RTN4R

NOGO Receptor 1 (RTN4R) regulates axonal growth, as well as axon regeneration after injury. The gene maps to the 22q11.2 schizophrenia susceptibility locus and is thus a strong functional and positional candidate gene.

The reticulon 4 receptor gene RTN4R encodes Nogo 1 receptor (NgR1) in Amyotrophic lateral sclerosis, to test if the variants were associated with variable expression of the gene and whether NgR1 protein expression was modified in a transgenic mouse model of ALS. Amy et al, genotyped three single nucleotide polymorphisms (SNPs; rs701421, rs701427, and rs1567871) of the RTN4R gene in 364 ALS French patients and 430 controls. They examined expression of RTN4R mRNA by quantitative PCR in control post mortem human brain tissue. They determined the expression of NgR1 protein in spinal motor neurons from a SOD1 G86R ALS mouse model. They observed significant associations between ALS and RTN4R alleles. Messenger RNA expression from RTN4R in human cortical brain tissue correlated significantly with the genotypes of rs701427. NgR1 protein expression was reduced in Nogo A positive motor neurons from diseased transgenic animals. In conclusion, these observations suggest that a functional RTN4R gene variant is associated with ALS. This variant may act in concert with other genetic variants or environmental influences [1)].

Schizophrenia

Hsu et al evaluate evidence for genetic association between common RTN4R polymorphisms and schizophrenia in a large family sample of Afrikaner origin and screen the exonic sequence of RTN4R for rare variants in an independent sample from the U.S. They also employ animal model studies to assay a panel of schizophrenia-related behavioral tasks in an Rtn4r-deficient mouse model. They found weak sex-specific evidence for association between common RTN4R polymorphisms and schizophrenia in the Afrikaner patients. In the U.S. sample, they identified two novel non-conservative RTN4R coding variants in two patients with schizophrenia that were absent in 600 control chromosomes. In the complementary mouse model studies, they identified a haploinsufficient effect of Rtn4r on locomotor activity, but normal performance in schizophrenia-related behavioral tasks. We also provide evidence that Rtn4r deficiency can modulate the long-term behavioral effects of transient postnatal N-methyl-D-aspartate (NMDA) receptor hypofunction.

The results do not support a major role of RTN4R in susceptibility to schizophrenia or the cognitive and behavioral deficits observed in individuals with 22q11 microdeletions. However, they suggest that RTN4R may modulate the genetic risk or clinical expression of schizophrenia in a subset of patients and identify additional studies that will be necessary to clarify the role of RTN4R in psychiatric phenotypes. In addition, the results raise interesting issues about evaluating the significance of rare genetic variants in disease and their role in causation [2)].

Thomas et al, previously reported NgR1 as receptor for the epilepsy-linked protein LGI1. NgR1 regulates synapse number and synaptic plasticity, whereas LGI1 antagonizes NgR1 signaling and promotes synapse formation. Impairments in synapse formation are common in neurological disease and we hypothesized that an LGI1-NgR1 signaling pathway may contribute to the development of schizophrenia.

Variants in NgR1 and LGI1 may be associated with schizophrenia and variants in NgR1 found in schizophrenic patients have impaired LGI1-NgR1 signaling. Impaired LGI1-NgR1 signaling may contribute to disease progression [3)].

1)
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2)
Hsu R, Woodroffe A, Lai WS, Cook MN, Mukai J, Dunning JP, Swanson DJ, Roos JL, Abecasis GR, Karayiorgou M, Gogos JA. Nogo Receptor 1 (RTN4R) as a candidate gene for schizophrenia: analysis using human and mouse genetic approaches. PLoS One. 2007 Nov 28;2(11):e1234. PubMed PMID: 18043741; PubMed Central PMCID: PMC2077930.
3)
Thomas RA, Ambalavanan A, Rouleau GA, Barker PA. Identification of genetic variants of LGI1 and RTN4R (NgR1) linked to schizophrenia that are defective in NgR1-LGI1 signaling. Mol Genet Genomic Med. 2016 Mar 11;4(4):447-456. eCollection 2016 Jul. PubMed PMID: 27468420.