Shank3 mutations and HCN channelopathy: one size *does not* fit all

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Autism, from the Greek autos ("self") and ismos ("action") was initially described as a congenital lack of interest in other people. Approximately 1 in 88 children in the United States is currently diagnosed with autism spectrum disorder (ASD). ASD symptoms begin early in childhood and include social-interaction deficits and stereotyped, repetitive behavioral interests that interfere with daily activities.

Recent large-scale genomic studies suggest an association between ASD and mutations in the SHANK3 gene (SH3 and multiple ankyrin repeat domains protein 3) (Leblond et al., 2014), which encodes a scaffolding protein enriched at the postsynaptic density fraction (PSD) of glutamatergic synapses. The full length SHANK3 protein contains several domains for protein–protein interactions: ANK domain, SH3 domain, PDZ domain, proline-rich region domain and SAM domain.

In mice, the Shank3 gene has 22 exons, 6 intragenic promoters and 5 alternative splicing exons, resulting in diverse protein isoforms, namely isoforms lacking some interaction domains (Monteiro and Feng, 2017). Likely due to these intragenic promoters, multiple research groups have failed to fully delete all SHANK3 isoforms in mutant mouse lines. Out of 13 mouse lines that have been generated with experimental Shank3 mutations, 9 mutant lines show aberrant social behaviors, and 9 display repetitive behavior. These mutant mice carrying experimental mutations are thus highly valuable for understanding Shank3 role, but also reveal that each mutation within the Shank3 gene has unique physiological impact and should perhaps be studied individually.

A recent study has shown that SHANK3 mutations can cause Ih channelopathy and that SHANK3 protein can directly bind to hyperpolarization-activated cyclic nucleotide-gated channel proteins (HCN) mediating Ih currents (Yi et al., 2016). Previous reports have also indicated that HCN2 transcripts are enriched in the olfactory bulb, hippocampus, thalamus and brain stem (Moosmang et al., 1999). Interestingly, in the brain, Shank3 mRNA is

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enriched in cortex, hippocampus, striatum, cerebellum and thalamus (Wang et al., 2014), and some authors have suggested associations between thalamic abnormalities and ASD.

In a recent issue of The Journal of Physiology Zhu et al. (2018) compared for the first time the physiological consequences of two different Shank3 mutations in neurons of the thalamus. The key finding of this study is the demonstration that Shank3 deficiency in thalamic neurons can cause HCN channelopathy and altered intrinsic neuronal properties. Interestingly the authors demonstrate that Shank3$^{\Delta 13\text{-}16}$ mutation, a mutation where SHANK3 protein lacks its PDZ domain of interaction, causes a reduction in HCN2 expression and Ih current amplitude in thalamocortical neurons. Moreover, thalamocortical neurons carrying this Shank3$^{\Delta 13\text{-}16}$ mutation share similar defects in basic electrical properties as thalamocortical neurons lacking HCN2. In contrast, this finding is not observed for thalamocortical neurons carrying Shank3$^{\Delta 4\text{-}9}$ mutation, a mutation where SHANK3 protein lacks its ANK domain for protein–protein interactions. These data thus emphasize the existence of isoform-specific functions, where particular Shank3 domains might be important for Ih currents but not others. These findings also help to explain how different Shank3 gene mutations may result in distinct phenotypic consequences in different transgenic mice. Importantly when thinking about patients with SHANK3 mutations, careful genotype–phenotype patient stratification will be required for testing specific pharmacological agents. Although HCN channels might be appealing targets for drug development, patients carrying different Shank3 gene mutations may differently benefit from such drugs, or not.

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