CURRENT TREND AND RECENT DEVELOPMENT OF AUTISM SPECTRUM DISORDER (ASD) – A REVIEW

Mahamad Shabudin NS[1] and Shuid AN[1].
[1]Community Health Department, Advanced Medical and Dental Research Institute, University of Science, Malaysia.

Correspondence:
Ahmad Naqib bin Shuid,
Community Health Department,
Advanced Medical and Dental Research Institute,
University of Science, 13200, Penang, Malaysia
Email: naqib@usm.my

Abstract
Autism spectrum disorder (ASD) is a neurological and developmental disorder that may appear early during childhood and lasts throughout a person's life with different symptom severity. Not just that, ASD have also been associated with other neurological diseases such as intellectual disability (ID) and epilepsy. Genetic or environmental factors may play a role in the development of ASD. Research has shown that changes in specific genes may increase the chance of a child developing ASD. Specific environmental influences may also increase the risk of developing ASD. Most people often misinterpret ASD behaviors. Families of patients with ASD often overlook ASD as a redundant disease that does not need proper medical attention. This situation might result from family's ego state, lacking knowledge of ASD and the cost required for diagnosing and treating ASD patients. Lacking knowledge among people with ASD patient indicates that there is not much information about ASD. Thus, this review aims to disseminate knowledge and provide updates on ASD. This review will also highlight the challenges in screening techniques used to detect autism. This review will also discuss the possible risks of developing autism and recent advances in ASD related research.

Keywords: Autism spectrum disorder, autism, screening and genome mutation

Introduction

Autism spectrum disorder (ASD) is a neurological disorder with symptoms that can range from mild to severe (33) and the Diagnostic and Statistical Manual of Mental disorders - 5th edition (DSM-5) is the latest criteria for used ASD diagnostics. Asperger's syndrome, Rett syndrome, childhood disintegrative disorder, Kanner's syndrome and pervasive developmental disorder are the five major types of ASD (22). A person with ASD also have been found to be associated with other illnesses, such as schizophrenia, dementia, or Parkinson's disease (21, 26, 50). ASD lasts throughout a person's life and may begin early in childhood. ASD is also considered a common environmental and genetic disorder. (33, 34). Environmental factors such as pesticides, pollution, diabetes, immune system disorder, late conception and prematurity have been found to be associated with ASD. Discoveries of the de novo mutations in genes of subjects with ASD that were unknown before has led to advances in epigenetics, polygenic risk, and how genes interact with their environments (34).

According to the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), a person diagnosed with autism must meet five standard criteria specifically ruled out for ASD diagnosis. The five criteria include a) problems with interaction and communication with others. b) limited and repetitive interests and behaviour, c) signs that appear early but may not be fully visible until later in life or hidden by pick-up techniques later in life. d) symptoms that significantly affect current functioning, and e) Intellectual disability. Autism often causes communication and social difficulties. It can also cause agitation when their daily routine changes, engage in repetitive activities and react oddly to certain situations. In developed countries, ASD prevalence is as minimum as 1.5%, with recent surges, especially among others without intellectual handicaps (3, 12). Males are more frequently diagnosed with autism in comparison to females, with research ratios of 2:1 to 5:1 and prognosis of 4:1 (8, 33). Many autistic people have above-average to average intelligence, with 30% having an intellectual impairment (ID) (8). Several studies have also found that 9 % of adults with ASD and from this 60 and 70 % having at least one common

mental disorder. For instance, attention deficit hyperactivity disorder (ADHD) or other mood disorders (30).

Current Trend in ASD Research
Differences in Gender

Researchers, for some reason, have a long history of ignoring female representatives in any study, including autism. However, this prejudice is shifting, as indicated by many studies examining gender variations in autism. Autistic females seem to have more genetic abnormalities than autistic male. Researchers are working to identify the reasons for these discrepancies. For instance, in 2021, Zhang et al. found evidence supporting the 'female protective effect' in brain activity. This fact still baffles a lot of scientists to this day. The X chromosome has a disproportionate influence on brain development, which may contribute to creating gender differences in ASD patients early on. Even the resting-state brain activity patterns differ between autistic male and female (4).

Genome mutation

Researchers have mostly looked at genes, which make up only 2% of the genome, in their search for mutations linked to autism. This year, autism researchers made significant strides in investigating huge DNA regions that do not code for proteins. A sequencing investigation has identified that the first three random mutations within non-coding areas might be associated with the disorder. The analysis demonstrates that non-coding mutations have a role in the 'second strike' theory of autism genetics, magnifying the effect of the transformation in the chromosomal region linked to autism at the 16p11.2 locus and the 22q11.2 locus. A novel atlas of gene expression in the fetal brain for mid-gestation indicates that non-coding mutations may also affect when and where autism-related genes are most active throughout brain development. A postmortem of brain tissue showed that mutations in enhancers, non-coding regions that boost gene expression, happen much more often in people with autism than in those who didn't have it (9).

New advances in screening

Researchers implemented several new strategies to improve autism screening (42). Especially the quest to test newborns for uncommon genetic disorders related to autism (13). When combined, developmental screening and surveillance are two methods that can be used within the context of the patient and family medical home to assist in the earlier detection of children who may have developmental issues. All children should be given standardized developmental screening tests at nine months, 18 months, and 30 months. Additional testing may be suggested if the test administration reveals concerns about a child's development. With the guidance of a pediatric health care professional, screening could be done by other clinic workers. The screening for ASD must be done at 18 months and Twenty-four months with the specified ASD screening test, such as general developmental screening, until precise and reliable measures can be used for confirmation for different ages. (30).

Risk of developing ASD
ASD genetic make-up

Neurodevelopmental abnormalities have been connected with exposure to ubiquitous environmental pollutants, such as endocrine disruptor. As risk factors or causes of autism, functional effects on particular biological areas, like synaptic function and epigenetic regulation, have been identified. The results of experiments show convergences and complicated interplay between gene mutation and toxic exposures in the controlled circuits altered through multiple environmental variables and genetic alterations. Besides a poorly defined load of low-risk variations, cumbersome, predominantly single nucleotide polymorphisms (SNPs) (27). Numerous extremely penetrant uncommon variants frequently copy number variants (CNVs), whose multi-functionality is impacted mainly by the genetic background variety. Common SNPs dispersed throughout the genome are predicted to be responsible for ASD at a minimum of 20% susceptibility and to act synergistically or additively with other factors (1, 17, 29). The genetic variation pattern that causes ASD shows the peculiar effect, highly penetrant gene mutation or CNVs that are inherited or, more often, happen on their own in the germinal cells. Because these mutations are bad for reproduction, they are rare in the general public (20).

Environmental factors

Several environmental factors affect the start of ASD and how it develops. These include stress level, hormonal balance, maternal nutrition, exposure to environmental chemicals, and substance abuse such as pesticides, metals, air pollutants and plastic derivatives (23, 40). In 2017, Tran and Miyake found that the chances of prenatal developing ASD increase significantly with exposure to tobacco smoke. Through the neuroendocrine axis, a mother's stress level has also been linked to changes in the epigenetic programming that can stop neurons from developing properly (35). Furthermore, epidemiological studies have shown that introducing prenatal to selective serotonin re-uptake inhibitors (SSRIs) and valproic acid upsurges the ASD incidence among children, and exposure to paracetamol might hinder language development (7, 12). Also, heavy metal exposure, like arsenic, mercury and lead, are strongly linked to brain development problems and bad neurodevelopmental outcomes linked to ASD (19, 45). The endocrine-

disrupting chemicals (EDCs) effects study on foetal central nervous system (CNS) is especially worrying because they can mess up the delicate hormonal balance and cause epigenetic responses that can have long-term adverse effects on neural progenitors (2, 46, 52).

Recent Development in ASD
Treatments and Interventions

ASD treatment ranges from drug treatments to specialised behavioural therapies. In young children, high-intensity applied behaviour analysis (ABA) was related to neurodevelopmental and linguistic ability improvements compared to community controls (52). Early intensive behavioural intervention (EIBI) is one of the well established treatments for ASD children founded on behaviour analysis. It can give significant relief to core ASD symptoms, notably communication skills when implemented over a long time frame at an average of 20 to 40 hours per week (15). The National Institute for Health and Care Excellence (NICE) developed procedures for how to care for and help people with autism. Based on these procedures, it appears that social learning programmes for individuals or groups that incorporate behavioural therapy strategies into a social learning framework may be able to assist in the improvement of social interaction issues. Among these are peer feedback, reinforcement to teach the rules of how to act in social situations, imitation, and video models (41). ASD is difficult to treat psychopharmacologically because of the disorder's wide range of presentational characteristics and frequent co-morbidities. Insured children with ASD reportedly receive psychopharmacological therapies in close to half of the cases, most frequently in the form of stimulants, antidepressants, anticonvulsants, antipsychotics, and alpha-2 agonists (36). Up to date, there are no medications that have been approved to treat the primary ASD signs, including repetitive activities or difficulties with social communication. Both aripiprazole and risperidone are licenced and approved by the Food and Drug Administration of the United States for treating irritability linked to ASD (18).

Prevention that can be taken to minimise the ASD risk.

Sharma and Mehan (2021) revealed that PI3K-AKT/mTOR pathway needs to be upregulated because it is involved in the pathogenesis of autism. In mammalian receptors, the PI3K-AKT/mTOR pathway is essential for signalling or biochemical functions, including metabolism, cell survival, protein synthesis, differentiation, and development of cells. The upregulation of the PI3K-AKT/mTOR pathway has been linked to various abnormalities in the human brain, including autism (42). PI3K-AKT/mTOR signalling is linked to genetic changes and neurological apoptosis in various neuro complications. Blocking the PI3K/AKT/mTOR pathway can have neuroprotective effects on many neurological conditions such as ASD, fragile X syndrome, Huntington's disease, Down syndrome, depression, Parkinson's disease and epilepsy (16, 24, 25, 39, 47, 56). So far, what has been seen suggests that giving IGF-1 to an infant could reduce or prevent neurological problems, especially the development of ASD. More and more proof is that autism is caused by issues with the IGF1/IGFR/IRS1/PI3K/AKT/mTOR intracellular signalling pathway. This specific pathway affects the way IGF-1 is translated to help myogenesis. When the tyrosine kinase receptor sites on IGFR, which are at the boundary within both the intracellular and the extracellular environments, are turned on, it affects several signalling pathways, causing changes in how blood flows and how cells use energy. On the other hand, phosphorylated AKT is lower within the brain of an autistic person (5, 11, 37). This might occur if the surrounding cells had less IGF and the IRS1 protein in the PI3K/AKT chain was a polymorphic form (52). Autism also can be prevented during the pregnancy phase through folic acid treatment. This treatment has demonstrated a remarkable clinical development in the fundamental ASD. Pregnancy-related complications, abnormal foetal development and infertility are all significantly contributed to by autoimmune folate receptors as well as folate deficiency. About 70% of children diagnosed with ASD have autoimmune responses against folic acid receptor alpha (FRα). A substantial proportion of these children respond to oral folate with significant improvement in social interaction, language, and speech (43). A study revealed an early diagnosis and treatment with high-dose folate and a diet without animal milk might be effective if the mother's FR antibodies are harmful or if both parents' antibodies are negative (6). Lastly, an appropriate amount of vitamin D is crucial during pregnancy (49). Vitamin D influences brain function via growth, neurotrophic and neuroprotective actions, maturation, neuronal differentiation, and calcium signalling regulation (28). The current study showed that vitamin D in utero could harmfully affect foetal growth and raise the likelihood of developing ASD development (31, 38, 55).

Competing interests

The authors declare that they have no competing interests.

References

1. Anney R, Klei L, Pinto D, Almeida J, Bacchelli E, Baird G, *et al*. Individual common variants exert weak effects on the risk for autism spectrum disorders. Human Molecular Genetics. 2012;21(21): 4781–4792.
2. Baccarelli A, Bollati V. Epigenetics and environmental chemicals. Current Opinion in Pediatrics. 2009;21(2): 243–251.

3. Baxter AJ, Brugha TS, Erskine HE, Scheurer RW, Vos T, Scott JG. The epidemiology and global burden of autism spectrum disorders. Psychological Medicine. 2015;45(3):601–613.
4. Bedford SA, Park MTM, Devenyi GA, Tullo S, Germann J, Patel R, *et al.* Large-scale analyses of the relationship between sex, age and intelligence quotient heterogeneity and cortical morphometry in autism spectrum disorder. Molecular Psychiatry. 2020;25(3):614–628.
5. Bibollet-Bahena O, Almazan G. IGF-1-stimulated protein synthesis in oligodendrocyte progenitors requires PI3K/mTOR/Akt and MEK/ERK pathways. J Neurochemistry. 2009;109(5):1440–1451.
6. Bobrowski-Khoury N, Ramaekers VT, Sequeira JM, Quadros EV. Folate Receptor Alpha Autoantibodies in Autism Spectrum Disorders: Diagnosis, Treatment and Prevention. Journal of Personalized Medicine. 2021;11(8):710.
7. Boukhris T, Sheehy O, Mottron L, Bérard A. Antidepressant Use During Pregnancy and the Risk of Autism Spectrum Disorder in Children. JAMA Pediatrics. 2016;170(2):117.
8. Braconnier ML, Siper PM. Neuropsychological Assessment in Autism Spectrum Disorder. Curr Psychiatry Rep. 2021;23(10):63.
9. Brugha TS, Spiers N, Bankart J, Cooper SA, McManus S, Scott FJ, *et al.* Epidemiology of autism in adults across age groups and ability levels. British Journal of Psychiatry. 2016;209(6):498–503.
10. Chawner SJRA, Doherty JL, Anney RJL, Antshel KM, Bearden CE, Bernier R, *et al.* A Genetics-First Approach to Dissecting the Heterogeneity of Autism: Phenotypic Comparison of Autism Risk Copy Number Variants. American Journal of Psychiatry. 2021;178(1), 77–86.
11. Chen J, Alberts I, Li X. Dysregulation of the IGF-I/PI3K/AKT/mTOR signaling pathway in autism spectrum disorders. International Journal of Developmental Neuroscience. 2014;35(1), 35–41.
12. Christensen DL, Baio J, Braun KVN, Bilder D, Charles J, Constantino, *et al.* Prevalence and Characteristics of Autism Spectrum Disorder Among Children Aged 8 Years — Autism and Developmental Disabilities Monitoring Network, 11 Sites, United States, 2012. MMWR. Surveillance Summaries. 2016;65(3), 1–23.
13. Christensen J, Grønborg TK, Sørensen MJ, Schendel D, Parner ET, Pedersen L H, Vestergaard M. Prenatal Valproate Exposure and Risk of Autism Spectrum Disorders and Childhood Autism. JAMA. 2013;309(16), 1696.
14. Dattaro L. The push to screen newborns for rare autism-linked genetic conditions. Spectrum. 2021. Frankel F, Myatt R, Sugar C, Whitham C, Gorospe CM, Laugeson E. A Randomized Controlled Study of Parent-assisted Children's Friendship Training with Children having Autism Spectrum Disorders. Journal of Autism and Developmental Disorders. 2010;40(7), 827–842.
15. Franz DN, Capal JK. mTOR inhibitors in the pharmacologic management of tuberous sclerosis complex and their potential role in other rare neurodevelopmental disorders. Orphanet Journal of Rare Diseases. 2017; 12(1), 51.
16. Gaugler T, Klei L, Sanders SJ, Bodea CA, Goldberg AP, Lee AB, *et al*. Most genetic risk for autism resides with common variation. Nature Genetics. 2014;46(8): 881–885.
17. Genovese A, Butler MG. Clinical Assessment, Genetics, and Treatment Approaches in Autism Spectrum Disorder (ASD). International Journal of Molecular Sciences. 2020;21(13):4726. Giordano G, Costa LG. Developmental Neurotoxicity: Some Old and New Issues. ISRN Toxicology. 2012; 1–12.
18. Grandjean P, Landrigan P. Developmental neurotoxicity of industrial chemicals. The Lancet. 2006;368(9553):2167–2178.
19. Grove J, Ripke S, Als TD, Mattheisen M, Walters RK, Won H, *et al*. Identification of common genetic risk variants for autism spectrum disorder. Nature Genetics 2019;51(3);431–444.
20. Hamlyn J, Duhig M, McGrath J, Scott J. Modifiable risk factors for schizophrenia and autism — Shared risk factors impacting on brain development. Neurobiology of Disease. 2013;53;3–9.
21. Hodges H, Fealko C, Soares N. Autism spectrum disorder: definition, epidemiology, causes, and clinical evaluation. Transl Pediatr. 2020;(9 Suppl 1): S55-S65.
22. Homberg JR, Kyzar EJ, Scattoni ML, Norton WH, Pittman J, Gaikwad S, *et al.* Genetic and environmental modulation of neurodevelopmental disorders: Translational insights from labs to beds. Brain Research Bulletin. 2016; 125:79–91.
23. Huang X, Zhang H, Yang J, Wu J, McMahon J, Lin Y, *et al.* Pharmacological inhibition of the mammalian target of rapamycin pathway suppresses acquired epilepsy. Neurobiology of Disease. 2010;40(1):193–199.
24. Humbert S, Bryson EA, Cordelières FP, Connors NC, Datta SR, Finkbeiner S, *et al*. The IGF-1/Akt Pathway Is Neuroprotective in Huntington's Disease and Involves Huntingtin Phosphorylation by Akt. Developmental Cell. 2002;2(6), 831–837.
25. Ivashko-Pachima Y, Hadar A, Grigg I, Korenková V, Kapitansky O, Karmon G. Discovery of autism/intellectual disability somatic mutations in Alzheimer's brains: mutated ADNP cytoskeletal impairments and repair as a case study. Molecular Psychiatry. 2021:26(5):1619– 1633.
26. Jeste SS, Geschwind DH. Disentangling the heterogeneity of autism spectrum disorder through genetic findings. Nature Reviews Neurology. 2014;10(2):74–81.

27. Kesby JP, Eyles DW, Burne THJ, McGrath JJ. The effects of vitamin D on brain development and adult brain function. Molecular and Cellular Endocrinology. 2001;347(1– 2): 121–127.
28. Klei L, Sanders SJ, Murtha MT, Hus V, Lowe JK, Willsey AJ, *et al*. Common genetic variants, acting additively, are a major source of risk for autism. Molecular Autism. 2012;3(1):9.
29. Lever AG, Geurts HM. Psychiatric co-occurring symptoms and disorders in young, middle-aged, and older adults with autism spectrum disorder. Journal of Autism and Developmental Disorders. 2016;46(6):1916–1930.
30. Lee BK, Eyles DW, Magnusson C, Newschaffer CJ, McGrath JJ, Kvaskoff D, *et al*. Developmental vitamin D and autism spectrum disorders: findings from the Stockholm Youth Cohort. Molecular Psychiatry. 2021;26(5):1578–1588.
31. Lipkin PH, Macias MM, Norwood KW, Brei TJ, Davidson LF, Davis BE, *et al*. Promoting Optimal Development: Identifying Infants and Young Children With Developmental Disorders Through Developmental Surveillance and Screening. Pediatrics. 2020;145(1).
32. Lord C, Brugha TS, Charman T, Cusack J, Dumas G, Frazier T, *et al.* Autism spectrum disorder. Nature Reviews Disease Primers. 2020;6(1):5.
33. Lord C, Elsabbagh M, Baird G, Veenstra-Vanderweele, J. Autism spectrum disorder. The Lancet. 2018;392(10146):508–520.
34. Lyall K, Croen L, Daniels J, Fallin MD, Ladd-Acosta C, Lee BK, *et al*. The Changing Epidemiology of Autism Spectrum Disorders. Annual Review of Public Health. 2017;38(1):81–102.
35. Maccari S, Krugers HJ, Morley-Fletcher S, Szyf M, Brunton PJ. The Consequences of Early-Life Adversity: Neurobiological, Behavioural and Epigenetic Adaptations. Journal of Neuroendocrinology. 2014;26(10):707–723.
36. Madden JM, Lakoma MD, Lynch FL, Rusinak D, Owen-Smith AA, Coleman KJ, *et al*. Psychotropic Medication Use among Insured Children with Autism Spectrum Disorder. Journal of Autism and Developmental Disorders. 2017;47(1):144–154.
37. Manning BD, Cantley LC. AKT/PKB Signaling: Navigating Downstream. Cell. 2007;129(7):1261–1274.
38. McGrath J, Saari K, Hakko H, Jokelainen J, Jones P, Järvelin MR, *et al*. Vitamin D supplementation during the first year of life and risk of schizophrenia: a Finnish birth cohort study. Schizophrenia Research. 2004;67(2–3):237–245.
39. Neis VB, Moretti M, Rosa PB, Dalsenter Y de O, Werle I, Platt N, *et al*. The involvement of PI3K/Akt/mTOR/GSK3β signaling pathways in the antidepressant-like effect of AZD6765. Pharmacology Biochemistry and Behavior. 2020; 198:173020.
40. Pelch KE, Bolden AL, Kwiatkowski CF. Environmental Chemicals and Autism: A Scoping Review of the Human and Animal Research. Environmental Health Perspectives. 2019;127(4):046001.
41. Pilling S, Baron-Cohen S, Megnin-Viggars O, Lee R, Taylor C. Recognition, referral, diagnosis, and management of adults with autism: summary of NICE guidance. BMJ. 2012;344: e4082–e4082.
42. Rahi S, Mehan S. Understanding Abnormal SMO-SHH Signaling in Autism Spectrum Disorder: Potential Drug Target and Therapeutic Goals. Cellular and Molecular Neurobiology. 2022;42(4):931–953.
43. Ramaekers VT, Sequeira JM, DiDuca M, Vrancken G, Thomas A, Philippe C, *et al.* Improving Outcome in Infantile Autism with Folate Receptor Autoimmunity and Nutritional Derangements: A Self-Controlled Trial. Autism Research and Treatment. 2019:1–12.
44. Rao R. Web app tracks pupil size in people, mice. Spectrum. https://doi.org/10.53053/QTFW8070 Reichow B, Hume K, Barton EE, Boyd B A. Early intensive behavioral intervention (EIBI) for young children with autism spectrum disorders (ASD). Cochrane Database of Systematic Reviews, 2018;(10).
45. Saunders NR, Dziegielewska KM. Developmental neurotoxicity of industrial chemicals. The Lancet. 2007;369(9564):821.
46. Schug TT, Blawas AM, Gray K, Heindel JJ, Lawler CP. Elucidating the Links Between Endocrine Disruptors and Neurodevelopment. Endocrinology. 2015;156(6):1941– 1951.
47. Sharma A, Mehan S. Targeting PI3K-AKT/mTOR signaling in the prevention of autism. Neurochemistry International. 2021; 147:105067.
48. Sharma R, Rahi S, Mehan S. Neuroprotective potential of solanesol in intracerebroventricular propionic acid induced experimental model of autism: Insights from behavioral and biochemical evidence. Toxicology Reports. 2019; 6:1164–1175.
49. Sourander A, Upadhyaya S, Surcel HM, Hinkka-Yli-Salomäki S, Cheslack-Postava K, Silwal S, *et al*. Maternal Vitamin D Levels During Pregnancy and Offspring Autism Spectrum Disorder. Biological Psychiatry. 2021;90(11):790–797.
50. Starkstein S, Gellar S, Parlier M, Payne L, Piven J. High rates of parkinsonism in adults with autism. Journal of Neurodevelopmental Disorders. 2015;7(1):29.
51. Steinman, G. The putative etiology and prevention of autism. 2020:1–34.
52. Steinman G. The putative etiology and prevention of autism. Prog Mol Biol Transl Sci. 2020; 173:1-34.
53. Tiura M, Kim J, Detmers D, Baldi H. Predictors of longitudinal ABA treatment outcomes for children with autism: A growth curve analysis. Research in

Developmental Disabilities. 2017; 70:185–197.
54. Tran NQV, Miyake K. Neurodevelopmental Disorders and Environmental Toxicants: Epigenetics as an Underlying Mechanism. International Journal of Genomics. 2017, 1–23.
55. Tran NQV, Miyake K. Neurodevelopmental Disorders and Environmental Toxicants: Epigenetics as an Underlying Mechanism. International Journal of Genomics. 2017:1–23.
56. Vinkhuyzen AAE, Eyles DW, Burne THJ, Blanken LME, Kruithof CJ, Verhulst F*, et al.* Gestational vitamin D deficiency and autism spectrum disorder. BJPsych Open. 2017;3(2):85–90.
57. Yui K, Sasaki H, Imataka G, Okanishi T. The role of antioxidant proteins in improvement of autism core symptoms in two patients with tuberous sclerosis treated with mTOR inhibitor everolimus. Global Medicine and Therapeutics. 2018;1(1).
58. Zhang Y, Li N, Li C, Zhang Z, Teng H, Wang, Y., *et al*. Genetic evidence of gender difference in autism spectrum disorder supports the female-protective effect. Translational Psychiatry. 2020;10(1), 4.