



Universiteit  
Leiden  
The Netherlands

## **Huntington disease and other polyglutamine diseases : using CAG repeat variations to explain missing heritability**

Gardiner, S.L.

### **Citation**

Gardiner, S. L. (2019, October 10). *Huntington disease and other polyglutamine diseases : using CAG repeat variations to explain missing heritability*. Retrieved from <https://hdl.handle.net/1887/79259>

Version: Publisher's Version

License: [Licence agreement concerning inclusion of doctoral thesis in the Institutional Repository of the University of Leiden](#)

Downloaded from: <https://hdl.handle.net/1887/79259>

**Note:** To cite this publication please use the final published version (if applicable).

Cover Page



Universiteit Leiden

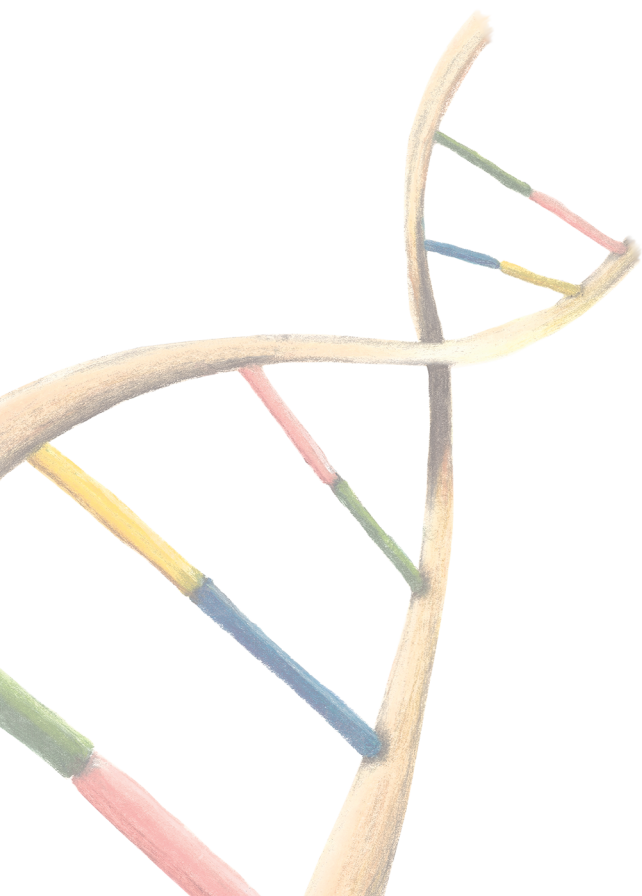


The handle <http://hdl.handle.net/1887/79259> holds various files of this Leiden University dissertation.

**Author:** Gardiner, S.L.

**Title:** Huntington disease and other polyglutamine diseases : using CAG repeat variations to explain missing heritability

**Issue Date:** 2019-10-10



# Chapter

INTRODUCTION

1



# INTRODUCTION

## Huntington disease

In 1872, George Huntington described a peculiar form of chorea which he termed 'hereditary chorea'. In his writing, he described three striking characteristics of this movement disorder: its heritability, its tendency to insanity and its adult onset. Moreover, he stated that 'once it begins, it clings to the bitter end', emphasizing its fatality. Huntington concludes the article by stating that he wanted to draw attention to this form of chorea as a 'mere medical curiosity' and that he does not consider it of any great practical importance.<sup>1</sup>

We now know this hereditary form of chorea as Huntington disease (HD). The prevalence of HD in the Western population is 10.6-13.7 individuals per 100 000.<sup>2</sup> A lower prevalence of 1-7 per million is seen in Japan, Taiwan and Hong Kong. Lower rates are also seen in black populations.<sup>2</sup> The current description of this progressive neurodegenerative disorder still compares considerably well to the symptoms presented in 1872. HD is characterized by motor, cognitive and neuropsychiatric disturbances. The motor impairments can be hyperkinetic with the involuntary dance-like movements known as chorea, as well as hypokinetic characterized by bradykinesia, dystonia, balance and gait disturbances.<sup>3,4</sup> Problems with cognitive function include impaired emotion recognition, processing speed, visuospatial processing and executive function. In addition, patients are also known to suffer from apathy, anxiety, irritability, depression, obsessive compulsive behaviour and psychosis.<sup>5,6</sup> Both cognitive disturbances and neuropsychiatric symptoms can be observed long before the onset of motor symptoms.<sup>7</sup> Furthermore, HD patients suffer from several peripheral abnormalities, including unintended weight loss, muscle wasting, and autonomic failure.<sup>8</sup> As Huntington also described, HD patients do not recover and this devastating disease is inevitably fatal. Although ample research has been conducted over the years, the disease remains incurable.

HD has an autosomal dominant inheritance pattern. The mutation responsible was discovered in 1993. HD is caused by a cytosine-adenine-guanine (CAG) triplet repeat expansion in exon 1 of the huntingtin gene (*HTT*) located on chromosome 4p16.3.<sup>9</sup> Once the CAG repeat number exceeds 39 repeats, the development of the disease is inevitable, while a reduced penetrance is observed in individuals with repeat numbers between 36 and 39. The repeat sequence is highly unstable and genetic anticipation can be seen especially when the gene is passed down the paternal line.<sup>10</sup> Several disease characteristics have an inverse association with the CAG repeat expansion: age of onset, clinical progression and body mass index (BMI).<sup>4,11-15</sup>

## Polyglutamine diseases

Eight other hereditary neurodegenerative disorders are caused by a similar CAG triplet repeat expansion in the protein coding region of the respective mutated genes. The trinucleotide



CAG encodes the amino acid glutamine. Therefore, these diseases, including HD, are defined as polyglutamine diseases and the affected genes as polyglutamine disease-associated genes (PDAGs). The associated polyglutamine proteins are primarily expressed in the central nervous system. Aside from HD, the polyglutamine diseases include six spinocerebellar ataxias (SCAs): SCA1, SCA2, SCA3, SCA6, SCA7 and SCA17 as well as dentatorubral-pallidoluysian atrophy (DRPLA) and spinal and bulbar muscular atrophy (SBMA). All polyglutamine diseases are inherited in an autosomal dominant manner. The only exception is SBMA, which has an X-linked inheritance pattern.<sup>16,17</sup>

### SCA1

The prevalence of SCA1 worldwide is approximately 0.2-2 individuals per 100 000.<sup>18,19</sup> The primary symptom in SCA1 is progressive cerebellar ataxia characterized by disturbances in balance and gait. Oculomotor movements are also affected.<sup>20-21</sup> Furthermore, patients frequently suffer from pyramidal, extrapyramidal and bulbar symptoms.<sup>22</sup> In advanced stages, muscle atrophy arises. Cognitive disturbances have also been reported in the final stages with impaired executive function being the most common defect.<sup>23-26</sup> The age of symptom onset in SCA1 can vary from 4 to 74 years, but is usually around the third decade of life. Disease duration is between 10-20 years.<sup>27,28</sup>

### SCA2

In Europe, about 0.1-5.8 per 100 000 people suffer from SCA2.<sup>19,29-34</sup> SCA2 is characterized by progressive cerebellar ataxia, dysarthria and oculomotor deficits, including extremely slow saccades, nystagmus and sometimes ophthalmoparesis.<sup>29</sup> Additionally, patients can suffer from intention and postural tremors, myoclonus, parkinsonism, sleep disturbances, autonomic dysfunction and initial hyperreflexia followed by peripheral neuropathy with hypo- or areflexia.<sup>21,35-38</sup> Several studies have reported cognitive deficits in 5-25% of the patients.<sup>23,39</sup> Psychiatric symptoms have also been described.<sup>40</sup> Onset of symptoms is usually in the fourth decade of life with a disease duration of 10-15 years.

### SCA3

SCA3 or Machado-Joseph disease is considered the most common autosomal dominant ataxia. However, prevalence differs greatly per population investigated.<sup>41-44</sup> Because the symptoms of SCA3 are so variable, its clinical features are divided into four disease subtypes.<sup>45-48</sup> Type 1 has an early age of onset between 10-30 years and is characterized by pyramidal and extrapyramidal symptoms. Cerebellar ataxia is less prominent. Type 2 is the most common SCA3 subtype with an age of onset between 20-50 years. Type 2 represents a more classic cerebellar-plus syndrome involving notable cerebellar ataxia, dysarthria and pyramidal symptoms. In type 3, aside from cerebellar ataxia, symptoms include peripheral neuropathy leading to muscle atrophy and areflexia. Age of onset of type 3 is typically later (40-75 years). Type 4 has a variable age of onset and is characterized by parkinsonism.<sup>49-52</sup> Symptoms that are not restricted to a subtype include oculomotor symptoms, cranial nerve deficits, sleep disturbances, involuntary weight

loss and autonomic problems.<sup>47,48</sup> Furthermore, SCA3 patients are also known to suffer from mild cognitive impairments.<sup>53-58</sup> Disease duration is reported to range between 6-29 years.<sup>59,60</sup>

### SCA6

The overall prevalence of SCA6 is between 0.02-0.45 per 100 000 individuals.<sup>33,61-69</sup> The disease is considered a 'pure' cerebellar ataxia and is primarily characterized by slow progressive cerebellar ataxia, dysarthria and nystagmus.<sup>70,71</sup> In 40-50% of the patients, pyramidal symptoms such as hyperreflexia and extensor plantar responses have been noted.<sup>71</sup> Furthermore, signs of basal ganglia involvement including dystonia and blepharospasm are reported in 25% of the cases.<sup>72</sup> Cognitive function is usually not impaired. The mean age of onset of SCA6 is between 43-52 years, (range 19-71 years). Although the disease causes a high morbidity, the lifespan of patients is unaltered.<sup>73</sup>

### SCA7

The prevalence of SCA7 is about 0.06-0.23 per 100 000 individuals.<sup>19,33,74,75</sup> The mean age of onset is about 32 years with a range of 1-72 year. Clinical features differ substantially between patients with an adult onset and patients with an onset in infancy or early childhood.<sup>76</sup> In adulthood, SCA7 is characterized by progressive cerebellar ataxia, slowed ocular saccades, dysarthria, dysphagia and pyramidal symptoms, such as hyperreflexia and spasticity.<sup>77</sup> A distinctive feature of SCA7 is retinal degeneration with progressive cone-rod dystrophy leading to eventual blindness.<sup>78-80</sup> Decline in cognitive function and episodes of psychosis have also been reported.<sup>81</sup> When symptoms start in childhood the disease has a rapid and aggressive progression. Furthermore, muscle atrophy and hypotonia are common features, while cerebellar ataxia and visual impairment may be less evident.<sup>82</sup> The mean disease duration is about 20 years.<sup>83</sup>

### SCA17

Less than 100 families with SCA17 have been reported. The prevalence in the north east of England is about 0.16 per 100 000 individuals and the prevalence in Japan is estimated at around 0.47 per 1000 000.<sup>84,85</sup> SCA17 is also known as Huntington Disease-Like 4 and symptoms of this disease indeed resemble HD characteristics. SCA17 presents itself with cerebellar ataxia, pyramidal signs and involuntary movements including chorea and dystonia. Parkinsonism has also been reported. Furthermore, SCA17 patients are known to suffer from psychiatric symptoms, as well as dementia.<sup>86-88</sup> The mean age of onset is 34.6 years with a broad range of 3-75 years and a mean disease duration of about 20 years.<sup>83,89</sup>

### *Dentatorubral-pallidolusian atrophy*

Dentatorubral-pallidolusian atrophy (DRPLA) is most common in Japan with a prevalence of 0.48 per 100 000 individuals.<sup>90</sup> However, individuals with DRPLA have also been reported in European and North and South American populations.<sup>91-95</sup> Clinical





presentation of DRPLA differs with age of onset. When disease onset is before the age of 20, a progressive myoclonus epilepsy phenotype is observed. Symptoms include various forms of generalized seizures, myoclonus, cerebellar ataxia and progressive intellectual deterioration.<sup>96-98</sup> After the age of 20, a non-progressive myoclonus epilepsy phenotype is described. The symptoms of this phenotype include cerebellar ataxia and involuntary movements such as choreoathetosis.<sup>98</sup> Cognitive impairment and psychosis are also seen in adults.<sup>97,99</sup> The onset ranges from 0-72 years with a mean age of onset of 31.5 years. Disease duration on average is 8 years with a range of 0-35 years.<sup>100</sup>

### *Spinal and bulbar muscular atrophy*

Spinal and bulbar muscular atrophy (SBMA) or Kennedy disease is the only polyglutamine disease with an X-linked inheritance pattern. The affected gene encodes the androgen receptor. As females have lower levels of circulating androgens and thus lower levels of androgen receptor stimulation, SBMA is only fully penetrant in males. The estimated prevalence is 1 per 300 000 males.<sup>101</sup> SBMA characteristics can be divided into neurological and androgen insensitivity symptoms. Neurological symptoms include muscle weakness and cramps with eventual atrophy of the proximal and distal muscles, and an action tremor. When the bulbar muscles become involved, patients start to exhibit dysarthria and dysphagia. The main life-threatening problem in SBMA patients is the risk of aspiration pneumonia and ventilation failure due to these deficiencies. Otherwise, life expectancy is unaltered.<sup>102,103</sup> Neurological symptoms usually begin around middle age (30-50 years), whereas androgen sensitivity symptoms start in adolescence.<sup>103,104</sup> Androgen sensitivity symptoms include, gynecomastia, testicular atrophy and oligospermia or azoospermia. These symptoms are often of greater concern to the patients than the neurological symptoms.<sup>105,106</sup>

### **Characteristics of CAG trinucleotide repeats**

The expanded CAG repeat sequences that cause polyglutamine diseases, constitute a major class of repetitive nucleotide motifs in DNA called tandem repeats, including microsatellites and minisatellites. Microsatellites consist of 1-6 repeated base pair motifs and thus the trinucleotide CAG repeats are considered microsatellites. Tandem repeats in general constitute ~3% of the human genome, a larger proportion than the entire protein coding sequences combined.<sup>107</sup>

The number of CAG repeats that result in the development of a polyglutamine disease, differ per disease and per affected gene (*ATXN1*, *ATXN2*, *ATXN3*, *CACNA1A*, *ATXN7*, *TBP*, *HTT*, *ATN1* and *AR*) (**Table 1**).<sup>31,108-133</sup> However, all polyglutamine diseases have an inverse association between the number of CAG repeats and the age of symptom onset. In addition, disease severity, progression and clinical presentation are frequently associated with the sequence length.<sup>38,77,97,127,134-138</sup> These polyglutamine disease characteristics

**Table 1.** Characteristics of polyglutamine disease-associated genes.

Disease	PDAG	Locus	Protein	Repeat	CAG repeat number		
					normal	intermediate	pathological
HD	<i>HTT</i>	4p16.3	Huntingtin	(CAG) <sub>n</sub>	6-26	27-35	36-121
SCA1	<i>ATXN1</i>	6p23	Ataxin-1	(CAG) <sub>n</sub> (CAT) <sub>n</sub> (CAG) <sub>n</sub> <sup>a</sup>	6-35 (6-44) <sup>c</sup>	36-38	39-91 (45-91) <sup>c</sup>
SCA2	<i>ATXN2</i>	12q24.12	Ataxin-2	[(CAG) <sub>n</sub> (CAA) <sub>n</sub> (CAG) <sub>n</sub> ] <sub>n</sub> <sup>b</sup>	14-31 <sup>d</sup>	32 <sup>d</sup>	33-500 <sup>d</sup>
SCA3	<i>ATXN3</i>	14q32.12	Ataxin-3	(CAG) <sub>2</sub> CAA AAG CAG CAA(CAG) <sub>n</sub>	11-44	45-59	60-87
SCA6	<i>CACNA1A</i>	19p13.13	CACNA1A	(CAG) <sub>n</sub>	4-18	19	20-33
SCA7	<i>ATXN7</i>	3p14.1	Ataxin-7	(CAG) <sub>n</sub>	4-19	28-33	34-460
SCA17	<i>TBP</i>	6q27	TBP	[(CAG) <sub>n</sub> (CAA) <sub>n</sub> (CAG) <sub>n</sub> ]	25-40 <sup>d</sup>	-	41-66 <sup>d</sup>
DRPLA	<i>ATN1</i>	12p13.31	Atrophin-1	(CAG) <sub>n</sub>	3-38	39-47	48-93
SBMA	<i>AR</i>	Xq12	Androgen receptor	(CAG) <sub>n</sub>	6-34	-	36-73

CAG=cytosine-adenine-guanine. PDAG=polyglutamine disease-associated genes. CACNA1A=calcium channel, voltage-dependent P/Q type,  $\alpha$ 1A subunit; TBP=thymine-adenine-thymine-adenine (TATA) box binding protein; SCA=spinocerebellar ataxia; HD=Huntington Disease; DRPLA=Dentatorubropallidolusian atrophy; SBMA=spinal bulbar muscular atrophy. <sup>a</sup> Could be interrupted by 1-4 CAT trinucleotide repeats. <sup>b</sup> Could be interrupted by 1-4 CAA trinucleotide repeats. <sup>c</sup> Range if CAT trinucleotide repeat interruptions are present. <sup>d</sup> Includes potential CAA trinucleotide repeat interruptions.



are examples of how variations in the number of repeats within a sequence modulate the genetic function of the associated gene. Variations in repeat number cannot only change associated protein properties, such as flexibility and binding affinity when located within coding sequences, but also alter the local DNA structure and transcription activity when present in noncoding regions.<sup>139</sup> Consequently, differences in tandem repeat length throughout the human genome can affect a variety of biological processes, including development, brain function and behaviour.<sup>140,141</sup>

Tandem repeats are genetically highly unstable and prone to mutation as a result of DNA strand slippage during replication.<sup>142</sup> As a result, polyglutamine diseases are subject to genetic anticipation, which is the decrease in age of onset with each successive generation due to a generational increase in CAG repeat length.<sup>143</sup> Mutation rate can be influenced by factors such as number of repeats and purity of the repetition (i.e. the presence of interruptions).<sup>144,145</sup>

The capability of CAG repeat polymorphisms and tandem repeat polymorphisms in general to affect genetic function and their high mutability as described in the previous section, produces an extensive source of genetic variation, which can be exploited for rapid evolutionary adaptation.<sup>146</sup> Tandem repeats facilitate efficient and continuous adaptive adjustment of quantitative traits. Therefore, these polymorphisms have earned the metaphorical characterization as 'evolutionary tuning knobs'.<sup>139,147</sup>

### **'Missing heritability': unravelling complex genetic disorders**

Despite the evident association between CAG repeat number and age of onset in polyglutamine diseases described in the previous section, the CAG repeat number in the mutated polyglutamine disease-associated gene (PDAG) can only explain 36-80% of the variation in age of onset.<sup>135,148</sup> Thus, a large amount of variability remains unexplained so that other environmental or genetic factors must be involved.<sup>148,149</sup> Lacking explanatory genetic factors are referred to as 'missing heritability'. Interestingly, several studies have shown that CAG repeat numbers in the unaffected allele *in trans*,<sup>150-154</sup> as well as variations in CAG repeat numbers in non-causal PDAGs within the 'normal' range had an additional effect on the onset of polyglutamine disease symptoms (**Table 2**).<sup>153,155-158</sup> These findings suggest that CAG repeat numbers within 'normal' ranges can also affect polyglutamine disease characteristics and clarify part of the 'missing heritability' in age of symptom onset.

In many common disorders, such as depression, obesity and dementia, a large amount of 'missing heritability' is also involved. These disorders are heritable, but genetically complex. Several genes are thought to play a part in their heritability and genome wide association studies (GWAS) have made a substantial contribution to the genetic mapping these polygenic disorders. However, a large amount of 'missing heritability' remains.<sup>159-163</sup>



**Table 2.** Disorders associated with ‘normal’ ranged variations in polyglutamine disease-associated genes.

PDAG		Disorder	Affected aspect	Reference
<i>HTT</i>	<i>in trans</i>	HD	age of onset	[152,154]
		SCA3	age of onset	[153]
		Cognition	grey matter volume globus pallidus	[184]
			brain structure	[185]
			general intelligence	[185]
<i>ATXN1</i>	<i>in trans</i>	SCA1	age of onset	[151,153]
		SCA3	age of onset	[157,158]
		SCA6	age of onset	[153]
		ALS	risk	[170,171]
<i>ATXN2</i>		SCA3	age of onset	[153,157]
		ALS	risk	[167-170]
<i>ATXN3</i>	<i>in trans</i>	SCA3	age of onset	[150,157]
		SCA2	age of onset	[155]
		SCA6	age of onset	[153]
		SCA7	age of onset	[153]
<i>CACNA1A</i>	<i>in trans</i>	SCA6	age of onset	[151,153]
		SCA2	age of onset	[156]
<i>ATXN7</i>	<i>in trans</i>	SCA7	age of onset	[153]
		SCA2	age of onset	[153]
<i>TBP</i>		SCA7	age of onset	[153]
		Schizophrenia	risk	[172,173]
<i>ATN1</i>		SCA3	age of onset	[153]
<i>AR</i>		AD	risk	[174]
		Cognition	cognitive test scores	[183]
		Metabolism	obesity	[179]
			body fat mass	[182]
			serum leptin concentration	[182]
			serum insulin concentration	[182]
		Ovarian cancer	risk	[180,181]
		Prostate cancer	risk	[177,178]
Violent criminal behavior	risk	[175,176]		

PDAG=polyglutamine disease-associated genes. SCA=spinocerebellar ataxia. ALS=amyotrophic lateral sclerosis. HD=Huntington disease. AD=Alzheimer disease.

An explanation could be that aside from single nucleotide polymorphisms (SNPs), GWAS are unable to assess other genetic polymorphisms, including tandem repeat

variations. Investigating tandem repeat variations, such as CAG repeat polymorphisms, as an additional source of heritability could prove beneficial in explaining the ‘missing heritability’ in these polygenic disorders.<sup>164-166</sup>

Recent research has demonstrated that ‘normal’ CAG repeat polymorphisms in PDAGs can indeed modify clinical aspects of polygenic disorders. For instance, intermediate CAG repeat numbers in *ATXN2* increased the risk of amyotrophic lateral sclerosis (ALS)<sup>167-169</sup> and different studies indicated a similar association between ALS and the CAG repeat number in *ATXN1*.<sup>170,171</sup> Larger CAG repeat numbers in *TBP* were found to be associated with schizophrenia.<sup>172,173</sup> Furthermore, *AR* repeat polymorphisms were associated with obesity, body fat mass, serum concentrations of leptin and insulin, Alzheimer disease, violent criminal behaviour, ovarian and prostate cancer.<sup>174-182</sup> In addition, lower scores on three cognitive tests in elderly men were associated with longer *AR* repeat sequences.<sup>183</sup> Moreover, larger CAG repeat numbers in *HTT* were associated with increased grey matter volume in the globus pallidus, and advantageous changes in brain structure and general intelligence (IQ) in children aged 6-18 years.<sup>184,185</sup> When combined, these results indicate that CAG repeat variations below the expanded polyglutamine disease-associated range can act as interesting novel genetic modifiers of health and disease (**Table 2**).<sup>166</sup>

## Scope of this thesis

The primary focus of this thesis was to investigate the relatively untapped potential of CAG repeat polymorphisms as genetic modifiers of both Mendelian and polygenic disorders. To achieve this objective, we initially examined the association between CAG repeat variations within the ‘normal’ range in polyglutamine disease-associated genes (PDAGs) and age of onset in HD (**Chapter 2.1**). In addition, we explored whether differences in bioenergetic profile between HD patients could further clarify these age of onset differences (**Chapter 2.2**). Furthermore, we extended our study by investigating the association between ‘normal’ ranged CAG repeat variations in PDAGs and the heritability of more common polygenic disorders that have symptoms in common with the polyglutamine diseases. These symptoms include cognitive impairment (Alzheimer disease and age-related cognitive decline, **Chapter 3**), psychiatric symptoms (depression, **Chapter 4**) and unintended weight loss (BMI, **Chapter 5**). After genotyping the participants from the cohorts included in these studies, we were also able to describe the prevalence of intermediate and pathological polyglutamine disease-associated alleles in this general population devoid of polyglutamine disease diagnoses (**Chapter 6**). Finally, we discuss the broader role of tandem repeat variations in the search for genetic risk factors of hereditary disorders and mechanisms to target these mutations in order to prevent and treat disease (**Chapter 7**).

## REFERENCES

1. Huntington G. On Chorea. *The Medical and Surgical Reporter: A Weekly Journal* 1872; **26**(15): 317-21.
2. Bates GP, Dorsey R, Gusella JF, et al. Huntington disease. *Nature reviews Disease primers* 2015; **1**: 15005.
3. Dorsey ER, Beck CA, Darwin K, et al. Natural history of Huntington disease. *JAMA neurology* 2013; **70**(12): 1520-30.
4. Rosenblatt A, Liang KY, Zhou H, et al. The association of CAG repeat length with clinical progression in Huntington disease. *Neurology* 2006; **66**(7): 1016-20.
5. Tabrizi SJ, Langbehn DR, Leavitt BR, et al. Biological and clinical manifestations of Huntington's disease in the longitudinal TRACK-HD study: cross-sectional analysis of baseline data. *The Lancet Neurology* 2009; **8**(9): 791-801.
6. Craufurd D, Thompson JC, Snowden JS. Behavioral changes in Huntington Disease. *Neuropsychiatry, neuropsychology, and behavioral neurology* 2001; **14**(4): 219-26.
7. Papoutsis M, Labuschagne I, Tabrizi SJ, Stout JC. The cognitive burden in Huntington's disease: pathology, phenotype, and mechanisms of compensation. *Movement disorders : official journal of the Movement Disorder Society* 2014; **29**(5): 673-83.
8. van der Burg JM, Bjorkqvist M, Brundin P. Beyond the brain: widespread pathology in Huntington's disease. *The Lancet Neurology* 2009; **8**(8): 765-74.
9. MacDonald ME, Ambrose CM, Duyao MP, et al. 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* 1993; **72**(6): 971-83.
10. Telenius H, Kremer B, Goldberg YP, et al. Somatic and gonadal mosaicism of the Huntington disease gene CAG repeat in brain and sperm. *Nature genetics* 1994; **6**(4): 409-14.
11. Duyao M, Ambrose C, Myers R, et al. Trinucleotide repeat length instability and age of onset in Huntington's disease. *Nature genetics* 1993; **4**(4): 387-92.
12. Stine OC, Pleasant N, Franz ML, Abbott MH, Folstein SE, Ross CA. Correlation between the onset age of Huntington's disease and length of the trinucleotide repeat in IT-15. *Human molecular genetics* 1993; **2**(10): 1547-9.
13. Ravina B, Romer M, Constantinescu R, et al. The relationship between CAG repeat length and clinical progression in Huntington's disease. *Movement disorders : official journal of the Movement Disorder Society* 2008; **23**(9): 1223-7.
14. Rosenblatt A, Kumar BV, Mo A, Welsh CS, Margolis RL, Ross CA. Age, CAG repeat length, and clinical progression in Huntington's disease. *Movement disorders : official journal of the Movement Disorder Society* 2012; **27**(2): 272-6.
15. Aziz NA, van der Burg JM, Landwehrmeyer GB, Brundin P, Stijnen T, Roos RA. Weight loss in Huntington disease increases with higher CAG repeat number. *Neurology* 2008; **71**(19): 1506-13.
16. Orr HT. Polyglutamine neurodegeneration: expanded glutamines enhance native functions. *Current opinion in genetics & development* 2012; **22**(3): 251-5.
17. Durr A. Autosomal dominant cerebellar ataxias: polyglutamine expansions and beyond. *The Lancet Neurology* 2010; **9**(9): 885-94.
18. Opal P, Ashizawa T. Spinocerebellar Ataxia Type 1. In: Adam MP, Ardinger HH, Pagon RA, et al., eds. *GeneReviews*((R)). Seattle (WA): University of Washington, Seattle
19. University of Washington, Seattle. *GeneReviews* is a registered trademark of the University of Washington, Seattle. All rights reserved.; 1993.
20. Moseley ML, Benzow KA, Schut LJ, et al. Incidence of dominant spinocerebellar and

1

2

3

4

5

6

7

&

- Friedreich triplet repeats among 361 ataxia families. *Neurology* 1998; **51**(6): 1666-71.
21. Ferrarin M, Gironi M, Mendozzi L, Nemni R, Mazzoleni P, Rabuffetti M. Procedure for the quantitative evaluation of motor disturbances in cerebellar ataxic patients. *Medical & biological engineering & computing* 2005; **43**(3): 349-56.
  22. Rivaud-Pechoux S, Durr A, Gaymard B, et al. Eye movement abnormalities correlate with genotype in autosomal dominant cerebellar ataxia type I. *Annals of neurology* 1998; **43**(3): 297-302.
  23. Gilman S. Progression rates of dominant spinocerebellar ataxias. *Neurology* 2011; **77**(11): 1026-7.
  24. Burk K. Cognition in hereditary ataxia. *Cerebellum (London, England)* 2007; **6**(3): 280-6.
  25. Burk K, Globas C, Bosch S, et al. Cognitive deficits in spinocerebellar ataxia type 1, 2, and 3. *Journal of neurology* 2003; **250**(2): 207-11.
  26. Klinka I, Minnerop M, Schmitz-Hubsch T, et al. Neuropsychological features of patients with spinocerebellar ataxia (SCA) types 1, 2, 3, and 6. *Cerebellum (London, England)* 2010; **9**(3): 433-42.
  27. Fancellu R, Paridi D, Tomasello C, et al. Longitudinal study of cognitive and psychiatric functions in spinocerebellar ataxia types 1 and 2. *Journal of neurology* 2013; **260**(12): 3134-43.
  28. Genis D, Matilla T, Volpini V, et al. Clinical, neuropathologic, and genetic studies of a large spinocerebellar ataxia type 1 (SCA1) kindred: (CAG)*n* expansion and early premonitory signs and symptoms. *Neurology* 1995; **45**(1): 24-30.
  29. Matilla-Duenas A, Goold R, Giunti P. Clinical, genetic, molecular, and pathophysiological insights into spinocerebellar ataxia type 1. *Cerebellum (London, England)* 2008; **7**(2): 106-14.
  30. Geschwind DH, Perlman S, Figueroa CP, Treiman LJ, Pulst SM. The prevalence and wide clinical spectrum of the spinocerebellar ataxia type 2 trinucleotide repeat in patients with autosomal dominant cerebellar ataxia. *American journal of human genetics* 1997; **60**(4): 842-50.
  31. Riess O, Laccone FA, Gispert S, et al. SCA2 trinucleotide expansion in German SCA patients. *Neurogenetics* 1997; **1**(1): 59-64.
  32. Cancel G, Durr A, Didierjean O, et al. Molecular and clinical correlations in spinocerebellar ataxia 2: a study of 32 families. *Human molecular genetics* 1997; **6**(5): 709-15.
  33. Lorenzetti D, Bohlega S, Zoghbi HY. The expansion of the CAG repeat in ataxin-2 is a frequent cause of autosomal dominant spinocerebellar ataxia. *Neurology* 1997; **49**(4): 1009-13.
  34. van de Warrenburg BP, Sinke RJ, Verschuuren-Bemelmans CC, et al. Spinocerebellar ataxias in the Netherlands: prevalence and age at onset variance analysis. *Neurology* 2002; **58**(5): 702-8.
  35. Bird TD. Hereditary Ataxia Overview. In: Adam MP, Ardinger HH, Pagon RA, et al., eds. GeneReviews((R)). Seattle (WA): University of Washington, Seattle
  36. University of Washington, Seattle. GeneReviews is a registered trademark of the University of Washington, Seattle. All rights reserved.; 1993.
  37. Rub U, Schols L, Paulson H, et al. Clinical features, neurogenetics and neuropathology of the polyglutamine spinocerebellar ataxias type 1, 2, 3, 6 and 7. *Progress in neurobiology* 2013; **104**: 38-66.
  38. Engel KC, Anderson JH, Gomez CM, Soechting JF. Deficits in ocular and manual tracking due to episodic ataxia type 2. *Movement disorders : official journal of the Movement Disorder Society* 2004; **19**(7): 778-87.
  39. Velazquez-Perez L, Seifried C, Santos-Falcon N, et al. Saccade velocity is controlled by polyglutamine size in spinocerebellar ataxia 2. *Annals of neurology* 2004; **56**(3): 444-7.
  40. Schols L, Amoiridis G, Buttner T, Przuntek H, Epplen JT, Riess O. Autosomal dominant cerebellar ataxia: phenotypic differences

- in genetically defined subtypes? *Annals of neurology* 1997; **42**(6): 924-32.
41. Burk K, Globas C, Bosch S, et al. Cognitive deficits in spinocerebellar ataxia 2. *Brain : a journal of neurology* 1999; **122** ( Pt 4): 769-77.
  42. Storey E, Forrest SM, Shaw JH, Mitchell P, Gardner RJ. Spinocerebellar ataxia type 2: clinical features of a pedigree displaying prominent frontal-executive dysfunction. *Archives of neurology* 1999; **56**(1): 43-50.
  43. Matilla T, McCall A, Subramony SH, Zoghbi HY. Molecular and clinical correlations in spinocerebellar ataxia type 3 and Machado-Joseph disease. *Annals of neurology* 1995; **38**(1): 68-72.
  44. Ranum LP, Lundgren JK, Schut LJ, et al. Spinocerebellar ataxia type 1 and Machado-Joseph disease: incidence of CAG expansions among adult-onset ataxia patients from 311 families with dominant, recessive, or sporadic ataxia. *American journal of human genetics* 1995; **57**(3): 603-8.
  45. Gan SR, Ni W, Dong Y, Wang N, Wu ZY. Population genetics and new insight into range of CAG repeats of spinocerebellar ataxia type 3 in the Han Chinese population. *PLoS one* 2015; **10**(8): e0134405.
  46. Zhao Y, Tan EK, Law HY, Yoon CS, Wong MC, Ng I. Prevalence and ethnic differences of autosomal-dominant cerebellar ataxia in Singapore. *Clinical genetics* 2002; **62**(6): 478-81.
  47. Rosenberg RN. Machado-Joseph disease: an autosomal dominant motor system degeneration. *Movement disorders : official journal of the Movement Disorder Society* 1992; **7**(3): 193-203.
  48. Coutinho P, Andrade C. Autosomal dominant system degeneration in Portuguese families of the Azores Islands. A new genetic disorder involving cerebellar, pyramidal, extrapyramidal and spinal cord motor functions. *Neurology* 1978; **28**(7): 703-9.
  49. Paulson HL. Dominantly inherited ataxias: lessons learned from Machado-Joseph disease/spinocerebellar ataxia type 3. *Seminars in neurology* 2007; **27**(2): 133-42.
  50. Riess O, Rub U, Pastore A, Bauer P, Schols L. SCA3: neurological features, pathogenesis and animal models. *Cerebellum (London, England)* 2008; **7**(2): 125-37.
  51. Lu CS, Chang HC, Kuo PC, et al. The parkinsonian phenotype of spinocerebellar ataxia type 3 in a Taiwanese family. *Parkinsonism & related disorders* 2004; **10**(6): 369-73.
  52. Buhmann C, Bussopulos A, Oechsner M. Dopaminergic response in Parkinsonian phenotype of Machado-Joseph disease. *Movement disorders : official journal of the Movement Disorder Society* 2003; **18**(2): 219-21.
  53. Gwinn-Hardy K, Singleton A, O'Suilleabhain P, et al. Spinocerebellar ataxia type 3 phenotypically resembling parkinson disease in a black family. *Archives of neurology* 2001; **58**(2): 296-9.
  54. Tuite PJ, Rogaeva EA, St George-Hyslop PH, Lang AE. Dopa-responsive parkinsonism phenotype of Machado-Joseph disease: confirmation of 14q CAG expansion. *Annals of neurology* 1995; **38**(4): 684-7.
  55. Zawacki TM, Grace J, Friedman JH, Sudarsky L. Executive and emotional dysfunction in Machado-Joseph disease. *Movement disorders : official journal of the Movement Disorder Society* 2002; **17**(5): 1004-10.
  56. Kawai Y, Takeda A, Abe Y, Washimi Y, Tanaka F, Sobue G. Cognitive impairments in Machado-Joseph disease. *Archives of neurology* 2004; **61**(11): 1757-60.
  57. Braga-Neto P, Pedrosa JL, Alessi H, et al. Cerebellar cognitive affective syndrome in Machado Joseph disease: core clinical features. *Cerebellum (London, England)* 2012; **11**(2): 549-56.
  58. Roeske S, Filla I, Heim S, et al. Progressive cognitive dysfunction in spinocerebellar ataxia type 3. *Movement disorders :*





- official journal of the Movement Disorder Society* 2013; **28**(10): 1435-8.
59. Lopes TM, D'Abreu A, Franca MC, Jr., et al. Widespread neuronal damage and cognitive dysfunction in spinocerebellar ataxia type 3. *Journal of neurology* 2013; **260**(9): 2370-9.
  60. Garrard P, Martin NH, Giunti P, Cipelotti L. Cognitive and social cognitive functioning in spinocerebellar ataxia : a preliminary characterization. *Journal of neurology* 2008; **255**(3): 398-405.
  61. Sudarsky L, Corwin L, Dawson DM. Machado-Joseph disease in New England: clinical description and distinction from the olivopontocerebellar atrophies. *Movement disorders : official journal of the Movement Disorder Society* 1992; **7**(3): 204-8.
  62. Sequeiros J, Coutinho P. Epidemiology and clinical aspects of Machado-Joseph disease. *Advances in neurology* 1993; **61**: 139-53.
  63. Geschwind DH, Perlman S, Figueroa KP, Karrim J, Baloh RW, Pulst SM. Spinocerebellar ataxia type 6. Frequency of the mutation and genotype-phenotype correlations. *Neurology* 1997; **49**(5): 1247-51.
  64. Ikeuchi T, Takano H, Koide R, et al. Spinocerebellar ataxia type 6: CAG repeat expansion in alpha1A voltage-dependent calcium channel gene and clinical variations in Japanese population. *Annals of neurology* 1997; **42**(6): 879-84.
  65. Matsuyama Z, Kawakami H, Maruyama H, et al. Molecular features of the CAG repeats of spinocerebellar ataxia 6 (SCA6). *Human molecular genetics* 1997; **6**(8): 1283-7.
  66. Matsumura R, Futamura N, Fujimoto Y, et al. Spinocerebellar ataxia type 6. Molecular and clinical features of 35 Japanese patients including one homozygous for the CAG repeat expansion. *Neurology* 1997; **49**(5): 1238-43.
  67. Riess O, Schols L, Bottger H, et al. SCA6 is caused by moderate CAG expansion in the alpha1A-voltage-dependent calcium channel gene. *Human molecular genetics* 1997; **6**(8): 1289-93.
  68. Stevanin G, Durr A, David G, et al. Clinical and molecular features of spinocerebellar ataxia type 6. *Neurology* 1997; **49**(5): 1243-6.
  69. Schols L, Kruger R, Amoiridis G, Przuntek H, Epplen JT, Riess O. Spinocerebellar ataxia type 6: genotype and phenotype in German kindreds. *Journal of neurology, neurosurgery, and psychiatry* 1998; **64**(1): 67-73.
  70. Pujana MA, Corral J, Gratacos M, et al. Spinocerebellar ataxias in Spanish patients: genetic analysis of familial and sporadic cases. The Ataxia Study Group. *Human genetics* 1999; **104**(6): 516-22.
  71. Jiang H, Tang B, Xia K, et al. Spinocerebellar ataxia type 6 in Mainland China: molecular and clinical features in four families. *Journal of the neurological sciences* 2005; **236**(1-2): 25-9.
  72. Garcia-Planells J, Cuesta A, Vilchez JJ, Martinez F, Prieto F, Palau F. Genetics of the SCA6 gene in a large family segregating an autosomal dominant "pure" cerebellar ataxia. *Journal of medical genetics* 1999; **36**(2): 148-51.
  73. Gomez CM, Thompson RM, Gammack JT, et al. Spinocerebellar ataxia type 6: gaze-evoked and vertical nystagmus, Purkinje cell degeneration, and variable age of onset. *Annals of neurology* 1997; **42**(6): 933-50.
  74. Gomez CM. Spinocerebellar Ataxia Type 6. In: Adam MP, Ardinger HH, Pagon RA, et al., eds. GeneReviews(R). Seattle (WA): University of Washington, Seattle
  75. University of Washington, Seattle. GeneReviews is a registered trademark of the University of Washington, Seattle. All rights reserved.; 1993.
  76. Globas C, Bosch S, Zuhlke C, Daum I, Dichgans J, Burk K. The cerebellum and cognition. Intellectual function in spinocerebellar ataxia type 6 (SCA6). *Journal of neurology* 2003; **250**(12): 1482-7.
  77. Filla A, Mariotti C, Caruso G, et al. Relative frequencies of CAG expansions in spinocerebellar ataxia

- and dentatorubropallidoluysian atrophy in 116 Italian families. *European neurology* 2000; **44**(1): 31-6.
78. Storey E, du Sart D, Shaw JH, et al. Frequency of spinocerebellar ataxia types 1, 2, 3, 6, and 7 in Australian patients with spinocerebellar ataxia. *American journal of medical genetics* 2000; **95**(4): 351-7.
  79. Giunti P, Stevanin G, Worth PF, David G, Brice A, Wood NW. Molecular and clinical study of 18 families with ADCA type II: evidence for genetic heterogeneity and de novo mutation. *American journal of human genetics* 1999; **64**(6): 1594-603.
  80. Garden G. Spinocerebellar Ataxia Type 7. In: Adam MP, Ardinger HH, Pagon RA, et al., eds. GeneReviews(R). Seattle (WA): University of Washington, Seattle
  81. University of Washington, Seattle. GeneReviews is a registered trademark of the University of Washington, Seattle. All rights reserved.; 1993.
  82. Aleman TS, Cideciyan AV, Volpe NJ, Stevanin G, Brice A, Jacobson SG. Spinocerebellar ataxia type 7 (SCA7) shows a cone-rod dystrophy phenotype. *Experimental eye research* 2002; **74**(6): 737-45.
  83. Ahn JK, Seo JM, Chung H, Yu HG. Anatomical and functional characteristics in atrophic maculopathy associated with spinocerebellar ataxia type 7. *American journal of ophthalmology* 2005; **139**(5): 923-5.
  84. Hugosson T, Granse L, Ponjavic V, Andreasson S. Macular dysfunction and morphology in spinocerebellar ataxia type 7 (SCA 7). *Ophthalmic genetics* 2009; **30**(1): 1-6.
  85. Benton CS, de Silva R, Rutledge SL, Bohlega S, Ashizawa T, Zoghbi HY. Molecular and clinical studies in SCA-7 define a broad clinical spectrum and the infantile phenotype. *Neurology* 1998; **51**(4): 1081-6.
  86. Enevoldson TP, Sanders MD, Harding AE. Autosomal dominant cerebellar ataxia with pigmentary macular dystrophy. A clinical and genetic study of eight families. *Brain : a journal of neurology* 1994; **117** ( Pt 3): 445-60.
  87. Monin ML, Tezenas du Montcel S, Marelli C, et al. Survival and severity in dominant cerebellar ataxias. *Annals of clinical and translational neurology* 2015; **2**(2): 202-7.
  88. Craig K, Keers SM, Walls TJ, Curtis A, Chinnery PF. Minimum prevalence of spinocerebellar ataxia 17 in the north east of England. *Journal of the neurological sciences* 2005; **239**(1): 105-9.
  89. Maruyama H, Izumi Y, Morino H, et al. Difference in disease-free survival curve and regional distribution according to subtype of spinocerebellar ataxia: a study of 1,286 Japanese patients. *American journal of medical genetics* 2002; **114**(5): 578-83.
  90. Cellini E, Forleo P, Nacmias B, et al. Spinocerebellar ataxia type 17 repeat in patients with Huntington's disease-like and ataxia. *Annals of neurology* 2004; **56**(1): 163; author reply -4.
  91. Toyoshima Y, Yamada M, Onodera O, et al. SCA17 homozygote showing Huntington's disease-like phenotype. *Annals of neurology* 2004; **55**(2): 281-6.
  92. Toyoshima Y, Onodera O, Yamada M, Tsuji S, Takahashi H. Spinocerebellar Ataxia Type 17. In: Adam MP, Ardinger HH, Pagon RA, et al., eds. GeneReviews(R). Seattle (WA): University of Washington, Seattle
  93. University of Washington, Seattle. GeneReviews is a registered trademark of the University of Washington, Seattle. All rights reserved.; 1993.
  94. Stevanin G, Brice A. Spinocerebellar ataxia 17 (SCA17) and Huntington's disease-like 4 (HDL4). *Cerebellum (London, England)* 2008; **7**(2): 170-8.
  95. Tsuji S, Onodera O, Goto J, Nishizawa M. Sporadic ataxias in Japan--a population-based epidemiological study. *Cerebellum (London, England)* 2008; **7**(2): 189-97.
  96. Burke JR, Wingfield MS, Lewis KE, et al. The Haw River syndrome: dentatorubropallidoluysian atrophy



- (DRPLA) in an African-American family. *Nature genetics* 1994; **7**(4): 521-4.
97. Le Ber I, Camuzat A, Castelnovo G, et al. Prevalence of dentatorubral-pallidoluysian atrophy in a large series of white patients with cerebellar ataxia. *Archives of neurology* 2003; **60**(8): 1097-9.
  98. Martins S, Matama T, Guimaraes L, et al. Portuguese families with dentatorubropallidoluysian atrophy (DRPLA) share a common haplotype of Asian origin. *European journal of human genetics : EJHG* 2003; **11**(10): 808-11.
  99. Wardle M, Morris HR, Robertson NP. Clinical and genetic characteristics of non-Asian dentatorubral-pallidoluysian atrophy: A systematic review. *Movement disorders : official journal of the Movement Disorder Society* 2009; **24**(11): 1636-40.
  100. Paradisi I, Ikonomu V, Arias S. Spinocerebellar ataxias in Venezuela: genetic epidemiology and their most likely ethnic descent. *Journal of human genetics* 2016; **61**(3): 215-22.
  101. Naito H, Oyanagi S. Familial myoclonus epilepsy and choreoathetosis: hereditary dentatorubral-pallidoluysian atrophy. *Neurology* 1982; **32**(8): 798-807.
  102. Ikeuchi T, Koide R, Tanaka H, et al. Dentatorubral-pallidoluysian atrophy: clinical features are closely related to unstable expansions of trinucleotide (CAG) repeat. *Annals of neurology* 1995; **37**(6): 769-75.
  103. Tsuji S. Dentatorubral-pallidoluysian atrophy. *Handbook of clinical neurology* 2012; **103**: 587-94.
  104. Adachi N, Arima K, Asada T, et al. Dentatorubral-pallidoluysian atrophy (DRPLA) presenting with psychosis. *The Journal of neuropsychiatry and clinical neurosciences* 2001; **13**(2): 258-60.
  105. Hasegawa A, Ikeuchi T, Koike R, et al. Long-term disability and prognosis in dentatorubral-pallidoluysian atrophy: a correlation with CAG repeat length. *Movement disorders : official journal of the Movement Disorder Society* 2010; **25**(11): 1694-700.
  106. La Spada A. Spinal and Bulbar Muscular Atrophy. In: Adam MP, Ardinger HH, Pagon RA, et al., eds. GeneReviews((R)). Seattle (WA): University of Washington, Seattle
  107. University of Washington, Seattle. GeneReviews is a registered trademark of the University of Washington, Seattle. All rights reserved.; 1993.
  108. Mariotti C, Castellotti B, Pareyson D, et al. Phenotypic manifestations associated with CAG-repeat expansion in the androgen receptor gene in male patients and heterozygous females: a clinical and molecular study of 30 families. *Neuromuscular disorders : NMD* 2000; **10**(6): 391-7.
  109. Atsuta N, Watanabe H, Ito M, et al. Natural history of spinal and bulbar muscular atrophy (SBMA): a study of 223 Japanese patients. *Brain : a journal of neurology* 2006; **129**(Pt 6): 1446-55.
  110. Rhodes LE, Freeman BK, Auh S, et al. Clinical features of spinal and bulbar muscular atrophy. *Brain : a journal of neurology* 2009; **132**(Pt 12): 3242-51.
  111. Warner CL, Griffin JE, Wilson JD, et al. X-linked spinomuscular atrophy: a kindred with associated abnormal androgen receptor binding. *Neurology* 1992; **42**(11): 2181-4.
  112. Sinnreich M, Sorenson EJ, Klein CJ. Neurologic course, endocrine dysfunction and triplet repeat size in spinal bulbar muscular atrophy. *The Canadian journal of neurological sciences Le journal canadien des sciences neurologiques* 2004; **31**(3): 378-82.
  113. Lander ES, Linton LM, Birren B, et al. Initial sequencing and analysis of the human genome. *Nature* 2001; **409**(6822): 860-921.
  114. Orr HT, Chung MY, Banfi S, et al. Expansion of an unstable trinucleotide CAG repeat in spinocerebellar ataxia type 1. *Nature genetics* 1993; **4**(3): 221-6.
  115. Zuhlke C, Dalski A, Hellenbroich Y, Bubel S, Schwinger E, Burk K. Spinocerebellar ataxia type 1 (SCA1): phenotype-genotype

- correlation studies in intermediate alleles. *European journal of human genetics* : *EJHG* 2002; **10**(3): 204-9.
116. Pulst SM, Nechiporuk A, Nechiporuk T, et al. Moderate expansion of a normally biallelic trinucleotide repeat in spinocerebellar ataxia type 2. *Nature genetics* 1996; **14**(3): 269-76.
  117. Mao R, Aylsworth AS, Potter N, et al. Childhood-onset ataxia: testing for large CAG-repeats in SCA2 and SCA7. *American journal of medical genetics* 2002; **110**(4): 338-45.
  118. Kawaguchi Y, Okamoto T, Taniwaki M, et al. CAG expansions in a novel gene for Machado-Joseph disease at chromosome 14q32.1. *Nature genetics* 1994; **8**(3): 221-8.
  119. Costa Mdo C, Paulson HL. Toward understanding Machado-Joseph disease. *Progress in neurobiology* 2012; **97**(2): 239-57.
  120. Ishikawa K, Tanaka H, Saito M, et al. Japanese families with autosomal dominant pure cerebellar ataxia map to chromosome 19p13.1-p13.2 and are strongly associated with mild CAG expansions in the spinocerebellar ataxia type 6 gene in chromosome 19p13.1. *American journal of human genetics* 1997; **61**(2): 336-46.
  121. Shizuka M, Watanabe M, Ikeda Y, Mizushima K, Okamoto K, Shoji M. Molecular analysis of a de novo mutation for spinocerebellar ataxia type 6 and (CAG)<sub>n</sub> repeat units in normal elder controls. *Journal of the neurological sciences* 1998; **161**(1): 85-7.
  122. Mariotti C, Gellera C, Grisoli M, Mineri R, Castucci A, Di Donato S. Pathogenic effect of an intermediate-size SCA-6 allele (CAG)<sub>(19)</sub> in a homozygous patient. *Neurology* 2001; **57**(8): 1502-4.
  123. Yabe I, Sasaki H, Matsuura T, et al. SCA6 mutation analysis in a large cohort of the Japanese patients with late-onset pure cerebellar ataxia. *Journal of the neurological sciences* 1998; **156**(1): 89-95.
  124. David G, Abbas N, Stevanin G, et al. Cloning of the SCA7 gene reveals a highly unstable CAG repeat expansion. *Nature genetics* 1997; **17**(1): 65-70.
  125. Lebre AS, Brice A. Spinocerebellar ataxia 7 (SCA7). *Cytogenetic and Genome Research* 2003; **100**(1-4): 154-63.
  126. Nardacchione A, Orsi L, Brusco A, et al. Definition of the smallest pathological CAG expansion in SCA7. *Clinical genetics* 1999; **56**(3): 232-4.
  127. van de Warrenburg BP, Frenken CW, Aulsems MG, et al. Striking anticipation in spinocerebellar ataxia type 7: the infantile phenotype. *Journal of neurology* 2001; **248**(10): 911-4.
  128. Koide R, Kobayashi S, Shimohata T, et al. A neurological disease caused by an expanded CAG trinucleotide repeat in the TATA-binding protein gene: a new polyglutamine disease? *Human molecular genetics* 1999; **8**(11): 2047-53.
  129. Nanda A, Jackson SA, Schwankhaus JD, Metzger WS. Case of spinocerebellar ataxia type 17 (SCA17) associated with only 41 repeats of the TATA-binding protein (TBP) gene. *Movement disorders : official journal of the Movement Disorder Society* 2007; **22**(3): 436.
  130. Maltecca F, Filla A, Castaldo I, et al. Intergenerational instability and marked anticipation in SCA-17. *Neurology* 2003; **61**(10): 1441-3.
  131. Semaka A, Creighton S, Warby S, Hayden MR. Predictive testing for Huntington disease: interpretation and significance of intermediate alleles. *Clinical genetics* 2006; **70**(4): 283-94.
  132. Kremer B, Goldberg P, Andrew SE, et al. A worldwide study of the Huntington's disease mutation. The sensitivity and specificity of measuring CAG repeats. *The New England journal of medicine* 1994; **330**(20): 1401-6.
  133. Koide R, Ikeuchi T, Onodera O, et al. Unstable expansion of CAG repeat in hereditary dentatorubral-pallidoluysian atrophy (DRPLA). *Nature genetics* 1994; **6**(1): 9-13.
  134. Shimojo Y, Osawa Y, Fukumizu M, et al. Severe infantile dentatorubral pallidoluysian atrophy with extreme expansion of CAG repeats. *Neurology* 2001; **56**(2): 277-8.



135. La Spada AR, Wilson EM, Lubahn DB, Harding AE, Fischbeck KH. Androgen receptor gene mutations in X-linked spinal and bulbar muscular atrophy. *Nature* 1991; **352**(6330): 77-9.
136. Kuhlénbaumer G, Kress W, Ringelstein EB, Stogbauer F. Thirty-seven CAG repeats in the androgen receptor gene in two healthy individuals. *Journal of neurology* 2001; **248**(1): 23-6.
137. Bettencourt C, Hensman-Moss D, Flower M, et al. DNA repair pathways underlie a common genetic mechanism modulating onset in polyglutamine diseases. *Annals of neurology* 2016; **79**(6): 983-90.
138. Fan HC, Ho LI, Chi CS, et al. Polyglutamine (PolyQ) diseases: genetics to treatments. *Cell transplantation* 2014; **23**(4-5): 441-58.
139. Sequeiros J, Seneca S, Martindale J. Consensus and controversies in best practices for molecular genetic testing of spinocerebellar ataxias. *European journal of human genetics : EJHG* 2010; **18**(11): 1188-95.
140. Stevanin G, Durr A, Brice A. Clinical and molecular advances in autosomal dominant cerebellar ataxias: from genotype to phenotype and pathophysiology. *European journal of human genetics : EJHG* 2000; **8**(1): 4-18.
141. Globas C, du Montcel ST, Baliko L, et al. Early symptoms in spinocerebellar ataxia type 1, 2, 3, and 6. *Movement disorders : official journal of the Movement Disorder Society* 2008; **23**(15): 2232-8.
142. Ashizawa T, Figueroa KP, Perlman SL, et al. Clinical characteristics of patients with spinocerebellar ataxias 1, 2, 3 and 6 in the US; a prospective observational study. *Orphanet journal of rare diseases* 2013; **8**: 177.
143. Doyu M, Sobue G, Mukai E, et al. Severity of X-linked recessive bulbospinal neuronopathy correlates with size of the tandem CAG repeat in androgen receptor gene. *Annals of neurology* 1992; **32**(5): 707-10.
144. Igarashi S, Tanno Y, Onodera O, et al. Strong correlation between the number of CAG repeats in androgen receptor genes and the clinical onset of features of spinal and bulbar muscular atrophy. *Neurology* 1992; **42**(12): 2300-2.
145. Kashi Y, King DG. Simple sequence repeats as advantageous mutators in evolution. *Trends in genetics : TIG* 2006; **22**(5): 253-9.
146. Fondon JW, 3rd, Hammock EA, Hannan AJ, King DG. Simple sequence repeats: genetic modulators of brain function and behavior. *Trends in neurosciences* 2008; **31**(7): 328-34.
147. Nithianantharajah J, Hannan AJ. Dynamic mutations as digital genetic modulators of brain development, function and dysfunction. *BioEssays : news and reviews in molecular, cellular and developmental biology* 2007; **29**(6): 525-35.
148. Kunkel TA. Nucleotide repeats. Slippery DNA and diseases. *Nature* 1993; **365**(6443): 207-8.
149. Mirkin SM. Expandable DNA repeats and human disease. *Nature* 2007; **447**(7147): 932-40.
150. Chambers GK, MacAvoy ES. Microsatellites: consensus and controversy. *Comparative biochemistry and physiology Part B, Biochemistry & molecular biology* 2000; **126**(4): 455-76.
151. Ellegren H. Microsatellites: simple sequences with complex evolution. *Nature reviews Genetics* 2004; **5**(6): 435-45.
152. Kashi Y, King D, Soller M. Simple sequence repeats as a source of quantitative genetic variation. *Trends in genetics : TIG* 1997; **13**(2): 74-8.
153. King DG. Evolution of simple sequence repeats as mutable sites. *Advances in experimental medicine and biology* 2012; **769**: 10-25.
154. van Dellen A, Hannan AJ. Genetic and environmental factors in the pathogenesis of Huntington's disease. *Neurogenetics* 2004; **5**(1): 9-17.
155. Andrew SE, Goldberg YP, Hayden MR. Rethinking genotype and phenotype correlations in polyglutamine expansion disorders. *Human molecular genetics* 1997; **6**(12): 2005-10.

156. Durr A, Stevanin G, Cancel G, et al. Spinocerebellar ataxia 3 and Machado-Joseph disease: clinical, molecular, and neuropathological features. *Annals of neurology* 1996; **39**(4): 490-9.
157. van de Warrenburg BP, Hendriks H, Durr A, et al. Age at onset variance analysis in spinocerebellar ataxias: a study in a Dutch-French cohort. *Annals of neurology* 2005; **57**(4): 505-12.
158. Aziz NA, Jurgens CK, Landwehrmeyer GB, et al. Normal and mutant HTT interact to affect clinical severity and progression in Huntington disease. *Neurology* 2009; **73**(16): 1280-5.
159. Tezenas du Montcel S, Durr A, Bauer P, et al. Modulation of the age at onset in spinocerebellar ataxia by CAG tracts in various genes. *Brain : a journal of neurology* 2014; **137**(Pt 9): 2444-55.
160. Djousse L, Knowlton B, Hayden M, et al. Interaction of normal and expanded CAG repeat sizes influences age at onset of Huntington disease. *American journal of medical genetics Part A* 2003; **119a**(3): 279-82.
161. de Castilhos RM, Furtado GV, Gheno TC, et al. Spinocerebellar ataxias in Brazil-frequencies and modulating effects of related genes. *Cerebellum (London, England)* 2014; **13**(1): 17-28.
162. Pulst SM, Santos N, Wang D, et al. Spinocerebellar ataxia type 2: polyQ repeat variation in the CACNA1A calcium channel modifies age of onset. *Brain : a journal of neurology* 2005; **128**(Pt 10): 2297-303.
163. Chen Z, Zheng C, Long Z, et al. (CAG)n loci as genetic modifiers of age-at-onset in patients with Machado-Joseph disease from mainland China. *Brain : a journal of neurology* 2016; **139**(Pt 8): e41.
164. Tezenas du Montcel S. Reply: Replicating studies of genetic modifiers in spinocerebellar ataxia type 3: can homogeneous cohorts aid? *Brain : a journal of neurology* 2015; **138**(Pt 12): e399.
165. Hyde CL, Nagle MW, Tian C, et al. Identification of 15 genetic loci associated with risk of major depression in individuals of European descent. *Nature genetics* 2016; **48**(9): 1031-6.
166. Locke AE, Kahali B, Berndt SI, et al. Genetic studies of body mass index yield new insights for obesity biology. *Nature* 2015; **518**(7538): 197-206.
167. Lee SH, Harold D, Nyholt DR, et al. Estimation and partitioning of polygenic variation captured by common SNPs for Alzheimer's disease, multiple sclerosis and endometriosis. *Human molecular genetics* 2013; **22**(4): 832-41.
168. Ridge PG, Mukherjee S, Crane PK, Kauwe JS. Alzheimer's disease: analyzing the missing heritability. *PloS one* 2013; **8**(11): e79771.
169. Davies G, Armstrong N, Bis JC, et al. Genetic contributions to variation in general cognitive function: a meta-analysis of genome-wide association studies in the CHARGE consortium (N=53949). *Molecular psychiatry* 2015; **20**(2): 183-92.
170. Hannan AJ. Tandem repeat polymorphisms: modulators of disease susceptibility and candidates for 'missing heritability'. *Trends in genetics : TIG* 2010; **26**(2): 59-65.
171. Hannan AJ. TRPing up the genome: Tandem repeat polymorphisms as dynamic sources of genetic variability in health and disease. *Discovery medicine* 2010; **10**(53): 314-21.
172. Hannan AJ. Tandem repeats mediating genetic plasticity in health and disease. *Nature reviews Genetics* 2018.
173. Wang MD, Gomes J, Cashman NR, Little J, Krewski D. Intermediate CAG repeat expansion in the ATXN2 gene is a unique genetic risk factor for ALS--a systematic review and meta-analysis of observational studies. *PloS one* 2014; **9**(8): e105534.
174. Neuenschwander AG, Thai KK, Figueroa KP, Pulst SM. Amyotrophic lateral sclerosis risk for spinocerebellar ataxia type 2 ATXN2 CAG repeat alleles: a meta-analysis. *JAMA neurology* 2014; **71**(12): 1529-34.
175. Sproviero W, Shatunov A, Stahl D, et al. ATXN2 trinucleotide repeat length





- correlates with risk of ALS. *Neurobiology of aging* 2017; **51**: 178.e1-e9.
176. Conforti FL, Spataro R, Sproviero W, et al. Ataxin-1 and ataxin-2 intermediate-length PolyQ expansions in amyotrophic lateral sclerosis. *Neurology* 2012; **79**(24): 2315-20.
  177. Lattante S, Pomponi MG, Conte A, et al. ATXN1 intermediate-length polyglutamine expansions are associated with amyotrophic lateral sclerosis. *Neurobiology of aging* 2018; **64**: 157.e1-e5.
  178. Ohi K, Hashimoto R, Yasuda Y, et al. TATA box-binding protein gene is associated with risk for schizophrenia, age at onset and prefrontal function. *Genes, brain, and behavior* 2009; **8**(4): 473-80.
  179. Chen CM, Lane HY, Wu YR, et al. Expanded trinucleotide repeats in the TBP/SCA17 gene mapped to chromosome 6q27 are associated with schizophrenia. *Schizophrenia research* 2005; **78**(2-3): 131-6.
  180. Lehmann DJ, Butler HT, Warden DR, et al. Association of the androgen receptor CAG repeat polymorphism with Alzheimer's disease in men. *Neurosci Lett* 2003; **340**(2): 87-90.
  181. Cheng D, Hong CJ, Liao DL, Tsai SJ. Association study of androgen receptor CAG repeat polymorphism and male violent criminal activity. *Psychoneuroendocrinology* 2006; **31**(4): 548-52.
  182. Rajender S, Pandu G, Sharma JD, Gandhi KP, Singh L, Thangaraj K. Reduced CAG repeats length in androgen receptor gene is associated with violent criminal behavior. *International journal of legal medicine* 2008; **122**(5): 367-72.
  183. Qin Z, Li X, Han P, et al. Association between polymorphic CAG repeat lengths in the androgen receptor gene and susceptibility to prostate cancer: A systematic review and meta-analysis. *Medicine* 2017; **96**(25): e7258.
  184. Weng H, Li S, Huang JY, et al. Androgen receptor gene polymorphisms and risk of prostate cancer: a meta-analysis. *Scientific reports* 2017; **7**: 40554.
  185. Gustafson DR, Wen MJ, Koppanati BM. Androgen receptor gene repeats and indices of obesity in older adults. *International journal of obesity and related metabolic disorders : journal of the International Association for the Study of Obesity* 2003; **27**(1): 75-81.
  186. Schildkraut JM, Murphy SK, Palmieri RT, et al. Trinucleotide repeat polymorphisms in the androgen receptor gene and risk of ovarian cancer. *Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology* 2007; **16**(3): 473-80.
  187. Zhu T, Yuan J, Xie Y, Li H, Wang Y. Association of androgen receptor CAG repeat polymorphism and risk of epithelial ovarian cancer. *Gene* 2016; **575**(2 Pt 3): 743-6.
  188. Zitzmann M, Gromoll J, von Eckardstein A, Nieschlag E. The CAG repeat polymorphism in the androgen receptor gene modulates body fat mass and serum concentrations of leptin and insulin in men. *Diabetologia* 2003; **46**(1): 31-9.
  189. Yaffe K, Edwards ER, Lui LY, Zmuda JM, Ferrell RE, Cauley JA. Androgen receptor CAG repeat polymorphism is associated with cognitive function in older men. *Biol Psychiatry* 2003; **54**(9): 943-6.
  190. Muhlau M, Winkelmann J, Rujescu D, et al. Variation within the Huntington's disease gene influences normal brain structure. *PloS one* 2012; **7**(1): e29809.
  191. Lee JK, Ding Y, Conrad AL, et al. Sex-specific effects of the Huntington gene on normal neurodevelopment. *Journal of neuroscience research* 2017; **95**(1-2): 398-408.

