"*The Alzheimer's disease gene SORL1 – discovery of a novel exon implying synaptic functions besides APP trafficking*"

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Independent approaches employing human genetics, clinical pathology, or exploratory studies in animal models have identified the *SORL1* gene as a risk factor for Alzheimer's disease (AD). More recently, identification of carriers with a destructed *SORL1* allele only in AD patients but never in non-demented individuals, has lead to the proposal that *SORL1* is an autosomal dominant AD gene. Importantly, these findings suggest that reduced SORL1 activity is noncompatible with healthy aging of the human brain

SORL1 encodes a neuronal sorting receptor (SORL1), and work from several groups including my own, have shown that SORL1 functions as a sorting determinant of intracellular APP, where SORL1 activity inhibits amyloidogenic processing in line with an observed decreased SORL1 expression in AD brains. However, the physiological role of SORL1 is still not clear.

SORL1 is present in most neurons throughout the central nervous system, but is surprisingly strong expressed in Purkinje cells, suggesting important functions in the cerebellum.

We have identified a novel SORL1 splice variant specifically expressed in human Purkinje cells where its transcript is exported out of the soma into the dendritic tree suggesting an important function regulated by local synaptic translation. This transcript is significantly reduced in AD patients, suggesting a cerebellar contribution to cognitive processing.