Accepted Article

Title: Perturbed proteostasis in autism spectrum disorders

Running title: Perturbed proteostasis in autism

Authors: Susana R. Louros and Emily K. Osterweil

Affiliation:
Centre for Integrative Physiology/Patrick Wild Centre
University of Edinburgh
Hugh Robson Building, George Square
Edinburgh, EH8 9XD, UK

*Corresponding author:
Emily K. Osterweil, PhD
Centre for Integrative Physiology/Patrick Wild Centre
University of Edinburgh
Hugh Robson Building, George Square
Edinburgh, EH8, 9XD, UK
Tel: +44 (0)131 650 3722
Email: Emily.osterweil@ed.ac.uk

Key Words: Autism, ASD/ID, proteasome, ubiquitin, synaptic plasticity, translation

Abbreviations:
αCaMKII - αCa^{2+}/calmodulin dependent kinase II
AMPAR - α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor
Arc/Arg3.1 - activity-regulated cytoskeleton-associated protein
AS - Angelman Syndrome

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/jnc.13723
This article is protected by copyright. All rights reserved.
Abstract:
Dynamic changes in synaptic strength rely on de novo protein synthesis and protein degradation by the ubiquitin proteasome system (UPS). Disruption of either of these cellular processes will result in significant impairments in synaptic plasticity and memory formation. Mutations in several genes encoding regulators of mRNA translation and members of the UPS have been associated with an increased risk for the development of autism spectrum disorders (ASD). It is possible that these mutations result in a similar imbalance in protein homeostasis (proteostasis) at the synapse. This review will summarize recent work investigating the role of the UPS in synaptic plasticity at glutamatergic synapses, and propose
that dysfunctional proteostasis is a common consequence of several genetic mutations linked to ASD.

**Protein synthesis and degradation in ASD/ID**

Functioning neural circuits require synaptic connections capable of strengthening or weakening in response to activity. This plasticity, measured electrophysiologically as the long-term potentiation or depression of synaptic strength (LTP/D), is particularly important for experience dependent memory formation. It is well established that *de novo* protein synthesis plays a fundamental role in supporting LTP/D and that it is required for the creation of new memories. Given this important role in synaptic plasticity, it is perhaps not surprising that mutations in several genes that encode regulators of protein synthesis have been identified as risk factors for the development of autism spectrum disorders with accompanying intellectual disability (ASD/ID) (Table 1) (Kelleher & Bear 2008, Bhakar et al. 2012). These include mutations in the *FMR1* and *TSC1* or 2 genes, which respectively give rise to the neurodevelopmental disorders fragile X syndrome (FXS) and Tuberous Sclerosis Complex (TSC), as well as many regulators of the Ras-MAPK and mTOR translation control pathways (Krab et al. 2008, Kelleher & Bear 2008). Studies in animal models of these disorders reveal that protein synthesis downstream of group I metabotropic glutamate receptors (mGluR1/5) is commonly disrupted, leading to dysfunctional LTD (Auerbach et al. 2011, Osterweil et al. 2010, Barnes et al. 2015, Krab et al. 2008, Bateup et al. 2011, Dolen et al. 2007). Subsequent studies in multiple other mouse models of ASD/ID reveal a similar dysregulation of protein synthesis and LTD (Table 1). Importantly, normalizing mRNA translation corrects aberrant synaptic plasticity and several other pathological phenotypes in many of these mutant models.

Interestingly, the changes in protein synthesis observed in many mouse models of ASD/ID do not appear to be accompanied by significant changes in protein expression. One explanation is that there is a compensatory change in the rate of protein degradation in order to prevent large shifts in the abundance of the synaptic proteome. If so, it may be that this in itself contributes to the neurological phenotypes seen in these mutant models. Indeed, the coordination between protein synthesis and breakdown of proteins by the ubiquitin proteasome system (UPS) is thought to play an important role in the regulation of ubiquitin function and plasticity (Hanus & Schuman 2013). Although the role of the UPS in neurodevelopmental disorders has received relatively little attention, one of the most commonly mutated genes linked to ASD/ID encodes the ubiquitin E3 ligase Ube3a (Kishino...
et al. 1997). Moreover, mutations in over a dozen other UPS genes have been identified as risk factors for ASD/ID (Table 2). An intriguing possibility is that imbalance in the combined process of protein synthesis and breakdown (proteostasis) could be a common contributor to the development of ASD/ID (Figure 1).

In this review, we will summarize work linking ubiquitination and proteasome activity to changes in synapse function. Our emphasis will be on studies investigating the role of the UPS in the plasticity of excitatory synapses that contribute to learning and memory. The links between UPS dysfunction, protein synthesis, and the development of ASD/ID will be discussed.

UPS regulation by synaptic activity

The process of protein degradation is essential for the function of all eukaryotic cells, including neurons. Pathologically misfolded proteins must be removed, short-lived proteins must be quickly degraded in response to activity, and more stable constituents must be turned over to maintain the infrastructure of the cell. The majority of cytosolic and nuclear proteins are degraded by the UPS, which is comprised of the 26S proteasome and the ubiquitin ligases that tag proteins for degradation (for extensive review see Weissman 2001, Schmidt & Finley 2014). The proteasome consists of multi-subunit 19S regulatory particles, and a 20S catalytic core that hydrolyzes ATP in order to break down target proteins (Weissman 2001). For recognition by the proteasome, proteins destined for degradation must be tagged with a polyubiquitin chain. The covalent attachment of ubiquitin to the target protein involves three different enzymes: the E1 ligase that activates monoubiquitin, the E2 ligase that conjugates additional ubiquitin monomers to form a chain, and finally the E3 ligase that selectively conjugates the polyubiquitin chain to its target protein (Schmidt & Finley 2014, Suryadinata et al. 2014). It is the affinity of E3 ligases for select protein targets that determines the specificity of the UPS for only those proteins that require degradation. Interestingly, the addition of a single ubiquitin to a target protein, rather than a polyubiquitin chain, may serve as a tag for intracellular trafficking rather than degradation. Generally, proteins bound to lysine 48 (K48) chains are directly targeted for proteasomal degradation while a lysine 63 (K63) chain or a single ubiquitin molecule may result in significant effects in subcellular localization or activity of proteins (Suryadinata et al. 2014).
In neurons, the UPS has been implicated in several fundamental processes including morphogenesis, dendritic spine structure, synaptic activity, and the regulation of synaptic strength (for excellent reviews of these topics see Bingol & Sheng 2011, Tai et al. 2010, Hegde 2010, Hamilton & Zito 2013). Several lines of evidence show that the proteasome is regulated by neuronal activity through alterations in four factors: subunit composition, proteolytic activity, location within the cell and interaction with other proteins. Pioneering studies in cultured neurons showed that manipulation of neuronal activity resulted in a dramatic change in the ubiquitination and degradation of the postsynaptic proteome (Ehlers 2003). Subsequent work revealed that proteasomes can be translocated from dendritic shafts into postsynaptic dendritic spines within minutes upon KCl-induced depolarization, leading to overall increased local proteolysis (Bingol & Schuman 2006). More recent studies expressing a proteasome substrate GFP in cultured hippocampal neurons demonstrated that proteasomal breakdown is directly related to network activity. Blockade of action potential firing with the sodium channel blocker tetrodotoxin (TTX) decreased the degradation rate of GFP whereas increasing neuronal activity with the GABA-A receptor (GABA-AR) antagonist bicuculline lead to more degradation (Djakovic et al. 2009).

The majority of studies focused on UPS activity in synaptic function have examined excitatory neurotransmission through the activation of ion channel linked NMDA-type glutamate receptors (NMDARs) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs) at the postsynaptic membrane. Experiments in cultured neurons show that agonist induced activation of NMDARs leads to disassembly of the 26S proteasome, resulting in decreased proteolytic activity and a dissociation of E3 ligases from the proteasome (Tai et al. 2010). In addition, it may be that the NMDAR acts to stabilize proteasomes at synapses in order to facilitate the trafficking of AMPARs. Proteomic examination of hippocampal neurons from mice lacking the NMDAR subunit GluN2B reveals a decrease in the abundance of several proteasome subunits in purified postsynaptic density fractions (Ferreira et al. 2015).

NMDARs also regulate UPS function through the activation of the abundant postsynaptic protein α-Ca²⁺/calmodulin dependent kinase II (αCaMKII). Evidence from cultured neurons shows that Ca²⁺-dependent activation of αCaMKII through either NMDARs or L-type voltage-gated Ca²⁺ channel results in an increased association with proteasomes, and the recruitment of proteasomes into synapses (Djakovic et al. 2009). The stimulation of proteasome activity by αCaMKII involves phosphorylation of the regulatory subunit Rpt6,
which increases the catalytic activity of the 20S core (Bingol et al. 2010). Evidence showing that αCaMKII itself can be ubiquitinated suggests that its effects on the proteasome could be autoregulatory (Na et al. 2012), however the specific E3 ligases regulating this process remain unknown.

**UPS regulation of the postsynaptic proteome**

Several studies have shown that manipulation of the UPS has a significant impact on both the structure and function of the postsynaptic compartment. Recent studies using 2-photon live imaging in organotypic hippocampal slice culture showed that pharmacological inhibition of the UPS dramatically reduces the rate of dendritic spine outgrowth (Hamilton et al. 2012). This regulation of spine outgrowth by the UPS was seen to rely on the interaction between GluN2B and αCaMKII. Although the UPS substrates involved in dynamic spine morphogenesis have not been extensively characterized, the ubiquitination of the actin regulatory protein spine-associated Rap GTP activating protein (SPAR) has been implicated in dendritic spine shrinkage and synapse weakening (Pak et al. 2001).

The UPS regulates numerous proteins that have a direct impact on synaptic transmission. This includes major postsynaptic scaffolding proteins such as PSD95, GKAP and Shank, as well as major plasticity related proteins (PrPs) such as Arc/Arg3.1 and αCaMKII (Ehlers 2003). Additionally, NMDARs and AMPARs themselves are major UPS substrates, as are a number of other neurotransmitter receptors including mGluR1/5, inhibitory GABARs, Kainate receptors, Glycine receptors, nicotinic acetylcholine receptors, and dopamine receptors (Lin & Man 2013). A recent study performed a systematic analysis of the ubiquitome in the adult rat brain using a new monoclonal antibody to purify ubiquitinated peptides. By mass spectrometry analysis the authors identified a wide range of ubiquitination events on 45 key components of the presynaptic region and of the postsynaptic density including PSD-95, CaMKII and receptors for AMPA, NMDA, GABA, serotonin and acetylcholine. Interestingly, several UPS proteins were also found to be ubiquitinated, including E1, E2, E3 ligases, 10 DUBs and several proteasome subunits (Na et al. 2012).

Degradation of the NMDAR is mediated by ubiquitination of the obligatory GluN1 subunit by the E3 ligase Fbxo2, which directs receptors to cytosolic proteasomes (Kato et al. 2005). The GluN2B subunit of the NMDAR is also ubiquitinated by the E3 ligase mind bomb 2 (Mib2) (Jurd et al. 2008). Both mGluR1a and mGluR5 can be ubiquitinated by the E3 ligase seven in absentia homolog 1A (Siah1a) leading to proteasomal degradation (Moriyoshi
The ubiquitination of mGluR1a may be regulated by synaptic plasticity, as it has been shown to require the association with the Homer3 scaffolding protein (Rezvani et al. 2012).

One of the most well described postsynaptic targets of the UPS is the AMPAR. A recent study showed that all four AMPAR subunits (GluA1-4) are rapidly ubiquitinated upon brief application of AMPA or biccuculline in cultured neurons (Widagdo et al. 2015). The increase in neuronal activity leads to ubiquitination of GluA1 by the E3 ligase Nedd4-1, which internalizes AMPARs and directs them to endosomes and lysosomes for degradation (Schwarz et al. 2010). This process can be counteracted by the de-ubiquitinase (DUB) USP8 in response to NMDAR activation, which promotes AMPAR reinsertion into the postsynaptic membrane (Scudder et al. 2014). Recently, in vivo and in vitro studies demonstrated that the DUB USP46 also targets GluA1, regulating AMPAR surface expression, endocytosis, and the strength of synaptic transmission (Huo et al. 2015). During homeostatic plasticity, GluA1 is also targeted by the E3 ligase Cdh1-APC and degraded by the proteasome, a process that involves signaling through ephrin receptor EphA4 (Fu et al. 2011). Altogether, these studies indicate that ubiquitination is an important regulatory signal for controlling AMPAR function. This may explain the observed importance of the UPS for maintaining LTP and LTD, both of which occur through changes in AMPAR trafficking.

The role of the UPS in synaptic plasticity

Early experiments performed in Aplysia revealed a critical role for the UPS in the long-term facilitation (LTF) of synaptic strength at sensory-motor synapses (Hegde et al. 1997). This observation was supported by subsequent experiments in rat hippocampal CA1 showing that the proteasome inhibitor MG132 blocks both the early protein synthesis-independent phase of LTP (E-LTP), and the late phase LTP (L-LTP) that requires protein synthesis (Karpova et al. 2006). Later experiments revealed that application of the specific proteasome inhibitor lactacystin enhanced E-LTP but blocked L-LTP at hippocampal CA1 synapses (Fonseca et al. 2006, Dong et al. 2008). The specific effect of proteasome inhibitors on L-LTP but not E-LTP suggested that the requirement for protein degradation was related to the requirement for new protein synthesis. Further studies proved this correct, showing that the augmentation of LTP by proteasome inhibitors is blocked by the presence of the protein synthesis inhibitor anisomycin. This indicated that proteasome inhibition increases the induction of LTP by stabilizing locally translated proteins in dendrites (Dong et al. 2008). Supporting this interpretation, a recent study linked the enhancement of E-LTP by
proteasome inhibition to increases in the levels of the translation initiation factors eIF4E and eF1A (Dong et al. 2014). This study further suggested proteasome inhibition might impair the consolidation of L-LTP due to an accumulation of Paip2 and 4E-BP2, two translational repressors (Dong et al. 2014).

Another way in which the UPS may modulate LTP is in the regulation of brain-derived neurotropic factor (BDNF). Recent work showed that application of BDNF induced a rapid and transient decrease in proteasome activity in hippocampal synaptoneurosome fractions, and that the proteasome activator IU1 blocked the enhancement of E-LTP by BDNF (Santos et al. 2015). Similar to previous studies, the authors show that proteasome inhibitors block the expression of L-LTP and the effect of BDNF upon LTP consolidation (Santos et al. 2015). These results support earlier findings, and underscore the conclusion that the combination of both the degradation and synthesis of proteins is required to support the long term strengthening of synapses.

Besides the role of proteasome activity in LTP some studies reported direct modulation of E3 ligases and DUBs by synaptic activity. Upon AMPAR stimulation Nedd4-1 is redistributed to dendritic spines in a persistent and rapid manner while NMDAR stimulation selectively activates USP8. Therefore, Nedd4-1 and USP8 are regulated at synapses to control synaptic strength in an opposite fashion, regulating AMPAR ubiquitination and function. Moreover, bicuculline-induced downscaling of AMPARs and synaptic strength is accompanied by an increase in Nedd4-1 and a decrease in USP8 protein levels, respectively showing that E3 ligases and DUBs can be modulated during Hebbian and homeostatic plasticity (Scudder et al. 2014).

The induction of LTD at hippocampal CA1 synapses can be induced by either the weak stimulation of NMDARs or through stimulation of mGluR1/5, both of which elicit changes in synaptic efficacy through AMPAR endocytosis (Dudek & Bear 1992, Huber et al. 2001). Although they can occur at the same set of synapses, a major distinction is that mGluR-LTD requires new protein synthesis whereas NMDAR-LTD does not (Huber et al. 2000). Interestingly, the role of the UPS may also differentiate these forms of LTD. Multiple studies have shown that proteasome inhibitors reduce the AMPAR endocytosis and LTD downstream of NMDAR activation (Colledge et al. 2003, Citri et al. 2009, Patrick et al. 2003, Bingol & Schuman 2004). The role of the UPS in mGluR-LTD, however, is not as clear. Initial studies showed that incubation of hippocampal slices with the proteasome inhibitors MG132 or lactacystin resulted in impairment of mGluR-LTD (Hou et al. 2006). The authors proposed that the UPS sensitivity of mGluR-LTD was due to a breakdown of the

This article is protected by copyright. All rights reserved.
translation repressor fragile X mental retardation protein (FMRP), the protein lost in FXS (Hou et al. 2006). Recent work identifies Cdh1-APC as the E3 ligase responsible for FMRP degradation, and shows that mice lacking this ligase exhibit impaired mGluR-LTD (Huang et al. 2015). Along the same lines, another recent study showed that mGluR-LTD requires the rapid degradation of Arc/Arg3.1, a process that is counterbalanced by the RNA binding protein Sam68 (Klein et al. 2015). Together, these results support the idea that the UPS is required for the induction of mGluR-LTD.

In contrast to these results, other studies find that the UPS may be inhibitory for mGluR-LTD. A study directly comparing both forms of LTD showed that the proteasome inhibitors MG132 and lactacystin inhibit NMDAR-LTD but enhance mGluR-LTD.

Additionally, application of UBEI-41/PYR-41, a novel cell-permeable compound that irreversibly inhibits the E1 activating enzyme, was shown to enhance both the AMPAR internalization and LTD induced by the mGluR1/5 agonist DHPG (Citri et al. 2009). Other work shows that application of proteasome inhibitors enhances the transition from early-to late-phase LTD (Li et al. 2015). The seemingly dual nature of the UPS in LTD may be due to the regulation of different target proteins: those that are ubiquitinated to facilitate the induction of LTD and those that are broken down to limit the extent of LTD. Further investigation into the identity of these target proteins may clarify the opposing results regarding the function of the UPS during long-term plasticity.

Requirement of the UPS for learning and memory

The key role of proteasomal degradation in the expression of long-term synaptic plasticity has led to investigation of the UPS in learning and memory. A variety of different behavioral paradigms have been used to study the impact of synaptic plasticity on learning and memory formation. Using these paradigms, it has been shown that new mRNA translation facilitates memory formation by stabilizing molecular and synaptic changes during both consolidation (after learning) and reconsolidation (after memory reactivation) (reviewed in Jarome & Helmstetter 2014). In order to determine the role of the UPS in these aspects of memory formation, initial studies tested the effects of lactacystin infused into the hippocampus directly after training on an inhibitory avoidance (IA) learning task. The results showed that lactacystin infusion resulted in a full retrograde amnesia, similar to what is seen with protein synthesis inhibitors. Concomitantly, IA training resulted in an increase in protein ubiquitination and UPS activity in the hippocampus. These findings were the first to indicate that the UPS is crucial for the establishment of long-term memory in rats (Lopez-Salon et al.)

This article is protected by copyright. All rights reserved.
Since then, it has been demonstrated that the inhibition of the proteasome in multiple brain regions results in impairments in memory consolidation (Jarome & Helmstetter 2014).

The reconsolidation of memory is also sensitive to proteasome inhibition. Studies in the hippocampus showed that infusion of lactacystin blocked the extinction of fear conditioning and prevented the memory-impairing effect of the protein synthesis inhibitor anisomycin when given after retrieval, but did not affect memory formation when administered after training. Based on this, the authors proposed that the UPS is required for the destabilization of preexisting memories, allowing for modification by reconsolidation or extinction (Lee et al. 2008). However, this conflicts with more recent work showing that both consolidation and reconsolidation depend on protein synthesis and also on protein degradation by UPS (Figueiredo et al. 2015).

Nevertheless, there is a clear relationship between the requirement for new protein synthesis and UPS function in the acquisition of memory. Indeed, the time at which memory retention is sensitive to proteasome inhibitors is the same 3-4 hour post-acquisition time window that is sensitive to protein synthesis inhibitors (Bourtchouladze et al. 1998, Figueiredo et al. 2015). One possibility is that the degradation of translation inhibitors is needed to promote protein-synthesis dependent plasticity (Bingol & Sheng 2011). It is also possible that the non-proteolytic function of the UPS is required. Supporting this notion, the monoubiquitination of the translation regulator cytoplasmic polyadenylation element binding protein 3 (CPEB3) was shown to be critical for the consolidation of hippocampus dependent memories (Pavlopoulos et al. 2011). Further work is needed to understand the precise mechanisms by which the UPS contributes to the formation of new memories, and the potential regulation of protein synthesis.

**UPS mutations in ASD/ID**

The impact of proteasome dysfunction on human cognition has been an active field of research with respect to neurodegenerative disorders such as Alzheimer’s, Parkinson’s and Huntington’s disease. In these disorders it is widely accepted that proteasomal dysfunction is, at least in part, responsible for the formation of protein inclusions in specific neuronal subtypes that ultimately will cause neurodegeneration (Dantuma & Bott 2014). However, very little is known about the role of the UPS in neurodevelopmental disorders.

One notable exception to this is Angelman Syndrome (AS), a neurodevelopmental disorder caused by disruption of the E3 ligase Ube3a, which is characterized by ID, developmental delay, seizures, motor disruptions and an unusually positive demeanor.
This article is protected by copyright. All rights reserved.
Another interesting target of Ube3a is the mammalian target of rapamycin (mTOR) suppressor protein Tsc2 (Zheng et al. 2008). Recent work suggests that breakdown of Tsc2 by Ube3a may contribute to pathology in the Ube3a\(^{m/p+}\) mouse of AS, as treatment with the mTOR inhibitor rapamycin rescued motor deficits and abnormal dendritic branching (Sun et al. 2015). Despite these results, it is important to consider that the Ube3a substrates described so far contribute to only a subset of phenotypes associated with AS. It may be that the key Ube3a substrates have not yet been identified or, more likely, that the disruption of Ube3A leads to a multiplicative effect involving multiple downstream targets. Indeed, recent in vitro studies reveal that Ube3a promotes the ubiquitination of the 26S proteasome itself, suggesting that it can have a significant impact on overall UPS function (Jacobson et al. 2014).

In addition to UBE3A, mutations in over a dozen other UPS genes, mainly E3 ligases, have been identified as ASD/ID risk factors (Table 2). Large-scale studies have identified copy number variations (CNVs) that result in the deletion of the E3 ligase gene PARK2, and duplication in the E3 ligase genes RFWD2 and FBXO40 (Glessner et al. 2009). A more recent study focused on rare de novo CNVs in ASD families from the Simons Simplex Collection identified a duplication of the DUB gene USP7 (Sanders et al. 2011). The function of these genes in brain development and synaptic plasticity remains to be clarified. However, mutation of the Uba6 gene encoding an E1 ubiquitin activating ligase has recently been shown to result in phenotypes reminiscent of ASD mouse models, including increased dendritic spine density, altered levels of Shank3 and Ube3a, and behavioral deficits including anxiety, reduced social interaction and impaired communication (Lee et al. 2013, Lee et al. 2015). Additional studies should address the question of whether a phenotypes related to ASD/ID are common neurobiological consequences of UPS gene mutation.

**Problematic proteostasis in ASD/ID**

As large-scale genetic studies continue to identify novel mutations linked to ASD/ID, it is becoming more essential to understand the functional consequences of these mutations. Studies in mutant mouse models suggest that synaptic protein synthesis is dysregulated in several genetic causes of ASD/ID. Considering the clear functional connection between protein synthesis and breakdown, it is not unreasonable to suspect that changes in UPS function would result in similar pathology (Figure 1A). Evidence from the studies of UBE3A mutation illustrate that changes in UPS activity can lead to the multiple pathological changes
seen in ASD/ID. However, whether other UPS gene mutations lead to neuropathology reminiscent of ASD or ID remains to be determined.

Another important question is whether disorders that arise due to disruption of protein synthesis also result in changes in UPS function. In this case, pathological changes would not be due to changes in protein levels per se, but rather an increase in protein turnover (Figure 1B). This could impair synaptic function by increasing the ratio of new to old proteins, which could have a drastic impact on regulation and function. Alternatively, the compensatory change in the UPS could lead to aberrant breakdown of inappropriate target proteins, or altered ubiquitin-regulated trafficking of these targets. Teasing this apart would be of particular importance for guiding potential treatment strategies. Indeed, it is possible that the alterations in protein synthesis and compensatory changes in UPS function could contribute to different symptom domains of ASD/ID. Examination of the disruptions that occur in the collective process of proteostasis may therefore be an important next step in understanding the pathogenesis of ASD/ID.

ARRIVE guidelines have been followed: Yes
=> if No, skip complete sentence
=> if Yes, insert "All experiments were conducted in compliance with the ARRIVE guidelines."

Conflicts of interest: none
=> if 'none', insert "The authors have no conflict of interest to declare."
=> otherwise insert info unless it is already included

Acknowledgements:
The authors are grateful for support from the Wellcome Trust and Royal Society (Sir Henry Dale fellowship 104116/Z/14/Z), as well as the Medical Research Council (MRC MRC MR/M006336/1).
### Table 1. ASD/ID mutations in genes encoding regulators of mRNA translation.

Several genetic mutations that confer risk for developing ASD or ID are found in genes related to protein synthesis. These include regulators of the Ras-MAPK and mTOR signalling pathways that control mRNA translation at synapses. Synaptic plasticity and learning phenotypes are seen in mouse models of many of these disorders (ND = not determined).

| GENE | DISORDER | FUNCTION | PHENOTYPES | REFERENCES |
|------|----------|----------|------------|------------|
| FMR1 | Fragile X syndrome (ID, ASD) | Translation repressor | Enhanced mGluR-LTD, Impaired LTP, Impaired learning and memory | (reviewed in (Damell & Klann 2013, Bhakar et al. 2012)) |
| CYFIP1 | ASD | Translation repressor | Enhanced mGluR-LTD, Enhanced extinction of inhibitory avoidance | (Bozdagi et al. 2012, Wang et al. 2015, Nishimura et al. 2007) |
| SYNGAP1 | ID, ASD | Ras-MAPK negative regulator | Enhanced mGluR-LTD, Impaired LTP, Learning and memory deficits | (Komiyama et al. 2002, Barnes et al. 2015, Jeyabalan & Clement 2016) |
| NF1 | Neurofibromatosis type 1 (ID) | Ras-MAPK negative regulator | Impaired LTP, Abnormal spatial learning | (Costa et al. 2002, Silva et al. 1997, Sanders et al. 2011) |
| TSC1/2 | Tuberous sclerosis complex (ID, ASD) | Rheb-mTOR negative regulator | Impaired mGluR-LTD, Abnormal LTP, Learning and memory deficits | (Auerbach et al. 2011, Ehninger et al. 2008) |
| PTEN | Cowden syndrome (ID, ASD) | PI3K-mTOR negative regulator | Impaired LTP and LTD, Impaired spatial memory | (Butler et al. 2005, Kwon et al. 2006, Sperow et al. 2012) |
| RPL10 | ID, ASD | Ribosomal protein | ND | (Klauck et al. 2006, Thevenon et al. 2015, Brooks et al. 2014) |
| RPS6KA2 | ASD | Ribosomal p90 S6 kinase (MAPK pathway) | ND | (Marshall et al. 2008) |
| RPS6KA3 | ID, ASD | Ribosomal p90 S6 kinase (MAPK pathway) | Impaired spatial learning | (Matsumoto et al. 2013, O’Roak et al. 2012, Zeniou et al. 2002, Zeniou-Meyer et al. 2010) |
| EIF4E | ASD | Initiation factor | Enhanced mGluR-LTD, Impaired social behaviour, Repetitive behaviours | (Neves-Pereira et al. 2009, Kelleher et al. 2012, Gkogkas et al. 2013, Santini et al. 2013) |
| EEF1A2 | ASD/ID | Elongation factor | ND | (Nakajima et al. 2015, de Ligt et al. 2012) |
| RBMS3 | ASD | RNA binding protein | ND | (O’Roak et al. 2011) |
| HRAS | Costello syndrome (ASD) | Ras GTPase | Enhanced LTP, Enhanced spatial learning, Enhanced fear conditioning | (Herault et al. 1993, Comings et al. 1996, Herault et al. 1995, Alfieri et al. 2014, Kelleher et al. 2012, Manabe et al. 2000, Kushner et al. 2005) |
| BRAF | Costello syndrome/Noonan syndrome (ID, ASD) | MAPK activator | Impaired LTP, Impaired spatial learning, Impaired contextual discrimination | (Alfieri et al. 2014, Chen et al. 2006) |
| PTPN11 | Noonan syndrome (ID) | Ras pathway regulator | Impaired LTP, Impaired spatial learning | (Tartaglia et al. 2001, Deciphering Developmental Disorders 2015, Krumm et al. 2015, Lee et al. 2014) |
| SOS1 | Noonan syndrome (ID) | Ras pathway regulator | ND | (Tartaglia et al. 2007, Roberts et al. 2007) |
Table 2. ASD/ID risk factors in ubiquitin proteasome system (UPS) genes. Mutations in several UPS genes have been identified as risk factors for ASD or ID. These include multiple genes encoding ubiquitin E3 ligases and de-ubiquitinases that regulate protein degradation. With the exception of mutations in UBE3A, the functional consequences of these gene mutations have not been determined (ND).

Figure 1. Dysregulation of protein synthesis or degradation results in unbalanced proteostasis.

(A) Mutations in several genes that regulate mRNA translation and ubiquitin proteasome system function have been implicated in ASD/ID (see Tables 1-2). This includes regulators of translation control signalling pathways (TSC1/2, NF1, PTEN, SYNGAP1, PTPN11, HRAS), protein synthesis regulators (FMR1, CYFIP1, EIF4E, RBMS3, RPL10, RPSS6KA2,3), E3 ubiquitin ligases (UBE3A,B,C, CULLIN3,7, PARK2, FBXO40, RFWD2, HERC2, HECW2, HUWE1), de-ubiquitinases (USP7, USP45, USP9Y), and the proteasome protein PSMD10. The proteins encoded by these genes collectively contribute to the proteostasis involved in synaptic plasticity. (B) The pathogenic excess in synaptic protein synthesis observed in

This article is protected by copyright. All rights reserved.
animal models of ASD/ID (i.e., \textit{FMR1}, \textit{SYNGAP1}, and \textit{CYFIP1}) may lead to a homeostatic increase in UPS function. Similarly, mutations in E3 ligases, such as Ube3A, that decrease UPS function may result in a compensatory decrease in protein synthesis. In both cases, the imbalance in proteostasis would lead to a change in the composition of new versus old plasticity related proteins (PrPs) in the synaptic proteome without necessarily affecting overall protein levels.

References:
Alfieri, P., Caciolo, C., Piccini, G. et al. (2015) Behavioral phenotype in Costello syndrome with atypical mutation: a case report. \textit{Am J Med Genet B Neuropsychiatr Genet}, \textbf{168B}, 66-71.
Alfieri, P., Piccini, G., Caciolo, C. et al. (2014) Behavioral profile in RASopathies. \textit{Am J Med Genet A}, \textbf{164A}, 934-942.
Auerbach, B. D., Osterweil, E. K. and Bear, M. F. (2011) Mutations causing syndromic autism define an axis of synaptic pathophysiology. \textit{Nature}, \textbf{480}, 63-68.
Barnes, S. A., Wijetunge, L. S., Jackson, A. D. et al. (2015) Convergence of Hippocampal Pathophysiology in Syngap+/- and Fmr1-/y Mice. \textit{J Neurosci}, \textbf{35}, 15073-15081.
Basel-Vanagaite, L., Dallapiccola, B., Ramirez-Solis, R. et al. (2012) Deficiency for the ubiquitin ligase UBE3B in a blepharophimosis-ptosis-intellectual-disability syndrome. \textit{Am J Hum Genet}, \textbf{91}, 998-1010.
Bateup, H. S., Takasaki, K. T., Saulnier, J. L., Denefrio, C. L. and Sabatini, B. L. (2011) Loss of Tsc1 in vivo impairs hippocampal mGluR-LTD and increases excitatory synaptic function. \textit{J Neurosci}, \textbf{31}, 8862-8869.
Bhakar, A. L., Dolen, G. and Bear, M. F. (2012) The Pathophysiology of Fragile X (and What It Teaches Us about Synapses). \textit{Annual review of neuroscience}, \textbf{35}, 417-443.
Bingol, B. and Schuman, E. M. (2004) A proteasome-sensitive connection between PSD-95 and GluR1 endocytosis. \textit{Neuropharmacology}, \textbf{47}, 755-763.
Bingol, B. and Schuman, E. M. (2006) Activity-dependent dynamics and sequestration of proteasomes in dendritic spines. \textit{Nature}, \textbf{441}, 1144-1148.
Bingol, B. and Sheng, M. (2011) Deconstruction for reconstruction: the role of proteolysis in neural plasticity and disease. \textit{Neuron}, \textbf{69}, 22-32.
Bingol, B., Wang, C. F., Arnott, D., Cheng, D., Peng, J. and Sheng, M. (2010) Autophosphorylated CaMKIIalpha acts as a scaffold to recruit proteasomes to dendritic spines. \textit{Cell}, \textbf{140}, 567-578.
Bourtchouladze, R., Abel, T., Berman, N., Gordon, R., Lapidus, K. and Kandel, E. R. (1998) Different training procedures recruit either one or two critical periods for contextual memory consolidation, each of which requires protein synthesis and PKA. \textit{Learn Mem}, \textbf{5}, 365-374.
Bozdagi, O., Sakurai, T., Dorr, N., Pilorge, M., Takahashi, N. and Buxbaum, J. D. (2012) Haploinsufficiency of Cyfip1 produces fragile X-like phenotypes in mice. \textit{PLoS One}, \textbf{7}, e42422.
Brooks, S. S., Wall, A. L., Golzio, C. et al. (2014) A novel ribosomopathy caused by dysfunction of RPL10 disrupts neurodevelopment and causes X-linked microcephaly in humans. \textit{Genetics}, \textbf{198}, 723-733.

This article is protected by copyright. All rights reserved.
Butler, M. G., Dasouki, M. J., Zhou, X. P. et al. (2005) Subset of individuals with autism spectrum disorders and extreme macrocephaly associated with germline PTEN tumour suppressor gene mutations. *J Med Genet*, **42**, 318-321.

Chahrour, M. H., Yu, T. W., Lim, E. T. et al. (2012) Whole-exome sequencing and homozygosity analysis implicate depolarization-regulated neuronal genes in autism. *PloS Genet*, **8**, e1002635.

Chen, A. P., Ohno, M., Giese, K. P., Kuhn, R., Chen, R. L. and Silva, A. J. (2006) Forebrain-specific knockout of B-raf kinase leads to deficits in hippocampal long-term potentiation, learning, and memory. *J Neurosci Res*, **83**, 318-321.

Citri, A., Soler-Llavina, G., Bhattacharyya, S. and Malenka, R. C. (2009) N-methyl-D-aspartate receptor- and metabotropic glutamate receptor-dependent long-term depression are differentially regulated by the ubiquitin-proteasome system. *Eur J Neurosci*, **30**, 1443-1450.

Codina-Sola, M., Rodriguez-Santiago, B., Homs, A. et al. (2015) Integrated analysis of whole-exome sequencing and transcriptome profiling in males with autism spectrum disorders. *Mol Autism*, **6**, 21.

Colledge, M., Snyder, E. M., Crozier, R. A., Soderling, J. A., Jin, Y., Langeberg, L. K., Lu, H., Bear, M. F. and Scott, J. D. (2003) Ubiquitination regulates PSD-95 degradation and AMPA receptor surface expression. *Neuron*, **40**, 595-607.

Comings, D. E., Wu, S., Chiu, C., Muhleman, D. and Sverd, J. (1996) Studies of the c-Harvey-Ras gene in psychiatric disorders. *Psychiatry Res*, **63**, 25-32.

Cooper, E. M., Hudson, A. W., Amos, J., Wagstaff, J. and Howley, P. M. (2004) Biochemical analysis of Angelman syndrome-associated mutations in the E3 ubiquitin ligase E6-associated protein. *J Biol Chem*, **279**, 41208-41217.

Costa, R. M., Federov, N. B., Kogan, J. H., Murphy, G. G., Stern, J., Ohno, M., Kucherlapati, R., Jacks, T. and Silva, A. J. (2002) Mechanism for the learning deficits in a mouse model of neurofibromatosis type 1. *Nature*, **415**, 526-530.

Dantuma, N. P. and Bott, L. C. (2014) The ubiquitin-proteasome system in neurodegenerative diseases: precipitating factor, yet part of the solution. *Front Mol Neurosci*, **7**, 70.

Darnell, J. C. and Klann, E. (2013) The translation of translational control by FMRP: therapeutic targets for FXS. *Nat Neurosci*, **16**, 1530-1536.

de Ligt, J., Willemsen, M. H., van Bon, B. W. et al. (2012) Diagnostic exome sequencing in persons with severe intellectual disability. *N Engl J Med*, **367**, 1921-1929.

Deciphering Developmental Disorders, S. (2015) Large-scale discovery of novel genetic causes of developmental disorders. *Nature*, **519**, 223-228.

Djakovic, S. N., Schwarz, L. A., Barylko, B., DeMartino, G. N. and Patrick, G. N. (2009) Regulation of the proteasome by neuronal activity and calcium/calmodulin-dependent protein kinase II. *J Biol Chem*, **284**, 26655-26665.

Dolen, G., Osterweil, E., Rao, B. S., Smith, G. B., Auerbach, B. D., Chattarji, S. and Bear, M. F. (2007) Correction of fragile X syndrome in mice. *Neuron*, **56**, 955-962.

Dong, C., Bach, S. V., Haynes, K. A. and Hegde, A. N. (2014) Proteasome modulates positive and negative translational regulators in long-term synaptic plasticity. *J Neurosci*, **34**, 3171-3182.

Dong, C., Upadhya, S. C., Ding, L., Smith, T. K. and Hegde, A. N. (2008) Proteasome inhibition enhances the induction and impairs the maintenance of late-phase long-term potentiation. *Learn Mem*, **15**, 335-347.
Dudek, S. M. and Bear, M. F. (1992) Homosynaptic long-term depression in area CA1 of hippocampus and effects of N-methyl-D-aspartate receptor blockade. Proc Natl Acad Sci USA, 89, 4363-4367.

Ehlers, M. D. (2003) Activity level controls postsynaptic composition and signaling via the ubiquitin-proteasome system. Nat Neurosci, 6, 231-242.

Ehninger, D., Han, S., Shilyansky, C., Zhou, Y., Li, W., Kwiatkowski, D. J., Ramesh, V. and Silva, A. J. (2008) Reversal of learning deficits in a Tsc2+/− mouse model of tuberous sclerosis. Nat Med, 14, 843-848.

Ferreira, J. S., Schmidt, J., Rio, P., Aguas, R., Rooyakkers, A., Li, K. W., Smit, A. B., Craig, A. M. and Carvalho, A. L. (2015) GluN2B-Containing NMDA Receptors Regulate AMPA Receptor Traffic through Anchoring of the Synaptic Proteasome. J Neurosci, 35, 8462-8479.

Figueiredo, L. S., Dornelles, A. S., Petry, F. S., Falavigna, L., Dargel, V. A., Kobe, L. M., Aguzzoli, C., Roesler, R. and Schroder, N. (2015) Two waves of proteasome-dependent protein degradation in the hippocampus are required for recognition memory consolidation. Neurobiol Learn Mem, 120, 1-6.

Flex, E., Ciolfi, A., Caputo, V. et al. (2013) Loss of function of the E3 ubiquitin-protein ligase UBE3B causes Kaufman oculocerebrofacial syndrome. J Med Genet, 50, 493-499.

Fonseca, R., Vabulas, R. M., Hartl, F. U., Bonhoeffer, T. and Nagerl, U. V. (2006) A balance of protein synthesis and proteasome-dependent degradation determines the maintenance of LTP. Neuron, 52, 239-245.

Froyen, G., Belet, S., Martinez, F. et al. (2012) Copy-number gains of HUWE1 due to replication- and recombination-based rearrangements. Am J Hum Genet, 91, 252-264.

Froyen, G., Corbett, M., Vandewalle, J. et al. (2008) Submicroscopic duplications of the hydroxysteroid dehydrogenase HSD17B10 and the E3 ubiquitin ligase HUWE1 are associated with mental retardation. Am J Hum Genet, 82, 432-443.

Fu, A. K., Hung, K. W., Fu, W. Y., Shen, C., Chen, Y., Xia, J., Lai, K. O. and Ip, N. Y. (2011) APC(Cdh1) mediates EphA4-dependent downregulation of AMPA receptors in homeostatic plasticity. Nat Neurosci, 14, 181-189.

Gkogkas, C. G., Khoutorsky, A., Ran, I. et al. (2013) Autism-related deficits via dysregulated eIF4E-dependent translational control. Nature, 493, 371-377.

Glessner, J. T., Wang, K., Cai, G. et al. (2009) Autism genome-wide copy number variation reveals ubiquitin and neuronal genes. Nature, 459, 569-573.

Greer, P. L., Hanayama, R., Bloodgood, B. L. et al. (2010) The Angelman Syndrome protein Ube3A regulates synapse development by ubiquitinating arc. Cell, 140, 704-716.

Hamilton, A. M., Oh, W. C., Vega-Ramirez, H., Stein, I. S., Hell, J. W., Patrick, G. N. and Zito, K. (2012) Activity-dependent growth of new dendritic spines is regulated by the proteasome. Neuron, 74, 1023-1030.

Hamilton, A. M. and Zito, K. (2013) Breaking it down: the ubiquitin proteasome system in neuronal morphogenesis. Neural plasticity, 2013, 196848.

Hanus, C. and Schuman, E. M. (2013) Proteostasis in complex dendrites. Nat Rev Neurosci, 14, 638-648.

Harlalka, G. V., Baple, E. L., Cross, H. et al. (2013) Mutation of HERC2 causes developmental delay with Angelman-like features. J Med Genet, 50, 65-73.

Hegde, A. N. (2010) The ubiquitin-proteasome pathway and synaptic plasticity. Learn Mem, 17, 314-327.
Hegde, A. N., Inokuchi, K., Pei, W., Casadio, A., Ghirardi, M., Chain, D. G., Martin, K. C., Kandel, E. R. and Schwartz, J. H. (1997) Ubiquitin C-terminal hydrolase is an immediate-early gene essential for long-term facilitation in Aplysia. Cell, 89, 115-126.

Herault, J., Perrot, A., Barthelemy, C. et al. (1993) Possible association of c-Harvey-Ras-1 (HRAS-1) marker with autism. Psychiatry Res, 46, 261-267.

Herault, J., Petit, E., Martineau, J. et al. (1995) Autism and genetics: clinical approach and association study with two markers of HRAS gene. Am J Med Genet, 60, 276-281.

Hou, L., Antion, M. D., Hu, D., Spencer, C. M., Paylor, R. and Klann, E. (2006) Dynamic translational and proteasomal regulation of fragile X mental retardation protein controls mGluR-dependent long-term depression. Neuron, 51, 441-454.

Huang, J., Ikeuchi, Y., Malumbres, M. and Bonni, A. (2015) A Cdh1-APC/FMRP Ubiquitin Signaling Link Drives mGluR-Dependent Synaptic Plasticity in the Mammalian Brain. Neuron, 86, 726-739.

Huber, K. M., Kayser, M. S. and Bear, M. F. (2000) Role for rapid dendritic protein synthesis in hippocampal mGluR-dependent long-term depression. Science, 288, 1254-1257.

Huber, K. M., Roder, J. C. and Bear, M. F. (2001) Chemical induction of mGluR5- and protein synthesis--dependent long-term depression in hippocampal area CA1. J Neurophysiol, 86, 321-325.

Huo, Y., Khatri, N., Hou, Q., Gilbert, J., Wang, G. and Man, H. Y. (2015) The deubiquitinating enzyme USP46 regulates AMPA receptor ubiquitination and trafficking. J Neurochem, 134, 1067-1080.

Jacobson, A. D., MacFadden, A., Wu, Z., Peng, J. and Liu, C. W. (2014) Autoregulation of the 26S proteasome by in situ ubiquitination. Mol Biol Cell, 25, 1824-1835.

Jarome, T. J. and Helmstetter, F. J. (2014) Protein degradation and protein synthesis in long-term memory formation. Front Mol Neurosci, 7, 61.

Jeyabalan, N. and Clement, J. P. (2016) SYNGAP1: Mind the Gap. Front Cell Neurosci, 10, 32.

Jiang, Y. H., Armstrong, D., Albrecht, U., Atkins, C. M., Noebels, J. L., Eichele, G., Sweatt, J. D. and Beaudet, A. L. (1998) Mutation of the Angelman ubiquitin ligase in mice causes increased cytoplasmic p53 and deficits of contextual learning and long-term potentiation. Neuron, 21, 799-811.

Jurd, R., Thornton, C., Wang, J., Luong, K., Phamluong, K., Kharazia, V., Gibb, S. L. and Ron, D. (2008) Mind bomb-2 is an E3 ligase that ubiquitinates the N-methyl-D-aspartate receptor NR2B subunit in a phosphorylation-dependent manner. J Biol Chem, 283, 301-310.

Karpova, A., Mikhailova, M., Thomas, U., Knopfel, T. and Behnisch, T. (2006) Involvement of protein synthesis and degradation in long-term potentiation of Schaffer collateral CA1 synapses. J Neurosci, 26, 4949-4955.

Kato, A., Rouach, N., Nicoll, R. A. and Bredt, D. S. (2005) Activity-dependent NMDA receptor degradation mediated by retrotranslocation and ubiquitination. Proc Natl Acad Sci USA, 102, 5600-5605.

Kelleher, R. J., 3rd and Bear, M. F. (2008) The autistic neuron: troubled translation? Cell, 135, 401-406.

Kelleher, R. J., 3rd, Geigenmuller, U., Hovhannisyan, H., Trautman, E., Pinard, R., Rathmell, B., Carpenter, R. and Margulies, D. (2012) High-throughput sequencing of mGluR signaling pathway genes reveals enrichment of rare variants in autism. PLoS One, 7, e35003.

This article is protected by copyright. All rights reserved.
Kishino, T., Lalande, M. and Wagstaff, J. (1997) UBE3A/E6-AP mutations cause Angelman syndrome. *Nat Genet*, **15**, 70-73.

Klauck, S. M., Felder, B., Kolb-Kokocinski, A. et al. (2006) Mutations in the ribosomal protein gene RPL10 suggest a novel modulating disease mechanism for autism. *Mol Psychiatry*, **11**, 1073-1084.

Klein, M. E., Castillo, P. E. and Jordan, B. A. (2015) Coordination between Translation and Degradation Regulates Inducibility of mGluR-LTD. *Cell Rep*.

Komiyama, N. H., Watabe, A. M., Carlisle, H. J. et al. (2002) SynGAP regulates ERK/MAPK signaling, synaptic plasticity, and learning in the complex with postsynaptic density 95 and NMDA receptor. *J Neurosci*, **22**, 9721-9732.

Krab, L. C., Goorden, S. M. and Elgersma, Y. (2008) Oncogenes on my mind: ERK and MTOR signaling in cognitive diseases. *Trends Genet*, **24**, 498-510.

Krumm, N., Turner, T. N., Baker, C. et al. (2015) Excess of rare, inherited truncating mutations in autism. *Nat Genet*, **47**, 582-588.

Kuhnle, S., Mothes, B., Matentzoglu, K. and Scheffner, M. (2013) Role of the ubiquitin ligase E6AP/UBE3A in controlling levels of the synaptic protein Arc. *Proc Natl Acad Sci U S A*, **110**, 8888-8893.

Kushner, S. A., Elgersma, Y., Murphy, G. G. et al. (2005) Modulation of presynaptic plasticity and learning by the H-ras/extracellular signal-regulated kinase/synapsin I signaling pathway. *J Neurosci*, **25**, 9721-9734.

Kwon, C. H., Luikart, B. W., Powell, C. M., Zhou, J., Matheny, S. A., Zhang, W., Li, Y., Baker, S. J. and Parada, L. F. (2006) Pten regulates neuronal arborization and social interaction in mice. *Neuron*, **50**, 377-388.

LaSalle, J. M., Reiter, L. T. and Chamberlain, S. J. (2015) Epigenetic regulation of UBE3A and roles in human neurodevelopmental disorders. *Epigenomics*, **7**, 1213-1228.

Lee, J. Y., Kwak, M. and Lee, P. C. (2015) Impairment of social behavior and communication in mice lacking the Uba6-dependent ubiquitin activation system. *Behav Brain Res*, **281**, 78-85.

Lee, P. C., Dodart, J. C., Aron, L., Finley, L. W., Bronson, R. T., Haigis, M. C., Yankner, B. A. and Harper, J. W. (2013) Altered social behavior and neuronal development in mice lacking the Uba6-Use1 ubiquitin transfer system. *Mol Cell*, **50**, 172-184.

Lee, S. H., Choi, J. H., Lee, N. et al. (2008) Synaptic protein degradation underlies destabilization of retrieved fear memory. *Science*, **319**, 1253-1256.

Lee, Y. S., Ehninger, D., Zhou, M. et al. (2014) Mechanism and treatment for learning and memory deficits in mouse models of Noonan syndrome. *Nat Neurosci*, **17**, 1736-1743.

Li, Q., Korte, M. and Sajikumar, S. (2015) Ubiquitin-Proteasome System Inhibition Promotes Long-Term Depression and Synaptic Tagging/Capture. *Cerebral cortex*.

Lin, A. W. and Man, H. Y. (2013) Ubiquitination of neurotransmitter receptors and postsynaptic scaffolding proteins. *Neural plasticity*, **2013**, 432057.

Lopez-Salon, M., Alonso, M., Vianna, M. R., Viola, H., Mello e Souza, T., Izquierdo, I., Pasquini, J. M. and Medina, J. H. (2001) The ubiquitin-proteasome cascade is required for mammalian long-term memory formation. *Eur J Neurosci*, **14**, 1820-1826.

Mabb, A. M., Je, H. S., Wall, M. J., Robinson, C. G., Larsen, R. S., Qiang, Y., Correa, S. A. and Ehlers, M. D. (2014) Triad3A regulates synaptic strength by ubiquitination of Arc. *Neuron*, **82**, 1299-1316.
Mabb, A. M., Judson, M. C., Zylka, M. J. and Philpot, B. D. (2011) Angelman syndrome: insights into genomic imprinting and neurodevelopmental phenotypes. *Trends in neurosciences*, **34**, 293-303.

Manabe, T., Aiba, A., Yamada, A., Ichise, T., Sakagami, H., Kondo, H. and Katsuki, M. (2000) Regulation of long-term potentiation by H-Ras through NMDA receptor phosphorylation. *J Neurosci*, **20**, 2504-2511.

Mandel-Brehm, C., Salogiannis, J., Dhamne, S. C., Rotenberg, A. and Greenberg, M. E. (2015) Seizure-like activity in a juvenile Angelman syndrome mouse model is attenuated by reducing Arc expression. *Proc Natl Acad Sci U S A*, **112**, 5129-5134.

Marshall, C. R., Noor, A., Vincent, J. B. et al. (2008) Structural variation of chromosomes in autism spectrum disorder. *Am J Hum Genet*, **82**, 477-488.

Matsumoto, A., Kuwajima, M., Miyake, K., Kojima, N., Nakashima, N., Jnimo, E. F., Kubota, T., Momoi, M. Y. and Yamagata, T. (2013) An Xp22.12 microduplication including RPS6KA3 identified in a family with variably affected intellectual and behavioral disabilities. *J Hum Genet*, **58**, 755-757.

Matsuura, T., Sutcliffe, J. S., Fang, P., Galjaard, R. J., Jiang, Y. H., Benton, C. S., Rommens, J. M. and Beaudet, A. L. (1997) De novo truncating mutations in E6-AP ubiquitin-protein ligase gene (UBE3A) in Angelman syndrome. *Nat Genet*, **15**, 74-77.

Moriyoshi, K., Iijima, K., Fujii, H., Ito, H., Cho, Y. and Nakanishi, S. (2004) Seven in absentia homolog 1A mediates ubiquitination and degradation of group 1 metabotropic glutamate receptors. *Proc Natl Acad Sci U S A*, **101**, 8614-8619.

Na, C. H., Jones, D. R., Yang, Y., Wang, X., Xu, Y. and Peng, J. (2012) Synaptic protein ubiquitination in rat brain revealed by antibody-based ubiquitome analysis. *J Proteome Res*, **11**, 4722-4732.

Najmabadi, H., Hu, H., Garshasbi, M. et al. (2011) Deep sequencing reveals 50 novel genes for recessive cognitive disorders. *Nature*, **478**, 57-63.

Nakajima, J., Okamoto, N., Tohyama, J. et al. (2015) De novo EEF1A2 mutations in patients with characteristic facial features, intellectual disability, autistic behaviors and epilepsy. *Clin Genet*, **87**, 356-361.

Nava, C., Lamari, F., Heron, D. et al. (2012) Analysis of the chromosome X exome in patients with autism spectrum disorders identified novel candidate genes, including TMLHE. *Transl Psychiatry*, **2**, e179.

Neves-Pereira, M., Muller, B., Massie, D., Williams, J. H., O'Brien, P. C., Hughes, A., Shen, S. B., Clair, D. S. and Miedzybrodzka, Z. (2009) Deregulation of EIF4E: a novel mechanism for autism. *J Med Genet*, **46**, 759-765.

Nishimura, Y., Martin, C. L., Vazquez-Lopez, A. et al. (2007) Genome-wide expression profiling of lymphoblastoid cell lines distinguishes different forms of autism and reveals shared pathways. *Hum Mol Genet*, **16**, 1682-1698.

O’Roak, B. J., Deriiziotis, P., Lee, C. et al. (2011) Exome sequencing in sporadic autism spectrum disorders identifies severe de novo mutations. *Nat Genet*, **43**, 585-589.

O’Roak, B. J., Vives, L., Girirajan, S. et al. (2012) Sporadic autism exomes reveal a highly interconnected protein network of de novo mutations. *Nature*, **485**, 246-250.

Osterweil, E. K., Krueger, D. D., Reinhold, K. and Bear, M. F. (2010) Hypersensitivity to mGluR5 and ERK1/2 leads to excessive protein synthesis in the hippocampus of a mouse model of fragile X syndrome. *J Neurosci*, **30**, 15616-15627.

Pak, D. T., Yang, S., Rudolph-Correia, S., Kim, E. and Sheng, M. (2001) Regulation of dendritic spine morphology by SPAR, a PSD-95-associated RapGAP. *Neuron*, **31**, 289-303.

This article is protected by copyright. All rights reserved.
Patrick, G. N., Bingol, B., Weld, H. A. and Schuman, E. M. (2003) Ubiquitin-mediated proteasome activity is required for agonist-induced endocytosis of GluRs. *Current biology : CB*, **13**, 2073-2081.

Pavlopoulos, E., Trifilieff, P., Chevaleyre, V., Fioriti, L., Zairis, S., Pagano, A., Malleret, G. and Kandel, E. R. (2011) Neuralized1 activates CPEB3: a function for nonproteolytic ubiquitin in synaptic plasticity and memory storage. *Cell*, **147**, 1369-1383.

Pignatelli, M., Piccinin, S., Molinaro, G. et al. (2014) Changes in mGlu5 receptor-dependent synaptic plasticity and coupling to homer proteins in the hippocampus of Ube3A hemizygous mice modeling angelman syndrome. *J Neurosci*, **34**, 4558-4566.

Piton, A., Gauthier, J., Hamdan, F. F. et al. (2011) Systematic resequencing of X-chromosome synaptic genes in autism spectrum disorder and schizophrenia. *Mol Psychiatry*, **16**, 867-880.

Puffenberger, E. G., Jinks, R. N., Wang, H. et al. (2012) A homozygous missense mutation in HERC2 associated with global developmental delay and autism spectrum disorder. *Hum Mutat*, **33**, 1639-1646.

Rezvani, K., Baalman, K., Teng, Y., Mee, M. P., Dawson, S. P., Wang, H., De Biasi, M. and Mayer, R. J. (2012) Proteasomal degradation of the metabotropic glutamate receptor 1alpha is mediated by Homer-3 via the proteasomal S8 ATPase: Signal transduction and synaptic transmission. *J Neurochem*, **122**, 24-37.

Roberts, A. E., Araki, T., Swanson, K. D. et al. (2007) Germline gain-of-function mutations in SOS1 cause Noonan syndrome. *Nat Genet*, **39**, 70-74.

Salyakina, D., Cukier, H. N., Lee, J. M. et al. (2011) Copy number variants in extended autism spectrum disorder families reveal candidates potentially involved in autism risk. *PLoS One*, **6**, e26049.

Sanders, S. J., Ercan-Sencicek, A. G., Hus, V. et al. (2011) Multiple recurrent de novo CNVs, including duplications of the 7q11.23 Williams syndrome region, are strongly associated with autism. *Neuron*, **70**, 863-885.

Santini, E., Huynh, T. N., MacAskill, A. F., Carter, A. G., Pierre, P., Ruggero, D., Kaphzan, H. and Klann, E. (2013) Exaggerated translation causes synaptic and behavioural aberrations associated with autism. *Nature*, **493**, 411-415.

Santos, A. R., Mele, M., Vaz, S. H. et al. (2015) Differential role of the proteasome in the early and late phases of BDNF-induced facilitation of LTP. *J Neurosci*, **35**, 3319-3329.

Schmidt, M. and Finley, D. (2014) Regulation of proteasome activity in health and disease. *Biochim Biophys Acta*, **1843**, 13-25.

Schwarz, L. A., Hall, B. J. and Patrick, G. N. (2010) Activity-dependent ubiquitination of GluA1 mediates a distinct AMPA receptor endocytosis and sorting pathway. *J Neurosci*, **30**, 16718-16729.

Scudder, S. L., Goo, M. S., Cartier, A. E., Molteni, A., Schwarz, L. A., Wright, R. and Patrick, G. N. (2014) Synaptic strength is bidirectionally controlled by opposing activity-dependent regulation of Nedd4-1 and USP8. *J Neurosci*, **34**, 16637-16649.

Silva, A. J., Frankland, P. W., Marowitz, Z., Friedman, E., Laszlo, G. S., Ciuffi, D., Jacks, T. and Bourchuladze, R. (1997) A mouse model for the learning and memory deficits associated with neurofibromatosis type I. *Nat Genet*, **15**, 281-284.

Smith, S. E., Zhou, Y. D., Zhang, G., Jin, Z., Stoppel, D. C. and Anderson, M. P. (2011) Increased gene dosage of Ube3a results in autism traits and decreased glutamate synaptic transmission in mice. *Sci Transl Med*, **3**, 103ra197.
Sperow, M., Berry, R. B., Bayazitov, I. T., Zhu, G., Baker, S. J. and Zakharenko, S. S. (2012) Phosphatase and tensin homologue (PTEN) regulates synaptic plasticity independently of its effect on neuronal morphology and migration. *J Physiol*, **590**, 777-792.

Sun, J., Liu, Y., Moreno, S., Baudry, M. and Bi, X. (2015) Imbalanced mechanistic target of rapamycin C1 and C2 activity in the cerebellum of Angelman syndrome mice impairs motor function. *J Neurosci*, **35**, 4706-4718.

Suryadinata, R., Roesley, S. N., Yang, G. and Sarcevic, B. (2014) Mechanisms of generating polyubiquitin chains of different topology. *Cells*, **3**, 674-689.

Tai, H. C., Besche, H., Goldberg, A. L. and Schuman, E. M. (2010) Characterization of the Brain 26S Proteasome and its Interacting Proteins. *Front Mol Neurosci*, **3**.

Tartaglia, M., Mehler, E. L., Goldberg, R. et al. (2001) Mutations in PTPN11, encoding the protein tyrosine phosphatase SHP-2, cause Noonan syndrome. *Nat Genet*, **29**, 465-468.

Tartaglia, M., Pennacchio, L. A., Zhao, C. et al. (2007) Gain-of-function SOS1 mutations cause a distinctive form of Noonan syndrome. *Nat Genet*, **39**, 75-79.

Thevenon, J., Michot, C., Bole, C. et al. (2015) RPL10 mutation segregating in a family with X-linked syndromic Intellectual Disability. *Am J Med Genet A*, **167A**, 1908-1912.

Vandewalle, J., Langen, M., Zschatzsch, M. et al. (2013) Ubiquitin ligase HUWE1 regulates axon branching through the Wnt/beta-catenin pathway in a Drosophila model for intellectual disability. *PLoS One*, **8**, e81791.

Wang, J., Tao, Y., Song, F., Sun, Y., Ott, J. and Saffen, D. (2015) Common Regulatory Variants of CYFIP1 Contribute to Susceptibility for Autism Spectrum Disorder (ASD) and Classical Autism. *Ann Hum Genet*.

Weissman, A. M. (2001) Themes and variations on ubiquitylation. *Nature reviews. Molecular cell biology*, **2**, 169-178.

Widagdo, J., Chai, Y. J., Ridder, M. C., Chau, Y. Q., Johnson, R. C., Sah, P., Huganir, R. L. and Anggono, V. (2015) Activity-Dependent Ubiquitination of GluA1 and GluA2 Regulates AMPA Receptor Intracellular Sorting and Degradation. *Cell Rep*.

Yi, J. J., Berrios, J., Newbern, J. M., Snider, W. D., Philpot, B. D., Hahn, K. M. and Zylka, M. J. (2015) An Autism-Linked Mutation Disables Phosphorylation Control of UBE3A. *Cell*, **162**, 795-807.

Zeniou, M., Pannetier, S., Fryns, J. P. and Hanauer, A. (2002) Unusual splice-site mutations in the RSK2 gene and suggestion of genetic heterogeneity in Coffin-Lowry syndrome. *Am J Hum Genet*, **70**, 1421-1433.

Zeniou-Meyer, M., Gambino, F., Ammar, M. R., Humeau, Y. and Vitale, N. (2010) The Coffin-Lowry syndrome-associated protein RSK2 and neurosecretion. *Cell Mol Neurobiol*, **30**, 1401-1406.

Zheng, L., Ding, H., Lu, Z., Li, Y., Pan, Y., Ning, T. and Ke, Y. (2008) E3 ubiquitin ligase E6AP-mediated TSC2 turnover in the presence and absence of HPV16 E6. *Genes Cells*, **13**, 285-294.
