INTRODUCTION

Genetic cerebellar ataxias are a group of disabling disorders that share progressive incoordination of movement due to dysfunction and degeneration of the cerebellum as their main hallmark. The advent of next-generation sequencing technologies greatly advanced the identification of genes involved in ataxia. However, despite the increasing number of genes identified, treatment attempts are still limited to relieving symptoms and do not target the underlying biological mechanisms. Development of effective therapies is hampered by an enormous genetic heterogeneity, the rarity of some of the subtypes, and the limited knowledge of biological processes in which ataxia genes exert their function. Identification of shared biological modules between genes mutated in ataxia (from here onwards referred to as ataxia genes) would provide a basis for therapeutic strategies that could be applied to larger cohorts of ataxia patients, in spite of their heterogeneous genotypic background. In recent years, efforts have been made to identify common denominators of genetic ataxias. A number of ataxia genes were found to share interaction partners at protein level and to be involved in processes such as RNA splicing, regulation of transcription, and cell cycle.

In this study, we systematically analyse the genes to date implicated in cerebellar ataxia, their functional biological pathways and their expression in the developing human brain. Our integrative study identifies common denominators that underlie progressive cerebellar degeneration and ataxia, including a cerebellum-specific mechanism affected in a subgroup of ataxia disorders that may account for region-specific degeneration and defective stress defence pathways as underlying mechanism to the large majority of ataxia disorders to which the cerebellum is in particular sensitive.

MATERIALS AND METHODS

Cerebellar ataxia gene selection and classification

The Human Phenotype Ontology database (download November 2015) was used to search for genes associated with ataxia. A list of 347 genes was obtained (online supplementary table S1) and manually curated using PubMed and OMIM. Genes associated with progressive cerebellar ataxia as prominent clinical manifestation, either in isolation or as part of a more complex phenotype, were included. Primary metabolic disorders, genes associated with cerebellar hypoplasia and genes inconsistently associated with cerebellar ataxia were excluded.

Gene ontology analysis

The webtool G-profiler (rev 1760, build October 2018) was used to perform gene ontology analysis.
**Enrichment analysis**

Enrichment scores for GO terms were calculated as followed: \((a/b)/(c−a)/(d−b)\), where \(a\) is the number of genes in the ataxia category associated with that GO term, \(b\) is the total number of genes in the ataxia category, \(c\) is the total number of genes in the genome category associated with that GO term or, for GO analysis of BrainSpan data, the total number of genes associated with that GO term remaining after filtering out low expressed genes from BrainSpan data and \(d\) is the total number of annotated human genes present in Ensembl (20,313 genes) or, for GO analysis of BrainSpan data, the total number of genes remaining after filtering out low expressed genes from BrainSpan data (16,956 genes).

**Protein-protein interaction network**

Protein-protein interactions (PPI) between CA genes were obtained from GeneMANIA, HPRD and BioGrid and included physical interactions, predicted interactions, shared protein domains and pathways. All interactions were combined and assembled in a reference network using Cytoscape (V.3.1.1.) and duplicates were removed from the reference network.

**Physical interaction enrichment score**

We used the physical interaction enrichment (PIE) algorithm to account for biases in the number of reported protein interactions for disease-associated genes in the generated reference PPI network. PIE scores and associated \(p\) values were calculated against 10,000 random protein groups obtained by number-matched subsamplings selected from the reference PPI network for all four ataxia gene categories, as previously described.

**BrainSpan developmental transcriptome analysis**

The publicly available developmental transcriptome RNA sequencing (RNAseq) data from the Human BrainSpan atlas was used for ataxia gene expression analysis. BrainSpan provides RNaseq count data represented as RPKM of 11 targeted neocortical human brain regions and 5 targeted non-neocortical brain regions. Details on samples, sequencing protocols and RNA expression analysis can be found at the BrainSpan website (http://www.brainspan.org). First, low expressed genes, with an average expression <0.05 RPKM over brain developmental stages and regions, were filtered out. Data were then binned into nine stages, spanning important developmental milestones of the prenatal and postnatal human brain. On average, three samples per developmental stage and brain structure were available (online supplementary table S2). Samples were not sex-matched. EdgeR (V.3.16.5) and Limma (V.3.30.7), provided by the online service Bioconductor, were used to identify the differentially expressed genes between the 16 brain regions separately over the developmental stages. Genes were considered to be differentially expressed between two brain regions if their adjusted \(p\) value passed the <0.05 threshold (Benjamini-Hochberg correction for the number of differentially expressed genes). No Log2FC threshold was set for the differential expression analysis. Graphpad Prism V.5.0 contingency tables and Chi Square and Fisher’s exact (in case of groups containing less than five genes) two-tailed tests were used to calculate whether ataxia gene expression was significantly enriched in the cerebellum compared with the rest of the brain. GENE-E (V.3.0.215, www.broadinstitute.org) was used to hierarchically cluster average RPKM values of ataxia genes in the cerebellum over the nine defined developmental stages.

**RESULTS**

A systematic catalogue of genes associated with progressive cerebellar ataxia

We generated a manually curated systematic catalogue of 103 disorders consistently associated with progressive cerebellar ataxia, corresponding to 71 annotated protein-coding genes (online supplementary table S1). Of the 71 genes that met our criteria, mutations in 42 of the genes follow recessive inheritance and mutations in 31 of the genes follow dominant inheritance. Two genes, SPTBN2 and AFG3L2, have been described in both dominant and recessive ataxia. Generally, mutations associated with recessive ataxia are loss of function mutations, whereas dominant ataxias can be caused by a combination of gain and/or loss of function mutations. Several genetic ataxias are caused by unstable repeat expansions that can occur in non-coding and coding regions of the genome. Eight of these (ATXN1, ATXN2, ATXN3, ATXN7, ATXN8, CACNA1A, TBP and ATN1) contain/represent translated trinucleotide repeats that encode for polyQ residues and follow dominant inheritance.

**Genes involved in ataxia function in common biological processes**

Differences in the type of mutations and phenotypes between recessive and dominant ataxias suggest that in spite of shared clinical features, different biological mechanisms might underlie these disorders. To examine whether recessive, dominant and polyQ ataxia genes are associated with distinct biological functions, GO analysis was performed on the three gene categories. Recessive ataxia genes were significantly enriched for catalytic activity, acting on DNA (\(p=2.23 \times 10^{-4}\)), DNA repair (\(p=2.02 \times 10^{-4}\)) and cellular response to stress (\(p=8.30 \times 10^{-4}\)) (figure 1A). Dominant ataxia genes were significantly enriched for nuclear matrix (\(p=0.031\)), somatodendritic compartment (\(p=0.015\)) and dendrite (\(p=0.018\)) (figure 1B). Ataxia genes encoding polyQ expansions were significantly enriched for regulation of cellular biosynthetic process (\(p=0.025\)), nuclear periphery (\(p=5.56 \times 10^{-5}\)), nuclear matrix (\(p=2.31 \times 10^{-5}\)) and nuclear inclusion body (\(p=0.007\)) (figure 1C). Despite these differences, the shared clinical hallmarks of genetic ataxias suggest that ataxia genes/proteins might affect common biological pathways or processes. To identify such common biological themes, we also analysed the combined ataxia gene catalogue. We found a significant enrichment for most of the GO terms revealed by the separate analyses of genes underlying ataxia subtypes, including cellular response to stress (\(p=0.002\)) and DNA repair (\(p=6.32 \times 10^{-4}\) (recessive), somatodendritic compartment (\(p=0.004\) (dominant) and nuclear inclusion body (\(p=0.034\)) (polyQ) (figure 1D). Interestingly, analysis of the contribution of recessive and dominantly inherited ataxia genes to the identified GO terms revealed a shared contribution to nearly all processes (figure 1D).
Figure 1  Cerebellar ataxia genes function in common biological processes. Gene ontology (GO) terms significantly enriched among (A) recessive ataxia genes, (B) dominant ataxia genes, (C) dominant ataxia genes with polyglutamine (polyQ) expansion, (D) all ataxia genes (all GO terms passed Bonferroni correction for multiple testing, p<0.05).
supporting an overlapping molecular pathology underlying both dominant and recessive ataxias. Moreover, several GO terms, such as those linked to calcium ion transmembrane transport (p = 0.004), neuron projection (p = 8.41e-5) and adult walking behaviour (p = 0.010), were only highlighted if the analysis was applied to the complete catalogue of ataxia genes and might be more representative of the shared hallmarks between recessive and dominant progressive cerebellar ataxias. Alternatively, they were not detected in the analyses of the separate groups due to limited statistical power of the smaller group sizes.

Genes involved in ataxia show high connectivity on the protein level

Physical and functional interactions of proteins provide the basis of biological pathways and are crucial to understand cellular function. We evaluated whether our catalogue of ataxia proteins shows significant molecular connectivity. For this, we collected PPI data from three large databases and combined these into a reference network (figure 2A). We found that 46 of the proteins physically interacted with other proteins present in the ataxia catalogue. Of these 46 proteins, 17 proteins were connected in small modules (pairs, trimers and hexamers), whereas 29 proteins formed a single major network with 30 interactions (figure 2A). Interestingly, within these modules and networks, proteins associated with recessive, dominant and polyQ progressive ataxia are jointly represented, demonstrating a biological overlap regardless of inheritance type or mutational mechanism (figure 2A).

To assess the significance of the identified connectivity, PIE scores and associated p values were calculated for all, and separately for recessive, dominant and polyQ ataxia proteins. This analysis revealed that ataxia proteins as a whole group interact twofold more than randomly expected (p < 0.001) (figure 2B). Recessive ataxia proteins interacted 2.1-fold more (p < 0.001), dominant ataxia proteins interacted 2.8-fold more (p < 0.001) and polyQ-associated ataxia proteins interacted 3-fold more (p < 0.05) (figure 2B). Thus, ataxia proteins are significantly interconnected. Since interactions between proteins underlie biological processes and pathways, we continued examining whether these represent specific biological processes. Individual small protein modules within the ataxia interactome (figure 2A, left side) were significantly enriched for processes such as calcium ion homeostasis (p = 0.003) and calcium ion transmembrane transport activity (p = 0.006), m-AAA complex (p = 4.36e-8), unfolded protein binding (p = 0.024), potassium ion transport (p = 0.026) and potassium channel activity (p = 0.007) (figure 2A, left side). The large module within the ataxia interactome was significantly enriched for DNA repair (p = 1.21e-4), DNA metabolism process (p = 1.78e-5), cellular response to stress (p = 0.009) and nuclear inclusion body (p = 0.001) (figure 2A, right side). Together, these results illustrate that ataxia proteins function in common biological networks and processes.

A subset of ataxia genes shows high relative expression specifically in the cerebellum

The basis for the preferential regional vulnerability of neurons in the cerebellum in genetic ataxias is mostly unknown. Temporal and spatial patterns of ataxia gene expression in the brain may significantly contribute to specific or preferential cerebellar degeneration when disturbed. To address this, we turned to the publicly available BrainSpan Transcriptional Atlas of the Developing Human Brain, as resource. After exclusion of low expressed genes, a transcription matrix of 16,956 genes representing the 16 brain regions was left that was binned into nine different developmental stages (figure 3A). We then calculated for each of the 16,956 genes per developmental period whether it was differentially expressed in the cerebellum, compared pairwise with any of the other 15 brain regions. From the resulting matrix, the ataxia genes were extracted and the percentage of ataxia genes differentially expressed (adj. p < 0.05) in the cerebellum compared with one or more other brain regions was calculated (data summary: online supplementary table S3, data per stage: online supplementary tables S4–S12) and visualised in a heatmap (figure 3B). Of note, the expression levels of three ataxia genes, TGM6, PIK3R5 and MTPAP, did not pass the threshold of very low expressed genes and were therefore excluded from further analyses. The expression of most ataxia genes in the cerebellum was not different from any of the other 15 brain regions (online supplementary table S3), and their average did not differ from the average genome-wide expression (online supplementary figure S1). However, the vast majority of those ataxia genes that did show differential expression to other brain regions, did so to all 15 of them (figure 3B, black square, online supplementary table S3). Their high relative expression level was specific to the cerebellum, suggesting their distinct requirement in this region of the brain. Interestingly, this pattern showed a sharp onset at birth, suggesting that these genes serve cerebellar function specifically at postnatal stages (figure 3B, black square).
Elevated cerebellar-specific expression predisposes to ataxia

We continued determining whether elevated relative expression in the cerebellum predisposes to ataxia. To address this, we calculated whether the amount of ataxia genes that were specifically elevated in the cerebellum for each developmental stage was higher than randomly expected, considering the genome-wide frequency of cerebellar elevated genes. Ataxia genes were more frequently elevated in the cerebellum during the postnatal stages 5–9 (infancy: p<0.001, early childhood: p<0.001, late childhood: p<0.001 and adolescence: p<0.01) than randomly expected (figure 3C). The following genes were specifically elevated in the cerebellum during one or more of the analysed developmental stages: ADCK3, ATM, ATN1, CACNA1A, DMT1, GRID2, GRM1, ITPR1, KCNA3, KCND3, SPTBN2, SYNE1 and TRPC3 (online supplementary tables S3–S12). To further examine whether a specific mode of inheritance or mutational mechanism was underlying this group of genes, the analysis was repeated for the recessive, dominant and polyQ ataxia gene categories. Also here, the expression of genes involved in either of these three categories was enriched in the cerebellum.
during postnatal development stages (figure 3D–F), suggesting that all of them contribute to the finding of cerebellum-specific postnatal enrichment of ataxia gene expression. Finally, we asked whether the genes that were not specifically elevated in the cerebellum during one of the nine developmental stages, were specifically elevated in one of the other 15 brain regions. We found that a small group of ataxia genes was specifically elevated in either the thalamus (GBA2, UCHL1, PRICKLE1 and ANO10) or striatum (CCDC88C and PDYN) during certain developmental stages compared with rest of brain. Not a single ataxia gene was significantly elevated in one of the remaining 13 specific brain regions. In summary, systematic analyses of brain expression across brain regions revealed that the expression of a subgroup of ataxia genes is specifically enriched in the postnatal cerebellum, likely driving the pathological features of these disorders.

**Cerebellar-specific expression patterns separate ataxia genes in distinct biological modules**

We next asked which functional biological modules are underlying the identified group of genes with cerebellar-specific expression. GO term analysis was performed on the lists of ataxia genes that showed enriched cerebellar expression during one or more of the developmental stages and ataxia genes that did not (online supplementary tables S3–S12). This revealed that ataxia genes that were specifically elevated in the cerebellum during one of the developmental stages were significantly enriched for neuronal and ion-related processes such as neuron apoptotic process \((p=0.030)\), hindbrain morphogenesis \((p=0.006)\), regulation of cytosolic calcium ion concentration \((p=0.031)\), synapse \((p=0.042)\) and transmembrane transporter activity \((p=0.024)\) (figure 3G). Ataxia genes that were not specifically elevated in the cerebellum during one of the developmental stages were significantly enriched for processes such as DNA repair \((p=0.003)\), cellular response to stress \((p=0.011)\) and inclusion body \((p=0.032)\) (figure 3G).

**Temporal gene expression patterns in the cerebellum cluster genes involved in progressive ataxia into two groups**

Finally, we also explored developmental expression profiles of ataxia genes in the cerebellum over time, to examine whether this provides further clues about dependence of the cerebellum on certain biological processes during specific stages of development (figure 4A, B). We hierarchically clustered the temporal expression patterns of ataxia genes in the cerebellum over the nine developmental stages, which unbiasedly separated the genes in two distinct clusters (figure 4B). Genes present in cluster 1 showed significant higher expression during prenatal stages compared with genes in cluster 2, and genes present in cluster 2 showed significant higher expression during postnatal stages compared with genes present in cluster 1 (figure 4A). Recessive, dominant and polyQ-associated ataxia genes contributed randomly to the two clusters (data not shown). However, genes expressed higher during prenatal stages (cluster 1) were enriched for DNA repair \((p=0.031)\) and cellular response to stress \((p=0.035)\), whereas genes with higher postnatal expression (cluster 2) were enriched for processes related to the cellular component synapse \((p=0.029)\), calcium ion transmembrane transport \((p=0.035)\) and metal ion transport \((p=0.028)\) (figure 4C). Ataxia genes can thus be distinguished based on their temporal expression profiles in the cerebellum, which links to specific biological processes.

**DISCUSSION**

We have here systematically mapped shared molecular pathways, processes and expression characteristics among ataxia causing genes, to increase our understanding of the biology of genetic ataxias and to identify mechanistic hubs that can serve as targets for therapeutic interventions. In comparison to previous studies, we generated a manually curated catalogue of genes involved in genetic ataxia and performed analyses across dominant and recessive forms of the disorder. Furthermore, we applied a strategy that integrated ataxia gene expression in developing human brain, GO and protein interaction network analysis, to get a comprehensive understanding of the vulnerability of the cerebellum and the molecular modules and processes affected in genetic ataxias.

Data in this study highlight the different biological processes that are implicated in recessive, dominant and polyQ ataxias, with recessive ataxias linked to cellular response to stress and DNA repair-related processes; dominant ataxias to dendrite-related processes and polyQ ataxias to nuclear inclusion body. The deleterious effect of the type of mutation on the protein, the expression timing profile, specificity and levels of the affected protein in the cerebellum and the sensitivity of the cerebellum to disruption of these processes might explain these different findings. Despite this, we found a shared contribution of recessive and dominant ataxia genes to nearly all biological processes, while processes such as calcium ion transmembrane transport were only enriched when applying GO analysis to the complete ataxia gene panel. In agreement with previous studies, we found that ataxia genes operate in networks with significantly enriched protein connectivity, demonstrating global coherence independent of inheritance mode or mutational mechanism. Notably, polyQ proteins interacted directly with other non-polyQ dominant and recessive ataxia proteins. This indicates that, in addition to common toxic gain-of-function mechanisms such as the formation of nuclear inclusion bodies, the disruption of the biological processes that these genes operate in likely contributes to the disease pathogenesis. This notion derived from our systematic analysis is supported by gene-focused studies, for example, of mouse models of SCA1, where ATXN1 loss-of-function phenotypes were very similar to ATXN1 gain-of-function phenotypes, and of SCA17 models demonstrating that impaired transcriptional activity of polyQ-expanded TBP contributes to disease pathogenesis. Together, our findings strongly support an overlapping molecular pathology between recessive and dominant ataxia subtypes. The identified protein modules represent different biological processes and ataxia proteins can broadly be separated in two themes: a large stress module and smaller ion homeostasis/synapse modules. The common end point of these modules is progressive degeneration of the cerebellum, and analysis of ataxia gene expression in the developing human brain suggested that these two modules might contribute differently to cerebellar vulnerability, depending on their specific and temporal cerebellar expression pattern (figure 5). Brain expression analysis demonstrated that elevated gene expression specifically in the postnatal cerebellum predisposes to ataxia. Genes with this pattern of expression are significantly overrepresented among ataxia genes. The normally high gene activity levels may explain the specific vulnerability of the cerebellum to deleterious mutations in these genes. Interestingly, the corresponding genes encode ion channels, calcium receptors, calcium-activated proteins enriched for transmembrane transporter activity and regulators of cytosolic calcium ion concentration. Most of them
Figure 4  Ataxia genes can be separated in two distinct clusters based on their temporal expression levels in the cerebellum. (A) Average reads per kilobase per million mapped reads (RPKM) value for ataxia genes present in cluster 1 and cluster 2 of figure 4B, for the indicated developmental stages. (red: cluster 1, blue: cluster 2, error bars represent SD). (B) Hierarchical clustering of ataxia gene expression levels during cerebellar development using Spearman’s correlation. Data were obtained from BrainSpan and mean RPKM values were calculated for the indicated developmental stages. Heatmap colour codes are based on median RPKM value per row (developmental stage), divided by the row standard deviation (blue: low expression in cerebellum compared with median, red: high expression in cerebellum compared with median). (C) Significantly enriched gene ontology (GO) terms for cluster 1 and cluster 2 from figure 4B (all GO terms passed Bonferroni correction for multiple testing, p<0.05).
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Figure 5 Ataxia genes can broadly be divided in two themes that affect neuronal homeostasis and when disrupted predispose to progressive cerebellar ataxia. Module 1: 13 genes are specifically elevated in the cerebellum during one or more developmental stages. Of these 13 genes, 7 are linked to Ion/Synapse function and 5 out of these 7 genes showed increased expression during postnatal cerebellar development compared with prenatal cerebellar development. Module 2: 55 genes do not show increased expression in the cerebellum. Of these 55 genes, 23 genes are linked to cellular response to stress and 12 out of these 23 genes show increased expression during prenatal cerebellar development compared with postnatal cerebellar development (data displayed in figures 2–4).

are part of the smaller ion homeostasis/synapse module we identified (figure 3). These results are similar to those obtained by Bettencourt et al, demonstrating that disruptive calcium signaling is important in a dominant ataxia gene, transcript-enriched, co-expression module relevant to Purkinje cells (PC).4 The cerebellum contains a unique neuronal cell type, the PC, that is central to ataxia pathobiology. PCs might be particularly vulnerable for alterations in ion homeostasis due to their extensive dendritic arbour that exhibit intense and highly regulated firing properties.21–23 The striking complexity of PC firing regulates sensorimotor integration and is highly dependent on calcium channels and calcium-activated potassium channels.21 In several ataxia models, PCs show reduced firing rate and dysregulated calcium homeostasis, even before the onset of clinical symptoms and PC degeneration.17 24 25 Reduced PC excitement enhances the excitability of efferent deep cerebellar nuclei neurons and this is sufficient to cause cerebellar ataxia even in the absence of PC degeneration.26 This shows that calcium homeostasis in PCs is crucial for proper sensorimotor integration and disruption of these processes likely affects PC firing properties, eventually leading to cerebellar degeneration and the onset of ataxia. Calcium is also an important messenger in intracellular signaling pathways, proteostasis mechanisms at ER and Golgi membranes and mitochondrial activity.27 28 The metabolic activity of PCs is high.29 Deficits in neuronal energy production and intracellular organelle systems that influence ion fluxes may thus be further factors that account for increased vulnerability of PCs. The energy provided for metabolism is provided by mitochondrial oxidative phosphorylation in the form of ATP. Increased calcium uptake by mitochondria leads to extensive oxidative phosphorylation and overproduction of reactive oxygen species (ROS).27 28 ROS overproduction in turn can lead to detrimental oxidative modifications of lipids, proteins and nucleic acids.30 31 Interestingly, the large identified protein module is enriched for the cellular stress response, and proteins present in this module are among others involved in mitochondrial maintenance, DNA repair, unfolded protein response and regulation of apoptotic and autophagic processes. We found that overall, these genes were not more elevated in the cerebellum during any of the analysed developmental stages. Thus, elevated cerebellar gene expression cannot account for preferential cerebellar degeneration. This suggests that, compared with other neuronal cell types, the PCs might be more vulnerable to insults related to a distorted cellular stress response. Interestingly, approximately half of the cellular stress response genes show higher expression during embryonic stages, arguing for a developmental predisposition in these cases. Ataxia genes with a function in DNA repair were abundantly represented in the stress module (figure 3). DNA breaks arising from oxidative damage are a major threat for the genome stability of mature postmitotic neurons. They are usually repaired by base excision repair and single strand break repair (SSBR).32 Interestingly, genetic ataxias such as SCAN1 and AOA1, are associated with DNA SSBR deficiencies, and animal models of these show

increased sensitivity to ROS.29 32 The genes mutated in these disorders, TPDI and APTX, do not show enriched cerebellar expression during any of the nine analysed developmental stages, which may indicate that SSBR is a key homeostatic process required for PCs for reasons unrelated to expression, such as their high metabolic activity, oxidative load and intrinsic firing properties. There is also a distinct subset of genes implicated in recessive ataxias that are involved in double strand break (DSB) repair. Double-stranded DNA breaks commonly occur during rapid proliferation of central nervous system (CNS) development and are less likely to occur in the matured nervoussystem.33 The cerebellum might be in particular vulnerable to disruption of DSB repair due to its development up until the first postnatal years, which will lead to the formation of the most abundant cell type in the CNS: the cerebellar granule neurons.29 This postnatal period of rapid and massive cell proliferation may generate replication stress-associated DNA damage that might affect the cerebellar granule neurons, and indirectly other cerebellar cell types such as the PCs to which they signal.32 Interestingly, ATM, a kinase that is involved in detection of DSBs and is mutated in ataxia telangiectasia (AT), shows enriched expression in the cerebellum exactly during this postnatal developmental stage. Since ATM is involved in DSB-induced apoptotic signalling, dysfunctional neurons may fail to be efficiently eliminated in the early AT cerebellum, and degenerate only later on.32 34 35 This is in agreement with the development of disorders, such as ataxia telangiectasia, that can fail to be efficiently eliminated in the early AT cerebellum, and degenerate only later on.32 34 35 This is in agreement with the fact that ATM-deficient PCs, DSB repair might also be required for cerebellar maintenance.32 34 35 Therefore, DSB repair is likely a key homeostatic process that maintains PC integrity.

In conclusion, while a number of molecular processes are involved in progressive cerebellar ataxia pathology, these interact and form a common end point: disrupted neuronal homeostasis, to which the cerebellum is either exclusively susceptible, or more than other brain regions. More experimental data are required to understand the dependence of the cerebellum on different aspects of neuronal homeostasis, such as calcium signaling, ROS and DNA repair, particularly in absence of region-specific expression levels. However, based on the here identified biological themes, it seems conceivable to propose therapeutic interventions that target deregulated calcium and ROS levels, or mechanisms that can decrease the harmful downstream effects of these deleterious insults.

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