as anxiety and depression.

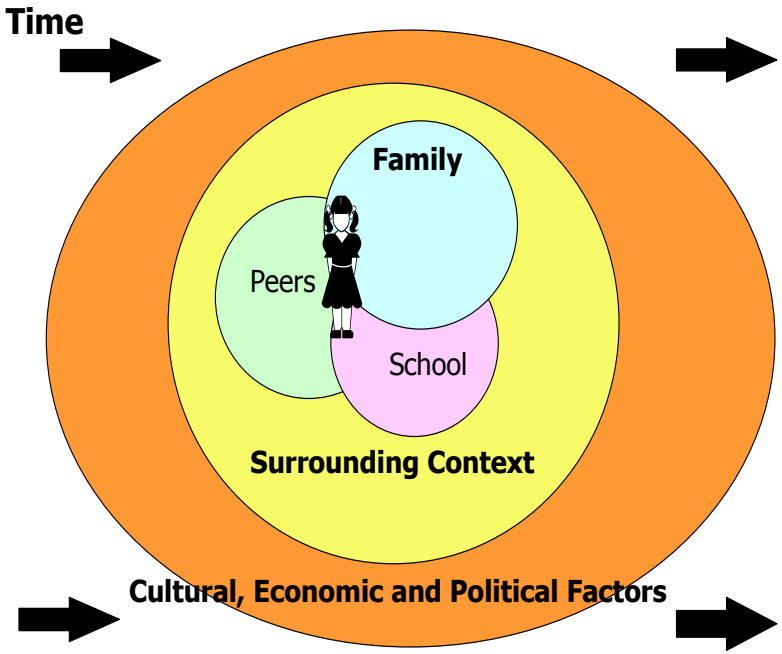
How to build a healthy brain*



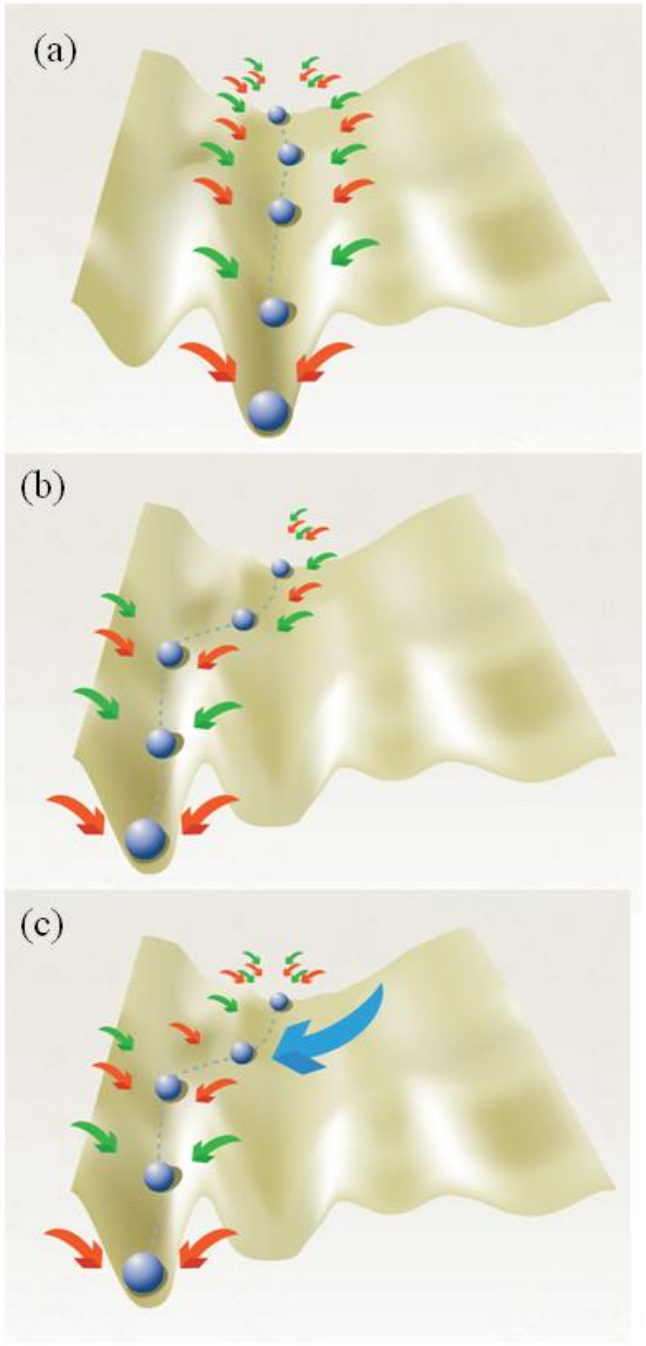
**some assembly required*



The instructions to build a brain emerge in a dynamic and contingent fashion

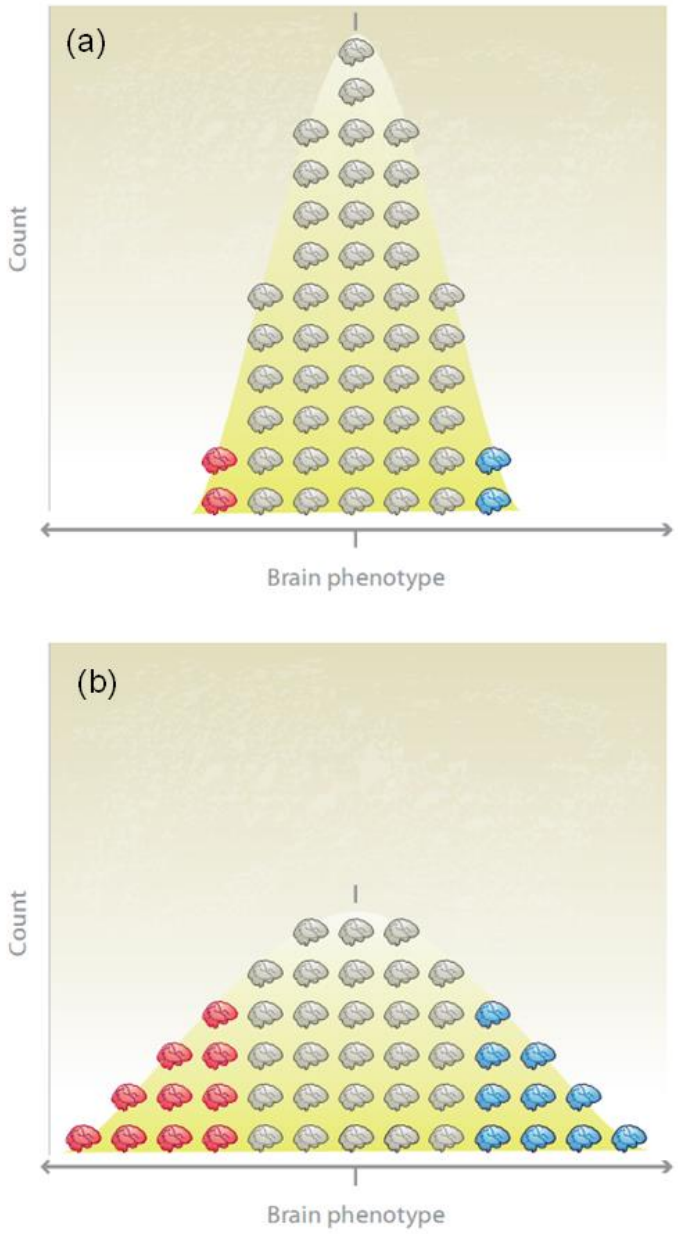


- The organism draws instructions from *genetic* and *environmental* factors.
- Brain development is a tightly regulated cascade.
  - *Timing*
  - *Position*



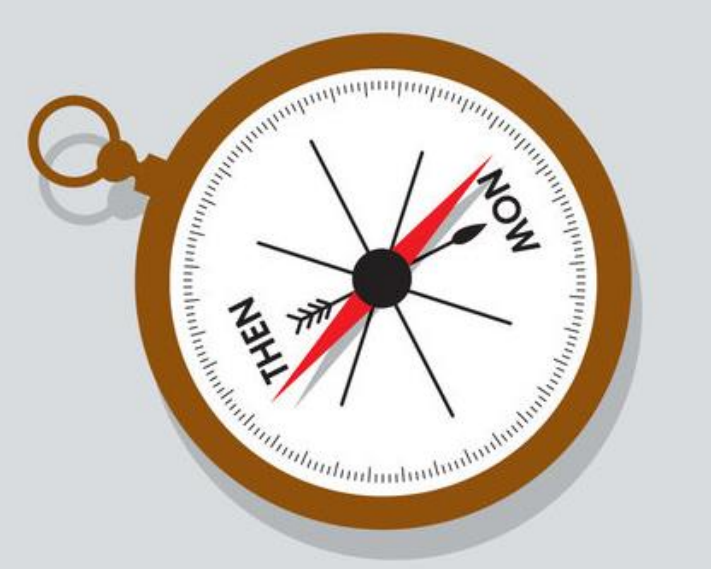
- Genetic and nongenetic factors emerge over time and the instructions for brain development are derived from these instructions in real time.
- *Experience-expectant* factors (ubiquitous - common)
  - 'Environmental knock-out'
- Rare and disruptive exposures

McGrath JJ, Hannan AH, Gibson G. (2011) Decanalization, brain development and risk of schizophrenia. ***Translational Psychiatry*** 1, e14.



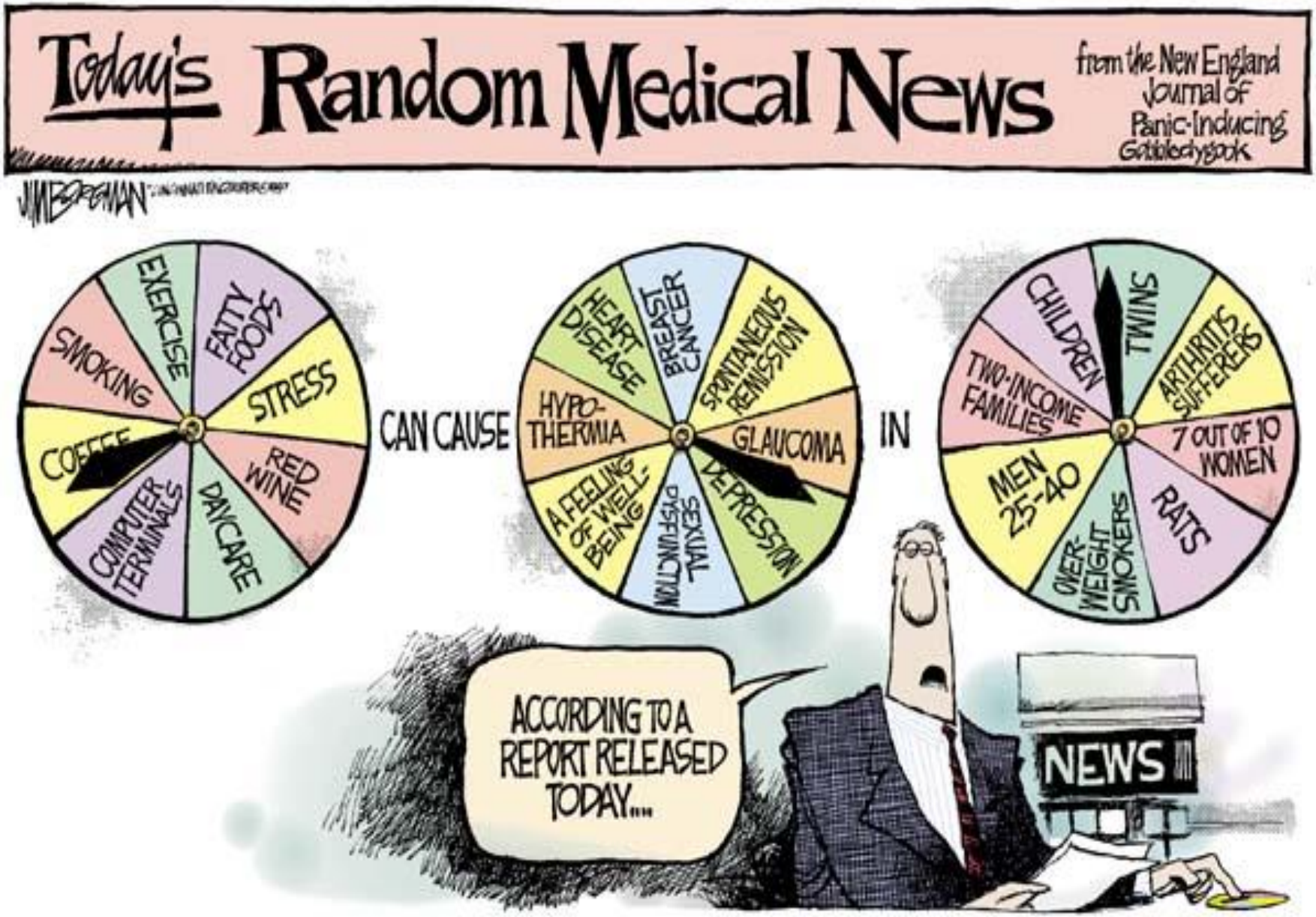
- Decanalization can influence the variance of the phenotype (population level)
- Systems buffered with redundancies are less likely to decanalize
- Implications for the expanded neocortex
  - *Last in = first to break*

McGrath JJ, Hannan AH, Gibson G. (2011) Decanalization, brain development and risk of schizophrenia. ***Translational Psychiatry*** 1, e14.



Brown AS, McGrath JJ. (2011) The prevention of schizophrenia. ***Schizophr Bull*** 37; 257-61.

McGrath JJ, Lawlor DA. (2011) The search for modifiable risk factors for schizophrenia. ***Am J Psychiatry*** 168:1235-8.

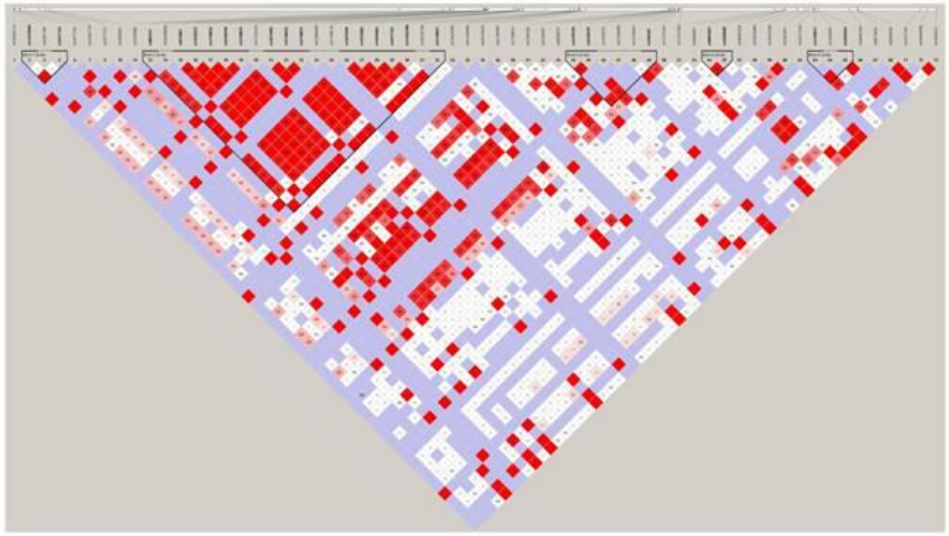


Cartoon by Jim Borgman, first published by the Cincinnati Inquirer and King Features Syndicate 1997 Apr 27; Forum section: 1 and reprinted in the New York Times, 27 April 1997, E4.

The limits of observational epidemiology

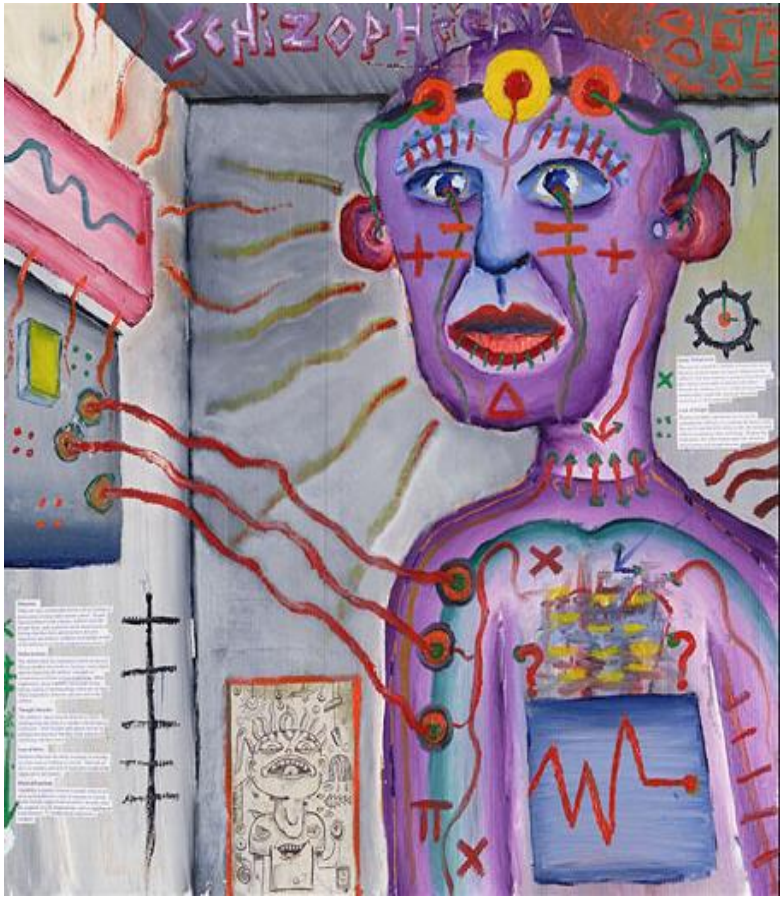
- The curse of observation epidemiology
- In the absence of RCTs, how else can we interrogate clues from epidemiology?
- Is the association the result of unmeasured residual confounding?
- Animal models/experiments as tools to explore biological plausability
- *Can genetics help?*

Tag SNPs versus Proxy risk factors



- Season of birth
- Urban residence during early life
- Migrant/ethnic status
- Paternal age

Candidate modifiable risk factors

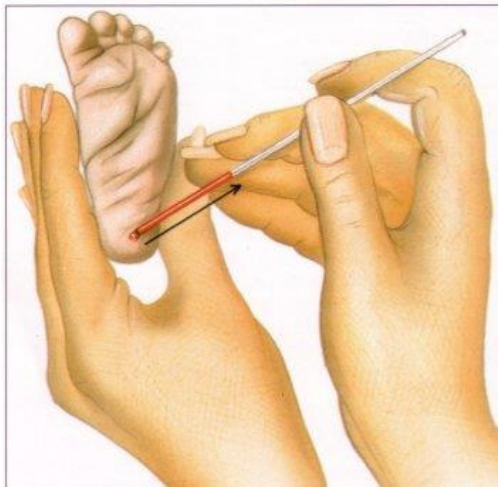


- Trauma exposure
- Early cannabis use
- Pregnancy and birth complications
- Infection (or maternal immune activation?)
- Prenatal nutrition
  - Vitamin D, folate, iron
- Advanced paternal age

Trauma exposure is linked to adverse health outcomes (including schizophrenia)

Scott J, Varghese D, McGrath (2010). As the twig is bent, the tree inclines – Adult mental health consequences of childhood adversity. ***Archives of General Psychiatry*** 67 (2). 111-112

Analytic epidemiology



- Preben Bo Mortensen (Aarhus University)
- Population-based samples
- Record linkage
- Biobank - neonatal dried blood spots

www.ncrr.au.dk

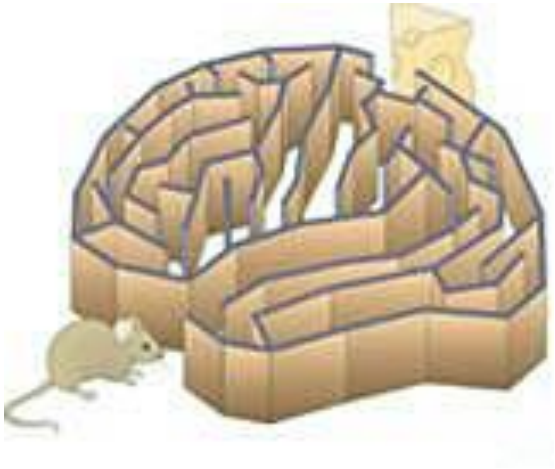
Danish Neonatal Dried Blood Spots

Prenatal health

- Infection
  - Antibodies to infectious agents
- Maternal immune response
  - Cytokines and bioimmune markers

Borglum AD, et al. Genome-wide study of association and interaction with maternal cytomegalovirus infection suggests new schizophrenia loci. ***Mol Psychiatry*** in press

Vitamin D and brain health



Low vitamin D disrupts brain development and adult brain function

Low neonatal vitamin D is associated with an increased risk of schizophrenia

Low childhood vitamin D is associated with an increased risk of later psychotic experiences

McGrath J, Burne TH, Feron F, Mackay-Sim A, Eyles DW (2010). Developmental vitamin D deficiency and risk of schizophrenia: A 10 year update. ***Schizophrenia Bulletin*** 36; 1073-8.

Cannabis use and risk of schizophrenia

- Consistent evidence from prospective cohort studies (early use, heavy use)
- Single SNP GxE evidence

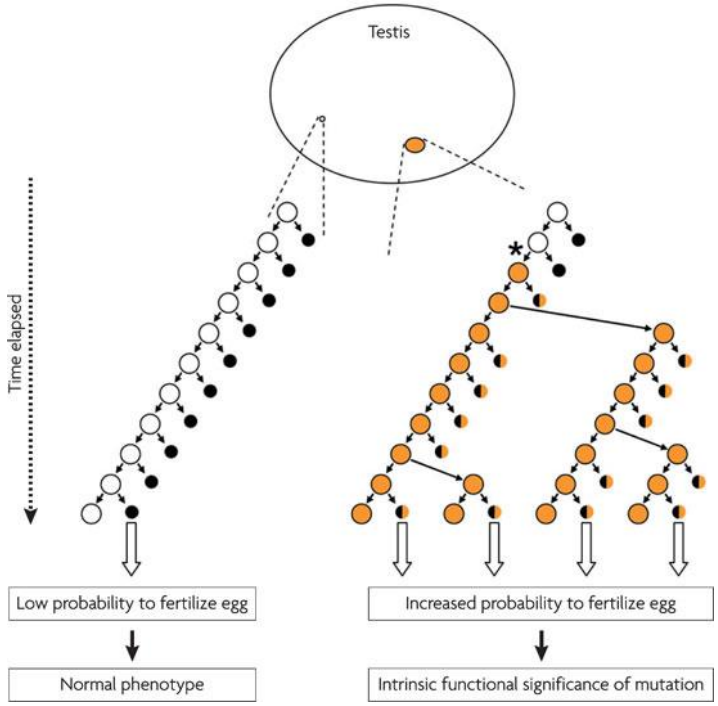
Di Forti M, Iyegbe C, Sallis H, et al. Confirmation that the AKT1 (rs2494732) genotype influences the risk of psychosis in cannabis users. (2012) ***Biol Psychiatry*** 72:811-6

Advanced paternal age and risk of neurodevelopmental disorders

August 2012

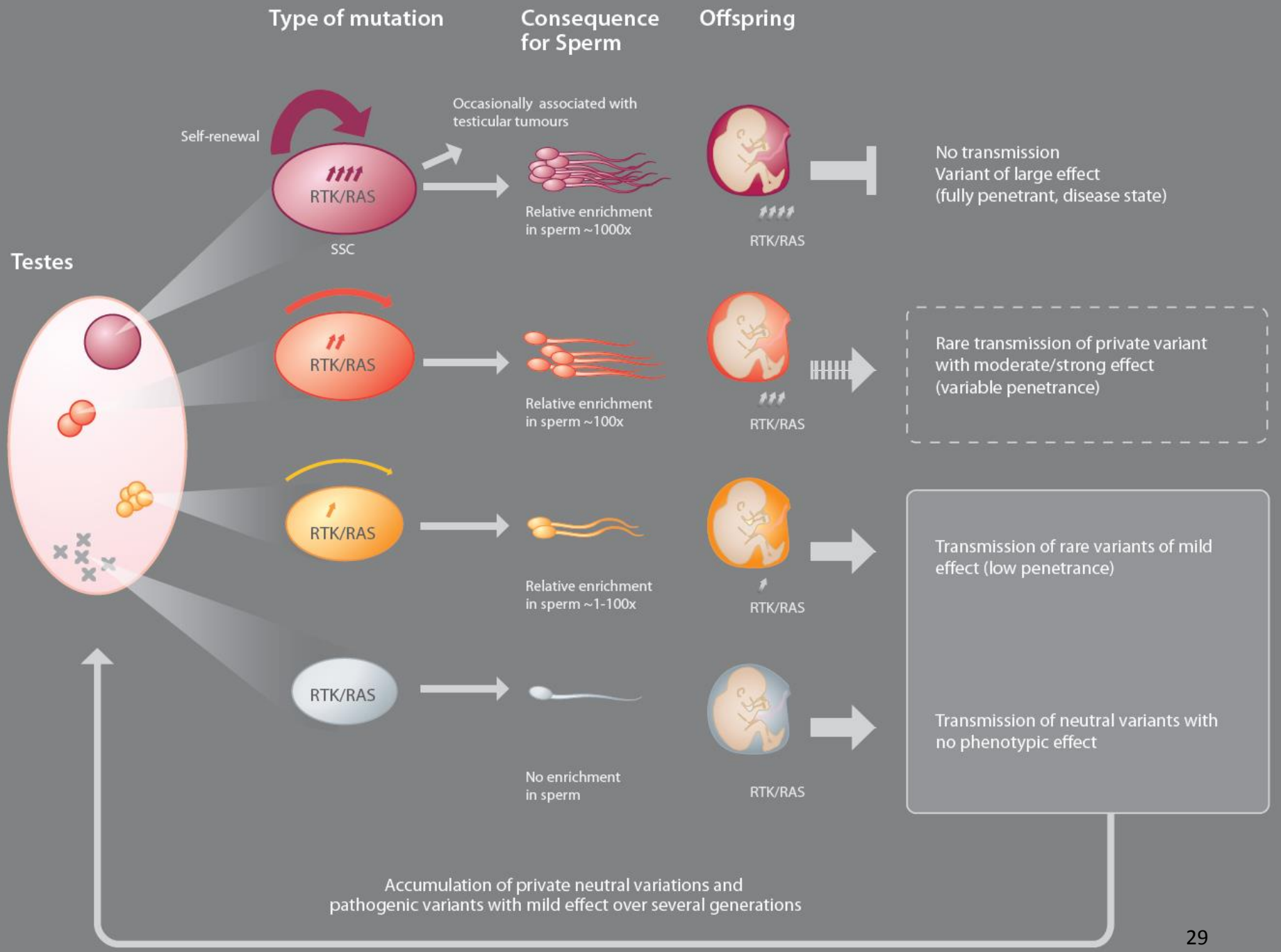
- The offspring of older fathers have an increased risk of schizophrenia – *Dolores Malaspina* (2001)
- Growing epidemiological support
- Animal models
- Clues from genetics
  - An increase of about two de novo mutations per year of paternal age.

Advanced paternal age and "selfish" selection

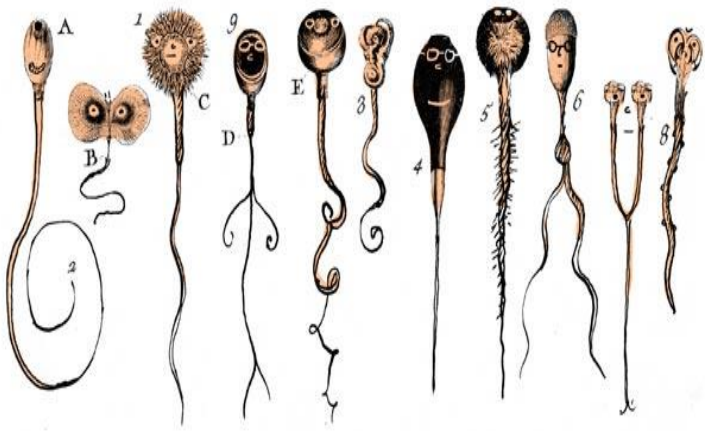


- Spermatogonial stem cells divide every 16 days
- Mutations that increase cell proliferation will result in clonal expansion
- Age-related mutations will be skewed by this within-testes selective process

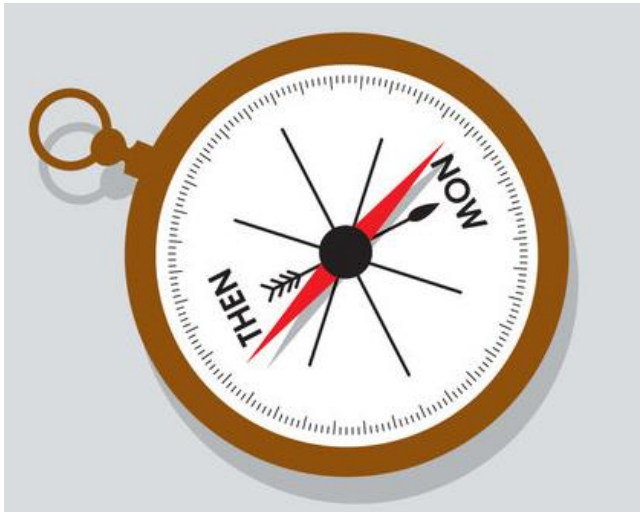
Goriely A, McGrath J, et al. (2013) "Selfish spermatogonial selection": a novel mechanism for the association between advanced paternal age and neurodevelopmental disorders. ***American Journal of Psychiatry****;170:599-608*.


Type of mutation
Consequence for Sperm
Offspring
Testes
Self-renewal
RTK/RAS
SSC
Occasionally associated with testicular tumours
Relative enrichment in sperm ~1000x
RTK/RAS
No transmission
Variant of large effect
(fully penetrant, disease state)
RTK/RAS
Relative enrichment in sperm ~100x
RTK/RAS
Rare transmission of private variant with moderate/strong effect (variable penetrance)
RTK/RAS
Relative enrichment in sperm ~1-100x
RTK/RAS
Transmission of rare variants of mild effect (low penetrance)
RTK/RAS
No enrichment in sperm
RTK/RAS
Transmission of neutral variants with no phenotypic effect
Accumulation of private neutral variations and pathogenic variants with mild effect over several generations

Speculation: *environmental exposures influence the rate of age-related mutagenesis*



Combining genes and environmental factors



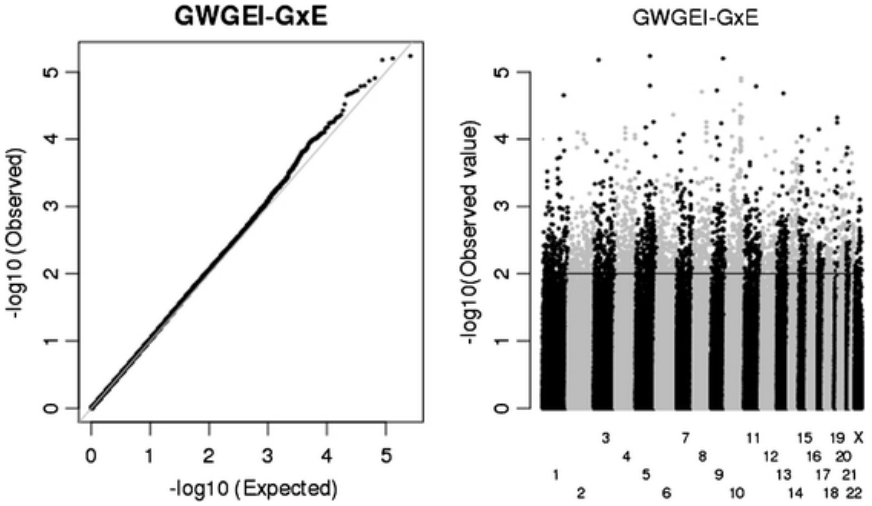
- Family history as a proxy marker
- Single SNPs in candidate genes (COMT, AKT1 etc)
- iPsych (Denmark)
- EU- GEI *2010-2015*
  - www.eu-gei.eu

Key references on GxE

- **What are the statistical nuances?**
  - Zammit S, Lewis G, Dalman C, Allebeck P. Examining interactions between risk factors for psychosis. *Br J Psychiatry* Sep 2010;197:207-211.
- **What are the problems with the literature?**
  - Duncan LE, Keller MC. A critical review of the first 10 years of candidate gene-by-environment interaction research in psychiatry. *Am J Psychiatry* 2011;168:1041-9
- **What has already been done for schizophrenia single SNP x E?**
  - Modinos G, Iyegbe C, Prata D, et al. Molecular genetic gene-environment studies using candidate genes in schizophrenia: A systematic review. *Schizophr Res* 2013;150:356-65

GWAS plus environmental factors

- SNPs associated with BMI
- Role of college education (E Proxy measure – for behaviour, diet etc)



Boardman JD, et al. Is the Gene-Environment Interaction Paradigm Relevant to Genome-Wide Studies? The Case of Education and Body Mass Index. ***Demography*** 2013 (on line)

Figure 2. GWAS in heavy coffee-drinkers.

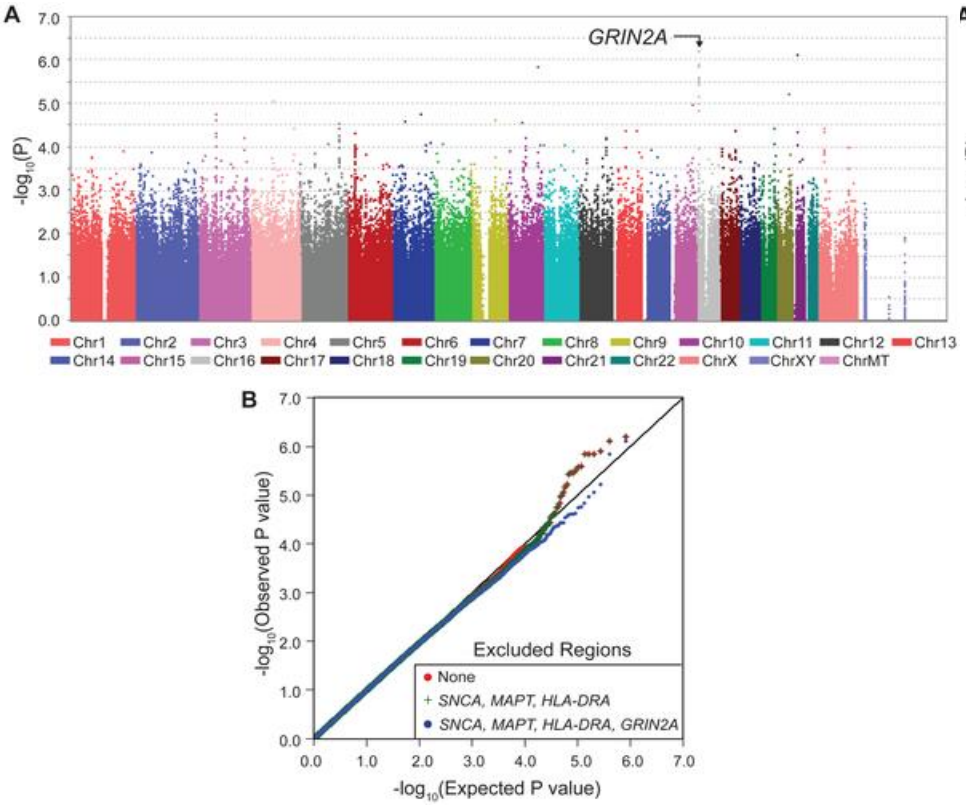
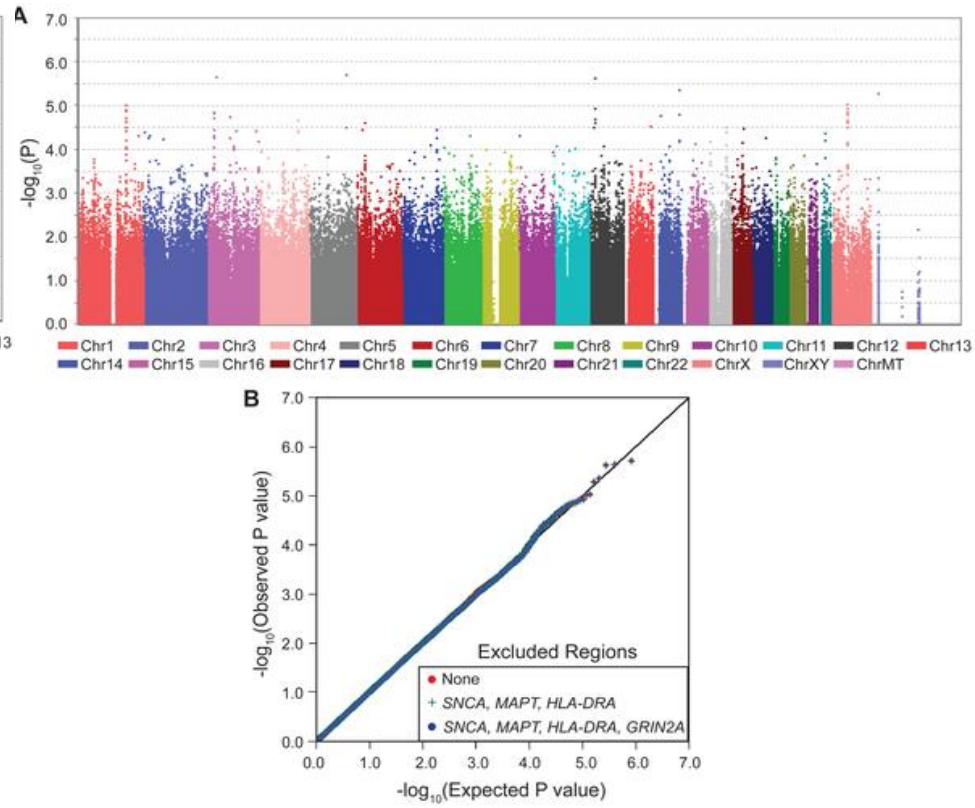
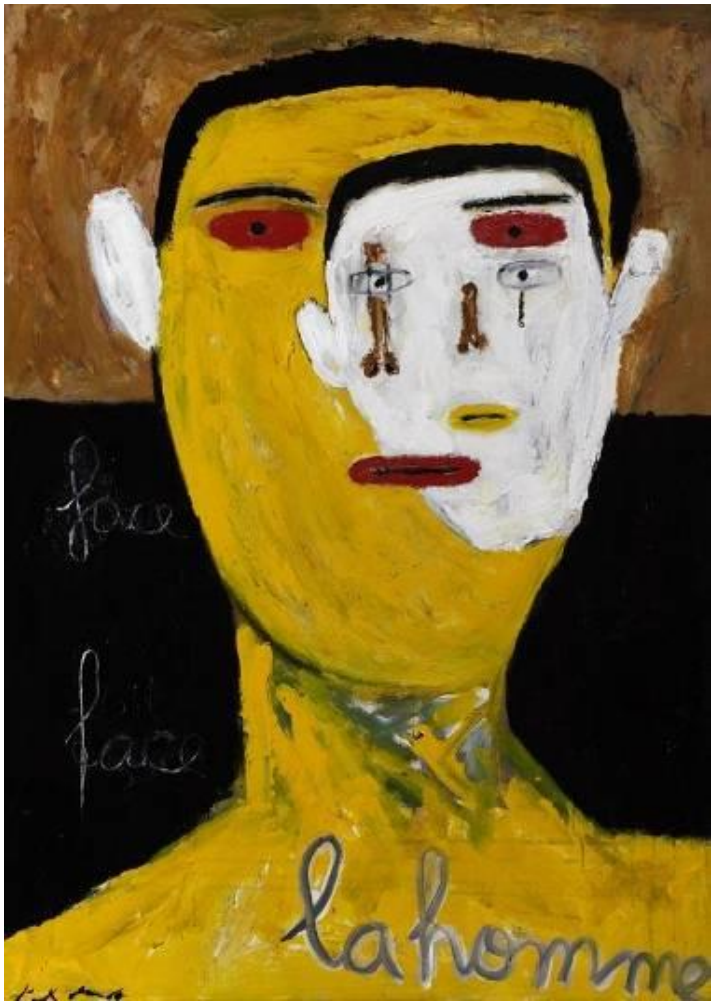


Figure 3. GWAS in light coffee-drinkers.



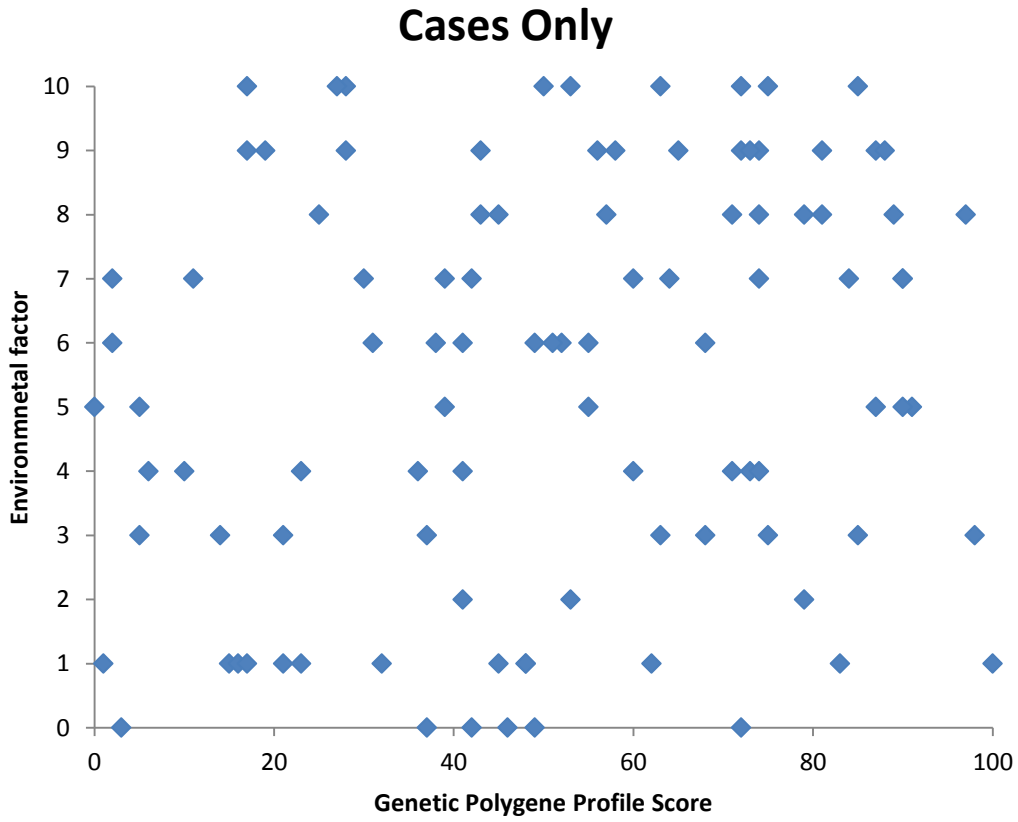
Hamza TH, Chen H, Hill-Burns EM, Rhodes SL, et al. (2011) Genome-Wide Gene-Environment Study Identifies Glutamate Receptor Gene GRIN2A as a Parkinson's Disease Modifier Gene via Interaction with Coffee. PLoS Genet 7(8): e1002237. doi:10.1371/journal.pgen.1002237
http://www.plosgenetics.org/article/info:doi/10.1371/journal.pgen.1002237

Future options
Genomic risk profile scores



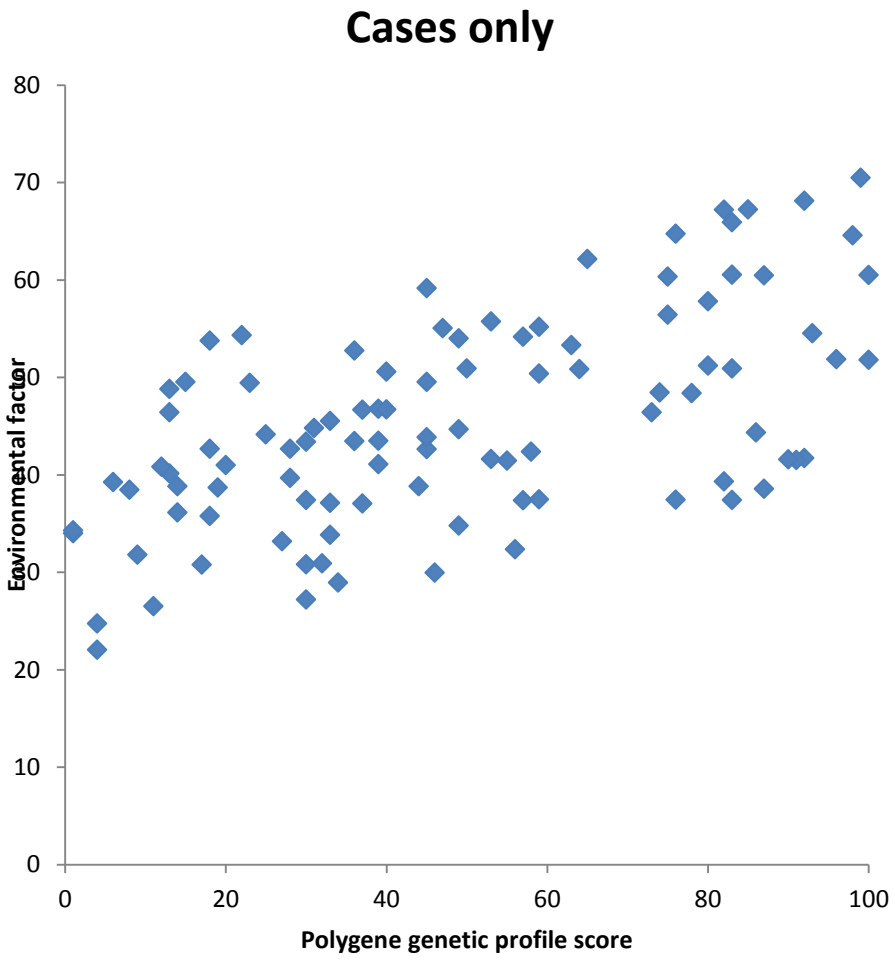
- Provide a *continuous measure of liability* rather than the dichotomous or categorical measure of family history.
- Can the addition of environmental risk factors improve the predictive value of polygene score (utility)?
- Can bespoke profile scores be generated on cases and controls stratified by an exposure (e.g. Season of birth, trauma, cannabis)?
  - Improved utility?
  - Provide clues to underlying pathways?
  - Can we reverse engineer profile scores to help generate novel candidate exposures?

Case only – explore correlation between G and E



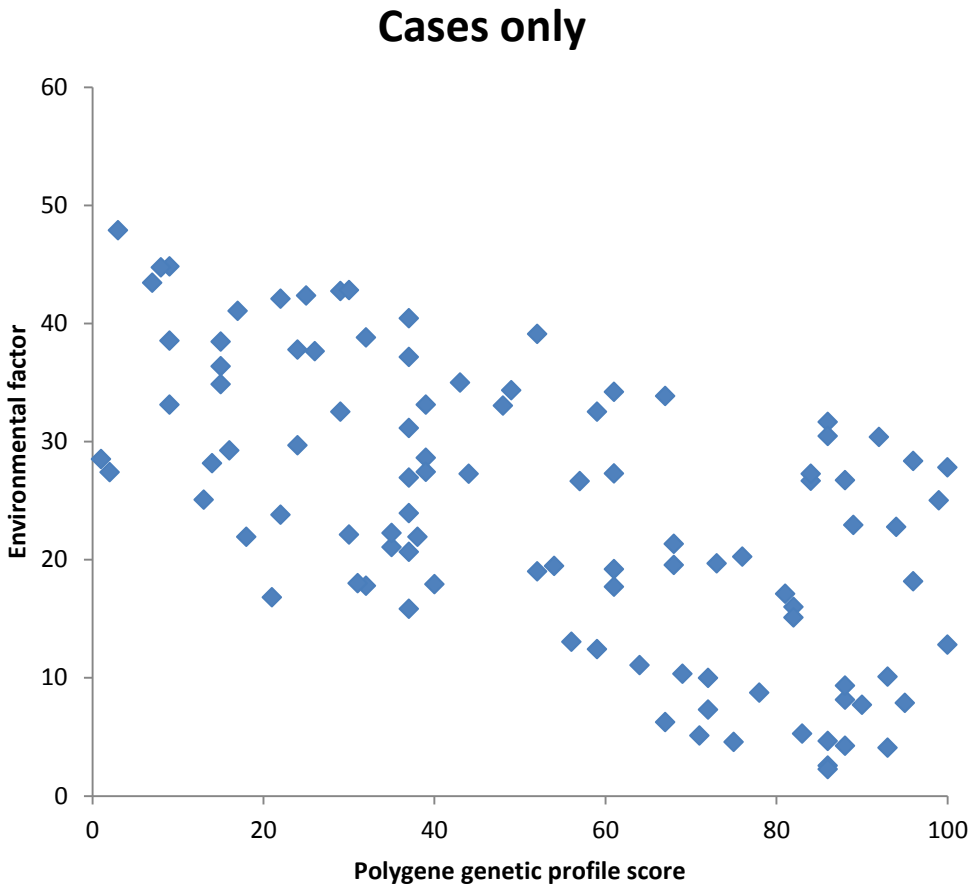
- No correlation between profile score and E factor within cases
  - does this weaken the case that the profile score captures variants related to the E factor?

Case only – explore correlation between G and E



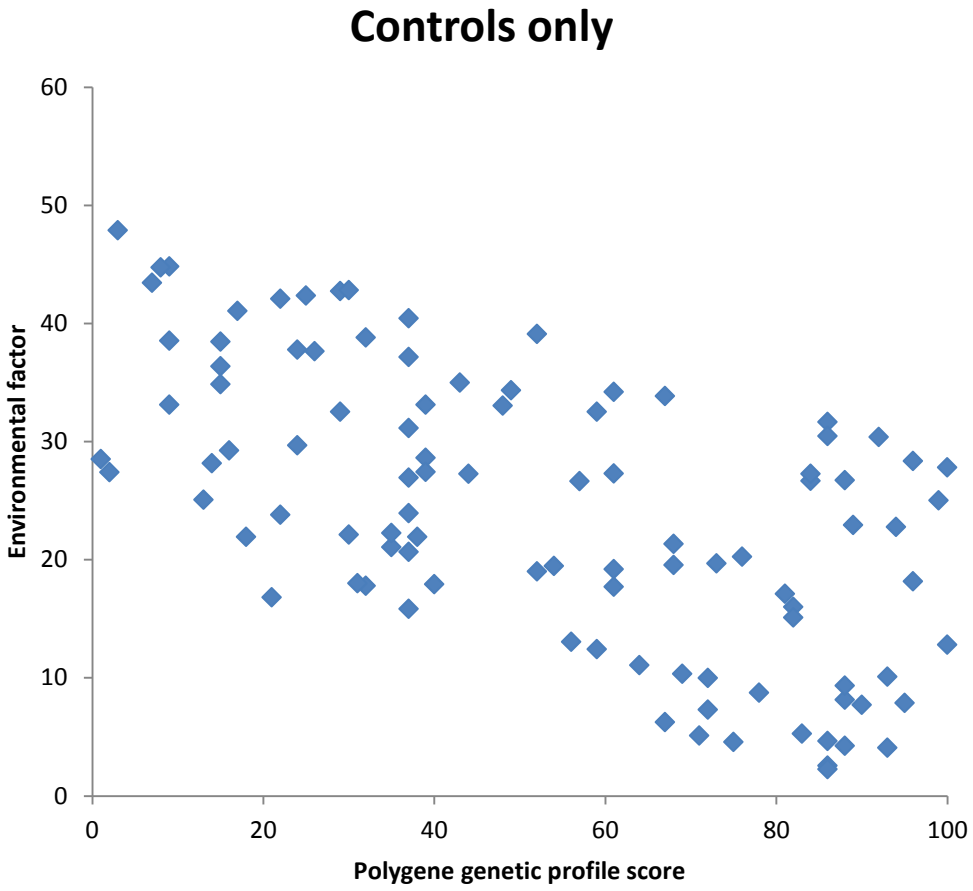
- Positive correlation between profile score and E factor within cases
  - Does this profile score capture variants related to the E factor?

Case only – explore correlation between G and E



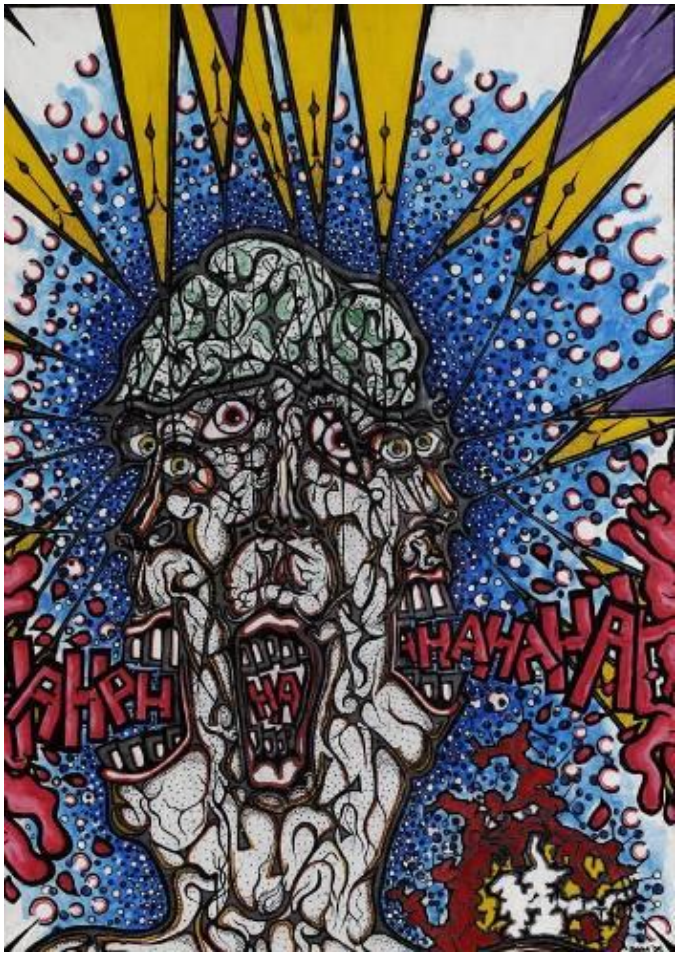
- Negative correlation between profile score and E factor within cases
  - Does this environmental factor generate *phenocopies* in those with low profile scores?

Controls only – explore correlation between G and E



- Negative correlation between profile score and E factor within controls
  - Has the low risk environmental factor protected high-risk subjects?

SNP-based heritability



- Genome-wide similarities in genotypes between all pairs of individuals have been able to estimate the proportion of variance tagged by SNPs
  - Stratify cases according to exposures of interest
  - genome-wide similarities may be greater within these strata versus between the strata.

Lee SH, Wray NR, Goddard ME, Visscher PM. Estimating missing heritability for disease from genome-wide association studies. *Am J Hum Genet* Mar 11 2011;88(3):294-305.

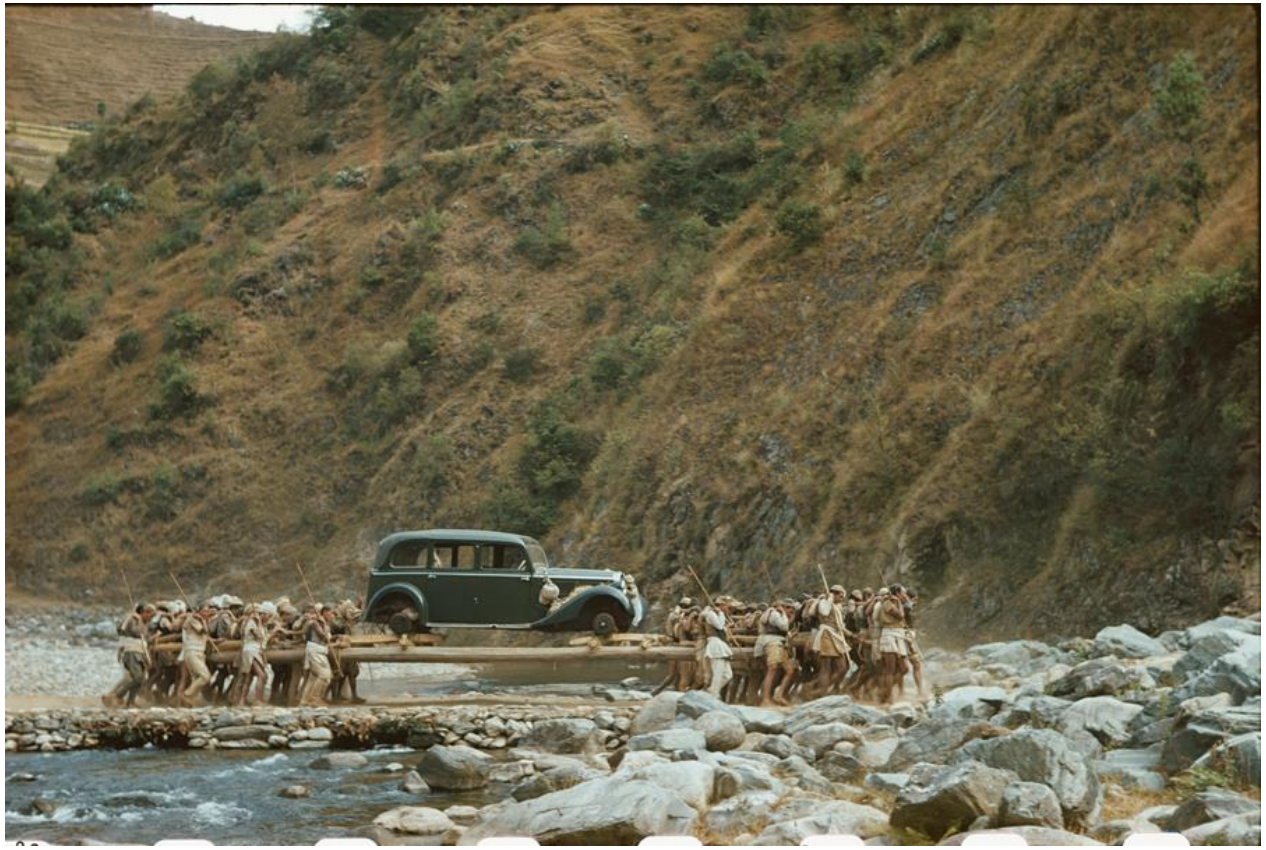
Other methods that may help combine genes and environment

- Mendelian randomization
  - Which E-related phenotypes maybe be amenable to SNP-based instruents?
  - Pleotropy and the brain
- Genomewide methylation as a proxy for past exposures
- Data mining?
  - GWAS versus electronic records for *exposures* (including treatment) and *phenotypes*

GWAS meets epidemiology
the next steps

- Enrich PGC samples with quick and cheap E factors
- Harmonize datasets for candidate exposures
- Invest time and energy in new methods
- Use the clues from GWAS studies as a ‘lens’ on the environment
  - Power issues and replication samples will hinder progress, but we can generate new hypotheses
- Clues from epidemiology are too valuable to waste!

Where GWAS and Epidemiology Meet: the state of play

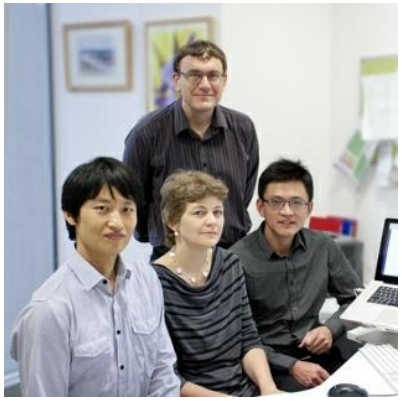


Porters transport a car on long poles across a stream in Nepal, January 1950.

PHOTOGRAPH BY VOLKMAR K. WENZTEL, NATIONAL GEOGRAPHIC http://natgeofound.tumblr.com/

Acknowledgments

- Brisbane colleagues
  - Darryl Eyles
  - Tom Burne
  - Naomi Wray
  - Peter Visscher
- Danish collaborators
  - Preben Bo Mortensen
  - Carsten Pedersen



National Health and Medical Research Council, John Cade Fellowship

Questions and Discussion