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

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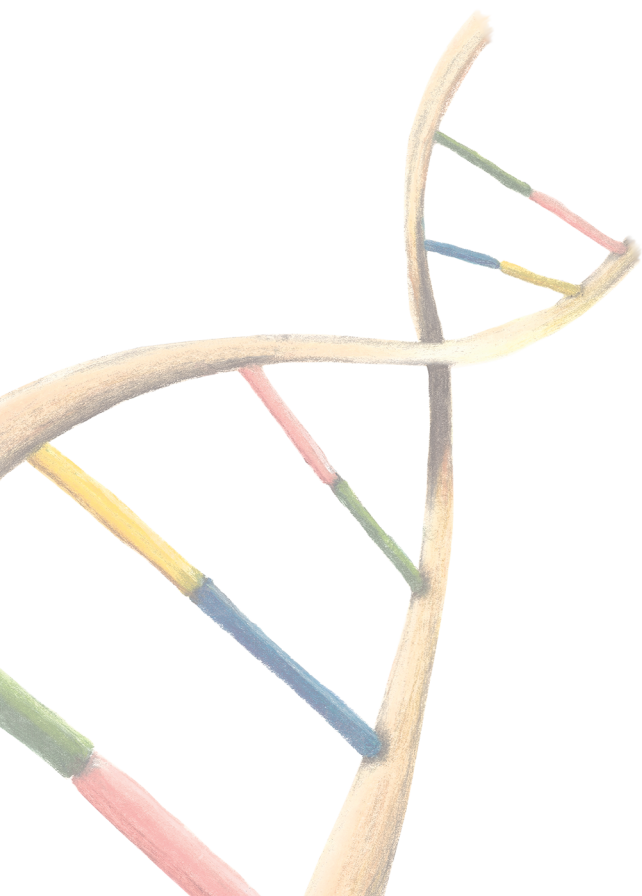


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# Chapter

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

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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**).

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