Translational Analysis of Patients with ANKS1B Neurodevelopmental Syndrome and Corresponding Mouse Model.

Albert Einstein College of Medicine

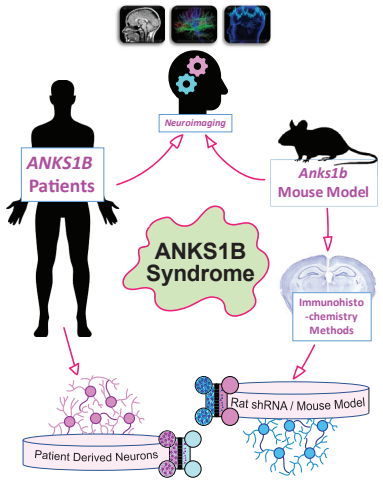
Montefiore Inspired Medicine

Ilana V. Deyneko, Changhoon Cho, Abigail Carbonell, Bryen Jordan, Sophie Molholm

Abstract:

Haploinsufficiency of the gene ANKS1B underlies a rare genetic disease that presents as a neurodevelopmental syndrome. This gene encodes the protein AIDA-1, which was shown to be present throughout the brain by mouse proteomic analysis. This potentially indicates a wide-spread influence of AIDA-1 on many neuronal functions, but it is unclear which areas of the brain are most affected by this disorder. Several families with deletions in this gene have recently been identified; a few of these families were brought in for more in-depth neuropsychological testing and neuroimaging at our institute. The symptoms of the affected patients include Autism, Attention Deficit/Hyperactivity Disorder, speech and motor deficits, and global developmental delays. Based on a clinical read of structural MRI scans from 11 patients, the majority of the patients (n=9) had abnormal findings such as dysgenesis or thin body of the corpus callosum and hyperintensities in white matter. Additionally, we have completed histological staining of our ANKS1B deletion mouse model to look at the affects of AIDA-1 loss on the brain. Based on these findings, we plan to study the effects of this syndrome on specific areas of the brain within the patient population with a focus on the corpus callosum. We will be using rigorous, automatic processes to analyze patient MRI scans.

Translational Methods for Studying Disease:



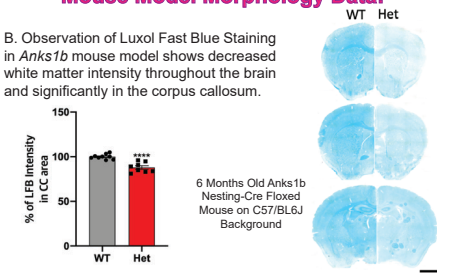
MRI Abnormalities Found in Patient Populations:

A. A sample of our patient population with abnormalities in their clinical MRI reads. The corpus callosum and white matter were particularly affected. Of 11 patients that recieved MRI scans, 9 presented with abnormalities.

Patient	Age	MRI Read (Carbonell et al. 2019)
EIN-1-2	6	Small T2 hyperintensities in Rt caudate nucleus head, remote ischemic injury or atypical perivascular space. T1 hypointensity in corpus callosum midbody. Thin corpus callosum body.
TOR-2	2.4	Nonspecific tiny T2 hyperintensity in Lt para ventricular WM, may represent prominent perivascular space. Corpus callosum subtle thinning in body region.
GEN-1	3	Dysgenesis of corpus callosum.
GEN-5	N/A	Partial agenesis of corpus callosum.
DEC-2	15	Enlarged ventricles, thin corpus callosum.
DEC-6	8	Shallow arachnoid cyst in middle of cranial fossa anteriorly on left.
DEC-7	35	Enlargement of lateral and 3rd ventricles (35yrs), CT brain reportedly normal at 3 months, possible L frontal old infarction at 12 months post open heart surgery.
DEC-10	6	T2 hyperintensity in posterior corona radiata WM.
DEC-11	7	T2 hyperintensity Rt hippocampus.

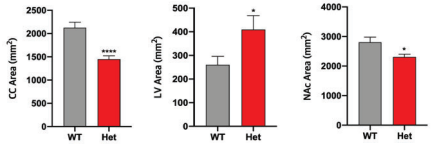
Mouse Model Morphology Data:

B. Observation of Luxol Fast Blue Staining in *Anks1b* mouse model shows decreased white matter intensity throughout the brain and significantly in the corpus callosum.



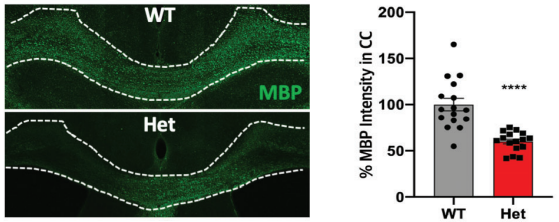
Areas that were significantly different comparing WT to Het Mouse

C. Corpus Callosum D. Lateral Ventricle E. Nucleus Accumbens

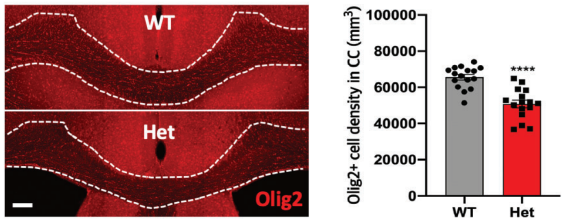


Affected Myelination in the Corpus Callosum in Anks1b Mouse Model

F. In the mouse corpus callosum, there is significantly reduced myelin protein.



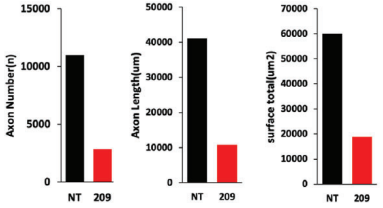
G. There is also a significantly reduced number of oligodendrocytes in Het mice.

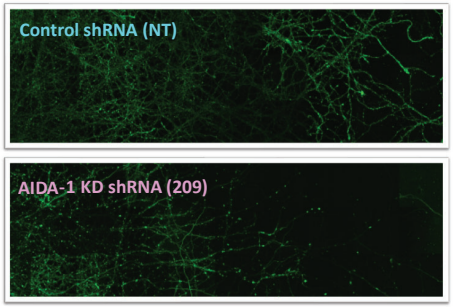


Immunostaining for Myelin Basic Protein and Olig2+ Cells

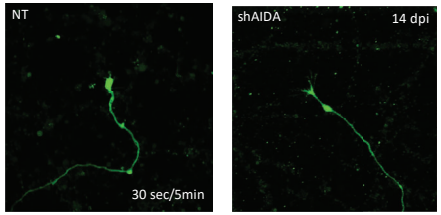
Impaired Axon Growth Observed in Neuron Cell Cultures

H. To look more closely at the affects of AIDA-1 loss, we cultured human derived axons in a microfluidics chamber. AIDA-1$^{-/-}$ axon growth is significantly diminished.





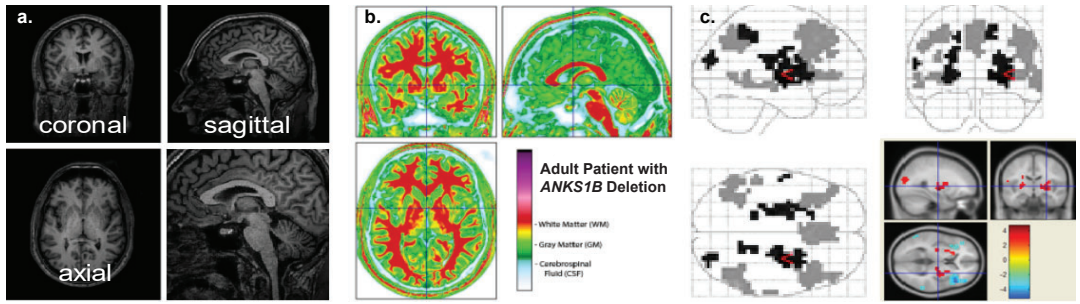
I. Reduced growth may be due to impaired axon guidance. There appear to be deficits at the growth cone of axons in the microfluidics cultures usign human derived neurons.



Next Step: Unbiased Voxel-Based Morphometry (VBM) Analysis for Single-Patient Studies

J. Using a semiautomatic Matlab system in conjunction with SPM12b and CAT12c software, we will segment brain tissue as Gray Matter (GM) or White Matter (WM) (2b). We will then perform an unbiased screen across brain regions and visualize ROIs using XJviewd (2c). Bottom-right of 2c demonstrates an example of clusters projected onto canonical brain. This facilitates automatic fragmentation of the whole brain into clusters where statistically significant differences are observed between ANKS1B patients and the normalized NT (2c).

K. We can complete analgous experiments in our mouse model as well.



Refernces:

Carbonell, A. U. et al. Haploinsufficiency in the ANKS1B gene encoding AIDA-1 leads to a neurodevelopmental syndrome. Nat. Commun. 10, (2019)

Hinkley, L. B. N. et al. The role of corpus callosum development in functional connectivity and cognitive processing. PLoS One 7, (2012).

Mühlau, M. et al. Voxel-based morphometry in individual patients: A pilot study in early Huntington disease. Am. J. Neuroradiol. 30, 539–543 (2009).