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Research Article

# Cdk5 and Folate Gene Variants may Regulate Efficacy of Pharmaceutical Intervention in ADHD Probands

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**Keywords** ADHD; CDK5; Folate; MPH

## Abstract

**Aim:** Therapeutic intervention forms crucial part in ADHD management. However, treatment is often discontinued due to adverse outcome. We attempted to find out gene variants which may predict treatment outcome.

**Patients & Methods:** ADHD patients recruited through DSM-IV, were assessed through Conner's Parent Rating Scale and Drug side effect rating scale. CDK5 and folate gene variants were analyzed by sequencing and RFLP based genotyping.

**Results:** MPH treatment caused significant improvement in presence of MTHFR rs1801131 "C", while ATX caused improvement in presence of MTR rs1805087 "G". Behavioural problem and hyperactivity improved in presence of CDK5 rs2069459 "TT". Studied variants showed significant independent as well as interactive effects which correlated with phenotypes.

**Conclusion:** We hypothesize that genes encoding for CDK5 and folate may modulate post-treatment outcome of ADHD by affecting function of MPH.

## Introduction

Attention Deficit Hyperactive Disorder (ADHD) is a complex neurobehavioral disorder diagnosed by hyperactivity, impulsivity, and attention deficit [1]. The disorder is highly heritable with a male biasness and probands frequently suffer from various co-morbid psychiatric disorders [1]. Genetic association studies revealed small but significant roles of several genes in the disease etiology [2,3]. An explorative analysis also showed possible role of Cyclin Dependent Kinase 5 (CDK5) gene variants [4]. Epigenetic regulation of ADHD associated traits was confirmed by the involvement of folate metabolic system gene variants [5,6] and association of risk gene variants with vitamin $B_{12}$ deficiency and mild hyperhomocysteinemia [5-7].

Since symptoms of inattention, cognitive deficit, and behavioural problems, often lead to scholastic underachievement as well as social problems, successful management of ADHD probands require therapeutic intervention as well as behavioural training. Psychostimulants like methylphenidate (MPH), amphetamine, dextroamphetamine, etc. form the primary line of intervention. Non-stimulant medications like atomoxetine (ATX) are also in use. However, due to a number of reasons including side effects and inadequate improvement, treatment is frequently discontinued often leading to a disastrous situation. Based on these facts, we tried to identify gene variants which can be used for targeted therapeutic intervention. In the Indian ADHD probands dopamine transporter gene variants were reported to be useful for therapeutic intervention [8]. Since CDK5 [4] and folate system gene variants [5-7] have shown significant association with phenotypic traits related to ADHD, we tried to know whether these gene variants have any role in the therapeutic intervention of subjects with ADHD.

## Materials and Methods

### Subject recruitment

ADHD probands were recruited following the Diagnostic and Statistical Manual for Mental Disorders-IV-text revised (DSM-IV-TR) criteria [9]. ADHD associated traits like hyperactivity (HA), inattention (IA), ADHD index (AI) and behavioural problems (BPr) were assessed by the Conners' Parent Rating Scale-Revised (CPRS-R) [10]. Based on age of the probands, clinical history, and ease of drug availability, probands were prescribed either MPH (0.3 mg/kg body weight /day for

1st week, then 0.6 mg/kg body weight /day for the rest of the tenure) or ATX (0.8mg/kg body weight /day for the 1st week then 1.2mg/kg body weight /day for the rest of the tenure) and re-assessed using the CPRS-R criteria after 8 weeks of treatment. Side effects caused by the treatment were recorded based on Drug Side Effect Rating Scale [11]. All the methods were performed in accordance with the relevant guidelines / regulations and the study protocol was approved by the Institutional Human Ethics Committee (Approval No. 02-110414) comprising of Scientists, Clinicians, Human Rights Advocate and Social worker.

### Genotyping and data analysis

Peripheral blood was collected after obtaining informed written consent for participation and processed for genotyping through sequencing [4] or RFLP-based methods [5-7]. Three variants from CDK5 and seven variants important for the folate metabolic system were selected based on earlier observations [4-7]. Henceforth, for convenience, the studied sites will be referred as SNP 1-10 (rs2069454-SNP1, rs2069456- SNP 2, rs2069459- SNP 3, rs1051266-SNP 4, rs2236225- SNP 5, rs1801131- SNP 6, rs1801133- SNP 7, rs1805087- SNP 8, rs1801394- SNP9, rs3733890- SNP10). Detailed description on the variants, their functional role and association report are provided in Table 1.

Correlation between gene variants and treatment outcome was analyzed in ADHD probands treated with either MPH (N=39) or ATX (N=25). Post-treatment improvement in symptoms was calculated by 1-Tn/To (Tn=post-treatment score, To=initial score). Detailed description on the method is provided in Figure 1.

## Results

### Post treatment changes in trait scores of probands with different alleles

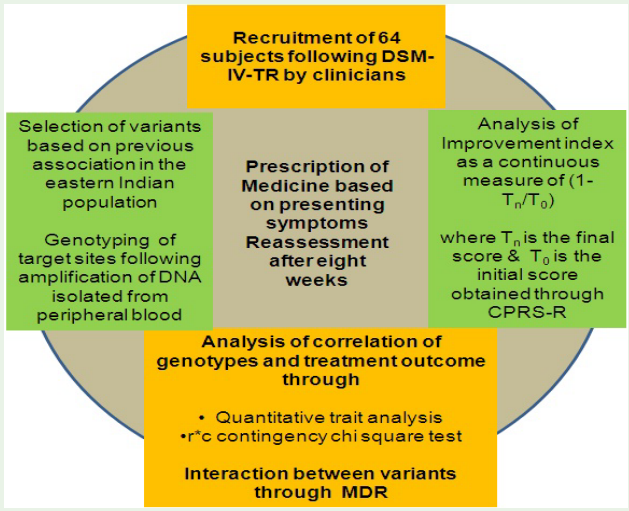


**Figure 1:** Detailed description on the protocol used for the study.

Significant impact of folate system genes on ADHD associated traits was noticed following treatment with MPH as well as ATX. In presence of SNP6 "C", all the three trait scores showed statistically significant improvement after MPH treatment (Table 2), while in presence of SNP10 "A" these symptoms were more devastating. ATX treatment improved BPr and HA in probands with SNP8 "G" (Table 2). CDK5 gene variants (SNP1-3) failed to exhibit any significant associations.

### Association between genotypes and treatment outcome

MPH induced improvement in BPr was noticed in higher frequency of probands having SNP 3"TT" and SNP 10"AA" genotypes

**Table 1:** Details of SNPs studied for contribution on pharmacotherapy.

| Gene | rsID | Presented as | Allelic shift | Effect of substitution | Association reports on ADHD from India | Cross reference |
|---|---|---|---|---|---|---|
| CDK5 | rs2069454 | SNP1 | G>C | Transcriptional activation by "C" through NKX2 | Haplotype with "G" was associated with inattention. Haplotypes with "G/C" showed association with reduced impulsivity and behavioural problem | Maitra et al, 2017. [4] |
| | rs2069456 | SNP2 | A>C | Transcriptional activation by "A" through HSF | A showed association with reduced impulsivity and behavioural problem, while C was associated with improved attention | |
| | rs2069459 | SNP3 | G>T | Splice site generation | Subjects with "T" showed improvement in ADHD Index during longitudinal follow up | |
| MTHFR | rs1801131 | SNP4 | A>C | Nonsynonymous substitution in Exon 8 -affect thermostability | AA showed association with ADHD Index & behavioural problem, while C could be linked to IQ deficit | Saha et al., 2014; 2018 [5,7] |
| | rs1801133 | SNP5 | C>T | Nonsynonymous substitution in Exon 5-increases enzyme thermolability | The "C" allele exhibited association with behavioural problem, inattention, hyperactivity-impulsivity, and IQ defcit | Saha et al. 2014; 2017; 2018 [5-7] |
| MTR | rs1805087 | SNP6 | A>G | Nonsynonymous substitution in Exon 26-reduces affinity of binding with co-factor | "G" showed association with ADHD Index | Saha et al. 2018 [6] |
| MTRR | rs1801394 | SNP7 | A>G | Nonsynonymous substitution in Exon 2- reduces enzyme efficacy | Association of the "A" allele was noticed with behavioural problem | Saha et al. 2018 [6] |
| RFC1 | rs1051266 | SNP8 | G>A | Nonsynonymous substitution in Exon 2-alters splicing and transcription | Probands with "G" allele exhibited higher behavioural problem | Saha et al. 2014; 2018 [6,7] |
| BHMT | rs3733890 | SNP9 | G>A | Nonsynonymous substitution in Exon 6-may alter homocysteine metabolism | Probands with "AG" genotype exhibited higher ADHD Index | Saha et al. 2018 [6] |
| MTHFD | rs2236225 | SNP10 | C>T | Nonsynonymous substitution in Exon 20-alters splicing | Association between hyperactivity/impulsivity was noticed in presence of the "CC" genotype | Saha et al. 2017 [5] |

**Table 2:** Effect of MPH treatment on ADHD phenotype of subjects harbouring different gene variants.

| Medication | rs ID (SNP No.) | Allele | Trait | Add value | CI | $\chi^2$ (P) |
|---|---|---|---|---|---|---|
| MPH | rs1801131 (SNP6) | C | IA | 3.41 | 0.12 to 6.70 | 5.48 (0.02) |
| | | | HA | 2.73 | -0.07 to 5.54 | 4.42 (0.04) |
| | | | AI | 3.58 | 0.37 to 6.80 | 6.36 (0.01) |
| | rs3733890 (SNP10) | A | IA | -3.27 | -6.99 to 0.44 | 3.78 (0.05) |
| | | | HA | -3.19 | -6.62 to 0.24 | 4.16 (0.04) |
| | | | AI | -5.99 | (-10.55 to -1.42) | 6.49 (0.002) |
| ATX | rs1805087 (SNP8) | G | BPr | 4.47 | -0.83 to 9.77 | 2.84 (0.09) |
| | | | HA | 4.44 | 0.05 to 8.83 | 4.17 (0.04) |

N.B. MPH: Methylphenidate; ATX: Atomoxetine; CI: Confidence interval; BPr: Behavioural problem; IA: Inattention; HA: Hyperactivity; AI: ADHD Index.

(Table 3). Improvement in HA was noticeable in higher frequency of probands with SNP3 "GG" and SNP7 "CC" (Table 3).

ATX treatment led to improvement in IA in higher frequency of probands with SNP3 "GG" and SNP6 "AA", while those with SNP3 "GG" and SNP4 "AA" exhibited better scores for AI (Table 3).

## Association with drug induced side effects

CDK5 variants failed to show any significant impact on drug induced side effects. Out of the folate gene variants, only SNP9 influenced side effects. Probands with SNP 9"G" reported night mare (AV:0.37, CI" 0.04 to 0.71, X2=5.65, P=0.02) and irritability (AV:0.65, CI: 0.10 to 1.19, X2=9,47, P=0.002) following MPH treatment, while those with the "A" allele showed insomnia (AV: 1.14, CI: 0.03 to 2.25, $X^2$=9.77, P=0.002). In subjects with SNP9 "G", nail biting was lower

**Table 3:** Association between frequency of probands harbouring different genotypes and change in trait scores after pharmaceutical intervention.

| Medication | Trait | rs ID (SNP No.) | Genotype | Imp | Not-Imp | $\chi^2$ (P)* | LRS(P) |
|---|---|---|---|---|---|---|---|
| MPH | BPr | rs2069459 (SNP3) | GG | 0.37 | 0.42 | 23.0 (0.0001) | 4.55 (0.09) |
| | | | GT | 0.42 | 0.58 | | |
| | | | TT | 0.21 | 0 | | |
| | | rs3733890 (SNP10) | GG | 0.46 | 0.50 | 30.7 (0.0001) | 6.55 (0.04) |
| | | | GA | 0.29 | 0.50 | | |
| | | | AA | 0.25 | 0 | | |
| | HA | rs2069459 (SNP3) | GG | 0.52 | 0.15 | 44.9 (0.0001) | 7.57 (0.02) |
| | | | GT | 0.30 | 0.76 | | |
| | | | TT | 0.18 | 0.08 | | |
| | | rs1801133 (SNP7) | CC | 0.88 | 0.60 | 20.4 (0.0001) | 3.86 (0.05) |
| | | | CT | 0.12 | 0.40 | | |
| | | | TT | 0.0 | 0.0 | | |
| ATX | IA | rs2069459 (SNP3) | GG | 0.44 | 0.22 | 29.3 (0.0001) | 4.86 (0.09) |
| | | | GT | 0.56 | 0.56 | | |
| | | | TT | 0 | 0.22 | | |
| | | rs1801131 (SNP6) | AA | 0.40 | 0.22 | 37.6 (0.0001) | 4.86 (0.09) |
| | | | AC | 0.53 | 0.33 | | |
| | | | CC | 0.07 | 0.45 | | |
| | HA | rs1801394 (SNP9) | AA | 0.13 | 0.50 | 52.7 (0.0001) | 6.64 (0.04) |
| | | | AG | 0.54 | 0.10 | | |
| | | | GG | 0.33 | 0.40 | | |
| | AI | rs2069459 (SNP3) | GG | 0.47 | 0.12 | 46.6 (0.0001) | 6.82 (0.03) |
| | | | GT | 0.53 | 0.63 | | |
| | | | TT | 0 | 0.25 | | |
| | | rs1051266 (SNP4) | GG | 0.25 | 0.75 | 64.7 (0.0001) | 8.09 (0.02) |
| | | | GA | 0.38 | 0.25 | | |
| | | | AA | 0.37 | 0.0 | | |

N.B. MPH: Methylphenidate; ATX: Atomoxetine; BPr: Behavioural problem; IA: Inattention; HA: Hyperactivity; AI: ADHD Index; Imp: Improved; Not-Imp: Not-Improved; *Power>90%; LRS: Likelihood Ratio Statistics.

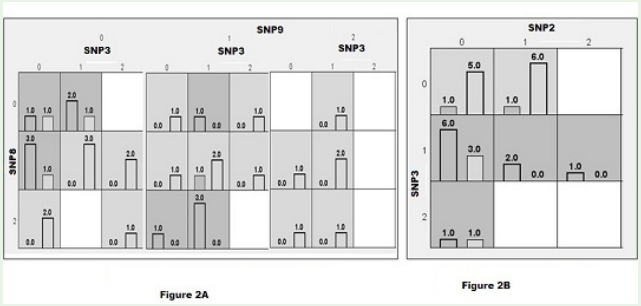


**Figure 2:** Graphical model exhibiting synergistic effect of SNPs on improvement in trait scores following MPH treatment; 2A: Behavioural problem, 2B: Hyperactivity.

between SNP1 and SNP10 (Figure 3A). SNP1, SNP3 and SNP8 showed mild interactions in the group showing improvement (Figure 3B), while strongest interaction was observed between SNP2 and SNP4 for reduced HA (Figure 3C). For diminishing AI, SNP1, SNP3, and SNP8 showed positive interactions (Figure 3D).

## Discussion

In the present analysis, we tried to explore the role of CDK5 and folate system gene variants in the efficacy of treatment of ADHD probands and the data obtained for the first time showed that CDK5 and folate variants may influence treatment outcome of ADHD probands.

Cdk5 mediated DA signalling, apart from being extremely complicated, is region specific. We earlier reported that two haplotypes

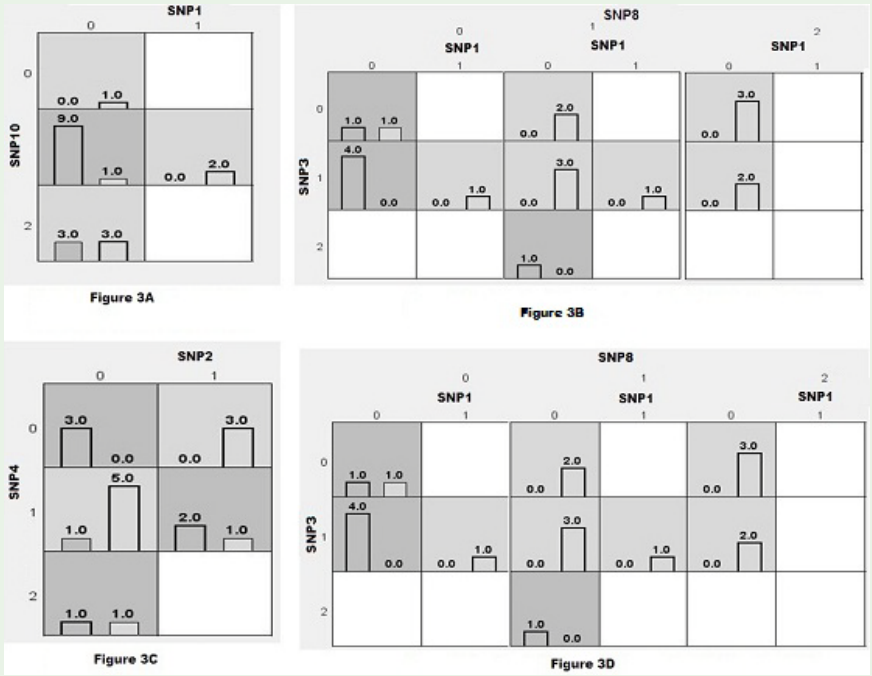


**Figure 3:** Graphical model exhibiting synergistic effect of SNPs on trait scores following ATX treatment; 3A: Behavioral problem, 3B: Inattention, 3C: Hyperactivity, 3D: ADHD Index.

(AV:-0.36, CI: -0.71to -0.02, $X^2$=5.95, P=0.01) as compared to the other group.

### Analysis of interaction between gene variants

Graphical models for the most significant interactions (CVC>8) observed in ADHD probands treated with MPH and ATX are presented in Figure 2 & 3 respectively. The right column of each box represents the improved group while the left column represents the non-improved group. Numbers under the name of each SNP is the genotype (wild type homozygous-0, heterozygous-1 and derived homozygous - 2). In the MPH treated group, BPr was found to be influenced by synergistic interactions between SNP3, SNP8, and SNP9 (Figure 2A) with SNP3 "T" participating in almost all interactions. Post-treatment improvement in HA was affected by strong interactions between SNP2 and SNP3 (Figure 2B). In the ATX treated group, BPr was higher in probands showing interactions

formed by SNP1- SNP2- SNP3 variants may reduce the level of impulsivity (Imp) and behavioural problem (Bpr), by attenuating dopaminergic transmission [4]. SNP 2 "A" was speculated to have a protective role against all the traits including IA, HA, Imp and BPr [4]. During longitudinal follow up, SNP3 "T" showed association with decrease in disease severity of drug naive patients [4]. The present analysis revealed improvement in BPr of individuals harbouring SNP3 "TT" following MPH treatment supporting our previous finding of its beneficial effect. Our earlier analysis also suggested an improvement in AI which could actually be due to improvement in BPr noticed by the parents. But ATX treated group showed betterment in IA and AI in presence of SNP3 "GG". This difference in treatment outcome may be due to differential effect of Cdk5 on neurotransmitters which merits further in depth investigation.

All the folate-homocysteine metabolic pathway genes investigated in the present study are important for maintaining the level of

S-adenosine methionine, a vital component for neurotransmitter synthesis and most of them have shown significant association with ADHD traits in the studied population [5-7]. In the present study, SNP6 "C" showed association with reduced trait scores after MPH treatment, thus indicating a beneficial effect in presence of this allele. Improvement in BPr scores was noticed in presence of SNP3 "TT" and SNP10 "AA" genotypes. On the other hand, in probands having SNP3 "GG" and SNP7 "CC", HA score was reduced indicating an improvement following treatment. Independent analysis on alleles however showed that in presence of SNP10 "A", disease associated symptoms were more distressing. This difference in outcome could be due to the absence of the "AA" genotype in the non-improved group, thus indicating necessity of further investigation on SNP10. Probands with SNP3 "GG", SNP4 "AA", SNP6 "AA", and SNP8 "G" benefitted from ATX treatment. MPH induced side effects were higher in subjects with SNP9 "G".

MDR analysis revealed different interactive patterns between gene variants for different trait scores re-establishing the fact that distinct pathways govern each trait. Treatment outcome was found to be influenced by interactive effects between CDK5 and folate gene variants. Detailed analysis revealed that this interaction was higher for the ATX treated group as compared to the MPH treated. However, number of subjects in each group was low and genetic association analysis alone may not be sufficient to understand the actual scenario inside the brain, indicating the necessity of further in depth investigation to understand the complicated pathophysiology of ADHD.

Major drawbacks of the present study are 1) limitation in number of subjects, 2) inclusion of only few genetic variants and 3) short term follow up after treatment. However, this study provides further support for association between ADHD, CDK5 and folate system gene variants. MPH mediated alteration in DA signalling was hypothesized to be modulated through DARPP32/PPI pathway and Cdk5 was speculated to have a role in this [12] while folate may be a co-modulator [13]. Based on this information, we for the first time carried out analysis on correlation between CDK5 as well as folate system gene variants and post-treatment changes in behavioural attributes of ADHD probands. Data obtained indicates that MPH induced betterment of ADHD subjects could be mediated through CDK5 and folate gene variants, a process possibly regulated by modulation of dopaminergic transmission.

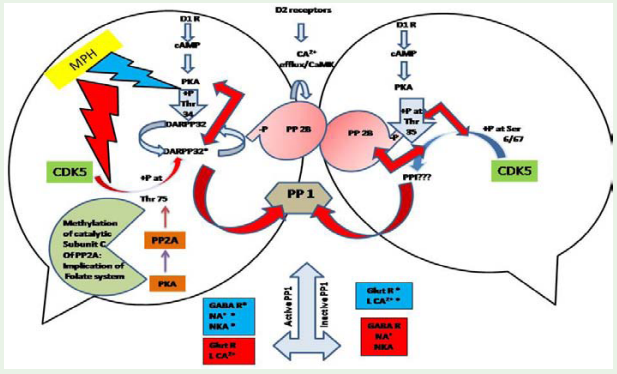


**Figure 4:** Schematic presentation of the possible regulatory effect of Cdk5 and folate system on dopaminergic transmission.

Cdk5 was reported to reduce DA signalling in the medium spiny neurons [14] while loss of Cdk5 activity enhanced action of Protein Kinase A (PKA) and DA signalling in the striatum [12]. An earlier investigation showed that MPH may influence D1 signalling by counteracting the effect of Cdk5 [15]. Therefore MPH, along with blocking DAT, may improve DA signalling through modulation of Cdk5 [15]. Our earlier investigation showed that folate deficiency, which influences SAM-mediated generation of neurotransmitters [16], may affect symptoms of ADHD [5-7] possibly through altered neurotransmission. Data obtained in the present study indicate that addition of folate as an adjuvant during pharmacotherapy could be a better option for ADHD probands with folate deficiency. Based on the above information, we propose a hypothetical model on how pharmacotherapy of ADHD could be affected by Cdk5 and folate system (Figure 4).

During D1 surged cAMP signalling, PPI and DARPP- 32 are phosphorylated at the 35$^{th}$ and 34$^{th}$ Thr residue [16,17]. As a result of this phosphorylation, they become potent inhibitor of protein phophatase1 (PP1) and make passage for D1 mediated cAMP signalling further to activate the glutamate receptors. On the other hand, Cdk5 phosphorylates DARPP-32 at 75$^{th}$ Thr residue thereby blocking D1 mediated signalling [14], and 6$^{th}$, 67$^{th}$ Ser of PPI with an ambiguous effect [17,18]. This Cdk5 induced DARPP-32 phosphorylation was shown to be due to calcium influx mediated depolarization while PPI phosphorylation was found to be non-specific to cations [18], indicating more specific effect of Cdk5 on DARPP-32. Phosphorylation of DARPP32 at the 34$^{th}$ Thr residue is promoted by MPH. On the other hand, it lowers phosphorylation at the 75$^{th}$ Thr residue, a site regulated by Cdk5 [15], making Cdk5 an important candidate for understanding function of MPH. Additionally, MPH driven blockade of Cdk5 may induce glutamatergic surge, a common detrimental effect associated with prolonged psychostimulant usage [19]. However, PPI is of more frequent occurrence than DARPP-32 [18] thus restricting the effect of MPH on DA signalling to specific regions of the brain.

An earlier study showed that the effect of Cdk5 activity on Thr 75 of DARPP-32 could be blocked by PP2A βδ holo enzyme through activation of PKA [13,20]. Activity of PP2A, on the other hand, depends on methylation of its catalytic domain [21]. Study on neural cell lines showed that folate deficiency may induce inadequate methylation of PP2A, thereby leading to characteristic symptoms of neurodegeneration [22]. Low folate status and hyperhomocysteinemia was shown to down regulate PP2A methylation [23]. Folate deficiency was also reported to induce DA receptor 4 hypomethylation, thereby increasing the chance for neurodegeneration [24].

## Conclusion & Future perspective

The present study revealed that ADHD probands having risk genetic variants of CDK5 responded differently to MPH treatment and we hypothesize that this could be due to differential action of MPH and Cdk5 on DARPP-32, indicating the necessity of genetic analysis before pharmaceutical intervention with MPH. Additionally, subjects carrying risk gene variants of the folate metabolic system may suffer from compromised folate metabolism, thus affecting the methylation pattern as well as neurotransmitter synthesis, resulting in a cascade of events upsetting adequate response to pharmacotherapy. In Caucasian patients with Major depressive disorder, CpG island

hypomethylation have already shown to have significant impact on treatment outcome [25]. Based on our observations, we speculate that better symptomatic recovery could be provided to ADHD patients through vitamin supplementation along with MPH treatment. Therapeutic intervention and vitamin supplementation to deficient individuals may provide faster remediation to ADHD associated symptoms thereby reducing the chances of treatment discontinuation.

## Summary Points

- Genetic as well as epigenetic factors play regulatory roles in the etiology of ADHD.
- Pharmacological intervention is often required. However, due to inadequate improvement and side effects, treatment is often discontinued.
- Personalized treatment may provide better relief.
- We investigated genetic variants, that influences ADHD associated traits, to identify their contribution in therapeutic intervention.
- Data obtained indicate that the studied risk gene variants, modulating neural transmission, may affect treatment outcome.
- Therapeutic intervention considering these facts may provide faster relief.

## Disclosures

### Ethical conduct of research statement

This work has not published elsewhere and will not be submitted simultaneously for publication elsewhere. We hereby declare that the work was carried out on Indian ADHD subjects after obtaining informed written consent for participation and the project was approved by Human Ethical Committee of the Institute. We also declare that all the authors have approved the final manuscript for publication and there is no conflict of interest. The publication, if accepted, will not be published elsewhere without the written consent of the copyright holder.

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