Sarah Hughes- Lay Summary

"Controlling the message": How the messenger RNA derived from genes linked to autism spectrum disorder affect brain development.

SMARCB1 is one of many genes associated with autism spectrum disorder. However, we currently have no idea how SMARCB1 is needed for normal brain development. This is important as patients with autism spectrum disorder have subtle changes in the structure of their brain. As we grow, our brains are built by adding various cells like neurons derived from neuronal stem cells (NSCs). This process is abnormal in patients that have inherited mutations in autism spectrum disorder-risk genes. Thus, we will test a theory that changes in the function of genes associated with autism spectrum disorder affect NSC growth or function lead to altered formation of the normal pattern of neurons in the brain and thus, affect cognition.

Our genes are encoded in our DNA. Within cells, DNA is normally wrapped up in various proteins to form chromatin. These proteins change the local availability of DNA such that a gene can be functionally turned on or off. Turning a gene 'on' involves making a copy of the genes DNA as a messenger RNA (mRNA) which provides instructions for the cell to make proteins. Our study is focused on known autism spectrum disorder-associated genes encoding the chromatin remodeling proteins which change how DNA and proteins interact. These proteins are needed to ensure the proper cell type (such as in a NSC) turns critical genes on or off as needed at the proper point in development. These changes in gene activity are essential for normal development of all tissues, including the brain. Currently the specific role of the chromatin remodeling genes during brain development is not very well understood.

This project focuses specifically on one chromatin remodeling gene called SMARCB1, which encodes a protein that, in combination with several others, regulates genes encoded in our DNA. However, it is very difficult to study these proteins in complex laboratory animals like rats or mice. Thus, we are going to use a much more simple laboratory animal the fruit fly. This is possible as fruit flies have a SMARCB1 equivalent gene called Snr1. We confirmed that like human SMARCB1, fly Snr1 is required for the proper cell growth and differentiation of NSCs in the developing brain. Interestingly we also find that a group of proteins interact with the Snr1 mRNA affecting if Snr1 protein is made or not. This type of cellular regulation of Snr1 protein in NSCs in the developing brain is a new theory and has not been studied before.

The advantage of using simple animals like flies is that we can relatively easily determine how, where and when Snr1 mRNA is regulated in cells within the developing brain. We have already identified different parts of the Snr1 mRNA that seem to be important for this regulatory event in NSCs. The next step is to determine which of the proteins we found that bind Snr1 mRNA directly affects the process of making Snr1 mRNA into protein. It also is likely that different proteins interact with different parts of Snr1 mRNA, affecting where and when it functions within the NSCs of flies. The final step of our study will be once we have clearly sorted which proteins interact with which part of the Snr1 mRNA. With this knowledge in hand we will look in the more complicated mouse brain to confirm the similar processes in the mammalian brain. Similarly, we will begin to link these changes in the cell in terms of SMARCB1 mRNA activity in terms of brain development by determining how changing this process changes learning and memory behavior of mice.

Increased understanding of the how cells control production of this critical chromatin remodeling protein is important to supporting ongoing searches for drugs that target these processes. With the

advent of mRNA-based drugs we are also excited about identifying completely new therapeutic options for autism spectrum disorder patients in the future.