ANKS1B

Disease/Syndrome Features:
In 2017, chromosome microarray analyses identified a ~370 kb deletion in the *ANKS1B* gene in individuals from a single family presenting with speech apraxia, motor dyspraxia, developmental delays, and autism spectrum disorders (ASD). This deletion was paternally inherited and present in 3 out of 4 children [1]. Since then, 11 additional individuals in the USA, Europe, and the Middle East displaying speech and motor deficits, autism, and developmental delays were found to have related deletions [1]. The *ANKS1B* gene is only found in vertebrates, and with highest homology orthologs present in mammals. The gene spans ~1.2 mb across chromosome 12 band 23.1 (12q23.1) and contains approximately 30 exons, with the exact number depending on the genome repository. Deletions identified in probands are roughly 100 to 400 kb in size and result in the loss of 3-7 exons in the 5' region of *ANKS1B*. No deletions in the 3' region have been identified, and all probands identified to date are heterozygous. Normal transcription of *ANKS1B* results in multiple variants that can be broadly classified as large *ANKS1B* variants containing the 5' exons, or shorter variants lacking the exons deleted in probands [2]. This suggests that the deletions identified in humans so far would only affect expression of larger *ANKS1B* transcripts.

Almost all subjects with *ANKS1B* deletions show speech impairments, including delayed achievement of developmental milestones for speech. In some cases, a formal diagnosis of speech apraxia or developmental articulation disorder has been made. Motor phenotypes are also observed, including delays in developing fine motor and/or gross motor skills. Developmental coordination disorder and Tourette's are among the motor disorders diagnosed. Several subjects have also been diagnosed with autism spectrum disorder. Cognitive impairment is a variable finding, with subjects ranging from normal IQ to intellectual disability. On neuroimaging, three subjects show thinning of the corpus callosum by anatomical MRI, two show enlargement of brain ventricles. In most cases, heterozygous deletions were inherited from a parent with a normal to mild phenotype.

Protein/Pathway:
ANKS1B encodes the protein AIDA-1 (amyloid precursor protein intracellular domain associated-1 protein). AIDA-1 is an adaptor protein implicated in synaptic and nuclear function[1] that is enriched in the cerebral cortex, hippocampus, and cerebellum[2]. AIDA-1 is principally expressed in neurons where it is one of the most abundant proteins at postsynaptic densities (PSDs)[3-6]. At the PSD it binds to NMDARs and the adaptor protein PSD95 [3] through the first two PDZ domains on PSD95**.** Synaptic activity causes AIDA-1 to shuttle into the nucleus and regulate Cajal body stability and nucleolar morphology [3,7]. Recent work shows that AIDA-1 is required for the transport of GluN2B subunits of NMDARs into hippocampal synapses [8]. Loss of AIDA-1 leads to GluN2B accumulation in the endoplasmic reticulum (ER), reduces levels of GluN2B at synapses, decreases GluN2B-mediated currents, and impairs NMDAR-mediated long-term potentiation (LTP) and long-term depression (LTD) in the hippocampus [8]. A growing number of studies implicate *ANKS1B* in disease. As with NMDARs and their

associated proteins [9-11], recent studies link *ANKS1B* to neuropsychiatric disorders including schizophrenia [12-15], and autism spectrum disorders (ASD) [16-19]. Analysis of the AIDA-1 interactome using quantitative proteomic techniques has uncovered roles in protein networks involved in synaptic function and the etiology of neurodevelopmental disorders [1], which provides potential causal links between disruption of this gene and the associated disorders.

Mice lacking *ANKS1B* in the nervous system (using a Nestin-Cre driver) have been developed, but only heterozygotes are viable. Homozygotes die late in embryogenesis or perinatally for unknown reasons, which may explain the lack of probands identified with homozygous deletions. Mice with homozygous deletion specifically in neurons of the forebrain (using a CaMKIIa-cre driver) are viable and show impaired synaptic function and reduced NMDA-dependent plasticity in the hippocampus [8]. Synapses in stratum radiatum of mutant mice show increased conductance of the NMDA receptor subunit GluN2A with a corresponding decrease in GluN2B-mediated currents. In the absence of AIDA-1, GluN2B subunits become enriched in the endoplasmic reticulum, suggesting AIDA-1 regulates the intracellular transport or maturation of NMDA receptor subunits [8]. Heterozygous mice display behavioral correlates of neurodevelopmental disorders. Mutant mice display deficits in sociability as measured using the three chambered sociability test, mild hyperactivity, and show deficits both in acoustic startle and pre-pulse inhibition [1]. Tests of fine motor skills using tape removal show deficits in the absence of AIDA-1. Results suggest heterozygotes may represent a viable model of a novel *ANKS1B*-related neurodevelopmental syndrome.

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Support Groups and Information:
Anks1b Deletion (private Facebook group)

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