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HD and SCA1: Tales from two 30-year journeys since gene discovery

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Abstract

One of the more transformative findings in human genetics was the discovery that the expansion of unstable nucleotide repeat mutations underlie a group of inherited neurological diseases. A subset of these unstable repeat neurodegenerative diseases is due to the expansion of a CAG trinucleotide repeat encoding a stretch of glutamines, i.e. the polyglutamine repeat (polyQ) neurodegenerative diseases. Among the CAG/polyglutamine repeat diseases are Huntington's disease (HD) and Spinocerebellar Ataxia type 1 (SCA1) where the expansions are within widely expressed proteins. While both HD and SCA1 are autosomal dominantly inherited and cause typically mid-life to late-onset movement disorders with cognitive decline, they each are characterized by distinct clinical characteristics and predominant sites of neuropathology. Importantly, the respective affected proteins Huntingtin-HTT (HD) and Ataxin1-ATXN1 (SCA1) have unique functions and biological properties. Here we review HD and SCA1, with a focus on how their disease-specific and shared features may provide informative insights.

In Brief

Here Thompson and Orr review features of the CAG repeat neurodegenerative diseases Huntington's disease and Spinocerebellar Ataxia type 1 (SCA1). The affected proteins Huntingtin-HTT and Ataxin1-ATXN1 have key unique functions and biological properties that define characteristics associated with each disorder.

Introduction

The class of unstable CAG repeat mutations has grown to include nine autosomal dominant neurodegenerative disorders, each having diverse symptomatology and regional neuropathology. Here we focus on the CAG/polyglutamine repeat expansion diseases Spinocerebellar Ataxia Type 1 (SCA1) and Huntington's disease (HD). This year marks

the 30th anniversary since discoveries of the affected genes and identification of their CAG repeat expansion mutations in 1993.[1,2] There is considerable variability in disease features, both between the two diseases and within each disease context. In the case of SCA1, both symptom age of onset and severity appear to be primarily due to differences in the size of the repeat expansion in affected individuals[3], although given somatic repeat instability in the striatum, there may be yet undiscovered modifier genes. With HD, it is a combination of the size of the CAG repeat and modifier genes.[4–7] Within the range of disease-causing repeats, longer expansions are generally associated with earlier symptom onset and a broader range of neurological symptoms. As these diseases progress, symptoms include weight loss, muscle wasting, cognitive deficits, and respiratory complications that are a primary cause of premature lethality. HD also has significant psychiatric symptoms, including depression and psychosis. Falls and cardiac events are additional causes of death. A consistent pathological feature of each disease is the presence of nuclear inclusions and aggregates of the polyQ expanded protein in cells throughout distinct regions of the CNS.[8,9] Collectively, “aggregation” encompasses a range of structures from oligomers and protofibrils to fibrils and inclusions that are likely to have differential effects on pathogenesis. While the pathogenic role of visible inclusions remains controversial, we note that for both mHTT and mATXN1 inclusions, data indicates that they may not be critical for early pathogenesis and might, in part, function as part of a coping response to the toxic proteins, at least in initial stages of disease. Another interesting feature of each disease is the presence of enhanced somatic repeat instability in MSNs of the striatum. Curiously, in HD, striatal instability appears to promote disease onset and progression, while in SCA1 it primarily seems to influence progression of motor dysfunction with age.

Here we provide an overview of progress made towards better understanding the molecular aspects involved in HD and SCA1. We focus on how their commonalities and differences combine to help develop a pathogenic map for each. HD and SCA1 share key features, such as a very similar relationship between repeat length and age of disease onset, cell selective degeneration, and tissue pattern of somatic repeat instability.[10] To a significant extent, the protein context in which the polyglutamine stretch is located impacts pathogenesis in both diseases. The role of protein context in driving SCA1/ATXN1 pathogenesis is particularly important, such that entry of mutant protein into the nuclei of affected cells is critical to initiate the pathogenic pathway that leads to cellular dysfunction and eventual degeneration. In contrast, the role of protein context in HTT/HD is more complex, with both nuclear and cytosolic contributions to pathogenesis and the potential loss of normal HTT functions contributing to disease.

Clinical and Genetic Features:

SCA1 and HD patients typically have symptom onset between the ages of 35–50 years, with a slow disease progression. In SCA1 ataxia, a broad-based gait with variable stride lengths and unstable turns is most often the initial sign, and progresses to limb incoordination, speech disturbance, and oculomotor abnormalities, ultimately culminating in death, often by respiratory failure. Initial symptoms in HD often consist of a choreiform gait together with loss of cognitive function, particularly of executive function, as well as psychiatric impairment, most often depression, psychosis, and obsessive-compulsive

disorder. While similar to an ataxic gait, a choreiform gait includes abrupt, irregular, sudden movements that often become violent with ballismus, i.e. characterized by spontaneous involuntary movements, muscular weakness, and incoordination of movements of the proximal extremities.

In HD, greater than 39 CAG repeats invariably causes disease, with 40–55 repeats causing adult-onset disease. More rarely, there is a juvenile onset form of HD, showing more Parkinson-like rigidity, caused by repeat expansions above ~55 repeats.[11] Between ~27–35 repeats, individuals will not develop HD, but may have a greater chance of passing a disease range expansion to their offspring, specifically transmitted through the paternal lineage.[12]. Repeat lengths between 35–39 show variable penetrance. CAG repeat length accounts for a large portion (~60%) of the age at which symptoms occur, with repeat length the primary driver of age-of-juvenile onset HD.[13] However, genetic modifier genes, particularly in pathways involved in DNA damage repair, significantly influence the age-of-disease onset as demonstrated through GWAS studies.[4] Recent studies demonstrate that CAG repeat interruptions by one or more CAAs in the 3' end of the pure CAG repeat, representing a major modifier, promotes later onset.[5,14] This raises important considerations in the context of genetic counseling and providing CAG repeat lengths to patients. The increasing complexity of the CAG repeat expansion in HD is that it can be bidirectionally transcribed to produce both CAG and CUG antisense expansion transcripts, in turn producing repeat-associated non-AUG (RAN) proteins.[15–17] Additionally, the HTT CAG repeats may interfere with cellular homeostasis at the RNA level, in part by producing increased levels of small CAG-repeated RNAs.[15]

In general, the relationship between repeat tract length and age of SCA1 disease onset is similar to that for HD. However, the CAG tract in *ATXN1* is often interrupted with CAT triplets encoding histidine. Thus, unaffected and affected *ATXN1* alleles fall into two classes: those without and those with a CAT interruption. Unaffected alleles range from 19 to 44 CAG repeats, with CAT interruptions in tracts over 21 repeats such that there is no stretch of CAGs longer than 21 repeats on unaffected alleles. Affected *ATXN1* alleles have 38 to 82 CAG repeats, with as many as 10% of affected alleles having CAT interruptions with a pure CAG tract of at least 38 repeats.[18–20] It is notable that the presence of a histidine interruption in an expanded polyQ tract of ATXN1 reduces inclusion formation in transfected cells.[19] However, with the recent demonstration that the *ATXN1* CAG repeat is subject to somatic repeat instability,[18,21,22] we speculate that the impact on pathogenesis of the *ATXN1* CAT interruptions is not at the protein level, but instead at the DNA level, similar to HD where interruption of the CAG repeat by a CAA alters the age of onset.

SCA1-associated pathology typically includes pronounced cerebellar (Purkinje and dentate nuclei neurons) and brainstem degeneration (pons and inferior olive) with a variable degree of damage to more anterior (e.g. basal ganglia) and posterior (e.g. spinal cord) regions of the nervous system.[23,24] Perturbations in neuronal circuitry in SCA1 patients include several components of the cerebellar motor system. Affected afferent components include the mossy fibers that arise in the spinocerebellar tracts, vestibular nuclei, basal pontine nuclei, and climbing fibers from the olivary nuclei. Other proprioceptive sensory pathways also can be impaired. Affected efferent components include the deep nuclei of the cerebellum, as well

as their targets in the red nuclei and thalami. While pathology in these sites accounts for the ataxic features in patients, equally important is ancillary neuronal degeneration outside that system, particularly in cranial nerve nuclei related to eye movements and swallowing, with dysphagia often being a mechanism of death. The pars compacta of the substantia nigra is relatively spared, but the pallidum and thalamus have mild involvement. The basal forebrain cholinergic nuclei, cerebral cortex and hippocampus may have mild neuronal loss.

Neuropathologically, in HD there is overall brain volumetric loss, with selective degeneration of striatal medium spiny neurons (MSNs), also known as spiny projection neurons (SPNs). The degree of degeneration and neuropathology is classified through a system of grading severity through macroscopic and microscopic criteria (Vonsattel scale).[25] Degeneration particularly affects the indirect pathway D2 receptor expressing neurons in the striatum (caudate and putamen)[26,27], typically progressing from the tail of the caudate nucleus to the head and body (for review[28]). In post-mortem tissue, the volume of the striatum is markedly reduced depending on the Vonsattel grade. The caudate changes in shape, and there is an enlargement of ventricles, reflecting the loss of the MSNs, dendritic arbors, and myelinated axonal projections.[28] Thinning of the cerebral cortex, proceeding from the posterior to anterior regions, is a common early feature of disease. Further, altered corticostriatal circuitry,[27] circuitry between the striatum and globous pallidus and substantia nigra pars reticulata[26], and reduced BDNF,[29] in part from impaired vesicular trafficking of BDNF and its receptor TrkB,[30] normally provided to the striatum through corticostriatal synapses, significantly affects function and contributes to an imbalance in signaling and the degeneration of striatal neurons.[31] Mutant Htt expression changes striatal excitatory synaptic activity, decreasing glutamate uptake and increasing N-methyl-d-aspartate receptor (NMDAR) signaling. Furthermore, neuronal Ca^{2+} influx and intracellular Ca^{2+} handling are impacted.[32] While the caudate and putamen are the most overtly affected areas of the brain, other regions are also being re-examined and may have potentially greater contribution to disease than previously thought. One example is the cerebellum, which does not show overt neuropathology. However, in HD brains where there is reduced cerebellar volume and altered cerebellar diffusion, there is an association with impairments to motor function and psychiatric symptoms in early-stage HD.[33]

HD and SCA1: Linking neurodevelopment with neurodegeneration

While HD and SCA1 are typically designated as late-onset neurodegenerative disorders, in both cases the affected proteins are expressed from the first days of life. Indeed, there is evidence from an evolutionary perspective of the necessity for longer CAG repeats in the human brain,[34] that when expanded beyond the disease threshold, can cause neuronal dysfunction and disease. Intermediate length repeats in HTT that do not cause disease but are in a range that could expand into a pathogenic range, may actually confer some cognitive and longevity advantages.[35,36] Evidence from both mouse and patient studies support the concept of there being neurodevelopmental components to HD[37,38] and from mouse studies in SCA1.[39] That HTT is essential for development is apparent from the early findings that deletion of the mouse *HTT* homolog, *Hdh*, is embryonic lethal.[40,41] These studies were followed by insights from conditional forebrain *Htt* knockout mice that Htt is required for mouse neurodevelopment, e.g. Htt is required for neurogenesis, excitatory

synapse and cortical-striatal circuit development.[40,42–44]. In contrast, mice lacking *Atxn1* are viable and fertile, but have learning deficits in the absence of ataxia.[45] Using conditional mouse models of SCA1[39] and HD[46], it was found that expression of only polyQ expanded HTT and ATXN1 early, during a critical developmental period, was sufficient to yield disease-like symptoms later in adult mice. Suppression of RORα-mediated transcription during development due to impairment of YAP/YAPdeltaC function by expanded ATXN1 is a developmental pathway altered in SCA1 mice.[47] Thus, alterations in development likely have a critical role in the pathogenesis of both HD and SCA1.

Additional data supports the idea that neurodevelopmental alterations induced by expression of mHTT are a substantial component of HD. mHTT alters division of neuronal progenitors, yielding a thin cerebral cortex.[48] Likewise, HD patient-derived neurons show changes in gene expression and organoid circuitry that are consistent with an altered developmental program.[49–53] Bulk and single nuclei RNAseq studies suggest impaired maturation across multiple cell types, including striatal neurons, astrocytes and oligodendrocytes (e.g[54–58]). Imaging studies show that HD mutation carriers, long before disease symptoms develop, have a smaller intracranial volume as early as seven years of age.[59]. One study using a BACHD mouse model of HD, showed that stopping expression of mHTT at postnatal day 21 did not prevent the development of HD phenotypes[46], suggesting early effects of mHTT expression. A retrospective neuropathological study of 130 HD brains as a discovery cohort, followed by 720 HD brains as a validation cohort, from two independent brain banks showed an increased occurrence of developmental malformations in HD brains.[60] Lastly, human fetuses carrying the HD mutation show a pattern of alterations in cortical development, including deficits in neuroprogenitor cells.[42] Thus, the HD mutation causes both neurodevelopmental abnormalities, potentially involving impairment of normal HTT function, and neurodegeneration later in life. There is enormous plasticity and potential cognitive reserve in the brain that may compensate for many years before the effects of potential neurodevelopmental deficits overcome synaptic reserve and symptoms emerge.[61] In the face of these developmental effects, results from the recent Young Adult Study (HD-YAS) are encouraging for therapies. The study showed that in over 130 young adults predicted to be ~24 years from symptomatic onset, that through a battery of cognitive and psychiatric tests, there were no observed changes in any of these outcomes.[62]

Protein structure/function/localization: Implications for Pathogenesis

Ataxin-1 (ATXN1) and Huntingtin (HTT) are ubiquitously expressed throughout the body. ATXN1 has 816 amino acids (100 kDa)[2,63] and HTT is a 350 kDa 3,144 amino acid protein (Figure 1). In addition to the polyQ tract, several functional motifs/domains have been identified in ATXN1 and HTT. As outlined below, the very large size of HTT and complexity of HTT's normal functions introduce obstacles in the study of HTT/HD relative to ATXN1/SCA1.

A distinctive feature of HTT are several HEAT repeats (Huntingtin, Elongation factor 3, protein phosphatase 2A, TOR1) which are degenerate ~38 amino acid motifs that typically appear in tandem arrays distributed throughout its length.[64,65] HEAT repeats form a well-defined secondary structure important for protein-protein interactions, of which a large

number have been described. To date, as reported in HdinHD[66], there are over 4700 protein interactions defined through studies in yeast, cells, mice, human cell lines, and human tissue, particularly through interactions with the first 17 amino acid domain and HEAT repeats. This ability to interact with a diverse array of cellular proteins, as well as the fact that HTT is involved in multiple cellular processes - including trafficking, transcription, mitochondrial function, selective autophagy, and synaptic biology, among others - has suggested that HTT serves as a critical cellular scaffold for these functions.[12,64,67] HTT is normally a primarily cytoplasmic protein, although HTT shuttles between the nucleus and cytosol, and can be localized to the nucleus via a karyopherin b1/b2 proline-tyrosine (PY)-NLS in the amino terminal 17 amino acids of HTT.[68] HTT mRNA normally shuttles between the nucleus and cytoplasm, with 50% mRNA shown to be localized to the nucleus, but only in neuronal cells.[69] However, HTT also has a strong cytosolic retention sequence NES[70,71] in the amino terminus, which typically maintains the protein in the cytoplasm. When this domain is deleted in mutant BACHD mouse models, mHTT accumulates in the nucleus and animals have more severe disease, robust transcriptional changes, and visible aggregates[72]. In the disease state, mutant HTT shows strong nuclear accumulation that has been strongly associated with pathogenesis over the years[73–75], although both nuclear and cytoplasmic mHTT appear to contribute to pathogenesis.[76] One mechanism whereby HTT becomes “stuck” in the nucleus is the aggregation that occurs upon nuclear localization, potentially masking the ability of the NES to function.[73] This 17 amino acid region also appears to be involved in interactions with organelles and membranes, having similarity in structure to the amphipathic helix of mitochondrial targeting sequences[77] and is involved in mitochondrial protein import[78], which is impaired in HD. Altered mitochondrial function is a key hallmark of HD, with evidence for mitochondrial and bioenergetic dysfunction in HD years before the identification of the HD gene (e.g.[79]) and early rodent models of HD based on mitochondrial toxins including quinolinic acid[80] and 3-nitropropionic acid (for review[81]). Other studies also suggest impaired mitophagy as an early event in HD.[82–85] Several studies support a role of mitochondrial dysfunction in the Purkinje cell/cerebellar[86–88] as well as the extra-cerebellar pathophysiology of SCA1.[89] Results reported by Sánchez et al. indicate that ATXN1 regulates bioenergetics homeostasis in the mouse cerebellum.[90]

Disruption to the nuclear pore has been shown,[91,92] similar to that observed in ALS, with disrupted transport of Rangap1 in iPSC neurons and tissues as well as Lamin-B1, RAN and RANGAP1 mislocalization in striatal neurons expressing mHTT and disrupted nucleocytoplasmic transport, which is likely to impact the localization of mHTT as well. In short, the unique size and extensive interaction of HTT with cellular proteins and organelles provide a basis for the broad dysregulation throughout brain cells in the presence of the expanded repeat.

At the C-terminus of ATXN1 there is a monopartite nuclear localization signal (NLS) motif that directs localization of ATXN1 to the nucleus.[93] In tissue culture cells, ATXN1 with a WT polyQ tract shuttles between the cytoplasm and nucleus. In contrast, ATXN1 with an expanded polyQ tract is transported to the nucleus but is unable to be exported out of the nucleus.[94] Notably, ATXN1 with an expanded polyQ tract having a single amino acid substitution, K772T, within its NLS that prevents ATXN1 from entering nuclei of Purkinje cells, is no longer pathogenic.[93] To examine the role of ATXN1 nuclear

localization broadly in SCA1-like disease pathogenesis, CRISPR-Cas9 was used to develop a mouse with an amino acid alteration (K772T) in the nuclear localization sequence of the expanded ATXN1 protein. Characterization of these mice indicates proper nuclear localization of mutant ATXN1 contributes to many disease-like phenotypes, including motor dysfunction, cognitive deficits, and premature lethality.[95] Thus, a prominent aspect of SCA1 pathogenesis throughout the brain is related to the function(s) of ATXN1 in the nucleus. Interestingly, using a similar CRISPR-Cas9 approach to modify the interaction of mATXN1 interaction with Cic and its phosphorylation at S776 (see below) in SCA1 knockin mice improved their motor performance and improved somewhat their survival. However, these modifications had no effect on cognitive abilities of the SCA1 knockin mice or their failure to gain weight.[96,97] Overall, the results indicate that once in the nucleus, mATXN1 disease-associated pathways are largely unique to each brain region affected.

Wild-type and expanded ATXN1 interact with a variety of nuclear components including RNA,[94,98] several regulators of transcription, SMRT[99], Capicua[100], Senseless/Gfi-1[99], the Rorα/Tip60 complex[39,101], RFX1, ZKSCAN1, and ZBTB5.[96] Paramount among these ATXN1 interactions with transcription factors is the interaction with the transcriptional repressor Capicua (Cic) subserved by the 139 aa region of ATXN1 encoding the ataxin-1/HBP1 (AXH) domain. The AXH domain folds, independently forming an OB-fold containing both a protein-protein interaction surface as well as an oligonucleotide-binding surface. The crystal structure of the AXH domain of ATXN1 bound to Cic revealed interactions at the residue level that are critical for forming an ATXN1/Cic complex.[102] In addition, this study suggested that Cic/AXH interaction alters the configuration of the ATXN1 homodimer such that interaction with other ATXN1 binding partners would be impaired.

In the case of mATXN1, deletion of the amino acids important for its self-association and inclusion formation eliminated mATXN1inclusions without altering disease onset or progression in a Purkinje cell-specific transgenic mouse model of SCA1.[93] Further evidence that mATXN1 inclusions are not pathogenic and might even be protective was reported in a *Atxn1* knockin model of SCA1.[103] In these mice, neurons that were last to form inclusions, e.g. cerebellar Purkinje cells, were the first to show pathology. Correspondingly, regions where inclusions formed early in disease progression, e.g. the cerebral cortex and the hippocampus, were the last to show signs of pathology, if at all. The conclusion from this work was that neurons in which mATXN1 was the most soluble were also the most susceptible to degeneration. Similarly, analysis of brain regions in transgenic and knockin mouse models of HD showed widespread distribution of inclusions, including in regions that do not show cell death (see below).[104,105]

Aggregation of the mutant HTT protein is a hallmark of HD. Multiple forms of aggregates that are not necessarily inclusions can be observed in HD mouse models even by light microscopy. For instance, in one full length YAC transgenic model (YAC128 mice), inclusions are relatively rare but significant aggregation can be detected even at 3 months of age.[106] Using a murine striatal neuronal culture system, Arrasate et al. found that the amount of diffuse mHTT, and not visible inclusion formation, predicted neuronal death.[107] Many neurons died without visible inclusions, and inclusion formation was a predictor of

neuron survival. However, polyQ-expanded HTT aggregates from oligomers to fibrils can lead to global collapse in neuronal proteostasis, which is already reduced as a consequence of aging.[108,109] In an elegant study, Gidalevitz, et al. showed that the expansion confers a precise propensity to aggregate, causes toxicity, and disrupts protein quality control in *C. elegans* in a manner analogous to temperature-sensitive mutants.[110] Therefore, the role of aggregation in disease may be complex and reflect a continuum of disrupted protein homeostasis. In recent work, aggregating species within autophagosomes in iPSC-derived neurons may reflect early evidence of disrupted proteostasis that can be further studied and therapeutically targeted.[111] Finally, the discovery of sense and antisense repeat-associated non-ATG (RAN) translation proteins (polyAla, polySer, polyLeu, and polyCys) that accumulate in HD human brains may contribute to the formation of aggregating protein.[17] These RAN products are found to accumulate in brain regions with aggregation, neuronal loss, and microglial activation, including caudate/putamen and white matter. While not typically found in the cerebellum in adult onset, they do accumulate in juvenile-onset cases[112]

Posttranslational Modifications of HTT and ATXIN1: contributions to pathogenesis

Some of the many post-translational modifications (PTMs) have been reported to impact toxicity of polyQ expanded HTT and ATXN1. In the case of ATXN1, just past the NLS, S776 is one of seven phosphorylation sites of ATXN1 (Figure 1).[113] Phosphorylation of S776 is critical for polyQ expanded ATXN1-induced Purkinje cell degeneration. Replacement of S776 with an Ala, which cannot be phosphorylated, diminishes the ability of ATXN1[82Q] to induce Purkinje cell disease in transgenic mice.[44] Substituting an Asp at position 776, mimicking phosphorylation, enhances the ability of ATXN1[82Q] to induce Purkinje cell disease and converts ATXN1[30Q] into a protein able to induce ataxia when expressed in Purkinje cells.[114] An important biochemical outcome of S776 phosphorylation is that it reduces proteolytic clearance of ATXN1. Phosphorylation of S776 also activates a binding motif for the chaperone 14-3-3.[115] When complexed with 14-3-3, S776 of ATXN1 cannot be dephosphorylated, thus increasing its stability in cells.

For HTT, there are numerous PTMs that modulate normal HTT function and are altered or contribute to pathogenic consequences when the HTT protein is mutated. Phosphorylation sites have been identified throughout HTT through mass spec screens and targeted approaches[116] including Ser-421 (S421), classically thought of as neuroprotective[117–120], but which has emerged as having more complex functions.[121] Phosphorylation of HTT within the N17 domain at T3, S13 or S16, alone or in combination, modulates mHTT aggregation, subcellular localization and toxicity.[122–125] Kinases for those sites have also been defined – e.g. CK2 for T3[122], which is reduced in HD,[126] IKK beta for S13,[123] and TBK1 for S13 and S16, using in vitro site specific phosphorylation of exon 1 fragments.[127,128] Other critical phosphorylation sites have also been defined, including phosphorylation of huntingtin at S434, 181 and 1201, which are phosphorylated by CDK5. Acetylation at K444[129] and palmitoylation of HTT at C214[130] are implicated in turnover and pathogenesis of mHTT.

Addition of a small ubiquitin-like modifier (SUMO) is another post-translational modification that both HTT and ATXN1 undergo[70,131,132], however, its contribution to pathogenesis in each case is complex and may be distinct. SUMOylation of proteins is often related to their homeostasis and clearance, protein interactions, and regulation of their activity in the nucleus[133]. SUMOylation of synaptic proteins outside the nucleus has emerged as critical to synaptic plasticity[134]. In the case of HD, SUMO can act as a molecular glue to facilitate the assembly of large protein complexes in DNA damage repair foci.[135,136]. SUMOylation of ATXN1 was mapped to at least five lysine residues: Lys16, Lys194 preceding the polyglutamine tract, Lys610, Lys697 and Lys746.[132] SUMOylation of ATXN1 decreases in ATXN1 with an expanded polyglutamine tract, and with phosphorylation at serine 776. SUMOylation of ATXN1 is dependent on the NLS of ATXN1. The possible dependence of ATXN1 SUMOylation on nuclear localization is suggestive of other nuclear proteins, e.g. PML, Sp100, and histone deacetylase 4, where SUMOylation regulates their nucleocytoplasmic trafficking as well as their ability to function as transcriptional regulators.[133] In contrast, insoluble SUMOylated proteins aberrantly accumulate in the striatum of human HD postmortem tissue[131], reflecting impaired protein homeostasis. For HTT as with ATXN1, there is cross-talk between phosphorylation and SUMOylation of HTT, however in the case of HTT, phosphorylation of S13 regulates SUMOylation of HTT and clearance of HTT.[123,137] HTT also has a large number of SUMO Interaction Motifs (SIMs)[131] which promote interactions with other SUMOylated proteins and contribute to the formation of protein complexes and could be involved in HTT's scaffold functions. Given the large number of PTMs on HTT, one way to evaluate the contribution of SUMO to HD pathogenesis has been to identify the E3 SUMO ligases that facilitate the modification. Two key enzymes were shown to regulate SUMOylation of HTT – the E3 SUMO ligase-like G protein Ras Homolog Enriched in Striatum (RHES), and the E3 SUMO ligase Protein Inhibitor of Activated STAT1 (PIAS1).[131,138] Reduction of Rhes or PIAS1 both show improvement in multiple neurodegenerative phenotypes, including reduced neurotoxicity *in vitro*,[138] improved phenotypes in a fly model of mHTT[131], improved HD mouse model symptoms,[139 140] restored synaptic gene expression[141], and prevention of mHTT-associated aberrant structures.[111] Indeed, reduction of SUMO1 itself resulted in significantly improved outcomes in HD mice.[142]

While the study of these modifications is complex in both diseases, with increasing complexity through the large number of potential interactions between PTMs, they can provide insights into disease pathogenesis and alternative therapeutic strategies. For HD, the impact of PTMs is broad across multiple cellular processes and there are likely to also be distinct temporal considerations, whereby PTMs may have unique contributions depending on disease stage. In contrast, for SCA1, phosphorylation and SUMOylation appear to have the most significant relation to nuclear localization of ATXN1, and thus on pathogenesis.

Cell Type Specificity in SCA1 and HD

A variety of transcriptomic and epigenetic approaches have been utilized to better understand HD and SCA1 pathogenic alterations at a molecular and tissue-specific level and inform how therapies might have broad or cell type selective effects. Distinct alterations

in transcription are found in various affected brain regions and cell types of HD and SCA1 mice, reviewed in[143,144], respectively.

A hallmark of HD is early and reproducible transcriptional dysregulation in the brain, particularly in the striatum.[145–148] HD striata displays a set of neuronal genes, largely characterized as downregulated. Indeed, a set of 266 genes represent a “signature” of altered striatal gene expression across multiple HD mouse models[149], that fit within distinct modules of co-expressed genes[150]. Many of these are involved in neuronal activity and enriched for genes essential to striatal function (e.g. DRD2, DRD1, DARPP32, PDE10A, PENK1). Initial hypotheses relating to transcriptional changes in HD suggested that aberrant interactions of mHTT with transcriptional regulators such as CBP, SP1, REST, and others, might drive these changes; however, no single transcription factor appears to account for the consistent transcriptional dysregulation (for review[151–153]). A number of histone modifications and epigenetic factors also contribute to dysregulation,[50,154] including marks selectively decreased at super-enhancers[155] and potentially long noncoding RNAs derived from enhancers (eRNAs).[156] Additionally, the concept of an accelerated epigenetic aging through altered DNA methylation patterns has been implicated in HD.[157] The binding of HTT to DNA has also been proposed to regulate transcription.[158] Most likely is that mHTT alters RNA biology in a myriad of complex processes, including aberrant splicing, processing, and posttranscriptional modifications, as well as localization and clearance of RNA regulatory proteins.

An intriguing aspect of HD pathology is the progressive impact of mHTT on the multiple cell types of the striatum. In HD mice early in disease, D2 dopamine receptor positive striatal spiny projection neurons (SPNs) of the indirect pathway iSPNS are affected, leading to hyperkinetic motor performance.[159,160] As the disease progresses, other cell types become affected, including D1 dopamine receptor expressing SPNs of the direct pathway, resulting in a transition to hypokinetic motor symptoms. In addition to indirect and direct SPNs, the striatum can be divided into molecularly distinct matrix and striosome cells. Striosome cells wind through the surrounding matrix-designated cells. A recent study used single-nucleus RNA-sequencing of SPNs from HD mouse and patient material to examine transcriptomic profiles of striosome and matrix SPNs.[161] Curating the striatal single-nucleus RNA-sequence data from a stage 1 HD patient and two HD mouse models allowed the investigators to group data into D1SPN, D2SPN, matrix, and striosome clusters. The findings support the conclusion that direct SPN and indirect SPN, along with the striosome-matrix subdivisions, are inter-dependently and differentially altered in HD, with the striosome-matrix pathway being compromised early and the directindirect pathway altered late in disease progression.

In SCA1 mice, analyses of transcriptional changes in the two most vulnerable and earliest brain regions affected in SCA1 patients - the cerebellum and inferior olive - shows that each affected region has a set of changes in gene expression that is unique to that region. The cerebellum is distinguished by alterations in gene expression encoding ion channel and neurotransmitter receptors that are corrected by manipulations that correct motor performance.[162] On the other hand, the inferior olive is characterized by alterations in expression of defense response/immune related genes.[163] Expanding further on the regional

uniqueness of SCA1-associated transcriptional changes, RNA sequence analysis of genes whose expression is corrected to WT levels in SCA1 knockin mice (in which nuclear entry of mATXN1 was decreased) found that transcriptomic aspects of SCA1 pathogenesis differ between the cerebellum, brainstem, cerebral cortex, hippocampus, and striatum.[95]

Extensive insights have emerged from single-cell approaches to investigate cell type-specific gene expression changes in HD, demonstrating specific genes and pathways altered in oligodendrocytes and astrocytes, in addition to striatal neuron-specific signatures of D1 and D2 neurons.[55,56,58] Network-based modeling approaches using these data are now providing therapeutic targets derived from predictions of upstream regulatory genes that may drive either cell type-specific treatment, or broader therapeutic effects in the HD brain.

Somatic repeat instability

An intriguing aspect to the molecular genetics of HD and SCA1 is somatic repeat instability and its contribution to disease onset and progression (Figure 2). While it is well established that both the *HTT* and ATXN1 CAG repeats are unstable upon transmission to offspring, studies in both human and mouse brain clearly show that the *HTT* expanded CAG repeat also has a high degree of further expansions in somatic tissues, i.e. somatic repeat instability.[21,164] Somatic expansion of the expanded CAG *HTT* repeat occurs in a repeat length and time-tissue/cell type dependent fashion. Genome-wide association studies (GWAS) in HD patients, and molecular studies in HD mouse models, indicate that DNA mismatch repair genes modify rate of HD onset and control CAG somatic expansion, respectively.[165] In particular, genes such as MSH3 promote repeat instability and reduce the age of onset, whereas protective polymorphisms (SNPs) in genes including FAN1 reduce repeat instability and age of disease onset. In general, the brain typically has a higher level of somatic *HTT* expanded CAG repeat instability than peripheral tissue. However, the striatum and liver are also prone to *HTT* expanded CAG repeat expansion, while in the cerebellum the repeat is much more stable.[21] Using fluorescence activated nuclear sorting (FANS) and deep molecular profiling, a recent study showed that in human brain samples, mHTT CAG tract expansions occur in striatal MSNs and cholinergic interneurons, and in cerebellar Purkinje cells.[166]

The relatively high level of somatic repeat instability manifested by the striatum underlies the high degree to which the striatal neurons are susceptible to pathogenesis in HD as well as rate of disease onset. Preclinical therapeutic approaches targeting the striatal *HTT* expanded CAG repeat instability. Notably, naphtyridine-azaquinolone (NA), a small molecule that binds to the repeat expansion intermediate slipped-CAG stretches, induces *HTT* expanded CAG repeat contractions in HD patient cells and in striatal MSNs in an HD mouse model.[167] When administered to R6/2 HD mice, NA reduces the presence of the pathological marker polyQ HTT protein aggregates in MSNs. Other approaches to mediate CAG repeat contractions utilize CRISPR-Cas9 targeting of the repeats, e.g. SpCas9-NG-mediated repair[168] or CAG^{EX} RNA-targeting CRISPR-Cas13d system (Cas13d-CAG^{EX}) to eliminate toxic CAG^{EX} RNA.[169] Reduction of DNA repair proteins that are involved in repeat instability through aberrant mismatch repair, e.g. MSH3, MLH1, and others,

are targets for intervention and have been shown in HD mice to prevent somatic repeat expansion and exert significant therapeutic benefit.[10,170–174]

In SCA, magnetic resonance imaging (MRI) of patients show that loss of cerebellar volume is essentially complete at diagnosis. As SCA1 patients age, MRI analyses show a progressive loss in striatal volume.[175,176] Moreover, a recent study found striatal volume to be a predictor of motor decline with increasing patient age after onset of ataxia.[175] In knockin SCA1 mice, cerebellar injection of iRNA virus targeting *ATXN1* restores motor function early in disease, at 6 weeks of age.[97,177] In contrast, using a conditional knockout SCA1 mouse model, deletion of expanded ATXN1 from striatal MSNs resulted in an improvement of motor performance that did not manifest until late in disease, at 31 weeks-of-age.[178] These results indicate that the relative time course of disease in cerebellum and striatum in *SCA1 knockin* mice parallels the MRI findings in SCA1 patients. Interestingly, the pattern of somatic repeat instability of expanded *ATXN1* in the striatum and cerebellum of both SCA1 knockin mice and a SCA1 patient parallels that seen in HD, i.e. a high level of somatic repeat instability in the striatum and a much lower level in the cerebellum.[21,22,179] It is intriguing to speculate that striatal cells are less sensitive to length of the polyQ tract in ATXN1 than Purkinje cells and thus, striatal cells require somatic expansion of the ATXN1 repeat with age for initiation of striatal pathogenesis. An important caveat is that somatic repeat instability of *ATXN1* and *HTT* have been examined using whole cerebellar extracts. In the cerebellum, granule neurons far outnumber Purkinje cells. It is therefore critical that data on somatic repeat instability within these genes be obtained specifically for Purkinje cells to assess the extent to which ATXN1 instability might be greater in Purkinje cells than *HTT and* contribute to Purkinje cells being among the first neurons affected in SCA1.

Conclusions and perspectives

Considerable progress has been made towards understanding the molecular genetics of HD and SCA1. These two diseases are due to an expanded CAG trinucleotide repeat within genes that have similar spatial and temporal expression patterns, i.e. genes expressed widely throughout the body and early after birth. Moreover, HD and SCA1 have very similar relationships between inherited CAG repeat length and age of disease onset, as well as tissue pattern of somatic repeat instability, i.e. high instability in the striatum and low in the cerebellum.[21]. Yet, at disease onset HD shows prominent cerebral cortex and striatum pathology, while SCA1 shows prominent pathology in the cerebellar cortex and inferior olive. Indeed, HD may even have compensatory mechanisms in cerebellum that confer some neuroprotection. As the disease progresses, regions of pathology become broader and overlapping, and very large repeats that cause juvenile onset disease show significant overlap across regions affected in HD[13] and SCA1, perhaps reflecting more of a polyglutamine-opathy (e.g. term attributed to Henry Paulson). We argue that these features of HD and SCA1 support the concept that the native biology of the affected proteins and/or genes are critical aspects of disease pathogenesis in each, and in the case of HD, the mutation may cause impaired normal function that contributes to disease as well as having dominant effects. Perhaps the strongest evidence supporting a critical role for an aspect of normal protein in pathogenesis is in SCA1, where making a single amino acid change in the nuclear

localization sequence of mATXN1 improves a spectrum of SCA1-like disease phenotypes in a knockin SCA1 mouse model.[95]

As is often the case with neurodegenerative diseases, research is typically focused on elucidating disease mechanisms in brain regions/cell types that manifest prominent pathology. In the case of widely expressed genes like HTT and ATXN1, it is critical to understand the extent to which a disease phenotype is due to pathology in regions beyond those where prominent pathology has become a “standard” feature of disease. In SCA1, research has focused largely on Purkinje cells of the cerebellar cortex. While it is clear that Purkinje cell dysfunction and loss contribute to the motor deficits seen in SCA1, these patients also typically experience profound loss of neurons in other regions of the cerebellum system critical for proper motor performance, such as the dentate and olivary nuclei. The dentate nucleus receives projections from Purkinje cells, the sole efferent pathway from the cerebellar cortex, and connects the cerebellar cortex to other regions of the brain. Climbing fibers from the inferior olive project to Purkinje cell dendrite and are critical for regulating complex spike activity of Purkinje cells. Furthermore, with disease progression, additional regions may then contribute to motor deficits (see above). An important translational contribution of preclinical animal studies will be correlating disease symptom onset and progression with complete pathoanatomical explanations.

An interesting facet of HD is the developing concept of an interdependent functional relationship between the cerebellum and striatum, where dysfunction in one region is compensated by function in the other. As described by van der Plas et al.[38], in premanifest HD, the cerebellum compensates for dysfunction in the striatal indirect pathway. When comparing children carrying an expanded *HTT* allele to children not carrying an expanded *HTT* allele, functional MRI shows there is increased connectivity between the cerebellum and striatum. This increase in striatal-cerebellum connectivity decreases as mutant *HTT* carriers age, setting the stage for onset of motor deficits. It is intriguing to speculate that a similar striatal-cerebellar compensational relationship exists in SCA1. In contrast to HD, the striatum seemsrelatively unaffected early in SCA1 compared to the cerebellum, compensating for cerebellar dysfunction. As SCA1 progresses and induces dysfunction in the striatum, striatal compensation is lost.

The development of disease-modifying treatments requires finding therapeutic targets that are drivers of disease. HD and SCA1 are each associated with numerous shared and unique disease-associated pathological features, e.g. polyQ protein aggregates, altered protein homeostasis, impaired ion channel activity, mitochondrial dysfunction, and unconventional repeat-associated non-ATG translation, making identification of pathogenic drivers of disease challenging. Therefore, current potential disease-modifying treatments with a high potential of having substantial efficacy are those that target the lowering of the mutant gene or protein expression. These include RNA targeting therapies such as ASOs and RNAi viral vectors, and DNA-targeting approaches like CRISPR-Cas9 to reduce either the CAG repeat length or mutant gene transcription.[169,180] Importantly, mouse models of HD and SCA1 strongly indicate that the earlier the therapeutic approach is applied, the more effective the outcome will be. This point is nicely illustrated for SCA1 using a conditional mouse model to block mutant gene expression at various times during disease progression,

stopping mutant ATXN1 expression at an early stage of disease (6 weeks of age), nuclear inclusions were cleared from Purkinje cells and motor function was completely restored (Zu et al., 2004). Notably, stopping mutant ATXN1 expression at a late stage of disease showed that Purkinje cells retain some ability to repair damage caused by mutant ATXN1. In HD mice, early treatment of cortical circuit deficits delays onset of HD-like symptoms.[181] The importance of early treatment has been illustrated by the recent total HTT lowering trial[180], where the further the patient is from age of symptom onset, the worse the outcome. Finally, additional therapeutic approaches are being evaluated in parallel to target modifiers of disease onset. These include DNA damage repair proteins, drivers of altered protein homeostasis (autophagy activators), metabolic regulators (PPARdelta agonist) as well as cell-based therapies and other interventions (enhancing glutamatergic transmission[181]) to restore lost circuitry and other mechanism-based treatments.

In closing, we note that an interesting aspect of polyQ tracts is that humans have a very clear prevalence towards longer alleles (Figure 3). The polyglutamine tract of HTT has an evolutionary property of correlating with increasing brain complexity. The HTT glutamine tract first emerged in fish, and as complexity of the brain progresses along an evolutionary continuum, there is a corresponding elongation of the HTT glutamine tract, suggesting that the glutamine stretch is a mediator of brain complexity and provides a selective advantage for longer non-pathogenic HTT polyglutamine tracts.[182] Evidence that the longer polyQ tracts in non-pathogenic HTT is advantageous includes the presence of their effect on normal brain structure, with more CAGs associated with enhanced cognitive function.[36] Using mouse embryonic stem cells, it was recently found that increased length of non-pathogenic CAGs in HTT improved the cells' neurogenic potential.[34] As mentioned above, this selective advantage may then cause a disadvantage when the repeat is expanded beyond the pathogenic threshold.

Like HTT, the polyglutamine tract of ATXN1 is longer and more variable in humans (Figure 3). However, in contrast to the relative early evolutionary emergence of the HTT glutamine tract, the ATXN1 glutamine appears much later in mammals. The evolutionary development of the ATXN1 glutamine tract is not along a continuum with increased brain complexity as seen with HTT. Rather, it appears a categorical event occurred in mammals and was later solidified in primates which selected for an increase in the length of the ATXN1 glutamine stretch on affected alleles. It will be interesting to understand the functional basis for this apparent selective increase in the length of the ATXN1 glutamine stretch as primates evolved. We speculate that similar to what is thought to be the case for the evolutionary increase in the HTT glutamine tract, the glutamine tract lengthening in ATXN1 relates to the role ATXN1 has in brain function.

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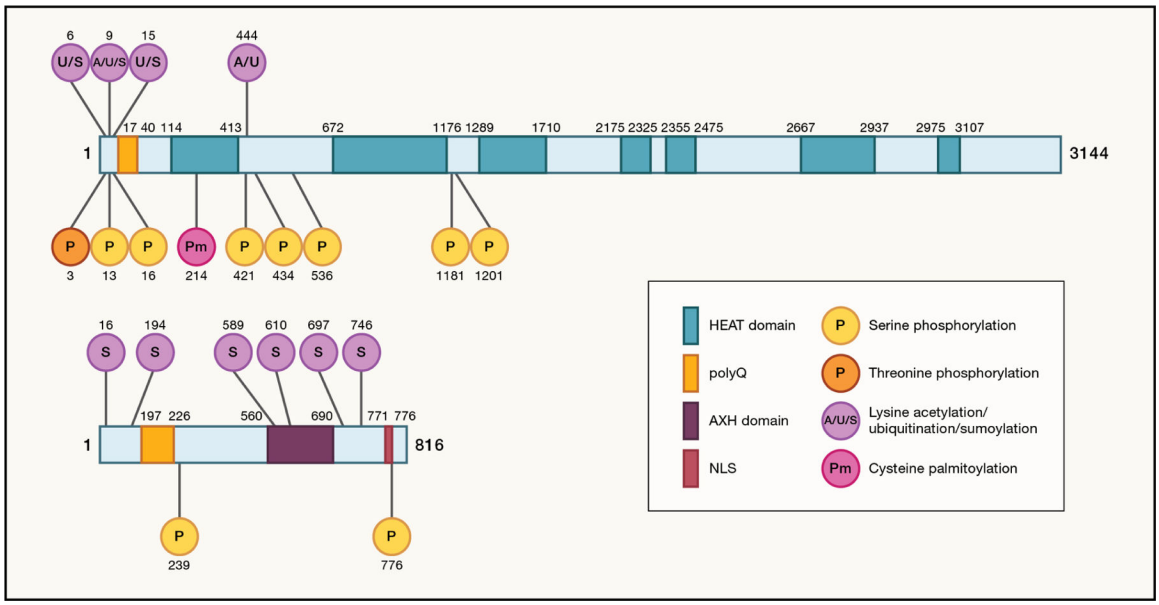

Figure 1.

Schematic Depiction of the HTT and ATXN1 Proteins showing functional motifs and sites of posttranslational modifications.

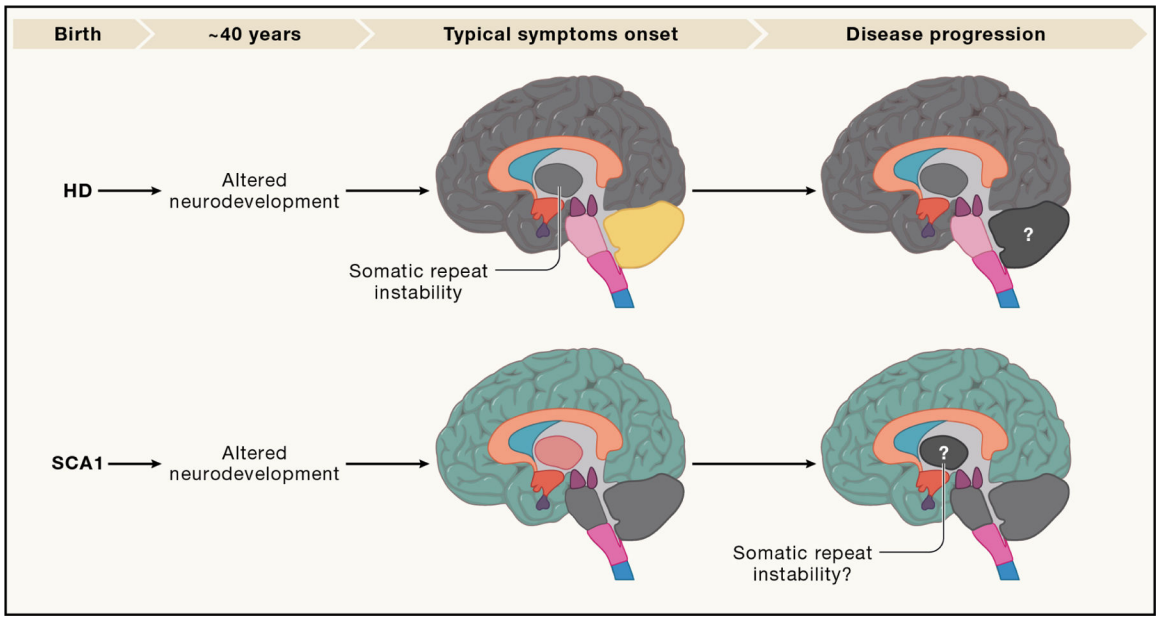

Figure 2.

Impact of striatal somatic repeat instability on HD and SCA1 disease presentation and progression. Sites of typical prominent pathology at disease presentation are indicated by **grey shading** along with timing of somatic repeat instability during progression. Possible sites pathology at late stages of disease progression are depicted by a white ?. For impact of mutations on specific cellular processes, please see reviews[12,162]

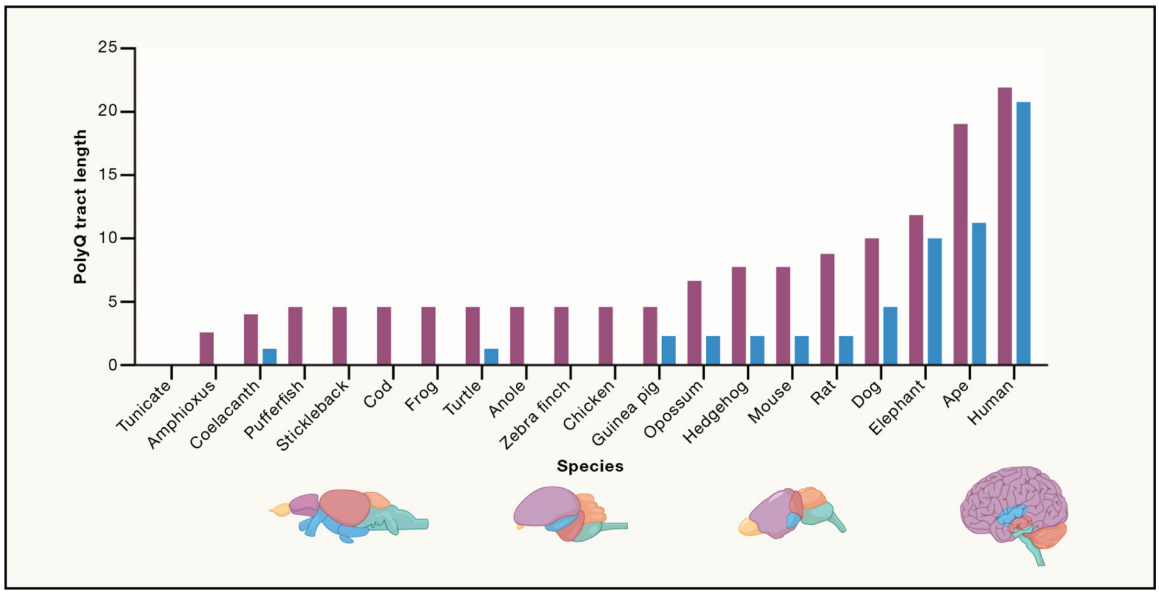

Figure 3. The Relationship Between the Evolutionary Emergence of CAG Repeats in *HTT* (blue bars) and *ATXN1* (red bars) with and Emergence of Brain Structure Complexity.

CAG repeat data are from ensemble, uniprot, ncbi. From left to right, brains represent the zebrafish, zebrafinch, mouse and human, color coded for various brain regions.