

Alea iacta est and Dyson spheres:
Strategies for integrating genetics into neurotrauma
research and management



*David Menon,
University of Cambridge*



Disclaimers, Potential Conflicts, Scope

Disclaimers

- This talk is built on 35 years in TBI research exploring “*What the patient brings to the disease*” (to quote Geoff Manley): A fascination with how host factors modify disease course or outcome
- However, I am not a geneticist or a spinal cord injury researcher

Potential Conflicts

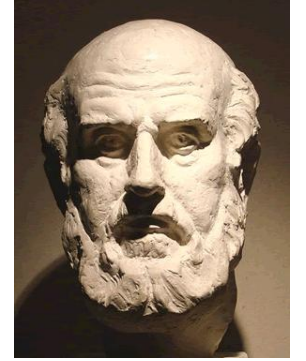
- In last 5 years, Consultant, Trial Steering Committee, Data Management Committee, or lectures for several industry partners (Analog Garage, Astrocyte Pharma, Axoft , Dompe, Integra, Invex, Neurotrauma Sciences, PressuraNeuro)
- None of these are relevant to the current talk

Scope

- Associations between **genetic variation and neurotrauma outcome in humans** – no preclinical models or differential expression of genes – in either neural tissue or peripheral blood

Themes

- From prophecies to predictions



“No head injury is too severe to despair of, nor too trivial to ignore.”

Hippocrates



IMPACT

Prognostic calculator

Based on extensive prognostic analysis the IMPACT investigators have developed prognostic models for predicting 6 month outcome in adult patients with moderate to severe head injury (Glasgow Coma Scale ≤ 12) on admission. By entering the characteristics into the calculator, the models will provide an estimate of the expected outcome at 6 months. We present three models of increasing complexity (Core, Core + CT, Core + CT + Lab). These models were developed and validated in collaboration with the CRASH trial collaborators on large numbers of individual patient data (the [IMPACT database](#)). The models discriminate well, and are particularly suited for purposes of classification and characterization of large cohorts of patients. Extreme caution is required when applying the estimated prognosis to individual patients.



Prediction models for 6 month outcome after TBI

Admission Characteristics Value

Core

Age (14-99 years)

Motor Score

Pupils

Core+CT

Hypoxia

Hypotension

CT Classification

tSAH on CT

Epidural mass on CT

[Select]
Diffuse Injury I
Diffuse Injury II
Diffuse Injury III
Diffuse Injury IV
Evacuated Mass Lesion
Nonevacuated Mass Lesion

[Select] ▼

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List of subpages

- Background
- Mission & Aims
- Collaboration
- Investigators
- Advisory Board
- IMPACT database
- Prognostic calculator
- IMPACT recommendations
- Common Data Elements (Draft)
- Data Sharing
- Acknowledgements

IMPACT

Prognostic models in TBI

1. Clinical Practice

- informing relatives
- support treatment decisions
- allocating resources

2. Research

- Classification:
 - adjust for baseline characteristics
 - ordinal analyses:
 - sliding dichotomy
 - proportional odds model
- Clinical trials

3. Quality assessment of health-care delivery

Predicting outcome after traumatic brain injury: practical prognostic models based on large cohort of international patients

MRC CRASH Trial Collaborators

Head injury prognosis



These prognostic models may be used as an aid to estimate mortality at 14 days and death and severe disability at six months in patients with traumatic brain injury (TBI). The predictions are based on the average outcome in adult patients with Glasgow coma score (GCS) of 14 or less, within 8 hours of injury, and can only support - not replace - clinical judgment. Although individual names of countries can be selected in the models, the estimates are based on two alternative sets of models (high income countries or low & middle income countries).

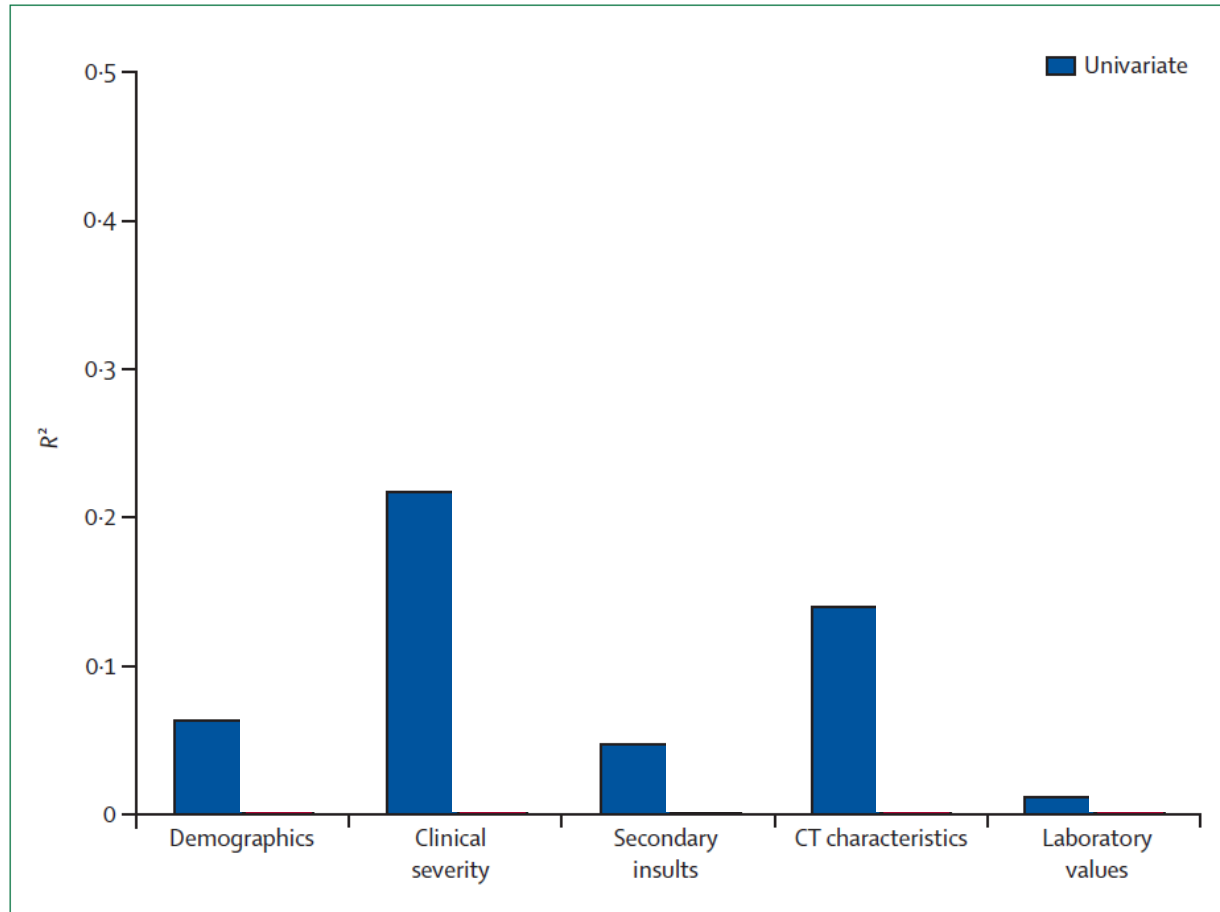
Country	Argentina
Age, years	≤40
Glasgow coma score	11
Pupils react to light	One
Major extra-cranial injury?	No
CT scan available?	☐

Prediction

Risk of 14 day mortality (95% <u>CI</u>)	10.0% (8.0 - 12.5)
Risk of <u>unfavourable outcome</u> at 6 months	23.9% (19.7 - 28.8)

Early prognosis in traumatic brain injury: from prophecies to predictions

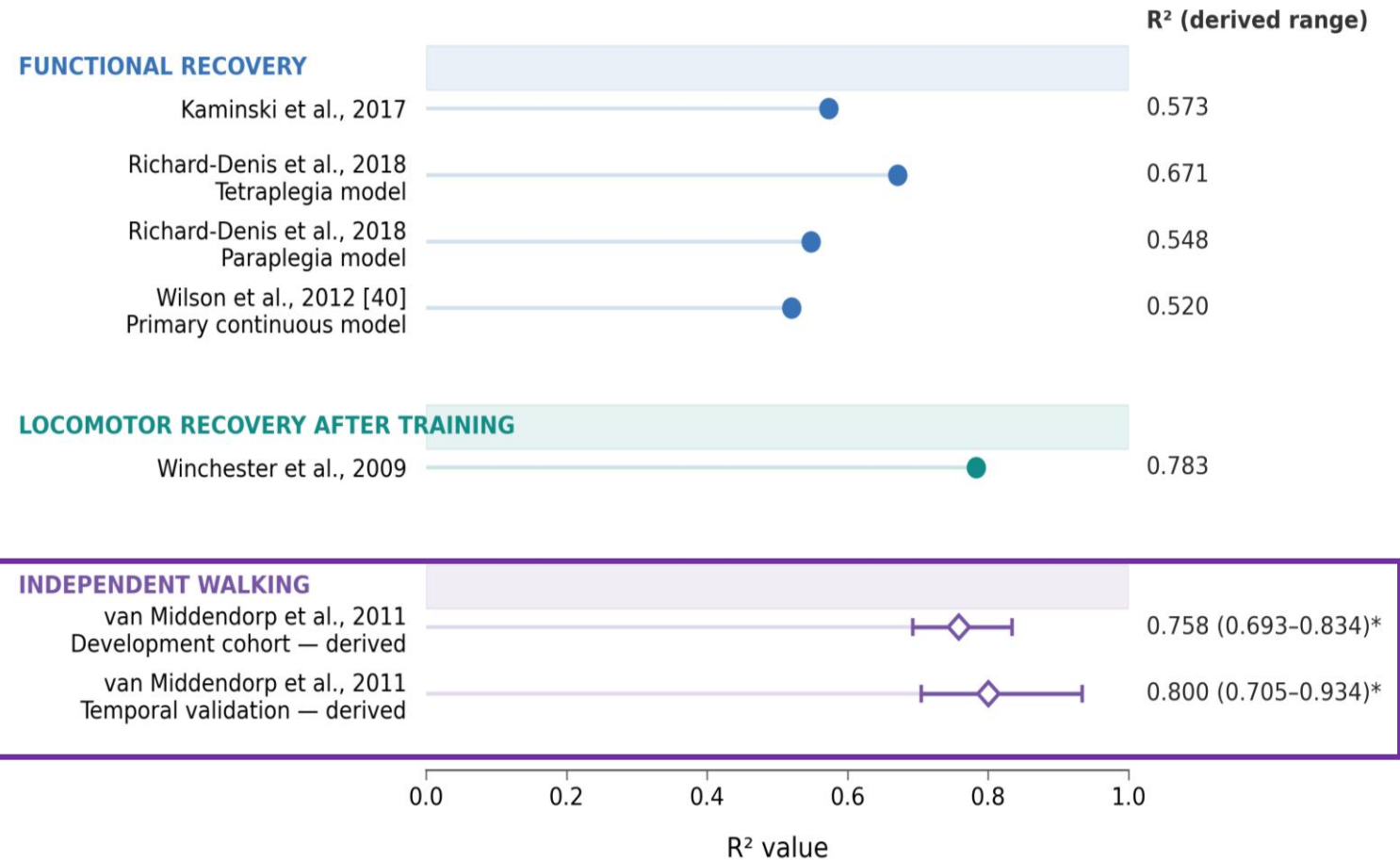
Hester F Lingsma, Bob Roozenbeek, Ewout W Steyerberg, Gordon D Murray, Andrew I R Maas



Multivariable Prediction Models for Traumatic Spinal Cord Injury: A Systematic Review

Ramtin Hakimjavadi, Shahin Basiratzadeh, Eugene K. Wai,
Natalie Baddour, Stephen Kingwell, Wojtek Michalowski,
Alexandra Stratton, Eve Tsai, Herna Viktor, and Philippe Phan

- Partial R^2 inconsistently reported in SCI. (figures for van Middendorp model are approximate estimates derived from published data)
- So, less easy to compare with TBI
- However, in general, higher than TBI prediction models (Nagelkerke partial R^2 0.55 – 0.8)
- Possibly less potential than TBI to increase prognostic precision (**for some outcomes**)?



Themes

- From prophecies to predictions
- *Alea iacta est*: Biological underpinning of host phenotypes



Genetics and *iacta alea est*.....

- Overall model of disease progression/outcome in TBI/SCI includes:
 - Severity: GCS, injury level/completeness
 - Neuroimaging
 - Blood biomarker(s)
 - Modulators: Age, sex, hypoxia, hypotension, extracranial injury
 - Premorbid disease and pre-injury therapy

What could genetic association analysis deliver?

- Characterise impact of host response in TBI
- Quantifying/characterising its impact could:
 - Improve prognostication
 - Discover/refine pathophysiology
 - Identify/prioritize targets for drug development informed by human data
 - Identify subpopulations for Rx or Trials of new drugs
 - Wider neurobiology – e.g. in aging/dementia (*“the experiment of disease/injury”*)

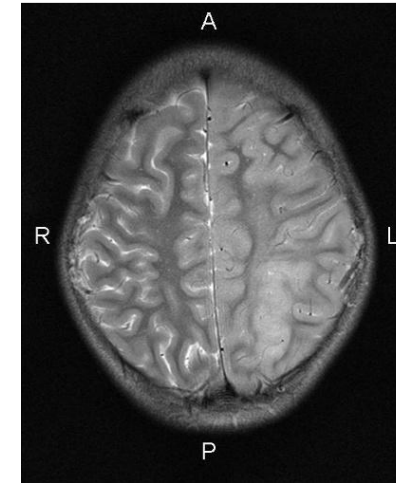
Themes

- From prophecies to predictions
- *Alea iacta est*: Biological underpinning of host phenotypes
- Candidate gene studies – pros and cons

Early seizures and cerebral oedema after trivial head trauma associated with the *CACNA1A* S218L mutation

A H Stam,¹ G-J Luijckx,² B T Poll-Thé,³ I B Ginjaar,⁴ R R Frants,⁵ J Haan,^{1,6} M D Ferrari,¹ G M Terwindt,¹ A M J M van den Maagdenberg^{1,5}

- *CACNA1A* (FHM1) is one of three genes for Familial Hemiplegic Migraine
- Dominant inheritance, encodes Cav2.1 (P/Q) Ca²⁺ channel subunit,
- *CACNA1A* S218L mutation*
 - alters Ca²⁺ flux
 - increases spreading depression
 - associated with fatal cerebral oedema after minor TBI



Coma after heading a football



Late cerebellar atrophy

*(Kors et al; *Ann Neurol* 2001; 49: 753)

Many other candidate genes investigated –
targets based on pathophysiology or role in other diseases

Apolipoprotein E4 Polymorphism and Outcomes from Traumatic Brain Injury: A Living Systematic Review and Meta-Analysis

Charles A. McFadyen, Frederick A. Zeiler, Virginia Newcombe, Anneliese Synnot, Ewout Steyerberg, Russel L. Gruen, Jonathan Rosand, Aarno Palotie, Andrew I.R. Maas, and David K. Menon

Study or Subgroup

Alexander 2007
Chiang 2003
Diaz-Arrastia 2003
Friedman 1999
Hiekkanen 2009
Millar 2003
Nathoo 2003
Olivecrona 2010
Ponsford 2011
Pruthi 2010
Teasdale 1997
Teasdale 2005
Willemse-van Son 2008
Yousuf 2015

Total (95% CI)
Total events
Heterogeneity: $\tau^2 = 0.09$
Test for overall effect: $Z = 2.00$

Genetic Influences on Patient-Oriented Outcomes in Traumatic Brain Injury: Living Systematic Review of Non-Apolipoprotein E Single-Nucleotide Polymorphisms

Frederick A. Zeiler, Charles McFadyen, Virginia F.J. Newcombe, Anneliese Synnot, Emma L. Donoghue, Samuli Ripatti, Ewout W. Steyerberg, Russel L. Gruen, Thomas W. McAllister, Jonathan Rosand, Aarno Palotie, Andrew I.R. Maas, & David K. Menon

- 1. Catechol-O-methyltransferase (COMT)
- 2. Monoamine oxidase -A (MAO-A)
- 3. Serotonin transporter (SLC6A4)
- 4. Glutamic acid decarboxylase (GAD)
- 5. Vesicular monoamine transporter (VMAT)
- 6. Vesicular glutamate transporter (VGLUT)
- 7. Dopamine receptor D2 (DRD2)
- 8. Adenosine receptor (AR)
- 9. Tumour necrosis factor- α (TNF α)
- 10. Interleukin-1 (IL-1)
- 11. Interleukin-6 (IL-6)
- 12. Interleukin-1 Receptor agonist (IL-1RAcP)
- 13. Lectin polymorphisms (e.g. MBL)
- 14. Nitric Oxide Synthase 3 (NOS-3)
- 15. Angiotensin Converting Enzyme (ACE)
- 16. Aquaporin (AQP)
- 17. Mitochondrial genes
- 18. ATP Binding Cassette (ABC)
- 19. Brain Derived Neurotrophic Factor (BDNF)
- 20. Calcineurin
- 21. Alpha Synuclein (α Syn)
- 22. Neuroglobin
- 23. Aromatase
- 24. Period
- 25. Poly-ADP Ribose polymerase
- 26. Kidney & Brain Expressed Protein (KIBP)
- 27. Methylene tetrahydrofolate reductase (MTHFR)

Genetic drivers of cerebral blood flow dysfunction in TBI: a speculative synthesis

Frederick A. Zeiler, Eric P. Thelin, Joseph Donnelly, Andrew R. Stevens, Peter Smielewski, Marek Czosnyka, Peter J. Hutchinson and David K. Menon

Of key relevance to:

- Cerebrovascular physiology
- Autoregulation
- Intracranial pressure

Potential sites of genetic modulation

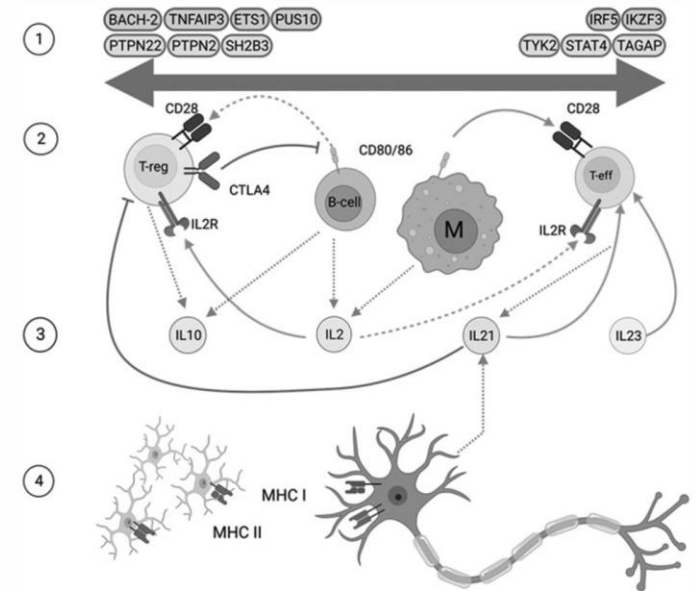
- Vascular receptor biology
- Ligand coding
- Ligand synthesis & breakdown
- Ion channels
- Smooth muscle function
- Metabolism
- BBB transporters
- ECM matrix modulators

Candidate Genetic and Molecular Drivers of Dysregulated Adaptive Immune Responses After Traumatic Brain Injury

Michał Duchniewicz,¹ John Y.W. Lee,² David K. Menon,² and Edward J. Needham^{2,3}

Table 1. Genes Commonly Implicated in Association Studies Across Multiple Autoimmune Disorders

HLA Family	BACH2	CTLA4	IL-2RA	CD28
IL-21	SH2B3	STAT4	TYK2	ETS1
IKZF3	IL-10	IL-12B	IL-2	IRF5
PTPN2	PTPN22	PUS10	TAGAP	TNFAIP3



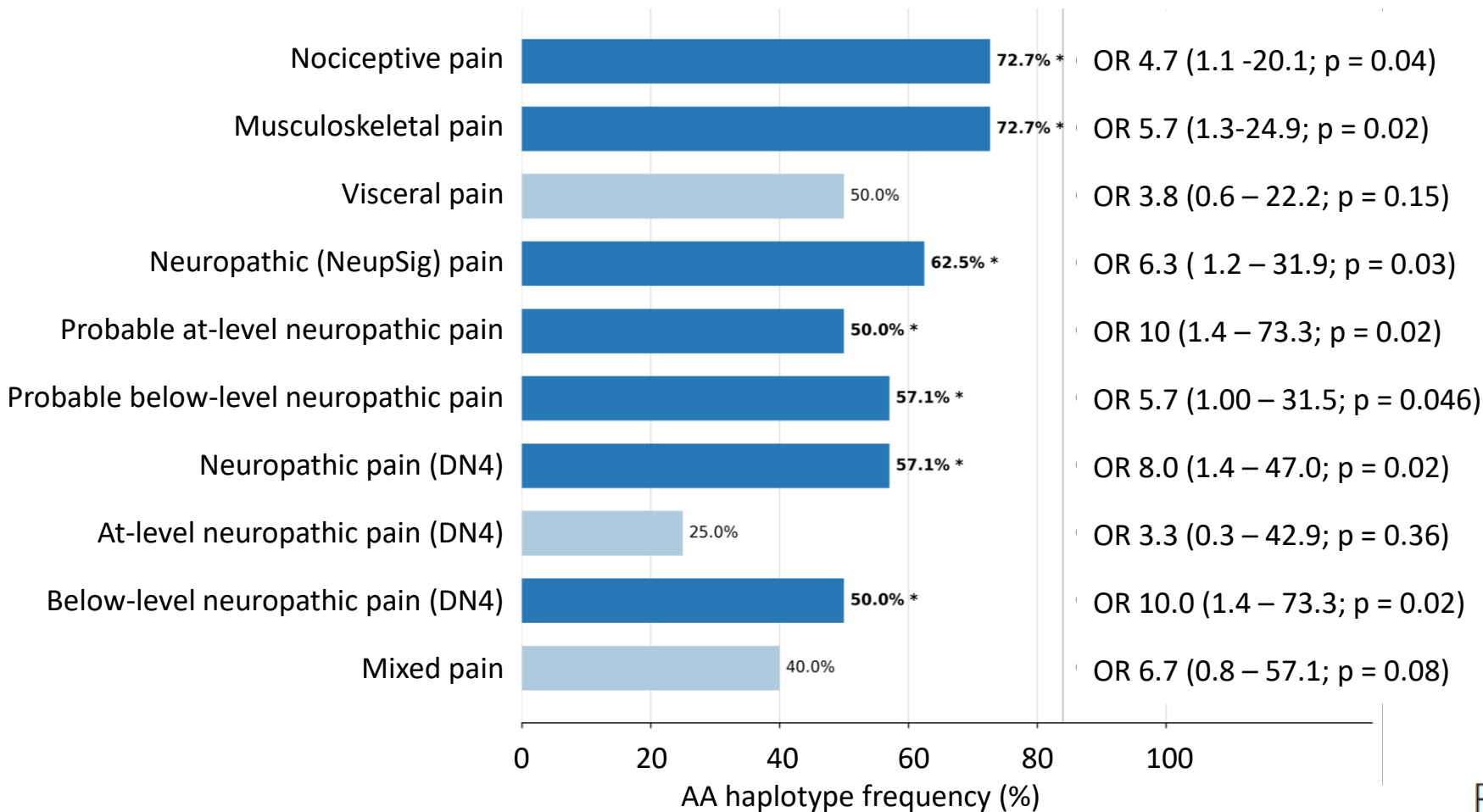
Candidate gene analyses in SCI

Gene	Study	N	Outcome	Association
Apolipoprotein E (ϵ 4 allele)	Jha et al, 2008	89 cervical SCI (83 European)	motor recovery (<i>no adjustment for injury severity</i>)	Subjects carrying the variant showed less motor recovery
Apolipoprotein E (ϵ 4 allele)	Sun et al, 2011	100 cervical SCI (Han Chinese)	motor recovery (<i>no adjustment for injury severity</i>)	Subjects carrying the variant showed less motor recovery
Brain-Derived Neurotrophic Factor (BDNF Val66Met polymorphism)	Leech et al, 2017	11 incomplete SCI	serum BDNF level during rehabilitation exercise	Subjects with variant showed blunted BDNF increase with exercise
α 7-Nicotinic Acetylcholine Receptor CHRFAM7A (α 7nAChR Δ 2bp variant)	Lin et al, 2021	45 severe/mild SCI (European Americans)	Inflammatory mediators	↑↑ acute proinflammatory cytokines in severe SCI with Δ 2bp, but less consistent over time & in mild SCI.
Transient Receptor Potential Ankyrin 1 (<i>rs11988795</i> & <i>rs13255063</i> in TRPA1)	Vidal et al, 2017	24 SCI (Spanish)	neuropathic pain	Subjects carrying the variant were more likely to be free of neuropathic pain.

Prevalence and characterization of pediatric-onset spinal cord injury pain as reported by youth: an observational and case control association study with TRPA1 gene single nucleotide polymorphisms

Marta Ríos-León, Beatriz Huidobro-Labarga, Inmaculada Castillo-Aguilar, Antonio Segura, Elisa López-Dolado, Julian Taylor

AA haplotype (rs11988795/rs13255063) frequency by SCI pain subtype (total n=66)

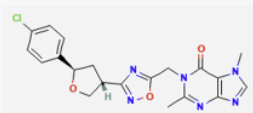


TRPA1 antagonists administered to humans

Exact structures are shown where the clinical candidate has been publicly disclosed

Nedizantrep (GDC-6599)

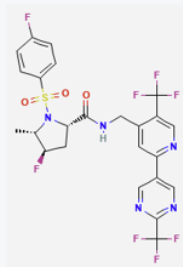
Phase II; chronic cough



Publicly disclosed structure

GDC-0334

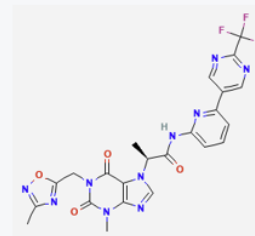
Phase I; asthma programme



Publicly disclosed structure

LY3526318 (HX-260)

Phase I/II; chronic pain



Publicly disclosed structure

BI 1839100

Phase I/II; cough in pulmonary fibrosis

Exact clinical-candidate
structure not publicly
disclosed

No unique structure can be drawn reliably

ISC 17536 (GRC 17536)

Phase II; painful diabetic neuropathy

Exact clinical-candidate
structure not publicly
disclosed

No unique structure can be drawn reliably

ODM-108

Phase I; neuropathic-pain programme

Exact clinical-candidate
structure not publicly
disclosed

No unique structure can be drawn reliably

CB-189625 (CB-625)

Phase I; acute surgical pain

Exact clinical-candidate
structure not publicly
disclosed

No unique structure can be drawn reliably

HX-100

Phase I; pain/asthma programme

Exact clinical-candidate
structure not publicly
disclosed

No unique structure can be drawn reliably

Problems with many candidate gene studies

- Low genetic coverage
- Selection bias: The streetlight effect
- High false positive rate
- Often small sample sizes
- Inconsistent correction for covariates of relevance
- Publication bias
- Poor replication



Themes

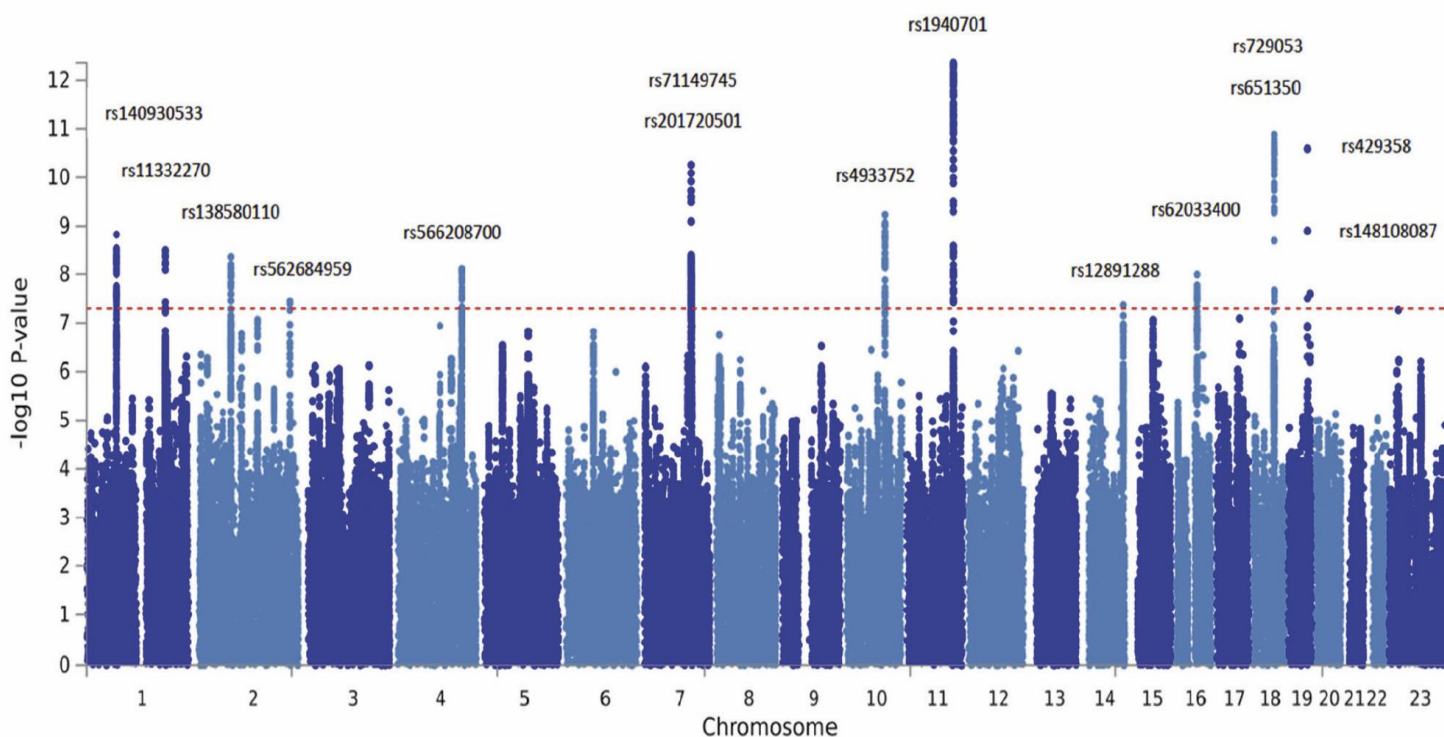
- From prophecies to predictions
- *Alea iacta est*: Biological underpinning of host phenotypes
- Candidate gene studies – pros and cons
- Genome wide associations – unbiased estimates of genetic risk

ARTICLE



Genome-wide association study of traumatic brain injury in U.S. military veterans enrolled in the VA million veteran program

Victoria C. Merritt^{1,2,3} , Adam X. Maihofer^{1,2}, Marianna Gasperi^{1,2,3}, Catherine Chanfreau-Coffinier⁴ , Murray B. Stein^{1,2,5} , Matthew S. Panizzon^{1,2,6}, Richard L. Hauger^{1,2,3,6}, Mark W. Logue^{7,8,9,10} , Lisa Delano-Wood^{1,2,3} and Caroline M. Nievergelt^{1,2,3}

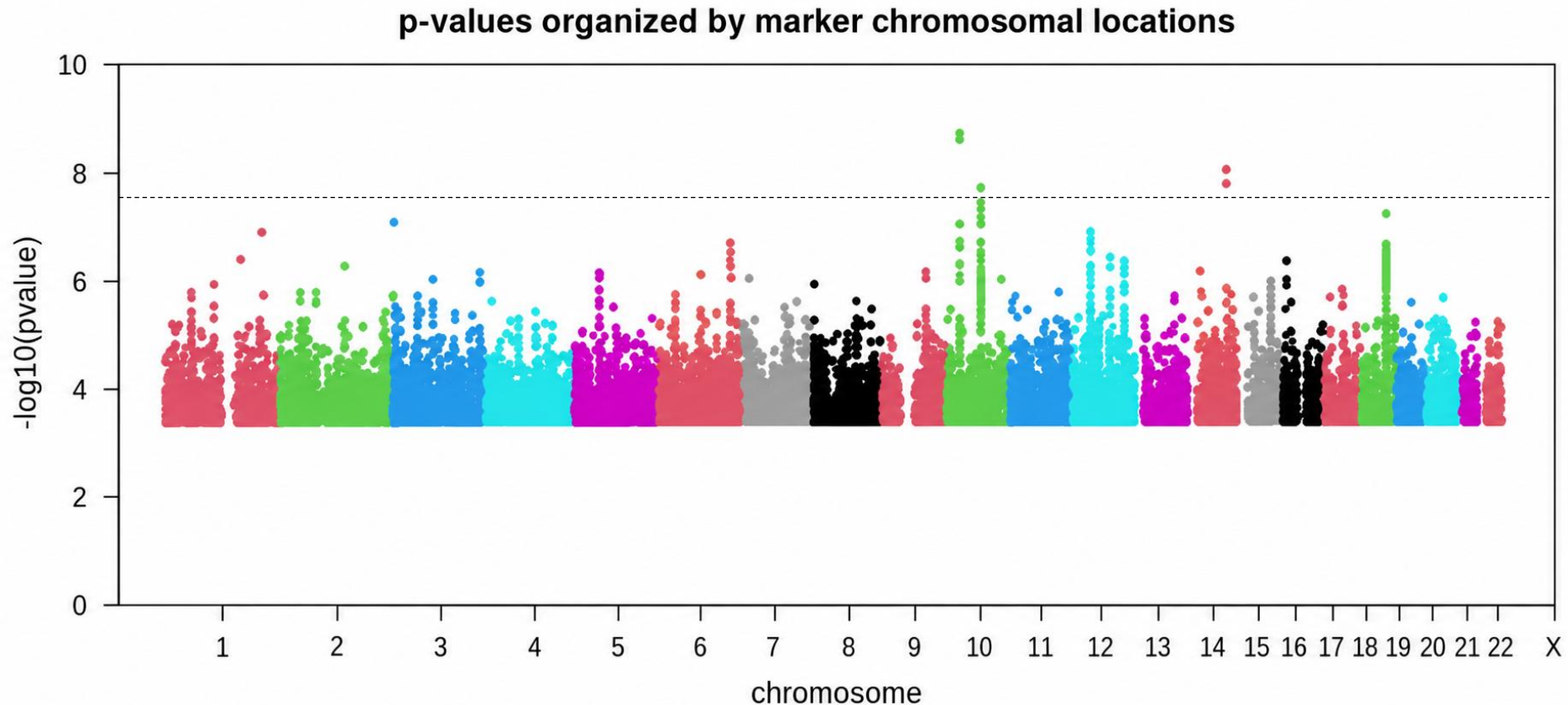


- GWAS of TBI **incidence** in VA Million Veteran Program
 - N = 304,485 (111,494 TBI, 192,991 controls).
 - SNP-based heritability was 0.060 (6%).
 - 15 genome-wide significant loci ($p < 5 \times 10^{-8}$)
- Gene-based analyses: 14 significant genes
- Top genes: NCAM1, APOE, FTO, and FOXP2.
- Tissue expression analysis - brain enrichment
- Genetic correlations
 - Risk-taking behaviors/psychiatric disorders,
 - Stronger for risk-taking vs. psychiatric traits.
 - Less for neurocognitive variables.
- Genetic architecture similar to polygenic psychiatric disorders, **not** neurodegenerative disorders

Genome-wide study of SCI incidence/prevalence

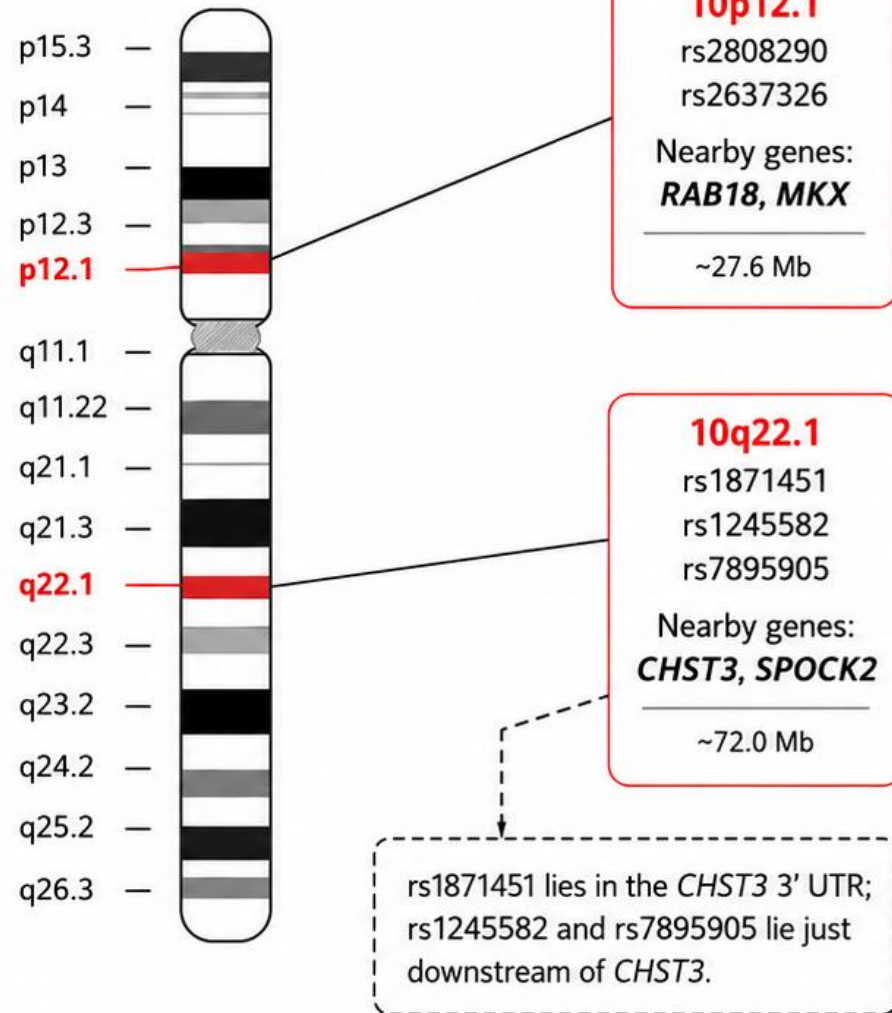
Meta-analysis of NSSCI (Spinal Cord Injury) in AFR, AMR, and EUR Million Veteran Program (MVP) participants

- 27,144 cases
- 373,343 controls



SNP locations and nearby genes : Conjectures and caveats

Chromosome 10



Neurological relevance of nearby genes

- **RAB18** – Strong neurological relevance. Loss of function causes Warburg Micro / Martsolf syndromes, with severe neurodevelopmental abnormalities including callosal and cortical malformations.
- **CHST3** – High neurobiological interest. Regulates chondroitin-6-sulfation in brain extracellular matrix and perineuronal nets, with relevance to synaptic plasticity and axonal regeneration.
- **SPOCK2** – Brain-expressed extracellular-matrix proteoglycan and plausible secondary candidate gene at the 10q22.1 locus.
- **MKX** – Best known for tendon / connective-tissue biology; currently limited direct neurological evidence compared with the other three genes.

However, these are all >>> 1 Mbase from SNP (Usual threshold for linkage disequilibrium).

More robust conclusions need LD data, fine-mapping or eQTL/chromatin-contact evidence

Issues with phenotyping in MVP GWAS/PheWAS

Nervous System Problems						
	YES	YEAR DIAGNOSED				TAKE MEDS
Migraine headaches	☐					☐
Other headaches	☐					☐
Memory loss or impairment	☐					☐
Dementia (includes Alzheimer's, vascular, etc.)	☐					☐
Concussion or loss of consciousness	☐					☐
Traumatic brain injury	☐					☐
Spinal cord injury or impairment	☐					☐
Epilepsy / Seizure	☐					☐
Parkinson's disease	☐					☐
Amyotrophic lateral sclerosis (Lou Gehrig's disease)	☐					☐
Multiple sclerosis	☐					☐
Other nervous system problem	☐					☐

- SCI recorded as binary survey-derived phenotype (“Spinal Cord Injury”; *NSSCI*)
- MVP metadata show NSSCI categorized under Surveys / Disease Diagnosis
- Reflect if participant reported diagnosis/history of spinal cord injury/impairment
- No AIS grade, neurological level, completeness, MRI features, mechanism, Rx
- The GWAS treated this as a case–control binary trait.
- Explains high prevalence: **27,144/400,487** $\approx$ **6.8%** (vs. 0.19-0.25% general population)



Gaziano JM et al.

Million Veteran Program: A mega-biobank to study genetic influences on health and disease. J Clin Epidemiol 2016; 70: 214

- Evidence of genetic influence on risk of sustaining TBI/SCI
- What about unbiased estimates of genetic impact on outcome?

A genome-wide association study of outcome from traumatic brain injury

Mart Kals,^{a,b,1} Kevin Kunzmann,^{c,1} Livia Parodi,^{d,e,f,1} Farid Radmanesh,^g Lindsay Wilson,^h Saef Izzy,^g Christopher D. Anderson,^{e,f,g} Ava M. Puccio,ⁱ David O. Okonkwo,ⁱ Nancy Temkin,^j Ewout W. Steyerberg,^{k,l} Murray B. Stein,^m Geoff T. Manley,ⁿ Andrew I.R. Maas,^o Sylvia Richardson,^c Ramon Diaz-Arrastia,^p Aarno Palotie,^{a,d,f} Samuli Ripatti,^{a,f,q} Jonathan Rosand,^{d,e,f,*} and David K. Menon^{r,**}; on behalf of The Genetic Associations In Neurotrauma (GAIN) Consortium (with contribution from the CENTER-TBI, TRACK-TBI, CABI, MGB, and TBIcare studies)

5289 patients (4710 European ancestry)

Heritability (LD score regression): ~25%

No SNP significant at genome-wide levels
($p < 5 \times 10^{-8}$)

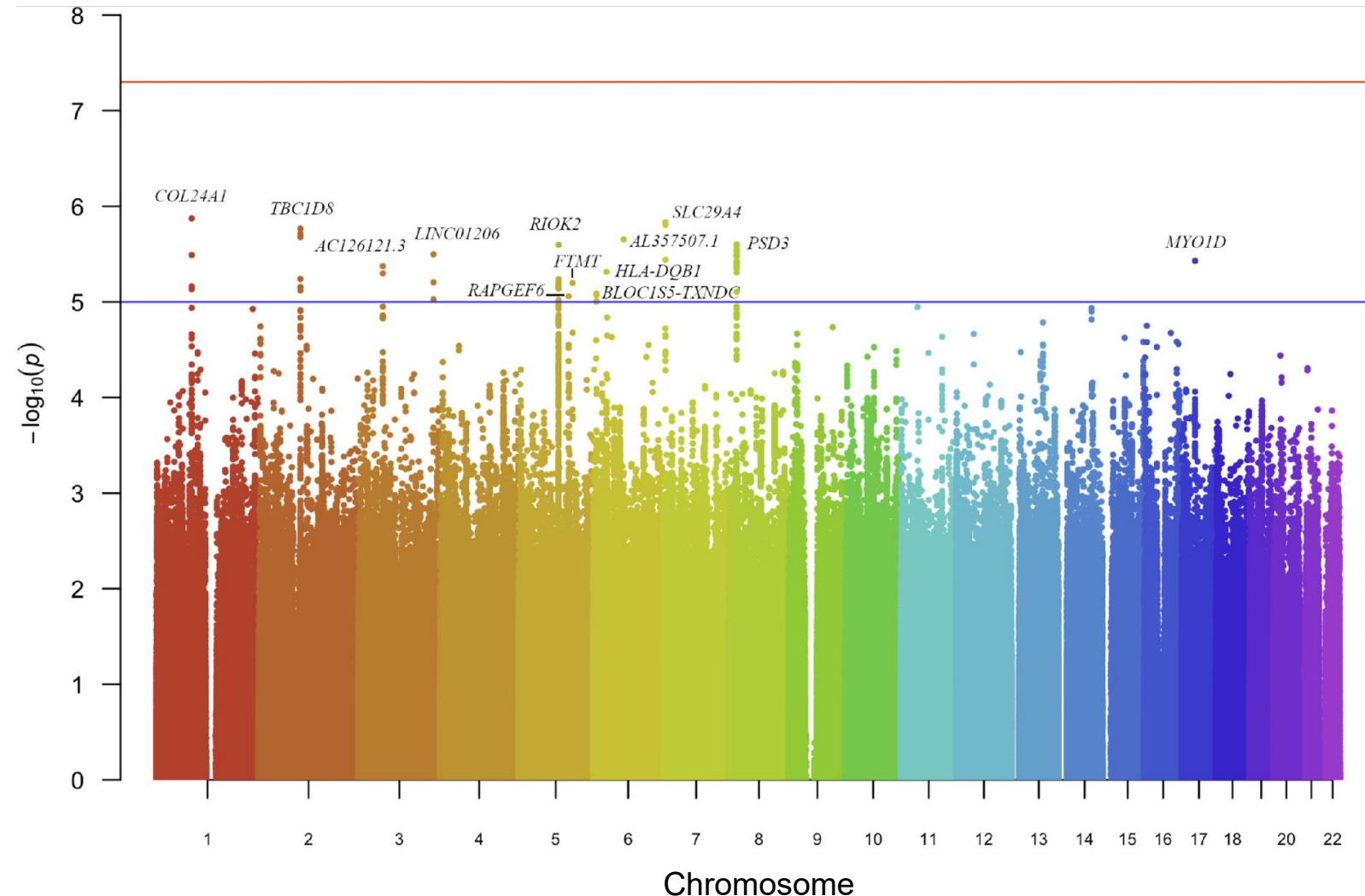
83 variants (13 loci) met pre-specified
exploratory threshold ($p < 10^{-5}$)

75 SNPs from past candidate gene studies:

- **rs1800450 in *MBL2* sig ($p 5.24 \times 10^{-4}$)**
- Other past SNPs not significant
- This includes APOEε4

Conclusions/plans:

Underpowered - plan for extended study
Explore combined subthreshold effects



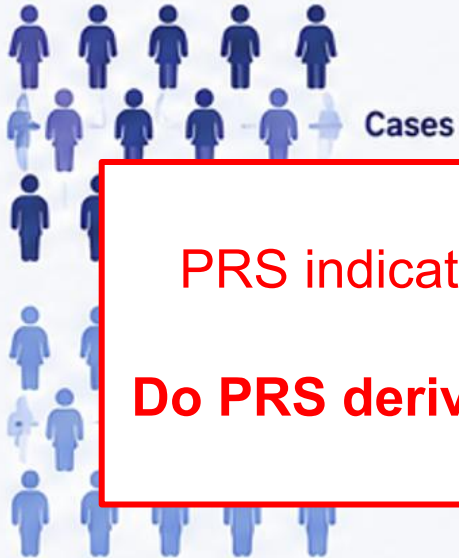
Themes

- From prophecies to predictions in
- *Alea iacta est*: Biological underpinning of host phenotypes
- Candidate gene studies – pros and cons
- Genome wide associations – unbiased estimates of genetic risk
- Polygenic risk score – borrowing power from GWAS in other diseases

Calculating a PRS

1 IDENTIFY VARIANTS ASSOCIATED WITH TRAIT

Genome-wide association study (GWAS)



Compare genomes of cases and controls to find variants associated with the trait

2 ESTIMATE EFFECT SIZES

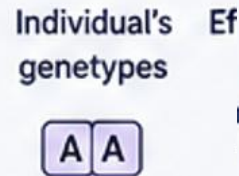
For each variant, estimate the effect (β) on the trait

Variant (SNP)	Effect size (β)
rs101234	+0.08

Thousands to millions of variants, each with a very small effect

3 CALCULATE GENETIC RISK

Count risk alleles and weight them by effect size



$$PRS = \sum (r_i \beta_i)$$

Sum across all variants

4 GENERATE POLYGENIC RISK SCORE (PRS)

The sum of weighted effects across all variants



5 RANK INDIVIDUALS IN THE POPULATION

Compare PRS across individuals

Distribution of PRS in population



Top 5%
Higher risk

Individuals in the right tail have higher genetic risk than the population average

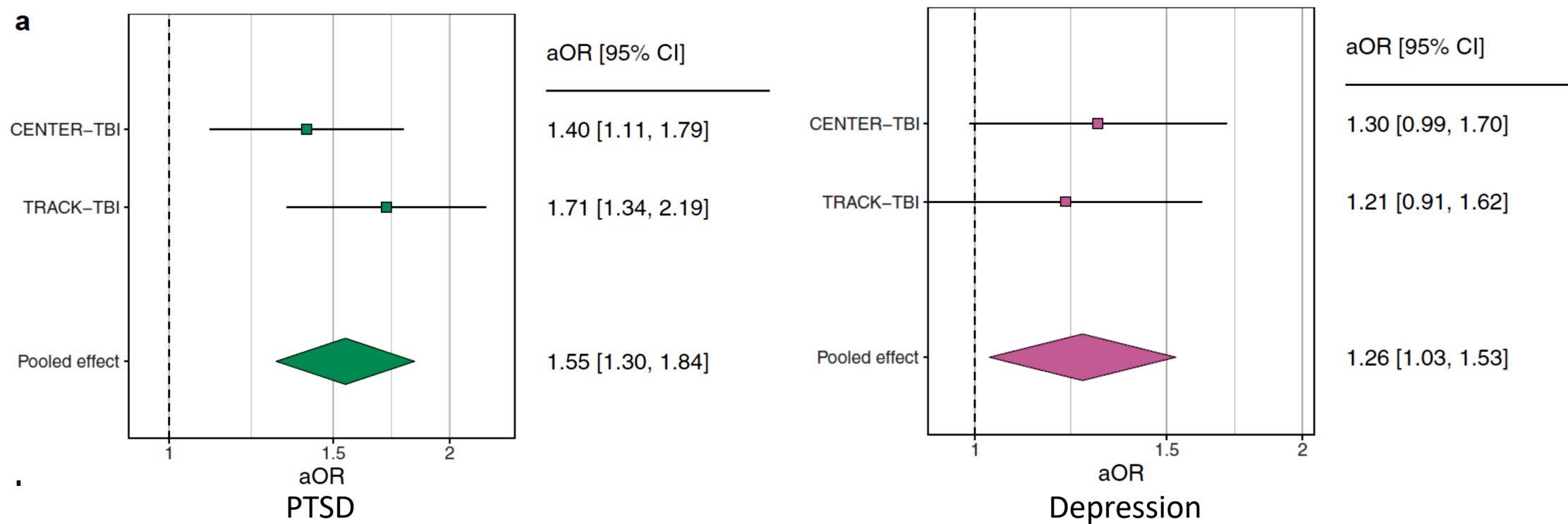
PRS indicates probabilistic risk and could provide a basis for exploring shared biology

Do PRS derived from GWAS in other diseases associate with related TBI outcomes?

Genetic vulnerability and adverse mental health outcomes following mild traumatic brain injury: a meta-analysis of CENTER-TBI and TRACK-TBI cohorts

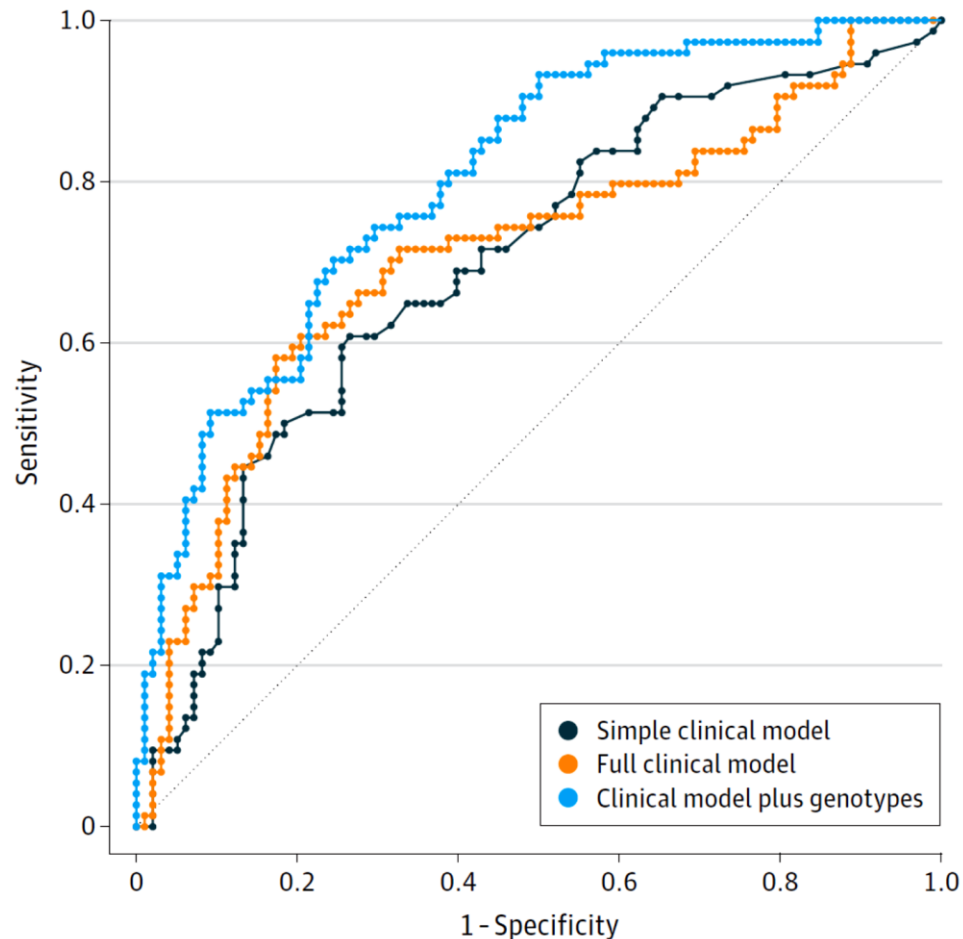
Mart Kals,^{a,b,*} Lindsay Wilson,^c Daniel F. Levey,^{d,e} Livia Parodi,^{f,g,h} Ewout W. Steyerberg,ⁱ Sylvia Richardson,^j Feng He,^k Xiaoying Sun,^k Sonia Jain,^k Aarno Palotie,^{l,f,h} Samuli Ripatti,^{l,h,m} Jonathan Rosand,^{f,g,h} Geoff T. Manley,^{n,o} Andrew I. R. Maas,^{p,q} Murray B. Stein,^{r,s,t,u} and David K. Menon,^{b,u,**} on behalf of The Genetic Associations In Neurotrauma (GAIN) Consortium (with contribution from the CENTER-TBI and TRACK-TBI studies)

Polygenic risk scores from PTSD and major depression applied to 1869 patients from CENTER-TBI & TRACK-TBI
Prediction of PTSD (PCL-5 ≥ 33) & depression (PHQ-9 ≥ 15); adjusted for known predictors, including prior psychiatric disease



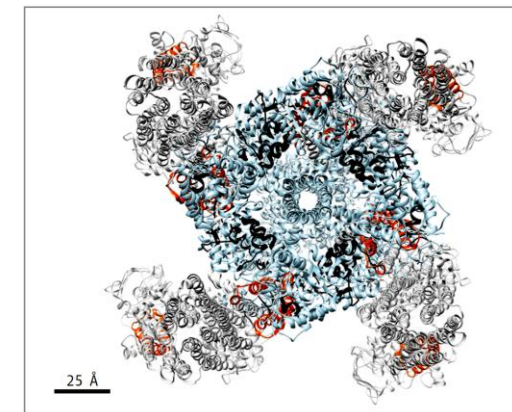
Genetic Variants Associated With Intraparenchymal Hemorrhage Progression After Traumatic Brain Injury

Ruchira M. Jha, MD, MSc; Benjamin E. Zusman, MD, MSc; Ava M. Puccio, PhD; David O. Okonkwo, MD, PhD; Matthew Pease, MD; Shashvat M. Desai, MBBS; Matthew Leach, MD; Yvette P. Conley, PhD; Patrick M. Kochanek, MD

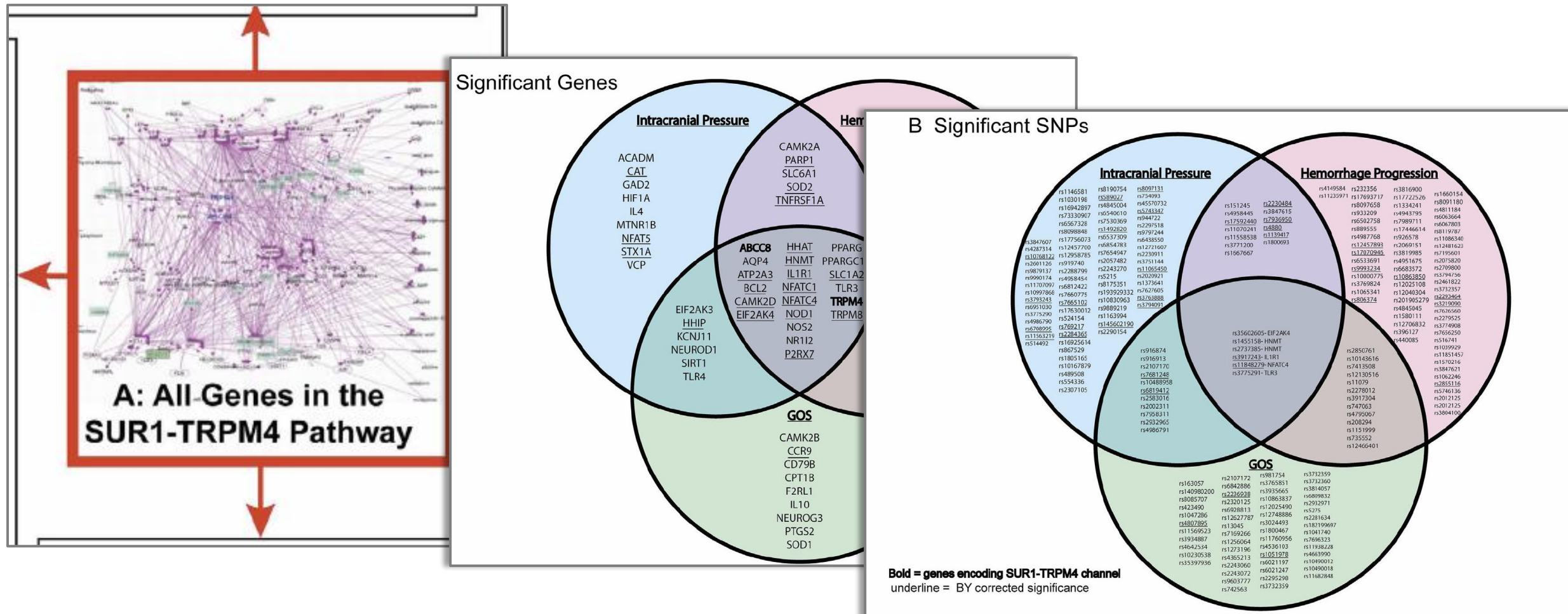


- Single centre study of 321 patients (95 with DC)
- SUR1-TRPM4 channel complex (includes sulphonylurea receptor)
- Implicated in pathophysiology of contusion (tICH) expansion in TBI.
- 40 variants in *ABCC8* (SUR1) and *TRPM4* explored as drivers of tICH
 - 4 SNVs in *ABCC8* increased risk of tICH progression
 - 4 SNVs in *TRPM4* decreased risk of tICH progression.
- Genetic information improved prediction of tICH expansion
- SNVs shown to influence SUR1-TRPM4 channel function *in silico*.

■ SUR1 subunits
■ TRPM4 subunits



ANN NEUROL 2026;99:459–477

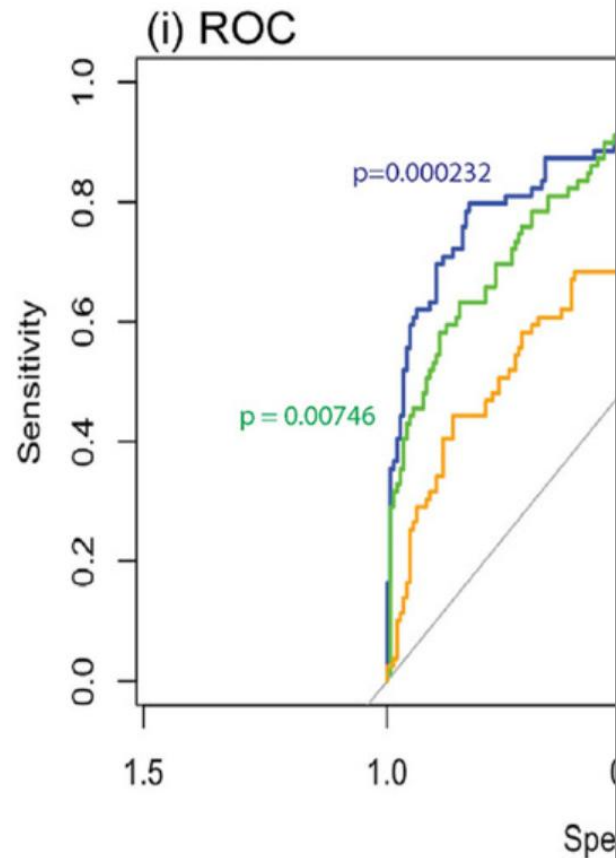


Polygenic Vulnerability to Intracranial Hypertension, Hemorrhage Progression, and Outcome in TBI

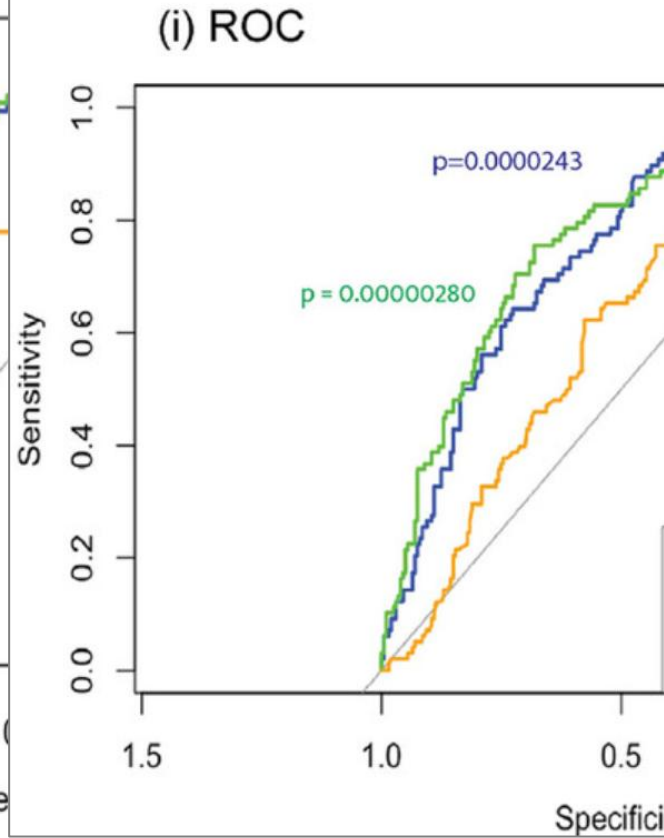
ANN NEUROL 2026;99:459–477

Margaux E. Miller, Benjamin E. Zusman, Chia-Ling Phuah, Erin McNally, David O. Okonkwo, Matthew Pease, Shashvat M. Desai, Anupama Rani, Nasathapot Namphol, Aditya Kumar, MD, Raemier A. Javelosa, Adam T. Eberle, Semeon Afework, Joshua Catapano, Charles S. Cox Jr MD, Patrick M. Kochanek, Yvette P. Conley, Ava M. Puccio, Ruchira M. Jha, the BRAIN Investigators

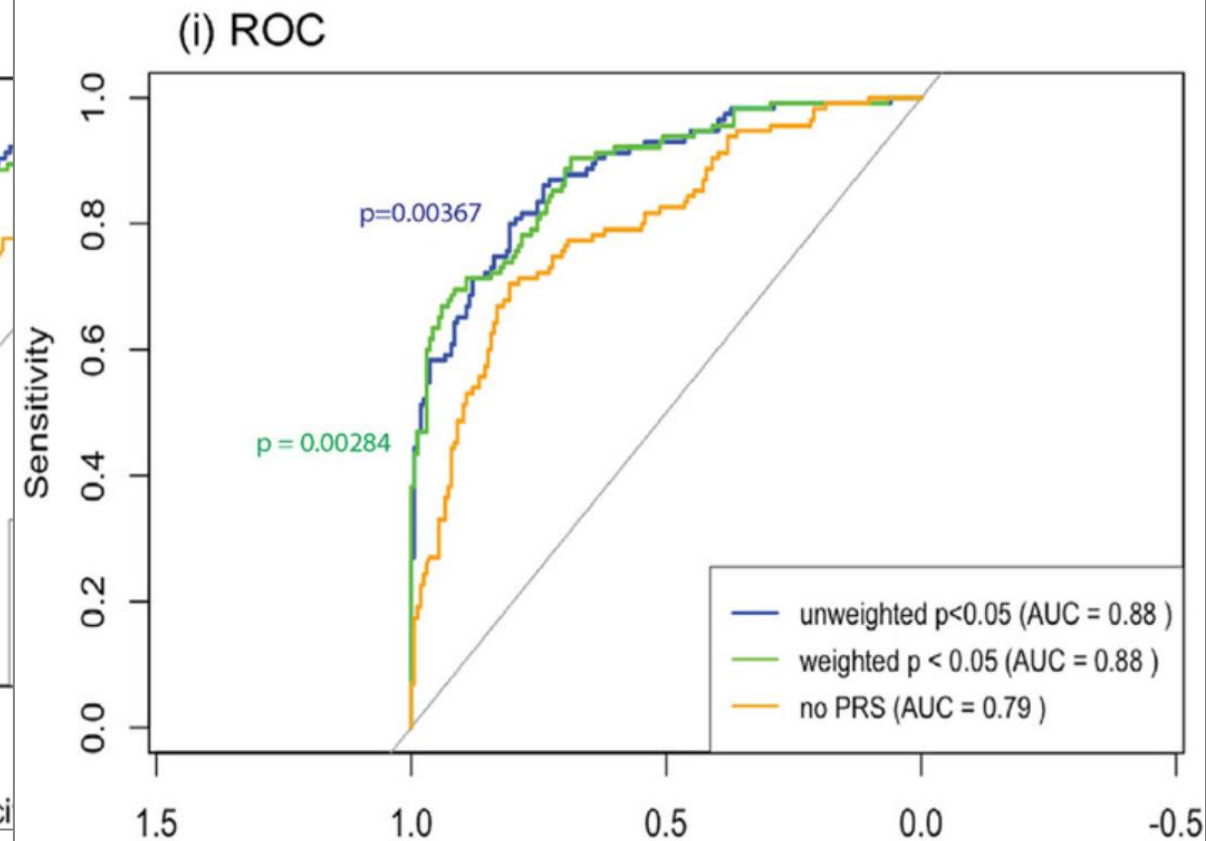
A 0-6h IPH Progression



D Peak ICP



E 12 Month GOS

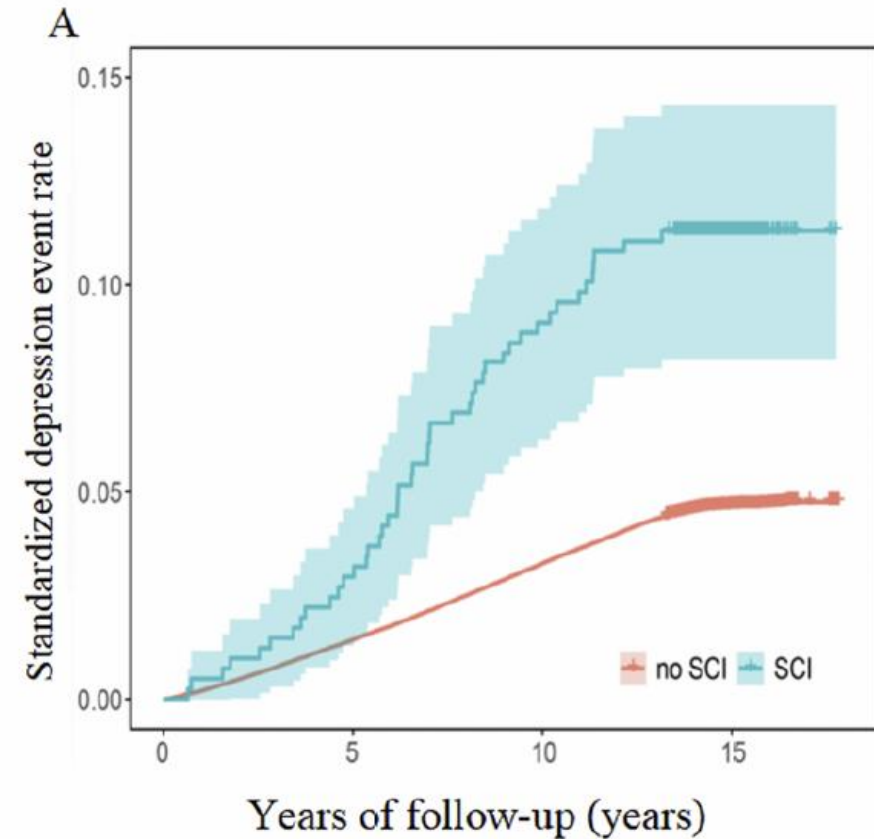


Brain structural changes and their role in increasing depression risk following spinal cord injury: evidence from the UK biobank

Wu Zhou, Bo Hei, Lei Huang, Jiayu Liu, Jixia Fang, Qun Gao, Bin Wang, Zihan Ding & Chengcai Li

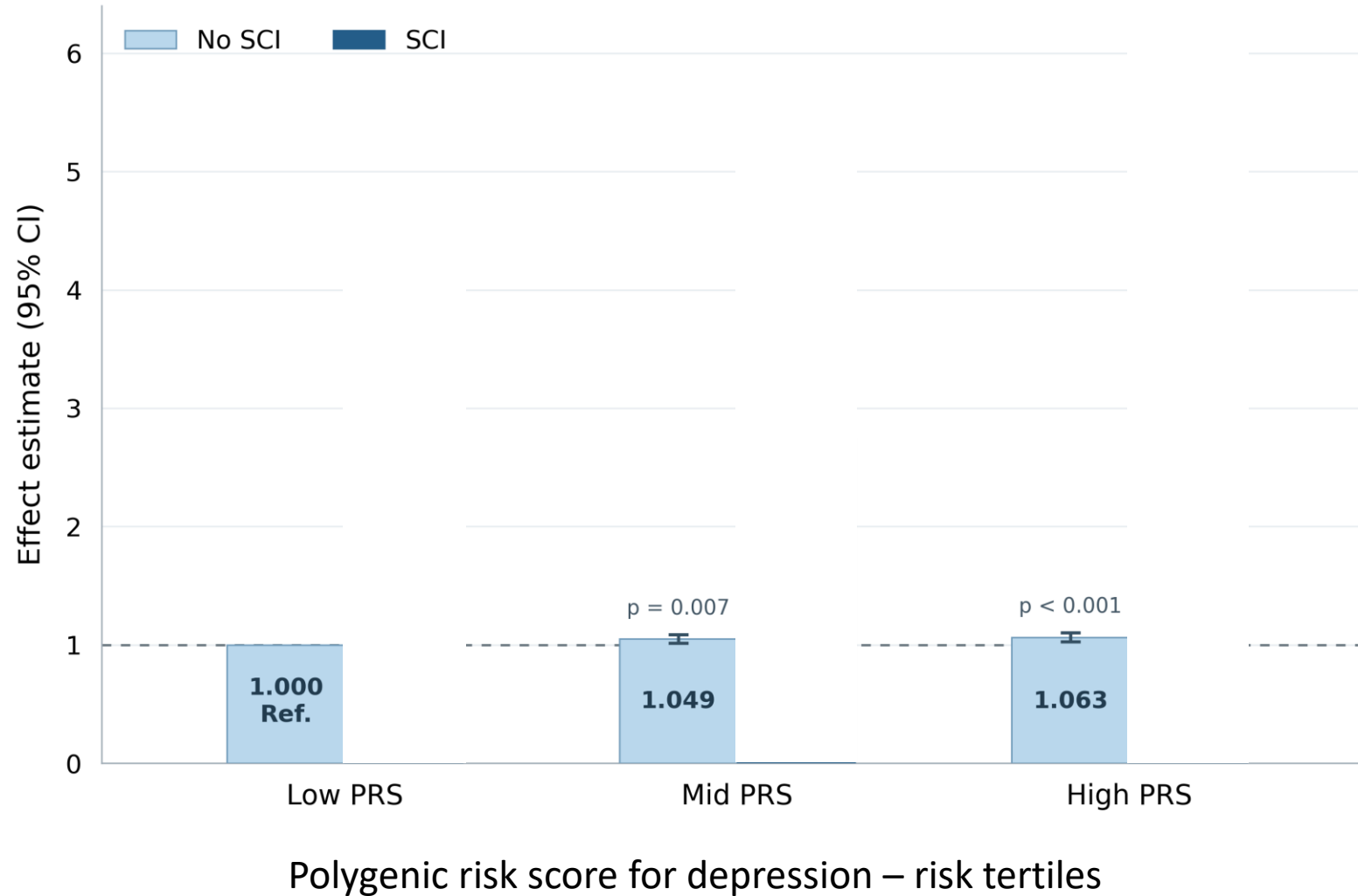
Based on data from UK BioBank:

- 407 SCI subjects and 431,890 non-SCI subjects
- Case identification based on ICD-10 codes for
 - SCI (S14, S24, S34, T06, T09)
 - Depression (F32, F33)



Model 3: PRS and SCI groups

Reference: low PRS with no SCI



Expected (small) increase in depression with increasing PRS tertiles in non-SCI population

SCI increases overall risk of depression (OR: 2 – 4)

SCI **substantially** sensitises to increased risk associated with PRS categories (~ 5-10 fold)

Increase across PRS bins (lowest PRS tertile as reference):

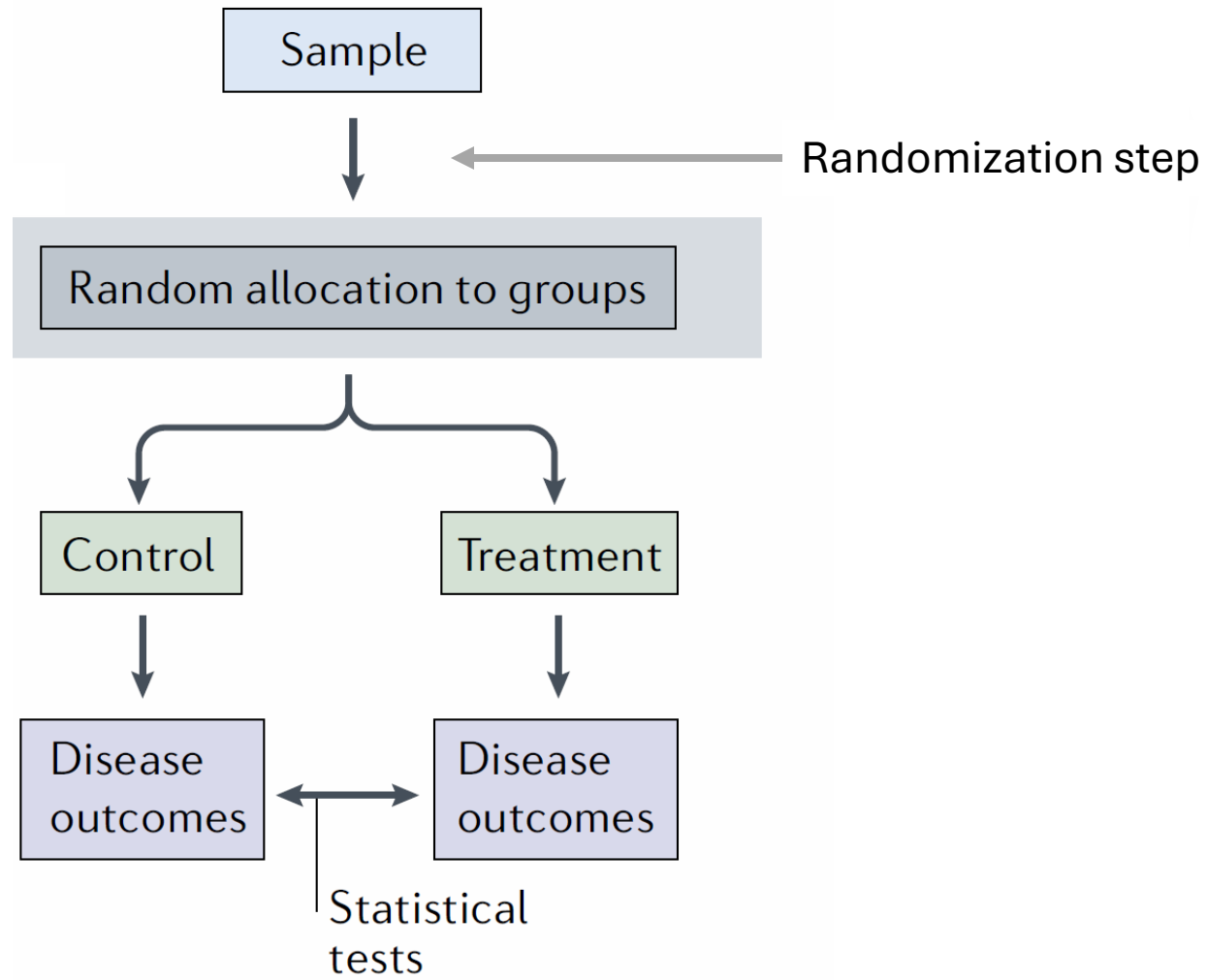
- If no SCI: Ref -> 5% -> 6.5%
- If yes SCI: Ref -> 27% -> 70%

**Classical demonstration
of Gene x Environment
interaction**

Themes

- From prophecies to predictions
- *Alea iacta est*: Biological underpinning of host phenotypes
- Candidate gene studies – pros and cons
- Genome wide associations – unbiased estimates of genetic risk
- Polygenic risk score – borrowing power from GWAS in other diseases
- Endotypes and precision medicine

Randomized controlled trial



Mendelian randomization

Eleanor Sanderson^{1,2}✉, M. Maria Glymour³, Michael V. Holmes^{1,4,5}, Hyunseung Kang⁶, Jean Morrison⁷, Marcus R. Munafò^{1,8,9}, Tom Palmer^{1,2}, C. Mary Schooling^{10,11}, Chris Wallace^{12,13}, Qingyuan Zhao¹⁴ and George Davey Smith^{1,2,9}

Advantage over direct measurement of target molecule

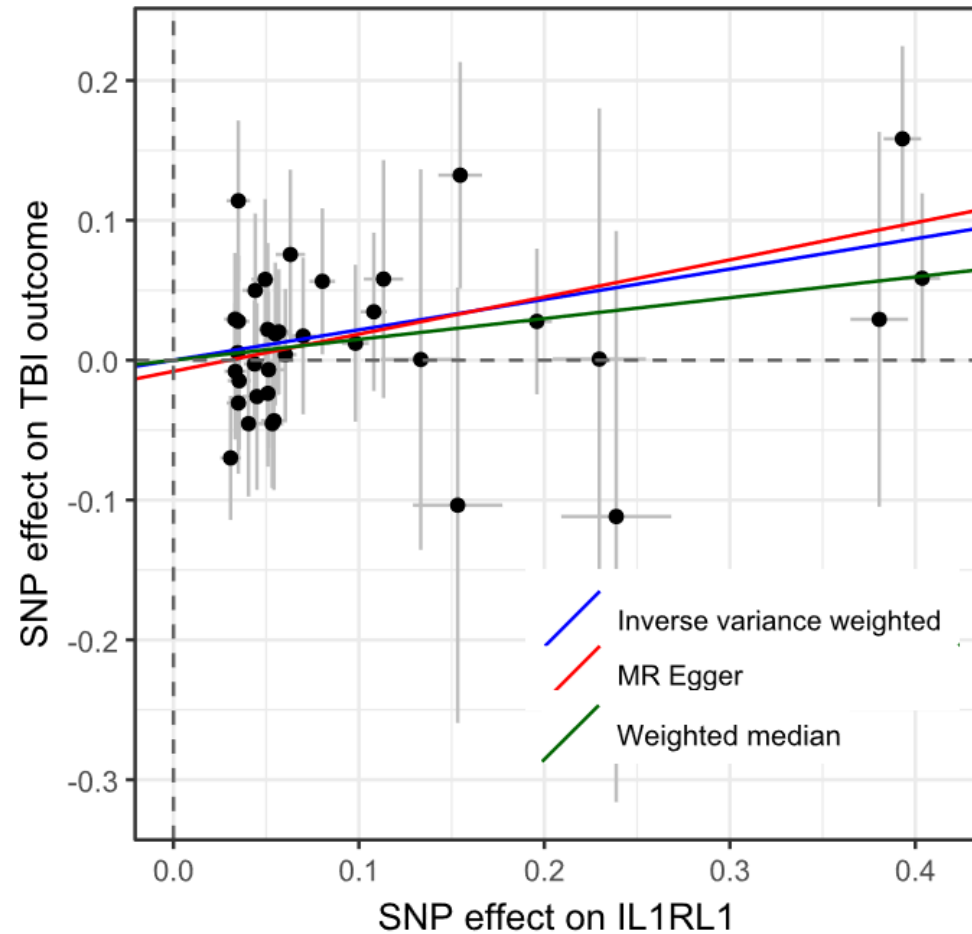
- Unconfounded by injury severity – early *iacta alea est!*
- Allows (retrospective) interrogation of targets
- Assess multiple targets at negligible extra cost



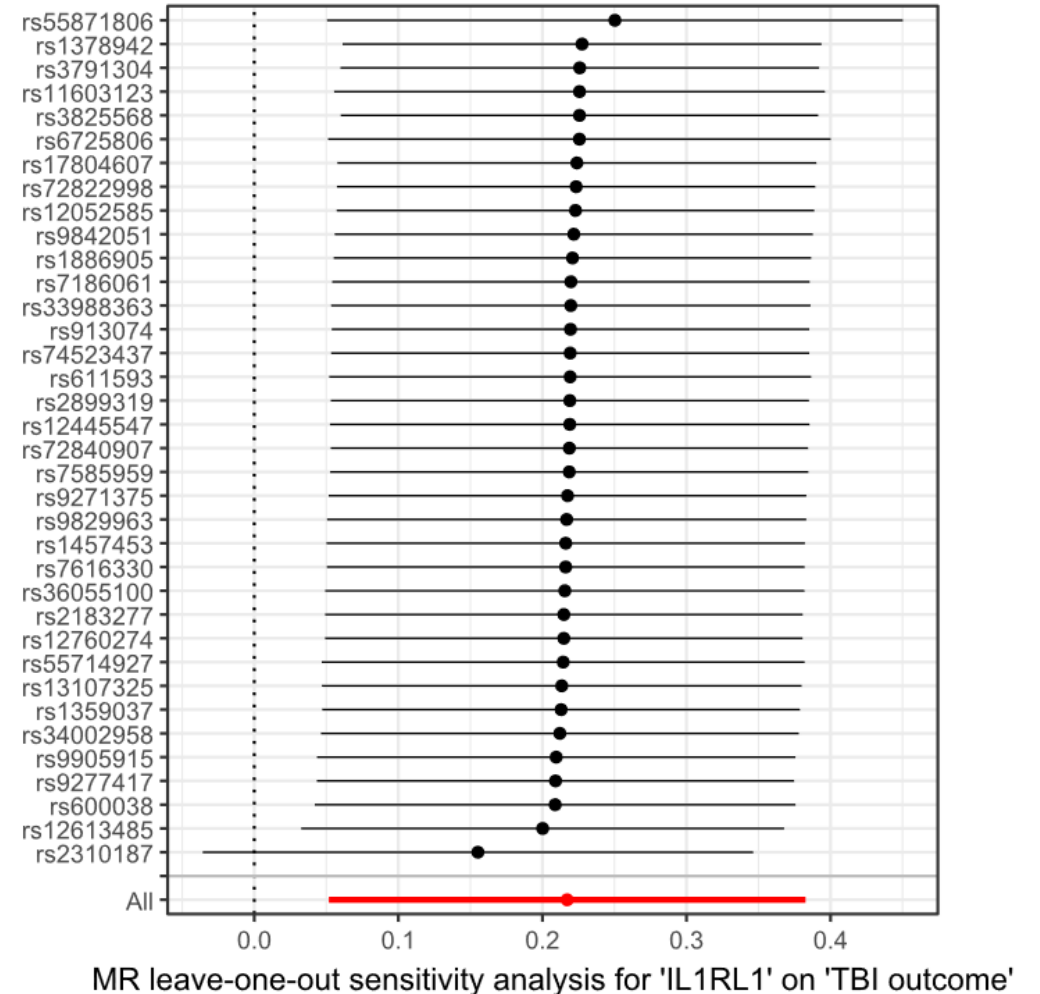
Many sources of error:
need to be excluded
for reliable results

Mendelian Randomization Analysis Identifies the Interleukin (IL)-1 Cytokine Family as a Causal Driver of Traumatic Brain Injury Prognosis.

A



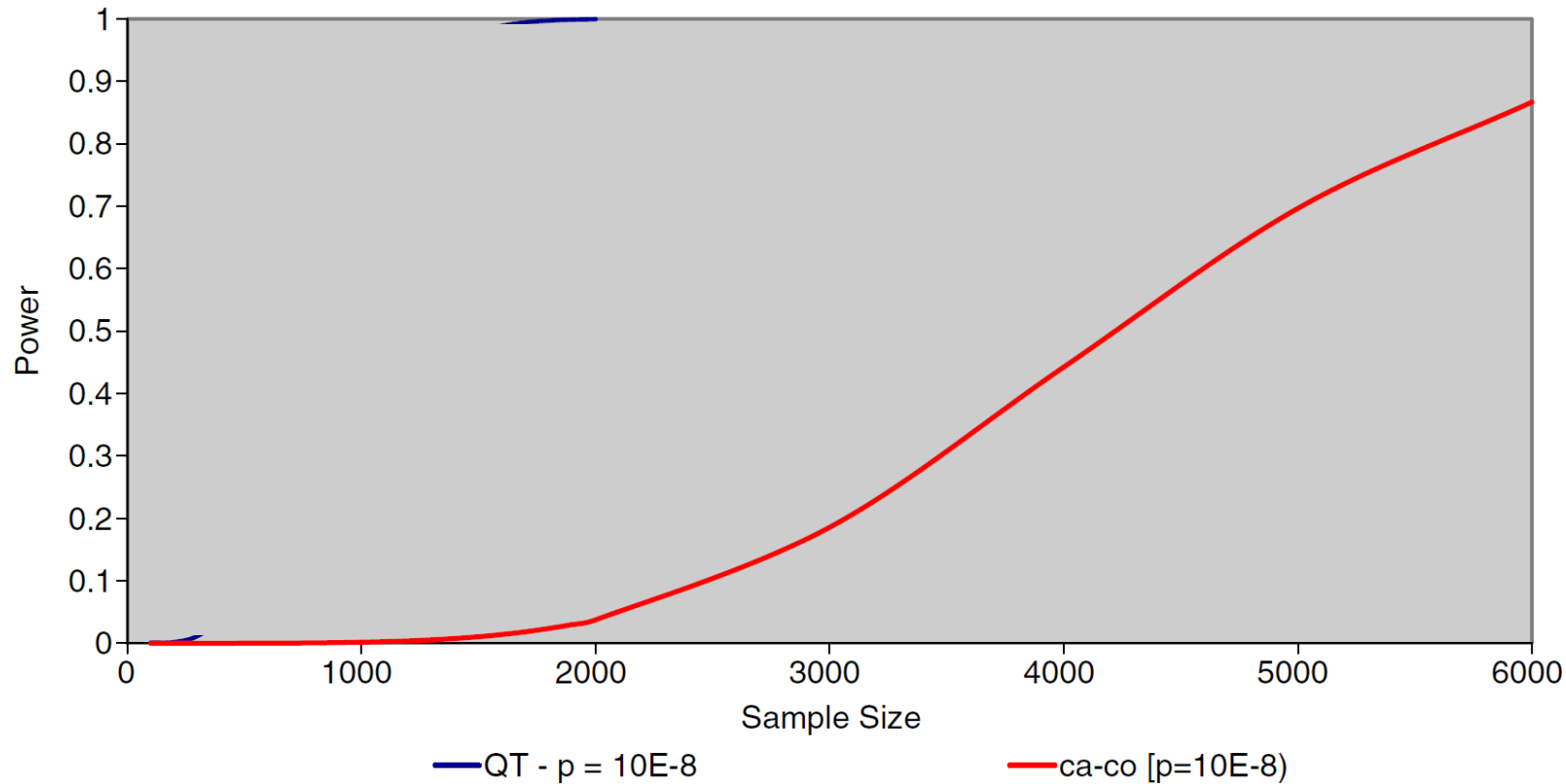
B



Themes

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- Endotypes and precision medicine
- Increasing power – sample size, analysis options, and logistics

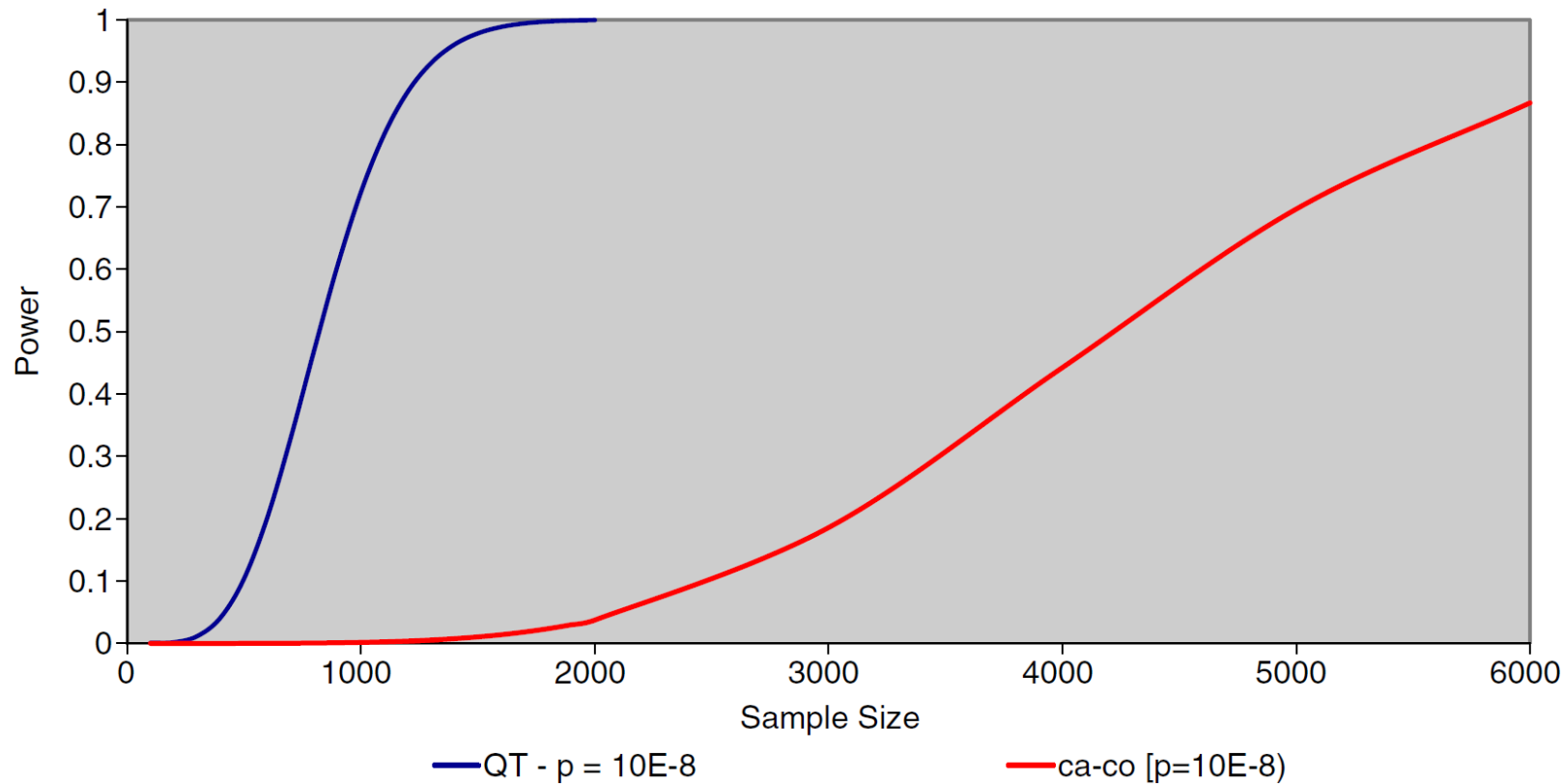
Genetic analysis of quantitative phenotypes in AD and MCI: imaging, cognition and biomarkers



Sample sizes for GWAS $p < 10^{-8}$ for:

- **Cases/Controls** vs **Quantitative Trait**
- *Simulated with OR 1.5, MAF = 0.1*
10% of QT variance explained by SNP

Genetic analysis of quantitative phenotypes in AD and MCI: imaging, cognition and biomarkers



Sample sizes for GWAS $p < 10^{-8}$ for:

- Cases/Controls vs Quantitative Trait
- Simulated with OR 1.5, MAF = 0.1 **10%** of QT variance explained by SNP

Possible quantitative Traits in SCI

- Clin progress (motor recovery slope?)
- Progression on imaging (serial MRI?)
- GFAP/NFL levels/trajectories
- Therapy intensity level
- Rehabilitation progress
- Mental health outcomes

Science 1960; 131: 1667

Search for Artificial Stellar Sources of Infrared Radiation

FREEMAN J. DYSON
Institute for Advanced Study, Princeton, New Jersey

Search for Artificial Stellar
Sources of Infrared Radiation



Freeman Dyson theorized that hypothetical advanced alien megastructures would use energy photovoltaic shells in habitats around their star to solve energy problems; these would give off far infrared radiation and searching for that byproduct would be a viable method for searching for extraterrestrial life.

How would an advanced alien civilisation address the issue of generating knowledge and clinical evidence pertaining to genetic drivers in TBI/SCI?

1. Use information from a prospective GWAS project – a small proportion (probably $\ll 0.01\%$ of global cases) - a solar farm approach

OR

2. Collect data from all clinical trials (or all the $\sim 200,000$ SCIs that occur annually) - a Dyson sphere of evidence generation
 - Currently 1750-2000 patients enrolled in SCI Clinical trials
 - Estimated accrual of ~ 3000 patients/yr to SCI registries

Data Hub

Legacy/New Studies
& National audits
($n > 100,000$)
Population cohorts
($n > 2$ million)

Curate &
Harmonize

HDR UK
TBI-REPORTER Node On DPUK TRE
UK SeRP

- Biofluids/DNA
- Tissue/Cell banks
- Brain donation
- Neuroimaging
- Impact data
- TRL RTC data
- Outcomes

- Establish generic processes for
- Regulatory templates
 - Sampling, banking & retrieval
 - Assay harmonisation
 - Image acquisition & transfer
 - Digital biomarker pipelines

Biomarker Resource

Admission DNA & serum sample banked from
every patient in associated prospective studies

Promote:

- Open access (*FAIR*)
- Patient & public input
- Access for neglected cohorts
- Engagement (16 UK centres)

Leverage:

- Global UK leadership
- Legacy data/samples
- UK research infrastructure
- NHS data linkage
- Links with sporting bodies

Underpin:

- Academia/Industry Ib/Ila trials
- Biomarker informed research
- De-risked drug development

Facilitate:

- Phase IIb/III adaptive platform
- Research training
- Robust legacy solutions
- Policy development

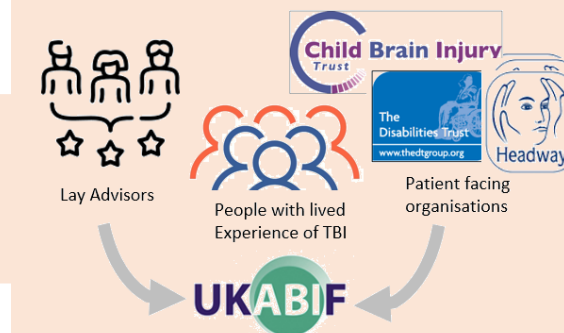
Experimental Medicine Network

Pathfinder centres ($n \sim 8$)
Definitive network (n 12-16)

- Advanced neuroimaging
- Biosample processing
- Special expertise (PET, ECOG, HR ICU, brain microdialysis)

*Framework for **early-stage** trials*

- Template protocol/Ethics
- Integrated into NIHR CRN
- MHRA engagement
- Industry engagement



Patient & Public Involvement/Engagement



Chloe Hayward



Peter Hutchinson



Adel Helmy



Fiona Lecky



David Menon



James Piercy



David Sharp



Emma Squires



Willie Stewart



Simon Thompson



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TBI reporter

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Welcome to TBI-REPORTER

UK TBI-Repository and Data Portal Enabling Discovery

Traumatic Brain Injury (TBI) is a major cause of death and disability. In the UK alone, TBI care costs over £10 billion each year and globally it costs over \$400 billion. TBI can lead to long-term health issues such as dementia, epilepsy, mental health problems, and a shorter lifespan. While we have gained some understanding of the underlying processes driving TBI related health outcomes, drug trials have often failed and progress in clinical care has been slow. However, over the years, each of the individual studies investigating TBI and its outcomes has gathered potentially very informative data that, to date, has not been widely available to researchers outside of the original studies.

Learn about what PPIE is and how to use it.

[Learn more](#)

Read more about our program governance documents and meeting notes.

[Documents](#)

Meet our amazing team.

[Meet the team](#)

Take home messages

- ~50% of outcome variance in TBI and ~20-30% in SCI unexplained by known or emerging risk factors
- Genetically driven host response likely to contribute to remaining unexplained variance
- Past evidence from candidate gene studies - but these have drawbacks
- **Best estimate that in TBI ~25% of outcome variance is heritable (what is the proportion in SCI?)**
- **However, even with ~5000 patients, GAIN was not powered to identify contributory variants in TBI**
- **Solution:**
 - Bank DNA in every ongoing TBI/SCI study (observational or interventional) – Cost ~\$20/patient
 - Clinical variables, covariates and outcome are available “for free” from such studies
 - Genotyping costs are low : ~\$50-75 per sample
 - Extending GAIN will cost <\$100k per 1000 patients, or <\$ 1 million for a further 10,000 patients
 - Advantages in exome or whole genome sequencing, but costs range from \$300-1000/sample
 - However, costs are falling all the time, and if DNA is banked, much more may be possible

“You can’t start a fire ...

You can’t start a fire without a spark....

Translational Research to Inform Practice (TRIP)

Key questions:

- To what extent does genetic variance modulate disease course and outcome in neurotrauma?
- What approaches can we use to determine such modulation?
- What can such information be used for?

Summary of presentation in lay terms:

- Accumulating evidence that genetic variation does impact disease course/outcome in TBI/SCI
- Current studies have delivered intriguing, but not definitive, results
- Better evidence can be obtained through improved study design and increased study size
- An efficient way to increase study size is to include all patients (or at least all patients recruited to any research study) in genetic analysis
- These approaches may lead to improved understanding of disease, deliver new treatment targets, and aid prognostication

How would pre-clinical work would better inform your research?

- By validation of any genetic hits in human neurotrauma in preclinical models.