



## Case Report

# Kennedy disease in two sisters with biallelic CAG expansions of the androgen receptor gene

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## Abstract

We present a retrospective 21-year follow-up of two sisters with X-linked biallelic CAG expansions in the androgen receptor (*AR*) gene causing Kennedy disease. Two sisters inherited CAG expansions from their mother who was a carrier and their father who had Kennedy disease. Genetic testing revealed alleles comprising 43/45, and 43/43 CAG repeats in the younger and older sister, respectively. They were referred to a neurologist for further evaluation. Both reported similar symptoms with chronic backache, pain and cramps in upper- and lower extremities, and fasciculations in their faces and extremities. Neurological examination demonstrated postural hand tremor in both and EMG revealed chronic neurogenic changes. Reevaluation of the patients at ages 74 and 83 showed slight progression of clinical manifestations. As opposed to male patients, these two females showed minimal disease progression and have maintained normal level of function into old age. © 2021 The Author(s). Published by Elsevier B.V.

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## 1. Introduction

Kennedy disease or spinobulbar muscular atrophy (SBMA), is known as an X-linked, lower motor neuron and muscle disease caused by expanded CAG repeats (CAG > 37) in the first exon of the androgen receptor (*AR*) gene. It is a rare disorder with a prevalence in Europe ranging from 1 to 2.5/100,000 in men [1,2]. The onset of neurologic symptoms is usually between age 30–50, and inversely correlated with the CAG repeat length [3]. Common symptoms are cramps, fasciculations and progressive wasting of bulbar and limb muscles as well as androgen insensitivity resulting in gynecomastia and reduced fertility in men [3]. Recent studies

report a wide variety of systemic manifestations [4,5]. Female heterozygous carriers are usually asymptomatic, but some report cramps and postural tremor [6]. Information on disease manifestation and progression in females with biallelic *AR* CAG expansions is sparse [7]. The two elderly sisters with Kennedy disease presented here have been subjected to 21 years of follow-up. The aim of this case report is to bring forth more evidence on Kennedy disease symptoms, signs, progression and prognosis in females.

## 2. Case report

The two sisters, studied in this report, belong to a large family with many men with Kennedy disease (Fig. 1). When the sisters' cousin (Fig. 1. II.5) was confirmed to have Kennedy disease, his family was offered genetic counseling and testing. The sisters (Fig. 1. II.1 and II.2) were found to have biallelic expansions and accordingly they were referred

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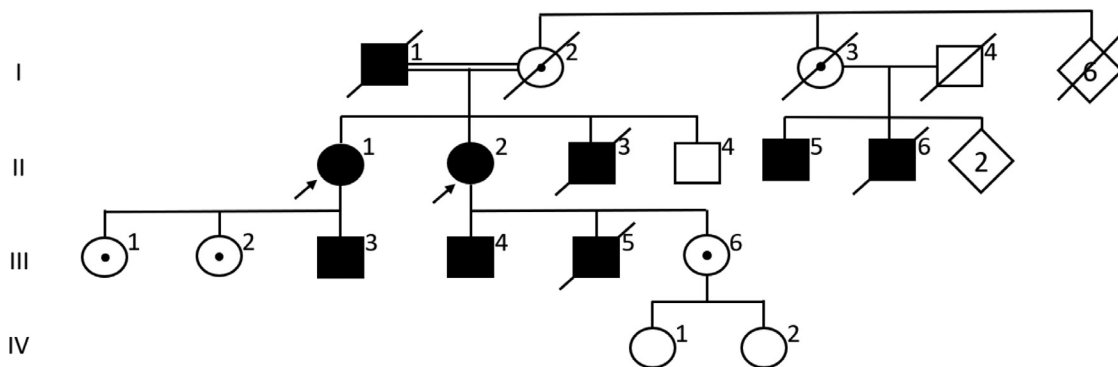


Fig. 1. Family pedigree. The index in this family is individual II.5. He was diagnosed with Kennedy disease at age 53, and is a first cousin of the two sisters (II.1 and II.2) who are indicated by black arrows. The sisters' parents (I.1 and I.2) were first cousins. Their mother (I.2) carried an expansion and their father (I.1) had symptoms of Kennedy disease, but never underwent genetic testing. The sisters had one brother (II.3) with severe Kennedy disease. Their sons (II.3, III.4 and III.5) all have Kennedy disease, while their daughters (III.1, III.2 and III.6) are obligate carriers.

for neurological evaluation. According to information from the two sisters, their daughters are healthy obligate carriers, with normal body mass indexes (BMI), and show no signs of neurologic or metabolic diseases (Fig. 1. III. 1, 2 and 6), but their sons were severely affected by Kennedy disease (Fig. 1. III. 3, 4 and 5).

The youngest sister (II.1) is compound heterozygous for 43 and 45 CAG repeats in the *AR* gene. She had a medical history of cancer cervix *in situ* when she was 30 years old. She was 53 years old when first assessed at our neurological department. She reported shoulder and back pain, cramps in muscles of her arms and legs and fasciculations in both arms and legs. Except for fasciculations, the neurological examination was normal. Meanwhile, she had been diagnosed with diabetes mellitus type 2, elevated cholesterol levels including LDL and triglycerides, elevated liver enzymes, hepatic steatosis, hypertension and hypothyroidism. Due to subjective memory impairments, she underwent neuropsychological testing and brain MRI at 58, both with normal results. A neurological follow-up at the age of 59 describes additionally postural hand tremor. At 73 she fell on ice and had a proximal humerus fracture. At age 74, symptoms and findings on neurological examination were assessed as unchanged at the neurological outpatient department. However, in recent years her voice gradually became weaker. Although she had no swallowing difficulties, a videofluoroscopy at age 74 found a slight residue in the vallecula. She also developed moderate urinary incontinence and constipation. CK levels were normal, ranging between 45 and 167 U/L. EMG in proximal and distal arm and leg muscles when she was 53, 59 and 74 years of age showed a moderate to pronounced chronic neurogenic pattern with sparse spontaneous activity which did not change significantly (Fig. 2). Results from nerve conduction studies were normal at the initial investigation. Later examinations revealed minimal abnormalities like a mild carpal tunnel syndrome and slightly prolonged F-response latencies at the last examination (Table 1). Muscle MRI findings in the lower extremities at 74 years of age was in accordance to her age.

She has been fit and lean her whole life, and her BMI at 74 years of age was  $51/1.58 \text{ m}^2 = 20.5$ .

The oldest sister (II.2) is homozygous for 43 CAG repeats in exon 1 of the *AR* gene. She had a past medical history of aseptic meningitis, migraine, adenoma in her right breast (14 years old), colon cancer (48 years old) and ductal carcinoma *in situ* in both breasts (68 years old). Polysomnography examination demonstrated sleep apnea syndrome, and osteopenia was verified on bone density measurements when she was 73 years old. After a fall, 81 years old, vertebral fractures were detected on Th12, L1 and on several ribs.

She was consulted at our neurological outpatient department at the age of 62, reporting symptoms that began in her late fifties. She complained about pain in her shoulders, arms and back, and to a lesser extent in her thighs and calves. Furthermore, she described cramps and fasciculations in her face and extremities. At the onset of her neurological symptoms, she had slightly elevated HbA1c, elevated cholesterol levels including LDL, hypertension, elevated liver enzymes and mild urinary incontinence. The neurological examination was normal. She was followed-up at the age of 65, 73, 77 and 83. These examinations revealed addition of a postural tremor in her hands at 65 years of age, subjectively a slight increase in her cramps and fasciculations, and her voice becoming weaker from 73 years of age. The neurological consultations did not reveal other changes during follow-up. Blood glucose, cholesterol levels and liver enzymes stayed stable. At the neurological consultation at the age of 83, symptoms were described as unchanged with pain, cramps, fasciculations and postural hand tremor. She had no other bulbar symptoms than a slightly weak voice. She complained of urinary incontinence and constipations that had slightly progressed from her late fifties. Her CK levels have been normal with values between 115 and 170 U/L. EMG, performed when she was 62, 65 and 83 years old, all showed a chronic neurogenic pattern of moderate degree with a few fibrillations and fasciculation potentials (Fig. 2). The abnormalities were most pronounced in hand- and leg

Table 1.  
Nerve conduction studies of the two sisters (II.1 and II.2) with Kennedy disease.

Patient	II. 1		II. 2	
	1999	2020	1999	2020
<i>Year</i>				
<i>Median nerve</i>				
DL, ms	3.8	3.8	3.6	3.8
CMAPa, mV	6.0	6.8	6.5	5.7
CV, m/s	57.5	60.7	60.5	56.7
F-latency, ms	22.4	<b>24.5</b>	22.6	22.4
SNAPa, uV 70	<b>17.9</b>	104	36.2	
Sensory DL, ms 2.0	<b>2.41</b>	2.1	2.3	
<i>Peroneal nerve</i>				
DL, ms	4.6	3.6	3.6	3.3
CMAPa, mV	6.0	1.4	9.0	3.6
CV, m/s	43.9	41.2	49.2	48.7
F-latency, ms	40.8	<b>48.6</b>	40.4	44.0
<i>Tibial nerve</i>				
DL, ms	5.4	3.8	4.6	3.2
CMAPa, mV	7.0	7.1	8.6	6.2
CV, m/s	42.0	45.6	46.3	47.9
F-latency, ms	45.6	<b>49.8</b>	46.0	46.8
<i>Sural nerve</i>				
SNAPa, uV	10.0	2.8	2.7	<b>1.5</b>
CV, m/s	45.0	54.9	42.9	55.8

Abbreviations: DL, distal latency; CMAPa, compound muscle action potential amplitude; CV, conduction velocity; SNAP, sensory nerve action potential amplitude.

\*Abnormal values in bold are evaluated from Z-scores taking age and height into account.

muscles and did not change significantly over time. Nerve conduction studies were essentially normal (Table 1). At 83 years of age muscle MRI of the lower extremities did not show any significant signs of neuropathy or myopathy. She has been fit and lean into old age, and her BMI at 83 years of age was  $60\text{ kg}/1.6\text{ m}^2 = 23.4$ .

### 3. Discussion

By following two sisters with biallelic expanded AR CAG repeats, from detection of the expansions until old age, we observed minimal disease progression on neurological examination, EMG, neurography and lower extremity muscle MRI. Their daughters are healthy, obligate carriers of the AR gene expansion. In contrast, the motor manifestations in their sons and other male relatives with Kennedy disease were severe and typical for Kennedy disease.

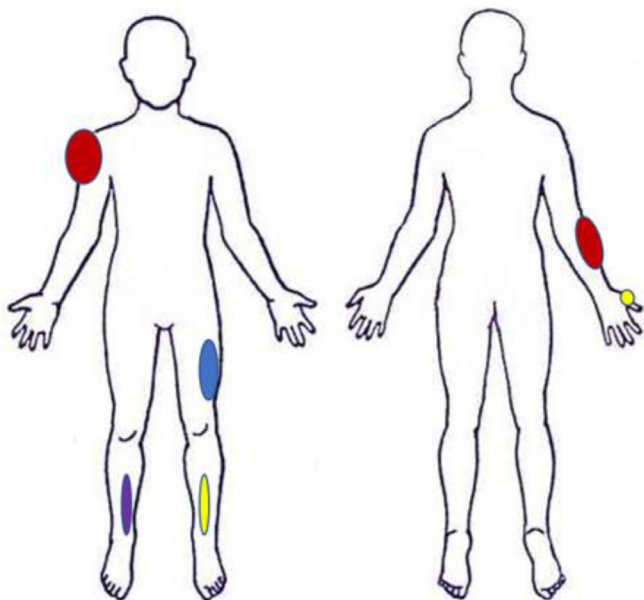
Female heterozygous carriers are usually asymptomatic, but a few may manifest with mild bulbar symptoms later in life, and many may have slight neurogenic and myopathic changes on EMG and in muscle biopsy [6,8,9]. We found only one report on females with biallelic AR CAG expansions in the range associated with Kennedy disease. Although observations on the natural disease progression in these females are lacking, Schmidt and colleagues describe the clinical feature of two Canadian sisters aged 34 and 42 with biallelic CAG repeat expansions of 46/47 and 47/48, respectively [7]. Similar to the patients reported here, both Canadian patients had cramps, fasciculations and postural tremor as well as otherwise normal neurological examinations [7]. In contrast to the two patients reported here, the EMG examinations were normal in the two Canadian patients.

These findings taken together could point towards an average age of onset being around 40–50 in biallelic females which is similar to males [3]. However, the degree of EMG abnormalities may vary between affected females or may appear over time (Fig. 2).

Although muscle cramps and tremor are often the first symptoms of Kennedy disease [3], the currently described two cases suggest that motor manifestations hardly progress in women. Contrary to male patients with Kennedy disease, the two sisters described here remained physically fit with little disease related disability at advanced age. Furthermore, in contrast to women with either one or two expanded AR alleles, men with Kennedy disease have pronounced progression in bulbar and extremity muscle weakness, tremor and fasciculations [3,10]. The prognosis in men is rather discouraging, most patients develop dysarthria and dysphagia, and about half of the patients become wheelchair dependent at the age of 60 [3,10]. Additionally, most male patients with Kennedy disease have sensory manifestations, which is rarely reported in female carriers [10]. No impact on sensory nerves was found in the two female patients reported here (Table 1).

The CAG expansion in the AR gene causes both a toxic gain of function and a loss of function of the androgen receptor. The differences in the neurological manifestations between males and females with Kennedy disease is mostly explained by the fact that binding of androgens to the AR induce toxicity to neurons and muscle cells [11]. Higher androgen levels in men produce more abnormal and toxic protein aggregates, leading to more manifested neurological symptoms in males as compared to females. In line with this, reducing androgen levels proves to reduce disease manifestations in transgenic SBMA mouse models [12–14].

## The youngest sister (II.1)



## The oldest sister (II.2)

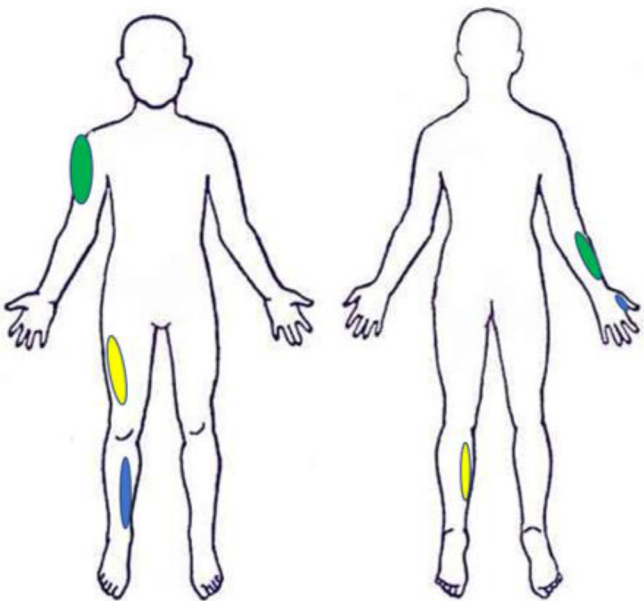


Fig. 2. Distribution of electromyographic changes in the youngest (II.1) and the oldest (II.2) sister. Red color denotes pronounced chronic neurogenic changes; violet pronounced subacute neurogenic changes with denervation activity; blue moderate chronic neurogenic changes; yellow slight chronic neurogenic changes; green normal findings.

Randomized controlled trials of drugs with antiandrogen effect did not meet significance for their primary endpoints, but this could be due to low statistical power and the slow progression of Kennedy disease making it difficult to find proper clinical endpoints [15,16]. However, the studies

met significance for several secondary endpoints [15,16]. Furthermore, the pooled analysis of two randomized trials showed indications of benefit for a testosterone lowering drug (Leuprorelin) [17]. The two sisters presented here with biallelic CAG expansions in the *AR* gene, may provide further evidence that lower levels of androgens in women produce less toxicity, and they escape the whole neurological picture of SBMA.

Contrary to the neurological picture, the two sisters seem to be at least equally affected as men with Kennedy disease in manifestations outside the nervous system. Both presented with hypertension, non-alcoholic liver steatosis, hyperlipidemia and elevated blood glucose levels arising at the same time as the neurological symptoms. The article about two Canadian patients with CAG expansions on both alleles does not give information on extraneurological findings, and we do not know if the metabolic manifestations in the two patients reported here are caused by the *AR* receptor expansions [7]. Since both have normal BMI and their daughters are healthy with normal BMI, the metabolic changes are less likely caused by other inherited disorders or lifestyle habits. Additionally, heterozygous carriers do not seem to be affected by metabolic abnormalities indicating that expansions on two alleles could be necessary to express metabolic changes [18]. Females have much lower levels of androgens than males. It is therefore less likely that the findings outside the nervous system are caused by the toxic gain of function mechanism in the *AR*. Because *AR* is important for normal liver function, we speculate that the metabolic abnormalities observed in the patients may be caused by a loss of *AR* function in the liver giving steatosis, and disturbed homeostasis of glucose and lipids [19].

- Kennedy disease in females with biallelic CAG expansions progresses minimally and they maintain good function into old age.
- EMG over the course of female Kennedy disease with biallelic CAG expansions does not change significantly.
- In women with postural tremor, muscle pain, cramps and fasciculations, Kennedy disease is a possible differential diagnosis.
- Kennedy disease in females with biallelic CAG expansions may have as many manifestations outside the nervous system as men.

#### Declaration of Competing Interest

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines. None of the authors has any conflict of interest to disclose. No financial support for the research/manuscript was received.

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