Seminar Daring Universitas Indonesia

The importance of genomic studies in Indonesian population

Beben Benyamin
beben.benyamin@unisa.edu.au

Australian Centre for Precision Health &
Allied Health and Human Performance

Adelaide, 14 October 2020

University of South Australia

- I am senior lecturer in biostatistics (I teach statistics, genetics, epidemiology and public health)

- I research statistical genetic and epidemiology of complex diseases and trait

- https://people.unisa.edu.au/Beben.Benyamin
- https://scholar.google.com.au/citations?user=wMoqGWQAAAAJ&hl=en

Menyongsong Kedokteran Presisi dengan Genom Indonesia

BEBEN BENYAMIN

Dosen Senior dan Peneliti di Bidang Genetika Statistik, University of South Australia, Adelaide

Jago. Julukan itu diberikan kepada Rohani, kakek 80 tahun dari suku Bajo, Pulau Togean (Sulawesi), karena ketangguhannya menyelam. Seperti kebanyakan lelaki Bajo, Rohani bisa menyelam untuk berburu ikan dan hewan laut lainnya sampai kedalaman 70 meter selama beberapa menit. Uniknya, semua itu dilakukan tanpa menggunakan alat penyelam. Bermodal kacamata berbingkai kayu, kemampuan menyelam orang Bajo di luar batas kemampuan manusia biasa.

Kisah hidup Rohani diang-

logi sekuensing atau pengeja huruf DNA canggih, berbagai penelitian berbasis genom diharapkan bisa dilakukan di Indonesia, baik secara mandiri maupun kolaborasi. Selama ini mayoritas penelitian tentang asal-usul manusia Indonesia dan penelitian kedokteran berbasis genom Indonesia mengamati segmen kecil dalam genom, misalnya satu gen atau satu kromosom Y saja. Dengan teknologi yang baru diresmikan, sekarang penelitian dapat dilakukan pada seluruh bagian genom yang memuat sekitar 20.000 gen. Gen sendiri merupakan unit kecil dari genom yang memberikan instruksi pembuatan protein.

Di dunia tonggak penelitian genom manusia sendiri sebenarnya dimulai seperempat abad lalu dengan dibentuknya *Human Genome Project*. Proyek sains raksasa yang menghabiskan USD3 miliar ini bertujuan memetakan 3 miliar huruf DNA penyusun ge-

ngaruhi penyakit tersebut telah diidentifikasi. Teknik ini dikenal dengan sebutan *genome-wide association study* (GWAS).

Berbagai penyakit dan karakteristik yang bisa diamati tidak luput dari penelitian. Ilmuwan tidak hanya meneliti kondisi yang sering kita sebut sebagai penyakit "genetik" saja, seperti talasemia atau hemofilia. Sekarang hampir semua penyakit dan karakteristik yang selama ini dianggap tidak banyak dipengaruhi genetik pun tak luput dari penelitian GWAS. Dari rambut ikal sampai tangan kidal. Dari asma sampai skizofrenia. Semua dicari gen penyebabnya.

Walaupun sulit, laksana mencari jarum di tumpukkan jerami, buah dari proyek raksasa ini sudah mulai bisa dipetik. Ribuan perubahan huruf DNA telah berhasil dikaitkan dengan berbagai penyakit dan karakteristik manusia. Sebagian temuan

suku Bajo bisa menyelam sangat dalam dan lama tanpa menggunakan alat penyelam?

Mereka memulai dengan membandingkan ukuran limpa orang Bajo dengan orang Saluan. Suku Saluan dijadikan sebagai pembanding karena letaknya berdekatan, tapi tidak mempunyai tradisi menyelam seperti suku Bajo. Ukuran limpa diteliti karena pada mamalia penyelam andal seperti anjing laut, ukuran limpanya lebih besar daripada proporsi bagian tu-

nomnya sudah banyak dipelajari. Ternyata mereka menemukan bahwa variasi pada gen *PDE10A* dan *BDKRB2* di suku Bajo terseleksi secara turun-temurun. Proses seleksi ini diperkirakan berlangsung selama ribuan tahun.

Dari analisa lanjutan, mereka juga berhasil membuktikan bahwa variasi di dua gen tersebut berkorelasi positif dengan ukuran limpa (*PDE10A*) dan sifat refleks menyelam (*BDKRB2*). Penelitian seperti ini menjawab kenapa suatu suku mempunyai karakteristik unik dibanding orang kebanyakan. Tak kalah penting, penelitian seperti ini juga bisa membawa dampak pada penelitian kedokteran. Penelitian tentang kemampuan menyelam suku Bajo bisa membuka penelitian baru tentang hipoksia, kondisi berkurangnya oksigen dalam tubuh.

Keunikan Lain

Kedokteran Presisi dengan Genom Indonesia

Dalam satu dekade terakhir, dunia sedang bergerak menuju praktik kedokteran masa depan. Praktik kedokteran karena keunikan pasien, baik dari segi genom, lingkungan, maupun gaya hidupnya, dijadikan acuan perawatan. Kalau selama ini boleh dibilang bahwa pengobatan disamaratakan bagi setiap pasien, di era *precision medicine* (kedokteran presisi) praktik tersebut akan menjadi masa lalu.

Sampai saat ini mayoritas (80%) penelitian genom menggunakan sampel dari orang keturunan Eropa. Hanya 20% menggunakan sampel dari belahan dunia lain, termasuk Afrika, Asia, dan Amerika Latin. Sedangkan penggunaan sampel dari Indonesia untuk penelitian-penelitian genom mutakhir, terutama di bidang kedokteran, masih terbatas. Bahkan, dibanding dengan negara-negara te-

pemimpinan ilmuwan Indonesia dalam bidang ini sangat menentukan. Penggunaan sampel genom Indonesia untuk mengatasi masalah-masalah kedokteran di Indonesia tidak bisa ditunda-tunda lagi. Kita tidak bisa hanya mengandalkan hasil penelitian genom Eropa atau negara lain.

Untuk itu, adanya dukungan pemerintah dengan dibentuknya Pusat Genom Nasional merupakan angin segar perlu diapresiasi. Tapi tentu saja jangan berhenti di sana. Kita ketahui bahwa penelitian genom memakan biaya yang mahal. Karena itu, dukungan dana penelitian yang besar dengan durasi panjang dan berkelanjutan menjadi keharusan. Pelatihan-pelatihan bidang genom untuk memperkuat sumber daya manusianya juga perlu segera ditingkatkan.

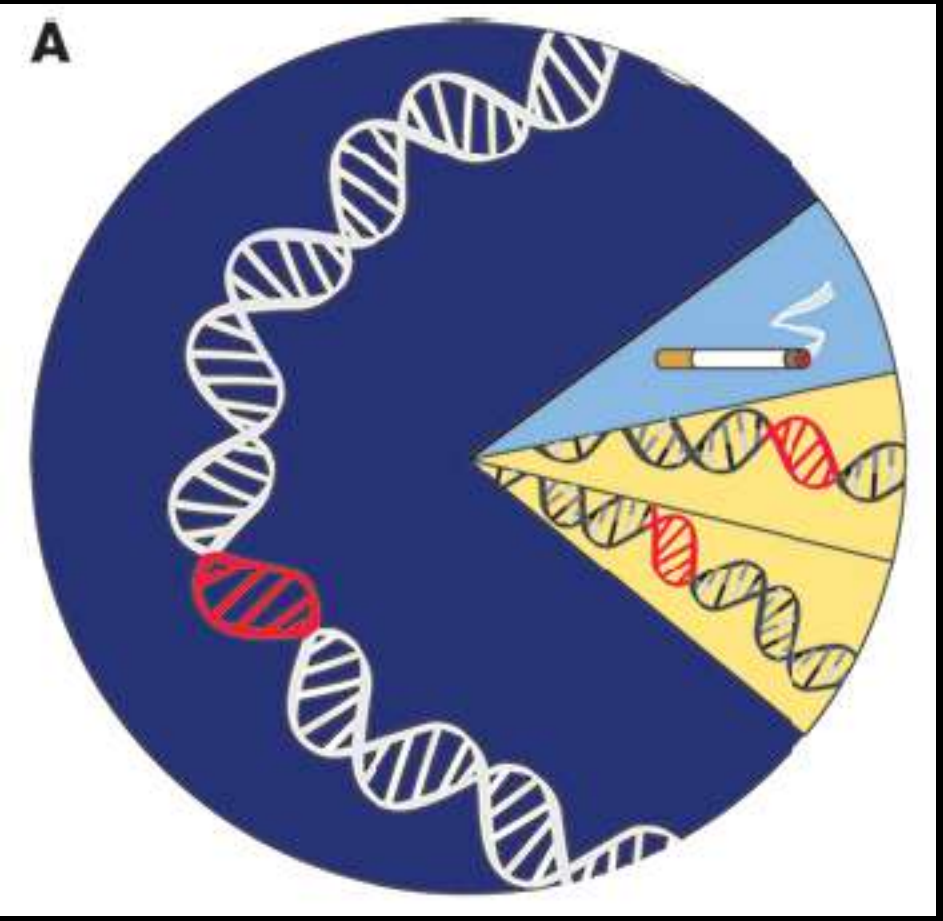
Selain itu, sudah saatnya Indonesia membentuk Biobank Indonesia. Biobank ini ditujukan untuk menjadi pusat ko-

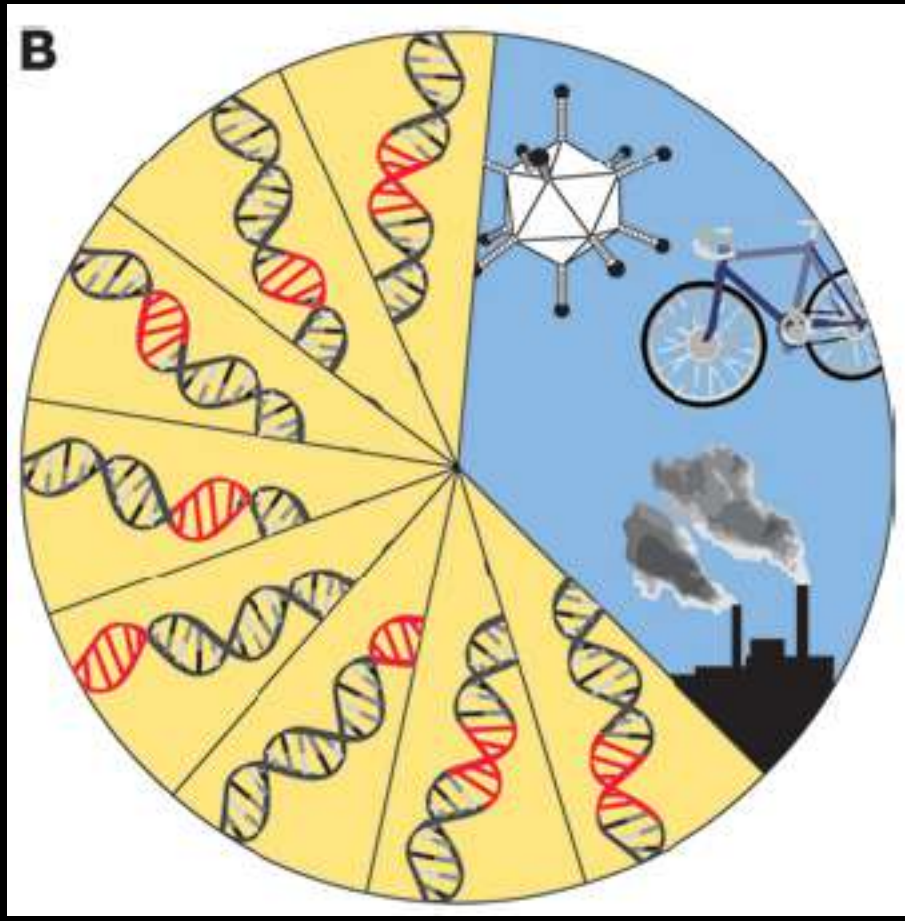
http://koran-sindo.com/page/news/2018-05-22/1/0/Menyongsong_Kedokteran_Presisi_dengan_Genom_Indonesia

University of South Australia

University of South Australia

Mendelian disease *vs* Complex disease





Cystic fibrosis, Huntington's disease

Schizophrenia, type 2 diabetes

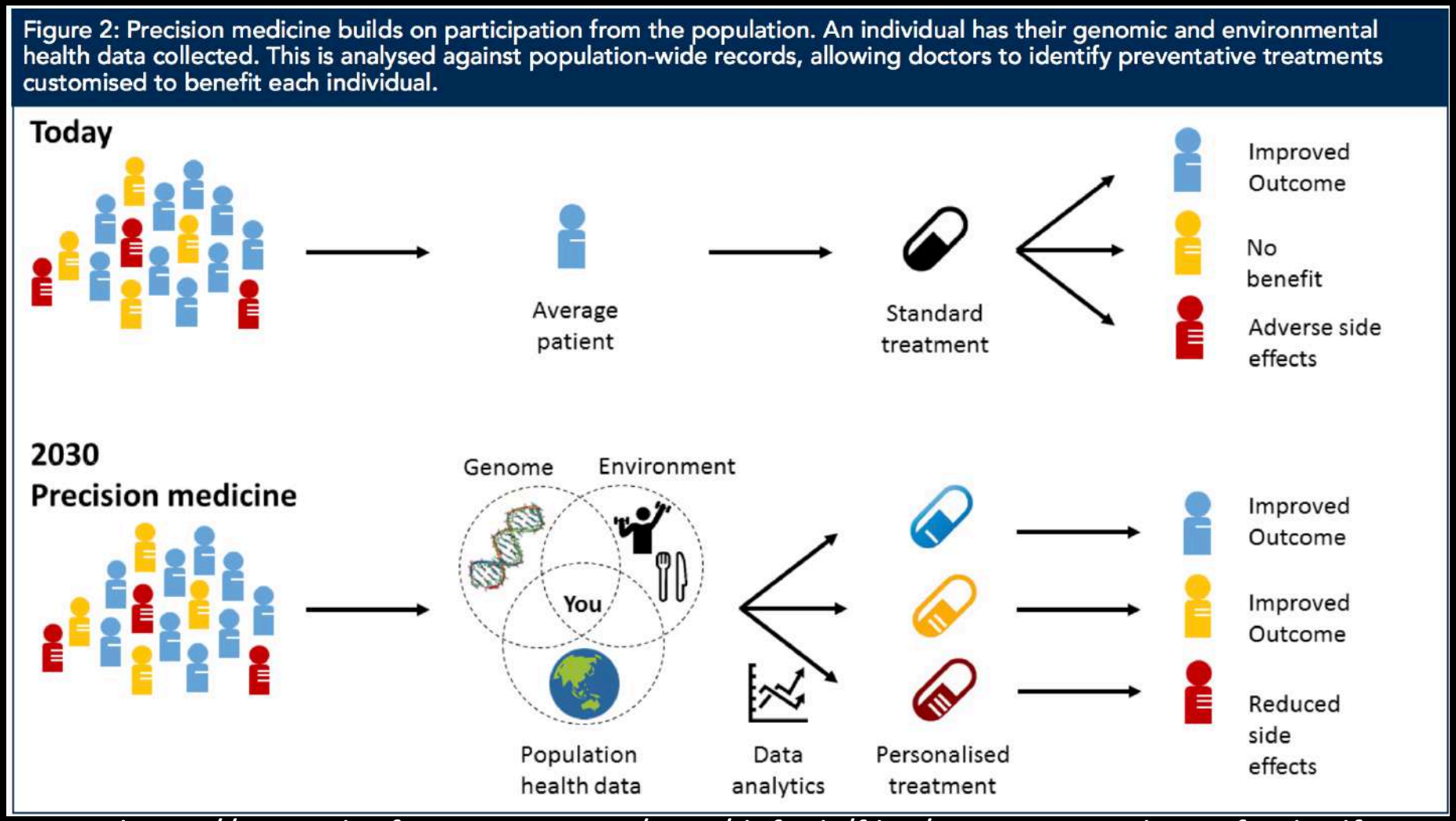
Manolio et al. JCI 2008

My research questions

1. What causes this phenotypic variation?
   - What are the relative contribution of genetic and environmental factors on complex trait or disease?
2. How do we find genes affecting individual differences?
3. How do we use this genomic information in medicine?

University of South Australia

Goal: Precision (personalized) medicine



https://www.chiefscientist.gov.au/sites/default/files/Precision-medicine-final.pdf

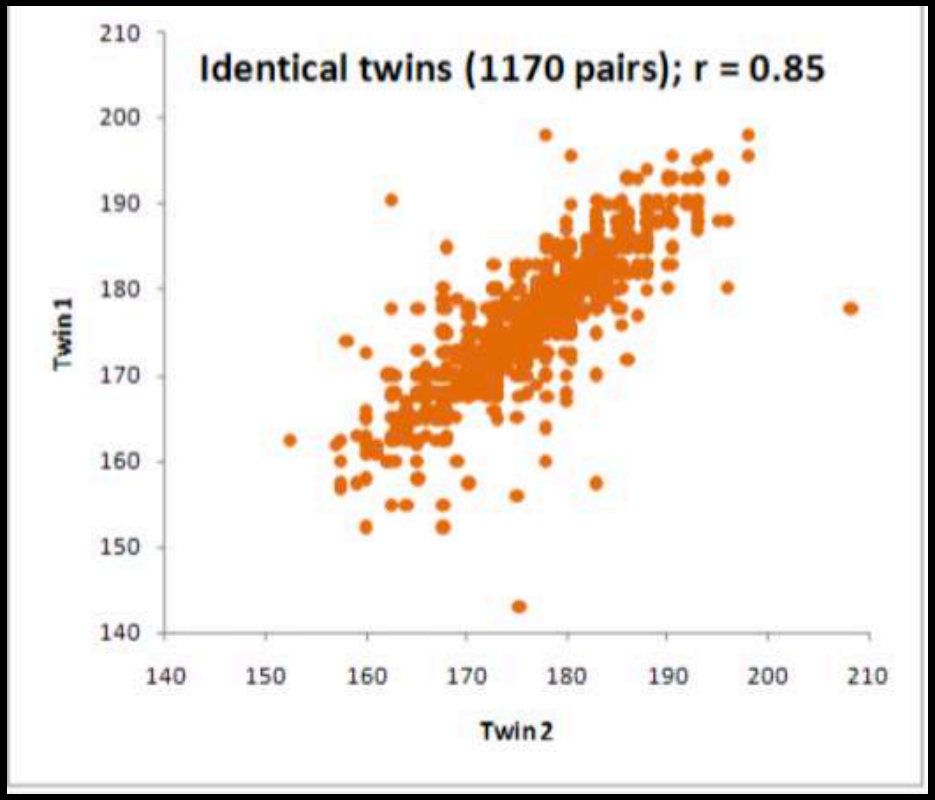
University of South Australia

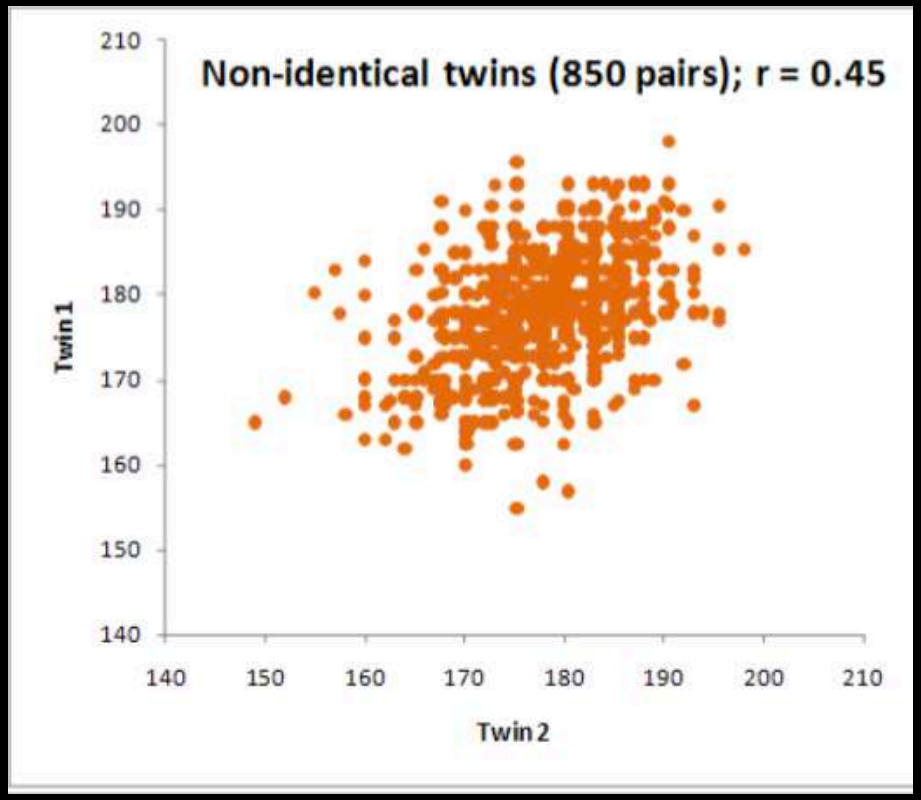
1. **What are the relative contribution of genetic and environmental factors on complex disease?**

2. **How do we find genes affecting complex disease?**

3. **How do we use this genomic information in medicine?**

How do we estimate the genetic contribution to complex traits?





Heritability: Proportion of phenotypic variance explained by genetic factors.

Heritability (h^2) = 2*(rMZ-rDZ) ~ 80%

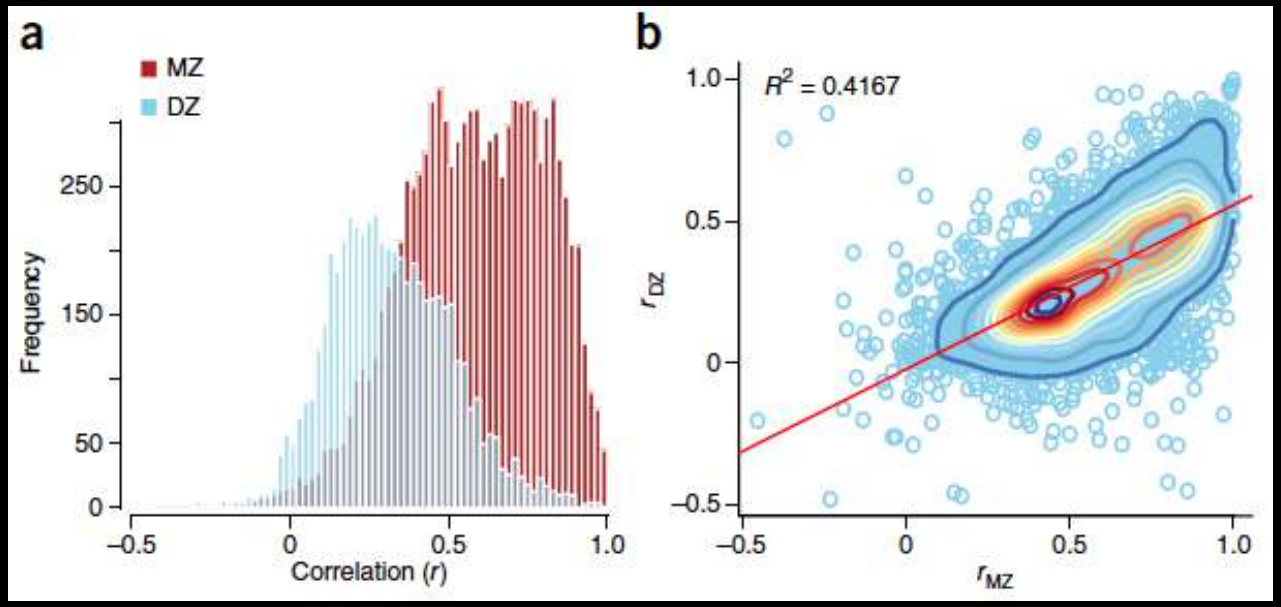
Courtesy of Peter Visscher (UQ)

Meta-analysis of all twin studies in the last 50 years

University of South Australia

2,748 papers, published between 1958 and 2012, reporting on 17,804 traits on a total of 14,558,903 twin pairs

- The average heritability of all human traits is 49%.
- Common environmental variance contribute to a 17% of the phenotypic variance.



Meta-analysis of the heritability of human traits based on fifty years of twin studies

Tinca J C Polderman[1,10], Beben Benyamin[2,10], Christiaan A de Leeuw[1,3], Patrick F Sullivan[4–6], Arjen van Bochoven[7], Peter M Visscher[2,8,11] & Danielle Posthuma[1,9,11]
[10]These authors contributed equally

VOLUME 47 | NUMBER 7 | JULY 2015 NATURE GENETICS

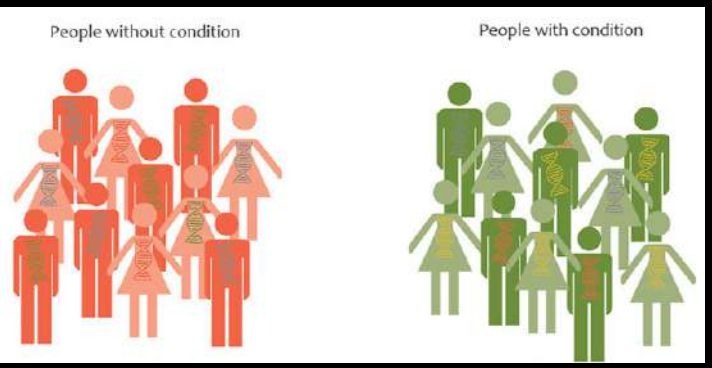
University of South Australia

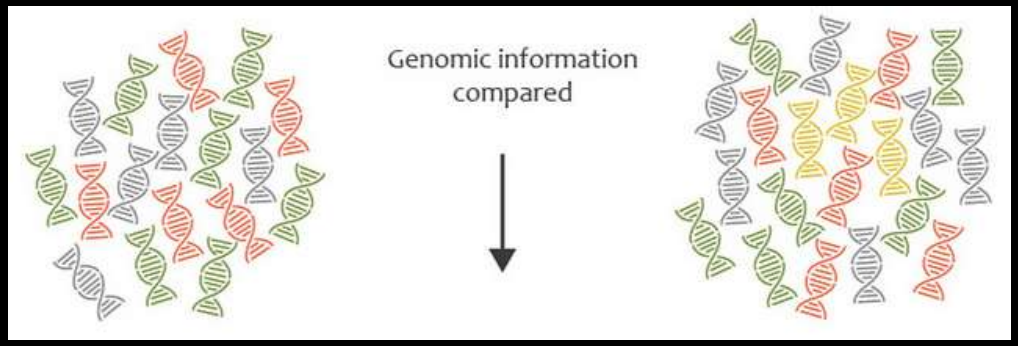
1. What are the relative contribution of genetic and environmental factors on complex disease?

2. **How do we find genes affecting complex disease?**

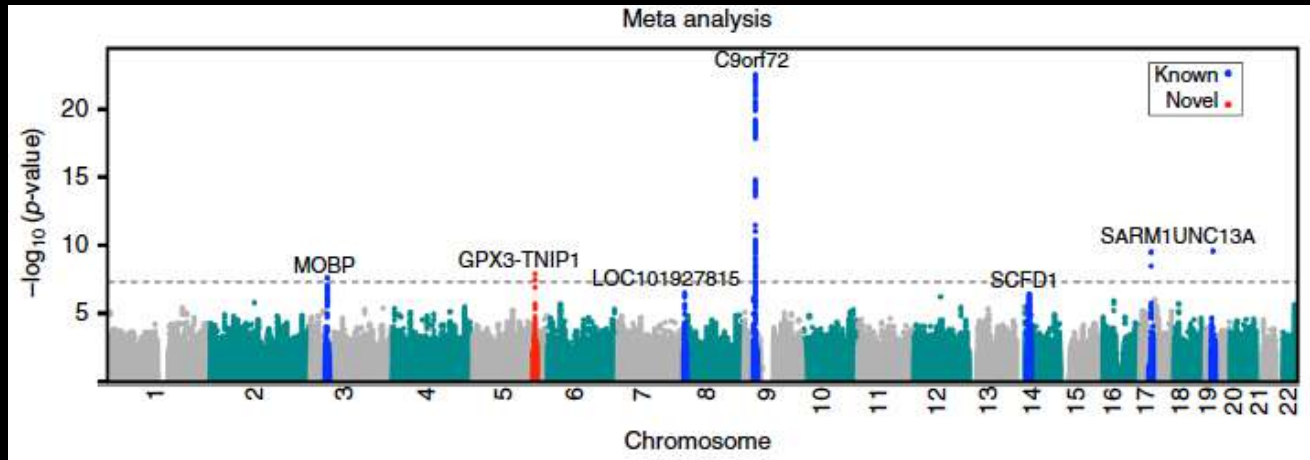
3. How do we use this genomic information in medicine?

Genome-wide Association Study (GWAS)





www.genomicseducation.hee.nhs.uk



Benyamin Nature Communication (2017)

Challenges: Most studies are of European ancestry: Can the findings be transferred into other populations?

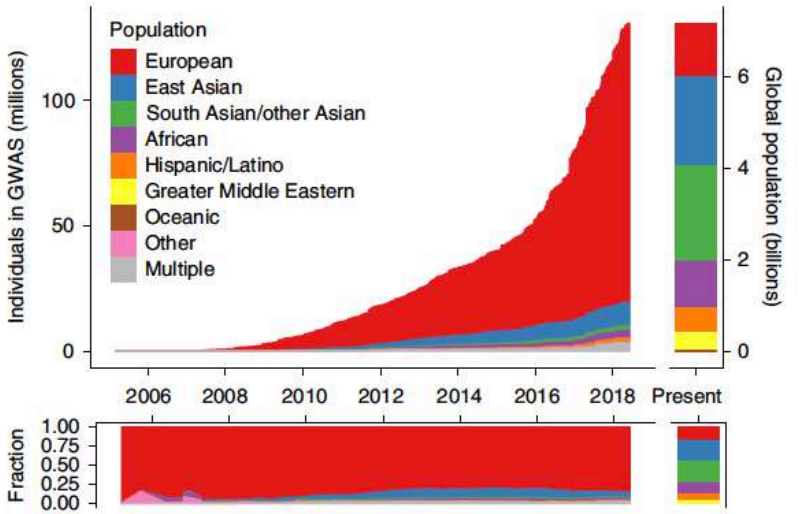
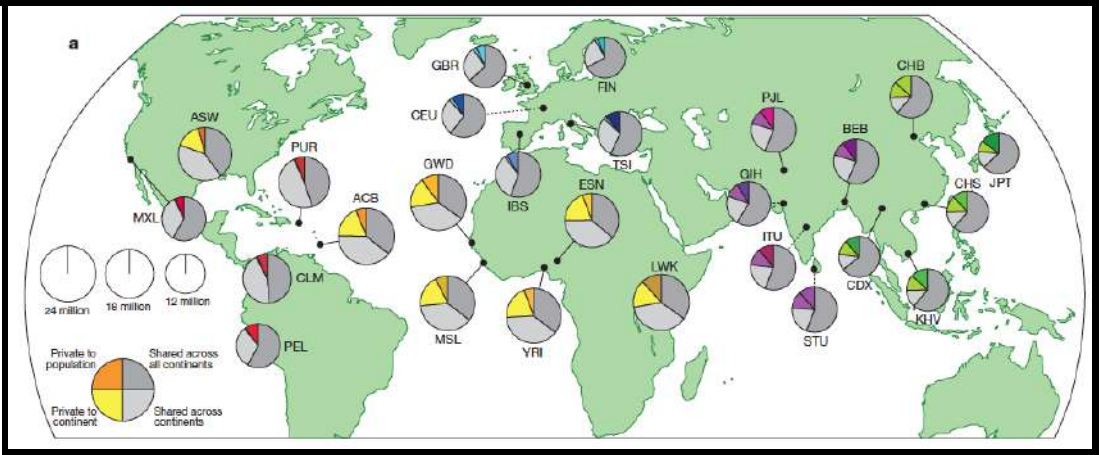


Fig. 1 | Ancestry of GWAS participants over time, as compared with the global population. Cumulative data, as reported by the GWAS catalog[76]. Individuals whose ancestry is 'not reported' are not shown.

Martin et al Nat Gen,2019



1000Genome Project 2015

- Lactose intolerant in different populations due to mutations in *LCT* gene.
- Strength of association can be different between populations (*MHC* gene for schizophrenia).

- South East Asian populations homes to a half billion people are not well represented.

University of South Australia

University of South Australia

Differences in drug response between ethnic groups

Drug[A]	Therapeutic Area[A]	Referenced Subgroup[A]	Prevalence
Codeine	Anesthesiology	*CYP2D6* Ultra-rapid metabolizers	more common in Caucasians (1-10%) and less in Chinese and Japanese (0.5-1%)[B].
Warfarin	Cardiology or Hematology	*VKORC1* A allele carriers (e.g., –1639G>A)	Allele frequencies for AA genotype (lower warfarin dose requirement): 14.2% in Caucasians versus 82.1% in Chinese [2].
Amitriptyline	Psychiatry	*CYP2D6* poor metabolizers	~6-10% in Caucasians vs ~2% in Asians[1]
Clopidogrel	Cardiology	*CYP2C19* poor metabolizers	poor metabolizers: 3-5% in Caucasian vs 15-20% in Asians[3]
Carbamazepine	Neurology	*HLA-B*1502* allele carriers	>15% in Hong Kong, about 10% in Taiwan, but largely absent (0-1%) in Caucasians[C].
Erlotinib	Oncology	*EGFR* exon 19 deletion or exon 21 substitution (L858R) positive	*EGFR* activating mutation frequencies: ~ 50-60% of NSCLC in Asia-Pacific versus only 12-13% in UK [5].
Irinotecan	Oncology	*UGT1A1*28* allele carriers	Allele frequencies for *UGT1A1 7/7* genotype (high incidence of neutropenia) is 12-13% in Caucasians, 23% in Blacks and lower (2-8%) in Asians [2,12].

[A]AS in FDA; Table of pharmacogenomic biomarkers in drug labeling (http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm);
[B]FDA NDA 206323 from www.accessdata.fda.gov/scripts/cder/daf/index.cfm;
[C]FDA NDA 016608 from www.accessdata.fda.gov/scripts/cder/daf/index.cfm.

Epilepsy drug – > Steven Johnsons Syndrome

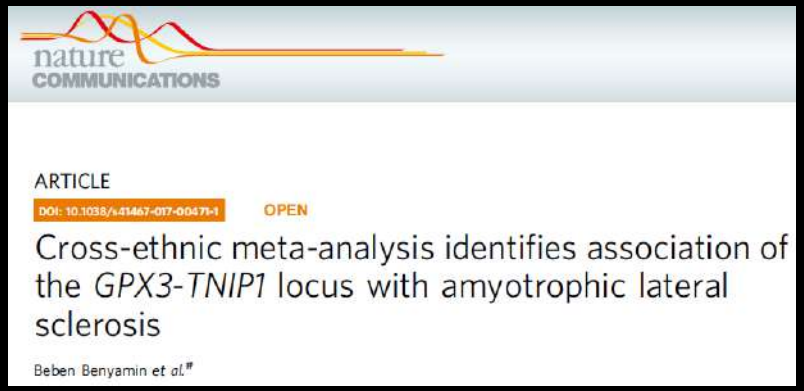
Table 1: Examples of drugs exhibiting ethnic differences in pharmacogenomic variants.

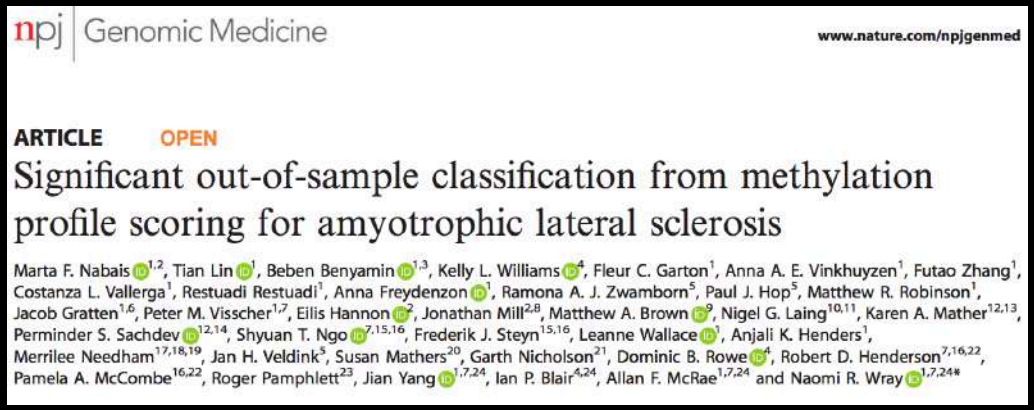
Lee et al., J Pharmacogenomics Pharmacoproteomics 2017, 8:1

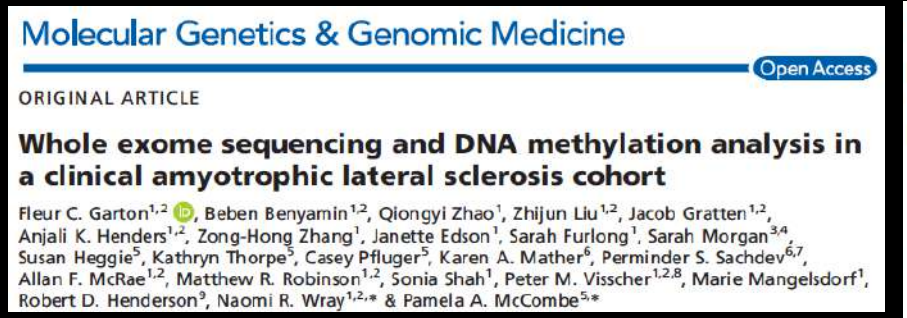
Answers: Genomic studies using Indonesian and Chinese samples

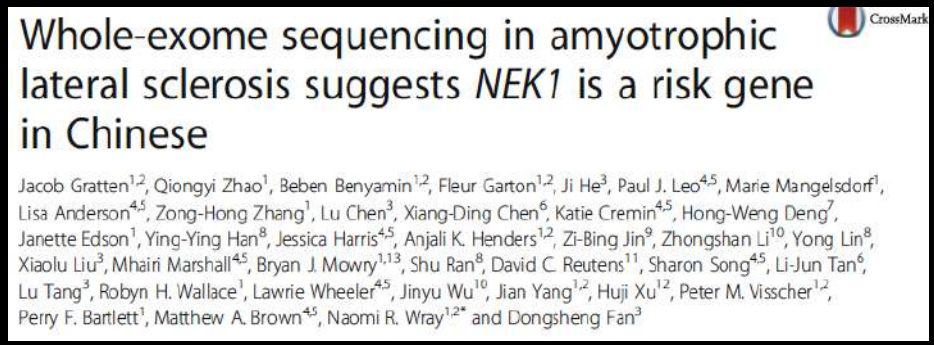
- Trans-ethnic genomic and epigenomic studies of motor neuron disease using samples from China (1,300 cases and 3,000 controls) combined with European samples (12,000 cases and 23,000 controls).

- We found genes affecting motor neuron diseases (*GPX3-TNIP1*)









Answers: Genomic studies using Indonesian and Chinese samples

- 23K cases and 35K controls from East Asian populations (including 2000 cases/controls from Indonesia) – 19 loci
- Genetic correlation between EAS and EUR (rG= 0.98±0.03)
- MHC locus, the strongest signal in EUR was not significant in EAS. This reflects the complexity of MHC region (linkage disequilibrium) and limited power in EAS (MHC MAF is lower in EAS)

Association of rs1344706 in the ZNF804A gene with schizophrenia in a case/control sample from Indonesia

Sibylle G. Schwab [a,*], Agung A.A. Kusumawardhani [b], Nan Dai [c,d], WenWen Qin [c,d], Mutiara D.B. Wildenauer [c,d], Feranindhya Agianandа [b], Nurmiati Amir [b], Ronald Antoni [b], Tiana Arsianti [b], Asmarahadi Asmarahadi [b], Hervita Diatri [b], Prianto Djatmiko [b], Irmansyah Irmansyah [b], Siti Khalimah [b], Irmia Kusumadewi [b], Profitasari Kusumaningrum [b], Petrin R. Lukman [b], Lukman Mustar [b], Martina W. Nasrun [b], Safyuni Naswati [b], Prasetiyawan Prasetiyawan [b], Gerald M. Semen [b], Kristiana Siste [b], Heriani Tobing [b], Natalia Widiasih [b], Tjhin Wiguna [b], Widayanti Dewi Wulandari [b], Indonesian Schizophrenia Genetics Consortium [1], Beben Benyamin [e], Dieter B. Wildenauer [c,d,f]

nature genetics

ARTICLES

https://doi.org/10.1038/s41588-019-0512-x

Comparative genetic architectures of schizophrenia in East Asian and European populations

Max Lam[1,2,3,4,5,6,72], Chia-Yen Chen[4,5,7,8,9,72], Zhiqiang Li[10,11], Alicia R. Martin[4,5,7], Julien Bryois[12], Xixian Ma[13], Helena Gaspar[14], Masashi Ikeda[15], Beben Benyamin[16,17,18], Brielin C. Brown[19,20], Ruize Liu[4,5], Wei Zhou[11,21], Lili Guan[22,23,24], Yoichiro Kamatani[25,26], Sung-Wan Kim[27], Michiaki Kubo[28], Agung A. A. Kusumawardhani[29], Chih-Min Liu[30,31], Hong Ma[22,23,24], Sathish Periyasamy[32,33], Atsushi Takahashi[26,34], Zhida Xu[35], Hao Yu[22,23,24], Feng Zhu[36,37,38], Schizophrenia Working Group of the Psychiatric Genomics Consortium[39], Indonesia Schizophrenia Consortium[39], Genetic REsearch on schizophreniA neTwork-China and the Netherlands (GREAT-CN)[39], Wei J. Chen[30,31,40], Stephen Faraone[41], Stephen J. Glatt[42], Lin He[11,43,44], Steven E. Hyman[5,45], Hai-Gwo Hwu[30,31,40], Steven A. McCarroll[5,46], Benjamin M. Neale[4,5,7], Pamela Sklar[47], Dieter B. Wildenauer[48], Xin Yu[22,23,24], Dai Zhang[22,23,24], Bryan J. Mowry[32,33], Jimmy Lee[49], Peter Holmans[50], Shuhua Xu[13,51,52,53], Patrick F. Sullivan[54], Stephan Ripke[4,5,55], Michael C. O'Donovan[50], Mark J. Daly[4,5,7,56], Shengying Qin[11,57,71], Pak Sham[58,59,71], Nakao Iwata[15,71], Kyung S. Hong[60,71], Sibylle G. Schwab[61,62,71], Weihua Yue[22,23,24,63,71*], Ming Tsuang[64,71*], Jianjun Liu[2,65,71*], Xiancang Ma[37,38,66,71*], René S. Kahn[67,68,69,71*], Yongyong Shi[1,10,11,70,71*] and Hailiang Huang[4,5,7,71*]

medRxiv

THE PREPRINT SERVER FOR HEALTH SCIENCES

CSH Cold Spring Harbor Laboratory BMJ Yale

HOME | ABO

Search

Comment on this paper

Mapping genomic loci prioritises genes and implicates synaptic biology in schizophrenia

Schizophrenia Working Group of the Psychiatric Genomics Consortium, Stephan Ripke, James TR Walters, Michael C O'Donovan

doi: https://doi.org/10.1101/2020.09.12.20192922

University of South Australia

University of South Australia

Challenges and opportunities

- The explosion of big data in genomics (and new omics data) combined with health records (biobanks).
  - How can we make sense this complexity?
  - How can we analyze this data efficiently?
  - How can we use this data in precision health?

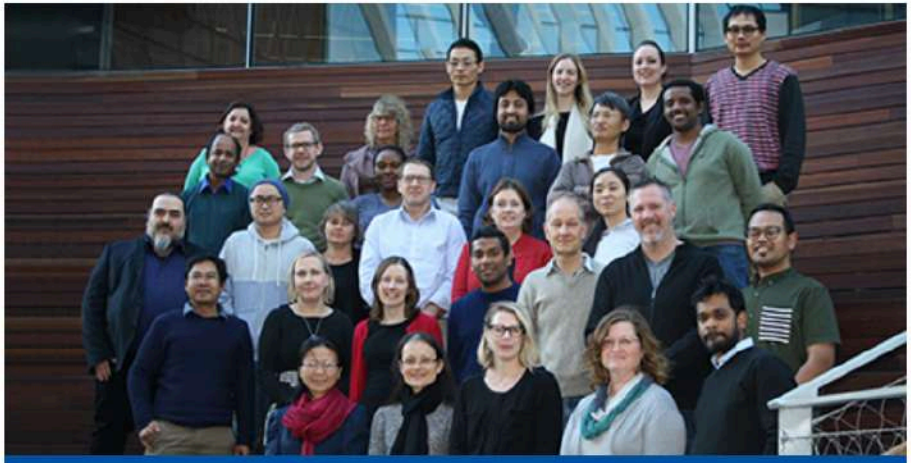
- A half of billion of people is South East Asians (half of them are Indonesians), but they are not well represented in this genomic revolution.
  - How can we intensify the collaboration with scientists from this region to participate in this genomic revolution?

University of South Australia

Australian Centre for Precision Health

About us

Australian Centre for Precision Health (ACPreH) is part of the University of South Australia Cancer Research Institute. We are based at the South Australian Health and Medical Research Institute, with a genotyping facility at University of South Australia City East campus. We are active researchers, with many of us also involved in teaching UniSA health sciences, medical science and pharmacy-based degrees.



Our people

Mission

University of South Australia

Australian Centre for Precision Health

https://www.unisa.edu.au/research/cri/our-research/australian-centre-for-precision-health/

Population Health

Epidemiological analyses, including cancer, nutritional, genetic, lifecourse, spatial and social epidemiology.

Predicting risk and identifying determinant's of disease and strategies for prevention

Medical statistics, longitudinal modelling

Data linkage, big data

Genomics

Genetic and phenotypic risk prediction modelling

Gene-environment interaction

Establishing causality, and predicting the totality of risk (phenomewide analyses, Mendelian randomization)

Large scale genomics analyses, including gene discovery

Translation

Informing appropriateness of care and patient safety

Cancer screening; developing cancer monitoring systems

Increasing survival, preventing disease and improving care.

Informing cost effectiveness and social policy

Developing E-health (iHealth) applications

Benefit to population: accurate and evidence based disease prediction, prevention and care

Prevention with precision: identifying and overcoming individual vulnerabilities

Data to health: using advanced statistical methods to turn big data to knowledge

Collaboration for impact: Listening to people, contributing to policy and global research consortia

University of South Australia

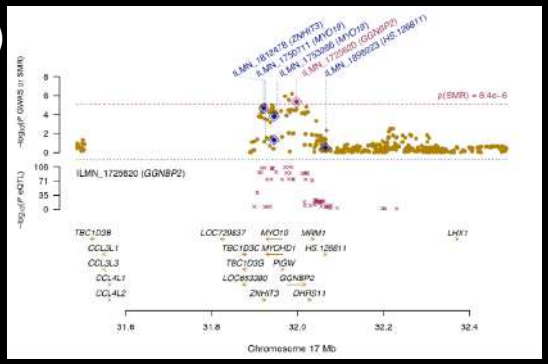
Research Opportunities (Masters, PhD, Collaboration)

Dr Beben Benyamin

Australian Centre for Precision Health, University of South Australia

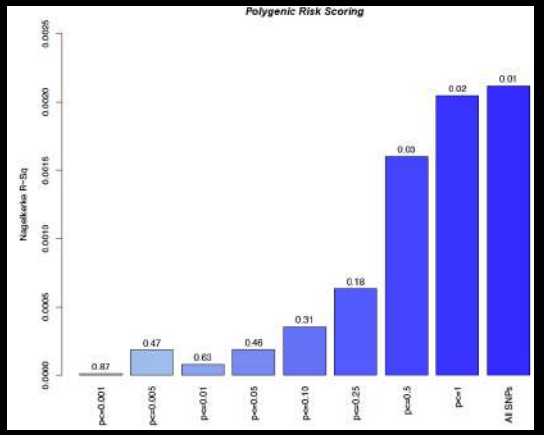
(http://u.unisa.edu.au/research/cri/our-research/australian-centre-for-precision-health/)

- **Background:**
  - We differ in a range of characteristics/traits and our susceptibility to disease also varies.
  - These differences are caused by genetic and environmental factors (and their interactions)
  - Understanding these factors are important and useful in psychology, medicine and other fields



- **Broad aims:**
  - To understand the genetic and environmental causes underpinning individual difference neuropsychiatric traits/diseases
  - To identify underlying genetic variation affecting neuropsychiatric traits/diseases
  - To use these genomic and other omics information in precision medicine (e.g. disease prediction, tailored treatment, drug development)

- **Approaches:**
  - Using advanced computing and statistical methods applied to genomics and other omics (e.g. epigenomics, transcriptomics) combined with phenotypic and clinical data
  - Data obtained through collaborations with other researchers and clinicians as well as sourced from publicly available resources, such as UK Biobank (500,000 individuals)



- **Available projects:**
  - Integrative genomic and epigenomic analyses to dissect neurodegenerative diseases, such as motor neuron disease
  - Trans-ethnic genomic analysis for neuropsychiatric diseases, such as schizophrenia in European and Asian populations
  - Inferring the causal effects of risk factors, such as sleep or exercise on disease

Acknowledgment

University of South Australia:
Prof Elina Hypponen
Dr Ang Zhou

QIMR Berghofer:
Prof Nick Martin
Dr John Whitfield

University of Wollongong:
A/Prof Sibylle Schwab

University of Queensland:
Prof Peter Visscher
Prof Naomi Wray
Dr Fleur Garton

Peking University:
Prof Dongsheng Fan
Dr Ji He

University of Indonesia/RSCM:
Dr AAA Agung Kusumawardhani

University of Western Australia:
Prof Dieter Wildenauer

Harvard University:
Dr Hailiang Huang

Terima Kasih!

- If you are interested to do Masters/PhD study or research collaboration, please contact me at: beben.benyamin@unisa.edu.au

University of South Australia