Figures and figure supplements

Molecular pathway analysis towards understanding tissue vulnerability in spinocerebellar ataxia type 1

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Figure 1. Schematic illustrating the cross-tissue and cross-model comparisons conducted to identify common and unique molecular alterations across SCA1 affected tissues. Transcriptomics data from Atxn1^{154Q/2Q} KI inferior olive and cerebellum were first analyzed individually (1-2) before comparing the two tissues (3). Using the ATXN1-82Q Tg inferior olive, comparison of the Atxn1^{154Q/2Q} KI and ATXN1-82Q Tg inferior olive was assessed (4) before evaluating similarities and differences between ATXN1-82Q Tg affected tissues (5). Finally, a cerebellar cross-model comparison was conducted (6).

DOI: https://doi.org/10.7554/eLife.39981.002
Figure 2. Defense Response-related genes are significantly enriched in the 12 week old $\text{Atxn1}^{154Q/2Q}$ KI inferior olive. (A) PolyQ-expanded Atxn1 is expressed in the inferior olive of $\text{Atxn1}^{154Q/2Q}$ KI mice ($n = 2$ animals per genotype). * marks Atxn1-2Q and ** marks Atxn1-154Q. (B) Illustration of the Defense Response-related genes enrichment in the inferior olive. (C) Enrichment analysis of Defense Response-related genes in the inferior olive of $\text{Atxn1}^{154Q/2Q}$ KI mice. (D) Biological pathway enrichment analysis of Defense Response-related genes in the inferior olive of $\text{Atxn1}^{154Q/2Q}$ KI mice. (E) Heatmap of interferon stimulated genes (ISGs) expression in the inferior olive of $\text{Atxn1}^{154Q/2Q}$ KI mice. (F) RT-qPCR analysis of interferon stimulated gene expression in the inferior olive of $\text{Atxn1}^{154Q/2Q}$ KI mice. (G) Immunofluorescence images of Iba1 and Gfap expression in the inferior olive of control and $\text{Atxn1}^{154Q/2Q}$ KI mice. (H) Iba1+ cell counts and Gfap fluorescence intensity in the inferior olive of control and $\text{Atxn1}^{154Q/2Q}$ KI mice. (I) $\text{Ift7}$ expression in BV2 cells.
Figure 2 continued

brain region examined. (C) Total number of up- and down-regulated genes in the Atxn1^{154Q/2Q} KI inferior olive (FDR p-value < 0.05; n = 3 males per genotype). (D) Biological pathway enrichment for all differentially regulated inferior olive genes. X-axis marks enrichment score, with the significance cut-off marked by the vertical black line (p-value < 0.05), in this and all following graphs unless mentioned otherwise. (E) Interferon Stimulated Genes (ISGs) are significantly up-regulated in Atxn1^{154Q/2Q} KI. Orange coloring marks up-regulated genes. (F) Validation of up-regulated ISGs in 12 week old Atxn1^{154Q/2Q} KI inferior olive using RT-qPCR. All samples normalized to Gapdh and Actb reference genes. n = 3 males per group. *** p-value < 0.001. Error bars indicate SEM in this and all following graphs. (G) Immunofluorescence staining for Iba1-positive cell counts and Gfap fluorescence intensity imaged in the 12 week old Atxn1^{154Q/2Q} KI and WT control inferior olives. Scale bar is 300 μm. (H) Iba1 cell body counts and Gfap fluorescence intensity quantified relative to WT controls as a percentage. *p < 0.05; t-test; n.s. = non significant (n = 3 males and females per genotype). (I) Irf7 mRNA expression is significantly up-regulated in BV2 cells expressing human ATXN1-82Q (*p < 0.05, t-test; n = 4 wells per condition). DOI: https://doi.org/10.7554/eLife.39981.003
Figure 2—figure supplement 1. Response to Organic Substance and Hormone Metabolic Process genes are differentially regulated in the 5 week old Atxn1154Q/2Q KI inferior olive. (A) Illustration of the tissue examined. (B) Total number of up- and down-regulated genes in Atxn1154Q/2Q KI inferior olive at 5 weeks of age (FDR p-value < 0.05; n = 3 males per genotype). (C) Biological pathway enrichment for all differentially regulated inferior olive genes. X-axis marks enrichment score, with the significance cut-off marked by the vertical black line (p-value < 0.05). Genes with an FDR p-value < 0.05 were used to generate the enriched pathway list. (D) Response to Organic Substance and (E) Hormone Metabolic Process-related genes are largely up-regulated. Y-axis represents the normalized FPKM expression of each gene relative to control samples as a percentage. (* FDR p-value < 0.05; ** FDR p-value < 0.01; n = 3 males per genotype used in RNA-seq).

DOI: https://doi.org/10.7554/eLife.39981.004
Figure 2—figure supplement 2. Features of the Defense Response, including Interferon Signaling and IRF Activation, are predicted to have increased activity in the 12 week old Atxn\(^{154Q/2Q}\) KI inferior olive. (A) Biological pathway enrichment using Qiagen’s IPA in the 12 week old Atxn\(^{154Q/2Q}\) KI inferior olive differentially expressed genes. X-axis marks the enrichment score using a Benjamini-Hochberg corrected p-value. Bars that surpass the vertical threshold at 1.3 indicate significant enrichment for that pathway. Orange coloring indicates IPA-predicted activation of that pathway, while blue suggests possible inhibition based on z-score. Grey is not predicted. (B) Predicted upstream regulators for all differentially expressed Atxn\(^{154Q/2Q}\) KI inferior olive genes at 12 weeks. Orange nodes indicate predicted activation of those transcriptional regulators, blue indicates predicted suppression, and grey has no predicted activation or inhibition. Orange edges connecting transcriptional regulators indicate predicted activation, yellow are findings inconsistent with previous research, and grey is not predicted.

DOI: https://doi.org/10.7554/eLife.39981.005
Figure 2—figure supplement 3. Subset of genes associated with the enriched biological pathway Neurological System Process are down-regulated in the 12 week old Atxn1154Q/2Q KI inferior olive. (A) Down-regulated genes within the Neurological System Process pathway (** FDR p-value < 0.01; n = 3 males per genotype used in RNA-seq analysis). (B) Validation of Calb1 down-regulation using RT-qPCR. All samples were normalized to Gapdh and Actb reference genes (** p-value < 0.01 t-test; n = 3 males per genotype).

DOI: https://doi.org/10.7554/eLife.39981.006
Figure 2—figure supplement 4. Divergent gene expression changes and minimal biological pathway overlap in the temporal comparison of the Atxn1^{154Q/2Q} KI inferior olive. (A) Schematic of the time-point comparison in Atxn1^{154Q/2Q} KI inferior olive between 5 and 12 weeks. (B) Total number of divergent significant genes between 5 and 12 weeks. (C) Correlation of Log Fold Change (LFC) for both age groups. (D) Top canonical pathways for the 5 and 12 week Atxn1^{154Q/2Q} KI inferior olive. (E) Normalized expression of selected neuroactive genes in Atxn1^{154Q/2Q} KI inferior olive at 5 and 12 weeks. (F) Analysis of selected genes for the response to organic substance pathway. (G) Analysis of selected genes for the system process pathway.
differentially regulated genes in the Atxn1$^{154Q/2Q}$ KI inferior olive relative to appropriate WT controls that are common, and uniquely altered, across time-points (FDR p-value < 0.05; n = 3 males per genotype for RNA-seq). (C) Dot plot of log fold changes for genes altered in the 5 and 12 week Atxn1$^{154Q/2Q}$ KI inferior olive. X-axis marks log fold change values in the 5 week Atxn1$^{154Q/2Q}$ KI, and the Y-axis marks log fold change values for the 12 week dataset. Pink nodes mark genes significantly altered only at the 5 week time-point, blue nodes mark genes significantly altered only at the 12 week time-point, and black marks genes significant at both time-points. (C') Log fold change of genes up- or down-regulated at both the 5 and 12 week time-points only. Linear regression analysis identified the slope and R$^2$ of these log fold changes (slope = $1.03 \pm 0.07$; R$^2$ = 0.90). A total of 29 genes were plotted in this analysis. (D) Clustering of GO terms identified from the Atxn1$^{154Q/2Q}$ KI inferior olive 5 week and 12 week differentially regulated gene lists relative to the appropriate WT controls. (E) A subset of genes associated with Neuropeptide Hormone Activity were commonly down-regulated at each time-point. (F) A subset of Response to Organic Substance genes were up-regulated, and (G) some System Process-related genes were dysregulated when assessed in the 5 and 12 week time-point. * FDR p-value < 0.05; ** FDR p-value < 0.01.

DOI: https://doi.org/10.7554/eLife.39981.007
Figure 3. Chemical Synaptic Transmission genes, including GABAergic and glutamatergic genes, are differentially regulated in the 12 week old Atxn1<sup>154Q/2Q</sup> KI cerebellum. (A) Illustration of the tissue examined. (B) Total number of up- and down-regulated genes in the 12 week old Atxn1<sup>154Q/2Q</sup> KI cerebellum (FDR p-value < 0.05; n = 3 males per genotype for RNA-seq). (C) Biological pathway enrichment for all differentially regulated cerebellar genes. (D) GABAergic and glutamatergic receptors and receptor subunits are altered in the cerebellum (* FDR p-value < 0.05, ** FDR p-value < 0.01; n = 3 males per group).

DOI: https://doi.org/10.7554/eLife.39981.014
Figure 3—figure supplement 1. Few genes and pathways are significantly enriched in the 5 week Atxn1^{154Q/2Q} KI cerebellum. (A) Illustration of the tissue examined. (B) Total number of up- and down-regulated genes in Atxn1^{154Q/2Q} KI cerebellum at 5 weeks of age (FDR p-value < 0.05; n = 3 males per genotype for RNA-seq). (C) Biological pathway enrichment for all differentially regulated genes in the 5 week old Atxn1^{154Q/2Q} KI cerebellum. (D) Reproductive Process and (E) Transcription Factor Binding-related genes are largely down-regulated in the 5 week Atxn1^{154Q/2Q} KI cerebellum. * FDR p-value < 0.05 (n = 3 males per genotype used in RNA-seq).

DOI: https://doi.org/10.7554/eLife.39981.015
Figure 3—figure supplement 2. Consistent gene expression changes in the Atxn\textsuperscript{154Q/2Q} KI cerebellum across the 5 and 12 week time-points. (A) Schematic of the time-point comparison in Atxn\textsuperscript{154Q/2Q} KI cerebellum. (B) Total number of differentially regulated genes in the Atxn\textsuperscript{154Q/2Q} KI cerebellum that are commonly altered in both the 5 and 12 week time-point relative to appropriate WT controls (FDR p-value < 0.05; n = 3 males per genotype for RNA-seq). (C) Dot plot of log fold changes for genes altered in the 5 and 12 week Atxn\textsuperscript{154Q/2Q} KI cerebellum. (C') Log fold change of genes up- or down-regulated at both the 5 week and 12 week time-points only. Linear regression analysis identified the slope and R\textsuperscript{2} of these log fold changes (slope = 1.30 ± 0.13; R\textsuperscript{2} = 0.86). A total of 17 genes were plotted in this analysis. (D) A subset of genes were commonly down-regulated and (E) commonly up-regulated at both time-points. * FDR p-value < 0.05; ** FDR p-value < 0.01 (n = 3 males per genotype for each time-point).

DOI: https://doi.org/10.7554/eLife.39981.016
Figure 3—figure supplement 3. Nominally significant differentially regulated genes in the 5 week old Atxn1^{154Q/2Q} KI cerebellum overlapped with previously published microarray datasets and revealed significantly enriched pathways. (A) Subset of genes with a nominal p-value < 0.01 that overlapped with a previously published dataset (* nominal p-value < 0.01 but FDR p-value > 0.05; n = 3 males per genotype used in RNA-seq). (B) Total number of up- and down-regulated genes in Atxn1^{154Q/2Q} KI cerebellum at 5 weeks of age (p-value < 0.01; n = 3 males per genotype for RNA-seq). (C) Biological pathway enrichment for all differentially regulated cerebellum genes with a nominal p-value < 0.01.

DOI: https://doi.org/10.7554/eLife.39981.017
Figure 3—figure supplement 4. Consistent gene expression changes and pathway enrichment in the 5 week and 12 week Atxn1<sup>154Q/2Q</sup> KI cerebellum with an expanded 5 week p-value cutoff. (A) Schematic of the time-point comparison in Atxn1<sup>154Q/2Q</sup> KI cerebellum. (B) Total number of differentially regulated genes in the Atxn1<sup>154Q/2Q</sup> KI cerebellum relative to appropriate WT controls that are common, and uniquely altered, in each time-point.

Figure 3—figure supplement 4 continued on next page.
C) Dot plot of log fold changes for genes altered in the 5 and 12 week Atxn1^{154Q/2Q} KI cerebellum. Nominal p < 0.01 for the 5 week dataset, FDR p-value < 0.05 for the 12 week dataset. (C') Log fold change of genes up- or down-regulated in both the 5 week and 12 week time-points only. Dysregulated gene were excluded from this analysis. Linear regression analysis identified the slope and R^2 of these log fold changes (slope = 1.53 ± 0.10; R^2 = 0.78). A total of 73 genes were plotted in this analysis. (D) Clustering of GO terms identified from the Atxn1^{154Q/2Q} KI cerebellum 5 week and 12 week differentially regulated gene lists relative to the appropriate WT controls. For this analysis, genes with a nominal p-value < 0.01 were used to generate the GO list for the 5 week Atxn1^{154Q/2Q} KI cerebellum, and FDR p-value < 0.05 was used for the 12 week cerebellum. (E) A subset of genes associated with CNS Development were commonly up-regulated and (F) a subset of Synaptic Signaling genes were commonly down-regulated when assessed in the 5 and 12 week time-point. * nominal p-value < 0.01; ** FDR p-value < 0.01 (n = 3 males per genotype for each time-point).

DOI: https://doi.org/10.7554/eLife.39981.018
Figure 4. Cross-tissue comparison of pathway enrichment reveals common and unique features of the 12 week old Atxn\textsuperscript{154Q/2Q KI inferior olive and cerebellum. (A) Schematic of the cross-tissue comparison conducted. (B) Clustering of GO terms from the 12 week old inferior olive and cerebellum differentially expressed genes lists. In this and all following figures, nodes represent GO terms and edges connect nodes that share common genes. Edge width corresponds to the number of genes shared between nodes, and edge length represents the similarity coefficient between nodes. Color-
coded nodes represent GO terms from either the inferior olive (pink), cerebellum (blue), or GO terms shared by both tissues (purple). All GO terms were significantly enriched within the datasets (FDR p-value < 0.05). (C) Total number of differentially regulated genes that are common, and uniquely altered, in the 12 week old Atxn1154Q/2Q Ki inferior olive and cerebellum (FDR p-value < 0.05). (D) A subset of genes commonly up-regulated and (E) commonly down-regulated in both the inferior olive and cerebellum relative to WT controls (* FDR p-value < 0.05; ** FDR p-value < 0.01; n = 3 males per genotype for RNA-seq).

DOI: https://doi.org/10.7554/eLife.39981.025
Figure 4—figure supplement 1. Minimal gene overlap in the 5 week old Atxn1<sup>154Q/2Q</sup> KI cerebellum and inferior olive in the cross-tissue comparison. (A) Schematic of the cross-tissue comparison in the 5 week old Atxn1<sup>154Q/2Q</sup> KI inferior olive and cerebellum. (B) Total number of differentially regulated genes in the Atxn1<sup>154Q/2Q</sup> KI inferior olive and cerebellum relative to appropriate WT controls that are common, and uniquely altered, in each tissue (nominal p-value < 0.01 for cerebellum dataset; FDR p-value < 0.05 for inferior olive dataset; n = 3 males per genotype for RNA-seq). (C) Clustering of GO terms identified from the Atxn1<sup>154Q/2Q</sup> KI cerebellum and inferior olive differentially regulated gene lists relative to the appropriate WT controls. For cerebellum, nominal p-value < 0.01 was used to generate the list of enriched pathways, while FDR p-value < 0.05 was used for the inferior olive. (D) Genes differentially regulated in both the inferior olive and cerebellum relative to the appropriate WT controls were up-regulated, dysregulated, and down-regulated. * nominal p-value < 0.01; ** FDR p-value < 0.01 (n = 3 males per genotype for each time-point). DOI: https://doi.org/10.7554/eLife.39981.026
Figure 5. The Defense Response is enriched in both the 12 week old Atxn1^{154Q/2Q} KI inferior olive and ATXN1-82Q Tg inferior olive. (A) ATXN1 mRNA expression in the 12 week old ATXN1-82Q Tg cerebellum and inferior olive (**p < 0.001, t-test; n = 3 males per genotype). (B) PolyQ-expanded ATXN1 is present in the cerebellum, but not in the inferior olive (n = 2 males per genotype). * marks Atxn1-2Q, ** marks ATXN1-82Q. (C) Schematic of the cross-model, 12 week old inferior olive comparison. (D) Total number of differentially regulated genes that are common, and uniquely altered, in the inferior olive of Atxn1^{154Q/2Q} KI and ATXN1-82Q Tg mice (FDR p-value < 0.05). (E) Clustering of GO terms from the Atxn1^{154Q/2Q} KI and ATXN1-82Q Tg inferior olive differentially expressed genes lists. (F) Heatmap of log fold changes in Defense Response-related genes relative to control littermates from both the 12 week Atxn1^{154Q/2Q} KI and 12 week ATXN1-82Q Tg inferior olive. (G) Total number of differentially regulated genes linked to Defense Response that are common, and uniquely altered, in the 12 week old Atxn1^{154Q/2Q} KI and ATXN1-82Q Tg inferior olive (FDR p-value < 0.05).

DOI: https://doi.org/10.7554/eLife.39981.031
Figure 5—figure supplement 1. The majority of genes significantly altered in the 5 week ATXN1-82Q Tg inferior olive are up-regulated. (A) Illustration of the tissue examined. (B) Total number of up- and down-regulated genes in ATXN1-82Q Tg inferior olive at 5 weeks of age (FDR p-value < 0.05; n = 3 males per genotype for RNA-seq). (C) Biological pathway enrichment for all differentially regulated inferior olive genes. (D) Vasculature Development and (E) Enzyme-Linked Receptor Protein Signaling Pathway-related genes are largely up-regulated. * FDR p-value < 0.05; ** FDR p-value < 0.01 (n = 3 males per genotype used in RNA-seq).

DOI: https://doi.org/10.7554/eLife.39981.032
**Figure 5—figure supplement 2.** Differentially regulated genes identified in the 12 week ATXN1-82Q Tg inferior olive are associated with Blood Vessel Morphogenesis, Response to Organic Substance, and Defense Response-related pathways. (A) Illustration of the tissue examined. (B) Total number of up- and down-regulated genes in the 12 week old ATXN1-82Q Tg inferior olive (FDR p-value < 0.05; n = 3 males per genotype for RNA-seq). (C) Biological pathway enrichment for all ATXN1-82Q Tg differentially regulated inferior olive genes at 12 weeks. (D) Blood Vessel Morphogenesis and Response to Organic Substance-related genes are up- and down-regulated. * FDR p-value < 0.05; ** FDR p-value < 0.01 (n = 3 males per genotype used in RNA-seq).

DOI: https://doi.org/10.7554/eLife.39981.033
Figure 5—figure supplement 3. Divergent gene expression changes and minimal biological pathway overlap in the temporal comparison of the ATXN1-82Q Tg inferior olive. (A) Schematic of the time-point comparison in ATXN1-82Q Tg inferior olive. (B) Total number of differentially regulated genes in the ATXN1-82Q Tg inferior olive relative to appropriate WT controls that are common, and uniquely altered, across the 5 and 12 week time-points (FDR p-value < 0.05; n = 3 males per genotype for RNA-seq). (C) Dot plot of log fold changes for genes significantly altered in the 5 and 12 week ATXN1-82Q Tg inferior olive relative to appropriate controls. (C') Log fold change of genes significantly up-regulated at both the 5 week and 12 week time-points only. Linear regression analysis identified the slope and $R^2$ of these log fold changes (slope = 0.91 ± 0.12, $R^2 = 0.87$). A total of 10 genes were plotted in this analysis. Dysregulated genes were excluded from this analysis. (D) Clustering of GO terms identified from the ATXN1-82Q Tg inferior olive 5 week and 12 week differentially regulated gene lists relative to the appropriate WT controls. (E) A subset of genes associated with Response to Organic Substance and Vasculature Development were commonly up-regulated and (F) a subset of Response to Organic Substance genes
Figure 5—figure supplement 3 continued

were dysregulated when assessed in the 5 and 12 week time-points. * FDR p-value < 0.05; ** FDR p-value < 0.01 (n = 3 males per genotype for each time-point).

DOI: https://doi.org/10.7554/eLife.39981.034
Figure 6. Divergent gene expression changes and low biological pathway overlap between 12 week old ATXN1-82Q Tg inferior olive and cerebellum. 
(A) Schematic of the cross-tissue comparison in ATXN1-82Q Tg mice. (B) Total number of differentially regulated genes that are common, and uniquely altered, in the inferior olive and cerebellum of 12 week old ATXN1-82Q Tg mice (FDR p-value < 0.05; n = 3 males per genotype). (C) A subset of genes commonly up-regulated in the inferior olive and cerebellum, and genes altered in opposing directions (** FDR p-value < 0.01; n = 3 males per genotype for RNA-seq). (D) Clustering of GO terms from the ATXN1-82Q Tg inferior olive and cerebellum differentially expressed genes lists.

DOI: https://doi.org/10.7554/eLife.39981.039
Figure 6—figure supplement 1. Chemical Synaptic Transmission and Regulation of Cell Communication are the most enriched pathways in the 5 week ATXN1-82Q Tg cerebellum. (A) Illustration of the tissue examined. (B) Total number of up- and down-regulated genes in ATXN1-82Q Tg cerebellum at 5 weeks of age (FDR p-value < 0.05; n = 3 males per genotype for RNA-seq). (C) Biological pathway enrichment for all differentially regulated 5 week old ATXN1-82Q Tg cerebellum genes (p-value < 0.05). (D) Genes linked to Chemical Synaptic Transmission and (E) Regulation of Cell Communication are largely down-regulated. * FDR p-value < 0.05; ** FDR p-value < 0.01 (n = 3 males per genotype used in RNA-seq).

DOI: https://doi.org/10.7554/eLife.39981.040
Figure 6—figure supplement 2. Pathways related to Synaptic Signaling are enriched in the 12 week ATXN1-82Q Tg cerebellum. (A) Illustration of the tissue examined. (B) Total number of up- and down-regulated genes in ATXN1-82Q Tg cerebellum at 12 weeks of age (FDR p-value < 0.05; n = 3 males per genotype for RNA-seq). (C) Biological pathway enrichment for all differentially regulated cerebellum genes (p-value < 0.05). (D) Genes linked to Synaptic Signaling and (E) Regulation of Signaling are down- and up-regulated. * FDR p-value < 0.05; ** FDR p-value < 0.01 (n = 3 males per genotype used in RNA-seq).

DOI: https://doi.org/10.7554/eLife.39981.041
Figure 6—figure supplement 3. Common gene expression changes and pathway enrichment in the 5 and 12 week ATXN1-82Q Tg cerebellum. (A) Schematic of the time-point comparison in ATXN1-82Q Tg cerebellum. (B) Total number of differentially regulated genes in the ATXN1-82Q Tg cerebellum. (C) Log fold change of 5 and 12 week ATXN1-82Q Tg cerebellum. (D) Gene ontology and cellular processes. (E) Commonly up-regulated and down-regulated genes.

Figure 6—figure supplement 3 continued on next page.
cerebellum relative to appropriate WT controls that are common, and uniquely altered, across the 5 and 12 week time-points (FDR p-value < 0.05; n = 3 males per genotype for RNA-seq). (C) Dot plot of log fold changes for genes altered in the 5 and 12 week ATXN1-82Q Tg cerebellum. (C') Log fold change of genes significantly up- or down-regulated at both the 5 week and 12 week time-points only. Linear regression analysis identified the slope and $R^2$ of these log fold changes (slope = 1.47 ± 0.03; $R^2 = 0.89$). A total of 316 genes were plotted in this analysis. Dysregulated genes were excluded from this analysis. (D) Clustering of GO terms identified from the ATXN1-82Q Tg cerebellum 5 week and 12 week differentially regulated gene lists relative to the appropriate WT controls. (E) A subset of genes were commonly up-regulated and down-regulated at both time-points relative to WT controls. * FDR p-value < 0.05; ** FDR p-value < 0.01 (n = 3 males per genotype for each time-point).

DOI: https://doi.org/10.7554/eLife.39981.042
Figure 6—figure supplement 4. Divergent gene expression changes and pathway enrichment in the 5 week ATXN1-82Q Tg inferior olive and cerebellum. (A) Schematic of the cross-tissue comparison in ATXN1-82Q Tg inferior olive and cerebellum at 5 weeks of age. (B) Total number of differentially regulated genes in the ATXN1-82Q Tg cerebellum and inferior olive relative to appropriate WT controls that are common, and uniquely altered (FDR p-value < 0.05; n = 3 males per genotype for RNA-seq). (C) Clustering of GO terms identified from the ATXN1-82Q Tg inferior olive and cerebellum 5 week differentially regulated gene lists relative to the appropriate WT controls.

DOI: https://doi.org/10.7554/eLife.39981.043
Figure 7. Genes commonly regulated in the cerebellum across 12 week old SCA1 mouse models are altered in opposing directions. (A) Schematic of the cross-model comparison in 12 week old Atxn1^{154Q/2Q} KI and ATXN1-82Q Tg cerebellum. (B) Number and directionality of shared differentially regulated genes in the Atxn1^{154Q/2Q} KI and ATXN1-82Q Tg cerebellum (FDR p-value < 0.05; n = 3 males per genotype for RNA-seq). (C) Log fold change for genes commonly altered in both the Atxn1^{154Q/2Q} KI and ATXN1-82Q Tg cerebellum, and the proportion of commonly altered genes within each quadrant. (D) Common genes up-regulated or down-regulated in the cerebellum from both mouse models (Quadrant I and III), and genes regulated in opposing directions (Quadrant II and IV) at 12 weeks of age (* FDR p-value < 0.05, ** FDR p-value < 0.01; n = 3 males per genotype for RNA-seq).

DOI: https://doi.org/10.7554/eLife.39981.047
Figure 8. Summary of biological and molecular pathway enrichment across SCA1 mouse models in each brain region over time. Differentially regulated genes in the 5 week old inferior olive and cerebellum from both SCA1 mouse models are associated with specific biological and molecular pathways, a subset of which are listed. The 5 week old Atxn1<sup>154Q/2Q</sup> KI cerebellum pathways are derived when using a nominal p-value < 0.01. In the cerebellum, the majority of differentially regulated genes are down-regulated at both the 5 and 12 week time-points (blue arrow). In the SCA1 inferior olive, the majority of genes are up-regulated at 5 weeks of age, which is followed by a shift toward gene down-regulation (orange and blue gradient arrow). In SCA1 mice at 12 weeks of age, there are enriched biological and molecular pathways that are both conserved, and unique, to specific affected tissues.

DOI: https://doi.org/10.7554/eLife.39981.048