Genome Medicine

Minireview

A role for neurotransmission and neurodevelopment in attention-deficit/hyperactivity disorder

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Abstract

Attention-deficit/hyperactivity disorder (ADHD) has a moderate to high genetic component, probably due to many genes with small effects. Several susceptibility genes have been suggested on the basis of hypotheses that catecholaminergic pathways in the brain are responsible for ADHD. However, many negative association findings have been reported, indicating a limited success for investigations using this approach. The results from genome-wide association studies have suggested that genes related to general brain functions rather than specific aspects of the disorder may contribute to its development. Plausible biological hypotheses linked to neurotransmission and neurodevelopment in general and common to different psychiatric conditions need to be considered when defining candidate genes for ADHD association studies.

Introduction

Although the etiology of attention-deficit/hyperactivity disorder (ADHD) is not completely understood, it is well known that the disorder has a moderate to high genetic component, with an estimated heritability of 76% [1]. The mode of transmission is likely to be due to many susceptibility genes with small effects. Moreover, recent research findings have highlighted the relevance of gene-gene and gene-environment interactions in explaining the heterogeneous ADHD phenotype [2-4]. Several susceptibility genes have been proposed in almost 15 years of molecular research on ADHD, mainly on the basis of neurobiological hypotheses for ADHD. However, the success of these investigations can be considered as limited, because many studies were not able to replicate the positive results [1,4]. Here, we review the main results obtained so far in the ADHD molecular genetics field and suggest new ways of investigation that might help to clarify the genetic component of ADHD.

The first molecular genetic studies of ADHD

The dopaminergic theory proposed to explain the neurobiology of the disorder [5], initially largely based on pharmacological evidence, states that abnormal levels of dopamine cause ADHD. This led in 1995 to the first association study by Cook *et al.* [6], who investigated a 40 bp variable number tandem repeat (VNTR) in the 3' untranslated region of the dopamine transporter gene (*DAT1*) in ADHD families. Using the family-based approach called 'haplotype relative risk', an association with the ten-repeat allele was detected. In the following year, LaHoste *et al.* [7] investigated another dopaminergic gene, the dopamine D4 receptor gene (*DRD4*). In this study [7], the frequency of a 48 bp VNTR in exon 3 was compared between ADHD cases and controls and an association with the seven-repeat allele was observed. These two genes, specifically through these variants, became the most studied genes in ADHD molecular genetics, with some positive and some negative results. Other polymorphisms in the two genes and in genes coding for other dopaminergic components were also investigated, although in fewer studies. Several other candidate genes were extensively studied on the basis of noradrenergic and serotonergic hypotheses for ADHD, as were genes encoding components of other neurotransmission systems and functions [8-10]. Meta-analyses have suggested that the *DAT1*, *DRD4*, dopamine D5 receptor (*DRD5*), dopamine β hydroxylase (*DBH*), serotonin transporter (*5HTT*), serotonin 1B receptor (*5HT1B*) and synaptosomal-associated protein of 25 kDa (*SNAP25*) genes are susceptibility genes for ADHD. However, the odds ratios for these genes range from 1.00 to 1.30, so they can have only a very small effect on ADHD symptoms [1,4,11].

The existence of many negative association reports, together with the small effects detected in meta-analyses, suggests that the putative susceptibility genes can be responsible for only a minority of ADHD cases, explaining only a tiny part of its development or phenotypic heterogeneity. Moreover, the candidate gene approach may not be the only strategy

ADHD, attention-deficit/hyperactivity disorder; *BAIAP2*, brain-specific angiogenesis inhibitor 1-associated protein 2 gene; *BDKRB2*, bradykinin receptor B2 gene; *DAT1*, dopamine transporter gene; *DRD4*, dopamine D4 receptor gene; SNP, single nucleotide polymorphism; VNTR, variable number tandem repeat.

for detecting susceptibility genes in complex diseases like ADHD [2,4,12]. Genome-wide linkage and association scans, in which hundreds to thousands of genetic markers are evaluated, have shown promising results. The first ADHD genome scan [13] screened 404 polymorphisms in 126 affected sibling pairs. Evidence for linkage was obtained for regions in chromosomes 5, 10, 12 and 16. After this initial report [13], other genome scans testing for linkage were conducted, suggesting different loci on several chromosomes [4,14]. The meta-analysis by Zhou *et al.* [15] identified 16q23.1 to q terminal as the genomic region with the most consistent linkage evidence across these studies, a region in which, surprisingly, no genes related to previous neurobiological ADHD hypotheses are mapped.

Because linkage approaches seem to be more useful for genes of moderate to major effects [16], researchers have turned to genome-wide association studies. In a recent review, Franke and colleagues [17] have shown that none of the individual investigations report any association that remains significant at the genome-wide level after correction for multiple testing. However, the most important finding is that there is little evidence supporting a role for the 'classic' ADHD genes, namely the ones related to dopaminergic, noradrenergic and serotonergic systems, in the genome-linkage scans. On the other hand, genes related to other neurotransmission and cell-cell communication systems are suggested, including processes such as cell division, adhesion and polarity, neuronal migration and plasticity, extracellular matrix regulation and cytoskeletal remodeling processes. Thus, although without statistically significant results (probably because of the insufficient power in all the studies), the findings from genome-wide approaches indicate a whole range of new and promising possibilities for ADHD molecular genetic studies [17].

Genes associated with neurodevelopment as predisposing genes for ADHD

A recent report by Ribasés and colleagues [18] is one example of this new emphasis on candidate gene investigations. Considering the abnormal left-right brain asymmetries observed in several ADHD neurobiological studies, the authors [18] selected six functional genes shown to be expressed differentially between brain hemispheres in a previous report by Sun *et al.* [19]. These are the genes encoding brain-specific angiogenesis inhibitor 1-associated protein 2 (*BAIAP2*), dapper antagonist of β-catenin homolog 1 (*DAPPER1*), LIM domain only 4 (*LMO4*), neurogenic differentiation 6 (*NEUROD6*), ATPase, Ca^{++} transporting plasma membrane 3 (*ATP2B3*) and inhibitor of DNA binding 2 (*ID2*). An initial case-control study was conducted in a sample of 587 participants with ADHD (children and adults) and 587 matched control individuals from Spain. The results obtained were then tested in two other case-control samples from Germany and Norway (639 and 417 adult ADHD participants and 612 and 469 control individuals, respectively). From a total of 30 single nucleotide polymorphisms (SNPs) investigated in these six genes, an association with *BAIAP2* was detected, by both the single- and multiple-marker analyses, in the adult ADHD Spanish sample. In the replication study, the association with this locus was also observed in the German sample, although there was a slight difference in the putative risk SNPs. No positive results were obtained for the Norwegian patients. From these findings, the authors [18] concluded that genetic factors possibly influencing abnormal cerebral lateralization may be involved in ADHD etiology, with *BAIAP2* acting specifically in cases of persistent ADHD.

BAIAP2 is located at 17q25 and encodes the 53 kDa insulin receptor tyrosine kinase substrate protein (IRSp53), a molecule that participates in the signal transduction pathways of insulin and insulin-like growth factors. This protein is highly expressed in the left cortex and seems to be involved in neuronal proliferation, survival and maturation [18]. The *BAIAP2* locus is not only a new gene to be investigated in ADHD, but it also indicates that genes related to general brain functions, rather than specific aspects of the disorder, may contribute to ADHD development; common variants in these genes could then confer susceptibility to a group of related psychiatric disorders. Further evidence for this hypothesis has recently been provided by Gratacòs and colleagues [20], who observed an association of the bradykinin receptor B2 gene (*BDKRB2*) with panic disorder, substance abuse, bipolar disorder, obsessive-compulsive disorder and major depression. *BDKRB2* is located at 14q32 and encodes a transmembrane receptor for the non-peptide bradykinin, which activates various second messenger systems. In response to this signal, several processes are modulated, including blood-brain barrier permeability, blood pressure regulation, pain perception, release of glutamate from astrocytes, neuronal differentiation and nitric oxide production [20].

Conclusions

The investigations performed so far on ADHD are far from conclusive. Many more studies are still needed to raise new biological hypotheses linked to neurotransmission and neurodevelopment in general in order to define new candidate genes for association studies with ADHD. Knowledge of such genes will allow us to identify specific diagnostic biological markers. In addition, defining target genes is the first step toward the development of novel drug therapies for ADHD.

Competing interests

LAR has served as a speaker and/or consultant for Eli Lilly, Janssen-Cilag and Novartis in the past 5 years. Currently, his only industry-related activity is taking part in the advisory board/speakers' bureau for Eli Lilly and Novartis (less than US$10,000 per year and reflecting less than 5%

of his gross income per year). The ADHD and Juvenile Bipolar Disorder Outpatient Programs chaired by him received unrestricted educational and research support from the following pharmaceutical companies in the past three years: Abbott, Bristol-Myers Squibb, Eli Lilly, Janssen-Cilag, Novartis and Shire. TR and MHH declare that they have no competing interests.

Authors' contributions

TR and MHH conceived the article and helped to draft the manuscript. LAR helped to draft the manuscript. All authors read and approved the final manuscript.

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