Moving towards a neurodevelopmental understanding of Schizophrenia

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Neuro-developmental genetic risk factors have been implicated as playing a major role in schizophrenia pathogenesis. Furthermore, neuro-anatomical and neurochemical alterations have been identified in post-mortem brain sections of schizophrenia patients. This includes a decrease in expression of reelin, an extracellular matrix protein that plays a pivotal role in neuronal migration during brain development and which has previously been associated with schizophrenia susceptibility. The N-terminus of reelin contains a reeler domain, a domain which has only been identified in one other protein, F-spondin, which is also an extracellular matrix protein involved in neural crest cell-migration.

As the reeler domain occurs only in proteins essential for neuronal migration, we hypothesised it plays a critical role in neurodevelopment, probably through protein-protein interactions. To test this hypothesis we screened a foetal brain cDNA library, using the reeler domain as bait in yeast two-hybrid analysis.

Several putative reeler-ligands have been identified, including proteins with functions relating to vesicular transport and docking, and neuronal maturation. Further investigations of these interactions have identified a novel reelin ligand, KIAA0893, which shares domains with proteins with membrane-associated and signalling functions as well as cytoskeletal rearrangements.

The identification of novel components of the reelin pathway will facilitate further understanding of schizophrenia pathogenesis and may identify novel drug targets for schizophrenia therapy.