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Exploring genetic and environmental contributions to autism spectrum disorder: insights from rodent models*

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Autism Spectrum Disorder (ASD) is a complex neurodevelopmental condition with diverse genetic and environmental origins. Rodent models, particularly mice, have proven invaluable in studying the underlying mechanisms of ASD, offering insights into the genetic mutations and neurobiological processes that may contribute to the disorder in the human population. This review examines key rodent models to study genetic and environmental factors affecting the etiology and pathogenesis of ASD. While these models successfully mimic many core ASD symptoms, they face limitations in fully replicating the social and cognitive complexities of human ASD. Future research should prioritize improving models of gene-environment interactions and exploring humanized approaches to bridge

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the gap between animal studies and clinical applications. These efforts are essential for advancing our understanding of ASD and developing effective therapeutic strategies.

KEY WORDS*:* autism spectrum disorder / genetic / environment / rodent model / behavior

Introduction

Autism spectrum disorder (ASD) is a group of neurodevelopmental conditions characterized by decreased social interaction, altered communication, and the occurrence of repetitive behaviors [American Psychiatric Association 2013]. The etiology of ASD is intricate and incompletely understood, with both genetic and environmental factors recognized as essential contributors to neurodevelopmental and behavioral outcomes [Bölte *et al.* 2019, Wiśniowiecka-Kowalnik and Nowakowska 2019]. The initial approach for investigating the influence of genes on the occurrence of ASD focused on the comparison of autism concordance rates between monozygotic and dizygotic twins. Evidence demonstrates a significantly higher concordance rate in monozygotic compared to dizygotic sibling pairs [Bailey *et al.* 1995], indicating a substantial genetic contribution to ASD in siblings born to the same embryo. Moreover, whole-genome sequencing studies have identified hundreds of gene mutations linked with ASD, suggesting that genetic factors are important in the etiology of ASD [Pinto *et al.* 2010, Klei *et al.* 2012, Yu *et al.* 2013]. In addition to genetic variation, epidemiological studies have identified various environmental risk factors that contribute to ASD, including obstetric complications, preeclampsia, maternal infection, maternal stress, advanced maternal age, and metabolic conditions during pregnancy [Kolevzon *et al.* 2007, Hultman *et al.* 2011, Walder *et al.* 2014, Zerbo *et al.* 2015, Wang *et al.* 2017, Croen *et al.* 2019, Katz *et al.* 2021].

The heterogeneous nature of ASD demands a multi-disciplinary investigative approach. Animal models provide a valuable framework for comprehending the impact of genetic and environmental influences on ASD, as well as their interactions. Animal models serve as testing grounds for potential therapies, allowing researchers to study the efficacy and safety of medications or treatments before their biomedical application to humans. The use of rodent models in ASD research has grown substantially, as shown in recent reviews summarizing the contributions and limitations of these models in exploring ASD pathophysiology [Berg and Silverman 2022, Silverman *et al.* 2022, Ornoy *et al.* 2024]. Despite these advancements, there is growing skepticism regarding the translational validity of animal models in ASD research. Critics have argued that rodent models cannot fully capture the social and cognitive complexity of human ASD [Möhrle *et al.* 2020, Silverman *et al.* 2022]. Some question the value of animal studies for direct patient benefit, suggesting that animal models have not yet provided actionable outcomes for individuals with ASD [Chadman 2017, McCracken *et al.* 2021]. While these critiques highlight important limitations, animal models remain essential for dissecting genetic and molecular processes that may underlie ASD pathology. For instance, rodent models have enabled the identification of

specific genetic mutations, such as those in Shank3 and Mecp2, which are implicated in ASD, as well as preclinical testing of pharmacological targets like metabotropic glutamate receptor 5 (mGluR5) antagonists as well as neuropeptide oxytocin, which have shown therapeutic promise in early trials [Chahrour *et al.* 2016, Bernaerts *et al.* 2020]. For example, animal models have been instrumental in elucidating the potential benefits of oxytocin for ASD individuals. Studies involving rodent models have demonstrated that oxytocin administration can enhance social interactions and reduce repetitive behaviors [Teng *et al.* 2013, Szabó *et al.* 2024]. Thus, while recognizing the limitations of rodent models, it is essential to highlight their unique advantages in studying the biological basis of ASD, potentially guiding future therapies. Integrating new methodologies and models could help connect preclinical findings with clinical applications, facilitating the translation of insights from animal research to human ASD.

Three criteria are generally used to validate an animal model: construct validity, face validity, and predictive validity [Willner 1986, Crawley 2004]. Construct validity requires that the cause of the behavioral symptoms in the animal model corresponds to the etiological factors affecting ASD occurrence in humans (e.g., a genetic mutation, neuroanatomical abnormality, or environmental factor implicated in ASD). In this context, rodent models offer valuable tools to understand the role of genetic and environmental factors in producing specific symptoms of autism. Face validity requires that the behavioral abnormalities detectable in animal models resemble the specific behavioral disorders affecting human patients, such as social deficits and repetitive behaviors that define ASD. Diagnosis of ASD is made only by behavioral symptoms. Therefore, behavioral tests are used to assess face validity in animal models. Predictive validity requires that the therapy or treatment that helps to cure the disease's symptoms in humans would alleviate the behavioral abnormalities in animals (e.g., improving social deficits or reducing repetitive behaviors). As ASD is currently untreatable, predictive validity cannot yet be determined in animal models of ASD [Crawley 2004, Ellegood and Crawley 2015].

Here, we summarize the literature regarding current research trends utilizing rodent models to investigate the etiology, pathophysiology, and potential therapeutic interventions for ASD.

Rodent models to study the multifactorial origin of ASD

Rodent models have long been at the forefront of research into ASD and other neurodevelopmental disorders. These models, typically involving mice and rats, offer valuable insights into the etiology and neuropathogenesis of ASD due to their genetic and neurobiological similarities with humans. Using rodent models, researchers can study the underlying mechanisms of ASD, including genetic factors, neural circuitry, and behavioral phenotypes. Additionally, rodent models provide a platform for investigating potential therapeutic interventions and exploring the developmental trajectories of ASD.

Rodent models of ASD genetics

Recently, rodent models have been widely employed to investigate the genetic alterations associated with autism development, including gene knock-out (KO) models or knock-in (KI) humanized mice. Researchers can study the associated neurobiological alterations and the resulting behavior by inducing targeted genetic mutations in mice. Those models contributed to understanding the genetic bases of ASD by allowing the identification of critical molecular pathways and neural circuits involved. For instance, the SHANK3 mutation appears in a relatively large number of autism cases in humans [Patel *et al.* 2018]. Mutations occurring in the homologous mouse genes have been generated in many KO models [Silverman *et al.* 2010], demonstrating that mice carrying Shank3 gene deletions exhibit not only self-injurious repetitive grooming and deficits in social interactions [Peça *et al.* 2011], thus mirroring ASD symptomatology but also neuroanatomical alterations [Guo *et al.* 2019]. Studying these mice provides insights into the role of Shank3 in synaptic function and neural circuitry, contributing to our understanding of how disruptions in this specific gene can lead to autism-related behaviors.

Additionally, Shank3 mutant mice are a model for exploring potential therapeutic interventions targeting synaptic dysfunction in autism [Peça *et al.* 2011, Yoo *et al.* 2019]. The following example is Mecp2 KO mice that lack the functional Mecp2 protein, leading to behavioral and neurobiological changes reminiscent of Rett syndrome [Nagarajan *et al.* 2006]. Another known genetic causes of ASD are mutations in the Fmr1 gene, which lead to Fragile X syndrome. Fmr1 KO mice, lacking the Fmr1 gene, exhibit behavioral and neurobiological abnormalities similar to those seen in individuals with Fragile X syndrome and autism. These mice display deficits in social interactions, cognitive flexibility, and sensory processing. Research on Fmr1 KO mice reveals the essential molecular and synaptic disruptions caused by the absence of the Fmr1 gene, laying the foundation to develop targeted therapies for individuals with Fragile X syndrome and related autism spectrum disorders [Spencer *et al.* 2005, Borreca *et al.* 2023].

Rodent models of environmental factors associated with ASD

On the other hand, animal models exposed to environmental factors are an essential tool for studying the influence of the environment on gene expression, epigenetic processes, and their contribution to autistic behavior. Suboptimal prenatal environments, such as exposure to toxicological and immunological insults, are known to increase the risk of autism in human offspring and induce ASD-like behaviors in animal models. Many rodent models have been developed, including mice and rats prenatally exposed to the anticonvulsant valproic acid (VPA), to model prenatal exposure and its effects on brain development and functions. Offspring exposed to VPA during prenatal development exhibit autism-like behaviors, including anxiety,

repetitive actions, social interaction deficits, and memory impairments [Mehta *et al.* 2011, Taheri *et al.* 2024]. Furthermore, the maternal immune activation (MIA) model has been developed to investigate the effects of maternal infections on ASD occurrence. The maternal immune system is strongly connected with fetal brain development, and its inflammatory responses may be very harmful in terms of cortical layer development and functions [Baines *et al.* 2020]. It was demonstrated that offspring conceived by pregnant dam infected with a virus or injected intraperitoneal with synthetic double-stranded RNA [poly(I: C)], a mimic of viral genome, display behavioral symptoms reminiscent of ASD: social deficit, abnormal communication, and repetitive behaviors [Malkova *et al.* 2012]. This model allows researchers to investigate the neurobiological consequences of prenatal immune activation, offering insights into the potential role of immune-related factors in developing autism [Carbone *et al.* 2023].

Epidemiological evidence shows that advanced parental age is a risk factor in the development of ASD [Yip *et al.* 2006, Janecka *et al.* 2019]. Similarly, rodent models of advanced paternal and maternal age have demonstrated that parental age affects offspring neurodevelopment and behaviors resembling the core symptoms of ASD [Sampino *et al.* 2014, 2017, Mai *et al.* 2022]. For instance, offspring of older mothers have altered cognitive functions, such as memory, learning defects, and cognitive inflexibility [Ziętek and Sampino 2023]. On the other hand, it has been reported that offspring of aged fathers show increased distress response after isolation from the nest, emitting an increased rate of ultrasound of vocalization (USV) calls at a higher sound amplitude compared to pups derived from younger fathers, decreased sociability, increased grooming activity, and anxiety-like responses in adulthood, which was partially transmitted to the next generation [Sampino *et al.* 2014]. In the other study, mouse offspring of older males did not exhibit social preference behavior, suggesting a social behavior deficit [Tanaka *et al.* 2022]. Conversely, another study showed that advanced paternal age reduced the number and duration of syllables and altered the syllable composition. Pups born to aged fathers exhibited more divergent vocal patterns with a limited repertoire. Thus, the study indicates that advanced paternal age significantly affects offspring's vocal development [Mai *et al.* 2022].

The BTBR mouse as a model of idiopathic autism

The BTBR T^{+} Itpr3^{tf}/J (BTBR) inbred strain displays strong behavioral face validity to ASD symptoms, and it is recognized as a model of idiopathic autism with genetic origin. BTBR pups show an unusual repertoire of ultrasound vocalization when socially isolated [Wöhr *et al.* 2011], while adult BTBR exhibit altered courtship vocalizations [Scattoni *et al.* 2008], reduced sociability, and high levels of repetitive self-grooming [McFarlane *et al.* 2008], high anxiety, defective short-term memory, and/or attention [Chao *et al.* 2018] therefore its behavioral traits resembling core ASD symptoms. Moreover, BTBR mice display neuroanatomical abnormalities, including disrupted axonal networks with the absence of the corpus callosum and a severe reduction

of the hippocampal commissure [Wahlsten *et al.* 2003]. Widespread abnormalities in neuronal structure and connectivity have been observed, particularly changes in the shape and position of different brain structures, including the hippocampus and amygdala, a decreased size of frontal and parietal-temporal lobes, and an increase in the size of the cerebellum [Mercier *et al.* 2012, Ellegood *et al.* 2015], as well as smaller cortical thickness in dorsal and lateral cortices compared to the C57BL6 control strain have been reported [Faraji *et al.* 2018]. Furthermore, immune dysregulation has been widely observed in humans with ASD [Hsiao 2013, Robinson-Agramonte *et al.* 2022]. The immune system of the BTBR mice exhibits a marked proinflammatory profile [Heo *et al.* 2011], including increases in pro-inflammatory cytokines such as IL-1β, TNFα and IL-6, and chemokines such as MCP-1 in plasma/sera, cerebral spinal fluid (CSF) and brain tissue [Careaga *et al.* 2015]. Additionally, BTBR mice exhibit multiple systemic dysregulations, such as gastrointestinal abnormalities [Golubeva *et al.* 2017], circadian disruptions [Vijaya Shankara *et al.* 2022], and altered eating behaviors [Tordoff and Ellis 2013], paralleling human ASD comorbidities.

Overall, social deficits, altered vocalization patterns, and increases in stereotypic/repetitive behaviors in BTBR mice extensively mirror the breadth of behavioral deficits representative of the domain core symptoms of ASD, thus representing a valuable tool to investigate ASD etiology and the biological mechanisms underlying its pathogenesis.

Rodent models of gene-environment (G x E) interactions

Growing evidence indicates that ASD results from a combination of genetic vulnerability and environmental factors interacting during critical prenatal developmental windows, which lead to altered fetal brain development and the manifestation of behavioral symptoms later in postnatal life [Jones *et al.* 2014, Esposito *et al.* 2018, Emberti Gialloreti *et al.* 2019]. Studying gene-environment interaction in human populations is challenging due to the high degree of genetic variability and the presence of numerous confounding factors. Animal models help dissect the specific contributions of genes and environmental insults in disease development. In this context, KO and environment-induced mouse models of ASD are countless. However, few studies have investigated gene-environment interactions in the context of ASD etiology [Tordjman *et al.* 2014]. For instance, Cntnap2 KO mice (genetic factor, G) exposed to VPA during embryonic development (environmental factor, E) have been employed to investigate the specific vulnerability of mice carrying an autism-linked genetic variant to the effects of prenatal VPA exposure. The results showed that the social deficits observed in the respective Cntnap2-KO and VPA models improved in the G × E model when both factors co-occurred.

Moreover, the Cntnap2-KO × VPA interaction did not significantly change repetitive self-grooming or hyperactivity behaviors, although each factor induced these behavioral symptoms when provided independently [Kim *et al.* 2019]. These

findings suggest that the interaction of two risk factors does not always aggravate ASD symptoms but can also alleviate them, which may be vital to understanding individual differences in behavioral phenotypes and symptom severity. Another study testing G x E interaction in the context of autism was conducted by Smith et al., which investigated the effects of MIA on IL-6 KO and wild-type mice. The results showed that maternal poly(I: C) treatment does not affect social interaction and open-field behavior of the IL6-KO offspring, thus demonstrating the importance of IL-6 in mediating the adverse effects of MIA in mice [Smith *et al.* 2007]. A similar study investigated the effects of MIA on two different genetic backgrounds, the BTBR ASD model and the C57BL6 control. The results showed that MIA increases vocalizations, impairs social behaviors, and increases repetitive behavior in the marble burying test in both strains. However, many of these effects were substantially more robust in BTBR mice, suggesting that MIA leads to behavioral changes in offspring in a strain-dependent manner [Schwartzer *et al.* 2013].

Furthermore, another study evaluated the effect of early-life stress on the BTBR and C57BL6 genetic backgrounds, showing that early postnatal stress affects exploratory and social behavior and locomotor activity in BTBR and C57BL6 at juvenile and adolescent ages. However, these effects were sex- and strain-dependent. Unexpectedly, these effects did not enhance the manifestations of autism-like behavior in BTBR mice [Reshetnikov *et al.* 2021]. Moreover, another study aimed to determine if an enriched environment could alleviate ASD-like symptoms in Shank3 complete KO mice. The findings revealed that contrary to previous studies involving other mouse models of ASD, environmental enrichment had minimal impact on behavior. Specifically, enriched rearing did not improve repetitive behaviors, anxiety-like behavior, or motor performance. These results suggest that a one-size-fits-all approach to behavioral intervention for ASD may not be practical for all genetic mutations [Hulbert *et al.* 2018].

Various mechanisms have been proposed through which environmental factors might contribute to autistic behaviors and clinical variants of ASD, including inflammation, immune activation, and oxidative stress. However, the relevance of these factors may not be directly causal but somewhat influenced by genetic factors. Therefore, it is crucial to investigate when, how, and to what extent ASD risk factors interact with specific genetic mutations to alter neurodevelopmental processes and determine disease occurrence.

Methodological approaches for analysis of autism-like behaviors in rodents

Understanding ASD through animal models relies on well-established behavioral tests that aim to replicate core symptoms, including social deficits, communication challenges, and repetitive behaviors.

Social interaction tests are fundamental in evaluating social behavior. These assays assess the subject's interaction with another rodent, typically in a three-chambered

apparatus allowing for social preference tests. The social interaction test provides insights into social motivation and social memory by measuring the amount of time spent with another animal of the same species compared to an inanimate object or empty space. This test has high construct validity for ASD models, as it captures one of the primary social deficits observed in the disorder. However, it has limited scope in replicating the full spectrum of human social behavior. Furthermore, the results may be influenced by factors such as strain-specific sociability, environmental stress, or handling, which can add variability to outcomes [Rein *et al.* 2020].

Rodents communicate through ultrasonic vocalizations (USV). These vocalizations can be evaluated to study communication deficits that parallel the language difficulties often present in ASD. USV assays are especially useful for studying communication during early developmental stages. Variations in call frequency, length, and structure can provide clues about deficits in communication behaviors in ASD models. Nevertheless, rodent USVs do not precisely translate to human speech, limiting direct relevance. Furthermore, environmental conditions and the age or stress levels of the test animals may affect USV, complicating the interpretation of results [Caruso *et al.* 2020].

Repetitive behaviors, another core behavioral symptom of ASD, are often evaluated through self-grooming, marble-burying, and digging tests. These behaviors reflect compulsive or repetitive actions akin to those seen in individuals with ASD. Tests like self-grooming and marble-burying allow researchers to observe and quantify repetitive actions in a controlled environment, providing face validity for ASD models. On the other hand, the repetitiveness in rodent models may differ in nature and intensity from that observed in ASD. Additionally, repetitive behaviors may be influenced by factors unrelated to ASD, such as anxiety, making it essential to interpret findings within a broader context of behavioral tests [Silverman *et al.* 2010, Takumi *et al.* 2020].

Concluding remarks and perspectives

ASD remains a complex neurodevelopmental condition with multifactorial origins involving both genetic predispositions and environmental influences. Rodent models, particularly mice, have proven invaluable for studying the genetic, neurobiological, and behavioral facets of ASD. These models offer a platform to investigate specific genetic mutations, such as Shank3, Mecp2, and Fmr1, associated with ASD-like behaviors, enabling us to dissect the underlying molecular pathways and neural circuits involved in the disorder. Likewise, environmental models, such as prenatal exposure to VPA and MIA, provide insights into how early-life environmental factors influence ASD pathology. However, despite the significant contributions of rodent models, their translational relevance to human ASD is not without limitations. However, these models exhibit face and construct validity in reproducing many behavioral and neurobiological aspects of ASD. However, due to the lack of effective treatments for

ASD, animal models may help to develop new therapies. Furthermore, while rodent models successfully replicate specific core ASD symptoms, such as social deficits and repetitive behaviors, the complex social and cognitive abilities of humans present inherent limitations in fully capturing the breadth of ASD phenotypes (i.e., theory of mind).

Future research should focus on refining rodent models to better encompass the heterogeneity of ASD. Integrating models of G x E interactions, as shown by studies combining genetic knockouts with environmental insults, offers a promising tool to capture the multifactorial nature of ASD. Specifically, using genetically diverse mouse strains further emphasizes the importance of considering individual genetic backgrounds in ASD research. This approach may yield more personalized therapeutic strategies in the future.

Moreover, emerging techniques such as CRISPR-Cas9 genome editing and advanced imaging technologies are poised to enhance the precision and depth of investigations into the neurobiological underpinnings of ASD. These tools and advances in transcriptomics and proteomics could lead to identifying novel molecular targets for intervention.

Finally, developing more humanized animal models and alternative models, such as organoids derived from human stem cells, may bridge the gap between preclinical findings and clinical applications. These approaches will likely provide a more precise understanding of the dynamic interplay between genetic risk factors and environmental exposures that shape ASD development.

In conclusion, rodent models continue to play an indispensable role in unraveling the etiology and pathophysiology of ASD. As our understanding of the genetic and environmental contributors to ASD grows, our capacity to develop tailored therapeutic interventions that address the specific needs of individuals on the autism spectrum will rise. By advancing the methodology and conceptual frameworks in ASD research, the field moves closer to translating preclinical discoveries into practical clinical solutions.

REFERENCES

1. AMERICAN PSYCHIATRIC ASSOCIATION, 2013 - Diagnostic and Statistical Manual of Mental Disorders. ***American Psychiatric Association***.
2. BAILEY A., LE COUTEUR A., GOTTESMAN I., BOLTON P., SIMONOFF E., YUZDA E., RUTTER M., 1995 - Autism as a strongly genetic disorder: evidence from a British twin study. ***Psychological Medicine*** 25, 1, 63-77.
3. BAINES K.J., HILLIER D.M., HADDAD F.L., RAJAKUMAR N., SCHMID S., RENAUD S.J., 2020 - Maternal immune activation alters fetal brain development and enhances proliferation of neural precursor cells in rats. ***Frontiers in Immunology*** 11, 1145.
4. BERG E.L., SILVERMAN J.L., 2022 - Animal models of autism. ***The Neuroscience of Autism*** 157-196.

5. BERNAERTS S., BOETS B., BOSMANS G., STEYAERT J., ALAERTS K., 2020 - Behavioral effects of multiple-dose oxytocin treatment in autism: a randomized, placebo-controlled trial with long-term follow-up. ***Molecular Autism*** 11, 1-6.
6. BÖLTE S., GIRDLER S., MARSCHIK P.B., 2019 - The contribution of environmental exposure to the etiology of autism spectrum disorder. ***Cellular and Molecular Life Sciences*** 76, 7, 1275-1297.
7. BORRECA A., DE LUCA M., FERRANTE A., BOUSSADIA Z., PIGNATARO A., MARTIRE A., AMMASSARI-TEULE M., 2023 - Fmr1-KO mice failure to detect object novelty associates with a post-test decrease of structural and synaptic plasticity upstream of the hippocampus. ***Scientific Reports*** 13, 1, 755.
8. CARBONE E., BUZZELLI V., MANDUCA A., LEONE S., RAVA A., TREZZA V., 2023 - Maternal immune activation induced by prenatal lipopolysaccharide exposure leads to long-lasting autistic-like social, cognitive, and immune alterations in male Wistar rats. ***International Journal of Molecular Sciences*** 24, 4, 3920.
9. CAREAGA M., SCHWARTZER J., ASHWOOD P., 2015 - Inflammatory profiles in the BTBR mouse: how relevant are they to autism spectrum disorders? ***Brain, Behavior, and Immunity*** 43, 11-16.
10. CARUSO A., RICCERI L., SCATTONI M.L., 2020 - Ultrasonic vocalizations as a fundamental tool for early and adult behavioral phenotyping of Autism Spectrum Disorder rodent models. ***Neuroscience & Biobehavioral Reviews*** 116, 31-43.
11. CHADMAN K.K., 2017 - Animal models for autism in 2017 and the consequential implications to drug discovery. ***Expert Opinion on Drug Discovery*** 12, 12, 1187-1194.
12. CHAHROUR M., O'ROAK B.J., SANTINI E., SAMACO R.C., KLEIMAN R.J., MAZINI M.C., 2016 - Current Perspectives in Autism Spectrum Disorder: From Genes to Therapy. ***The Journal of Neuroscience*** 36, 45, 11402-11410.
13. CHAO O.Y., YUNGER R., YANG Y.M., 2018 - Behavioral assessments of BTBR T+Itpr3tf/J mice by tests of object attention and elevated open platform: implications for an animal model of psychiatric comorbidity in autism. ***Behavioural Brain Research*** 347, 140-147.
14. CRAWLEY J.N., 2004 - Designing mouse behavioral tasks relevant to autistic-like behaviors. ***Mental Retardation and Developmental Disabilities Research Reviews*** 10, 4, 248-258.
15. CROEN L.A., QIAN Y., ASHWOOD P., ZERBO O., SCHENDEL D., PINTO-MARTIN J., DANIELE FALLIN M., LEVY S., SCHIEVE L.A., YEARGIN-ALLSOPP M., SABOURIN K.R., AMES J.L., 2019 - Infection and fever in pregnancy and autism spectrum disorders: findings from the Study to Explore Early Development. ***Autism Research*** 12,10, 1551-1561.
16. ELLEGOOD J., ANAGNOSTOU E., BABINEAU B.A., CRAWLEY J.N., LIN L., GENESTINE M., DICICCO-BLOOM E., LAI J.K.Y., FOSTER J.A., PEÑAGARIKANO O., GESCHWIND D.H., PACEY L.K., HAMPSON D.R., LALIBERTÉ C.L., MILLS A.A., TAM E., OSBORNE L.R., KOUSER M., ESPINOSA-BECERRA F., XUAN Z., POWELL C.M., RAZNAHAN A., ROBINS D.M., NAKAI N., NAKATANI J., TAKUMI T., VAN EEDE M.C., KERR T.M., MULLER C., BLAKELY R.D., VEENSTRA-VANDERWEELE J., HENKELMAN R.M., LERCH J.P., 2015 - Clustering autism: using neuroanatomical differences in 26 mouse models to gain insight into the heterogeneity. ***Molecular Psychiatry*** 20, 1, 118-125.
17. ELLEGOOD J., CRAWLEY J.N., 2015 - Behavioral and neuroanatomical phenotypes in mouse models of autism. ***Neurotherapeutics*** 12, 3, 521-533.
18. EMBERTI GIALLORETI L., MAZZONE L., BENVENUTO A., FASANO A., ALCON A.G., KRANEVELD A., MOAVERO R., RAZ R., RICCIO M.P., SIRACUSANO M., ZACHOR D.A., MARINI M., CURATOLO P., 2019 - Risk and protective environmental factors associated with autism spectrum disorder: evidence-based principles and recommendations. ***Journal of Clinical Medicine*** 8, 2, 217.

19. ESPOSITO G., AZHARI A., BORELLI J.L., 2018 - Gene × environment interaction in developmental disorders: where do we stand and what's next? ***Frontiers in Psychology*** 9, 2036.
20. FARAJI J., KARIMI M., LAWRENCE C., MOHAJERANI M.H., METZ G.A.S., 2018 - Non-diagnostic symptoms in a mouse model of autism about neuroanatomy: the BTBR strain reinvestigated. ***Translational Psychiatry*** 8, 1, 234.
21. GOLUBEVA A.V., JOYCE S.A., MOLONEY G., BUROKAS A., SHERWIN E., ARBOLEYA S., FLYNN I., KHOCHANSKIY D., MOYA-PÉREZ A., PETERSON V., REA K., MURPHY K., MAKAROVA O., BURAVKOV S., HYLAND N.P., STANTON C., CLARKE G., GAHAN C.G.M., DINAN T.G., CRYAN J.F., 2017 - Microbiota-related changes in bile acid & tryptophan metabolism are associated with gastrointestinal dysfunction in a mouse model of autism. ***EBioMedicine*** 24, 166-178.
22. GUO B., CHEN J., CHEN Q., REN K., FENG D., MAO H., YAO H., YANG J., LIU H., LIU Y., JIA F., QI C., LYNN-JONES T., HU H., FU Z., FENG G., WANG W., WU S., 2019 - Anterior cingulate cortex dysfunction underlies social deficits in Shank3 mutant mice. ***Nature Neuroscience*** 22, 8, 1223-1234.
23. HEO Y., ZHANG Y., GAO D., MILLER V.M., LAWRENCE D.A., 2011 - Aberrant immune responses in a mouse with behavioral disorders. ***PLoS ONE*** 6, 7, e20912.
24. HSIAO E.Y., 2013 - Immune dysregulation in autism spectrum disorder. In International Review of Neurobiology, ***Elsevier*** 113, 269-302
25. HULBERT S.W., BEY A.L., JIANG Y., 2018 - Environmental enrichment has minimal effects on behavior in the Shank3 complete knockout model of autism spectrum disorder. ***Brain and Behavior*** 8, 11, e01107.
26. HULTMAN C.M., SANDIN S., LEVINE S.Z., LICHTENSTEIN P., REICHENBERG A., 2011 - Advancing paternal age and risk of autism: new evidence from a population-based study and a meta-analysis of epidemiological studies. ***Molecular Psychiatry*** 16, 12, 1203-1212.
27. JANECKA M., HANSEN S.N., MODABBERNIA A., BROWNE H.A., BUXBAUM J.D., SCHENDEL D.E., REICHENBERG A., PARNER E.T., GRICE D.E., 2019 - Parental age and differential estimates of risk for neuropsychiatric disorders: findings from the Danish Birth Cohort. ***Journal of the American Academy of Child & Adolescent Psychiatry***. 58,6, 618-627.
28. JONES E.J.H., GLIGA T., BEDFORD R., CHARMAN T., JOHNSON M.H., 2014 - Developmental pathways to autism: a review of prospective studies of infants at risk. **Neuroscience & Biobehavioral Reviews** 39, 1-33.
29. KATZ J., REICHENBERG A., KOLEVZON A., 2021 - Prenatal and perinatal metabolic risk factors for autism: a review and integration of findings from population-based studies. ***Current Opinion in Psychiatry*** 34, 2, 94-104.
30. KIM J.W., PARK K., KANG R.J., GONZALES E.L., OH H.A., SEUNG H., KO M.J., CHEONG J.H., CHUNG C., SHIN C.Y., 2019 - Gene-environment interaction counterbalances social impairment in mouse models of autism. ***Scientific Reports*** 9, 1, 11490.
31. KLEI L., SANDERS S.J., MURTHA M.T., HUS V., LOWE J.K., WILLSEY A.J., MORENO-DE-LUCA D., YU T.W., FOMBONNE E., GESCHWIND D., GRICE D.E., LEDBETTER D.H., LORD C., MANE S.M., MARTIN C.L., MARTIN D.M., MORROW E.M., WALSH C.A., MELHEM N.M., CHASTE P., SUTCLIFFE J.S., STATE M.W., COOK E.H., ROEDER K., DEVLIN B., 2012 - Common genetic variants, acting additively, are a major source of risk for autism. ***Molecular Autism*** 3, 1, 9.
32. KOLEVZON A., GROSS R., REICHENBERG A., 2007 - Prenatal and perinatal risk factors for autism: a review and integration of findings. ***Archives of Pediatrics & Adolescent Medicine*** 161, 4, 326.

33. MAI L., INADA H., KIMURA R., KANNO K., MATSUDA T., TACHIBANA R.O., TUCCI V., KOMAKI F., HIROI N., OSUMI N., 2022 - Advanced paternal age diversifies individual trajectories of vocalization patterns in neonatal mice. ***iScience*** 25, 8, 104834.
34. MALKOVA N.V., YU C.Z., HSIAO E.Y., MOORE M.J., PATTERSON P.H., 2012 - Maternal immune activation yields offspring displaying mouse versions of the three core symptoms of autism. ***Brain, Behavior, and Immunity*** 26, 4, 607-616.
35. McCRACKEN J.T., ANAGNOSTOU E., ARANGO C., DAWSON G., FARCHIONE T., MANTUA V., MCPARTLAND J., MURPHY D., PANDINA G., VEENSTRA-VANDERWEELE J., 2021 - Drug development for Autism Spectrum Disorder (ASD): Progress, challenges, and future directions. ***European Neuropsychopharmacology*** 48, 3-31.
36. MCFARLANE H.G., KUSEK G.K., YANG M., PHOENIX J.L., BOLIVAR V.J., CRAWLEY J.N., 2008 - Autism-like behavioral phenotypes in BTBR T+tf/J mice. ***Genes, Brain, and Behavior*** 7, 2, 152-163.
37. MEHTA M.V., GANDAL M.J., SIEGEL S.J., 2011 - mGluR5-antagonist mediated reversal of elevated stereotyped, repetitive behaviors in the VPA model of autism. ***PLoS ONE*** 6, 10, e26077.
38. MERCIER F., KWON Y.C., DOUET V., 2012 - Hippocampus/amygdala alterations, loss of heparan sulfates, fractones and ventricle wall reduction in adult BTBR T+tf/J mice, animal model for autism. ***Neuroscience Letters*** 506, 2, 208-213.
39. MÖHRLE D., FERNÁNDEZ M., PEÑAGARIKANO O., FRICK A., ALLMAN B., SCHMID S., 2020 - What we can learn from a genetic rodent model about autism. ***Neuroscience & Biobehavioral Reviews*** 109, 29-53.
40. NAGARAJAN R., HOGART A., GWYE Y., MARTIN M.R., LASALLE J.M., 2006 - Reduced MeCP2 expression is frequent in autism frontal cortex and correlates with aberrant MECP2 promoter methylation. ***Epigenetics*** 1, 4, 172-182.
41. ORNOY A., ECHEFU B., BECKER M., 2024 - Animal Models of Autistic-like Behavior in Rodents: A Scoping Review and Call for a Comprehensive Scoring System. ***International Journal of Molecular Sciences*** 25, 19, 10469.
42. PATEL J., LUKKES J.L., SHEKHAR A., 2018 - Overview of genetic models of autism spectrum disorders. ***In Progress in Brain Research***, 241, 1-36. Elsevier.
43. PEÇA J., FELICIANO C., TING J.T., WANG W., WELLS M.F., VENKATRAMAN T.N., LASCOLA C.D., FU Z., FENG G., 2011 - Shank3 mutant mice display autistic-like behaviours and striatal dysfunction. ***Nature*** 472, 7344, 437-442.
44. PINTO D., PAGNAMENTA A.T., KLEI L., ANNEY R., MERICO D., REGAN R., CONROY J., MAGALHAES T.R., CORREIA C., ABRAHAMS B.S., ALMEIDA J., BACCHELLI E., BADER G.D., BAILEY A.J., BAIRD G., BATTAGLIA A., BERNEY T., BOLSHAKOVA N., BÖLTE S., BOLTON P.F., BOURGERON T., BRENNAN S., BRIAN J., BRYSON S.E., CARSON A.R., CASALLO G., CASEY J., CHUNG B.H.Y., COCHRANE L., CORSELLO C., CRAWFORD E.L., CROSSETT A., CYTRYNBAUM C., DAWSON G., DE JONGE M., DELORME R., DRMIC I., DUKETIS E., DUQUE F., ESTES A., FARRAR P., FERNANDEZ B.A., FOLSTEIN S.E., FOMBONNE E., FREITAG C.M., GILBERT C., GILLBERG C., GLESSNER J.T., GOLDBERG J., GREEN A., GREEN J., GUTER S.J., HAKONARSON H., HERON E.A., HILL M., HOLT R., HOWE J.L., HUGHES G., HUS V., IGLIOZZI R., KIM C., KLAUCK S.M., KOLEVZON A., KORVATSKA O., KUSTANOVICH V., LAJONCHERE C.M., LAMB J.A., LASKAWIEC M., LEBOYER M., LE COUTEUR A., LEVENTHAL B.L., LIONEL A.C., LIU X.Q., LORD C., LOTSPEICH L., LUND S.C., MAESTRINI E., MAHONEY W., MANTOULAN C.R., MARSHALL C.R., MCCONACHIE H., MCDOUGLE C.J., MCGRATH J., MCMANON W.M., MERIKANGAS K.R., MIGITA O., MINSHEW N.J., MIRZA G.K., MUNSON J., NELSON S.F., NOAKES C., NOOR A., NYGREN G., OLIVEIRA K., PAPANIKOLAOU J.R., PARR J., PARRINI B., PATON A., PICKLES A., PILORGE M., PIVEN J., PONTING C.P., POSEY D.J., POUSTKA

A., POUSTKA F., PRASAD A., RAGOUSSIS J., RENSHAW K., RICKABY J., ROBERTS W., ROEDER K., ROGE B., RUTTER M., BIERUT L.J., RICE J.P., SALT J., SANSOM K., SATO D., SEGURADO A.F., SEQUEIRA L., SENMAN N., SHAH N., SHEFFIELD V.C., SOORYA L., SOUSA I., STEIN O., SYKES N., STOPPIONI V., STRAWBRIDGE R., TANCREDI K., TANSEY B., THIRUVAHINDRAPDURAM A.P., THOMPSON A.P., THOMSON S., TRYFON A., TSIANTIS J., VAN ENGELAND H., VINCENT J.B., VOLKMAR F., WALLACE S., WANG K., WANG Z., WASSINK T.H., WEBBER C., WEKSBERG R., WING K., WITTEMEYER K., WOOD S., WU J., YASPAN B.L., ZURAWIECKI D., ZWAIGENBAUM L., BUXBAUM J.D., CANTOR R.M., COOK E.H., COON H., CUCCARO M.L., DEVLIN B., ENNIS S., GALLAGHER L., GESCHWIND D.H., GILL M., HAINES J., HALLMAYER J., MILLER J., MONACO A.P., NURNBERGER JR J.I., PATERSON A.D., PERICAK-VANCE M.A., SCHELLENBERG G.D., SZATMARI P., VICENTE A.M., VIELAND V.J., WIJSMAN E.M., SCHERER S.W., SUTCLIFFE J.S., BETANCUR C., 2010 - Functional impact of global rare copy number variation in autism spectrum disorders. ***Nature*** 466, 7304, 368-372.

45. REIN B., MA K., YAN Z., 2020 - A standardized social preference protocol for measuring social deficits in mouse models of autism. ***Nature Protocols*** 15, 10, 3464-3477.
46. RESHETNIKOV V.V., AYRIYANTS K.A., RYABUSHKINA Y.A., SOZONOV N.G., BONDAR N.P., 2021 - Sex-specific behavioral and structural alterations caused by early-life stress in C57BL/6 and BTBR mice. ***Behavioural Brain Research*** 414, 113489.
47. ROBINSON-AGRAMONTE M.D.L.A., NORIS GARCÍA E., FRAGA GUERRA J., VEGA HURTADO Y., ANTONUCCI N., SEMPRÚN-HERNÁNDEZ N., SCHULTZ S., SINISCALCO D., 2022 - Immune dysregulation in autism spectrum disorder: What do we know about it? ***International Journal of Molecular Sciences*** 23, 6, 3033.
48. SAMPINO S., JUSZCZAK G.R., ZACCHINI F., SWIERGIEL A.H., MODLINSKI J.A., LOI P., PTAK G.E., 2014 - Grand-paternal age and the development of autism-like symptoms in mice progeny. ***Translational Psychiatry*** 4, 4, e386.
49. SAMPINO S., STANKIEWICZ A.M., ZACCHINI F., GOSCIK J., SZOSTAK A., SWIERGIEL A.H., DRAGO G., MODLINSKI J.A., PTAK G.E., 2017 - Pregnancy at advanced maternal age affects behavior and hippocampal gene expression in mouse offspring. ***The Journals of Gerontology: Series A*** 72, 11, 1465-1473.
50. SCATTONI M.L., GANDHY S.U., RICCERI L., CRAWLEY J.N., 2008 - Unusual repertoire of vocalizations in the BTBR T+tf/J mouse model of autism. ***PLoS ONE*** 3, 8, e3067.
51. SCHWARTZER J.J., CAREAGA M., ONORE C.E., RUSHAKOFF J.A., BERMAN R.F., ASHWOOD P., 2013 - Maternal immune activation and strain specific interactions in the development of autism-like behaviors in mice. ***Translational Psychiatry*** 3, 3, e240.
52. SILVERMAN J.L., YANG M., LORD C., CRAWLEY J.N., 2010 - Behavioural phenotyping assays for mouse models of autism. ***Nature Reviews Neuroscience*** 11, 7, 490-502.
53. SILVERMAN J.L., THURM A., ETHRIDGE S.B., SOLLER M.M, PETKOVA S.P., ABEL T., BAUMAN M.D., BRODKIN E.S., HARONY-NICOLAS H., WÖHR M., HALLADAY A., 2022 - Reconsidering animal models used to study autism spectrum disorder: Current state and optimizing future. ***Genes, Brain and Behavior*** 21, 5, e12803.
54. SMITH S.E.P., LI J., GARBETT K., MIRNICS K., PATTERSON P.H., 2007 - Maternal immune activation alters fetal brain development through interleukin-6. ***Journal of Neuroscience*** 27, 40, 10695-10702.
55. SPENCER C.M., ALEKSEYENKO O., SERYSHEVA E., YUVA-PAYLOR L.A., PAYLOR R., 2005 - Altered anxiety-related and social behaviors in the Fmr1 knockout mouse model of fragile X syndrome. ***Genes, Brain and Behavior*** 4, 7, 420-430.

56. SZABÓ J., MLYNÁR M., FEJEŠ A., RENCZÉS E., BORBÉLYOVÁ V., OSTATNÍKOVÁ D., CELEC T.P., 2024 - Intranasal oxytocin in a genetic animal model of autism. ***Molecular Psychiatry*** 29, 2, 342-347.
57. TAHERI F., JOUSHI S., ESMAEILPOUR K., EBRAHIMI M.N., TAHERIZADEH Z., TAHERI P., SHEIBANI V., 2024 - Transmission of behavioral and cognitive impairments across generations in rats subjected to prenatal valproic acid exposure. ***Birth Defects Research*** 116, 2, e2309.
58. TAKUMI T., TAMADA K., HATANAKA F., NAKAI N., BOLTON P.F., 2020 - Behavioral neuroscience of autism. ***Neuroscience & Biobehavioral Reviews*** 110, 60-76.
59. TANAKA M., SATO A., KOTAJIMA-MURAKAMI H., KASHII H., HAGINO Y., IDE S., IKEDA K., 2022 - Interaction between social behavior and paternal age in offspring of the same paternal mice. ***Neuropsychopharmacology Reports*** 42, 3, 343-346.
60. TENG B.L., NONNEMAN R.J., AGSTER K.L., NIKOLOVA V.D., DAVIS T.T., RIDDICK N.V., BAKER L.K., PEDERSEN C.A., JARSTFER M.B., MOY S.S, 2013 - Prosocial effects of oxytocin in two mouse models of autism spectrum disorders. ***Neuropharmacology*** 72, 187-196.
61. TORDJMAN S., SOMOGYI E., COULON N., KERMARREC S., COHEN D., BRONSARD G., BONNOT O., WEISMANN-ARCACHE C., BOTBOL M., LAUTH B., GINCHAT V., ROUBERTOUX P., BARBUROTH M., KOVESS V., GEOFFRAY M.M., XAVIER J., 2014 - Gene-environment interactions in autism spectrum disorders: Role of epigenetic mechanisms. ***Frontiers in Psychiatry*** 4, 5, 53.
62. TORDOFF M.G., ELLIS H.T., 2013 - Taste dysfunction in BTBR mice due to a mutation of Itpr3, the inositol triphosphate receptor 3 gene. ***Physiological Genomics*** 45, 18, 834-855.
63. VIJAYA SHANKARA J., HORSLEY K.G., CHENG N., RHO J.M., ANTLE M.C., 2022 - Circadian responses to light in the BTBR mouse. ***Journal of Biological Rhythms*** 37, 5, 498-515.
64. WAHLSTEN D., METTEN P., CRABBE J.C., 2003 - Survey of 21 inbred mouse strains in two laboratories reveals that BTBR T/+ tf/tf has severely reduced hippocampal commissure and absent corpus callosum. ***Brain Research*** 971, 1, 47-54.
65. WALDER D.J., LAPLANTE D.P., SOUSA-PIRES A., VERU F., BRUNET A., KING S., 2014 - Prenatal maternal stress predicts autism traits in 6½ year-old children: Project Ice Storm. ***Psychiatry Research*** 219, 2, 353-360.
66. WANG C., GENG H., LIU W., ZHANG G., 2017 - Prenatal, perinatal, and postnatal factors associated with autism: A meta-analysis. ***Medicine*** 96, 18, e6696.
67. WILLNER P., 1986 - Validation criteria for animal models of human mental disorders: Learned helplessness as a paradigm case. ***Progress in Neuro-Psychopharmacology and Biological Psychiatry*** 10, 6, 677-690.
68. WIŚNIOWIECKA-KOWALNIK B., NOWAKOWSKA B.A., 2019 - Genetics and epigenetics of autism spectrum disorder-current evidence in the field. ***Journal of Applied Genetics*** 60, 1, 37-47.
69. WÖHR M., ROULLET F.I., CRAWLEY J.N., 2011 - Reduced scent marking and ultrasonic vocalizations in the BTBR T+tf/J mouse model of autism. ***Genes, Brain and Behavior*** 10, 1, 35-43.
70. YIP B.H., PAWITAN Y., CZENE K., 2006 - Parental age and risk of childhood cancers: A population-based cohort study from Sweden. ***International Journal of Epidemiology*** 35, 6, 1495-1503.
71. YOO Y.E., YOO T., LEE S., LEE J., KIM D., HAN H.-M., BAE Y.C., KIM E., 2019 - Shank3 mice carrying the human Q321R mutation display enhanced self-grooming, abnormal electroencephalogram patterns, and suppressed neuronal excitability and seizure susceptibility. ***Frontiers in Molecular Neuroscience*** 12, 155.
72. YU T.W., CHAHROUR M.H., COULTER M.E., JIRALERSPONG S., OKAMURA-IKEDA K., ATAMAN B., SCHMITZ-ABE K., HARMIN D.A., ADLI M., MALIK A.N., D'GAMA A.M., LIM E.T., SANDERS S.J., MOCHIDA G.H., PARTLOW J.N., SUNU C.M., FELIE J.M., RODRIGUEZ J., NASIR R.H., WARE J., JOSEPH R.M., HILL R.S., KWAN B.Y., AL-SAFFAR M., MUKADDES

N.M., HASHMI A., BALKHY S., GASCON G.G., HISAMA F.M., LECLAIR E., PODURI A., ONER O., AL-SAAD S., AL-AWADI S.A., BASTAKI L., BEN-OMRAN T., TEEBI A.S., AL-GAZALI L., EAPEN V., STEVENS C.R., RAPPAPORT L., GABRIEL S.B., MARKIANOS K., STATE M.W., GREENBERG M.E., TANIGUCHI H., BRAVERMAN N.E., MORROW E.M., WALSH C.A., 2013 - Using whole-exome sequencing to identify inherited causes of autism. ***Neuron*** 77, 2, 259-273.

73. ZERBO O., QIAN Y., YOSHIDA C., GRETHER J.K., VAN DE WATER J., CROEN L.A., 2015 - Maternal infection during pregnancy and autism spectrum disorders. ***Journal of Autism and Developmental Disorders*** 45, 12, 4015-4025.
74. ZIĘTEK M.M., SAMPINO S., 2023 - Embryonic factors mediate the maternal age-induced programming of offspring postnatal behavior in mice. ***Biology of Reproduction*** 109, 1, 45-52.