World Journal of Biology Pharmacy and Health Sciences
eISSN: 2582-5542
Cross Ref DOI: 10.30574/wjbphs
Journal homepage: https://wjbphs.com/

(REVIEW ARTICLE)

Check for updates

Genetic mutations in mouse models for the comorbidity of autism spectrum disorders and epilepsy: A systematic review

Modibo Kouyate [1, 4, *], Modibo Sangare [1, 2], Oumar Sidibe [1], Mahamadou Diakite [2], Afif Ben-Mahmoud [3], Hyung-Goo Kim [3] and Mounia Abik [4]

[1] *Sciences and technology department, Graduate School of the USTTB (DSSTM), University of Sciences, Techniques and Technologies of Bamako (USTTB), Bamako, Mali.*
[2] *Immunogenetic Lab, University of Sciences, Techniques and Technologies of Bamako (USTTB), University of Sciences, Techniques and Technologies of Bamako (USTTB), Bamako, Mali.*
[3] *Neurological Disorders Research Center, Qatar Biomedical Research Institute, Hamad Bin Khalifa University, Doha, Qatar.*
[4] *Information Retrieval and Data Analytics department, School of Computer Science and Systems Analysis (ENSIAS), Rabat, Marocco.*

World Journal of Biology Pharmacy and Health Sciences, 2023, 16(03), 273-280

Publication history: Received on 09 November 2023; revised on 26 December 2023; accepted on 29 December 2023

Article DOI: https://doi.org/10.30574/wjbphs.2023.16.3.0517

Abstract

The complex relationship between autism spectrum disorders (ASD) and epilepsy is yet to be well established. The increased prevalence of epilepsy in ASD and vice versa has resulted in each disorder being considered a "comorbidity" of the other. Their common co-occurrence has been suggestive of certain shared neurobiological mechanisms or pathways. Specifically, the discovery of novel genetic mutations in the comorbidity has pointed to abnormalities in synaptic formation and function, which alter the balance between normal neuronal excitation and inhibition. Animal models in general, and mouse models using knockout, knock-in, or CRISPR-Cas9 technology, can be informative in sorting out the relationship in the comorbidity and gaining insights into its medical and behavioral complexities. As a result of the growing mechanistic information on the comorbidity, we can expect the development of genetic mutation and pathway-specific targeted treatments. A coordinated global effort between researchers on epilepsy and ASD is crucial, including conducting timely systematic reviews and meta-analyses on animal models. This study aimed to review the genetic mutations commonly used to develop mouse models for the comorbidity of ASD and epilepsy.

Keywords: ASD; Epilepsy; Mouse models; Knock-out; Knock-in; Comorbidity; Intellectual disability

1. Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by impaired social interaction, and deficits in verbal and nonverbal communication, as well as stereotyped behaviors and restricted interests. Individuals with ASD often experience challenges such as a lack of achievement in neurodevelopmental milestones, learning and memory deficits, poor motor skills, hyperactivity, hyperexcitability, altered responsiveness, aggression, anxiety, fear, sensory processing issues, altered sleep patterns, and gastrointestinal distress. ASD prevalence is higher in boys than in girls (Baron-Cohen et al., 2011). The male to female ratio in ASD has been reported as 4:1 (Loomes, Hull, & Mandy, 2017). However, recent research suggests that the ASD sex-bias favoring boys may be due to under- or misdiagnosis in girls. Girls often present distinct, subtler behavioral profiles compared to boys, due to a variety of compensatory behaviors and camouflaging of symptoms (Lai et al., 2015; Park et al., 2016; Rynkiewicz et al., 2016).

* Corresponding author: Modibo Kouyate; https://orcid.org/0009-0005-2260-6788

ASD and epilepsy are prevalent and pervasive lifelong disorders for which conventional medical interventions are either not readily available or need drastic improvements (Sundelin et al., 2016). ASD and epilepsy are heterogeneous human disorders that have various etiologies and pathogeneses. There is a considerable risk of frequent epilepsy in ASD, which results in increased morbidity and mortality (Besag FM and al 2017, Sundelin et al., 2016).

ASD represents a common co-morbidity in patients with epilepsy and vice versa. In other words, individuals with epileptic disorders are ten (10) times more likely to be diagnosed with ASD (Sundelin et al., 2016). Moreover, 30% of patients with ASD are concomitantly diagnosed with epilepsy, and another 30% develop epilepsy at some point in their lives (Clarke et al., 2005; Seidenberg et al., 2009; Tuchman & Rapin, 2002). Interestingly, the association between epilepsy and ASD has been diagnosed more often in girls than in boys (Tuchman et al., 2010b).The most significant predictors of ASD in patients with epilepsy are early onset of with the condition, low cognitive functioning, and intellectual disability. Thus, patients with severe epileptic encephalopathies of infancy and childhood (i.e., Ohtahara, West and Lennox-Gastaut syndromes) and those children with symptomatic epilepsies have the highest incidences of ASD.

Many studies have independently reported a high prevalence of ASD in children with epilepsy, and similarly, children with ASD frequently have epilepsy. Concordant conclusions have been drawn regarding the importance of intellectual disability (ID) as the link between ASD and epilepsy. On one hand, individuals with ASD and are at a substantially higher risk of developing epilepsy compared to those with relatively normal intellectual function. On the other hand, the comorbidity of ASD and epilepsy has been associated with both a high probability and severity of ID (Amiet et al., 2008). This trend is consistent across multiple studies and was the primary focus and conclusion of an extensive meta-analysis (Amiet C, 2018). Similarly, children with epilepsy and ID are at a substantially increased risk of autism compared to those with epilepsy who have normal intellect (Berg A, 2011).

A meta-analysis of reports published between 1963 and 2006 on ASD and epilepsy aimed to assess the relative risk (RR) of epilepsy in ASD with respect to ID and gender. The findings included: (i) Epilepsy was more prevalent in subjects with ASD, who also had ID compared to those without ID ($p<0.001$) (ii) The combined prevalence of epilepsy was 21.5% in those with both ASD and ID, versus 8% in those without ID. (iii) The male to female ratio of ASD in those with epilepsy was roughly 2:1, in contrast to 3.5:1 in those without epilepsy. This analysis clearly indicated that ID significantly increases the risk of epilepsy in those with ASD. It also suggested that the rate of epilepsy was higher in people with ASD who have ID One plausible explanation was the difference in intellectual quoficient (IQ) distribution. In other words, those with ASD, but without ID, would have an IQ curve shifted to the left, implying that their average or median IQ would be considerably lower than that in the general population. Consequently, the risk of epilepsy would be higher in this lower IQ group (Amiet et al., 2018).

Several neurodevelopmental syndromes with known genetic etiology, such as Rett, Dravet, Angelman, Dup15q and/or Landau Kleffner syndromes, exhibit the co-existence of epilepsy and ASD as parallel conditions (Tuchman et al., 2010b). Both ASD and epilepsy have multifactorial etiologies. The frequent co-occurence of ASD and epilepsy suggests shared neurological and biological abnormalities. Several biological pathways, including gene transcription regulation, cellular growth, synaptic channel function, and maintenance of synaptic structure, seem to play a role in the progression of both disorders (Sundelin et al., 2016). Recent research suggests that a combination of genetic and environmental factors exert a strong influence on both ASD and epilepsy (Meltzer & Van de Water, 2017; Ornoy et al., 2016; Sandin et al., 2017; Shorvon, 2014; Wipfler et al., 2018).

Animal models are important tools for studying the roles of genetic and environmental factors, and their interplay in influencing the onset and severity of disorders, including ASD and epilepsy. Mouse models play an essential role in the drug discovery process. In preclinical trials, they are crucial for demonstrating the metabolism, absorption, general safety, and even the efficacy of new medications (Zuberi & Lutz, 2016). Several mouse models have been proposed to study the comorbidity of ASD and epilepsy. Compared to DDY mice, the EL mouse is considered as a superior natural model, since its expressed behavioral abnormalities closely resemble those observed in individuals with ASD. A deeper understanding of the common genetic, molecular, and cellular mechanisms of ASD and epilepsy in mouse models will pave the way for novel therapeutic approaches for both conditions (Meidenbauer, J. J. 2011).

Our research question was “which mouse model most closely mimics the ID and/or impaired social interaction observed in patients with the comorbidity of ASD and epilepsy? We hypothesized that current mouse models closely replicate these characteristics. Our study systematically reviewed all published mouse models on this comorbidity from 2013 to 2023 to identify the most suitable one for clinical research on ID and/or impaired social interaction.

2. Material and methods

2.1. Information sources and search strategy

We followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. We conducted a systematic review of articles using PubMed, Google Scholar, Europe PMC, Medline/PubMed from 2013 to 2023.

We first searched our keywords individually: murine model, genes mutations, autism, epilepsy. For each keyword, we used synonyms. For instance, for autism, we used: 'autism OR autism spectrum disorders OR autistic disorders OR Asperger syndrome'. Similarly, for epilepsy, we searched for 'epilepsy OR seizure disorders OR convulsion'. For murine models, we used 'murine models OR mice model OR mouse patterns. We then combined the keywords using the advanced search, employing 'AND' between different keywords and 'OR' between synonyms. We then evaluated the full text based on our inclusion and exclusion criteria. We registered all full-text articles in Zotero.

2.2. Study selection

We reviewed titles and abstracts to ensure that all publications included met the inclusion criteria: availability of free full text, relevance to ASD and epilepsy comorbidity, and the specified year of publication. We merged articles that were duplicates, meaning they had the same author and were published in the same year.

3. Results

3.1. Study selection

In the PRISMA flowchart (Figure 1), our document search approach is outlined. Initially, we found 5,386 articles (2,246 in PubMed, 2,125 in Europe PMC, 1,015 in Google scholar) discussing genes of ASD and/or epilepsy and the available animal models. All these articles have been saved in Zotero using the 'remove duplicates' feature. Based on eligibility criteria-relevance to murine models of autism and epilepsy, availability of the full text, and publication in the last decade (2013-2023), 1,050 articles were excluded. After further refinement of our criteria, we selected14 articles for our study. We chose review articles because they provide an assessment of existing research and insights. While they may not present new findings, they often offer unique perspectives and potential new directions (Table 1).

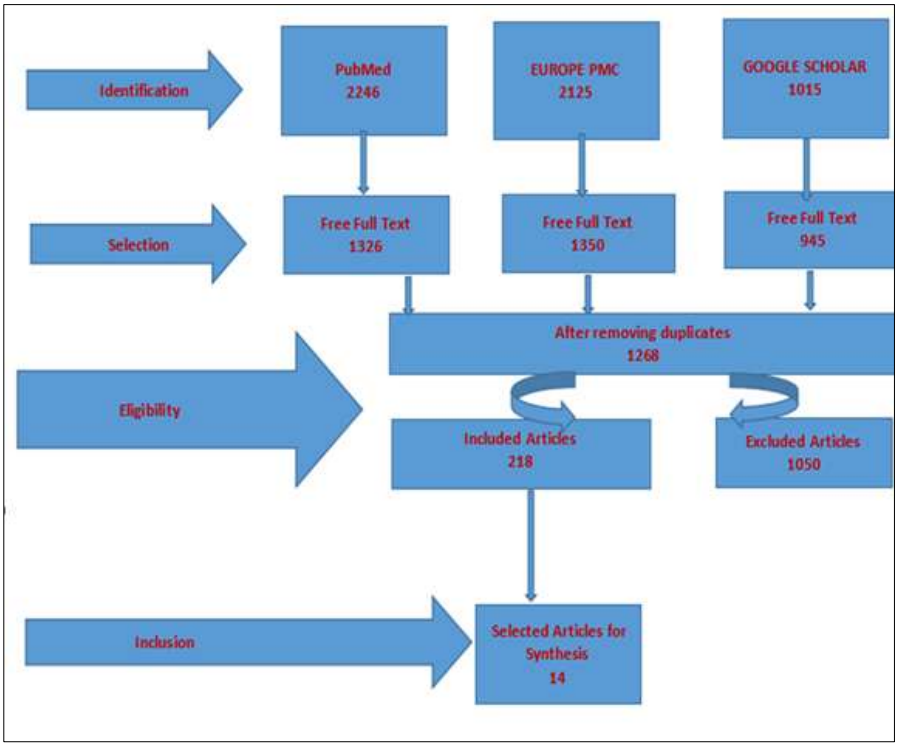

Figure 1 Prisma flowchart of article search Strategy and selection

Table 1 Gene Technology mouse ages in selected articles

S. N	First_Authors and year of publication	Journal_of_Publication	Country	Gene technology*	Mouse Age
1	Bolneo et al., 2022	International Journal of Molecular Sciences	Australia	GFP	1-6 months old
2	Shapiro et al., 2022	Frontiers in Pharmacology	USA	qRT-PCR	3-4 months old
3	Nicole A.et al., 2021	Neurobiology of Disease	USA	CRISPR/Cas9	2-3 months old
4	Brault et al., 2021	PLOS Genetics	USA	Crisper_Ca9	1-6 months old
5	Rossi et al., 2021	International Journal of Molecular Sciences	Italy	CRISPR/Cas9	13 weeks old
6	Lossi et al., 2019	Journal of Clinical Medicine	USA	CRISPR/Cas9	3 weeks old
7	Uddin et al., 2018	*American Journal of Human Genetics*	USA	Western Blot	3 weeks old
8	Tu et al., 2017	Nature Communications	USA	Microrray	2-5 weeks old
9	Wesseling et al., 2017a	Molecular Autism	UK	LC-MS	7 days old
10	Wesseling et al., 2017b	Molecular Autism	UK	LC-MS	7 days old
11	Provenzano et al., 2016	Frontiers in Neurosciences	USA	Crisper_Ca9	3-5 months old
12	Nethralaya et al., 2016	Frontiers in Neurosciences	USA	CRISPR/Cas9	2-3 months old
13	Kuzniewska et al., 2015	Molecular Neurobiology	USA	Western Blot	2-6 months old
14	Corradi et al., 2013	Human Molecular Genetics	USA	Crisper_Cas9	2-3 months old

*LC-MS : Liquid chromatography-Mass Spectrometry, qRT-PCR : quantitative real time-Polymerase Chain Reaction, RT_qRT-PCR : Reverse transcriptase quantitative real time-Polymerase Chain Reaction, GFP : Green Fluorescent Protein.

4. Discussion

In this review, we have examined 14 peer-reviewed research articles that discuss 14 different mouse models developed to simulate 16 unique genetic mutations associated with the comorbidity of ASD and epilepsy. The sex ratio was 6:1, consistent with the male predominance in ASD patients. The mice were typically three (3) months old adults (Table2). The models were produced based on the following four mouse strains: C57BL/6J (n=11), B6C3B (n=1), 55Rbns (n=1) and 101/RlEp (n=1). Models from C57BL/6J strain were derived from 11 different genes:

Tsc1, SFR, SCN8A, KCNB1, GAMT, EN2/BTBR, GAD67/VGAT, RELN, MEF2C, KLF13, SYNGAP1.

In contrast, the models based on 55Rbns, 101/RlEp, and B6C3B strains were tied to OTUD7A, SYN2, and DYRK1A, respectively, all of which are autosomal. These genes were either knocked out (n=8) or knocked down (n=6)

(Table 2). The following technologies were employed: Liquid chromatography-mass Spectrometry

(LC-MS) for the TSC1 gene model, quantitative Real Time-Polymerase Chain Reaction (qRT-PCR) for the EN2/BTBR genes, Reverse Transcriptase_ quantitative Real Time-Polymerase Chain Reaction (RT qRT-PCR) for the DYRK1A gene,

Green Fluorescent Protein (GFP) for GAD67/VGAT genes while the remaining models were produced using CRISPR-CAS9 technology, which is predominantly used for generating knockout models in living organisms (Table 2). Impaired reciprocal social interaction was observed in 93% (13/14) of the models, and ID was found in all models, 100% (14/14), irrespective of age, sex, strain or gene mutation (Table 3). We would like to address the limitations of mouse models, as highlighted in the report (Weuring, Geerligs, & Koeleman, 2021). First, mouse models in autism have been developed to target the presence or absence of a specific developmental diagnostic criterion in ASD, making it challenging to evaluate the spectrum's degree of severity. Second, epilepsy is one of the most common medical comorbidities frequently seen in ASD patients (Hus & Segal, 2021). Third, the genetic etiology in ASD has been identified in ~ 25–35% of ASD patients.

Table 2 Sex, Strain/species, gene, locus and mouse models in selected article

	First Author last name and Year of publication	Sex	Species/Strain	Gene_Name	Locus	Mouse Model*
1	Bolneo et al., 2022	Male	C57BL/6J	*GAD67/VGAT*	7q.12	GAD67$^{+/-}$ and VGAT$^{-/-}$
2	Shapiro et al., 2022	Male	C57BL/6J	*SCN8A*	12q.13	Scn8aR1620L$^{-/+}$ (RL/+)
3	Nicole A.et al., 2021	Male	C57BL/6J	*KCNB1*	20q13	Kcnb1G379R$^{-/+}$
4	Brault et al., 2021	Male	B6C3B	*DYRK1A*	21q22.13	Dyrk1aC$^{-/-}$
5	Rossi et al., 2021	Female	C57BL/6J	*GAMT*	19p13.3	GAMT$^{-/-}$
6	Lossi et al., 2019	Male	C57BL/6J	*RELN*	7q22.1	Reln $^{-/-}$
7	Uddin et al., 2018	Male	55Rbns	*OTUD7A*	15q13.3	Df(h15q13)$^{-/-}$ mice
8	Tu et al., 2017	Male	C57BL/6J	*MEF2C*	5q14.3	Mef2c$^{+/-}$ (Mef2c-het)
9	Wesseling et al., 2017a	Female	C57BL/6J OlaHsD	*Tsc1*	16p13.3	Tsc1$^{+/-}$
10	Wesseling et al., 2017b	Male	C57BL/6J	*KLF13*	15q13.3	Df(h15q13) $^{-/-}$
11	Provenzano et al., 2016	Male	C57BL/6_and_BTBR	*EN2/BTBR*	q36.3	En2$^{+/-}$ x_and_BTBRT$^{+/-}$ Itpr3tf/J
12	Nethralaya et al., 2016	Male	C57BL/6J	*SYNGAP1*	6p21.3	Syngap1$^{-/+}$
13	Kuzniewska et al., 2015	Male	C57BL/6 _Srf 7f	*SFR*	3p21.31	Srf$^{-/-}$ CaMKCreERT2
14	Corradi et al., 2013	Male	101/RIEp	*SYN2*	3p25.2	SYN2 KO$^{-/-}$

$^{-/+}$ (KD), $^{-/-}$(KO).

Table 3 Comparative clinical symptoms in mouse models of ASD and epilepsy comorbidity

	First Authors and year of publication	Gene Name	Observed ASD symptoms in ASD/epilepsy mice*				
			1	2	3	4	5
1	Bolneo et al., 2022	*GAD67/VGAT*	+	N/S	N/S	+	+
2	Shapiro et al., 2022	*SCN8A*	+	+	+	+	+
3	Nicole A.et al., 2021	*KCNB1*	+	+	N/S	N/S	+
4	Brault et al., 2021	*DYRK1A*	+	N/S	N/S	+	+
5	Rossi et al., 2021	*GAMT*	+	N/S	N/S	+	+
6	Lossi et al., 2019	*RELN*	+	+	+	+	+
7	Uddin et al., 2018	*OTUD7A*	+	N/S	N/S	+	+
8	Tu et al., 2017	*MEF2C*	+	+	+	+	+
9	Wesseling et al., 2017a	*Tsc1*	+	+	+	+	+
10	Wesseling et al., 2017b	*KLF13*	+	+	+	N/S	+
11	Provenzano et al., 2016	*EN2/BTBR*	+	N/S	N/S	+	+
12	Nethralaya et al., 2016	*SYNGAP1*	N/S	N/S	N/S	N/S	+
13	Kuzniewska et al., 2015	*SFR1*	+	N/S	N/S	+	+
14	Corradi et al., 2013	*SYN2*	+	+	+	+	+

+= presence of the phenotype 1= impaired social reciprocal interaction, 2= impaired verbal and nonverbal ommunication 3= Stereotyped Repetitive Behaviors, 4= Restricted Interests, 5= mental retardation Presence slight, moderate or severe) or absence of mental retardation(MR) #TSC1 gene : Tuberous sclerosis 1 gene or amartin,SFR1 gene : SWI5 Dependent Homologous Recombination Repair Protein 1 gene,SCN8A gene : sodium oltage-gated channel alpha subunit 8 sub-unit A gene,EN2/BTBR gene : "Engrailed Homeobox 2"/"Black and Tan Rachyury" gene, DYRKLA gene : Dual-specificity tyrosine phosphorylation-regulated kinase gene,KCNB1 : otassium voltage-gated channelsubfamily B member 1gene, GAMT gene : GuanidinoacetateN-Methyltransferase ene, GAD67/VGAT gene : Glutamic Acid Decarboxylase 67/Vesicular GABA Transporter gene, MEF2C gene : Myocyte Enhancer Factor 2,OTUD7A gene:OTU Deubiquitinase 7A gene ; SYN2 gene : Synapsin II, SYNGAP1gene : ynaptic Ras GTPase Activating Protein 1 gene, RELN gene : Reelin, KLF13 gene: KLF Transcription Factor 13 N/S - lot Specified

Nearly all the genetic mutations in the various mouse models (both knockouts and knock in) are involved in the regulation of pre- and post-synaptic transmission of neurotransmitters, knowledge of which could significantly benefit ASD and epilepsy research. Despite these limitations, mouse models remain an appealing tool for investigating the comorbidity of ASD and epilepsy. Of all 14 mouse models (Table 2), the PK1 R104Q knock-in mouse displayed the most the key characteristics and behavioral phenotypes consistent with ASD and epilepsy comorbidity in patients (Todd and Bassuk, 2018). In humans, the PK1 R104Q mutation causes progressive myoclonic epilepsy (PME). This homozygous mutation leads to a lowered seizure threshold and autism-like phenotypes in mice, mirroring the phenotypes observed in patients with heterozygous mutation. Behavioral studies of PK1+/− mice revealed abnormal social behavior and repetitive behaviors (Paemka et al., 2013). Another mutation, PK1 D482N, was implicated as a causative variant of ASD (Todd and Bassuk, 2018). Therefore, PK1 stands out as a prime candidate for studying comorbidity of epilepsy and ASD. In addition to the PK1 R104Q knock-in mouse, BTBR T+tf/J (BTBR) mice are known for displaying behaviors consistent with the diagnostic criteria for ASD (originally a triad, now a dyad), including impaired social interaction and communication, as well as increased repetitive behaviors. Notable similarities and differences have been observed between male and female BTBR mice (Kiffmeyer et al., 2022; Meyza et al., 2013).

Syngap1-/+ mice (Table 2) not only demonstrate decreased pain sensation and motor function impairment, but also reproduce cognitive deficits typically observed in ASD associated with ID. SYNGAP1-related intellectual disability

(SYNGAP1-ID) is characterized by developmental delay (DD) or intellectual disability (ID) in 100% of affected individuals, generalized epilepsy in approximately 84%, autism spectrum disorder (ASD), other behavioral abnormalities in up to 50%, and sleep disturbances. SYNGAP1 (Synaptic Ras-GTPase-activating protein) has been identified as a cause of ID with comorbid ASD and epilepsy in children. As a negative regulator of Ras, Rap and of AMPA receptor trafficking to the postsynaptic membrane, SYNGAP1 not only regulates synaptic plasticity, but also neuronal homeostasis. Recent studies on the neurophysiology of SYNGAP1, using Syngap1 mouse models, have provided deeper insights into how downstream signaling proteins and synaptic plasticity are regulated by SYNGAP1 (Holder Jr, Hamdan, & Michaud, 2019; Jeyabalan & Clement, 2016; Nakajima et al., 2019; Paul et al., 2019; Smith-Hicks et al., 2021).

Even though Neuroligin mouse model NL3R451C mice did not appear in our search, compelling evidence from the literature indicates that it displays aggressive and repetitive behaviors that closely mimic the phenotype observed in ASD patients with ASD. The aggressive phenotype is reversible with risperidone (Burrows et al., 2015)

Taken together, we observed that each of the aforementioned four mouse models captures different symptoms of ASD or the comorbidity of ASD and epilepsy to varying extents. Reflecting on the polygenic nature of ASD and epilepsy with genetic origins, there is potential for improving existing models. An optimized model would provide a more comprehensive representation of ASD and epilepsy, taking into account other comorbidities. Future drug development studies may then more accurately target specific symptoms in ASD and epilepsy in KO mice. Such advancements in mouse models could significantly impact behavioral testing methods, data analysis, and critical interpretation (Silverman et al., 2022).

Our study has some limitations. Firstly, many of the 16 selected papers did not sufficiently detail the lifespan of the mouse models. Factors such as the number of seizures corresponding to the phenotype, the duration of the seizures, and latency times were sometimes omitted. Furthermore, certain human-specific symptoms, like language/speech expression, are not feasible to study in animal models. Secondly, the mice studied ranged in age from as young as 3 weeks to as old as six months. Consequently, behavioral testing results may vary even within the same mouse model at different ages.

5. Conclusion

Our review aimed to identify the most suitable model for clinical research on ID and/or impaired social interaction in such comorbidity. The mouse models PK1 R104Q knock-in, BTBR *T+tf*/J (BTBR), and Syngap1-/+ mice emerged as the most appropriate, in decreasing order of suitability. In the future, we plan to conduct an in silico a gene-gene interaction analysis for the individual genes used to generate the aforementioned three mouse models. Additionally, we will consider another gene to propose a 4-gene polygenic model for ASD and epilepsy.

Compliance with ethical standards

Acknowledgments

We thank Madagui Dolo for her assistance in developing the search terms for the database search.

Disclosure of conflict of interest

The authors declare no competing interests relevant to the content of this article.

Author contributions

All authors participated in conceptualizing and designing the study. MK handled material preparation, data collection and analysis. He also wrote the initial draft of the manuscript, which was subsequently reviewed and commented by all authors. HGK revised and finalized the manuscript. All authors read and approved the final manuscript.

References

[1] Amiet, C., Gourfinkel-An, I., Bouzamondo, A., Tordjman, S., Baulac, M., Lechat, P., . . . Cohen, D. (2008). Epilepsy in autism is associated with intellectual disability and gender: evidence from a meta-analysis. Biol Psychiatry, 64(7), 577-582. doi:10.1016/j.biopsych.2008.04.030

[2] Burrows, E. L., Laskaris, L., Koyama, L., Churilov, L., Bornstein, J. C., Hill-Yardin, E. L., & Hannan, A. J. (2015). A neuroligin-3 mutation implicated in autism causes abnormal aggression and increases repetitive behavior in mice. Mol Autism, 6, 62. doi:10.1186/s13229-015-0055-7

[3] El-Fishawy, P., & State, M. W. (2010). The genetics of autism: key issues, recent findings, and clinical implications. Psychiatr Clin North Am, 33(1), 83-105. doi:10.1016/j.psc.2009.12.002

[4] Holder Jr, J. L., Hamdan, F. F., & Michaud, J. L. (2019). SYNGAP1-related intellectual disability.

[5] Hus, Y., & Segal, O. (2021). Challenges Surrounding the Diagnosis of Autism in Children. Neuropsychiatr Dis Treat, 17, 3509-3529. doi:10.2147/NDT.S282569

[6] Jeyabalan, N., & Clement, J. P. (2016). SYNGAP1: Mind the Gap. Front Cell Neurosci, 10, 32. doi:10.3389/fncel.2016.00032

[7] Kiffmeyer, E. A., Cosgrove, J. A., Siganos, J. K., Bien, H. E., Vipond, J. E., Vogt, K. R., & Kloth, A. D. (2022). Deficits in cerebellum-dependent learning and cerebellar morphology in male and female BTBR autism model mice. NeuroSci, 3(4), 624-644. doi:10.3390/neurosci3040045

[8] Loomes, R., Hull, L., & Mandy, W. P. L. (2017). What Is the Male-to-Female Ratio in Autism Spectrum Disorder? A Systematic Review and Meta-Analysis. J Am Acad Child Adolesc Psychiatry, 56(6), 466-474. doi:10.1016/j.jaac.2017.03.013

[9] Meyza, K. Z., Defensor, E. B., Jensen, A. L., Corley, M. J., Pearson, B. L., Pobbe, R. L., . . . Blanchard, R. J. (2013). The BTBR T+ tf/J mouse model for autism spectrum disorders-in search of biomarkers. Behav Brain Res, 251, 25-34. doi:10.1016/j.bbr.2012.07.021

[10] Nakajima, R., Takao, K., Hattori, S., Shoji, H., Komiyama, N. H., Grant, S. G. N., & Miyakawa, T. (2019). Comprehensive behavioral analysis of heterozygous Syngap1 knockout mice. Neuropsychopharmacol Rep, 39(3), 223-237. doi:10.1002/npr2.12073

[11] Paemka, L., Mahajan, V. B., Skeie, J. M., Sowers, L. P., Ehaideb, S. N., Gonzalez-Alegre, P., . . . Bassuk, A. G. (2013). PRICKLE1 interaction with SYNAPSIN I reveals a role in autism spectrum disorders. PLoS One, 8(12), e80737. doi:10.1371/journal.pone.0080737

[12] Paul, A., Nawalpuri, B., Shah, D., Sateesh, S., Muddashetty, R. S., & Clement, J. P. (2019). Differential Regulation of Syngap1 Translation by FMRP Modulates eEF2 Mediated Response on NMDAR Activity. Front Mol Neurosci, 12, 97. doi:10.3389/fnmol.2019.00097

[13] Silverman, J. L., Thurm, A., Ethridge, S. B., Soller, M. M., Petkova, S. P., Abel, T., . . . Halladay, A. (2022). Reconsidering animal models used to study autism spectrum disorder: Current state and optimizing future. Genes Brain Behav, 21(5), e12803. doi:10.1111/gbb.12803

[14] Smith-Hicks, C., Wright, D., Kenny, A., Stowe, R. C., McCormack, M., Stanfield, A. C., & Holder, J. L., Jr. (2021). Sleep Abnormalities in the Synaptopathies-SYNGAP1-Related Intellectual Disability and Phelan-McDermid Syndrome. Brain Sci, 11(9).doi:10.3390/brainsci11091229

[15] Weuring, W., Geerligs, J., & Koeleman, B. P. C. (2021). Gene Therapies for Monogenic Autism Spectrum Disorders. Genes (Basel), 12(11). doi:10.3390/genes12111667

[16] Wisniowiecka-Kowalnik, B., & Nowakowska, B. A. (2019). Genetics and epigenetics of autism spectrum disorder-current evidence in the field. J Appl Genet, 60(1), 37-47. doi:10.1007/s13353-018-00480-w

[17] Zuberi, A., & Lutz, C. (2016). Mouse Models for Drug Discovery. Can New Tools and Technology Improve Translational Power? ILAR J, 57(2), 178-185. doi:10.1093/ilar/ilw021.