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Research report

Genetic control of social behavior: Lessons from mutant mice

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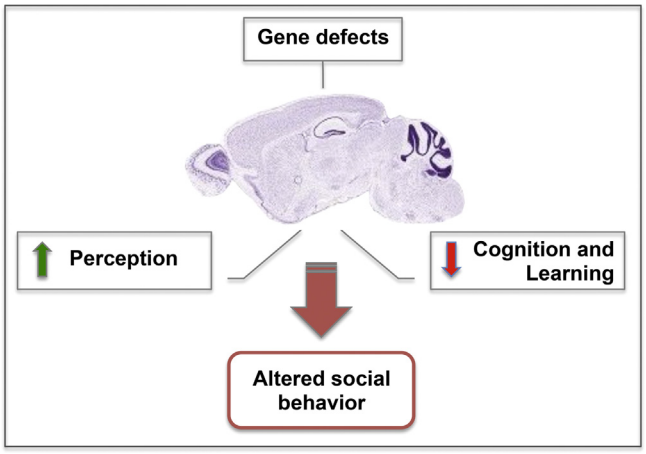
HIGHLIGHTS

- Altered social behavior is a pathological trait of autism spectrum disorder (ASD).
- In mice, mutations in ASD genes result in altered social behavior.
- Mouse models are a crucial tool to develop novel treatments for ASD.

GRAPHICAL ABSTRACT



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ABSTRACT

Social behavior is evolutionary conserved, and is thought to be evolved since it increased reproductive and survival fitness of living species. In humans, disturbances of social behavior are a peculiar pathological trait of neurodevelopmental disorders, namely autism spectrum disorder (ASD). ASD is defined by deficits in two core domains (social interaction/communication and repetitive/restrictive behaviors), which emerge during early postnatal development. ASD has a strong genetic component: copy number variations, de novo and familial mutations, as well as epigenetic modifications have been reported in a huge number of genes. Recent studies in mice demonstrate that mutations in a wide variety of ASD-associated genes can cause neurodevelopmental defects, which subsequently result in social behavior disturbances during early postnatal age and adulthood. From these studies, it clearly emerges that functionally interrelated cellular mechanisms underlie social behavior and its disturbances in ASD. Indeed, most of ASD-associated genes control neuronal differentiation and migration, growth of neuronal connections and synaptic function. Here we will present the recent advances in understanding the genetic

Abbreviations: ASD, autism spectrum disorders; BTBR, BTBR T^{+} *Itpr3tf/J* mouse strain; cKO, conditional knockout; CNS, central nervous system; CNTNAP2, contactin-associated protein-like 2; DREADD, designer receptors exclusively activated by designer drugs; DSM-5, Diagnostic and Statistical Manual of Mental Disorders: 5th edition; EEG, electroencephalogram; *En*, engrailed; *Fmr1*, Fragile X mental retardation gene 1; GABA, gamma-aminobutyric acid; GO, gene ontology; HE, hemizygous; HT, heterozygous; HM, homozygous; KI, knockin; KO, knockout; LTD, long term depression; LTP, long term potentiation; Mecp2, methyl-cytosine binding protein 2; mPFC, medial prefrontal cortex; mTOR, mammalian target of rapamycin; Nlgn, neuroligin; Nrxn, neurexin; Oxt, oxytocin; Oxtr, oxytocin receptor; PFC, prefrontal cortex; PV, parvalbumin; Scn1a, sodium channel 1a; SFARI, Simon Foundation Autism Research Initiative; Tg, transgenic; Tsc, tuberous sclerosis complex; WT, wild-type.

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determinants of social behavior, as they emerge from the study of ASD mouse models, and discuss the importance of these studies for the development of novel therapeutic approaches to overcome social disturbances in ASD.

1. Introduction

Social behavior is defined as interactions among individuals, normally within the same species, which usually provide mutual benefits to all individuals involved. Social behavior likely evolved because it increased the individual's fitness, providing the species with a higher chance to reproduce and survive [1]. Deciphering the genes that influence the development and function of brain circuits mediating social behavior represents a fascinating and complex challenge.

In humans, disturbances of social behavior are a characteristic trait of developmental disorders of the central nervous system (CNS), namely autism spectrum disorder (ASD). ASD is a group of complex neurodevelopmental disorders whose diagnosis is exclusively made on a behavioral basis. According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), ASD is defined by deficits in two core domains (social interaction and communication, and repetitive/restrictive behaviors), which emerge in early phases of postnatal development [2].

It has long been known that ASD has a very high degree of heritability. However, only the recent advances in genetics and genomics have allowed the identification of an increasingly high number of gene variants associated to ASD: copy number variations, de novo and familial mutations, epigenetic modifications have been reported in candidate as well as novel genes [3–5]. Strong evidence indicates that functionally interrelated cellular mechanisms underlie the disorder. Indeed, most of ASD-associated genes code for proteins involved in synaptic signaling, transcriptional/post-transcriptional mechanisms and cell adhesion, which crucially operate in CNS development, controlling the birth and differentiation of neuronal subtypes, neuronal migration, synapse formation and maintenance of neuronal connections [3,5]. Thus, knowledge from genetic studies of ASD has provided new insights to enhance our understanding of the molecular mechanisms underlying social behavior abnormalities.

Most of these data resulted from the analysis of mouse models of ASD. The mouse (*Mus musculus*) is a highly social species, which shows a wide variety of social behaviors (such as reciprocal interactions, play, territorial marking, aggressive behaviors, sexual behaviors and parental cares). These peculiar behavioral traits pushed many research laboratories to investigate social behavior disturbances in mice bearing mutations or deletions of ASD-associated genes. Several ASD mouse models have been generated, providing a powerful tool to investigate the molecular, neuroanatomical and behavioral consequences of gene dysfunction in ASD. From these studies, it clearly emerges that social behavior disturbances in ASD have marked genetic determinants of neurodevelopmental origin. Another important asset of these studies is the possibility to test novel treatments to rescue social and other ASD-related behaviors in the laboratory animal [6,7].

In this review we will discuss recent findings from ASD mouse models, which greatly contributed to unravel the genetic basis of social behavior. We will focus on specific sets of genes involved in neural development and synaptic activity, describing how they may contribute to shape the structure and function of brain areas involved in social behavior. Finally, we will provide examples of ASD gene mutations resulting in altered social behavior in mice, and discuss the importance of these studies for the development of novel therapeutic approaches for ASD.

2. Behavioral assays to study social interactions in mice

Investigating social behavior in mice entails a constellation of behavioral assays, which have been used to unravel social disturbances in ASD mouse models; however, not all readouts of these tests are relevant to ASD. Here, we will focus only on the most relevant types of assays for detecting social interaction abnormalities, which ensure a pure measure of simple interest in reciprocal approach excluding sexual, mating, aggressive, agonistic and parental care components, and whose readouts are considered to be relevant for ASD [6]. In Sections 2.1–2.4 we will briefly describe these assays (reciprocal social interactions, three-chamber, partition and social preference tests). For a detailed discussion of these experimental approaches, the reader is referred to the comprehensive review by Silverman et al. [6].

2.1. Reciprocal social interactions

This test is straightforward and conducted in an open field or home cage environment, where two unfamiliar mice are placed together. Parameters relevant to social interactions such as approaching, following, sniffing, climbing and allogrooming are routinely evaluated using a video-tracking system [6].

2.2. Three-chamber social approach test

In this test, the subject mouse is placed in a plexiglas box partitioned into three chambers. One side chamber contains an unfamiliar mouse (target) enclosed in a small wire cage with widely spaced wire bars, which permit visual, olfactory, auditory and some tactile contact but prevent aggressive and sexual interactions. The opposite side chamber contains the novel object (an inverted wire pencil cup), while the center chamber is completely empty. During the test, the subject mouse is placed in the center chamber, and given the choice to spend time with the non-social novel object or target mouse. Measures are taken of the amount of time spent in entries into each side of the test box, as well as time spent sniffing the wire cages [8].

It should be pointed out that a certain cohort to cohort variation has been noted in data coming from the three-chamber test. Moreover, it is not clear if this test is sensitive enough to detect defective reciprocal social interactions, since some studies of genetic ASD models show deficits in reciprocal social interactions, but not in the three-chamber test (Table 1).

2.3. Partition test

In this test, two unfamiliar mice are placed into a standard cage divided in two compartments by a perforated transparent partition, allowing the subject mouse to see, hear, and smell the target mouse through the holes in the plastic transparent divider precluding any direct physical contact. Time spent at the partition and numbers of approaches represent the amount of interest in the social partner [9].

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