Disrupted in Schizophrenia 1 regulates the processing of reelin in the perinatal cortex

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ARTICLE INFO

Article history:
Received 12 January 2017
Received in revised form 3 April 2017
Accepted 4 April 2017
Available online xxxx

Keywords:
ADAMTS-4
Schizophrenia
DISC1
Reelin
Transgenic mouse
Neurodevelopment

ABSTRACT

Disrupted in Schizophrenia 1 (DISC1) is a prominent gene in mental illness research, encoding a scaffold protein known to be of importance in the developing cerebral cortex. Reelin is a critical extracellular protein for development and lamination of the prenatal cortex and which has also been independently implicated in mental illness. Regulation of reelin activity occurs through processing by the metalloproteinases ADAMTS-4 and ADAMTS-5. Through cross-breeding of heterozygous transgenic DISC1 mice with heterozygous reeler mice, which have reduced reelin, pups heterozygous for both phenotypes were generated. From these, we determine that transgenic DISC1 leads to a reduction in the processing of reelin, with implications for its downstream signalling element Dab1. An effect of DISC1 on reelin processing was confirmed in vitro, and revealed that intracellular DISC1 affects ADAMTS-4 protein, which in turn is exported and affects processing of extracellular reelin. In transgenic rat cortical cultures, an effect of DISC1 on reelin processing could also be seen specifically in early, immature neurons, but was lost in calretinin and reelin-positive mature neurons, suggesting cell-type specificity. DISC1 therefore acts upstream of reelin in the perinatal cerebral cortex in a cell type/time specific manner, leading to regulation of its activity through altered proteolytic cleavage. Thus a functional link is demonstrated between two proteins, each of independent importance for both cortical development and associated cognitive functions leading to behavioural maladaptation and mental illness.

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1. Introduction

Disrupted in Schizophrenia 1 (DISC1) is a long standing candidate gene for major mental illness, and in particular schizophrenia, bipolar disorder and major depression. The DISC1 gene was initially identified in a large family in which it was disrupted by a chromosomal translocation linked to these three conditions (Millar et al., 2000; Thomson et al., 2016). It was reinforced as a gene pertaining to schizophrenia and other conditions through genetic association studies in specific populations (reviewed in Chubb et al., 2008; Bradshaw and Porteous, 2012; Thomson et al., 2013) and via a separate mutation in another family (Sachs et al., 2005), although no single SNP or haplotype has been associated with one of these conditions globally. Functionally, DISC1 is an intracellular scaffold protein established to play a role in cortical development, impacting on both migration of cortical neurons and lamination of the prenatal cortex and which has also been independently implicated in mental illness. Regulation of reelin activity occurs through processing by the metalloproteinases ADAMTS-4 and ADAMTS-5. Through cross-breeding of heterozygous transgenic DISC1 mice with heterozygous reeler mice, which have reduced reelin, pups heterozygous for both phenotypes were generated. From these, we determine that transgenic DISC1 leads to a reduction in the processing of reelin, with implications for its downstream signalling element Dab1. An effect of DISC1 on reelin processing was confirmed in vitro, and revealed that intracellular DISC1 affects ADAMTS-4 protein, which in turn is exported and affects processing of extracellular reelin. In transgenic rat cortical cultures, an effect of DISC1 on reelin processing could also be seen specifically in early, immature neurons, but was lost in calretinin and reelin-positive mature neurons, suggesting cell-type specificity. DISC1 therefore acts upstream of reelin in the perinatal cerebral cortex in a cell type/time specific manner, leading to regulation of its activity through altered proteolytic cleavage. Thus a functional link is demonstrated between two proteins, each of independent importance for both cortical development and associated cognitive functions leading to behavioural maladaptation and mental illness.

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with specific species of the reelin protein later shown to be deregulated in this condition, bipolar disorder and depression (Fatemi et al., 2001). Similar results have also been reported since by others, while a considerable number of genetic association studies also associated it with schizophrenia and autism spectrum disorders (reviewed in Ishii et al., 2016). Negative genetic association findings to mental illness have also been reported, although one positive finding was at the genome-wide level (Shifman et al., 2008). Additionally, mice heterozygous for the reeler mutation display phenotypes reminiscent of aspects of schizophrenia (Tueting et al., 1999; Rogers et al., 2013; Schmitt et al., 2013).

Given the roles of these two proteins in both cortical development and the pathogenesis of mental illness, we sought to discern whether they operated in a common pathway. Such links between DISC1 and reelin have been hypothesised previously (Deutsch et al., 2010; Bader et al., 2012), and the two proteins share several common pathway elements, which are known to include LIS1, GSK3β, Akt and APP (Assadi et al., 2003; Ohkubo et al., 2003; Brandon et al., 2004; Hashimoto et al., 2006; Jossin and Coffinet, 2007; Hoe et al., 2009; Mao et al., 2009; Young-Pearse et al., 2010). Our results, however, show, for the first time a direct functional link between DISC1 and reelin, with DISC1 found to alter the post-translational regulation of reelin by proteolytic cleavage.

2. Materials and methods

2.1. Animals

All animal work was approved by the LANUV (State Agency for Nature, Environment and Consumer Protection), North Rhine-Westphalia, Germany. A transgenic rat line expressing human DISC1 under the Syrian hamster PrP promoter, on a Sprague-Dawley background, has been described in detail previously (Trossbach et al., 2016). The same cosmid system and technique were used to introduce human DISC1 under the same promoter into a C57BL/6 N mouse. The presence of the transgene in a stable founder line was confirmed at both the transcript and protein level within the brain (Fig. 1A–B, Supplemental Fig. 1). Heterozygotes were generated by crossing the transgenic mouse with wild type C57BL6/N mice. As the mouse experiments were performed using heterozygous DISC1 mice crossed with heterozygous reeler mice, the ensuing litter included wild type pups which were used as controls for their transgenic littermates. Pups with both the DISC1 and reeler alleles were not allowed to grow past one week of age. For the generation of brain homogenates, animals were sacrificed by decapitation and the whole brain rapidly extracted and flash-frozen in liquid nitrogen. Tail samples were taken for genotyping. Frozen brains were homogenized to a brain rapidly extracted and homogenates, animals were sacrificed by decapitation and the whole brain rapidly extracted and flash-frozen in liquid nitrogen. Tail samples were taken for genotyping. Frozen brains were homogenized to a final concentration of 7.5% (w/v) in 50 mM HEPES pH 7.5, 250 mM sucrose, 5 mM MgCl₂, 100 mM KAc, 1% Triton X-100, containing protease and phosphatase inhibitor cocktails and DNaseI. Homogenates were incubated with gentle spinning at 4 °C for 2 h and then mixed with 2× SDS loading buffer.

2.2. Antibodies

The 20E12 monoclonal antibody was raised against a recombinant fragment of mouse reelin (amino acids 24–500) using previously described protocols (Korth et al., 1999). The final antibody was shown to be specific for reelin (Fig. 1C–E) and was used at ×500 dilution for western blot (WB) and ×300 for immunocytochemistry (ICC). Anti-DISC1 monoclonal antibody 14F2 (×500 for WB), anti-DISC1 polyclonal antibody FFD5 (×300 for ICC), and polyclonal anti-ADAMTS-4 (×500 for WB) have been described previously (Lelieveld et al., 2008; Ottis et al., 2011; Hisanaga et al., 2012), the latter being a gift from Prof. Mitsuharu Hattori (Nagoya City University, Japan). Commercial antibodies were used against α-actin (Sigma-Aldrich, #A2066, ×5000 for WB), Akt (Cell Signaling Technology, #2920 and #4690, ×1000 each for WB), calretinin (GeneTex, #GTX103261, ×300 for ICC), coflin (Santa Cruz Biotechnology #sc-12,912-R, ×200 for WB, and Cell Signaling Technology #3318, ×1000 for WB), Dab1 (Merck Millipore, #AB5840, ×1000 for WB), EBF2 (antibodies-online, #bs-11740R, ×100 for ICC), Erk (Cell Signaling Technology, #4379 and #9107, ×1000 each for WB), GSK3β (Cell Signaling Technology #5585 and BD Transduction Laboratories #610201, ×1000 each for WB) reelin (Merck Millipore, #MAB5364, ×1000 for WB) and α-τubulin (Sigma-Aldrich, #T9026, ×2000 for WB).

2.3. Cell and neuronal culture

HEK293 (human kidney derived) cells expressing recombinant reelin or GFP as a control ( Förster et al., 2002) were a gift from Dr. Eckart Förster (Centre for Molecular Neurobiology Hamburg, Germany) and were grown in D-MEM with 5% foetal calf serum, penicillin and

Please cite this article as: Bradshaw, N.J., et al., Disrupted in Schizophrenia 1 regulates the processing of reelin in the perinatal cortex, Schizophr. Res. (2017), http://dx.doi.org/10.1016/j.schres.2017.04.012
and then antibodies applied in PBS/0.05% Tween for 1 h. Membranes were blocked for 1 h in PBS/0.05% Tween/5% milk powder, media.

Two species of the same protein, or when examining protein in cell normalized to actin or tubulin (as shown in the corresponding blot) as PBS/0.05% Tween. After washing, proteins were visualized using an Od-

2.6. Real time PCR

ysis was performed using a StepOnePlus Real-Time PCR Cycler (Applied Biosystems) and the Platinum SYBR Green qPCR SuperMix-UDG (Invitrogen). Relative expression levels were calculated using StepOnePlus Software 2.0 (Applied Biosystems) with the 2^-ΔΔCt method. ODAMTS-4 expression levels were normalized twice; first to the housekeeping gene ARF1 and then to the expression levels of untreated controls. The following primer sets were used: ODAMTS-4: 5'- CCTGACCACTTTGACACAGC-3' and 5'-CTGACTGAGCCCATCATCT'- ARF1: 5'-GACACGATCTCTACAAGC-3' and 5'-TCCACACAGTGAAGGCTGTAG-3'.

2.7. Statistics

Distribution of genotypes among crosses of transgenic DISC1 and reeler mice were analysed by chi-squared test. Comparisons of protein signals between three or more genotypes or treatments were performed by one-way ANOVA, with Dunnett’s multiple comparison test. Comparisons of only two genotypes were performed using Walsh’s t-test. All error bars represent standard error of the mean.

3. Results

3.1. Transgenic DISC1 alters the processing of reelin in the perinatal mouse brain

To investigate potential interplay between the DISC1 and reelin proteins during neurodevelopment, reeler heterozygous mice were crossed with heterozygous mice expressing human DISC1 (Fig. 1A–B, see Section 2.1 and Supplemental Fig. 1). Heterozygous reeler were chosen over homozygous reeler mice because DISC1 mouse models (both knockdown animals and those expressing mutant variants of the protein) show subtle behavioural and cognitive deficits (Lipina and Rodér, 2014) which would likely not be detectable on the background of the gross rearrangements in cortical layering associated with the homozygous reeler mouse (Ogawa et al., 1995). Genotyping confirmed the presence of all four genotypes (wild type: WT, DISC1 heterozygote: Dhet, reeler heterozygote: Rhet, and animals heterozygous for both: DhetRhet), although the distribution was not Mendelian (Fig. 2A), demonstrating that at least one of the genetic alterations affects viability. The reeler phenotype was the more detrimental to viability. Curiously, the DhetRhet genotype was more abundant than the Rhet alone, potentially implying that transgenic DISC1 can partially rescue viability defects due to reeler, however with the numbers of animals used, no statistically significant interaction was detected by the χ² test (p = 0.10).

To probe possible interactions between transgenic DISC1 and reelin in these animals, five litters of pups from such breedings were sacrificed within twelve hours of birth (P0-P0.5) and brain homogenates prepared.

Western blotting of the brains showed a reduction in the total level of reelin by approximately 45% could be confirmed in the presence of a reeler allele (WT vs. Rhet, Fig. 2B&C, Supplemental Fig. S2 A&B), however this loss was unevenly distributed. Three species were detected using our N-terminal derived antibody, consistent with 450 kDa full length reelin, and two known processed fragments (Lambert de Rouvroit et al., 1999) described in the literature as being 350 kDa and 240 kDa. In the brain homogenates of animals with the reeler allele, signal intensity of the total level of reelin was reduced to approximately 35% of WT (p < 0.05), but not in the total level of all reelin species (full length and processed), with a corresponding decrease in processed reelin. This implied that expression of transgenic DISC1 was inhibiting the processing of reelin in the brains of these animals. The increase in the proportion of reelin which was full...
measured Dab1 phosphorylation in this assay due to the use of flash frozen as opposed to fresh brain tissue (a necessity due to crossed mouse litters being born on different dates). Therefore the level of total Dab1 was instead assayed, as reelin also influences the degradation of Dab1 (Arnaud et al., 2003). While the presence of a reeler allele reduced Dab1 protein levels by 18 ± 5% (WT vs. Rhet, Fig. 2E&F, Supplemental Fig. S2C, p = 0.056), this was restored in the presence of a DISC1 allele (Rhet vs. DhetRhet, Fig. 2E&F, p < 0.05). This would be consistent with the DISC1-related restoration of normal levels of specifically full length reelin rescuing the deficit in Dab1 activity, even while levels of total reelin are decreased. Both DISC1 and reelin have previously been reported to affect Akt signalling (Hashimoto et al., 2006; Jossin and Goffinet, 2007), a downstream element of Dab1, and indeed the presence of a DISC1 allele did increase the phosphorylation of Akt (Fig. 2G&H, Supplemental Fig. S2D), with a similar trend effect of the reeler allele, although the effects were not seen to be cumulative. No significant effect was seen however on three other downstream elements of reelin signalling: Erk1, GSK3β or coflin (Supplemental Fig. S3).

3.2. Intracellular DISC1 can affect extracellular reelin in cell culture through the ADAMTS-4 enzyme

Processing of reelin at both of its major cleavage sites occurs through two enzymes of the A Disintegrin and Metalloproteinase with Thrombospondin motifs family, ADAMTS-4 and ADAMTS-5 (Hisanaga et al., 2012; Kostic et al., 2012). While both proteins could be detected in the P0-P0.5 mouse brain samples, their expression levels were too weak, and the available antibodies too lacking in specificity, to reliably quantify. However, it should be noted that as a soluble extracellular matrix protein, ADAMTS should be diffusible in extracellular space. Therefore, to investigate a potential relationship between DISC1 and ADAMTS in reelin processing, cell media containing freshly prepared recombinant reelin was incubated for 18 h with transgenic SH-SY5Y neuroblastoma cells that express DISC1 in response to doxycycline (Trossbach et al., 2016), but no detectable endogenous DISC1 protein. Cells were variously treated with doxycycline, EGCG (a selective inhibitor of ADAMTS-4 and 5, Vankemmelbeke et al., 2003) and/or vehicle controls. The ensuing conditioned media was then analysed by western blot (Fig. 3A) showing no effect of DISC1 expression on total reelin levels, unlike EGCC which led to a 50% total reelin reduction (Fig. 3B). Notably however, DISC1 expression led to an increase in the proportion of reelin in the media which was full length, suggesting that DISC1 was inhibiting reelin processing, as in the transgenic mice (Fig. 3C). Furthermore, this effect was not seen using DISC1-expressing cells which had also been treated with EGCG, suggesting that the effect of DISC1 on reelin processing is dependent on ADAMTS-4/5 (Fig. 3C).

It is notable in this experiment that overexpression of intracellular DISC1 is able to affect the processing of recombinant reelin in the cell media, despite the two proteins presumably never coming into direct contact with each other. To determine whether ADAMTS-4 may provide the link between them, HEK293 cells expressing exogenous reelin were transfected for 6 h with human DISC1 and/or murine ADAMTS-4 and then incubated for 42 h in fixed volumes of media. As expected, expression of ADAMTS-4 led to an increase in reelin processing in the conditioned media (Fig. 3D&E), whereas this was not seen following expression of both ADAMTS-4 and DISC1. This was, seemingly because the expression of DISC1 led to a dramatic decrease in levels of cellular ADAMTS-4 (Fig. 3D&F), whereas in contrast the expression of ADAMTS-4 had no significant effect on levels of DISC1 protein. Both the levels of ADAMTS-4 within the cell (predominantly the 105 kDa form, retaining its pro-domain) and extracellular ADAMTS-4 (the known 70 kDa active form, Wang et al., 2004) were affected. An equivalent effect of DISC1 on ADAMTS-4 mRNA levels was not seen however (Fig. 3G), suggesting that the DISC1 protein may instead effect the stability or turnover of ADAMTS-4 in the cell. This effect of DISC1 on ADAMTS-4 levels could also be seen in another cellular system.
transgenic HEK293 cells which over-express human ADAMTS-4 in response to doxycycline (Fig. 3H, described in Section 2.3). In this case, transient over-expression of human DISC1 led to an approximately 50% reduction in levels of both the pro-form and the active, mature form of ADAMTS-4 (Fig. 3H&I).

3.3. Transgenic DISC1 alters reelin processing in a cell type dependent manner in rat cortical cultures

To determine whether the effect of DISC1 on reelin processing was generalizable to other experimental systems, our existing DISC1-transgenic rat model was employed (Trossbach et al., 2016). Primary cortical neuronal cultures were prepared from six E18 transgenic embryos, as well as from six wild type Sprague-Dawley rat embryos (“control embryos”), and seeded onto plates at a consistent density. After 24 h in vitro, fresh media (without reelin) was added and allowed to condition for 48 h before western blotting. Levels of full length reelin and of the larger of the two processed species were fairly consistent, but too low to accurately quantify. However, the 130 kDa form was approximately 40% lower in media conditioned with transgenic cultures compared to those from control cultures (Fig. 4A,B). No reelin species of 130 kDa or higher could be detected in cell lysates. Therefore, like in the mouse brain homogenates, processing of reelin is decreased in rat cortical cultures in the presence of a transgenic DISC1 allele. Notably however, media conditioned with neurons instead up to 8 days in vitro did not show this effect (Fig. 4C), suggesting the effect of DISC1 on reelin processing to be developmentally time-dependent. Levels of ADAMTS-4/5 in the cells/media were too low to accurately measure, meaning that it cannot be conclusively demonstrated if the enzymes were responsible for the effect in this system.

To investigate this effect, cortical neuronal cultures were examined by immunofluorescence. After 1–3 days in vitro, reelin was seen to be strongly expressed by a small population of cells, <1% of those in culture, with a distinctive morphology (Fig. 4D). These cells also expressed Ebf2 (Early B-cell Factor 2, Fig. 4E), but were negative for the calretinin (Fig. 4F), which would be consistent with Cajal-Retzius cells. In contrast,
such cells could not be seen in cultures after 8–10 days in vitro. Instead at this time point, a much more abundant population of reelin-expressing cells were seen to be present, which were calretinin-positive and with a more classically neuronal morphology (Fig. 4G). The effect of DISC1 on reelin therefore appears to be specific to certain cell types.

The presence of human DISC1 in both sets of reelin positive cells, was confirmed in the transgenic cultures (Fig. 4H).

4. Discussion

Despite their established importance for both mental illness and cortical development, no strong functional links between DISC1 and the reelin pathway have previously been established. It has been shown that knockdown or over-expression of either Dab1 or APP leads to mislocalisation of DISC1 (Young-Pearse et al., 2010), indicating DISC1 to lie downstream of them and thus most likely of reelin signalling, however here we demonstrate for the first time that DISC1 also has a function upstream of reelin, through regulating its proteolytic cleavage.

Reelin is naturally processed in vivo from a 450 kDa full length protein, with the N-terminal section of the protein, required for its function, with the N-terminal cleavage, without altering total reelin levels. It remains to be determined whether this is an effect of the presence of additional functional DISC1, or due to the presence of insoluble aggregated DISC1, which can also be detected in these transgenic mice, as it was in our previously described transgenic rat (Trossbach et al., 2016). Furthermore, as complete brain homogenate was employed, it is not possible to determine if the effect of DISC1 on reelin occurs in specific brain regions, as might be hypothesised based on the decrease of reelin expression in the prefrontal cortex which has been associated with schizophrenia (Habl et al., 2012). Nevertheless, the effect of DISC1 on N-terminal cleavage of reelin could also be confirmed in primary neurons derived specifically from the cortex of rats, as determined by measuring levels of the processed 130 kDa reelin species, although levels of the other processed species were too low to easily detect and quantify. These differential effects of DISC1 on individual reelin species are of particular interest given it has previously been reported that full length reelin is increased in the blood of schizophrenia patients, whereas one of its major breakdown products (described by the authors as 180 kDa, but seemingly corresponding to the 130 kDa described here) were lowered in patients with bipolar disorder or depression (Fatemi et al., 2001).

ADAMTS-4 is an extracellular protease, originally identified as a processor of cartilage aggrecan (Tortorella et al., 1999). Both ADAMTS-4 and the closely related enzyme ADAMTS-5 are also known to act on reelin, cleaving reelin at two sites yielding the 350 kDa and 130–170 kDa reelin species (Hisanaga et al., 2012; Krstic et al., 2012). Notably, it was ADAMTS-4, which plays the more prominent role in reelin processing (Krstic et al., 2012), which was affected by over-expression of DISC1 (Section 3.2). Furthermore, in cell culture, DISC1 was shown to affect the processing of extracellular reelin, except following the inactivation of ADAMTS-4/5 with EGCG, suggesting an ADAMTS enzyme to be the mechanism by which this effect is relayed out of the cell. In concordance with this, expression of DISC1 was shown to modulate levels of ADAMTS-4 both within and outside the cell, suggesting DISC1 to have an effect on ADAMTS-4 prior to it becoming exported. The subsequent effect of ADAMTS-4 on reelin can be assumed to occur outside of the cell, in this case in the cell media.

In cortical cultures from E18 rats (Section 3.3), the effect of DISC1 was detectable in the first 3 days in vitro, while reelin was expressed solely by EBF-positive cells with a distinctive morphology, but not following the emergence of reelin-expressing cells resembling interneurons, demonstrating a cell-type specific effect. We have interpreted these early cells to most likely be Cajal–Retzius cells based on their expression timing and the presence of reelin and Ebf2, but not calretinin, although in the absence of positional data, this designation must be treated as provisional (Anstötz et al., 2014). Decline in Cajal–Retzius cell numbers occurs principally in rats around two weeks after birth, as a result of caspase 3-dependent apoptosis, although loss of reelin expression occurs prior to cell death (Chowdhury et al., 2010; Anstötz et al., 2014; Anstötz et al., 2016). If these reelin and EBF2-positive, but calretinin-negative cells are indeed Cajal–Retzius cells, then the slight differences in timing likely reflect the lack of localization-specific signalling in cell culture compared to the highly ordered cerebral cortex. The absence of cells positive for both reelin and calretinin in the P0–P2 rat cortex has also been reported previously (Martinez-Galan et al., 2014).

In this paper, it has been demonstrated that an established mental illness-related protein involved in neurodevelopment, DISC1, and a major neurodevelopmental protein implicated in mental illness, reelin, exist in a common pathway in the perinatal cortex within two different transgenic rodent models, with DISC1 inhibiting the processing of reelin by ADAMTS-4/5. Common areas of function of the two proteins,
particularly with regard to their individually identified roles in neuronal migration are therefore of considerable interest when considered in light of the neurodevelopmental hypothesis of schizophrenia (Murray and Lewis, 1987; Weinberger, 1987; Fatemi and Folsom, 2009). Further analysis of the consequences of DISC1 on reelin would thus reveal more regarding their common neurodevelopmental functions, with potential implications for the early development of pathological features that influence mental illness in later life.

Author disclosure

Role of funding source

The role of the exclusively governmental funding sources was to enable research through financing positions, investment or running material. Funding sources did not have any influence on results or conclusions of the work at any time.

Contributors

N.J.B. and C.K. designed the work, analysed data and drafted the manuscript. N.J.B., S.V.T. and S.Wa. performed the experiments. S.V.T. generated the novel DISC1-transgenic mice and managed animal experiments. S.K. and I.P. generated the novel anti-reelin monoclonal antibody. S.Wa. and S.We. generated the novel ADAMTS-4-expressing cells. All authors contributed to and have approved the final manuscript.

Conflict of interest

The authors declare that they have no conflicts of interest with the contents of this article.

Acknowledgements

We thank Irene Rolle for assistance with antibody characterization and Prof. Dr. Hans Bock for advice and discussion.

This work was supported by the Alexander von Humboldt Stiftung (1142747 to N.J.B.), the Forschungskommission der Medizinischen Fakultät der Heinrich-Heine-Universität Düsseldorf (9772547 to N.J.B. and 9772513 to S-We.), the Fritz Thyssen Stiftung (10.14.2.140 to C.K.) and Prof. Dr. Hans Bock for advice and discussion.


Ma, Y., Chen, X., Frank, C.L., Madison, J.J., Koehler, A.N., Doad, M.K., Tassa, C., Berry, E., Sodha, T., Singh, K.K., Biechele, T., Petryshen, T.L., Moon, R.T., Haggarty, S.J., Tsai, L-H.,


Please cite this article as: Bradshaw, N.J., et al., Disrupted in Schizophrenia 1 regulates the processing of reelin in the perinatal cortex. Schizophr. Res. (2017), http://dx.doi.org/10.1016/j.schres.2017.04.012