Compulsive-like behaviors in DISC1-mice

Nadezhda Chizhova, ICG SB RAS, Novosibirsk, Russia
chnadezhda1995@gmail.com
Kristina Smirnova, NSU, Novosibirsk, Russia & PhBMRI, Novosibirsk, Russia
vedelina@mail.ru

MOTIVATION AND AIM

The *DISC1* gene (*Disrapted-In-Schizophrenia-1*) encodes a multifunctional scaffold protein that regulates many aspects of nervous system`s development and is involved in signaling and associated with a number of human psychopathologies (Brandon et al, 2009).

It was shown that a deletion occurred in the exon 2-3 region led to an increase in the marble burying test, which is one of the most common tests for obsessive-compulsive-like behavior (Wulaer et al, 2018; Alonso et al, 2015). Currently genetic lines of mice with point mutations, fall into this region, have been created: *DISC1*-Q31L$^{-/-}$ and *DISC1*-L100P$^{-/-}$ (models of depression and schizophrenia resp.) (Clapcote et al, 2007; Lipina et al, 2010 and 2011). We have previously shown that homozygous males with the *DISC1*-Q31L mutation, but not the *DISC1*-L100P, bury more balls in the marble burying test, which is a sign of compulsive behavior in these mice (Smirnova et al, 2020).

The aim of this study is to evaluate the compulsive behavior in *DISC1*-Q31L$^{+/-}$, *DISC1*-L100P$^{+/-}$ and *DISC1*-L100P$^{+/-}$ /Q31L$^{+/-}$ mice, as well as to assess genotype`s and, accordingly, behavior`s contribution of homozygous mother.

Animals

♂ \ ♀	WT	Q31L-HOM	L100P-HOM
WT	WT	-	-
Q31L-HOM	Q31L-HET	-	L100P-HET(f) / Q31L-HET(m)
L100P-HOM	L100P-HET	Q31L-HET(f) / L100P-HET(m)	-

Parental Crossbreeding Scheme

All mice were kept in vivarium of PhBMRI.

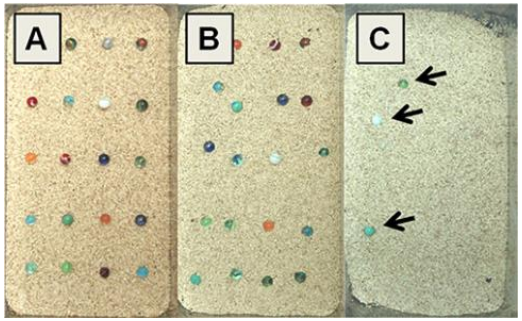
Behavioral tests

Testing of the obtained experimental mice was performed at the age of about 3 months. The marble burying test was carried out in the home room according to the protocol (Angoa-Pérez et al, 2013). The open field test was conducted in accordance with the description (Seibenhener & Wooten, 2015).

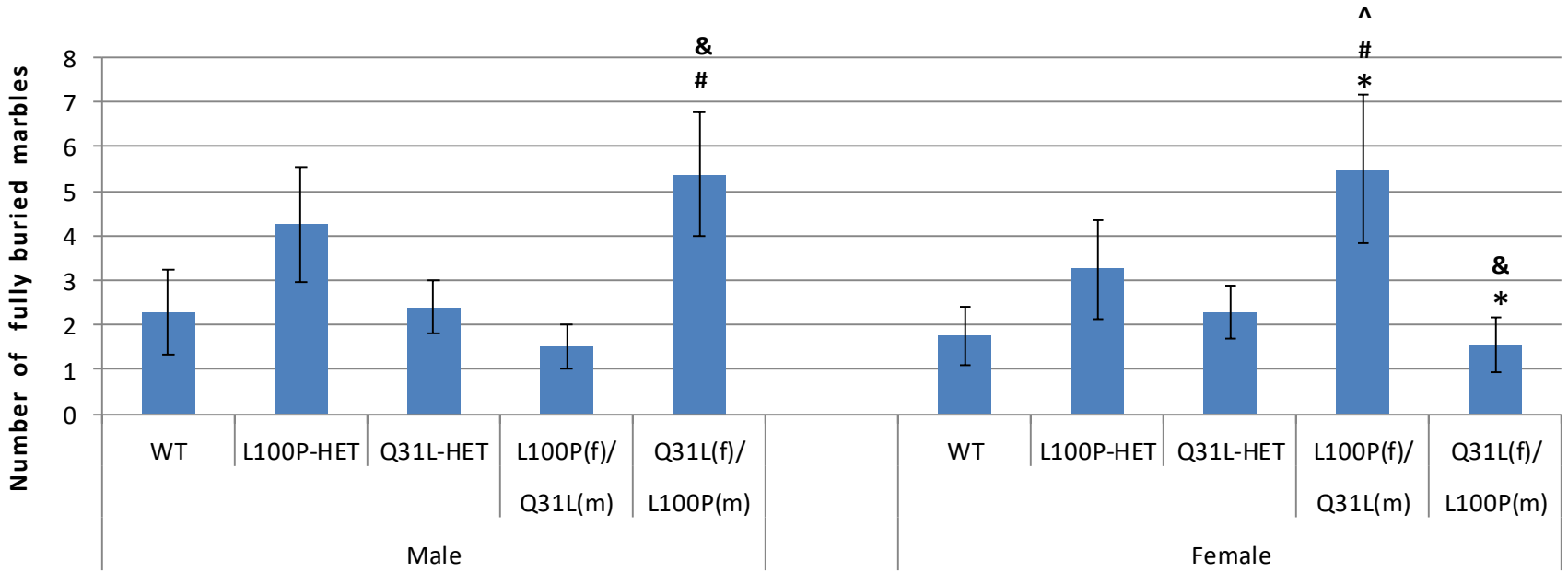
All conditions for working with animals were observed in accordance with international standards (Council of the European Communities Directive 86/609/EES).

Results

1. In the marble burying test the differences between the following groups were found:
   - Males Q31L(f)/L100P(m) and females L100P(f)/Q31L(m) buried more balls than the same sex WT mice
   - Males Q31L(f)/L100P(m) instilled more balls than same females and than L100P(f)/Q31L(m) males
   - Males L100P(f)/Q31L(m) buried less balls compared to females
   - Females L100P(f)/Q31L(m) instilled more balls compared to Q31L(f)/L100P(m) and heterozygous Q31L females
2. In the open field test was revealed differences in activity only between Q31L(f)/L100P(m) (made more racks) and heterozygous Q31L males



Cages before (A) and after (C) the marble burying test (photographsfrom Angoa-Pérez et al, 2013)



The number of buried marbles in the test for compulsive behavior in *DISC1*-mutant mice (mean±SEM). *- p<0.05 vs same genotype males; # - p<0.05 vs same sex WT ; ^ - p<0.05 vs same sex Q31L-HET; & - p<0.05 vs same sex L100P(f)/Q31L(m)*.

Conclusion

The lack of increased activity in the studied groups of mutant mice allows us to consider the results of the marble burying test to be correct for determining their compulsive-like behavior.

The presence of single mutant allele (both *DISC1*-Q31L and *DISC1*-L100P) is not sufficient for the expression of compulsive-like behavior in mice. However, mice that combine both mutations are predisposed to this behavior and exhibit it depending on their sex and mother's genotype: this behaviour characterize heterozygous males whose mothers were homozygous for *DISC1*-Q31L mutation, and females whose mothers were homozygous for *DISC1*-L100P mutation.

Given the results of our previous work, we suppose that the homozygosity of mothers with *DISC1*-Q31L mutation leads to compulsive-like behavior as in males *DISC1*-L100P$^{+/-}$/Q31L$^{+/-}$, and in males *DISC1*-Q31L$^{-/-}$, whereas females with two mutations are similarly affected by the homozygosity of mothers with the *DISC1*-L100P mutation, but not *DISC1*-Q31L.

This conclusion can be confirmed or disproved in subsequent experiments, where (1) compulsive-like behavior would be studied in females homozygous for these mutations and (2) the mother genotype`s influence on compulsive-like behavior would be explored in heterozygous for *DISC1*-Q31L and *DISC1*-L100P mutations mice separately.

Acknowledgment

Mice were provided by UNU "Biological collection - genetic biomodels of neuropsychic diseases" (No. 493387) PhBMRI (Petrova et al, 2018).

The study was supported by budgetary funding for basic scientific research of the Scientific Research Institute of Physiology and Basic Medicine (theme No. AAAA-A16-116021010228-0).