Chapter

Role of Copy Number Variations in ADHD

Danijela Krgović

Abstract

Copy number variations (CNV) have an important role in etiology of neurodevelopmental disorders (NDD). Among them, individuals with attention-deficit and hyperactivity disorders (ADHD) have 1.33 times higher overall rate of CNVs larger than 100 kb compared to healthy controls. These CNVs are often shared with other NDDs and neuropsychiatric disorders such as schizophrenia (SCZ) and autism spectrum disorder (ASD), although duplications of 15q13.3 and 16p13.11 have been found enriched in ADHD cohorts. CNVs provide new opportunities for studying and management of psychiatric disorders including ADHD. Therefore this chapter provides a brief overview of the literature on this topic and presents the benefits of CNV genetic diagnostics in ADHD patients.

Keywords: attention-deficit and hyperactivity disorders (ADHD), neuropsychiatric disorders, neurodevelopmental disorders (NDDs), copy number variations (CNV), chromosomal microarrays (CMA), whole genome sequencing (WGS)

1. Introduction

Attention-deficit and hyperactivity disorders (ADHD) is a childhood-onset neuropsychiatric disorder affecting 5–6% of children [1]. The follow-up studies of children with ADHD showed that symptoms are evident even in adulthood in approximately two-third of patients [2] and that disorder is present in 2.5% of adults [1, 3]. The twin studies suggest a high heritability of ADHD, estimated to be at approximately 70% [4]. This is comparable to the heredity of other neuropsychiatric disorders, such as autism spectrum disorder (ASD) and schizophrenia (SCZ) [5]. Genetic studies shown a complex genetic etiology comprising both common variants such are single nucleotide polymorphisms (SNPs) [6], as well as rare variants causing a loss-of-function in single gene in form of single nucleotide variants (SNVs) [7], and deletions or duplications of multiple genes in form of copy number variations (CNVs) [8–10]. A SNP-based genome wide heritability studies can explain the genetic origin of the ADHD in approximately 22% cases, which still does not explain the large proportion of heredity set out in twin studies [6]. To some extent the difference can be explained by rare variants in form of SNVs and CNVs [11].

In 2010, a chromosomal microarrays (CMA) which are used for detection of genomic CNVs, became first-tier clinical diagnostic test for individuals with developmental delay and/or intellectual disability (DD/ID), ASD, and/or multiple congenital anomalies. Namely, a review of 33 studies including 21,698 patients tested by CMA showed that a pathogenic CNV could be determined in an average of 12.2% patients across all studies [12]. Since then, rare CNVs have been described

across different neurodevelopmental disorders (NDDs) [13]. In individuals with ADHD a 1.33 times higher overall rate of CNVs larger than 100 kb compared to the healthy controls was observed [14].

Therefore, an important role of CNVs in etiology of ADHD is further discussed in this chapter.

2. What are CNVs?

CNVs are genomic structural variations causing the deletion or duplication of coding and non-coding segments of DNA. They vary in size, spanning from single gene to encompassing multiple genes. They can be common or rare events in genome acting as a disease cause.

CNVs occur in genome due to the segmental duplications present in certain regions in human genome. These repetitive sequences represent CNV "hotspots" as they make these regions prone to mutational mechanism called non-allelic homologs recombination. The process occurs during sperm or egg formation, therefore CNV prevalence remains relatively constant regardless of the severity of genomic disorder [15].

The CMA technology was designed to detect deletions and duplications across human genome randomly, without the need of specific suspected diagnosis of genomic disorder made by clinician. The technology enables us to identify the recurrent as well as novel disease associated CNVs [15]. Rare CNVs have been described as microdeletions or microduplications involved in many NDDs [12, 16–20].

Rare CNVs are considered to be present in less than <0.1% of general population. Disease associated CNVs are rare but collectively explain approximately 20% of DD/ID, 10% of ASD, and 5% of SCZ cases. However for other neuropsychiatric conditions the role of rare CNVs in disease pathophysiology is less clear, therefore diagnostics yield for CMA remains to be determined [17].

An important role in prevalence of rare CNV has its relative overall penetrance. CNVs with high overall penetrance are expected to be absent from general population whereas low penetrance CNVs have higher chance to be found in general population, where CNV carriers may have mild clinical manifestation [21, 22].

Different NDDs also share same CNVs effecting the same genes [4, 17] indicating on their clinical pleiotropy [13].

3. Role of CNVs in ADHD

ADHD has a complex genetic architecture. The larger sample size and advances in technology enabled to study an effect of different classes of genetic variations in disease development. This revealed that ADHD is polygenic disorder like other neuropsychiatric disorders and its genetic architecture involves both the thousands of common variants with individually small effect size (SNPs), as well as rare variants causing a loss-of-function in single gene (SNVs) or small or larger genome deletions or duplications (CNVs) [23]. From all the genetic variants that contribute to etiology of ADHD, CNVs probably have the most evident clinical evidence, since they are enriched in several neuropsychiatric disorders [15].

ADHD is often associated with syndromic disorders [5]. For example, ADHD symptoms are present in more than 60% of patients with Williams-Beuren syndrome caused by microdeletion of chromosome region 7q11.23 [24] and approximately 40% patients with 22q11 deletion syndrome, also known as DiGeorge syndrome [25].

A parent-offspring trio studies showed a higher rate of de novo CNVs in children with NDDs. The highest is observed in 10% of children with ID/DD [26]. For ASD

patients a 3- to 5-fold higher rate is observed than in control [27]. Similar rate was observed in SCZ-trio studies [28]. Only recently, studies of ADHD patients have reached the number of patients, which would unable similar studies to be performed as in ASD and SCZ patients [5]. Most recent trio-based study of ADHD patients have shown that overall mutation rate of de novo CNVs was 4.6% and similar to the rate observed in children with ADS, but slightly higher than in SCZ study [29]. Their rate was also higher than from previously trio-based ADHD study, which was 1.7% [30]. From the 14 de novo CNVs found in 13 ADHD probands, four CNVs: duplications of 15q13.1, 16p13.11 and 22q11.21 and deletion of 16p12.1, have been previously implicated in neuropsychiatric disorders or NDDs, once again highlighting their clinical pleiotropy [29].

In the study of Gudmundsson et al., a presence of 19 rare neuropsychiatric CNVs, that confer risk of ASD and SCZ, have been tested in 8883 ADHD probands. Presence was confirmed in 2.15% of individuals, compared to the 0.86% of controls. Only one CNV carrier had comorbid diagnosis of ADHD and ASD, and none for SCZ. Eight of the tested CNVs were significantly associated with ADHD risk: deletion of 2p16.3 (*NRXN1*), 15q11.2, 15q13.3, and 22q11.21 and duplications of 1q21.1 distal, 16p11.2 proximal, 16p13.11, and 22q11.21 [10]. Among them, deletion of DiGeorge region (22q11 deletion) was established to have highest risk of ADHD, since in addition to high frequency of SCZ in DiGeorge patients, ADHD has been observed in 37% of the children [31]. A high significance to ADHD was also confirmed for 15q13.3 deletion. Deletions of this region is associated with various NDDs [32] with the higher rate of neuropsychiatric disorders, along with 6.5% of ADHD [3, 33].

3.1 Does ADHD-specific CNVs exist?

There is still no ADHD-specific CNV identified. Although, there are still some incocistency about frequency of rare CNVs in ADHD patients [30, 34–38], studies of CNVs in ADHD patients show a higher burden of this structural variants compared to the control [8, 9, 30, 39, 40].

The CNVs found in patients with ADHD often coincide with ASD and SCZ chromosomal loci [41–43], which is also evident in clinical comorbidity of ADHD with this two disorders [44]. Stronger comorbidity is set for ASD [45] by common CNV-affected genes [8, 9, 30] and biological pathways [46]. Overlap of the disease-associated genes between ASD and ADHD was also observed in SNVs studies [7].

A large genome-wide CNV analysis was performed recently in 2691 patients diagnosed with different NDDs, in order to determine the pleiotropy of CNVs. For example, genes like *NRXN1*, *EXOC3*, and *PCMTD2* were found in ASD, ADHD and SCZ or ASD, ADHD and obsessive compulsive disorder (OCD) or ASD, OCD and SCH patients respectively. Recurrent and non-recurrent CNV regions were also identified to be involved in multiple NDDs, as 16p13.11 and 15q11-q13 duplications in SCZ, OCD, ASD and ADHD. The study also showed that clinically relevant CNV was detected in 9.4% (N 40/427) ADHD patients, similar to the percentage in ASD (11.4%) and SCZ (10.8%) patients [13]. Studies like this show an importance of CNVs in genetics of NDDs and complex genetic architecture of this disorders.

Interestingly, not much has been done in studying the CNVs implicated in ID/DD, since ADHD patients who have comorbid ID/DD are usually exclude from such studies [23].

A recent study of CNV involved genes obtained from 11 published studies was performed with aim to define ADHD-associated candidate genes. Among 2241 localized genes from 1532 CNVs, 26 genes were established to have highest credibility as ADHD candidate genes. This genes also share common biological topic such as transcription, mitochondrial biology, mRNA metabolism, and cytoskeleton [47].

3.2 Ambiguity of the rare CNVs

By researching of the genome and CNV mapping, it was estimated that sequence included in CNVs contribute to the 4.8–9.5% of the genome. Additionally, it was postulated that about 100 genes can be deleted by CNVs and have no apparent phenotype [19]. Furthermore, an average mutation rate in individuals in the general population should be take into account, consequently rare variants could be false positive [48].

Therefore, the meaning of a rare unknown CNV identified in ADHD patient should be carefully interpreted.

4. The importance of CNV in diagnostics of ADHD

Reaching the genetic diagnosis in ADHD patient can have many advantages for the patient as well as clinician. Molecular diagnosis can benefit in patients' care in management and treatment (e.g. preference or avoidance of particular medications) as well as prognosis [15].

Genetic counseling is also important. The family based and twin studies of ADHD patients revealed a strong familial and genetic overlap of ADHD with ASD and ID. The individuals with monozygotic twin with ASD have an increased risk for ADHD compared to the risk observed in dizygotic twin studies. The association is higher for higher-functioning than lower-functioning ASD [23]. Siblings of ADHD probands have ninefold higher risk to ADHD compared to the siblings in controls [49]. ADHD is also strongly associated with lower IQ and ID indicating that they share heritability [23]. Additionally, family members of ADHD individuals are at elevated risk for neurodevelopmental and neuropsychiatric disorders. Knowing the genetic cause may have an impact on their management and treatment [23].

CNVs will lead to understanding how genes affect biological pathways involved in ADHD. For example, CNVs in glutameric genes were liked to cognitive and clinical impairments of ADHD [4]. In study of Thapar et al. found CNVs in ADHD patients were enriched in genes for which it was previously known to be involved in SCZ, Fragile X ID, and partly with autism [50]. More recently 26 ADHD-associated candidate genes were identified that share common biological topic such as transcription, mitochondrial biology, mRNA metabolism, and cytoskeleton [47].

Other features can be explain by CNVs. The duplications of *CHRNA7* gene were observed in higher rate in ADHD patients [9]. This gene encodes alpha-7 nicotinic acetylcholine receptor. A higher rate of smokers have been observed in ADHD patients [51]. Namely, nicotine administration reduce hyperactivity and impulsivity [52] since nicotine modulates dopaminergic neurons by interacting with nicotinic acetylcholine receptors [53].

Moreover, knowledge of the cause of the disease assist in better understanding and felicitate the acceptance of the condition, improves genetic counseling and also refine possible future new treatments [15].

Although there are still no clear guidelines when to perform genetic testing for rare variants in ADHD patients, testing for CNVs is recommended in individuals with comorbid mild ID or ASD [23].

5. Future prospects

Technologies such as whole genome sequencing (WGS) that enable us to detect SNVs as well as structural variants in the genome in a single experiment, will facilitate the detection of even smaller CNVs, which we could not detect with CMA due to technology limitations.

Pathogenicity of rare large CNVs in NDDs and neuropsychiatric disorders is mostly defined, whereas a significance of a small nonrecurrent CNVs (<500 kb) is still ambiguous. In the study of 4417 patients referred to CMA testing 383 (8.67%) patient had at least one small, nonrecurrent CNV. Of these, 142 (3.21%) patients were carriers of pathogenic or likely pathogenic CNV, from which in 80 patients a single gene or exonic deletion of the gene was found [54].

A CNV study in adult ADHD patients did not found enrichment for large CNVs, however they did found significant increase of small CNVs [14]. Therefore, the relevance of new technologies in studying of genomic disorders will facilitate new genotype–phenotype correlation [15].

6. Conclusions

CNVs provide new opportunities for studying and management of psychiatric disorders including ADHD.

Detection of small CNVs of few kilo base in size is still difficult due to method limitations, although WGS of the ADHD patients promises their discovery. On the other hand, for the detection of large rare CNVs that occurs with frequency less than 1%, large sample size are needed [5].

Furthermore, parent-offspring trio studies of de novo CNVs and SNVs will contribute in disease etiology, since de novo aberrations in genome are more likely deleterious [28]. Identification of disease-associated genes and knowledge of their molecular functions will lead to better understanding of their disease pathology and hopefully enable better diagnostic and treatment [47].

Genetic counseling for polygenic disorders with complex genetic architecture as is ADHD is challenging, due to variable phenotypic outcomes and incomplete penetrance encountered in majority of genetic disorders. Therefore understanding the molecular etiology for clinicians is useful in patient management, in terms of improving risk predictions, screening for extra-psychiatric features, treatment, etc. [15]. New discoveries are also a starting point for identifying and assessing novel treatments in ADHD patients [23].

Though psychiatric genetics is unlikely to change the treatment of patients, it will eventually contribute to more personalized medicine [5]. Therefore the role of CNVs in clinical practice for ADHD patients remains to be seen.

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Conflict of interest

No conflict of interest.

Author details

Danijela Krgović[1,2]

1 Division of Gynecology and Perinatology, Medical Genetics Laboratory, University Medical Centre Maribor, Maribor, Slovenia

2 Department of Molecular Biology, Faculty of Medicine, University of Maribor, Maribor, Slovenia

*Address all correspondence to: danijela.krgovic@ukc-mb.si; danijela.krgovic1@um.si

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