QUT Health

How Genetics can provide more effective responses to addictive behaviour

APSAD Conference
10 November 2015

Professor Ross Young
Executive Dean, QUT Health

QUT Health

Overview

1. Potential biological influences on social learning and substance use, with a focus on DRD2.
2. Environmental and genetic effects influence substance misuse, comorbidity and response to treatment, with a focus on PTSD.
3. The promise of epigenetic mechanisms of mental illness uniting biological and social psychological risk in addictive behaviour.

QUT Health

- Genetics and understanding of the underlying mechanisms of addiction

QUT Health

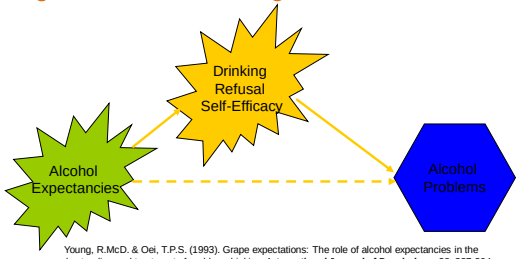
Public views on the development of addiction – family members (Meurk et al, 2015)

Table 3. *Beliefs about how addiction developed*

My family member developed an addiction because of:	Agree/strongly agree (%)	Neither agree nor disagree (%)	Disagree/strongly disagree (%)	Not relevant family member (%)
The enjoyment they got out of taking drugs	82	11	7	0
Their problems coping with stress	82	9	2	7
Poor self-esteem	78	13	9	0
Their personality	73	22	4	2
The easy access they had to drugs	67	16	13	4
Their genetic makeup	64	20	7	9
Chemistry in their brain	58	29	7	5
The fact they were a risk taker	55	27	13	5
Peer pressure to use drugs	47	22	24	7
Not fitting into 'normal' society	45	20	25	9
Mental illness	40	29	13	18
Relationship problems	38	20	25	16
Childhood bullying	25	15	35	25
Marriage breakdown and/or re-partnering of parents	20	16	20	44
Learning difficulties	20	5	38	36
A traumatic life event, not otherwise specified	20	35	18	27
Childhood sexual abuse	13	11	16	60
Dependency on medications prescribed for pain	12	4	24	61

QUT Health

Cognitive-social learning model of addiction



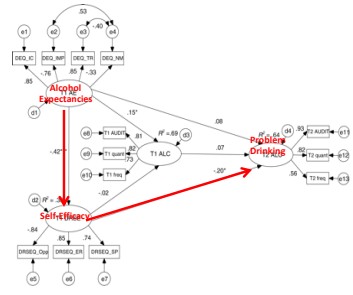
Young, R.McD. & Oei, T.P.S. (1993). Grape expectations: The role of alcohol expectancies in the understanding and treatment of problem drinking. ***International Journal of Psychology***, 28, 337-364.

REPLICATED IN CANNABIS

Connor, J.P., Gullo, M.J., Feeney, G.F.X., Kavanagh, D.J., Young, R.McD. (2014). The relationship between cannabis expectancies and cannabis refusal self-efficacy in a treatment population. ***Addiction*. 109, 111-119**

QUT Health

Expectancies predict the establishment of drinking behaviour over time



- **Prospective**
- **Young Adolescents (13-14 years old)**
- **n= 192**

Connor, J.P., George, S.M., Gullo, M., Kelly, A.B, Young (2011). A prospective study of alcohol expectancies and self-efficacy as predictors of young adolescent alcohol misuse. *Alcohol and Alcoholism*, 46, 161-169.

QUT Health

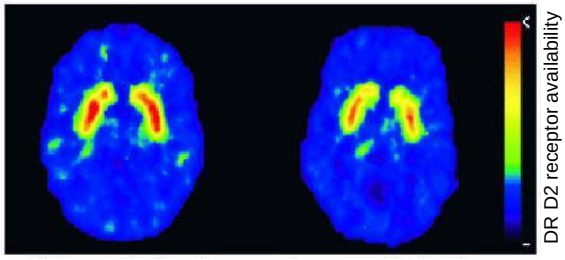
Important considerations for genetic research and mental health

- Replication
- Avoid biological reductionism
- Look beyond associations with diagnosis - symptoms and functional outcomes
- Complexity of multiple genes and their expression
- Environmental influences and their measurement
- Longitudinal studies
- Consider ethical issues including stigma, complexity and discrimination from the start.

QUT Health

By Larry Young, Emory University

QUT Health



High receptor level unpleasant

Low receptor level pleasant

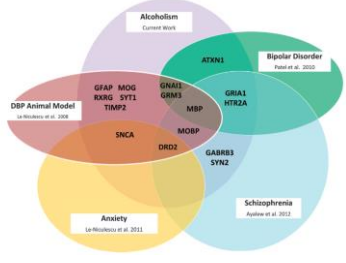
QUT Health

Convergent Functional Genomics (Levey et al; 2014)

- Gene level integration of GWAS, genetic, gene expression data, animal and human studies. Pathway analyses.
- Panel (n=135 genes, 713 SNP's) genetic risk prediction for alcohol dependence. Three independent cohorts (N= 3079 dependence cases, N= 500 alcohol abuse, N= 3329 controls).
- Top candidate genes (n=11):
  - SNCA synuclein alpha
  - GFAP, glial fibrillary acidic protein
  - DRD2
  - GRM3 glutamate receptor, metabotropic 3
  - MBP, myelin basic protein
  - MOBP, myelin-associated oligodendrocyte basic protein

QUT Health

Top candidate genes show significant overlap with other disorders (Levey et, al 2014).



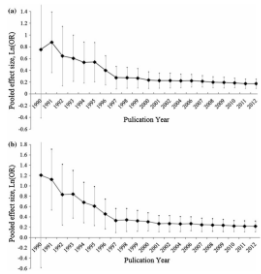
QUT Health

Taq 1A DRD2/ANKK1 "controversy"

- DRD2 Long arm chromosome 11 (G protein coupled receptor).
- Taq 1A located in exon 8 of adjacent ANKK 1 gene (signal transduction), modify DRD2 gene expression ?
- Initially considered in terms of "reward" (Blum et al; 1996), broadened to motivational states, working memory, mood, executive function (Volkow, et al; 2011).
- Stronger evidence for a primary role of dopamine in stimulant and alcohol dependence than opiate, nicotine or cannabis dependence (Nutt et al., 2015).
- Initial meta analyses positive (Young et al, 2004), past possible publication bias considered (Munafo, Matheson & Flint; 2007), recently refuted in meta-analysis N=18,000; N=61 case control studies (Wang et al; 2013).

QUT Health

Lack of DRD2/ANKK1 publication bias (Wang et al;2013)



QUT Health

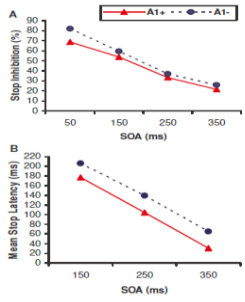
Broad risk related to DRD2/ANKK1 status (White, Young et al; 2009)

- N=72 Healthy adults (TAFE)
- Acute psychosocial stress (speech preparation) vs relaxation

- Reinforcer cued approach impulsivity (Card Arranging Responsiveness Objective Test)
- Delayed discounting (Two Choice Impulsivity Paradigm)
- Response Inhibition (Go-Stop)

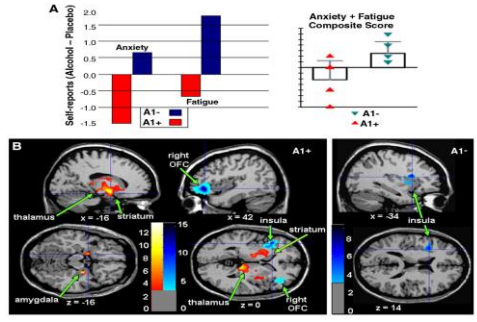
QUT Health

A1+ status Go-Stop: "rash impulsive" endophenotype (White, Young, et al ;2009)



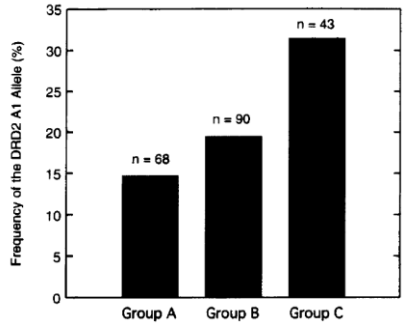
QUT Health

Ethanol decreased anxiety and fatigue in A1+ individuals & increased in A1- (London et al; 2009)



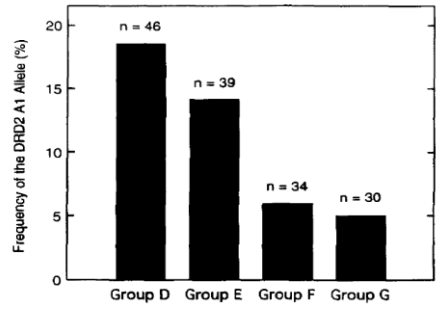
QUT Health

DRD2/ANNK1 A1 + status and severity/FH+ in alcohol dependence (Lawford, Young et al, 1997)



QUT Health

Similar effects evident in stratified controls (Lawford et al, 1997).



QUT Health

ANKK1/DRD2 A1+ status is associated with heavier consumption

Measure	A_1+ Allele		A_1- Allele		Effect Size
N= 84 alcohol dependent	Mean	SD	Mean	SD	P
Cigarettes per day	36.20	16.79	27.48	14.27	.014
Nicotine content (mg)	1.36	.41	1.17	.47	.063
Fagerstrom	7.07	2.61	6.24	2.83	.191
Drinking Frequency	6.20	1.58	6.06	1.37	.662
Drinking Quantity (St. Drinks)	21.70	10.56	16.69	8.40	.019
Alcohol Dependence Scale (ADS)	33.76	9.34	29.94	8.89	.067
Nicotine dose per week (mg)	364.09	202.81	235.11	167.56	.002
Ethanol dose per week (g)	1365.67	768.14	1031.29	587.17	.028

Connor,J.P., Young, R.McD., Lawford, B.R., Saunders, J.B., Ritchie, T.L., & Noble, E.P. (2007). Heavy nicotine and alcohol dependence is associated with D2 dopamine receptor (DRD2) polymorphism *Addictive Behaviors, 132 310-319*

QUT Health

DRD2/ANNK1 A1+ status is associated with social pressure refusal self-efficacy (Young, Lawford et al; 2004)

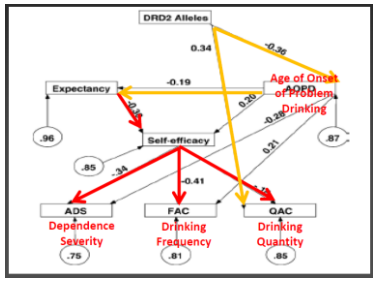
Table 2
Analysis of variance of drinking expectancy profile (alcohol expectancy and drinking refusal self-efficacy) factors grouped according to TaqI A DRD2 allelic status

	A1+ Allele	A1− Allele	*P*
Alcohol expectancy			
Affective change[a]	29.0 ± 10.3 (24)	33.9 ± 20.2 (28)	
1/Affective change	0.039 ± 0.015	0.036 ± 0.016	0.572
Tension reduction[a]	13.5 ± 3.0 (24)	19.5 ± 22.7 (28)	
1/Tension reduction	0.079 ± 0.020	0.075 ± 0.030	0.628
Drinking refusal self-efficacy			
Social pressure	39.3 ± 14.6 (23)	52.3 ± 22.5 (28)	0.009
Negative affect	40.3 ± 19.2 (23)	48.9 ± 21.9 (28)	0.098
Opportunistic drinking	29.6 ± 10.7 (23)	35.9 ± 18.1 (28)	0.099

The A1+ allele consists of A1A1 and A1A2 genotypes; the A1 − allele consists of the A2A2 genotype. Values for allelic groups are presented as the mean ± standard deviation with number of samples (*n*) in parentheses.
[a] Affective change and tension reduction were significantly skewed and were normalized by 1/x transformation for statistical analysis.

QUT Health

DRD2/ANNK1, Expectancy and Self-Efficacy predict drinking problems



Alcohol Dependent Patients (n= 143)

QUT Health

DTNBP1: hippocampal function is associated with SZ, PTSD, opiate and nicotine dependence, not alcohol dependence (Voisey, Swagell, Hughes at al, 2010)

- Dsybindin DTNBP1
- Lower DTNBP1 associated with hippocampal loss in schizophrenia.
- C957T (rs 6277)
- DTNBP1 (rs 9370822)
- Opiate, nicotine, alcohol dependence, PTSD, controls

Controls	N=250	148 males	36.8 yrs
Opiate	N=120	70 males	28.7 yrs
PTSD	N=127	127 males	52.3 yrs
Alcohol	N=231	231 males	42.1 yrs
Nicotine	N=147	68 males	43.3 yrs

QUT Health

Table 2: Genotype association of *DTNBP1* SNP rs9370822

Sample Set	Genotype counts AA (%)	AC (%)	CC (%)	*p*-value[a]
control	113 (47.9)	101 (42.8)	22 (9.3)	
Schizophrenia[b]	58 (37.2)	66 (42.3)	32 (20.5)	0.004 0.002[†]
Odds ratio	1.00	1.27	2.83	
p-value		0.57	0.002	
PTSD	36 (30)	62 (51.7)	22 (18.3)	0.002 0.0004[†]
Odds ratio	1.00	1.93	3.14	
p-value		0.02	0.00	
Nicotine dependence	46 (33.8)	70 (51.5)	20 (14.7)	0.022 0.007[†]
Odds ratio	1.00	1.70	2.23	
p-value		0.04	0.05	
Opiate dependence	45 (39.8)	47 (41.6)	21 (18.6)	0.04 0.027[†]
Odds ratio	1.00	1.17	2.40	
p-value		1.00	0.03	
Alcohol dependence	92 (41.63)	103 (46.6)	26 (11.76)	0.36 0.16[†]
Odds ratio	1.00	1.25	1.45	
p-value		0.51	0.49	

[a] *p*-value determined by Pearson's χ^2 test
[†] *p*-value determined using the extended Mantel-Haenszel test for trend
[b] previously published data [24]

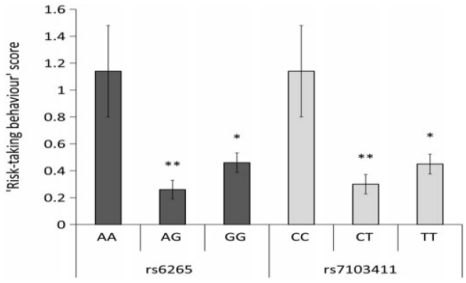
QUT Health

Brain Derived Neurotrophic Factor and dopamine (Cheah et al; 2014)

- Replication across two samples
- SZ Group 1 N=157, mean age = 36.2 years, battery included standard screening tools eg AUDIT.
- SZ Group 2 ASRB N=235, mean age = 43.9 years, Diagnostic Interview for Psychosis (DIP)
- AD Group N=231, mean age = 40.7 years
- Control Group N=125, mean age = 45 years (assessed with DIP)
- rs6265 (P=0.009) and rs7103411 (P=0.013) associated with male AD in schizophrenia but not AD alone.

QUT Health

Comorbid alcohol use and risk taking in Schizophrenia related to BDNF status (Cheah, et al; 2014)



QUT Health

Summary: Cautious conclusions re genetic risk and underlying mechanisms of addiction

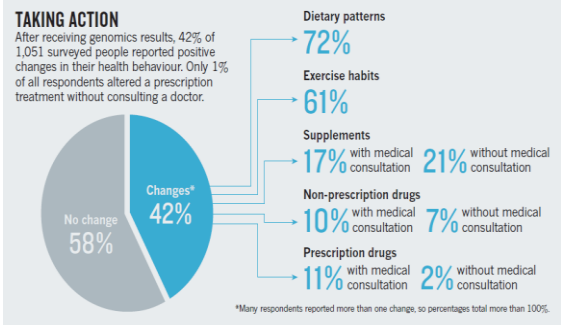
- Genetic risks are probabilistic and often viewed in the popular media as linear and causal.
- Traits related to addiction are influenced by multiple genes, including Taq 1A DRD2/ANKK1
- DRD2/ANKK1 re alcohol:
  - Underlying rash impulsiveness
  - Early onset
  - Acute Insula/striatal activation
  - Drinking refusal self-efficacy
- Move beyond individual associations –understanding comorbid risk will require development of gene "panels"

QUT Health

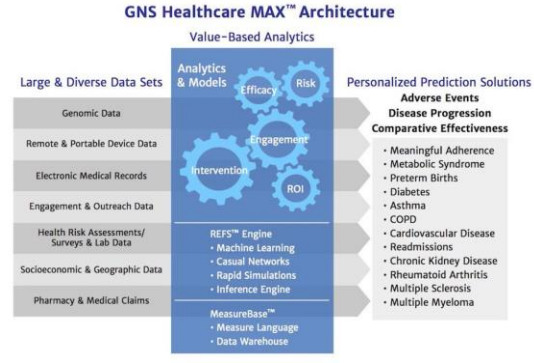
- Can genetic risk assist with the development of more effective and targeted treatments?

QUT Health

QUT Health

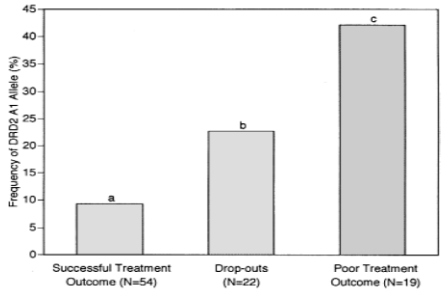


QUT Health



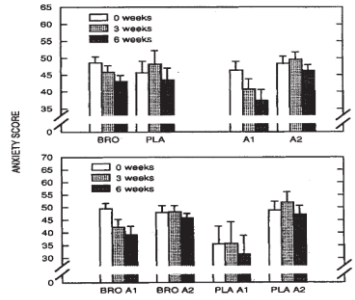
QUT Health

Methadone response poorer in those with DRD2/ANKK 1 A1+ status (Lawford et al; 2000)



QUT Health

Anxiety reduction followed a shorter time course associated A1+ status (Lawford, Young et al, 1995)



QUT Health

QUT Health

PTSD and comorbid alcohol misuse (Steindl, Young, Creamer & Crompton, 2003)

- Alcohol use as a coping strategy or a means of self medication for specific PTSD symptoms.
- No consensus re the order of treatment, some anxiety treatment experts recommending the alcohol treatment should come first.
- N=608 participants ACPMH treatment centres (N=607 males), average age = 51.4 years (SD=4.5). Average service = 7.8 years (SD=8.2 years). 9 month follow-up.

QUT Health

Reducing alcohol use was a key to PTSD symptom improvement

- Alcohol use at baseline was not predictive of outcome, continued problematic use of alcohol was.
- Those who became low risk drinkers over the 9 months showed less avoidance, numbing and arousal at follow up compared with unchanged hazardous drinkers. Arousal strongest effect across groups.
- Early improvement in drinking, produced greater changes in PTSD symptoms post program. Early PTSD change did not predict later changes in alcohol use.
- Understanding challenges to altering alcohol use, including genetic risk.

QUT Health

The body of genetic work in PTSD paints a similar picture to the addictions (Voisey, et al, 2014)

- N=68 Candidate gene association studies, N= 31 genes
- N= 6 Genome Wide Association Studies identifying 4 genes
- N=17 Epigenetic studies, N=48 genes + GWAS

	Pre - 2009	Post - 2009
Various	13	13
Combat	11	10
Natural disasters	4	3
Genocide	0	4
Other (eg urban)	2	8

QUT Health

Which genes show the most relevance to combat related PTSD and comorbidity?

ANKK1 (N=5)	rs 1800497	343 cases	699 controls
APOE (N=3)	rs 7412; rs 429358	221 cases	259 controls
SLC6A4	rs 25531	51 cases	31 controls
BDNF	rs 6265	370 cases	206 controls
COMT	rs 4680	51 cases	48 controls
PRKCA	rs 4790904	391 cases	570 controls
DBH	rs 1611115	133 cases	34 controls
DTNB1	rs 9370822	127 cases	250 controls
KPNA3	rs 2273816	121 cases	237 controls
NOS1AP	rs 386231	121 cases	237 controls
NPY	rs 16139	77 cases	202 controls
NR3C1	rs 6189; rs 6190 rs 56149945	118 cases	41 controls

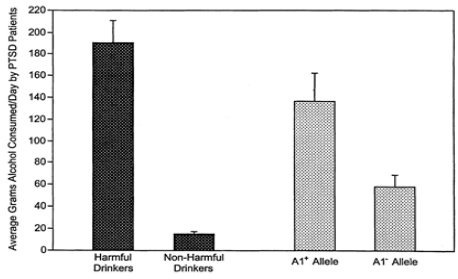
QUT Health

DRD2/ANKK1 status and comorbid alcohol use in PTSD (Young, Lawford, Noble et al, 2002)

- Increase in substance misuse parallels the increase in PTSD symptoms (Bremer et al, 1996).
- N= 91 male Vietnam Veterans with PTSD, mean age = 52 years.
- All reported exceeding 60 g alcohol per day off duty in Vietnam; 41.8% exceeded 60 g per day currently and 23.1 % were abstainers. 37.1 % were current smokers (non-harmful drinkers, mean 8.9 cigarettes per day; harmful drinkers, 16.9 cigarettes per day).

QUT Health

Average grams of alcohol consumed per day by post-traumatic stress disorder (PTSD) harmful and non-harmful drinkers and by PTSD patients with and without the DRD2 A1 allele.

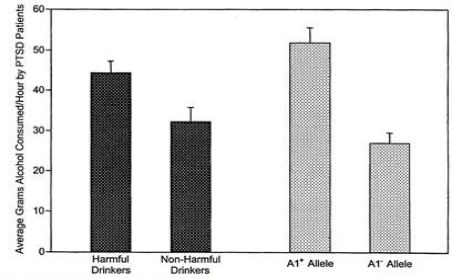


R. McD. Young et al. Alcohol and Alcoholism 2002;37:451-456

ALCOHOL AND ALCOHOLISM

QUT Health

Average grams of alcohol consumed per hour by post-traumatic stress disorder (PTSD) harmful and non-harmful drinkers and by PTSD patients with and without the DRD2 A1 allele.



R. McD. Young et al. Alcohol and Alcoholism 2002;37:451-456

ALCOHOL AND ALCOHOLISM

QUT Health

Taq 1A A1+ status show different SSRI treatment outcomes in PTSD (Lawford, Young, Noble et al, 2003)

- SSRI antidepressants, only 20-30 % of patients experience significant or full remission (Berger, et al, 2009)
- Paroxetine, 20 mg per day for 2 weeks, 40 mg day for 6 weeks. Main outcome measure GHQ-28.
- N= 63 Vietnam Veterans.
- N= 18 discontinued, trend for A1- patients to experience more adverse events (Chi-square = 3.21, p=0.064).
- N=45, mean age = 51.8 years.

QUT Health

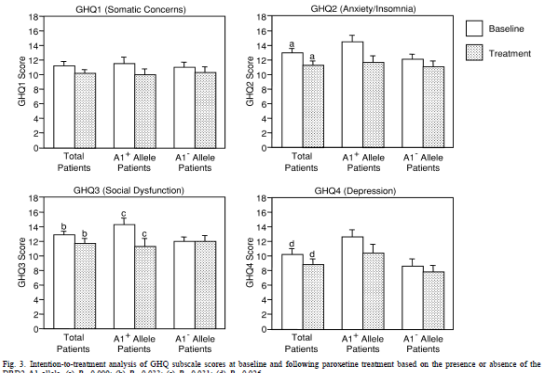


Fig. 3. Intention-to-treatment analysis of GHQ subscale scores at baseline and following paroxetine treatment based on the presence or absence of the DRD2 A1 allele. (a) $P = 0.009$; (b) $P = 0.033$; (c) $P = 0.031$; (d) $P = 0.026$.

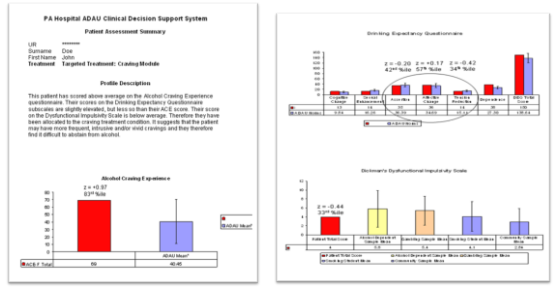
QUT Health

Princess Alexandra Hospital Current Trial UTN = U1111-1146-1931 (Connor, et al; 2015)

- RCT of targeted vs usual CBT
- Clinical Decision Support System (DSS) profiling
  - Craving
  - Impulsivity
  - Expectancy
- Combined pharmacotherapy (Naltrexone + Acamprosate)
- Genetic response by Psychological profiles and pharmacotherapy

QUT Health

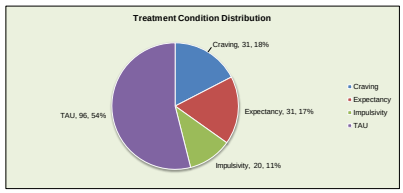
Targeted Treatment: Patient Profile Example



QUT Health

Targeted Treatment: Allocation Breakdown To Date

Currently enrolled in Targeted Alcohol Treatment Program
(n=178, 48 completed @ 12 weeks)



Opioid receptors
OPRM1,
OPRD1, OPRL1, OPRK1 (PDYN),
POMC and PNOC

GABA GABRG1,
GABRA2,
GABRA4 and GABRB1.

Dopamine DRD2, ANKK1, DRD4, DAT as well as COMT.

Serotonin HTR2A, HTR1B,
HTR3A and HTR3B

QUT Health

Summary: The treatment implications of genetic work to date are limited

- Technological advances now include “desk top” rapid and inexpensive genetic analysis (eg for P450 activity)
- There is little replicated evidence that pharmacogenetic approaches are “stand alone” treatments in addiction
- Pharmacogenetic approaches may assist in targeting specific medications but predicitive testing outcomes with any one gene are likely to be modest
- Integration of multiple genetic influences with treatment components is needed

QUT Health

Epigenetics will connect environment, social learning and mental illness

- Identical twins can have very different risk for disease.
- Epi means: upon, on, over, near, at, before and after.
- Epigenetics originally referred to “The interaction between genes and environment to bring the phenotype into being” (Waddington, 1940). Now it is considered to be the “extra layers of instructions that influence gene activity without altering the DNA sequence”.
- In a milestone identical twin study these epigenetic effects increased with age (Fraga et al, 2005).
- DNA methylation
- Histone modification

QUT Health

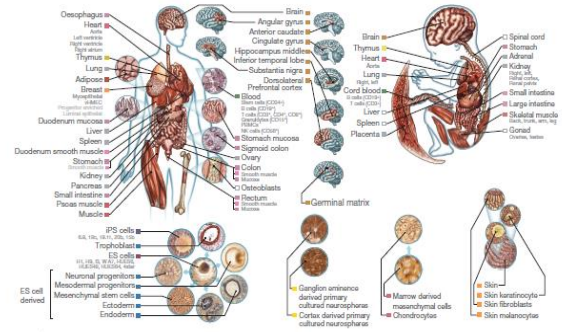


Figure 1 | Tissues and cell types profiled in the Roadmap Epigenomics Consortium. Primary tissues and cell types representative of all major lineages in the human body were profiled, including multiple brain, heart, muscle, gastrointestinal tract, adipose, skin and reproductive samples, as well as immune lineages, ES cells and iPS cells, and differentiated lineages derived from ES cells. Box colours match groups shown in Fig. 2b. Epigenome identifiers (EIDs, Fig. 2c) for each sample are shown in Extended Data Fig. 1.

QUT Health

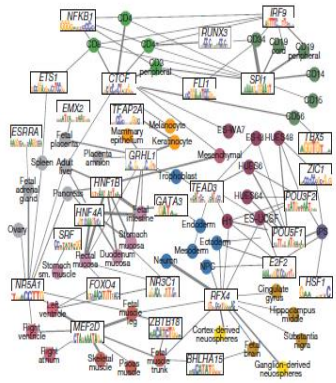


Figure 8 | Linking regulators to target tissues and cell types. Module-level regulatory motif enrichment (Supplementary Fig. 11) and correlation between regulator expression and module activity patterns (Extended Data Fig. 8a) are used to link regulators (boxes) to their likely target tissue and cell types (circles). Edge weight represents motif enrichment in the reference epigenomes of highest module activity.

QUT Health

Epigenetics as the link between childhood risk exposure and adult problems

- Susceptibility and disease.
- Dutch Armed Forces (van Zuiden et al, 2011, 2012). Low mRNA levels of GR inhibitor FK506 binding protein 5 (FKBP5) and high GC induced leucine zipper (GILZ) mRNA levels associated with PTSD symptoms
- 9/11 mRNA FKBP5 and GR inhibitor STAT5B reduced in PTSD patients (Mehta et al, 2011).
- FKBP5 DNA demethylation mediates the interaction between childhood trauma exposure and adult trauma reaction (Klengel et al, 2013)

QUT Health

Immune dysregulation may be the key to linking epigenetics and mental health

- Inflammatory markers are elevated in PTSD and depression (eg IL-6, IL-1β, IL-2),
- Hypermethylation of inflammatory initiator genes (eg IL-8) and demethylation of inflammatory regulator genes (eg FKBP5)
- Breen et al (2015), N = 188 US Marines. Blood pre and post deployment. RNA expression
- Weighted Gene Co-expression Network Analysis
- N= 10,184 genes used
- Dysregulated gene networks for innate immunity; hemostasis and wound healing

QUT Health

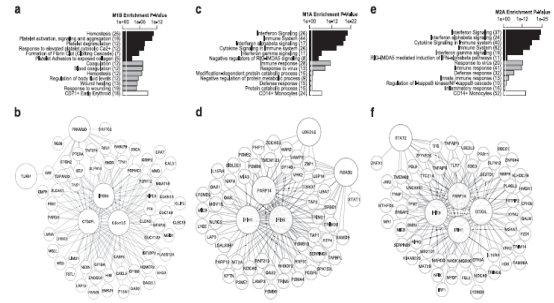


Figure 3. Module characterization for *Dataset 1*. Enrichment analysis and correlation networks for modules M1B (**a** & **b**) and M1A (**c** & **d**) identified post-deployment, and module M2A (**e** & **f**) identified pre-deployment in *Dataset 1*. Enrichment analysis was used to identify the top 6 REACTOME ontology terms (black bars), the top 6 DAVID ontology terms (grey bars) and the most significant cell-type signature (white bar) over-represented in the list of genes within each module. All terms were deemed significant as assessed by a hypergeometric test FDR corrected *P*-value < 0.05 displayed as a white line. The total number of genes within each significant term is denoted within the brackets associated with that term. Gene-networks were constructed selecting the top 150 most significant connections ranked by *kME*. Nodes represent genes and edges represent correlations. The top 5 hub genes, those most correlated to *ME* values, are shown in larger sizes.

QUT Health

Most of the epigenetic research in addictions has focussed on smoking (Anderson et al;2015)

Table 2. Genes with significantly associated CpGs for smoking in seven or more studies.

AHRR/cg05575921	15 studies
F2RL3/cg03636183	13 studies
2q37.1	10 studies
CNTNAP2	10 studies
GFI1	10 studies
MYO1G	9 studies
GPR15	9 studies
6p21.33	8 studies
GNG12	7 studies

QUT Health

Illumina PsychArray Chip

Overview

The Infinium PsychArray BeadChip is a cost-effective, high-density Illumina microarray, developed in collaboration with the Psychiatric Genomics Consortium[1] and several leading research institutions for large-scale genetic studies focused on psychiatric predisposition and risk. Content for the PsychArray includes 271,000 proven tag SNPs found on the HumanCore BeadChip, 277,000 markers from the HumanExome BeadChip, and ~50,000 markers associated with common psychiatric disorders. Additional SNPs include genetic variants associated with the research of common psychiatric conditions such as:

- Schizophrenia
- Bipolar disorder
- Autism-spectrum disorders
- Attention deficit hyperactivity disorder
- Major depressive disorder
- Obsessive compulsive disorder
- Anorexia nervosa
- Tourette's syndrome

QUT Health

The future: Study of epigenetic mechanisms of PTSD and influence on substance use and health

- N=300 Vietnam Veterans to date, N=150 with PTSD. Nearly all exposed to combat. Plans to recruit Iraq/Afghanistan Veterans from 2016. Current data cross sectional – follow up planned.
- Substance use and social, psychological and medical outcomes.
- Pathology, potential biomarkers (blood, saliva).
- Genetic analysis using the Illumina PsychArray Chip
- Cardiovascular, respiratory, sleep, cancer, GI, Endocrine, Immune, Sensory, Neurological and Dermatological data.
- Psychological symptoms and resilience
- Subset: Blood - epigenetic whole genome RNA transcriptome
- Subset: Semen - epigenetic inheritance via methylation can occur via changes in male germ cells

QUT Health

Addiction and physical health outcomes associated with PTSD may be epigenetic

- Influence of alcohol and smoking on multiple disorders
- Co-morbid psychiatric illness
- Cardiovascular disease, hypertension, hypercholesterolemia
- Diabetes, obesity, hyperthyroidism
- Sleep apnoea, periodic limb movement disorder, sleep paralysis
- Gastrointestinal reflux, IBS
- Bronchitis
- Autoimmune disorders eg psoriasis
- Cancer ?
- "Ill defined" disorders, "conversion", "somatisation", "Gulf War" syndrome.

QUT Health

Genome wide DNA methylation in the human brain in Schizophrenia (Wockner et al, 2014)

N=24 (average = 71.3 years) controls, N=24 (average = 51.6 years) diagnosed with schizophrenia

Post-mortem samples 0.4-1.0 grams frontal brain tissue.

Illumina Infinium Human Methylation 450 Gene Chip

485,000 GpG sites (and miRNA promoter sites)

Adjusted for age and PMI, 4641 probes differentially methylated from 2929 genes.

Cluster analysis of the top 3000 most variable probes

Could identify those with disease from controls: DTNBP1, COMT, DRD2* genes. May have crucial roles in utero.

QUT Health

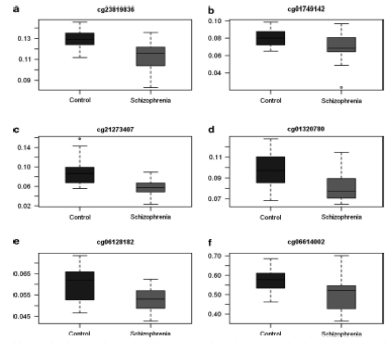


Figure 1. Box plots of β-values for the control and schizophrenia groups for probes associated with genes of interest. The median β-value is denoted by the solid middle line (a) 'cg27026005' is promoter associated (PA) and located on a CpG island, it is associated with *AKT1*. (b) 'cg01749142' is also PA and located on a shore, it is associated with *AKT1*. (c) 'cg21273407' is located on a CpG island, it is associated with *NOS1*. (d) 'cg23401624' is located on a CpG island and is PA, it is associated to *DNMT1*. (e) 'cg06128182' is located on a CpG island and is PA, it is associated to *DNMT1*. (f) 'cg06614002' is located on a shore and is associated with *SOX10*.

QUT Health

Summary: Epigenetic models are likely to lead to more effectively integrated models of addiction

- Genes can be influenced by internal and external environmental triggers causing methylation or histone modification.
- Epigenetic models embrace nature and nurture. Our learned behaviour and the environments we select are influenced by our genes and in turn can influence our genes.
- Environmental influences may precipitate genetic changes that alter intergenerational physical and mental health. This has the potential may unite disciplines in more complex models of addiction and develop a new "culture" of research and practice.
- Epigenetic effects do not imply biologically based interventions. Public health initiatives to increase safety in childhood, robust psychological skills, effective social support, a more adaptive and caring community may be the best epigenetic interventions at our disposal

QUT Health

Collaborators in addiction research

- **Genetics of addiction**
  - Professor Bruce Lawford (QUT/RBWH/GPH), Professor Ernest Noble (UCLA), Professor Phillip Morris (QUT), Dr Joanne Voisey (QUT)
- **Alcohol related cognitions**
  - Associate Professor Jason Connor (UQ), Associate Professor Adrian Kelly (UQ), Professor Tian Oei (UQ), Dr Penelope Hasking (Monash)
- **CBT and Pharmacotherapy**
  - Associate Professor Jason Connor (UQ), Associate Professor Gerald Feeney (PAH), Professor David Kavanagh (QUT)
- **Comorbidity**
  - Professor Bruce Lawford (QUT/RBWH/GPH), Professor David Kavanagh (UQ), Professor Sharon Dawe (Griffith), Associate Professor Leanne Hides (QUT)
- **Models of addiction (including behavioural addictions)**
  - Professor Bruce Lawford (QUT/RBWH/GPH), Associate Professor Jason Connor (UQ), Associate Professor Lina Ricciardelli (Deakin), Professor Barry Jones (University of Glasgow), Professor Katy White (QUT)

Previous and current postgraduate students in alcohol research

- Roseliza Abrahman
- Greg Currie
- Associate Professor Adrian Kelly
- Hilary Mack
- Steven Luxmoore
- Associate Professor Jason Connor
- Dr Ruth Bourma
- Dr Carey Walmsley
- Dr Stan Steindl

Dr Melanie White
Dr Claudia Aguero
Dr Kim Johnston
Dr Amy Mullens
Dr Mihn Tam Nguyen
Dr Fred Thorberg
Dr Louise Starfelt
Dr David Crompton
Sern-Yi Cheah
Wole Oloyede

QUT Health

We gratefully acknowledge the funders of our work

- ARC
- NH&MRC
- Commonwealth Department of Health
- QUT
- University of Queensland
- Griffith University
- CRC for Diagnostics
- ATN Universities Research Challenge
- Australian Brewers Foundation
- Cancer Council Queensland
- TPCH Foundation
- RBWH Foundation
- PAH Foundation
- Australian Rotary Research Fund
- Queensland Health
- Vic Health
- Pharmacia
- Janssen-Cilag
- Astra-Zeneca
- Roche
- RSL Queensland