

CES1 and SLC6A2 Genetic Variants As Predictors of Response To Methylphenidate in Autism Spectrum Disorders

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Purpose: Autistic spectrum disorders (ASD) children and adolescents usually present comorbidities, with 40–70% of them affected by attention deficit hyperactivity disorders (ADHD). The first option of pharmacological treatment for these patients is methylphenidate (MPH). ASD children present more side effects and poorer responses to MPH than ADHD children. The objective of our study is to identify genetic biomarkers of response to MPH in ASD children and adolescents to improve its efficacy and safety.

Patients and Methods: A retrospective study with a total of 140 ASD children and adolescents on MPH treatment was included. Fifteen polymorphisms within genes coding for the MPH target NET1 (*SLC6A2*) and for its primary metabolic pathway (*CES1*) were genotyped. Multivariate analyses including response phenotypes (efficacy, side-effects, presence of somnolence, irritability, mood alterations, aggressivity, shutdown, other side-effects) were performed for every polymorphism and haplotype.

Results: Single marker analyses considering gender, age, and dose as covariates showed association between *CES1* variants and MPH-induced side effects (rs2244613-G (p=0.04), rs2302722-C (p=0.02), rs2307235-A (p=0.03), and rs8192950-T alleles (p=0.03)), and marginal association between the *CES1* rs2302722-C allele and presence of somnolence (p=0.05) and the *SLC6A2* rs36029-G allele and shutdown (p=0.05). A *CES1* haplotype combination was associated with efficacy and side effects (p=0.02 and 0.03 respectively). *SLC6A2* haplotype combination was associated with somnolence (p=0.05).

Conclusion: *CES1* genetic variants may influence the clinical outcome of MPH treatment in ASD comorbid with ADHD children and adolescents.

Keywords: *CES1*, *SLC6A2*, autistic spectrum disorders, ASD, methylphenidate, attention deficit hyperactivity disorders, ADHD

Introduction

Autistic spectrum disorders (ASD) are neurodevelopmental disorders that affect social communication and are characterized by repetitive/restricted behaviors. The prevalence of ASD in the population is 1–2%,¹ with a boy/girl ratio of 3:1.² A combination of genetic, epigenetic and environmental mechanisms is thought to contribute to the development of ASD.^{2,3} There is no specific pharmacological treatment for ASD's nuclear symptoms, although about a third of patients receive psychotropic medications to treat comorbid conditions such as ADHD, aggression, irritability, hyperactivity and self-injurious behaviors, anxiety, or mood disorders.^{4,5} Attention deficit hyperactivity disorders (ADHD) are the most prevalent comorbidity, affecting between 40% and 70% of ASD patients.⁶ Methylphenidate (MPH) is the drug of choice to treat ADHD symptoms in ASD patients.⁷ However, almost half of patients experience a poor response to medication

and/or have adverse reactions or augmented comorbid symptoms.⁵ The efficacy of MPH is lower and the presence of side effects is greater in ASD children presenting ADHD than the presence of side effects observed in ADHD.⁸ Previous evidence has proven the influence of genetic variants on the efficacy and safety of pharmacological treatments.^{5,9,10} However, only a limited number of pharmacogenetic studies have been conducted on ASD patients. Further research on the genetic factors determining MPH response in ASD patients is required.

Methylphenidate increases extracellular concentrations of dopamine and norepinephrine into the presynaptic neuron by blocking their reuptake through inhibition of the dopamine (DAT1) and norepinephrine (NET1) transporters (www.pharmgkb.org MPH pathways). MPH also has weak effects at blocking the reuptake of serotonin at the serotonin transporter, although this is clinically not significant.¹¹ Previous studies have associated genetic variants in the genes coding for DAT1 (*SLC6A3*)^{12–14} and NET1 (*SLC6A2*) with clinical outcomes in ADHD patients.^{15–22} MPH main biotransformation is performed by carboxylesterase 1 (CES1)²³ (www.pharmgkb.org MPH pathways). Genetic variants in this enzyme have been associated with the response to treatment in ADHD patients.^{24,25} Several studies have reported that CES 1 variants may affect the metabolism and induce adverse events of MPH and other drugs metabolized by CES1,^{26–32} although these findings have not been universally replicated.³¹ However, there is a lack of evidence of NET1 and CES1 genetic variants' role in the response to MPH in ASD subjects. The main objective of our study is to investigate the influence of NET1 and CES1 genetic variants on the response to MPH in the ASD comorbid with ADHD population.

Methods

Study Samples

Retrospective study with inclusion criteria: Children and adolescents from 6 to 18 years old who meet the criteria for ASD and ADHD (according to DSM-5 criteria) treated with MPH for a minimum of 8 weeks were investigated and data extraction conducted from 8 to 12 weeks post treatment initiation. Exclusion criteria: patients younger than 6 years old and older than 18 years old, patients with ADHD without ASD. The assessment of treatment response was conducted using the Aberrant Behavior checklist (ABC-CV, Aman et al 1985), Autism Treatment Evaluation Checklist (ATEC) (Rimland & Edelson, 1999), Clinical Global Impression-Impression-efficacy index (CGI-E) to Autism and ADHD symptoms, Conners Rating Scale-Revised (CRS-R) for parents and teachers for the assessment of ADHD symptoms (Conners, 1997), Child Behaviour Checklist (CBCL) for parents and Teacher's Report Form (TRF) for teachers to assess general child psychopathology symptoms. The evaluation of response to pharmacological treatment was obtained retrospectively from the parents' CGI-E categorical scores (0=poor response, 1=some response, 2=good response, 3=very good response). Global side-effects were evaluated with a global score (0=no side effects, 1=mild side effects lasting less than two weeks, 3=moderate side effects lasting more than 2 weeks, 4=bad side effects with long-lasting side effects of duration more than a month or intolerable side effects resulting in suppression of medication). Specific symptomatology such as presence or absence of aggression, shutdowns, irritability, mood alterations, and somnolence were reported by parents through interviews. Informed consent was obtained from all participants or their legal care givers prior to the introduction to the study. The study was approved by the Ethics committee of the Hospital Universitari Mútua Terrassa (Acta 03/2018) and complies with the principles of the Declaration of Helsinki.

Genetic Characterization

Fifteen polymorphisms within genes coding for the MPH target NET1 (*SLC6A2*) and for its primary metabolic pathway (*CES1*) were genotyped (see [Table 1](#) for full list). Polymorphisms were selected based on previously reported associations with response to pharmacological treatment.^{15,17,18,20–22,27–33}

DNA was extracted from whole blood and saliva samples using a commercial kit (E.Z.N.A. SQ Blood and saliva DNA Kit II, Omega Bio-Tech, USA) and following manufacturers' instructions.

Polymorphisms were genotyped using iPLEX[®] Gold chemistry and the MassARRAY platform (UCIM-SCSIE_Central research unit of University of Valencia_Epigenetic and genotype department). The results of the genotyping of a *SLC6A3* 3UTR_VNTR variant from a previous study were included to analyze possible synergistic interactions between the three

Table 1 Genotype and Allele Frequencies of Investigated Polymorphisms in the Study Sample (N = 140)

| GENE | SNPs | Genotype Frequency | | | Allele Frequency | | | |
|------|----------------|--------------------|-----|-----|------------------|------|---|------|
| | | w/w | w/m | m/m | w | | m | |
| CESI | rs2244613_CESI | 61% | 34% | 5% | T | 0.78 | G | 0.22 |
| | rs2302722_CESI | 41% | 53% | 5% | A | 0.68 | C | 0.32 |
| | rs2307235_CESI | 62% | 35% | 3% | C | 0.79 | A | 0.21 |
| | rs2307240_CESI | 89% | 11% | 0% | C | 0.94 | T | 0.06 |
| | rs8192935_CESI | 44% | 42% | 14% | G | 0.65 | A | 0.35 |
| | rs8192950_CESI | 41% | 41% | 19% | G | 0.61 | T | 0.39 |
| | rs9921399_CESI | 57% | 37% | 6% | T | 0.75 | C | 0.25 |
| NETI | rs1861647_NET | 42% | 47% | 11% | G | 0.66 | A | 0.34 |
| | rs1992303_NET | 91% | 09% | 0% | G | 0.95 | A | 0.05 |
| | rs2242446_NET | 57% | 42% | 1% | T | 0.78 | C | 0.22 |
| | rs36021_NET | 26% | 54% | 20% | A | 0.53 | T | 0.47 |
| | rs36029_NET | 34% | 50% | 17% | A | 0.59 | G | 0.41 |
| | rs3785143_NET | 83% | 16% | 1% | C | 0.91 | T | 0.09 |
| | rs3785152_NET | 83% | 15% | 2% | C | 0.91 | T | 0.09 |
| | rs5569_NET | 42% | 40% | 18% | G | 0.62 | A | 0.38 |

Abbreviations: w, wild type; m, variant type.

genes.³⁴ This sample has ≥ 70 –85% statistical power to detect associations with ORs ≥ 3 with genetic variants with MAF=0.05–0.10, respectively (95% CI, two-sided, calculated with EpiInfo v. 7.2.5.0).

Statistical Analyses

Multivariate analyses including response phenotypes (efficacy, side-effects, presence of somnolence, irritability, mood alterations, aggressivity, shutdown, other side-effects) as the dependent variables and gender, age, and dose as covariables were performed for every polymorphism analyzed. Haplotype analyses were also conducted using the same model. Statistical analyses were performed using the statistical package PLINK (version 1.07.2) (Purcell et al, 2007) and SPSS Statistics (IBM, version 28.0).

Results

One hundred and forty children and adolescents (85,7% boys, average age=8,7 \pm 3,7 SD years old) met the inclusion criteria. Genotyping success rates were $>95\%$ for all polymorphisms and individuals (see Table 1). All polymorphisms were in Hardy-Weinberg equilibrium. Single marker analyses considering gender, age and dose as covariates showed association between the *CESI* rs2244613-G ($p=0.04$, $\beta=0.35$, 95% CI=0.02–0.69), rs2307235-A ($p=0.03$, $\beta=0.37$, 95% CI=0.04–0.70), and rs8192950-T ($p=0.03$, $\beta=0.29$, 95% CI=0.04–0.53) alleles and higher risk to suffer side effects. The *CESI* rs2302722-C allele ($p=0.02$, $\beta=-0.39$, 95% CI=-0.72–(-0.06)) was associated to lesser risk of side effects. Marginal associations were also observed between the *CESI* rs2302722 variant and presence of somnolence ($p=0.05$, OR=0.35 (0.12–1.02) for C allele) and the *SLC6A2* rs36029 variant, with the G allele showing lesser levels of shutdown ($p=0.05$, OR=0.21 (0.04–1.02)). Regarding haplotype analyses, a *CESI* haplotype combination was associated with efficacy ($p=0.02$), side effects ($p=0.03$), and aggressivity ($p=0.05$). A *SLC6A2* haplotype combination was associated with somnolence ($p=0.05$).

Analyses of *SLC6A3*, *SLC6A2* and *CES1* combined polymorphisms showed no association suggesting no synergistic interaction. Tables 2 and 3 summarize the results. It is important to note that none of the findings mentioned in this section remained statistically significant after Bonferroni corrections for multiple analyses.

Discussion

The present study aimed to find genetic predictors of response to MPH in ASD individuals. Several significant associations were observed that may contribute to individualize MPH treatment in ASD children and adolescents.

We investigated genetic variants in the enzyme *CES1*, the main metabolic pathway of MPH and their relation to treatment response in ASD patients. Four *CES1* variants (rs2244613, rs2307235, rs2302722 and rs8192950) showed significant associations with MPH-induced side-effects in our ASD cohort (Table 2). Previous studies of *CES1* variants reported conflicting results regarding treatment response.^{26,27,30,35,36} The *CES1* rs2244613, rs2307235, and rs2302722 variants were reported to be associated with MPH plasma concentrations in healthy volunteers.²⁶ The rs2244613-G, and the rs2307235-A alleles were associated with a decreased function of *CES1* and the rs2302722-C allele was associated with a better function of *CES1*. These observations are in concordance with our findings since a decreased function of *CES1* will lead to a higher risk of side-effects and the rs2302722-C allele was associated with a lower risk (Table 2). Johnson and collaborators found association between the *CES1* rs2244613-A allele and MPH-induced sadness in ADHD children.³⁰ However, we found that the A allele was associated with a lower risk of side-effects. Aside from a false positive finding, population differences may explain these contradictory observations. Replication in independent samples is required to confirm the validity and the direction of this association. The *CES1* rs8192850-G allele had previously been associated with a decreased risk of recurrent ischemic events in patients treated with clopidogrel.²⁷ In our study, the presence of the rs8192850-G allele was also associated with a decreased risk of side-effects (see Table 2). No significant associations were found with the other *CES1* variants investigated (rs9921399, rs2307240 and rs8192935). We were not able to replicate previous findings of association between these SNPs and other *CES1* substrates.^{29,31} *CES1* haplotype distribution analyses revealed significant associations with efficacy and side effects. However, these associations were of similar magnitude that the ones observed in the individual marker analyses suggesting no underlying interactions.

We also investigated genetic variants in *NET1*, a direct target of MPH, and their possible association with response in ASD patients. We observed a marginal association between a *SLC6A2* rs36029 and shutdown in ASD individuals treated with MPH. A previous study with 3,4-methylenedioxymethamphetamine (MDMA) reported an association between the rs36029-G allele and decreased cardiovascular activity (mean arterial pressure). These results agree with our findings showing a relation between G allele and decreased of side-effects.³³ We were not able to replicate the associations between the *SLC6A2* rs3785152, rs36021, rs5569 and rs1992303 polymorphisms and response to MPH in ADHD patients previously reported,^{17,18,20–22} nor we could replicate the associations reported between the other *SLC6A2* variants investigated (rs3785143, rs1861647 and rs2242446) and pharmacological treatment response in other pathologies.^{15,19,32,33} Differences in pathologies and treatment combinations may explain the dissimilarity. Finally, a *SLC6A2* haplotype combination was associated with somnolence (see Table 3). A previous study reported an association between a *SLC6A2* haplotype combination of the rs2242446-T and rs3785143-C alleles and higher scores in attention problems in ADHD children treated with MPH, suggesting a similar association.¹⁵

We combined the information obtained in this study with the information on the dopamine transporter *SLC6A3* gene from a previous study to investigate possible synergistic effects.³⁴ However, we did not find any statistically significant association supporting a synergistic effect.

Our study has some limitations. The sample size is moderate, which may have affected the statistical significance of the findings. However, it is one of the largest ASD cohorts with pharmacogenetic information to date. Secondly, none of the reported associations survived Bonferroni corrections for multiple analyses. However, Bonferroni corrections are highly conservative and may undervalue the observed associations. As is the case in most pharmacogenetic studies, our findings require replication in independent samples to confirm their validity.

In summary, genetic variants in *CES1* may influence the presence of side effects in MPH treatment in ASD subjects. If confirmed, these genetic variants may be used as predictors of clinical outcomes and have the potential to be implemented in clinical settings for the safe use of MPH in these patients.

Table 2 Summary of Statistical Analyses on Investigated Genetic Variants and MPH Response (N=140 Covariates Age, Sex, Dose)

| Gene | SNPs | Allele | Efficacy | | | Side Effects | | | Somnolence | | | Irritability | | | Mood | | | Aggressivity | | | Shutdown | | | Others Side Effect | | |
|------|----------------|--------|----------|-------|------|--------------|-------|------|------------|------|------|--------------|------|------|-------|------|------|--------------|------|------|----------|------|------|--------------------|------|------|
| | | | Wald | BETA | p | Wald | BETA | p | STAT | OR | p | STAT | OR | p | STAT | OR | p | STAT | OR | p | STAT | OR | p | STAT | OR | p |
| CESI | rs2244613_CESI | G | 0.56 | 0.10 | 0.58 | 2.10 | 0.35 | 0.04 | -0.04 | 0.98 | 0.97 | 1.07 | 1.75 | 0.29 | -0.07 | 0.95 | 0.95 | -1.37 | 0.21 | 0.17 | 1.23 | 2.35 | 0.22 | -0.11 | 0.94 | 0.91 |
| | rs2302722_CESI | C | 1.68 | 0.30 | 0.10 | -2.35 | -0.39 | 0.02 | -1.93 | 1.00 | 0.05 | -1.29 | 0.49 | 0.20 | -0.24 | 0.86 | 0.81 | 1.13 | 2.35 | 0.26 | -1.33 | 0.32 | 0.18 | 0.46 | 1.27 | 0.65 |
| | rs2307235_CESI | A | 0.47 | 0.09 | 0.64 | 2.21 | 0.37 | 0.03 | 0.59 | 1.34 | 0.55 | 1.70 | 2.46 | 0.09 | 0.74 | 1.63 | 0.46 | -1.35 | 0.21 | 0.18 | 1.31 | 2.44 | 0.19 | -0.55 | 0.72 | 0.58 |
| | rs2307240_CESI | T | -1.63 | -0.56 | 0.11 | 1.19 | 0.39 | 0.24 | 1.60 | 4.01 | 0.11 | -0.77 | 0.42 | 0.44 | 0.03 | 1.04 | 0.97 | 0.00 | 0.00 | 1.00 | 0.16 | 1.21 | 0.87 | 0.56 | 1.70 | 0.57 |
| | rs8192935_CESI | A | 1.08 | 0.16 | 0.28 | 1.69 | 0.23 | 0.10 | 0.46 | 1.21 | 0.64 | 0.96 | 1.53 | 0.34 | -1.43 | 0.34 | 0.15 | -0.79 | 0.60 | 0.43 | 0.58 | 1.41 | 0.56 | -1.35 | 0.46 | 0.18 |
| | rs8192950_CESI | T | 0.74 | 0.10 | 0.46 | 2.27 | 0.29 | 0.03 | 0.95 | 1.43 | 0.34 | 0.46 | 1.20 | 0.65 | -0.84 | 0.61 | 0.40 | -1.18 | 0.48 | 0.24 | 0.56 | 1.36 | 0.58 | -0.64 | 0.75 | 0.53 |
| | rs9921399_CESI | C | 1.00 | 0.17 | 0.32 | -0.09 | -0.01 | 0.93 | 0.87 | 1.48 | 0.39 | -0.34 | 0.84 | 0.73 | 0.18 | 1.11 | 0.86 | -0.12 | 0.91 | 0.90 | -1.30 | 0.34 | 0.19 | -0.93 | 0.60 | 0.35 |
| NETI | rs1861647_NET | A | 0.56 | 0.09 | 0.58 | 0.93 | 0.15 | 0.36 | -0.14 | 0.93 | 0.89 | -0.93 | 0.62 | 0.35 | -1.37 | 0.39 | 0.17 | -1.38 | 0.23 | 0.17 | -0.91 | 0.53 | 0.36 | -0.79 | 0.66 | 0.43 |
| | rs1992303_NET | A | -0.05 | -0.02 | 0.96 | -1.29 | -0.50 | 0.20 | 0.13 | 1.14 | 0.90 | -0.44 | 0.60 | 0.66 | -0.65 | 0.42 | 0.52 | 0.22 | 1.34 | 0.82 | 0.00 | 0.00 | 1.00 | -0.60 | 0.49 | 0.55 |
| | rs2242446_NET | C | 1.64 | 0.27 | 0.11 | -0.48 | -0.08 | 0.63 | 0.24 | 1.12 | 0.81 | -0.89 | 0.62 | 0.37 | -0.84 | 0.53 | 0.40 | -0.27 | 0.80 | 0.79 | 1.30 | 2.24 | 0.20 | 0.11 | 1.06 | 0.91 |
| | rs36021_NET | T | 0.06 | 0.01 | 0.96 | -0.78 | -0.11 | 0.44 | 0.20 | 1.08 | 0.85 | -0.43 | 0.83 | 0.66 | -0.81 | 0.66 | 0.42 | 0.67 | 1.59 | 0.50 | 0.87 | 1.69 | 0.38 | -0.55 | 0.79 | 0.59 |
| | rs36029_NET | G | -0.60 | -0.09 | 0.55 | 0.47 | 0.07 | 0.64 | 0.84 | 1.40 | 0.40 | 0.19 | 1.09 | 0.85 | 1.04 | 1.74 | 0.30 | 0.55 | 1.44 | 0.58 | -1.93 | 0.21 | 0.05 | 0.54 | 1.27 | 0.59 |
| | rs3785143_NET | T | -0.88 | -0.23 | 0.38 | -1.38 | -0.34 | 0.17 | 1.15 | 2.12 | 0.25 | -0.29 | 0.80 | 0.77 | 0.60 | 1.67 | 0.55 | 1.11 | 2.63 | 0.27 | 0.78 | 1.88 | 0.43 | 0.71 | 1.64 | 0.48 |
| | rs3785152_NET | T | 0.34 | 0.09 | 0.73 | 1.25 | 0.30 | 0.21 | 1.54 | 3.21 | 0.12 | 0.52 | 1.51 | 0.60 | 0.41 | 1.45 | 0.68 | 0.53 | 2.03 | 0.60 | -0.27 | 0.73 | 0.79 | 1.10 | 2.34 | 0.27 |
| | rs5569_NET | A | 0.69 | 0.11 | 0.49 | 1.35 | 0.18 | 0.18 | 0.09 | 1.04 | 0.93 | -0.85 | 0.68 | 0.39 | -0.47 | 0.78 | 0.64 | -0.29 | 0.81 | 0.77 | -0.63 | 0.68 | 0.53 | -0.38 | 0.84 | 0.70 |

Note: Coloured cells: statistically significant results.

Abbreviations: STAT, coefficient statistic considering covariates age, gender and dose; p, significance p value; OR, odds ratio.

Table 3 Summary of Significant Haplotype Findings

| Phenotype | Gene | p value | STAT | Allele Combination | Polymorphisms in Haplotype |
|--------------|--------|---------|------|--------------------|--|
| Efficacy | CES1 | 0.02 | 5.35 | TCCCATC | rs2244613 rs2302722 rs2307235 rs2307240 rs8192935 rs8192950 rs9921399 |
| Side-Effects | CES1 | 0.03 | 4.70 | TCCCGGT | rs2244613 rs2302722 rs2307235 rs2307240 rs8192935 rs8192950 rs9921399 |
| Somnolence | SLC6A2 | 0.05 | 3.85 | GGTTACCG | rs1861647 rs1992303 rs2242446 rs36021 rs36029 rs3785143 rs3785152 rs5569 |
| Aggressivity | CES1 | 0.05 | 3.98 | TACCATC | rs2244613 rs2302722 rs2307235 rs2307240 rs8192935 rs8192950 rs9921399 |

Abbreviations: STAT, stat coefficient statistic considering covariates age, gender and dose; p, significance p value.

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Disclosure

Mr Marc Cendros works for Eugenomics, a private company offering pharmacogenetics counselling and genetic testing, but his work on this article has been completely independent of his work at Eugenomic. The authors report no other conflicts of interest in this work.

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