Research in Autism Spectrum Disorders 82 (2021) 101729

Contents lists available at ScienceDirect

Research in Autism Spectrum Disorders

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

Resequencing and association analysis of *GAP43* with autism spectrum disorder and schizophrenia in a Japanese population

Reza K. Arta [a], Yuichiro Watanabe [a,*], Emiko Inoue [a], Yoshihiro Nawa [b], Ryo Morikawa [a], Jun Egawa [a], Itaru Kushima [b,c], Hirofumi Igeta [a], Satoshi Hoya [a], Atsunori Sugimoto [a], Andi J. Tanra [d], Norio Ozaki [b], Toshiyuki Someya [a]

[a] *Department of Psychiatry, Niigata University Graduate School of Medical and Dental Sciences, 757 Asahimachidori-ichibancho, Chuo-ku, Niigata, 951-8510, Japan*
[b] *Department of Psychiatry, Nagoya University Graduate School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya, 466-8550, Japan*
[c] *Medical Genomics Center, Nagoya University Hospital, 65 Tsurumai-cho, Showa-ku, Nagoya, 466-8550, Japan*
[d] *Research Unit of Psychiatry and Neurobehaviour, Faculty of Medicine, Hasanuddin University, Jl P Kemerdekaan km11, Tamalanrea, Makassar, Indonesia*

ARTICLE INFO

Number of reviews completed is 2

Keywords:
Autism spectrum disorder
GAP43
Japanese
Schizophrenia

ABSTRACT

Background: Growth-associated protein 43 (GAP43), a synaptic protein involved in axonal growth and synaptic plasticity, is implicated in the pathophysiology of autism spectrum disorder (ASD) and schizophrenia. To examine the role of rare *GAP43* variants in the genetic etiology of ASD and schizophrenia in a Japanese population, we performed resequencing and association analysis.
Methods: First, we resequenced the *GAP43* coding region in 295 ASD patients, 323 schizophrenia patients and 304 controls. Second, we genotyped rs561268447 in 273 ASD patients, 1,150 schizophrenia patients and 1,022 controls. Third, we performed an association analysis of rs561268447 in 568 ASD patients, 1,473 schizophrenia patients and 10,127 controls.
Results: We identified a rare putatively damaging missense variant (rs561268447) in an ASD patient via resequencing. However, we did not detect the variant in 2,445 individuals via genotyping. The variant was not significantly associated with ASD or schizophrenia in the association analysis.
Conclusion: This study does not provide evidence for the contribution of rare *GAP43* variants to ASD or schizophrenia susceptibility in the Japanese population.

1. Introduction

Autism spectrum disorder (ASD) and schizophrenia are neurodevelopmental disorders (Lord et al., 2020; Smeland, Frei, Dale, & Andreassen, 2020; Sullivan & Geschwind, 2019). A recent systematic review and meta-analysis of epidemiological studies indicated a significant association between ASD and schizophrenia (Zheng, Zheng, & Zou, 2018). ASD and schizophrenia share genetic risk factors, including common variants (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2019; Matoba et al., 2020), rare coding variants (Satterstrom et al., 2020; Singh et al., 2020) and rare copy number variations (Kushima et al., 2018).

Growth-associated protein 43 (GAP43; also known as neuromodulin) is an activity-dependent presynaptic phosphoprotein that is

* Corresponding author.
E-mail address: yuichiro@med.niigata-u.ac.jp (Y. Watanabe).

https://doi.org/10.1016/j.rasd.2021.101729
Received 22 October 2020; Received in revised form 7 January 2021; Accepted 18 January 2021

involved in developmental neurite outgrowth (Holahan, 2017; Igarashi et al., 2020). GAP43 also regulates memory formation involving synaptic plasticity and long-term potentiation (Holahan, 2017).

Several lines of evidence have suggested that GAP43 is implicated in the pathophysiology of ASD and schizophrenia. In a post mortem study of adults with autism, increased GAP43 expression was accompanied with an excessive number of thin axons specifically in the superficial white matter below the anterior cingulate cortex (Zikopoulos & Barbas, 2010, 2013). Changes in GAP43 mRNA or protein levels have also been reported in the brains of schizophrenia patients (Blennow, Bogdanovic, Gottfries, & Davidsson, 1999; Chambers, Thomas, Saland, Neve, & Perrone-Bizzozero, 2005; Eastwood & Harrison, 1998; Fung, Sivagnanasundaram, & Weickert, 2011; Hakak et al., 2001; Perrone-Bizzozero et al., 1996; Sower, Bird, & Perrone-bizzozero, 1995; Tian, Wang, Bezchlibnyk, & Young, 2007; Weickert, 2001), although other studies failed to find such changes (Eastwood & Harrison, 2001; Fromer et al., 2016; Halim et al., 2003; Honer et al., 1999; Webster, Shannon Weickert, Herman, Hyde, & Kleinman, 2001). *Gap43* heterozygous knockout mice show autistic-like behaviors, including resistance to change, stress-induced behavioral withdrawal and anxiety, and low social interaction (Zaccaria, Lagace, Eisch, & McCasland, 2010). Of nine patients with a 3q13.2-q13.31 deletion encompassing 28 genes including *GAP43*, three had ASD (Shuvarikov et al., 2013). Shen et al. (2012) resequenced the promoter region and exons of *GAP43* in 586 schizophrenia patients and 576 controls of Han Chinese descent. They identified four rare variants exclusively in patients. Taken together, these findings indicate *GAP43* to be a candidate gene for ASD and schizophrenia.

To examine the role of rare *GAP43* variants in the genetic etiology of ASD and schizophrenia in a Japanese population, we performed resequencing and association analysis.

2. Methods

2.1. Participants

This study was approved by the Ethics Committee on Genetics of Niigata University, and the Ethics Committee of the Nagoya University Graduate School of Medicine and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants and/or their families.

All participants were unrelated and of Japanese descent. For resequencing *GAP43* coding regions, we included 295 patients with ASD, 323 patients with schizophrenia and 304 controls (Table 1). For genotyping of rare non-synonymous variants identified via resequencing, we included 273 patients with ASD, 1,150 patients with schizophrenia and 1,022 controls. These individuals did not overlap those selected for resequencing.

Each participant was subjected to psychiatric assessment, as previously described (Kushima et al., 2018). In brief, patients were diagnosed in accordance with the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition criteria for ASD or schizophrenia. Controls had no personal or family history (first-degree relatives) of psychiatric disorders.

We used the genomes or exomes of 8,801 Japanese individuals as additional controls, including 7,600 from the GEnome Medical alliance Japan Whole Genome Aggregation (GEM-J WGA) Panel (https://togovar.biosciencedbc.jp/?) and 1,201 from the Human Genetic Variation Database (HGVD) v2.3 (http://www.genome.med.kyoto-u.ac.jp/SnpDB/; Higasa et al., 2016).

2.2. Resequencing the GAP43 coding region

We resequenced the coding region of *GAP43* isoform 1 and isoform 2 (RefSeq accession number, NM_001130064 and NM_002045, respectively) in 922 individuals using Sanger sequencing, as previously described (Nunokawa et al., 2010). Primer sequences used for amplification are listed in Supplementary Table 1. We prioritized rare non-synonymous variants with an alternative allele frequency < 0.001 in GEM-J WGA and HGVD v2.3.

2.3. Genotyping

We genotyped a rare missense variant (rs561268447), identified via resequencing, in 2,445 individuals using the TaqMan 5′-exonuclease assay (Thermo Fisher Scientific, Waltham, MA, USA; Supplementary Table 2), as previously described (Watanabe, Muratake, Kaneko, Nunokawa, & Someya, 2006).

2.4. In silico analysis

We predicted the functional impact of the variants identified via resequencing using Polymorphism Phenotyping v2 (PolyPhen-2;

Table 1
Characteristics of participants.

Sample	Autism spectrum disorder			Schizophrenia			Control		
	n	Men (%)	Mean age ± SD	*n*	Men (%)	Mean age ± SD	*n*	Men (%)	Mean age ± SD
Resequencing	295	230 (78.0%)	19.8 ± 9.4	323	181 (56.0%)	41.6 ± 13.0	304	111 (36.5%)	37.2 ± 11.1
Genotyping	273	207 (75.8%)	19.2 ± 10.5	1150	619 (53.8%)	46.3 ± 15.7	1022	607 (59.4%)	40.2 ± 14.7

http://genetics.bwh.harvard.edu/pph2/; Adzhubei et al., 2010) and Combined Annotation Dependent Depletion (CADD; https://cadd.gs.washington.edu/; Rentzsch, Witten, Cooper, Shendure, & Kircher, 2019).

2.5. Statistical analysis

We assessed the association of rs561268447 with ASD or schizophrenia using Fisher's exact test. A post-hoc power calculation was performed using the Genetic Power Calculator (http://zzz.bwh.harvard.edu/gpc/cc2.html; Purcell, Cherny, & Sham, 2003). We estimated the sample size to adequately detect the association of rs561268447 with ASD or schizophrenia with a power of 0.80 and an α of 0.05, assuming a disease prevalence of 0.01, a risk allele frequency of 0.000099, and a genotypic relative risk for heterozygous risk allele carriers of 8.9 under the dominant model of inheritance.

3. Results

Resequencing the *GAP43* coding region in 295 ASD patients, 323 schizophrenia patients, and 304 controls identified six variants (Table 2; Fig. 1). Of these, rs561268447 was a rare missense variant identified in an ASD patient. This variant was predicted to be probably damaging by PolyPhen-2. The CADD score for rs561268447 was 28.1, predicting the variant to be in the 1% most deleterious substitutions for the human genome compared with all possible substitutions. Another missense variant (rs369966812), identified in a schizophrenia patient, was also predicted to be damaging by *in silico* analysis. However, we did not prioritize this variant because the allele frequency of this variant was greater than 0.001 in GEM-J WGA and HGVD v2.3.

We then genotyped rs561268447 in 273 ASD patients, 1,150 schizophrenia patients and 1,022 controls (Table 3). However, all 2,445 individuals were homozygous for the reference allele of the variant. Next, we performed an association analysis of rs561268447 with ASD and schizophrenia in 568 ASD patients, 1,473 schizophrenia patients and 10,127 controls. Although the rare allele frequency was higher in ASD patients than in controls (0.00088 and 0.000099, respectively), the association between rs561268447 and ASD was not significant (odds ratio = 8.9, 95% confidence interval = 0.8–98.5, and $p = 0.151$).

4. Discussion

In the present study, we identified a rare, putatively damaging missense variant (rs561268447) in an ASD patient via resequencing the *GAP43* coding region. However, rs561268447 was not significantly associated with ASD or schizophrenia in 568 ASD patients, 1,473 schizophrenia patients and 10,127 controls. Our results do not support the contribution of rare *GAP43* variants to ASD or schizophrenia susceptibility.

Our findings are in line with those from a large-scale meta-analysis of whole-exome sequencing (WES) data from ASD or schizophrenia patients, which indicated no significant association between rare *GAP43* variants and these neurodevelopmental disorders. The Autism Sequencing Consortium (https://asc.broadinstitute.org/) found two nonsense *GAP43* variants (rs1266389660 and rs199629932) in family-based samples (6,430 patients, 2,179 unaffected siblings, and both parents) and case-control samples (5,556 patients and 8,809 controls). The Schizophrenia Exome Sequencing Meta-analysis consortium (https://schema.broadinstitute.org/) observed a splice site *GAP43* variant (rs778502148) in 24,248 schizophrenia patients, 97,322 controls and 3,402 parent-affected offspring trios (Singh et al., 2020). Resequencing the promoter region and exons of *GAP43* in 586 patients and 576 controls, Shen et al. (2012) identified four rare variants, including a variant in the promoter region (rs118747541), a synonymous variant

Table 2
GAP43 variants identified via resequencing.

Position[a]	Allele[b]	dbSNP ID	Amino acid[c]	Genotype[d]			*In silico* analysis		Mutant allele frequency	
				ASD	Schizophrenia	Control	PolyPhen-2	CADD	GEM-J	HGVD
115382655	C/T	rs28399377	His10His/–	260/33/2	291/28/4	283/21/0	–	0.984	0.046	0.0448
115394897	A/G	rs561268447	Asp59Gly/ Asp23Gly	294/1/0	323/0/0	304/0/0	Probably damaging	28.1	0.0001	–
115394928	G/A	rs747505118	Lys69Lsy/ Lys33Lsy	295/0/0	323/0/0	303/1/0	–	12.01	0.0005	0.0008
115395157	G/A	rs369966812	Glu146Lys/ Glu110Lys	295/0/0	322/1/0	304/0/0	Probably Damaging	27.7	0.002	0.0038
115395221	C/T	rs755305822	Ser167Leu/ Ser131Leu	295/0/0	322/1/0	303/1/0	Benign	23.9	0.001	0.0012
115395321	G/A	rs6292	Glu200Glu/ Glu164Glu	272/21/2	298/22/3	288/16/0	–	11.07	0.032	0.0316

ASD, autism spectrum disorder; CADD, Combined Annotation Dependent Depletion; GEM-J, GEnome Medical alliance Japan; HGVD, the Human Genetic Variation Database; PolyPhen-2, Polymorphism Phenotyping v2.

[a] Position according to GRCh37.

[b] Reference/alternative allele.

[c] Isoform 1/isoform 2.

[d] Homozygous for reference allele/heterozygous/homozygous for mutant allele.

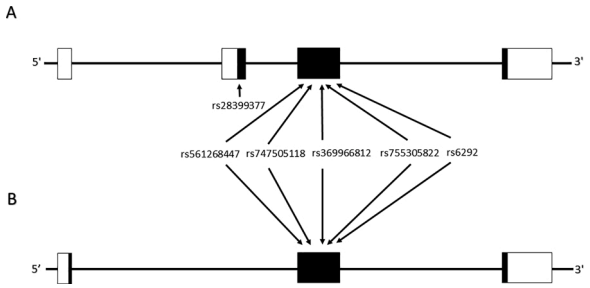

Fig. 1. Genomic structure of *GAP43* isoform 1 (A) and isoform 2 (B). Isoform 1 and isoform 2 have four and three exons (rectangles), respectively. Black and white rectangles represent coding and untranslated regions, respectively. Arrows indicate locations of coding variants identified via resequencing.

Table 3
Association analysis of rs561268447.

Sample	Allele[a]		
	ASD	Schizophrenia	Control
Resequencing	589/1	646/0	608/0
Genotyping	546/0	2,300/0	2,044/0
GEM-J WGA	–	–	15,198/2
HGVD	–	–	2,402/0
Combined	1,135/1	2,946/0	20,252/2

ASD, autism spectrum disorder; GEM-J, GEnome Medical alliance Japan Whole Genome Aggregation; HGVD, the Human Genetic Variation Database.
[a] Reference/alternative allele.

(rs76253894) and two missense variants (rs57478210 and rs76766788), exclusively in schizophrenia patients. However, statistical evidence did not indicate association between these variants and schizophrenia. Taken together, these findings do not provide evidence for *GAP43* being a risk gene with a large effect for ASD or schizophrenia.

GAP43 is a presynaptic protein involved in axonal growth and degeneration (Holahan, 2017). GAP43 is also localized at postsynaptic sites and plays an important role in synaptic plasticity (Han et al., 2013). Converging evidence from genetic, postmortem brain and animal model studies suggests that synaptic proteins are implicated in the pathophysiology of ASD and schizophrenia (Forrest, Parnell, & Penzes, 2018; Lima Caldeira, Peça, & Carvalho, 2019). Large-scale WES studies with gene ontology annotation of ASD and schizophrenia have demonstrated significant enrichment of synaptic genes. Chemical synaptic transmission (GO:0007268) was enriched among putative ASD-associated genes in 21,219 family-based and 14,365 case-control samples (Satterstrom et al., 2020). Enrichment in the postsynapse gene set (GO:0098794) was observed for ultra-rare protein-coding variants in 24,248 patients, 97,322 controls and 3,402 parent-affected offspring trios (Singh et al., 2020). Of note, *de novo* putatively damaging missense variants, including a *GAP43* variant (rs1368974710), showed enrichment in the post synaptic density gene set in 176 bipolar disorder trios (Goes et al., 2019). Further studies should be performed to assess whether synaptic genes, including *GAP43*, contribute to ASD and schizophrenia susceptibility.

Our study has some limitations. First, our sample size (568 ASD patients, 1,473 schizophrenia patients and 10,127 controls) may not provide adequate statistical power to detect an association of rs561268447 with ASD or schizophrenia because the risk allele frequencies were extremely low (0.000099 in controls). Assuming a risk allele frequency of 0.000099 and a genotypic relative risk for heterozygous risk allele carriers of 8.9 under the dominant model of inheritance, approximately 6000 patients and 6000 controls are needed to adequately detect association with a power of 0.80. We were not able to use additional samples to assess an association of rs561268447 with ASD or schizophrenia. Therefore, we cannot exclude the possibility that our negative results may be caused by an insufficient sample size. However, our observations are consistent with those from the Autism Sequencing Consortium (https://asc.broadinstitute.org/) and the Schizophrenia Exome Sequencing Meta-analysis consortium (https://schema.broadinstitute.org/). Additionally, with the exception of rs561268447, we did not identify rare, putatively damaging variants by resequencing the *GAP43* coding region in 922 individuals. Taken together, our results indicate that coding variants in *GAP43* do not exert a large effect on ASD or schizophrenia susceptibility in the Japanese population. Second, we resequenced the coding region of *GAP43*. Therefore, we may have overlooked non-coding variants. Recent whole-genome sequencing studies have demonstrated that rare non-coding variants play roles in the genetic etiology of ASD and schizophrenia (Halvorsen et al., 2020; Takata, 2019; Trost et al., 2020; Turner & Eichler, 2019; Zhou et al., 2019). To identify non-coding risk variants in specific genes for ASD and schizophrenia, further studies with larger sample sizes are needed.

In conclusion, our present study does not provide evidence for the contribution of rare *GAP43* variants to ASD or schizophrenia susceptibility in the Japanese population.

Contributors

RKA, YW, EI and JE designed the study. RKA, YW, JE and AT wrote the first draft of the manuscript. RKA, YW, EI and YN conducted experiments. YW, EI, YN, RM, JE, IK, HI, SH, AT, NO and TS contributed to sample collection. All authors contributed to and approved the final manuscript.

Funding

This work was supported by Grants-in-Aid for Scientific Research (17K16371 to EI) from the Japan Society for the Promotion of Science, and AMED Grants JP20ek0109411 (to IK), JP20km0405216 (to IK), JP20dm0107087 (to NO) and JP20dm0207075 (to NO). The funding sources had no involvement in the study design, in the collection, analysis or interpretation of data, in the writing of the report, or in the decision to submit the article.

Declaration of Competing Interest

The authors report no declarations of interest.

Acknowledgments

The authors thank the patients, their families, and the healthy volunteers for their participation, and Ms. Yamazaki for excellent technical assistance. We thank Jeremy Allen, PhD, from Edanz Group (https://en-author-services.edanzgroup.com/ac) for editing a draft of this manuscript.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at https://doi.org/10.1016/j.rasd.2021.101729.

References

Adzhubei, I. A., Schmidt, S., Peshkin, L., Ramensky, V. E., Gerasimova, A., Bork, P., … Sunyaev, S. R. (2010). A method and server for predicting damaging missense mutations. *Nature Methods, 7*(4), 248–249. https://doi.org/10.1038/nmeth0410-248.

Blennow, K., Bogdanovic, N., Gottfries, C. G., & Davidsson, P. (1999). The growth-associated protein GAP-43 is increased in the hippocampus and in the gyrus cinguli in schizophrenia. *Journal of Molecular Neuroscience, 13*(1–2), 101–109. https://doi.org/10.1385/jmn:13:1-2:101.

Chambers, J. S., Thomas, D., Saland, L., Neve, R. L., & Perrone-Bizzozero, N. I. (2005). Growth-associated protein 43 (GAP-43) and synaptophysin alterations in the dentate gyrus of patients with schizophrenia. *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 29*(2), 283–290. https://doi.org/10.1016/j.pnpbp.2004.11.013.

Cross-Disorder Group of the Psychiatric Genomics Consortium. (2019). Genomic relationships, novel loci, and pleiotropic mechanisms across eight psychiatric disorders. *Cell, 179*(7), 1469–1482. https://doi.org/10.1016/j.cell.2019.11.020.

Eastwood, S. L., & Harrison, P. J. (1998). Hippocampal and cortical growth-associated protein-43 messenger RNA in schizophrenia. *Neuroscience, 86*(2), 437–448. https://doi.org/10.1016/S0306-4522(98)00040-2.

Eastwood, S. L., & Harrison, P. J. (2001). Synaptic pathology in the anterior cingulate cortex in schizophrenia and mood disorders. A review and a Western blot study of synaptophysin, GAP-43 and the complexins. *Brain Research Bulletin, 55*(5), 569–578. https://doi.org/10.1016/S0361-9230(01)00530-5.

Forrest, M. P., Parnell, E., & Penzes, P. (2018). Dendritic structural plasticity and neuropsychiatric disease. *Nature Reviews Neuroscience, 19*(4), 215–234. https://doi.org/10.1038/nrn.2018.16.

Fromer, M., Roussos, P., Sieberts, S. K., Johnson, J. S., Kavanagh, D. H., Perumal, T. M., … Sklar, P. (2016). Gene expression elucidates functional impact of polygenic risk for schizophrenia. *Nature Neuroscience, 19*(11), 1442–1453. https://doi.org/10.1038/nn.4399.

Fung, S. J., Sivagnanasundaram, S., & Weickert, C. S. (2011). Lack of change in markers of presynaptic terminal abundance alongside subtle reductions in markers of presynaptic terminal plasticity in prefrontal cortex of schizophrenia patients. *Biological Psychiatry, 69*(1), 71–79. https://doi.org/10.1016/j.biopsych.2010.09.036.

Goes, F. S., Pirooznia, M., Tehan, M., Zandi, P. P., McGrath, J., Wolyniec, P., … Pulver, A. E. (2019). De novo variation in bipolar disorder. *Molecular Psychiatry*. https://doi.org/10.1038/s41380-019-0611-1.

Hakak, Y., Walker, J. R., Li, C., Wong, W. H., Davis, K. L., Buxbaum, J. D., … Fienberg, A. A. (2001). Genome-wide expression analysis reveals dysregulation of myelination-related genes in chronic schizophrenia. *Proceedings of the National Academy of Sciences of the United States of America, 98*(8), 4746–4751. https://doi.org/10.1073/pnas.081071198.

Halim, N. D., Weickert, C. S., McClintock, B. W., Hyde, T. M., Weinberger, D. R., Kleinman, J. E., … Lipska, B. K. (2003). Presynaptic proteins in the prefrontal cortex of patients with schizophrenia and rats with abnormal prefrontal development. *Molecular Psychiatry, 8*(9), 797–810. https://doi.org/10.1038/sj.mp.4001319.

Halvorsen, M., Huh, R., Oskolkov, N., Wen, J., Netotea, S., Giusti-rodriguez, P., … Szatkiewicz, J. P. (2020). Increased burden of ultra-rare structural variants localizing to boundaries of topologically associated domains in schizophrenia. *Nature Communications, 11*(1), Article 1842. https://doi.org/10.1038/s41467-020-15707-w.

Han, M. H., Jiao, S., Jia, J. M., Chen, Y., Chen, C. Y., Gucek, M., … Li, Z. (2013). The novel caspase-3 substrate gap43 is involved in ampa receptor endocytosis and long-term depression. *Molecular & Cellular Proteomics, 12*(12), 3719–3731. https://doi.org/10.1074/mcp.M113.030676.

Higasa, K., Miyake, N., Yoshimura, J., Okamura, K., Niihori, T., Saitsu, H., … Matsuda, F. (2016). Human genetic variation database, a reference database of genetic variations in the Japanese population. *Journal of Human Genetics, 61*(6), 547–553. https://doi.org/10.1038/jhg.2016.12.

Holahan, M. R. (2017). A shift from a pivotal to supporting role for the growth-associated protein (GAP-43) in the coordination of axonal structural and functional plasticity. *Frontiers in Cellular Neuroscience, 11*, 1–19. https://doi.org/10.3389/fncel.2017.00266.

Honer, W. G., Falkai, P., Chen, C., Arango, V., Mann, J. J., & Dwork, A. J. (1999). Synaptic and plasticity-associated proteins in anterior frontal cortex in severe mental illness. *Neuroscience, 91*(4), 1247–1255. https://doi.org/10.1016/S0306-4522(98)00679-4.

Igarashi, M., Kawasaki, A., Ishikawa, Y., Honda, A., Okada, M., & Okuda, S. (2020). Phosphoproteomic and bioinformatic methods for analyzing signaling in vertebrate axon growth and regeneration. *Journal of Neuroscience Methods, 339*, Article 108723. https://doi.org/10.1016/j.jneumeth.2020.108723.

Kushima, I., Aleksic, B., Nakatochi, M., Shimamura, T., Okada, T., Uno, Y., … Ozaki, N. (2018). Comparative analyses of copy-number variation in autism spectrum disorder and schizophrenia reveal etiological overlap and biological insights. *Cell Reports, 24*(11), 2838–2856. https://doi.org/10.1016/j.celrep.2018.08.022.

Lima Caldeira, G., Peça, J., & Carvalho, A. L. (2019). New insights on synaptic dysfunction in neuropsychiatric disorders. *Current Opinion in Neurobiology, 57*, 62–70. https://doi.org/10.1016/j.conb.2019.01.004.

Lord, C., Brugha, T. S., Charman, T., Cusack, J., Dumas, G., Frazier, T., … Veenstra-VanderWeele, J. (2020). Autism spetrum disorder. *Nature Reviews Disease Primers, 6*(1), 5. https://doi.org/10.1038/s41572-019-0138-4.

Matoba, N., Liang, D., Sun, H., Aygün, N., McAfee, J., Davis, J., … Stein, J. (2020). Common genetic risk variants identified in the SPARK cohort support DDHD2 as a candidate risk gene for autism. *Translational Psychiatry, 10*(1), 265. https://doi.org/10.1038/s41398-020-00953-9.

Nunokawa, A., Watanabe, Y., Kaneko, N., Sugai, T., Yazaki, S., Arinami, T., … Someya, T. (2010). The *dopamine D3 receptor* (*DRD3*) gene and risk of schizophrenia: Case-control studies and an updated meta-analysis. *Schizophrenia Research, 116*(1), 61–67. https://doi.org/10.1016/j.schres.2009.10.016.

Perrone-Bizzozero, N. I., Sower, A. C., Bird, E. D., Benowitz, L. I., Ivins, K. J., & Neve, R. L. (1996). Levels of the growth-associated protein GAP-43 are selectively increased in association cortices in schizophrenia. *Proceedings of the National Academy of Sciences of the United States of America, 93*(24), 14182–14187. https://doi.org/10.1073/pnas.93.24.14182.

Purcell, S., Cherny, S. S., & Sham, P. C. (2003). Genetic power calculator: Design of linkage and association genetic mapping studies of complex traits. *Bioinformatics, 19*(1), 149–150. https://doi.org/10.1093/bioinformatics/19.1.149.

Rentzsch, P., Witten, D., Cooper, G. M., Shendure, J., & Kircher, M. (2019). CADD: Predicting the deleteriousness of variants throughout the human genome. *Nucleic Acids Research, 47*(D1), D886–D894. https://doi.org/10.1093/nar/gky1016.

Satterstrom, F. K., Kosmicki, J. A., Wang, J., Breen, M. S., De Rubeis, S., An, J. Y., … Buxbaum, J. D. (2020). Large-scale exome sequencing study implicates both developmental and functional changes in the neurobiology of autism. *Cell, 180*(3). https://doi.org/10.1016/j.cell.2019.12.036, 568-584.e23.

Shen, Y. C., Tsai, H. M., Cheng, M. C., Hsu, S. H., Chen, S. F., & Chen, C. H. (2012). Genetic and functional analysis of the gene encoding GAP-43 in schizophrenia. *Schizophrenia Research, 134*(2–3), 239–245. https://doi.org/10.1016/j.schres.2011.11.016.

Shuvarikov, A., Campbell, I. M., Dittwald, P., Neill, N. J., Bialer, M. G., Moore, C., … Rosenfeld, J. A. (2013). Recurrent HERV-H-mediated 3q13.2-q13.31 deletions cause a syndrome of hypotonia and motor, language, and cognitive delays. *Human Mutation, 34*(10), 1415–1423. https://doi.org/10.1002/humu.22384.

Singh, T., Poterba, T., Curtis, D., Akil, H., Eissa, M. A. I., Barchas, J. D., … Daly, M. J. (2020). Exome sequencing identifies rare coding variants in 10 genes which confer substantial risk for schizophrenia. *medRxiv*. https://doi.org/10.1101/2020.09.18.20192815.

Smeland, O. B., Frei, O., Dale, A. M., & Andreassen, O. A. (2020). The polygenic architecture of schizophrenia - rethinking pathogenesis and nosology. *Nature Reviews Neurology, 16*(7), 366–379. https://doi.org/10.1038/s41582-020-0364-0.

Sower, A. C., Bird, E. D., & Perrone-bizzozero, N. I. (1995). Increased levels of GAP-43 protein in schizophrenic brain tissues demonstrated by a novel immunodetection method. *Molecular and Chemical Neuropathology, 24*, 1–11. https://doi.org/10.1007/BF03160108.

Sullivan, P. F., & Geschwind, D. H. (2019). Defining the genetic, genomic, cellular, and diagnostic architectures of psychiatric disorders. *Cell, 177*(1), 162–183. https://doi.org/10.1016/j.cell.2019.01.015.

Takata, A. (2019). Estimating contribution of rare non-coding variants to neuropsychiatric disorders. *Psychiatry and Clinical Neurosciences, 73*(1), 2–10. https://doi.org/10.1111/pcn.12774.

Tian, S. Y., Wang, J. F., Bezchlibnyk, Y. B., & Young, L. T. (2007). Immunoreactivity of 43 kDa growth-associated protein is decreased in post mortem hippocampus of bipolar disorder and schizophrenia. *Neuroscience Letters, 411*(2), 123–127. https://doi.org/10.1016/j.neulet.2006.10.031.

Trost, B., Engchuan, W., Nguyen, C. M., Thiruvahindrapuram, B., Dolzhenko, E., Backstrom, I., … Yuen, R. K. C. (2020). Genome-wide detection of tandem DNA repeats that are expanded in autism. *Nature, 586*(7827), 80–86. https://doi.org/10.1038/s41586-020-2579-z.

Turner, T. N., & Eichler, E. E. (2019). The Role of *de novo* noncoding regulatory mutations in neurodevelopmental disorders. *Trends in Neurosciences, 42*(2), 115–127. https://doi.org/10.1016/j.tins.2018.11.002.

Watanabe, Y., Muratake, T., Kaneko, N., Nunokawa, A., & Someya, T. (2006). No association between the *brain-derived neurotrophic factor* gene and schizophrenia in a Japanese population. *Schizophrenia Research, 84*(1), 29–35. https://doi.org/10.1016/j.schres.2006.03.011.

Webster, M. J., Shannon Weickert, C., Herman, M. M., Hyde, T. M., & Kleinman, J. E. (2001). Synaptophysin and GAP-43 mRNA levels in the hippocampus of subjects with schizophrenia. *Schizophrenia Research, 49*(1–2), 89–98. https://doi.org/10.1016/S0920-9964(00)00052-9.

Weickert, C. S. (2001). Reduced GAP-43 mRNA in dorsolateral prefrontal cortex of patients with schizophrenia. *Cerebral Cortex, 11*(2), 136–147. https://doi.org/10.1093/cercor/11.2.136.

Zaccaria, K. J., Lagace, D. C., Eisch, A. J., & McCasland, J. S. (2010). Resistance to change and vulnerability to stress: Autistic-like features of GAP43-deficient mice. *Genes, Brain, and Behavior, 9*(8), 985–996. https://doi.org/10.1111/j.1601-183X.2010.00638.x.

Zheng, Z., Zheng, P., & Zou, X. (2018). Association between schizophrenia and autism spectrum disorder: A systematic review and meta-analysis. *Autism Research, 11*(8), 1110–1119. https://doi.org/10.1002/aur.1977.

Zhou, J., Park, C. Y., Theesfeld, C. L., Wong, A. K., Yuan, Y., Scheckel, C., … Troyanskaya, O. G. (2019). Whole-genome deep-learning analysis identifies contribution of noncoding mutations to autism risk. *Nature Genetics, 51*(6), 973–980. https://doi.org/10.1038/s41588-019-0420-0.

Zikopoulos, B., & Barbas, H. (2010). Changes in prefrontal axons may disrupt the network in autism. *Journal of Neuroscience, 30*(44), 14595–14609. https://doi.org/10.1523/JNEUROSCI.2257-10.2010.

Zikopoulos, B., & Barbas, H. (2013). Altered neural connectivity in excitatory and inhibitory cortical circuits in autism. *Frontiers in Human Neuroscience, 7*, 1–24. https://doi.org/10.3389/fnhum.2013.00609.