View metadata, citation and similar papers at core.ac.uk

brought to you by CORE

provided by Edinburgh Research Explorer

THE UNIVERSITY of EDINBURGH

Edinburgh Research Explorer

Of mice, men, and NLGN4

Citation for published version:
Osterweil, E 2019, 'Of mice, men, and NLGN4', *Science Translational Medicine*.
https://doi.org/10.1126/scitranslmed.aaz0307

Digital Object Identifier (DOI):
10.1126/scitranslmed.aaz0307

Link:
Link to publication record in Edinburgh Research Explorer

Document Version:
Peer reviewed version

Published In:
Science Translational Medicine

General rights
Copyright for the publications made accessible via the Edinburgh Research Explorer is retained by the author(s) and / or other copyright owners and it is a condition of accessing these publications that users recognise and abide by the legal requirements associated with these rights.

Take down policy
The University of Edinburgh has made every reasonable effort to ensure that Edinburgh Research Explorer content complies with UK legislation. If you believe that the public display of this file breaches copyright please contact openaccess@ed.ac.uk providing details, and we will remove access to the work immediately and investigate your claim.

Download date: 31. Jul. 2020

Editor's Choice Summary

Issue date: (we will complete)
DOI: 10.1126/scitranslmed.axxXXXX (we will complete)
Volume: (we will complete)
E-locator: (we will complete)

Overline: Autism Spectrum Disorder

Title: Of mice, men, and *NLGN4*

One-sentence summary: Expression of the autism risk factor *NLGN4* is divergent between human and mouse neurons.

Your name: Emily K. Osterweil
Your affiliation:
Centre for Discovery Brain Sciences, Simons Initiative for the Developing Brain
University of Edinburgh, Edinburgh, UK EH8 9XD
Emily.osterweil@ed.ac.uk

Text of summary

Genetically modified mouse models are of clear value for teasing apart the mechanisms contributing to altered brain function in Autism Spectrum Disorder (ASD). One drawback is that the gene of interest may be functionally divergent in humans. This issue is highlighted in a recent study by Marro et al., which investigates the expression and function of the highly penetrant ASD gene *NLGN4* in human embryonic stem cell (hESC)-derived neurons. The role of the neuroligin-4 protein encoded by *NLGN4* has been described based on studies of the mouse ortholog *Nlgn4*, which is poorly conserved. These studies indicated that neuroligin-4 is modestly expressed in brainstem, retina, and spinal cord, where it is restricted to inhibitory neurons. In contrast, Marro et al. found that neuroligin-4 is highly expressed in post-mortem samples of human cortex and is concentrated in excitatory synapses. They went on to show that overexpression of a mutant *NLGN4* with the R704C mutation identified in ASD increases both excitatory synapse number and excitatory transmission in hESC-derived neurons. In contrast to previous studies of neuroligin-4 in mice, these results suggest that *NLGN4* mutations may contribute to pathophysiology in humans through enhanced rather than diminished excitatory drive.

This work illustrates the importance of investigating disease-relevant mutations in human cellular systems, especially with respect to poorly conserved genes such as *NLGN4*. Now researchers can investigate the extent to which other *NLGN4* mutations disrupt synaptic function in human neurons and test potential therapeutic strategies to target excitatory transmission. A major limitation of this study is that it is restricted to an in vitro culture system, which makes it difficult to assess the full impact of *NLGN4* mutation on nervous system function. Nevertheless, the divergence of neuroligin-4 expression and function revealed by this work is an important reminder that models of both mouse and (wo)man are needed to fully understand the genetic basis of ASD.

Highlighted Article

Marro SG, Chanda S, Yang N, Janas JA, Valperga G, Trotter J, Zhou B, Merrill S, Yousif I, Shelby H, Vogel H, Kalani MYS, Südhof TC, Wernig M.
Neuroligin-4 Regulates Excitatory Synaptic Transmission in Human Neurons.
Neuron. 2019 Aug 21;103(4):617-626.e6. doi: 10.1016/j.neuron.2019.05.043.

URL of citation

https://www.cell.com/neuron/pdf/S0896-6273(19)30496-9.pdf