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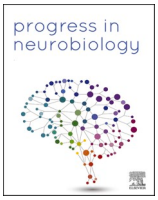

Cerebellar impairments in genetic models of autism spectrum disorders: A neurobiological perspective

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ABSTRACT

Functional and molecular alterations in the cerebellum are among the most widely recognised associates of autism spectrum disorders (ASD). As a critical computational hub of the brain, the cerebellum controls and coordinates a range of motor, affective and cognitive processes. Despite well-described circuits and integrative mechanisms, specific changes that underlie cerebellar impairments in ASD remain elusive. Studies in experimental animals have been critical in uncovering molecular pathology and neuro-behavioural correlates, providing a model for investigating complex disease conditions. Herein, we review commonalities and differences of the most extensively characterised genetic lines of ASD with reference to the cerebellum. We revisit structural, functional, and molecular alterations which may contribute to neurobehavioral phenotypes. The cross-model analysis of this study provides an integrated outlook on the role of cerebellar alterations in pathobiology of ASD that may benefit future translational research and development of therapies.

1. Introduction

Autism spectrum disorder (ASD) is an umbrella term for a range of neurodevelopmental disabilities. The condition sets on in early childhood and is manifested by the deficit of cognition and social communication, restricted interests, and repetitive behavior (Lord et al., 2020; Bhat, 2021). Although ASD is primarily viewed as a disorder related to impairments of distributed neural mechanisms, increasing neurophysiological and imaging data suggests a differential sensitivity of selected functional sub-systems of the brain (Barnea-Goraly et al., 2014; Hazlett et al., 2017; Nordahl et al., 2020, 2012; Stoodley, 2014). The variations in ASD sensitivity of neural circuits imply the involvement of specific molecular and cellular mechanisms associated with different impairements, a notion supported also by reports of autism-like phenotypes prompted by focal inflammation or early age traumatic injury of selected brain structures (Casanova et al., 2013; DeLong and Bauman, 1987; Singh et al., 2016; Hrdlicka et al., 2019). Over recent years, there has been a growing emphasis on the prefrontal and orbitofrontal cortices (Leisman et al., 2023; Mohapatra and Wagner, 2023; Long et al., 2016; Courchesne and Pierce, 2005), limbic structures such as the amygdala and hippocampus (Fu et al., 2022; Wong et al., 2020; Haznedar et al., 2000; Baron-Cohen et al., 2000; Zalla and Sperduti, 2013), and the cerebellum (Becker and Stoodley, 2013; Fatemi et al., 2012; Hampson and Blatt, 2015; Mosconi et al., 2015; Rogers et al., 2013; Rudolph et al., 2023; Su et al., 2021; Sydnor and Aldinger, 2022; Wang et al., 2014) as principal brain regions affected by ASD.

As a critical computational hub of the brain, the cerebellum, through local and long-range connections, coordinates and controls a wide variety of motor and non-motor functions, including speech, cognition and social behaviour (Rudolph et al., 2023; Schmahmann, 2019; Lawrenson et al., 2018; Buckner, 2013; Hull and Regehr, 2022). Through processing and integration of extensive sensory and associative inputs and provision of dynamic feedback to the forebrain, midbrain-brainstem, and spinal cord networks, cerebellum organizes and coordinates complex motor and cognitive processes to support learned and new behaviors essential for adaptation and survival (Manto et al., 2012; Moberget and Ivry, 2016; Popa and Ebner, 2018). Accordingly, deficits of cerebellar functions due to cellular and molecular impairments can have

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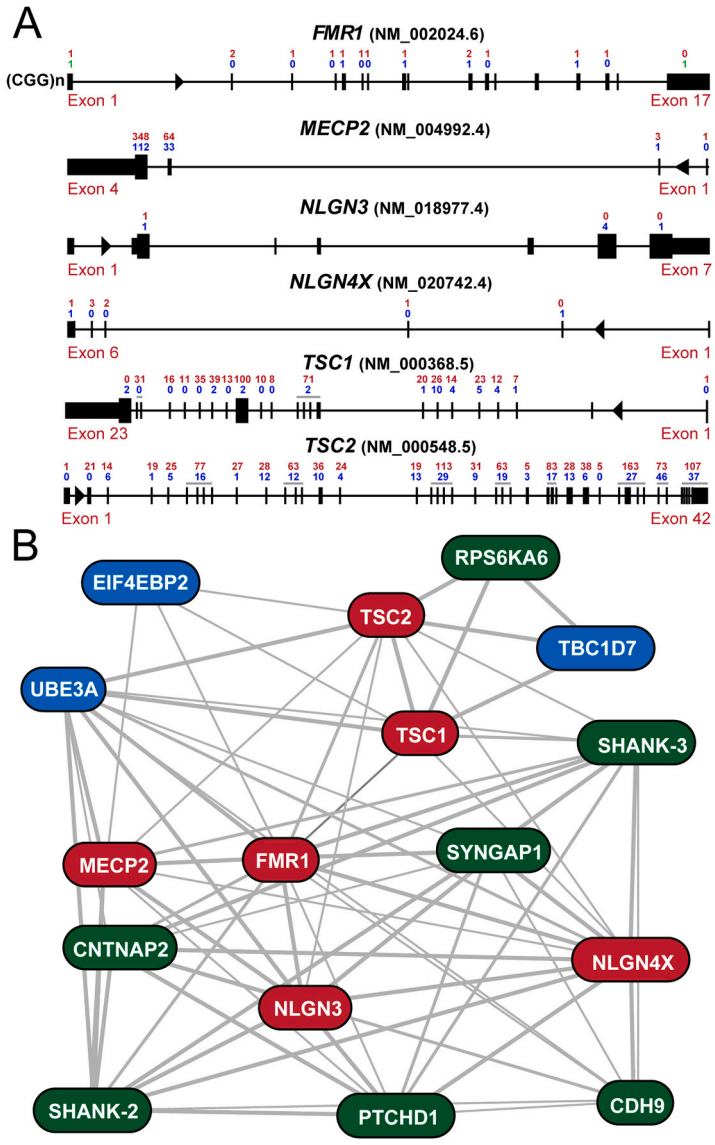
detrimental effects on these processes, contributing towards various neurological, neurodevelopmental and psychiatric disorders, including ASD (Rudolph et al., 2023; Gillig and Sanders, 2010; Schmahmann and Caplan, 2006; Hariri, 2019; Ovsepian et al., 2013). Neuroimaging in ASD patients revealed cerebellar abnormalities, including hypoplasia of the vermis, grey and white matter irregularities with cerebellar undergrowth, which are present in early life and can persist into adulthood (Courchesne et al., 1988; Bruchhage et al., 2018; Palmen and van Engeland, 2004; DiCicco-Bloom et al., 2006; Webb et al., 2009; Aldinger et al., 2013). Postmortem examinations showed loss of Purkinje cells (PCs), more elaborate Bergmann glial networks, activation of astrocytes and microglia, and loss of myelin and lobular atrophy (Kern, 2003; Bauman and Kemper, 2005; Vargas et al., 2005; Sundberg and Sahin, 2015). There has also been strengthening molecular and ultrastructural evidence for synaptic impairments in ASD, which can affect processes and mechanisms at post and presynaptic levels (Durand et al., 2007; Ebrahimi-Fakhari and Sahin, 2015; Granak et al., 2023; Jiang et al., 2022; Kutna et al., 2021; Yeo et al., 2022). Increasing neurophysiological data suggests detrimental effects of synaptic dysfunctions on computational and integrative mechanisms of the cerebellum (Hausser and Clark, 1997; Hausser et al., 2004; Hoebeek et al., 2005; Ovsepian and Friel, 2012; Muscinelli et al., 2023). Although results of preclinical studies support the critical relevance of cerebellar impairments to ASD, there is a pressing need to unravel the specific mechanisms underlying their phenotypic convergence and resemblance to clinical signs of ASD in humans.

This study presents a first cross-model analysis and integrated outlook on cerebellar alterations in the most extensively studied preclinical models. Reviewed herein findings, along with the increasing body of literature, open new vistas in the ASD field in consolidating the



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Node	STRING cluster/Functional annotation
CDH9	Pr-pr interactions at synapses; Transmitter- gated channel activity; Inhibitory chemical synaptic transmission; Regulation of presynapse assembly; Postsynaptic cell membrane; Neurexins and neuroligins
CNTNAP2	Pr-pr interactions at synapses; Clustering of voltage-gated K^+ channels; Synaptic membrane adhesion; Postsynaptic cell membrane; Neurofascin interactions
EIF4EBP2	Eukaryotic translation initiation factor 4E; RNA transport
FMR1	Dendritic transport of ribonucleoprotein complex; Deadenylation - dependent mRNA decay; Messenger ribonucleoprotein complex; RNA transport
MECP2	Histone deacetylase complex; Sin3 complex; NuRD complex; RNA Polymerase II Transcription; Transcription of receptors, channels, GABA signaling
NLGN3, 4X	Pr-pr interactions at synapses; Transmitter - gated channel activity; Neurotransmitter receptor complex; Regulation of presynapse assembly; Neurexins and neuroligins
PTCHD1	Pr-pr interactions at synapses; Transmitter - gated channel activity; Inhibitory chemical synaptic transmission; Neurotransmitter receptor complex; Regulation of presynapse assembly; Neurexins and neuroligins
RPS6KA6	MAPK signaling, mTOR signaling, Long-term potentiation, Postsynaptic signal transmission; L1CAM interactions; Activation of NMDA receptors; Axon guidance
SHANK2	Pr-pr interactions at synapses; Transmitter - gated channel activity; Neurotransmitter receptor complex; Regulation of presynapse assembly; Neurexins and neuroligins
SHANK3	Pr-pr interactions at synapses; Transmitter - gated channel activity; Neurotransmitter receptor complex; Regulation of presynapse assembly; Neurexins and neuroligins; Glutamatergic synapse; Axon guidance
SYNGAP1	Pr-pr interactions at synapses; Transmitter - gated channel activity; Inhibitory chemical synaptic transmission; Neurotransmitter receptor complex; Regulation of presynapse assembly; Neurexins and neuroligins; Ras/MAPK signaling
TBC1D7	mTOR signaling; Ribosomal protein S6 kinase activity; Membrane trafficking (Rab-regulation)
TSC1, 2	mTOR signaling; Ribosomal protein S6 kinase activity; RNA Polymerase II Transcription; PI3K-Akt signaling; Membrane trafficking (Rab regulation)
UBE3A	Oxygen-dependent proline hydroxylation of HIF Alpha; Ubiquitin conjugating enzyme activity; Ubiquitin mediated proteolysis

Fig. 1. Mutations, molecular networks and putative functions of ASD genes implicated in cerebellar impairment of most extensively studied preclinical models. (A) Loci and frequency of neurodevelopmental disease-causing sequence variants of *FMR1*, *MECP2*, *NLGN3*, *NLGN4X*, *TSC1* and *TSC2* deposited in the HGMD database (v4.1) – a schematic representation (representative RefSeq HGMD genes derived from UCSC Genome Browser). Large CGG repeat expansions in 5′UTR are the main pathogenic variants in *FMR1*. Red, blue and green numbers indicate the frequency of reported likely gene disrupting (LGD), missense and regulatory variants, respectively. (B) Full STRING (v12.0) protein network indicating both functional and physical protein associations. Red nodes are the proteins of interest, and blue and green nodes are the first shells of interactors. Green nodes represent proteins with strong synaptic effects; blue nodes represent proteins with more global regulators and homeostatic roles. Edges represent protein-protein associations where line thickness indicates confidence or the strength of data support (minimum interaction score 0.40). (C) The table shows each network node's STRING cluster/functional annotation (B).

cerebellum as a critical hub for cognitive, social and motor functions and impairments. They also may provide clues for engagement with and manipulations of molecular pathways and mechanisms that may benefit future translational research and therapeutic interventions.

2. Investigated genetic models and their relevance to human ASD: a brief overview

ASD is genetically highly diverse (Persico and Napolioni, 2013; Ghafouri-Fard et al., 2023; Huguet et al., 2013; Rolland et al., 2023; Rylaarsdam and Guemez-Gamboa, 2019) (Fig. 1A, C). Over 230 high-confidence genes linked to ASD have been described, with the majority expressed in the cerebellum (Lord et al., 2020; Sydnor and Aldinger, 2022; Huguet et al., 2013; Mapelli et al., 2022; Aldinger et al., 2019). Such heterogeneity with major knowledge gaps makes the comprehensive review and synthesis extremely challenging. At present, a meaningful analysis of ASD phenotypes necessitates a reductionistic approach with focus on selected characteristics or mechanisms. Given the growing number of studies showing ASD-like impairments in social, cognitive and visuospatial domains in patients with cerebellar diseases (Ahmadian et al., 2019; Argyropoulos et al., 2020; Jacobi et al., 2021), we focus our analysis on the cerebellar pathology associated with impairments of *Fmr1*, *Mecp2*, *Nlgn3/4*, and *Tsc1/2* genotypes, which are the most extensively characterised preclinical models (Fig. 1 A-C).

In humans, aberrations in *FMR1*, *MECP2*, *NLGN3/4x*, and *TSC1/2* genes have been associated with Fragile X-syndrome (FXS), Rett syndrome, X-link Neuroligin 3/4 and tuberous sclerosis complex (TSC), respectively (Kutna et al., 2021; Rylaarsdam and Guemez-Gamboa, 2019; Zoghbi and Bear, 2012). Fmr1 (fragile X messenger ribonucleoprotein) is enriched in the brain and plays a crucial role in neurodevelopment and cognitive functions (Bernardet and Crusio, 2006; Fyke and Velinov, 2021). *Fmr1* loss-of-function in animal models is considered a model for fragile X mental retardation (Richter and Zhao, 2021). Mice with the *Fmr1* deficiency show autism-like hyperactivity, cognitive impairments, and repetitive behaviour (Bernardet and Crusio, 2006; Petroni et al., 2022). The critical role of Fmr1 in regulating protein translation and its enrichment in neurons implies that neurobehavioral effects associated with its deficiency might be due to impairments in protein synthesis involved in synaptic development and plasticity and neural circuit remodelling (Richter and Zhao, 2021; Thomazeau et al., 2021). Fmr1 is especially prominent in dendrites, where intense RNA translation and protein synthesis support local demands (Sutton and Schuman, 2006; Sun et al., 2021).

The importance of protein synthesis in ASD is also underscored by its link with *Mecp2* deficit, which is known to regulate chromatin activity through DNA transcription (Palmer et al., 2008; Smrt et al., 2007). The Mecp2 protein plays a vital role in embryogenesis (Tate et al., 1996), with the effects in genetic loss-of-function models confined to a specific tissue type or developmental stage (Varghese et al., 2017). *Mecp2* deficiency in the forebrain mimics behavioural aspects of Rett syndrome in humans (Gemelli et al., 2006), with *Mecp2*+/- mice being used as an ASD model (Young and Zoghbi, 2004). Notably, mild *Mecp2* overexpression results in improved motor and contextual learning and enhanced synaptic plasticity at an early age, followed by age-dependent deterioration, leading to frequent seizures, hypoactivity and premature death (Collins et al., 2004). Impaired learning, memory, and synaptic transmission have also been reported (Na et al., 2012). In addition to dysregulation of protein translation, specific changes in synaptic functions and BDNF signalling have been reported in *Mecp2* models, causing impairment of neural mechanisms (Martinowich et al., 2003).

Neurons and brain tissue appear to be the primary site of the pathobiology in *Nlgn3/4* models of ASD. Encoding for Neuroligin-3/4 cell-adhesion proteins responsible for connecting the pre- and post-synaptic elements at a synaptic junction, *Nlgn3/4* loss-of-function leads to break down of synaptic contacts between neurons, with detrimental effects on brain development, neurotransmission, and synaptic plasticity (Liu et al., 2022; Monday et al., 2018). *NLG3* plays especially prominent role in ASD, with two ASD-related variants described in mouse models: (1) *Nlgn3* KO with reduced vocalisation and a lack of social novelty preference (Radyushkin et al., 2009), attributed to synaptic dysfunction and abnormal plasticity (Baudouin et al., 2012), and (2) a point mutation (*Nlgn3*-R451C) associated with impaired social interactions and enhanced spatial learning (Tabuchi et al., 2007).

Finally, *Tsc1/2* loss-of-function mice and rat models display ASD-like cognitive deficits, behavioural impairments, and psychiatric signs in ~50 % of heterozygotes (Kutna et al., 2021; Scheidenhelm and Gutmann, 2004). *Tsc1* and *Tsc2* nulls are lethal due to a deficiency in encoded hamartin and tuberin proteins, respectively (Rennebeck et al., 1998; Kobayashi et al., 2001). These two proteins form a heterodimer that inhibits the mammalian target of rapamycin (mTOR) signalling, with their shortage linked to out-of-control protein synthesis with related impairments (Lipton and Sahin, 2014). *Tsc1/Tsc2* deficit in neurons leads to disruption of synaptic functions with abnormal neuroplasticity, while their depletion in glial cells is associated with gliomas (Kutna et al., 2021; Pokorna et al., 2024). Like other ASD models, loss of function *Tsc1* and *Tsc2* mutations are linked with repetitive behaviour and abnormal social interaction in mice and rats (Granak et al., 2023; Tsai and Sahin, 2011; Tsai et al., 2012; Waltereit et al., 2011). As discussed in the following, these changes are associated with the dysregulation of specific proteins involved in the synaptic vesicle cycle and exocytosis (Czapski et al., 2021), as well as general dysregulation of neural functions, loss of myelin and neurodegeneration (Granak et al., 2023; Kutna et al., 2021, 2022).

3. Cerebellar alterations in *Fmr1* ASD models

Loss-of-function *FMR1* mutations lead to FXS manifested by intellectual deficiency, hyperactivity, seizures, as well as cerebellar motor signs (Hagerman et al., 2017; Tobia and Woodruff-Pak, 2009). Fragile X-associated tremor and ataxia syndrome (FXTAS), mainly reported in adult males harboring inherited *FMR1* premutation, is characterized by varying cerebellar ataxia and intention tremor (Hagerman et al., 2017; Koekkoek et al., 2005). MRI of human FXS and FXTAS show hypoplasia in the cerebellar vermis with increased T2 signals in the middle peduncles (Gothelf et al., 2008). Alterations of vermis in FXS appear as early as one year and persist into adulthood (Gothelf et al., 2008; Hoeft et al., 2010). Intellectual disabilities of FXS correlate positively with changes in the volume of vermis in patients (Gothelf et al., 2008). PCs are shown to be reduced in their numbers and dendritic tree complexity in postmortem examinations (Greco et al., 2011; Salcedo-Arellano et al., 2020). Spongiosis and discoloration of cerebellar white matter and atrophy of grey matter were also revealed by histopathological assessment of the FXTAS samples (Greco et al., 2011, 2002).

Fmr1 KO mice show disturbances in social interaction, repetitive behavior and hyperactivity, impaired memory, and deficiencies in motor coordination and balance (Koekkoek et al., 2005; Ding et al., 2014; Pietropaolo et al., 2011). Deficits in eyeblink conditioning were also found when *Fmr1* was conditionally knocked out in PCs, indicating specific involvement of the cerebellum in FXS phenotypes (Koekkoek et al., 2005). Analysis of general and PC-specific *Fmr1* KO mice showed elongated and irregularly shaped dendritic spines of PCs, with the total number unaffected (Koekkoek et al., 2005) (Fig. 2, A-C). These changes involve intricate molecular interplay in dendrites and dendritic spines. The PC spine density is finely regulated by competing climbing fibre (CF) and parallel fibre (PF) inputs via highly complex regulatory processes (Kakizawa et al., 2000). Retarded elimination of multiple CF inputs of developing PCs in Fmr1 deficient mice may reflect a compensatory response to slowed spine maturation and attenuated PF inputs (Koekkoek et al., 2005). The rate of cerebellar myelination in *Fmr1* KO mice is slowed down (Pacey et al., 2013), possibly due to impairments of oligodendrocyte functions (Fig. 2, C). On the other hand, increased GFAP expression in the cerebellum from early postnatal weeks

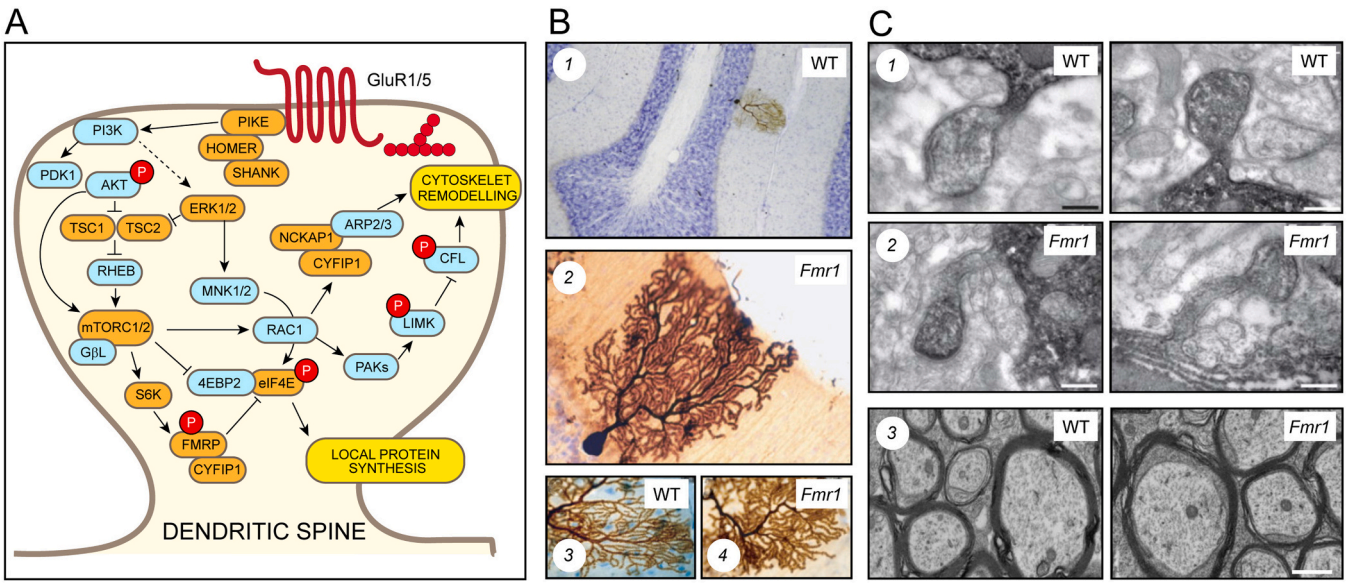

Fig. 2. Molecular interactions and the effects of *Fmr1* deficiency on the cerebellum of mouse models of ASD. The illustrative material is used from published literature. (A) The expansion of a polymorphic CGG repeat of human FMR1 by more than 200 units causes methylation of the promotor region of the gene and silences it, leading to a deficiency of protein FMRP. Due to the essential role of FMRP in neural signalling and protein synthesis, its deficit has multiple effects on cerebellar structures and cellular organisation. (B, C) Micrographs showcasing the impact of *Fmr1* deficiency on the dendritic tree (B, light microscopic images of WT [1,3] and *Fmr1*$^{-/-}$ [2,4]) and spine morphology of PCs in mice (C, WT [1] and *Fmr1*$^{-/-}$ [2]). Note the longer and more irregularly shaped spines in *Fmr1* null mutants. Scale bars in micrographs of the wild types represent 271 nm, 283 nm, and 260 nm, respectively (Koekkoek et al., 2005). (C, 3) Comparison of cerebellar axons at postnatal day 15 (electron microscopic images) of WT and *Fmr1*$^{-/-}$ genotypes, showing fewer myelinated axons and looser myelin sheath in the cerebellum in the latter. Scale bars, 500 nm (Pacey et al., 2013). Images reused with permission.

into adulthood suggests astrocyte activation, accompanied by higher expression of Tumour Necrosis Factor Receptor 2 and Leukaemia Inhibitory Factor (Pacey et al., 2013, 2015). Finally, there are emerging data on the reduction of Sonic hedgehog signalling in Bergmann glia as well as a decreased proliferation of cerebellar granular cell precursors, leading to thinning of the external granule layer in *Fmr1* KO mice (Lee et al., 2022; Cheng et al., 2018) (Table 1).

Assessment of glutamatergic transmission in the cerebellum of *Fmr1* KO mice showed an increase in group 1 metabotropic glutamate receptor (mGluR1) dependent LTD (Iliff et al., 2013; Shakhawat et al., 2024). This change has been suggested to contribute towards epileptogenic activity, motor hyperactivity, and structural remodelling of the cerebellum, as pharmacological inhibition or genetic silencing of mGluR1 has restored cerebellar functions and synaptic connections (Iliff et al., 2013; Santoro et al., 2012). Collectively, these findings agree with functional and structural changes in the cerebellum, assigning FMR1 protein the role of a critical regulator of cerebellar development, control of dendritic spine dynamics and mGluR-dependent synaptic plasticity, with downstream effects on a range of molecular pathways and functions.

4. Cerebellar alterations in *Mecp2* ASD models

In humans, *MECP2* mutations are associated with Rett syndrome, manifested by stereotypic movements, impaired motor coordination and speech disorders (Leonard et al., 2017). Anatomical investigations in patients with Rett syndrome have revealed cerebellar atrophy with general hypoplasia during early childhood, among other changes in the cerebellum and throughout the entire central nervous system (Murakami et al., 1992; Oldfors et al., 1990). Microscopic examination revealed loss of PCs through atrophy, astrocytic gliosis in the molecular and granular cell layers, and loss of myelin (Oldfors et al., 1990).

Given the high expression of Mecp2 in the cerebellum of mice, it is hardly surprising that deficiency in the *Mecp2* gene leads to substantial structural and functional alterations therein in preclinical models (Sanfeliu et al., 2019; Achilly et al., 2021) **(**Fig. 3**)**. MRI studies of Mecp2B (deletion of *Mecp2* exons 3 and 4) (Belichenko et al., 2008; Saywell et al., 2006) and Mecp2J (in-frame deletion of *Mecp2* exon 3) (Belichenko et al., 2008) mice revealed a reduction in cerebellar volume. *Mecp2* KO also showed a reduced cerebellar volume (Saywell et al., 2006; Steadman et al., 2014) attributed primarily to smaller granular cells and their enhanced packing density (Belichenko et al., 2008). A reduction in cerebellar volume has also been reported in Mecp2tm1.1-Bird/J and Mecp2tm2Bird/J lines, while Mecp2tm1Hzo mutants expressing loxP-flanked thymidine kinase genes that disrupt exon four show cerebellar enlargement (Allemang-Grand et al., 2017). Steadman and co-workers (Steadman et al., 2014) used a mild truncation model *Mecp2* 308$^{-/-}$ to observe an increase in the cerebellar volume in homozygous mutant adult females but not in heterozygous (females) or hemizygous (males) (Steadman et al., 2014). Histochemical analysis showed no difference in PC density, anterior/posterior granule layer thickness, or anterior/posterior molecular layer thickness in Mecp2R308/Y mice compared to wild type littermates. In contrast, PC examination revealed decreased density in dendritic spines (Kloth et al., 2015) **(**Fig. 3 A**)**. The *Mecp2* knock-in model reproduced previous findings of the changes in granule cells and confirmed that these alterations can lead to wider histopathological impairments in the cerebellum (Rangasamy et al., 2016).

In *Mecp2* deficiency-KO mice, impaired motor functions manifest primarily as tremors, hypoactivity, myoclonic seizures, and kyphosis, consistent with cerebellar deficits (Shahbazian et al., 2002). The timing of scoring functional impairments is crucial as the deficit in cerebellar motor learning and coordination gradually worsens during development. *Mecp2*-null mice show developmentally onsetting loss of motor control, disrupted autonomic regulation and impaired learning and memory (Lonetti et al., 2010; Robinson et al., 2012). In the grid walking test, *Mecp*$^{2+/-}$ mice display a higher number of slips and impaired walking than *Mecp*$^{2+/+}$ genotype (Samaco et al., 2013). Targeted depletion of Mecp2 from the cerebellum disrupted motor learning, which could be compensated by additional training (Achilly et al.,

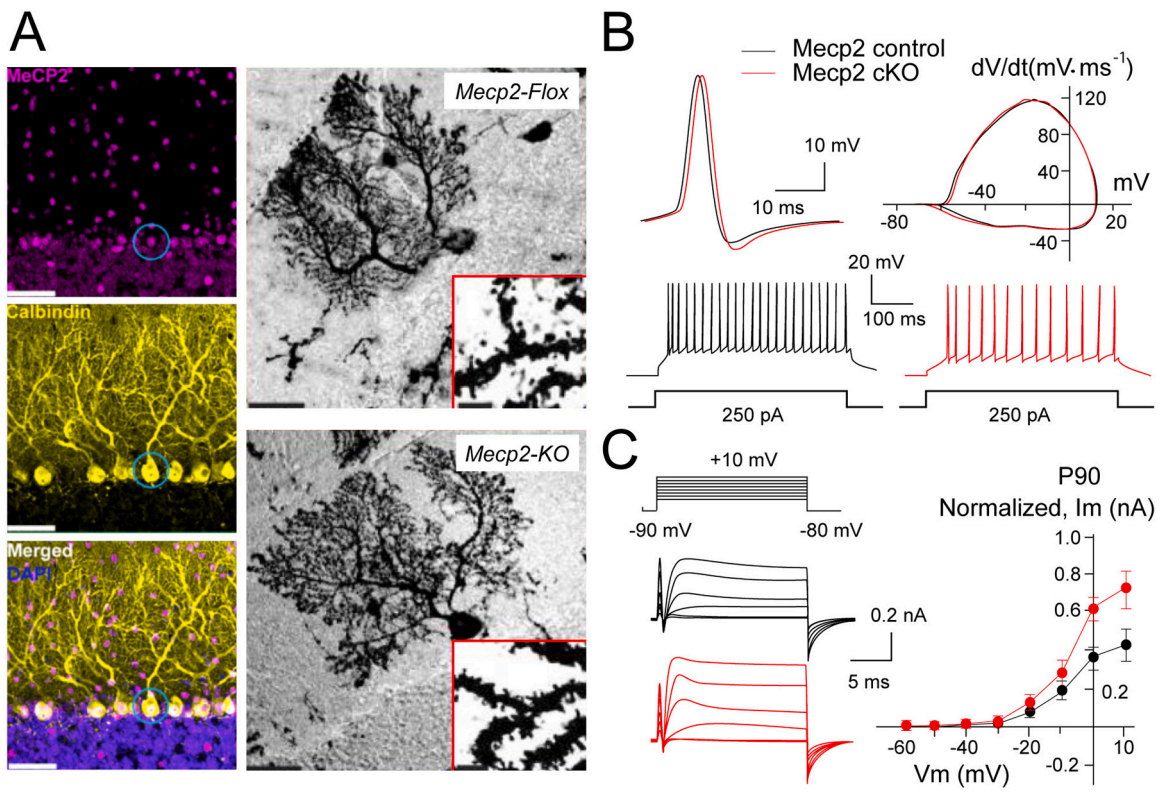

Fig. 3. The impact of *Mecp2* loss-of-function on PC morphology and evoked activity. The illustrative material is used with permission from published literature. (A, left top to bottom) Visualisation of Mecp2 expression in cerebellar neurons of 6-month-old WT mice: Mecp2 (magenta), Calbindin (yellow) in the PC layer and merged image with DAPI staining. Scale, 25 μm. (A, right top to bottom) Golgi stain of PCs in Flox and KO mice. Scale bar, 25 μm. The inset panels show the dendritic spines of the PCs (Achilly et al., 2021). Scale bars, 5 μm. (B) Top pair: representative action potentials induced by injection of depolarising current in PCs of WT and *Mecp2* cKO PCs (left) with phase-plane plots (Vm vs dV/dt) (Vm, membrane potential; dV, delta change of voltage; dt, delta change of time) for action potentials (right). Middle and bottom traces: examples of spikes trains in PCs from control and cKO mice (P30) (middle) in response to a 200-ms somatic current injection (bottom). (C) Left: typical SK2 currents (middle and bottom) induced by voltage steps (top) in control and cKO mice (red and black, respectively) at P90. Right: current-voltage (I-V) curves derived from P90 mice, with currents normalised to the maximal value (Xu et al., 2023). Recordings collected from PCs of vermis. Images reused with permission.

2021). In transgenic mice expressing the entire human MECP2 locus, mild overexpression of wild-type Mecp2 results in improved motor and contextual learning with enhanced LTP (Collins et al., 2004). Of note, *Mecp2* KO mice did not exhibit impaired non-motor phenotypes such as deficit in social interaction and cognition decline despite the evidence for the key role of the cerebellum in these functions (Van Overwalle et al., 2020).

Analysis of neuronal activity in mice lacking Mecp2 in the cerebellum showed irregular PC firing (Achilly et al., 2021), potentially due to altered parallel fibre inputs from granule cells. An *in vitro* study of granule cell activity demonstrated that Mecp2 depletion leads to increased susceptibility to apoptosis in response to hypoxia and excitotoxicity (Russell et al., 2007). Impairments in other neurotransmitter systems are also likely to contribute to the manifestations of *Mecp2* deletion, with the reduction in the 5-HT and dopamine levels reported in the cerebellum of *Mecp2*-KO mice (Dai et al., 2022). While the specific mechanisms underlying changes in neuronal processes and cerebellar functions remained unidentified, dysregulation of synaptic protein translation and alterations in BDNF signalling reported in *Mecp2* models (Martinowich et al., 2003; Chang et al., 2006) will likely contribute to the pathological process. A recent study has demonstrated that selective Mecp2 deletion in PCs dampens their intrinsic excitability by reducing the small-conductance calcium-activated potassium channel (SKCa) and TrkB – the high-affinity receptor for BDNF (Xu et al., 2023) (Fig. 3 B, C). Behavioural tests show this change correlates with autistic-like phenotypes and reduced vestibulo-cerebellar motor learning. Notably, enhancing the TrkB activity in PCs is sufficient to rescue their electrophysiological function and behavioural deficit caused by Mecp2 loss-of-function, suggesting potential intervention targets and avenues for therapeutic engagement (Xu et al., 2023).

5. Cerebellar alterations in *Nlgn3/4* ASD models

Data from *Nlgn3/4* animal models of ASD suggest a range of structural and functional alterations in the cerebellum. *Nlgn3* R451C KI in male mice showed differential changes across cerebellar regions, with enlarged crus II of the ansiform lobule and in paraflocculus (Steadman et al., 2014). *Nlgn4* KO developing male mice showed decreased cerebellar volume (Jamain et al., 2008) while *Nlgn3* KO male mice aged 13–15 weeks demonstrated augmented motor activity in an open field, impaired response to social novelty, and decreased vocalisation, with none decisively attributable to the cerebellum (Jamain et al., 2008; Rothwell et al., 2014). The rotarod performance remained normal (Rothwell et al., 2014). Interestingly, another report showed impairments in cerebellum-dependent motor coordination in *Nlgn3* KO mice in the Erasmus ladder test (Baudouin et al., 2012). The conditional KO of *Nlgn3* restricted to PCs did not produce the same alteration, with the *Nlgn3*$^{-/-}$ mice performed normally (Baudouin et al., 2012) whereas analysis of KI Nlgn3 R451C showed an enhanced rotarod performance in terms of longer latencies to fall (Chadman et al., 2008). Conditional loss-of-function mutations of *Nlgn3* in PCs in mice induced a hyperactivity phenotype in an open field; however, it failed to reproduce the rotarod motor learning impairments (Rothwell et al., 2014). Notably, another study found no differences in open fields or rotarod in Nlgn3

deficient mice (Tabuchi et al., 2007). Data on *Nlgn4* mutant models is scarce, with no evidence of cerebellar effects.

Sudhof and co-workers have analysed the effects of single, double, and triple conditional KO of *Nlgn1, 2* and *3* in the structure and functions of PCs (Zhang et al., 2015). Deletion of *Nlgn1–3* caused loss of distal CF-PC but not the PF-PC synapses. These differences could be attributed to the fact that PF synapses utilise neurexin-cerebellin-GluRd2 for stabilising and proper functioning of synaptic connections (instead of Nlgn). Also, the study shows that in inhibitory basket/stellate cell synapses, the deletion of neuroligins did not change synapse numbers but resulted in increased size and nearly complete loss of their function (Zhang et al., 2015). Conditional KO studies also showed that the Nlgn 1–3 proteins are essential for NMDAR signalling in cerebellar stellate interneurons (Zhang and Sudhof, 2016). Nevertheless, what makes Nlgn3 more unique is that it is involved in the development and function of excitatory glutamatergic and inhibitory GABAergic synapses. *Nlgn3* KO mice also showed a significant invasion of CF terminals into the distal molecular layer (Baudouin et al., 2012). This effect was Nlgn-3 specific as it was not observed in the cerebellum of *Nlgn1* KO mice, with the targeted re-expression of Nlgn3 in PC suppressing ectopic synapse formation in PCs of conditional *Nlgn-3* KO mice (Baudouin et al., 2012). Like in Nlgn3 KO models, in *Nlgn3* R451C leads to retardation of cerebellar development, with PCs keeping excitatory inputs from multiple CFs up to day 16. These changes may leave a lasting effect on the function of the cerebellar circuit, which may contribute to ASD-like behaviour (Lai et al., 2021) (Fig. 4 A - B).

Electrophysiological studies showed *Nlgn* −3 R451C knock-in but not *Nlgn*-3 KO mice exhibit increased spontaneous inhibitory synaptic transmission in the cerebral cortex and cerebellum (Tabuchi et al., 2007; Lai et al., 2021), suggesting knock-in as a gain-of-function state **(**Fig. 4 **C)**. Notably, at glutamatergic inputs of PCs, *Nlgn3* KO mice displayed an occlusion in mGluR-LTD, and disturbed mGluR–dependent synaptic plasticity due to increased expression of synaptic mGluR1α protein, which colocalised with Nlgn-3 in the heads of PC dendritic spines. Re-expression of *Nlgn3* restored wild type mGluR1α protein levels and removed ectopic synapses from the distal PC dendrites (Baudouin et al., 2012). Taken together, these findings suggest *Nlgn3* might function as a circuit-specific synapse organiser, with its deficit leading to motor impairments contributed by the dysfunctions of mGluR-mediated LTD at PCs. Interestingly, constitutive *Nlgn3* KO mice showed no change in mGluR1/5 protein levels or PF LTD, with CF EPSCs or IPSCs of PC-specific *Nlgn3* KO mice remaining unaltered (Zhang et al., 2015; Piochon et al., 2014).

6. Cerebellar alterations in *Tsc1/2* ASD models

Clinical reports of *TSC* loss-of-function describe a range of neurocognitive and motor impairments, including signs of cerebellar deficiency characteristic of ASD (Kutna et al., 2021; Jurkiewicz et al., 2006; Weisenfeld et al., 2013). The results of functional neuroimaging studies show a positive correlation between cerebellar pathology and the severity of social deficits (Eluvathingal et al., 2006; Traut et al., 2018). Postmortem examination of the cerebellum revealed various abnormalities, including swelling and degeneration of PCs and activation of astrocytes and microglia, with enhanced cytokine activity amongst the most widely reported (Sundberg and Sahin, 2015; Boer et al., 2008; Skefos et al., 2014). Occasional lesions (~30 % of *Tsc* patients) are observed in various cerebellar structures, mainly in children of older (> six years) age (Martí-Bonmatí et al., 2000). Correlation analysis suggested a link between autistic behaviour and the occurrence of cerebellar tubers (Eluvathingal et al., 2006; Weber et al., 2000). The true extent of cerebellar contribution to the neurobehavioral phenotype of *Tsc* ASD remains unclear, meriting in-depth analysis in preclinical models.

The *Tsc1/2* deficiency models generally replicate cellular abnormalities described in postmortem brain studies of human ASD (Kutna

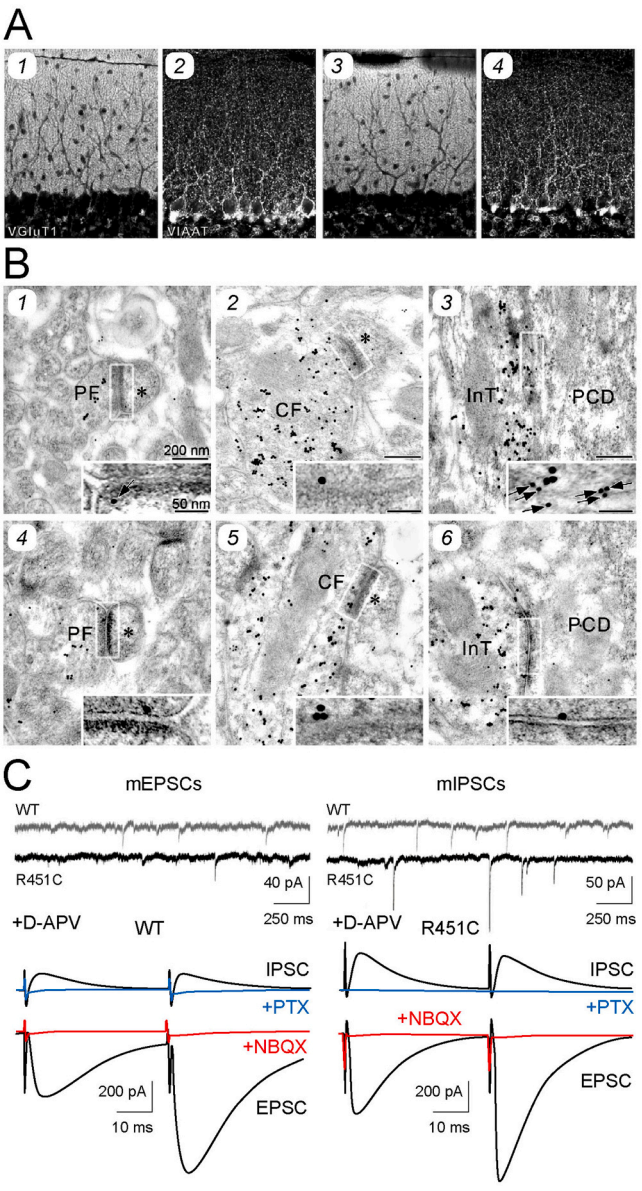

Fig. 4. Effects of Nlgn3 loss-of-function (NLGN3-451C mutation) on PC morphology and synaptic activity. The illustrative material is used with permission from published literature. (A) Representative immunofluorescence images for the excitatory PF marker VGluT1 (1, 3) and the inhibitory synaptic terminal marker vesicular inhibitory amino acid transporter (VIAAT) (2, 4) of the cerebellum in wild type and *Nlgn3* loss-of-function mice showing no overt differences. (B) Selective reduction in Nlgn3 expression at inhibitory interneurons to PC synapses in NLGN3-R451C mice. Post-embedding immunogold electron microscopy for metal particle labelled Nlgn3 protein in wild-type (1−3) and NLGN3-R451C (4−6) mice. Note that PC spines (asterisks) contacting PF inputs labelled for VGluT1 (1, 4) and PC spines (asterisks) contacting CF terminals labelled for VGluT2 (2, 5) show similar levels of Nlgn3 protein. Unlike this, the level of Nlgn3 protein in *Nlgn3* loss-of-function line is visibly reduced at contacts of PC dendrites (PCD) with presynaptic terminals of inhibitory interneurons (InT). (C) Top traces: representative traces of mEPSC (left) recorded from PCs of wild-type and NLGN3-R451C mutant mice at −70 mV in the presence of 1 μM tetrodotoxin and 100 μM PTX and (right) mIPSC in the presence of 1 μM tetrodotoxin, 10 μM NBQX, and 5 μM R-CPP. Bottom traces: representative recordings of evoked AMPAR- and GABAAR-mediated synaptic currents in wild-type (left) and NLGN3-R451C (right) mice. Scale bars, 10 ms and 200 pA. Note higher amplitude of evoked IPSCs in R451C and significantly higher inhibitory vs excitatory (I/E) ratio.
Images are reused with permission from (Lai et al., 2021)

et al., 2021). Both *Tsc1*$^{-/-}$ and $^{+/-}$ mice showed PC loss, which becomes evident in Tsc1$^{-/-}$ mice at two months of age, with selective depletion of Tsc1 in PCs resulting in autism-like behaviours (Tsai et al., 2012). *Tsc* regulates dendritic spine density, which is increased in loss-of-function *Tsc1* PCs (Fig. 5 A). Numerous axonal varicosities and abnormal collaterals are observed in *Tsc1* deficient mice, consistent with known roles for *Tsc* in regulating neurite growth and morphology (Tsai and Sahin, 2011; Tsai et al., 2012). Reith and co-workers selectively deleted *Tsc2* (*Tsc2*f/-; Cre) from PCs starting at postnatal day six, which led to increased cell size and subsequent death from apoptosis (Reith et al., 2013). Neurodegeneration in this model was cell-type specific and associated with motor deficits. The cell death was countered by mTORC1 inhibitor rapamycin (Reith et al., 2013). Kutna and co-workers analysed *Tsc2*$^{+/-}$ rat cerebellum, reporting enlargement of the vermis with moderate age-related loss of myelin in the deep white matter, mild astrogliosis and increased microglial activity (Kutna et al., 2022) (Fig. 5 D, E). The number of PCs in adult Tsc2$^{+/-}$ rats decreased while the number of NeuN-positive neurons in the molecular layer remained intact. Depletion of myelin-basic protein (MBP) in the central white matter of *Tsc2*+/- suggests impairments of oligodendroglia shielding of mossy and climbing fibres and axons of PCs, in agreement with human and mouse reports (Tsai et al., 2012; Cupolillo et al., 2016; Jay et al., 1998). Higher Iba1 and GFAP activity observed in the same model imply gliosis and the presence of inflammatory responses (Kutna et al., 2021, 2022).

In the context of mTORC1 signalling and PC function, it is noteworthy that both *Tsc1*$^{-/-}$ and *Tsc1*$^{+/-}$ mice showed reductions in PC excitability (including reduced firing rates), the effects being present in both genotypes (Tsai et al., 2012) (Fig. 5 B, C). These observations suggest that cerebellar impairments related to *Tsc* deficiency might provide a potential mechanistic ground for the ASD-like neuro--behavioral phenotype. Evidence from behaving animals shows that *tsc2*flox/- *i.e.* a Cre mouse model with targeted depletion of the *Tsc2* protein in PCs increases repetitive motor activity, implying that *Tsc2* loss-of-function in PCs alone can lead to an autism-like phenotype (Reith et al., 2013). Overall, the emerging evidence from *Tsc1/2* models showing cellular and molecular alterations in the cerebellum and their effects on cerebellar functions warrant further studies to identify the mechanisms behind the phenotypic convergence with neuro-behavioral signs in human ASD.

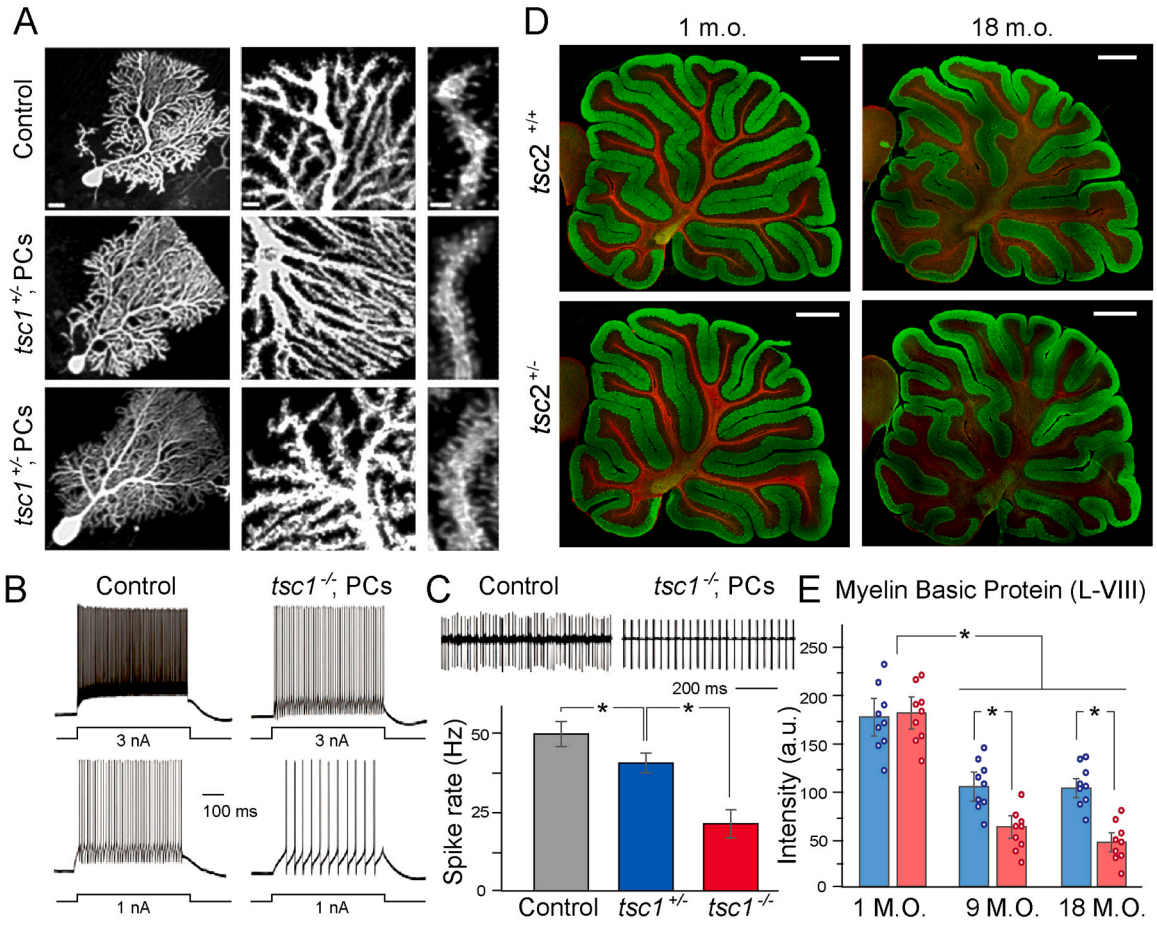

Fig. 5. The impact of *Tcs1/2* loss-of-function on PC morphology, electrophysiological activity and myelination of central white matter in mice and rats. The material is used with permission from published literature. (A) Comparison of PCs of *tsc1*$^{+/+}$, *tsc1*$^{+/-}$, *tsc1*$^{-/-}$ genotypes showing increased spine density in mice showing ASD-like phenotype. Scale bars: 20 μm, 5 μm and 2 μm, respectively. (B) Whole-cell recordings of evoked firing activity of PCs (two pulse intensities) demonstrating reduced excitability in *tsc1*$^{-/-}$ genotypes compared to WT controls. (C) Recordings of spontaneous spiking activity of PCs in a cell-attached mode in *tsc1*$^{+/+}$ and in *tsc1*$^{-/-}$ genotypes (top) demonstrating a reduction in discharge rates of PCs with a graphical representation of data from a population of PC spike rate analysis in *tsc1*$^{+/+}$, *tsc1*$^{+/-}$, *tsc1*$^{-/-}$ genotypes. Asterisks indicate significant differences between the population data. (D) Representative micrographs of the cerebellar vermis of *Tsc2*+/+ and *Tsc2*+/- rats (18 m.o.) stained for myelin basic protein (red) and parvalbumin (green). Scale bar – 0.7 mm. Note the more pronounced age-dependent drop in myelin basic protein expression in *Tsc2*+/- genotype. (E) Summary bar graphs of the distribution of the mean signal intensity of parvalbumin (blue) and myelin basic protein (pink) of *Tsc2*$^{+/+}$ and *Tsc2*$^{+/-}$ rats of 3 age groups, respectively.
Images reused with permission from (Kutna et al., 2022) and from (Tsai et al., 2012).

7. Cerebellar alterations in other genetic models of ASD

Cerebellar alterations have also been analysed in several other pre-clinical models with defects in high-confidence ASD genes. Although the lack of detailed analysis of effects did not allow multi-parametric cross-comparison with the discussed above models, the overlap of molecular pathways and shared neurobehavioral phenotypes makes the brief overview of their effects well warranted.

Cyfip1 gene encodes Cyfip1 protein, which interacts as a binding partner to Fmrp1 in regulating protein translation. A recent report

Table 1
Summary of critical alterations found in cerebellum of *Fmr1*, *Mecp2*, *Nlgn3/4*, and *Tsc1/2* genetic models of ASD with references. Colours represent the frequency of reported changes shared across models, from high to low (purple, red, orange, yellow, green and white). Gray slots mark areas where there is not data. Abbreviations: PC - Purkinje cell; PF-PC - parallel fibre-Purkinje cell input; CF-PC - climbing fibre-Purkinje cell input, mIPSC - miniature inhibitory postsynaptic currents; LTD – long-term depression. High level, increased - ↑; low level, reduced - ↓.

Genes	Model genotype	Cerebellar morphology	PC structure, spines	Synaptic changes	Functional	Ref.
Fmr1	*Fmr1* Null *Fmr1* KO mice	No data	Elongated PC spines	Enhanced LTD in PCs	Cerebellar eyeblink conditioning ↓	106
	Fmr1 KO mice	Volume ↓, Myelination ↓	No data	No data	No data	116
	Fmr1 KO mice	No data	No data	No data	Deficit in alternation behavior, make mice	76
	Fmr1 KO mice	Thinning external granule layer	No data	No data	No data	117
	CGG knock - 120-150 CGG repeats mice	No data	No data	Enhanced mGluR1 LTD in PCs	Motor hyperactivity	119
	Fmr1 KO mice	No data	No data	Enhanced PF-PC LTD	Impaired oculomotor learning	120
Mecp2	*Mecp2* cKO mice	Thinning molecular layer	Altered PC	No data	Irregular firing in PC	126
	$Mecp2^{tm1.1Bird}$ mice $Mecp2^{tm1.1Jae}$ mice	Volumes ↓	No data	No data	No data	127
	Mecp2-/y mice	Size, volume ↓ Fissures ↓	No data	No data	No data	128
	$Mecp2^{tm1Hzo}$ mice $Mecp2^{tm1.1Bird/J}$ mice $Mecp2^{tm2Bird/J}$ mice	Volume ↑ Volume ↓ Volume ↓	No data	No data	No data	130
	Mecp2, 308-truncation mice	Volume ↑	No data	No data	No data	129
	$Mecp2^{R308/Y}$ mice	No data	PC spine density ↓	No data	PC firing ↓	131
	Mecp2 A140V KI mice	GN soma size ↓	No data	No data	No data	132
	Mecp2 null mice	No data	Stellate cell input–PC ↑, Basket cells input-PC ↑	No data	Loss of motor control, impaired learning	134
	pCP2-Cre mice *Mecp2*f/f (female) *Mecp2*f/y (male)	No change	No data	No data	PCs excitability ↓	141
Nlgn 1-4	*Nlgn*-3 R451C KI mice	Size, volume ↑ (crus II, paraflocculus)	No data	No data	No data	129
	Nlgn-3-KO mice *Nlgn*-R451C mice	No data	No data	No data	Motor hyperactivity. repetitive behaviour	143
	Nlgn-3-KO mice	No data	PC dendrites ↑	mGluR LTD at PF-PC synapses ↓	No data	92
	Nlgn (1,2 and 3) KO mice	No data	CF inputs PC ↓	Inhibitory synapse ↑ CF synapses PC ↓	CF AMPAR-EPSC ↓	145
	PV-Cre/ *Nlgn*-123 cKO mice	No change	No data	Inhibitory stellate cells ↓	NMDAR input ↓	146
	Nlgn-3-R451C mice	No change	CF input to PC ↓	No data	PC mIPSC frequency ↑ PC I/E balance ↑	147
	Nlgn-4-KO mice	Volume ↓	No data	No data	No data	142
Tsc1	$L7^{Cre}$; $Tsc1^{+/+ (L7Cre)}$ $Tsc1^{flox/flox}$ mice	No data	PC loss, Spine density ↑ , Abnormal axon collaterals	No data	PC firing ↓ R-Input ↓ PC excitability ↓	100
Tsc2	$Tsc2^{+/flox}$, $Tsc2^{+/KO}$ mice	No data	PC loss	No data	No data	157
	$Tsc2^{+/-}$ rats	Vermis ↑ Myelination ↓ Microglia ↑	PC loss	No change	No data	103

showed that transgenic mice overexpressing Cyfip1 protein display enrichment of the synaptic organiser neurexin-1 at CF inputs of PC primary dendrites and concomitantly enhanced CF-EPSCs in PCs (Busch et al., 2023).

Shank3 gene encodes an important scaffold protein of postsynaptic density (PSD) involved in recruiting several critical synaptic proteins, including AMPA, mGluR and NMDA glutamate receptors, and cytoskeletal proteins (Naisbitt et al., 1999; Ross and Aizenman, 2023). The human equivalent *SHANK3* gene is one of the leading genes of ASD, with over a hundred models available. *Shank3* mutant mice exhibit ASD-like behaviours, with loss of function leading to neurobehavioral signs. In the cerebellar context, *Shank3* expression is limited to granule cells, unlike *Shank1* and *Shank2* enriched in PC dendrites (Bockers et al., 2004). The effects of high-risk ASD mutations *Shank3* on cerebellar morphology and synaptic functions are a subject of future investigation.

Scn2A gene encodes for the pore-forming α subunit of $Na_V1.2$ channel (Scn2a and human equivalent SCN2A protein). Mutations in *SCN2A* have been associated not only with epileptic syndromes but also with intellectual disability and ASD (Varghese et al., 2017). In the cerebellum, $Na_V1.2$ is enriched at the axon initial segment in granule cells (Osorio et al., 2005), with loss of function impairing high-frequency transmission and plasticity at MF input to PCs.

Csmd3 a novel giant gene (the equivalent of human CSMD3), encodes a protein with CUB and sushi multiple domains (CSMDs) implicated in ASD (Shimizu et al., 2003; Xi et al., 2023). While the underlying mechanisms of CSMD3 in ASD are largely unknown, it was recently shown that the loss of CSMD3 protein results in abnormal morphology, increased intrinsic excitability and impaired synaptic plasticity in PCs, including abnormal development of dendrites and spines. Combined Ca^{2+} imaging and electrophysiological recordings showed an enhanced excitability of PCs, increased excitatory synaptic inputs, and an impaired long-term depression at the PF inputs (Xi et al., 2023).

8. Integrated outlook on cerebellar impairments in ASD models

As emerges from the above discussion, in genetic models of ASD, signs resembling human ASD can be induced by global as well as cell-specific gene manipulations. Analysis and cross-model comparison of changes in the cerebellum show they can be loosely grouped into six categories: (1) changes in cerebellar morphology and volume; (2) alterations in neuronal development and dendritic geometry; (3) aberration in dendritic spines and spine developments; (4) impairment of cerebellar myelination (5) gliosis with activation of astrocytes and microglia and (6) abnormal synaptic transmission and plasticity (Table 1, Fig. 6). While some impairments are present in many or all four models, others are genotype-specific and show substantial mode-to-model variability.

The most common characteristic emerging from our analysis is altered cerebellar morphology and volume (Fig. 6). In *Fmr1*, *Mecp2* and *Nlgn4* KO male mice, the cerebellar volume is reduced (Saywell et al., 2006; Steadman et al., 2014; Jamain et al., 2008; Huber, 2006), owing to abnormal proliferation of granule cells (Lee et al., 2022; Cheng et al., 2018), change in the density of cell packing (Belichenko et al., 2008) and potentially also to loss of specific groups of neurons (Kutna et al., 2022; Russell et al., 2007; Reith et al., 2013). Alterations in the morphology of the dendritic tree of *Fmr1* global and PC-specific KO (Koekkoek et al., 2005) also might contribute to reduced cerebellar volume. Remarkably, *Nlgn3* R451C KI cerebellum showed differential changes across regions, with crus II of the ansiform lobule and in paraflocculus enlarged in homozygote females (Steadman et al., 2014). In contrast, the Mecp2tm1Hzo mice and *Tsc2*$^{+/-}$ rats showed a gender-independent general enlargement of the cerebellar vermis (Kutna et al., 2022). Unlike *Fmr1* and *Mecp2* showing no evidence for gliosis, the larger cerebellar volume *Tsc2*$^{+/-}$ rat might result from astrogliosis and enhanced proliferation of microglia (Kutna et al., 2022). Other impairments of neuronal and glial morphology and connectivity, including retarded

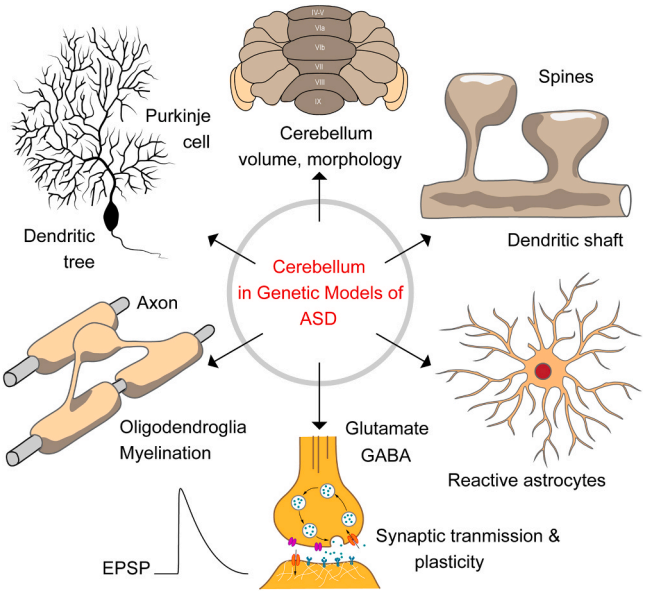

Fig. 6. A summary diagram illustrating cerebellar alterations described in genetic models of ASD. Overall, six groups of effects have been identified in *Fmr1*, *Mecp2*, *Nlgn3/4*, and *Tsc1/2* cerebellum: (1) modifications in cerebellar morphology and volume, (2) abnormal geometry and expansion of the dendritic tree of PCs, (3) changes in the shape and development of dendritic spines in PCs, (4) retardation in development of myelin sheath and oligodendroglia deficiency with myelin loss, (5) activation of astrocytes and microglia and (6) structural and functional alterations in glutamatergic synapses and impairments of synaptic plasticity. Detailed descriptions of these changes are listed in Table 1 and discussed throughout the review.

elimination of CF inputs and slowed maturation of PC dendritic spines (Koekkoek et al., 2005; Uchigashima et al., 2021), might also impact the cerebellar volume and morphology of ASD models (Table 1).

Changes in dendritic morphology and connectivity in ASD infer alterations in synaptic structure and functions, which is the next broadly shared trait in preclinical models, also showing considerable model-specific variability. Elongated and distorted spines of PCs in global and PC-specific *Fmr1* KO mice without changes in spine density (Koekkoek et al., 2005) imply altered excitatory inputs, in line with abnormal synaptic activity and mGluR1-dependent LTD (Iliff et al., 2013). Similar effects have been observed in PCs of *Nlgn3* KO mice showing reduced mGluR-dependent synaptic plasticity (Baudouin et al., 2012). Unlike *Fmr1* KO mice, the dendritic spine density of PCs in *Nlgn3/4* KO was lower than in wild-type controls (Kloth et al., 2015). Of note, impairments of excitatory synapses in ASD models can be input-specific, given the differential response of CF-PC versus the PF-PC synapses in *Nlgn1–3* KO mice (Zhang et al., 2015; Piochon et al., 2014). Importantly, cerebellar GABAergic interneurons also could contribute to ASD signs, as showcased by abnormal NMDA signalling at stellate interneurons of conditional KO of Nlgn 1–3 genotypes (Zhang and Sudhof, 2016). The alterations in excitatory and inhibitory drive in PCs would degrade the efferent code in time and frequency dimensions (Hausser and Clark, 1997; Hausser et al., 2004; Hoebeek et al., 2005; Ovsepian and Friel, 2012). In line with the results of *Nlgn* studies, PC excitability and firing activity have also been altered in global *Tsc1*$^{-/-}$ and *Tsc1*$^{+/-}$ mice (Tsai et al., 2012), which could be attributed to phenotypic convergence of the effects of multiple genes and gene groups. Notably, selective Mecp2 deletion in PCs also dampened their intrinsic excitability by reducing the SKCa (Xu et al., 2023), suggesting that ASD mutations could have dual, pre- and postsynaptic effects.

Changes in cerebellar volume and morphology could also result from abnormalities of glial cells, with high-risk ASD mutations reported to affect oligodendrocytes, astrocytes and microglia (Vargas et al., 2005;

Kutna et al., 2021, 2022; Pacey et al., 2013, 2015; Cheng et al., 2018). In the cerebellum, global *Fmr1* KO slows down myelination (Pacey et al., 2013), affecting oligodendrocyte shielding of mossy and climbing fibres and axons of PCs (Buyanova and Arsalidou, 2021; Barron et al., 2018; Brodal, 1998). Analysis of the white matter of *Tsc2*$^{+/-}$ also showed decreased myelination, as evident from reduced MBP, which aligns with the oligodendroglial pathology (Kutna et al., 2022). Both ASD models also show elevated GFAP expression, suggesting astrocyte activation (Kutna et al., 2022; Pacey et al., 2013), with TSC2$^{+/-}$ also displaying signs of increased microglial activity (Kutna et al., 2022). Given the fine grading of the myelination of various axon types in the cerebellum (Buyanova and Arsalidou, 2021; Brodal, 1998) and the role of astrocytes and microglia in synaptic homeostasis (Tewari et al., 2024; Chung et al., 2015; Garland et al., 2022), these changes will likely alter the information processing and flow within the cerebellar circuits and communication with functional targets.

Overall, presented so far evidence from ASD models implies that global and cell-type specific changes in the cerebellum can affect multiple non-motor functions, mimicking signs of human ASD. While the nature of neural computations contributing towards mechanisms and shared phenotypes between various models and human ASD remain elusive, neuro-behavioural impairments induced by both, global and cell-specific genetic manipulations support the premise that the ASD phenotypes taxing cerebellum can result from its general deficit, which aligns with the developmental nature of the disease condition.

9. Summary and conclusions

The fundamental premise of the functional system-centred model of ASD is that the symptoms of the disease might be related to impairments in selected groups of neurons or functional networks. Through extensive connections with the brain stem, basal ganglia, thalamus and cerebral cortex, the cerebellum controls and coordinates a wide range of neural mechanisms, contributing to motor and non-motor functions (Schmahmann, 2019; Ovsepian et al., 2013; Muscinelli et al., 2023; Schmahmann et al., 2019). Mounting evidence from neuroimaging studies of patients and postmortem examination of brain tissue strongly suggest that the abnormalities and damage in the cerebellum can lead to symptoms of ASD, prompting discussions and research of the "little brain" as one of the critical neural hubs affected (Kutna et al., 2021; Kloth et al., 2015; Piochon et al., 2014; D'Mello and Stoodley, 2015; O'Halloran et al., 2012). Due to significant risks to patient safety and ethical considerations, most mechanistic analysis of cerebellar impairments in ASD is carried out in animal models.

In this article, we revisited the evidence suggesting structural, functional, and molecular changes in the cerebellum of the four most widely characterised rodent models of ASD to identify commonalities that might account for or contribute towards their phenotypic convergence. The effects of mutations in *Fmr1*, *Mecp2*, *Nlgn3/4* and *Tsc1/2*, were critically reviewed with reference to cerebellar impairments and impact on motor, cognitive and affective domains. Although it is not possible to draw a direct link between changes observed in the cerebellum of animal models and clinical signs of ASD in humans, some morpho-functional alterations revealed herein through the analysis and cross-comparison of preclinical models provide clues into the pathobiology of ASD and underscore the potential significance of cerebellar impairments. The first and most prominent group of cellular impairments traversing many preclinical reports is synaptopathy and related impairments of CF and PF glutamatergic inputs and altered synaptic plasticity of PCs. These changes impair PC output and cerebellar computation, which is detrimental to integrative processes. The second group of cellular abnormalities that also emerges from most studies is the pathological response of glial cells manifested in dysfunction of oligodendrocytes with loss of myelin and activation of astrocytes and microglia. Given the critical role of myelination in neuronal communication, the loss of myelin would alter the conductive mechanisms and flow of information within the cerebellar circuits and functional targets. Finally, many reports indicate compensatory remodelling of cerebellar circuits, exemplified by ectopic synaptic contacts and maintenance of multiple climbing fibre inputs of PCs at the later developmental stages. As discussed, these changes along with degenerative processes can lead to abnormalities in cerebellar morphology and volume, reported in most analysed genotypes.

Although the specific ASD-related impairments of cerebellar mechanisms and their impact on large-scale network dynamics need to be explicitly shown, altered coding of time-varying information of individual PCs and disturbed temporal relations within cerebellar neurons and long-range targets might play a critical role (Fortier et al., 1993; de Solages et al., 2008). We anticipate that discussed herein discoveries in preclinical models will stimulate future research and understanding of the pathobiology of human ASD, to guide future translational studies and therapeutic interventions.

CRediT authorship contribution statement

Saak Ovsepian: Writing – review & editing, Writing – original draft, Visualization, Supervision, Project administration, Methodology, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Reza Asadollahi:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation. **Valerie O'Leary:** Writing – review & editing, Writing – original draft, Visualization. **Susan Shorter:** Writing – review & editing, Conceptualization. **Viera Kutna:** Writing – review & editing, Formal analysis, Data curation, Conceptualization. **Artem Grigoryan:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation. **Konstantin Yenkoyan:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Project administration, Methodology, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of Competing Interest

The authors have no conflict of interest to report.

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Authors' contributions

K.Y., S.S., V.K. and S.V.O. conceived the study. K.Y., A.G., R.A., and S.V.O., wrote the manuscript. K.Y., V.B.O., and S.V.O. prepared the illustrative material. K.Y., A.G., V.K., S.S., V.B.O., R.A., and S.V.O. revised and commented on various draft versions. All authors have reviewed and approved the final version of the manuscript for submission.

Data Availability

No data was used for the research described in the article.

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