

# Advances in molecular genetic studies of attention deficit hyperactivity disorder in China

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**Summary:** Attention deficit hyperactivity disorder (ADHD) is a common psychiatric condition in children worldwide that typically includes a combination of symptoms of inattention and hyperactivity/impulsivity. Genetic factors are believed to be important in the development and course of ADHD so many candidate genes studies and genome-wide association studies (GWAS) have been conducted in search of the genetic mechanisms that cause or influence the condition. This review provides an overview of gene-association and pharmacogenetic studies of ADHD from mainland China and elsewhere that use Han Chinese samples. To date, studies from China and elsewhere remain inconclusive so future studies need to consider alternative analytic techniques and test new biological hypotheses about the relationship of neurotransmission and neurodevelopment to the onset and course of this disabling condition.

**Keywords:** ADHD, genetics, candidate gene studies, GWAS, China

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## 1. Introduction

Attention deficit hyperactivity disorder (ADHD) is a highly prevalent childhood-onset neuropsychiatric condition, with an estimated worldwide-pooled prevalence of 5 to 12% in school-age children<sup>[1,2]</sup> and 2 to 5% in adults.<sup>[3]</sup> On average 50% (32.8 to 84.1%) of children with ADHD continue to meet DSM-IV criteria for ADHD as adults.<sup>[4]</sup> In China, reported prevalence ranges from 4.31 to 5.83%.<sup>[5,6]</sup> ADHD is characterized by age-inappropriate and impaired levels of inattention, hyperactivity and impulsivity. These three primary clinical characteristics may be expressed to different extents among children with ADHD, as reflected in the DSM-IV subclassification of ADHD into primarily inattentive (ADHD-I), primarily hyperactive/impulsive (ADHD-HI), and combined (ADHD-C) subtypes.<sup>[7]</sup> The ratio of boys to girls with ADHD is between 3:1 and 9:1. ADHD is associated with prolonged dysfunction including low self-esteem, substance abuse, delinquency, and other types of psychological problems. These limitations cause a heavy burden to the individual, their families, and society.

ADHD is a complex condition caused by the interaction of genetic, social, and environmental factors.<sup>[8]</sup> Adoption and twin studies have helped disentangled the genetic and environmental sources of transmission of ADHD. A review<sup>[9]</sup> of 20 twin studies from the United States, Australia, Scandinavia, and the European Union reported a mean heritability estimate of 76%, indicating that ADHD is one of the most heritable psychiatric disorders. Molecular genetics studies suggest that ADHD is a multifactorial polygenic disorder with minor contribution from each individual susceptibility gene. Multiple neural pathways have been implicated in the development of ADHD including the dopaminergic, norepinephrinergetic, serotonergic, and cholinergic pathways.<sup>[10]</sup> Current findings from both candidate gene studies and genome-wide association studies (GWAS) have failed to find a major gene for ADHD.

The present review introduces the Chinese contribution to the molecular genetics of ADHD. Three English databases (PubMed, Embase, Google Scholar) and one Chinese database (CNKI) were searched for relevant

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reports published prior to June 2014. The medical subject heading terms and/or text words used for the search were as follows: 'attention deficit hyperactivity disorder' or 'ADHD' or 'ADD' or 'attention deficit' or 'hyperactivity' or 'hyperkinetic syndrome' AND 'genetic' or 'polymorphism' or 'gene'. Identified studies were selected if they were conducted in mainland China, Hong Kong, or Taiwan. The reference lists of selected studies were reviewed to identify any additional studies and additional papers from China not identified in the search but considered relevant by the authors. Based on these published reports, our review starts with an overview of candidate gene studies, considers ADHD endophenotypes, presents results from the first GWAS of ADHD in Chinese Han children, and concludes with a discussion of pharmacogenomics studies.

## 2. Candidate gene studies

### 2.1 Dopaminergic system (DA system)

The dopaminergic theory, proposed by Levy,<sup>[11]</sup> suggests that DA deficits in specific brain regions, such as cortical areas and the striatum, results in ADHD symptoms. Supporting evidence from animal model studies and from pharmacology, brain imaging, and genetic studies has made the dopaminergic theory the most popular theory about the genetic etiology of ADHD.<sup>[12]</sup>

#### 2.1.1 Dopamine transporter genes (*DAT*, *SLC6A3*)

The dopaminergic theory about the neurobiology of ADHD led to the first gene association study for ADHD by Cook and colleagues.<sup>[13]</sup> They investigated a 40 bp variable number tandem repeats (VNTR) located in the 3' untranslated region (3' UTR) of the dopamine transporter gene (*DAT1*) in ADHD families. Using the family-based haplotype relative risk (HRR) measure, an association with the 10-repeat allele (10R) was detected.<sup>[13]</sup> Results of a meta-analysis of the association between the 10R allele of *DAT1* and ADHD supported the hypothesis about the involvement of dopamine system genes in ADHD.<sup>[14]</sup> Chen and colleagues<sup>[15]</sup> also found evidence of increased transmission of the 10-repeat allele in a Taiwanese sample, but other studies in Chinese samples by Qian<sup>[16]</sup>, Wang<sup>[17]</sup>, and Cheuk<sup>[18]</sup> did not replicate these findings. Qian<sup>[16]</sup> found that long repeat alleles (11–12 repeats) were associated with ADHD. Qian also reported<sup>[19]</sup> no association between ADHD and the new polymorphism G352A/G in *DAT1* exon 15 but did find a non-significant association ( $p=0.077$ ) between ADHD and the 352G allele in a small ( $n=22$ ) subsample of girls. Xu<sup>[20]</sup> found a significant association between the T allele of promoter polymorphism -67A/T and ADHD in the Taiwanese population and in combined samples from the United Kingdom and Taiwan. Shang and colleagues<sup>[21]</sup> screened 15 polymorphisms across the *DAT1* gene and found significant associations between the inattentive subtype of ADHD and three haplotype blocks (intron 2 through intron 6, intron 8 through

intron 11, and 3'UTR) and the haplotype rs27048 (C)/rs429699 (T).

#### 2.1.2 The dopamine D4 receptor gene (*DRD4*)

LaHoste and colleagues<sup>[22]</sup> were the first to compare the frequency between ADHD cases and controls of a 48 bp VNTR located in exon 3, which encodes a receptor expressed primarily in the prefrontal cortex. They found an association between the 7-repeat allele (7R) and ADHD. This is the strongest and most consistently replicated molecular genetic finding in ADHD; it has been reported in Caucasian and several non-Caucasian populations.<sup>[23-28]</sup> However, Qian and her colleagues<sup>[15]</sup> did not find the 7R or longer repeats, but did report that long repeat genotypes and alleles ranging from 4 to 6 repeats may increase the risk for ADHD in Han Chinese children. A study from Hong Kong indicated that the 4-repeat allele was the predominant polymorphism in the population (84.4%) and that alleles with 4 to 7 repeats were significantly more frequent in children with ADHD.<sup>[29]</sup> In a meta-analysis that included both studies, the association between ADHD and the longer repeats was statistically significant in males (OR=1.70, 95% CI 1.20–2.40,  $p=0.003$ ) and most closely associated with the ADHD-C subtype (OR=1.74, 95% CI 1.16–2.59,  $p=0.007$ ).<sup>[29]</sup> Another small study in ADHD probands ( $n=32$ ) observed an increase in prevalence of the 2R allele (33%) compared to controls (20%).<sup>[30]</sup> Another report based on a small ADHD sample ( $n=32$ ) proposed that the observed increased prevalence of the 2R allele in Han Chinese ADHD probands (33%) compared to the prevalence of the 7R allele (20%) was still consistent with the 7R allele hypothesis of ADHD in European-ancestry children.<sup>[30]</sup> Zhao and colleagues did not find an association between *DRD4* and ADHD, but did find that *DRD4* was associated with the internalizing behaviors of ADHD.<sup>[31]</sup> A study by Guan<sup>[32]</sup> focusing on a 521 C/T in the promoter region of *DRD4* indicated that the T allele and the TT genotype were more prevalent in children with ADHD with disruptive behavior disorder (DBD). Li<sup>[33]</sup> reported that carriers of the *DRD4* rs916455 C allele were more likely to have persistent ADHD symptoms in adulthood. In a Taiwanese sample, researchers did not find an association between ADHD and two markers in the *DRD4* gene – the exon 3 VNTR and a 5' 120 bp duplication.<sup>[34]</sup>

Besides *DRD4* and *DAT1*, Qian<sup>[35]</sup> also investigated the 241 A>G polymorphism of *DRD2*, which showed no significant difference between ADHD cases and controls even after stratification by gender or subtype; she also found no evidence of gene–gene interactions among dopamine candidate genes.<sup>[35]</sup> Guan and colleagues performed a comprehensive association analysis study screening 245 single nucleotide polymorphism (SNPs) of 23 candidate genes (including *DRD1*, *DRD2*, *DRD3* and *DRD4*) in a sample of Han Chinese descent; they found that the rs7638876 of *DRD3* was associated with ADHD-C (Normal  $p=0.037$ , Empirical  $p=0.293$ ).<sup>[36]</sup>

Another study in Taiwan found no association between ADHD and the *DRD2* TaqI A polymorphism.<sup>[37]</sup>

## 2.2 Noradrenergic system (NE system)

Although stimulant medications appear to act primarily by regulating dopamine levels in the brain, noradrenergic and serotonergic functions may also be affected by ADHD medications. After treatment with low-dose methylphenidate (MPH), NE efflux within the prefrontal cortex (PFC) increased by 280% and DA by 130%.<sup>[38]</sup> The presumed method of action of atomoxetine, an effective treatment for ADHD, is increased extracellular levels of norepinephrine and dopamine in PFC.<sup>[39]</sup> Among NE system genes, researchers have primarily focused on the noradrenaline transporter (*NET1/SLC6A2*) and on the adrenergic alpha receptors 2A and 2C (*ADRA2A* and *ADRA2C*).

### 2.2.1 *NET1*

*NET1* may be involved in the etiology of ADHD, but studies have yielded conflicting results.<sup>[40-42]</sup> The rs363039 of *NET1* appears to be associated with ADHD-C (Normal  $p=0.018$ , Empirical  $p=0.267$ ).<sup>[36]</sup> Wang and colleagues<sup>[43]</sup> reported that *NET1* was probably a susceptibility gene of pure ADHD, especially for the pure ADHD-I subtype. Liu and colleagues found that the rs3785143 of *NET1* was associated with the comorbidity of oppositional defiant disorder (ODD) and ODD symptoms in ADHD probands,<sup>[44]</sup> a finding that has been replicated in three studies from other countries.<sup>[45-47]</sup>

### 2.2.2 *ADRD2A*, *ADRA2C*

Evidence from neurobiological, neuro-pharmacological, and animal models support suggestions that *ADRD2A* is a candidate gene of ADHD.<sup>[48-50]</sup> Wang<sup>[51]</sup> examined the association of the *ADRA2A* MspI and DraI polymorphisms with ADHD in 268 nuclear families of Han Chinese, and found no biased transmission of alleles of either polymorphism; the mm genotype of the MspI polymorphism was marginally related to lower ADHD symptom scores in ADHD cases ( $p=0.051$ ), which was opposite to the findings in several Caucasian samples.<sup>[52, 53]</sup> On the other hand, Guan<sup>[36]</sup> reported a significant association between ADHD-C and the rs7682295 of *ADRA2C* ( $p<0.05$ ).

## 2.3 Serotonergic system (5-HT system)

Serotonin has been shown to influence a variety of behaviors relevant to ADHD, including impulsivity, aggression, dis-inhibition, and attention, thus it is thought to play a causal role in ADHD.<sup>[54-56]</sup> The main candidate genes studied within the serotonergic system are those coding for the serotonin transporter (*5-HTT/SLC6A4*), the 1B and 2A serotonin receptors (*HTR1B*) and (*HTR2A*), and tryptophan hydroxylase (*TPH2*) genes. Additionally, there is some evidence of potential

involvement of the genes for 2C serotonin receptors (*HTR2C*), the serotonin 4 receptor gene (*HTR4*), and the 1D serotonin receptors (*HTR1D*).

### 2.3.1 *5-HTT/SLC6A4*

Three polymorphisms of *5-HTT* are well characterized: a 44 bp in/del promoter polymorphism (5-HTTLPR), a 16–17 bp VNTR polymorphism in intron-2 (STin2), and a SNP in the 3'-untranslated region. Li<sup>[57]</sup> found no association between the STin2 VNTR and ADHD, but did find preferential transmission of the S allele of the 5-HTTLPR polymorphism to probands with ADHD-C and trios with comorbid ADHD and learning disorder (LD). Zhao<sup>[58]</sup> observed an association between serotonin transporter promoter polymorphisms and some ADHD symptoms; ADHD cases homozygous for the short allele showed more withdrawn or somatic complaint scores than subjects with the long allele. Xu<sup>[34]</sup> found no association between 5-HTT polymorphisms and ADHD in samples from the United Kingdom and Taiwan.

### 2.3.2 *HTR1*, *HTR2*, *HTR4*, *HTR5*, *HTR6*

Studies about the association between ADHD and T102C of *HTR2A* in Chinese samples have been inconsistent.<sup>[59-61]</sup> Li and colleagues<sup>[61]</sup> investigated association between ADHD and several serotonin transporters (including *HTR2A*, *HTR1B*, *HTR2C* and *HTR4*); they found no association between ADHD and T102C and the G1438A of *HTR2A*, but they did find that polymorphisms of A1438G are related to functional remission in ADHD.<sup>[62]</sup> They also found significant over-transmission of the C-759T/G-697C haplotype within the *HTR2C* gene<sup>[63]</sup> and under transmission of the C83097T/G83198A haplotype in the *HTR4* gene in Han Chinese cases, but there was no association between ADHD and markers in *HTR5A* or *HTR6*.<sup>[61]</sup> For *HTR1D*, the A allele of the 1236A>G polymorphism exhibited a significant preferential transmission to probands of ADHD-C<sup>[64]</sup> and the C allele of the 1350T>C polymorphism showed preferential transmission to probands with comorbid ADHD and DBD.<sup>[65]</sup> However, a family association study in a Taiwanese sample<sup>[66]</sup> did not replicate previous reports of the association between ADHD and the rs6295 of *HTR1A*.<sup>[67]</sup>

## 2.4 Enzyme system

Molecular studies have provided compelling evidence for the association of ADHD with genes that encode enzymes involved in the metabolism of catecholamine and serotonin.

### 2.4.1 *Catechol-O-methyltransferase (COMT)*

*COMT* catalyzes a major step in the degradation of dopamine, norepinephrine, and epinephrine; about 60% of the DA degradation in the PFC is performed by *COMT*.<sup>[68]</sup> The most popular marker for the *COMT* gene is the Val/Met functional SNP (rs4680). In spite of the

negative findings from a Hong Kong meta-analysis<sup>[69]</sup> and a recent systematic review,<sup>[70]</sup> this marker is currently the most actively researched SNP listed on the ADHD gene database<sup>[71]</sup> (<http://adhd.psych.ac.cn/>). In China, Qian and colleagues<sup>[72,73]</sup> did not find an association between *COMT* and ADHD but did find some sex-specific associations: compared to controls, the Met allele was preferentially transmitted to boys with ADHD and the Val allele was preferentially transmitted to girls with ADHD; they also found that male ADHD comorbid with ODD was associated with homozygosity of the high-activity Val allele, while the ADHD-I was associated with the low-activity Met allele. Other studies in Chinese samples also failed to identify a significant association between ADHD and *COMT*.<sup>[74-77]</sup> Zhang and colleagues<sup>[78]</sup> reported that the rs6267 of *COMT* was not associated with the susceptibility to ADHD but it was associated to some of the clinical characteristics of ADHD.

#### 2.4.2 Tryptophan hydroxylase (TPH and TPH-2)

TPH is the rate-limiting enzyme in the synthesis of serotonin, and TPH polymorphisms have been associated with aggression and impulsivity.<sup>[79]</sup> Two family-based studies in Chinese samples have examined the TPH gene in ADHD. One study of 69 Han Chinese trios found no association between ADHD and a SNP (A218C) in intron 7.<sup>[80]</sup> Another study examined two SNPs among more than 350 Han Chinese youth with ADHD (including those with and without learning disability) and their families; neither SNP showed biased transmission individually, but a haplotype composed of the A-218 and G-6526 alleles appeared to be under-transmitted.<sup>[81, 82]</sup> These findings have been replicated in independent samples.<sup>[44, 83-85]</sup> Another study found two tagging SNPs that were associated with comorbid ADHD and tic disorder (TD) in a Chinese Han sample.<sup>[86]</sup> In a Taiwanese sample, Hsu<sup>[66]</sup> failed to replicate the result of a preferential transmission for two polymorphisms in *TPH2*'s regulatory region initially reported in German families with ADHD.

#### 2.4.3 Dopamine beta-hydroxylase (DBH)

*DBH* catalyzes the primary enzyme responsible for conversion of DA to NE, and is found in sympathetic terminals, adrenal glands, and in the prefrontal cortex.<sup>[87]</sup> Many studies have focused on a TaqI restriction polymorphism (rs2519152) of *DBH*, and two meta-analysis reported a significant association between rs2519152 and ADHD.<sup>[10, 88]</sup> Guo and colleagues also found that the A2 allele was a risk factor for ADHD.<sup>[89]</sup> A -1021C>T polymorphism in the 5' flanking region of *DBH* has been shown to account for as much as 50% of plasma *DBH* activity and to be associated with ADHD in the Han Chinese; Zhang and colleagues<sup>[36]</sup> found the this polymorphism was associated with the ADHD-C subtype in male trios.<sup>[90]</sup> Guan identified four statistically significant SNPs of *DBH* in ADHD-I and one statistically significant SNP (rs1076150) in ADHD-C.<sup>[36]</sup> Using a much

larger sample, Ji also found an association between three SNPs (including rs1076150) and ADHD-HI.<sup>[91]</sup>

#### 2.4.4 Monoamine oxidase A (MAOA)

*MAOA* also plays an important role in the metabolism of monoamine neurotransmitters including 5-HT, NE, and DA. A linkage study showed that ADHD might be in linkage with the *MAOA* gene.<sup>[92-94]</sup> A small (n=86) study identified significant associations between two SNP *MAOA* polymorphisms and ADHD remission.<sup>[95]</sup> Guan and colleagues observed nominal associations with all of the 12 SNPs of *MAOA* tested, among which 9 consecutive SNPs approached statistical significance with ( $p < 0.02$ ).<sup>[36]</sup> The identified locations were identical to those reported in an IMAGE (International Multisite ADHD Genetics) study of 776 Caucasian families.<sup>[96]</sup> Liu and colleagues assessed five SNPs in 1253 ADHD trios, and found that rs5905859, rs3027400, and rs1137070 were related to ADHD-HI trios, providing support for the association between *MAOA* and impulsivity.<sup>[97]</sup> Using a Taiwanese sample, Xu<sup>[98]</sup> replicated previously published findings from a Caucasian sample that the G-allele of 941G/T in *MAOA* was associated with ADHD.

#### 2.4.5 Monoamine oxidase B (MAOB)

*MAOB* preferentially metabolizes dopamine, while *MAOA* preferentially metabolizes serotonin and norepinephrine. Li and colleagues<sup>[99]</sup> screened exons and the 5' and 3' flanking regions of the *MAOB* gene and found two novel polymorphisms (2276C>T and 2327C>T) that were closely associated with ADHD. However, Jiang conducted a transmission disequilibrium test (TDT) to assess the linkage between a VNTR polymorphism at the *MAOA* (CA) (n) or *MAOB* (GT) (n) locus, and found no significant linkage between ADHD and *MAOB*.<sup>[92]</sup>

#### 2.4.6 Dopamine decarboxylase (DDC)

Dopa decarboxylase catalyses the formation of functional dopamine through decarboxylation of a precursor tyrosine derivative and it participates in the synthesis of trace amine compounds that are believed to act as modulators of central neurotransmission.<sup>[100]</sup> In a high-density screen, the rs6592952 of *DDC* was associated with ADHD-I (at trend level only).<sup>[36]</sup>

### 2.5 Genes of synaptic vesicle proteins

Psychiatric and neurological diseases are often characterized by the occurrence of aberrant synaptic formation, function, and plasticity, or by malformed dendritic spines. Dysfunctions in neuroplasticity mechanisms and in synapses may be involved in the pathophysiology of ADHD.<sup>[101,102]</sup> A case-control study by Zhao reported a significant association between 1065G>T of *Synaptosomal-associated protein 25*

(*SNAP25*) and ADHD.<sup>[103]</sup> Guan assessed *Synaptophysin* (*SYP*), *SNAP25*, *Syntaxin 1A* (*STX1A*), *Synaptotagmin 1* (*SYT1*), and *Vesicle-associated membrane protein2* (*VAMP2*) in a high-density screen study; they found that the rs5906754 of *SYP* was associated with ADHD-I (a non-significant trend), and *SNAP25* was significantly associated with ADHD-I ( $p < 0.05$ ).<sup>[104]</sup> Liu replicated this result in a larger sample of Han Chinese subjects using both family-based and case-control methods.<sup>[105]</sup>

## 2.6 Other candidate genes

Other candidate genes for ADHD studied include brain derived neurotrophic factor (*BDNF*), brain-specific angiogenesis inhibitor 1-associated protein 2 (*BAIAP2*), circadian locomotor output cycles kaput (*CLOCK*), Zinc finger protein 804A gene (*ZNF804A*), amphetamine-regulated transcript (*CARTPT*), and C-kinase-1 (*PICK1*) genes, Cholinergic receptor.

*BDNF* is a protein that supports survival of central nervous system neurons and stimulates growth and differentiation of developing neurons. Most genetic studies focused on the functional Val66-Met polymorphism (rs6265), which affects intracellular trafficking and activity-dependent secretion of *BDNF*. Cao and Li found that the rs6265 was associated with ADHD or its subtypes.<sup>[106,107]</sup> However, Xu and colleagues<sup>[108]</sup> failed to replicate these associations with Val66 in samples from the United Kingdom or Taiwan. Xu and colleagues<sup>[108]</sup> also examined the 270C>T SNP in the 5'-noncoding region of intron1 and found significant over-transmission of the C270T allele in Taiwanese, but not British, ADHD families. Li and colleagues found a higher prevalence of the Val allele in females with ADHD compared to female controls and a non-significant lower plasma *BDNF* level in Val allele carriers than in Met/Met genotype carriers ( $p = 0.071$ ).<sup>[109]</sup>

*BAIAP2* is thought to be associated with cerebral asymmetry. A study by Liu and colleagues showed that *BAIAP2* was associated with childhood ADHD – especially ADHD-I – in individuals of Han Chinese descent.<sup>[110]</sup> The haplotype AAGG, which consists of rs4969239-rs4969358-rs6565531-rs8079626 was associated with ADHD children who had comorbid learning disorders.<sup>[111]</sup>

Xu and colleagues<sup>[112]</sup> found increased transmission of the T allele of the rs1801260 polymorphism of *CLOCK* in both Taiwanese and British ADHD cases, but they didn't find significant associations between rs1344706 or *ZNF804A* and ADHD.<sup>[113]</sup> Hsu and colleagues investigated the polymorphisms of *CARTPT* and *PICK1*, but they failed to identify any statistically significant associations between ADHD and the genotyped SNPs in the two genes.<sup>[114]</sup>

## 3. Endophenotype

Endophenotype is a heritable trait associated with a disease that is measurable and, thus, it serves as an intermediate marker between genotype and phenotype.

Endophenotypes may include neurophysiological, biochemical, neuroanatomical, cognitive, and neuropsychological (including configured self-report data) measures. Promising cognitive endophenotypes for ADHD include the intelligence quotient (IQ), executive function (EF), memory, and attention.<sup>[115]</sup> Clarifying the relationships between these endophenotype measures and genetic variants of ADHD will help identify the brain functions affected by ADHD and help characterize the pathways from genes to behavior.

Executive function consists of response inhibition, working memory, cognitive shifting, planning, and verbal fluency. Studies by Shuai and Qian revealed that Chinese Han children with ADHD have impaired executive functioning in performance-based tests and in everyday life scenarios.<sup>[116,117]</sup> Response inhibition is of particular interest to ADHD researchers because of its close association with the core symptoms of ADHD. Qian<sup>[118]</sup> reported associations between *COMT* Val158Met in ADHD cases and measures of response inhibition (evaluated by Stroop), memory (evaluated by the Wechsler Memory Scale), and attention (evaluated by the Number Cancellation Test); Zhang found this polymorphism in ADHD cases was associated with the results of the Wisconsin Card Sorting Test (which assesses executive functioning).<sup>[119]</sup> Ji and colleagues<sup>[120]</sup> found that ADHD patients with the TT genotype of *DBH* 1021C/T performed significantly better than ADHD children with CT or CC genotypes on the Stroop task (assessing response inhibition). Liu<sup>[97]</sup> found relationships between the genetic profile of *MAOA* in ADHD cases, laboratory-based tests of impulsivity, and parents' scores about their child on the 'inhibit' factor of the Behavior Rating Inventory of Executive Function. Similarly, a study from Taiwan found that genetic variation in *DAT1* predicts measures of spatial working memory.<sup>[121]</sup>

There is a significant literature suggesting that IQ is highly heritable.<sup>[122]</sup> Chinese researchers have examined the association between specific genes and IQ in individuals with ADHD. Qian<sup>[123,124]</sup> found that the *HTR2A* -1438 A/G polymorphism and interaction between the *STIN2* VNTR and *HTR2A* -1438 A/G might be associated with IQ. She also found that *MAOA-uVNTR*, *COMT* Val158Met, and their interaction significantly predicted the IQ of boys with ADHD; they also reported an inverted U-shaped relationship between IQ in ADHD and the activity of dopamine.<sup>[123,125,126]</sup>

## 4. Genome wide association studies

To date, the eight GWAS conducted for ADHD have been inconclusive; no genome-wide significant associations have been identified for any SNP.<sup>[3,83,127-133]</sup> But the results from GWAS do suggest that genes playing a role in ADHD are related to the processes that enhance neuronal plasticity, including neuronal migration, cell adhesion, cell division, and signaling via the potassium channel-system.<sup>[134,135]</sup> In China, Yang and colleagues first conducted GWAS in 1040 ADHD cases and 963 controls; they found no significant SNPs, but they did

find an increased burden of large, rare copy number variants (CNVs) in the ADHD subjects ( $p=0.038$ ). Pathway analyses identified several genetically determined cellular components, including neuron projections and synaptic components<sup>[133]</sup>; these findings support hypotheses about the neurodevelopmental pathophysiology for ADHD.<sup>[136]</sup> However, given the evident complexity and heterogeneity of the etiological pathways to ADHD, very large samples of cases will need to be collected (possibly from collaborative international studies) and followed over time to identify the different clinical trajectories of specific types of genetic profiles. Considering the complex heterogeneity of ADHD, international collaboration is needed to obtain a larger sample.

### 5. Pharmacogenomic studies

Genetics has the potential to provide an invaluable contribution to the pharmacological management of ADHD. However, no pharmacogenetic study has yet identified genes that can predict the effectiveness and side effects of different ADHD medications. Most of pharmacogenetic investigations in ADHD have focused on response to methylphenidate (MPH), a first-line option in the psychopharmacologic treatment of ADHD.<sup>[137,138]</sup> Yang and colleagues<sup>[139]</sup> studied the reduction in ADHD-RS scores among 45 children and adolescents who received MPH at doses of 0.45 to 0.60 mg/kg per day; they reported a significant association between the *SLC6A5* polymorphism G1287A and responsiveness to MPH (based on decreases in scores for hyperactivity and impulsiveness but not in scores for inattentiveness). However, these findings were not replicated by international researchers.<sup>[140,141]</sup>

Atomoxetine is a norepinephrine reuptake inhibitor with demonstrated efficacy for the treatment of ADHD.<sup>[142]</sup> Yang and colleagues<sup>[143]</sup> evaluated the association between twelve SNPs in *SLC6A2*, *ADRA2A*, and *ADRA1A* and the response or remission status after atomoxetine treatment. The results suggested that DNA variants of both *SLC6A2* and *ADRA2A* in the adrenergic neurotransmitter system might alter the response to atomoxetine.

Possible explanations of the inconsistent results of ADHD pharmacogenetic studies include differences in study design, medication dosing regimens, and outcome measures. Advances in ADHD pharmacogenetics can potentially identify novel, targeted treatments for different subgroups of patients; the use of such patient-specific treatments could substantially improve the efficacy and safety of ADHD treatment.

### 6. Summary and future directions in ADHD genetic research

This article reviewed the main molecular genetic studies about ADHD among Han Chinese samples in mainland China and elsewhere. Overall, the findings have been inconsistent and disappointing. There are several possible reasons for the failure of GWAS and

candidate gene studies to identify high heritability genes associated with ADHD:

- (a) ADHD may be result of the cumulative effect of multiple genetic factors with small individual effects that can only be identified in studies with very large sample sizes;
- (b) ADHD may be caused by gene–gene and gene–environment interactions that are not being identified by current studies;
- (c) genetic factors other than the SNPs investigated in most current studies (e.g., copy number variants, structural variants in DNA, etc.) may play important roles in the etiology of ADHD;
- (d) current diagnostic criteria for the clinical identification of ADHD may not reflect the underlying biological and genetic subtypes of the condition; and
- (e) the subjects studied in the different studies vary widely in age, ethnicity, gender, comorbidity, and diagnostic characteristics.

Clearly there needs to be a re-focusing of effort to move this field forward. The old methods are not generating much useful information so we should be actively trying new methods. More attention needs to be focused on the genetic correlates of other aspects of neuronal functioning that may prove more productive than the ‘usual suspects’ that have been the focus of attention in ADHD molecular genetic studies over the last 15 years: including processes such as cell division, adhesion and polarity, neuronal migration and plasticity, extracellular matrix regulation, and cytoskeletal remodeling. Studies that integrate genetic findings with imaging assessments of brain structure and function<sup>[144]</sup> are needed to identify the changes in the brain that link genetic to behavioral changes. Longitudinal studies are needed to identify the genetic and environment factors that predict spontaneous recovery prior to adulthood versus a lifetime course of illness. Finally, the research culture and funding mechanisms that promote the conduct of large numbers of small-sample, underpowered studies – a problem that is particularly evident in China – needs to change. Large collaborative studies between centers that rigorously ensure standardization of procedures are essential to achieving the sample sizes needed to identify uncommon, but etiologically important, genetic variants.

### Conflict of interest

The authors declare no conflict of interest.

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## 注意缺陷多动障碍在中国的分子遗传学研究进展

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**概述:** 注意缺陷多动障碍 (attention deficit hyperactivity disorder, ADHD) 是全球常见的儿童精神障碍, 通常包括注意力不集中和多动/冲动的症状。一般认为遗传因素在 ADHD 的发生和发展过程中起到重要作用, 因此展开了很多针对该障碍遗传机制中病因或影响因素的候选基因研究和全基因组关联研究 (GWAS)。本文就在中国大陆开展的以及在其他地方开展的使用汉族华人样本的 ADHA 基因关联研究和药理学研究做了一个综述。迄今为止, 上述研究依然

没有明确结论, 所以将来的研究需要考虑其他的分析技术来验证这种致残性障碍发生和发展过程中神经递和神经发育之间关联的新生物学假说。

**关键词:** 注意缺陷多动障碍, 遗传, 候选基因研究, 全基因组关联研究, 中国

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