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Bardet-Biedl Syndrome Type 10 Mice Display Reduced Anxiety-like Behavior

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Abstract

Bardet-Biedl Syndrome (BBS) is an autosomal recessive genetic disorder characterized by polydactyly, obesity, and vision loss. Some BBS patients experience developmental delay and difficulties in emotional regulation, but neurological features of this disorder are understudied. BBS mouse models have defects in fear conditioning and reduced anxiety-like behaviors in open field tests. The purpose of this study is to characterize the anxiety-like behavior in *Bbs10* knockout mice prior to severe visual impairment using elevated plus maze. *Bbs10*$^{-/-}$ mice made significantly more entries into the open arms and traveled greater distances compared to littermate controls, suggestive of reduced anxiety-like behaviors.

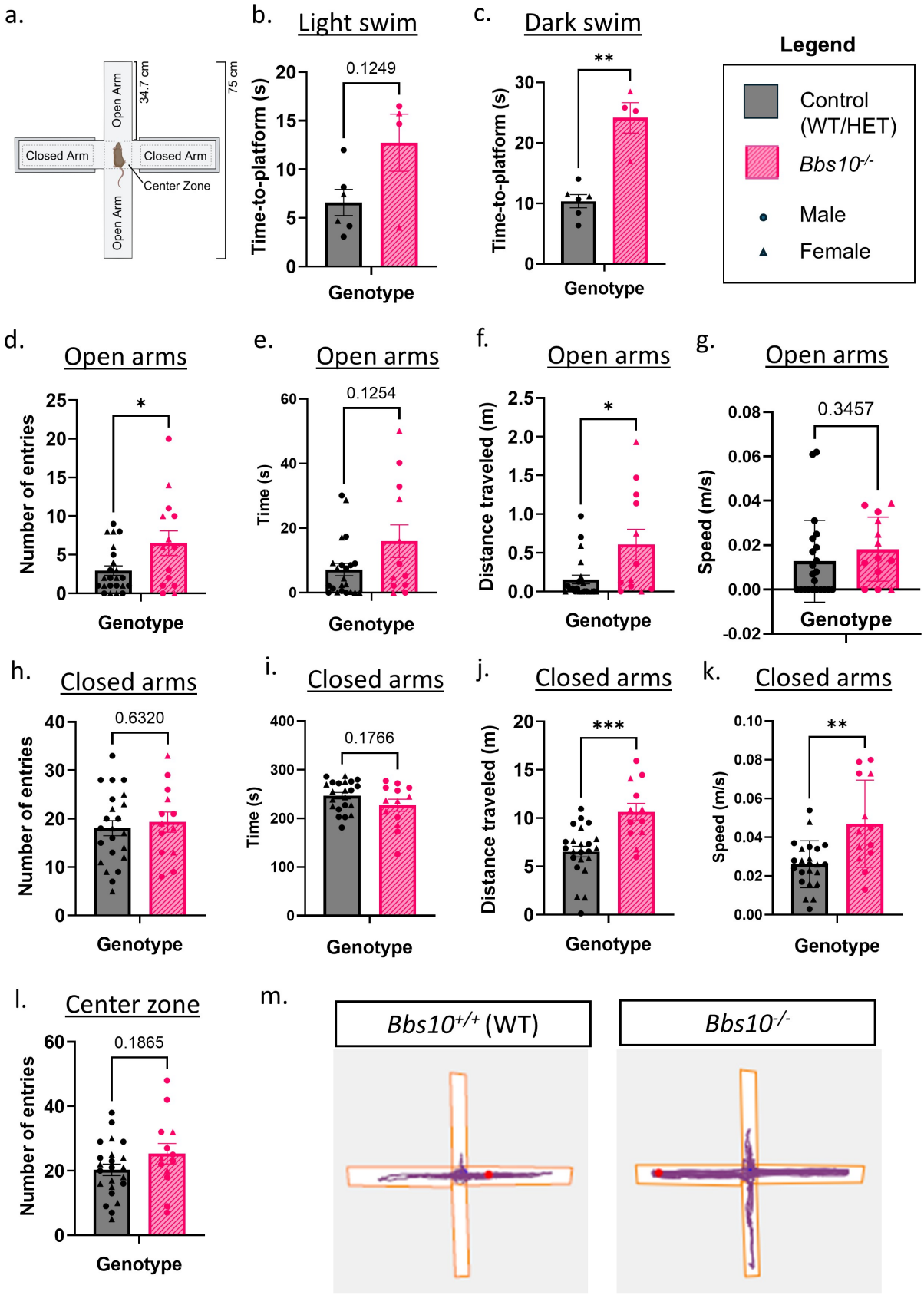


Figure 1. *Bbs10*$^{-/-}$ mice show increased open arm exploration in the elevated plus maze:

The elevated plus maze apparatus (a). Time-to-platform in light-adapted functional vision test for *Bbs10*$^{-/-}$ mice and wild-type (WT) or heterozygous (HET) control littermates (b). Time-to-platform in dark-adapted functional vision test for

controls and *Bbs10*$^{-/-}$ mice (c). Number of entries into open arms for controls and *Bbs10*$^{-/-}$ mice (d). Time spent in open arms for controls and *Bbs10*$^{-/-}$ mice (e). Distance traveled in open arms for controls and *Bbs10*$^{-/-}$ mice (f). Locomotion speed in open arms for controls and *Bbs10*$^{-/-}$ mice (g). Number of entries into closed arms for controls and *Bbs10*$^{-/-}$ mice (h). Time spent in closed arms for controls and *Bbs10*$^{-/-}$ mice (i). Distance traveled in closed arms for controls and *Bbs10*$^{-/-}$ mice (j). Locomotion speed in closed arms for controls and *Bbs10*$^{-/-}$ mice (k). Number of entries into center square for controls and *Bbs10*$^{-/-}$ mice (l). Trajectories in elevated plus maze test for a typical control mouse and a *Bbs10*$^{-/-}$ mouse (m).

Description

Bardet-Biedl Syndrome (BBS) is a rare, autosomal recessive disorder characterized by obesity, vision loss, and behavioral/neurological traits. BBS genes encode proteins that jointly regulate trafficking in an organelle called the primary cilium (Nachury 2018). Mutations in at least 26 different BBS genes can independently cause BBS with overlapping clinical features (Dollfus et al. 2024; Forsyth and Gunay-Aygun 2003 [Updated 2023 Mar 23]). Many BBS genes, including *BBS1*, *2*, *4*, *5*, *7*, *8*, *9* and *18*, encode proteins that form a complex - the BBSome (Loktev et al. 2008; Nachury et al. 2007). The BBSome is a cargo adaptor to the ciliary trafficking machinery. *BBS10*, *BBS6* and *BBS12* encode chaperonin proteins responsible for assembly of the BBSome (Seo et al. 2010). Mutations in *BBS10* constitute the second most common cause of BBS among BBS genes, accounting for approximately 21 % of all BBS cases (Stoetzel et al. 2006). In children with BBS, night blindness is typically noted before onset of significant vision loss. Parents of children with BBS first noted night blindness in their children at an average age of 8.5 years, and their children were registered as “blind” at an average age of 15.5 years (Beales et al. 1999). Behavioral/neurological features are not as well understood. Clinical reports associate BBS with autism-spectrum disorder in some patients (Chatterjee et al. 2014; Jain et al. 2026). In mouse models of BBS, altered ciliary functions impact migration, differentiation, and proliferation of neurons in the brain, which could be associated with neurological phenotypes in patients (Carter et al. 2012). In one study, approximately 50% of subjects with BBS experienced developmental delays, with development of speech being delayed by up to 2 years in 47% of the subjects (Beales et al. 1999). This study also noted an inappropriate affect and a disinhibited demeanor in approximately half of the enrolled patients (Beales et al. 1999). Neurological features of BBS merits further study.

In mouse models of BBS, including *Bbs1*$^{M390R/M390R}$ mice and mice with postnatal deletion of *Bbs8*, long-term context-dependent fear conditioning was impaired, despite intact short-term context-dependent fear conditioning (Pak et al. 2021). In a study dissecting anxiety-related phenotypes of *Bbs6*$^{-/-}$ and *Bbs8*$^{-/-}$ mice, *Bbs8*$^{-/-}$ mice exhibited increased latency to immobility in the forced swim test, and a trend was also seen in *Bbs6*$^{-/-}$ mice (Rodig et al. 2022). BBS mice may be more resistant to depression compared to littermates. BBS8 is a member of the BBSome complex and BBS6 is a member of the chaperonin complex (Seo et al. 2010). In the open field test, *Bbs6*$^{-/-}$ mice traveled significantly greater distances compared to that in littermate controls, a trend also observed in *Bbs8*$^{-/-}$ mice compared to their littermates (Rodig et al. 2022). Additionally, *Bbs8*$^{-/-}$ mice spent significantly less time in the corners of the open field arenas, a tendency also seen in *Bbs6*$^{-/-}$ mice. Together, these data showed that *Bbs6*$^{-/-}$ and *Bbs8*$^{-/-}$ mice had decreased anxiety-like phenotypes, at least in a non-social context.

The goal of this study is to determine whether *Bbs10*-null mice (*Bbs10*$^{-/-}$) have an anxiety-like phenotype using the elevated plus maze behavior test. The elevated plus maze test is a well-validated behavioral assay using a plus-shaped apparatus, with two of the four arms “closed” (surrounded by opaque walls) and the other two arms “open” (Figure 1a). Rodents naturally prefer dark, enclosed spaces, and this innate preference drives them towards the closed arms. They also have an innate fear for height and for lighted areas, hence the natural tendency to avoid open arms. The preference of the mice to explore closed versus open arms in elevated plus maze informs the degree of their anxiety-like behavior (or lack thereof) (Walf and Frye 2007). The BBS10 mouse model, on the 129S6/SvEvTac incipient genetic background, harbors a deletion encompassing parts of exon 1 and 2 of the *Bbs10* gene. Mice that are null for *Bbs10* (*Bbs10*$^{-/-}$) recapitulate phenotypes seen in humans, including vision loss and obesity (Mayer et al. 2022). However, their behavioral phenotypes have not been fully characterized.

In this study, the anxiety-like phenotype of *Bbs10*$^{-/-}$ mice and control littermates was examined when they were between postnatal day 22 and 24, an age when impairment in functional day vision of *Bbs10*$^{-/-}$ mice is mild. Both wild-type (WT) littermates and littermates heterozygous (HET) for the *Bbs10*-null allele were used as controls due to the recessive nature of BBS. To ascertain their functional vision in light-adapted conditions, a visually-guided swim assay was performed between the ages of 34 days to 60 days old, shortly after they completed the elevated plus maze tests. In this vision test, each mouse was trained to locate a platform in a water maze, then underwent 20 different platform-finding trials, with the platform position randomly placed for each trial. For this experiment, a datapoint is the averaged time-to-platform metric of 20 trials of the test mouse in a given lighting condition. In these and in subsequent bar graphs, male mice are shown as

circles, and female mice are shown as triangles to enable the visualization of sex compositions of the groups. Due to sample size limitations, this study was not powered to investigate sex differences in behavioral traits, and males and females were combined for analysis. The averaged time it took for *Bbs10*$^{-/-}$ mice to locate a platform in lighted conditions was 12.7 ± 2.9 s (n = 4), compared to the averaged time it took for control littermates, which was 6.6 ± 1.3 s (n = 6). Even though the time-to-platform metrics were not significantly different between groups (p = 0.125), *Bbs10*$^{-/-}$ mice tended to take longer to find the platform, indicating onset of a mild visual impairment in the light (Figure 1b). At this age, *Bbs10*$^{-/-}$ mice had statistically significant impairment in dark-adapted functional vision in the swim assay (Figure 1c; *Bbs10*$^{-/-}$: 24.139 ± 2.5 s; control: 10.374 ± 1.1 s; p= 0.006). In the elevated plus maze, 22 - 24 days old *Bbs10*$^{-/-}$ mice made twice as many entries into the open arms compared to those made by their control littermates (Figure 1d, *Bbs10*$^{-/-}$: 6.92 ± 1.658 entries; control: 2.957 ± 0.611 entries; p = 0.040), and *Bbs10*$^{-/-}$ mice tended to spend more time in the open arms compared to controls (Figure 1e; *Bbs10*$^{-/-}$: 15.967 ± 5.064; control: 7.159 ± 1.897; p = 0.125). *Bbs10*$^{-/-}$ mice traveled on average 3.7 times greater distances in the open arms of the elevated plus maze compared to distances traveled by their littermate controls (Figure 1f; *Bbs10*$^{-/-}$: 0.606 ± 0.196 m; control: 0.155 ± 0.057 m; p = 0.0462). Locomotion speed in the open arms was not significantly different between *Bbs10*$^{-/-}$ and controls (*Bbs10*$^{-/-}$: 0.018 ± 0.004 m/s; control: 0.013 ± 0.004 m/s; p = 0.346; Figure 1g).

Number of entries into the closed arms was not significantly different between *Bbs10*$^{-/-}$ and littermate controls (*Bbs10*$^{-/-}$: 19.308 ± 2.080; control: 18.043 ± 1.572; p = 0.632; Figure 1h). Time spent in the closed arms was also not significantly different between *Bbs10*$^{-/-}$ and littermate controls (*Bbs10*$^{-/-}$: 227.085 ± 12.412; control: 246.859 ± 6.665; p = 0.177; Figure 1i). However, *Bbs10*$^{-/-}$ mice travelled significantly greater distances in the closed arms despite not spending significantly more time there (*Bbs10*$^{-/-}$: 10.658 ± 0.886 m; control: 6.690 ± 0.488 m; p = 0.0003; Figure 1j). *Bbs10*$^{-/-}$ mice had significantly greater locomotion speed in the closed arms of the elevated plus maze compared to littermate controls (*Bbs10*$^{-/-}$: 0.047 ± 0.006 m/s; control: 0.026 ± 0.003 m/s; p = 0.0068; Figure 1k). The number of entries into the center zone was not different between *Bbs10*$^{-/-}$ mice compared to littermate controls (Figure 1l). Typical trajectories of a wild-type control and a *Bbs10*$^{-/-}$ mouse (both females) on the elevated plus maze test are shown in Figure 1m. In Figure 1m, the starting position of the animal is shown as a blue dot, and the position of the animal at the end of the test is shown as a red dot.

BBS mice are runty during postnatal development but develop obesity in adulthood (Mayer et al. 2022). To determine whether bodyweights were a confounding factor in locomotion and behavior, weights were recorded. At 22 – 24 days old, juvenile *Bbs10*$^{-/-}$ mice have significantly reduced bodyweights and have not yet developed obesity (*Bbs10*$^{-/-}$: 6.083 ± 0.338 g; controls: 12.518 ± 0.243 g; p <0.0001).

Together, these data show that mice lacking the *Bbs10* gene make an increased number of entries into the open arms of the elevated plus maze, a finding typically interpreted as a decreased level of anxiety and/or fear experienced by the animals. Hypermobility was also detected in these juvenile *Bbs10*$^{-/-}$ mice, at least prior to onset of obesity. Since these experiments were performed in juvenile mice prior to severe vision loss, these phenotypes likely reflect intrinsic behavioral features of *Bbs10*$^{-/-}$ mice.These observations in *Bbs10*$^{-/-}$ echo findings made in *Bbs6*$^{-/-}$ and *Bbs8*$^{-/-}$ mice.Future studies could be performed in mice with brain-specific deletion of BBS genes to completely remove visual impairment as a confounding factor in behavior. The lower degrees of anxiety in BBS mouse models could be plausibly associated with the disinhibited affect observed in BBS patients, although a direct link has not been established and more studies are needed. These behavioral differences could also reflect a greater drive for exploration and/or a greater sense of curiosity.

Methods

Animal husbandry and mouse model

This study was performed in strict accordance with the recommendations in the Guide for the Care and Use of Laboratory Animals of the National Institutes of Health. All animals were handled according to approved Institutional Animal Care and Use Committee (IACUC) protocol #4031421 of the University of Iowa. The BBS10 mouse model was acquired from the KOMP2 Center at the Jackson Laboratory, and it is now distributed through the Mutant Mouse Resource and Research Centers (MMRRC) as C57BL/6N-*Bbs10*$^{tm1.1(KOMP)Vlcg}$/*JMmucd*. This mouse model was generated from the embryonic stem cell line *Bbs10*$^{tm1(KOMP)Vlcg}$ (VG13389A-A11, MMRRC). The characterization of this mouse model and genotyping procedures were described in detail elsewhere (Mayer et al. 2022). Mice were crossed onto the 129S6 genetic background for at least 7 generations. Animals were housed according to IACUC recommendations. Both male and female mice were used in this study.

Elevated plus maze

Each side arm of the elevated plus maze apparatus measured 34.7 cm long, and the walls of the closed arms were 15 cm tall. The center square measured 5.6 cm wide, which was also the width of each of the side arms. The side arms had an elevation of 49.7 cm from the bottom of the apparatus, and the entire apparatus was positioned on a table that was 60.4 cm tall. The apparatus was made of dark, opaque plastic. Mice between 22-24 days old were placed in the intersection of the four arms of the elevated plus maze, designated the center, facing an open arm. Their behavior and movement were video recorded for 5 minutes. These mice were not tested in any other behavioral assays prior to this experiment. For each animal, it was their first exposure to the elevated plus maze test. Video recording and automatic video tracking of the animal's body and time spent in each compartment were performed in ANYMAZE software version 6.32. The floor of the side arms were covered in white tape to increase contrast for automatic video tracking. An observer also manually marked the number of times an animal placed 2 forepaws into the open arm compartment as an additional metric. The elevated plus maze test was performed under typical fluorescent ceiling light, between 12 to 5 pm. The maze was cleaned by 70 % ethanol between animals to mask scent. Males and females were tested on separate days when possible. If they must be tested on the same day, all the male animals were tested first, the white tape was replaced in addition to cleaning, and then all the female animals were tested. At the conclusion of each day, 10 % bleach was used to clean the apparatus.

Visually-guided swim assay

The visually-guided swim assay, adapted from the Morris water maze, was performed as previously described (Hassan et al. 2023). Briefly, over four training days, a mouse was trained to identify and swim to a platform in a water maze for five trials per day. The location of the platform was randomized at every trial to prevent memorization. Following training, a mouse was tested over four testing days, for five trials per day, with randomized platform positions. After testing in lighted conditions, functional vision was measured under dark-adapted conditions under a dim red light. Under dark-adapted conditions, a mouse was trained over 2 training days, then tested over 4 testing days for 5 trials per day, with randomized platform positions. Time-to-platform metrics over 20 trials were independently averaged for light-adapted and dark-adapted conditions. Occasionally, a test mouse has been found to prefer swimming or to repeatedly float with no desire to reach the platform. The following criteria for exclusion were used. All data from a mouse (light and dark) will be discarded if during the test phase a mouse's mean swim time is greater than one standard deviation from their genotype's median and subjective evidence of swimming preference (i.e., consistent floating, that is floating more than three times over four test days or more than three corrections of floating per test episode, escaping the researcher by jumping into the water from the platform) is also present (Hassan et al. 2023). For swim assays, each animal is considered a biological datapoint and standard error of the mean was calculated using the averaged time-to-platform of each animal.

Statistical analysis

Scientific visualization was performed using GraphPad PRISM 11.0.2, and statistical analysis was performed using 2-tailed Welsh's *t*-test with assumption of unequal standard deviation. Error bars in graphs and in manuscript text represent standard error of the mean. Grubbs' tests were performed and datapoints meeting criteria for outliers (alpha < 0.05) were excluded.

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