Pharmacogenetics (PGx) Predictors of Methylphenidate Efficacy in Childhood ADHD

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Abstract

Stimulant medication has long been effective in treating attention-deficit hyperactivity disorder (ADHD) and is currently the first line pharmacological treatment for children. Both methylphenidate and amphetamine modulate extracellular catecholamine levels through interaction with dopaminergic, adrenergic, and serotonergic system components; it is therefore likely that catecholaminergic molecular components influence the effects of ADHD treatment. Using meta-analysis, we sought to identify predictors of pharmacotherapy to further the clinical implementation of personalized medicine. We identified 36 studies (3,647 children) linking the effectiveness of methylphenidate treatment with DNA variants. Pooled-data revealed a statistically significant association between single nucleotide polymorphisms (SNPs) rs1800544 *ADRA2A* (odds ratio: 1.69; 95% confidence interval: 1.12-2.55), rs4680 *COMT* (odds ratio: 1.40; 95% confidence interval: 1.04-1.87), rs5569 *SLC6A2* (odds ratio: 1.73; 95% confidence interval: 1.26-2.37), and rs28386840 *SLC6A2* (odds ratio: 2.93; 95% confidence interval: 1.76-4.90), and, repeat variants VNTR 4 *DRD4* (odds ratio: 1.66; 95% confidence interval: 1.16-2.37) and VNTR 10 *SLC6A3* (odds ratio: 0.74; 95% confidence interval: 0.60-0.90), whereas the following variants were not statistically significant: rs1947274 *LPHN3* (odds ratio: 0.95; 95% confidence interval: 0.71-1.26), rs5661665 *LPHN3* (odds ratio: 1.07; 95% confidence interval: 0.84-1.37) and VNTR 7 *DRD4* (odds ratio: 0.68; 95% confidence interval: 0.47-1.00). Funnel plot asymmetry amongst *SLC6A3* studies was identified and attributed largely to small study effects. Egger's regression test and Duval and Tweedie's 'trim and fill' were used to examine and correct for publication bias. These findings have implications for advancing our therapeutic approach to childhood ADHD treatment.

Introduction

- There are currently five FDA-approved medications for the treatment of ADHD
  - Stimulants: methylphenidate (MPH) and amphetamine (AMP)
  - Non-stimulants: atomoxetine (ATX), extended-release guanfacine, and extended-release clonidine
- Stimulants are the first-line treatment option; response and tolerance varies[1]
- Some serious adverse reactions (tic disorder, QT prolongation, depression, psychosis, and mania), although rare, have been linked to the use of MPH[2-5]
- Non-serious adverse events (insomnia, loss of appetite) also occur[6]
- Currently there are no clinical guidelines to address these issues with a personalized medicine approach

Genetics of MPH response

- Several genetic markers have been associated with the inter-individual variable response to MPH
- Variants in the MPH-metabolizing carboxylesterase 1A1 gene (*CES1A1*) have been associated with reduced enzyme activity, thus influencing the plasma concentration of MPH before it reaches the brain[7-9]
- Many polymorphisms in monoaminergic pharmacodynamics genes have also been studied in order to detect their association with response efficacy to stimulant medication, but have yielded conflicting evidence[10]
- Currently there is no way to predict the response to MPH
- PGX testing has the potential to improve response likelihood, tolerability and adherence

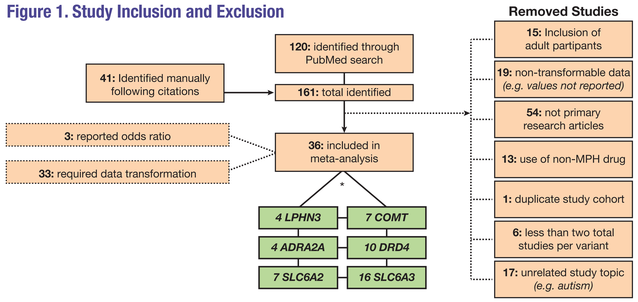
Objective

- To conduct a meta-analysis evaluating the aggregate body of pharmacodynamics literature in an effort to identify clinically significant predictors of MPH response in children

Methods

- A systematic review of NCBI PubMed database was conducted using a series of search terms
- 161 studies were identified, of which 36 met pre-defined criteria (**Figure 1**)

Figure 1. Study Inclusion and Exclusion



- Pre- and post-treatment outcome measures and/or effect sizes were analyzed to evaluate differential treatment response
- Effect sizes were converted to odds ratios[11]
- A fixed-effect model was applied in Review Manager (RevMan) to perform the meta-analysis
- Meta-regression was utilized to assess the relationship between covariates (age, sex, and study quality) and effect sizes

Results

Pooled results correlating MPH efficacy to SNPs

Figure 2A. SLC6A2 rs28386840

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI	Year
Kim 2010	0.9586	0.385	46.1%	2.61 [1.23, 5.55]	2010
Park 2012	0.6129	0.5351	23.9%	1.85 [0.65, 5.27]	2012
Hong 2012	1.6278	0.4777	30.0%	5.09 [2.00, 12.99]	2012
Total (95% CI)			**100.0%**	**2.93 [1.76, 4.90]**	

Heterogeneity: Chi² = 2.18, df = 2 (P = 0.34); I² = 8%
Test for overall effect: Z = 4.12 (P < 0.0001)

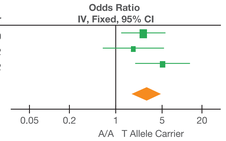


Figure 2B. SLC6A2 rs5569

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI	Year
Yang 2004	0.3033	0.5451	8.7%	1.35 [0.47, 3.94]	2004
McGough 2009	0.5412	0.4262	14.3%	1.72 [0.75, 3.96]	2009
Kim 2010	0.5666	0.3839	17.6%	1.76 [0.83, 3.74]	2010
Song 2011	1.0463	0.3966	16.5%	2.85 [1.31, 6.19]	2011
Lee 2011	-0.2231	0.4063	15.7%	0.80 [0.36, 1.77]	2011
Hong 2012	0.8199	0.3909	17.0%	2.27 [1.06, 4.88]	2012
Park 2012	0.6646	0.5098	10.0%	1.94 [0.72, 5.28]	2012
Total (95% CI)			**100.0%**	**1.73 [1.26, 2.37]**	

Heterogeneity: Chi² = 5.92, df = 6 (P = 0.43); I² = 0%
Test for overall effect: Z = 3.40 (P = 0.0007)

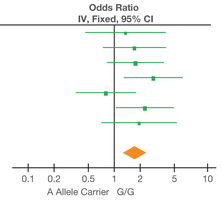


Figure 2C. ADRA2A rs1800544

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI	Year
Polanczyk 2007	0.7536	0.3673	33.0%	2.12 [1.03, 4.36]	2007
da Silva 2008	1.252	0.5184	16.6%	3.50 [1.27, 9.66]	2008
Froehlich 2011	-0.85	0.4233	24.8%	0.43 [0.19, 0.98]	2011
Kim 2013	1.088	0.4169	25.6%	2.97 [1.31, 6.72]	2013
Total (95% CI)			**100.0%**	**1.69 [1.12, 2.55]**	

Heterogeneity: Chi² = 14.73, df = 3 (P = 0.002); I² = 80%
Test for overall effect: Z = 2.48 (P = 0.01)

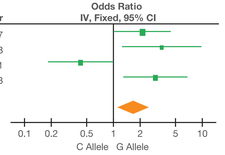


Figure 2D. COMT rs4680

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI	Year
Cheon 2008	0.644	0.3463	18.5%	1.90 [0.97, 3.75]	2008
Kereszturi 2008	1.187	0.3873	14.8%	3.28 [1.53, 7.00]	2008
McGough 2009	0.384	0.4413	11.4%	1.47 [0.62, 3.49]	2009
Salatino-Oliveira 2011	-0.9355	0.3748	15.8%	0.39 [0.19, 0.82]	2011
Froehlich 2011	0.9625	0.4327	11.8%	2.62 [1.12, 6.11]	2011
Yatsuga 2014	-0.018	0.5235	8.1%	0.98 [0.35, 2.74]	2014
Park 2014	0.163	0.3359	19.6%	1.18 [0.61, 2.27]	2014
Total (95% CI)			**100.0%**	**1.40 [1.04, 1.87]**	

Heterogeneity: Chi² = 19.96, df = 6 (P = 0.003); I² = 70%
Test for overall effect: Z = 2.25 (P = 0.02)

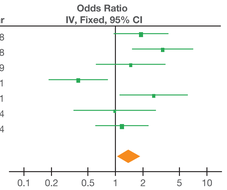


Figure 2E. LPHN3 rs6551665

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI	Year
Choudhry 2012	0.6638	0.3096	16.5%	1.94 [1.06, 3.56]	2012
Labbe 2012	-0.389	0.1808	48.5%	0.68 [0.48, 0.97]	2012
Song 2014	0.5062	0.3234	15.2%	1.66 [0.88, 3.13]	2014
Bruxel 2015	0.355	0.2827	19.8%	1.43 [0.82, 2.48]	2015
Total (95% CI)			**100.0%**	**1.07 [0.84, 1.37]**	

Heterogeneity: Chi² = 12.96, df = 3 (P = 0.005); I² = 77%
Test for overall effect: Z = 0.54 (P = 0.59)

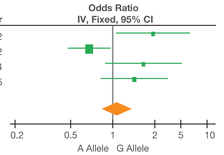
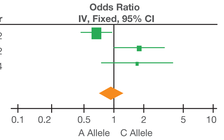


Figure 2F. LPHN3 rs1947274

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI	Year
Labbe 2012	-0.4057	0.1811	64.2%	0.67 [0.47, 0.95]	2012
Choudhry 2012	0.588	0.2964	23.9%	1.80 [1.01, 3.22]	2012
Song 2014	0.5379	0.4205	11.9%	1.71 [0.75, 3.90]	2014
Total (95% CI)			**100.0%**	**0.95 [0.71, 1.26]**	

Heterogeneity: Chi² = 10.44, df = 2 (P = 0.005); I² = 81%
Test for overall effect: Z = 0.38 (P = 0.70)



Conclusions

- Genetic variants in *SLC6A2* (rs28386840 and rs5569), *COMT* (rs4680), *ADRA2A* (rs1800544), *SLC6A3* (10-repeat VNTR), and *DRD4* (4-repeat VNTR) were shown to be potential candidates for predicting MPH efficacy in children with ADHD.
- Interventions accounting for individual variation addressed in this meta-analysis may improve outcomes of childhood ADHD treatment and should be considered in future clinical trials.

Pooled results correlating MPH efficacy to VNTRs

Figure 3A. DRD4 4-repeat VNTR

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI	Year
McGough 2006	0.3809	0.5267	11.9%	1.46 [0.52, 4.11]	2006
Cheon 2007	1.674	0.5418	11.3%	5.33 [1.84, 15.42]	2007
McGough 2009	0.4939	0.4223	18.5%	1.64 [0.72, 3.75]	2009
Froehlich 2011	0.916	0.4287	18.0%	2.50 [1.08, 5.79]	2011
Hong 2012	0.05799	0.3629	25.1%	1.06 [0.52, 2.16]	2012
Ji 2013	0.02098	0.4653	15.3%	1.02 [0.41, 2.54]	2013
Total (95% CI)			**100.0%**	**1.66 [1.16, 2.37]**	

Heterogeneity: Chi² = 8.23, df = 5 (P = 0.14); I² = 39%
Test for overall effect: Z = 2.79 (P = 0.005)

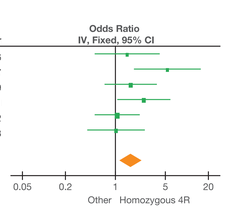


Figure 3B. DRD4 7-repeat VNTR

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI	Year
Seeger 2001	-0.3868	0.5366	13.0%	0.68 [0.24, 1.94]	2001
Hamarman 2004	-2.209	0.5919	10.7%	0.11 [0.03, 0.35]	2004
McGough 2006	-0.4534	0.5303	13.3%	0.64 [0.22, 1.80]	2006
Tharoor 2008	-0.03208	0.2902	44.4%	0.97 [0.55, 1.71]	2008
Kereszturi 2008	-0.1123	0.4467	18.7%	0.89 [0.37, 2.15]	2008
Total (95% CI)			**100.0%**	**0.68 [0.47, 1.00]**	

Heterogeneity: Chi² = 11.36, df = 4 (P = 0.02); I² = 65%
Test for overall effect: Z = 1.97 (P = 0.05)

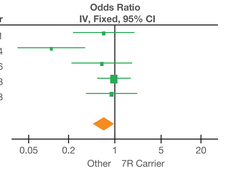
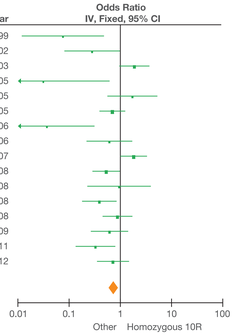


Figure 3C. SLC6A3 10-repeat VNTR

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI	Year
Winsberg 1999	-2.5802	0.935	1.3%	0.08 [0.01, 0.47]	1999
Roman 2002	-1.266	0.629	2.8%	0.28 [0.08, 0.97]	2002
Kirley 2003	0.6317	0.3374	9.7%	1.88 [0.97, 3.64]	2003
Cheon 2005	-3.459	1.511	0.5%	0.03 [0.00, 0.61]	2005
Stein 2005	0.5423	0.5654	3.4%	1.72 [0.57, 5.21]	2005
Langley 2005	-0.3577	0.2875	13.3%	0.70 [0.40, 1.23]	2005
Gilbert 2006	-3.3008	1.0845	0.9%	0.04 [0.00, 0.31]	2006
McGough 2006	-0.4897	0.5165	4.1%	0.61 [0.22, 1.69]	2006
Joober 2007	0.6	0.2975	12.5%	1.82 [1.02, 3.26]	2007
Tharoor 2008	-0.6366	0.3061	11.8%	0.53 [0.29, 0.96]	2008
Bellgrove 2008	-0.05572	0.72	2.1%	0.95 [0.23, 3.88]	2008
Purper-Ouakil 2008	-0.9416	0.3873	7.3%	0.39 [0.18, 0.83]	2008
Kereszturi 2008	-0.1251	0.3331	9.9%	0.88 [0.46, 1.70]	2008
McGough 2009	-0.4856	0.4195	6.3%	0.62 [0.27, 1.40]	2009
Froehlich 2011	-1.116	0.4474	5.5%	0.33 [0.14, 0.79]	2011
Hong 2012	-0.3277	0.3591	8.5%	0.72 [0.36, 1.46]	2012
Total (95% CI)			**100.0%**	**0.74 [0.60, 0.90]**	

Heterogeneity: Chi² = 47.37, df = 15 (P < 0.0001); I² = 68%
Test for overall effect: Z = 2.92 (P = 0.004)



References

1. Faraone SV, Biederman J, Spencer TJ, Aleardi M. Comparing the efficacy of medication for ADHD using meta-analysis. *Med Gen Med* 2006; 8: 4.
2. Efron D, Jarman F, Barker M. Side effects of methylphenidate and dexamphetamine in children with attention deficit hyperactivity disorder: a double-blind, crossover trial. *Pediatrics* 1997; 100: 662–666.
3. Aron AR, Dowson JH, Sahakian BJ, Robbins TW. Methylphenidate improves response inhibition in adults with attention-deficit/hyperactivity disorder. *Biol Psychiatry* 2003; 54: 1465–1468.
4. Pliszka SR. The use of psychostimulants in the pediatric patient. *Pediatr Clin North Am* 1998; 45:1085–1098.
5. Ari ME, Cetin Il, Ekici F, Kocabas A, Eminoglu S, Guney E et al. Assessment of cardiovascular risks due to methylphenidate in six months of treatment in children with Attention Deficit and Hyperactivity Disorder. *Bulletin of Clinical Psychopharmacology* 2014; 24: 248–252.
6. Storeba OJ, Ramstad E, Krogh HB, Nilausen TD, Skoog M, Holmskov M et al. *Methylphenidate for children and adolescents with attention deficit hyperactivity disorder (ADHD).* John Wiley & Sons, Ltd: Chichester, UK, 2015.
7. Hosokawa M, Endo T, Fujisawa M, Hara S, Iwata N, Sato Y et al. Interindividual variation in carboxylesterase levels in human liver microsomes. *Drug Metab Dispos* 1995; 23: 1022–1027.
8. Zhu H-J, Patrick KS, Yuan H-J, Wang J-S, Donovan JL, DeVane CL et al. Two CES1 gene mutations lead to dysfunctional carboxylesterase 1 activity in man: clinical significance and molecular basis. *Am J Hum Genet* 2008; 82: 1241–1248.
9. Walter Soria N, Belaus A, Galván C, Ana Pasquali M, Velez P, del Carmen Montes C et al. A simple allele-specific polymerase chain reaction method to ²detect the Gly143Glu polymorphism in the human carboxylesterase 1 gene: importance of genotyping for pharmacogenetic treatment. *Genet Test Mol Biomarkers* 2010; 14: 749–751.
10. Stein MA, McGough JJ. The pharmacogenomics era: promise for personalizing ADHD therapy. *Child Adolesc Psychiatr Clin N Am* 2008; 17: 475-xii.
11. Borenstein M, Hedges LV, Higgins JPT, and Rothstein HR. *Introduction to Meta-Analysis.* John Wiley & Sons, Ltd: Chichester, UK, 2009.

Presented at the 25th Annual World Congress of Psychiatric Genetics. October 13–17, 2017. Orlando, Florida, USA