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Sommario	Shank proteins are the major scaffold proteins that organize the postsynaptic density at the excitatory synapses. Shank1-3 proteins are associated with type I mGluRs via an interaction with Homer in the proline-rich domain. Phelan-McDermid (PMS) syndrome is characterized by intellectual impairment, absent or delayed speech, and autistic-like behaviors. Loss of Shank3 is now considered to cause the neurobehavioral symptoms of PMS. Furthermore, a significant number of SHANK3 mutations have been identified in patients with Autism Spectrum disorders ASD, and SHANK3 truncating mutations are associated with moderate to profound ID. In this study, we investigated the molecular mechanisms associated with the ASD-like behaviors observed in Shank311-/- mice in which exon 11 has been deleted. Our results indicate that Shank3 is essential to mediating mGlu5 receptor signaling by recruiting Homer1b/c to the PSD, specifically in the striatum and cortex. Moreover, augmenting mGlu5 receptor activity by administering 3-Cyano-N-(1,3-diphenyl-1H-pyrazol-5-yl)benzamide (CDPPB) ameliorated the functional and behavioral defects that were observed in Shank311-/- mice, suggesting that pharmaceutical treatments that increase mGlu5 activity may represent a new approach for treating patients that are affected by PMS and SHANK3

	mutations.
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