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significant overlap in the genes changing (trends), or are there fundamentally different transcripts changing in between the mice with the larger expansions (Q113 and Q129) and those with the smaller expansion (Q76)?" To address this question, we further investigated the relationships of significantly dysregulated genes in the Q76, Q113 and Q129 mice at the age of 12 weeks determined by cross-platform analysis (correspond to the red bars in Figs. 2A–D). Interestingly, over half of downregulated genes in the Q76 mice were also downregulated both in the Q113 and Q129 mice (Supplementary Fig. 5), suggesting that downregulated genes were essentially similar across three transgenic strains although the numbers of them were drastically increased depending on the size of expanded CAG repeats. On the other hand, there was no overlap in the upregulated genes in the cerebrum of the Q76 mice with those of the Q113 and Q129 mice. In the cerebellum of the Q76 mice, only a limited portion of the upregulated genes overlapped with those of the Q113 mice and Q129 mice. These observations suggest that the upregulated genes are relatively specific to the Q113 and Q129 mice, which can be regarded as the specific response to the very largely expanded polyglutamine stretches.

Discussion

DRPLA transgenic mouse lines harboring variable lengths of expanded CAG repeats exhibit CAG repeat length- and age-dependent phenotypic changes resembling those in human DRPLA

CAG-repeat-length-dependent phenotypic variation is a cardinal feature commonly observed in polyglutamine diseases including DRPLA. To accurately evaluate the CAG-repeat-length-dependent phenotypic variations in transgenic mice, various parameters including the promoter, the context, the insertion site, and the copy number of the transgene need to be identical. To accomplish this, we have generated DRPLA transgenic mouse strains carrying various lengths of CAG repeats (Q76, Q96, Q113, and Q129) on a homogeneous genetic background. The transgenic mouse strain with the longest CAG repeat expansion (Q129) exhibits very severe and progressive phenotypes closely resembling those of early-onset human DRPLA, such as ataxia, epilepsy, and myoclonus, whereas the transgenic strain with the shortest CAG repeat expansion (Q76) shows no obvious DRPLA phenotype (Sato et al., 2009). The mouse lines with moderately expanded CAG repeats (Q96 and Q113) showed intermediate phenotypes depending on the CAG repeat length (Fig. 1). Thus, we have successfully reproduced the CAG-repeat-length-dependent phenotypic features of DRPLA in the transgenic models we generated in this study. This study is the first in vivo demonstration of the CAG repeat length and age dependence of mouse phenotypes and gene expression changes in polyglutamine diseases.

The transgenic strains with expanded CAG repeats of 96 and above showed obvious motor deficits, whereas the strain with 76 CAG repeats (Q76) did not seem to show any decline in motor performance (Fig. 1), despite the existence of region-specific accumulation of the mutant DRPLA protein in the brain (Sato et al., 2009). Seventy-six CAG repeats are sufficiently long to induce the development of the disease phenotypes of DRPLA in humans. The number of CAG repeats in DRPLA patients is generally increased to over 50, whereas that in normal individuals is usually under 30. The lifespans are tremendously different between humans and mice. As we have indicated, the accumulation of the mutant proteins is not only a CAG-repeat-length-dependent but also a time-dependent process. In the case of our Q76 transgenic strain, the lifespan of the mice is probably too short to develop motor deficits resulting from progressive intranuclear accumulation of mutant DRPLA proteins, which take years or decades to show up in DRPLA patients.

In this study, we demonstrated that transgenic mice with relatively short CAG repeats (Q76 and Q96) show deficits in spatial learning and memory in the early stage of the disease. Previous studies on other mouse DRPLA models did not pay much attention to memory disturbance, while motor phenotypes were mainly highlighted. This study is the first to show cognitive impairment of DRPLA transgenic mice. Cognitive impairment and character changes are, in fact, major symptoms in DRPLA patients. Besides DRPLA, cognitive impairment is the common clinical presentation of polyglutamine diseases, particularly Huntington's disease. In previous studies, cognitive impairment was reproduced in transgenic mice with Huntington's disease (Lione et al., 1999; Van Raamsdonk et al., 2005). Since our series of DRPLA transgenic mice clearly showed CAG-repeat-length-dependent deterioration of DRPLA phenotypes, we were able to easily observe the cognitive impairment (Q76 and Q96) before these phenotypes were masked by motor impairment.

Cross-platform analyses confirmed CAG-repeat-length- and age-dependent changes in expression profiles

Microarray-based expression profiling is widely used to search for the genes related to disease pathogenesis. In general, the genes identified as "significantly dysregulated" need to be confirmed by independent experiments, usually by real-time RT-PCR or northern blot analyses. However, it is impractical to confirm a large number of genes by those approaches. To overcome this limitation, we performed a comprehensive cross-platform analysis using two different microarray platforms, which employ completely different probe designs and algorithms, to confirm the significantly dysregulated genes identified by single-platform analysis. The combined use of Affymetrix arrays and Agilent arrays has shown that there is a high correlation between these two platforms, and the number of correlated genes is by far larger than that of anticorrelated genes, strongly supporting the validity of the cross-platform analysis for the high-throughput confirmation of microarray data.

As shown in Fig. 4, two-dimensional cluster analyses of the cross-platform data revealed three clusters. In cluster 1, genes were downregulated with increasing CAG repeat length and age. In contrast to cluster 1, genes were upregulated with increasing CAG repeat length and age in cluster 2. In cluster 3, genes were exclusively upregulated in the Q129 mice at an early stage. These findings further confirm that the length of expanded CAG repeats and age, which are the major determinants of neuronal intranuclear accumulation of mutant DRPLA proteins, also play a critical role in the severity of transcriptional dysregulation.

Although the changes in the expression profiles are very mild in Q76 (Fig. 4), a substantial number of downregulated genes in the Q76 mice were also downregulated in the Q113 and Q129 mice, confirming that mice with smaller expansions show essentially the same trends as with larger ones in terms of downregulation of genes (Supplementary Fig. 5). In contrast, there was no overlap in the upregulated genes in the cerebrum of Q76 mice with those of the Q113 or Q129 mice. In the cerebellum of the Q76 mice, only a limited portion of the upregulated genes overlapped with those of Q113 mice or Q129 mice. Thus, upregulation of genes is rather specific to the Q113 and Q129 mice, presumably reflecting the cellular response to the very largely expanded polyglutamine stretches.

Downregulated genes are associated with calcium signaling, neuropeptide signaling, and neuronal development

The overrepresentation of gene annotation terms related to calcium signaling and calcium binding proteins was observed to be the prominent feature of the genes in cluster 1 (Table A). Previous microarray studies have mainly indicated that neurotransmitters and their receptors are downregulated in animal models of polyglutamine diseases (Luthi-Carter et al., 2000, 2002), but none of them have identified the specifically dysregulated genes related to calcium signaling pathways. In this study, we have specifically identified the downregulated genes

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related to calcium signaling (e.g., *Plcb1*, *Ppp3Ca*, *Pde1b*, *Itpka*, *Itpr1*, and *Atp2b2*) and calmodulin binding, which, consistent with recent findings indicating the possible involvement of calcium signaling in the pathogenesis of Huntington's disease (Panov et al., 2002; Tang et al., 2003, 2005; Varshney and Ehrlich, 2003), may represent dysfunction in calcium signaling and contribute to the molecular mechanism of neuronal dysfunction in DRPLA.

Specifically, the downregulation of inositol 1,4,5-triphosphate receptor 1 (*Itpr1*) deserves special attention. The expression level of *Itpr1* has been demonstrated to be decreased in mouse models of Huntington's disease (Luthi-Carter et al., 2000) and SCA1 (Lin et al., 2000). The *Itpr1*-encoded protein forms a complex with Huntingtin, which affects calcium signaling (Tang et al., 2003), and *Itpr1* KO mice show ataxia and epileptic seizures (Matsumoto et al., 1996). Large deletions involving *Itpr1* have recently been identified in patients with SCA15 (Hara et al., 2008; van de Leemput et al., 2007). Thus, the downregulation of *Itpr1* identified in this study further indicates that the dysfunction of calcium signaling caused by the downregulation of calcium-signaling-related genes including *Itpr1* is potentially involved in the pathogenesis of polyglutamine diseases including DRPLA.

Previously, we reported the downregulation of hypothalamic neuropeptide genes in Q129 mice (Sato et al., 2009). Confirming this finding, our present study also demonstrated the CAG repeat length- and age-dependent downregulation of hypothalamic neuropeptide genes in the cerebrum of DRPLA transgenic mice, such as *Penk1*, *Npy*, *Cart*, and *Sst*. The downregulation of these hypothalamic neuropeptide genes may contribute to the phenotypic manifestations potentially caused by the dysfunction of the hypothalamus that we have observed in the DRPLA transgenic mice, such as progressive body weight loss and central diabetes insipidus (Sato et al., 2009). The downregulation of hypothalamic neuropeptide genes and hypothalamic dysfunction have also been observed in a mouse model of Huntington's disease (Kotliarova et al., 2005). Previous studies have demonstrated the decreased expression levels of hypothalamic neuropeptides [i.e., proenkephalin (Iadarola and Mouradian, 1989) and somatostatin (Cramer et al., 1981)] in the cerebrospinal fluid of patients with Huntington's disease. It is possible that the downregulation of hypothalamic neuropeptide genes causes subclinical endocrinological dysfunctions, which then may contribute to mood changes or psychotic symptoms in DRPLA patients.

Table

Function categories of the gene clusters. A. Function categories of the gene clusters in the cerebrum. B. Function categories of the gene clusters in the cerebellum. The table shows the gene ontology (GO) terms of the genes significantly enriched in each cluster in either the cerebrum or cerebellum of the DRPLA transgenic mice and their biological process and molecular function categories. The GO terms were selected on the basis of a p-value ≤0.05, which is calculated using EASE. Other similar significant terms, cellular component category terms, and KEGG pathways are not included to minimize redundancy. Terms are considered "similar" if two terms have the same the parent term or both the parent and child (or grandchild) terms are included together. Complete data are shown in the Supplementary Table 2A, B.

A. Cerebrum

Biological process	p value	Molecular function	p value
Cluster 1			
Metal ion transport	0.00549	Calmodulin binding	0.00001
Calcium ion transport	0.01266	Protein binding	0.00014
Cell-cell adhesion	0.01499	Binding	0.00461
Neuropeptide signaling pathway	0.01520	Actin binding	0.00522
Intracellular signaling cascade	0.01607	Calcium ion binding	0.00700
Cation transport	0.02138	Ion binding	0.01175
Negative regulation of biological process	0.02405	Metal ion binding	0.01175
Neurotransmitter transport	0.02608	Cation binding	0.01796
Negative regulation of cellular process	0.03944	Cytoskeletal protein binding	0.02326
Di-, tri-valent inorganic cation transport	0.03974	Cation transporter activity	0.02351
Ion transport / Cell signaling		Protein binding / Ion binding	
Cluster 2			
Cellular metabolism	0.00488	RNA binding	0.00057
Cell division	0.00967	Nucleotide binding	0.00138
Biopolymer metabolism	0.01282	Nucleic acid binding	0.00470
Protein modification	0.02550	Binding	0.01242
Cellular protein metabolism	0.02965	Protein serine/threonine kinase activit	0.02170
Biopolymer modification	0.03112	Enzyme regulator activity	0.04203
Cellular macromolecule metabolism	0.03273	Protein kinase activity	0.04395
Embryonic development	0.03417	Cyclin-dependent protein kinase regulator activi	0.04617
Phosphate metabolism	0.04921		
Phosphorus metabolism	0.04921		
Protein modification / Nucleotide/nucleic acid binding		Protein kinase	
Cluster 3			
Positive regulation of cellular process	0.00321	Copper ion binding	0.00862
Negative regulation of apoptosis	0.00348	Binding	0.01624
Negative regulation of programmed cell death	0.00365	Insulin-like growth fa	0.04298
Regulation of cell proliferation	0.00369	Integrin binding	0.04498
Negative regulation of cellular process	0.00745		
Apop tosis	0.00902		
Fatty acid biosynthesis	0.00920		
Cell-substrate adhesion	0.00952		
Regulation of apoptosis	0.00975		
Programmed cell death	0.00978		
Cell death/apoptosis			

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Table (*continued*)

B. Cerebellum

Biological process	p value	Molecularfunction	p value
Cluster 1			
Cell development	0.0000	Protein binding	0.0000
Neuron differentiation	0.0001	Calciumion binding	0.0001
Neuron development	0.0001	Receptor binding	0.0005
Positiveregulationoflocomotion	0.0001	Cation binding	0.0009
Positiveregulationof cellmotility	0.0001	GTPase regulator activity	0.0010
Celldifferentiation	0.0002	Ion binding	0.0019
Neurogenesis	0.0003	Metalion binding	0.0019
Development	0.0004	Binding	0.0020
Intracellular signaling cascade	0.0004	Enzyme regulator activity	0.0060
Nervous systemdevelopment	0.0006	Lipid binding	0.0070
Cellmigration/differentiation/development		Ion binding	
Cluster2			
Cellular physiological process	0.0000	Protein binding	0.0000
Negative regulation of biological process	0.0000	Nucleotide binding	0.0000
Protein processing	0.0000	Purine nucleotide binding	0.0002
Protein metabolism	0.0000	RNA binding	0.0004
Primary metabolism	0.0001	ATP binding	0.0005
Biopolymer modification	0.0003	Protein dimerizatio nactivity	0.0011
Metabolism	0.0003	Transferase activity, transferring phosphorus-	0.0016
Macromolecule metabolism	0.0004	Protein serine/threonine kinaseactivity	0.0018
Cellular protein metabolism	0.0005	Kinase activity	0.0043
Cell organization and biogenesis	0.0005	cAMP-dependentproteinkinaseactivity	0.0052
Protein modification		Nucleotide/nucleic acid binding	Protein kinase
Cluster 3			
Biopolymer metabolism	0.0002	Obsolete molecular function	0.0001
Cellular physiological process	0.0005	Binding	0.3100
RNA splicing, via transesterification reactions	0.7000	Nucleic acid binding	0.1800
RNA splicing	0.0008	RNA binding	0.0319
DNA packaging	0.0011	Protein binding	0.0331
DNA metabolism	0.0014	Chondroitin sulfate proteoglycan	0.0335
Regulationof cell proliferation	0.7100	Nucleotide binding	0.8330
mRNA processing	0.0025	Copper ion binding	0.0420
Regulation of transcription, DNA-dependent	0.0029		
Transcription	0.0034		
RNA splicing		Regulation of transcripton	Nucleotide/nucleic acid binding

The genes downregulated in the cerebellum (cluster 1) are found to be mostly related to neuronal developmental processes. In particular, the downregulation of the genes related to myelination (e.g., *Cldn11*, *Ugt8a*, *Plp1*, and *Large*) are noteworthy, since these genes may play a role in the formation of white matter lesions, which are characteristically observed in DRPLA patients. Our previous morphometric study has also demonstrated that spine density is reduced in the neurons of Q129 DRPLA mice (Sakai et al., 2006). Neuropathological observations have long revealed that the entire brain of DRPLA patients is somehow proportionally small in addition to the region-specific neuronal loss in the dentatorubral and pallidoluysian systems. Considering these findings, developmental abnormalities of neurons are also considered as important pathological processes in DRPLA, besides neuronal degeneration.

We previously demonstrated the age-dependent downregulation of genes in the cerebrum of Q129 DRPLA transgenic mice (Sato et al., 2009). Among the 46 genes from that study, 10 genes were also identified to be associated with age-dependent as well as CAG-repeat-length-dependent downregulation in our present study (included in cluster 1). Four of the 10 genes encode transcription factors (*Dbp*, *Egr1*, *Bhlhb2*, and *Mef2c*), three encode neuropeptides (*Sst*, *Npy*, and *Penk1*), one encodes a signaling molecule (*Prkcd*), one encodes a vesicular transporter (*Rab33a*), and one encodes a cytoskeletal and structural molecule (*Cldn11*). Six of the 21 genes listed as CREB-dependent genes are included in cluster 1 (*Sst*, *Penk1*, *Egr1*, *Bhlhb2*, *Mef2c*, and *Cldn11*). Intriguingly, the genes found to be downregulated in both our present and previous studies are functionally categorized into the same categories: neuropeptide genes, transcription factor genes, or CREB target genes. We previously demonstrated that CREB-dependent transcriptional activation is strongly suppressed by expanded polyQ stretches in cellular models (Nucifora et al., 2001; Shimohata et al., 2000, 2005), which strongly indicates that expanded-polyQ-mediated transcriptional suppression is involved in the pathogenesis of DRPLA. Our findings further support recent studies that demonstrated the therapeutic effectiveness of potent transcriptional activators, such as sodium butyrate (Ferrante et al., 2003; Ying et al., 2006), SAHA (Hockly et al., 2003), and phenylbutyrate (Gardian et al., 2005), against polyglutamine diseases.

Upregulated genes are associated with protein modification, apoptosis, and transcriptional regulation

The upregulated genes in transgenic models of polyglutamine diseases have been paid less attention than the downregulated genes, since they were regarded as the result of cellular stress responses and inflammation (Luthi-Carter et al., 2000, 2002). In this study, however, we have identified a cluster of genes that are upregulated with increasing

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CAG repeat length and age (cluster 2), which have important biological functions, such as those encoding nucleotide-binding proteins, kinases, and phosphatases. Furthermore, most of these genes encode the proteins localized in the nucleus where the DRPLA protein acts as a transcriptional coregulator. Therefore, it is likely that the upregulation of these genes indicates their involvement in the intrinsic molecular interactions underlying the neuronal degeneration in the disease (Shen et al., 2007), instead of being simply a response to stress or inflammation.

It is interesting that the genes classified into cluster 3 in both the cerebrum and cerebellum in this study, which are exclusively upregulated in the Q129 transgenic strain from a very early stage, are mainly related to cell death and apoptosis (*Cdkn1a*, *Sgk*, *Trp53inp1*, *Tsc22d3*, and *Agt*). The *Cdkn1a*-encoded protein inhibits cell cycle progression in G1 by binding to G1 cyclin-CDK complexes, and cell cycle arrest in the G(0)/G(1) phase has been shown to enhance the cellular toxicity of truncated ataxin-3 with expanded polyQ stretches, which is the product of *MJD1* — the causative gene for Machado–Joseph disease/SCA3 (Yoshizawa et al., 2000). Thus, the upregulation of *Cdkn1a* in the brain of the DRPLA transgenic mice may indicate a similar role of the gene in enhancing the neuronal toxicity of the mutant DRPLA protein with expanded polyglutamine stretches. The upregulation of genes whose function is neuroprotective (negative regulation of apoptosis or programmed cell death), such as *Sgk*, may indicate a protective response to the neuronal toxicity of the mutant DRPLA protein containing expanded polyQ stretches. Interestingly, the expression level of *Sgk* has also been reported to be elevated in the brain of patients with Huntington's disease (Rangone et al., 2004).

Conclusions

We have unprecedentedly generated DRPLA transgenic mouse strains carrying various lengths of expanded CAG repeats, and demonstrated significant CAG repeat length- and age-dependent changes in behavioral phenotypes and gene expression profiles in the transgenic mice. We have identified specific gene clusters that are differentially dysregulated in the brains of the animals and new pathways that are potentially involved in the pathogenesis of DRPLA. This study is the first to comprehensively reproduce the CAG repeat length- and age-dependent features of human DRPLA in animal models, and has provided new insights into the pathogenic mechanisms leading to neuronal degeneration and dysfunction in DRPLA as well as in other polyglutamine diseases.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at doi:10.1016/j.nbd.2012.01.014.

References

Carter, R.J., et al., 1999. Characterization of progressive motor deficits in mice transgenic for the human Huntington's disease mutation. J. Neurosci. 19, 3248–3257.
Cramer, H., et al., 1981. Huntington's chorea — measurements of somatostatin, substance P and cyclic nucleotides in the cerebrospinal fluid. J. Neurol. 225, 183–187.
David, G., et al., 1997. Cloning of the SCA7 gene reveals a highly unstable CAG repeat expansion. Nat. Genet. 17, 65–70.
Dennis Jr., G., et al., 2003. DAVID: Database for Annotation, Visualization, and Integrated Discovery. Genome Biol. 4, P3.
Erkner, A., et al., 2002. Grunge, related to human Atrophin-like proteins, has multiple functions in *Drosophila* development. Development 129, 1119–1129.
Ferrante, R.J., et al., 2003. Histone deacetylase inhibition by sodium butyrate chemotherapy ameliorates the neurodegenerative phenotype in Huntington's disease mice. J. Neurosci. 23, 9418–9427.
Gardian, G., et al., 2005. Neuroprotective effects of phenylbutyrate in the N171-82Q transgenic mouse model of Huntington's disease. J. Biol. Chem. 280, 556–563.
Hara, K., et al., 2008. Total deletion and a missense mutation of ITPR1 in Japanese SCA15 families. Neurology 71, 547–551.
Hockly, E., et al., 2003. Suberoylanilide hydroxamic acid, a histone deacetylase inhibitor, ameliorates motor deficits in a mouse model of Huntington's disease. Proc. Natl. Acad. Sci. U. S. A. 100, 2041–2046.
Huang da, W., et al., 2009. Systematic and integrative analysis of large gene lists using DAVID bioinformatics resources. Nat. Protoc. 4, 44–57.
Iadarola, M.J., Mouradian, M.M., 1989. Decrease in a proenkephalin peptide in cerebrospinal fluid in Huntington's disease and progressive supranuclear palsy. Brain Res. 479, 397–401.
Ikeuchi, T., et al., 1995. Dentatorubral-pallidoluysian atrophy (DRPLA): close correlation of CAG repeat expansions with the wide spectrum of clinical presentations and prominent anticipation. Semin Cell Biol. 6, 37–44.
Imbert, G., et al., 1996. Cloning of the gene for spinocerebellar ataxia 2 reveals a locus with high sensitivity to expanded CAG/glutamine repeats. Nat. Genet. 14, 285–291.
Kawaguchi, Y., et al., 1994. CAG expansions in a novel gene for Machado–Joseph disease at chromosome 14q32.1. Nat. Genet. 8, 221–228.
Koide, R., et al., 1994. Unstable expansion of CAG repeat in hereditary dentatorubral-pallidoluysian atrophy (DRPLA). Nat. Genet. 6, 9–13.
Koide, R., et al., 1999. A neurological disease caused by an expanded CAG trinucleotide repeat in the TATA-binding protein gene: a new polyglutamine disease? Hum. Mol. Genet. 8, 2047–2053.
Kotliarova, S., et al., 2005. Decreased expression of hypothalamic neuropeptides in Huntington disease transgenic mice with expanded polyglutamine-EGFP fluorescent aggregates. J. Neurochem. 93, 641–653.
La Spada, A.R., et al., 1991. Androgen receptor gene mutations in X-linked spinal and bulbar muscular atrophy. Nature 352, 77–79.
Lin, X., et al., 2000. Polyglutamine expansion down-regulates specific neuronal genes before pathologic changes in SCA1. Nat. Neurosci. 3, 157–163.
Lindblad, K., et al., 1996. An expanded CAG repeat sequence in spinocerebellar ataxia type 7. Genome Res. 6, 965–971.
Lione, L.A., et al., 1999. Selective discrimination learning impairments in mice expressing the human Huntington's disease mutation. J. Neurosci. 19, 10428–10437.
Luthi-Carter, R., et al., 2000. Decreased expression of striatal signaling genes in a mouse model of Huntington's disease. Hum. Mol. Genet. 9, 1259–1271.
Luthi-Carter, R., et al., 2002. Polyglutamine and transcription: gene expression changes shared by DRPLA and Huntington's disease mouse models reveal context-independent effects. Hum. Mol. Genet. 11, 1927–1937.
Matsumoto, M., et al., 1996. Ataxia and epileptic seizures in mice lacking type 1 inositol 1,4,5-trisphosphate receptor. Nature 379, 168–171.
Nagafuchi, S., et al., 1994. Dentatorubral and pallidoluysian atrophy expansion of an unstable CAG trinucleotide on chromosome 12p. Nat. Genet. 6, 14–18.
Naito, H., Oyanagi, S., 1982. Familial myoclonus epilepsy and choreoathetosis: hereditary dentatorubral-pallidoluysian atrophy. Neurology 32, 798–807.
Nakamura, K., et al., 2001. SCA17, a novel autosomal dominant cerebellar ataxia caused by an expanded polyglutamine in TATA-binding protein. Hum. Mol. Genet. 10, 1441–1448.
Nucifora Jr., F.C., et al., 2001. Interference by huntingtin and atrophin-1 with cbp-mediated transcription leading to cellular toxicity. Science 291, 2423–2428.
Orr, H.T., et al., 1993. Expansion of an unstable trinucleotide CAG repeat in spinocerebellar ataxia type 1. Nat. Genet. 4, 221–226.
Panov, A.V., et al., 2002. Early mitochondrial calcium defects in Huntington's disease are a direct effect of polyglutamines. Nat. Neurosci. 5, 731–736.
Pulst, S.M., et al., 1996. Moderate expansion of a normally biallelic trinucleotide repeat in spinocerebellar ataxia type 2. Nat. Genet. 14, 269–276.
Rangone, H., et al., 2004. The serum- and glucocorticoid-induced kinase SGK inhibits mutant huntingtin-induced toxicity by phosphorylating serine 421 of huntingtin. Eur. J. Neurosci. 19, 273–279.
Sakai, K., et al., 2006. Neuronal atrophy and synaptic alteration in a mouse model of dentatorubral-pallidoluysian atrophy. Brain 129, 2353–2362.
Sanpei, K., et al., 1996. Identification of the spinocerebellar ataxia type 2 gene using a direct identification of repeat expansion and cloning technique, DIRECT. Nat. Genet. 14, 277–284.
Sato, T., et al., 2009. Severe neurological phenotypes of Q129 DRPLA transgenic mice serendipitously created by en masse expansion of CAG repeats in Q76 DRPLA mice. Hum. Mol. Genet. 18, 723–736.
Sato, A., et al., 1999a. Adenovirus-mediated expression of mutant DRPLA proteins with expanded polyglutamine stretches in neuronally differentiated PC12 cells. Preferential intranuclear aggregate formation and apoptosis. Hum. Mol. Genet. 8, 997–1006.

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Sato, T., et al., 1999b. Transgenic mice harboring a full-length human mutant DRPLA gene exhibit age-dependent intergenerational and somatic instabilities of CAG repeats comparable with those in DRPLA patients. Hum. Mol. Genet. 8, 99–106.
Shen, Y., et al., 2007. Functional architecture of atrophins. J. Biol. Chem. 282, 5037–5044.
Shimohata, T., et al., 2000. Expanded polyglutamine stretches interact with TAFII130, interfering with CREB-dependent transcription. Nat. Genet. 26, 29–36.
Shimohata, M., et al., 2005. Interference of CREB-dependent transcriptional activation by expanded polyglutamine stretches — augmentation of transcriptional activation as a potential therapeutic strategy for polyglutamine diseases. J. Neurochem. 93, 654–663.
Tang, T.S., et al., 2003. Huntingtin and huntingtin-associated protein 1 influence neuronal calcium signaling mediated by inositol-(1,4,5) triphosphate receptor type 1. Neuron 39, 227–239.
Tang, T.S., et al., 2005. Disturbed Ca^{2+} signaling and apoptosis of medium spiny neurons in Huntington's disease. Proc. Natl. Acad. Sci. U. S. A. 102, 2602–2607.
The Huntington's Disease Collaborative Research Group, 1993. A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. The Huntington's Disease Collaborative Research Group. Cell 72, 971–983.
van de Leemput, J., et al., 2007. Deletion at ITPR1 underlies ataxia in mice and spinocerebellar ataxia 15 in humans. PLoS Genet. 3, e108.
Van Raamsdonk, J.M., et al., 2005. Cognitive dysfunction precedes neuropathology and motor abnormalities in the YAC128 mouse model of Huntington's disease. J. Neurosci. 25, 4169–4180.
Varshney, A., Ehrlich, B.E., 2003. Intracellular Ca2+ signaling and human disease: the hunt begins with Huntington's. Neuron 39, 195–197.
Wood, J.D., et al., 2000. Atrophin-1, the dentato-rubral and pallido-luysian atrophy gene product, interacts with ETO/MTG8 in the nuclear matrix and represses transcription. J. Cell Biol. 150, 939–948.
Yamada, M., et al., 2001. Widespread occurrence of intranuclear atrophin-1 accumulation in the central nervous system neurons of patients with dentatorubral-pallidoluysian atrophy. Ann. Neurol. 49, 14–23.
Yamasaki, N., et al., 2008. Alpha-CaMKII deficiency causes immature dentate gyrus, a novel candidate endophenotype of psychiatric disorders. Mol. Brain. 1, 6.
Ying, M., et al., 2006. Sodium butyrate ameliorates histone hypoacetylation and neurodegenerative phenotypes in a mouse model for DRPLA. J. Biol. Chem. 281, 12580–12586.
Yoshizawa, T., et al., 2000. Cell cycle arrest enhances the in vitro cellular toxicity of the truncated Machado–Joseph disease gene product with an expanded polyglutamine stretch. Hum. Mol. Genet. 9, 69–78.
Zhang, S., et al., 2002. Drosophila atrophin homolog functions as a transcriptional corepressor in multiple developmental processes. Cell 108, 45–56.
Zhuchenko, O., et al., 1997. Autosomal dominant cerebellar ataxia (SCA6) associated with small polyglutamine expansions in the alpha 1A-voltage-dependent calcium channel. Nat. Genet. 15, 62–69.

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