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A decade from discovery to therapy: Lingo-1, the dark horse in neurological and psychiatric disorders

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A decade from discovery to therapy: Lingo-1, the dark horse in neurological and psychiatric disorders

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Abstract

Leucine-rich repeat and immunoglobulin domain-containing protein (Lingo-1) is a potent negative regulator of neuron and oligodendrocyte survival, neurite extension, axon regeneration, oligodendrocyte differentiation, axonal myelination and functional recovery; all processes highly implicated in numerous brain-related functions. Although playing a major role in developmental brain functions, the potential application of Lingo-1 as a therapeutic target for the treatment of neurological disorders has so far been under-estimated. A number of preclinical studies have shown that various methods of antagonizing Lingo-1 results in neuronal and oligodendroglial survival, axonal growth and remyelination; however to date literature has only detailed applications of Lingo-1 targeted therapeutics with a focus primarily on myelination disorders such as multiple sclerosis and spinal cord injury; omitting important information regarding Lingo-1 signaling co-factors. Here, we provide for the first time a complete and thorough review of the implications of Lingo-1 signaling in a wide range of neurological and psychiatric disorders, and critically examine its potential as a novel therapeutic target for these disorders.

Key Words: Lingo-1 signaling; gene expression; neurological pathologies; psychiatric disorders; therapeutic strategies

1. Introduction

Myelination is a fundamental progressive process occurring throughout the brain from embryonic stages of development through to adolescence. During the last decade, novel signaling pathways, largely involving myelin associated inhibitory proteins including: myelin associated glycoprotein (MAG), oligodendrocyte-myelin glycoprotein (OMgp) and neurite outgrowth inhibitor (Nogo) were found to inhibit the growth of neurons and myelination. Mechanisms involved in these processes largely implicate a receptor complex comprised of the p75 neurotrophin receptor and the (then) newly discovered Nogo Receptor (NgR) (Caroni and Schwab, 1988; Chen et al., 2000; Domeniconi et al., 2002; Fournier et al., 2001; GrandPré et al., 2000; Liu et al., 2002; Kevin C. Wang et al., 2002a, 2002b). The mechanism by which NgR regulates axonal growth is initiated by the high affinity binding of Nogo to the NgR, however the NgR itself does not contain a transmembrane domain and as such requires a transmembrane co-receptor in order to elicit intracellular signals. While p75 has been shown to elicit the transduction of inhibitory NgR signals (Kevin C. Wang et al., 2002a), certain NgR containing cell types not expressing p75, were still found to be able to transduce inhibitory NgR signals (Kevin C. Wang et al., 2002a), leading to the discovery of TNF receptor orphan Y (TROY) as a functional homolog of p75 within the signaling complex (Shao et al., 2005). The functional ternary receptor complex was suggested to be complete when a third co-receptor was discovered in the form of Lingo-1 (Leucine-rich repeat and Ig domain-containing, Nogo receptor-interacting protein) (Mi et al., 2004) and the Lingo-1/NgR/p75 or TROY complex was born.

Lingo-1 was first identified as LERN1 (leucine-rich repeat neuronal protein 1), a transmembrane leucine-rich protein coded for by the novel gene *LRRN6A* discovered by Carim-Todd and collaborators (Carim-Todd et al., 2003) on human chromosome 15q24-26 just over a decade ago. It was suggested that due to the developmental expression profile of *LRRN6A*, the predicted protein structure of LERN1 and its similarity to proteins already identified as having a vital role in nervous system development and maintenance, that the *LRRN6A* gene and LERN1 protein would be highly relevant for further study in neurobiology. While a number of previously uncharacterized central nervous system-specific proteins were being assessed for their ability to bind to NgR, Lingo-1 was

discovered as we know it today, Leucine-rich repeat and Ig domain-containing, Nogo receptor-interacting protein (Mi et al., 2004). Lingo-1 has been widely studied in relation to multiple sclerosis and spinal cord injury due to its prominent role in myelination and myelin related processes, however there has always been lack of information in relation to psychiatric disorders. Considering the ever growing evidence that the essential developmental functions of neurite outgrowth and myelination are disrupted in psychiatric disorders like schizophrenia, it seems timely and topical to consider the role of Lingo-1 in neuropsychiatric disorders. Here we provide a comprehensive review on Lingo-1, a relatively new candidate that since discovery has been studied across a wide range of neurological disorders, and why it is a promising candidate for future research in neuropsychiatric disorders and their therapeutic approaches.

Note: For the purpose of this review, the terms *LRRN6A* and LERN1 will no longer be used and the gene and protein will be referred to as *Lingo-1* and Lingo-1 respectively.

2. Lingo-1: the Gene, Structure, Expression and Function

The identification and characterization of the *Lingo-1* gene (Carim-Todd et al., 2003) was an important first step to uncovering the function of Lingo-1. The *Lingo-1* locus on human chromosome 15q24-26 is a region that has been widely implicated in a number of psychiatric, addictive and anxiety related disorders, and genomic alterations in this chromosomal region are considered to be susceptibility factors for schizophrenia, depression, autism, panic disorders, anxiety and phobic disorders (Gratacòs et al., 2001; McInnes et al., 2010).

The *Lingo-1* gene maintains a very high degree of conservation across a large number of unrelated vertebrate species, including both mouse and rat (Carim-Todd et al., 2003). Furthermore, two additional paralogous genes have been mapped to human chromosomes 9 and 19 which were identified as *LRRN6B* and *LRRN6C*, coding for proteins LERN2 and LERN3 (Carim-Todd et al., 2003) also known as Lingo-3 and Lingo-2 respectively (Chen et al., 2006).

The Lingo-1 structure has been shown to be highly stable in a tetrameric conformation in both its crystal form and in solution, facilitated by its leucine-rich repeat-Ig-composite fold (Mosyak et al.,

2006). Due to the tetramer burying such a large surface area into the cell membrane it is thought that this may in fact serve as an efficient and stable scaffold for a binding platform, facilitating the assembly of the Lingo-1/NgR/p75 or TROY complex, localizing signaling functions to the sites of neuronal pathways that terminate axon growth (Mosyak et al., 2006). Accordingly, knowing that Lingo-1 forms tetramers may provide an answer to the still unresolved questions about the stoichiometry of the Lingo-1/NgR/p75 or TROY receptor complex. It has been hypothesized that Lingo-1 may form tetramers relative to the monomers on the cell surface, meaning that each signaling complex may consist of four of each receptor component (4:4:4) rather than one (1:1:1) as previously thought. It is apparent that Lingo-1 is involved in a number of central nervous system processes, in addition to having the ability to bind a number of signaling molecules, thus its functional roles within the central nervous system and its mechanisms of oligomerization may vary depending on the where and when it is expressed (Mosyak et al., 2006). Just recently the crystalline tetrameric formation of Lingo-1 has been confirmed by Pepinsky et. al., in addition to showing for the first time that Lingo-1 is also present as a tetramer on cells expressing full-length Lingo-1 (Pepinsky et al., 2014). This tetrameric formation on transfected cells is indicative of oligomer formation being an intrinsic property of Lingo-1 in the absence of its ligands or co-receptors (Pepinsky et al., 2014).

Proteins containing leucine-rich repeats have been shown to play an important role in protein-protein interactions (Kajava et al., 1995; Kobe and Deisenhofer, 1994; Kobe and Kajava, 2001) in a wide variety of cellular processes (Carim-Todd et al., 2003) including ligand recognition (Brose et al., 1999; Chen et al., 2001; Li et al., 1999; Vourc'h et al., 2003; Kevin C. Wang et al., 2002b). Their implication in important neurodevelopmental functions such as neuronal differentiation and growth (Halegoua et al., 1991) and the regulation of axon guidance, axon branching, cell-migration and regeneration processes (Bormann et al., 1999; Brose and Tessier-Lavigne, 2000; Ishii et al., 1996; Nguyen-Ba-Charvet and Chédotal, 2002), results consequently in their involvement in neurological diseases such as hereditary epilepsy and X-linked stationary night blindness (Bech-Hansen et al., 2000; Kalachikov et al., 2002; Morante-Redolat et al., 2002; Pusch et al., 2000). Since Lingo-1 is a leucine rich repeat protein, and considering its genetic locus is in a chromosomal region associated

with a high risk for a number of psychiatric disorders, *Lingo-1* makes for an ideal candidate for study in a vast array of neurological disorders.

Within the healthy adult human brain *Lingo-1* RNA expression was found to be abundantly and almost exclusively expressed in the central nervous system (Carim-Todd et al., 2003). A closer look at the distribution of *Lingo-1* across the adult human brain showed that expression was highest in the cerebral cortex (Carim-Todd et al., 2003), a region heavily involved in sensory-motor function, cognition and working memory; the hippocampus (Carim-Todd et al., 2003), responsible for long term memory and the encoding and retrieval of multi-sensory information; the amygdala (Carim-Todd et al., 2003), a region highly implicated in the stress response (Stork and Pape, 2002), as well as the thalamus; with a more constant and basal level of expression across the remainder of the brain (Carim-Todd et al., 2003). In the context of neurological and psychiatric disorders, these brain regions that have been identified as highly expressing *Lingo-1* transcripts, have also been heavily implicated in neuropsychological disorders such as stress and panic disorders (Stork and Pape, 2002), Parkinson's Disease (Inoue et al., 2007) and Alzheimer's Disease (Zhu et al., 2007), as well as schizophrenia (Fung et al., 2010), temporal lobe epilepsy (Goffin et al., 2011) and amnesia (Jarrard, 2001), thus potentially implicating *Lingo-1* in a wide variety of central nervous system disorders.

To confirm the findings of a differential expression pattern of *Lingo-1* across the adult human brain, and due to the high degree of identity (99.5%) between human and mouse orthologs of *Lingo-1*, levels of *Lingo-1* mRNA have been examined in both the adult mouse brain (Carim-Todd et al., 2003), as well as across different stages of neurodevelopment from embryonic stages to adulthood in both the mouse (Carim-Todd et al., 2003) and the rat (Mi et al., 2004). Both mouse and rat results confirmed first of all that the expression of *Lingo-1* is highly specific and is confined to the adult central nervous system. Similarly, the highest levels of expression were again found in the neocortex (Carim-Todd et al., 2003; Mi et al., 2004), hippocampus, thalamus and amygdala, in addition to the entorhinal cortex and various other components of the limbic system (Carim-Todd et al., 2003). While *Lingo-1* is a highly expressed central nervous system transcript in the adult human, rat and mouse brain, it is ubiquitously expressed in the embryonic mouse up until embryonic day E7.5 (Carim-Todd et al.,

2003). By E17.5 *Lingo-1* is expressed exclusively within the central nervous system with the highest levels detectable within the neocortex, hippocampus, piriform cortex, and amygdala (Carim-Todd et al., 2003) corresponding to similar regions that presented with the highest expression levels in the adult mouse, rat and human, thus demonstrating that *Lingo-1* is likely to have a highly conserved function throughout development across a variety of mammalian species.

Neuronal sprouting and myelination are developmental milestones and are an integral part of neurodevelopment. Furthermore, *Lingo-1* has been shown to be expressed early in embryonic development as described above. Accordingly in normal brain development, *Lingo-1* is a potent negative regulator of myelination and neurite outgrowth, both of which are key neurodevelopmental processes. *Lingo-1* was also reported to be expressed on oligodendrocytes where it plays an important role in the inhibition of oligodendrocyte differentiation and axon myelination (Mi et al., 2005). Myelination was shown to be inhibited by endogenous *Lingo-1* and antagonism of *Lingo-1* was able to reverse this inhibition (Mi et al., 2005). In support of these findings, electron microscope studies have shown increased numbers of myelinated axons within the spinal cord of *Lingo-1* knockout mice compared to their wild type littermates (Mi et al., 2007, 2005). In contrast, transgenic mice overexpressing *Lingo-1* show a delayed onset of myelination (X. Lee et al., 2007). A study by Mi *et al.* not only showed that *Lingo-1* interacts with both NgR and p75, as a part of the receptor complex, but also proved that it is capable of activating ras homolog gene family member A (RhoA), a small GTP-binding protein, and mediating the activity of myelin inhibitors. The *Lingo-1* cytoplasmic domain was reported to be essential in providing the signal to activate RhoA, and thus to inhibit axonal outgrowth and myelination (Mi et al., 2004). Without the intracellular domain of *Lingo-1*, neurite outgrowth is restored *in vitro*, due to the interruption of the interaction between *Lingo-1* and its co-receptor binding partners (Mi et al., 2004).

3. *Lingo-1* Signaling Pathways

In addition to the NgR/p75 or TROY co-receptors, *Lingo-1* is able to interact with additional co-factors and/or co-receptors, leading to the activation of further downstream signaling pathways,

resulting in the regulation of neuronal survival, axon regeneration, oligodendrocyte differentiation, and myelination processes in the brain (Figure 1).

3.1. NgR/p75 or TROY Complex

NgR is encoded by the *NgR* gene (also known as *RTN4R*), located at locus 22q11.2 in humans, a chromosomal region that has been previously identified as being involved in many psychiatric disorders. A faulty NgR possibly caused by mutations within the gene itself, could result in abnormal axonal connections. This hypothesis has caused much interest among researchers due to the large number of neuropathologies that present with axonal abnormalities.

Studies have also shown that NgR plays a role in synaptic plasticity (Budel, 2007; Josephson et al., 2003; McGee and Strittmatter, 2003; Trifunovski et al., 2004), thus it has been considered that any aberrant enhancement of neuronal plasticity during neural development may be caused by a reduction or complete loss of NgR function during the last phases of development (Budel, 2007; Budel et al., 2008). Alteration of activity-driven synaptic plasticity at Schaffer collateral-CA1 synapses; and abnormalities of dendritic spine shape have been previously observed in several animal studies, notably including the use of *NgR* null mice (Lee et al., 2008; Raiker et al., 2010), suggesting a key role of NgR in both of these processes.

NgR is expressed primarily on the axons of a subpopulation of neurons, including cerebral cortical pyramidal neurons and cerebellar Purkinje cells (Kevin C Wang et al., 2002). In normal brain development, oligodendrocytes are responsible for regulating axonal growth via the Nogo protein and its receptor, NgR. Nogo binds to the leucine-rich repeat domains of NgR and facilitates the inhibition of axon growth (Hu and Strittmatter, 2004). NgR is a 473-residue protein, anchored to the neuronal membrane by a Glycosyl Phosphatidyl Inositol component. NgR protein is primarily comprised of a leucine-rich repeat ectodomain domain (similar to the one of Lingo-1), capped by N-terminal and C-terminal cysteine rich molecules (He et al., 2003).

To our knowledge, levels of NgR protein expression in post-mortem tissue have only ever been reported in the hippocampus in a cohort for Alzheimer's Disease (Zhu et al., 2007). Interestingly,

NgR expression was increased in the hippocampus of patients suffering from Alzheimer's Disease suggesting that NgR may play a common role in a larger scope of brain disorders. The levels of expression of the neurotrophin receptor p75, one of the direct binding partners involved in the downstream signaling of NgR with Lingo-1 or TROY, was also found to be higher in post-mortem brain tissue from Alzheimer's Disease patients (Fujii and Kunugi, 2009), supporting the implication of the NgR/p75 pathway in this disorder.

The Lingo-1 co-factor p75, is a well-defined member of the tumor necrosis factor receptor (TNFR) superfamily and was originally identified as a low-affinity neurotrophin receptor (Rabizadeh and Bredesen, 2003). The *p75* gene is located at the human chromosomic region 17q21-22 and codes for a 427 amino acid residue protein (Lotta et al., 2014). p75 has a well-established role in the nervous system, controlling the survival and differentiation of neurons (Dechant and Barde, 2002).

While selective knockdown of *p75* in mice results in severe ataxia making detailed behavioural testing near impossible (von Schack et al., 2001), it has been shown that interfering with the function of the p75 receptor suppresses neurotrophin activity and results in schizophrenia related endophenotypes (Rajakumar et al., 2004). p75 is a receptor for all mature and developing neurotrophins (Barker, 2004). Considering the implication of brain-derived neurotrophic factor (BDNF), the most widely studied neurotrophin and ligand for p75, with neurodegenerative and neuropsychiatric diseases such as Alzheimer's disease, depression and schizophrenia, it is reasonable to consider that the neurotrophic receptor p75 itself, may play vital roles in the pathogenesis of a wide variety of neurological disorders (Fujii and Kunugi, 2009). The loss of the *p75* gene from neurons has been shown to render them incapable of activating RhoA, subsequently inhibiting neurite outgrowth in the presence of myelin inhibitors (Mi et al., 2004; Kevin C. Wang et al., 2002b), providing another plausible link to a neurodevelopmental role in psychiatric disorders.

As part of the Lingo-1/NgR complex, the p75 neurotrophin receptor is specifically responsible for transmitting intracellular signals. Certain neurons lacking p75 show neither RhoA activation, nor do they exhibit neurite growth inhibition in the presence of myelin associated inhibitors, suggesting that

p75 plays a significant role in the transduction of inhibitory NgR signals in vitro (Kevin C Wang et al., 2002). On the other hand, some NgR containing cell types not expressing p75, have still been found to transduce inhibitory NgR signals (Kevin C. Wang et al., 2002a), leading to the discovery of TROY as a functional homolog of p75 within the signaling complex (Shao et al., 2005).

TROY is a type I membrane protein belonging to the same tumor necrosis factor subfamily as p75, and is encoded by the *TNFSF19* gene at human chromosome 13q12.11-12.3. Despite TROY belonging to the same family as p75, unlike p75, TROY is widely expressed in adult neurons where it can substitute for p75 in the Lingo-1/NgR/p75 signaling complex in the presence of myelin associated inhibitors in neurons lacking p75 (Park et al., 2005; Shao et al., 2005). TROY is abundantly expressed throughout neurodevelopment in neural stem cells located in the ventricular and subventricular zones, and is also found to be more abundantly present throughout the adult central nervous system than its homolog p75 (Hisaoka et al., 2003; Kojima et al., 2000; Park et al., 2005; Shao et al., 2005). TROY and Lingo-1 are expressed together in subpopulations of reactive astrocytes, macrophages/microglia and neurons, but not in oligodendrocytes (Sato et al., 2007). Dominant-negative forms of p75 or TROY, in addition to both *p75* and *TROY* knockout mice, have reduced levels of activated RhoA and enhanced neurite outgrowth in the presence of myelin inhibitors (Park et al., 2005; Shao et al., 2005; Kevin C. Wang et al., 2002b).

Neurotrophic growth factors are well known to regulate many aspects of neuronal development and function (Huang and Reichardt, 2001; Segal, 2003). Lingo-1 can also interact with the complex neurotrophin, nerve growth factor (NGF)/Trk receptor tyrosine kinase (RTK) TrkA, which leads to the regulation of the expression of genes involved in oligodendrocyte differentiation and myelination, such as oligodendrocyte transcription factor 2 (olig 2) and natural killer cell-associated antigen 2 homeobox 2 (nkx2.2) (Zhou et al., 2001).

The Lingo-1/NgR/p75 or TROY complex was the first cellular complex identified to determine the functions of Lingo-1 in the brain. The characterization of the serine threonine kinase With No Lysine K (WNK1) as both a modulator of the trimolecular receptor complex and as a direct downstream

signaling partner of Lingo-1 has highlighted the importance and expansive nature of Lingo-1 functions in the brain.

3.2. WNK1

WNK1, a part of a distinct subfamily of serine threonine kinases implicated in the binding of ATP and catalyzing phosphoryl transfer (Hanks et al., 1988), is expressed abundantly in the brain (Choate et al., 2003; Xu et al., 2000). WNK1 has been shown to be co-localized with Lingo-1 in cortical cultured neurons (Zhang et al., 2009) in addition to being shown as a direct binding partner to Lingo-1 through co-immunoprecipitation experiments with both brain tissue and cell lysates (Zhang et al., 2009).

Considering that little is known about the regulation and function of WNK1 in the central nervous system, there are an abundance of genetic studies regarding *WNK1* gene (located on chromosome 12p13.3) mutations. Interestingly, the disruption of the *WNK1* gene in mice leads to death of the embryo at day 13 (Zambrowicz et al., 2003), suggesting an essential role of WNK1 in embryonic and neural development, which is a critical period implicated in a number of neurological and neuropsychiatric disorders. Furthermore, large intronic deletions in the *WNK1* gene, leading to an increase in *WNK1* mRNA, have been linked to an inheritable hypertension syndrome (Wilson et al., 2003), in addition to genetic variations located in the regulatory 5' region of the *WNK1* gene also being associated with hypertension (Han et al., 2011). *WNK1* gene expression has also been consistently reported to be upregulated in the prefrontal cortex of schizophrenia sufferers in genome wide association studies (Maycox et al., 2009; Mistry et al., 2012), suggesting a role in this disorder as well.

The suppression of WNK1 expression by RNA interference has been shown to promote neurite extension and eliminate the inhibitory response to Nogo in cortical cultured neurons. In addition, the overexpression of WNK1 (123-510) reduces Nogo-induced inhibition of neurite extension rather than strengthening it, and inhibits the activation of RhoA (Zhang et al., 2009). The over expression of WNK1 (123-510) was also found to significantly reduce the interaction between endogenous WNK1

and Lingo-1, suggesting that this serine threonine kinase may serve as a binding platform for Lingo-1, however the kinase activity may not be necessary for Lingo-1 signaling (Zhang et al., 2009).

3.3. Myt1 and Myt1l

Myelin Transcription Factor 1 (Myt1) and its homologue Myelin Transcription Factor 1-like (Myt1l) are postmitotic neuronal specific zinc finger proteins expressed in the developing brain (Armstrong et al., 1995; Bellefroid et al., 1996). They are coded for by two independent genes *Myt1* and *Myt1l* respectively on human chromosomes 20q13.33 and 2p25.3. Myt1 expression appears to be present in both neural and glial lineages, however in the adult brain, Myt1 is not expressed on neurons (Armstrong et al., 1997). In contrast, Myt1l does not appear to be found in either the glial lineage, nor on glial cells in the adult brain, however its transcripts are most abundantly expressed in the prenatal brain during the development of neurons and in differentiating neurons suggesting that it plays an important role in neuronal differentiation (Kim et al., 1997).

Myt1l has been reported to directly interact with the intracellular domain of Lingo-1, suggesting that Lingo-1 may regulate Myt1l transcription factor activity by affecting its subcellular localization (Llorens et al., 2008). It is thought that this may occur in two different ways: firstly Lingo-1 may interact with Myt1l to regulate its transcription factor activity by retaining it in the cytoplasm; or secondly, Lingo-1 may transduce intracellular signals by docking additional Myt1l cofactors or modifying enzymes (Llorens et al., 2008). Myt1 and Myt1l display a high degree of identity, and therefore are highly likely to share the same binding sites, considering the ability of the Myt1l protein to bind the oligonucleotide sequence containing the proteolipid protein site that was originally intended to clone Myt1. It has therefore been suggested that Lingo-1 may interact with Myt1 in oligodendrocytes the way that Lingo-1 interacts with Myt1l in neurons. Since it is known that Lingo-1 expression in oligodendrocytes and neurons is necessary for preventing myelination, it seems reasonable to hypothesize that these effects are mediated by an interaction between Lingo-1 and Myt1 and Lingo-1 and Myt1l in oligodendrocytes and neurons respectively (Llorens et al., 2008). *Lingo-1* and *Myt1* gene expression have been found to be increased when adult nerve cells were exposed to

traumatic injuries and in demyelinated lesions in rodent and human central nervous system injuries respectively (Mi et al., 2004; Vana et al., 2007).

3.4. EGFR/PI3-K/Akt Pathway

The Epidermal Growth Factor Receptor (EGFR), also known as ErbB-1, triggers the activation of the Phosphoinositide 3-kinase (PI3-K)/Akt signaling pathway leading to DNA synthesis and cell proliferation including neuronal survival and growth (Brunet et al., 2001; Inoue et al., 2007; Oda et al., 2005). The binding of myelin inhibitors to NgR, has been shown to trigger phosphorylation of EGFR in a Ca^{2+} dependent manner (Koprivica et al., 2005), however EGFR activation by its own ligand, Epidermal Growth Factor (EGF), is not sufficient to inhibit axonal-outgrowth (Koprivica et al., 2005), thus it is reasonable to speculate that receptor transactivation of EGFR by the NgR complex may activate a different set of signaling cascades (Schwab et al., 2006). More recently studies have shown that some LRR Ig-containing proteins are able to influence growth factors by modulating pathways related to EGFR signaling (Goldoni et al., 2007; Gur et al., 2004), indicating that it may in fact be due to Lingo-1 signaling that NgR is able to affect EGFR. Lingo-1 has since been shown to directly bind to EGFR using the EGFR-like tyrosine phosphorylation site in its cytoplasmic domain to negatively regulate the EGFR/Akt signaling pathway, which has been notably implicated in the pathophysiology of schizophrenia (Huang and Chen, 2009; Inoue et al., 2007; Koros and Dorner-Ciossek, 2007). Through immunoprecipitation, cell culture and brain tissue experiments, endogenous Lingo-1 was found to reduce EGFR levels mediated by a direct physical interaction (Inoue et al., 2007).

However the complete mechanisms underlying the inhibition of EGFR expression and function by Lingo-1 remain unclear. It has been suggested that this inhibition may be caused by Lingo-1 accelerating the internalization and degradation of EGFR and so reducing the availability of EGFR on the neuronal membrane. Another potential mechanism suggests that Lingo-1 can directly inhibit the phosphorylation of EGFR and thus decrease PI3-K/Akt signaling pathway activity, resulting in decreased neuronal survival and growth (Inoue et al., 2007). The potential role of Lingo-1 as an

inhibitor of neuronal survival through the Akt signaling pathway enhances the hypothesis of a role of Lingo-1 signaling in the pathogenesis of a number of neuropsychiatric disorders. Considering the role of Lingo-1 in directly negatively regulating the EGFR/PI3-K/Akt signaling pathway, Lingo-1 has been investigated in relation to dopamine neuron survival, growth and function (Inoue et al., 2007). It was found that all of these factors were improved with Lingo-1 antagonism, and that inhibiting Lingo-1 also increased EGFR and phospho-Akt levels in the absence of myelin inhibitors and promoted retinal cell survival (Fu et al., 2008; Inoue et al., 2007).

Interestingly, downstream Lingo-1 signaling partners WNK1 and Myt1 have also been shown to be implicated in EGFR/PI3-K/Akt signaling. WNK1 has been identified as a substrate for Akt signaling, and the phosphorylation of WNK1 is inhibited by PI3-K inhibitors, thus suggesting that WNK1 is phosphorylated via the PI3-K/Akt signaling pathway (Jiang et al., 2005). Furthermore, Myt1 was reported to be inhibited and significantly downregulated by Akt phosphorylation (Okumura et al., 2002).

Since Lingo-1 signaling plays a pivotal role in repressing neurite outgrowth, oligodendrocyte differentiation and myelination and keeping in mind its expression at an early stage of development, the implication of Lingo-1 and its signaling pathways in a wide variety of neurological pathologies seems apparent.

4. Role of Lingo-1 in Neurological Pathologies

A wide range of central nervous system diseases including spinal cord injury, traumatic brain injury, multiple sclerosis, Parkinson's disease and essential tremor, as well as Alzheimer's disease, epilepsy and glaucoma; are neurodegenerative disorders resulting in neuronal death, axon degeneration, gliosis and demyelination. Lingo-1 and its signaling partners have been shown to be implicated in all of these disorders, due to their role in the inhibition of axonal outgrowth, neuronal death, oligodendrocyte differentiation and myelination (see Figure 1 and Supplementary Materials). Furthermore, a number of preclinical studies have shown that various methods of antagonizing Lingo-1 result in neuronal and oligodendroglial survival, axonal growth and remyelination.

4.1. Spinal Cord Injury, Traumatic Brain Injury and Multiple Sclerosis

The vast majority of studies on Lingo-1 in neuropathological states are performed in relation to multiple sclerosis and traumatic injury to the central nervous system due to the inhibitory role of Lingo-1 in neurite outgrowth, oligodendrocyte differentiation and myelination, hindering the regeneration of the injured nervous system, whether from endogenous or exogenous processes.

Spinal cord injury results in damage to the axonal tracts that are responsible for controlling motor and sensory function (Ji et al., 2006). *Lingo-1* has been shown to be detected in the axonal tracts of adolescent rat spinal cords following injury (Mi et al., 2004). Further to this, a five-fold increase in *Lingo-1* mRNA levels was detected at 14 days post injury (Mi et al., 2004). Lingo-1-Fc, a soluble form of Lingo-1, has also been shown to antagonize Lingo-1 signaling pathways by inhibiting the binding of Lingo-1 to NgR, resulting in vast improvements in the functional recovery of rats following lateral hemisection of the spinal cord. Additionally these rats displayed elevated levels of axonal sprouting and increased oligodendrocyte and neural survival due to Lingo-1-Fc blocking RhoA activation (Ji et al., 2006). Lingo-1-Fc treatment was also found to enhance plasticity in the injured spinal cord through the promotion of sprouting of collateral neurons; however whether Lingo-1-Fc is able to promote cortical plasticity remains to be determined (Ji et al., 2006). These data demonstrate a functional role of Lingo-1 *in vivo* and suggest that Lingo-1 may be a viable target for the treatment of spinal cord injury.

Traumatic brain injury characteristically involves the necrotic and apoptotic death of cells in the brain in vulnerable areas such as the cerebral cortex and hippocampus (Conti et al., 1998; Raghupathi, 2004; Royo et al., 2003), two areas known to highly express Lingo-1 in both the adult stage of life and throughout development (Carim-Todd et al., 2003; Mi et al., 2004). RhoA signaling is largely responsible for the neuronal response to neuronal inhibitory proteins and the regeneration (or lack thereof) of damaged axons (Dubreuil et al., 2006). Significant RhoA upregulation (Brabeck et al., 2004) and activation has been reported in both the cortex and hippocampus following traumatic brain injury (Dubreuil et al., 2006). The activation of Rho GTPases occurs during synaptic remodeling,

neuronal activity and synaptic plasticity in the central nervous system (Luo, 2002; O’Kane et al., 2004, 2003). Since it is widely established that Lingo-1 mediates axonal outgrowth, oligodendrocyte differentiation and axon myelination largely due to its interaction with, and activation of RhoA, it has been hypothesized that Lingo-1 plays a significant inhibitory role in this debilitating neurological disorder. In support of this, the NgR inhibitor MAG has been shown to consistently improve a number of behavioural outcomes in rats using an experimental traumatic brain injury paradigm (Thompson et al., 2006). Furthermore, Lingo-1 antagonism using Lingo-1-Fc, has been shown to inhibit RhoA activation both *in vitro* in cultured cerebellar granule neurons (Mi et al., 2004), and *in vivo* in models of spinal cord injury (Ji et al., 2006). Since Lingo-1-Fc is able to block the interactions between Lingo-1 and NgR, it seems reasonable that blockade of RhoA activation occurred at the level of Lingo-1/NgR/p75 or TROY complex.

In addition to its role as part of the NgR trimolecular receptor complex in neuronal processes, Lingo-1 has also been shown to be expressed on oligodendrocytes where it able to negatively modulate oligodendrocyte differentiation and axon myelination (Mi et al., 2005). Lingo-1-Fc was found to have a neuroprotective effect on the survival of both neurons and oligodendrocytes after spinal cord injury in rats (Ji et al., 2006). Furthermore antagonizing endogenous Lingo-1 either by Lingo-1 RNA interference, dominant-negative Lingo-1, an anti-Lingo-1 antibody, or soluble Lingo-1; resulted in more highly differentiated and mature oligodendrocytes (with more branching and increases in the lengths of processes), in addition to the formation of abundant myelin sheaths (Mi et al., 2005). As a result of these experiments, Lingo-1 antagonists were examined as a potential candidate in the treatment for multiple sclerosis. Although the underlying molecular mechanisms constituting the presentation of multiple sclerosis remain unknown, the degree of inflammatory demyelination in this debilitating disorder correlates significantly with the extent of axonal damage that begins in the early stages of multiple sclerosis (Lassmann, 2003).

Lingo-1 protein expression has been shown to be decreased in both the prefrontal cortex and cerebellar cortex of multiple sclerosis brains, while expression of its co-receptor TROY was found to be significantly increased in the same brain regions compared to samples from subjects without

multiple sclerosis (Satoh et al., 2007). However due to the very limited sample size used in this study, the results have to be considered with caution. In contrast to this result, the immunoreactivity of both Lingo-1 and TROY were found to be enhanced in subpopulations of astrocytes and macrophages/microglia from the prefrontal and parietal cerebral cortex in multiple sclerosis brains (Satoh et al., 2007). Additionally, levels of NgR are up-regulated in reactive astrocytes and macrophages/microglia in chronic active demyelinating lesions of multiple sclerosis (Satoh et al., 2005), suggesting the implication of the Lingo-1/NgR/TROY signaling complex in the glial-neuronal and glial-glial interactions underlying multiple sclerosis. Considering these significant interactions, Garcia-Martin *et. al.* (García-Martín et al., 2013) set out to investigate two Lingo-1 variants (rs9652490 and rs11856808), previously associated with other neurological pathologies including essential tremor (Stefansson et al., 2009; Vilariño-Güell et al., 2010a) and Parkinson's disease (Vilariño-Güell et al., 2010a, 2010b). Despite no significant associations being found between these genetic variants and multiple sclerosis in a Caucasian Spanish population (García-Martín et al., 2013), evidence continues to stack up further implicating Lingo-1 in the pathogenesis of multiple sclerosis. This is further illustrated by animal studies. Myelination of central nervous system axons in *Lingo-1* knockout mice was found to present earlier in life compared to their wild-type littermates (Mi et al., 2007). In addition these mice have a greater resistance to the development of MOG-induced experimental autoimmune encephalomyelitis (EAE) (Mi et al., 2007), a model commonly used to model human demyelinating diseases including multiple sclerosis. Furthermore, treatment with Lingo-1 antagonizing antibodies and by RNA interference, leads to functional recovery and increases the axonal integrity of mice with (EAE) (Mi et al., 2007; Wang et al., 2014). Lingo-1 antagonism has been shown to induce both oligodendrocyte differentiation and remyelination using three different demyelination animal models; the EAE model, and pharmacological toxin-induced models of demyelination: lysophosphatidylcholine-(LPC) and cuprizone (Mi et al., 2009).

The promising results of antagonizing Lingo-1 to treat demyelination has led to the development of BIIB033 (also known as Li81); the first fully human, IgG1 monoclonal Lingo-1 antibody to enter clinical development (Mi et al., 2013). BIIB033 has been specially engineered to have reduced Fc

gamma and complement effector functions compared with wild type IgG, and binds human Lingo-1 with high affinity and specificity (Mi et al., 2013). Stage I clinical trials have demonstrated that BIIB033 is safe for use in humans, both in healthy controls, and multiple sclerosis patients, and has been found to be well tolerated, up to 100 mg/kg, and is able to cross the blood brain barrier resulting in cerebral spinal fluid levels of greater than 90% effective concentration when given at intravenous doses of greater than 10 mg/kg (Tran et al., 2012, 2014). Further to this, structural studies examining how BIIB033 binds to Lingo-1 have shown that its binding to the convex surface of the leucine-rich repeat domain of Lingo-1 within repeats 4-8, blocks the Lingo-1-Lingo-1 contact points and prevents oligomerization of the protein (Pepinsky et al., 2014). This indicates that BIIB033 interferes with the ability of Lingo-1 to form homotetramers, with the rearrangement of the quaternary structure of Lingo-1 providing a model for how the antibody inhibits Lingo-1 function in oligodendrocytes (Pepinsky et al., 2014). Phase II clinical trials for BIIB033 are currently underway, and will provide vital information on the impact of targeting Lingo-1 as a treatment for multiple sclerosis (Brugarolas and Popko, 2014).

4.2. Parkinson's Disease and Essential Tremor

Parkinson's disease and essential tremor are age-related movement disorders which have a prevalence of approximately 1-2% and 3-6% of individuals over the age of 65 respectively (de Rijk et al., 2000; Louis et al., 2009). While the clinical presentation of Parkinson's disease and essential tremor do overlap, essential tremor patients typically present with tremor on action, or postural tremor, whereas Parkinson's symptoms are typically more severe in that they present as tremor at rest, usually asymmetrical, in addition to experiencing bradykinesia, rigidity and postural instability (Fekete and Jankovic, 2011; Shahed and Jankovic, 2007).

Lingo-1 was first implicated in Parkinson's disease, when it was discovered that levels of Lingo-1 are upregulated in the substantia nigra of post mortem Parkinson's disease brains compared to matched controls and in neurotoxic animal models of Parkinson's disease (Inoue et al., 2007). Lingo-1 antagonism by a variety of pharmacological and genetic mechanisms produces neuroprotective effects

on dopaminergic neurons in the midbrain (Inoue et al., 2007). Dopamine neuron survival and a significant reduction in behavioural abnormalities were observed in *Lingo-1* knockout mice compared to wild-types (Inoue et al., 2007). Similar effects were also observed in wild-type mice *in vivo*, and *in vitro* in cultured dopaminergic neurons treated with Lingo-1 antagonists (Inoue et al., 2007). The treatment of dopaminergic neurons with a dominant-negative form of Lingo-1, an anti-Lingo-1 antibody, and Lingo-1-Fc resulted in a significant improvement in neuronal survival during a mitochondrial toxicity paradigm used to model Parkinson's disease *in vitro* (Inoue et al., 2007). Interestingly, the neuroprotection observed in *in vivo* and *in vitro* studies, was accompanied by an activation of the EGFR/PI3-K/Akt signaling pathway which is also implicated in the pathology of Parkinson's disease (Brunet et al., 2001; Farkas and Krieglstein, 2002; Iwakura et al., 2005; Onyango et al., 2005; Timmons et al., 2009). As mentioned above in section 3.4, Lingo-1 is able to directly bind to EGFR (Inoue et al., 2007), therefore the pharmacological inhibition of Lingo-1 by the Lingo-1 antagonists, suppresses its binding to EGFR resulting in activation of the EGFR/PI3-K/Akt signaling in the *in vitro* and *in vivo* models of Parkinson's disease (Inoue et al., 2007).

Expression of Lingo-1 protein has been found to be significantly increased in the cerebellum (particularly at the basket cell pinceau along the purkinje cell axon initial segment), but not in the occipital cortex of essential tremor patients (Kuo et al., 2013). The highly enriched pinceau processes labeled with Lingo-1 were not only more commonly observed in the cerebellum of essential tremor patients compared to controls, but were also significantly more elongated in the cerebellum of essential tremor patients compared to those seen in both cerebellar degenerative disorder patients and controls (Kuo et al., 2013). This suggests that Lingo-1 pinceau are a common feature of both essential tremor and cerebellar degenerative disorder, however the longer pinceau processes are specific to the essential tremor pathology, providing a novel pathological link between Lingo-1 and essential tremor.

While environmental factors are proposed to play a role in the onset of both Parkinson's disease and essential tremor, a number of genetic factors have been recognized to contribute to both disorders (Deng et al., 2007; Spanaki and Plaitakis, 2009). There is an abundance of genetic evidence implicating *Lingo-1* with both Parkinson's disease and essential tremor (Vilariño-Güell et al., 2010a,

2010b), with an equal number of studies claiming no implication of *Lingo-1* genetic variations with these disorders (Białecka et al., 2010; Wu et al., 2011). As a result, in 2012 meta-analyses were conducted on the results of genetic studies for both Parkinson's disease and essential tremor and it was confirmed that the *Lingo-1* single nucleotide polymorphisms (SNPs) rs9652490 and rs11856808 of which both had been claimed to be both associated and not associated with essential tremor, were in fact associated with the disorder (Jiménez-Jiménez et al., 2012). In the case of Parkinson's disease the rs9652490 SNP was found not to have an association with Parkinson's disease following the meta-analysis (Wu et al., 2012).

4.3. Alzheimer's Disease

Alzheimer's disease is the most prevalent cause of dementia in humans and is typically characterized by the early loss of neocortical synapses, the formation of neurofibrillary tangles and the accumulation of neuritic plaques within the hippocampus and temporal cortical regions of the brain (Khachaturian, 1985). One of the most hypothesized causes of the memory decline in the aging brain is the failure of synaptic plasticity with age (Foster, 1999). *Lingo-1*/NgR/p75 or TROY signaling was examined in the hippocampus and cerebral cortex from rats in an aging brain study (Trifunovski et al., 2006). While there were no significant alterations observed in the mRNA expression of any of the receptor components or in the expression of the ligands *OMgp* or *MAG*; *Nogo* mRNA was found to be significantly reduced in hippocampal subregions, specifically the CA1, CA3, CA4 and dentate gyrus, with age. Additionally, a downregulation of *NgR* mRNA expression was supposedly caused by activity induced alterations in brain activity, which is required to induce plastic changes within the brain (Josephson et al., 2003). In addition, a simultaneous increase in both NgR and its ligand *Nogo* were hypothesized to be required to induce a locked conformational state in hippocampal and cortical microcircuitry in order to maintain the plastic changes (Josephson et al., 2003). Thus the decrease in *Nogo* mRNA expression in the hippocampus of aged animals may be related to the age-dependent decline of brain plasticity.

In contrast to these animal studies, Zhu *et al.* have reported the expression of NgR to be increased in the hippocampus of Alzheimer's disease patients (Zhu et al., 2007). While there was not an overall significant difference in the number of immunopositive NgR neurons in Alzheimer's disease compared to control patients, there was a significant increase in the ratio observed between NgR immunopositive neurons to the total number of neurons within the hippocampus of Alzheimer's patients compared to that of the control group. Additionally, NgR was found to be co-localized with the hyperphosphorylated tau protein, which is largely responsible for the formation of neurofibrillary tangles, in hippocampal cells of Alzheimer's disease patients compared to controls.

The hypothesis of dysfunctional Lingo-1 signaling in Alzheimer's disease is also supported by a report of enriched *Lingo-1* expression within the limbic system (Carim-Todd et al., 2003), a region largely affected in Alzheimer's disease (Thiebaut de Schotten et al., 2014). In addition, NgR was found to be involved in the formation and deposition of amyloid- β peptide (Park et al., 2006), the main component in plaque formations (Hu et al., 2002). Due to its role in neuronal apoptosis and cell death, and more recent implication in the formation of neurofibrillary tangles, p75 also has a proposed role in the pathogenesis of Alzheimer's disease (Hu et al., 2002). Similarly, Lingo-1 has been shown to directly bind to amyloid precursor protein, the precursor for amyloid- β peptide, and to modulate its processing by increasing the production of amyloid- β peptide from amyloid precursor protein when it is overexpressed (Bai et al., 2008); however this was not found to be modulated by the leucine-rich repeats of Lingo-1 (Stein and Walmsley, 2012). Additionally, Lingo-1 is able to regulate amyloid precursor protein proteolysis by interacting with amyloid precursor protein in the endosome/lysosome pathway where Lingo-1 can control and regulate the amount of amyloid precursor protein available for processing (de Laat, 2012). All of the above evidence supports the hypotheses that Lingo-1/NgR/p75 signaling is implicated in the pathophysiology of Alzheimer's disease.

Furthermore, pharmacological blockade of EGFR antagonizes the formation of amyloid- β oligomers induced by EGFR activation, and improves memory impairment in animal models of Alzheimer's disease, suggesting that EGFR would be an ideal target for Alzheimer's disease therapy (Wang et al., 2012). Since Lingo-1 can directly activate EGFR and due to its role in neuronal survival, we can

hypothesis that Lingo-1 may also be involved in the pathophysiology of Alzheimer's disease through its interaction with EGF and EGFR.

4.4. Tuberous Sclerosis, Focal Cortical Dysplasia and Temporal Lobe Epilepsy

Tuberous sclerosis, focal cortical dysplasia and temporal lobe epilepsy are all very different types of neurological disorders; however they all have a common symptom: seizures. The expression of components of the Nogo-A signaling system have been investigated in samples taken from pediatric patients with tuberous sclerosis and focal cortical dysplasia type IIb, who were undergoing surgical procedures for the treatment of epilepsy. Both of these disorders are characterized by malformations of the cortex during development and as mentioned above, are both frequently associated with seizures (Yu et al., 2012). Both protein and mRNA levels for Nogo-A, NgR, Lingo-1, TROY and RhoA but not p75 were found to be upregulated in the cortex of patients from both tuberous sclerosis and cortical dysplasia compared to controls. Interestingly Nogo-A, NgR, Lingo-1 and TROY were all highly expressed in misshapen cells including dysmorphic neurons, balloon cells and giant cells (Yu et al., 2012). Lingo-1 and TROY were also identified in reactive astrocytes of the patient samples compared to controls. Together this research suggests that Nogo-A along with its signaling complex Lingo-1/NgR/TROY, but not Lingo-1/NgR/p75 may contribute to the development and/or progression of seizure activity in malformations of cortical development.

In addition the Lingo-1/NgR/TROY signaling complex was found to be altered in an animal model of temporal lobe epilepsy; the BALB/cByJ-Kv1.1^{mceph/mceph} (also known as *mceph/mceph*) mouse (Lavebratt et al., 2006). Temporal lobe epilepsy is the most common type of adult focal epilepsy that presents with progressive complex partial seizures with pathological brain overgrowth, or megalencephaly. Temporal lobe epilepsy principally affects the hippocampus and ventral cortex. Megalencephaly is a developmental disorder affecting around 2% of children worldwide and is largely thought to be caused by genetic abnormalities in the PI3-K/Akt signaling pathway which is known to be activated by Lingo-1 signaling. NgR mRNA expression was found to be significantly increased in the dentate gyrus in *mceph/mceph* mice compared to wild-types, with no other brain

regions displaying significant genotypic alterations in *NgR* expression. The *NgR* expression was however specifically restricted to neurons and predominantly observed in regions associated with high plasticity such as the cortex and hippocampus, both of which were also significantly enlarged in *mceph/mceph* mice compared to wild-types (Lavebratt et al., 2006). Additionally, *Lingo-1* showed expression patterns throughout the brain similar to that of *NgR*, however a significant increase in *Lingo-1* was observed in the CA3 region of the hippocampus, in addition to in the dentate gyrus ventral cortex and amygdala in the *mceph/mceph* mice compared to wild-types (Lavebratt et al., 2006). The third member of the tripartite receptor complex *TROY* was the only component in the complex to be significantly downregulated in the brains of *mceph/mceph* mice; with the most prominent decrease being evident in the cortex and dentate gyrus, with slightly smaller reductions being evident in the CA1 region of the hippocampus and ventral cortex. Again these were all brain regions that were significantly enlarged in *mceph/mceph* mice compared to wild-types. Importantly, all of the dysregulations in the expression of *NgR*, *Lingo-1* and *TROY* mRNA in the *mceph/mceph* mice were normalized when the mice were treated with carbamazepine, a commonly used anticonvulsant drug used for the treatment of epilepsy, with *Lingo-1* dropping to levels even below that of wild-type mice following treatment (Lavebratt et al., 2006). Additionally, the cortical overgrowth in brain regions that were enlarged due to the genetic abnormality in the *mceph/mceph* mice was prevented by the treatment with carbamazepine. Furthermore, an alteration of the EGF/mTOR (mammalian target of rapamycin) signaling pathway has also been reported in the pathophysiology of epilepsy (Cho, 2011). Due to the direct inhibitory effects of the EGF/EGFR signaling pathways, the implication of *Lingo-1* through the EGF-mTOR pathway also seems appropriate in the context of epilepsy.

Altogether, these results suggest that the *Lingo-1*/*NgR*/*TROY* and EGF/EGFR signaling pathways are involved in temporal lobe epilepsy, and that treatment with carbamazepine may be an effective treatment not only for seizures, but also for megalencephaly.

4.5. Glaucoma

Since the optic nerve is still considered to be a part of the central nervous system, the role of Lingo-1 in optic nerve disorders has been investigated. Glaucoma is a neurodegenerative disease characterized by abnormally high intraocular pressure and is the leading cause of blindness due to retinal ganglion cell death. Both Lingo-1 and NgR were found to be significantly upregulated in retinal ganglion cells following the use of an ocular hypertension paradigm in rats (Fu et al., 2011, 2008). Antagonizing the function of Lingo-1, either using Lingo-1-Fc or an anti-Lingo-1 antibody, or antagonizing NgR using soluble NgR (sNgR-Fc) has been shown to not only reduce the number of retinal ganglion cells that were lost after ocular hypertension, but also promote the survival of retinal ganglion cells following optic nerve transection (Fu et al., 2011, 2008). Lingo-1-Fc treatment was also shown to block RhoA signaling and promote Akt activation (Fu et al., 2008), thus the mechanism underlying Lingo-1 antagonist induced neuroprotection is evidently mediated through the RhoA and PI3-K/Akt signaling pathways. Conversely, another two studies have shown that Lingo-1 may exert its neuroprotective effects on retinal ganglion cells following ocular hypertension by its interaction with BDNF/TrkB (tropomyosin receptor kinase B). Lingo-1 and BDNF were found to be co-expressed in retinal ganglion cells (Fu et al., 2009). Additionally Lingo-1 is able to form a complex with TrkB following ocular hypertension injury (Fu et al., 2010). Furthermore it was demonstrated that Lingo-1 antagonists (Lingo-1-Fc and an anti-Lingo-1 antibody) caused an upregulation of phospho-TrkB phosphorylation, leading to the survival of retinal ganglion cells (Fu et al., 2010). However a combined treatment of BDNF and Lingo-1-Fc resulted in activation of more TrkB than a treatment of BDNF alone (Fu et al., 2009). Since the neuroprotective effects could be inhibited by an anti-BDNF antibody, this indicates that the regulation of the BDNF/TrkB signaling pathway by Lingo-1 is responsible for mediating the survival of the retinal ganglion cells.

Most recently, myocilin has been identified as being involved in the Lingo-1/NgR mediated oligodendrocyte differentiation and myelination of the optic nerve (Kwon et al., 2014). Myocilin is a glycoprotein secreted by optic nerve astrocytes, and mutations in its gene *MYOC*, were the first genetic implications known to cause glaucoma, more specifically open-angle glaucoma (Stone et al.,

1997). In both *in vivo* and *in vitro* studies, myocilin was found to mediate oligodendrocyte differentiation through direct interaction with both Lingo-1 and NgR (Kwon et al., 2014). Furthermore myocilin is involved in the myelination of the optic nerve in mice, and the differentiation of optic nerve oligodendrocytes is significantly delayed in *Myocilin* knockout mice, leading to decreased thickness of the myelin sheaths on the optic nerves of these mice compared to wild types. Overall these novel results have shown that myocilin plays a role in oligodendrocyte differentiation and myelination through its interactions with the Lingo-1/NgR complex.

5. Lingo-1 Signaling: A New Role in Psychiatric Disorders

Dysfunction of axonal growth and myelination has been prominently implicated by gene expression, histopathology and imaging studies, in a wide range of neuropsychiatric disorders including depression (Alexopoulos et al., 2002; Aston et al., 2005; Bae et al., 2006; Hannestad et al., 2006), obsessive compulsive disorder (Cannistraro et al., 2007; Jayarajan et al., 2012; Szeszko et al., 2005), post-traumatic stress disorder (Abe et al., 2006; Kim et al., 2005, 2006), bipolar disorder (Adler et al., 2006, 2004), autism (Keller et al., 2007; Lange et al., 2010; J. E. Lee et al., 2007), and attention deficit hyperactivity disorder (Castellanos et al., 2003; Filipek et al., 1997; Rüsche et al., 2007; Semrud-Clikeman et al., 2000). However the vast majority of studies have shown an implication of axonal growth and myelination dysfunction in schizophrenia (Barley et al., 2009; Bartzokis et al., 2003; Hakak et al., 2001; Schmitt et al., 2004; Shenton et al., 2001; Tkachev et al., 2003; Uranova et al., 2001; Walterfang et al., 2011, 2006).

Until recently, no studies had ever specifically investigated a link between Lingo-1 in schizophrenia. We have provided the first evidence of an implication of Lingo-1 in schizophrenia, by observing alterations in the expression profiles of Lingo-1 and its signaling partner proteins in the dorsolateral prefrontal cortex (DLPFC) and hippocampus (CA1 and CA3) from post-mortem schizophrenia brains (Fernandez-Enright et al., 2014); regions highly relevant to the schizophrenia pathophysiology providing highly sought after, novel directions for therapeutic strategies.

Although Lingo-1 itself had never been implicated in schizophrenia, a number of nicotinic receptor genes and the myelination gene *Lipidosin*, located within the vicinity of the *Lingo-1* locus at chromosomal region 15q24, had previously been shown to be associated with schizophrenia, along with several other myelination genes which were also reported to be downregulated in the prefrontal cortex in this disorder (Hakak et al., 2001; Tiwari et al., 2005; Tkachev et al., 2003; Weidenhofer et al., 2006). With Lingo-1 being a known myelination inhibitor and a negative modulator of oligodendrocyte differentiation when overexpressed (Mi et al., 2005), the investigation of the role of Lingo-1 in schizophrenia seemed timely and topical.

Previous studies have described significant reductions in prefrontal lobe white matter volume in patients with schizophrenia (Breier et al., 1992; Buchanan et al., 1998). However, a decrease in white matter anisotropy was consistently reported in schizophrenia patients, irrespective of their white matter volume (Buchsbaum et al., 1998; Lim et al., 1999; Tang et al., 2007). Thus, schizophrenia patients could present with compromised neuronal connectivity and/or directional coherence of white matter fibers (Lim et al., 1999), possibly due to the reported upregulation of Lingo-1 in schizophrenia (Fernandez-Enright et al., 2014).

In support of the possible role of Lingo-1 in myelin dysfunction in schizophrenia, *Lingo-1* knockout mice have been shown to have a higher and more differentiated percentage of mature oligodendrocytes than wild types (Mi et al., 2007, 2005). The typical onset of myelination in wild type mice occurs at PN5, however *Lingo-1* knockout mice had already developed myelinated fibers at PN1. Additionally, no obvious changes were observed in the peripheral nervous system sciatic nerve, suggesting that myelination effects were limited to the central nervous system (Mi et al., 2005).

As described above in section 4, Lingo-1 has been repeatedly implicated in a wide variety of central nervous system disorders resulting in emotional and mental disturbances, loss of motor skills and cognitive deficits; however in addition to its novel implication in schizophrenia (Fernandez-Enright et al., 2014), there is also evidence implicating the *Lingo-1* chromosomal region 15q24 in a range of

neuropsychiatric disorders including autism spectrum disorder, and anxiety disorders such as panic and phobic disorders.

To date, 15q24 deletion syndrome has been examined in a number of autism spectrum disorder cohorts, and from these studies, 15q24 deletion syndrome has been identified in approximately 0.1-0.2% of individuals with autism spectrum disorders (Marshall et al., 2008; McInnes et al., 2010). However to our knowledge, of the individuals identified as having 15q24 deletion syndrome to date, 21% of subjects present with autism spectrum disorder (Marshall et al., 2008; McInnes et al., 2010), and another 7% present with autistic features (McInnes et al., 2010; Sharp et al., 2007). Despite these implications, the true frequency of autism spectrum disorders in patients with 15q24 deletion syndrome is currently not known, as not all 15q24 deletion syndrome patients have been assessed for autism.

Further to this, mild mental retardation and/or developmental delay is present in all patients identified as having microduplications in the 15q24 chromosomal region (El-Hattab et al., 2010, 2009; Kiholm Lund et al., 2008), in addition to one patient also testing positive for both Asperger's syndrome, and attention deficit hyperactivity disorder (El-Hattab et al., 2009). Moreover interstitial duplications in 15q24-26, engulfing *Lingo-1* in its entirety, have been significantly associated with panic, agoraphobia and social phobia in families, and with panic disorder in non-familial cases, with 90% of patients fitting the diagnosis of one or more of the anxiety disorders having the chromosomal duplication (Gratacòs et al., 2001). Despite a number of groups trying to reproduce this finding, none have successfully done so (Henrichsen et al., 2004; Tabiner et al., 2003; Weiland et al., 2003; Zhu et al., 2004), therefore the finding by Gratacòs et. al. must be considered with caution.

While *Lingo-1* and its co-receptor NgR are highly involved in neurodevelopmental processes such as axonal outgrowth, they also play important roles in the mature brain. Both of these proteins have been previously reported to regulate experience-dependent synaptic plasticity (Josephson et al., 2003; McGee et al., 2005; Trifunovski et al., 2004), one of the important foundations in the development of learning and memory which has been shown to be dysfunctional in schizophrenia.

The results of our novel study, in concert with the current literature, suggest that downregulation of NgR and concurrent upregulation of Lingo-1 may be activity dependent characteristics of synaptic plasticity in schizophrenia. There is an abundance of evidence now supporting the concept that alterations in activity dependent plasticity (Shatz, 2009; Stephan et al., 2006), and changes in the restriction of myelin based plasticity genes in the postnatal brain, may be the underlying factor for the many cognitive and behavioural deficits reported in schizophrenia (C. J. Carter, 2006; C. S. Carter, 2006; Davis et al., 2003; Davis and Haroutunian, 2003; Hakak et al., 2001). It has previously been considered that aberrant enhancement of neuronal plasticity during neural development in schizophrenia may be caused by a reduction or complete loss of NgR function (Budel, 2007; Budel et al., 2008); this is supported by our study demonstrating a downregulation of NgR in schizophrenia subjects (Fernandez-Enright et al., 2014). Furthermore, this is also supported by the presence of genetic variations in the *NgR* gene in 1-2% of the schizophrenia population (Budel, 2007; Budel et al., 2008; Karayiorgou et al., 1995; Sinibaldi et al., 2004). Deletion of the chromosomal region 22q11, has an association with a risk of schizophrenia 25 times greater than the general population, making the 22q11 deletion one of the strongest known genetic risk factors for schizophrenia (Bassett et al., 2003; Bassett and Chow, 1999). Further to this, children and adolescents with the 22q11 deletion have been found to have a high incidence of anxiety, depression, social withdrawal, attention deficit hyperactivity disorder, bipolar disorder, obsessive-compulsive behaviors and occasionally autism (Carlson et al., 1997; Kozma, 1998; Papolos et al., 1996; Woodin et al., 2001). Moreover, a spontaneous 3 Mb deletion at 22q11 has been found in 5.3% of patients in the largest cohort of very-early onset childhood onset schizophrenia subjects to date (Sporn et al., 2004). Additionally, SNPs with functional roles and/or those resulting in a change in amino-acids (R377W, R227C, R399W, rs74315508, rs74315509 and L18L) within the *NgR* gene have been previously identified in schizophrenia subjects (Budel et al., 2008; Sinibaldi et al., 2004). Interestingly, two non-synonymous changes (rs74315508 and rs74315509) were found in patients who displayed predominantly negative symptoms which were strongly resistant to conventional and novel drug treatments (Sinibaldi et al., 2004).

It has been well documented that memory impairment exists in schizophrenia (Aleman et al., 1999; Barch et al., 2001; Callicott et al., 2000; Weinberger et al., 1986). If impaired working memory is a hallmark of schizophrenia, then a downregulation of NgR, and *NgR* gene mutations known to be present in the schizophrenia population (Budel, 2007; Budel et al., 2008), could be considered possible grounds for the development of this memory dysfunction taking into consideration the role of NgR in regulating synaptic plasticity. In support of this hypothesis, *NgR* deficient mice have been shown to exhibit impaired working memory, despite their spatial memory acquisition remaining intact (Franowicz et al., 2002). NgR is the only established myelin associated inhibitor to display a memory phenotype (Akbik et al., 2012); however since *NgR* knockout mice have also been shown to display multiple schizophrenia related endophenotypes, a stronger link has been made between NgR downregulation or loss, and schizophrenia (Budel, 2007). Additionally *NgR* knockout mice are now considered to be an animal model for schizophrenia (Budel et al., 2008; Kim et al., 2004).

Either the p75 neurotrophin receptor or its functional homolog TROY make up the remainder of the Lingo-1/NgR signaling complex, however despite the overwhelming evidence implicating NgR in schizophrenia, only a few studies have reported levels of expression of p75 in the post-mortem schizophrenia brain, where no change was reported in the hippocampus of schizophrenia subjects compared to controls in the Stanley consortium brains, however a decrease in p75 binding was seen in bipolar disorder subjects compared to controls in the same study (Dunham et al., 2009). Meanwhile, alterations in p75 signaling proteins have been found in the post-mortem fusiform gyrus from autism patients compared to controls; PI3-K and Akt were found to be significantly downregulated, and a trend towards an upregulation of the p75 neurotrophin receptor was also found (Fahnestock and Nicolini, 2014). Similar alterations were observed in the lateral temporal neocortex of rats using the valproic-acid induced rat model of autism (Fahnestock and Nicolini, 2014). Selective knockout of the *p75 neurotrophin receptor* from the cerebellar Purkinje cells of mice, results in autism-like behaviors including diminished social interaction, a lack of interest in novel environments, in addition to a decrease in the complexity of the dendritic arborization of their cerebellar Purkinje cells (Lotta et al., 2014). When it comes to anxiety related disorders, there is conflicting information regarding p75. On

one hand *p75* knockout mice have been shown to display increased anxiety behavior and difficulties recovering from stress compared to wild-types, with altered cholinergic transmission both at baseline and in response to acute stress (Martinowich et al., 2012). On the other hand, there is evidence to show that *p75* knockout mice show markedly reduced anxiety levels, despite having increased fear memory compared to wild-type controls (Olsen et al., 2013). Furthermore, *p75* knockout mice were found not to have altered anxiety-like behavior compared to wild-types in the elevated-plus maze, light-dark, hole-board, T-maze or forced swim tests, however in a test for despair and depression-like behaviors the knockout mice displayed increased mobility in the tail-suspension test compared to the wild-type controls (Catts et al., 2008). Considering that *p75* is more highly expressed in the developing brain compared to the adult brain, where its expression is limited to certain neuronal subpopulations (Shao et al., 2005), examination of *TROY* in the central nervous system in relation to schizophrenia and other psychiatric disorders is warranted. Since *TROY* is a major partner of the Lingo-1/NgR/*TROY* complex, and considering the significant upregulation reported in the CA1, with no change in the CA3 of schizophrenia patients (Fernandez-Enright et al., 2014), additional mechanisms may be involved in the regulation of this protein which will need to be further investigated. Furthermore, a significant downregulation of *TROY* gene expression was found in the fibroblasts of major depressive disorder patients compared to matched healthy controls (Garbett et al., 2014), further implicating the Lingo-1/NgR/*TROY* complex in a wider variety of neuropsychiatric disorders.

Previous studies have shown that WNK1 is a negative regulator of cell growth via phosphorylation of the PI3-K/Akt signaling pathway (Jiang et al., 2005), and its overexpression was shown to be a negative regulator of Nogo-induced inhibition of neurite extension and RhoA (Zhang et al., 2009). WNK1 protein expression was found to be elevated in schizophrenia compared to control brains within the CA1, but not CA3 or DLPFC in schizophrenia compared to controls (Fernandez-Enright et al., 2014). This result was supported by previous literature reporting a consistent upregulation of *WNK1* gene expression in DLPFC post-mortem tissue from schizophrenia sufferers compared to controls (Maycox et al., 2009). Interestingly, overexpression of WNK1 has also been reported to

significantly reduce the interaction between endogenous WNK1 and Lingo-1, suggesting that it may serve as a binding platform for Lingo-1, however its kinase activity may not be necessary for Lingo-1 signaling (Zhang et al., 2009). Furthermore, disruption of the *WNK1* gene in mice leads to death of the embryo at day 13 (Zambrowicz et al., 2003), suggesting an essential role of WNK1 in embryonic and neural development, which is a critical period implicated in a number of neuropsychiatric disorders. In support of this hypothesis, a young patient with autism spectrum disorder and a tendency for anxiety, has been found to have a 1.5 Mb terminal deletion of the chromosomal region 12p13.33, which encompasses the *WNK1* gene in its entirety, in addition to 12 other genes (Silva et al., 2014). Furthermore, Thevenon *et. al.* have shown that a number of patients with either *de novo* or inherited 12p13.33 microdeletions, present with not only a number of developmental abnormalities, but also with a number of psychiatric disorders including autism spectrum disorder, attention-deficit hyperactivity disorder, and anxiety (Thevenon et al., 2013). This is supported by a finding of a 6 Mb deletion at 12p13.3 in 2 patients presenting with attention deficit hyperactivity disorder (one of whom resided in a psychiatric center) encompassing around 50 genes including *WNK1* (Madrigal et al., 2012). Differential expression of gene transcripts has been found in military personnel suffering from traumatic brain injury from blast exposure, who also suffer from post-traumatic stress disorder and depression (Heinzelmann et al., 2014). *WNK1* was found to be among the genes found to be significantly upregulated in these military personnel compared to controls, further implicating *WNK1* in a wider scope of psychiatric disorders.

Myelin transcription factor 1 (Myt1) and its highly conserved homolog, Myt1-like (Myt1l), are two other well-characterized direct intracellular binding partners of Lingo-1. Although disruption of the *Myt1l* gene has been reported in a Dutch schizophrenia population (Vrijenhoek et al., 2008), and polymorphisms in the *Myt1l* gene have been recently reported to be associated with schizophrenia in a Chinese Han population, specifically in female schizophrenia subjects (Li et al., 2012), little else is known about the implication of the Myt1 gene and protein in schizophrenia. Interestingly, the *Myt1* gene has been predicted to regulate the expression of *Neuregulin-1*, an extensively studied schizophrenia candidate gene, in schizophrenia patients (Law et al., 2006). Similar to the expression

profile of Lingo-1, we have reported significantly higher levels of Myt1 protein in the DLPFC of schizophrenia subjects compared to controls, but like Lingo-1, levels of Myt1 were not significantly altered in the CA1 or CA3 hippocampal regions (Fernandez-Enright et al., 2014). Considering the role of Lingo-1 and Myt1 in oligodendrocyte and myelin dysfunction, it was not surprising to find an increase in levels of both these proteins in the DLPFC of schizophrenia patients. Furthermore, both *Myt1l* and *Myt1* genes have been further implicated in other neuropsychiatric disorders, including autism through a microduplication at 2p25.3 engulfing 7 exons of the terminal portion of *Myt1l* (Meyer et al., 2012) and depression through SNP association (Wang et al., 2010); additionally, microduplications in the *Myt1l* gene have been identified as being present in 2% of childhood onset schizophrenia subjects from the same cohort of children who also display 22q11 deletions (Lee et al., 2012). Further to this, *Myt1* has been implicated in mental retardation, through its subtelomeric deletion on 20q (Kroepfl et al., 2008), autism spectrum disorder, through a 1.4 Mb copy number variation gain at 20q13.33 encompassing the *Myt1* gene in its entirety as well as 43 other genes (Moessner et al., 2007), in addition to having a potential role in attention deficit hyperactivity disorder, demonstrated thorough a genome-wide pathway analyses which identified the cdc25 pathway of which Myt1 is involved, as being a candidate causal pathway for attention deficit hyperactivity disorder (Lee and Song, 2014).

As mentioned above in section 3.4, Lingo-1 is able to negatively regulate the EGFR/PI3-K/Akt signaling pathway (Inoue et al., 2007), also involved in neuronal survival and axon regeneration (Brunet et al., 2001). Since Lingo-1 can directly inhibit EGFR independently of EGF activation, leading to inhibition of PI3-K/Akt signaling pathways (Inoue et al., 2007); a downregulation of EGFR induced by Lingo-1's inhibitory action may be partly involved in the regional specificity of Lingo-1 expression in the DLPFC we observed compared to hippocampus in schizophrenia brains (Fernandez-Enright et al., 2014). In the same post-mortem schizophrenia brain cohort, higher levels of EGFR protein in the DLPFC (Brodmann area 46) but not hippocampal regions in schizophrenia *versus* control brains have been reported (Swaminathan et al., 2013). In the context of schizophrenia pathophysiology, we postulate that greater levels of EGFR in the DLPFC may play a role in Lingo-1

upregulation observed in this region, leading to inhibition of PI3-K/Akt signaling pathways in schizophrenia. Moreover, the EGFR/PI3-K/Akt signaling pathway has also been implicated in autism, post-traumatic and psychosocial stress disorders, as well as depression through a number of genetic and neurobiological studies. *EGFR* gene regulation was found to be significantly upregulated in the same cohort of military personnel suffering blast traumatic brain injury, post-traumatic stress disorder and depression as those who also had an upregulation of *WNK1* (Heinzelmann et al., 2014). Furthermore, both SNP and copy number variation studies have implicated the EGFR/PI3-K/Akt signaling pathway in autism spectrum disorders (Cuscó et al., 2009; Toyoda et al., 2007). On the biochemical level, the evidence is a little more conflicting; as increased serum levels of EGF have been reported in children with autism (İşeri et al., 2011), while in adults with high-functioning autism, decreased levels of EGF have been found (Suzuki et al., 2007). This discrepancy suggests that EGF plays a differential role in the progression of autism throughout development from childhood through to adulthood. Significantly increased levels of EGF were also found in women exposed to prolonged psychosocial stress (Åsberg et al., 2009). This is supported by a rodent study which found that Akt signaling is significantly increased in the ventral tegmental area in response to stressful stimuli using a social defeat paradigm (Krishnan et al., 2008).

In addition TrkB, another Lingo-1 binding partner, has been implicated in the pathophysiology of several psychiatric disorders including drug addiction, schizophrenia, anxiety and bipolar disorders, anorexia nervosa and suicide ideation (Gupta et al., 2013). Levels of *TrkB* mRNA were reported to be decreased in the prefrontal cortex from individuals with suicide ideation (Dwivedi et al., 2003) and in the hippocampus of patients suffering from schizophrenia and/or mood disorders (Iritani et al., 2003; Thompson Ray et al., 2011) compared to healthy controls. Mutations in *TrkB* have also been linked to anxiety disorders (Ernst et al., 2011) as well as susceptibility for nicotine (Beuten et al., 2007) and alcohol addiction (Xu et al., 2007). Considering the antagonist effect of Lingo-1 on TrkB receptor-phosphorylation (Fu et al., 2010), Lingo-1 may play a role in the disturbances of TrkB observed in a range of psychiatric disorders, thus emphasizing the importance to further characterize the relationship between Lingo-1 and its known and yet to be discovered signaling partners.

6. Conclusions and Future Directions

Little is known about Lingo-1, and it is probably involved in many more neurological disorders that we are not yet aware of due to its large range and wide reaching interactions with a variety of proteins within the central nervous system. We have provided a large body of evidence demonstrating that Lingo-1 signaling pathways are implicated in a wide range of central nervous system neurological disorders including spinal cord injury, traumatic brain injury and multiple sclerosis; in addition to Parkinson's disease, essential tremor, Alzheimer's disease, epilepsy and glaucoma. Furthermore, we have provided the first report implicating Lingo-1 and its signaling partner proteins in the schizophrenia pathophysiology, and provided sufficient evidence further implicating Lingo-1 signaling partners in the pathology of a number of neuropsychiatric disorders including autism spectrum disorder, depression, attention-deficit hyperactivity disorder, anxiety, drug addiction and post-traumatic stress disorder. Due to the role of the many Lingo-1 pathways as a negative regulator of myelination and neurite outgrowth, and considering the implication of both of these central processes in cognitive performance, antagonists of Lingo-1 appear to be a new potential candidate for the treatment of a number of neurological and psychiatric disorders.

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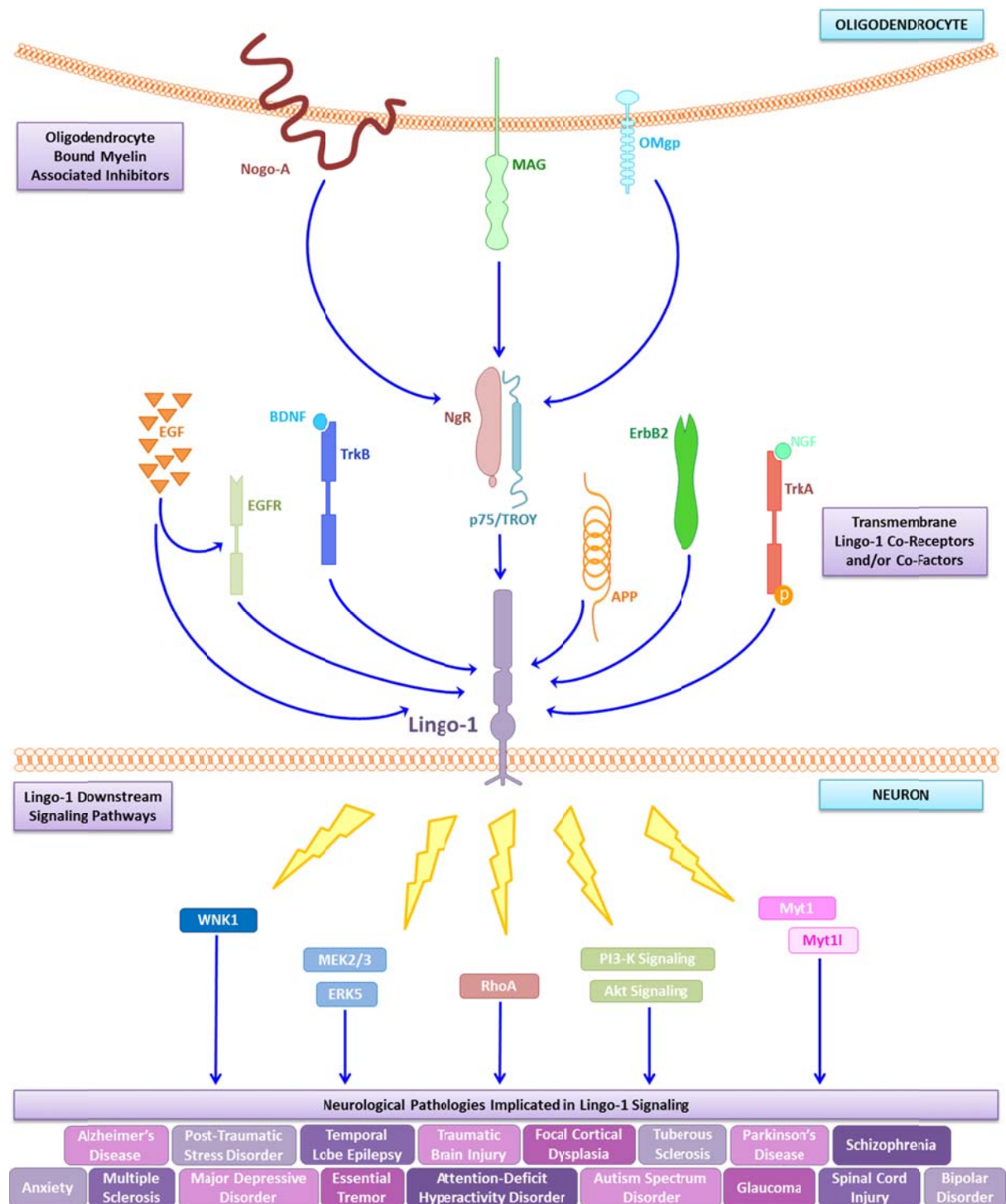
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Figure 1: Schematic representation of Lingo-1 signaling pathways implicated in neurological and psychiatric disorders. Oligodendrocyte bound, myelin associated inhibitory proteins - myelin associated glycoprotein (MAG), oligodendrocyte-myelin glycoprotein (OMgp) and neurite outgrowth inhibitor (Nogo-A) bind to the Nogo Receptor (NgR) with high affinity to inhibit neurite outgrowth and myelination processes. NgR lacks a transmembrane domain and requires either the p75 neurotrophin receptor (p75) or TNF receptor orphan Y (TROY) co-receptors, in addition to Lingo-1 to transduce its inhibitory signals. A number of other transmembrane proteins interacting with Lingo-1 on neurons are also implicated in a wide range of neurological disorders. These include: the epidermal growth factor receptor (EGFR) along with its ligand epidermal growth factor (EGF), brain-derived neurotrophic factor (BDNF) and its receptor tropomyosin receptor kinase B (TrkB), amyloid precursor protein (APP), receptor tyrosine-protein kinase erbB-2 (ErbB2), and tropomyosin receptor kinase A (TrkA) with its ligand nerve growth factor (NGF). These transmembrane protein-protein interactions with Lingo-1 result in the activation of a number of downstream signaling proteins which are further implicated in numerous neurological and psychiatric disorders; these include WNK lysine deficient protein kinase 1 (WNK1), mitogen activated protein kinase 2/3 (MEK2/3), extracellular signal reduced kinase 5 (ERK5), ras homolog gene family, member A (RhoA), phosphatidylinositide 3-kinase (PI3-K), protein kinase B (PKB, also known as Akt), and finally myelin transcription factor 1 (Myt1) and its homolog myelin transcription factor 1-like (Myt1l).

Figure 1



A decade from discovery to therapy: Lingo-1, the dark horse in neurological and psychiatric disorders

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Evidence for the involvement of Lingo-1 signaling and/or Lingo-1 binding proteins in neurodegenerative and neuropsychiatric disorders.

Disease	Protein(s)	Species/Model/Cell Line	Study Details	Findings	Reference
Alzheimer's Disease	APP, Lingo-1	Mouse, CD1	Mice underwent time-controlled transcardiac perfusion cross-linking (tcTPC) following anesthesia. Interactome maps for APP were obtained by immunoprecipitation and two-dimensional liquid chromatography and mass spectrometry.	Novel interactions between Lingo-1 and APP were found in the interactome map. This was validated and confirmed by a series of co-immunoprecipitation experiments using antibodies directed at APP or Lingo-1. <i>In situ</i> hybridization studies showed that Lingo-1 and APP are co-localized in the mouse brain, with pronounced staining of CA1 to CA3 hippocampal neurons.	Bai Y. et. al. 2008
Alzheimer's Disease	APP, Lingo-1	Chinese Hamster Ovary (CHO) cells	CHO cells at 90% confluence were transfected with APP695 and Lingo-1 constructs. HA-tagged Lingo-1, and APP constructs were co-immunoprecipitated	APP was co-immunoprecipitated with Lingo-1 constructs that were lacking either the LRR domain or the cytoplasmic domain of Lingo-1. Co-immunoprecipitation failed with a Lingo-1 construct comprising only the transmembrane and cytoplasmic domain.	Stein T, and Walmsley AR. 2012

Disease	Protein(s)	Species/Model/Cell Line	Study Details	Findings	Reference
				The APP interaction with Lingo-1 occurs within the Lingo-1 ectodomain, but does not require the LRRs.	
Alzheimer's Disease	EGFR	Drosophila, <i>Aβ42</i> transgenic flies Mouse, <i>APP/PS1</i> double transgenic mice [strain: B6C3-Tg(APP ^{swe} .PSEN1dE9)85Dbo/J]	Flies underwent a Pavlovian olfactory associative immediate memory conditioning assay, both before and after being treated with EGFR inhibiting drugs Gefitinib and Erlotinib. Mice underwent a 7 day pretesting treatment with Gefitinib before being subjected to the Morris water maze task for 9 days. Phospho-EGFR levels were assessed in the hippocampus of the mice using western blotting.	Co-expression of EGFR in <i>Aβ42</i> -expressing Drosophila exacerbated memory loss; while inhibition of EGFR activity prevented memory loss in <i>Aβ42</i> -expressing Drosophila. Treatment with Gefitinib completely recovered impaired memory in the <i>APP/PS1</i> double transgenic mice. Phospho-EGFR was elevated in the hippocampus of <i>APP/PS1</i> double transgenic mice, and could be suppressed by treatment with Gefitinib.	Wang L. et. al. 2012
Alzheimer's Disease and Spinal Cord Injury	NgR, BDNF	Rat, Sprague-Dawley and spontaneously hypertensive rats (SHR)	Kainic acid (10 mg/kg i.p.) was administered to Sprague-Dawley rats. Rats were decapitated and brains removed and frozen at different time points post injection for <i>in situ</i> hybridization or autoradiography analysis. SHR rats were given either unlimited access or no access to running wheels, and were decapitated at different time points after being given access to running wheels. Spinal cord weight drop injuries were performed on Sprague-Dawley rats; spinal cords were collected at different time points after injury.	Kainic acid injections resulted in strong downregulation of <i>NgR</i> and strong upregulation of <i>BDNF</i> mRNA in dentate gyrus, hippocampus and neocortex. Running on wheels for 3 and 7 days resulted in a significant downregulation of <i>NgR</i> mRNA in the cortex, hippocampus and dentate gyrus. No robust regulation of <i>NgR</i> was observed in the spinal cord following spinal cord injury.	Josephson A. et. al. 2003
Alzheimer's Disease	NgR	Human post-mortem brains from Alzheimer's Disease subjects	Hippocampal samples were collected from 10 post-mortem female Alzheimer's brains and 10 age-matched non-demented female brains. Immunohistochemistry and double-labeling	NgR immunoreactivity was present in more than 50% of the pyramidal layer cells of the CA1 to CA4 subfields of the hippocampus. No significant difference in the number of	Zhu H-Y. et. al. 2007

Disease	Protein(s)	Species/Model/Cell Line	Study Details	Findings	Reference
			immunofluorescence were used to investigate the expression of NgR in the hippocampus of Alzheimer's Disease compared to control brains.	immunopositive cells in the CA1 to CA4 regions was observed between Alzheimer's and control subjects. A higher ratio of immunopositive cells to the total number of pyramidal cells was observed in the CA1 and CA2 hippocampal regions in Alzheimer's brains compared to control brains.	
Alzheimer's Disease	NgR, Nogo-A, APP	Human post-mortem brains from Alzheimer's Disease subjects Mouse, <i>APP^{swe}/PSEN-1(ΔE9)</i> double transgenic mouse Human Embryonic Kidney HEK-293T cells APP ^{swe} -N2A neuroblastoma cells	Histological analysis of Nogo-A and NgR immunoreactivity was performed in post-mortem sections from the hippocampus and Brodmann's area 20/36 from 6 Alzheimer's brains and 6 control brains. NgR localization was assessed in a transgenic mouse model of Alzheimer's disease. Immunoprecipitation studies were performed using the HEK-293T cells to determine interactions between Nogo-A and NgR with APP. Western blotting was used to examine expression of endogenous NgR and Aβ production in the N2A cell line. <i>APP^{swe}/PSEN-1(ΔE9)</i> double transgenic mice were bred with <i>NgR</i> null mice to examine the effect of the NgR/ APP interaction <i>in vivo</i> . <i>APP^{swe}/PSEN-1(ΔE9)</i> double transgenic mice were treated with soluble NgR(310)ecto-Fc protein to increase NgR APP interactions <i>in vivo</i> .	Nogo-A and NgR are mislocalized in Alzheimer's brain samples. Neither NgR nor Nogo-A co-localize with neurofibrillary tangles or dystrophic neurites. Results confirmed in transgenic mouse model. APP is physically associated with NgR. Overexpression of NgR decreases Aβ production in N2A neuroblastoma culture. Targeted disruption of NgR expression increases transgenic mouse Aβ levels, Aβ plaque deposition and dystrophic neurites. Infusion of a soluble NgR fragment reduces Aβ levels, amyloid plaque deposits and dystrophic neurites in a transgenic Alzheimer's disease mouse model.	Park JH. et. al. 2006
Alzheimer's Disease	Nogo-A, OMgp, MAG, NgR, Lingo-1, TROY	Rat, Fisher 344	In situ hybridization was used to examine mRNA levels of <i>Nogo-A</i> , <i>OMgp</i> , <i>MAG</i> , <i>NgR</i> , <i>Lingo-1</i> and <i>TROY</i> in the cortex and hippocampus and young (4 months), middle	No alterations in levels of <i>NgR</i> , <i>Lingo-1</i> , <i>TROY</i> , <i>OMgp</i> or <i>MAG</i> were observed. <i>Nogo-A</i> was significantly decreased in the	Trifunovski A. et. al. 2006

Disease	Protein(s)	Species/Model/Cell Line	Study Details	Findings	Reference
			aged (16 months) and old (24 months) rats.	hippocampus of the aged rats.	
Alzheimer's Disease	p75	Human post-mortem brains from Alzheimer's Disease subjects	Expression of p75 was examined by immunocytochemistry in the hippocampus taken from the level of the lateral geniculate body from 10 female Alzheimer's Disease subjects compared to 10 non-demented controls.	<p>Increased intensity of p75 immunoreactivity in cell bodies and processed in the CA1 and CA2 of Alzheimer's subjects compared to controls.</p> <p>Increases in the ratio of p75 expressing neurons to thionin (Nissl) stained neurons in CA1 and CA2 of Alzheimer's compared to controls.</p> <p>Large proportion of p75 expressing cells co-localized with Alz-50 (recognizes tau protein) in CA1 and CA2 regions in Alzheimer's Disease subjects.</p>	Hu X-Y. et. al. 2002
Autism	BDNF, TrkB, PI3-K, Akt, mTOR, p75	Human post-mortem brains from autism subjects Rat, Valproic acid (VPA) – induced rat model of autism	Protein levels were examined by western blot in the fusiform gyrus of 11 autism and 13 control subjects and in the lateral temporal neocortices of VPA rats and control rats.	<p>Decreased TrkB, PI3K, Akt, mTOR and phospho-mTOR protein levels in autism compare to controls.</p> <p>Trending increase in truncated TrkB and p75 protein levels in autism compare to controls.</p> <p>Similar results observed in VPA rats.</p>	Fahnestock M, and Nicolini C. 2014
Autism	EGF	Human	Blood serum levels of EGF were examined by sandwich ELISA in 27 autistic children and 28 age-matched controls (age 2-11 years)	Increased levels of EGF serum levels in autistic children compared to controls.	İşeri E. et. al. 2011
Autism	EGF	Human, Japanese	Blood serum levels of EGF were examined by ELISA in 17 male autistic subjects and 18 age-matched control subjects (aged 19-28 years).	Decreased serum levels of EGF in high-functioning autism subjects compared to controls.	Suzuki K. et. al. 2007
Autism	EGF	Human, Caucasian	Genetic association study using 252 White trio families with a male offspring scored for autism. Hispanic and Latino families were	A significant haplotypic association between <i>EGF</i> gene and autism.	Toyoda T. et. al. 2007

Disease	Protein(s)	Species/Model/Cell Line	Study Details	Findings	Reference
			excluded.	The rs4698803 and rs6533485 SNPs showed a tendency towards an association with autism.	
Autism	Lingo-1	Human	Genetic screening for copy number variants across 15q24 was performed on 173 unrelated subjects with autism spectrum disorder. Additionally 1336 subjects with autism spectrum disorder from 785 families were also screened. Results were confirmed by array comparative genomic hybridization and quantitative PCR.	An atypical de novo deletion of 3.06 Mb in 15q23-24.1 was discovered in a boy with autism. He shared many features with the other 13 subjects with 15q24 microdeletion syndrome that have been described to date. Deletions in 15q24 represent rare causes of autism spectrum disorder.	McInnes LA. et. al. 2010
Autism	Myt1l	Human	Subjects were male half-siblings born to a common mother by different fathers. Both subjects score well above the cut-off for autism on the Autism Diagnostic Interview-Revised (ADI-R). The 2p25.3 duplication was identified in both male siblings using an Affymetrix 10K SNP microarray. Duplication of 2p25.3 was confirmed using fluorescence <i>in situ</i> hybridization, and Affymetrix 6.0 SNP arrays were used to more precisely delineate the duplication breakpoints.	Fluorescence <i>in situ</i> hybridization revealed evidence for duplication in both affected half-brothers. Their mother tested positive for duplication of 33-40% of the fluorescence <i>in situ</i> hybridization probes, revealing that she was mosaic in her lymphoblasts for the duplication. Affymetrix 6.0 revealed that the 2p25.3 duplication was approx. 281 kb and that only 63 kb of the <i>Myt1l</i> terminus (containing 7 exons) was duplicated.	Meyer KJ. et. al. 2012
Autism	p75	Mouse, Purkinje cell-selective <i>p75</i> knockout mice (Cre-loxP mice)	Immunohistochemistry was used to examine quantitative microanatomy of the Purkinje cells in the mice by genotype. Locomotor activity and social interaction were assessed.	Cre-loxP mice exhibit complete knockout of p75 in approx. 50% of their cerebellar Purkinje cells. Cre-loxP mice display decreased allogrooming, socialization and fighting with other mice. Cre-loxP mice display decreased non-ambulatory exploration of their environment than wild types; and display increased	Lotta LT. et. al. 2014

Disease	Protein(s)	Species/Model/Cell Line	Study Details	Findings	Reference
				jumping behavior compared to wild-types.	
Autism	PI3-K	Human, Caucasian	A comparative genomic hybridization array was performed on a cohort of 96 Spanish patients with idiopathic autism spectrum disorder.	238 copy number variations were detected, and of these, 13 were present specifically in the autistic population (i.e. 12 out of the 96 individuals)	Cuscó I. et. al. 2009
Autism	WNK1	Human	An 8-year old boy of European origin presented for evaluation of neurodevelopmental delay. G-banded chromosome analysis was performed on peripheral blood lymphocytes. Array comparative genomic hybridization was performed on DNA extracted from peripheral blood using a whole-genome, bacterial artificial chromosome-based microarray.	Comparative genomic hybridization revealed a 1.5 Mb terminal deletion at 12p13.33, encompassing 13 different genes: <i>B4GALNT3</i> , <i>CCDC77</i> , <i>ERC1</i> , <i>FBXL14</i> , <i>IQSEC3</i> , <i>KDM5A</i> , <i>LINC00942</i> , <i>LOC574538</i> , <i>NINJ2</i> , <i>RAD52</i> , <i>SLC6A12</i> , <i>SLC6A13</i> and <i>WNK1</i> .	Silva IMW. et. al. 2014
Autism, Attention Deficit Hyperactivity Disorder and Anxiety	WNK1	Human	A genetic study was performed on a series of 9 patients with 12p subtelomeric deletions, including 2 familial cases with severe speech sound disorders. The Human Genome CGH Microarray 44, 105, 180 or 244K from Agilent Technologies was utilized for analysis and fluorescence <i>in situ</i> hybridization and quantitative PCR were used to confirm results.	Subjects with either inherited or de novo 12p13.33 microdeletions present with developmental abnormalities, in addition to psychiatric disorders including autism spectrum disorder, attention-deficit hyperactivity disorder and anxiety.	Thevenon J. et. al. 2013
Essential Tremor	Lingo-1	Human	A meta-analysis was conducted on 11 association studies between Lingo-1 rs9652490 (3972 cases vs. 20714 controls), and 7 association studies between Lingo-1 rs11856808 (2076 cases vs. 18792 controls) and their risk for essential tremor.	There is a significant relationship between <i>Lingo-1</i> rs11856808 and essential tremor and familial essential tremor. The <i>Lingo-1</i> rs9652490 polymorphism was only related to a familial risk for essential tremor.	Jiménez-Jiménez FJ. et. al. 2012
Essential Tremor	Lingo-1	Human post-mortem brains from essential tremor subjects	Post-mortem tissue was obtained from essential tremor patients and age-matched controls.	Western blotting showed that Lingo-1 protein was significantly increased in the cerebellar cortex of essential tremor brains compared to	Kuo S-H. et. al. 2013

Disease	Protein(s)	Species/Model/Cell Line	Study Details	Findings	Reference
			Western blotting (using 10 essential tremor cases and 11 controls) and immunohistochemistry (11 essential tremor and 12 controls) were used to examine Lingo-1 protein in essential tremor compared to control brains.	controls; however levels were similar in the occipital cortex. Immunohistochemistry revealed that Lingo-1 was enriched in the distal axonal processes of basket cells, forming a pinceau structure around the Purkinje cell axon initial segment.	
Essential Tremor	Lingo-1	Human, Caucasian	Genome-wide association study was conducted on Icelandic subjects with essential tremor. Illumina HumanHap300 and HumanCNV370 chips were used.	rs9652490 and rs11856808 SNPs were both found to be significantly associated with essential tremor. Only the rs9652490 SNP was found to be significant at the genome-wide level.	Stefansson H. et. al. 2009
Essential Tremor and Parkinson's Disease	Lingo-1	Human, Caucasian	The cohort from this study included: 356 essential tremor patients from North America, 426 Parkinson's disease patients from North America, 618 Parkinson's disease patients from Norway; in addition to 428 controls from North America and 602 controls from Norway. All subjects were of Caucasian descent. Genotyping was performed using a TaqMan probe on an ABI7900.	There was a significant association between the <i>Lingo-1</i> SNP rs9652490 and both essential tremor and Parkinson's disease.	Vilariño-Güell C., Ross OA. et. al. 2010
Essential Tremor and Parkinson's Disease	Lingo-1	Human, Caucasian	A total of 1247 essential tremor patients, 633 Parkinson's disease patients, and 642 control subjects were used in this study. All subjects were Caucasian and from North America. Genomic DNA was extracted from peripheral blood lymphocytes and <i>Lingo-1</i> and <i>Lingo-2</i> genes were sequenced in 95 essential tremor and 96 Parkinson's disease patients (randomly selected). Haplotype-tagging SNPs identified by	Sequencing revealed 6 novel coding variants in <i>Lingo-1</i> (S4C, V107M, A277T, R423R, G537A, and D610D), in addition to 5 known polymorphisms (rs2271398, rs2271397, rs2271396, rs3743481, and rs61737308). The <i>Lingo-1</i> SNPs S4C, A277T, R423R, G537A and D610D were observed exclusively in cases (either essential tremor or both essential tremor and Parkinson's disease) and not in controls.	Vilariño-Güell C., Wider C. et. al. 2010

Disease	Protein(s)	Species/Model/Cell Line	Study Details	Findings	Reference
			sequencing were genotyped using a Sequenom MassArray iPLEX platform.	Associations with essential tremor were also observed for <i>Lingo-1</i> SNPs rs4886887, rs3144, rs8028808 and rs12905478; with rs4883887 and rs3144 being driven by the minor alleles. The <i>Lingo-1</i> SNP rs907396 was associated with a 5-year younger mean age of onset of essential tremor.	
Glaucoma	Lingo-1, RhoA, PI3-K, Akt	Rat, Sprague-Dawley	An experimental ocular hypertension model in female rats was used. Lingo-1 expression in retinas was investigated using immunohistochemistry and western blotting. Soluble Lingo-1 (Lingo-1-Fc) and anti-Lingo-1 antibody (mAb 1A7) were injected into vitreous body to examine effects of Lingo-1 antagonism on RGC survival after ocular hypertension and optic nerve transection.	Lingo-1 was expressed in RGCs and up-regulated after intraocular pressure elevation. Blocking Lingo-1 using Lingo-1-Fc, significantly reduced RGC loss both 2 and 4 weeks after ocular hypertension and promoted RGC survival after optic nerve transection. Lingo-1-Fc and mAb 1A7 treatment blocked the RhoA pathway and promoted Akt activation.	Fu Q-L. et. al. 2008
Glaucoma	Lingo-1, BDNF, TrkB	Rat, Sprague-Dawley	Experimental ocular hypertension model in rats was used to examine whether BDNF combined with Lingo-1 antagonists can promote long-term RGC survival after ocular hypertension. Immunohistochemistry and western blotting were used to assess TrkB and Lingo-1 expression.	BDNF alone shows slight neuroprotection to RGCs 4 weeks after ocular hypertension. Combined BDNF and Lingo-1-Fc treatment prevents RGC death in the same condition. Lingo-1 is co-expressed with BDNF receptor TrkB in the RGCs BDNF combined with Lingo-1-Fc activated more TrkB in the injured retina compared to BDNF alone.	Fu Q-L. et. al. 2009
Glaucoma	Lingo-1, NgR, Myocilin	Mouse, <i>Myocilin</i> -null mice (<i>Myoc</i> -null mice)	Myocilin-null mice were compared to wild type mice in all experiments.	Myocilin is expressed and secreted by optic nerve astrocytes.	Kwon HS. et. al. 2014

Disease	Protein(s)	Species/Model/Cell Line	Study Details	Findings	Reference
			Quantitative PCR, immunoprecipitation, western blotting, immunohistochemistry and co-immunoprecipitation experiments were used to examine the role of Myocilin in the optic nerve and the interaction of Myocilin with the NgR/Lingo-1 complex.	<p>Differentiation of optic nerve oligodendrocytes is delayed in <i>Myocilin</i>-null mice.</p> <p>Optic nerves of <i>Myocilin</i>-null mice contain reduced levels of MBP, myelin proteolipid protein and 2'3'-cyclic nucleotide 3'-phosphodiesterase compared to wild types. <i>Myocilin</i>-null mice have reduced myelin sheath thickness on optic nerve axons compared to wild types.</p> <p>Myocilin stimulates oligodendrocyte differentiation through the NgR/Lingo-1 receptor complex.</p> <p>Myocilin interacts physically with Lingo-1 and may be considered to be a Lingo-1 ligand.</p>	
Glaucoma	Lingo-1, TrkB, BDNF	<p>Rat, Sprague-Dawley</p> <p>Human Embryonic Kidney HEK-293T cells overexpressing both <i>Lingo-1</i> and <i>TrkB</i></p>	<p>Adult female Sprague-Dawley rats underwent a laser eye procedure to induce unilateral ocular hypertension.</p> <p>Lingo-1-Fc or 1A7 (2 µg in 2µL PBS) were administered intravitreally to the rats on Day 0, then anti-BDNF (1 µg/µL) was injected into the experimental eye on Day 0 (30 min after 1A7 or Lingo-1-Fc injection), then at 4, 7 and 10 days after laser treatment.</p> <p>Immunoprecipitation studies using both HEK-293T cells and cells from injured retinas were conducted to assess if TrkB and Lingo-1 form an interacting complex.</p> <p>BDNF and TrkB expression levels in the rat retinas were assessed by western blotting.</p> <p>Retinal levels of BDNF were quantified by</p>	<p>Lingo-1 forms a receptor complex with TrkB and negatively regulates its activation in the retina after ocular hypertension injury.</p> <p>Lingo-1 antagonists 1A7 antibody or Lingo-1-Fc treatment up-regulates phospho-TrkB activation and leads to RGC survival after ocular hypertension injury.</p> <p>Treatment with an anti-BDNF antibody blocks the neuronal protective effect of the Lingo-1 antagonists.</p> <p>Blocking Lingo-1 promotes the activation of TrkB after the induction of ocular hypertension.</p>	Fu Q-L. et. al. 2010

Disease	Protein(s)	Species/Model/Cell Line	Study Details	Findings	Reference
			<p>ELISA.</p> <p>BDNF-positive RGCs in the retina were quantified by immunohistochemistry.</p>		
Glaucoma	NgR	Rat, Sprague-Dawley	<p>Adult female Sprague-Dawley rats were subjected to either a laser eye procedure to induce unilateral ocular hypertension, or an optic nerve transection procedure.</p> <p>After the first laser eye procedure or immediately following optic nerve transection, an intravitreal injection of soluble sNgR-Fc (2µg in 2 µL PBS) was given.</p> <p>Rats were sacrificed at 5 days, 2 weeks or 4 weeks in the ocular hypertension model and at 1 week in the optic nerve transection model. Rats in the 4 week group received treatments once per week.</p> <p>Expression of NgR in the normal and injured rat retina was assessed by immunohistochemistry.</p> <p>The effect of sNgR-Fc on synaptic input after the induction of ocular hypertension was assessed by immunohistochemical analysis of c-Fos expression.</p> <p>Retinal NgR expression was measured by western blotting.</p>	<p>NgR was expressed in RGCs and was upregulated after intraocular pressure elevation.</p> <p>Treatment with soluble sNgR-Fc significantly reduced RGC loss at both 2 and 4 weeks after the induction of ocular hypertension.</p> <p>sNgR-Fc treatment promoted RGC survival after optic nerve transection.</p> <p>sNgR-Fc attenuated synaptic degeneration at 5 days, 2 weeks and 4 weeks.</p>	Fu Q-L. et. al. 2011
Major Depression	Myt1l	Human, Chinese Han	<p>A total of 1139 major depressive patients (487 males and 652 females) and 1140 controls (374 males and 766 females) were genotyped from a Chinese Han population.</p> <p>8 tag SNPs were genotyped (rs1617213,</p>	<p>3 SNPs were found to have significant allelic and genotypic associations with major depressive disorder (rs3748989, rs3748988 and rs7592630).</p> <p>After correction by SNPSpD rs3748989</p>	Wang T. et. al. 2010

Disease	Protein(s)	Species/Model/Cell Line	Study Details	Findings	Reference
			rs6759709, rs6727410, rs11687068, rs3748989, rs3748988, rs4305302 and rs7592630), using the ABI 7900 DNA detection system with Taq-Man probes from Applied Biosystems.	retained genotypic and allelic significance, and rs3748988 retained genotypic significance.	
Major Depression	TROY (TNFRSF19)	Human Fibroblasts	<p>Cultured dermal fibroblast samples from patients with major depressive disorder and matched controls were assayed for genome-wide mRNA expression using an Agilent 2100 Bioanalyzer microarray assay. Results were validated by quantitative PCR.</p> <p>Quantitative PCR was also used to assess over 1000 microRNA (miRNA) species.</p>	<p>Fibroblasts from major depressive patients showed a strong mRNA expression pattern change in molecular pathways including cell-to-cell communication, innate/adaptive immunity, and cell proliferation.</p> <p>The same fibroblasts showed altered expression of a distinct panel of 38 miRNAs.</p> <p><i>TNFRSF19</i> mRNA is downregulated in fibroblasts from major depressive disorder patients compared to matched healthy controls.</p>	Garbett KA. et. al. 2014
Megalencephaly	BDNF, TrkB, Nogo-A, Lingo-1, NgR, TROY, OMgp	Mouse, <i>BALB/cByJ-Kv1.1^{mceph/mceph}</i>	<p><i>BALB/cByJ-Kv1.1^{mceph/mceph}</i> (also known as <i>mceph/mceph</i>) mice and wild type mice were treated with carbamazepine (3.5 g/kg pellets) from postnatal week 6 to 12. The expected daily intake of carbamazepine was 0.5 g/kg body weight per rat.</p> <p>Levels of <i>BDNF</i>, <i>TrkB</i>, <i>Nogo-A</i>, <i>Lingo-1</i>, <i>NgR</i>, <i>TROY</i>, and <i>OMgp</i> mRNA were assessed by <i>in situ</i> hybridization in <i>mceph/mceph</i> mice compared to wild types along with the effects of carbamazepine treatment on mRNA levels.</p>	<p><i>BDNF</i> mRNA was significantly increased in the CA3, ventral cortex, amygdala and CA1 of <i>mceph/mceph</i> mice compared to wild types.</p> <p><i>TrkB</i> mRNA was significantly upregulated in the dentate gyrus of <i>mceph/mceph</i> mice compared to wild types.</p> <p><i>Nogo-A</i> mRNA hybridization was increased in the CA3 of <i>mceph/mceph</i> mice compared to wild types.</p> <p><i>NgR</i> mRNA was increased in the dentate gyrus in <i>mceph/mceph</i> mice compared to wild types.</p> <p><i>Lingo-1</i> mRNA was increased in the CA3, dentate gyrus, ventral cortex and amygdala in <i>mceph/mceph</i> mice compared to wild types.</p>	Lavebratt C. et. al. 2006

Disease	Protein(s)	Species/Model/Cell Line	Study Details	Findings	Reference
				<p><i>TROY</i> mRNA was decreased in the cortex, dentate gyrus CA1 and ventral cortex of <i>mceph/mceph</i> mice compared to wild types.</p> <p>OMgp mRNA levels were upregulated in the amygdala of <i>mceph/mceph</i> mice compared to wild types.</p> <p>Treatment with carbamazepine completely normalized all of the dysregulations in the expression of <i>BDNF</i>, <i>Nogo-A</i>, <i>NgR</i>, <i>Lingo-1</i> and <i>TROY</i> mRNA in the <i>mceph/mceph</i> mice. <i>TrkB</i> and <i>OMgp</i> levels were not normalized by carbamazepine treatment.</p>	
Multiple Sclerosis	Lingo-1	Mouse, myelin oligodendrocyte glycoprotein-induced experimental autoimmune encephalomyelitis (EAE) mice; created from C57/BL6 mice	<p>Lentiviral vectors encoding Lingo-1 short hairpin RNA (LV/Lingo-1-shRNA) were constructed to inhibit Lingo-1 expression.</p> <p>EAE mice received intracerebroventricular injections (5µL) of LV/Lingo-1shRNA into both lateral ventricles over a 5 min time period followed by an additional 2 min delay to allow for diffusion before removal of the cannula.</p> <p>Locomotor activity was assessed at different time points (1, 3, 7, 14, 21 and 30 days after injection).</p> <p>Levels of myelination were examined by luxol fast blue staining.</p> <p><i>Lingo-1</i> mRNA and protein expression were examined from cortical samples by real-time PCR and western blotting respectively.</p>	<p><i>Lingo-1</i> mRNA and protein expression was higher in untreated EAE mice compared to wild types at all time points examined.</p> <p><i>Lingo-1</i> mRNA and protein levels were significantly downregulated by LV/Lingo-1-shRNA treatment compared to the untreated EAE mice.</p> <p>Locomotor activity scores were significantly lower in the LV/Lingo-1-shRNA treated groups than in the untreated mice.</p> <p>Significant demyelination was observed in the EAE mice compared to the wild type mice. LV/Lingo-1-shRNA treatment resulted in significantly higher myelination than the untreated group, but myelination levels remained lower than in the wild type mice.</p>	Wang C-J. et. al. 2014
Multiple Sclerosis	Lingo-1	Human, Caucasian	The cohort used for this study consisted of 293 unrelated Caucasian Spanish patients (203	<i>Lingo-1</i> SNPs rs9652490 and rs11856808 were found not to have any significant allelic	García-Martín E. et. al. 2013

Disease	Protein(s)	Species/Model/Cell Line	Study Details	Findings	Reference
			<p>females and 90 males, average age 43.9±11.4) and 318 healthy, unrelated controls (221 females and 97 males, average age 43.7±12.4), matched for age and gender.</p> <p>Genomic DNA was obtained from peripheral leukocytes and the <i>Lingo-1</i> SNPs rs9652490 and rs11856808 were genotypes using KASPar assays.</p>	<p>or genotypic associations with multiple sclerosis.</p> <p>Allelic and genotypic frequencies were found to be unrelated to the age of onset of multiple sclerosis, gender and the clinical course of the disease.</p>	
Multiple Sclerosis	Lingo-1	Human	<p>Two separate randomized, placebo-controlled Phase 1 clinical trials were performed. Single ascending doses (0.1 to 100 mg/kg) and multiple ascending doses (0.3 to 100 mg/kg; 2 doses separated by 14 days) of BIIB033 or placebo were administered intravenously to 64 healthy adult volunteers and 42 subjects with relapsing-remitting or secondary progressive multiple sclerosis respectively.</p> <p>Safety assessments included adverse event monitoring, neurologic examinations, conventional and non-conventional MRI, EEG, optical coherence tomography, retinal examinations and evoked potentials.</p> <p>Serum and cerebrospinal fluid samples were collected to measure BIIB033 concentrations.</p>	<p>BIIB033 infusions were well tolerated.</p> <p>The frequency of adverse effects was similar between BIIB033 and placebo; headache was the most frequently reported adverse effect.</p> <p>Doses at 10 mg/kg or higher resulted in BIIB033 concentrations similar to or higher than the concentration associated with 90% of the maximum remyelination effect in rats.</p>	Tran J. et. al. 2014
Multiple Sclerosis	Lingo-1	<p>Rat, myelin oligodendrocyte glycoprotein-induced experimental autoimmune encephalomyelitis (EAE) rats</p> <p>Mouse, <i>Lingo-1</i> knockout</p>	<p>Myelin oligodendrocyte glycoprotein-induced experimental autoimmune encephalomyelitis (EAE) was induced in both mice and rats (<i>Lingo-1</i> knockout mice vs. wild type C57BL6J mice, and Sprague-Dawley rats).</p> <p>3 days after EAE induction, rats were treated with either intrathecal injections of either an isotype control antibody, or anti-Lingo-1 (185 mg/day for 2 weeks); or intraperitoneal</p>	<p><i>Lingo-1</i> knockout mice have an earlier onset of myelination compared to wild-types.</p> <p>While both wild-type and <i>Lingo-1</i> knockout mice displayed EAE symptoms, the EAE scores were significantly higher in <i>Lingo-1</i> knockout mice.</p> <p>Electron microscopy showed that lower EAE scores reflect remyelination.</p>	Mi S. et. al. 2007

Disease	Protein(s)	Species/Model/Cell Line	Study Details	Findings	Reference
			<p>injections of the same antibodies (8mg/kg twice per week for 2 weeks).</p> <p><i>Lingo-1</i> knockout and wild-type control mice also underwent EAE induction.</p> <p>All animals were perfused 30-36 days after EAE induction and spinal cord tissues were prepared for diffusion tensor imaging, immunocytochemistry and electron microscopy analysis to assess the levels of de/re-myelination in the different treatment groups.</p>	<p><i>Lingo-1</i> knockout EAE animals showed an abundance of newly formed myelin sheaths, and had more myelinated fibers overall compared to wild-type EAE mice.</p> <p>Blocking Lingo-1 function either by gene knockout or through treatment with an anti-Lingo-1 antibody, promotes functional recovery in the EAE model.</p> <p>Functional recovery is correlated with improved axonal integrity and axonal myelination.</p> <p>Demyelination in the spinal cord of anti-Lingo-1 treated EAE rats was five times lower than in the control group.</p> <p>More myelination and/or remyelinated axons were found in anti-Lingo-1 treated rats.</p>	
Multiple Sclerosis	Lingo-1, TROY, p75, NgR	Human post-mortem brains from multiple sclerosis subjects	<p>Post-mortem brain samples from the frontal cerebral cortex or the cerebellar cortex were obtained from autopsied brains from 5 multiple sclerosis patients and 10 non-multiple sclerosis cases.</p> <p>Immunoreactivity and protein expression levels were assessed for both Lingo-1 and TROY proteins by immunohistochemistry and Lingo-1, TROY, p75 and NgR proteins by western blot respectively.</p>	<p>Immunohistochemistry revealed that Lingo-1 and TROY are expressed in the cerebral cortex, brainstem and spinal cord from both multiple sclerosis and non-multiple sclerosis brains; and that this expression is in neurons, reactive astrocytes, and macrophages/microglia, but not oligodendrocytes.</p> <p>Western blot revealed overall higher levels of TROY expression in multiple sclerosis brains compared to non-multiple sclerosis brains., whereas Lingo-1 levels were found to be reduced in all multiple sclerosis cases.</p> <p>Expression pattern of p75 was generally the same as that of TROY, and NgR showed a</p>	Satoh J. et. al. 2007

Disease	Protein(s)	Species/Model/Cell Line	Study Details	Findings	Reference
				trend for higher levels in the cerebellum vs. lower levels in the cerebrum.	
Multiple Sclerosis	Lingo-1, RhoA	Primary cell culture, dorsal root ganglion (DRG) neurons from E14-17 Long Evans rats Rat, Long Evans Mouse, <i>Lingo-1</i> knockout	Primary dorsal root ganglion (DRG) cell cultures of embryonic E14-17 Long Evans rats were grown in vitro for testing with: Lingo-1-Fc, dominant-negative (DN)-Lingo-1, full-length (FL)-Lingo-1 or <i>Lingo-1</i> RNAi. The number of total and mature oligodendrocytes was quantified by western blot analysis and electron microscopy. Myelinated axons in the 2-week-old cultures were quantified by counting the number of myelinated internode bundles that were derived from single MBP ⁺ oligodendrocytes. Immunohistochemistry was used to examine expression of O4, MBP, CNPase, and Lingo-1 in tissue sections from mice and in cell cultures. Lingo-1 expression was examined in rat optic nerve sections by <i>in situ</i> hybridization. mRNA extracted from rat brains was subjected to RT-PCR to quantify <i>Lingo-1</i> mRNA. Oligodendrocyte progenitor cells were treated for 2 days with Lingo-1-Fc or control-Fc. RhoA-GTP and RhoA amounts were quantified. Expression levels of the myelin proteins MBP and MAG in cells were determined by western blotting.	RT-PCR in purified populations of CNS cells showed Lingo-1 is expressed highly in neurons, a low expression in oligodendrocytes; however it is not expressed in astrocytes. <i>In situ</i> hybridization and immunohistochemistry in sections from adult optic nerve tissue confirmed the expression of Lingo-1 in oligodendrocytes. RT-PCR showed that <i>Lingo-1</i> RNAi infected oligodendrocytes had reduced levels of endogenous Lingo-1 expression. This reduction in Lingo-1 resulted in more highly differentiated and mature oligodendrocytes, increased length of cell processes and more abundant myelin sheath structures. DN-Lingo-1 infected oligodendrocytes showed increased differentiation and resulted in a five-fold increase in the number of mature oligodendrocytes; in addition to a five-fold increase in the amount of MBP expressed. Overexpression of <i>FL-Lingo-1</i> inhibited differentiation; the cells had less developed processes and an 80% reduction in the number of mature oligodendrocytes. Additionally, these cells also displayed 90% lower amounts of MBP expressed. A2B5 ⁺ oligodendrocyte progenitors treated with Lingo-1-Fc differentiated into mature oligodendrocytes in a concentration dependent manner. The treatment also resulted in	Mi S. et. al. 2005

Disease	Protein(s)	Species/Model/Cell Line	Study Details	Findings	Reference
			<p>DRG neuron and oligodendrocyte cultures were grown for 4 weeks in the presence of Lingo-1-Fc (10 µg/ml) or control-Fc.</p> <p>Ultrastructural analysis of spinal cords from <i>Lingo-1</i> knockout mice and the DRG cultures was performed using electron microscopy.</p>	<p>oligodendrocytes with longer processes and more abundant myelin sheaths.</p> <p>Treatment of oligodendrocytes with Lingo-1-Fc, DN-Lingo-1 or <i>Lingo-1</i> RNAi resulted in reduced levels of RhoA.</p> <p>Lingo-1-Fc and DN-Lingo-1 treatment on oligodendrocyte and neuron co-cultures resulted in concentration dependent robust axonal myelination. MAG, MOG, OMgp, CNPase and MBP were also upregulated. Furthermore FL-Lingo-1 decreased MBP expression by 50%.</p> <p>Primary cell cultures from <i>Lingo-1</i> knockout mice have more highly differentiated and a larger percentage of mature oligodendrocytes than wild-type cultures.</p> <p>Spinal cords from <i>Lingo-1</i> knockout mice contained more myelinated fibers than wild-type spinal cords.</p>	
Multiple Sclerosis	Lingo-1	<p>Rat, myelin oligodendrocyte glycoprotein-induced experimental autoimmune encephalomyelitis (EAE) rats</p> <p>Rat, oligodendrocyte cultures, dorsal root ganglion (DRG) neuron cultures, co-culture myelination assays and oligodendrocyte differentiation assays</p> <p>Rat, Sprague-Dawley</p>	<p>1A7 or isotype control antibody (4 µg) was injected intravitreally into the right eye of EAE rats from disease onset for 2 weeks.</p> <p>Oligodendrocyte cultures, dorsal root ganglion (DRG) neuron cultures, co-culture myelination assays and oligodendrocyte differentiation assays were prepared.</p> <p>300 µm sections were taken from the brains of PN2 mice at the junction of the corpus callosum to the hippocampus. Sections were cultured in serum containing either anti-Lingo-1 (10 µg/ml) or control antibody for 4 days.</p>	<p>Optic nerves of antibody treated EAE rats showed evidence of extensive myelination compared to rats treated with control antibody; myelin sheaths of treated rats were thinner than those in untreated rats, suggesting that they were remyelinated.</p> <p>1A7 antibody treatment produced robust myelination in co-cultures of DRG and OPCs compared to treatment with the isotype antibody control. Western blotting showed a dose dependent increase in MBP expression in the co-cultures treated with the 1A7 antibody.</p> <p>Incubation of P2 forebrain slices with 1A7</p>	Mi S. et. al. 2009

Disease	Protein(s)	Species/Model/Cell Line	Study Details	Findings	Reference
		<p>Mouse, C57BL/6</p> <p>Mouse, <i>Lingo-1</i> knockout</p>	<p>Sagittal cerebellar slices were taken from PN10 rats and grown for 7 days before treatment with 5 mg/ml lysophosphatidylcholine (LPC) to induce demyelination. Slices were then incubated with 1A7 or control antibody (10 µg/ml) for 3 days, and remyelination was visualized by MBP immunostaining.</p> <p>Rats received direct injections of LPC into the spinal cord, followed 3 days later by treatment with 1A7 or control antibody (1.5 µg in 2 µl). LPC-treated rat spinal cords were sectioned and toluidine blue staining and electron microscopy were used to assess levels of remyelination versus demyelination.</p> <p>Immunohistochemistry was used to visualize myelination with anti-MBP, oligodendrocyte precursor cells (OPCs) with anti-NKx2.2 and Lingo-1 positive (Lingo-1⁺) OPCs with anti-Lingo-1 in the lesions of 1A7 antibody and control treated rats.</p> <p>Cuprizone treated mice received stereotaxic injections of 1A7 of isotype control antibody at weeks 2.5 and 3 of cuprizone feeding. Mice were euthanized 4 and 6 weeks after antibody injection.</p> <p><i>Lingo-1</i> knockout and wild-type mice also received cuprizone treatment for 4 weeks to assess the number of myelinated axons.</p>	<p>for 4 days resulted in approximately 30-fold increased staining of MBP-positive cells and 20-fold increase in myelinated axon clusters distributed in the periventricular area and cerebral cortex.</p> <p>Exposure to 1A7 antibody for 3 days after removal of LPC from P10 cerebellar slices resulted in an extensive reorganization of the MBP⁺ fibers which had previously been punctuated and disorganized by the LPC.</p> <p>Lingo-1 was strongly expressed in OPCs compared with mature oligodendrocytes, and increased numbers of Lingo-1⁺ cells were seen in 7-day post-LPC spinal cord lesions. The number of NKx2.2⁺ and Lingo-1⁺ cells was also increased in the lesions. Toluidine blue stained sections and electron microscopy showed a three-fold increase in myelinated fibers in 1A7-treated animals compared with control animals.</p> <p>1A7-treated lesions displayed less Lingo-1⁺ OPCs and more mature MBP⁺ oligodendrocytes than antibody controls; treatment with Lingo-1 antagonists also enhanced re-myelination in the LPC rat and slice models.</p> <p>Cuprizone treated mice that also received 1A7 treatment showed substantially more MBP staining, indicative of increased myelin, than control treated mice. This was confirmed by ultrastructural analysis by electron microscopy.</p> <p><i>Lingo-1</i> knockout mice had significantly more myelinated axon fibers after 4 weeks of cuprizone treatment compared to wild-types.</p>	

Disease	Protein(s)	Species/Model/Cell Line	Study Details	Findings	Reference
Multiple Sclerosis	Nogo-A, NgR, p75, APP	Human post-mortem brains from multiple sclerosis subjects	<p>Post-mortem brain samples from the frontal cerebral cortex or the cerebellar cortex were obtained from autopsied brains from 4 multiple sclerosis patients, 6 non-multiple sclerosis cases with neurologic/neuropsychiatric disorders, and 6 neurologically normal cases.</p> <p>Immunoreactivity and protein expression levels were assessed for Nogo-A, NgR, APP and p75 proteins by immunohistochemistry and Nogo-A and NgR proteins by western blot respectively.</p>	<p>Immunohistochemistry revealed a substantial number (20%-60%) of surviving oligodendrocytes and remaining myelin sheaths in multiple sclerosis cases expressed intense levels of Nogo-A. Adjacent sections revealed that APP reactive axons were hardly detectable in any case examined, and that these axons did not co-localize with Nogo-A expressing oligodendrocytes.</p> <p>Immunohistochemistry also showed that a large number (>60%) of astrocytes, microglia and neurons have an intense immunoreactivity for NgR.</p> <p>p75 was most prominently expressed in the nerve fibers of substantia gelatinosa in the spinal cord, tractus solitaries in the brain stem and the vascular wall of the cerebrum. p75 was not expressed on oligodendrocytes, astrocytes or microglia/macrophages.</p>	Satoh J-I. et. al. 2005
Multiple Sclerosis	Nogo-A, NgR	Mouse, myelin oligodendrocyte glycoprotein-induced experimental autoimmune encephalomyelitis (EAE) C57BL/6 mice	<p>Myelin oligodendrocyte glycoprotein-induced experimental autoimmune encephalomyelitis (EAE) was induced in C57BL6J mice. Mice were euthanized at 4 different time points (Day 0 – naïve, Day 10 – preclinical, Days 18-22 – acute, and Day 50 – chronic).</p> <p><i>Nogo-A</i> expression was examined by <i>in situ</i> hybridization in the olfactory bulb, cortex, piriform cortex, hippocampus, thalamus, cerebellum, brain stem and spinal cord.</p> <p><i>Nogo-A</i> and NgR mRNA was quantified using semiquantitative RT-PCR using RNA extracted from both brain and spinal cord tissues.</p>	<p><i>In situ</i> hybridization and RT-PCR revealed that <i>Nogo-A</i> expression is reduced at preclinical and acute phases, followed by an upregulation during the chronic phase.</p> <p><i>Nogo-A</i> mRNA was expressed in neurons and oligodendrocytes.</p> <p>Immunohistochemistry and western blotting showed that Nogo-A protein expression was increased in the chronic phase and was inversely correlated with axonal regeneration and axonal injury.</p> <p>Cortical NgR protein and mRNA levels were increased in the chronic phase.</p>	Theotokis et.al. 2012

Disease	Protein(s)	Species/Model/Cell Line	Study Details	Findings	Reference
			<p>Nogo-A and NgR protein expression was examined by immunohistochemistry and western blotting analyses in brain and spinal cord sections.</p> <p>Double immunofluorescent labeling was performed to identify the different types of Nogo-A positive cells throughout the different EAE time-points. Macrophages were double stained with Nogo-A/Mac-3, microglia/macrophages were stained with Nogo-A/lectin, myelin was stained with Nogo-A/CNPase, neurons were stained with Nogo-A/NeuN, and astrocytes were stained with Nogo-A/GFAP.</p>		
Optic Nerve Regeneration	NgR	Mouse, <i>NgR</i> knockout mice	<p>The abrupt loss of ocular dominance plasticity at the end of the critical period, at which the cerebral cortex is sensitive to experience-dependent plasticity, was examined in single unit cortical recordings from anesthetized mice.</p> <p>Wisteria floribunda agglutinin-stained sections of the visual cortex were examined to assess the cellular site of chondroitin sulfate proteoglycans (CSPGs).</p> <p>Homogenates of visual cortex were analyzed by western blotting for MBP, NgR, Nogo-A and MAG.</p> <p>Immunohistochemical layer-specific analysis was used to assess MBP expression between PN26 and PN60 in <i>NgR</i> knockout mice.</p> <p>Electrophysiological responsiveness of the binocular visual cortex was characterized in <i>NgR</i> knockout mice exposed to unmodified visual stimuli.</p>	<p>CSPG-positive perineuronal nets surround parvalbumin-positive inhibitory neurons, leaving all other neurons unaffected.</p> <p>Myelin associated proteins including ligands for NgR were easily detectable in the postnatal visual cortex. The abundance of NgR ligands Nogo-A and MAG was consistent in the visual cortex over the time course of the critical period, whereas NgR tends to increase slightly. The total concentration of MBP remained nearly constant; however layer-specific levels of intracortical myelin mature considerably as the critical period ends.</p> <p>The onset and distribution of cortical myelination in <i>NgR</i> knockout mice is indistinguishable from that of wild-type mice.</p> <p><i>NgR</i> and <i>Nogo-A</i> mutant mice are sensitive to monocular deprivation after the critical period compared to wild-types, as assessed by their weighted ocular dominance (WOD) scores.</p>	McGee AW. et. al. 2005

Disease	Protein(s)	Species/Model/Cell Line	Study Details	Findings	Reference
				<p>Since WOD scores of <i>NgR</i> knockout mice were indistinguishable from the wild-type mice, visual system development and immature cortical plasticity are normal in the absence of NgR.</p> <p>Physiological NgR signaling from myelin-derived Nogo-A, MAG and OMgp consolidate the neural circuitry established during experience-dependent plasticity.</p> <p>Overall, <i>NgR</i> knockout mice display normal levels of plasticity during the critical period, however it continues abnormally, such that ocular dominance at 45 or 120 days postnatal is subject to the same plasticity as at juvenile ages.</p>	
Parkinson's Disease	Akt	Human post-mortem brains from Parkinson's disease subjects	<p>Frozen tissue from the midbrain and paraffin-embedded sections of substantia nigra pars compacta from 5 idiopathic Parkinson's disease cases and 5 controls (matched for age, gender, post-mortem delay and tissue pH) were obtained from the Netherlands Brain Bank. Tissue was dissected using a perpendicular cut to the brainstem at the level of the superior colliculus.</p> <p>Western blotting for Akt and phospho^{Ser473}-Akt was performed on fractions prepared from midbrain tissue containing the substantia nigra pars compacta.</p> <p>Immunofluorescent microscopy was also performed for Akt and phospho^{Ser473}-Akt in addition to tyrosine hydroxylase.</p>	<p>Western blot of midbrain fractions from Parkinson's disease compared to control brains showed reduced levels of both total and active phospho^{Ser473}-Akt in Parkinson's disease.</p> <p>Immunofluorescence microscopy of the substantia nigra pars compacta confirmed these results.</p> <p>Double immunofluorescence microscopy showed that Akt and phospho^{Ser473}-Akt are expressed at high levels in tyrosine hydroxylase immunopositive dopaminergic neurons in the control human brain.</p> <p>Loss of these neurons in Parkinson's disease was accompanied by a marked decrease in Akt and phospho^{Ser473}-Akt.</p>	Timmons S. et. al. 2009

Disease	Protein(s)	Species/Model/Cell Line	Study Details	Findings	Reference
Parkinson's Disease	EGF	Rat, Hanover-Wistar (E14 primary cell cultures from ventral mesencephalon)	<p>E14 embryos were collected from pregnant Hanover-Wistar rats and primary cells collected from the ventral mesencephalon floor were cultured.</p> <p>Immunostaining on cultured cells was performed to differentiate between nuclei of proliferating cells, or glial cells from tyrosine hydroxylase positive dopaminergic neurons.</p> <p>Immunohistochemistry using anti-tyrosine hydroxylase and anti-heparin-binding epidermal growth factor-like growth factor (HB-EGF) was performed.</p> <p>Western blotting using anti-pTyr, anti-ERK(pT202/pY204), anti-Akt(pS473) and anti-Tyr, was performed on ventral mesencephalic cells that had been treated with HB-EGF for 7 days.</p>	<p>Heparin-binding epidermal growth factor-like growth factor (HB-EGF) is expressed in close proximity to developing dopaminergic neurons.</p> <p>HB-EGF promotes survival of midbrain dopaminergic neurons.</p> <p>HB-EGF mediates its neuroprotective effects via astrocytes.</p> <p>Endogenous HB-EGF contributes to the survival of dopaminergic neurons.</p> <p>Survival promoting effect of HB-EGF is mediated via the EGFR/Akt and MAPK signaling pathways.</p>	Farkas LM. et. al. 2002
Parkinson's Disease	EGF, EGFR, ErbB2	<p>Human post-mortem brains from Parkinson's disease subjects</p> <p>Rat, Wistar</p>	<p>Post-mortem samples were collected from the prefrontal cortex (BA9) and putamen from 9 chronic Parkinson's disease brains (4 male, 5 female) and 10 controls (6 male, 4 female).</p> <p>Male Wistar rats received intra-nigral infusions of 6-hydroxydopamine (2 μL of 4 mg/mL) or saline under pentobarbital anesthesia to induce dopaminergic lesions.</p> <p>A second group of male Wistar rats received a subcutaneous implantation of an osmotic minipump filled with human recombinant EGF (0.3 mg/mL) or saline, in addition to the intra-nigral infusions. These rats were infused continuously at a rate of 0.5 μL/h for 7 days.</p>	<p>Protein levels of EGF and tyrosine hydroxylase were decreased in the prefrontal cortex and striatum of patients.</p> <p>Heparin-binding epidermal growth factor-like growth factor (HB-EGF) and transforming growth factor alpha (TGF-α) were not significantly altered in either region.</p> <p>EGR receptors (ErbB1, ErbB2 but not ErbB3 or ErbB4) were downregulated in the same forebrain regions.</p> <p>In the rats treated with nigral 6-hydroxydopamine infusion to induce dopaminergic lesions, the same results were replicated.</p>	Iwakura Y. et. al. 2005

Disease	Protein(s)	Species/Model/Cell Line	Study Details	Findings	Reference
			<p>Enzyme immunoassays were performed on collected brain tissues to determine growth factor concentrations.</p> <p>Protein levels of ErbB family members, tyrosine hydroxylase and neuron-specific enolase were determined by western blotting.</p>	<p>EGF and ErbB1 were reduced in the striatum in the lesioned hemisphere compared to the control hemisphere of the treated rats.</p> <p>Subchronic supplementation of EGF in the striatum of the Parkinson's disease rat model was able to locally prevent the dopaminergic neurodegeneration as measured by tyrosine hydroxylase immunoreactivity.</p>	
Parkinson's Disease	Lingo-1	Human, mixed ethnicity	<p>A meta-analysis from 12 case-control studies was performed for the <i>Lingo-1</i> SNP rs9652490.</p> <p>A total of 6053 Parkinson's disease cases and 5997 controls, across 4 studies in Asians and 8 studies in non-Asians were included in the meta-analysis.</p>	<p>The meta-analysis showed an overall lack of association of rs9652490 and Parkinson's disease.</p> <p>Separate analysis in subjects of Asian origin of non-Asian origin also failed to show any ethnic dependent association.</p>	Wu Y. et. al. 2012
Parkinson's Disease	Lingo-1	Human, Chinese	<p>The <i>Lingo-1</i> SNP rs9652490 was examined in two independent case-control Chinese populations involving a total of 1305 subjects (649 Parkinson's disease patients and 656 controls) from Taiwan and Singapore.</p> <p>The cohort from Taiwan (421 Parkinson's disease patients and 411 controls) was genotyped using TaqMan Assays.</p> <p>The cohort from Singapore (228 Parkinson's disease patients and 245 controls) was genotyped using the Sequenom MassArray system.</p>	<p>There were no significant genotypic or allelic associations with the risk of Parkinson's disease in either of the two case-control populations, nor were there any associations in the pooled analysis.</p> <p>Meta-analysis including all published data to date and the present study's data failed to demonstrate any modulatory role of the Lingo-1 rs9652490 SNP in Parkinson's disease.</p>	Wu Y-R. et. al. 2011
Parkinson's Disease	Lingo-1	Human, Caucasian	<p>The <i>Lingo-1</i> SNP rs9652490 was examined in a cohort of 162 Polish Parkinson's disease patients (73 females and 89 males) and 177 controls (81 females and 96 males). All subjects were of Caucasian origin.</p>	<p>Genotyping frequencies were similar in both Parkinson's disease patients and controls.</p> <p>There were no significant differences in either genotypic or allelic frequencies between cases</p>	Bialecka M. et. al. 2010

Disease	Protein(s)	Species/Model/Cell Line	Study Details	Findings	Reference
			Genotyping was performed using the Sequenom MassArray system	and controls. When the Parkinson's disease group was split into early onset and late onset Parkinson's disease, there were still no significant differences in genotypic or allelic frequencies between case and control groups.	
Parkinson's Disease	Lingo-1, EGFR, Akt	Human post-mortem brains from Parkinson's disease subjects Rat, Sprague-Dawley Mouse, <i>Lingo-1</i> knockout Mouse, C57BL/6	<i>In situ</i> hybridization and semi-quantitative RT-PCR was used to assess levels of <i>Lingo-1</i> in the post-mortem human substantia nigra of Parkinson's disease brains compared to age matched controls. <i>Lingo-1</i> levels were assessed by <i>in situ</i> hybridization and/or immunohistochemistry on adult rat brains and rat primary <i>in vitro</i> embryonic cultures from E15 rat brains. The function of Lingo-1 in dopaminergic neurons was studied <i>in vitro</i> in the presence of Lingo-1 antagonists: Lingo-1-Fc protein, an anti-Lingo-1 antibody (1A7) or a dominant-negative (DN) form of Lingo-1. Stereotaxic striatal injections of 6-hydroxydopamine (6-OHDA) and intraperitoneal injections of <i>N</i> -methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) were used to create neurotoxin induced experimental models of Parkinson's disease in <i>Lingo-1</i> knockout and wild-type mice. Lingo-1-Fc protein (6.5 µg/µL; total 2 µL) or the Fc-fragment (as a control) was injected unilaterally into the striatum of C57BL/6 mice. Seven days after treatment, mice received intraperitoneal injections of MPTP. Mice were euthanized 1 week later.	<i>Lingo-1</i> mRNA levels were found to be significantly higher in the substantia nigra of Parkinson's disease patients than controls. In the ventral midbrain of normal adult rats, <i>Lingo-1</i> mRNA was expressed in many neuronal types, and was co-localized with tyrosine hydroxylase positive dopaminergic neurons. In primary ventral midbrain cultures, Lingo-1 protein was also found to be present in tyrosine hydroxylase neurons. In the cells treated with DN-Lingo-1, 1A7 antibody or Lingo-1-Fc, dopaminergic neurons had longer neurites than control cultures. Additionally, DN-Lingo-1 transduction also resulted in increased levels of p-Akt and elevated levels of EGFR. Motor asymmetry was significantly lower in 6-OHDA treated <i>Lingo-1</i> knockout compared to wild-type mice. 6-OHDA produced a significant loss of tyrosine hydroxylase neurons in the substantia nigra pars compacta of both wild-type and knockout mice; while MPTP resulted in a lower number of tyrosine hydroxylase neurons in the wild-type compared to <i>Lingo-1</i> knockout mice.	Inoue H. et. al. 2007

Disease	Protein(s)	Species/Model/Cell Line	Study Details	Findings	Reference
			EGFR and Lingo-1 interactions were examined in cultured cells and wild-type or <i>Lingo-1</i> knockout ventral midbrain tissues using co-immunoprecipitation.	<p>MPTP treated wild-type mice also had lower levels of striatal dopamine compared to vehicle-treated wild-type mice. Dopamine levels were not significantly different in vehicle-treated and MPTP-treated <i>Lingo-1</i> knockout mice.</p> <p>There was a higher number of surviving tyrosine hydroxylase neurons in the 6-OHDA treated <i>Lingo-1</i> knockout compared to wild-type mice. There were also increased levels of the neuroprotective form of Akt (p-Akt) in the ventral midbrain of the MPTP-treated knockout compared to wild-type mice.</p> <p>In the wild-type mice that had received 6-OHDA treatment, there was a significantly higher level of Lingo-1 protein in the striatum 3 days after injury.</p> <p>Lingo-1-Fc treatment resulted in unilateral increase in the number of tyrosine hydroxylase neurons, and in dopamine levels in the substantia nigra pars compacta.</p> <p>Lingo-1 decreases EGFR protein levels in a dose-dependent manner. The anti-Lingo-1 antibody 1A7 blocked the binding of Lingo-1 to EGFR. EGFR activation was suppressed by Lingo-1, and the 1A7 antibody was able to attenuate these effects; therefore Lingo-1 can reduce EGFR levels by direct physical interaction.</p>	
Schizophrenia, Major Depressive Disorder, Bipolar	BDNF, TrkB, p75	Human post-mortem brains from schizophrenia, major depressive disorder and bipolar disorder subjects	Post-mortem anterior hippocampal and cerebellum brain samples were obtained from the Stanley Foundation Neuropathology Consortium. The cohort consisted of 15 schizophrenia subjects, 15 major depressive	Reductions in BDNF were seen in all layers of the right but not left hippocampus in major depressive disorder patients, with no changes in the dentate gyrus.	Dunham JS. et. al. 2009

Disease	Protein(s)	Species/Model/Cell Line	Study Details	Findings	Reference
Disorder			<p>disorder subjects, 15 bipolar disorder subjects and 13 age and gender matched controls.</p> <p>Protein levels of BDNF, TrkB and p75 were assessed in the hippocampal samples by western blotting and immunautoradiography.</p> <p>Genomic DNA was extracted from the cerebellum samples from each subject, and genotyping was performed using the Sequenom iPLEX platform, for several SNPs located in the <i>BDNF</i>, <i>NTRK2</i> and <i>NGFR</i> genes (full list not disclosed).</p>	<p>A similar but less pronounced pattern was observed for bipolar disorder.</p> <p>Bipolar, but not major depressive patients had bilateral reductions in p75 in hippocampal layers, but not in the dentate gyrus. No changes in TrkB were seen in any diagnosis.</p> <p>BDNF density was reduced in subjects who carried the minor allele for rs12273363 and rs7127505.</p> <p>TrkB density was decreased in subjects who carried the minor allele for rs1187323 and rs1187326.</p> <p>p75 density was increased in subjects who carried the minor allele for rs11466117.</p>	
Schizophrenia	EGFR	Human post-mortem brains from schizophrenia subjects	<p>Post-mortem brain samples from the dorsolateral prefrontal cortex (BA46) were obtained from 37 schizophrenia subjects and 37 matched controls.</p> <p>EGFR mRNA expression was assessed by <i>in situ</i> hybridization and quantitative real-time PCR.</p> <p>Protein levels were assessed by western blotting</p>	<p>Increased EGFR protein was seen in the dorsolateral prefrontal cortex of schizophrenia subjects compared to controls.</p> <p>There were no significant differences in mRNA levels between patients and controls.</p> <p>Protein levels were significantly correlated with mRNA levels in both the schizophrenia group and in the control group.</p> <p>Subjects with no history of suicidality had significantly higher levels of EGFR protein and mRNA compared to those with suicidality.</p>	Swaminathan V. et. al. 2014
Schizophrenia	Lingo-1, NgR, p75, TROY, WNK1, Myt1	Human post-mortem brains from schizophrenia subjects	Post-mortem brain samples from the dorsolateral prefrontal cortex (BA46) were obtained from 37 schizophrenia subjects and	Significant increases in Lingo-1 and Myt1 were observed in the DLPFC of schizophrenia brains compared to controls. Additionally, a	Fernandez-Enright F. et. al. 2014

Disease	Protein(s)	Species/Model/Cell Line	Study Details	Findings	Reference
			<p>37 matched controls. Samples were taken from the middle one-third (rostral-caudally) of the middle frontal gyrus from coronal slabs anterior to the genu of the corpus callosum.</p> <p>Post-mortem brain samples from the hippocampus (CA1 and CA3 regions), taken from the level of the lateral geniculate nucleus were obtained from 20 schizophrenia subjects and 20 matched controls from the same cohort as the DLPFC samples.</p> <p>Protein levels for Lingo-1, NgR, p75, TROY, WNK1, Myt1 and MBP were assessed by western blotting in all 3 brain regions.</p>	<p>significant decrease in NgR was observed in the same region.</p> <p>Both TROY and WNK1 were significantly increased in the CA1 hippocampal region in schizophrenia compared to control subjects.</p> <p>NgR was significantly increased in the CA3 of schizophrenia subjects compared to controls.</p> <p>No significant changes in MBP levels were reported in any brain region.</p> <p>Confounding factors had no impact on levels of protein expression.</p>	
Schizophrenia	Myt1l	Human, Chinese	<p>Genomic DNA samples were collected from 528 paranoid schizophrenia patients (264 males and 264 females (mean age 27.32±8.03 years)) and 528 healthy controls (264 males and 264 females (mean age 27.73±8.01 years)).</p> <p>Genotyping was performed for 6 SNPs in the <i>Myt1l</i> gene (rs17039584, rs10190125, rs17338616, rs10432710, rs6742365, rs2385135) using the Illumina GoldenGate assay on a BeadStation 500G Genotyping System.</p>	<p>The SNP rs17039584 was significantly associated with schizophrenia, even after Bonferroni correction.</p> <p>The SNP rs10190125 was found to be significantly associated with schizophrenia in female patients.</p> <p>The SNP rs6742365 was associated with a family history of schizophrenia in females.</p>	Li W. et. al. 2012
Schizophrenia	Myt1l	Human, Caucasian	<p>A genome-wide screen for copy number variations was performed on a small cohort of 54 Dutch schizophrenia subjects, using an Affymetrix GeneChip 250K SNP array.</p> <p>4 of the novel copy number variations were chosen based on their gene content for further validation by multiplex ligation-dependent</p>	<p>A total of 90 copy number variations were identified, 77 of which had previously been reported in unaffected control cohorts.</p> <p>13 novel copy number variations were identified in this study, of which 7 did not affect any gene, nor were they located in highly conserved regions.</p>	Vrijenhoek T. et. al. 2008

Disease	Protein(s)	Species/Model/Cell Line	Study Details	Findings	Reference
			<p>probe amplification or genomic quantitative PCR.</p> <p>The second part of this study involved studying copy number variations within the 4 loci in a large Dutch case control cohort consisting of 752 schizophrenia subjects and 706 unaffected controls.</p>	<p>The four copy number variations validated included 2 duplications in chromosomal regions 2p25.3 (affecting 4 genes – including <i>Myt1l</i>) and 5p15.2 (affecting 7 genes), and 2 deletions in chromosomal regions 2p16.3 (affecting the <i>NRXN1</i> gene) and 9q33.1 (affecting the <i>ASTN2</i> gene).</p> <p>Within the larger cohort, an additional 8 copy number variations were identified (7 in patients and 1 in a control subject). The 4 variations that affect coding sequences were found only in the patient cohort, including 1 previously unreported copy number variation at 2p25.3, a 3.8 Mb duplication affecting 11 genes including <i>Myt1l</i>.</p>	
Schizophrenia	Myt1	Human post-mortem brains from schizophrenia subjects	<p>Post-mortem hippocampal and cerebellar tissue was collected from 44 schizophrenia patients (29 males and 15 females; of which 24 were African American and 20 were Caucasian), and 84 normal controls (62 males and 22 females; of which 53 were African American, 25 were American Caucasian, 5 were Hispanic and 1 was Asian). Subjects were matched for age, brain pH and post-mortem interval.</p> <p>Hippocampal <i>Neuregulin1</i> (<i>NRG1</i>) mRNA expression was measured by quantitative RT-PCR using an ABI Prism 7900 sequence detection system with 384-well format.</p> <p>Genomic DNA was extracted from cerebellar tissue. A total of 10 SNPs within <i>NRG1</i> were genotyped; 4 from the de-CODE core haplotype (SNP8NRG221132, SNP8NRG221533, SNP8NRG241930 and SNP8NRG243177) and 6 additional SNPs</p>	<p><i>NRG1</i> type I mRNA expression levels were increased in the hippocampus of schizophrenia patients compared to controls. No significant differences were observed for any of the other <i>NRG1</i> isoforms.</p> <p>None of the SNPs examined showed any effect on the expression of type II or type III <i>NRG1</i> isoforms.</p> <p>There was a genotype x diagnosis interaction for SNP8NRG221132 and type I <i>NRG1</i> mRNA expression; however there was no main effect of genotype.</p> <p>There was a significant main effect of SNP8NRG243177 on type IV <i>NRG1</i> expression.</p> <p>Individuals heterozygous for the (T) risk allele in SNP8NRG243177 have 21% more type IV <i>NRG1</i> mRNA than those individuals</p>	Law AJ. et. al. 2006

Disease	Protein(s)	Species/Model/Cell Line	Study Details	Findings	Reference
			<p>from HAPMAP (rs10096573, rs4268090, rs4298458, rs4452759, rs4733263 and rs4476964). Genotyping was performed using the TaqMan 5' exonuclease allelic discrimination assay.</p> <p>Putative transcription factor binding site analysis was performed using MATINSPECTOR software, a computational suite for promoter informatics.</p>	<p>homozygous for the (C) major allele.</p> <p>Individuals homozygous for the (T) risk allele in SNP8NRG243177 have 49% more type IV <i>NRG1</i> mRNA than those individuals homozygous for the (C) major allele.</p> <p>This effect appeared more pronounced in the schizophrenia group, despite no diagnosis x genotype interaction being present.</p> <p>The SNP8NRG243177 was found to be within a putative binding site for serum response factor (SRF) and myelin transcription factor 1 (Myt1). Carrying the risk (T) allele results in a predicted loss of binding to both of these transcription factors.</p> <p>The SNP8NRG243177 variant was found to be within a predicted transcription factor binding domain for SRF, with the risk (G) allele abolishing SRF binding.</p>	
Schizophrenia	NgR	Human	<p>A total of 695 patients with schizophrenia, schizoaffective disorder or schizophreniform disorder were screened for 22q11 interstitial deletions.</p> <p>A separate study consisting of 18 velocardial facial syndrome patients, of which 4 also had schizophrenia, were screened to test they hypothesis that a more extensive deletion may be present in the subgroup of velocardial facial syndrome patients who also have a diagnosis of schizophrenia.</p>	<p>2 deletions were identified and characterized by fluorescence <i>in situ</i> hybridization. Both were hemizyously deleted for cosmids N25 (D22S75) and DO832 (D22S502).</p> <p>No correlation exists between the extent of the deletion and the additional schizophrenia phenotype; however the prevalence of schizophrenia in this small sample (22%) is much higher than that of the general population (1%).</p>	Karayorgou M. et. al. 1995
Schizophrenia	NgR, Nogo-A	Human, mixed ethnicities	The case control cohort for SNP genotyping consisted of 636 Caucasians (336	rs701428 was found to be weakly associated with schizophrenia, with the minor allele	Budel S. et. al. 2008

Disease	Protein(s)	Species/Model/Cell Line	Study Details	Findings	Reference
		<p>Cells, E7 chick retinal explants</p> <p>Cells, E13 chick dorsal root ganglion (DRG) explants</p> <p>Cells, dissociated E20 rat DRG cultures</p> <p>Mouse, <i>NgR</i> knockout</p>	<p>schizophrenia and 300 controls) and 296 African Americans (196 schizophrenia and 100 controls). DNA was also obtained from 1122 Chinese Trios (621 schizophrenia patients and 501 controls).</p> <p>A total of 7 SNPs in the <i>NgR</i> gene (rs701421, rs701428, rs1567871, rs696880, rs854927, rs9606296 and rs701427) were genotyped using a TaqMan SNP Genotyping Assay.</p> <p>DNA from a separate cohort of 542 schizophrenia probands and <i>NgR</i> variant pedigrees, along with 650 healthy controls were obtained for DNA sequencing. The entire translated region, plus approx. 500 bp of the 5' and 3' untranslated region was sequenced.</p> <p>E7 chick retinal explants and E13 chick DRG cells (expressing wild type <i>NgR</i> or the novel <i>NgR</i> variants) were used for growth cone collapse experiments.</p> <p>E20 rat DRG cultures were used for neurite outgrowth experiments.</p> <p>Cognitive assessment in <i>NgR</i> knockout and wild-type mice was assessed in the spatial delayed alternation task.</p> <p><i>NgR</i> knockout and wild-type mice also underwent prepulse inhibition testing.</p>	<p>enriched in the Caucasian group. 4 novel missense variations were identified in the cohort of 542 schizophrenia probands (R377W, R377Q, R227C and R399W), with 3 of the 4 novel variants predicted to disrupt protein function (R377W, R227C and R399W). While R377Q and R377W are not within the ligand-binding domain, they are in the region of the protein that is required for signal transduction, and may disrupt signaling.</p> <p>Wild-type <i>NgR</i> sensitizes E7 chick retinal explants to Nogo-A, whereas the R377Q or R377W variants do not. Similarly MAG-mediated inhibition of neurite outgrowth in E20 rat DRG neurons is supported by wild-type <i>NgR</i> but not by the <i>NgR</i> R377 variant.</p> <p>E13 chick DRG neurons express <i>NgR</i> and are responsive to Nogo-A, whereas R377Q and R377W substituted proteins block the function of the endogenous <i>NgR</i> and function as dominant negatives.</p> <p><i>NgR</i> knockout mice have impaired working memory in the spatial delayed alternation task.</p> <p>A small subset of <i>NgR</i> knockout mice exhibit decreased prepulse inhibition.</p>	
Schizophrenia	NgR	Human, Caucasian	Genomic DNA from a total of 120 unrelated schizophrenia patients (77 males and 43 females) and 300 controls (180 males and 120 females) were screened for mutations in the <i>NgR</i> gene using denaturing high performance	3 mutant alleles were detected in the schizophrenia patients. 2 were missense mutations and 1 was a synonymous codon variant.	Sinibaldi L. et. al. 2004

Disease	Protein(s)	Species/Model/Cell Line	Study Details	Findings	Reference
			<p>liquid chromatography. All subjects were of Italian origin.</p> <p>The crystallographic structure of NgR was used to evaluate the functional relevance of the R119W and R196H mutations.</p>	<p>1 patient was heterozygous for a cytosine to thymine transition resulting in an arginine to tryptophan substitution (R119W). This mutation is located in the 3rd leucine-rich repeat which is expected to be an important functional domain.</p> <p>Another patient was heterozygous for a guanine to adenine transition resulting in an arginine to histidine substitution (R196H). This mutation is located in the 6th leucine-rich repeat.</p> <p>These change mutations were not found in any of the 600 control chromosomes.</p> <p>Both of the missense mutations were predicted to alter the electrostatic binding properties of NgR, and may result in alterations in the function and/or stability of the NgR, possibly affecting its ability to bind to other components of the receptor complex (p75 and Lingo-1).</p> <p>The patient with R119W mutation suffered deficit syndrome schizophrenia, while the patient with R196H suffered early onset and disorganized schizophrenia. The negative symptoms of both patients were strongly resistant to both conventional and novel drug treatments.</p>	
Schizophrenia	WNK1	Human	<p>Microarray technology by Affymetrix was used to determine the expression of over 30,000 mRNA transcripts in the post-mortem anterior prefrontal cortex (BA 10) in 28 schizophrenia and 23 control brains collected from Charing Cross Hospital.</p>	<p>A total of 51 gene expression changes were common to both groups of schizophrenia patients, and of these changes, 49 of them showed the same direction of disease-associated regulation.</p> <p><i>WNK1</i> was shown to be upregulated in both</p>	Maycox PR. et. al. 2009

Disease	Protein(s)	Species/Model/Cell Line	Study Details	Findings	Reference
			The results of this study were then compared to an independent dataset acquired from the prefrontal cortex (BA 9) of 16 schizophrenia, and 27 control brains, collected from the Harvard Brain Bank.	prefrontal cortical regions of the post-mortem schizophrenia brain from both the Charing Cross and the Harvard Brain Bank cohorts.	
Spinal Cord Injury	Lingo-1	Rat, Sprague-Dawley Rat, Long Evans	<p>ELISA competition assay was used to determine if Lingo-1-Fc can inhibit Lingo-1 binding to NgR.</p> <p>Sprague-Dawley rats underwent a lateral hemisection procedure at cervical vertebra C7, to completely interrupt the rubrospinal tract components. Long-1-Fc was administered locally using a gel foam sponge soaked with 20 µg/10 µL Lingo-1-Fc protein placed at the site of injury.</p> <p>Long Evans rats underwent a dorsal hemisection procedure at thoracic vertebra T7 to completely interrupt the main dorsomedial and the dorsolateral corticospinal tracts. An intrathecal catheter was inserted into the subarachnoid space at T7 and a mini-osmotic pump delivered Human Lingo-1-Fc fusion protein (25 µM), Human IgG isotype control protein (5 mg/mL) or PBS at a rate of 0.25 µL/h.</p> <p>Functional recovery, RhoA activation and histological analyses were performed to assess the effectiveness of the Lingo-1-Fc treatment following spinal cord injury.</p>	<p>Lingo-1-Fc significantly decreased the binding of Lingo-1 to NgR.</p> <p>Lingo-1-Fc treatment significantly improved both forelimb and hindlimb functional recovery, promoted axonal sprouting and decreased RhoA activation in both dorsal and lateral hemisection models.</p> <p>Lingo-1-Fc treatment also increased oligodendrocyte and neuronal survival after either rubrospinal or corticospinal tract transection.</p>	Ji B. et. al. 2006
Spinal Cord Injury	Lingo-1	Rat, Long Evans Primary cell culture, cerebellar granular neurons from P7 rats	<p>Long Evans rats underwent a dorsal laminectomy procedure at thoracic level T6 and T7. A dorsal hemisection was performed to completely disrupt the main dorsomedial and the minor dorsolateral corticospinal tracts.</p>	<p>In situ hybridization and immunohistochemistry showed that <i>Lingo-1</i> is expressed in neurons.</p> <p>Lingo-1 mRNA was detected in PN2, PN4</p>	Mi S. et. al. 2004

Disease	Protein(s)	Species/Model/Cell Line	Study Details	Findings	Reference
		Cells, COS-7	<p>Rats were euthanized and tissues were collected for <i>Lingo-1</i> expression analysis.</p> <p>RT-PCR was used to quantify <i>Lingo-1</i> mRNA levels in rat brains and injured spinal cords.</p> <p><i>In situ</i> hybridization was used to detect <i>Lingo-1</i> mRNA in rat brain, spinal cord and dorsal root ganglia.</p> <p>Primary cerebellar granular neurons were cultured from P7 rats, and were seeded onto slides pre-coated with OMgp-Fc, Nogo-66-GST, myelin, Lingo-1-Fc, or control-Fc.</p> <p>Immunohistochemistry was used to detect levels of Lingo-1, NgR and p75 in rat brain sections and PN7 rat cerebellar granular neurons.</p> <p>A separate lot of cerebellar granular neurons were transfected with <i>dominant negative (DN)-Lingo-1</i>, and vector control. <i>DN-Lingo-1</i> expression in the cells was verified by western blotting.</p> <p>COS-7 cells transfected with <i>Lingo-1</i>, <i>NgR</i> and <i>p75</i> were immunoprecipitated and analyzed by western blotting.</p> <p>COS-7 cells were transfected with <i>NgR</i> and <i>p75</i>, or with <i>NgR</i>, <i>p75</i> and <i>Lingo-1</i>, and analyzed for alkaline phosphatase (AP)-OMgp, AP-Nogo or AP-Lingo-1 binding by ELISA.</p> <p>GTP-bound and total RhoA proteins were detected in <i>Lingo-1</i>-, <i>p75</i>-, and <i>NgR</i>-transfected COS-7 cells by western blotting.</p>	<p>and PN8 cultured cerebellar granular neurons.</p> <p>Immunohistochemistry revealed that Lingo-1 expression was higher in the PN7 cerebellar granular neurons than in the corresponding adult tissue.</p> <p>Immunohistochemistry also showed that Lingo-1 was detected in rat spinal cord axonal tracts following injury.</p> <p>Quantitative RT-PCR showed that <i>Lingo-1</i> was increased 5-fold 14 days following injury.</p> <p>COS-7 cell culture experiments showed that Lingo-1 and NgR are able to bind to each other.</p> <p>RhoA activation in <i>Lingo-1</i>-, <i>p75</i>-, and <i>NgR</i>-transfected COS-7 cells showed that Lingo-1, NgR and p75 can together mediate the inhibitory activities of myelin.</p> <p><i>DN-Lingo-1</i> transfected neurons showed diminished responses to inhibitory substrates, evidenced by the presence of longer neurites than the cells transfected with the control vector.</p>	

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Spinal Cord Injury	NgR	Mouse, <i>NgR</i> knockout	<p><i>NgR</i> knockout mice were generated from C57BL/6J mice.</p> <p><i>NgR</i> knockout and wild-type mice were subjected to open field testing for locomotor activity and rotarod testing for motor coordination and learning.</p> <p>Myelin inhibitory proteins Nogo-A, MAG OMgp and CNS myelin were examined for growth cone collapsing activity in wild-type versus <i>NgR</i> knockout PN14 DRG cultures.</p> <p>Mice underwent a dorsal laminectomy procedure at thoracic level T6 and T7. A dorsal hemisection was performed at T6 to completely disrupt the dorsal and dorsolateral corticospinal tracts. Complete transections were performed at T8.</p> <p>The corticospinal and rubrospinal tracts were traced with injections of biotin dextran amine (BDA).</p> <p>Locomotor recovery in <i>NgR</i> knockout versus wild-type mice following a midthoracic dorsal hemisection injury was assessed by open field testing.</p>	<p><i>NgR</i> knockout mice display hypoactivity and motor impairment.</p> <p>DRG neurons lacking <i>NgR</i> do not bind Nogo-A, and their growth cones are not collapsed by Nogo-A.</p> <p>Recovery of motor function after dorsal hemisection of the spinal cord is improved in <i>NgR</i> knockout mice.</p> <p>Corticospinal fibers do not recover in <i>NgR</i> knockout mice after hemisection; however some raphespinal and rubrospinal fibers do regenerate.</p>	Kim JE. et. al. 2004
Spinal Cord Injury	Lingo-1, NgR, p75, TROY	Mouse, BALB/c	<p>Distribution and intensity of mRNA signal and immunoreactivity for receptors of myelin associated inhibitors was assessed by <i>in situ</i> hybridization for <i>NgR</i>, <i>Lingo-1</i>, <i>p75</i> and <i>TROY</i>, and immunohistochemistry for p75.</p> <p>Neuronal cell groups that project into the spinal cord and express one or more of the receptors for myelin inhibition were examined using co-localization of <i>in situ</i> hybridization</p>	<p><i>In situ</i> hybridization, immunohistochemistry and neuronal tracing revealed that NgR and Lingo-1 are strongly expressed in several neuronal populations of the adult mouse brain projecting into the spinal cord, including: the corticospinal, reticulospinal, raphespinal and vestibulospinal tracts.</p> <p>p75 expression was restricted to the neuronal populations in the descending pathways from</p>	Barrette et. al. 2007

Disease	Protein(s)	Species/Model/Cell Line	Study Details	Findings	Reference
			<p>or immunofluorescence labeling of the neuronal tracer Fluoro-Gold (FG) injected into the thoracic spinal cord.</p> <p>Spinal cord sections were stained with an anti-glial fibrillary acid protein (GFAP, a marker of astrocytes) antibody, Luxol fast blue (LFB)/cresyl violet (CV) and FluoroJade B (FJB), to examine the extent of tissue loss and axonal damage in mice subjected severe spinal cord contusions.</p>	<p>the brainstem. TROY was absent from most brain regions and from all neuronal projection systems.</p> <p>In the mice that underwent severe spinal cord contusions, GFAP astrocytes accumulated around the site of the injury forming a glial scar. 3D spinal cord reconstructions and labeling with FJB revealed that axons from several projection systems were injured.</p> <p>Quantitative analysis of <i>in situ</i> hybridization signals for receptors of myelin associated inhibitors revealed no significant difference in average number of positive cells and hybridization signal per cell between naïve and spinal cord injury mice. There was also no change in the expression profile of receptors for myelin associated inhibitors over time post-spinal cord injury.</p>	
Spinal Cord Injury	TROY	<p>Chinese Hamster Ovary (CHO) cells</p> <p>Cells, COS-7</p> <p>Mouse, <i>TAJ</i> knockout</p> <p>Primary cell culture, PN7 cerebellar granular neurons and dorsal root ganglion (DRG) neurons from <i>TAJ</i> knockout mice</p>	<p>CHO cells at 90% confluence were transfected with various combinations of human <i>NgR</i>, rat <i>p75</i>, and human <i>Lingo-1</i> constructs.</p> <p>ELISA plates coated with soluble <i>NgR</i> were incubated with serial dilutions of alkaline phosphatase (AP)-<i>TAJ</i>, AP-<i>p75</i> or control-AP to quantify bound AP-<i>TAJ</i>.</p> <p>COS-7 cells were transfected with combinations of full-length human <i>TAJ</i>, human <i>NgR</i>, human <i>Lingo-1</i> and rat <i>p75</i>. Western blotting was used to assess levels of <i>NgR</i>, <i>Lingo-1</i> and <i>TAJ</i>/TROY.</p> <p>Quantitative RT-PCR was performed for <i>TAJ</i>, <i>p75</i>, <i>NgR</i>, and <i>Lingo-1</i> on whole mouse brain homogenates taken over a developmental</p>	<p>AP-<i>TAJ</i> was found to bind to cells which expressed <i>NgR</i>, <i>NgR</i>/<i>Lingo-1</i> and <i>NgR</i>/<i>Lingo-1</i>/<i>p75</i>, but not to vector transfected cells or CHO cells expressing only <i>p75</i> or <i>Lingo-1</i>.</p> <p><i>TAJ</i> binds to <i>NgR</i> and can replace <i>p75</i> in the <i>p75</i>/<i>NgR</i>/<i>Lingo-1</i> complex to activate <i>RhoA</i> in the presence of myelin inhibitors.</p> <p><i>TAJ</i> and <i>p75</i> showed differential expression patterns in the rat brain across developmental time-points, with <i>p75</i> expression peaking at E14 and E18 but dropping into adulthood. <i>TAJ</i> was expressed at its highest between PN0-PN8. Higher levels of <i>TAJ</i> were observed in PN23 and adult samples compared to expression of <i>p75</i>. Levels of <i>Lingo-1</i> and <i>NgR</i></p>	Shao et. al. 2007

Disease	Protein(s)	Species/Model/Cell Line	Study Details	Findings	Reference
			<p>time-course (embryonic day E14 and E18, and postnatal day PN0, PN4, PN8, PN23 and adult brains).</p> <p>COS-7 cells were transfected with various combinations of <i>TAJ</i>, <i>NgR</i>, and <i>Lingo-1</i>. The cells were subsequently treated with AP-OMgp, GST-Nogo-66, MAG-Fc or control. Western blotting was then used to assess for levels of RhoA in the various cells.</p> <p>Cerebellar granular neurons and DRG neurons from TAJ knockout mice were assessed for neurite outgrowth <i>in vitro</i>.</p>	<p>mRNA resembled those of <i>TAJ</i>, with highest expression being at PN4 and declining slowly into adulthood.</p> <p><i>In vitro</i> exogenously added soluble TAJ reversed neurite outgrowth in normal cerebellar granular neurons and DRG neurons caused by myelin-associated inhibitor factors MAG, OMgp and Nogo.</p> <p>Neurons from <i>TAJ</i> knockout mice were more resistant to the suppressive action of the myelin inhibitors.</p>	
Stress and Depression	Akt, BDNF, TrkB	<p>Rat, Sprague-Dawley</p> <p>Mouse, C57BL/6</p> <p>Mouse, CD1 retired breeders</p> <p>Human, post-mortem brains from depressed subjects</p>	<p>Chronic fluoxetine was administered via subcutaneous implants of pellets in the dorsal interscapular region. The pellets delivered 20 mg/kg/day of fluoxetine or placebo over a 20-day interval.</p> <p>C57BL/6 mice were subjected to a social defeat paradigm using resident CD1 mice as the aggressors.</p> <p>Samples from post-mortem human ventral tegmental area and both the ventral tegmental area and nucleus accumbens from the C57BL/6 mice were used in western blotting assays for Akt, phospho-Akt, BDNF, and TrkB.</p>	<p>Susceptibility to social defeat was associated with a significant reduction in levels of active/phosphorylated Akt within the ventral tegmental area.</p> <p>Chronic antidepressant treatment in both mice and humans resulted in increased active Akt levels.</p> <p>Defeat induced reduction in Akt activation in susceptible mice was necessary and sufficient to induce depressive behaviors associated with susceptibility.</p> <p>Pharmacological reductions in Akt resulted in a significant rise in the firing frequency of ventral tegmental area dopamine neurons.</p>	Krishnan V. et. al. 2008
Traumatic Brain Injury	MAG	Rat, Sprague-Dawley	<p>Adult male rats were subjected to either lateral fluid percussion brain injury or sham injury.</p> <p>Treatment with either 8.64 µg anti-MAG monoclonal antibody or IgG control antibody, delivered by osmotic minipumps, began 1</p>	<p>At 72 hours post-injury, rats showed increased immunoreactivity for MAG in the ipsilateral cortex, thalamus and hippocampus of brain injured animals; anti-MAG was detected in the hippocampus, fimbria and ventricles.</p>	Thompson HJ. et. al. 2006

Disease	Protein(s)	Species/Model/Cell Line	Study Details	Findings	Reference
			<p>hour post injury and continued for 72 hours.</p> <p>One group of rats was euthanized at the 72 hour post injury time-point to verify drug diffusion and MAG immunohistochemistry.</p> <p>All other rats were evaluated for up to 8 weeks post-injury to assess neurologic motor, sensory and cognitive function using a battery of previously described tests, including but not limited to the rotarod test, adhesive paper test, and Morris water maze test.</p> <p>Hemispheric tissue loss was evaluated at 8 weeks post-injury.</p>	<p>Brain-injured rats that received anti-MAG antibody treatment showed significantly improved recovery of sensorimotor function at 6 and 8 weeks post-injury compared to the brain-injured IgG control treated rats.</p> <p>8 weeks post-injury, anti-MAG treated brain-injured rats showed significantly improved cognitive function and reduced hemispheric tissue loss compared to brain-injured controls.</p>	
Traumatic Brain Injury and Epilepsy	RhoA	Rat, Sprague-Dawley	<p>Male rats were subjected to a lateral fluid percussion brain injury; cortex and hippocampus from both hemispheres were collected 24 h to 3 days after injury.</p> <p>A second set of male rats were administered kainic acid (10 mg/kg i.p.) to induce seizure; brains were collected 24 h after injections and bilateral hippocampi were removed.</p> <p>GTP-RhoA pull down assays were performed on rat cortical and hippocampal tissue homogenates.</p>	<p>RhoA activation was increased from 24 h to 3 days post-injury in the cortex, and by 3 days in the hippocampus, ipsilateral to the injury.</p> <p>RhoA activation was also detected in the cortex and hippocampus contralateral to the injury, without alterations in the level of RhoA.</p> <p>Severe seizures resulted in bilateral RhoA activation in cortex and hippocampus.</p>	Dubreuil CI. et. al. 2006
Traumatic Brain Injury	RhoA	Human, post-mortem brains from traumatic brain injury subjects	<p>The post-mortem cohort consisted of brains from 25 patients who died after various survival times following closed traumatic brain injury, in addition to 4 brains of neuropathologically normal cases used as controls.</p> <p>Immunohistochemistry was used to detect RhoA expression throughout the brain at</p>	<p>The main cellular sources of RhoA after traumatic brain injury were monocytes/macrophages, granulocytes and neurons.</p> <p>Following closed traumatic brain injury there was a significant increase in the number of parenchymal cells expressing RhoA at the lesion site, but not in neighboring areas.</p>	Barabeck C. et. al. 2004

Disease	Protein(s)	Species/Model/Cell Line	Study Details	Findings	Reference
			different stages of survival (<7 hours, 12-48 hours, 4-16 days, and months) following closed traumatic brain injury.	<p>There were no significant differences in the number of RhoA positive cells in the very early stages following injury (<7 hours); RhoA expression was confined to shrunken eosinophilic neurons.</p> <p>RhoA expression was highest between 1-2 weeks post injury and was predominantly expressed in macrophages at this stage post-injury.</p> <p>In the later stages post-injury (months), additional staining was observed in reactive astrocytes.</p>	
Tuberous Sclerosis & Cortical Dysplasia	Nogo-A	Human, surgical specimens from pediatric patients undergoing surgery for epilepsy.	<p>Brain biopsy specimens were used to examine the expression patterns of the Nogo-A system in cortical lesions of 28 pediatric patients with tuberous sclerosis complex (TSC) (n=16) and focal cortical dysplasia type IIb (FCDIIb) (n=12). Control white matter cortical specimens were obtained from the brains of 10 normal-appearing brains of pediatric patients without a history of seizures or other neurological disorders at autopsy.</p> <p>Western blotting and immunohistochemistry were used to examine expression levels of Nogo-A, NgR, Lingo-1, TROY, p75 and RhoA in the brain specimens of FCDIIb, TSC and control subjects.</p> <p>Quantitative RT-PCR was used to examine relative levels of <i>Nogo-A</i> and <i>NgR</i> mRNA in all samples.</p>	<p>mRNA and protein levels of Nogo-A, NgR, Lingo-1, TROY and RhoA, but not p75 were upregulated in the cortices of patients compared to autopsy controls.</p> <p>Immunohistochemistry showed that Nogo-A and NgR were expressed strongly in misshapen cells, particularly in dysmorphic neurons, balloon cells and giant cells.</p> <p>TROY was diffusely expressed in the malformations of cortical development.</p> <p>The majority of Nogo-A/NgR positive cells were co-labeled with neuronal rather than astrocytic markers.</p>	Yu S-X. et. al. 2012

Abbreviations: 6-OHDA: 6- hydroxydopamine; ADI-R: Autism Diagnostic Interview-Revised; Akt: protein kinase B; AP: alkaline phosphatase; APP: amyloid precursor protein; ASTN2: astrotactin 2; BA: Brodmann's Area; BDA: biotin dextran amine; BDNF: brain derived neurotrophic receptor; CA1: Cornu Ammonis 1; CA2: Cornu Ammonis 2; CA3: Cornu Ammonis 3; CA4: Cornu Ammonis 4; CHO: Chinese Hamster Ovary; CNPase: 2',3'-Cyclic-nucleotide 3'-phosphodiesterase; CNS: central nervous system; CSPG: chondroitin sulfate proteoglycan; CV: cresyl violet; DN: dominant-negative; DRG: dorsal root ganglion; E: embryonic day; EAE: myelin oligodendrocyte glycoprotein-induced experimental autoimmune encephalomyelitis; EGF: epidermal growth factor; EGFR: epidermal growth factor receptor; ELISA: enzyme linked immunosorbent assay; ErbB2: receptor tyrosine-protein kinase erbB-2; Fc: fragment crystallizable; FCDIIb: focal cortical dysplasia type IIb; FG: Fluoro-Gold neuronal tracer; FJB: FluoroJade B; FL: full-length; GFAP: glial fibrillary acidic protein; GST: glutathione S-transferase; HA: hemagglutinin; HB-EGF: heparin-binding epidermal growth factor-like growth factor; HEK: human embryonic kidney; i.p. intraperitoneal; LFB: luxol fast blue; Lingo-1: leucine-rich repeat and Ig domain-containing, nogo receptor-interacting protein; LPC: lysophosphatidylcholine; LRR: leucine-rich repeats; LV/Lingo-1-shRNA: lentiviral vectors encoding Lingo-1 short hairpin RNA; mAb: monoclonal antibody; MAG: myelin associated glycoprotein; Mb: mega base pairs; mceph/mceph: BALB/cByJ-Kv1.1^{mceph/mceph} mice; miRNA: microRNA; MPTP: N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; mRNA: messenger RNA; mTOR: mammalian target of rapamycin; Myt1: myelin transcription factor 1; Myt1l: myelin transcription factor 1-like; NgR: nogo receptor; Nogo-A: neurite outgrowth inhibitor; NRG1: neuregulin1; NRXN1: neurexin-1-alpha; OMgp: oligodendrocyte-myelin glycoprotein; OPC: oligodendrocyte precursor cell; p75: p75 neurotrophin receptor; PCR: polymerase chain reaction; Phospho: phosphorylated; PI3-K: phosphatidylinositide 3-kinase; PN: postnatal day; RGC: retinal ganglion cell; RhoA: ras homolog gene family, member A; RNAi: RNA interference; RT-PCR: real-time polymerase chain reaction; SHR: spontaneously hypertensive rats; SNP: single nucleotide polymorphism; SRF: serum response factor; TAJ: TNF receptor orphan Y (TROY); tcTPC: time-controlled transcardiac perfusion cross-linking; TNFRSF19: Tumor necrosis factor receptor superfamily, member 19 (TROY); TrkB: tropomyosin receptor kinase B; TROY: TNF receptor orphan Y; TSC: tuberous sclerosis complex; VPA: Valproic acid; WNK1: WNK lysine deficient protein kinase 1; WOD: weighted ocular dominance.