Controversial Topics in Gambling: Alberta Gambling Research Institute's 13th Annual Conference

Aitchison, Katherine J.; Castellani, Brian; Chapman, Craig S.; Christensen, Darren R.; Crawford, Sandy; Currie, Cheryl; Downs, Carolyn; Euston, David; Forrest, David; Goodyear, Bradley G....

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conference proceedings

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“Genetics as a tool for research in Addictions”

Presentation to the Alberta Gambling Research Institute Conference
April 5, 2014

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http://www.psychiatry.med.ualberta.ca/AboutUs/FacultyMembers/AcademicStaff/Pages/default.aspx?P=225
http://www.mentalhealthresearch.ca/KeyInitiatives/Chairs/Pages/MentalIllnessandAddictionsResearchChair.aspx
• Alberta Addiction and Mental Health Research Partnership Program (AAMHRPP)

• Alberta Centennial Addiction and Mental Health Research Chairs (ACAMHRC) Program

• University of Alberta (UA)

• Alberta Health Services (AHS)

• Alberta Enterprise and Advanced Education (EAE)

• Research Administrative Assistants
Declaration of Interests (previous)

• Research grants:
  - Bristol-Myers Squibb and Otsuka Pharmaceuticals Limited;
    Johnson & Johnson Pharmaceutical Research and Development

• Research partnerships:
  - GlaxoSmithKline

• Invited member of Advisory Boards:
  - Johnson & Johnson, Lundbeck, Roche Diagnostics, and Bristol-
    Myers Squibb and Otsuka Pharmaceuticals Limited

• Consultancy fees:
  - Bristol-Myers Squibb, Lundbeck, Roche Molecular Systems,
    Roche Diagnostics, Johnson & Johnson Pharmaceutical
    Research and Development

• Consultancy fees and research support:
  - Roche Diagnostics and Roche Molecular Systems
The scale of the problem

- Mental health is Alberta’s largest economic health issue after heart disease
- Depression is the leading cause of disability worldwide in the 15-44y age group
- By 2030 the “global burden of disease” caused by mental illness (depression) will be >all physical disorders except heart disease
- Each yr, >600K Albertans visit a physician for mental health concerns
- The economic burden of addiction and mental health problems in Alberta has been said to be “staggering”

Creating Connections: Alberta’s Addiction and Mental Health Strategy, September 2011; Alberta Health Services and Government of Alberta
Alcohol use disorders

In both low- and middle-income countries, and high-income countries, alcohol use disorders are among the 10 leading causes of YLD.

The male burden for alcohol and drug use disorders is nearly seven times higher than that for females, and accounts for almost one third of the male neuropsychiatric burden.

This includes only the direct burden of alcohol dependence and problem use.

The total attributable burden of disability due to alcohol use is much larger.

Two twin studies of pathological gambling show consistent evidence for heritability (50%) (Slutske et al. 2010; Agrawal et al. 2012)

20% of the genetic risk for pathological gambling is accounted for by the genetic risk for alcohol addiction (Slutske et al. 2000; Lobo and Kennedy 2009)

The gene encoding the cannabinoid receptor 1 (CNR1) modulates addictive behavior across several substance abuse disorders (Benyamina et al. 2011)
Path diagram of the association between pathological gambling (PG) and alcohol dependence (AD) for a single individual. The variance in liability for PG and AD is decomposed into that caused by the effects of additive genetic influences (A), shared environmental (C) or nonadditive genetic (D) influences, and nonshared environmental influences, including measurement error (E). The correlation between PG and AD liability is similarly decomposed into that caused by additive genetic influences ($r_A$), shared environmental ($r_C$) or nonadditive genetic ($r_D$) influences, and nonshared environmental influences ($r_E$). Note that with data from monozygotic and dizygotic twins only, either C or D (but not both) can be estimated as a source of variation in liability for a trait within a given model.
Where are we going?

Next generation sequencing and genome-wide association studies (GWASs) have led to a sharp increase in publications on the genetics of addiction in the last decade (Helinski and Spanagel 2011).

## ADDICTION GWAS RESOURCE

### Results

<table>
<thead>
<tr>
<th>SNP Name</th>
<th>Phenotype</th>
<th>Chromosome</th>
<th>Position</th>
<th>Region</th>
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<th>Closest gene</th>
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What is pharmacogenetics?

Pharmacogenetics is: a type of personalised medicine in which genetic factors predicting clinical response and side effects including toxic reactions are identified, in order to improve clinical response to medications and reduce adverse effects thereof (Aitchison & Gill, 2002)

The provision of such relevant genetic information could save lives & lead to substantial cost savings in addictions and mental health, with enhancement of service delivery
Pharmacogenomics is the study of genomic contributors to a person’s response to drugs, toxins, dietary substances, etc.

- Using a whole genome approach (e.g. multiple markers across the genome)
- To develop effective, safe medications and better prescribing algorithms

NIH, Genetics Home Reference website.

Personalized Medicine

SNP profile A

SNP profile B

SNP profile C

SNP profile D

SNP profile E

SNP profile F
What can PGx help with...

• At present, about ⅓ of patients with depression do not receive effective treatment and >10% of all mental health patients are at risk of suffering serious toxic reactions to prescribed medications
  o Adverse drug reactions (ADRs) are a significant contribution to hospital admissions (*Pirmohammed et al, 2006*)
  o For approximately 50% of medications prescribed in not only psychiatry but in medicine as a whole, less than 50% will respond to them without having ADRs
• In Psychiatry, compliance is often problematic (50%) (*Bebbington et al, 1995*)
  o Initiation of treatment with correct dose of correct drug could significantly improve outcome
  o Failure to prescribe an effective medication can have drastic effects including suicide and homicide
For example...

In a recent study, when $HLA-B^*1502$ genotype was quantified in Asian patients who were potentially going to be prescribed carbamazepine, the frequency of a potentially lethal adverse drug reaction (*Stevens-Johnson syndrome and toxic epidermal necrolysis*) decreased to zero percent.

Pharmacogenomics for psychiatry
Cytochrome P450

• Found in a variety of organs including the brain, with varying abundance

• Different variants of a given isoform may be found in different tissues

• Developmental regulation of expression

• Site of gene x environment interaction
  - Drug-drug interactions
  - Effects of dietary constituents
  - Aging, disease

Miksys et al., 2002; Thompson et al., 1998; Aitchison et al., 2000
CYP2D6 substrates

- Over 50 commonly used medications
  - Antidepressants (TCAs, venlafaxine)
  - Antipsychotics (haloperidol, risperidone, etc.)
  - Beta-blockers, analgesics, etc.
  - Amphetamines

[www.medicine.iupui.edu/clinpharm/ddis](http://www.medicine.iupui.edu/clinpharm/ddis)
How relevant…

Find over 50 commonly used medications that interact with CYP2D6 at www.medicine.iupui.edu/clinpharm/ddis
CYP2D6

- 4 different phenotypes: UM, EM, IM, PM
- Varying frequency of phenotypes in different ethnic groups
  - UM: 29% in Ethiopians, 0.9-4% UK
  - IM: *10 in Orientals, *17 and *29 in Blacks
  - PM: 7% in Caucasians, 1% Orientals
- >70 alleles characterised
  - UM: gene amplification
  - See: www.cypalleles.ki.se
Outline

• Background

• Examples of application of PGx to addictions:
  - Ecstasy-induced toxicity
  - cannabis-induced psychosis

• Future directions
Outline

• Background

• Examples of application of PGx to addictions:
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• Future directions
Ecstasy-induced toxicity

- Definition of “ecstasy”
- The scale of the problem
- Physiological effects
- Pharmacogenetic risk factors
Ecstasy-induced toxicity

• Definition of “ecstasy”
• The scale of the problem
• Physiological effects
• Pharmacogenetic risk factors
What is “ecstasy”? 

• “Ecstasy” is a common “street” name for: 3,4-methylenedioxymethamphetamine (MDMA)

• A synthetic amphetamine analogue

• An entactogen and a stimulant
  - Entactogen: “en” (Greek: within), “tactus” (Latin: touch) and “gen” (Greek: produce)
    - Users report feelings of “love,” “empathy,” and “emotional closeness” to others
    - Madonna has apparently stated that her latest, controversial, album title (MDNA) is a triple entendre, including a reference to MDMA

  - Stimulant: owing to neurotransmitter release
Various “logos” for tablets containing MDMA

And “Molly,” etc.

No consistency of content (amount of MDMA, purity of substance)
Ecstasy-induced toxicity

• Definition of “ecstasy”
• The scale of the problem
• Physiological effects
• Pharmacogenetic risk factors
The scale of the problem

Every year there are several deaths of young people attributable to the consumption of substances marketed as “ecstasy” in the “rave scene” in Alberta, and a further number are admitted to hospital with significant resulting morbidity.

In January 2009, two First Nations men died in British Columbia following ingestion of “ecstasy.” This was followed by the “ecstasy”-induced deaths of two girls aged 14 and 15 at the Paul Band First Nation reserve in Alberta in March, 2009; two other young people attending the same social event required hospitalization. In April, 2009 a 14 year old girl also died following “ecstasy” ingestion at a dance party at a shopping mall in Edmonton, Alberta.

*Since Nov 2011, there have been 20 deaths for which MDMA was present on toxicological analysis (Graham Jones, Chief Toxicologist, personal communication).*

http://www.edmontonjournal.com/health/researcher+explores+chemicals+street+ecstasy/6320002/story.html
Morbidity and service burden – “A total of 27 patients were taken from a weekend-long electronic music festival at Northlands to Edmonton-area hospitals” (Alberta Health Services, The Edmonton Journal)
Factors influencing toxicity

- Experiments in rodents
  - Locomotor activity, hyperthermia
- Increased toxicity with
  - Overcrowding
  - Increased ambient temperature
  - Increased background noise
  - Poor murine hydration
- Toxic effects
  - Not dose related
  - Occur at ‘desired’ doses
  - Occur in those who previously tolerated MDMA
- Non-linear kinetics (de la Torre et al, 2000)
- Acute toxicity associated with elevated plasma concentrations (Greene et al, 2003)

Listening to loud music exacerbates the effects on the brain of taking ecstasy, researchers have found.

Italian scientists gave the drug to rats who were then exposed to music at nightclub noise levels. The researchers measured the electrical activity in the rats' brains and found that noise prolonged the effects of ecstasy by up to five days.

Experts said the study, published in the Biomed Central Neuroscience, showed music worsened users' "comedown".

This research suggests that exposure to loud music may worsen the comedown but it is unclear how this may contribute to longer term effects.

Martin Barnes, Drugscope

Story from BBC NEWS:
http://news.bbc.co.uk/go/pr/fr/-/1/hi/health/4716500.stm
Published: 2006/02/16 10:07:35 GMT
© BBC MMVI
Ecstasy-induced toxicity

- Definition of “ecstasy”
- The scale of the problem
- Physiological effects
- Pharmacogenetic risk factors
Physiological effects of “ecstasy”

• Release of oxytocin
  - Prosocial effect
     • Effect appears to be mediated by 5-HT1A receptors (Thompson et al, 2007)
     • Observed in a sample of regular “clubbers” (Wolff et al, 2006)

• Release of vasopressin (AVP)
  - Syndrome of inappropriate antidiuretic hormone (SIADH; Wolff et al, 2006)
     • Hyponatremia
     • Hypo-osmolality
     • Risk of cerebral oedema

• Release of neurotransmitters
  - Serotonin, dopamine, noradrenaline
     • Serotonin syndrome
     • Neuroleptic malignant-like syndrome
Physiological effects of “ecstasy”

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Vasopressin and oxytocin secretion in response to the consumption of ecstasy in a clubbing population

K Wolff, EM Tsapakis, AR Winstock, D Hartley, D Holt, ML Forsling and KJ Aitchison

J Psychopharmacol, 2006 May;20(3):400-10.
PubMed PMID: 16574714
Methods

• Responders to advert in ‘Mixmag,’ a UK magazine;
  • with Channel 4 News
• 48 ‘experienced’ clubbers (30 ♂)
• Predominantly Caucasian Londoners
• Mean age 24 (♀) and 26 (♂)
• No past medical or psychiatric history
• Written consent (and Research Ethics Committee approval)
• Pre- and post-clubbing:
  HR, sitting & standing BP; blood test [plasma Na, urea, cortisol, vasopressin, oxytocin, osmolality]; urine [osmolality, pH, urine drug screen]
Change in plasma oxytocin (n = 29) pre- and post-clubbing, grouped according to presence of MDMA in the post-clubbing urine sample.
Results: increase in AVP

Change in plasma vasopressin (n = 30) pre- and post-clubbing, grouped according to presence of MDMA in the post-clubbing urine sample.
Change in plasma sodium pre- and post-clubbing (n= 30), grouped according to presence of MDMA in the post-clubbing urine sample.
Change in plasma osmolality pre- and post-clubbing (n= 30), grouped according to presence of MDMA in the post-clubbing urine sample.
Which may lead to this...and other similar fatalities

(Cherney et al, 2002; Budisavljevic et al, 2003; Brvar et al, 2004; Wolff et al, 2006; Jones, personal communication, 2012)
Discussion

• Ingestion of MDMA was associated with the release of oxytocin in those attended a dance venue

• However, it was also associated with the induction of SIADH

• Clinical implications:
  - ‘Clubbers’ with early signs of hyponatraemia should in fact restrict their water intake
  - Those presenting to Emergency Medicine should have their plasma and urine osmolality assessed (data not shown), as well as plasma sodium

“As a public health intervention, encouraging the availability of commercially available oral rehydration salts containing sodium in clubbing venues should perhaps be considered. Such measures could be life-saving, and, conversely, inappropriate administration of water without knowledge of the water homeostatic state of the patient could be fatal.”
Physiological effects of “ecstasy”

• Release of oxytocin
  - Prosocial effect
    • Effect appears to be mediated by 5-HT1A receptors (Thompson et al, 2007)
    • Observed in a sample of regular “clubbers” (Wolff et al, 2006)

• Release of vasopressin (AVP)
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    • Hyponatremia
    • Hypo-osmolality
    • Risk of cerebral oedema

• Release of neurotransmitters
  - Serotonin, dopamine, noradrenaline
    • Serotonin syndrome
    • Neuroleptic malignant-like syndrome
MDMA & Serotonin Syndrome

• Releaser of serotonin, presynaptic $\alpha_2$-adrenoceptor antagonist

• Serotonin Syndrome:
  - Hyperthermia
  - Agitation/restlessness, tremor
  - Nausea, vomiting, diarrhea
  - Autonomic dysfunction: changes in blood pressure, tachycardia
  - Myoclonus, loss of coordination, overactive reflexes, hallucinations
  - Organ failure - death

• Hyperthermia is mediated by $\alpha_1$-adrenoceptors (cutaneous vasoconstriction) and central thermo-regulating centres involving dopamine and serotonin (Docherty & Green, 2010)
Rodent Behavioural Data

- ♀ Sprague-Dawley rats ~ human CYP2D6 EMs
- ♀ Dark Agouti rats ~ human CYP2D6 PMs
- ♀ Dark Agouti accumulated MDMA in brain and blood levels several fold higher than SDs treated with identical doses of MDMA (Chu et al, 1996)
- The hyperthermic response to MDMA as well as acute toxicity were enhanced in ♀ Dark Agouti rats (Colado et al, 1995)
- The PM phenotype may predispose to lethality by an as yet unknown mechanism (Malpass et al, 1999)
MDMA & Serotonin Syndrome
Ecstasy-induced toxicity

- Definition of “ecstasy”
- The scale of the problem
- Physiological effects
- Pharmacogenetic risk factors
Pharmacogenetic risk factors


Metabolism of 3,4-methylenedioxymethamphetamine

Drugs or xenobiotics may be
- Metabolised by CYP2D6 (substrates)
- Inhibitors of CYP2D6
  - MDMA is a potent inhibitor of CYP2D6 (Heydari et al, 2004)
  - Resulting in increased risk of drug-drug interactions/further toxicity

Distribution of CYP2D6 functionality shows inter-ethnic variability (Aitchison et al, 2000)
- Individuals with the IM variant show significantly reduced MDMA metabolism (Ramamoorthy et al, 2002)
  - The IM allele may be more readily inhibitable (Tandon et al, 2004)
Catechol-O-methyltransferase (COMT)

- Catalyzes the transfer of a methyl group
- One of the major degradative pathways for:
  - Catecholamine transmitters (DA, ADR, NA) and related drugs (e.g. L-DOPA)
- Level of COMT enzyme activity is variable
  - Trimodal distribution: low, intermediate, and high
  - Genetic polymorphism is associated with in a 3- to 4-fold difference in activity between the extremes of this distribution
- Associated with the Val158Met single nucleotide polymorphism (SNP), rs4680 in exon 4, a G>A substitution in amino acid codon 158, resulting in a valine to methionine substitution
  - Met/Met low activity, Val/Met intermediate, Val/Val high
Change in plasma sodium by CYP2D6

\( (p = 0.012) \)
Change in plasma osmolality by CYP2D6

(p = 0.009)

Mean ± 1 SE Plasma Osmolality Level (mosmol/kg)

Pre- or post-clubbing status

Ⅰ pre
Ⅰ post

CYP group for SIADH analysis
Change in plasma sodium by COMT ($p = 0.003$)

- **Mean ± 1 SE Plasma sodium**
  - Val/Met or Met/Met: 138 ± 1
  - Val/Val: 136 ± 1

- **Pre- or post-clubbing status**
  - Pre
  - Post

**COMT Val158Met polymorphism**
Change in plasma osmolality by COMT

\((p = 0.012)\)

Pre- or post-clubbing status

- \(\square\) pre
- \(\square\) post

Mean ± 1 SE Plasma osmolality

COMT Val158Met polymorphism

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<tr>
<th>COMT Polymorphism</th>
<th>Pre</th>
<th>Post</th>
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<td>Val/Met or Met/Met</td>
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<td>294</td>
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<tr>
<td>Val/Val</td>
<td>298</td>
<td>296</td>
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CYP2D6 and COMT genotype predicts ↑ risk of MDMA-induced SIADH in a UK sample
- To investigate this association in Alberta

Frequency of those at risk (in regular “clubbers” in the UK):
- 11/46 (23.9%) CYP2D6 EM/IM
- 8/48 (16.7%) COMT Val/Val, i.e. 83.3% had an at risk genotype

Public health implications:
- Should the pharmacogenetic associations be replicated, could offer pharmacogenetic testing to predict risk of toxicity: harm reduction
Change in plasma cortisol by MDMA status post-clubbing ($p < 0.001$)
Change in plasma cortisol by \textit{COMT} (two-tailed Bonferroni $p = 0.039$)
Change in plasma cortisol by CYP2D6 (two-tailed $p = 0.027$)
Change in plasma cortisol by CYP2D6 genotype group (two-tailed Bonferroni $p = 0.003$)
Change in cortisol: Discussion

- CYP2D6 and COMT genotype predicts risk of MDMA-induced hypercortisolemia in a UK sample

- No association found with the serotonin transporter (promoter polymorphism)
Summary and Conclusions

• “Ecstasy” is not a safe drug
  - Toxicity may occur in those who have previously tolerated the drug
  - Serotonin syndrome, neuroleptic-malignant like syndrome, SIADH, hypercortisolemia

• Constituents in addition to MDMA may exacerbate effects
  - e.g. Benzylpiperazine (BZP; Hudson et al, 2011)
  - Recent deaths in Alberta associated with PMMA

• Genetic risk factors
  - Common variants in metabolising enzymes place individuals at high risk of toxicity

• Knowledge transfer work conducted and further desirable
Outline

• Background

• Examples of application of PGx to addictions:
  - Ecstasy-induced toxicity
  - Cannabis-induced psychosis

• Future directions
Cannabis-induced psychosis

- Cannabis at <15 y = a risk factor for psychosis
  - However, not all who take cannabis will become psychotic
  - If we understood the vulnerability factors, then appropriate public health education measures could be taken

- Caspi et al (2005) reported an association between the COMT Val158Met SNP and cannabis-induced psychosis
  - COMT is involved in the metabolism of monoamines
    - Especially in the prefrontal cortex (dysfunctional in schizophrenia)

- However, not replicated by Zammit et al (2011)
  - Genotyped 6 SNPs in COMT, in a UK birth cohort (ALSPAC), employing questionnaire-based assessments for cannabis use at age 14y & psychotic experiences at age 16y
Percent with schizophreniform disorder at age 26

<table>
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<tr>
<th>COMT genotype</th>
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<th>Val/Val</th>
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<td>n</td>
<td>(151)</td>
<td>(311)</td>
<td>(148)</td>
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<td>(48)</td>
<td>(91)</td>
<td>(54)</td>
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Caspi et al., 2005, Biol Psychiatry
Reasons for Non-Replication

- Very few of interactions at the molecular-genetic level for candidate genes have been consistently replicated.
- Replication problems may be due to many factors, including:
  - Initial gene selection
  - Statistical power
  - Bias towards positive results
- Increased sample sizes, greater density of genetic markers and a stronger focus on true replication are necessary.
- However, another gene, which may relate to a common molecular mechanism with \textit{COMT}, shows promising data: \textit{AKT1}.

### AKT1

#### Table 2. Significant SNP × Cannabis Interactions (at P < .05) in 740 Unaffected Siblings

<table>
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<tr>
<th>SNP</th>
<th>Gene</th>
<th>Risk Variant</th>
<th>HWE P Value</th>
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<td>PRODH</td>
<td>A</td>
<td>.20</td>
<td>0.24</td>
<td>.0246</td>
</tr>
<tr>
<td>rs5746832</td>
<td>TBX1</td>
<td>G</td>
<td>.40</td>
<td>0.21</td>
<td>.0343</td>
</tr>
<tr>
<td>rs3037354</td>
<td>NPY</td>
<td>Deletion</td>
<td>.41</td>
<td>0.19</td>
<td>.0368</td>
</tr>
<tr>
<td>rs4606</td>
<td>RGS2</td>
<td>G</td>
<td>.23</td>
<td>0.25</td>
<td>.0340</td>
</tr>
</tbody>
</table>

Abbreviations: HWE, Hardy-Weinberg equilibrium; SNP, single-nucleotide polymorphism.

*a* The SNPs showing interaction at the Bonferroni-adjusted threshold ($P < .0003$).

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van Winkel (GROUP) 2011, Arch Gen Psych 68(2)
Table 3. Case-Only Follow-up of Significant SNPs in the At-Risk Paradigm

<table>
<thead>
<tr>
<th>SNP</th>
<th>Gene</th>
<th>Distribution, %</th>
<th>Effect Size, $\beta$</th>
<th>SE</th>
<th>$P$ Value</th>
<th>Risk Variant</th>
<th>Distribution, %</th>
<th>Effect Size, $\beta$</th>
<th>SE</th>
<th>$P$ Value</th>
<th>Risk Variant</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs1130233</td>
<td>AKT1</td>
<td>G/G: 54.9, A/G: 39.0, A/A: 6.1</td>
<td>0.37</td>
<td>0.17</td>
<td>.0003</td>
<td>A</td>
<td>G/G: 54.9, A/G: 39.0, A/A: 6.1</td>
<td>0.14</td>
<td>0.09</td>
<td>.097</td>
<td></td>
</tr>
<tr>
<td>rs2494732</td>
<td>AKT1</td>
<td>T/T: 32.5, C/T: 50.2, C/C: 17.3</td>
<td>0.42</td>
<td>0.22</td>
<td>.0001</td>
<td>C</td>
<td>T/T: 34.4, C/T: 46.6, C/C: 19.0</td>
<td>0.20</td>
<td>0.07</td>
<td>.007</td>
<td>C</td>
</tr>
<tr>
<td>rs673871</td>
<td>LHRTM1</td>
<td>A/A: 78.4, A/T: 20.0, T/T: 1.6</td>
<td>1.17</td>
<td>0.57</td>
<td>.0001</td>
<td>T</td>
<td>A/A: 78.1, A/T: 21.3, T/T: 0.6</td>
<td>-0.31</td>
<td>0.17</td>
<td>.084</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CIDI, Composite International Diagnostic Interview; G × E, gene × environment; SIS-R, Structured Interview for Schizotypy–Revised; SNP, single-nucleotide polymorphism.

*Outcome is CIDI lifetime use; both SNP (coded as 0, 1, or 2) and CIDI lifetime use (coded as 0, 1, 2, or 3) were analyzed as continuous variables, thus examining the hypothesis that increased risk allele loading was associated with increasing levels of lifetime use (i.e., examination of linear trend). One hundred twelve patients were excluded from the analysis because the most intensive period of use occurred after illness onset.

*Outcome is SIS-R positive schizotypy; SNPs (coded as 0, 1, or 2) were analyzed for linear trend in interaction with recent cannabis use (yes/no).

*Significant and directionally similar evidence for SNP × cannabis interaction in both the at-risk and the case-only G × E paradigm.
AKT1 (rs2494732)

- AKT1 (rs2494732) x cannabis interaction upheld in siblings of psychotic patients in case-only, case-sibling and case-control analyses (van Winkel et al, 2011)
- Individuals with C/C genotype twofold more likely to be diagnosed with a psychotic disorder when having used cannabis
- Daily users with C/C genotype demonstrated a sevenfold increase in odds of psychosis compared with T/T carriers (Di Forti et al, 2012)
- AKT1 also accounted for 2.2% of the variance in schizotypy in high risk/unaffected siblings (van Winkel et al, 2011)
- Possible mechanism of cannabinoid regulated AKT1/GSK-3 signaling downstream of the dopamine D₂ receptor
van Winkel (GROUP) 2011, Arch Gen Psych 68(2)

Figure. AKT1 rs2494732 x cannabis interaction in the at-risk and case-only paradigm. A, Mean positive schizotypy scores according to AKT1 rs2494732 genotype in 728 unaffected siblings with (n=55) and without (n=673) recent cannabis use. Genotyping was unsuccessful in 12 unaffected siblings. THC indicates tetrahydrocannabinol. B, Relative risks for weekly and daily lifetime cannabis use in the patients according to AKT1 rs2494732 genotype.
Figure 2. Odds ratio (OR) of psychosis for subjects with AKT1 rs 2494732 C/T or C/C genotype compared to T/T, according to their cannabis use.

Outline

• Background

• Examples of application of PGx to addictions:
  - Ecstasy-induced toxicity
  - Cannabis-induced psychosis

• Future directions
Future Directions

• Seek to further investigate/replicate findings in Alberta
  - Identify frequency of the at risk variants in Albertans
    • In an anonymised population basis
  - Investigate clinical associations
  - Neuroimaging and genetic studies: a powerful combination

• Inclusion of environmental factors in studies
  - Adverse Childhood Experiences
  - Recent Adverse Life Events
    • And how the above are mediated by epigenetics
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- Amanda Perreault
- Maggie Lalies

Neurochemical Research Unit
- Glen Baker
Thank you

Questions?
Aim: that Alberta should be a world leader in advancing leading-edge practice and innovation in order to improve the mental well-being of all Albertans
“uplifting the whole people”

— HENRY MARSHALL TORY, FOUNDING PRESIDENT, 1908