

The genetic overlap of attention deficit hyperactivity disorder and autistic spectrum disorder

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Abstract: Autistic spectrum disorders (ASD) and attention deficit hyperactivity disorder (ADHD) are classified as distinct disorders within the DSM-IV-TR (1994). The manual excludes simultaneous use of both diagnoses in case of overlap on a symptomatic level. However this does not always represent clinical observations and findings of previous studies. This review explores the genetic basis of the phenomenological overlap between ADHD and ASD. Based on an extensive review of twin-, linkage-, association studies, and reported structural genomic abnormalities associated with these disorders, we have identified seventeen regions on the human genome that can be related to both disorders. These regions of shared genetic association are: 2q35, 3p14, 4p16.1, 4p16.3, 5p15.31, 5p15.33, 7p12.3, 7p22, 7q21, 8q24.3, 14q12, 15q11–12, 16p13, 17q11, 18q21–23, 22q11.2, Xp22.3. The presented data are of interest for future genetic studies and appear to suggest the existence of a phenotype partition that may differ from the current classification of psychiatric disorders.

Keywords: ADHD, autism, genetic, overlap

Introduction

Attention deficit hyperactivity disorder (ADHD) is a common childhood psychiatric disorder, with a variety of symptoms and a worldwide prevalence between 8%–12% or around 2% when significant impairment is included within the diagnostic criteria.^{1,2} ADHD is one of the best-validated childhood diagnoses.³ Autistic spectrum disorders (ASD) are pervasive developmental disorders that originate in early childhood and include autistic disorder (AD), Rett syndrome, Asperger syndrome, and pervasive development disorders – not otherwise specified (PDD-NOS).⁴ The reported prevalence of ASD has increased over the past 20 years and current estimated prevalence figures range from 27.5 to 107.6 per 10,000.^{5,6}

The risk to develop ADHD and ASD is largely determined by genetic factors, as has been shown in several family and twin studies. On average, the genetic risk for ADHD is estimated to be 76% as can be deduced from twin studies from Europe, the United States, and Australia.^{7–13}

For ASD, twin studies in autism have provided concordance rates between 36%–96% for monozygotic twins and 0%–30% for dizygotic twin pairs of the same sex.¹⁴ Based on these findings, it is estimated that the genetic risk for autism is over 90%. It has also been suggested that twinning itself might be part of the etiology of ASD, but this has been contested.¹⁵

ADHD and ASD are traditionally considered distinct and the diagnosis of ADHD still belongs to the exclusionary criteria for ASD.¹⁶ However, cumulative evidence from behavioral studies, neurocognitive studies and genetic studies suggests an etiological overlap between ADHD and ASD.^{16–26} Both are early-onset psychiatric disorders

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placed within the realm of child- and adolescent psychiatry.⁴ A considerable amount of ADHD patients show problems in communication and social interaction as observed in ASD.^{23–25} In addition, autistic children often show high levels of impulsivity, inattention, and hyperactivity.^{16,20,21} It has been suggested by family and twin studies that these overlapping traits can be explained by common genetic influences.^{22–26}

This review focuses on the overlap in genetic association of ADHD and ASD, in order to provide a stronger basis for understanding the shared biological processes which affect cognitive domains which may underlie both disorders. The aim of this study is to provide a clear overview of all genomic regions associated to ADHD or ASD, thereby identifying regions of shared genetic overlap between these disorders.

Methods

This review is based upon a literature survey within the PubMed database and Google Scholar search engine. First, the latest reviews about the genetics of autism and ADHD were selected for a broad orientation. Next, a systematic evaluation by using combinations of keywords including ADHD, Autis*, gene*, overlap, molecu*, etc. within these databases was performed. Studies were selected based on several criteria including diagnostic methods and a fixed statistical threshold with regard to linkage and association studies. With regard to ADHD, studies on the combined subtype, as well as all studies including patients with the inattentive or with the hyperactive subtype were included in this review. For ASD the studies which involved subjects diagnosed with autistic disorder, Asperger's disorder and PDD-NOS according to DSM-IV (TR) criteria were included. For linkage studies to be included in this review, a logarithm of odd (LOD) score of 2.2 (suggestive linkage) or higher was required.²⁷ In order to minimize the risk of overinterpretation, linkage regions were conservatively defined as extending 10 kb at either side of the reported marker. Only the occurrence of other independent findings within this region was considered as possible overlap.

The significance threshold (corrected for multiple testing), reported in association studies was considered significant when $P < 0.05$, and reported P-values between 0.05 and 0.10 were considered as suggestive. Only regions indicated by significant results were included in this review, however, a genomic region was also included when supported by suggestive results of two or more studies. Studies on cytogenetic abnormalities and case reports involving patients with cytogenetic abnormalities were only included if a validated checklist and/or a diagnosis according to DSM or ICD classification

was described, as well as an interpretable annotation of the involved genomic region.

All overlapping linkage and cytogenetic regions meeting these criteria were considered as loci putatively containing risk genes for a common etiology between ADHD and ASD.

Results

The loci and genes found in both ASD and ADHD by the literature survey are represented below. Figure 1 provides a complete and schematic overview of all included studies. Table 1 describes the 17 regions of overlap including the boundaries and involved studies.

Discussion

This review provides an overview of a joint genetic basis for ASD and ADHD through association-, linkage-, and cytogenetic studies. Seventeen regions on the human genome can be related to both disorders including: 2q35, 3p14, 4p16.1, 4p16.3, 5p15.31, 5p15.33, 7p12.3, 7p22, 7q21, 8q24.3, 14q12, 15q11–12, 16p13, 17q11, 18q21–23, 22q11.2, Xp22.3. These regions reflect about 36% of the loci involved in ADHD, whereas they reflect about 14% of the regions related to ASD.

These findings suggest that at least some shared genetic risk factors exist between ADHD and ASD, which may have implications for our concepts of these disorders.

However, for an adequate interpretation of these findings it is important to bear in mind that several limitations exist in our evaluation of the literature.

First, it is possible that some studies with relevant information were missed during the literature search. For example, studies that do not find associations with the regions described in this review are possibly less likely to be submitted for publication, leading to a publication-based biased overview of associated regions.

Second, pragmatic decisions have been made regarding the representation of linkage studies. Unfortunately, no consensus exists about the precise distance around the linkage peak that should be considered important. Moreover, generally weak significance scores are found for both disorders. This can be explained by the genetic complexity of the disorders and the small sample sizes of certain studies. In order to minimize the risk of type 1 errors, we have opted for a fairly conservative definition of linkage (10 kb at either side of the reported marker) for the current analysis.

Third, it is quite possible that although loci for ASD and ADHD overlap, different genes within these overlap regions are related to each disorder.

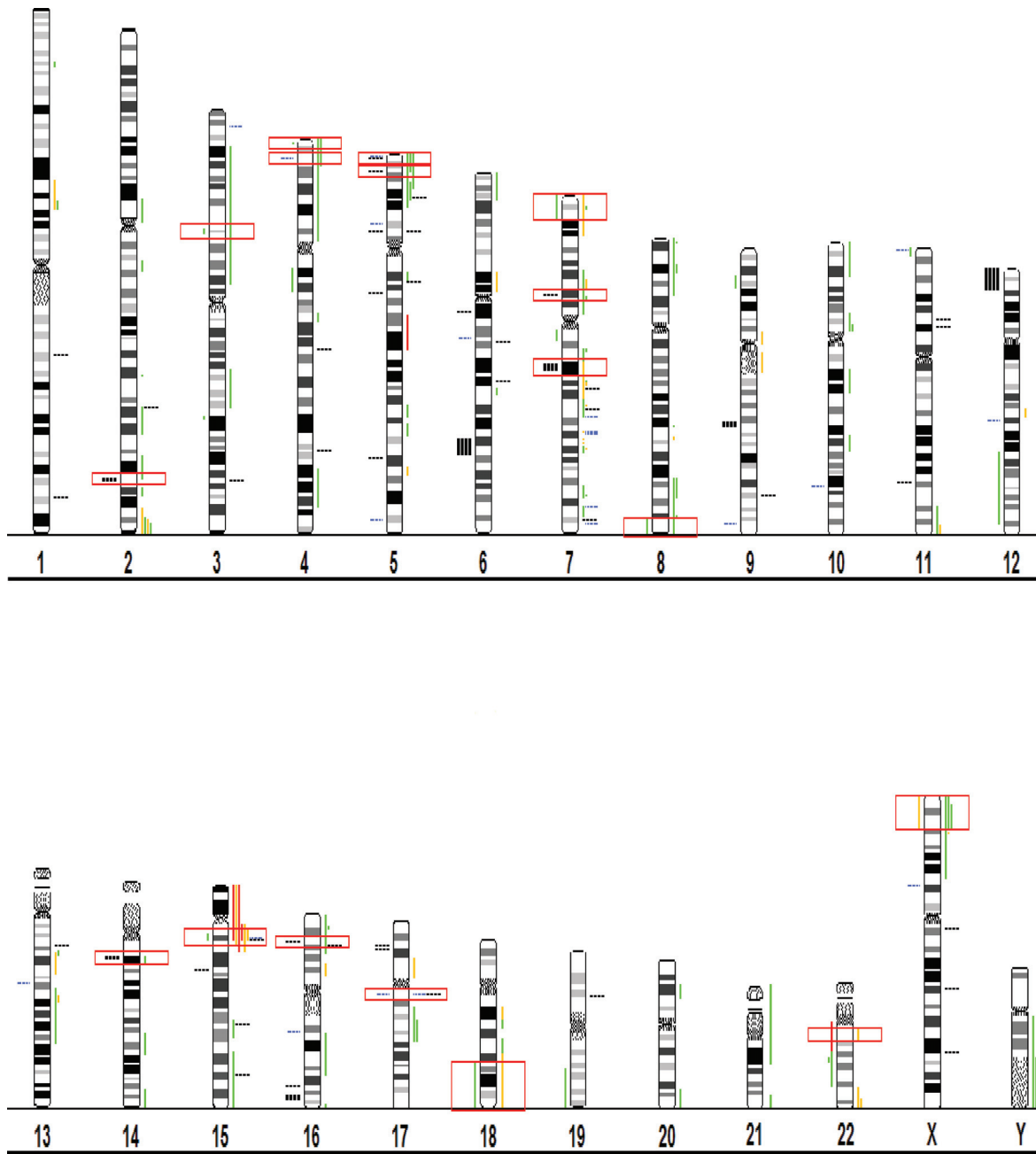


Figure 1 The genetic overlap of ADHD and ASD.

Notes: This figure shows 24 human chromosomes. On the left side of each chromosome the results of genetic studies on ADHD are provided. On the right side of each chromosome the genetic findings on ASD are given. Linkage studies are represented by black dotted horizontal lines. Association studies are indicated by blue dotted horizontal lines. Cytogenetic studies are vertical lines in the colors green, orange and red. A green line represents a region described by one study. An orange line represents a region described by two, three or four studies. A red line represents a region described by five or more studies. Regions containing overlap in genetic findings associated to both ASD and ADHD are accentuated by a red box surrounding the region of interest. All data included in this figure are exactly positioned. Further details can be found in Table I.

Abbreviations: ADHD, attention deficit hyperactivity disorder; ASD, autistic spectrum disorders.

Fourth, we have focused on positive association findings. This elicits the risk of type 1 errors, since the majority of reported loci show contradictory findings about putative association. This can be partly explained by different methods and sample sizes, as well as variety in ethnicity of the studied samples. We propose that the association with both ADHD

and ASD could be considered as additional evidence in support of the involvement of a locus.

Despite these limitations, the results of our analysis suggest that shared genetic etiologies may exist for ADHD and ASD, which may have implications for our clinical concepts of the disorders and the existing diagnostic procedures. The results

Table 1 Regions of overlap and involved studies

| Band | Region of overlap/involved gene | ADHD Studies | ASD Studies |
|---------------|---------------------------------|--------------|---------------|
| 2q35 | 217.16–217.71 Mb | 28 | 29 |
| 3p14 | 50.69–51.40 Mb | 30 | 31 |
| 4p16.3 | 1.8–2.2 Mb | 32 | 33, 34 |
| 4p16.1 | DRD5 | 35, 36 | 33, 34 |
| 5p15.33 | 1.44–1.50 Mb (SLC6A3) | 37–52 | 53, 54 |
| 5p15.31 | 7.70–7.72 Mb | 55 | 53, 54 |
| 7p22 | 0.00–7.20 Mb | 56 | 57–59 |
| 7p12.3 | 49.35–49.37 Mb | 18 | 60 |
| 7q21 | 77.95–81.40 Mb | 28 | 61, 62 |
| 8q24.3 | 140.0 Mb–8 qter | 56 | 63 |
| 14q12 | 24.30–24.98 Mb | 28 | 64 |
| 15q11–12 | 21.54–24.43 Mb (GABRB3) | 65 | 34, 53, 65–85 |
| 16p13 | 11.94–11.96 Mb | 86–88 | 89 |
| 17q11 | SLC6A4 (5HTT) | 90–94 | 95–101 |
| 18q21–18 qter | 52.0 Mb–18 qter | 102 | 103, 104 |
| 22q11.2 | 16.97–20.83 Mb | 105–111 | 112–115 |
| Xp22.3 | 0.00–10.0 Mb | 116–117 | 118 |

Notes: This table provides the information necessary to interpret the highlighted red boxes of Figure 1. Within each band a particular region of overlap is given, obtained by the methods described previously.

Abbreviations: ADHD, attention deficit hyperactivity disorder; ASD, autistic spectrum disorders.

of this paper provide a biological argument for applying a less stringent nosology. In fact, the existing exclusionary criteria for both disorders within the DSM-IV should be reconsidered. Moreover, this paper provides the biological argument to allow a more pragmatic view regarding treatment of overlapping symptoms, which could otherwise be missed.

Several methodological advantages of this study strengthen this interpretation of data.

First of all, the study provides a complete overview of associated genomic regions of both disorders. This is relevant, because a substantial genetic influence for both disorders was described, with a higher genetic risk for ASD than for ADHD. Our search for shared genetic association between ASD and ADHD is motivated by the clinical overlap between both disorders and the findings from twin and family studies.

Second, this review provides the basis for a bottom-up approach in research on the overlap of ADHD and ASD. Seventeen putative loci relevant for a molecular explanation of the overlap between ADHD and autism have been described. These include: 2q35, 3p14, 4p16.1, 4p16.3, 5p15.31, 5p15.33, 7p12.3, 7p22, 7q21, 8q24.3, 14q12, 15q11–12, 16p13, 17q11, 18q21–23, 22q11.2, Xp22.3. Although the interpretation of the results may not be straightforward and further research is clearly necessary, our findings do appear to provide robust, albeit indirect evidence for at least some shared genetic overlap between ASD and ADHD. This notion is consistent with the

findings of a recent twin study.²² The implicated regions of the current study may be of help when interpreting data from ongoing genome-wide association studies for ADHD and autism. Furthermore, these findings are in line with the emerging hypothesis that nosologically distinct psychiatric phenotypes, such as ADHD and ASD, or schizophrenia and bipolar disorder, may have shared biological etiologies.¹¹⁹

In conclusion, findings of our analysis are in support of shared genetic etiologies for ASD and ADHD. A pragmatic consequence of this finding may be that it provides some justification for a combined analysis of genetic association for ASD and ADHD. On a more conceptual level, our results suggest that the biology of ASD and ADHD does not seem to follow the boundaries laid out by our nosologic classification system.

Disclosure

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