Mutation Research-Reviews in Mutation Research 794 (2024) 108509

Contents lists available at ScienceDirect

Mutation Research-Reviews in Mutation Research

journal homepage: www.elsevier.com/locate/mutrev

A critical review of the impact of candidate copy number variants on autism spectrum disorder

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ARTICLE INFO

Keywords:
Autism spectrum disorder
Gene expression
Copy number variants
CNV
LncRNA
Integrative analysis

ABSTRACT

Autism spectrum disorder (ASD) is a complex neurodevelopmental disorder (NDD) influenced by genetic, epigenetic, and environmental factors. Recent advancements in genomic analysis have shed light on numerous genes associated with ASD, highlighting the significant role of both common and rare genetic mutations, as well as copy number variations (CNVs), single nucleotide polymorphisms (SNPs) and unique de novo variants. These genetic variations disrupt neurodevelopmental pathways, contributing to the disorder's complexity. Notably, CNVs are present in 10 %-20 % of individuals with autism, with 3 %-7 % detectable through cytogenetic methods. While the role of submicroscopic CNVs in ASD has been recently studied, their association with genomic loci and genes has not been thoroughly explored. In this review, we focus on 47 CNV regions linked to ASD, encompassing 1632 genes, including protein-coding genes and long non-coding RNAs (lncRNAs), of which 659 show significant brain expression. Using a list of ASD-associated genes from SFARI, we detect 17 regions harboring at least one known ASD-related protein-coding gene. Of the remaining 30 regions, we identify 24 regions containing at least one protein-coding gene with brain-enriched expression and a nervous system phenotype in mouse mutants, and one lncRNA with both brain-enriched expression and upregulation in iPSC to neuron differentiation. This review not only expands our understanding of the genetic diversity associated with ASD but also underscores the potential of lncRNAs in contributing to its etiology. Additionally, the discovered CNVs will be a valuable resource for future diagnostic, therapeutic, and research endeavors aimed at prioritizing genetic variations in ASD.

1. Introduction

Autism spectrum disorder (ASD) is defined as a complex and highly heterogeneous neurodevelopmental disorder (NDD), characterized by challenging in social interaction, repetitive patterns of activities, and restricted interests [1]. Additionally, individuals with ASD may experience various co-occurring conditions, such as schizophrenia, sleep disturbances, epilepsy, attention-deficit/hyperactivity disorder (ADHD),

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https://doi.org/10.1016/j.mrrev.2024.108509
Received 4 February 2023; Received in revised form 14 April 2024; Accepted 2 July 2024
Available online 6 July 2024

speech and language delays, anxiety, and intellectual disability (ID) [2,3]. The global prevalence of ASD is approximately 1 in 100 children, with a male to female ratio of four to five times higher, according to the Center for Disease Control (www.cdc.gov/ncbddd/autism/data.html, retrieved on 5 April 2024) [4–6]. Nonetheless, other studies hint at a potential adjustment in this ratio to closer to 3:1 or 2:1, likely influenced by evolving diagnostic criteria and enhanced recognition of ASD among females [7,8]. The etiology of ASD involves a complex interplay of genetic and environmental factors, which independently and synergistically contribute to the disorder's onset [9]. Genetic contributions to ASD are undoubtedly significant, encompassing a variety of elements such as single nucleotide polymorphisms (SNPs), alteration within non-coding regulatory regions (e.g., long non-coding RNAs or lncRNAs), common and rare variants, *de novo* mutations, epigenetic modifications, and copy number variants (CNVs) [10–12].

Previous research has highlighted the significant impact of CNVs on ASD [13,14] and other disease [15,16]. Among ASD patients, even within the same locus region, CNVs demonstrate significant clinical diversity, particularly in phenotypic characteristics, severity, and comorbidities [17]. As notable genetic contributors, CNVs are identified in 10 %-20 % of individuals diagnosed with ASD, although only 3 %-7 % are detectable using conventional cytogenetic methods [6,18,19]. The advent of chromosomal microarrays (CMA), genome-wide association studies (GWAS), and next-generation sequencing (NGS) techniques has revealed a broad spectrum of CNVs associated with ASD. To date, upward of 90 pathogenic CNVs, each with implicated causative genes or characterized by specific deletions or duplications related to ASD, have been identified. The majority of these CNVs were found to be inherited in a familial pattern; however, they can also occur de novo [6,10,20,21]. Although there is significant evidence that CNVs play a major role in ASDs, the incomplete penetrance and variability in expression of most CNVs pose challenges in pinpointing the specific genes implicated in ASD. Consequently, the identification of both known and unknown loci and candidate genes for ASD is needed to provide more information regarding genotype-phenotype correlations in the disorder.

The current study focuses on exploring 47 CNV regions (Table 1) that have been recently identified by our team using the novel CNV detection toolset SNATCNV [13] on a CNV dataset containing 6479 controls and 19,663 cases samples with ASD phenotypes, sourced from the SFARI (Simons Foundation Autism Research Initiative) dataset (https://gene.sfari.org/autdb/CNVHome.do). The methodologies employed for detecting ASD CNV regions have been detailed in our previous

Table 1
CNV regions identified by SNATCNV. Loci marked with an asterisk (*) contain at least one known ASD-associated genes.

Locus	region ID (hg19)	type	#case	#control	P *value*	#Brain-enriched / total		#Mice neuro phenotype
						coding	lncRNA	
1p36.32 *	chr1:10001–10270615	Del	240	41	5.10E-06	57/155	44/151	19
1q21.1	chr1:146113643–147727385	Dup	192	12	2.60E-17	5/10	5/15	0
1q21.1	chr1:146113643–147870095	Del	244	14	6.20E-18	5/11	5/22	0
2q23.1 *	chr2:148669357–148995585	Del	50	1	6.70E-06	3/3	2/2	2
2q37.3	chr2:242930600–243007359	Del	63	1	1.70E-07	0/0	0/3	0
2p16.3 *	chr2:51105853–51359022	Del	160	12	2.20E-10	1/1	1/1	1
3q29	chr3:195745603–197355603	Del	73	3	5.90E-07	12/28	9/34	2
4q16.3	chr4:1705715–2073645	Del	75	0	2.60E-10	5/11	0/4	2
6p25.3	chr6:259528–339802	Del	91	0	2.00E-12	1/1	0/0	0
6p25.3	chr6:259528–339802	Dup	92	2	2.10E-12	1/1	0/0	0
7q11.23 *	chr7:72742064–74142064	Del	146	3	1.50E-15	9/26	8/25	6
7q11.23 *	chr7:72742064–74142064	Dup	108	5	1.50E-11	9/26	8/25	6
8p23.1	chr8:10657597–10695288	Del	45	0	2.70E-06	0/3	0/0	0
8p23.1	chr8:7268819–7366446*	Del	54	1	2.90E-06	0/3	0/0	0
8p23.1	chr8:7721060–7752586	Dup	50	0	4.50E-08	0/1	0/0	0
8p23.1	chr8:8650757–11629240	Dup	72	2	4.10E-09	9/21	18/41	0
9q34.3	chr9:140441351–140936261	Del	58	0	5.80E-08	4/8	2/4	2
10q23.1 *	chr10:81960020–88800020	Del	118	15	3.90E-05	15/26	9/32	3
11p14.1 *	chr11:29635361–31653568	Del	69	5	4.50E-05	7/8	7/11	1
13q34	chr13:111699708–115085141	Del	66	0	5.20E-09	10/42	10/42	1
15q11.2	chr15:22798636–23088559	Del	245	32	4.20E-09	2/4	0/5	0
15q11–13.1*	chr15:23094431–29410239	Dup	280	23	2.80E-21	13/17	19/47	5
15q11–13.1*	chr15:24674739–28514614	Del	147	19	6.60E-06	8/10	15/35	3
15q13.3 *	chr15:30938215–32510863	Del	261	24	6.30E-14	5/11	3/13	2
15q13.3 *	chr15:32452709–32509897	Dup	90	7	7.90E-08	1/1	0/0	1
16p13.11	chr16:15248707–16292499	Del	171	26	1.80E-05	5/10	2/11	0
16p13.11	chr16:15502499–16292499	Dup	288	64	8.60E-07	5/10	1/9	0
16p12.2	chr16:21942499–22462224	Del	111	5	2.58E-12	5/8	2/6	0
16p11.2	chr16:28822499–29052499	Del	81	2	9.40E-09	1/9	0/8	0
16p11.2 *	chr16:29517499–30202499	Dup	275	28	5.80E-18	15/32	4/20	4
16p11.2	chr16:29517499–30367499	Del	373	16	8.10E-31	16/34	4/21	6
17p13.3	chr17:1038189–1673212	Dup	100	2	4.50E-13	6/22	1/17	4
17p11.2	chr17:16446387–18380166	Dup	87	0	8.50E-14	17/36	10/27	5
17p11.2	chr17:16789275–18299275	Del	61	1	2.70E-07	13/31	8/23	5
17p13.3	chr17:2302359–3502250	Dup	85	5	1.90E-08	9/13	6/12	3
17p13.3	chr17:911295–2593250	Del	65	3	5.10E-06	14/39	8/39	8
17q12	chr17:34815887–34856055	Dup	86	6	6.20E-08	0/3	0/0	0
17q12	chr17:34815887–36225887	Del	117	5	2.40E-10	5/17	5/12	1
17q21.31	chr17:43704217–44164182	Del	86	0	8.90E-12	3/4	4/7	3
22q11.21 *	chr22:18545000–21745000	Del	456	9	2.30E-47	20/54	10/37	5
22q11.21 *	chr22:19020000–20308799	Dup	193	25	1.60E-10	8/32	3/17	3
22q11.22	chr22:21910000–23650000	Del	89	9	6.30E-05	10/64	5/22	3
22q11.22	chr22:23046186–23134119	Dup	46	0	1.20E-07	0/7	0/5	0
22q13.2–33*	chr22:43000056–51224208	Del	259	40	1.60E-07	48/113	26/109	8
Xq28 *	chrX:152561384–154917042	Dup	127	14	2.50E-08	17/70	2/19	6
Xp22.33 *	chrX:619146–2700156	Dup	146	22	6.00E-07	4/15	6/11	0
Xp22.31 *	chrX:6490000–7885155	Del	80	7	3.80E-05	2/4	0/4	0

publication [13]. This study conducted an integrative bioinformatics analysis aiming to enhance our understanding of the genetic landscape of Autism. It provides an overview of both known and novel causative genes within the CNV regions, summarizing the existing evidence on the influence of detected genetic variations on the brain and nervous system (NS), and their potential risk factors for ASD.

2. Results and discussions

Our comprehensive analysis revealed 1632 genes including both protein-coding genes and long non-coding RNAs within 47 CNV regions implicated in ASD, with 659 of them showing significant expression in the brain. Utilizing a curated list of ASD-associated genes from SFARI, we identified 31 known genes located within 17 of these 47 loci. These 17 loci have been specifically highlighted in Table 1 for clarity. Additionally, this exploration has uncovered 567 novel candidate genes throughout the 47 ASD-associated CNV regions, which are detailed in Table S1 and illustrated in Fig. 1. Moreover, pathway and gene ontology analyses have been performed to better understand the functional implication of these genes. Further comprehensive discussions of these findings are planned for subsequent sections.

2.1. 1p36.22-p36.33 deletions

Our analysis identified a significant interstitial deleted region within the 1p36.22-p36.33 locus (chr1:10001–10270615) spanning 10.2 Mb and containing at least 306 genes. This deletion is associated with a variety clinical manifestation, such as congenital abnormalities, developmental delay (DD), ID, muscular hypotonia (MH), and seizures. It is noteworthy that such clinical manifestations have been observed in patients with varying sizes of deletions within the 1p36 region, both terminal and interstitial deletions [22–24], thus complicating the correlation between specific genotypes variations and the resulting phenotypic characteristics.

Within this identified region, we found 57 coding genes and 44 lncRNAs with significantly enriched expression in the brain. This part of

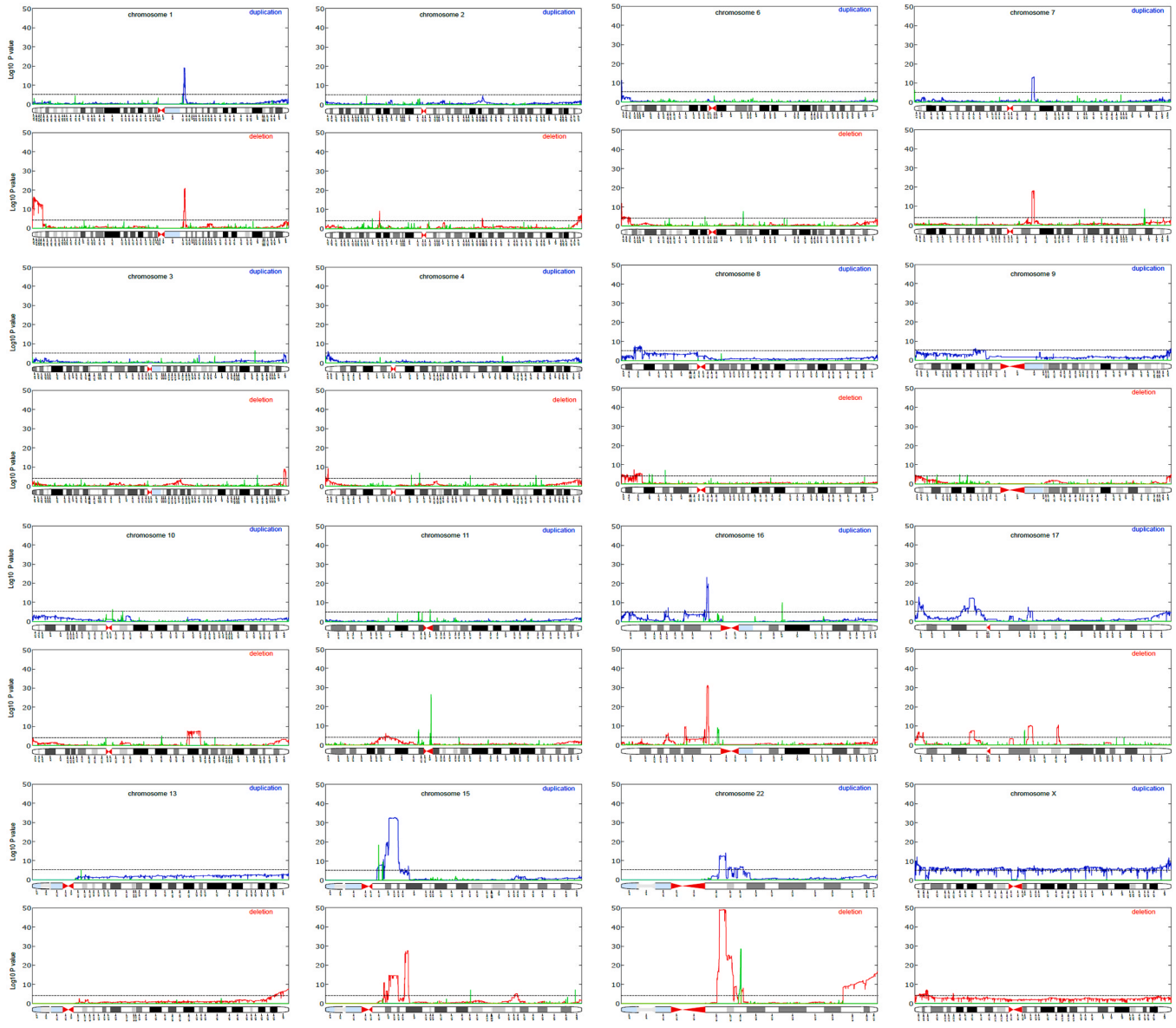

Fig. 1. ASD copy number variations on human chromosomes. Blue: statistically significant duplications identified in ASD individuals; Red: statistically significant deletions identified in ASD individuals; Green: copy number variants from healthy controls. Black dashed line indicates our threshold for significant regions (better *P-value* than 99.9999 percentile of 500,000 permutations). X-axis indicates genomic loci and y-axis indicates logarithm 10 *P-value*. *P-value* calculated through one-tailed Fisher exact test.

our study, which is focused on elucidating the potential roles of these genes in neurodevelopment and ASD pathogenesis, identified 19 coding genes with neural system phenotypes in mutant mouse models, such as *DNAJC11*, *DVL*, *VWA1, GNB1, GABRD, PRKCZ*, and *PERE*. Additionally, we discovered 16 lncRNAs that show dynamic expression patterns during the differentiation process from induced pluripotent stem cell (iPSC) to neuron, including *RP1–140A9, TP73-AS1, CATG00000045106, CATG00000004170, CATG00000004816*, and *CATG00000004823* [25–27].

The genes expressed in brain-derived tissue are considered to be among the major genetic contributors to autism [13]. For instance, *DVL1* (disheveled segment polarity protein 1), which has been identified as having a putative link to ASD, is notably absent in autistic individuals. Previously, Lijam et al. reported impaired social interaction behaviors (a hallmark characteristic of autism) in a mouse model lacking *Dvl1*[28]. According to our analysis, using the FANTOMCAT database [25], *DVL1* is highly expressed within the nervous system (NS) of the mouse [26,27], suggesting a significant role in neurodevelopment and potentially in the pathogenesis of ASD.

Similarity, *RERE* (arginine-glutamic acid dipeptide repeats), another brain-enriched gene significantly deleted in ASD patients, has been studied in zebrafish and mouse models [23]. This research has shown that mutation and haploinsufficiency of *RERE* can lead to NDDs, ID, DD, and renal issues [23,26,27,29–31]. These findings indicate that *RERE* mutation carriers and autistic individuals share common phenotypic traits, suggesting that this gene is a plausible and significant contributor to ASD. Additionally, the significant deletion of lncRNA *RP11-206L10* on 1p36, as identified in our study, support the potential function of this brain-enriched lncRNA in the neurodevelopmental regulation, aligning with previous reports that have been linked as residing in ID-associated CNVs [32].

2.2. 1q21.1 rearrangements

In this locus, CNVs have been detected in patients with a wide spectrum of developmental and neurological disorders, including DD, ID, schizophrenia, and ASD [33]. Our investigation of the 1q21.1 locus has revealed two notable structural abnormalities: a duplication spanning1.6 Mb (chr1:146113643–147727385) and a deletion covering 1.75 Mb (chr1:146113643–147870095), both of which significantly manifest in individuals with ASD. Analysis shows this locus contains 10 brain-enriched genes (5 protein-coding and 5 lncRNA genes), each undergoing significant deletion and/or duplication in ASD patients.

The microdeletion at 1q21.1 is linked to diverse phenotypes, including congenital heart disease (CHD) [34], schizophrenia [35], ID and microcephaly [24], whereas, microduplications at this locus are generally associated with ID, macrocephaly, and ASD [24,33,36]. The result of our study indicates that brain-enriched *RP11–337C18*, a significantly duplicated/deleted lncRNA with dynamic expression in an iPSC model of neuron differentiation, has potential role in neurodevelopmental process and is likely important in ASD. Furthermore, *BCL9* (B-cell CLL/lymphoma 9), as one of brain enriched coding gene within this locus, plays a critical role in signal transduction of the canonical Wnt pathway through promoting β catenin's transcriptional activity [37,38]. Previous association studies have implicated disruption in Wnt/β-catenin signaling in neurons as contributing factor to ASD phenotypes [38,39]. It has also been demonstrated that BCL9 modulates Wnt signaling through its interaction with the *ARX* gene, known to be associated with autism [40], suggesting the potential involvement of the *BCL9* gene in ASD pathogenesis.

2.3. 2p16.3 microdeletion

A significant deletion spanning 253 kb region (chr2:51105853–51359022) on 2p16.3 has been identified in individuals with ASD. This region contains one protein-coding gene, *NRXN1*, and one lncRNA, *AC007682*.1, both showing significant brain enrichment. *NRXN1* (neurexin 1) also demonstrates physiological and morphological effects on mutant mice [26,27]. This gene, belonging to the neurexins family of presynaptic cell-adhesion proteins crucial for synaptic connections, has already been linked to ID and DD. In addition, *NRXN1* is implicated in the pathogenesis of psychiatric disorders such as schizophrenia and ASD, with mutations showing incomplete penetrance and variable expressivity [41–44]. Furthermore, the identification of AC007682.1 as the sole brain-enriched lncRNA within this region suggests its potential involvement in ASD etiology.

2.4. 2q22.3-q23.1 microdeletions

In autistic individuals, we discovered a 326 kb region at 2q23.1, containing 5 brain-enriched genes (3 coding genes and 2 lncRNA genes) that are significantly deleted. Microdeletions in this region, varying in size from 0.2 Mb to 5.5 Mb, have been associated with a broad spectrum of clinical manifestations, including dysmorphic features, ID, seizures, behavioral problems, and ASD [45–48]. Among the identified brain-enriched coding genes, *MBD5* and *ACVR2A* have shown dynamic expression from iPSCs to neuronal differentiations and have been found to cause morphological changes in mutant mice [26,27]. *MBD5* (methyl-CpG binding domain protein 5) belongs to the methyl CpG-binding domain protein family, which encompasses *MECP2,* a well-known ASD-associated gene that is mutated in Rett syndrome [47,49,50]. It has been proposed that *MBD5* is a dosage-sensitive gene crucial for normal development, with autism-related mutations [48,51–53].

2.5. 2q37.3 microdeletion

The 2q37 deletion is known to be associated with brachydactyly mental retardation syndrome (BDMR), a condition characterized by ID, DD, behavioral abnormalities, and ASD [54,55]. The 2q37.3 microdeletion has also been linked to autism [56] and miscarriage [57], suggesting the presence of potentially important regulatory genes in this region might influence the progression of NDDs. Our analysis identified a 76.76 kb region significantly deleted at 2q37.3 (chr2:242930600–243007359) in autistic individuals, containing three lncRNA genes (*AC131097.3*; *AC093642.3*; *AC093642.4di*), underscoring their potential importance in ASD research.

2.6. 3q29 microdeletion

In the 3q29 region, microdeletions ranging from 0.8 Mb to 2.1 Mb have been associated with various phenotypes, including ID, neuropsychiatric and neurocognitive disorders, microcephaly, schizophrenia, bipolar disorder, and ASD [58–63]. The presence of low copy number repeats (LCRs) flanking this region suggests the role of non-allelic homologous recombination (NAHR) at deletion breakpoints [60]. Using SNATCNV, we detected one significantly deleted region (chr3:195745603–197355603) at 3q29 locus, which includes 21 brain enriched genes (12 coding and 9 lncRNA genes) out of 64 genes. Among these genes, *FBXO45, PAK2* and *DLG1* have shown impact on the NS in mutant mice [26,27], while *CATG00000067412*, *MFI2-AS1* and *AC128709.2*, three lncRNA genes implicated in iPSC to neuron differentiation with brain enrichment, highlight their plausible function in neurodevelopmental processes.

PAK2 (p21 (RAC1) activated kinase 2) is a serine/threonine kinase that regulates actin cytoskeleton dynamic, with potential signaling roles in cortical neurons [64–66]. It is highly expressed in the fetal brain and may contribute to neuronal differentiation [65,66]. It has also been documented that *PAK2* plays a crucial role in brain development and autism progression [60,67].

FBXO45 (F-box protein 45) is an ubiquitin ligase involved in the growth and formation of synapses [68,69], and has been implicated in the progression of schizophrenia and autism [70]. Studies in mice have

suggested roles for *Foxo45* in neuronal migration and development [71]. Overall, these findings, along with genotype-phenotype correlation studies for 3q29 deletion, indicate that *FBX045* might be a candidate gene involved in the progression of neuropsychiatric disorders [59].

DLG1 (discs large MAGUK scaffold protein 1) is a paralogue of *DLG3*, a gene engaged in the pathogenesis of ID when mutated [60]. This gene is required for normal development and is a component of a core transsynaptic complex (Neurexin/Neuroligin/DLG/SAPAP/Shank) whose mutations likely increase susceptibility to autism [70,72,73].

2.7. 4q16.3 microdeletion

The 4q16.3 deletion has been reported in patients with Wolf-Hirschhorn syndrome (WHS) [74]. Our analysis identified 15 genes (coding and non-coding) in a significantly deleted 367 kb region on 4q16.3 (chr4:1705715–2073645), of which five coding genes highly expressed in the brain. Among these, ***FGFR3*** and ***NAT8L*** stand out as potential candidates for involvement in neurodevelopmental processes, both are highly expressed in the NS and exhibit phenotypic manifestations in mutant mice [26,27]. Gene ontology analysis indicates that *FGFR3* is strongly associated with seizures and congenital abnormalities [75–77], which are very common in ASD. Additionally, it plays a role in the STAT cascade, which is involved in neural development [78], suggesting a possible role for *FGFR3* in autism.

2.8. 6p25.3 rearrangements

In our search for substantial CNVs related to autism spectrum disorder (ASD), we identified a novel 80.3Kb region (chr6:2595 28–339802) on the 6p25.3 chromosomal band, showing significant deletions and duplications. This region contains a single gene, ***DUSP22*** (Dual specificity phosphatase 22), which has previously been implicated in autism's pathogenesis through the JNK signaling pathway [79–82]. JNK signaling is considered to play a crucial role in the development of psychiatric diseases such as ID, schizophrenia and ASD [80]. The same study, in parallel to other findings [83], highlighted that *DUSP22* is an imprinted gene expressed maternally in the adult prefrontal cortex [82]. This finding further suggests its potential role as a contributor to the pathogenesis of ASD. Additionally, heterozygous deletion of the *DUSP22* gene has been reported in ASD cases [84].

2.9. 7q11.23 rearrangements

We have identified deletions and duplications ranging from 1.5 to 1.8 Mb at 7q11.23 locus, leading to Williams-Beuren Syndrome (WBS; MIM 194050) and 7q11.23 duplication syndrome (Dup7; MIM 609757), respectively [24,84–86]. Notably, the prevalence of WBS is 6–10 times higher in individuals with autism than in the general population [84], indicating that deletion may play a crucial role in the pathogenesis of autism. In autistic individuals, we detected a significantly deleted/duplicated region (chr7:72742064–74142064) spanning 1.4 Mb on the 7q11.23 chromosomal band, encompassing 51 genes (26 coding and 25 lncRNA genes). After narrowing down the list of the significantly deleted/duplicated brain-enriched genes (9 coding and 8 lncRNA genes) at 7q11.23 locus, we identified *STX1A*, *GTF2I*, *GTF2IRD1*, *CLIP2, FZD9*, *LIMK1*, *EIF4H* as genes associated with NS phenotype in mutant mouse, as well as *CATG00000096069*, *CATG00000092613*, *CATG00000096089* that display dynamic expression in iPSC models, suggesting their potential relevance in ASD. Furthermore, our analysis of *STX1A* suggests a potential role for this gene in autism, as it shows high expression in brain, significant deletions and duplications in ASD, and has effects on the NS when mutated in mice.

STX1A (syntaxin 1A) modulates serotonin transporter activity, which is found to be overexpressed in autism with high functioning and may potentially be involved in the pathogenesis of ASD [87–89]. ***GTF2I*** (the general transcription factor 2I) and ***CLIP2*** (CAP-Gly domain containing linker protein 2) are also other brain-enriched genes that may contribute to the etiology and clinical manifestation of autism [90,91].

2.10. 8p23.1 rearrangements

We have conducted a study on various deletions and duplications in the 8p23. region, which is known to be highly susceptible to genomic rearrangements. Different groups have reported changes in the range of 3.6 Mb to 6.5 Mb within this region [92–96]. Most interstitial deletions of 8p23.1 are *de novo* [96,97], while terminal deletions are typically inherited [96]. In our research, we narrowed down the regions of CNVs and uncovered four regions ranging from 38 kb to 3 Mb that were significantly deleted (chr8:10657597–10695288, chr8:7268819–7366446) or duplicated (chr8:7721060–7752586, chr8:8650757–11629240) on 8p23.1in autistic individuals.

Our analysis revealed that deletions in these regions are associated with an elevated risk of NDDs, psychiatric conditions, heart abnormalities, hyperactivity, and mild to moderate ID [24]. Conversely, duplications in these loci are linked to abnormal facial shape, behavioral/psychiatric abnormality, problems with learning/speaking, malformation of the heart, and ID [24]. Within these four regions, we detected 27 significantly duplicated brain-enriched genes (9 coding and 18 lncRNA genes). Although no ASD-associated genes were directly reported within these regions, our study highlighted several candidate genes. These include brain-enriched genes such as *TNKS, PINX1, MSRA, XKR6, FAM167A*, *NEIL2,* and genes associated with NS phenotypes in mutant mice, like *RP1L1* and *GATA4* [25–27]. Moreover, we identified that lncRNA *RP11–1E4.1* is significantly expressed in the brain and exhibits dynamic expression during iPSC to neuron differentiation, suggesting its potential impact on neurodevelopment and possible contribution to ASD phenotypes.

MSRA (methionine- sulfoxide reductase), located within a significantly duplicated region on chr8:8650757–11629240, plays a regulatory role in human fetal brain development [98] and has protective function against oxidative stress [99], which is proposed as a causative mechanism in ASD [100]. Furthermore, *MSRA* has been linked to bipolar disorder [101] and schizophrenia [102], and in a gene-based association within iPSYCH-PGC meta-analysis of ASD, it showed with ASD [103]. These findings, combined with our results, emphasize the possibility of a strong correlation between *MSRA* and autism.

PINX1 (PIN2/TRF1-interacting telomerase inhibitor 1) regulates telomere integrity, required for chromosomal stability [104,105]. Emerging evidence suggests that some genetic variations involved in ASD are linked to telomere shortening [106,107], making *PINX1* a potential candidate gene for telomere shortening in ASD patients.

TNKS (tankyrase 1), another brain enriched gene in the 3 Mb duplications region (chr8:8650757–11629240), is suggested to have a role in ID [25,96]. This gene is involved in regulating sister chromatid separation [108], intestine organoid growth [109], and the Wnt/β catenin signaling pathway [110]. Given that both activation and inhibition of canonical Wnt pathway have been implicated in increasing the risk of autism [38], *TNKS* could be considered as an ASD related gene.

2.11. 9q34.3 deletions

Several types of rearrangement have been observed at the 9q34.3 locus, including terminal and interstitial deletions, unbalanced translocations, and complex rearrangements, which are associated with 9q34.3 microdeletion syndrome [111]. These microdeletions, typically less than 3.5–4 Mb and involving multiple breakpoints at the telomeric regions, results in a spectrum of clinical features such as ID, microcephaly, MH, protruding tongue, heart impairment, congenital defects, and developmental impairment in fetuses [24,111].

Our study identified a 495 kb region at the 9q34.3 locus (chr9:140441351–140936261) containing 12 genes (8 coding and 4 lncRNA genes) that were significantly deleted in individuals with ASD.

Among these genes, *CATG00000107435* and *CATG00000107433* are two significantly deleted brain-enriched lncRNAs, while *CACNA1B* and *EHMT1* are brain enriched coding genes affecting the NS of mutant mice [26,27].

EHMT1 (euchromatin histone methyltransferase 1), identified as a genetic cause of ID syndrome associated with subtelomeric deletion of 9q34.3, primarily due to its haploinsufficiency [112,113]. This gene has been implicated in the development of autistic-like symptoms in knockout mice [114] and the onset of psychological issues, particularly mood disorders and ASD, in individuals with mosaicism status [115].

CACNA1B (calcium voltage-gated channel subunit alpha B) belongs to the calcium channel genes family, whose members modulates neural function and may potentially contribute to ASD [116,117]. According to gene ontology analysis, *CACNA1B* is associated with neurological speech impairment, a frequent challenge in ASD. Altogether, these findings and our results may indicate a possible role of this gene in ASD progression.

2.12. 10q22-q23 deletions

It has been demonstrated that deletions at the 10q22.3q23.2 locus are associated with cognitive and behavioral abnormalities as well as feature characteristic of autism [118]. These deletions affect various genes known for their role in neurodevelopmental, including *NRG3*, *GRID1*, *BMPR1A*, *SNCG*, *GLUD1*, among others [119]. Our bioinformatics analysis discovered a significantly deleted region spanning 6.84 Mb (chr10:81960020–88800020) in autistic patients. This region encompasses 26 coding genes and 32 lncRNA genes, with 24 of these genes (15 coding and 9 lncRNA genes) showing brain-enriched expression. The FANTOMCAT database revealed that *CATG00000000247*, *CATG00000000263*, *RP11–77P6.2*, and *RP11–96C23.5* are highly expressed during iPSC differentiation to neuron [25]. Moreover, *GRID1, OPN4*, and *SNCG* have been associated with neural system phenotypes in mutant mice [26,27], highlighting their potential roles in neural development.

GRID1 (glutamate receptor ionotropic, delta-1) is implicated in schizophrenia [120] and is considered to contribute the genetic landscape of autism [121–123]. ***BMPR1A*** (bone morphogenetic protein receptor type-1A), a gene significantly deleted in patients with ASD, is known to result in Juvenile Polyposis Syndrome (JPS) through loss of function mutations [124]. Microdeletions in *BMPR1A* are associated with severe polyposis, childhood malignancies and autism-related phenotypes such as cardiac abnormalities, macrocephaly and DD [125]. ***NRG3*** (neuregulin 3), another brain enriched gene within this locus, is identifies as susceptibility gene for schizophrenia [126], and 10q22-q23 microdeletions including this gene have been linked to NDDs such as cognitive impairment, DD, and autism [126,127].

2.13. 11p14.1-p13 deletions

Individuals with the 11p14.1 microdeletion have shown association with ADHD, obesity, and autism, while those carrying larger deletions in this chromosomal region have presented severe developmental delays, ID, language impairment and additional clinical features [128]. Using SNATCNV, we found a significantly deleted region spanning 2 Mb (chr11:29635361–31653568) on the 11p14.1-p13 loci which included 19 genes (8 coding and 11 lncRNA genes), 14 of which are brain-enriched (7 coding and 7 lncRNA genes). Among these genes, we identified ***KCNA4*** (potassium voltage-gated channel subfamily A member 4) as the most significantly deleted gene, which has an effect on the mouse NS when mutated [26,27]. This gene modulates the time interval and shape of the cardiac action potentials and heart rate [129], in addition to influencing neurotransmitter release [130,131]. Although direct studies linking KCNA4 to autism are lacking, it is known that dysfunction of neurotransmitter system and altered heart rate are linked to autism [132–135], suggesting a potential role for *KCNA4* in ASD. ***ELP4*** (elongator acetyltransferase complex subunit 4), another brain-enriched gene located within the 11p14.1-p13 CNVs, its deletion has been implicated in the progression of various NDDs, ranging from language impairment to epilepsy and ASD, indicating its likely significant role in this condition [136].

2.14. 13q34 deletion

The deletion at the 13q34 locus is associated with an increased risk of NDDs, including epilepsy, mild ID, and DD [137–139]. Our bioinformatics analysis of CNVs related to ASD using SNATCNV, revealed a significantly deleted 3.38 Mb region at 13q34 (chr13:111699708–115085141) in autistic patients. This region encompasses 42 coding genes and 42 lncRNA genes. Among the gens significantly deleted and showing enrichment in the brain and NS, *CATG00000016319, LINC00403, CATG00000018119, CATG00000018133, CATG00000016366,* and *CATG00000018138* displayed dynamic expression during neural differentiation of iPSCs, as well as ***ATP11A*** showed an effect on the mice's NS when mutated [26,27], may reflect their importance in the progression of NDDs.

Deletion of 13q34 harboring *ATP11A, MCF2L*, *F7*, *F10*, *PROZ*, *PCID2*, *CUL4A*, and *LAMP1* genes within our defined significantly deleted region, was detected in an Italian family suffering bleeding diathesis, multiorgan involvement, and language delay. This finding suggests the potential involvement of these genes in ASD-related manifestations such as language delay [140]. In addition, ***UPF3A***, another brain enriched gene significantly deleted in ASD, plays a compensatory role in patients with loss of *UPF3B* function [141]. *UPF3B* is a paralog of *UPF3A*, is known to have implications in ID, childhood onset schizophrenia, ADHD, and autism [142]. Furthermore, *UPF3A* gene plays pivotal role in Nonsense-Mediated mRNA Decay (NMD), a crucial mechanism for preventing the production of truncated and potentially harmful proteins [143,144]. Variations in *UPF3A* may influence NMD efficiency, potentially leading to the accumulation of defective proteins, particularly in neurons, thereby contributing to ASD pathogenesis. Additionally, the NMD pathway, involving *UPF3A*, regulates the expression of genes involved in neuronal development and synaptic function, potentially affecting ASD-risk genes [144,145].

2.15. 15q (15q11.2; 15q11.2-q13.1; 15q13.3) rearrangements

The proximal long arm of chromosome 15 contains a cluster of low copy DNA repeats (called duplicons) that facilitates the occurrence of NAHR during meiosis, incorporating five breakpoints known as BP1-BP5 [146,147]. This genomic architecture predisposes to rearrangements resulting in various NDDs including Prader-Willi syndrome (PWS), Angelman syndrome (AS), and ASD [148–150]. Furthermore, patients with 15q11.2 deletions and carriers of 15q11.2-q13.1 rearrangement have been presented a wide range of phenotypes including electroencephalogram (EEG) abnormalities, ID, microcephaly, seizures, schizophrenia, truncal ataxia, hypogonadism, MH, ASD, and truncal obesity [24,151,152]. Additionally, behavioral, cognitive and language impairments along with ASD, have been linked to larger deletions at 15q11-q13 [153], while facial abnormalities, ID, and seizures have been associated with 15q13.3 deletion [24]. Our bioinformatics analysis detected some relevant 15q CNVs in individuals with autism, including 15q11.2 deletion (chr15:22798636–23088559), 15q11.2-q13.1 duplication (chr15:23094431–29410239), 15q11.2-q13.1 deletion (chr15:24674739–28514614), 15q13.3 duplication (chr15:32452709–32509897) and 15q13.3 deletion (chr15:30938215–32510863).

A number of ASD-related genes have been identified within these regions, such as *UBE3A*, *GABRB3*, *GABRA5*, *GABRG3*, *HERC2*, *APBA2* [154–161] located on 15q11.2-q13.1, as well as *ARHGAP11B*, *FAN1*, *TRPM1*, and *CHRNA7* [162–165] mapped on 15q13.3, a region that harbors several genes indicating incomplete penetrance, variable expression, and dosage sensitivity [166]. In addition to these known

ASD-related genes, we defined a number of significantly deleted and/or duplicated genes within ASD CNVs that show enrichments in the brain and NS. These include *NDN* , *UBE3A*, *GABRB3*, *GABRA5*, *APBA2*, *OTUD7A*, and *CHRNA7,* which affect the NS of mutant mice [26,27]. We also identified *CATG00000024385*, *RP11–484P15*, *CATG00000022353*, *CATG00000022386*, *CATG00000024462*, and *CATG00000022467* lncRNA genes with dynamic expression during iPSCs differentiation to neuron, suggesting they may be candidate genes related to ASD.

One of the genes located on 15q11.2-q13.1, known as ***UBE3A*** (ubiquitin protein ligase E3A), is an imprinted multifunctional gene that acts as both ubiquitin ligase and transcriptional co-activator with regulatory roles at synapses [167–169]. Copy number changes in this gene leads to NDDs such as 15q11.2-q13.3 duplication syndrome and ASD [170], consistent with our findings suggesting that *UBE3A* may be involved in ASD. Linkage disequilibrium at *UBE3A* has also been reported in families with autism [154].

The ***GABRB3***, ***GABRA5***, and ***GABRG3*** genes, encoding gamma-aminobutyric acid (GABA) receptor subunits, play crucial roles in neurodevelopment, and deficiencies in their function cause autism and autism-related NDDs [171]. Another gene within the 15q13.3 locus that encodes a ligand-gated ion channel protein mediating signal transduction at synapses is ***CHRNA7*** (cholinergic receptor nicotinic alpha 7 subunit). The dosage-sensitivity of this gene seems to be involved in the cognitive and behavioral symptoms [172,173]. Furthermore, reduced expression of *CHRNA7* has been reported in the frontal cortex of individuals with Rett syndrome and autism [152].

Furthermore, ***NIPA1*** (NIPA magnesium transporter), significantly deleted in autistic individuals, encodes a magnesium transporter protein that mediates Mg^{2+} uptake and is likely implicated in some NDDs including ASD [174]. Van der Zwaag et al. have highlighted *NIPA1* and *CYFIPI* (another gene located at 15q11.2 CNVs) as autism risk genes with function in axonogenesis and synaptogenesis [175]. This compilation of evidence, in conjunction with our findings, strongly supports the relevance of these genes to ASD.

2.16. 16p (16p13.11; 16p12.2; 16p11.2) rearrangements

The 16p region is known as an autism-susceptibility locus, with numerous duplications and deletions reported [176–178]. Rearrangements within the 16p11.2 and 16p13.11 regions are associated with a broad spectrum of neurological disorders, including seizures/epilepsy, ID, and autism [179–183], while abnormalities such as facial dysmorphisms, ID, macrocephaly, and speech articulation are linked to 16p11.2 and 16p12.2 deletions [24,179]. Furthermore, carriers of 16p11.2 duplication also exhibit clinical manifestations including speech articulation abnormalities and microcephaly [179]. Along with these findings, our bioinformatics analysis identified six significant regions in individuals with autism, including two deletions at 16p11.2 (chr16:28822499–29052499; chr16:29517499–30367499) with sizes of 0.23 Mb and 0.85 Mb, a 0.68 Mb duplication at 16p11.2 (chr16:29517499–30202499), a 0.52 Mb deletion at 16p12.2 (chr16:21942499–22462224), a 1 Mb deletion at 16p13.11 (chr16:15248707–16292499), and a 0.8 Mb duplication at 16p13.11 (chr16:15502499–16292499).

As a result, we identified 60 genes (47 coding genes and 13 lncRNA genes) highly expressed in the NS, among which 35 are significantly deleted and 25 are significantly duplicated in ASD patients. Notably, *CATG00000028919* and *CATG00000028920*, the only two brain-enriched lncRNA genes at the 16p12.2 significantly deleted, represent dynamic expression during iPSCs differentiation to neuron. It is also noteworthy that *KCTD13, PRRT2*, *SEZ6L2*, *DOC2A*, *TBX6*, and *MAPK3* are NS-expressed genes impacting the neural system of mutant mice [26,27], indicating their potential roles in NDDs such as autism. In addition, ***TAOK2***, another gene within the 16p11.2 CNV region, is implicated in NDDs due to its critical function in dendrite morphogenesis [184,185].

KCTD13 (potassium channel tetramerization domain containing 13), located within 16p11.2 CNVs, plays a crucial role in regulating neurodevelopmental processes [186,187]. Research using zebrafish and mouse models has demonstrated that *KCTD13* regulates head size, leading to microcephaly and macrocephaly due to deletion or duplication, respectively [186]. These insights are consistent with our findings, suggesting that variations in *KCTD13* dosage are associated with autism [186]. Further, studies have found that dosage changes in *KCTD13* due to deletion and *de novo* structural alteration are consistently linked to autism [186,188], reinforcing the hypothesis that this gene may be integral to ASD progression.

MAPK3 (mitogen-activated protein kinase 3), another brain-enriched gene within the 16p region, is a member of the MAP kinase family involved in regulating brain growth, synaptic target selection and connectivity [189]. Disruptions in the MAP kinase pathway have been linked to various developmental disorders, including autism [190,191]. Our investigation has also revealed that ***SH2B1***, a brain-enriched gene involved in leptin and insulin signaling, glucose homeostasis regulation, and body weight, was significantly deleted in individuals with autism. This suggests it as a possible candidate gene within 16p11.2 CNV, potentially contributing to the observed comorbidity of obesity in some ASD cases.[192–194]. Recent explorations into the epigenetic patterns (abnormal methylation) of *SH2B1*, particularly in the neurotrophin signaling pathway known to influence cognitive and social functionalities, implicating its etiological role in ASD. [195,196]. These combined findings, alongside our research, emphasize the potential importance of *SH2B1* gene in the context of ASD.

2.17. 17p (17p13.3; 17p11.2) rearrangements

The short arm of chromosome 17 contains a high density of LCRs, which predispose this region to NAHR occurrence [197]. Specifically, the 17p13.3 locus as a genomic instability and recombination hotspot locus, harboring various deleted and duplicated CNVs associated with a range of NDDs and development of epileptogenesis [198,199]. Deletion of the gene-rich 17p13.3 locus have been linked to heart abnormalities, lissencephaly, microcephaly, midface retrusion, and Miller-Dieker syndrome [24,200], whereas duplication in this region have been associated with split-hand/foot malformation, autistic symptoms, postnatal overgrowth, psychomotor and developmental delay, and hypotonia [201,202].

Furthermore, deletion at the 17p11.2 locus results in Smith-Magenis Syndrome (SMS) characterized by hyperactivity, ID, MH, self-mutilation, short stature, sleep disturbance, and stereotypic behavior [24,203]. In contrast, Potocki-Lupski Syndrome, (PTLS), arising from duplication at this region, is associated with autism, hyperactivity, short attention span, and short stature [24,204].

Our bioinformatics analysis, aiming to identify additional genes related to autism in ASD-associated CNVs, revealed five significantly deleted or duplicated regions, including two duplications at 17p13.3 (635 kb at chr17:1038189–1673212 and 1.2 Mb at chr17:2302359–3502250), a 1.7 Mb deletion at 17p13.3 (chr17:911295–2593250), a 1.93 Mb duplication at 17p11.2 (chr17:16446387–18380166) and a 1.5 Mb deletion at 17p11.2 (chr17:16789275–18299275). In total, 259 genes were detected, 92 of which are highly expressed in the brain, including 59 coding genes and 33 lncRNA genes. Among these, 49 genes were significantly duplicated, and the rest significantly deleted. To further narrow down the number of possible autism-related genes in the specified regions, we identified significantly duplicated lncRNA genes *CATG00000030828*, *CATG00000032809*, *RP11–74E22.3*, and *CATG00000030472* as well as significantly deleted *CATG00000032796* and *CATG00000032809* at 17p13.3 CNV regions. These genes exhibit dynamic expression during the differentiation of iPSC to neuron, potentially indicating their role in neurodevelopmental processes and ASD development. Likewise, 16 coding genes, including *ASPA*, *TRPV1, RTN4RL1 YWHAE*, *RASD1*, *RAI1,* and *PAFAH1B1*, mapped to significantly deleted and duplicated regions,

affected the mouse NS when mutated [26,27], suggesting their potential roles in NDDs such as autism.

TRPV1 (transient receptor potential cation channel subfamily V member 1), a brain enriched gene located at 17p13.3, is significantly duplicated. It regulated by *SHANK3* [205], a gene remarkably implicated in autism for its role in synaptic formation, maturation, and maintenance [206–208], located within 22q13.3 CNVs. In sensory neurons, activation of *TRPV1* has impact on pain perception [209], aligning with the abnormal pain sensitivity is typically observed in ASD [210]. Therefore, *TRPV1,* alongside its adjacent gene *TRPV3*, may be involved in this ASD-associated phenotype.

RAI1, another ASD-related gene located at the 17p11.2 CNV region, is a dosage-sensitive gene thought to be responsible for the most phenotypes associated with SMS and PTLS [211,212]. *RAI1* haploinsufficiency has been observed in SMS, characterized by ID, neurobehavioral issues, obesity and disrupted circadian sleep-wake patterns [212]. Recent evidence linking ASD with circadian issues, sleep disruptions, behavior challenges, and altered circadian neuroendocrine responses, potentially due to compromised melatonin rhythm, aligns with this [213]. Moreover, *RAI1* exhibits dynamic expression during iPSCs differentiation to neuron, suggesting its possible contribution to autism in light of our findings.

Furthermore, the ***YWHAE*** gene (tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein epsilon) encodes a protein interacting with crucial signaling molecules like calmodulin and MAP3K. Duplication of *YWHAE* has been postulated to promote ERK-pathway activity, which is aberrantly activated in ASD patients [214–217]. Finally, ***PAFAH1B1*** (platelet activating factor acetyl hydrolase 1b regulatory subunit 1; also known as lissencephaly gene 1 (*LIS-1*), located within the 17p13.3 CNV regions, emerges as another candidate ASD-related gene due to its dynamic expression during iPSC to neuron differentiation and impact on the neural system of mutant mice [26,27]. Additionally, the presentation of lissencephaly in Miller-Dieker syndrome is caused by mutation or deletion in the *PAFAH1B1* gene [218], and its link to hypotonia and mild developmental delay in cases of duplications [217] highlight its potential role in ASD.

2.18. 17q (17q12; 17q21.31) rearrangements

Speech and motor delay, seizures, vision problems, and behavioral abnormalities are among the conditions linked to 17q12 recurrent duplication, which typically indicate reduced penetrance and variable expression [219]. The deletion of 17q12 significantly increase the risk for conditions such as schizophrenia and ASD [220] and is associated with different diseases including liver cancer, diabetes mellitus, and multiple renal cysts [24,221]. In addition, the 17q21.31 microdeletion and duplication have been identified as causes of Koolen-de Vries syndrome (KdVS), a disorder presenting DD/ID, neonatal/childhood hypotonia, dysmorphisms, congenital malformations, speech and language delay [24,222], as well as frontotemporal lobar degeneration (FTLD) and schizophrenia in a subset patients, respectively [223,224].

Our bioinformatics analysis has revealed three regions on chromosome 17q harboring CNVs significantly rearranged in ASD, including a 40 kb duplication at 17q12 (chr17:34815887–34856055), a 1.4 Mb deletion at 17q12 (chr17:34815887–36225887), and a 0.46 Mb deletion at 17q21.23 (chr17:43704217–44164182). Among these CNV regions, eight out of 24 coding genes and nine out of 19 lncRNA genes show high expression in the brain. Some of these genes may have an impact on neurodevelopment and autism, including *RP11–445F12*, *RP11–697E22,* and *MAPT-AS1* lncRNAs, which show dynamic expression during the differentiation of iPSC to neuron. Additionally, *LHX1*, *CRHR1*, *MAPT,* and *KANSL1* have demonstrated effects on the NS of mutant mice and are significantly deleted in ASD [26,27].

LHX1 (LIM homeobox 1), mapped to the17q12 locus, is a brain-enriched gene and implicated in various conditions, including autism [225]. It has also been suggested that *LHX1* is likely involved in brain development or function [226]. The ***MAPT*** (microtubule associated protein tau) and ***KANSL1*** (KAT8 regulatory NSL complex subunit 1) genes, located at the 17q21.31 CNV region, are noteworthy. *MAPT* encodes *tau* proteins that are involved in Alzheimer's disease (AD) and Parkinson's disease [227]. Furthermore, mutations and duplications of *MAPT* have been shown to be associated with frontotemporal lobar degeneration (FTLD), while its deletions are linked to various clinical manifestations like facial dysmorphism, hypotonia, and ID [228]. Interestingly, a study has revealed that reducing tau protein can prevent autism-like behaviors in mouse models [229]. Conversely, haploinsufficiency of *KANSL,* a chromatin modifier gene, results 17q21.31 microdeletion syndrome, characterized by ID, distinct facial features, and hypotonia [230].

2.19. 22q11.2 (22q11.21 and 22q11.22) rearrangements

A cluster of eight LCRs, labeled as *LCR22A-H* on the proximal long arm of chromosome 22, promotes NAHR, resulting in various rearrangements and the expansion of different combinations of recurrent CNVs in the this region [231]. The 22q11.21-q11.23 deletion leads to the 22q11.2 deletion syndrome (DiGeorge syndrome:DS), the most prevalent microdeletion syndrome, occurring in approximately 1/4000 live births and 1/1000 fetus [232]. Individuals with DS exhibit a wide range of clinical manifestations, including psychiatric and learning difficulties as well as ASD, with a noted increased prevalence of ASD in those affected by 22q11.2 deletion syndrome [233–236].

In our study, to identify significant chromosomal regions and ASD-related genes within CNVs at the 22q11.21-q11.22 loci in individuals with autism, we detected four critical regions. The 3.2 Mb region (chr22:18545000–21745000) at 22q11.21, featuring significant deletions, encompassed 54 coding genes and 37 lncRNA genes, 30 of which are highly expressed in the brain. This deletion is associated with various clinical features, such as heart abnormalities, delayed speech and language development, hypocalcemia, hypernasality, and T lymphocytopenia [24]. Remarkably, 22q11.21 stood out as the most significantly deleted region among the 47 regions we identified in relation to ASD.

Additionally, the 1.74 Mb region (chr22:21910000–23650000) at 22q11.22, also marked by significant deletions, contained 64 coding genes and 22 lncRNA genes, with 15 showing brain-enriched expression. Clinical phenotypes associated with 22q11.22 deletion includes facial dysmorphisms, intellectual disability (ID), short stature, and being small for gestational age [24].

In contrast, the 1.29 Mb region (chr22:19020000–20308799) at 22q11.21, featuring significant duplication and comprising 49 genes, including 11 brain-enriched genes (6 coding genes and 5 lncRNA genes). This duplication is linked to clinical features such as ID, hypernasality, and telecanthus [24]. Additionally, the 87.9 Kb region (chr22:23046186–23134119) at 22q11.22, marked by significant duplications, contains 7 coding genes and 5 lncRNA genes, with none showing brain-enriched expression.

We further discovered that *CRKL*, *RTN4R*, *ZDHHC8*, *SEPT5*, *MAPK1*, *GNAZ,* and *BCR,* which are significantly deleted, and *RTN4R*, *ZDHHC8*, and *SEPT5* genes significantly duplicated, have effects on the NS of mutant mice [26,27]. Likewise, lncRNA genes including *XXbac-B444P24*.14, *DGCR5*, *AC000068*.5, *CATG00000058233*, *CATG00000058251,* and *LL22NC03–86 G,* with remarkable deletion, and *XXbac-B444P24.14* and *AC000068.5* significantly duplicated, demonstrates dynamic expression in iPSC models.

SEPT5 (SEPTIN 5), a brain-enriched gene located within ASD CNV region, is a GTPase with cytokinesis activities and regulates neurotransmitter release at synapses. A genetic background-dependent relationship between *Sept5* deficiency and ASD-related phenotypes using a mouse model has been reported [237,238]. Another gene, ***MAPK1***, as a member of the MAPK family, is involved in proliferation, differentiation, apoptosis, development, and synaptic plasticity [239–241], and its deficiency results in brain impairment and autism-related characteristics

[242–244]. Furthermore, we identified ***CLTCL1*** (clathrin heavy chain-like 1) and ***GNB1L*** (G protein subunit beta 1 like) significantly deleted or duplicated in autistic individuals, are potential genes involved in ASD [245,246]. Along with coding genes linked to ASD, ***DGCR5***, a lncRNA gene with putative involvement in schizophrenia [247], has been proposed as a possible candidate autism-related gene.

2.20. 22q13.2-q13.33 deletion

The 22q13 deletion syndrome, known as Phelan-McDermid Syndrome (PMS), results from deletions ranging in size from 100 kb to over 9 Mb at 22q13.2-q13.33 loci. While larger deletions are associated with a variety of manifestations and neurological symptoms, including delayed speech and language development, DD, macrocephaly, hyperactivity, and ID; smaller deletions (median size of 3.39 Mb), are rarely associated with these phenotype and have been found in individuals with ASD [24,206].

In this study, an 8.2 Mb region (chr22:43000056–51224208) significantly deleted in ASD was identified, containing 113 coding genes and 109 lncRNA genes. Among 48 brain-specific coding genes, *SHANK3, MAPK8IP2, TTLL1*, *MLC1*, *BRD1, PANX2, MAPK11,* and *PLXNB2* were identified to impact on the NS of mutant mice [26,27], suggesting a possible connections between the function of these genes and neurodevelopmental processes. In addition, *CATG00000057830, RP3–388M5, CTA-217C2, CATG00000057926, RP3–402G11.26, CHKB-AS1, CATG00000058090,* and *CATG00000058095,* among the total of 26 brain-enriched lncRNA genes, showed dynamic expression during iPSC to neuron differentiation, as recorded in the FANTOMCAT database [25], which may indicate their importance in the development of neurological conditions, although no studies have directly demonstrated this correlation yet.

SHANK3, as a deleted gene in PMS, is the most well-known candidate gene for the neurological features observed in the 22q13 deletion syndrome and ASD. It plays a role in synaptic formation, maturation, and maintenance [206,207] and is associated with ASD phenotype [248]. Another candidate gene for chr22qter-associated disorders that is almost deleted in PMS and ASD cases [249] is ***MAPK8IP2*** (also known as *IB2*). It encodes a scaffold protein involved in JNK signaling [250] with high enrichment in postsynaptic densities. Both *MAPK8IP2* and *SHANK3* are brain-specific genes that are highly expressed during iPSC to neuron differentiation, with effects on the NS of mutant mice [26,27], implying roles for these genes in the development of NDDs, including autism. Moreover, ***PANX2*** is another significantly deleted brain-enriched gene at the 22q13.33 locus that has been shown to be differentially expressed in autism [251] and has effects on the mouse brain [26,27].

2.21. Xq28 duplication

The Xq28 sub-chromosomal band, a gene-rich region containing approximately 13 % of all X-linked genes, is associated with more than 40 of the roughly 300 X-linked disorders [252]. Rett syndrome (a disorder representing autistic phenotypes), Xq28 duplication syndrome, and *MECP2* duplication syndrome have all been reported to be linked to CNVs in this locus [253,254]. Chromosome microarray analysis has revealed Xq28 as the most common subtelomeric locus with copy number gains among individuals with DD, ID, dysmorphic features, multiple congenital anomalies, and seizure [255]. Further, it has been documented that delayed speech and language development, severe ID, MH, recurrent infections, seizures, and spasticity are some manifestations associated with Xq28 duplication syndrome [24,254].

Our bioinformatics analysis has identified a significant duplication spanning 2.35 Mb (chrX:152561384–154917042) in ASD, containing 19 brain-enriched genes (17 coding genes and 2 lncRNA genes) among 89 genes in total. Within this set, coding genes such as *MECP2* (already known to be ASD-associated), *GDI1, SLC6A8, L1CAM,* and *PLXNA3,* which show NS phenotypes in mutant mice [26,27] along with the *RP11–66N11.8* lncRNA exhibiting dynamic expression in iPSCs models, are suggested to be potentially promising candidate as NDD-related genes. Furthermore, genes including *MECP2* [256–258] and *SLC6A8* [259,260], and others like *RAB39B*, *RPL10, TMLHE,* and *SPRY3* within this region, have already established associations with ASD [261–263].

L1CAM (L1 cell adhesion molecule) and ***TMLHE*** (trimethyllysine hydroxylase, epsilon) are two candidate risk genes for ASD, with roles in the NS development [264] and the transmission of fatty acid through the mitochondrial membrane, respectively [265]. There is evidence that rare deletion mutations in *TMLHE* are present in some patients with ASD [265,266]. Furthermore, ***SPRY3*** (sprout RTK signaling antagonist 3), another autism susceptibility gene adjacent to *TMLHE*, shows high expression levels in the central and peripheral nervous system and ganglion cells in both mouse and human [267]. This aligns with our observations, which identify *SPRY3* as a highly significant duplicated NS specific gene at 8q28. ***GDI1*** (GDP dissociation inhibitor 1), another gene implicated in cognitive function [268] and enriched in the nervous system, has been found to be the most significantly duplicated gene in this region among autistic individuals. Considering the association between ID and *GDI1* duplication [254], along with its effect on the NS in mutant mice, underscores its potential as a candidate genes contributing to ASD and possibly other NDDs.

Furthermore, ***ATP2B3*** (ATPase plasma membrane Ca^{2+} transporting 3), with a function in Ca^{2+} extrusion, global and local Ca^{2+} homeostasis, and intracellular Ca^{2+} signaling [269], emerges as another brain-enriched gene significantly duplicated in individuals with autism. It is well known that Ca^{2+} signaling pathways have a vital role in the regulation of neuronal development and may be involved in the pathogenesis of ASD [270]. These findings suggest that *ATP2B3* might be a strong candidate gene for ASD.

2.22. Xp22.31 deletion

The Xp22.31 deletion has been associated with X-linked ichthyosis (XLI), a condition characterized by a spectrum of symptoms, including ocular changes, cryptorchidism, ID, epilepsy, hyperactivity, and autism [271,272]. We have detected a 1.4 Mb region (chrX:6490000–7885155) with a significant deletion in ASD, containing four coding genes and four lncRNA genes. Among these, ***STS*** is known as the causative gene for XLI and various NDDs [271,272], and ***PNPLA4*** is highly expressed in the brain. *PNPLA4* (Patatin Like Phospholipase Domain Containing) encodes an enzyme that belongs to the patatin-like family of phospholipases. In addition to having triglyceride lipase and transacylase activities, this enzyme may play a role in adipocyte triglyceride homeostasis and has been associated with human obesity. Recently, there have been suggestions that this gene could be implicated in X-linked ID due to its high expression level in the human brain [273]. It is important to note that this finding supports our results, indicating that *PNPLA4* might play a role in NDDs and ASD.

2.23. Xp22.33 duplication

The Xp22.33 region, extending across 4.4 Mb on the short arm of chromosome X, includes duplication (Xp22.33p22.32) associated with a variety of clinical conditions such as ID, DD, delayed speech and language development, short stature, and autism [24,274]. Our research has discovered a significant duplication spanning 2.08 Mb region on Xp22.33 (chrX:619146–2700156), containing 11 brain-enriched genes out of 26 (15 coding genes and 11 lncRNA genes), observed in individuals with autism.

One of these genes, ***ASMT*** (acetylserotonin O-methyltransferase), with enzyme activity in melatonin synthesis, is located at the pseudoautosomal region (PAR) of the X chromosome. This gene has regulatory effects on sleep, circadian rhythms, and memory, with a possible influence on cognitive functions [275–277]. *ASMT* is also considered a

potential autism susceptibility gene due to its rare deleterious mutations and SNP association among ASD patients [278,279]. In addition, *ASMTL* (acetylserotonin O-methyltransferase-like gene), which is an ASMT-like gene, and ASMTL-AS1 (ASMTL-AS1 antisense RNA 1) lncRNA divergent, both with significant duplication in ASD, are located at the Xp22.33 locus, implying a possible role for these genes in the progression of neurological disorders and autism. Furthermore, *CATG00000112948* lncRNA is one of the brain-enriched genes in this region that shows dynamic expression during iPSC to neuron differentiation, perhaps highlighting its relevance to NDDs and ASD.

2.24. Gene ontology analysis suggests role of neurons in ASD candidate genes with brain-enriched expression

Our results underscore the significance of brain-enriched genes in regulating neuronal structure, function, and intercellular communication in individuals with ASD. Utilizing WebGestalt (https://www.webgestalt.org), we conducted an in-depth analysis of the complex network involving these genes and their gene ontologies (GO). Our analysis identified the top 20 GO terms and biological pathways characterized by the False Discovery Rate (FDR) values < 0.05. Our findings revealed several GO terms pertinent to microtubule structure, notably including "cytoplasmic microtubule organization", "spindle" and “kinesin binding”. Notably, "cytoplasmic microtubule organization" exhibited the highest enrichment ratio, emphasizing the crucial role of microtubules in genes associated with ASD (Fig. 2). Microtubules play pivotal roles in cellular processes such as cell division, neurogenesis, and forming neural connections during embryonic development[280]. Conversely, "spindle" refers to microtubule structures are vital during mitosis and meiosis of eukaryotic cells [281]. Mounting evidence suggests that genetic variants disrupting microtubule function significantly impact NDDs, including ASD [282–284]. Further evidence supporting the role of microtubule organization in ASD is provided by the GO term "kinesin binding". Kinesins and related proteins bind to microtubules, regulating various microtubule functions such as chromatin segregation, cell division, and spindle formation [285]. Case studies have implicated mutations in Kinesin KIF21B and Kinesin 17 to altered social behaviors and increased risk of schizophrenia [286,287]. Critical genes in microtubule regulation such as ***PAFAH1B1***, ***TUBGCP5***, and ***TUBGCP6***, which are highly expressed in the brain and play essential roles in neurodevelopment, consistent with our findings. ***PAFAH1B1*** (platelet activating factor acetylhydrolase 1b regulatory subunit 1) encodes an enzyme that is part of a protein complex crucial for brain development, with mutations in PAFAH1B1 leading to lissencephaly syndrome [288]. Similarly, ***TUBGCP5*** (tubulin gamma complex component 5) and ***TUBGCP6*** (tubulin gamma complex component 6) belong to the ***TUBGCP*** family involved in microtubule activities and are associated with various brain disorders, including microcephaly and

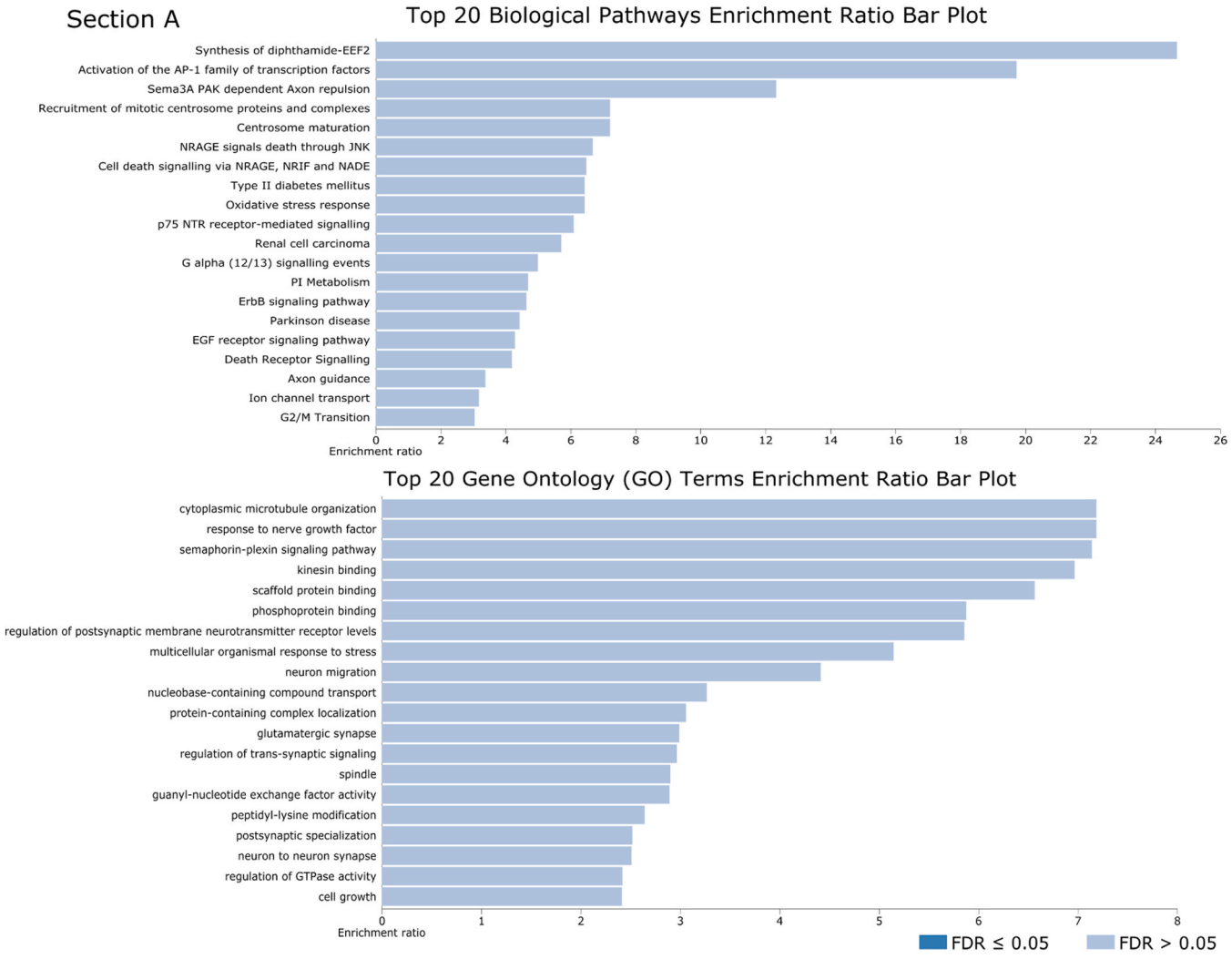

Fig. 2. Pathway and gene ontology analysis on the brain-enriched genes identified in our study. **A)** Top 20 biological pathways. **B)** Top 20 GO terms for molecular component. **C)** Top 20 GO terms for cellular component. A GO term network of biological process has been shown in Supplementary Fig. S1.

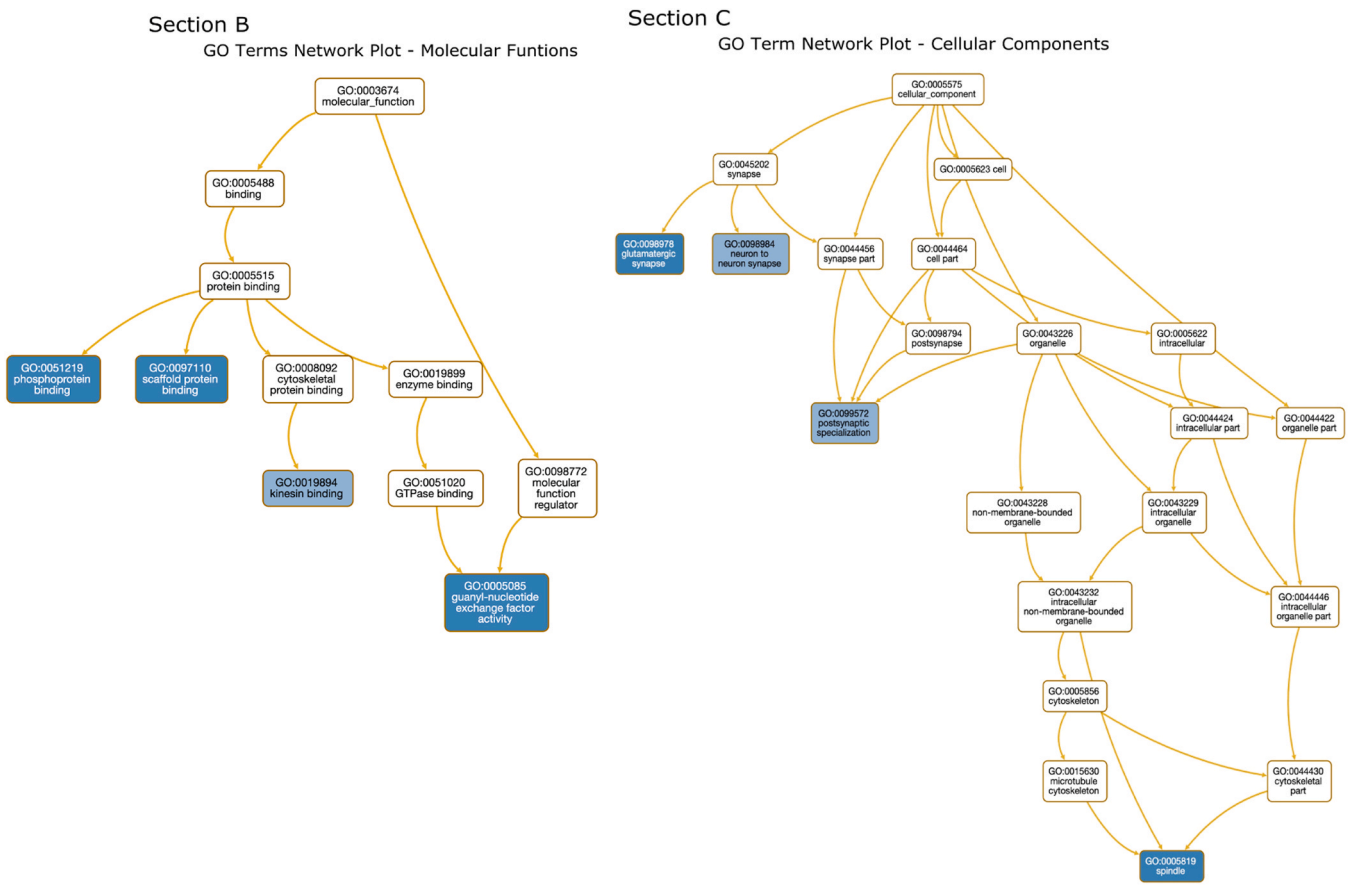

Fig. 2. (*continued*).

chorioretinopathy [289].

Our results also underscore the importance of GO terms associated with neuronal communication, including "glutamatergic synapse", "trans-synaptic signaling", "postsynaptic specialization", and "neuron to neuron synapse". Trans-synaptic and post-synaptic activities are regulated by alternative splicing of cellular adhesion molecule (CAM) RNA, which significantly impacts synapse maturation and signaling in mature synapses [290]. Glutamate, one of the predominant neurotransmitters in the brain and central nervous system (CNS), plays a crucial role in regulating ASD-related phenotypes such as neuronal excitability, brain volume, and synaptic plasticity [291,292]. Dysregulation in trans-synaptic or post-synaptic signaling, due to alteration in gene splicing and cellular adhesion, is enriched in ASD patients. This dysregulation may impair the establishment of normal synaptic communications, disrupted glutamatergic and gamma-aminobutyric acid signaling, and compromise synaptic plasticity, contributing to autism risk [290,293,294].

Among the top 20 biological pathways, 'Synthesis of diphthamide-EEF2' exhibits the highest enrichment ratio, indicating its prominence as a relevant biological pathway influenced by brain-enriched genes. Eukaryotic Elongation Factor 2 (***EEF2***) functions as a transcription factor, exerting post-translational regulation on diphthamide, a protein crucial for dynamic messenger RNA translation and ribosomal protein synthesis [295]. Variants affecting *EEF2* expression may lead to increased translational frameshifts and downregulation of diphthamide expression [296]. Conversely, ***DPH1*** (Diphthamide biosynthesis 1) directly regulates diphthamide expression levels [297]. Studies have shown that deficient diphthamide can lead to embryonic death and profound neurodevelopmental disorders affecting children's development, including intellectual disability and developmental delay [298,299].

2.25. Conclusion

Autism is a complex neurological condition with a multifaceted etiology, involving both genetic and environmental influences [7–9]. Ongoing research continues to explore the myriad risk factors associated with ASD, and our findings contribute valuable insights for further investigations, particularly in the context of genetics. Genetic variations have been shown to account for a significant portion of ASD heritability, with CNVs playing a substantial role in many ASD cases. In this study, using SNATCNV tool, alongside comprehensive bioinformatics analysis and an extensive literature review, underscores the substantial contribution of CNV to ASD.

Our investigation reveals that ASD-associated gene disruptions can result from both the deletion and duplication of CNVs, reflecting the intricate genetic landscape of this disorder. Notably, deletions often tend to have more pronounced effects on autism-related characteristics [300]. Both deletions and duplications elevate the risk of an ASD diagnosis and can impact nonverbal and verbal IQ as symptoms of ASD to varying degrees [300]. Deletions, often associated with haploinsufficiency, strongly affect language, motor skills, social communication, and behavior problems, potentially leading to ASD diagnoses. Core autism symptoms appear to be less affected by deletions. In contrast, duplications exert a more consistent genome-wide effect on autism risk, with nonverbal IQ playing a minor role in influencing this effect [300].

CNVs associated with autism ultimately influence neuronal development and function by disrupting gene expression within the brain, leading to phenotypic consequence in the NS of mutant mice. It is important to note that while mouse models provide valuable insights into the molecular and physiological aspects of ASD, they cannot fully replicate the intricate social behaviors observed in humans. To enhance

their utility, rigorous validation and analysis of behavioral testing are essential [301,302].

Our study aligns with previous research by identifying 567 candidate genes, encompassing both coding and non-coding genes, with the potential to be associated with ASD, many of which are brain-enriched lncRNA genes. Using iPSCs to model neuron differentiation has unveiled dynamic expression patterns in 83 lncRNA, highlighting their potential pivotal role in neurodevelopment process. In comparison to other studies conducted previously, our findings in this matter are consistent with the prior studies [303–305]. Considering the regulatory influence of lncRNA on gene expression, both in trans and cis situations, it is plausible that lncRNAs contribute to ASD by modulating the expression of protein-coding genes linked to this disorder [306,307]. Furthermore, our study presents a list of lncRNAs associated with ASD that warrant further investigation to uncover their potential function. To delve deeper into these non-coding genes, we suggest exploring chromatin interactions data analyses through publicly available tools such as MaxHiC [308] and MHiC [309], which can offer valuable insights related to our understanding of the genetic underpinnings of ASD within the scope of our study. Additionally, this research contributes valuable data to the expanding catalogue of CNVs associated with autism, significantly augmenting the pool of ASD risk genes encompassing both coding and non-coding genes. This substantial contribution serves to expedite future genetic investigations into ASD, including the development of potential therapeutic avenues and genetics diagnostic tools. Leveraging system-wide analysis of these candidate genes (coding and lncRNA genes) offer a promising framework for delving deeper into the intricate landscape of ASD.

It is essential to emphasize that each of the identified CNVs and ASD risk genes has the potential to play a pivotal role in providing precise explanations and personalized interventions for individuals affected by autism. This is particularly significant given the multifaceted nature of CNVs in the etiology of ASD.

Notably, while CNVs play a crucial role in the etiology of ASD, emerging research demonstrates that specific CNVs may confer genetic susceptibility, making certain individuals more susceptible to the influences of environmental factors. For instance, the increased risk of ASD in subjects with CNVs has been suggested to be associated with maternal infection, low folate concentration, and exposure to specific environmental toxins during pregnancy [310–312]. Deletions and duplications of DNA segments have distinct functional impacts ASD. Research suggests that deletions often associate more with DD and ID, while duplications might link to milder cognitive impacts [313]. Specific genomic regions, like 16p11.2, show different ASD-related phenotypes based on whether a deletion or duplication is present. The functional consequences of these CNVs also hinge on the genes they encompass, with certain genes being particularly sensitive to dosage changes. Additionally, genes affected by ASD-associated CNVs often converge on shared molecular pathways, and the type of CNV (deletion or duplication) might influence its role within these pathways.

These examples illustrate the dynamic interplay between CNVs and environmental factors in autism development. Our research findings, coupled with studies related to intricate interactions between genetic and environmental factors, could provide a deeper understanding of this interaction. Furthermore, our study has confirmed the effectiveness of the SNATCNV tool as a suitable and efficient method for detecting CNVs associated with ASD. This tool reliably identifies CNV regions and significantly reduces the genomic space associated with causative CNVs in ASD within a short time frame.

3. Materials and Methods

3.1. Samples collection

We used the CNV dataset provided by SFARI. The Simons Simplex Collection (SSC) serves as a central project and resource within SFARI. Operated by the Simons Foundation Autism Research Initiative in conjunction with 12 university-affiliated research clinics, the SSC oversees the identification and assessment of potential participants. These clinics, supported by guidance from the University of Michigan Autism and Communication Disorders Center, ensure consistency in participant selection procedures. Active enrollment concluded in 2011. Participation in the SSC required probands to receive a best-estimate clinical diagnosis of ASD and meet specific criteria on the Autism Diagnostic Interview-Revised (ADI-R) and Autism Diagnostic Observation Schedule (ADOS) assessments. For more information please visit (https://www.sfari.org/resoue/simons-simplex-collection).

The SFARI CNV dataset was downloaded through the public SFARI data portal. It comprises 19,663 samples collected from individuals with ASD, encompassing 47,189 CNVs. Additionally, there were 6479 samples from healthy controls, contributing 24,888 CNVs to this dataset. The CNVs dataset was compiled from multiple large ASD CNV datasets (with different microarray versions and different 'individual-level' CNV callers) by the Simons Foundation Autism Research Initiative (SFARI) and was downloaded (http://autism.mindspec.org/autdb; download date: July 2016). Since CNVs have been reported in different genome build versions such as hg17, hg18, and hg19, we initially converted all CNV coordinates to UCSC hg19 using UCSC Lift Genome Annotations tools [314]. Subsequently, we confirmed these locations using NCBI (National Center for Biotechnology Information) remap tools (www.ncbi.nlm.nih.gov/genome/tools/remap). We excluded 4500 CNVs for which there was no information provided about their genomic coordinates. Further information is provided in the Supplementary table S1 for more details.

3.2. Literature search strategy

Our literature searches were focused on human and mice papers available English language databases such as PubMed, Scopus, and Web of Science. We also used data and text mining techniques to extract supplementary related genes. Knowledge-based filtering system techniques have been also used to categorize the texts from the literatures search. Furthermore, we employed an in-house text-mining method to reevaluate the identified genes and resources from the literature. This method involves taking the gene name and/or symbol as input and searches for all phenotypes associated with these genes in the extracted papers from the literature. The search terms included "gene name", "phenotype", "Autism", "ASD", "non-coding RNA", "CNV", "copy number variations". Additionally, three authors were involved in the literature review process for this study, from initial literature search to the final synthesis of findings. This collaborative effort involved independent searches and record selection, followed by consensus discussions to resolve discrepancies, cross-checking each other's data extraction for bias minimization, and jointly synthesizing the analysis.

3.3. Identification of significant regions

To identify regions recurrently duplicated or deleted in ASD, we utilized the SNATCNV [13], which mined previously published ASD and control copy number variation databases collected and combined by the Simons Foundation Autism Research Initiative (https://gene.sfari.org/database/cnv). For every position in the genome, SNATCNV counted the number of deletion and duplication CNVs from 19,663 ASD patients and 6479 controls that overlapped and then calculated a *P-value* for each position using Fisher's exact test. To identify significant regions, SNATCNV calculated *P-values* for 500,000 random permutations of case/control labels to estimate the probability that an association emerges by chance. Consequently, we identified 47 CNV regions that are significantly deleted or duplicated for ASD case samples (Supplementary table S1).

The 47 CNV regions contain 856 protein-coding genes and 776 non-coding RNAs. We used normalized tag counts from the FANTOM5

(Functional Annotation of the Mammalian Genome) expression atlas [315] to identify nervous system enriched protein coding genes and non-coding RNAs within the 47 CNV regions. FANTOM5 is a collaborative international research initiative aimed at identifying and annotating the full set of functional elements in mammalian genomes, with a primary focus on the human genome including 1930 samples. To determine whether a gene had enriched expression in the 101 nervous system samples profiled by the FANTOM5 consortium (compared to the total set of 1829 samples profiled by FANTOM), we ranked samples by expression and then selected the top 101 samples. We then used Fisher's exact test to calculate a *P-value* indicating whether the top 101 samples were more likely to be nervous system samples or not. To establish a threshold on the *P-value*, we carried out 50,000 permutations randomizing the sample labels and determined the thresholds at the 99 % confidence interval. Subsequently, any gene with a *P-value* better than this permutation-specific threshold was identified as nervous system-enriched gene. For more details refer to our previous paper [13].

We also annotated protein-coding genes with the information from the Mouse Genome Informatics (MGI) resource (http://www.informatics.jax.org; June 12th 2018) to identify those genes showing nervous system phenotypes in mouse mutants (Supplementary table S1). FANTOM5 dataset was also used to identify non-coding RNAs with upregulation in iPSC to neuron differentiation. We then compared all genes in the 47 CNV regions to the 96 known causal genes from MSSNG [316] and SFARI [317]. MSSNG is an ambitious research project aimed to sequence the whole genomes of over 10,000 individuals with autism and their families in collaboration between Autism Speaks, a prominent autism advocacy organization, and Google. If a region contained one or more of these genes, we considered it as a region with known ASD genes. Subsequently, we performed a comprehensive literature search analysis for the remaining CNV regions to check for any previously ASD-associated genes in those regions. Our extended literature search was specifically focused on "gene name + autism" or "gene name + ASD". DECIPHER [24], SFARI [317], MSSNG [316] and two largest CNV studies of Global developmental delay to date by Coe *et al.* [318] and Cooper *et al.* [319] were used to annotate the CNV regions.

Furthermore, we conducted Over-representative Analysis (ORA) using WebGestalt (https://www.webgestalt.org/) to investigate gene ontologies (GO) and biological pathways associated with brain-enriched protein coding genes. This analysis aimed to elucidate the most pertinent biological, cellular, and molecular functions. For GO terms, we incorporated non-redundant databases covering biological processes, cellular components, and molecular functions. Additionally, we incorporated biological pathway databases such as KEGG, Reactome, Panther, and WikiPathway. We prioritized the top 20 GO terms and biological pathways based on descending order of False Discovery Rate (FDR), which serves as an indicator of the false positive rates associated with each term.

CRediT authorship contributions statement

HAR designed the study. HAR, SSA, SA, IR, ID, DB wrote and edited the manuscript with help from JH. HAR carried out all the analyses including the statistical analyses, region identification, text mining, gene prioritization, and gene ontology. YL performed the pathway and network analyses. SSA, SA curated the genes and regions. HAR generated all figures and tables. SA, SSA performed all the literature analysis. All authors have read and approved of the final version of the paper.

Funding

This work was supported by the UNSW Scientia Program Fellowship and the Australian Research Council Discovery Early Career Researcher Award (DECRA) under grant DE220101210 to HAR. The work was also supported by a grant to JI-TH from the Telethon-Perth Children's Hospital Research Fund.

Declaration of Competing Interest

The authors declare no competing financial/non-financial interests.

Data availability

there is a link to the data in the paper

Acknowledgements

Analysis was made possible with computational resources provided by the UNSW BioMedical Machine Learning Laboratory (BML) Servers with funding from the UNSW Scientia Program Fellowship. We kindly acknowledge Government of Western Australia, Department of Health, Clinical Excellence, for their support of this project through MERIT award to HAR.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mrrev.2024.108509.

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