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Research Report

Kufor-Rakeb Syndrome/PARK9: One Novel and One Possible Recurring Ashkenazi ATP13A2 Mutation

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Abstract. Kufor-Rakeb syndrome (KRS)/PARK9 presents with autosomal recessive young onset Parkinson's disease (YOPD), spastic paraparesis, abnormal eye movements and facial myokymia. KRS is caused by homozygous/compound heterozygous inactivating mutations in *ATP13A2*. Two affected siblings (born to non-consanguineous Jewish parents) presenting a similar KRS phenotype (onset age 27, 23), carried compound heterozygous pathogenic variants in *ATP13A2*: c.217_218insG and c.3057delC. Allele frequency of the c.3057delC mutation was about 100 times higher in Ashkenazi controls in our study (1/190 = 0.00526) and in the Genome Aggregation Database, (GnomAD, 27/10132 = 0.002665) versus non-Ashkenazi controls worldwide in GnomAD (9/264566 = 0.000034018, $p < 0.0001$). The c.217_218insG mutation is novel and not found in controls or GnomAD. The c.3057delC mutation should be included in the genetic workup of Ashkenazi YOPD patients.

Keywords: Parkinson's disease, Parkinsonism, Genetics, PARK9, Kufor-Rakeb syndrome, Ashkenazi

INTRODUCTION

Kufor-Rakeb syndrome (KRS) or PARK9 (OMIM #606693) is an autosomal recessive (AR) disorder clinically hallmarked by young onset of Parkinson's disease (PD), caused by homozygous or compound heterozygous inactivating mutations in the *ATP13A2* gene (OMIM# 606693). *ATP13A2,* localized to chromosome 1p36, encodes a transmembrane endo-/lysosomal-associated P5 type transport ATPase: ATP13A2 (OMIM*610513) [1–3]. Pathogenic *ATP13A2* mutations are loss-of-function mutations leading to alpha-synuclein accumulation [2, 4]. Clinically, the phenotype of KRS can be distinguished from that of idiopathic PD, both by young age at onset (before the 4th decade) and the additional neurological signs that accompany the parkinsonian features [2, 4–7]. The combination of parkinsonian, cerebellar signs, spastic paraparesis, supranuclear gaze palsy and facial-faucial-finger mini-myoclonus/myokymia, accompanied by early

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cognitive decline, render the PARK9 phenotype unique and distinct from other AR, young onset PD (YOPD) forms [2, 4, 6–8]. Moreover, the KRS/PARK9 phenotype is highly variable; the prominent clinical picture may be that of complicated hereditary spastic paraplegia (HSP), thus KRS/PARK9 is also termed SPG78 [2]. In addition, homozygous/compound heterozygous *ATP13A2* mutations have also been associated with neuronal ceroid lipofuscinosis (OMIM#606693), a neurodegenerative disorder characterized by the intracellular accumulation of autofluorescent lipopigments [9].

First described in a Jordanian family from the Kufor-Rakeb region, PARK9 is a rare disorder diagnosed in less than 50 patients in a few dozen families of diverse ethnicity, but not in Jewish communities [2–4, 7, 10, 11]. Certain genetic forms of movement disorders (e.g. PD-PARK8 or torsion dystonia-DYT1) cluster in Jewish individuals due to social and cultural seclusion leading to genetic isolation and endogamous marriage patterns [12]. Here we report two patients born to a non-consanguineous marriage of parents of Jewish Ashkenazi and non-Ashkenazi origin, who are compound heterozygous for *ATP13A2* mutations, one of which is a novel mutation.

MATERIALS AND METHODS

All family members gave written informed consent for diagnostic genetic testing. Genetic testing was performed at the VIB Center for Molecular Neurology, University of Antwerp, Belgium. Individual II-2 was genetically profiled using a massive parallel sequencing gene panel based on the multiplex amplification of specific targets for re-sequencing technology (Multiplicom, Niel, Belgium; http://www.multiplicom.com) for the exonic resequencing of genes associated with HSP: *SPAST, ATL1, KIF5A, REEP1, DYNC1H1, SPG7, CYP7B1, SPG11, SPG15, BICD2, ATP13A2, L1CAM* and *PLP1*. Mutations detected in the *ATP13A2* gene (localizing to exons 3 and 26) were independently validated by Sanger sequencing. The PCR products were purified with ExoSAP-IT (USB, Cleveland, OH), directly sequenced with a Big Dye Terminator v.3.1 kit (Applied Biosystems, Foster City, CA) and electrophoretically separated on an ABI3730xl DNA Analyzer (Applied Biosystems). Co-segregation analysis of the variants with the disease was performed for all available family members. Both *ATP13A2* sequence variants were also genotyped in 95 Ashkenazi and 92 non-Ashkenazi Jewish unrelated controls, recruited and ascertained for ethnicity at the Genetics Institute, Sheba Medical Center using an ethically approved protocol.

Primers were: ATP13A2_exon3_fw: CGCCCAGG CTGATGTTTATTG, ATP13A2_ex2_rv: TTGGCACCCAAGCATCCTCC, ATP13A2_ex26_fw: GGTGGGGCCTCTGCTATC, ATP13A2_ex26_rv: TGGGGTGGACAGGGAAGGG.

RESULTS

Clinical characteristics

Two siblings born to non-consanguineous Jewish parents, (mother Ashkenazi German, father non-Ashkenazi, Iraqi origin), were clinically diagnosed at the age of 34 and 29, with HSP and YOPD. Both siblings (the probands) exhibited a similar phenotype, however the brother (II-2) was more severely affected than his sister (II-3). Both II-2 and II-3, were born at term by vaginal delivery after uneventful pregnancies, achieved childhood developmental milestones and developed into normal young adults. II-2 worked with computers in a high-tech company and II-3 studied graphical design.

The disease of II-2 presented at age 27 with difficulties in driving lessons. By age 28, gait disturbance were noted. Neurological examination at that time revealed spastic paraparesis, for which Baclofen treatment was initiated. He gradually developed cognitive decline and motor slowness. Brain MRI showed diffuse cortical atrophy with no pathological signals in the basal ganglia. Spinal MRI revealed no pathology. Lumbar puncture was normal including normal Tau levels. Dopamine transporter (DaT) imaging (6 years after onset) showed considerably reduced tracer uptake activity in both caudate and putamen. The patient received levodopa treatment which partially ameliorated the symptoms, but was stopped after 6 months due to paranoidal delusions and loss of any clinical efficacy. The gait deteriorated with frequent falls, and 16 years after the onset II-2 became wheelchair bound.

II-3 became symptomatic at age 23 with a generalized seizure, which recurred at age 26. At 27, gait disturbances were first noted and progressed to frequent falls and to wheel-chair. A diagnosis of spastic paraparesis was made at age 29. She later developed bradykinesia and emotional incontinence. Brain MRI showed generalized atrophy with no pathological

Table 1
Clinical characteristics of compound heterozygous carriers of the c.3057delC*ATP13A2* mutation: our patients and the Chilean family members*

Subject	II-2	II-3	Chilean*
Mutation	c.3057delC c.217_218insG	c.3057delC c.217_218insG	c.3057delC c.1306+5G>A
Protein	p.Tyr1020Thrfs*3 p. Val73Glyfs*25	p.Tyr1020Thrfs*3 p.Val73Glyfs*25	p. Tyr1020Thrfs*3 p.Gly399_Leu435del
Gender/age at onset	M/27	F/23	10–18
Age at examination	45	43	18–33
n years education	16	16	0–5
Presenting symptom	Gait	Seizure	Bad school performance Bradykinesia
Progression	Slow	Slow	Slow
n years until wheelchair	16	4	1–23
Cognitive deficits	Mild dementia	–	+
Behavioral/psychiatric	Levodopa induced Induced delusions Hallucinations	Emotional lability	Hallucinations
Seizures	–	+	+
Neurological examination			
Pyramidal and peripheral motor system			
UL/LL spasticity	–/+	–/+	+
UL/LL weakness	–/+	–/+	+
Increased tendon reflexes	UL/LL+/+	+/+	+
Extensor plantar response	+	+	+
Extrapyramidal motor system			
Bradykinesia	+	+	+
UL/LL rigidity	+/–	+/–	+
Tremor	–	–	+(3/5)
Dystonia	–	–	–
Spinocerebellar system			
Dysarthria	+	+	NA
Limb/gait ataxia	–/+	–/+	+
Oculomotor disturbances			
Slow saccades	+	+	+(4/5)
Supranuclear gaze palsy	+	+	+(4/5)
Facial myokimia	+	+	+
Sensory system			
Surface/vibration/position	–/–/–	–/–/–	–
Levodopa response	Partial motor Amelioration, delusions	Not used	Not tolerated

*Described in 5 individuals. Data derived from [3–6]. Please note that the ATP13A2 protein (OMIM*610513) originally described as p. 1019GfsX1021 [3] or later as p.G1019GfsX3 [4] is newly annotated as p.Tyr1020Thrfs*3 (NM_022089.2, NP_071372.1, ClinVar ID 465253).

signals in the basal ganglia. DaT Scan (7 years after onset) showed bilateral reduced uptake of the tracer mainly in the putamen and less prominently in the caudate.

Clinical details and neurological examination are summarized in Table 1 and ancillary tests in Table 2.

Genetic findings

The probands II-2 and II-3 carried compound heterozygous pathogenic variants in the *ATP13A2* gene: c.217_218insG (p.Val73Glyfs*25) and c.3057delC (p.Tyr1020Thrfs*3). A clinically unaffected brother (II-1) was carrier of the p.Tyr1020Thrfs*3 variant, the mother the p.Tyr1020Thrfs*3 variant and the father, the p.Val73Glyfs*25 variant. The genetic variant p.Tyr1020Thrfs*3 (OMIM*610513, NM_022089.2, NP_071372.1, ClinVar ID 465253) was reported as pathogenic by Ramirez et al. [3], in a Chilean family. Variant p.Val73Glyfs*25 is novel and not reported previously. Table 1 summarizes the clinical characteristics and Table 2 the ancillary examinations of our patients and of the Chilean compound heterozygous family members [3–6].

ATP13A2 mutation c.3057delC (p.Tyr1020 Thrfs*3) was genotyped in 95 Ashkenazi controls

Table 2
Ancillary tests of compound heterozygous carriers of the c.3057delC*ATP13A2* mutation: our patients and the Chilean family members*

Subject	II-2	II-3	Chilean*
Mutation	c.3057delC c.217_218insG	c.3057delC c.217_218insG	c.3057delC c.1306+5G>A
Imaging			
Brain MRI	Generalized brain atrophy	Generalized brain atrophy	Generalized brain atrophy
Spinal MRI	Normal	Normal	Not done
Brain iron accumulation	–	–	+
DaT Scan			
Reduced tracer uptake	Bilateral Caudate, Putamen	Bilateral Caudate, Putamen	Bilateral Caudate, Putamen
Nerve conduction studies	Normal	Normal	Not done
CSF	Normal	Normal	Not done

*Described in 5 individuals. Data derived from [3–6].

and one heterozygous mutation carrier was detected. *ATP13A2* mutation c.217_218insG (p.Val73Glyfs*25) was genotyped in 94 non-Ashkenazi controls and none was found to harbor this mutation.

DISCUSSION

Here we describe two Jewish siblings of mixed Ashkenazi-non-Ashkenazi ancestry, who presented with YOPD, supranuclear gaze palsy, facial myokymia, spastic paraparesis and abnormal DAT scans, who carry compound heterozygous inactivating mutations in the *ATP13A2* gene. The phenotype of KRS/PARK9/SPG78 in these cases is supported by the genetic findings. The distinction of KRS/PARK9/SPG78 from other YOPD, especially from common ones such as PARK2 or from other complicated hereditary paraplegias is essential, as early diagnosis of some PD forms has therapeutic value. Indeed, levodopa treatment may be beneficial in KRS, if administered early in the course of the disease, even if the beneficial effects are temporary [2, 4, 10, 13], as for patient II-2. Early recognition is also important for careful follow-up due to possible early drug induced psychotic phenomena.

The c.3057delC mutation was previously described in compound heterozygous carriers in a Chilean family [3–6]. The Chilean phenotype is more severe than the one observed here, with childhood onset and early cognitive involvement expressed as low elementary school performance. The non-Ashkenazi variant described herein: (c.217_218insG ** ATP13A2*) is novel and was not detected in any of an ethnically matched healthy controls. The "Ashkenazi mutation" (c.3057delC **ATP13A2*) was detected in this report in 1/95 Ashkenazi healthy individuals (1%) (1/190 alleles, allele frequency 0.00526). This allele frequency is similar in magnitude to that reported in 5061 Ashkenazi individuals for this clinical variant (27/10132 alleles, allele frequency 0.002665, $\chi^2 = 0.465$, $p > 0.1$), in the Genome Aggregation Database: GnomAD (http://gnomad.broadinstitute.org/variant/1-17313566-AG-A). This is about 100 times higher than the world-wide allele frequency of 0.000034018 reported in GnomAD (9/264566 alleles, $\chi^2 = 515.420$, $p < 0.00001$) when excluding Ashkenazi Jewish controls (http://gnomad.broadinstitute.org/variant/1-17313566-AG-A). While a single mutation in a genetically homogenous population, such as Ashkenazi Jews combined with the paucity of the same mutation in other, genetically heterogeneous ethnic groups, is suggestive of a founder effect, a conclusive proof of this possibility requires the haplotyping of all identical mutation carriers. It could also be argued that a mutational hot spot is observed because the c.3057delC mutation was previously reported in a Chilean family [3, 6], and rarely in Latino (6/34402 alleles), European non-Finnish (2/124510 alleles) and other unspecified population groups (1/6438 alleles), (http://gnomad.broadinstitute.org/variant/1-17313566-AG-A). The discrepancy between the numbers in Ashkenazi Jews and other populations, suggests that the possibility of a hot spot is less likely. Interestingly, *ATP13A2* mutations cause combined mitochondrial lysosomal impairments, adding another gene to the list of lysosomal-related PD in Ashkenazi Jewish patients after *GBA* and *SMPD1* (OMIM *607608) p. Leu302Pro founder mutation of type A Niemann-Pick disease [2, 12, 14–17].

If the preliminary data on rate of the c.3057delC**ATP13A2* mutation is further validated in a larger population-based study, it may indicate that Ashkenazi Jewish couples could be offered genetic screen for that specific *ATP13A2* mutation, in order to prevent homozygosity in the offspring. PARK9 should be considered as a possible diagnosis within the spectrum of young onset PD, especially when accompanied additional neurological signs suggestive of KRS. The c.3057delC**ATP13A2* mutation should be included in the genetic work-up of Ashkenazi patients.

CONFLICTS OF INTEREST

The authors have no conflict of interest to report.

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