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Is dopamine transporter gene effective on therapeutic response of methylphenidate in ADHD patients?

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ABSTRACT

Attention-deficit/hyperactivity disorder (ADHD) is the most common neuropsychiatric illness, which affects about 5% of children worldwide. An 80% genetic background is responsible for ADHD due to its appearance in familial relationships. In addition, dopamine regulation in synaptic spaces, which have a central role in development of ADHD, is moderated by dopamine transporter neurotransmitter, which in turn is modulated by dopamine transporter gene named SLC6A3 or DAT1. Methylphenidate as the first line and most important prescribed medication for ADHD blocks dopamine transporter and increases the dopamine concentration in synaptic clefts. In theory, methylphenidate relay to dopamine transporter to play a role, and dopamine transporter synthesis is dependent on DAT1. This gene have 40 base pair in its 3`-untranslated region end that repeat from 3 to 11 times, with most frequent 9 and 10 repeats in human, forming several alleles in carriers including 9R and 10R and genotypes including 9R/9R, 10R/10R, 9R/10R. These genotypes, as the first suspected candidates, may explain why methylphenidate therapy is not sufficient some patients and how the side effects appear in some cases and not in all patients. Many studies have performed to investigate the association between responses to methylphenidate and genotypes and yet no consistency has occurred. This article has a rapid review on concerned literature.

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Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a common childhood neuropsychiatric disease involving about 8-12% of children and adolescent around the world (1). Its cardinal and central symptoms include inattention, impulsivity and hyperactivity. According to DSM-IV-TR (Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition-Text Revision), involved patients are placed to 3 clinical subtypes: significant hyperactivity, predominant attention deficit and mixing form containing both conditions (2). The etiology of ADHD is not clearly recognized, however, genetic contributors are estimated to be responsible for about 80% of the phenotype base of disease (3-5). Worldwide prevalence of ADHD varies from 5 to 10% of all children (6-8) and 2-4% of adults (9-11). ADHD causes significant morbidity for criminality including social, educational, physical and drug abuse problems as well as other anti-social behaviors, increasing admission to emergency departments (12) and falling in severe trouble with driving (13). Therefore, ADHD patients impose too much cost to the health care system and society (14).

Among many medical alternatives, which are prescribed for ADHD, dopamine transporter

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blocking agents such as methylphenidate (MPH) and amphetamine are the most common used and investigated drugs. MPH as a dopamine and noradrenaline transporter inhibitor causes an inhibitory influence on reuptaking of these neurotransmitters and finally increases the extracellular dopamine and noradrenaline in synaptic clefts especially in striatal areas of brain (15). This enhancement of neurotransmitter concentration within synapthic space is associated with significant clinical improvement of ADHD. Both cognitive and behavioral symptoms are subsided in involved children and adults, but some patients do not respond to MPH (16-18). Some volunteers remain spared from effects of MPH (19-21). Many studies, with medium to large size of population, have revealed the priority of MPH over placebo in ADHD cases (22-24). Regarding to MPH, there are a substantial variation in response to treatment among patients, while many of them have benefited greatly from MPH and a considerable proportion of patients failed to show improvement or earned small to moderate profit with MPH. Furthermore, side effect appearance was completely different among drug recipients, thus some of them refused to continue drug consumption (25). Currently, there is not any blurred evidence to address the causes of this variation. It might be multifactorial or even has a concerned relation with employed methodological issues in different studies (26). Pharmacogenitical approaches have been investigated in many studies because dopamine transporter dysregulation, which was primarily controlled by regulatory influence of genes, were most suspected factors in prediction of response to MPH treatment in ADHD. Pharmacogenitical explanations are able to cover not only inter-individual differences of patients in response to MPH, including both clinical symptoms and cognitive performances, but also appearing and severity of unwanted adverse effects in ADHD patients (27-30). Many conducted studies focused on the role of dopamine transporter regulation effect as the essential cause of ADHD. These transporters take the neurotransmitters such as dopamine from intra-synaptic space into the presynaptic neuron and cause a decrement in dopamine levels, which can be inhibited by MPH (31-33). A gene named SLC6A3, located on chromosome number 5 (chromosome 5p 15.3), is responsible for dopamine transporter protein synthesis (34,35).

This gene consists of a variable number of tandem repeat (VNTR) polymorphism that have been broadly investigated in recent years. In 3`-untranslated region of this gene, a series of 40 pairs of bases are binding together, with variable frequency in repeating. This recurrence extends from 3-11 times in human in which 9 and 10 is the most frequently repeating tandem (9R and 10R) (35-38). There is no consensus on any significant association between VNTR and MPH response in ADHD because single-photon emission computed tomographic studies (SPECT) have not been able to show any correlation between tandem repeat and striatum level of dopamine(39). Nonetheless, it seems that VNTR has a function in controlling of mRNA permanence, nuclear transferring to cytoplasm and protein synthesis (40-41). The authors who believed in the role of dopamine transporter gene (DAT1) as an origin for variable response to MPH in ADHD patients, concentrated on several objects as follow:

a. MPH therapy in ADHD directly implicates DAT, which in turn is regulated by DAT gene. b. A casual correlation between response to MPH and DAT provides a pharmacogenetic pattern for investigating.

c. Many studies have investigated the relation between DAT gene and ADHD etiology (3).

The amount of DAT in ADHD was studied in another survey (42) and searching for any association between DAT gene VNTR and accessibility of dopamine in human striatum was the objective aim of another study (39). The results obtained from different studies are not consistent, for example, some of them emphasized on 9R repeating allele on degree of response to MPH(26,43-46), while some accentuated its opposite (47-49) and some of them failed to present any correlation between VNTR and clinical reply to MPH (50-58). A meta-analysis study demonstrated a concordance between 10R homozygote alleles and poor clinical response to MPH in childhood ADHD (59). Many other studies have investigated this relationship (46,47,49,52-58). Twenty-two correlated studies are shown in Table 1 for a rapid looking. In this article, a brief and rapid review of related literatures are presented. As mentioned previously, there is not any consistency in results from conducted studies. While some of them have demonstrated a critical role for DAT1 gene in clinical response and better cognitive and behavioral performance after MPH therapy, others either denied or failed to show any relationship including both negative and positive relation between dopamine transporter gene and response to MPH in ADHD cases.

1. Kireley et al. investigated relationship of 10R VNTR DAT1 alleles with clinical response to MPH in 119 Irish ADHD cases, all in childhood age. (Chi2=7.918, df=1, P=0.005). They concluded a positive outcome for this gene variation to predict clinical response to MPH (47).

Table 1. Results of conducted studies investigating relation of dopamine modulating genes and metthylphenidate treatment from 1994 to2014

Author Year Reference	Sample	Ethnicity	Number	Study Design	Investigated Gene(s)	Comments
Edwin 1994 (60)	Children	Caucasian, Asian	57		Dopamine transporter gene (DAT1)	A significant association between DAT1 and reponse to MPH was demonstrated
Winsberg 1999 (43)	Children	African-American			Alleles of DRD2,DRD4 and DAT1	10R/10R DAT1 cases showed no response to MPH
Roman 2002 (44)	Yong male	Brazilian	50	Blind naturalistic study	Dopamine transporter gene (DAT1)	Non-10R/10R group showed 75% improvement with MPH in ABRS scale, while 47% improvement in 10R homozigote carriers. The former group obtained more scores in CGAS compare to 10R/10R genotypes with MPH.
Kirely 2003 (47)	Children	Irish	119	Retrospective study	Dopamine transporter gene (DAT1)	There was an association between 10R-repeat allele and response to MPH
Loo 2003 (58)	Children	American		Double-blind controlled trial	Dopamine transporter gene (DAT1)	10R/10R carriers showed poorer response to MPH.10R carriers showed opposite EEG change compare to 9R carriers
Cheun 2005 (45)	Children	Korean	11		DAT1 gene	100% of non-10R/10R genotype showed good response to MPH, while only 28.6% of 10R homozigotes showed good response to MPH.
Van der Meulen 2005 (50)	Children	Dutch	82		DAT1 /DRD4	Response to MPH was associated with one or two alleles of DRD4 but not 10R homozigosity of DAT1.
Stein 2005 (48)	Children	American	47	Double-blinded crossover trial	DAT1	9R/9R group showed a dose-related response to MPH.
Langley 2005 (51)	Children		263	Case-control study	DAT1	No significant relation was found between ADHD and response to MPH with DAT1 genotype
Zeni 2006 (54)	Children	Brazilian	111	Prospective controlled study	Dopaminergic (DAT1,DRD40) Serotonergic(HTR-1B,HTR2A, AND 5-HTT)	No significant relation was appeared between genotypes and either response to MPH or side effects.
Mc Gough 2006 (52)	Children	American	81	Doubl-blind placebo controlled cross-over	Dopamine receptor (DRD4), Synaptosomal-associated protein 25(SNAP25), DAT1	DRD4 was associated with response to MPH, SNAP25 was associated with side effects and DAT1 showed no significant association.

Gilbert 2006 (61)	Children	American	16	Randomized doubl-blind single-dose crossover study	Dopamine transporter gene (DAT1)	Both MPH and ATX did not increase SICI in 10R/10R genotypes, opposite to heterozygotes alleles.
Mick 2006 (53)	Adult		106	Randomized placebo-controlled parallel design	Dopamine transporter gene (DAT1)	There was no association between DAT1 VNTR polymorphism and response to MPH and cardiovascular side effects
Kooji 2008 (46)	Children		42	Double-blind controlled studies	Dopamine transporter(DAT1), Norepinephrine transporter(NET),Dopamine receptor D4(DRD4)	Response to MPH was significant increase in DAT1 polymorphism and not associated with other genotypes.
Joober 2007 (49)	Children	Canada	159	Prospective crossover trial	Dopamine transporter: variant VNTR alleles	Opposite to 9R/9R genotype,9R/10R and 10R/10R genotypes displayed a significant positive response to MPH, according to CGI-parents scale.
Tharoor 2008 (55)	Twin children	American	243		Allelic variation of DAT1,DRD4,nicotinic acethylcholin receptor,sertonine transporter promoter.	No significant association were displayed between genotype and response to MPH
Purper-Quakil 2008 (59)	Children		141 475	Meta- analysis	Dopamine transporter gene (DAT1)	Overpresentation of 10R/10R genotype in poor response to MPH group
Szobot 2011 (62)	Adolescent	Brazilian	17		Dopamine transporter gene (DAT1)	ADHD/SUDs with combined DRD4 7R and DAT1 10R/10R have poor response to MPH.
Contini 2012 (57)	Adult	Different ethnics	Reviewed 5 RCTs	Systematic review	Dopamine transporter gene (DAT1)	4 among 5 studies presented so far negative outcomes for relationship between DAT1 and response to MPH.
Hong 2012 (63)	Children and adolescents	Korean	103	Open-lable trial	DAT1,DRD4,alpha-2A adrenergic receptor gene(ADRA2A),Norepinephrine transporter gene (NET1)	Short-term response to MPH treatment might be predicted by genes implicated by dopaminergic and noradrenergic transporters.
Pasini 2013 (65)	children	Italian	108		DAT1 VNTR genotype	The 9R/9R group showed response to MPH treatment in inhibition and memory working in shortest period compare to 9R/10R and 10R/10R genotype.
Kambeitz 2014 (64)	Children adult	Several ethnicity	1 5 7 2 subjects from 16 studies	Systematic review	DAT1 alleles	Low responders to MPH, mostly belong to 10R/10R carriers

2. Winsberg et al. in 1997, resulted a negative predictor outcome for response to MPH therapy in association with 10R-repeat DAT1 gene in American-African ADHD children, tested with chi 2 (P=0.008)(43).

3. Edwin et al. evaluated the association of appropriate response to MPH and 10R DAT1 allele and found it out significant in 1995 (60).

4. Loo et al. discovered significant association between poor clinical response to MPH and EEG changes of decreased right frontal theta power, elevated parietal and central beta power and

lower theta/beta proportions with 10R-repeat DAT1 genotype, while inverse EEG changes was associated with 9R allele (58).

5. Cheun et al. in 2005, showed a negative relation between 10R/10R DAT1 genotype and poor response to MPH through measuring marked I^{123} DAT in basal ganglia by SPECT after 8-week treatment with MPH in 11 Korean ADHD children (45).

6. Stein et al. in 2005, evaluated dose-dependent response of MPH in ADHD cases with comparison to 9R and 10R alleles of DAT1 genotypes. They concluded that there was a clear curve pattern of response to increasing dose of MPH in 9R/9R VNTR genotype until 18 mg followed by absence of linear pattern in increasing dose of MPH from 18 mg to 36 mg and 54 mg (48).

7. Langely et al. in 2005, conducting a case control study with 257 ADHD cases and 263 normal subjects as control, denied any correlation between DAT1 genotypes, allele or haplotypes and clinical response to MPH (51).

8. Zeni et al. in 2006, investigated the relation between both dopaminergic (DRD4, DAT1) and serotonergic (HTR1B, HTR2A, and 5-HTT) gene polymorphism and response to MPH and appeared side effects, measured by Swanson, Nolan, and Pelham scale—version IV, Children Global Assessment Scale, Barkley's Stimulants Side Effects Rating scale, among 111 brazilian ADHD children. They concluded no association (54).

9. Mc Gough, in 2006, put 81 ADHD cases into 5 randomly designed groups and MPH was given in doses of 1.25 mg, 2.5 mg, 5 mg, 7.5 mg and placebo three times a day. In this investigation, a relation between side effects such as social withdrawal, picking and irritability were seen with DRD4 genotype in dose elevating, while tics, buccolingual movements and irritability were associated with SNAP 25 variant. Symptom reduction was associated with all variants (DRD4) promoter ($p=0.05$) and synaptosomal-associated protein 25 (SNAP25) alleles T1065G ($p=0.03$) and T1069C ($p=0.05$) except for DAT1 genotype (52).

10. Gilbert et al. 2006, investigated the association between 10R allele homo- or heterozygote of DAT1 gene and MPH and atomoxetin (ATX) effects on short interval cortical inhibition (SICI) measured by cortical transcranial magnetic electrode in ADHD subjects. SICI reduced in ADHD and was related to severity of clinical symptoms in ADHD. Both MPH and ATX had similar effects on SICI and these effect were aggravated in association with 10 R heterozygote of DAT1 (61).

11. Joober et al. in 2007, divided 159 ADHD children to 3 groups regarding to their genotype including 9R/10R DAT1, 10R/10R DAT1 and 9R/9R DAT1 genotypes. Assessment of children by parents and teachers concerned scales was performed after 2-week treatment by MPH. Obtained results from parent scale presented significant association between 9R/10R and homozygote 10R allele and response to MPH, while poor response was associated with homozygote 9R allele. Teacher scale was not significant with any of 3 genotypes. They concluded that some of polymorphisms in DAT1 gene could be associated with better performance in some children but not all ADHD children in response to MPH (49).

12. Kooji et al. 2007, demonstrated a significant association between heterozygote 10R allele of DAT1 and response to MPH in 42 ADHD adults. But it was not associated with 10R/10R DAT1 and the norepinephrine transporter, SLC6A2 (NET), and the dopamine receptor D4, DRD4 as well (46).

13. Taroor et al. 2008, failed to show any relationship between VNTR located in the 3'-UTR of the DAT1, DRD4 VNTR, CHRNA4 (rs1044396 and rs6090384) and the long (L(A) and L(G)) and short (S) forms of the serotonin transporter promoter region and the response to MPH in 243 ADHD cases who were assessed by their parents through a categorical scale. Although sample size had high power effect, its categorical scale was not sensitive enough (55).

14. Purper-Ouakil et al. in 2008, in an investigation for finding any relation between genotype and response to MPH, demonstrated overrepresentation of 10R/10R DAT1 genotype in low responder to MPH in 141 ADHD children that was in harmony with a meta-analysis of total 475 ADHD cases. Furthermore, they stated the possible role of study design on obtained results (59).

15. Pasini et al. 2013, studied 108 ADHD children with three distinct genotypes (9R/9R, 10R/10R, and 9R/10R) for investigating any relation between genotype and duration of MPH therapy. Measured outcomes were memory working, inhibition and programming. 9R/9R group were different with two other genotypes in response to MPH(62).

16. Hong et al. in 2012, investigated the independent effects and interaction of different genotypes on the response to MPH in 103 Korean ADHD children and adolescents. They showed that interaction of dopamine and noradrenalin genes on each other might predict short duration of response to MPH (63).

17. In a systematic review published electronically in 2012, the authors selected five eligible RCTs among electronic publication articles until January 2012. Apart from one study, all others presented no relation between genotyping in adult ADHD and response to MPH treatment. Currently, performed pharmacokinetic tests are not accepted

because they were not routine clinically (57).

18. In another systematic review with meta-analysis published in 2014, selected 16 articles consisted of 1572 ADHD cases. No confirmation was obtained for relation between DAT1 VNTR polymorphism and response to MPH. The only yielded result showed that carriers of 10R homozygote allele had poorer response to MPH compare to non-10R/10R carriers (64).

Conclusion

Literature review displays inconsistency about the influence of regulatory effects of dopamine transporter VNTR alleles on clinical outcomes after MPH treatment. Although sample size effects were enough in some of these studies, the resulted discrepancy might be due to the study design, applied scales and technical measure instruments. The most repeated fact is poor response of 10R/10R VNTR DAT1 genotype to MPH treatment in concerned investigations. Pharmacogenetic studies target the individual assessment for drug prescription in future to avoid adverse effects and provide more benefits or even shorter duration of medical therapy. Further and more accurate studies should be performed to achieve results that are more precise.

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Conflict of Interest

The authors declare no conflict of interest.

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