

A Review of Genetic Studies on Attention-deficit Hyperactivity Disorder in Han Chinese Population

中國漢族人注意力不足多動症的遺傳學研究回顧

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Abstract

Objective. To introduce the progress in genetic studies in attention-deficit hyperactivity disorder with particular emphasis on findings in Han Chinese.

Methods. The literature review included peer-reviewed articles on Medline, the China National Knowledge Infrastructure database, and references since 1980 were hand-picked.

Results. Several candidate genes have a substantial role in the aetiology of attention-deficit hyperactivity disorder. Possible confounding influences include: population admixture, environment and its interactions with genetic factors, diagnostic criteria, ethnicity, and genotype.

Conclusions. Diversity of the relationships of genes with attention-deficit hyperactivity disorder exists across different ethnic groups. Therefore, findings in western countries may not apply to other ethnic groups, including the Han Chinese population.

Key words: Attention deficit disorder with hyperactivity; Chinese; Genetic predisposition to disease; Genotype; Receptors, dopamine D4

摘要

目的：探討注意力不足多動症的遺傳學研究，尤其集中在中國漢族人的研究發展。

方法：回顧文獻包括Medline資料庫和中國知識基礎設施工程數據庫內經同儕評鑑的文章，以及自1980年出版經挑選的參考資料。

結果：導致注意力不足多動症方面，幾個候選基因扮演著很重要的角色。可能的混染影響包括：種群混合、環境及其與遺傳因素的相互作用、診斷標準、種族，以及基因類型。

結論：注意力不足多動症與基因的關係，在不同的種族存在著多樣性。因此西方國家的研究未必可應用於其他族群，如中國漢族人。

關鍵詞：注意力不足多動症、中國人、對疾病的遺傳易感性、基因型、多巴胺D4受體

Introduction

Attention-deficit hyperactivity disorder (ADHD) is a common childhood psychiatric problem characterised by hyperactivity, inattention and impulsivity,¹ and has a prevalence rate of 8 to 12% worldwide² and 3 to 8%

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in China.³⁻⁵ Family, twin, and adoption studies provide consistent evidence supporting the hypothesis that genetic factors lead to its familial aggregation.^{6,7} For example, Faraone and Biederman⁸ found that the risk of ADHD in parents of children with ADHD increased by 2- to 8-fold compared to healthy controls. Sprich et al⁹ reported that biological relatives of non-adopted ADHD children had a higher rate of the condition than adoptive relatives, while the risk in adoptive relatives was similar to the relatives of control children. In addition, twin studies concluded that ADHD has high heritability in the range of 75 to 91%.^{10,11}

During the past decade, there has been growing interest in molecular genetic studies of ADHD.¹² Moreover, molecular genetic methods including the candidate gene and genome scan approaches have been widely used to explore specific genetic factors by relating variations in DNA (genotype) to the diagnosis of ADHD (phenotype).¹³ Previous studies indicated that ADHD is polygenic and

Table. Recent genetic studies on attention-deficit hyperactivity disorder (ADHD) in the Han Chinese.

Study	Methods	ADHD sample	Candidate gene	Findings
Qian et al ²²	Case-control design	340 ADHD children and 226 healthy controls in Beijing	<i>DRD4</i>	2-Repeat allele was more common in ADHD children
Leung et al ²³	Case-control design	32 ADHD probands and 247 healthy controls in Hong Kong	<i>DRD4</i>	A significantly increased prevalence of 2-repeat allele in ADHD children
Chen et al ⁴³	Family-based design	110 Chinese probands in Taiwan	<i>DAT</i>	Increased transmission of the 10-repeat allele in ADHD patients
Qian et al ⁴⁶	Case-control design	337 ADHD children and 207 healthy controls in Beijing	<i>DAT</i>	G352G had a tendency to be over-transmitted to ADHD girls
Li et al ⁴⁹	One-group design	68 ADHD children in Beijing	<i>MAO</i>	There was significant association between <i>MAO</i> and ADHD remission
Li et al ⁶	Case-control design	272 Chinese ADHD trios and divided by subtype of ADHD in Beijing	5-HT _{1D}	An allele of the 1236A>G exhibited a significant preferential transmission to probands of ADHD
Li et al ⁶⁰	Family-based design	333 ADHD nuclear families in Beijing	5-HT _{2A} , 5-HT _{5A} , and <i>HTR6</i>	Five variants in 3 serotonin genes coding for <i>HTR2A</i> , <i>HTR5A</i> , and <i>HTR6</i> were not biased in transmission
Li et al ⁶¹	Family-based design	488 Families with ADHD patients in Beijing	5-HT _{2C}	The -759C allele, the -697G allele, and haplotype -759C/-697G were over-transmitted to affected probands while haplotypes -759C/-697C and -759T/-697C were under-transmitted
Li et al ⁶⁷	Family-based design	326 ADHD nuclear families in Beijing	5-HT ₄	C/G haplotype of the 83097C>T and 83198 A>G polymorphisms, the C/G/C haplotype of these polymorphisms and the -36 C>T polymorphism were under-transmitted to probands with ADHD
Li et al ⁶⁸	Family-based design	293 ADHD trios in Beijing	5-HTT	Over-transmission of the S allele of the 5-httlpr polymorphism to probands of ADHD, and no association between the STin2.VNTR and ADHD
Li et al ⁷³	Case-control design	132 Trios with probands of ADHD with learning disorder and 221 trios with probands of ADHD without learning disorder in Beijing	<i>TPH</i>	<i>TPH</i> gene and the haplotype 218A/-6526 G might be related to ADHD with learning disorder
Tang et al ⁷⁴	Family-based design	69 ADHD nuclear families in Shanghai	<i>TPH</i>	The <i>TPH</i> gene A218C polymorphism might not be a susceptibility factor of ADHD in the Chinese Han population

Abbreviations: *DRD4* = dopamine D4 receptor; *DAT* = dopamine transporter; *MAO* = monoamine oxidase; 5-HT = 5-hydroxytryptamine; and *TPH* = tryptophan hydroxylase.

multiple genes contribute small fractions to the total genetic effect.¹⁴ Meanwhile, ethnic difference is a common phenomenon in the genetic study in ADHD,¹⁵ which suggests the findings in western settings may not be applicable to other ethnic populations.¹⁰

To date, the choice of candidate genes has mainly focused on those encoding proteins involving dopaminergic and serotonergic pathways.¹⁰ Findings from numerous studies of ADHD candidate genes have been reviewed in considerable detail elsewhere.^{10,16} In this review, we summarise the progress of molecular genetic studies documenting the associations between the candidate genes and variants, and susceptibility

to ADHD in the Han Chinese (Table).

Methods

Peer-reviewed articles were searched on Medline and the China National Knowledge Infrastructure database, and references since 1980 were hand-picked.

Results

The Dopamine D4 Receptor Gene

Earlier neuroimaging and neuropsychological studies¹²

reported that the dopamine D4 receptor (*DRD4*) gene (influencing frontal-subcortical networks) is implicated in the pathophysiology of ADHD. Recent studies focused predominantly on a tandem repeat polymorphism in exon III of *DRD4* because of one variant, namely the 7-repeat allele that produces a blunted response to dopamine.¹⁷ Faraone et al¹⁸ documented the association between ADHD and *DRD4* in a meta-analysis and found the combined estimate of the odds ratios ranged from 1.4 (95% confidence interval [CI], 1.1-1.6) to 1.9 (95% CI, 1.4-2.2), which suggested that there was significant association between ADHD and the 7-repeat allele. Subsequently, a number of studies (though not all) confirmed this association.¹⁹⁻²¹ Qian et al²² investigated the association of the 48bp variable number tandem repeat polymorphism in the *DRD4* exon III among Han Chinese children in a case-control study, but did not find the 7-repeat allele in ADHD or healthy control subjects, although 2- and 4-repeat alleles were more common in the ADHD group. Similarly, Leung et al²³ also found a significantly increased prevalence of 2-repeat alleles rather than 7-repeat alleles in 32 Han Chinese children with ADHD. These findings suggest that allele frequencies of the *DRD4* gene vary between ethnic groups.¹³

The Dopamine D5 Receptor Gene

Initial studies reported increased transmission of the 148-bp allele to ADHD patients, with the strongest effect in families without a parental history of ADHD,²⁴ and recent studies on dopamine D5 receptor (*DRD5*) genes focused on a dinucleotide repeat which maps approximately 18.5 kb 5' to the start site of transcription.²⁵ The above associations were replicated by Tahir et al²⁶ and Comings et al.²⁷ Another 2 family-based analyses also replicated the association of the 148-bp allele with ADHD.^{28,29} In contrast, in some studies there was no evidence of associations with the dinucleotide repeat polymorphism³⁰ or the 148-bp allele.^{31,32} In a meta-analysis, Maher et al³³ found a significant association between *DRD5* and ADHD and concluded that the non-significant results of previous studies were probably due to insignificant statistical power. However, there is a lack of evidence that the dinucleotide repeat is functional, although *DRD5* has been suggested to be a susceptibility gene for ADHD.²⁵ To date, there is no study on *DRD5* in Chinese ADHD patients.

The Dopamine D2 and D3 Receptor Genes

There are scant studies on dopamine D2 receptor (*DRD2*) genes in comparison to those on *DRD4* and *DRD5*, and the conclusions were inconsistent. In 2 case-control studies, Comings et al^{34,35} found a significant association of TaqIA1 allele of *DRD2* with ADHD, but this finding was not replicated in 2 other family-based studies.^{36,37}

For dopamine D3 receptor (*DRD3*) genes, no allele was associated with ADHD, although an intron 5 MspI restriction and a Ser9Gly exon 1 polymorphism were reported to be in strong linkage disequilibrium in a family-based study in Canada.³⁸ Similar to *DRD5*, there has been

no study on *DRD2* and *DRD3* in the Chinese population.

Dopamine Transporter Gene

Dougherty et al³⁹ measured striatal dopamine transporter (*DAT*) gene activity and found that in ADHD patients, it was elevated by approximately 70%, and that it was reduced to normal levels following methylphenidate exposure. According to extensive studies during the past decade,^{40,41} evidence from both animal and other pharmacological studies showed that SLC6A3 (which encodes the *DAT* gene and maps to 5p15.3) was a suitable candidate gene for ADHD. For example, in a family-based study, Cook et al⁴² found a significant association of the 10-repeat allele of a tandem repeat polymorphism located in the 3' untranslated region of SLC6A3 with ADHD. Chen et al⁴³ analysed the SLC6A3 polymorphism in a sample of 110 Chinese probands in Taiwan with a Diagnostic and Statistical Manual of Mental Disorders—4th ed (DSM-IV) diagnosis of ADHD, and found evidence of increased transmission of the 10-repeat allele. In a meta-analysis, however, Curran et al⁴⁴ failed to find a significant association between ADHD and genetic variation at the SLC6A3. In a family-based twin study, Todd et al⁴⁵ also found no association with the 10-repeat allele with any subtypes of DSM-IV ADHD. Owing to these inconsistent findings, Faraone et al¹⁰ concluded that the effect of *DAT* on ADHD was probably modest, though further investigations were still warranted.

In another case-control study, Qian et al⁴⁶ in Beijing found that G352G, a new polymorphism in exon 15 of SLC6A3, had a tendency to be preferentially transmitted to ADHD girls, but no association was found between G352A and ADHD.

Monoamine Oxidase Gene

The monoamine oxidase (*MAO*) gene modulates one of the main metabolic enzymes for degradation of dopamine, serotonin, and norepinephrine transmitters, while those that code these 3 transmitters were the strongest candidate genes studied for ADHD.^{16,47} *MAO* has A and B types, that have similar structures and can degrade all the 3 neurotransmitters.⁴⁸ Their aetiological association with ADHD has therefore been investigated. In a case-control study, Manor et al²⁹ reported an association between a 30-bp tandem repeat in the promoter region of MAOA and ADHD in 129 patients with ADHD in Israel.

In China, Li et al⁴⁹ examined the association between adolescent outcome in 68 Chinese ADHD patients and *MAO* gene polymorphisms. They studied the 941T>G polymorphism in exon 8, 1460 C>T polymorphism in exon 14, the A>G polymorphism in the intron 13, the C>T polymorphism in the 3'UTR, and the 2327T>C polymorphism in exon 15, and encountered the association of MAOA with ADHD in remission. However, these findings need to be replicated due to the relatively small sample sizes.

Serotonin Receptor Genes 5-HT_{1B} and 5-HT_{1D}

HTR1B encodes the 5-HT_{1B} receptor and maps to

chromosome 6q13.⁵⁰ In animal studies, mice lacking this receptor manifested motor hyperactivity.⁵¹ Two family-based studies found the over-transmitted G allele gene coding for the serotonin *HTR1B* receptor in Caucasian samples.^{52,53} To date, there has been no study on the association between 5-HT_{1B} and ADHD in Chinese subjects.

HTR1D shares 77% amino acid sequence similarity and drug specificity with *HTR1B* and these 2 receptors were even named as serotonin-1D alpha and -1D beta.⁵⁴ *HTR1D* is responsible for regulating the release of serotonin in brain and variants in the *HTR1D* gene may disrupt this process in ADHD.⁵⁵ Bergen et al⁵⁶ found 3 polymorphisms in *HTR1D*, including 2190A>G, -628T>C, and -1123T>C, and showed significant transmission disequilibrium in ADHD patients. Li et al⁶ investigated 272 ADHD trios of Han Chinese ethnicity using a transmission disequilibrium test (TDT), and found the A allele of the 1236A>G exhibited a significant preferential transmission to probands of ADHD.

Serotonin Receptor 5-HT_{2A} Gene

The serotonin receptor 5-HT_{2A} (*HTR2A*) gene is located on chromosome 13q14-21; in animal studies, an antagonist of this receptor will lead to decreased dopamine-induced hyperactive behaviour in mice.⁵⁷ In Canada, Quist et al⁵⁸ found an association between the His 452Tyr allele of the 452His>Tyr polymorphisms of the *HTR2A* and ADHD, using the TDT test. While Zoroğlu et al⁵⁹ found no significant association between T102C and G1438A polymorphisms, and ADHD. A meta-analysis for the association between *HTR2A* and ADHD yielded a pooled odds ratio of 1.1, which was not significant.¹⁰ In a Chinese study involving 311 ADHD trios, Li et al⁶⁰ reported that 5 variants in 3 serotonin genes coding for *HTR2A*, *HTR5A*, and *HTR6* were not biased in transmission.

Serotonin Receptor 5-HT_{2C} Gene

The 5-HT_{2C} receptor mainly focuses on the choroid plexus, substantia nigra, globus pallidus, neocortex, hippocampus and raphe.⁶¹ This receptor partly controls dopamine function and plays an important role in the aetiology of ADHD.⁶² The serotonin receptors 5-HT_{2C} (*HTR2C*) gene has been mapped to chromosome Xq24.⁶³ Bobb et al¹⁶ reported lack of evidence for the association between *HTR2C* polymorphisms and ADHD in Caucasians. In contrast, in a family-based study by Li et al⁶¹ involving 488 Han Chinese families with ADHD patients, it was reported that the -759C allele, the -697G allele, and haplotype -759C/-697G were over-transmitted to affected probands, while haplotypes -759C/-697C and -759T/-697C were under-transmitted.

Serotonin Receptor 5-HT₄ Gene

The serotonin receptor 5-HT₄ (*HTR4*) gene is predominantly located on chromosome 5q32, and consists of 5 exons producing at least 8 variants.⁶⁴ 5-HT₄ receptors are more prevalent in the limbic system and frontal cortex, and facilitate dopamine release.⁶⁵ In animal studies, mice lacking this receptor showed attenuated novelty-induced exploratory

activity.⁶⁶ In a family-based study, Li et al⁶⁷ examined the relationship of the *HTR4* gene with the predisposition to ADHD. They found that the C/G haplotype of the 83097C>T and 83198A>G polymorphisms, the C/G/C haplotype of these polymorphisms, and the -36 C>T polymorphism were under-transmitted to probands. However, this finding needs to be replicated by independent studies.

Serotonin Transporter Gene

The serotonin transporter (5-HTT) gene was one of the most widely studied in ADHD during the past decade. It is located at 17q11.2 and comprises 3 candidate polymorphisms, including a 44bp insertion / deletion in the promoter region (5-HTTLPR), which results in a long (L) and a short (S) allele, a 17bp variable number of tandem repeats (VNTR) in intron 2 (STin2.VNTR) and a 3' untranslated region G/T SNP (3' UTR SNP).⁶⁸ Previous studies suggested a 44bp insertion / deletion in 5-HTTLPR and ADHD. In a case-control study, Seeger et al⁶⁹ reported an over-expression of the L/L genotype of hyperkinetic disorder with or without conduct disorder. Zoroğlu et al⁵⁹ also found an association between VNTR polymorphism (STin2) and ADHD. Kent et al⁷⁰ described a significant association of 3' UTR SNP and ADHD in a family-based study. In contrast, some studies had negative results.⁷¹ In a meta-analysis, Faraone et al⁷² surmised that the pooled odd ratios for the associations between the L allele and ADHD is 1.31 (95% CI, 1.09-1.59).

In a Han Chinese family-based study, Li et al⁶⁸ found an over-transmission of the S allele of the 5-HTTLPR polymorphism to probands of ADHD, and no association between the STin2.VNTR and ADHD. At the same time, the L/12 haplotype was found to be under-transmitted to probands with ADHD while the L/10 haplotype was over-transmitted.

Tryptophan Hydroxylase Gene

The tryptophan hydroxylase (*TPH*) gene encodes the rate-limiting enzyme in the process of 5-HT biosynthesis, therefore it is considered a candidate gene for ADHD. Two studies were carried out in Chinese ADHD patients. Li et al⁷³ explored the relationships between 2 *TPH* gene polymorphisms, A218C and A-6526G polymorphisms, and ADHD in 353 trios with probands of ADHD with or without learning disorder. He found haplotype of 218A/-6526G to be significantly not transmitted to the probands with ADHD with learning disorder. In another study in a Chinese population however, Tang et al⁷⁴ found no evidence of any association between the A218C polymorphism of *TPH* gene and susceptibility of ADHD. Therefore, further studies are warranted to clarify any possible association.

Discussion

Attention-deficit hyperactivity disorder is a highly heritable condition, and the genetic contribution to ADHD has been well-established in recent years. However, previous studies

reviewed in this paper indicated that the genetic architecture is quite complex. We introduced earlier studies involving 13 candidate genes of ADHD, and the corresponding findings are not conclusive. The Table summarises molecular studies involving 9 candidate genes conducted among Han Chinese subjects.

In a meta-analysis, the odds ratios for associations of candidate genes including *DRD4*, *DRD5*, *DAT*, *5-HTT* and *HTR1B* with ADHD ranged from 1.18 to 1.46, which supports the belief that many genes with small effects mediate the genetic vulnerability to ADHD.⁷⁵ Inconsistent findings in previous studies could have several explanations. First, population admixture could result in false-positive results in case-control study⁷⁶; second, given the small effects of candidate genes, negative findings could be due to lack of statistical power¹⁰; third, environmental factors have confounding effects on genetic studies of ADHD.¹³ Finally, differences in diagnosis of ADHD (phenotype), ethnicity, and genotype could have contributed to earlier inconsistent findings.⁷⁵ Therefore, it is recommended that meta-analyses, multi-centre or collaborative studies with large sample sizes, homogeneous samples with refined phenotype definitions and consideration of gene-gene and gene-environment interactions should be carried out in the future.¹⁰

In this review, we found the majority of associations between candidate genes and variants, and ADHD in the Han Chinese population to be not consistent with results reported in the West. This supports the belief that there is a diversity of the relationships between genes with ADHD, which differ according to ethnic groups. Further studies exploring these associations are warranted in China.

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