ESETISMERTETÉS

CASE REPORT

Novel heterozygous *STUB1* gene mutation causes SCA48 in a Hungarian patient

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Spinocerebellar ataxia type 48 (SCA48) is an autosomal dominantly inherited disease characterized by gait and limb ataxia, cerebellar dysarthria, cognitive impairment, psychiatric abnormalities and variable types of movement disorders. To date, more than 30 *STUB1* gene (NM_005861.4) mutations have been described in the genetic background of SCA48.

The aim of this short report was to demonstrate the first Hungarian SCA48 patient caused by a novel *STUB1* missense mutation (c.788G>C, p.Arg263Pro). The characteristics of detailed neurological phenotype, brain MRI and genetic assessment are presented and compared to previously published cases.

The most important neurological findings of the patient were gait ataxia, dysarthria, cognitive decline and psychiatric problems including depression, anxiety and mild impulsivity. The brain MRI demonstrated cerebellar atrophy with posterolateral predominance and frontal lobe cortical atrophy. Clinical exome sequencing examination identified the above-mentioned missense variant located in the significant ubiquitinase domain of the CHIP protein.

In this paper the first Hungarian SCA48 patient was described with characteristic neuropsychiatric signs and brain MRI abnormalities, due to a novel *STUB1* gene missense mutation.

Keywords: hereditary, spinocerebellar ataxia, *STUB1*, SCA48, SCAR16

Újabb *STUB1* génmutáció okozta SCA48 egy magyar páciensnél

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A spinocerebellaris ataxia 48-as típusa (SCA48) autoszomális domináns módon öröklődő betegség, aminek legjellemzőbb tünetei a járási és végtagataxia, a cerebellaris dysarthria, a kognitív deficit, a pszichiátriai eltérések és a különböző mozgászavarok. Eddig több mint 30 *STUB1* (NM_005861.4) génmutációt azonosítottak az SCA48 hátterében.

Az esetismertetés célja, hogy bemutassa az első magyar SCA48-as családot, akiknél a kórképet egy új *STUB1* misszensz mutáció (c.788G>C, p.Arg263Pro) okozza. Az esetismertetés részletes leírást ad a neurológiai fenotípusról, a koponya-MR-eltérésekről és a genetikai háttérről, illetve összehasonlítja ezeket a korábban közölt esetekben megfigyelt jellemzőkkel.

A beteg legfontosabb neurológiai tünetei a járási ataxia, a dysarthria és a kognitív hanyatlás voltak, melyek mellett pszichiátriai tünetek is jelentkeztek: depresszió, anxietas és enyhe impulzivitás. A koponya-MR-vizsgálat posterolateralis túlsúlyú kisagyi és frontális lebenyi kérgi atrophiát jelzett. A klinikai exomszekvenálás során a fent említett misszensz variáns igazolódott, ami a CHIP protein nagy jelentőségű ubiquitinase funkciójú doménjében található.

Jelen esetismertetés bemutatja az első magyar, új *STUB1* génmutáció okozta SCA48-as beteg jellegzetes neuropszichiátriai tüneteit és koponya-MR-eltéréseit.

Keywords: hereditaer, spinocerebellaris ataxia, *STUB1*, SCA48, SCAR16

Autosomal dominant cerebellar ataxias (ADCA), also known as spinocerebellar ataxias (SCA) are a group of progressive neurodegenerative diseases with remarkable clinical and genetic heterogeneity. In the last ten years 20 genes were identified in the background of SCAs. One of these genes was *STUB1* (STIP1 homology and U-box containing protein 1) (chromosome 16p13, NM_005861.4) encoding a multifunctional E3 ubiquitine ligase (CHIP)[1]. In 2013, *STUB1* was identified as a causative gene of autosomal recessive spinocerebellar ataxia 16 (SCAR16), but in 2018 Genis et al. published that heterozygous mutations of this gene can cause the autosomal dominantly inherited SCA48 as well[1, 2]. 28 French, twelve Italian, three Belgian, two North-American, one Spanish, one Turkish, one Dutch, one German and one British SCA48 families have been reported so far[2–9]. Based on these publications, SCA48 is a late-onset, progressive disorder characterized by cerebellar dysfunction, cognitive impairment, psychiatric features, dysphagia, hyperreflexia, urinary tract symptoms and movement disorders including Parkinsonism, chorea, dystonia and rarely tremor. The brain MRI in all SCA48 patients demonstrated vermian and hemispheric cerebellar atrophy which was more pronounced in the posterior areas (lobules VI and VII) of the cerebellum in most of the cases[2–9]. Besides this, T2-weighted imaging (T2WI) hyperintensity of dentate nuclei (DN) was reported in some Italian patients[10]. Moreover, the most recent publication described alterations on DAT-scan imaging in some French families[9]. Neurophysiological examinations did not find any central or peripheral nervous system abnormalities[2, 3, 5]. Neuropathologic findings revealed definite cerebellar atrophy and cortical shrinkage with variable severity[6, 7]. The histopathological assessment denoted Purkinje cell loss, p62-positive neuronal intranuclear inclusions in some cases and tau pathology in one patient[6, 7].

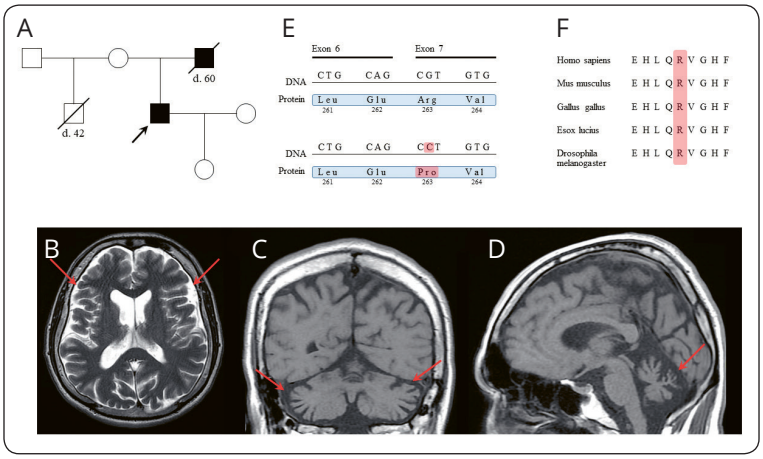

Figure 1. (A) *Family tree of the Hungarian SCA48 patients. The arrow indicates the proband, the black filled symbols the affected patients, the diagonal bands sign the dead subjects, whereas the number after the letter d. denotes the age at death.* **(B–D)** *Skull magnetic resonance imaging (MRI) of the proband.* **(B)** *Axial, T2-weighted images, the red arrows indicate frontal lobe atrophy.* **(C)** *Coronal, T1-weighted images, the red arrows denote cerebellar atrophy with predominance at the lateral parts of cerebellar hemispheres.* **(D)** *Sagittal, T1-weighted images, the red arrow shows cerebellar atrophy which is most prominent in the posterior vermian area.* **(E)** STUB1 *gene mutation of the patients. The upper part of the figure indicates the DNA sequence and wild-type encoded protein, whereas the red highlight of lower part depicts the c.788G>C change and the consequent Arg–Pro substitution of the CHIP protein.* **(F)** *The identified amino acid change is located within a highly conserved region of the protein across different species*

In this paper we describe the clinical and genetic characterization of the first Hungarian SCA48 case with a novel heterozygous *STUB1* gene missense mutation.

Case presentation

Clinical findings

The proband is 42 years old male, who was 35 when his gait ataxia appeared as an initial symptom of the disease. The first neurological examination was performed 5 years later and revealed marked gait ataxia, upper limb dysmetria, mild lower limb ataxia, cerebellar dysarthria and slightly reduced vibration sense in the legs. One year later he complained swallowing difficulties, mood disturbances and impulsive behavior. Further neurological findings were mildly saccadic smooth pursuit eye movements, increased tendon reflexes of the lower limbs and subtle bradykinesia with missing synkinesis. Scale for the Assessment and Rating of Ataxia (SARA) score was 12.5 out of 40 points. Neuropsychological assessment revealed cognitive deficit (Addenbrooke's Cognitive Examination 71/100 points, Mini-Mental State Examination 27/30 points) especially in the executive tests, visuospatial functions, anterograde and working memory capabilities. Psychiatric examination delineated anxiety and depression. Laboratory findings indicated mild hyperlipidemia and hyperuricemia with minimally elevated gamma-glutamyl transferase activity, whereas levels of TSH, alpha-fetoprotein, B12, tocopherol and other routine serum parameters were in the normal range. There was not found any pathological

alteration in the cerebrospinal fluid. Electroencephalography and electroneurography were normal. The psychiatric symptoms of the patients were ameliorated by benzodiazepine and citalopram treatment. However, his cognitive impairment and gait ataxia progressed and he can walk with sticks only.

The family tree of the patient is shown in **Figure 1.A**. The father of proband had similar gait problems and cognitive decline, however he had alcohol abuse problems as well and he died at 60 years of age. The mother of the proband did not have similar symptoms. The patient had a maternal half-brother who died at 42 years because of complications of advanced stage type 1 diabetes mellitus, nevertheless he did not have ataxia. The proband has an 11 years old daughter, who showed mild anxiety presumably the proband's progressive disease, but she does not have ataxia.

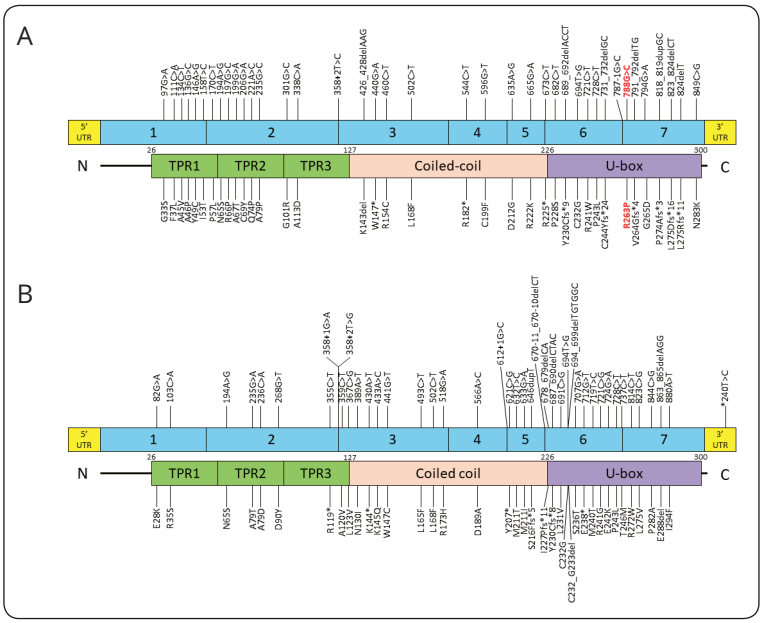

Figure 2. *Identified pathogenic mutations of the* STUB1 *gene and the consecutive amino acid changes of the protein.* **(A)** *The SCA48 causing variants, the red labeled variant is the mutation found in the proband.* **(B)** *Mutations described in SCAR16 patients*

MRI abnormalities

The brain MRI of the proband demonstrated cerebellar atrophy mainly in the posterior vermian and hemispheric areas. Additionally, supratentorial cortical atrophy was observed as well, especially in the frontal lobe. T2WI hyperintensity of the DN was not present **(Figure1.B–D)**.

Genetic findings

First of all, screening of the most frequent repeat expansion hereditary ataxias, including SCA1, 2, 3, 6 and Friedreich's ataxia were performed without any pathologically expanded repeat number in these genes. In the next step clinical exome sequencing was implemented. In a search for a causative mutation the Trusight One Expanded Sequencing Panel (Illumina, CA), covering the coding region of 6794 clinically relevant genes was applied using Illumina MiSeq (Illumina, CA). The 150 bp paired reads were aligned by Burrows Wheeler Aligner (BWA v0.7.9a) software. The variants were called by Genome Analysis Toolkit HaplotypeCaller (GATK v3.5) Best Practices; annotated by SnpEff and VariantStudio softwares. Variants were filtered based on severity and frequency against public variant databases including dbSNP, ClinVar, ExAC, EVS and in-house clinical exome database of 150 unrelated Hungarian patients. The clinical exome sequencing identified a heterozygous c.788G>C, p.Arg263Pro missense variant in the *STUB1* gene **(Figure 1.E)**. This mutation is not found in the gnomAD database (https://gnomad.broadinstitute.org) and is predicted to be deleterious by SIFT (0), PolyPhen2 (0.998) and Mutation Taster (0.999) softwares. The presence of the mutation was confirmed by targeted Sanger sequencing, whereas it was not identified in his mother and daughter. The identified arginine-proline change is located in the U-box domain of the protein, whose amino acid sequence is highly conserved across species **(Figure 1.F)**.

Discussion

In this paper we describe the clinical characteristics of the first genetically confirmed Hungarian SCA48 patient caused by a novel heterozygous mutation in the *STUB1* gene. Cerebellar symptoms, cognitive impairment and psychiatric disorders were the most prominent abnormalities of the proband which are consistent with the majority of previously published cases **(Table 1.A** and **B)**[2–9]. The brain MRI demonstrated the typical cerebellar atrophy with posterolateral predominance, however frontal lobe cortical atrophy was present as well without T2WI hyperintensity of the DN, thus the "crab sign" introduced by *Cocozza* et al. was not observed[10]. The identified *STUB1* gene missense variant results in an Arg–Pro substitution in the C-terminal U-box domain responsible for the ubiquitination activity of the CHIP protein which has an important role in protein quality control and its significance has been proven in

several neurodegenerative disorders including SCA1 and 3[11, 12]. To date, more than 70 *STUB1* mutations have been identified in SCA48 and SCAR16, more than two-thirds of them were located in the TPR or U-box domains **(Figure 2)**[1–9, 13–28]. Interestingly, some of them were associated with two modes of inheritance, including p.Asn65Ser, p.Leu168Phe, p.Cys232Gly and p.Pro243Leu. Additionally, there was a female predominance among SCA48 patients published by *Roux* et al. and *Lieto* et al.[5, 8]. This preponderance of women (66%) is noticeable in all previously described SCA48 patients as well **(Table 1.A** and **B)**. This observation supports the hypothesis proposed by Roux et al., that *STUB1* gene expression is lower in women than men in the brain, consequently females may be more sensitive to *STUB1* gene haploinsufficiency[8].

In summary, this paper demonstrates the first SCA48 patient in the Central and Eastern European region due to a novel *STUB1* gene missense mutation. This case report with the data of previously published subjects denotes well that there are no specific clinical features in SCA48 which would differentiate it from other SCAs. Thus next-

Table 1.A *Clinical phenotype of SCA48 patients published in the literature*

Mutation (cDNA)	97G>A	111C>A	134C>T	136G>C	146A>G	158T>C	170C>T	194A>G	199G>A
Mutation (protein)	G33S	F37L	A45V	A46P	Y49C	I53T	P57L	N65S	A67T
Nationality	Italian	North–American susp.	French	European	European	North–American susp.	Italian	European	Italian
Case number	6	3	1	3	10	4	4	5	1
Gender (M/F)	3M, 3F	1M, 2F	1F	3F	2M, 8F	3M, 1F	2M, 2F	5F	1F
Mean age at onset (y) [range]	30.67* [5–50]	40**	47	48.33 [38–60]	47.25 [37–76]	37 (21–60)	45.75 [40–60]	40.8 [27–55]	37
First detected symptoms/ signs	At 3/6 GTC 2/6 Dizz 1/6 Dys 1/6 Psy 1/6 Tr 1/6	At, Psy, PCh 1/3 NA 2/3	GD	U 3/3 Cl 2/3 Dip 1/3	Ap 1/10 At 1/10 U 4/10 Dys 4/10 Cl 5/10 W 1/10 NA 1/10	At: 3/4 Cl 3/4	Dys 3/4 U 3/4	U 4/5 Dy 1/5	Dys
Ataxia	++ 2/6 +++ 4/6	P 3/3	P SARA 28 SDFS 3	P 3/3	P 8/10 SARA 7.5–33 SDFS 2–7 NA 2/10	+ 2/4 +++ 1/4 – 1/4***	+ 1/4 P 3/4	P 5/5	++
Dysarthria	+ 3/6 ++ 3/6	P 1/3 NA 2/3	P	NA	P 4/10 – 1/10 NA 5/10	P 3/4 – 1/4	+++ 1/4 P 2/4 NA 1/4	P 1/5 NA 4/5	++
Dysphagia	P 3/6 – 3/6	– 1/3 NA 2/3	P	NA	– 3/10 NA 7/10	–	P 1/4 NA 3/4	NA 5/5	–
Tremor	+ 2/6 – 4/6	P 1/3 (WB) NA 2/3	–	– 3/3	– 6/10 NA 4/10	–	P 1/4	– 5/5	–
Parkinsonism	+ 4/6 ++ 1/6 – 1/6	– 1/3 NA 2/3	–	P 1/3	– 8/10 NA 2/7	–	P 2/4	– 5/5	–
Chorea	+ 2/6 ++ 2/6 – 2/6	– 1/3 NA 2/3	–	P 2/3	P 2/10 – 1/10 NA 7/10	–	– 4/4	– 5/5	+ (Ha)
Dystonia	P 3/6 – 3/6	– 1/3 NA 2/3	–	P 1/3 (He)	P 2/10 – 1/10 NA 7/10	–	–4/4	P 1/5	+ (Ha)

generation sequencing is the recommended genetic method in this disease group after testing the most common repeat expansion SCAs.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE – Written informed consent was obtained from all individual participants included in the study. Additional informed consent was obtained from all individual participants for whom identifying information is included in this article (Regional Human Biomedical Research Ethics Committee of the University of Szeged registration numbers are 150/2014. and 44/2016., respectively). All procedures performed in studies involving human participants were in accordance with the ethical standards of the Regional Human Biomedical Research Ethics Committee of the University of Szeged and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

CONFLICTS OF INTEREST – The authors declare no conflict of interest.

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197G>C	206G>A	221A>C	235G>C	301G>C	338C>A	358+2 T>C	426_428 delAAG	440G>A	460C>T	502C>T
R66P	C69Y	Q74P	A79P	G101R	A113D	–	K143del	W147*	R154C	L168F
French	European	European	European	European	European	European	European	European	European	European
2	2	1	1	5	2	1	3	1	1	1
2M	1M, 1F	1F	1F	2M, 3F	1M, 1F	1M	1M, 2F	1F	1F	1F
40 [20–60]	59 [44–74]	65	40	35 [25–50]	42 [40–44]	30	39.5 [27–52]	53	30	NA
At 1/2 Myo 1/2	U 2/2 CI 1/2	U, Dys	U, Dys	U 4/5 Dys 1/5	U 1/2 W 1/2	U	U 2/3	U, Dys	U	U
P 2/2 SARA 24–28 SDFS 3	P 2/2 SARA 7.5	P	P	P 5/5 SARA 6.5–12	P 2/2 SARA 12	P	P 3/3 SARA 4.5	P	P	NA
– 1/2 NA 1/2	NA	P	P	P 1/5 NA 4/5	NA	NA	NA	NA	NA	NA
– 2/2	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
– 2/2	P 1/2	NA	NA	P 1/5 – 4/5	– 2/2	–	– 3/3	–	–	NA
P 1/2	P 1/2	NA	NA	P 1/5 – 2/5 NA 2/5	– 2/2	–	P 1/3	–	P	NA
– 2/2	–	NA	NA	– 3/5 NA 2/5	P 1/2	–	– 3/3	–	–	NA
– 2/2	–	NA	NA	P 1/5 – 2/5 NA 2/5	– 2/2	–	P 1/3 (Ce)	–	–	NA

Continuation of Table 1.A

Mutation (cDNA)	97G>A	111C>A	134C>T	136G>C	146A>G	158T>C	170C>T	194A>G	199G>A
Increased tendon reflexes or EPR	+ 3/6 ++ 2/6 – 1/6	– 1/3 NA 2/3	P	NA	P 4/10 – 4/10 NA 2/10	P 4/4	P 3/4	NA	+
Psychiatric disorders	+ 2/6 ++ 3/6 +++ 1/6	P 2/3 NA 1/3	P (Irr)	P 1/3 (Ag)	2/10 (Mu, FS) – 5/10 NA 3/10	ASD 1/4 Alc 1/4	SH 1/4 Ag 1/4	NA	–
Cognitive dysfunction	+ 2/6 ++ 4/6	P 2/3 NA 1/3	P	P 2/3	P 8/10 NA 2/10	P 4/4	+ 1/4 – 2/4 NA 1/4	P 2/5 – 2/5 NA 1/5	MMSE 26/30
Other features	UTS 4/6 GTC 3/6 HL 1/6	GEN 1/3	UTS	Ny 1/3 SSa: 1/3	OMA 2/10 SSa 2/10 Dip 1/10 Pt 1/10 BSP 1/10 Myo 1/10	BSP 3/4 SD 2/4 Myo 1/4	Dip 2/4 Pt 2/4 BSP 1/4 SD 1/4 TA 1/4	HL 1/5 Sc 1/5	AEM, TC, UTC
Cerebellar atrophy on MRI or CT	++ 2/6 +++ 3/6 NA 1/6	++ 1/3 NA 2/3	+++	NA	P 2/10 +++ 1/10 NA 7/10	P 4/4	++ 1/4 NA 3/4	NA	+++
References	3	6	9	8	8, 9	6	5, 8	8	5

Table 1.B *Second half of the list: Clinical phenotype of SCA48 patients published in the literature*

Mutation (cDNA)	544C>T	596G>T 635A>G	665G>A	673C>T	682C>T	689_692 delACCT	694T>G	721C>T
Mutation (protein)	R182*	C199F D212G	R222K	R225*	P228S	Y230Cfs*9	C232G	R241W
Nationality	European	European	European	Italian	Italian	Italian	French	Italian
Case number	1	3	1	1	2	2	2	1
Gender (M/F)	1F	1M, 2F	1M	1F	2M	1M, 1F	1M, 1F	1F
Mean age at onset (y) [range]	65	27 [23–29]	50	50	45 [35–55]	39.5 [31–48]	44 [31–57]	46
First detected symptoms/ signs	CI	U 3/3 Dys 2/3	U, Dys	At, Dys	At 2/2	At 2/2 Dys 2/2	At 1/2 CI 1/2	CI, Dys
Ataxia	P	P 3/3	P	++	+++ 2/2	+ 1/2 +++ 1/2	P 2/2 SARA 18 SDFS 2–3	–
Dysarthria	NA	P 2/3	NA	++	++ 2/2	++ 1/2 +++ 1/2	P 1/2 NA 1/2	+

197G>C	206G>A	221A>C	235G>C	301G>C	338C>A	358+2 T>C	426_428 delAAG	440G>A	460C>T	502C>T
P 1/2 – 1/2	–	–	P	NA	P 1/2	P	P 1/3	P	–	NA
Dep 1/2 – 1/2	NA	NA	NA	Ap 1/5	NA	NA	– 3/3	NA	NA	NA
P 1/2	P 2/2	P	P	P 1/5	P 1/2	P	P 1/3 (CCAS)	P	P	P
Ny 1/2 SP 1/2 Myo 1/2	Cat 1/2 SSa 1/2 BSP 1/2 Ny 1/2 Op 1/2	FD	E	BSP 4/5 SSa 2/5 Ny 2/5 Op 2/5 Dip 1/5	Myo 1/2 BSP 1/2 W 1/2	–	BSP 2/3 Ny 1/3	–	SSa	NA
+++ 1/2 NA 1/2	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
9	8	8	8	8	8	8	8	8	8	8

728C>T	731_732 delGC	787–1G>C	788G>C	791_792 delTG	794G>A	818_819 dupGC	823_824 delCT	824delT	849C>G
P243L	C244Y fs*24	–	R263P	V264Gfs*4	G265D	P274Afs*3	L275D fs*16	L275R fs*11	N283K
European	Dutch	European	Hungarian	Italian	European	Italian	Italian Spanish Turkish	European	European
2	9	1	1	2	2	2	13	1	1
1M, 1F	NA	1F	1M	1M, 1F	1M, 1F	2F	3M, 10F	1F	1F
31.5 [30–33]	65.33 (50–72)	27	35	48 [40–56]	63.5 [60–67]	38 [34–42]	49.58 [33–70]	NA	48
U 2/2 Dys 1/2	Park 1/9 Psy 1/9 NA 7/9	U, Dys	At	At 1/2 Dys 1/2	U, Dys 1/2 At 1/2	At 2/2 Ch 1/2 CI 1/2	Anx 6/13 CI 5/13 CA 4/13 CAS 3/13 Dys 2/13 At 1/13	NA	Dys
P 2/2	P: 8/9 – 1/9	NA	++	+ 1/2 ++ 1/2	P 2/2 SARA 18.5–24 SDFS 3	+ 2/2	++ 4/13 +++ 3/13 P 3/13 – 3/13	P	P
P 1/2 NA ½	P 8/9 NA 1/9	NA	++	+ 1/2 ++ 1/2	P 1/2 NA 1/2	+ 2/2	+ 1/13 ++ 3/13 +++ 3/13 P 3/13 – 3/13	NA	P

Continuation of Table 1.B

Mutation (cDNA)	544C>T	596G>T 635A>G	665G>A	673C>T	682C>T	689_692 delACCT	694T>G	721C>T
Dysphagia	NA	NA	NA	–	P 2/2	P 1/2 – 1/2	– 2/2	–
Tremor	NA	P 1/3	P	–	+ 1/2 – 1/2	+ 1/2 (He) – 1/2	– 2/2	–
Parkinsonism	NA	– 1/3 NA 2/3	–	–	–	+ 1/2 – 1/2	– 2/2	–
Chorea	NA	– 1/3 NA 2/3	–	–	++ 1/2 – 1/2	+ 1/2 (Or) – 1/2	P 1/2 – 1/2	–
Dystonia	NA	– 1/3 NA 2/3	–	–	–	+ 2/2 (Ce)	P 1/2 – 1/2	–
Increased tendon reflexes	–	P 2/3 – 1/3	P	–	+ 1/2 – 1/2	+ 1/2 – 1/2	– 2/2	–
Psychiatric disorders	NA	NA	NA	+ (Ap)	+ 1/2 ++ 1/2	+ 1/2 (Dep) – 1/2	P 1/2 (Ag)	+ (Ap)
Cognitive dysfunction	P (CCAS)	P 2/3 – 1/3	–	MMSE 27/30	+ 1/2 ++ 1/2	MMSE 16/30 MMSE 27/30	P 2/2	MMSE 28/30
Other features	–	SSa 3/3 Ny 2/3	BSP, SSa	AEM	HL 1/2	BSP 2/2 LTL 1/2 Ny 1/2 UTS 1/2	DAT 2/2 SP 1/2	AEM, AD, HT, Hy
Cerebellar atrophy on MRI or CT	NA	NA		++	+++ 2/2	++ 1/2 +++ 1/2	+++ 2/2	+++
References	8	8		5	3	5	9	5

AEM: abnormal eye movements, AD: Addison's disease, Ag: aggressive behavioral, Alc: alcohol and drug abuse, Anx: anxiety disorder, Ap: apathy, Aph: aphasia, Apr: apraxia, ASD: autism spectrum disorder, At: ataxia, Bl: blepharospasm, Br: bradykinesia, BSP: broken smooth pursuit eye movements, CA: cerebellar atrophy, CAS: cognitive affective syndrome, Cat: cataract, CCAS: cerebellar cognitive affective syndrome, Ce: cervical, Ch: chorea, CI: cognitive impairment, DAT: DAT–scan abnormality, Del: delusion, Dep: depression, Dip: diplopia, Dizz: dizziness, DM: diabetes mellitus, Dys: dysarthria, E: epilepsy, EPR: extensor plantar, FD: facial dysmorphia, FS: frontal signs, GD: gait difficulty, GBA: generalized brain atrophy, GEN: gaze–evoked nystagmus, GP: gaze palsy, GTC: generalized tonic-clonic seizures, Ha: hands, He: head, HL: hearing loss, HT: Hashimoto's thyroiditis, Hy: hypogonadism, Imp: impulsivity, Irr: irritability, L: limbs, LTL: low testosterone levels, Me: meningioma, MMSE: Mini Mental

728C>T	731_732 delGC	787–1G>C	788G>C	791_792 delTG	794G>A	818_819 dupGC	823_824 delCT	824delT	849C>G
NA	NA	NA	+	–	– 1/2 NA 1/2	P 1/2 – 1/2	P 8/13 – 5/13	NA	NA
– 2/2	NA	–	–	–	P 1/2 – 1/2	–	– 13/13	P	NA
– 2/2	P 3/9 – 5/9 NA 1/9	–	–	+ 2/2	– 2/2	–	+ 1/13 P 3/13 – 9/13	–	NA
– 2/2	P 5/9 – 4/9	–	–	+ 1/2 (He) ++ 1/2 (Or, L)	+ 1/2 – 1/2	+ 1/2 (Ha) ++ 1/2 (He)	++ 1/13 (He, Or) P 2/13 – 9/13	–	NA
P 1/2 – 1/2	NA	–	–	–	– 1/2 NA 1/2	++ 1/2 (Bl, Ce, UL) – 1/2	+ 1/13 (Ce) P 3/13 – 9/13	–	NA
P 1/2 – 1/2	NA	P	+	–	– 2/2	+ 1/2 –1/2	P 2/13 – 9/13 NA 2/13	–	–
NA	P 5/9 – 4/9	Ap	++ (Anx, Dep, Imp)	++ 1/2 (Ap, Irr) – 1/2	Del 1/2 NA 1/2	++ 1/2 (Anx, Irr) – 1/2	Anx 7/13 OPD 2/13 Dep 1/13 – 5/13	NA	NA
– 2/2	P 9/9	P	P (CCAS)	MMSE 14/30 MMSE 16/30	P 2/2	MMSE 13/30 MMSE 17/30	CCAS 11/13 Apr 3/13 Pal 3/13 Aph 1/13 – 1/13 MMSE 24/30	–	–
–	BSP 4/9 GP 4/9 GBA 4/9	Myo	BSP, Br	BSP 2/2 SSa 1/2 Me 1/2	BSP 1/2 SSa 1/2 Cat 1/2 Ny 1/2 DAT 1/2	BSP 1/2 DM 1/2 UTS 1/2	UTS 7/13 SS: 3/13 Ny 1/13 Str 1/13	–	–
NA	P 6/9 – 2/9 NA 1/9	NA	+++	++ 1/2 NA 1/2	+++ 1/2 NA 1/2	++ 2/2	+ 3/13 ++ 3/13 +++ 1/13 P 1/13 NA 5/13	NA	NA
8	7	8	This study	5	8, 9	5	2, 4, 5	8	8

State Examination, Mu: mutism, Myo: myoclonus, NA: not available, Ny: nystagmus, OMA: oculomotor apraxia, Op: ophthalmoparesis, OPD: organic personality disorder, Or: oral, P: present without grade of severity, Pal: palilalia, Park: parkinsonism, PCh: personality changes, Psy: psychiatric disorders, Pt: ptosis, SARA: Scale for the Assessment and Rating of Ataxia, Sc: scoliosis, SD: saccadic dysmetria, SDFS: spinocerebellar disability functional score, SH: self-harm, SP: saccadic pursuit, SS: short stature, SSa: slow saccades, Str: stroke, TA: tongue atrophy, TC: thyroid cancer, Tr: tremor, U: unsteadiness, UL: upper limbs, UTS: urinary tract symptoms, W: weight loss, WB: wing-beating, +: mild, ++: moderate, +++: severe, –: not present, *: the first symptom in two patients was GTC at ages 5 and 12, while ataxia appeared at ages 22 and 40 in these subjects, ** only one patient's age at onset was available, ***: in the first 10 years of the disease.

Irodalom

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