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Review Article

Association of Copy Number Variations in Autism Spectrum Disorders: A Systematic Review

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Autism spectrum disorders (ASDs) are characterized by language impairments, social deficits, and repetitive behaviors. The onset of symptoms occurs by the age of 3 and shows a lifelong persistence. Genetics plays a major role in the etiology of ASD. Except genetics, several potential risk factors (environmental factors and epigenetics) may contribute to ASD. Copy number variations (CNVs) are the most widespread structural variations in the human genome. These variations can alter the genome structure either by deletion or by duplication. CNVs can be *de novo* or inherited. Chromosomal rearrangements have been detected in 5–10% of the patients with ASD and recently copy number changes ranging from a few kilobases (kb) to several megabases (Mb) in size have been reported. Recent data have also revealed that submicroscopic CNVs can have a role in ASD, and *de novo* CNVs seem to be a more common risk factor in sporadic compared with inherited forms of ASD. CNVs are being implicated as a contributor to the pathophysiology of complex neurodevelopmental disorders and they can affect a wide range of human phenotypes including mental retardation (MR), autism, neuropsychiatric disorders, and susceptibility to other complex traits such as HIV, Crohn's disease, and psoriasis. This review emphasizes the major CNVs reported to date in ASD.

1. Introduction to Autism Spectrum Disorders

Autism spectrum disorders (ASDs) include Asperger syndrome, autism, pervasive developmental disorder not otherwise specified, and childhood disintegrative disorder according to Diagnostic and Statistical Manual of Mental Disorders V (DSM-V) criteria [1–3]. ASDs, also termed as pervasive developmental disorders (PDDs), are characterized by impairments in reciprocal social interaction and communication with the presence of restricted and repetitive behaviors [4–8]. Many children with autism spectrum disorders also have intellectual disability, and most of them have lifelong disability requiring substantial social and educational support [5]. Autism was firstly described by Kanner in 1968 as a childhood developmental disorder [9]. Although ASDs are known to be highly heritable (90%), the underlying genetic mechanisms are still largely unknown and ASD affects ~1% of the population [10–14]. Unfortunately ASD is the most heritable disorder but is not a simple disorder and has a complex etiology [8, 15]. The genetic architecture of ASD comprises a diversity of rare single nucleotide variants, copy number variations (CNVs), chromosomal abnormalities, and common polymorphic variations. Candidate genes that contribute to ASD represent a spectrum of biological pathways including synaptic function and epigenetic mechanisms. Both gene-gene interactions and gene-environment interactions can be explaining the heterogeneity of ASD [1, 2]. Several studies have showed that there might be approximately 1,000 genes or loci to ASD contribution [13, 16, 17].

As summarized in Table 1, several genetic syndromes were associated with ASD. Except autism, clinical manifestations of schizophrenia, developmental delay, bipolar disorders, and intellectual disability are diverse and complex and include abnormalities in neuronal excitability, processing of complex information, and behaviors such as anxiety and impaired social interactions. There is a significant overlap in clinical manifestations in these mental disorders, such as impaired cognitive functions, seizures, and language problems. As a result of the studies, there is no clear clinical or

Table 1: The most common genetic syndromes associated with ASD.

Genetic syndromes	Gene/chromosome region
Fragile X Syndrome	*FMR1*
Rett Syndrome	*MECP2*
Neurofibromatosis type 1	*NF1*
Tuberous sclerosis	*TSC1*, *TSC2*
Prader Willi Syndrome	Del paternal allele at 15q11–q13
Angelman Syndrome	Del/mutation in maternal *UBE3A*
Smith-Lemli-Opitz Syndrome	*DHCR7*
Smith-Magenis Syndrome	17p11.2 del
Velocardiofacial/DiGeorge Syndrome	22q11.2 del
ARX Syndrome	*ARX*
Untreated phenylketonuria	*PAH*
Cornelia de Lange Syndrome	*SMC3*
Ch 22q11 duplication syndrome	22q11.2 dup
Potocki-Lupski Syndrome	17p11.2 dup
Down Syndrome	Trisomy of chromosome 21

neurobiological distinction between childhood schizophrenia, pervasive developmental disorder, and autism. Also these neurodevelopmental disorders can be included within the allelic spectrum of the same candidate gene. So, these observations strongly suggest that autism, schizophrenia, and intellectual disability may share similar pathogenic pathways and potential candidate genes in the same pathways [4, 18].

2. What Is CNV? How Can We Detect CNVs?

Structural genomic variations include any genetic variants that alter chromosomal structure such as inversions, translocations, duplications, and deletions. Genomic structural changes, such as gene copy number variations (CNVs), are extremely frequent in the human genome [31]. CNVs were defined as a segment of DNA larger than one kilobase presenting copy number differences by comparison of two or more genomes. Deletions may be heterozygous (in which one of the usual two copies is missing), homozygous (in which both copies are missing), or hemizygous (e.g., X-chromosome deletions in a male patient) [5]. They can change gene dosage, interrupting coding sequences, and influencing neighboring gene regulation so they have a great impact on gene expression and phenotypes [32]. Sometimes they can cause exon shuffling [33]. CNVs contribute significantly to genetic heterogeneity with an estimated 12–15% of the human genome. Approximately 14,400 CNV loci larger than 1 kb were identified to date [34]. The mutation rate for CNV (100–1000 times) is much higher than for SNP [35]. The locus-specific mutation rates for CNVs have been estimated to be ~100 to 10,000 times higher than those for nucleotide substitution rates [36]. Multiple studies of large control cohorts have shown that every person carries many copy number changes that are mostly benign [37, 38]. The most frequent CNV is less than 1 kb and 5–10% people have larger CNV including 500 kb [37, 39]. CNVs are largely composed of deletions and duplications and they can be *de novo* or inherited. *De novo* CNVs are more prevalent in sporadic genomic disorders [15]. The first CNV studies were published in the year of 2004 [38, 39]. It is possible that CNVs have an important role in modulating the phenotypic spectrum in single gene, multigenic, or complex diseases and several reports were related in neuropsychiatric diseases (i.e., autism spectrum disorders, schizophrenia, mental retardation, behavioral problems, epilepsy, and bipolar disorder) with specific CNVs [31, 34, 40–42].

Different experimental approaches can reveal specific CNVs. Fluorescence *in situ* hybridization (FISH) is the first molecular method for detection of submicroscopic genomic CNVs. MLPA (multiplex ligation-dependent probe amplification) is often used as a targeted method to assess copy number differences [43]. Microarray platforms represent a robust and high-resolution method of analysis. These arrays were originally designed for genome-wide genotyping, but they can also be used to detect CNVs. Comparative genomic hybridization (CGH) is another method which can detect copy number changes [2, 26, 41]. Unfortunately, oligonucleotide arrays cannot detect the CNVs smaller than 500 bp [33]. Array-CGH compares copy number of genomic loci between the patients and reference samples. These variations can range from submicroscopic imbalances (deletions or duplications) to an entire chromosome (aneuploidy) [43]. It is difficult to detect short CNVs with these platforms mentioned above.

Next generation sequencing, as a new approach, was being used from 2007; whole-exome sequencing (WES) has emerged as a cost effective and efficient means to identify rare genic SNV (single nucleotide variant) contributing to risk of multiple disorders including ASD [44, 45]. Next generation sequencing technology was used to detect <10 kb CNV with high resolution [33]. New methods have been developed to call CNV from WES data such as exome-hidden Markov model to normalize exome read depth and a hidden Markov model (HMM) to identify exonic CNV from WES data [13].

3. CNV Studies in ASD

Earlier studies mainly with simplex families in ASD showed an increased frequency of CNVs. But the evidence from these studies can only characterize some specific CNVs in ASD families with a broad variety of clinical features [1]. Duplications and deletions that affect lots of loci are associated with ASD [15]. Balanced genomic changes, such as translocations and inversions, also contribute to ASD [46]. CNVs with duplication in 15q13, deletions in 16p11.2 [11, 27, 47–49], 7q11.23 with Williams Syndrome locus, 22q11.2 with DiGeorge Syndrome locus, and 1q21.1 and 15q11-13 with Prader Willi-Angelman Syndrome locus [21, 49] are reported to date. Inherited duplications in the 15q11-q13 region have been reported to occur in ~1% to 3% of autism cases [40]. According to the genome-wide studies, copy number changes cause alterations in expression levels of genes within CNVs

[34]. Thus this structural variation may affect gene expression directly by disrupting genes and altering gene dosage or indirectly through a position effect or unmasking of recessive mutations or functional SNPs on the remaining allele. Unlikely, variants occurring in intronic or intergenic regions may have little or no effects on gene expression [28]. Specific chromosomal regions with CNVs are related with ASD except chromosomes 12, 19, 20, and 21. Some of these regions (such as chromosomes 1, 15, 16, and 22) are responsible for both ASD and schizophrenia [31]. Besides, multiple large CNV studies have been reported using different methodologies to examine different cohorts and the obtained data have great impact in the field of autism research to date [11, 20, 21, 26, 27, 47, 50–52]. According to large CNV studies, anyone can conclude that several rare *de novo* and inherited CNVs contribute to autism susceptibility. Additionally *de novo* CNVs are higher in simplex families than multiplex families (*de novo* CNVs are 3–5 times higher in ASD families than in controls).

Jacquemont et al. detected *de novo* CNVs in 24% of individuals with autism in a genome-wide association screen; one pair of affected siblings showed spontaneous CNVs in *NRXN1*. These findings may prove useful for guiding selection of appropriate analytic techniques and specific subgroups of autistic cases in future genetic studies [51]. Sebat et al. suggest that *de novo* CNVs are found much more frequently among pedigrees with only a single case with autism than in multiplex pedigrees. Their study focused on a sample of 264 families, including 118 "simplex" families, 47 "multiplex" families, and 99 control families with no diagnosis of autism. 17 CNVs were confirmed to be *de novo* in 16 individuals. The majority of these mutations are novel and only the largest of them (all CNVs were >4 Mb in size) have been reported previously in the literature. According to their data, all of the detected spontaneous CNVs were in different chromosomes (2p, 2q, 3p, 6p, 7p, 10q, 13q, 15q, 16p, 20p, and 22q). Spontaneous CNVs were present in 10% of affected individuals in sporadic cases, contrasting with substantially lower rates observed in controls (1%) and autism cases from multiplex families (3%) [27]. In the same year, another study investigated CNVs in ASD families and the authors concluded that inherited CNVs may increase the autism risk [20]. Cytogenetic chromosome abnormalities are found in 7.4% (129/1749) of ASD cases with a range from 0% to 54%. Balanced translocations and inversions accounted for 17% (22/129) of rearrangements. In their study, the rates of the *de novo* genomic CNV rearrangements were approximately 7% [11]. Christian et al. studied 397 unrelated subjects with ASD and 372 controls using a 19K BAC microarray. Fifty-one autism-specific CNVs were identified in 46 of 397 ASD patients with a rate of 11.6% [26].

Ozgen et al. enrolled four patients who implicate microcephalin 1 (*MCPH1*) in band 8p23.1 and this gene is an ASD susceptibility gene. A girl with a syndromic form of autistic disorder showed that she had a classic inv dup del(8)(qter-> p23.1::p23.1-> p21.2) containing at least three candidate genes: *MCPH1* and *DLGAP2* within the 6.9 Mb terminal deletion and *NEF3* within the concomitant 14.1 Mb duplication. Three further patients with *MCPH1* copy number changes were found using single-nucleotide polymorphism (SNP) array analysis in a cohort of 54 families with ASD patients. So they revealed that ASD can be a component of the classical inv dup del(8) phenotype and identified changes in copy number of *MCPH1* as a susceptibility factor for ASD in the distal short arm of chromosome 8 [53]. Gregory et al. studied 119 probands from multiplex autism families. Their analysis revealed that a genomic deletion containing the oxytocin receptor gene (*OXTR*) previously implicated in autism was present only in one proband and his mother [19]. Sykes et al. screened 330 families for SNP association and CNVs in *SHANK3*. They could not detect CNVs or SNP associations in their study group [54]. Cho et al. studied 28 ASD patients and 62 controls by array-CGH method. Two recurrent CNV regions in this study were found to be significantly associated with autism. Totally 38 CNVs were identified. One is on the 17p11.2 region (21.82–21.85 Mb). Although there are no known coding genes in this region, 17p11.2 has been suggested as an autism-related region. The other significantly associated one is on 8p23.1, which is one of the most recurrently observed copy number changes in their study. The 8p23.1 region is a well-known site of frequent chromosomal rearrangements. They conclude that decreased dosage of *DEFENSIN* was found to be a predisposing factor to idiopathic ASD [25]. 262 ASD patients were studied with the Agilent 244K human genome oligonucleotide CGH microarray. According to their results, deletion/duplication on chromosome 15q13.2q13.3 is related with developmental delay, autistic features, or the other neuropsychiatric issues such as attention deficit-hyperactivity disorder, expressive language delay, bipolar or mood disorder, anxiety disorders and/or obsessive-compulsive disorder, and subclinical EEG or MRI abnormalities [55]. 105 autism patients and 267 unrelated healthy controls using Illumina HumanHap300 Beadchips and Illumina Beadstudio analysis software were investigated. They also identified the same or similar genes from 13 published autism susceptibility loci (1q42, 2q31, 2q37, 3q26, 5p15, 7q22, 7q36, 15q11, 17q11, 18q21, 22q11, 22q13, and Xp22). Besides, they suggested that the occurrence of genomic gains and losses of genes associated with glycobiology is an important contributor to the development of ASD [29]. A total of 4187 CNV regions previously identified in HapMap populations were investigated in Fu et al.'s study with a different algorithm approach. The mutation rates of 104 (2.5%) CNV regions were estimated at the order of 10^{-3} per generation and these regions were classified as potential hotspots. 49 (47%) CNV hotspots include human genes, some of which are known to be functional CNV loci and have an important role of CNV in human health especially in common and complex diseases [56].

In another study, 1461 ASDs were investigated with oligonucleotide-based microarray analysis. Abnormalities were reported as 12.3% of these cases and the CNVs surveyed were mostly inherited (69%) among autistic individuals. These abnormalities included alterations in novel candidate genes such as *SNTG2*, *SOX5*, *HFE*, and *TRIP38* [23]. The exon array successfully identified six rare *de novo* autosomal heterozygous CNVs (including 1q21.3, 1q31.3, 2q13, and 3p26.1 locus) present in blood samples out of 99 probands in another

study. They also detected complex appearing *de novo* CNVs. Fifteen out of 17 of the complex CNVs were located in common CNV regions [57]. 223 ASD patients were screened with high-resolution whole genome array-based comparative genomic hybridization (array-CGH) to find out gene dose alterations associated with susceptibility to autism. Clinically significant CNVs were identified in 18 individuals (8%), of whom 9 cases (4%) had *de novo* aberrations and 13 cases carried rare inherited CNVs that may increase the risk of developing ASDs [23]. Using Affymetrix 500K arrays a heterozygous deletion at chromosome 10p12.1 as a novel CNV locus, was identified at a frequency of ~1.4% (6/427) and was observed to intersect *PTCHD3* gene. This deletion was found to be inherited in all ASD cases [58].

In 2012, 696 unrelated ASD cases were examined by array-CGH. 19.307 CNVs smaller than 100 kb were detected in ASD group. *CIB2*, *DAPP1*, and *SAE1* genes were reported as novel ASD candidate genes and all were inherited except for a *de novo* CNV in the *GPHN* gene [59]. Holt et al. studied 996 individuals with ASD and 1287 controls, respectively, for potential to generate fusion transcripts. They used an alternative mechanism whereby CNVs combine the 5′ and 3′ ends of two genes, creating a fusion gene. According to this methodology there is no evidence that fusion-gene generating CNVs lead to ASD susceptibility [60]. The highest CNV burden in Menashe et al.'s study was in the 16p11.2 locus. This genomic locus has long been known as a genetic risk factor of ASD. Additionally, they implicated three distinct ASD loci within the 15q11-q13 genomic locus [61]. Matsunami et al. used a custom array to obtain high-quality CNV results on 2,175 children with clinically diagnosed ASD and 5,801 children with normal development as a control group [30]. As a result, they confirmed the association of 31 of 185 published ASD-associated CNVs (including the regions of 1q, 2p, 2q, 3p, 4q, 5q, 6p, 8q, 10q, 12q, 15q, 16p, 17p, 20p, Xp, and Xq) in their dataset and they concluded these CNVs may be of clinical relevance in the evaluation of children with ASDs. Krumm et al. hypothesized that small genic inherited CNVs might contribute to sporadic autism and they searched for 411 families affected by sporadic ASD. They discovered a total of 847 transmitted, exonic, rare, autosomal CNVs, including 453 transmitted to probands and 394 transmitted to unaffected siblings. They used exome sequencing data in their study and this method enabled them to explore a smaller CNV landscape largely inaccessible by high-density SNP microarray data [62]. Poultney et al. used whole-exome sequencing in 811 individuals (432 ASD cases of European ancestry and 379 ancestry matched controls) to investigate small (1–30 kb) exonic CNVs. They found rare small deletions in subjects with ASD ($P = 0.0037$). 1–30 kb deletions were found in 28% of cases but only 21% of controls ($P = 0.017$) indicating that small CNVs could contribute to risk in as much as 7% of individuals with ASD [13]. Nava et al. screened 194 individuals with ASD for CNVs. A *de novo* triplication of chromosome 15q11-q12 of paternal origin, a deletion on chromosome 9p24, and a *de novo* 3q29 deletion were identified as the cause of the disorder in one individual in 2014 [63]. Finally in one study, 73 ASD probands from Austria were examined to obtain their CNV content. According to their findings, they identified a number of new genes or loci associated with autism, such as *GPHN*, *DLG2*, *HPCAL1*, *BDNF-OS*, and terminal 21q except several others previously identified such as *CDH13*, *AUTS2*, *DPP6*, *NRXN3*, *SH2B1*, and *CNTNAP2* [64]. The most studied chromosomal locus and CNVs related with ASD are summarized in Table 2.

4. MicroRNAs and CNV Association

MicroRNAs (miRNAs), as a class of small (21-nucleotide long) single stranded RNAs particularly abundant in the brain, are known to regulate gene expression at the transcript level with translational inhibition or mRNA cleavage by binding to the 3′ untranslated region (3′UTR) of target mRNAs [65, 66]. Polymorphisms in miRNA genes can affect the expression of many downstream-regulated genes. According to cancer research, it is obvious that the expression of miRNA genes can also be modified by CNVs [67]. Abnormalities in the translational control of multiple mRNA targets mediated by each miRNA could lead to the differences in phenotypes observed in ASD cases. Conversely, multiple miRNAs can target the same mRNA leading to convergent phenotypes arising from various CNV loci [65]. Another new class of RNA is described as large intergenic noncoding RNAs (lincRNAs), thought to be more than 4,000 in the human genome. These RNAs have several activities including X-chromosome inactivation and regulation of gene expression in stem cells, cancer cells, and development. In a case report, a 16-year-old female with a karyotype of 46,XX,t(2; 11)(p25.1; p15.1)dn has been revealed. The case with disruptions in *LINC00299* gene (long intergenic nonprotein coding RNA 299) has developmental disabilities of varying severity [68].

Recently a new study investigated firstly the genome-wide miRNA content of rare CNVs in schizophrenia. Obtained data demonstrated a genome-wide role for CNVs overlapping miRNAs in the genetic risk of schizophrenia [69]. This study could be a good example of studying CNV-miRNA analysis in other neurodevelopmental disorders. Another research was designed for better understanding the CNV-miRNA relationship in 213 probands with intellectual disability. miRNAs which have brain related functions have been found more prevalent in *de novo* CNV groups compared to common CNV groups [70]. Except CNV analysis in ASD recently one study focused on the contribution of miRNAs in copy number variable regions towards the development of autism. 11% of the CNV loci (41 out of 378) were shown to harbor miRNAs. Among the total 71 miRNAs, a few were previously reported to be related with autism. This can be accepted as a strong evidence for the role of CNV associated miRNAs in autism and suggested a possible mechanism that will account for the genetic heterogeneity and phenotypic variability of autistic patients [71]. Two miRNAs, hsa-mir-4436b-1 and hsa-mir-4436b-2, may be evaluated as strong pathogenic candidates in ASD since they have not been found in CNVs from unaffected individuals in another study [72].

Table 2: Top CNV loci for ASD susceptibility.

CNV locus	Study design	Patients	CNV type	Candidate gene	References
1q21.1	Illumina 1M-single array	996 ASD patients 1,287 controls	Deletion-duplication	*BCL9*	[10]
1q21.1	Array-CGH	119 ASD patients	Deletion-duplication		[19]
1q21.1	Affymetrix 10K SNP arrays	1,496 ASD families	Deletion-duplication		[20]
2p16.3	Affymetrix 10K SNP arrays	1,496 ASD families	Deletion-duplication	*NRXN1*	[20]
2p16.3	Illumina 1M-single array	996 ASD patients 1,287 controls	Deletion-duplication	*NRXN1*	[10]
2p16.3	Illumina HumanHap550 BeadChip	1,336 ASD patients 1110 controls	Deletion-duplication	*NRXN1*	[21]
2p16.3	Array-CGH	223 ASD patients	Deletion-duplication	*NRXN1*	[22]
3p26.3	Illumina 1M-single array	996 ASD patients 1,287 controls	Deletion-duplication	*CNTN4*	[10]
3p26.3	Illumina HumanHap550 BeadChip	1,336 ASD patients 1110 controls	Deletion-duplication	*CNTN4*	[21]
3p26.3	Array-CGH	223 ASD patients	Deletion-duplication	*CNTN4*	[22]
6q26	Illumina HumanHap550 BeadChip	1,336 ASD patients 1110 controls	Deletion-duplication	*PARK2*	[21]
6q26	Array-CGH	223 ASD patients	Deletion-duplication	*PARK2*	[23]
6q26	Illumina 1M-single array	996 ASD patients 1,287 controls	Deletion-duplication	*PARK2*	[10]
6q26	Affymetrix 10K SNP arrays	1,496 ASD families	Deletion-duplication	*PARK2*	[20]
7q11.22	Illumina HumanHap550 BeadChip	1,336 ASD patients 1110 controls	Duplication	*AUTS2*	[21]
7q11.22	Illumina 1M-single array	996 ASD patients 1,287 controls	Duplication	*AUTS2*	[10]
7q11.22	Array-CGH	96 ASD patients	Duplication	*AUTS2*	[24]
8p23.1	Array-CGH	28 ASD patients 62 controls	Deletion	*DEFENSIN* (*DEFA5*)	[25]
15q11-q13	Array-CGH	397 ASD patients 372 controls	Duplication	*UBE3A*, *GABRG3*, *GABRB3*, *GABRA5*	[26]
15q11-q13	Illumina 1M-single array	996 ASD patients 1,287 controls	Duplication	*UBE3A*, *GABRG3*, *GABRB3*, *GABRA5*	[10]

Table 2: Continued.

CNV locus	Study design	Patients	CNV type	Candidate gene	References
15q11-q13	Illumina HumanHap550 BeadChip	1,336 ASD patients 1110 controls	Duplication		[19]
15q11-q13	CGH	118 ASD patients 196 controls	Duplication	*UBE3A*, *GABRG3*, *GABRB3*, *GABRA5*	[27]
15q11-q13	Affymetrix GeneChip Human Mapping 500K Array	427 ASD patients 500 controls	Duplication	*UBE3A*, *GABRG3*, *GABRB3*, *GABRA5*	[11]
15q13.3	Illumina 1M-single array	996 ASD patients 1,287 controls	Deletion	*CHRNA7*	[10]
15q13.3	Array-CGH	119 ASD patients	Deletion	*CHRNA7*	[19]
15q13.3	Array-CGH	223 ASD patients	Deletion	*CHRNA7*	[22]
16p11.2	CGH	118 ASD patients 196 controls	Deletion-duplication	*A2BP1*	[27]
16p11.2	Affymetrix GeneChip Human Mapping 500K Array	427 ASD patients 500 controls	Deletion-duplication		[11]
16p11.2	Illumina HumanHap550 BeadChip	1,336 ASD patients 1110 controls	Deletion-duplication		[19]
16p11.2	Illumina 1M-single array	996 ASD patients 1,287 controls	Deletion-duplication	*MVP, GDPD3*	[10]
16p11.2	Array-CGH	223 ASD patients	Deletion-duplication		[22]
17p11.2	Array-CGH	28 ASD patients 62 controls	Deletion		[25]
22q11.21	Affymetrix 10K SNP arrays	1,496 ASD families	Deletion-duplication		[28]
22q11.21	Affymetrix GeneChip Human Mapping 500K Array	427 ASD patients 500 controls	Deletion-duplication		[11]
22q11.21	Illumina HumanHap550 BeadChip	1,336 ASD patients 1110 controls	Deletion-duplication		[21]
22q11.21	Illumina 1M-single array	996 ASD patients 1,287 controls	Deletion-duplication	DiGeorge Syndrome region	[10]
22q11.21	Array-CGH	223 ASD patients	Deletion-duplication	*PI4KA, SNAP29, TBX1, SLC7A4 SLC25A1, HIC2, UBE2L3, YPEL1, MAPK1*	[22]
22q13.33	Affymetrix 10K SNP arrays	1,496 ASD families	Deletion-duplication	*SHANK3*	[20]
22q13.33	Affymetrix GeneChip Human Mapping 500K Array	427 ASD patients 500 controls	Deletion-duplication	*SHANK3*	[11]

Table 2: Continued.

CNV locus	Study design	Patients	CNV type	Candidate gene	References
22q13.33	Illumina HumanHap550 BeadChip	1,336 ASD patients 1110 controls	Deletion-duplication	*SHANK3*	[21]
22q13.33	Illumina 1M-single array	996 ASD patients 1,287 controls	Deletion-duplication	*SHANK3*	[10]
22q13.33	Array-CGH	223 ASD patients	Deletion-duplication	*SHANK3*	[22]
22q13.33	Illumina HumanHap300 Beadchips	105 ASD patients 267 controls	Deletion-duplication	*SHANK3*	[29]
Xq27.2	Illumina iSelect array	2175 ASD patients 5801 controls	Deletion	*SPANXC*	[30]
Xq28	Illumina iSelect array	2175 ASD patients 5801 controls	Deletion	*MAGEA8*	[30]

5. Conclusion

Copy number variants and microRNAs (miRNAs) are new entities that have changed the level of gene expression and regulation. But little information is known about how CNVs influence miRNA metabolism and regulatory networks [24]. As summarized above, several human studies have established association between structural chromosomal abnormalities and ASD phenotypes suggesting that rare CNVs contribute to ASD risk. ASD is primarily a genetic disorder, but it has been also accepted that it shows genetic heterogeneity. While using the present technologies in CNV studies, we could mention that many more undiscovered CNVs may exist in the human genome, and therefore further studies are expected to improve our knowledge of the distribution and genetic susceptibility of CNVs. The latest advances in autism genetics highlight the complex mechanism of its pathophysiology. Although still in its infancy, the study of CNVs has already enriched our understanding of autism genetics. Additional work will be necessary to clarify the significance of these regions to autism susceptibility. In addition to more traditional explanatory models positing multiplicative effects of common variants, it seems that rare, spontaneous, and highly penetrant mutations may explain a portion of autism cases. Study design with simplex and multiplex families may prove useful for the selection of appropriate analytic techniques and specific subgroups of autism cases in future genetic studies. Despite these advances in our understanding of the likely importance of structural genetic variation in susceptibility to common complex disease, resolution is still limited by technology, and methods to detect copy number differences are unable to detect variation arising as a result of balanced rearrangements [28]. Efforts in molecular technologies with whole genome and whole-exome sequencing, as well as transcriptomic analysis and epigenetic studies, will further explain the mechanisms that contribute to ASD. As the studies go on and with the discovery of new pathways related to ASD will have a major impact on clinical diagnosis and classification of this complex disease.

Conflict of Interests

The author declares that there is no conflict of interests regarding the publication of this paper.

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