Collagen XIX Point Mutant Leads to Schizophrenia Related Behaviors Due to Synapse Impairment in Mice

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Schizophrenia is a complex brain disorder that affects 1% of the population and is characterized by alterations in cognitive function, acquisition and expression of behaviors not seen in healthy individuals, and loss of behaviors normally present in healthy individuals (Gonzalez-Burgos et al., 2012). Mounting evidence suggests that schizophrenia-associated behaviors result from alterations in the assembly and function of synapses (Liao et al., 2012). Labwork has identified roles for an extracellular matrix molecule that has been loosely associated with familial schizophrenia, Collagen XIX (COL19A1), in the assembly of inhibitory synapses. A family with a heterozygous mutation in COL19A1 that exhibited a number of neurologic and psychiatric symptoms was also identified. To study the impact of this mutation (Collagen XIX [p.Ala388Cysfs*56]), the previous project engineered mice to harbor a similar mutation (Collagen XIX [p.Ala385Cysfs*57]). The performance of these novel mutant mice and controls were measured in a series of tests, in which the mutant mice exhibited schizophrenia related behaviors. This project examined the underlying mechanisms behind these behaviors through immunohistochemistry, finding that the mutation led to loss of perisomatic inhibitory synapses, a type of synapse whose loss has been associated with schizophrenia. Using additional IHC and simulated interaction of Collagen XIX polypeptide strands, it was determined that this loss of synapses was likely due to deficits in their initial formation rather than from phagocytosis by activated microglia. Taken together, these studies identify a novel mutation in Collagen XIX that cause structural and behavioral changes similar to those associated with schizophrenia.