ASD & ADHD Pharmacogenetics: Current State of Evidence and Future Developments

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ASD and ADHD

A. Social communication and social interaction deficits

B. Restricted, repetitive patterns of behaviours, interests and activities

Comorbidities
- Depression
- Anxiety
- ADHD
- ID

ADHD
- Hyperactive / Impulsive
- Inattentive
- Combined
Importance of pharmacogenetic decision support tools for ASD & ADHD

Children with ASD and ADHD present difficulties for clinicians:

1. Heterogeneity of clinical presentation

2. Clinical presentation (communication, body language) can impede evaluation of treatment outcomes

3. Often treating comorbid symptoms (i.e. anxiety, depression, hyperactivity, aggression), not core ASD symptoms

4. We lack validated, objective measures of treatment response
Importance of pharmacogenetic decision support tools for ASD & ADHD

Trial and error approach to treatment burdens families:

1. Disruption to routines and home environment
2. Parents not sure whether the outcome is worth risks
3. Cost attending appointments and long wait times (difficult when needing to make changes to medication)

*How can we use genetic differences (e.g., SNPs) to identify an individual’s response to a drug, both in terms of therapeutic responses as well as adverse effects*
How do we select genes?

e.g. Dopamine Transporter Gene (DAT1) encodes the molecular target for Methylphenidate
Current treatment of ASD

1. Currently no approved treatments core symptoms of autism: social difficulties, repetitive behaviors.

2. Often treating comorbid symptoms (i.e. anxiety, depression, hyperactivity, aggression), not core ASD symptoms

3. 1 in 3 take some type of psychotropic medication. 1 in 10 take 3+ medications.
Pharmacogenetics of risperidone therapy in autism: association analysis of eight candidate genes with drug efficacy and adverse drug reactions

C T Correia, J P Almeida, P E Santos, A F Sequeira, C E Marques, T M Miguel, R L Abreu, G G Oliveira & A M Vicente

The Pharmacogenomics Journal 10, 418–430 (2010) | Download Citation

Impact of Pharmacogenetic Markers of CYP2D6 and DRD2 on Prolactin Response in Risperidone-Treated Thai Children and Adolescents With Autism Spectrum Disorders

Sukasem, Chonlaphat BPharm, PhD; Hongkaew, Yaowaluck MS; Ngamsamut, Nattawat MD; Puangpetch, Apichaya PhD; Vanwong, Natchaya MS; Chamnanphon, Montri MS; Chamkrachangpada, Bhunnada MS; Sinrachatanant, Ananya MD; Limsila, Penkhae MD, PhD

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Pharmacogenomics and efficacy of risperidone long-term treatment in Thai autistic children and adolescence

PGx studies in ASD: escitalopram

A pharmacogenetic study of escitalopram in autism spectrum disorders


Escitalopram pharmacogenetics: CYP2C19 relationships with dosing and clinical outcomes in Autism Spectrum Disorder

Jeffrey R. Bishop, Fedra Najjar, Leah H. Rubin, Stephen J. Guter, Thomas Owley, Matthew W. Mosconi, Suma Jacob, and Edwin H. Cook
Summary of PGx studies in ASD

1. **Very few** studies have examined the pharmacogenomic impact of medications in patients with ASD.

2. Very small sample sizes. Short trial durations.


Immense opportunity for research into PGx tools to improve medication and dose selection in patients with ASD.
Current treatment of ADHD

1. Stimulants remain first line psychopharmacological treatment: 70-80% respond to stimulant medications. Parents want to know if their child is part of the 20-30% who don’t respond.

2. Much longer history attempting to identify predictors of treatment response: e.g. attention span, baseline symptom severity, theta/beta EEG ratios, ERPs (P300, N2), candidate gene approach.

Dates back to the ‘70s but research has stalled.
Current treatment of ADHD

1. No consensus in Australia or internationally around what order of treatment to try, and dosage

2. “Start low, go slow”, but can lead to issues of non-compliance - initial dosing that is too small to have a worthwhile effect

3. Ceiling medication doses often have little to no grounding in medical or manufacturer literature
PGx studies in ADHD: stimulants

No evidence of association with DAT1 and MPH response

Kambeitz et al (2014) meta-analysis
Meta-analysis of 36 studies:
Several polymorphic variants significantly affected MPH treatment efficacy in children with ADHD:
- SLC6A2 (monoamine transporter): rs28386840 and rs5569
- COMT: rs4680
- ADRA2A: rs1800544

- Only 5 out of 36 studies reported tolerability data


- Alpha 2a receptor important for therapeutic effects of stimulants
**Need for better outcome measures**

1. **Adverse reactions**: aggression, weight gain/loss etc.
2. **Symptom improvement** *(responder vs non-responder; >25% symptom reduction; symptom normalisation)*
3. **Functional improvement** *(impairment, QoL etc)*
4. **Changes in neuropsychological function** *(e.g., RT variability)*
5. **Changes in physiological measures** *(EEG, fMRI, PET/SPECT)*
6. **Biochemical changes** *(Cytochrome P450 2D6 levels)*
Limitations & recommendations

1. Chronically low sample sizes

2. Need for prospective RCT designs

3. Need for dose titrations to clinical response

4. Use of neurocognitive biomarkers could enhance power

5. Larger collaborative studies needed
Overcoming clinical heterogeneity: Research Domain Criteria (RDoC) Approach

Research Domain Criteria (RDoC) Approach to autism & ADHD

PGx tools help to cut through some of the clinical heterogeneity of ASD & ADHD to help aid personalised treatment approaches.
RDoC and the future of PGx for neurodevelopmental disorders

1. Acknowledges the biological and genetic origins of neurodevelopmental disorders

2. A future for diagnostic criteria based on the causation of a disorder rather than symptoms alone

3. Optimizing drug selection and dosing based on genetic information, with objective measures to help inform treatment response

4. Improves diagnostic reliability, speed of diagnosis, and prediction of treatment outcomes
Questions?
Monash Autism/ADHD Genetics and Neurodevelopment (MAGNET) project
MAGNET project

EU-AIMS - Longitudinal European Autism Project (LEAP)

Monash Autism/ADHD Genetics and Neurodevelopment (MAGNET) Project