Poster

Investigating the effect of neurodevelopmental disorder missense variants on cognitive function with *Drosophila*

Anna Koutská[1], Tereza Koníková[1], Petra Havlíčková[2], Ivana Kutá-Smatanová[2], Michaela Fencková[1]

[1]*Laboratory of Neurogenetics, Faculty of Science, University of South Bohemia, Ceske Budejovice, Czech Republic*

[2]*Department of Chemistry, Faculty of Science, University of South Bohemia, Ceske Budejovice, Czech Republic*

fenckm00@prf.jcu.cz

Over 200 million people in the world are affected by Intellectual Disability (ID) and/or Autism Spectrum Disorder (ASD), debilitating and often co-occurring neurodevelopmental disorders [1; 2]. They have problems with cognitive and adaptive functioning, including learning, communication, and social skills. ID/ASD have mostly monogenic causes. Majority of the mutations (non-sense, frameshift, or splice-site) are likely gene disrupting (LGD). However, there is a growing number of de novo missense genetic variants with uncertain significance (VUS) that increase the disease risk to similar or even greater degree than LGD [3]. It is challenging to comprehend how VUS affects ID/ASD symptoms; hence it is important to develop an efficient model.

We are introducing 40 conserved recurrent VUS in Drosophila orthologs of ID/ASD genes with CRISPR-HDR. We will investigate their effect on cognitive function with habituation, a conserved form of learning that is based on suppressing a response to a repetitive but meaningless stimulus. Habituation is a prerequisite for higher cognitive functions [4; 5] and, as was shown previously, is affected in Drosophila LGD models of ID/ASD [6]. Thus, habituation is suitable for investigating the effect of VUS on cognitive function in ID/ASD. We use a high-throughput light-off jump habituation platform where the flies suppress their jump response to a light-off stimulus. This study should shed light on the effect of VUS on ID/ASD pathology and, most importantly, on cognitive function that cannot be easily assessed with simpler cell-based models.

[1] European intellectual disability research network (2003). 1-129. *European Commission.*

[2] Zablotsky B., Black LI, Maenner MJ etc. (2015) *Estimated prevalence of autism and other developmental disabilities following questionnaire changes in the 2014*. National Health Interview Survey: National health statistics reports, **87.**

[3] Iossifov I., O´Roak B. J., Sanders S. J., et al. (2014) *The contribution of de novo coding mutations to autism spectrum disorder,* Nature, **515**(7526), 216-221.

[4] Kavšek M. (2004) *Predicting later IQ from infant visual habituation and dishabituation: A meta-analysis.* JADP, **25**(3), 369-393.

[5] Domsch H., Lohaus A. and Thomas H. (2009) *Prediction of childhood cognitive abilities from a set of early indicators of information processing capabilities.* Infant Behavior and Development, **32**(1), 91-102.

[6] Fenckova M., Blok L.E.R., Asztalos L., et al. (2019*) Habituation Learning Is a Widely Affected Mechanism in Drosophila Models of Intellectual Disability and Autism Spectrum Disorders*. Biological Psychiatry, **86**(4), 294-305.

This work is supported by a grant from the Czech Science Foundation (grant no. 23-07810S) and an EMBO Installation grant (grant no. IG-5310-2023) to M. Fenckova.