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Clinical Spectrum of Kufor-Rakeb Syndrome in the Chilean Kindred with *ATP13A2* Mutations

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Video 

Abstract: We report the clinical features of the original Chilean family with Kufor-Rakeb syndrome (KRS) that led to the discovery of the *ATP13A2* gene at the PARK9 locus. KRS is a rare juvenile-onset autosomal recessive disease characterized by progressive Parkinsonism, pyramidal signs, and cognitive decline in addition to vertical gaze palsy and facial-faucial-finger minimyoclonus. Neurological and neuropsychological examination during a 10-year period, videotaping, neuroimaging, and measurement of DNA methylation of the *ATP13A2* promoter region were performed. The youngest 5 of 17 children of nonconsanguineous parents, carrying compound-heterozygous *ATP13A2* mutations, had normal development until ages ~10 to 12 years, when school performance deteriorated and slowness, rigidity, and frequent falls developed. Examination revealed bradykinesia, subtle postural/action tremor, cogwheel rigidity, spasticity, upward gaze palsy, smooth pursuit with saccadic intrusions, and dementia. Additional signs included facial-faucial-finger minimyoclonus, absent postural reflexes, visual/auditory hallucinations, and insomnia. Levodopa response could not be fully judged in this family. T2* magnetic resonance imaging sequences revealed marked diffuse hypointensity of the caudate (head and body) and lenticular nucleus bilaterally. Disease progression was slow including epilepsy, cachexia, and anarthria. Four affected members died after 28.5 ± 5.5 (mean ± SD) years of disease. Two heterozygous carriers, the mother and eldest sibling, showed jerky perioral muscle contractions and clumsiness of hand movements. There was no significant correlation between DNA methylation of the *ATP13A2* promoter region and disease progression. The marked caudate and lenticular nucleus T2*-hypointensity suggests that KRS might belong to the family of neurodegenerative diseases associated with brain iron accumulation. © 2010 Movement Disorder Society

Key words: juvenile Parkinsonism; *ATP13A2* mutations; minimyoclonus; saccadic pursuit; DNA methylation

Additional Supporting Information may be found in the online version of this article.

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Kufor-Rakeb syndrome (KRS) is an autosomal recessive form of juvenile Parkinsonism[1–4] (JP) first described in 1994 in a consanguineous family from Kufor-Rakeb, Jordan.[5] Starting at age 10 to 13 years, five affected siblings showed rigidity, bradykinesia, and mask-like faces, accompanied by cognitive deterioration and upward gaze palsy, with initial good response to levodopa (L-dopa) treatment. Brain imaging showed generalized brain atrophy.[5,6] A 10-year follow-up of the four surviving members identified new features, including facial-faucial-finger minimyoclonus, visual hallucinations, and oculogyric dystonic spasms.[7] Molecular genetic studies revealed three loss-of-function mutations in a lysosomal type-5 P-type ATPase (*ATP13A2*) in all five affected members of a Chilean family (compound-heterozygous state) and the Jordanian family (homozygous state).[8] Subsequently, two novel missense *ATP13A2* mutations have been described in two sporadic JP patients.[9,10]

The clinical picture associated with *ATP13A2* mutations (PARK9[11]) differs significantly from that associated to mutations in other recessive genes (*Parkin*, *DJ-1*, *PINK1*), which are clinically almost indistinguishable from sporadic PD.[12–16] However, very little detailed clinical information has yet been reported on patients suffering from KRS, which is currently limited to the Jordanian family and two isolated cases. Therefore, we performed a detailed, longitudinal family study to characterize the clinical features of affected individuals in the Chilean pedigree.

PATIENTS AND METHODS

A nonconsanguineous couple with 17 children living in Puente Alto, Chile had the youngest five siblings affected by KRS (Fig. 1). Four of them have been followed since 1999 (II-15 died in 1996). All examinations, tests, videotapes, and video-oculography were performed with informed consent and approval of the Hospital Sótero del Río and Luebeck Ethics Committees. A neurological assessment with the motor Unified Parkinson's Disease Rating Scale (UPDRS-III) was applied to the mother, four affected, and one asymptomatic sibling. Two affected and two asymptomatic members were videotaped. The mini-mental state of Folstein[17] (MMSE) was performed in three patients. Neurological evaluations, electroencephalograms, and CT scans performed before 1999 were obtained from medical records. Information on II-15 was gathered through the mother and older siblings. None of the affected had children. Currently, only II-14 is alive; three affected siblings (pneumonia) and the father (heart attack) died during the last 3 years.

Heterozygous and non-*ATP13A2* mutation carriers willing to participate (two refused), also underwent neurological examination, UPDRS-III, videotaping, and neuropsychological testing [MMSE, Frontal Assessment Battery (FAB),[18] Letter A fluency, Semantic fluency, Rey figure copy[19]]. Videotapes of these examinations were blindly reviewed by Drs. C.K. and J.H. to independently evaluate possible signs in heterozygous members.

Neuroimaging Studies

Magnetic resonance imaging (MRI) was performed in patient II-14 and heterozygous carriers I-2 and II-1 with a 1.5 T Magnetom Symphony Maestro Class MRI unit (Siemens, Erlangen, Germany) with maximum gradient amplitude of 25 mT/m. T2* sequences parameters (acquired with 6 echoes): slice number = 30/thickness = 2.5 mm/nogap/TR = 2510 milliseconds/TE = 53 milliseconds/flipangle = 30°/FOV/matrix/NEX = /180 × 150 mm^2/384 × 202/1. A 1-year follow-up measurement was performed in patient II-14 with a 3.0 T whole-body scanner (Philips, Achieva, Hamburg, Germany) using a T1-and T2-weighted FLASH three-dimensional MR sequence with the following T2-sequence parameters: slice number = 170/thickness = 1 mm/nogap/TR = 2500 milliseconds/TE = 260 milliseconds/flip angle = 90°/FOV224 224 170. MRIs were analyzed by two independent neuroradiologists blinded to the clinical/genetic status.

Promoter Methylation Analysis

Quantification of DNA methylation in the *ATP13A2* promoter region was carried out by bisulfite genomic sequencing using the pyrosequencing technology as described previously.[20] Briefly, bisulfite conversion of 1 μg DNA per sample was performed using the EpiTect Bisulfite Kit (Qiagen, Hilden, Germany) following the manufacturer's protocol. The CpG rich region was amplified by nested PCR using AmpliTaq Gold (Applied Biosystems) and biotinylated reverse primers for the inner PCRs. The biotinylated PCR products (25 μL) were cleaned up using Streptavidin Sepharose™ High Performance (GE Healthcare, Uppsala, Sweden) and a PyroMark Vacuum Prep Workstation (Biotage, Uppsala, Sweden) and the purified single-stranded PCR products were used for the pyrosequencing reactions. Pyrosequencing was carried out according to the manufacturer's protocol using Pyro Gold Reagents (Qiagen) and the PSQ96 MA Pyrosequencing System (Biotage).

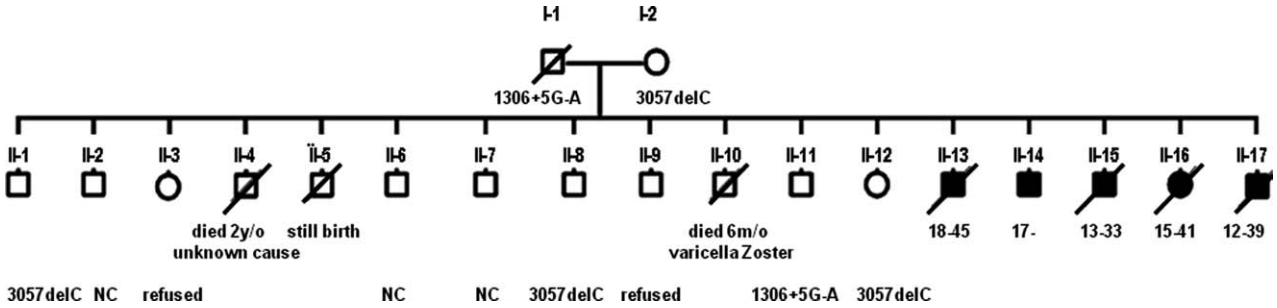

FIG. 1. Pedigree of the Chilean family with Kufor-Rakeb Syndrome. Pedigree symbols: circle, female; square, male; filled, affected; unfilled, unaffected; strike through, deceased. Age at onset-age at death of affected, carrier status, (NC = nonmutation carrier), and cause of infantile death are indicated underneath symbols. Since all family members (affected and unaffected) were included in this study, patients II-13, II-14, II-16, and II-17 correspond to patients II-8, II-9, II-10, and II-11 in the previous report.[8]

Quantification of DNA methylation was performed using the Pyro Q-CpG software (Biotage). Primer sequences and PCR conditions are available on request.

RESULTS

Clinical Findings

The father (I-1), a heavy drinker and municipal employee, refused formal neurological examination. Casual observation showed no major abnormalities. He died of myocardial infarction at age 84 years. The mother (I-2), a 79-year-old housekeeper has hypertension and frequent falls. Three of 17 children died young: still birth, varicella zoster (6 months), and unknown cause (2 years). The eldest nine siblings, ages 47 to 62 years, were healthy (II-1-3, II-6-9, II-11, and II-12). The youngest 5 (II-13-17) had normal development until ages 10 to 13 years (Fig. 1). Clinical features in all affected siblings were quite uniform. The disease started insidiously with deterioration in school performance and fatigue, interpreted as "laziness." The disease progressed slowly with difficulty rising from chairs, slowness of movements and speech, rigidity, and frequent falls. Detailed interrogation of the mother and school records revealed that intellectual deterioration was 3 to 5 years before the onset of motor symptoms, considered previously the AAO.[8] (Table 1).

Patient II-15 was the first to develop the disease. At age 10 years, he showed a decline of school performance and 2 to 3 years later, the teacher recommended medical evaluation because of slow movements. He was diagnosed with JP after thorough evaluation at a pediatric hospital, but medical records were unavailable. The disease progressed slowly to prostration. He died of pneumonia (age 33 years) in 1996, before this study was initiated. The disease was very similar to his siblings according to the mother and elder siblings' reports.

Patient II-16, the second to show symptoms, had normal development until around age 10 years when school performance deteriorated. Five years later, she developed fatigue and bradykinesia. Her first neurological evaluation (age 18 years) described slowed speech, slightly stooped gait, diminished arm swing, cogwheel rigidity in the elbows and wrists, and pursuit with saccadic intrusions (hereafter referred to as saccadic pursuit) on neuro-ophthalmologic assessment. Head CT was normal; EEG showed diffuse slowness. Walking and talking progressively deteriorated. Four years later, there was generalized rigidity, hypokinesia, cogwheel-rigidity with mild resting and postural tremor, hyperreflexia, spasticity, clonus, and bilateral Babinski signs. No cerebellar or sensory alterations were present. A CT scan showed cerebral and cerebellar atrophy. At age 37 years, she was almost mute, wheelchair-bound, had absent postural reflexes and generalized muscle atrophy with marked weight loss despite good appetite. At age 41 years, she was cachectic and mute; minimally obeyed commands with marked bradykinesia. Abundant facial and hand muscles minimyoclonus was present (video, Segment 1), very similar to the facial-faucial-finger minimyoclonus observed in the Jordanian family videos.[7] She died of pneumonia soon thereafter.

Patient II-17 suffered perinatal hypoxia after a prolonged pregnancy and Cesarean section, with left hemiparesis, left Babinski sign, spasticity and delayed developmental milestones. He walked at age 7 years, never learned to read or write. Around age 12 years, his walking and talking capabilities deteriorated. On his first neurologic evaluation (aged 33 years), he was cooperative, could nominate, repeat and comprehend two of three commands. There was spastic tetraplegia

TABLE 1. *Summary of clinical features of affected members*

	II-13[1]	II-14	II-15[2]	II-16[3]	II-17[4]
Age of onset (yr)	13	12	10	10	Around 12
Age at death (yr)	45		33	41	37
Duration of disease (yr)	35	>33	23	31	Around 25
Education	5th grade	4th grade	3rd grade	4th grade	0
Initial symptoms	Bad school performance, fatigue	Bad school performance, rigidity, bradykinesia	Slowness, fatigue, bad school performance	Fatigue, bad school performance	Slow progression, from birth, greater decline after ~12 yr
Extrapyramidal signs					
Tremor	−	−	+/−	−[5]	−
Cogwheel rigidity	++	++	++	−	−
Bradykinesia	++	+++	+++	+++	++
Hypomimia	++	+++	+++	+++	++
Ocular movements					
SN gaze palsy	Vertical	Vertical and horizontal	NA	Vertical and horizontal	Vertical
Saccadic pursuit	++	+++	NA	+++	++
Convergence	NA	Preserved	NA	NA	NA
Oculocephalic reflex	NA	Unaffected	NA	Preserved down	NA
Pyramidal signs					
Spasticity	++	+++	+++	Contractures	+++
Paresis	Mild, diffuse	Mod, diffuse	+++	Tetraparesis	Tetraparesis > left
Hyperreflexia	++	+++	+++	+++	+++
Babinski sign	Left	Right, left silent	Bilateral	Bilateral	Bilateral
Minimyoclonus					
Perioral	+	++	++[6]	+++	++
Face		++	++	+++	++
Hands	+	++	++	++	++
Insomnia	++	++	++	++	+
Hallucinations	Visual, severe	Auditory	−	Visual	−
Palmomentonean reflex	+	+	NA	+	+
End stage epileptic seizures	−	+	+	−	+
Age wheelchair-bound (yr)	32	34	15	25	12[4]
Loss of postural reflexes	+	+	+	+	+
Brain CT	28 yr: enlarged sulci	23 yr: enlarged sulci	NA	19 yr: normal, 21 yr: enlarged ventricles, 30 yr: diffuse atrophy	
Brain MRI		43 yr: mild diffuse atrophy, hypointensity of caudate			
EEG	Normal: 28 yr	NA	Not available	Slowness: 18 yr	NA
MMSE	NA	19/30: 39 yr		15/30: 37 yr	9/28[7]: 24 yr
L-dopa	Never tried	Not available initially, negative response, UDPRS change <20% at late stage	Not available initially, not tolerated (18 yrs after onset)	Not available initially, not tolerated (16 yr after onset)	Never tried
Trihexilphenidate	2–4 mg/day	2–4 mg/day	2–4 mg/day	Not tolerated	Never tried
Benzodiazepines	+	+	+	+	+

NA = not assessed.
[1]Last evaluation 1999 (age 38 years); refused further participation.
[2]Never evaluated by us, records unavailable.
[3]Last evaluation February 2007.
[4]Perinatal hypoxia; inaccurate AAO.
[5]Myoclonus.
[6]From mother/siblings' report.
[7]Illiterate, jerks, no clear parkinsonian tremor.
[8]Fifteen years after disease onset.

(>left), hyperreflexia, bilateral Babinski sign, and facial-faucial-finger minimyoclonus. He slowly progressed to prostration and died of pneumonia at age 37 years.

Patient II-13 hardly finished 5th grade at age 13 years and 5 years later showed slowness and rigidity. His first neurologic evaluation (at age 24 years) described bradypsychia, monotonous voice, stooped

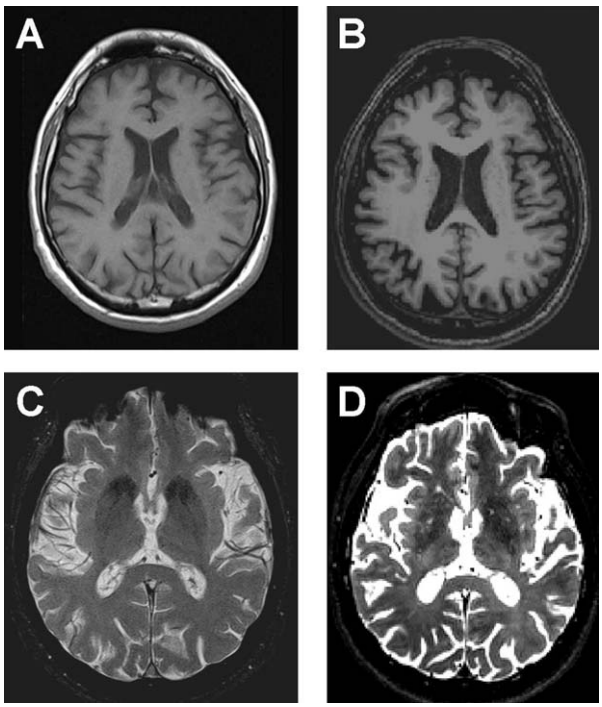

FIG. 2. T1 brain images showing generalized atrophy (**A**) without significant change 1 year later (**B**). T2* images showing decrease in signal intensity of the caudate and lenticular nucleus (**C**) without alterations of morphology or signal intensity in T1 sequences (A). The hypointensity increased at the dorsal portions of both nuclei after 1 year (**D**).

gait, reduced arm swing, left arm and bilateral wrist cogwheel-rigidity, generalized hyperreflexia, ankle clonus and left Babinski sign. There were no sensory or cerebellar signs. He showed diffuse brain atrophy on CT; EEG was normal. Trihexylphenidate had a mild effect, but the patient developed episodes of confusion and paranoid auditory hallucinations. Thioridazine 25 mg/day improved the hallucinations but worsened the extrapyramidal signs. At age 38 years, he was apathetic, with an unstable, stooped gait, upward gaze palsy, and facial-faucial-finger minimyoclonus. He died of pneumonia at age 45 years.

Patient II-14 had normal development until age 12 years, except for hypoacusis requiring audiphones. His first neurological evaluation (age 22 years) described generalized slowness, fine hand resting and postural tremor, stooped gait, diminished arm swing, bilateral wrist cogwheel rigidity, and generalized hyperreflexia, ankle clonus, and flexor plantar responses. Ocular movements, cerebellar, and sensory examinations were normal. CT revealed mild generalized brain atrophy. Trihexylphenidate (2–4 mg) was prescribed but increased auditory hallucinations. Disease progression was slow; at age 39 years, there was slurred speech, stooped and spastic gait with diminished postural reflexes. Upward gaze was normal, but saccadic horizontal smooth pursuit was present. The latest evaluation at age 44 years showed marked hypomimia, generalized bradykinesia, bilateral wrists/elbows cogwheel-rigidity, dystonic abduction of the left fifth finger on arm extension with slight postural tremor and interrupted movements on finger-nose testing. Marked diffuse spasticity and hyperreflexia, bilateral patellar cloni and right Babinski sign were observed, (video, segment 2). The patient was almost unable to walk unassisted with marked postural instability (video, segments 2 and 3). Minimyoclonic contractions of the perioral and frontal muscles were found (video, segment 4). Constructional apraxia, perseveration, and frontal release signs were also evident. At present, he spends the day sitting in a chair mumbling.

Eye movement examination revealed limited upward saccades correspondent to incomplete vertical gaze palsy. Saccades were slightly slow and hypometric with good initiation. Saccadic pursuit was present horizontally [confirmed by video-oculography (not shown)], as was slight gaze-evoked nystagmus horizontally ($\approx 40^{\circ}$), without spontaneous nystagmus in the primary position. The vestibulo-ocular reflex was undisturbed in all directions. Fixation was preserved (video, segment 4).

L-dopa was unavailable at the hospital at initial stages of the disease. Medical records indicated that L-dopa was tried in II-15 and II-16 at ages 28 and 26 years, respectively, but suspended due to nausea; II-13 and II-17 never received it. II-14 has taken L-dopa intermittently (nausea), with minimum improvement. Nevertheless, UPDRS-III was measured in patient II-14 before and after 20 and 45 minutes of administering 100 mg each of L-dopa/benserazide 100/25. The UPDRS improvement from 58 to 51–49 (12–15%) did not fulfill established criteria for responsiveness (>20%). Dyskinesias were never seen or recorded in medical records in any of the patients.

Neuroimaging

Serial follow-up MRIs of patient II-14 showed diffuse generalized cerebral and cerebellar atrophy without significant progression over the course of 1 year (Fig. 2A,B). T2* sequences revealed marked diffuse hypointensity of the caudate (head and body), and anterior lenticular nucleus bilaterally (Fig. 2C). In the follow-up examination, the dorsal portions of the caudate and anterior and posterior lenticular nucleus showed increase in hypointensity (Fig. 2D). MRIs performed in heterozygous carriers I-2 and II-1 (ages 81 and 62 years, respectively), revealed no T2* signal alterations.

TABLE 2. *Summary of carrier status and neurological evaluations of heterozygous carriers*

	I-1	II-1	II-2	II-6	II-8	II-11	II-12
Age (yr)	79	62	61	55	53	49	47
Carrier status	c.3057delC	c.3057delC	No	No	c.3057delC	c.1306+5G–A	c.3057delC
Clumsiness hand movements	+ left	+ left	–	–	–	–	–
Minimyoclonus	Perioral	Perioral	–	–	–	–	–
Gaze palsy	–	–	–	–	–	–	–
Neuropsychological tests							
MMSE	25	27	30	28	NA	29	29
FAB	9	17	18	17	NA	18	18
Letter A fluency	12	19	14	14	NA	13	11
Semantic fluency	7	22	21	22	NA	28	25
Rey figure copy	32	36	36	36	NA	36	36
Education (yr)	3	12	12	12	12	10	12

Expected values for neuropsychological testing: MMSE > 24, FAB > 15, letter A fluency > 9, semantic fluency > 12, Rey copy figures > 32.

Evaluation of Heterozygous and Nonmutation Carriers

Carrier I-2 (c.3057delC, the mother) showed normal speech and memory, mild hypomimia, stooped gait, and mildly decreased arm swing and postural reflexes. There was saccadic pursuit with preserved upward gaze, along with mild postural and intention tremor of the left arm, and bradykinesia on finger nose testing, tapping, and alternating movements, mild axial rigidity, postural instability, and left foot bradykinesia, without rigidity or resting tremor (UDPRS-III 13). Minicontractions of perioral muscles and slight jerky finger movements similar to those of II-16 and II-14 were observed. Carrier II-1 (c.3057delC, elder sibling), a 62-year-old guard-man that suffers from restless legs syndrome (untreated) showed subtle clumsiness and slowness of the left upper and lower extremities, and minicontractions of perioral muscles. Carriers II-8 (c.3057delC, 54-year-old guard-man), II-11 (c.1306 + 5G-A, 50-year-old cook), and II-12 (c.3057delC, 47 year-old, housekeeper), and noncarriers II-2 and II-6 (61-year-old guard-man, 55-year-old paramedic) showed no major neurologic alterations. Neuropsychological testing was normal in all examined members; except I-2 who had mildly reduced scores (FAB and semantic fluency), but only 3 years of education. Table 2 summarizes the heterozygotes' signs and neuropsychological tests.

Promoter Methylation Analysis

Although four of five affected members died approximately three decades after disease onset (28.5 ± 5.5, mean ± SD), patient II-14 is still alive showing a markedly milder disease progression compared with his haploidentical affected siblings. A possible explanation for this discordance is that yet unknown modulating factors might affect residual *ATP13A2* gene function in this patient. The *ATP13A2* promoter region contains a large CpG island with 96 putative DNA methylation sites surrounding the transcriptional start site. We quantified DNA methylation of the *ATP13A2* promoter region that was hypomethylated, with no significant correlation between DNA methylation and disease progression (Fig. 3).

DISCUSSION

Clinical Findings in Affected Compound Heterozygous *ATP13A2* Mutation Carriers

The clinical features of the Chilean family affected by KRS were very similar to those in the Jordanian family[5,7] with respect to age at onset and death, disease duration, and main symptoms with cognitive deterioration, extrapyramidal manifestations, pyramidal signs, and upward gaze palsy. The facial and hand minimyoclonus were strikingly similar, although chin myokymia or tremor of the lips and chin cannot be excluded. Although we did not find oculogyric spasm, saccadic pursuit was a constant sign. A slow and continuous progression was observed in our cases instead of the initial faster deterioration with later stabilization described in the Jordanian family.[7] Progressive deterioration was also described in the Brazilian and Japanese patients carrying missense homozygous mutations in *ATP13A2*.[10,11] The Brazilian case had onset (age 12 years) of an L-dopa-responsive severe akinetic-rigid Parkinsonism with supranuclear gaze palsy. Differing from the Chilean and Jordanian patients, he showed no cognitive decline or pyramidal signs. The Japanese woman had a later AAO (22 years), but was otherwise very similar to our patients, with amyotrophy, similar to patient II-16.

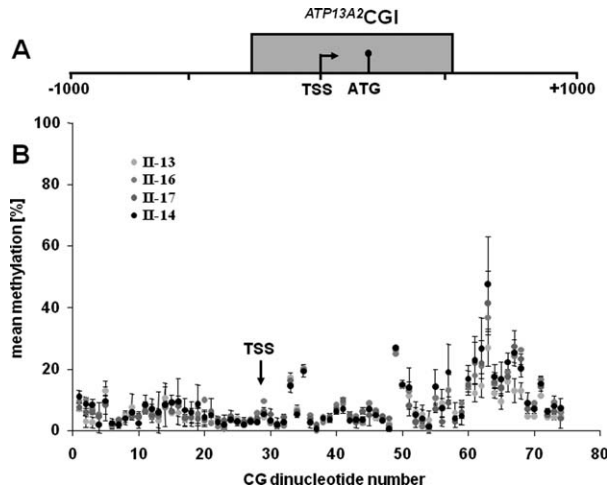

FIG. 3. **A**: Schematic representation of a putative CpG island within the genomic region 1,000 nucleotides upstream and downstream of the *ATP13A2* transcription start site (NCBI36:1:17184440: 17186440), which was identified using the CpG island finder and plotting tool (www.EBI.ac.uk/emboss). This algorithm identified a single putative CpG island (*ATP13A2*CGI) with a length of 805 bp within the respective genomic region ranging from −246 to +559 relative to the TSS. No other putative CpG islands were found in a region 3,000 nucleotides upstream and downstream of the TSS. *ATP13A2*CGI contains 96 CG dinucleotides in total. **B**: The mean DNA methylation level (±SEM) of 74 CG dinucleotides surrounding the TSS in four patients (II-13, II-14, II-16, and II-17) are shown. The quantification of DNA methylation of each CG dinucleotide in each patient was repeated at least three times ($n \geq 3$). Comparison of DNA methylation levels of each CG dinucleotide between the severely affected family members (II-13, II-16, and II-17) and the patient with less severe outcome (II-14) did not reveal significant correlations between disease severity and DNA methylation (*t*-test, $P \geq 0.05$). With mean overall methylation levels of 7.8% (II-13), 10.2% (II-14), 9.1% (II-16), and 8.6% (II-17), respectively, the ATP13A2CGI appears to be hypomethylated.

The response to L-dopa could not be fully judged on the Chilean family. It could not be evaluated at initial disease stages of the disease, and later administration in three patients was not tolerated due to nausea. Patient II-14 in this study had less than 20% improvement with 100 to 200 mg L-dopa treatment, which does not fulfill criteria of responsiveness. An incomplete late-stage response to L-dopa was also seen in the Jordanian family and the KRS Japanese patient.[11] Severe hallucinations and psychotic behavior associated with antiparkinsonian treatment have been reported previously. Hallucinations, visual (II-13 and II-16), and auditory (II-14), that could be attributed to medication were present in our patients; however, II-16 had visual hallucinations without medication suggesting they may be part of the disease.[20] Marked insomnia, possibly related to brain stem involvement was observed in advanced stages of the disease. The striking retropulsion is also of interest and may indicate striatal or pallidal involvement.

Evaluation of heterozygous carriers revealed the presence of very subtle neurological signs. These were clearly present in the mother (I-2) and elder sibling (II-1), but not in the younger heterozygous siblings, suggesting the existence of an age-related progression of signs. These very mild signs may point toward a possible phenotypic effect in heterozygous carriers that requires systematic follow-up investigation. Single heterozygous mutations in other putatively recessive PD genes have also been considered a potential susceptibility factor.[12,16,21] Larger, longitudinal studies, along with neuroimaging of the dopaminergic system will be required to test the hypothesis of heterozygous *ATP13A2* mutations acting as a possible risk factor for Parkinsonism.

Differential promoter methylation of *ATP13A2* did not explain variable disease expression as was recently shown for *SMN2* gene promoter methylation levels correlating with the progression of spinal muscular atrophy.[22]

Neuroimaging

A novel finding was an abnormal T2* MRI diffuse hypointensity of the caudate and lenticular nucleus in patient II-14 that progressed over the course of 1 year. The basal ganglia hypointensity probably represents ferritin deposits, since no associated hyperdensity was present on CT scans. Therefore, KRS may be a new member of the growing family of neurodegenerative diseases associated with brain iron accumulation (NBIA).[23] No *postmortem* studies have been performed in KRS to date, and the underlying mechanisms by which homozygous *ATP13A2* mutations might lead to increased iron deposition remain speculative. Interestingly, YPK9p, the yeast orthologue of the human ATP13A2 protein plays a role in the sequestration of divalent heavy metals.[24]

The detailed clinical description of the Chilean KRS family with *ATP13A2* mutations revealed that, similar to previous descriptions, disease onset is early and the clinical features outrange the typical symptoms of Parkinson's disease, including cognitive decline, supranuclear gaze palsy, spasticity, saccadic pursuit, minimyoclonus, insomnia, and caudate and lenticular ferritin deposits; an overall quite unique constellation. Other inherited JP, such as Parkinsonism due to *Parkin*, *PINK1*, and *DJ-1* mutations, and other causes of JP, such as dopa-responsive dystonia or spinocerebellar ataxias are clearly different from KRS.

Legends to The Video

Segment 1. Patient II-16 with end-stage disease, bed-ridden, and cachectic. Marked hypomimia, preserved horizontal gaze, and upward gaze palsy with preserved downward gaze on doll's eye maneuver. Abundant minimyoclonic contractions of facial muscles; palmomental and prehension reflexes present. Passive elevation of upper extremities elicits myoclonic movements of arms and hands. Bilateral Babinski and spasticity of lower extremities. She died 1 month after this recording.

Segment 2. Patient II-14. Marked hypomimia, severe generalized bradykinesia of fine hand movements greater on the left side. Hyperreflexia on upper and lower extremities, Babinski sign on the right, unequivocal on the left. Almost unable to walk unsupported, difficulty turning with start hesitation and freezing.

Segment 3. Patient II-14. Complete lack of postural reflexes.

Segment 4. Patient II-14. Abundant minimyoclonus of chin muscles. The patient was instructed to follow the examiner's finger to the right, then left, up, down, and up again. Note the pursuit with saccadic intrusions horizontally. Incomplete upward gaze palsy, preserved downward, and horizontal gaze. Undisturbed horizontal and vertical doll's eye movements (vertical vestibulo-ocular reflex not shown). Saccades were limited for upward gaze, slightly hypometric and had a slight reduced velocity. Saccade initiation was good.

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